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Fishman's PULMONARY DISEASES AND DISORDERS

VOLUME ONE & TWO

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Fishman's Pulmonary Diseases and Disorders

Volume 1

Notice

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Fishman's Pulmonary Diseases and Disorders

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Volumes 1 & 2

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To Barbara, Kristen, and Amy
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To Aaron, Brian, and Gayle
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To Martha, Jerry Flance, and Jack Pierce
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Preface

This book is now in its fourth edition. The first edition appeared in print in 1980. Each edition since then has provided a contemporary update of the growth of understanding of pulmonary disease and of the management of its clinical manifestations. Advances have been made in leaps and bounds. A 2006 review (Lopez et al.) summarized the impressive progress made in three key subsets of pulmonary medicine, chronic obstructive pulmonary disease (COPD), asthma, and critical care medicine.

COPD affords a practical illustration of the growth in understanding of a prevalent disease. The designation COPD, originally adopted as a convenient term for communication about the spectrum of chronic bronchitis and emphysema, now covers a wide range of clinical entities, ranging from predominant inflammation of the airways to disruption and over-expansion of the pulmonary paremchyma in emphysema.

COPD is the fourth leading cause of chronic morbidity and mortality in the United States. More than 12 million people have COPD and an additional 12 million do not know that they have the disease. Of all the leading killers, COPD is the only disease with mortality rates that are on the rise. World Health Organization projections indicate COPD will become the third leading cause of mortality worldwide by 2020.

Smoking is a predominant etiologic factor for COPD. However, as many as one of six people with COPD have never smoked. It is also understood that not all who smoke pay the price in terms of lung disease. The rates among women have dramatically increased since World War II. Vulnerability to harmful effects of smoking is believed to be rooted, at least in part, in genetic predisposition. This likelihood is currently under active investigation.

One particular limitation of the term "COPD" was recently highlighted by the advent of lung volume reduction surgery (LVRS) for the treatment of emphysema. It was clear from the outset that not all patients with emphysema are suitable candidates for LVRS. A major step toward the identification of those patients with emphysema who can be expected to benefit from the procedure was taken by the National Emphysema Treatment Trial (NETT). This trial, unique in its cosponsorship by three federal agencies—The National Heart, Lung & Blood Institute (NHLBI), The Health Care Finance Agency (HCFA) and the Agency for Health Care Policy and Research (AHCPR), began by excluding those patients with emphysema who were not likely to benefit from LVRS. These proved to be patients with a low FEV in conjunction with either homogeneous emphysema or a very low diffusing capacity for carbon monoxide (DLCO). In patients who proved to be eligible for LVRS, NETT took into account the risks posed by the surgical procedure and the fact that it affords no guarantee of successful outcome.

A second major study addressed the global impact of COPD. It has been estimated that in the United States almost 12 million people have COPD Smoking has long been known to be the predominant cause of COPD, but attempts at promoting widespread smoking cessation have largely been ineffective. Currently, COPD is being attacked on a variety of research fronts. Among these is the link between COPD and lung cancer. Other research is directed at clarifying the role of inflammation in the pathogenesis of COPD and trials of therapeutic interventions to minimize the ravages of the disease. Among the on-going trials are investigations which seek to determine the therapeutic effectiveness of novel agents, such as the phosphodiesterase inhibitors (PDE4 inhibitors). Other trials, using monoclonal antibodies seek to modify the inflammatory component of COPD. The global impact of COPD continues to provide impetus to the search for mechanisms that can be attacked therapeutically.

Looking back, the growth of pulmonary medicine has been punctuated and accelerated by certain iconic breakthroughs. Diagnostic radiology was revolutionized in the early 1990's by the introduction of spiral-computed tomography (CAT scan), which afforded a novel way to image the lung. Since then, improvements in the technology of the apparatus have enhanced its value as a diagnostic tool while enabling smaller doses of radiation to be delivered to the patients. Because of its ease of use and its availability, the use of the CAT scan has become widespread. In addition, continuing refinements hold promise of enhancing the

visualization of the microarchitecture of the lungs in health and disease.

Technological advances have played a key role in affording insights not only into the microarchitecture of the lungs but also into their physiological functions. Recent advances hold promise of even more to come. For example, the advent of virtual bronchoscopy has brought with it the likelihood of access to information about the bronchial tree and its surrounding structures without subjecting the patient to the stress of direct bronchoscopy. Moreover, the meaning of "virtual" continues to enlarge. Originally, the term referred to two-dimensional representations of the bronchial tree obtained by x-ray computed tomography (CT). Currently, the term also applies to more detailed images and less-intrusive methods obtained by such techniques as ultrasound or magnetic resonance imaging (MRI).

The newer imaging techniques not only afford static representations of the details of the airways and pulmonary parenchyma but also hold promise for functional studies, e.g., dynamic studies of pulmonary mechanics. Such studies would deal not only with the mechanics of the entire lung but also with the mechanics of regions of the lung. The increase in resolution on the one hand, and in the ease of acquisition of data on the other, has also enabled application of noninvasive imaging to the exploration of such functions of the lungs as ventilation-perfusion relationships.

Pulmonary medicine continues to be on the march. In recent years, the inclusion of sleep-disordered breathing has widened the scope of pulmonary medicine. National meetings devoted to pulmonary medicine attract ever-increasing audiences. This edition of "Pulmonary Diseases and Disorders" deals with the current understanding of lung diseases and the management of these diseases. Even a cursory comparison of this edition with previous editions reveals that considerable progress has been made in recent years. Despite this impressive progress, it is clear that much remains to be done. Patients and pulmonologists can look forward to further developments in the years ahead.

The experience and knowledge of each of the editors have been directed at ensuring that the specialized, as well as the general, aspects of pulmonary medicine have been expertly covered and well presented. Although the book is a collective arbeit, discussion and debate among the editors and authors have led to a collaborative and comprehensive work, integrated by a meeting of the minds and the sharing of the experiences. By the process of peer review, the book aspires to provide a readable and balanced coverage of what is latest and most meaningful in pulmonary diseases and disorders.

I have already indicated how much this book owes to the experts who comprise the editorial board. The editors, in turn, would have little to work with were it not for the splendid chapters contributed by the individual authors. And, in this edition, we also were aided by several medical fellows. My special thanks to Charles De La Cruz, Colin Gillespie, Howard Huang, Josh Kayser, Bianca Monteiro, Stephen Ryan, and Rael Sundy for their assistance. The editors also benefited greatly from close collaboration with the publisher whose personnel have listened carefully and implemented with patience and understanding.

I owe a great deal to those close to home. Betsy Ann Bozzarello, a collaborator for more than 20 years, managed to free time for me to devote to the book while she catalyzed and orchestrated the efforts of others. My family has provided the encouragement and peace of mind that such an effort inevitably calls for. My wife, Linda, has been unwavering in her tolerance and support. My daughter, Hannah, who is in her junior year at the University of Michigan and is trying her own hand at writing, is impressed by the enormity of the undertaking but remains optimistic about the outcome of such a venture. My sons, Mark and Jay, authors and editors in their own rights, share my conviction that this book is a worthwhile undertaking. Their spouses, Gayle and Martha, the former a nurse and the latter a pediatric pulmonologist, have also been supportive. I am greatly indebted to all of the above.

Alfred P. Fishman

SUGGESTED READING

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PART

I

Perspectives

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1

Milestones in the History of Pulmonary Medicine

Alfred P. Fishman

It has taken medicine more than 2000 years to reach its present level of clinical, scientific, and technologic sophistication. From the beginning, pulmonary medicine has been an integral part of this growth and development. About three hundred years ago, progress toward scientific medicine accelerated markedly, and it has continued to gain speed ever since: In the seventeenth century, research and experimentation began to tilt clinical medicine toward the exact sciences; by the eighteenth century, pathology had become an integral part of clinical medicine, and clinical-pathologic correlations began to succeed empiricism, dogmatism, and metaphysics in medicine. The age of the great clinicians dawned in Europe early in the nineteenth century, when autopsies became legally permissible and socially acceptable, and when physicians who cared for the patients ultimately performed the autopsy.

The road to current understanding and practice has been convoluted. Progress has been punctuated by delays, detours, and reversals. But it is possible to retrace the scientific trail by using iconic figures and discoveries to draw the map. Chapter 1 uses these milestones to trace the course of scientific pulmonary medicine up to the early twentieth century. The chapter goes no further, since more recent advances are more a matter of reporting than history. These advances are left to subsequent chapters in this book. This chapter deals only with certain of the key components of modern pulmonary medicine: alveolar-capillary gas exchange, lung volumes, mechanics of breathing, control of breathing, ventilation-perfusion relationships, and scientific clinical medicine.

ALVEOLAR-CAPILLARY GAS EXCHANGE

Ancient Greek Medicine

The beginnings of scientific medicine can be traced to ancient Greece in the sixth century B.C. Natural philosophers then speculated that air or some essential ingredient in air was inspired to generate a vital essence for distribution throughout the body.

Hippocrates, the "father of medicine," is as much a symbol of the Greek physician of the fifth and fourth centuries B.C., as the name of a real figure (Fig. 1-1). As an individual, he exemplified the caring physician who kept accurate records, made cautious inferences, and relied more on nature, rest,

Figure 1-1 The Hippocrates of Ostia. This damaged bust is believed to represent Hippocrates as perceived in antiquity. It was found in a family tomb in excavations near Ostia. *(Courtesy of Dr. Dickinson W. Richards.)*

and diet than on drugs for therapy. His name has been immortalized by affixing it to three major components of Greek medicine, even though none of these seems to be the work of a single individual. The first is the *Hippocratic corpus*, a collection of about 70 works that includes case reports, textbooks, lectures, and notebooks. The collection contains a description of Cheyne-Stokes breathing and the use of *Hippocratic succession* for the diagnosis of fluid and air in the pleural cavity. The second item is a collection of aphorisms, a compilation of brief generalizations relating to medicine. The third, which seems more attributable to Pythagoras (c. 530 B.C.) than Hippocrates, who lived about a century later (Table 1-1), is the *Hippocratic oath*, which not only represents the spirit of the physician of ancient Greece but has endured to modern times as a reflection of the ethical code of the physician.

Aristotle needs mention at this juncture because of his enduring influence on the intellect of humankind in his own time and for two millennia thereafter. Not until the seventeenth century were his doctrine of the four elements (earth, air, fire, and water) and that of Hippocrates (blood, phlegm, yellow bile, and black bile) laid to rest, thereby clearing the way for modern scientific medicine. Soon after Aristotle, about 300 B.C., an extraordinary medical school was founded at Alexandria in Egypt. One of the first teachers at this school, Erasistratus, postulated that the pneuma or spirit essential for life is somehow generated from interplay between air and blood. About four centuries after Erasistratus, Galen (Fig. 1-2) drew upon the medical, philosophic, and anatomic knowledge of his day to fashion a remarkable physiological schema. His construct was largely teleological. Unfortunately, it was so convincing that even though it was ultimately proved to be fanciful, it sufficed to retard scientific progress for a millennium and a half. Galen was a talented individual, well-educated, well-read, and well-positioned in society to popularize his beliefs. Moreover, his concepts fit well into the tenets of Christianity which was then beginning its ascendency; to contravert his authority was tantamount to blasphemy. Among his long-lasting, albeit erroneous, postulates, were the following: invisible pores in the ventricular septum that enabled the bulk of the blood to flow from the right ventricle to the left ventricle, thereby bypassing the lungs; a diminutive pulmonary circulation that served only to nourish the lungs; and two-way traffic in the pulmonary veins that enabled inspired air and effluent waste vapors to go their respective ways in the pulmonary veins (Fig. 1-3).

Every now and then, a voice did rise in protest—but without lasting effect. In the thirteenth century, Ibn An Nafis, writing in his *Canon of Avicenna*, objected that blood does not traverse the ventricular septum from right to left as Galen had proposed. However, this insight attracted little attention. Three hundred years later, Vesalius voiced similar misgivings. In the sixteenth century, Michael Servetus, a polymath trained in theology, geography, and anatomy, pictured the pulmonary circulation as the vehicle by which the inhaled spirit could be distributed throughout the body. In his theological treatise, *Christianismi Restitutio*, he pointed out that blood could not traverse the septum between the right and

Table 1-1

Landmark Figures in the Evolution of Modern Pulmonary Medicine

Alveolar-Capillary Gas Exchange

Ancient Greek Medicine

Hippocrates of CoS (c. 460–359 B.C.)
Aristotle (384–322 B.C.)
Erasistratus of Chios (c. 300–250 B.C.)
Galen of Pergamon (A.D. 129–99)
Ibn An Nafis (c. 1210–1288)
Leonardo da Vinci (1452–1519)
Miguel Servetus (1511–1553)
Andreas Vesalius of Brussels (1514–1564)
Realdus Columbus of Cremona (1516–1559)
Andreas Caesalpinus of Pisa (1519–1603)

William* Harvey *and the Oxford Physiologists

Galileo Galilei (1564–1642)
William Harvey (1578–1657)
Giovanni Alfonso Borelli (1608–1679)
Marcello Malpighi (1628–1694)
Robert Boyle (1627–1691)
Richard Lower (1631–1691)
Robert Hooke (1635–1703)
John Mayow (1640–1679)

Phlogiston:* The *Rise and Fall

Georg Erst Stahl (1660–1734)
John Black (1728–1799)
Joseph Priestley (1733–1804)
Carl Wilhelm Scheele (1742–1782)

Respiration and Metabolism

Antoine Laurent Lavoisier (1743–1794)
John Dalton (1766–1844)
Julius Robert von Mayer (1814–1878)
Carl von Voit (1831–1908)
Nathan Zuntz (1847–1920)

The Blood Gases

Joseph Black (1728–1799)
John Dalton (1766–1844)
Heinrich Gustav Magnus (1802–1870)
Felix Hoppe-Seyler (1825–1895)
Paul Bert (1833–1886)
Christian Bohr (1855–1911)
John Scott Haldane (1860–1936)
August Krogh (1874–1949)

Diffusion or Secretion of Oxygen

Joseph Barcroft (1872–1947)
Marie Krogh (1874–1943)

The Physical-Chemical Synthesis

Lawrence J. Henderson (1878–1942)

Mechanics of Breathing

John Hutchinson (1811–1861)
Karl Ludwig (1816–1895)
Franciscus Cornelius Donders (1818–1889)
Fritz Rohrer (1888–1926)
Wallace Osgood Fenn (1893–1971)

Control of Breathing

The Central Respiratory Centers

Thomas Lumsden (1874–1953)
Hans Winterstein (1878–1963)
Merkel Henry Jacobs (1884–1970)

The Peripheral Chemoreceptors

Ewald Hering (1834–1918)
Joseph Breuer (1842–1925)
Cornelius Heymans (1892–1968)

Scientific Clinical Medicine

Pathologic Anatomy

Gioranni Battista Morgagni (1682–1771)
Leopold Auenbrugger (1727–1809)
Jean Nicolas Corvisart (1755–1821)
René Theophile Hyacinthe Laënnec (1781–1826)

Microbiology

Robert Koch (1843–1910)

Physiology of the Pulmonary Circulation

Claude Bernard (1813–1878)
Auguste Chauveau (1827–1917)
Étienne Jules Marey (1830–1904)
Dickinson W. Richards (1895–1973)
André Frederic Cournand (1895–1988)
Werner Forssmann (1904–1979)

Figure 1-2 Galen of Pergamon as depicted in medieval times. No authentic reproduction exists of Galen in ancient times. *(From Galen's Therapeutica, published in Venice in 1500.)*

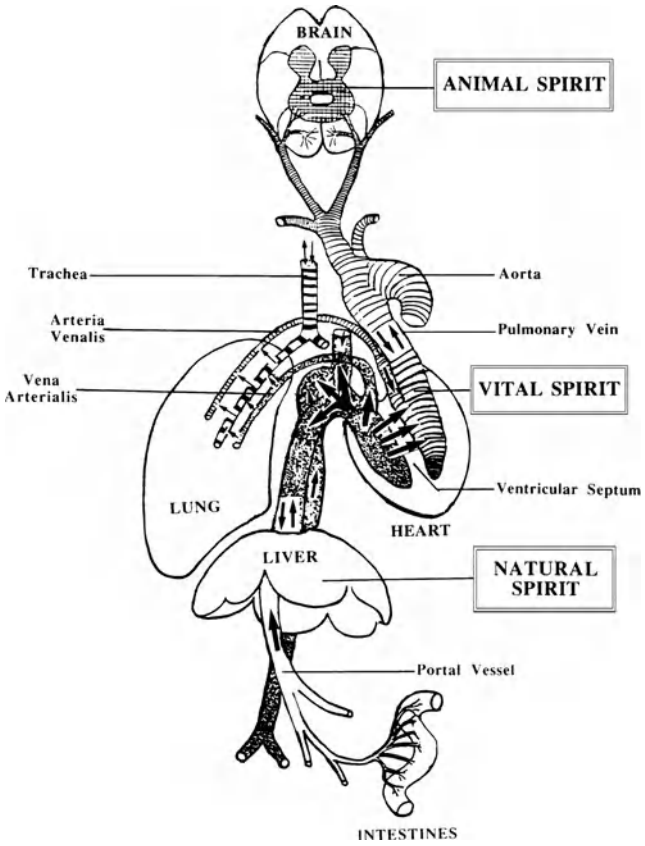

Figure 1-3 Galen's scheme of the circulation. The diagram shows the source and distribution of the three types of spirits. The validity of this scheme depended on invisible pores in the ventricular septum, two-way traffic in the pulmonary vein, and selective permeability of the mitral valve for sooty wastes but not for spirit-containing blood. Vena arterialis = pulmonary vein; arteria venalis = pulmonary artery. *(Modified after Singer C: A Short History of Scientific Ideas to 1900. London, Oxford University Press, 1959.)*

left ventricles and the lumen of the pulmonary artery was too large for a nutrient vessel. He became a hunted heretic, wanted for execution by both the Catholic Church and Calvin. He was warned by Calvin to stay out of Geneva. Both Servetus and Calvin then behaved predictably: Servetus showed up at a church where Calvin was preaching and Calvin had him captured and burned at the stake. In 1559, Realdus Columbus of Cremona, pupil of Vesalius, rediscovered the pulmonary circulation, as did Andreas Caesalpinus in 1571. Despite these challenging observations, Galen's schema was to last for more than another half century, i.e., until the physiological experiments of William Harvey.

William Harvey and the Oxford Physiologists

William Harvey (Fig. 1-4) was led to the discovery of the circulation of the blood by anatomic observations on the valves in systemic veins made by his mentor, Fabricus ab Aquapedente. Harvey's small book, *De Motu Cordis*, published in 1628, not only corrected a self-perpetuating error in Galenical teaching, but also marked the birth of modern physiology. However, the time was not yet ripe to relate the function of the heart to the physiology of breathing. To his dying day, Harvey clung to the idea that the main function of breathing is to cool the heart. Moreover, since he made no use of the microscope, he could not picture how the pulmonary arteries made connection with the pulmonary veins. Galileo invented the compound microscope in 1610. In 1661, using the compound microscope, Marcello Malpighi reported that alveoli were covered by capillaries and that blood and air were kept separate by the continuous alveolar-capillary barrier.

Harvey's description in 1628 of the circulation of the blood had three major consequences for pulmonary medicine: (1) it oriented pulmonary medicine toward the basic sciences and away from philosophy and empiricism; (2) it demolished the Galenic concept of the movement of the blood; and (3) it set the stage for an upcoming generation

Figure 1-4 William Harvey (1578–1657). This portrait of William Harvey is part of a family group in which William Harvey and his five brothers are gathered around their father, William Harvey.

of physiologists at Oxford University to explore breathing in terms of chemistry and physics.

The physiologists working at Oxford in the 1660s were greatly impressed by Harvey's disciplined approach to scientific inquiry. Many of these were medical practitioners who conducted research as a sideline. Four in particular began the systematic study of air and its constituents, thereby laying the foundations for contemporary respiratory physiology and medicine: Robert Boyle (Fig. 1-5), Robert Hooke, Richard Lower, and John Mayow. In 1660, Robert Boyle proved by means of his air pump that air is necessary for life. In 1667, Robert Hooke showed that insufflation of the lungs with air while breathing movements were arrested could keep an open-chest animal alive, i.e., that movement of the lungs was not essential for life. Richard Lower, the first to practice blood transfusion, took advantage of Hooke's continuously inflated lung preparation in the dog to observe that the dark venous blood becomes bright red as it traverses lungs insufflated with air. In 1674, Mayow interpreted the change in the color of blood from venous to arterial as due to the uptake of "nitro-aerial particles" (later to be called "oxygen") from the air.

Phlogiston: The Rise and Fall

Unfortunately, the discoveries and insights of the Oxford physiologists went largely unnoticed during the century that followed, overshadowed by the phlogiston theory of combustion. This theory, advanced by Stahl, postulated that all combustible materials were composed of two ingredients: phlo-

Figure 1-5 Robert Boyle (1627–1691). This engraving, from an original painting by Johann Kerseboom, hangs in the Royal Society, London. Boyle's invention of a pneumatic air pump and his publications concerning "the spring of air and its effect" stimulated considerable research on the physical properties of air and its role in respiration and combustion. He strongly influenced Hooke, Lower, and Mayow at Oxford.

giston, a principle that transformed into fire when heated, and an ash that was left behind after the fiery phlogiston escaped. The phlogiston theory was sufficiently malleable to accommodate almost every new discovery that could have overthrown it, including the rediscovery of carbon dioxide in 1754 by John Black and the independent discoveries of oxygen by Priestley and Scheele. Although the respiratory gases had been discovered by the end of the eighteenth century and many of their properties characterized, the discoveries were misapplied to support, rather than destroy, the phlogiston theory. The phlogiston theory was finally demolished by the experiments of Lavoisier.

Respiration and Metabolism

From the time of Hippocrates until early in the twentieth century, debate had continued about the site of heat production in the body. In 1777, Lavoisier suggested that air was composed of one respirable gas (which he later named "oxygine") and another (nitrogen) that remained unchanged in the

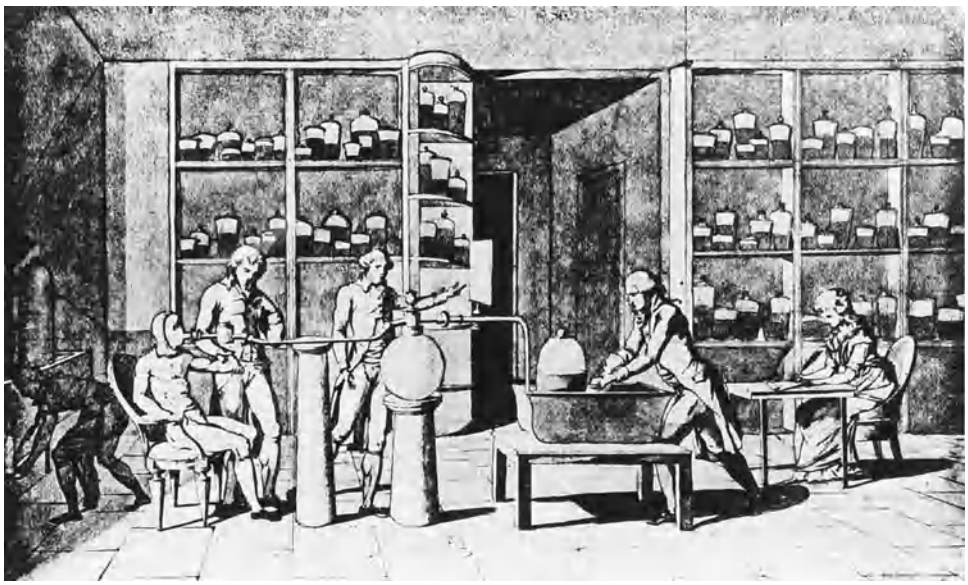

Figure 1-6 Scene from the laboratory of Antoine Laurent Lavoisier (1743–1794). His wife is acting as his assistant, and Sequin is the subject. Studies such as this led to the conclusion that respiration and circulation are similar processes.

course of respiration. Between 1782 and 1784, Lavoisier and Laplace concluded, on the basis of calorimetric experiments on guinea pigs, that "respiration is therefore a combustion, admittedly very slow, but otherwise exactly similar to that of charcoal" (Fig. 1-6). The similarity between respiration and combustion had previously been recognized by the Oxford physiologists, especially Mayow. By 1783, Lavoisier was accumulating evidence against the phlogiston theory and began to replace it with an entirely new system of chemistry.

As noted above, the ancients pictured the heart as the heat generator. Lavoisier favored the lungs. Others held that combustion occurred in the blood. Although Spallanzani had shown in the eighteenth century that isolated tissues take up oxygen and give off carbon dioxide; the idea that combustion occurred in the tissues was slow in gaining acceptance. Strength was infused into this hypothesis by Pflüger in 1878. He measured oxygen consumption and carbon dioxide production in dogs and calculated respiratory quotients. His research substantiated a concept that had been enunciated, but not named, by Lavoisier.

Once the idea that oxidation occurred in the tissues became generally accepted, investigators began to delve into the process involved in the utilization of foodstuffs by the tissues, energetics, growth, and repair. Carl von Voit and Max von Pettenkofer, using a respiration chamber, drew upon chemical balances and respiratory quotients in humans to distinguish the nature of the foodstuffs being burned and to show that the amounts of fat protein and carbohydrate burned varied with the mechanical work done by the subject. The law of conservation of energy was formulated by Julius Robert von Mayer between 1842 and 1845. Subsequently, Max Rubner showed that the law applied to the living body, and Herman von Helmholtz showed how its relevance to metabolism could be demonstrated experimentally. Application of these principles at the bedside was greatly facilitated by the development of a portable metabolic apparatus by Nathan Zuntz. Pioneering bedside studies of diverse metabolic states were conducted by a succession of distinguished investigators, including Magnus-Levy, Graham Lusk, F. G. Benedict, and Eugene F. DuBois.

The Blood Gases

The Oxford physiologists set the stage for the discovery of the blood gases. Using his vacuum pump, Robert Boyle extracted "air" from blood. John Mayow came close to discovering oxygen by showing that only part of air was necessary for life and that this part, his "nitro-aerial spirits," was removed both by respiration and fire (combustion). One of his famous experiments entailed enclosing a mouse and a lighted lamp in an air-tight container; the lamp went out first and then the mouse died. However, Mayow did not realize that the "nitro-aerial spirits" could be isolated as a gas.

One hundred years after Mayow, Joseph Priestley (Fig. 1-7) exposed a mouse to the gas released from heated mercuric oxide and found that the gas supported life better than did air; he also noticed that a flame burned more vigorously in this gas than in air. Priestley was not alone in his preoccupation with flame. In 1773, about a year before Priestley had obtained oxygen by heating mercuric oxide, Scheele discovered oxygen independently because of his interest in fire, and he designated oxygen as "fire air."

In 1662, Van Helmont, a Capuchin friar and talented chemist—a mystic with a drive to quantify—discovered carbon dioxide, coined the word *gas*, and called carbon dioxide "wild gas" ("gas sylvestre"). In 1755, Joseph Black rediscovered carbon dioxide. He showed that calcium carbonate (limestone) and magnesium carbonate (magnesia alba) lost

Figure 1-7 Joseph Priestley (1733–1804), the discoverer of oxygen. This figure shows a silver medal struck in his honor in 1783. A Presbyterian minister, he was radical in his religious and political beliefs, inventive in science, and conservative in the interpretation of his findings. *(From Fishman AP, Richards DW: Circulation of the Blood: Men and Ideas, New York, Oxford University Press, 1964, with permission.)*

Figure 1-8 Christian Bohr (1855–1911). At work in his laboratory, Bohr (far right) and his associates systematically explored the interplay between the respiratory gases and hemoglobin that led to the discovery of the ''Bohr effect." *(From Fishman AP, Richards DW: Circulation of the Blood: Men and Ideas, New York, Oxford University Press, 1964, with permission.)*

weight on heating, releasing "fixed air" (CO_2) in the process. This fixed air extinguished both flame and life. Lavoisier knew of the observations of Black and of Priestley and Scheele. He decided in 1778 that the gas obtained from heating mercuric oxide was not "fixed air" or "common air," but "highly respirable air" (oxygen).

The story of hemoglobin, the essential element in the transport of the respiratory gases by the blood, begins with Hoppe-Seyler, who, between 1866 and 1871, crystallized hemoglobin, explored its chemical properties, and assigned it a proper role in the transport of oxygen by the blood. At the turn of the nineteenth century, Dalton reported his experiments with the respiratory gases, which led to the development of his atomic theory. In 1872, taking advantage of Dalton's law, Paul Bert published the first oxygen dissociation curve, i.e., oxygen content at different barometric pressures; he pictured the curve as hyperbolic. Christian Bohr subsequently identified its s-shaped contour (Fig. 1-8) and in 1904, together with Hasselbach and August Krogh, showed that increasing carbon dioxide tension in blood drives out oxygen, i.e., the "Bohr effect." Shortly thereafter, the various influences, e.g., temperature and electrolytes, on the affinity of oxygen for hemoglobin—and consequently the position of the oxygen dissociation curve—began to be explored in detail by Barcroft and his associates. In 1914, Christiansen, Douglas, and Haldane reported that an increase in the oxygen tension of the blood drives out carbon dioxide, i.e., the "Haldane effect." In 1967, a new dimension was added to the understanding of the position and configuration of the oxygen dissociation curve by the demonstration that diphosphoglycerate, a chemical constituent of red cells, regulates the release of oxygen from oxyhemoglobin.

Diffusion or Secretion of Oxygen

Bohr is a central figure as an investigator and mentor in respiratory physiology. In 1904, he raised a troublesome issue that was not easily resolved, primarily because of limitations in methodology. He postulated that even though diffusion could account for the oxygen uptake at rest, it could not suffice during strenuous exercise, particularly at altitude. He held that oxygen secretion had to be involved. He held to this misconception during his lifetime, a conviction supported by two major lines of evidence. The first was indirect, i.e., oxygen secretion by the swim bladder of fish, which showed by extrapolation that active transport of oxygen in the lungs was possible. The second was based on observations made during his expedition to Pike's Peak in 1912, which showed (erroneously) that during exercise at altitude, arterial oxygen tension exceeded alveolar oxygen tension.

But, even before the report from high altitude, Bohr's former assistant August Krogh and his wife, Marie Krogh (Fig. 1-9) had marshaled new evidence to show that "the absorption of oxygen and the elimination of carbon dioxide in the lungs takes place by diffusion and diffusion alone." The final blow to the secretion theory was delivered by Marie Krogh. Based on the single-breath carbon monoxide method for determining diffusing capacity that she and her husband

Figure 1-9 August and Marie Krogh in 1922, at the time of their first visit to the United States so that August Krogh could deliver the Silliman Lecture at Yale. They demonstrated that diffusion, without secretion, could account for the transfer of O_2 and CO_2 across the alveolar-capillary membranes of the lungs. *(Courtesy of their daughter, Dr. Bodil Schmidt-Nielsen.)*

had developed in 1910, she was able to account for oxygen uptake in the lung by diffusion alone, even during strenuous exercise under conditions of low oxygen tension. Refinements in the carbon monoxide method by Roughton and others extended its clinical applicability and provided further evidence against the secretion theory. But Haldane would not let go. Throughout his life, despite mounting evidence to the contrary, he adhered to the idea that oxygen was secreted by the alveolar membrane.

Finally, the issue was settled by Joseph Barcroft (Fig. 1-10). Using a chamber to reproduce the hypoxic-strenuous exercise circumstances of the Pike's Peak expedition, he found that under all conditions, the arterial oxygen saturation of arterial blood was less than that of blood exposed to a sample of alveolar gas obtained at the same time. He subsequently confirmed these results by experiments done at high altitude, i.e., at Cerro de Pasco (1921–1922).

The Physical-Chemical Synthesis

Lawrence J. Henderson undertook the herculean task of depicting the reactions of oxygen and carbon dioxide in blood not as cause and effect but as interplay among physiochemical variables and functions (Fig. 1-10). In his theoretical considerations and practical applications via the Fatigue Laboratory at Harvard, he was greatly abetted by close collaboration with Van Slyke, Wu, and McLean at the Rockefeller Institute in New York, who were exploring the exchanges of blood constituents between red cells and plasma. In 1828, Henderson presented his synthesis in the form of a D'Ocagne nomogram that displayed the changes in the various elements that entered into the exchange of the respiratory gases between alveolar gas and blood: plasma; the red cell; hemoglobin; and chloride, bicarbonate, and hydrogen ions. He presented

Figure 1-10 Two founders of contemporary respiratory physiology in 1936. Sir Joseph Barcroft (1872–1947) *(left)* proved, in experiments on himself, that diffusion was the mechanism for gas exchange in the lungs and pioneered current understanding of the respiratory functions of the blood. Lawrence J. Henderson (1878–1942) *(right)* provided a mathematical analysis of blood as a physiochemical system and stimulated research on the complex interplay involved in respiratory gas exchange during exercise. *(From Fishman AP, Richards DW: Circulation of the Blood: Men and Ideas, New York, Oxford University Press, 1964, with permission.)*

nomograms not only for the normal subject at rest and during exercises, but also for individuals with anemia, nephritis, diabetic coma, and other major clinical entities. Henderson dealt with steady-state observations. Roughton and associates enlarged the physiochemical horizons further by discovering carbonic anhydrase in the red cell and dealing with transient phenomena relating to the transport of the respiratory gases and carbon monoxide in blood.

LUNG VOLUMES

Although Humphrey Davy had determined his own lung volume using hydrogen as the test gas in 1800, it was not until the 1840s that John Hutchinson laid the groundwork for modern pulmonary function testing: He devised a spirometer and used it to determine the subdivisions of the lung in a large number of healthy subjects, relating the measurements to height and age (Fig. 1-11). The many refinements since then are too numerous for mention in this chapter. A big step forward was the invention of the body plethysmograph many years later, which made possible the determination of the thoracic gas volume along with airway resistance and pulmonary capillary blood flow.

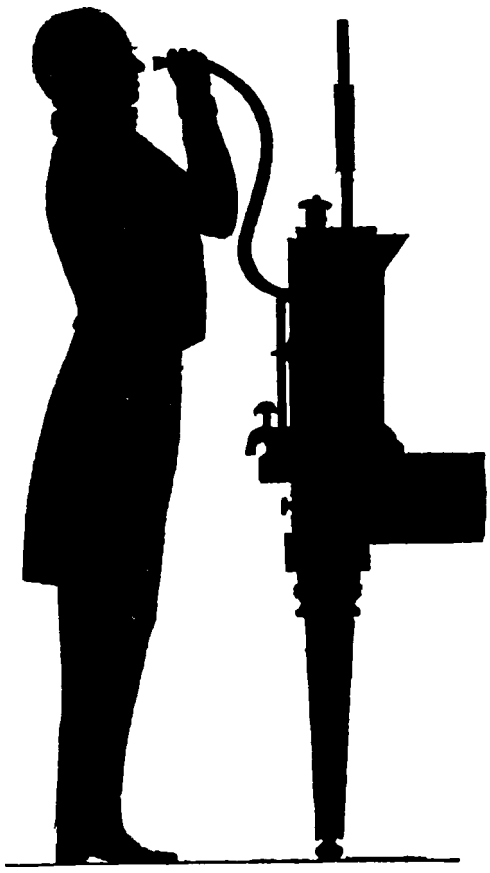

Figure 1-11 John Hutchinson's illustration of a subject about to undergo measurements of lung volumes. *[From Hutchinson J: Med Chir Soc (Lond) trans 29:137, 1846.]*

MECHANICS OF BREATHING

The ancients wondered about how air moved into and out of the lungs, and as far back as Erasistratus the diaphragm was recognized to be involved in breathing. Galen was aware that the lungs fill the chest cavity, they are moved by the actions of the thorax, and the large airways enlarge and lengthen during inspiration. He marveled at the long course of the nerves to the diaphragm and the innervation of the intercostal muscles. After Galen, interest in the mechanics of breathing waned except for sporadic observations and experiments by anatomists, notably Leonardo da Vinci and Andreas Vesalius. Interest resumed in the sixteenth century largely as a result of progress in physics and mathematics exemplified by the works of Borelli and Galileo.

The Respiratory Muscles

Mayow, one of the Oxford physiologists (Fig. 1-5), drew heavily on the work of colleagues, such as Boyle and Hooke, to develop considerable insight into the mechanics of breathing. He also built the first model on record of the chest as a bellows, which contained a bladder within it (Fig. 1-12). He understood that air moved into the lungs as the chest expanded because of the pressure and elasticity of ambient air, the chest expands because of the action of the intercostal muscles (internal and external), the diaphragm is the primary muscle of inspiration, and normal expiration is passive. After Mayow, little research was done on the role of the respiratory muscles in breathing until the mid-nineteenth century, when Donders distinguished between the respective roles played by the inspiratory muscles and elastic forces.

Elastic Properties of Lungs and Chest

Until the twentieth century, observations on the elastic properties of the lungs and chest cage in humans were fragmentary. Access to the pleural space was the major limiting factor. With few exceptions—notably Neergaard and Wirz, who used pleural pressures to determine elastic recoil in normal

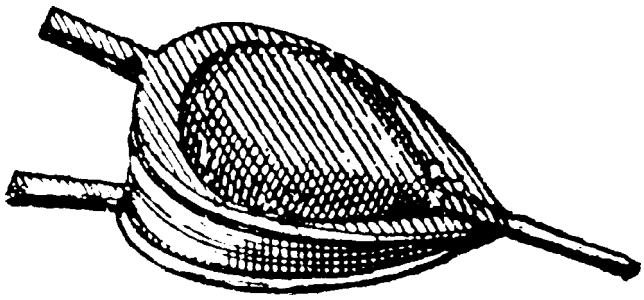

Figure 1-12 Mayow's model of the chest and lungs. The bellows encloses a bladder, the neck of which opens to the outside. A glass window on the upper side makes it possible to observe the bladder during inflation and deflation. *(From Mayow J: Medico-Physical Works, Crum A, Brown, Dobbin L (trans). Edinburgh, Alembic Club, Reprints, no 17, 1957. (Translated from Tractatus quinque medico-physics, 1674.)*

human subjects, and Christie, who recorded pleural pressures to demonstrate loss of pulmonary elasticity in emphysematous patients—measurements in humans were largely confined either to therapeutic interventions, e.g., induction of a pneumothorax or aspiration of pleural fluid, or experiments done at autopsy. The number of observations on the mechanical properties of the lungs increased dramatically when it was shown by Buytendijk, in 1949, and again by Dornhurst and Leathart, in 1952, that esophageal pressures provided an accurate measure of pleural pressures.

The role of alveolar surface tension in determining the elastic forces in the lungs began to be widely appreciated in the late 1950s, although the stage had been set long before then. In 1812, Laplace had published the law of surface tension. The implications of this law for the lungs began to be appreciated in 1929 when Neergaard compared pressure-volume curves of lungs filled with air with those filled with fluid. He concluded that unopposed surface tensions would favor alveolar collapse. Then, between 1954 and 1960, a remarkable outpouring of papers from different laboratories showed that a unique surfactant lined the alveoli, and this material was absent in premature infants with hyaline membrane disease (and alveolar collapse); these papers prompted extensive research, which continues to this day, on the chemical and physical properties of surfactant and on its sites of formation and removal.

Airway Resistance

A giant step forward began in 1916 when Rohrer, as part of his doctoral dissertation, presented a conceptual framework for determining flow/resistance in airways. His equations were based on precise anatomic measurements of airway dimensions in a human cadaver coupled with aerodynamic principles. During the following decade, he and his coworkers, Neergaard and Wirz, applied Poiseuille's law for laminar flow and his equations to the determination of airway resistance. Fleisch's pneumotachygraph with periodic interruptions of airflow was used as a strategy for measuring alveolar pressure. Measurements of alveolar pressure that were more useful clinically became available in 1956 with the introduction by DuBois and associates of the whole-body plethysmograph, which they coupled with the application of Boyle's law.

Synthesis of Mechanics

During the decade between 1915 and 1926, Rohrer and his colleagues provided a remarkably comprehensive synthesis of respiratory mechanics that included a description of the static pressure-volume characteristics of the respiratory system, the work of breathing; they also developed the principle of optimal frequencies of breathing to minimize respiratory work. Together with von Neergaard and Wirz, Rohrer developed and tested experimentally concepts involving pressures, flows, and volumes. The full significance of Rohrer's work was not appreciated until the publications by Fenn and his group at the University of Rochester starting in the 1940s. Although it is still premature to evaluate the contributions of W. O. Fenn, H. Rahn, and A. B. Otis to our present understanding of the mechanics of breathing, there is little doubt that this group shaped much of the contemporary thinking of respiratory physiologists and pulmonary physicians along this line.

CONTROL OF BREATHING

The control of breathing is a complex process that depends on the integrity of the entire respiratory system—lungs, airways, circulation, and control systems. Two dominant control systems exist: One is in the central nervous system, and the other is outside the brain. Control mechanisms in the central nervous system are influenced by the state of wakefulness or alertness and are subject to voluntary control. These mechanisms also are influenced reflexively by peripheral receptors of different kinds.

Localization of the Central Respiratory Centers

In 1812, Legallois, apparently intrigued by the gasping movements of the head after decapitation, identified an area in the medulla that was essential for life. In 1923, Lumsden systematically explored the effects of serial sections of the brain stem on respiration. This report marks the beginning of current lines of research on rhythmic breathing. He designated an area in the caudal pons responsible for a sustained inspirated drive as the "apneustic center" and an area in the rostral and lateral portions of the pons that presumably inhibited the apneustic drive as the "pneumotaxic center"; section of the vagi exaggerated the inhibition of the apneustic drive by the pneumotaxic center. Sixteen years later, Pitts and coworkers, using stereotactic stimulation of the cat medulla, identified inspiratory and expiratory centers and proposed a theory that could account for both rhythmic breathing and apneusis.

Chemical Stimulation of the Respiratory Centers

The chemical stimuli to breathing have been known for more than a century. In 1885, Miescher-Ruesch showed in humans that ventilation at rest is primarily regulated by carbon dioxide. Between 1887 and 1901, cross-perfusion experiments by Leon Fredericq underscored the role of carbon dioxide. But it was not until 1905 to 1909 that Haldane, Priestley, and Douglas paved the way to the modern understanding of the role of carbon dioxide under a variety of experimental conditions. In their experiments on humans, they relied heavily on the Haldane gas analyzer and an alveolar gas sampler of their own invention. However, their experiments did not distinguish clearly between CO_2 or H^+ in the stimulation of the respiratory centers. Winterstein and later Gesell advanced the idea that the chemical regulation of respiration is by the concentration of hydrogen ions within the respiratory centers.

The Winterstein theories provide a good example of the evolution of ideas prompted by new discoveries and

inventions. The original theory in 1911 attributed increments in ventilation caused by hypoxic or hypercapnic inspired mixtures to a single mechanism, i.e., acidification of arterial blood by either carbonic acid or lactic acid. In 1921, largely because of chemoreceptors, Jacob's demonstration of the rapid diffusion of carbon dioxide into starfish eggs implicated acidity within the respiratory centers, as well as arterial blood acidity, as the sites of stimulation. In order to account for the stimulation of breathing by hypoxia (the peripheral chemoreceptors had not yet been discovered), he invoked the release of asphyxiating substances (*Erstickungsstoffen*) within the respiratory centers themselves. A third theory in 1949, which attempted to incorporate the discovery of the peripheral chemoreceptors, finally gave way in 1955 to his fourth theory, which explained the effects of acid or hypoxia on both the central and peripheral chemoreceptors.

A major consequence of Winterstein's research was the impetus it gave to subsequent explorations of the chemical control of breathing. These explorations led to the identification of central chemoreceptors, distinct from mechanoreceptors, on the ventral surface of the medulla and clarification of the role of hydrogen ion activity as the central stimulus to breathing. It also prompted a search, which continues to this day, not only for the drives to ventilation arising from respiratory and metabolic acidosis, but also for a unifying theory for the chemical control of breathing.

The Reflex Regulation of Breathing

A considerable and diverse number of peripheral receptors can influence breathing reflexively by supplying information to respiratory centers located in the brain. These include pain receptors, stretch receptors in the muscles and distensible structures, and organs and chemoreceptors in major systemic arteries.

Mechanoreceptors

Until the work of Hering and his student, J. Breuer, little was known about the role of afferent impulses to the central control mechanisms in the control of breathing except that electrical stimulation of the vagus nerves influenced respiration. In 1868, Hering and Breuer reported that inflation of the lungs stopped respiration in expiration and promoted expiration and that, conversely, a decrease in lung volume ended expiration and promoted inspiration. They inferred that inflation had mechanically stimulated nerve endings in the lungs and the resulting impulses ascending the vagi were inhibitory to inspiration.

Peripheral Chemoreceptors

In 1841, Volkmann suggested the existence of chemoreceptors in the systemic circulation that were sensitive to blood-borne stimulants to respiration. In 1927, J. F. Heymans and C. Heymans first showed that the aortic bodies served this function, and in 1930, C. Heymans and Bouckaert demonstrated the peripheral chemoreceptive function of the carotid bodies. These were physiological observations that tallied well with the observations of F. De Castro, a student and later a colleague of Ramón y Cajal, who was sufficiently impressed by the histologic structure, location, and rich innervation of the carotid body to propose that it might be stimulated by blood-borne substances (Fig. 1-13).

VENTILATION-PERFUSION RELATIONSHIPS

In 1946, William Dock attributed the apical localization of tuberculosis to hypoperfusion of well-ventilated alveoli in the lung apices in the upright position. Shortly thereafter, ventilation–blood flow relationships were described in quantitative terms in papers by two separate groups: Rahn and Fenn, and Riley and Cournand.

SCIENTIFIC CLINICAL MEDICINE

Four remarkable figures may serve to illustrate different stages in the evolution of scientific pulmonary medicine: Morgagni, Laënnec, Koch, Cournand, and Richards. They represent pathologic anatomy, microbiology, and physiology.

Pathologic Anatomy

Two figures, almost a century apart, stand out in the contributions of pathologic anatomy to pulmonary medicine.

Morgagni

In the eighteenth century, a major contribution to scientific clinical medicine was made by Morgagni, a student of Valsalva (Fig. 1-14). Morgagni veered away from the undisciplined case reports of his predecessors. Instead, he adopted a logical system for relating findings at autopsy to their clinical manifestations. At age 79, he published a compilation of his lifelong experience in his famous work, *De Sedibus et Causis Morborum per Anatomen Indagatis. De Sedibus* includes about 700 cases. The clinical-pathological correlations in this work benefited greatly from the fact that Morgagni was both a seasoned clinician and a pathologist. One of the compilation's five books is devoted to diseases of the thorax. Among his descriptions were those of a tubercle undergoing liquefaction and the hepatization stage of pneumonia.

Laënnec

René Théophile Laënnec invented the stethoscope in 1816 (Fig. 1-15). At that time, clinical medicine in Europe, especially in France, was turning from metaphysic concepts and doctrinal systems to pathology as its scientific foundation. Eminent physicians, such as Bichat, Bayle, and Corvisart in France, and William and John Hunter and Baillie in England, were turning to the anatomic findings at autopsy to understand the signs and symptoms of their patients.

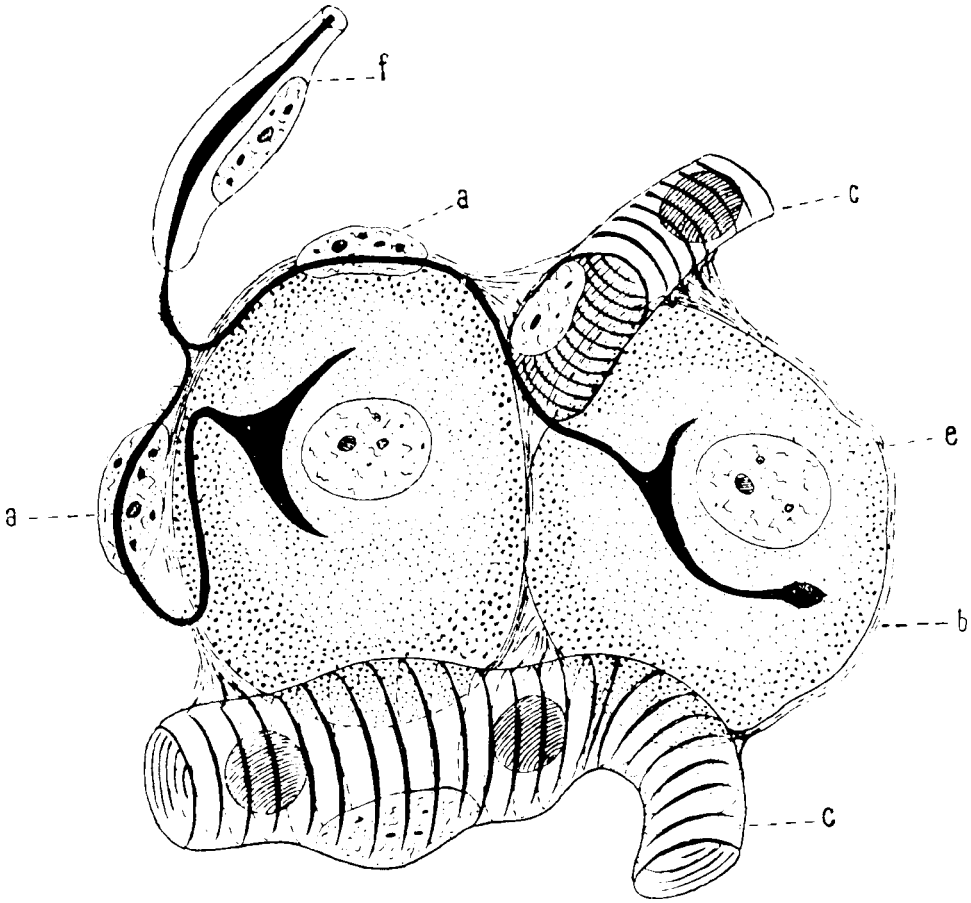

Figure 1-13 Drawing by De Castro showing the structure of the chemoreceptor. The glomus cells (*e*) present an ample cytoplasmic surface for contact with the perfusing blood delivered by the capillary (*c*); sensory nerve fiber (*f*) with sheath of myelin; Schwann cells (*a*) surround the unmyelinated fibers which form the terminal menisci; cell membrane (*b*). *(From De Castro F: Sur la structure de la synapse dans les chemocepteurs: leur mécanisme d'Excitation et R™ le dans la circulation sanguine locale. Acta Physiol Scand 22:14, 1951.)*

Percussion had been rediscovered by Corvisart: Although Auenbrugger had reported his "new invention" in 1761 in Latin, the idea had not caught on until Corvisart—eminent clinician and teacher and personal physician to Napoleon—published a translation in French in 1808. Corvisart's approach to medicine strongly influenced Laënnec. Laënnec applied the stethoscope and Corvisart's "sounding of the chest" to study individual patients with diseases of the lungs and heart throughout their clinical course to anatomical examination at autopsy. This was no simple matter. Since there were no pathologists in those days, the physician not only had to provide continuous care during the patient's lifetime but also had to arrange for and perform the autopsy, and then gather all that he had seen and learned and prepare it for publication.

In 1819, 2 years after the invention of the stethoscope, Laënnec published his famous monograph, *De l'Auscultation médiate*, which drew lessons from carefully documented cases that were studied throughout their clinical course and at autopsy. In this work, Laënnec built upon the monumental tome of Morgagni, who, a generation before, had related the clinical features of the diseases he described to the morbid anatomy, but had not been able to take the next step of relating the clinical course of individual patients to the anatomic findings after death.

Laënnec's monograph contains descriptions of physical signs, clinical-pathological correlations for tuberculosis, pneumonia, bronchiectasis, emphysema, and cancer of the lung, and instructions for the treatment of these conditions. The descriptions of tuberculosis were outstanding in the history of tuberculosis before Koch discovered the causative agent of the disease.

Microbiology

Tuberculosis provides a remarkably illuminating example of the impact of a novel basic science on clinical medicine. The disease can be traced back to the ancients, who were familiar with the diverse clinical syndromes that we now take for granted as due to tuberculosis, but had no way to relate them to a common etiologic agent. A synthesis by Morton in 1685 of all that was then known about tuberculosis focused on cavitary lesions, emaciation ("consumption"), and the tubercle but was shrouded in Galenic humors. Understanding of

Figure 1-14 Giovanni Battista Morgagni (1682–1771). The five volumes of his *De Sedibus* contain the clinical and pathologic descriptions of approximately 700 cases. *(Courtesy of the Library of the College of Physicians of Philadelphia.)*

Figure 1-15 Rene T.H. Laënnec (1781–1826). *[Drawn from life in 1825 by Charles James Blasius Williams (1805–1889) and reproduced in his autobiography, Memoirs of Life and Work, London, Smith, Elder & Co, 1884.]*

the disease accelerated in the eighteenth century when clinicians such as William Cullen began to sort out the various syndromes relating to phthisis, recognizing hemoptysis, empyema, catarrh, and asthma.

The tempo of discovery increased dramatically in the nineteenth century after the French Revolution. During the Napoleonic era, distinguished Parisian clinicians, including Bichat, Bayle, Louis, Broussais, and Laënnec, reported clinical-pathological correlations of tuberculosis. Both Bayle and Laënnec died of tuberculosis. However, little advance was made in understanding the pathogenesis of tuberculosis until Villemin, who, impressed by the analogy between glanders and syphilis on the one hand and tuberculosis on the other, and the fact that two of the three diseases had been shown to be infectious in origin, undertook experiments that showed that tuberculosis was an infectious disease that could be transmitted from humans to animals and from animals to animals.

Koch

In 1876, Koch was a general practitioner in the German township of Wollestein in the province of Posen, where he was responsible for the health care of 4000 inhabitants (Fig. 1-16). Between obstetrical deliveries and satisfying the medical and surgical needs of patients of all ages, he managed to conduct research on the microbial causes of communicable diseases. His laboratory was homemade, either the barn or living room; his major instrument was a microscope to examine bacteriologic and tissue specimens. In pursuing his research, he kept in mind the dictum of Jacob Henle, one of his teachers in medical school, who counseled that, "Before microscopic organisms can be regarded as the cause of contagion in man, they must be found constantly in the contagious material, they must be isolated from it and their strength tested." This lesson was to be the keynote of the future Koch postulates.

In 1876, Koch, the busy medical practitioner, sent a letter to Professor Ferdinand Cohn, director of the Botanical Institute in Breslau, indicating that he had discovered "the process of development of bacillus anthracis" and requesting permission to present his findings to Professor Cohn, "the foremost authority on bacteria." Koch had discovered the spores of anthrax bacilli. Cohn arranged for him to present his results before a formidable room full of distinguished scientists, i.e., Julius Cohnheim, Carl Weigert, Moritz Traube, Ludwig Lichtheim, and Leopold Auerbach. Koch's demonstration of the complete life history of the anthrax bacillus, including sporulation, was entirely convincing to these scientists. After the meeting, Cohnheim, upon his return home, announced to his colleagues, "This man has made a splendid discovery which is all the more astonishing because Koch has had no scientific connections and has worked entirely on his own initiative and has produced something absolutely complete. There is nothing more to be done. I consider this the greatest discovery in the field of bacteriology."

During the next 2 years, Koch described novel procedures for the examination, preservation, and photography

Figure 1-16 Robert Koch (1843–1910), announcing his discovery of the tubercle bacillus as the cause of tuberculosis. Berlin, March 28, 1882. *(Reproduced with permission from Knight D: Robert Koch: Founder of Bacteriology. New York: Franklin Watts, Inc., 1961, p 10.)*

of bacteria and demonstrated the role of microorganisms in traumatic infections while continuing his dual existence as a country doctor and an independent investigator. In 1880, Cohn and Cohnheim arranged for him to move to Berlin as a member of the Imperial Sanitary Commission. This move freed more time for research. By 1881, he made another breakthrough. This was the pour-plate method for isolating pure cultures. The ability that this technique afforded of producing transparent solid media coupled with his invention of new staining methods paved the way for him to tackle the microbial cause of tuberculosis.

His scientific approach, which has become immortalized as the "Koch postulates," consisted of four essential steps:

1. To prove that a microbe is the cause of a disease, it must be present in all cases of the disease. (He showed this for the tubercle bacillus using methylene blue and a counter stain.)
2. The microbe must be grown outside of the body in pure culture. (He devised blood-serum jelly as a culture medium for the slow-growing tubercle bacillus.)
3. The pure culture must be capable of causing the disease in healthy animals. (He proved this initially by inoculation and subsequently by allowing animals to breathe contaminated air.)
4. The same microbe must then be isolated from the inoculated (infected) animal and grown outside of the body in pure culture.

Koch's discovery of the tubercle bacillus and its modes of transmission revolutionized the treatment of tuberculosis. Before the discovery, tubercular patients were treated in sanitaria, which offered fresh air and altitude. Those who ran the sanitaria did not know that tuberculosis was a contagious disease: Sanitation was unregulated; neither sterilization nor fumigation was practiced; there were no laws about spitting; diagnostic capabilities were limited. Koch's discovery of the tubercle bacillus revolutionized therapy. For the rest of his life, while pursuing the causes of other diseases around the world—rinderpest in South Africa, Texas fever, tropical malaria, blackwater fever, bubonic plague in Bombay—he maintained his interest in tuberculosis. His interest led him into a major mistake, i.e., advocacy of tuberculin as a vaccine instead of its present use as a diagnostic test. In 1905, he was awarded the Nobel Prize. On April 7, 1910, the year of his death, he delivered a final address on the epidemiology of tuberculosis before the Berlin Academy of Sciences.

Physiology of the Pulmonary Circulation

Starting with William Harvey, studies of the pulmonary circulation have gone hand in hand with advances in pulmonary physiology and medicine. For many years, research on the pulmonary circulation was confined to animal experimentation. A giant step forward was made by the introduction of cardiac catheterization in humans.

Accurate measurement of pulmonary blood flow is a sine qua non for assessing pulmonary and cardiac performance in health and disease. The use of nitrous oxide in humans by Krogh and Lindhard was an important beginning in this direction, but not until mixed venous blood could be sampled for application of the Fick principle could reliable determinations of pulmonary blood flow be made.

Claude Bernard in 1846 and Chauveau and Marey in 1861 had catheterized the right side of the heart in animal experiments. Whether this technique could be used safely in humans was not known until 1929, when Werner Forssmann, a young surgeon in Germany, introduced a ureteral catheter into his own right atrium. In the 1940s, Cournand, Richards and their colleagues, resorted to right heart catheterization in order to obtain mixed venous blood for the determination of cardiac output by the Fick principle (Fig. 1-17). As everyone knows, the technique opened the way not only to the accurate determination of cardiac output, but also to exploring the heart and lungs in a wide variety of clinical cardiac and pulmonary disorders.

Until 1946, when von Euler and Liljestrand reported the effects of hypoxia and hypercapnia on the pulmonary

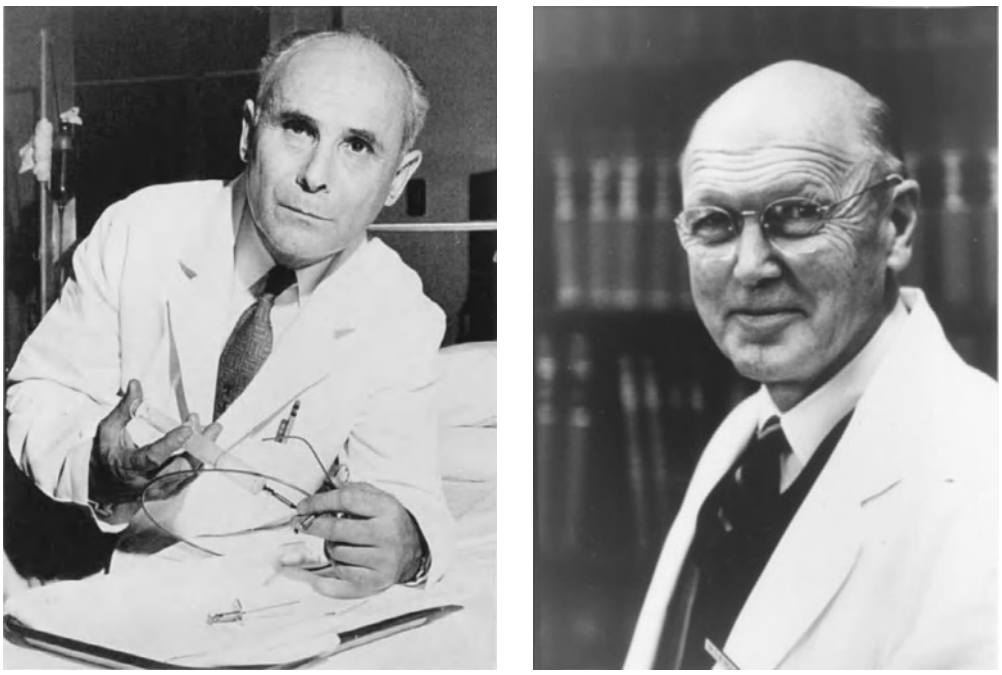

Figure 1-17 André Frederic Cournand (1895–1988) and Dickinson W. Richards (1895–1973). After Forssman's report of the uneventful catheterization of his own right heart, Cournand and Richards pioneered the use of cardiac catheterization for the study of the normal and abnormal pulmonary circulation and the standardization of pulmonary function tests.

circulation of the open chest of an anesthetized cat (Fig. 1-18), there was little understanding of the regulation of the pulmonary circulation. However, these studies, and the proposition of local control of the pulmonary circulation by local concentrations of the respiratory gases, paved the way to understanding pulmonary hypertension and the behavior of the pulmonary circulation on the one hand, in normal individuals at rest, after birth, during exercise, and at altitude, and on the other, in individuals with heart and/or lung disease.

The interposition of the pulmonary circulation between the right and left sides of the heart, an eventual step for life on earth, is not only prerequisite for gas exchange, but also serves a variety of other functions, e.g., mechanical, as a filter for particulate matter in blood returning to the heart, and metabolic, for the synthesis uptake, and breakdown for vital biologic functions and ingredients. Extensive studies have been conducted over the last few decades on the nonrespiratory functions of the lungs. From these studies has emerged considerable understanding of the diverse functions served by the branching pulmonary circulation and by its components, i.e., endothelium and smooth muscle and their interplay in the pulmonary circulation.

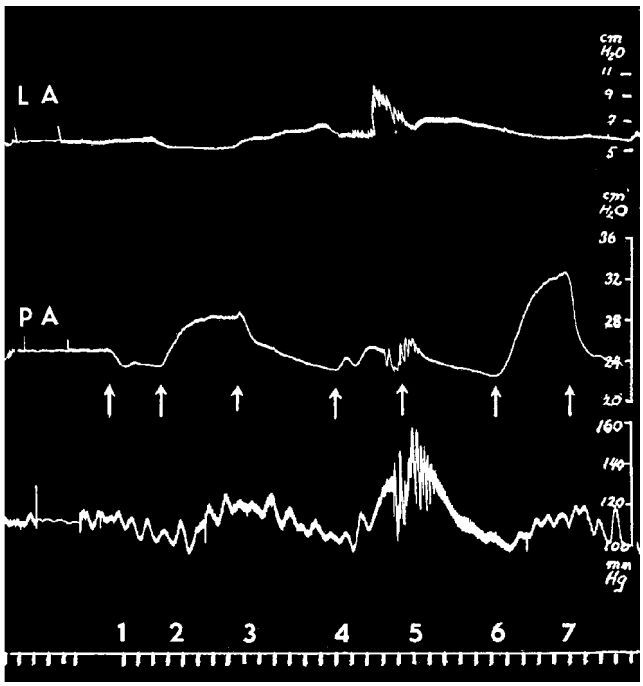

Figure 1-18 Effects of the blood gases on pulmonary arterial pressure in the open-chest cat, artificial respiration. LA = left atrial pressure; PA = pulmonary arterial pressure; lower trace = systemic arterial blood pressure. Numbers along the baseline represent the administration of test gases: 1 = O_2 (from air); 2 = 6.5% CO_2 in O_2; 3 = O_2; 4 = 18.7% CO_2 in CO_2; 5 = O_2; 6 = 10.5% O_2 in N_2; 7 = O_2. *(From Von Euler, US and Liljestrand, G: Observations on the pulmonary arterial blood pressure in the cat. Acta Physiol Scand 12:310, 1946.)*

TECHNOLOGICAL INVENTIONS AND IMPROVEMENTS

The road to contemporary pulmonary medicine could be just as easily traced by using technological advances as landmarks instead of people and discoveries. For example, the

introduction of the manometer for pressure recording, the use of chambers to simulate high altitude, the development of accurate blood-gas analyzers, and the application of sophisticated optical systems for viewing the lumens of the airways and the inside of the chest cavity are all notable milestones. However, probably no better example exists than the discovery of radiographs and the application of this discovery to the diagnosis, prevention, and management of pulmonary tuberculosis.

Wilhelm Conrad Roentgen (1845–1923) discovered radiographs in 1895 while experimenting with cathode ray tubes in his physics laboratory at the University of Wurzburg. Although others before him had seen radiographs as early as 1890, Roentgen was apparently the first to grasp the full significance of the discovery, and his publication, quite unpretentious, immediately attracted worldwide attention because of its prospects for the study of anatomic structures and pathological changes.

Within 2 years after Roentgen's discovery, fluoroscopy of the chest had been introduced into clinical practice, and its value in the early detection of tuberculosis and the diagnosis of pleural effusions was appreciated. In 1901, an atlas of chest radiographs was published, and the use of chest radiography increased greatly with each subsequent improvement in hot-cathode radiograph tubes and intensifying screens. The radiographic evaluation of tuberculosis was superior to physical examination per se for the diagnosis and characterization of pulmonary tuberculosis. By 1910, all patients admitted to sanatoriums were undergoing chest radiographic examination, and by 1917 tuberculosis was being classified according to radiograph findings.

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PART

II

Scientific Basis of Lung Function in Health and Disease

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CHAPTER 2

Functional Design of the Human Lung for Gas Exchange

Matthias Ochs • Ewald R. Weibel

At the end of a deep breath, about 80 percent of the lung volume is air, 10 percent is blood, and only the remaining 10 percent is tissue. Because this small mass of tissue is spread over an enormous area—nearly the size of a tennis court—the tissue framework of the lung must be extraordinarily delicate. It is indeed remarkable that the substance of the lung manages to maintain its integrity in the face of the multitude of insults that inevitably accompany a lifetime of exposure to ambient air and the complex necessity of keeping air and blood in intimate contact, but separate, for the sake of gas exchange.

Part of this success is undoubtedly attributable to the unique design of the lung, which ensures mechanical stability as well as nearly optimal conditions for the performance of the lung's primary function: to supply the blood with an adequate amount of oxygen even when the body's demands for oxygen are particularly high, as during heavy work.

THE LUNG AS AN ORGAN

At total lung capacity, the lung fills the entire chest cavity and can reach a volume, in the adult human, of some 5 to 6 L, largely depending on body size. Upon expiration, the lung retracts, most conspicuously from the lower parts of the pleural cavity, the posterior bottom edge of the lung moving upward by some 4 to 6 cm. This preferential lifting of the bottom edge is caused by retraction of the tissue throughout the entire lung, the surfaces of which are freely movable within the thoracic cavity.

The structural background for this mobility of a healthy lung is the formation, during morphogenesis, of a serosal space that is lined on the interior of the chest wall and on the lung surface by a serosa, the parietal and visceral pleurae,

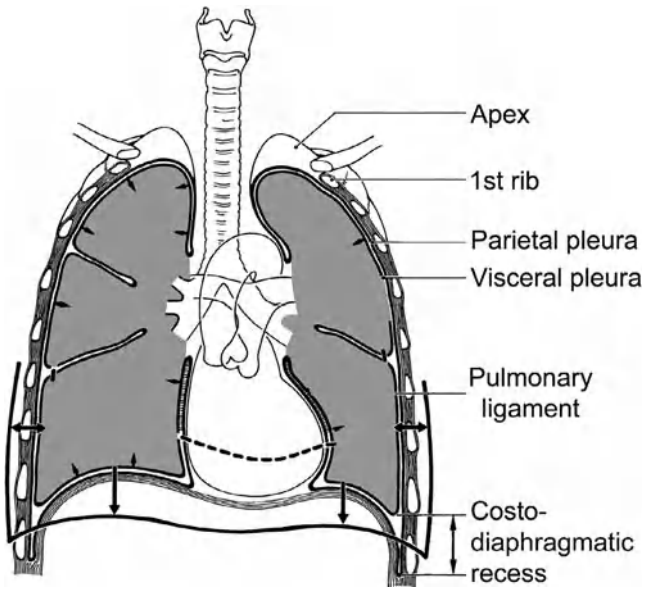


Figure 2-1 Frontal section of chest and lung showing pleural space. Single arrows indicate retractive force. Double arrows show the excursion of the lung bases and periphery between deep inspiration and expiration.

respectively (Fig. 2-1). However, this serosal space is minimal, since the visceral pleura is closely apposed to the parietal pleura, with only a thin film of serous fluid intercalated as a lubricant between the two surfaces. Both pleural surfaces are lined by a squamous epithelial layer, often called *mesothelium*, whose surface is richly endowed with long microvilli. The apical microvilli increase the surface area available, suggesting that pleural mesothelial cells are capable of participating in active transserosal transport of solutes. The total volume of pleural fluid is about 15 to 20 ml, with approximately 1700 cells/mm^3 (75 percent macrophages, 23 percent lymphocytes, 1 percent mesothelial cells). The volume and composition of the pleural fluid have to be tightly controlled to ensure an efficient mechanical coupling between chest wall and lung. Pleural fluid originates from pleural capillaries through microvascular filtration. Drainage occurs mainly via lymphatic stomata in the parietal pleura. Transcytosis through mesothelial cells in both directions might represent another mechanism involved in pleural fluid homeostasis.

The connective tissue of the visceral pleura consists of three layers. A superficial layer of predominantly elastic fibers follows the mesothelium, thereby forming an elastic "bag" that enwraps each lobe. A deep sheet of fine fibers follows the outline of alveoli and extends into the depth of the lung. Between these sheets lies a bed of loose connective tissue, containing free cells (histiocytes, plasma cells, and mast cells), that is often close to lymphatics and systemic arterial branches from the bronchial arteries.

The lung is maintained in a stable position within the chest by the hilum, where airways and blood vessels enter from the mediastinum, and by the pulmonary ligament, a long, narrow band of attachment between visceral and mediastinal pleura that extends downward from the hilum. Because of these attachments, a pneumothorax causes the lung to retract

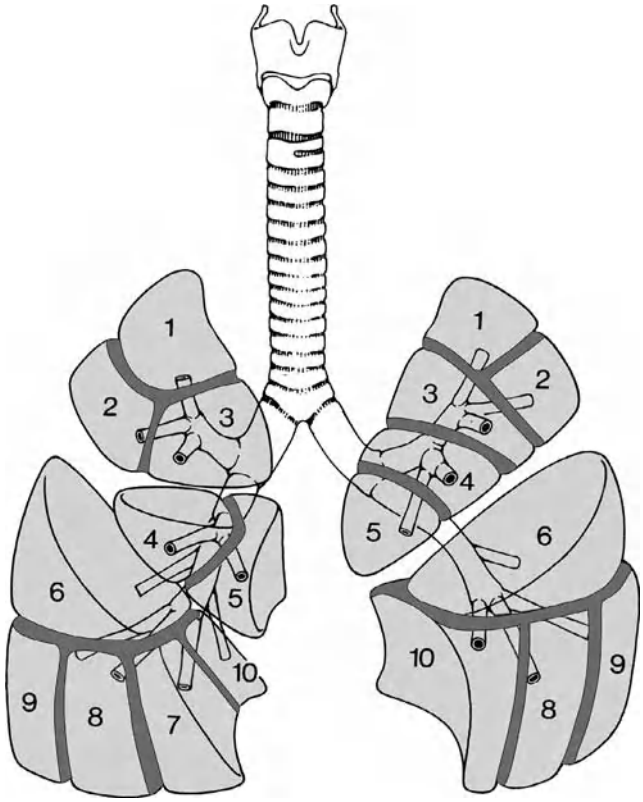


Figure 2-2 Bronchopulmonary segments of human lung. Left and right upper lobes: *(1)* apical, *(2)* posterior, *(3)* anterior, *(4)* superior lingular, and *(5)* inferior lingular segments. Right middle lobe: *(4)* lateral and *(5)* medial segments. Lower lobes *(6)*: superior (apical), *(7)* medial-basal, *(8)* anterior-basal, *(9)* lateral-basal, and *(10)* posterior-basal segments. The medial-basal segment *(7)* is absent in the left lung. (Note: The lungs are represented as turned inward slightly in order to display part of the lateral face.)

and form a lump of tissue that is attached to the mediastinal wall of the thoracic cavity.

The shape of the lung is congruent with that of the fully expanded pleural cavity. This shape is preformed in lung tissue and is hence also evident if an excised lung is inflated, revealing its three faces: the convex thoracic face apposed to the rib cage, the concave diaphragmatic face modeled by the diaphragmatic dome, and the mediastinal face, on which the contours of the heart are impressed beneath the hilum.

As the lung retracts during deflation, the acute edges between the thoracic face and the diaphragmatic and (anterior) mediastinal faces of the lung withdraw; the thoracic and diaphragmatic leaflets of the parietal pleura become apposed, thereby forming a costodiaphragmatic recess on each side (Fig. 2-1). Similarly, as the ventral edge of the lung retracts, the costal and mediastinal pleurae form a recess on each side, corresponding topographically to the borders of the sternum.

The port through which airways and blood vessels enter the lung is the hilum, i.e., the attachment of lung tissue to the mediastinum (Fig. 2-1). The airways reach the two hili by the mainstem, or principal, bronchi (Figs. 2-1 and 2-2). The left mainstem bronchus is longer than the right because it must pass under the aortic arch before it reaches the lung. The

two principal bronchi course downward and begin to divide sequentially shortly after entering the lung, first releasing the lobar bronchus to the upper lobe (Fig. 2-2). Since a middle lobe is formed only on the right side, there is no middle lobe bronchus on the left; instead, the corresponding parts form the lingula, which receives its airways from the superior bronchus of the upper lobe (Fig. 2-2). The last branch of the stem bronchus goes to the lower lobe.

The branching pattern of the human bronchial tree and of the pulmonary artery and veins are shown in a resin cast in Fig. 2-3. The pulmonary artery joins the bronchi while still in the mediastinum (Fig. 2-4*A*); its trunk lies to the left of the ascending aorta, and the right pulmonary artery turns dorsally to course between ascending aorta and right principal bronchus. In the hilum, the right pulmonary artery lies anterior to the right principal bronchus; the left pulmonary artery, however, "rides" on the principal bronchus and crosses over the superior lobar bronchus to the posterior side. From there on, the pulmonary artery branches in parallel with the bronchi; characteristically, each bronchus is associated with one closely apposed pulmonary artery branch, and this relationship is strictly maintained to the periphery, i.e., to the respiratory bronchioles.

In contrast, the pulmonary veins (Fig. 2-4*B*) follow a course independent of the bronchial tree; rather, they lie about midway between two pairs of bronchi and arteries; this

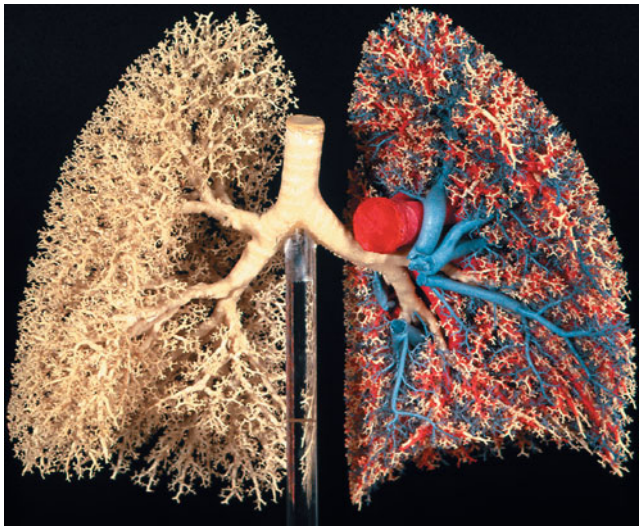


Figure 2-3 A resin cast of the human airway tree shows the dichotomous branching of the bronchi from the trachea and the systematic reduction of airway diameter and length with progressive branching. In the left lung the pulmonary arteries *(red)* and veins *(blue)* are also shown.

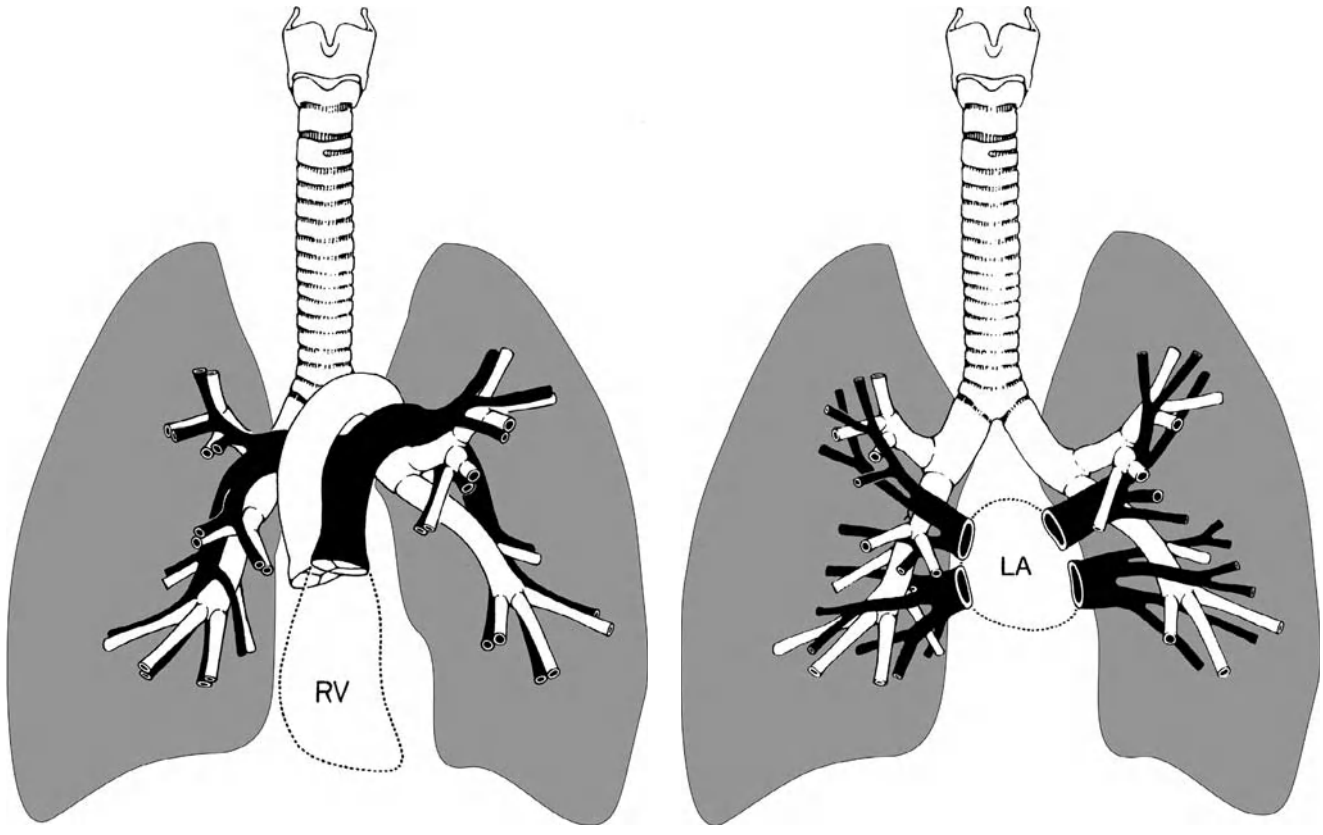


Figure 2-4 Schematic diagrams of the relation of the main branches of pulmonary arteries *(A)* and pulmonary veins *(B)* to the bronchial tree. The arteries follow the airways. Two main stems of pulmonary vein penetrate independently into the lung on each side. LA = left atrium; RV = right ventricle.

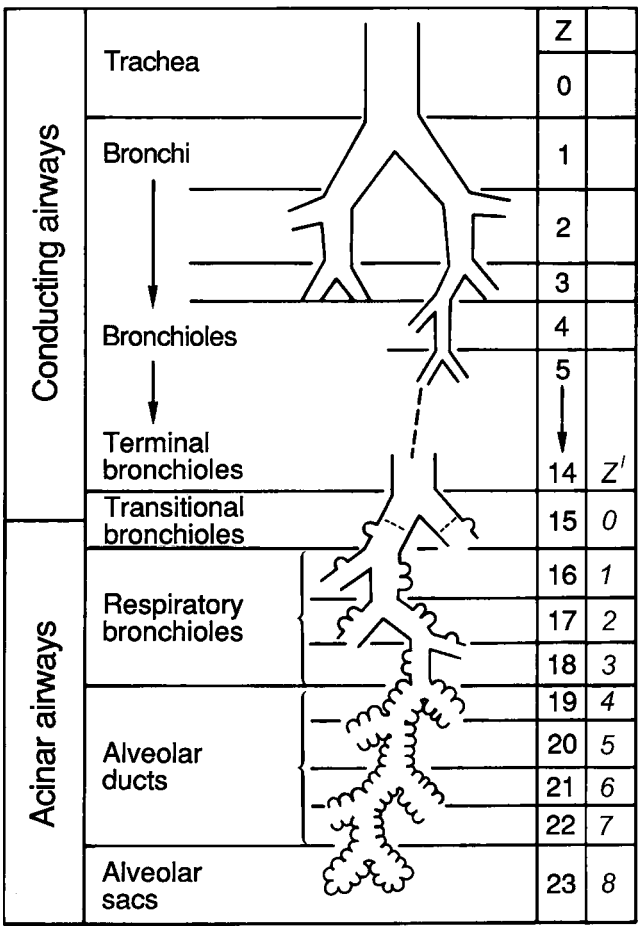


Figure 2-5 Model of airway branching in human lung by regularized dichotomy from trachea (generation z = 0) to alveolar ducts and sacs (generations 20 to 23). The first 14 generations are purely conducting; transitional airways (generation 15) lead into the acinar airways with alveoli that branch over eight generations (z′). *(Modified after Weibel ER: Morphometry of the Human Lung. Heidelberg, Springer-Verlag, 1963.)*

position is maintained to the periphery of the airway system. In the hilum, these veins are collected into at least two main veins on either side, which lead into the left atrium located at the back of the heart.

The airways systematically branch over an average of 23 generations of dichotomous branching, ending eventually in a blind sac (Fig. 2-5). The last nine generations of these airways are connected to tightly packed alveoli, airway chambers in which gas exchange takes place, whereas the central airways serve the function of conducting the air to the gas-exchange parenchyma. In such a system of sequential branching, the unit of lung parenchyma could be defined according to the portion of parenchyma that is supplied by a particular branch of the bronchial tree, and it is possible to conceive of as many types of units as there are generations unless clear definitions for such units are proposed. However, two units appear to be natural:

1. The *lobes*, which are demarcated by a more or less complete lining of pleura. There are three lobes on the right (superior, middle, and inferior lobes), and two on the left (superior and inferior lobes).
2. The *acinus*, which is defined as the parenchymal unit in which all airways have alveoli attached to their wall and thus participate in gas exchange. Along the airway tree, the acinus begins with a transitional bronchiole (Fig. 2-5).

Since all other units are somewhat arbitrarily defined, it is not surprising that some ambiguity exists in the literature about their meanings. Nonetheless, a certain convention has been adopted with respect to the following:

1. The *lung segments*, which are considered as the first subdivisions of lobes. Fig. 2-2 shows the location and distribution of the segments to the various lobes. The symmetry is imperfect because on the left the two segments corresponding to the right middle lobe are incorporated into the superior lobe as the lingula (segments 4 and 5) and because the medial-basal segment of the lower lobe is generally missing on the left (segment 7).
2. The *secondary lobule*, an old anatomic unit. It was introduced in the nineteenth century because "lobules" of about 1 cm^3 are visible on the surface of the lung. These lobules are delineated by connective tissue septa that are connected to the pleura. The secondary lobule is difficult to define in terms of the bronchial tree, but it does seem to comprise about a dozen acini. With reference to bronchograms, secondary lobules are supplied by airway branches that are about 1 mm in diameter.

The pulmonary blood vessels show a characteristic relationship to these units (Figs. 2-3 and 2-4). The pulmonary arteries, following the airways, course through the centers of the units and finally fan out into the capillaries located in the delicate alveolar septa of lung parenchyma. In contrast, the veins lie in the boundary between units and collect the blood from at least two or three adjacent units. This arrangement applies to acini and secondary lobules as well as to lung segments.

Therefore, it is evident that the units of lung parenchyma are bronchoarterial units, which share their venous drainage with neighboring units. This architecture has important functional and practical consequences. Except for the lobes, none of the units are separated from each other by complete connective tissue septa.

ORGANIZATION OF LUNG TISSUE

Basic Structural Elements

In looking at the tissue organization of the lung, we must first consider that the airways and the blood vessels each have their own lining by an uninterrupted cell layer. These layers extend all the way out to the gas-exchange region, but they show different properties in conducting as compared with respiratory structures. Likewise, the connective tissue forms a continuum throughout the lung all the way out to the pleura, but it, too,

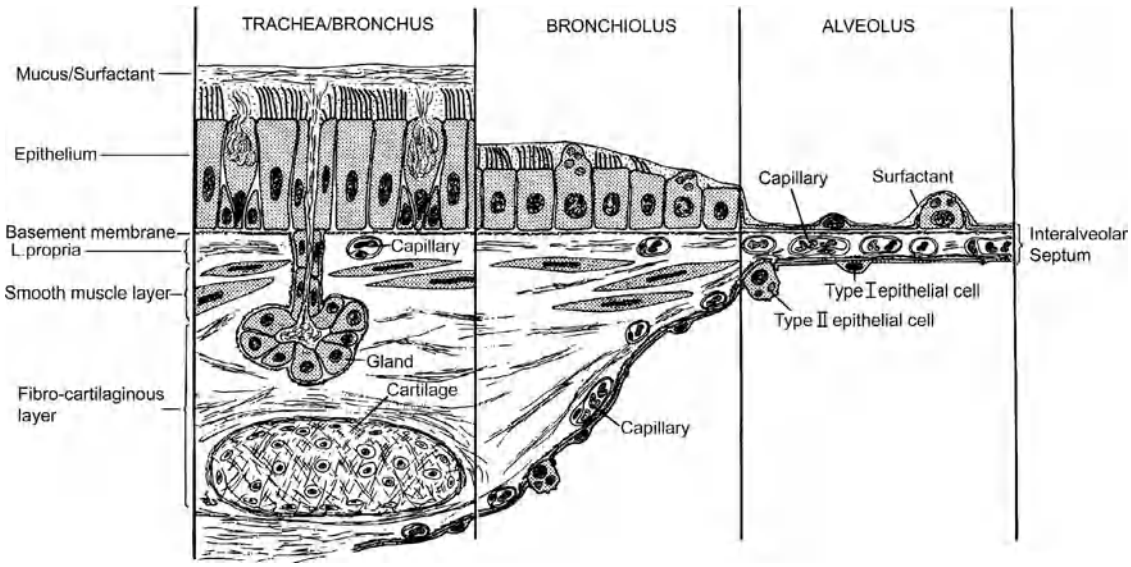


Figure 2-6 Airway wall structure at the three principal levels. The epithelial layer gradually becomes reduced from pseudostratified to cuboidal and then to squamous but retains its organization as a mosaic of lining and secretory cells. The smooth muscle layer disappears in the alveoli. The fibrous layer contains cartilage only in bronchi and gradually becomes thinner as the alveolus is approached.

will be differently organized in the different functional zones; whereas it is reduced to a minimum in the alveolar walls, it contributes a number of different ancillary structures to the wall of conducting airways and blood vessels, such as smooth muscle sheaths or cartilage. This connective tissue space also houses the nutritive vessels and nerves as well as the elaborate defense system related to lymphatic vessels. In the gas-exchange region, however, very few of these accessory structures are found.

The complexity of lung structure is also reflected at the cell biological level. There is no such thing as a standard "lung cell." Instead, we find some 40 different cell types, highly specialized both structurally and functionally, in the lung.

A word of caution is also necessary with respect to the extrapolation of structural findings in experimental animals, especially rodents, to the human lung. Noteworthy species differences include the bronchial circulation, the presence of respiratory bronchioles, the ultrastructural composition and distribution of non-ciliated bronchiolar (Clara) cells, the expression of surfactant proteins by Clara cells, the frequency of certain cell types like alveolar brush cells and lipid-containing interstitial cells (lipofibroblasts), and the ultrastructural organization of lamellar bodies in type II alveolar epithelial cells. All these structural elements have features characteristic for the human lung that are not found in rodents.

Wall Structure of Conducting Airways

The wall of conducting airways consists of three major components (Figs. 2-6 and 2-7): (1) a mucosa composed of an epithelial and a connective tissue lamina; (2) a smooth-muscle sleeve; and (3) an enveloping connective tissue tube partly provided with cartilage.

Epithelium

Although derived from one and the same anlage, the airway epithelium modifies its differentiation characteristics as we proceed from large bronchi over bronchioles to the alveolar region (Fig. 2-6). A simple epithelium exists as a lining of smaller bronchioles: as we move upward toward larger bronchi, the epithelium becomes higher and some basal cells appear, making the epithelium pseudostratified; at the point of transition into the gas-exchange region; that is, at the entrance into the complex of alveoli—the epithelium abruptly becomes extremely thin.

Fig. 2-6 also shows that the epithelium is not made of a uniform cell population but that it is, at each level, rather a mosaic of at least two cell types, in that secretory cells as well as some rarer special cells are interspersed into the complex of lining cells.

If we first have a closer look at the epithelium of larger conducting airways, we see that the lining cells are provided with a tuft of kinocilia at their apical cell face, whereas the secretory cells are goblet cells that produce and discharge to the surface a sticky mucus (Figs. 2-7, 2-8, and 2-9). This mucus spreads out as a thin blanket on top of the cilia and is capable of trapping dust particles that are still contained in the air entering the lung. Kinocilia (Fig. 2-10) are organelles of movement that are known to beat rhythmically in a given direction and at a frequency of about 20 Hz. In the airway epithelium, the cilia are oriented in such a fashion that their beat is directed outward. It is interesting that the cilia of airway epithelia develop at their tip fine claws with which they can grasp the mucus blanket in the phase of their forward beat, whereas on their return to the upright position they glide past the mucus blanket. The result of this is that the mucus blanket, together with trapped foreign material, moves outward or "up the

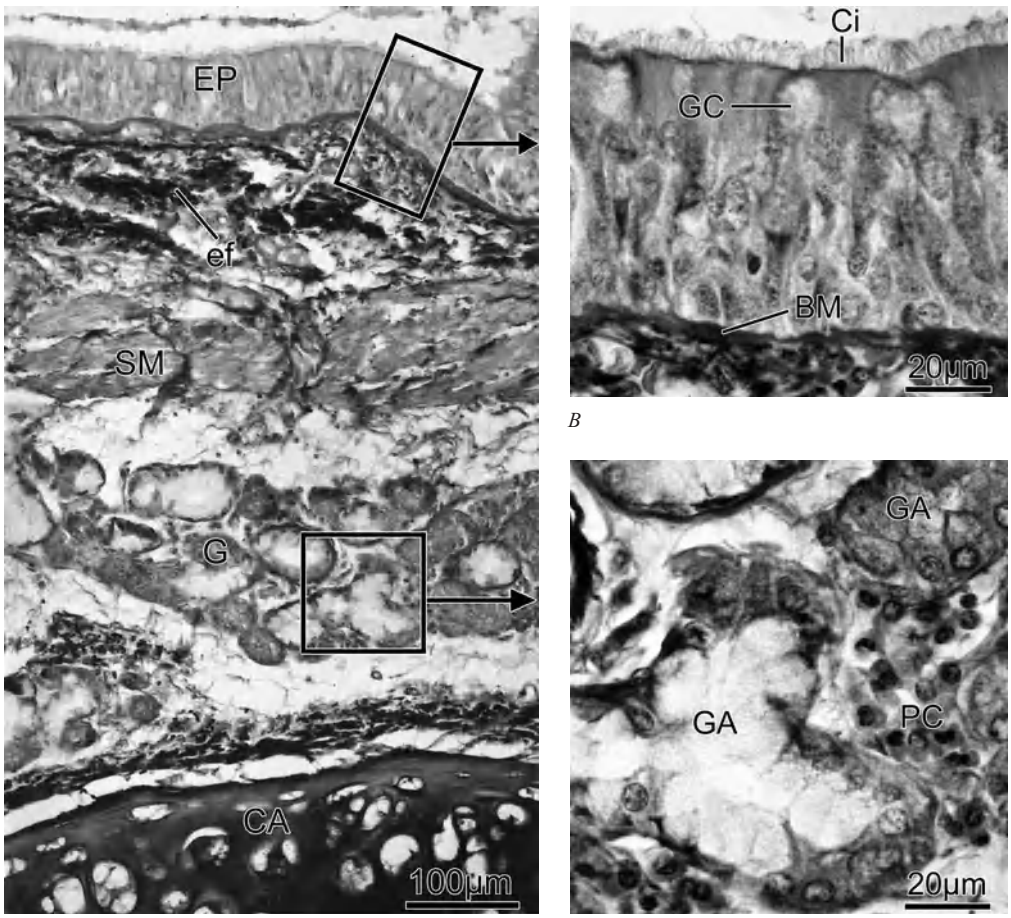


Figure 2-7 Light micrographs of bronchial wall. *A*. The layers from epithelium (EP) to cartilage (CA) with elastic fibers (ef), smooth-muscle bundles (SM), and glands (G). *B*. Higher power of pseudostratified epithelium with cilia (Ci). *C*. Details of gland with acini (GA) associated with groups of plasma cells (PC). BM = basement membrane; GC = goblet cell.

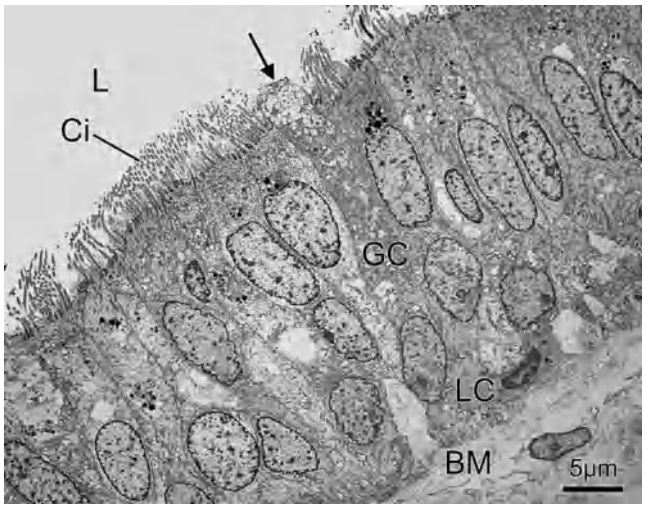


Figure 2-8 Electron micrograph of section across human bronchial epithelium made of high-columnar cells, most of which are ciliated (Ci). A goblet cell (GC) is cut lengthwise; note mucous droplets in process of accumulating at cell apex (*arrow*) and leukocyte (LC) caught in epithelium in process of diapedesis. BM = basement membrane; L = lumen.

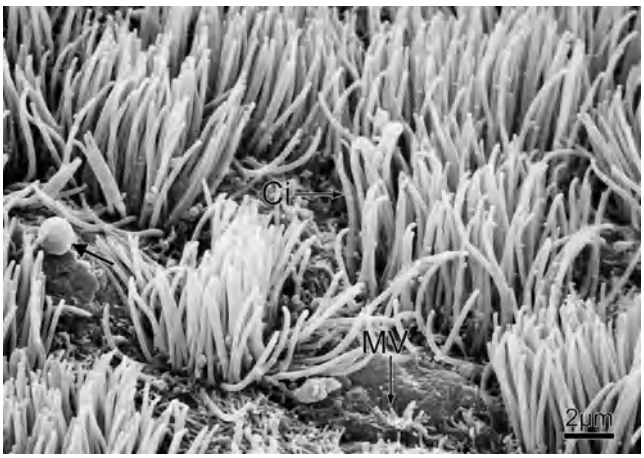
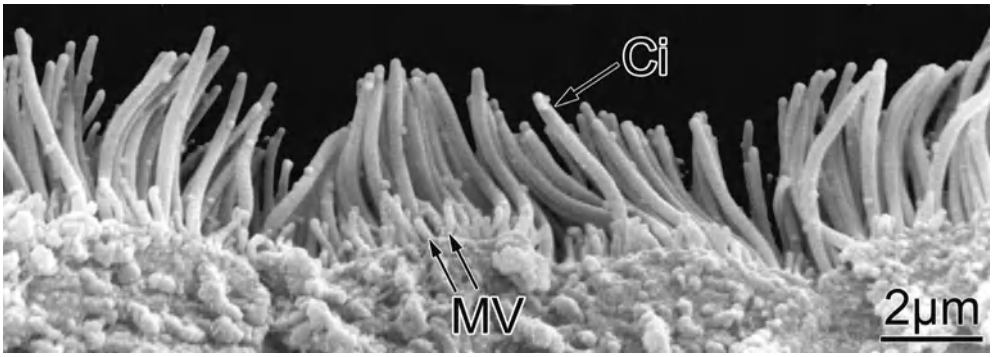


Figure 2-9 Surface view of bronchiolar epithelium shows tufts of cilia (Ci) forming on individual ciliated cells and microvilli (MV) on other cells. Note secretion droplet in process of release from goblet cell *(arrow)*.



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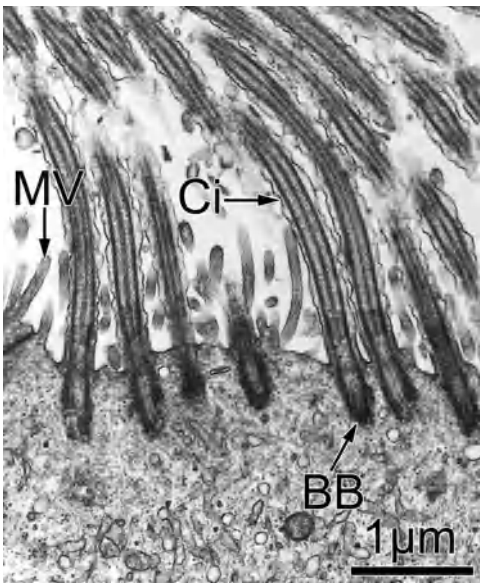

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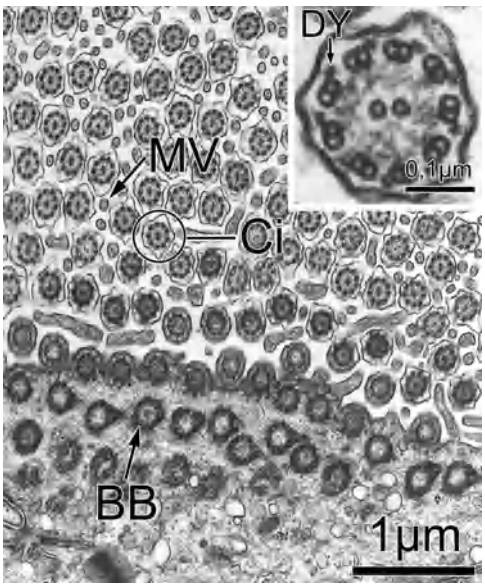


C

Figure 2-10 Cilia (Ci) from human bronchial epithelium seen on sections of epithelial cells in scanning electron micrograph *(A)*, and on thin sections in longitudinal *(B)*, and oblique cross section *(C)*. They are implanted in the epithelial cell by a basal body (BB). Cross-sectioned cilium at high power *(inset, C)* reveals its membrane, which is enveloping a typical set of two axial tubules and nine peripheral duplex tubules with dynein arm (DY) attached. Note abundant short microvilli (MV) interspersed between cilia.

airways" in a steady stream, a feature appropriately called the mucociliary escalator. Since the lining by ciliated cells is uninterrupted from the bronchioles, up the bronchi, to the trachea, this mucociliary escalator ends at the larynx, so that the normal fate of bronchial mucus is to be steadily discharged into the pharynx, whence it is swallowed, usually unnoticed. Only when an excessive amount of mucus accumulates in the trachea or in larger bronchi do we have to assist the system by coughing.

The secretory cell population shows a number of specialized features. In the bronchi of all sizes and in larger bronchioles one finds goblet cells interspersed between the ciliated cells; they form the mucus in their endoplasmic reticulum and Golgi complex, store it as droplets in their apical part, and discharge it in bulk (Figs. 2-8 and 2-9). In larger bronchi, one finds, in addition, small mucous glands located in the connective tissue; they are connected to the bronchial surface by long and narrow ducts (Figs. 2-6 and 2-7). In the normal bronchus the glandular acini are relatively small and composed of serous and mucous cells; enlargement of the acini and a relative increase of mucous cells are characteristics of chronic bronchitis.

Finally, a special secretory cell appears in the smaller bronchioles, the nonciliated bronchiolar (Clara) cell (Fig. 2-11). This cell population is very heterogeneous, thus displaying both interspecies and intraspecies variations. In the human lung, Clara cells account for about 11 and 22 percent of the total epithelial cell number in terminal and respiratory bronchioles, respectively. Besides the absence of cilia, Clara cells in conventional preparations are characterized by their dome-shaped apex that protrudes into the airway lumen. In contrast to rodents, where this cell is rich in smooth endoplasmic reticulum, Clara cells in the human lung lack significant amounts of smooth ER. They possess short lateral cytoplasmic extensions while their basal surface that rests on the basement membrane is practically free of infoldings.

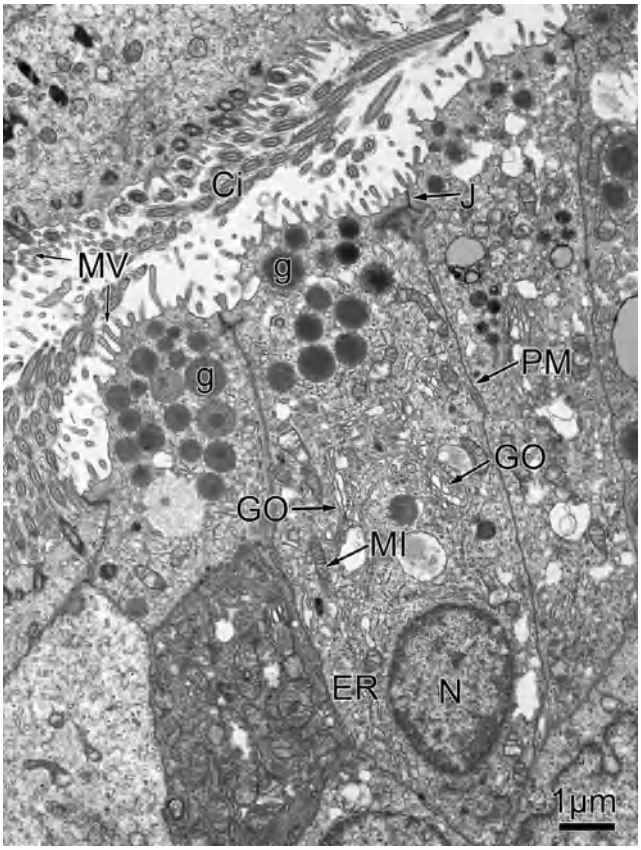


Figure 2-11 Clara cells from human bronchiolar epithelium contain dense secretion granules (g) at apex. Note abundant cytoplasmic organelles such as mitochondria (MI), Golgi complex (GO), or endoplasmic reticulum (ER) as well as microvilli (MV) at surface. Cell membranes are closely apposed and form tight junctions (J) at apical edge. Ci = cilia; N = nucleus; PM = plasma membrane.

Membrane-bound electron-dense granules of about 500 to 600 nm diameter are present, which underlines their secretory activity. Our understanding of the functions of Clara cells is still incomplete. In many aspects, Clara cells appear to be functionally related to the secretory cell type of the alveoli, the type II alveolar epithelial cell; ultrastructural features and expression patterns of lung adenocarcinoma cells show characteristics of both Clara and type II cells. Clara cell secretions add to the lining layer of the distal lung. Clara cells synthesize and secrete the so-called Clara cell secretory protein (CCSP), which has been shown to be structurally similar to rabbit uteroglobin. The exact function of CCSP in the human lung still remains to be elucidated. CCSP levels in BAL fluid are decreased in smokers and in patients with COPD or interstitial lung diseases. Animal studies suggest immunomodulatory functions for CCSP. Within the lung, the Clara cell is the primary site of cytochrome P450 monooxygenase activity. Thus, they are heavily involved in detoxification of xenobiotics. Clara cells, especially subpopulations associated with neuroepithelial bodies or localized at bronchiolo-alveolar duct junctions, also appear to act as progenitor cells for the bronchiolar epithelium.

There are also some additional rarer cells. Neuroendocrine cells are capable of secreting mediators (amines and

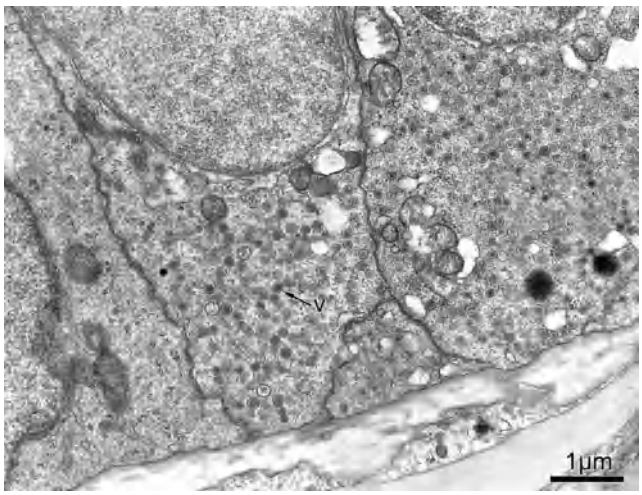


Figure 2-12 Basal part of neuroendocrine cell of human bronchiolar epithelium showing dense-cored vesicles (v). *(From Weibel ER: Lung cell biology, in Fishman A, Fisher AB (eds): Handbook of Physiology. Section 3: The Respiratory System. Bethesda, MD: American Physiological Society, 1985, vol 1, pp 47–91.)*

neuropeptides) into subepithelial capillaries. Prior to secretion, the bioactive substances are stored in dense-cored vesicles (Fig. 2-12). Occasionally, but only rarely in the adult human lung, these cells are organized in extensively innervated groups, then termed neuroepithelial bodies. Although it seems clear that neuroepithelial bodies have sensory, most likely oxygen-sensing, properties, their exact physiological function is still poorly understood. Another rare cell type of the airway epithelium is the brush cell. These cells are characterized by the presence of an apical tuft of blunt, broad microvilli with rootlike structures composed of filaments extending into the cytoplasm (Fig. 2-13). Glycogen

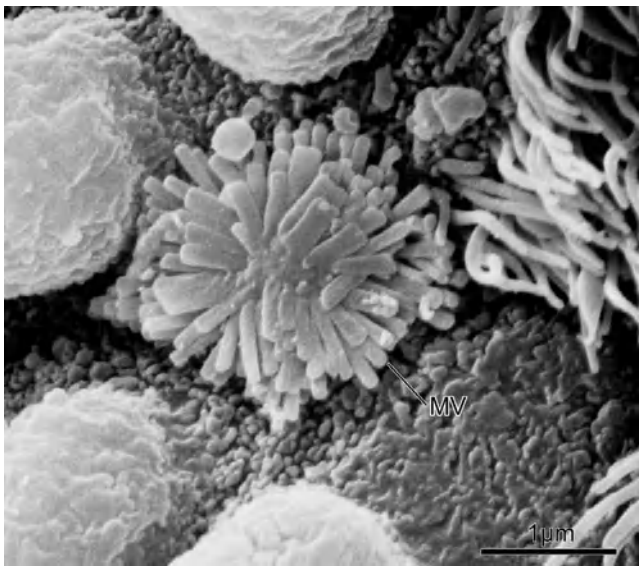


Figure 2-13 Brush cell from small bronchiole of rat lung containing broad microvilli (MV). *(From Weibel ER: Lung cell biology, in Fishman A, Fisher AB (eds): Handbook of Physiology. Section 3: The Respiratory System. Bethesda, MD: American Physiological Society, 1985, vol 1, pp 47–91.)*

granules, vesicles, and smooth endoplasmic reticulum are usually present as well. There is species variation in the occurence of brush cells. While common in rodents, they are only rarely found in the human lung. Their function still remains speculative. Owing to their ultrastructure and their strategic localization in the airways and at alveolar duct bifurcations, sensory/chemoreceptor as well as sentinel/immune surveillance functions have been proposed.

Interstitium

The layer of connective tissue in the bronchial mucosa consists predominantly of elastic fibers that are oriented longitudinally; these fibers serve to maintain a smooth outline of the longitudinal profile of the bronchial lumen no matter how much the bronchi are stretched as the lungs are inflated. In this connective tissue lamina there are foci of lymphoid cells; often they form small lymphoid follicles. However, bronchus-associated lymphoid tissue (BALT) is usually absent in normal adult human lungs and develops only after stimulation when inducible BALT might organize local immune responses.

Smooth-muscle bundles form a continuous sleeve in the connective tissue underlying the epithelial tube that extends from the major bronchi to the respiratory bronchioles; beyond the respiratory bronchioles, the bundles extend into the wall of alveolar ducts where the muscle fibers lie in the alveolar entrance rings. The bundles have an oblique course and encircle the mucosal tube in a criss-cross pattern; hence, their contraction results primarily in a narrowing of the lumen.

In the small bronchioles there is little else to the airway wall; the smooth muscle layer is ensheathed by a layer of delicate connective tissue that is in direct contact with adjacent alveoli (Fig. 2-6). In the larger bronchioles and even more in the bronchi, the outer connective tissue sheath forms a strong layer of fibers; in the bronchi, rings or plates of cartilage are incorporated into this layer.

The wall structure in the respiratory bronchioles is identical to that of terminal bronchioles except that in some regions the cuboidal epithelium is replaced by an alveolar epithelium of squamous cells (type I cells) closely apposed to capillaries. Very often, these single alveoli constitute outpouchings in these regions; sometimes simple "respiratory patches" form in the bronchiolar wall (see below).

Wall Structure of Conducting Blood Vessels

The endothelial lining of pulmonary arteries and veins is basically similar to that of capillaries. It is, however, thicker, and parts of its cytoplasm are richly endowed with organelles of various kinds (Fig. 2-14). Clearly, these cells are metabolically more active than those of the capillary endothelium. They are particularly rich in membrane-bound rod-shaped granules termed Weibel-Palade bodies, which represent the regulated secretory organelles of endothelial cells (Fig. 2-14). The lumen of Weibel-Palade bodies is filled with longitudinally arranged tubules. These tubules most likely represent von Willebrand factor, packed in a highly organized state. Other components of Weibel-Palade bodies include tissue-type plasminogen activator, endothelin-1, the leukocyte adhesion receptor P-selectin, interleukin-8, the tetraspanin CD63/LAMP-3, and the small GTPase Rab27a. Thus, Weibel-Palade bodies are actively involved in hemostasis as well as in vasoactive and inflammatory responses.

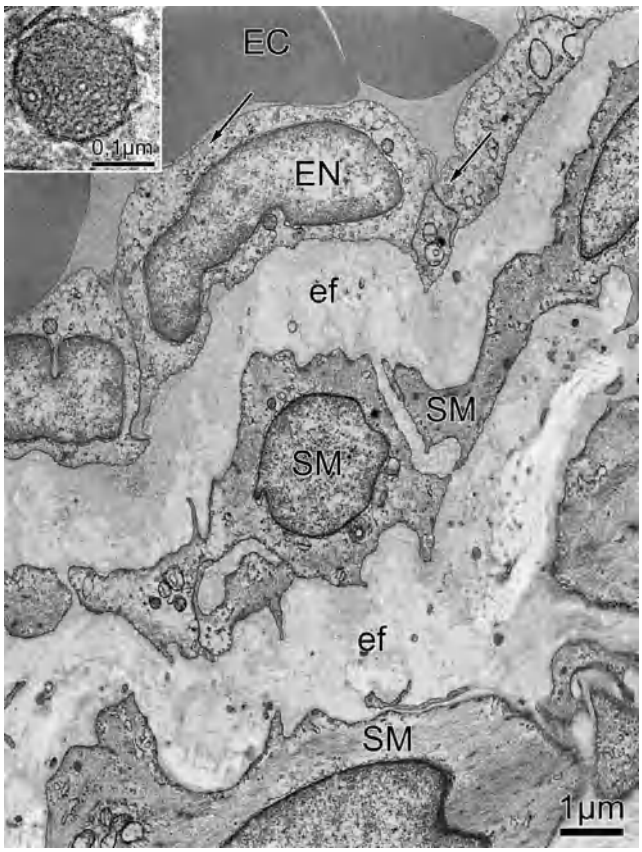


Figure 2-14 Part of wall of pulmonary artery from human lung. Endothelial cells (EN) form thick layer; their cytoplasm is rich in organelles. Specific granules of endothelium *(arrows),* a cross section of one of which is shown at high power in the inset, are enveloped by a membrane and contain tubules. The arterial wall is of the elastic type, formed of alternating layers of smooth muscle (SM) and elastic fibers (ef). EC = erythrocyte.

Many of the nonrespiratory metabolic functions of the lung—particularly the transformation of certain bioactive substances, such as angiotensin and prostaglandins—are performed in endothelial cells. Caveolae (or plasmalemmal vesicles) have been implicated in these processes. Caveolae are omega-shaped plasma membrane invaginations and associated vesicles with an outer diameter of about 70 nm. Their structural framework consists of members of the caveolin family of proteins associated with cholesterol and sphingolipids. Caveolae perform transport and signalling functions. All endocytic activity mediated by caveolae (thereby bypassing the clathrin-coated vesicle pathway) is pooled under the term potocytosis.

Accessory structures develop in the wall in accord with the functional properties of the vessels. Thus, the walls of the major pulmonary arteries that are close to the heart, and therefore exposed to the pressure oscillations of large amplitude prevailing in the outflow tract of the right ventricle, are

of the elastic type, i.e., layers of elastic lamellae are interconnected with smooth muscle cells as in the aorta; the tone of the smooth muscle regulates the elastic modulus of the vessel wall, thereby controlling the shape of the pulse wave. In the pulmonary arterial tree, this pattern prevails out to branches of about 1 mm diameter.

In contrast, branches less than l mm in diameter are of the muscular type, i.e., the smooth-muscle fibers encircle the vessel lumen; they can modify the vessel's cross section and can thus regulate blood flow through this vessel. Compared with systemic arteries, the thickness of the pulmonary arterial wall is reduced about in proportion to systolic pressure, i.e., by about a factor of 1:5; in pulmonary hypertension, the wall becomes thicker. Although arterioles are a well-defined entity in the systemic vascular bed, where they constitute the major site of arterial resistance, pulmonary arterioles are more difficult to locate and define. A single muscle layer—the histologic definition of an arteriole—does occur in branches about 100 μm in diameter, but the arterial bed continues out to the precapillaries, which consist of vessels 20 to 40 μm in diameter that are enwrapped by an incomplete smooth muscle sheath. This poverty of smooth muscle contributes importantly to the low resistance to blood flow that is normally afforded by the pulmonary arterial tree.

The structure of pulmonary veins is similar to that of systemic veins in the upper half of the organism. Their walls are rich in connective tissue and contain irregular bundles of smooth muscle. Larger veins contain a large amount of elastic tissue. More extensive in rodents, but to a certain degree also in humans, cardiac muscle tissue from the left atrial myocardium forms sleeves in the adventitia of pulmonary veins where they overlap with the smooth muscle of the venous wall. The arrangement of the myocardial sleeves correlates with the distribution of foci of ectopic beats initiating atrial fibrillation.

Nutritive Vessels and Nerves

The tissue of lung parenchyma is very well supplied with blood; the fact that it is venous is of no disadvantage, because O_2 is easily obtained from the air. Thus, nutrient supply from pulmonary arteries combined with O_2 supply from air appears to suffice not only for the parenchyma but also for bronchioles and the smaller pulmonary vessels, whose outer surface is almost directly exposed to air. The thicker-walled bronchi, with their glands and cartilage, require a nutrient blood supply from bronchial arteries. These derive in part directly from anterior branches of the aorta and partly from the upper intercostal arteries. They course alongside the esophagus and penetrate on both sides into the hilum. The bronchial arteries extend to the most peripheral bronchi but not into the walls of bronchioles. On the other hand, some branches supply large pulmonary vessels as *vasa vasorum,* whereas others course along larger septa to reach the pleura. Some bronchial arteries form anastomoses with peripheral branches of the pulmonary arteries. There have been long discussions about the role that such anastomoses may play. It seems that in the normal lung their importance has been overrated. However, in certain pathological conditions, such as bronchiectasis and tumors, the bronchial arteries and perhaps the bronchopulmonary anastomoses appear to play an important role. They also enlarge to form a collateral circulation when branches of the pulmonary artery are obliterated. The peribronchovascular space around larger pulmonary artery branches and bronchi with its capillaries from the bronchial circulation has also been proposed as a unique compartment since it is a preferential site of leukocyte infiltration and edema formation under pathological conditions. Furthermore, the bronchial circulation attenuates ischemia-reperfusion lung inujury. Consequently, interruption of the bronchial circulation without revascularization during lung transplantation often leads to bronchial anastomotic complications.

Except for a few bronchial veins in the hilar region, the bronchial system does not have its own venous drainage into the systemic veins. Instead, the bronchial veins, which begin as a peribronchial venous plexus, drain into pulmonary veins; this drainage seems to constitute one source of normal venous admixture to arterial blood.

The lung is innervated by the autonomic nervous system. The parasympathetic fibers are derived from the vagal nerves and the sympathetic fibers from the upper thoracic and cervical ganglia; together they form the pulmonary nervous plexus in the region of the hilum before entering the lung. The fiber bundles follow the major bronchi and blood vessels, finally penetrating into the acini; some nerves also supply the pleura. In addition, motor nerves influence the smooth-muscle tone of airways and blood vessels, and sensory nerves are involved in reflex functions (e.g., cough reflex, Hering-Breuer reflex). Moreover, the secretory function of glands as well as of type II alveolar epithelial cells is at least partly under control of this nervous system. Nerve fibers are easily found in the wall of bronchioles and bronchi, where they often follow the course of bronchial arteries. However, fibers in alveolar septa are small and scarce.

The Cells of the Alveolar Region

Basic Design of the Gas-Exchange Barrier

Efficient gas exchange in the lung depends on a very thin barrier of very large surface between air and blood. Actually, the barrier is so thin that it cannot be resolved into its constituents by light microscopy. Nevertheless, this barrier must be built of the three minimal tissue layers: an endothelium lining the capillaries, an epithelium lining the airspaces, and an interstitial layer to house the connective tissue fibers. The guiding principle in designing these cells must evidently be to minimize thickness and maximize extent. However, there is definitely a limit to this, set by the need to make the barrier and its constituent cells strong enough to resist the various forces that act on it: capillary blood pressure, tissue tension, and surface tension, in particular. Furthermore, the barrier must remain intact for a lifetime, and this requires continuous repair and turnover of the cells and their components. As a result, about half of the surface of the air-blood barrier

Table 2-1

Estimated Cell Volumes in the Human Lung

Cell or Tissue	Volume, ml	Percent Septal Tissue
Tissue (excl. blood)	284	—
Nonparenchyma	99	—
Alveolar septa	185	—
Cells	213	—
Nonparenchyma	50	—
Alveolar septa	163	—
Parenchymal cells	163	—
Alveolar epithelium type I	23	12.6
Alveolar epithelium type II	18	9.7
Capillary endothelium	49	26.4
Interstitial cells	66	35.8
Alveolar macrophages	7	3.9

Source: Weibel ER: The Pathway for Oxygen. Cambridge, MA: Harvard University Press, 1984.

is optimized for gas exchange in that the thin epithelial and endothelial cell extensions are only separated by a fused basement membrane. These areas are termed the thin parts of the air-blood barrier. Cell nuclei and connecting tissue fibers are concentrated in the so-called thick parts of the air-blood barrier.

In spite of this delicacy of tissue structure, we find that three-quarters of all the lung cells by volume or weight are contained in the lung parenchyma (Table 2-1). We also note that epithelium and endothelium make up about one-quarter each of the tissue barrier in the alveolar walls, whereas interstitial cells amount to 35 percent; the interstitial space with the connective tissue fibers makes up no more than 15 percent of the barrier.

Alveolar Epithelium

The alveolar epithelium is a mosaic of different cell types. The vast majority of the total surface is lined by a single layer of squamous cells; the remaining fraction—only about 3 percent (Table 2-2)—is occupied by cuboidal secretory cells; one usually calls the squamous lining cells type I and the secretory cells type II alveolar epithelial cells or pneumocytes. Type I and II cells occur with a numerical frequency of about 1:2. A very rare third cell type, the brush cell, can be found in some specific regions near the entrance of the acinus (see above).

The fine structural details of the different types of alveolar epithelial cells can only be fully visualized by electron microscopy, whereas molecular markers selective for either type I or II cells or some of their constituents can be detected and localized by light microscopy (Fig. 2-15; Table 2-3).

Type I Alveolar Epithelial Cells

At first glance, the squamous type I cells show rather simple design features (Fig. 2-16). Their small, compact nucleus is surrounded by a slim rim of cytoplasm, where one finds a modest basic set of organelles, a few small mitochondria,

Table 2-2

Morphometric Characteristics of Cell Population in Human Pulmonary Parenchyma

Cell Population	Percent of Total Cell Number*	Average Cell Volume, μm^3	Average Apical Cell Surface, μm^2
Alveolar epithelium			
Type I	8	1764	5098
Type II	16	889	183
Endothelium	30	632	1353
Interstitial cells	36	637	—
Alveolar macrophages	10	2492	—

* *Total cell number in human lung* 230×10^9.

Source: Date from Crapo J, Barry BE, Gehr P, et al., Cell number and cell characteristics of the normal human lung. Am Rev Respir Dis *125:332–337, 1982.*

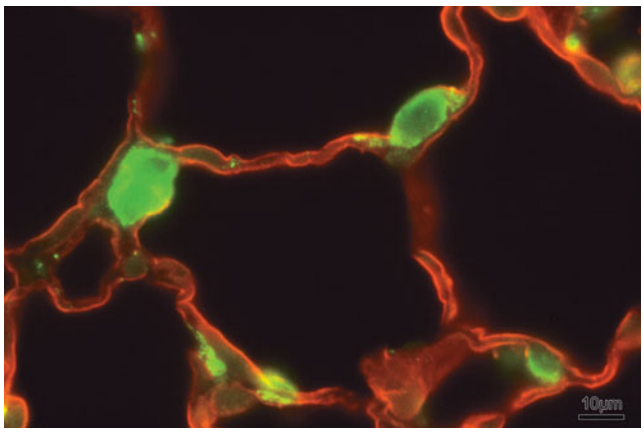


Figure 2-15 Immunofluorescent double labeling of alveolar epithelial cells. Type I cells are stained for Lycopersicum esculentum lectin (red), type II cells are stained for SP-D (green). Compare with Table 2-3. *(Micrograph courtesy of H. Fehrenbach.)*

and some cisternae of endoplasmic reticulum, seemingly the picture of a quiescent cell with no great metabolic activity.

At the edge of the perinuclear region, a very attenuated cytoplasmic leaflet emerges (Fig. 2-16) and spreads out broadly over the basal lamina. This leaflet is made essentially of the two plasma membranes forming the apical and basal cell face, respectively, with a very small amount of cytoplasmic ground substance interposed (Fig. 2-17). Here one rarely finds any organelles except for the numerous plasmalemmal vesicles implied in the transcellular transport of molecules. In fact, besides capillary endothelial cells, type I alveolar epithelial cells are among the richest in caveolae.

Table 2-3

Markers for Alveolar Epithelial Cells

Type I Cell	Type II Cell
HTI-56 (human)	Surfactant proteins:
T1α/RTI-40 (rat, mouse)	SP-A
Aquaporin 5	SP-B
Caveolin 1	SP-C
Receptors for advanced glycation end products (RAGE)	SP-D
	ABCA3
Carboxypeptidase M	RT II-70 (rat)
Lectins:	MMC4 (rat)
Lycopersicon esculentum	Alkaline phosphatase
Bauhinia purpurea	CD44
Ricinus communis 1	Lectins:
	Maclura pomifera

These markers allow a selective distiction between type I and type II alveolar epithelial cells and can be visualized at a light microscopic level by immunohistochemistry, enzyme histochemistry, or lectin histochemistry. However, other cell types of the distal bronchiolar and alveolar region, e.g., Clara cells, capillary endothelial cells or alveolar macrophages, might also stain positive for some of these markers.

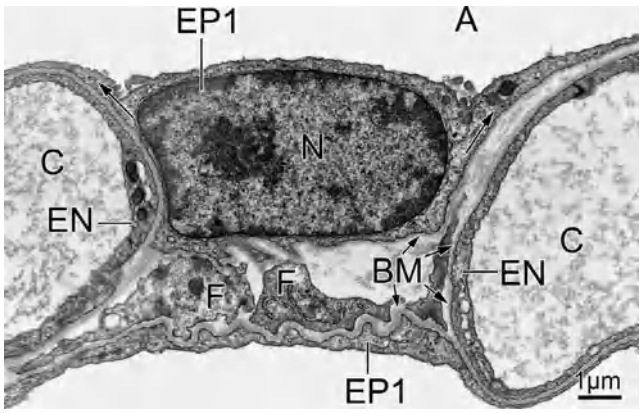


Figure 2-16 A type I alveolar epithelial cell (EP1) from human lung. The nucleus (N) is surrounded by very little cytoplasm, which extends as thin leaflets *(arrows)* to cover the capillaries (C). Note the basement membranes (BM) of the epithelium and endothelium (EN), which become fused in a minimal barrier. Interstitial space contains fibroblast processes (F).

The surface covered by one type I epithelial cell is about 4000 to 5000 µm^2. In some texts one may find the type I cell called the "small alveolar cell" because of its small nucleus; clearly this is a misnomer, as the type I cell is a rather large cell indeed, with respect to both surface and cell volume (Table 2-2). Terminal bars are formed where the cytoplasmic leaflets of epithelial cells meet (Fig. 2-18). If one looks at the surface of the alveolar epithelium in scanning electron micrographs (Fig. 2-19), one notes that the patches covered by single type I cells are variable in size and that even the largest are much smaller than the 4000 to 5000 µm^2 given above, a number derived by dividing the total alveolar surface by the total number of type I cell nuclei. Why is this? There seem to be three to four times as many type I cell domains

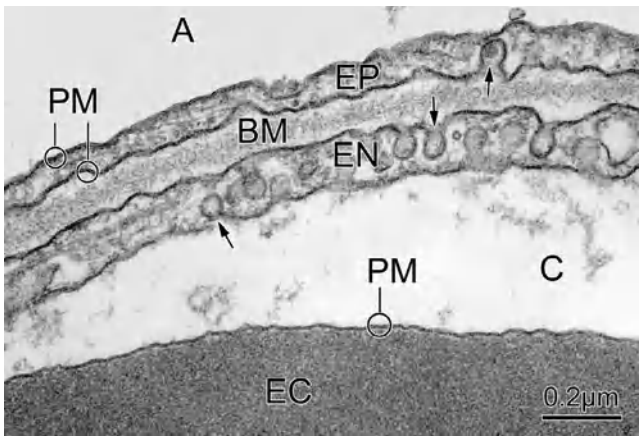


Figure 2-17 Thin, minimal tissue barrier between alveolar air (A) and capillary blood (C) is made of cytoplasmic leaflets of epithelium (EP) and endothelium (EN), joined by fused basement membranes (BM). Note that the epithelial and endothelial leaflets are bounded by plasma membranes (PM), as is the erythrocyte (EC). Arrows point to pinovytotic vesicles/caveolae. *(From Weibel ER: The Pathway for Oxygen. Cambridge, MA, Harvard University Press, 1984.)*

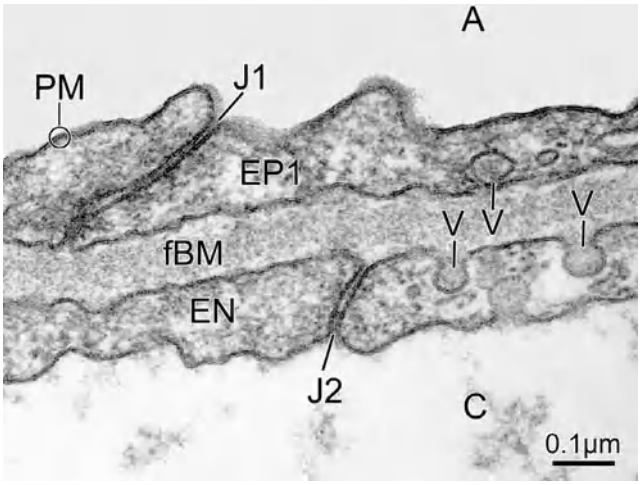


Figure 2-18 Minimal barrier part showing intercellular junctions. Between type I epithelial cells, a ''tight" junction (J1) is formed by close apposition of the cell membranes over a comparatively wide band; the junction between endothelial cells (J2) is ''leaky" because membranes become apposed over a narrow strip only. Note trilaminar structure of plasma membranes (PM), the occurrence of pinocytotic vesicles/caveolae (V) in both epithelium and endothelium (EN), and the fused basement membranes (fBM). A = alveolus; C = capillary; EP1 = type I epithelial cell.

encircled by terminal bars as there are nuclei. Indeed, this observation was already made some 125 years ago by Albert Kölliker; his interpretation was that part of the alveolar surface was lined by "non-nuclear" cytoplasmic plates rather than by complete cells. It turns out that an alternative explanation is possible. One finds that type I cells are not simple squamous cells but rather branched cells with multiple apical faces, as

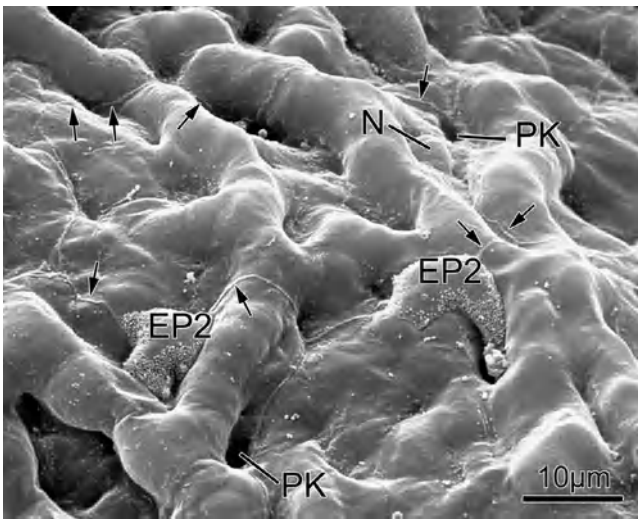


Figure 2-19 Surface of the alveolar wall in the human lung seen by scanning electron microscopy reveals a mosaic of alveolar epithelium made of type I and type II (EP2) cells. Arrows indicate boundary of the cytoplasmic leaflet of the type I cell which extends over many capillaries (C). Note the two interalveolar pores of Kohn (PK). N = nucleus of type I cell.

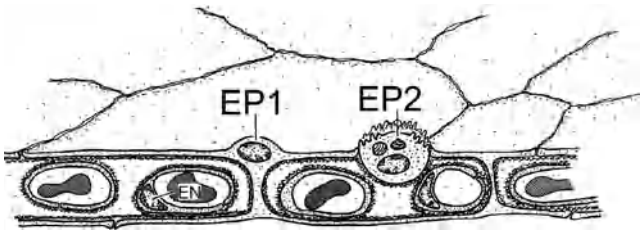


Figure 2-20 Diagram of the alveolar wall showing the complexity of a type I epithelial cell (EP1) and its relation to a type II cell (EP2) and endothelial cell (EN). *(From Weibel ER: The Pathway for Oxygen. Cambridge, MA, Harvard University Press, 1984.)*

shown diagrammatically in Fig. 2-20. Thus, what appears as non-nucleated plates are cytoplasmic domains connected to the perinuclear region by a stalk, spreading out on one side of the alveolar wall or the other; it is evident that several such domains may share a nucleus.

Although type I cells cover about 97 percent of the alveolar surface area, they have long been neglected as being "silent," providing solely a barrier function. Although their overall function in the human lung remains to be determined, recent animal and in vitro studies strongly suggest that type I cells are actively involved in alveolar ion and fluid homeostasis.

Type I cells are easily damaged, particularly because of their extensive surface area and their complex branching architecture. However, there is an additional problem: one finds that type I cells are not capable of multiplying by mitosis, neither during lung growth when more cells are needed to coat the expanding alveolar surface nor upon damage in the adult lung when cells need to be replaced. In both instances new type I cells are made by mitotic division and transformation of type II cells, a process that takes about 2 to 5 days.

This seems to work under normal circumstances. There are, however, conditions where this repair mechanism is too slow to cope with excessive damage, so that a syndrome of severe catastrophic respiratory failure, acute respiratory distress syndrome (ARDS), develops, which requires intensive care treatment. In such patients one finds large parts of the type I cell lining of the alveolar surface to be destroyed. As a consequence, the barrier has become leaky and the alveoli fill with alveolar edema, so that they can no longer take part in gas exchange.

With proper medical care, this alveolar edema can often be resolved within a few days. The alveoli become again filled with air, but in spite of this, gas exchange does not improve. What has happened is that the repair of the severely damaged alveolar epithelium requires a lot of new cells to be made by division of type II cells. These form a rather thick cuboidal lining of the barrier surface, a phenomenon termed cuboidal metaplasia, and this thick barrier offers a high resistance to O_2 flow. It takes several weeks until a thin barrier is restored by transformation of the cuboidal cell lining into delicate type I cells. During this process, the cells go through intermediate stages where they are often positive for both type II and type I cell markers.

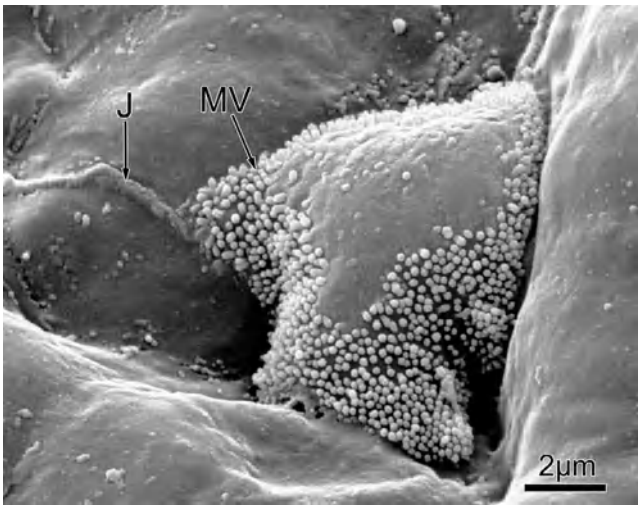


Figure 2-21 Higher magnification of a type II cell reveals a "crown'' of short microvilli (MV) and a central ''bald patch." Note junction lines of type I cells (J) meeting with the type II cell.

Type II Alveolar Epithelial Cells

The type II alveolar epithelial cell is a conspicuous but in fact relatively small cell whose mean volume is less than half that of the type I cell (Table 2-2), although it is often called the "large alveolar cell." Its shape is cuboidal, the apical cell surface bulges toward the lumen and is provided, mostly around its periphery, with a tuft of microvilli (Figs. 2-21 and 2-22). Often, type II cells seem to be preferentially located in the corners of alveoli or in close proximity to interalveolar pores of Kohn. They are usually found as solitary cells; only in cases of alveolar epithelial damage, proliferation of type II cells leads to focal clusters during the repair process. Occasionally, a single type II cell might supply two or even three adjacent alveoli with its apical surface. The basement membrane beneath type II cells is occasionally interrupted. Through these apertures, foot processes of type II cells can extend to the interstitium and come in close proximity to interstitial cells.

Type II cells contain a wealth of cytoplasmic organelles of all kinds (Fig. 2-22): mitochondria, a lot of endoplasmic reticulum with ribosomes, and a well-developed Golgi complex surrounded by a set of small lysosomal granules among which so-called multivesicular bodies—membrane-bounded organelles containing a group of small vesicles—stand out (Fig. 2-23). In addition, one finds the characteristic lamellar bodies, larger membrane-bounded secretory organelles that contain densely packed phospholipid lamellae. There are notable species differences in the ultrastructural organization of lamellar bodies. In rodents, the lamellae are mostly arranged in parallel stacks whereas in humans, concentrically arranged lamellae are mostly found which are attached to a projection core consisting of randomly arranged short stacks of densely packed membrane segments (Fig. 2-24). The periodicity of the lamellae is in the range of 4 to 6 nm. One human type II cell contains between 200 and 500 lamellar bodies, making up a total volume of about 2 cm^3 in the entire lung. With a diameter of approximately 1 µm, lamellar bodies are among the largest secretory organelles of all cells in the body. Owing to their equipment with lysosomal enzymes (e.g., acid phosphatase, cathepsins) and proteins (e.g., members of the LAMP protein family) and their acidic pH of about 5.5, lamellar bodies are regarded as secretory lysosome-related organelles.

Type II cells have two main functions: they serve as the cellular source of pulmonary surfactant and they contribute to the regeneration of the alveolar epithelium under physiological and pathological conditions. These properties form the basis of the concept of the type II cell as the "defender of the alveolus."

Surfactant prevents alveolar atelectasis by a surface area-dependent reduction of the alveolar surface tension (see below). Another function of surfactant as a result of the reduction of alveolar surface tension is to prevent the formation of intra-alveolar edema. In addition, certain surfactant components have important immunomodulatory functions in the innate host defense system. Taken together, the main functions of surfactant might be summarized as to keep alveoli open, dry, and clean. Surfactant is composed of around 90 percent lipids, mainly saturated phosphatidylcholine, and around 10 percent proteins, including the surfactant apoproteins termed SP-A, SP-B, SP-C, and SP-D. Besides its biochemical complexity, surfactant is also morphologically very heterogeneous, consisting of different surfactant subtypes with highly organized structure that represent different stages in metabolism (Figs. 2-24, 2-25, and 2-26).

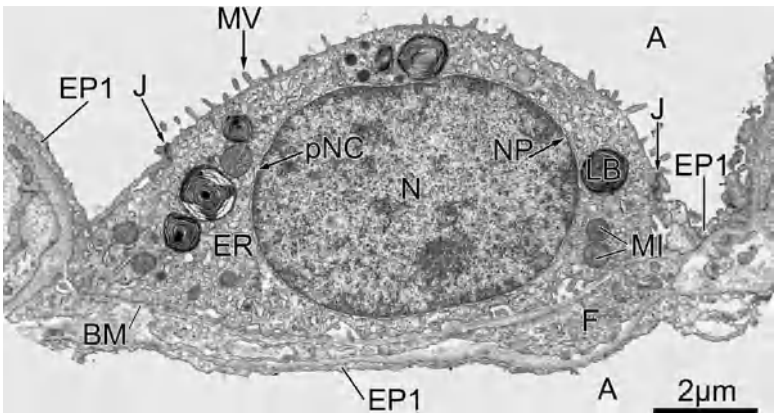


Figure 2-22 A type II epithelial cell from the human lung forms junction (J) with type I epithelial cells (EP1). Its cytoplasm contains osmiophilic lamellar bodies (LB) and a rich complement of organelles: mitochondria (MI), endoplasmic reticulum (ER), and so on. The nucleus (N) is surrounded by a perinuclear cisterna (pNC) which is perforated by nuclear pores (NP). A = alveolus; BM = basement membrane; F = fibroblast; MV = microvilli.

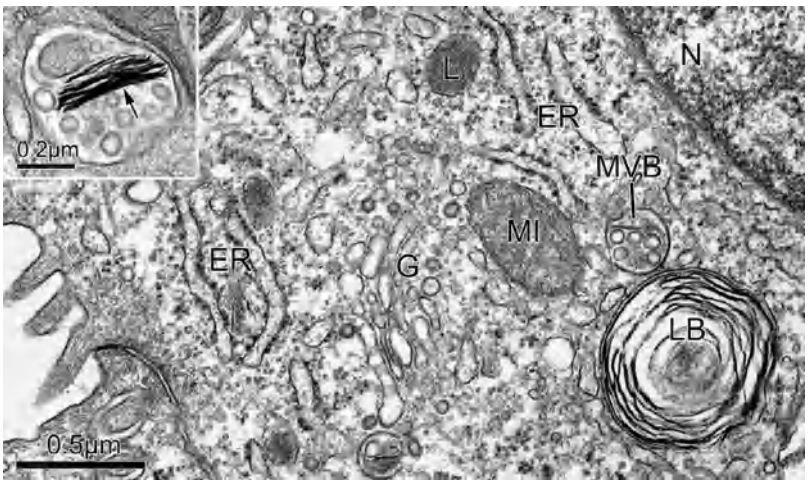
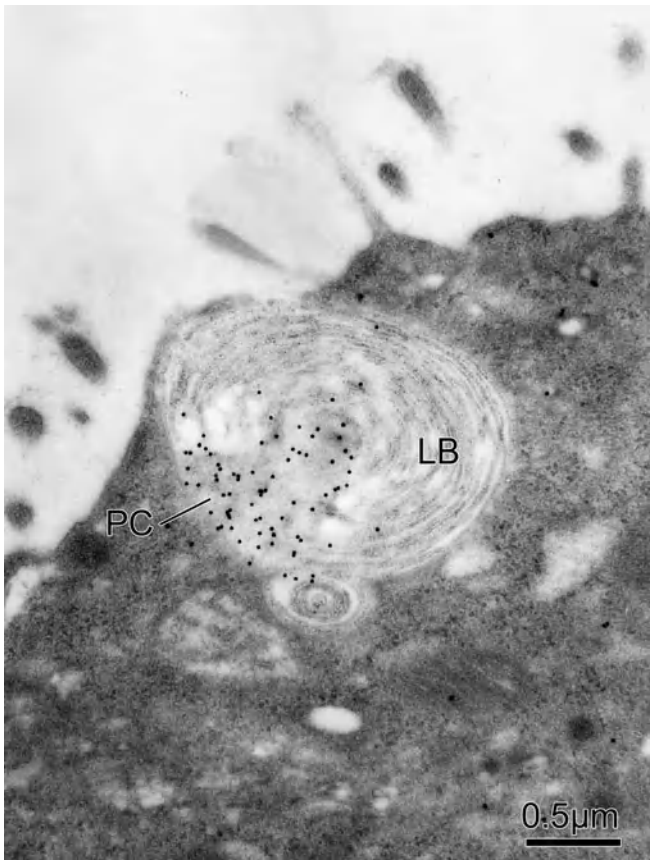


Figure 2-23 Cytoplasmic organelles of the type II cell implicated in the synthesis of surfactant are the endoplasmic reticulum (ER), Golgi complex (G), lysosomes (L), multivesicular bodies (MVB), and finally lamellar bodies (LB). The inset shows a large composite body with a stack of phospholipid lamellae (*arrow*). N, nucelus. *(From Weibel ER: The Pathway for Oxygen. Cambridge, MA, Harvard University Press, 1984.)*

The alveolar epithelium (including interalveolar pores of Kohn) is lined by a thin but apparently continuous fluid layer inserted between the apical cell membrane and the surface film, thus forming a duplex lining layer. Surfactant functions in and on this layer. It is synthesized, stored, secreted, and to a large extent recycled by type II cells. Therefore, an intracellular surfactant pool present in type II cells and an intra-alveolar surfactant pool present at the surface of the fluid alveolar lining layer as well as within its hypophase can be distinguished. The intracellular storage form of surfactant is represented by lamellar bodies. Prior to storage, the synthesis of surfactant material involves endoplasmic reticulum



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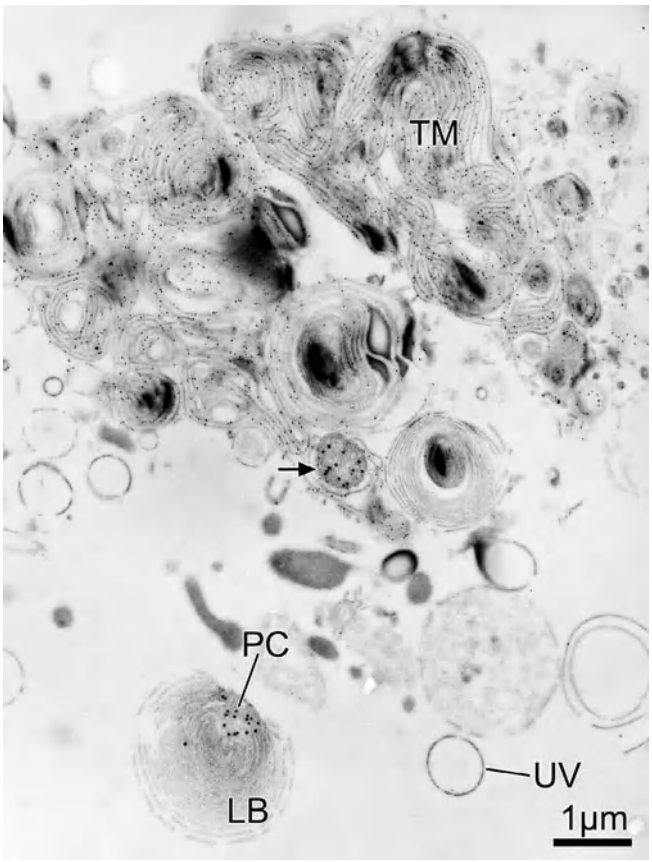


B

Figure 2-24 Immunogold labeling for SP-A (5-nm gold particles) and SP-B (15-nm gold particles) in the human lung. *A*. Within type II cells, SP-B is localized in the projection core (PC) of lamellar bodies (LB). *B*. In the alveolar lumen, SP-A is associated with tubular myelin figures (TM) whereas SP-B is found in the projection core (PC) of freshly secreted lamellar bodies (LB) and dense core particles (arrow) close to tubular myelin. UV = unilamellar vesicle.

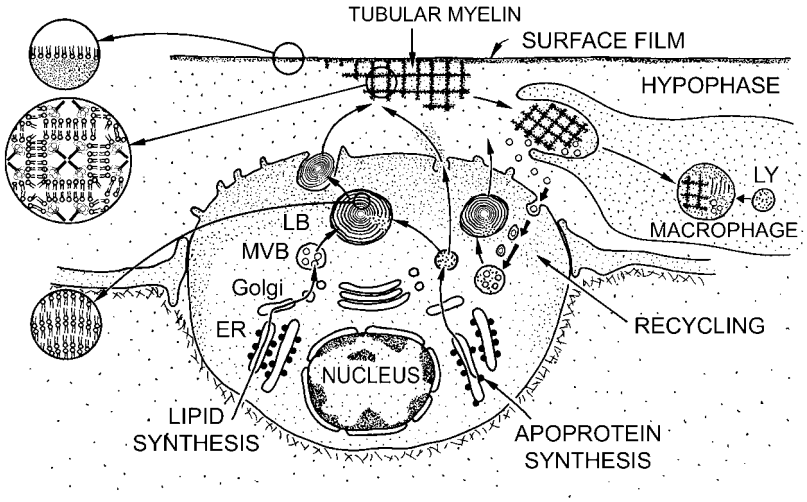


Figure 2-25 Schematic diagram of pathways for synthesis and secretion of surfactant lipids and apoproteins by a type II cell, for their recycling by type II cells, and for their removal by macrophages. Note the arrangement of phospholipids and apoproteins in the lamellar bodies, in tubular myelin, and in the surface film. *(Modified from Weibel ER: The Pathway for Oxygen. Cambridge, MA, Harvard University Press, 1984.)*

(at least partly), Golgi complex, and multivesicular bodies. In type II cells, multivesicular bodies participate in the post-translational processing of surfactant proteins as well as in endocytosis and subsequent recycling and/or degradation of surfactant material; thus, most probably representing the junction point between the biosynthetic and endocytotic pathway. In addition, transitional forms between multivesicular bodies and lamellar bodies, termed composite bodies, have been described. Surfactant material present in lamellar bodies is secreted into the alveolar lumen via exocytosis (Figs. 2-25 and 2-26).

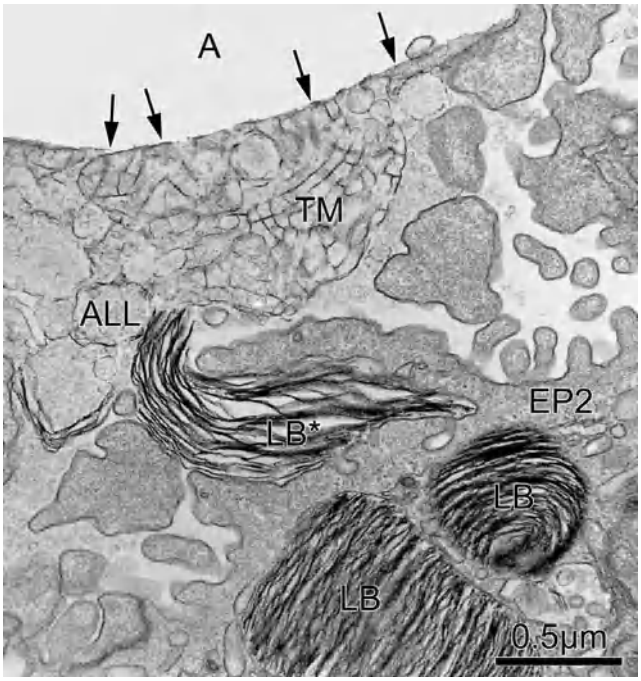


Figure 2-26 Apical part of type II cell (EP2) with lamellar bodies (LB); one of these (LB*) is seen in the process of being secreted into the alveolar surface lining layer (ALL). The free surface of the lining layer is covered by a thin black film of lipids (*arrows*), which is connected with tubular myelin (TM) in the hypophase. *(From Weibel ER, Gil J: Structure-function relationships at the alveolar level, in West JB, ed.: Bioengineering Aspects of the Lung. New York, Marcel Dekker, 1977, pp 1–81.)*

Most surfactant components are assembled in lamellar bodies prior to secretion (Figs. 2-24, 2-25, and 2-26)—at least the lipid fraction and the hydrophilic surfactant proteins SP-B and SP-C, whereas the hydrophilic surfactant proteins SP-A and SP-D seem to be secreted independently via a constitutive pathway bypassing the regulated exocytosis of lamellar bodies. Lamellar body secretion starts with the fusion of its limiting membrane with the apical plasma membrane, followed by formation of a fusion pore, and finally the slow release of surfactant material through the pore. The diameter of the pore is considerably smaller than that of the lamellar body. Thus, surfactant seems to be squeezed through the pore. The mechanisms that regulate surfactant secretion in vivo are still not fully elucidated. It seems that, among the various stimuli that can act via several different signalling pathways, mechanical stretch during ventilation—either as a direct effect on type II cells or indirectly via type I cells or capillary endothelial cells—is the physiologically most relevant.

Intraalveolar surfactant consists of several subtypes, namely freshly secreted lamellar body-like forms, tubular myelin, the surface film, and small unilamellar vesicles. After secretion, lamellar body-like forms in the hypophase associate with SP-A, which is separately secreted by type II cells, and undergo a major structural transformation into tubular myelin figures with a unique lattice-like structure. The precise physiological function of tubular myelin, however, is still unclear. Tubular myelin is thought to be the immediate precursor of the surface film, although the existence of an additional multilayered surface-associated surfactant reservoir underneath the surface film has been suggested. "Spent" surfactant components are found in the hypophase as small unilamellar vesicles. The major route of surfactant clearance is reuptake by type II cells. Within type II cells, surfactant material can either be recycled or degraded. Other routes of surfactant clearance include ingestion and lysosomal degradation by alveolar macrophages and clearance via the airways.

After differential centrifugation of intraalveolar surfactant material harvested by bronchoalveolar lavage, surface active large aggregates (LA), ultrastructurally largely corresponding to lamellar body-like forms and tubular myelin, and inactive small aggregates (SA), ultrastructurally largely corresponding to unilamellar vesicles, can be distinguished. Thus, the SA/LA ratio can be used to assess the biophysical activity of surfactant.

A surfactant film, most likely mainly transported upward from the alveoli, is also present in the airways. Here, surfactant prevents collapse of smaller airways, prevents transepithelial fluid influx, enhances mucociliary transport, and interacts with inhaled pathogens and particles. At least some of the surfactant proteins are also synthesized and secreted by Clara cells. Clara cells express SP-B, but not SP-C, which is exclusively expressed by type II cells. There is some controversy whether Clara cells express SP-A and SP-D. Although this is obviously the case in rodents, Clara cells in the normal adult human lung most likely express very low or no SP-A and SP-D. It seems that Clara cells are not involved in reuptake or recycling of surfactant components. However, the overall role of Clara cells in surfactant biology is not yet defined.

The surfactant apoproteins as the "smart molecules in the surfactant system" have important functions in surfactant subtype assembly, surfactant biophysics, surfactant homeostasis, and innate immunity. The hydrophilic proteins SP-A and SP-D belong to the collectin protein family involved in innate immunity. In addition, SP-A, together with SP-B, is important for tubular myelin formation, thus stabilizing active surfactant forms, while the hydrophobic proteins SP-B and SP-C and, in conjunction, SP-A enhance the adsorption of phospholipids into the surface film. SP-A might also inhibit surfactant secretion and stimulate surfactant reuptake by type II cells.

Differences in the ultrastructural organization of intracellular and intra-alveolar surfactant subtypes between humans and rodents are also reflected by a different distribution of surfactant proteins (Fig. 2-24). In the human lung, SP-A within type II cells is mainly found in small vesicles and multivesicular bodies and only rarely at the periphery of lamellar bodies. In the alveolar lumen, SP-A is associated with peripheral membranes of lamellar body-like forms in close proximity to tubular myelin, in the corners of the tubular myelin lattice structure, and partly at the surface film and unilamellar vesicles. SP-B in the human lung is localized in the projection core of lamellar bodies within type II cells and in dense core particles associated with tubular myelin in the alveolar lumen.

The crucial role of the surfactant system for the maintenance of the functional integrity of the lung is clearly demonstrated by surfactant dysfunction disorders, which can be caused either at birth by developmental deficiency (owing to lung immaturity or mutations affecting surfactant synthesis or secretion) or later by acquired dysfunction (owing to damage of type II cells or inhibition/inactivation of intraalveolar surfactant). A primary deficiency of surfactant in the immature lungs causes the respiratory distress syndrome of premature neonates (RDS). Surfactant dysfunction mutations causing either acute respiratory failure or chronic lung disease after birth have recently been identified in the genes encoding for SP-B, SP-C, and the ATP-binding cassette transporter ABCA3, which is present at the limiting membrane of lamellar bodies. Impairment of an originally intact surfactant system is involved in the pathogenesis of a variety of other lung diseases, such as acute lung injury/ARDS as well as obstructive, infectious, and interstitial lung diseases. Mechanisms leading to impaired surfactant activity include apoptotic or necrotic cell death of type II cells, damage of surfactant proteins and lipids by reactive oxygen and nitrogen species, and enzymatic damage by phospholipases or neutrophil elastase. In addition, plasma proteins entering the alveolar space during edema formation are also known to inactivate surfactant.

With a turnover time of about 4 to 10 hours and only a rather small intracellular surfactant reserve available for secretion onto the large alveolar surface, the ability to cope with a lack of active surfactant during lung injury is limited. Hence, there is a rationale to supplement the surfactant material available in cases of surfactant deficiency or damage. One of the major advances in neonatology in our time has been the development of surfactant replacement therapy for the treatment of RDS. The story of the treatment of premature babies with exogenous surfactant is indeed a paradigmatic example in which discoveries from basic research were successfully applied to an important clinical problem. The indications for surfactant replacement therapy have widened in recent years, with promising results in forms of respiratory failure not caused by a primary deficiency of endogenous surfactant but rather by impairment of an originally intact surfactant system. In these cases, however, the efficacy of exogenous surfactant therapy very much depends on the ability of the surfactant preparation to resist the inhibition/inactivation that caused alterations of the endogenous system.

Capillary Endothelium

The alveolar septa of the adult lung contain a single capillary network. The capillary endothelium is of the continuous (non-fenestrated) type. Alveolar capillaries are provided with pericytes, but they are rarer and less densely branched than pericytes of the systemic circulation. Pericytes are related to vascular smooth muscle cells in that they both are contractile perivascular cells. Thus, pericytes protect microvessel wall integrity by providing some mechanical support. However, in contrast to vascular smooth muscle cells, pericytes are embedded within the endothelial basement membrane, frequently forming contacts with capillary endothelial cells. They seem to contribute components to the capillary basement membrane and extracellular matrix and secrete vasoactive substances. In addition, pericytes are thought to be involved in the regulation of endothelial cell proliferation and differentiation and to act as progenitor cells for other cell types.

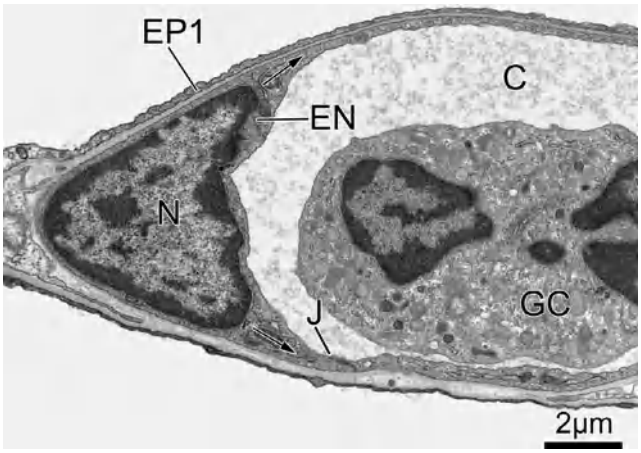


Figure 2-27 An endothelial cell (EN) of capillary (C) is similar in basic structure to a type I epithelial cell (EP1). The nucleus is enwrapped by little cytoplasm but thin leaflets extend as capillary lining *(arrows)*. Note the intercellular junction (J) and a white blood cell/granulocyte (GC), in the capillary. *(Modified from Weibel ER: The Pathway for Oxygen. Cambridge, MA, Harvard University Press, 1984.)*

Capillary Endothelial Cells

At first glance, capillary endothelial cells resemble type I alveolar epithelial cells, but in contrast to type I cells with their complex branching architecture, capillary endothelial cells form simple sheets (Fig. 2-27). Moreover, compared with the tight occluding junctions between alveolar epithelial cells that constitute a powerful seal of the intercellular cleft, the occluding junctions between capillary endothelial cells are rather leaky, allowing a nearly uninhibited exchange of water, solutes, and even some smaller macromolecules between the blood plasma and the interstitial space (Fig. 2-18). Occluding junctions between capillary endothelial cells are often located at the transition of the thin to the thick part of the air-blood barrier and are often covered by pericytes.

There is another notable and important difference between the two basically similar lining cells on the epithelial and endothelial side of the gas-exchange barrier: their size. Although the capillary surface is some 10 to 20 percent smaller than the alveolar surface, the capillary endothelial cells are about four times more numerous than type I cells; this means that the surface covered by one type I epithelial cell must be about four times larger, namely 4000 to 5000 μm^2, as compared with about 1000 μm^2 in endothelial cells (Table 2-2).

Numerous caveolae are found in capillary endothelial cells (Figs. 2-17 and 2-18). However, at the bulging part of the capillaries, some parts of the endothelial cell extensions are free of caveolae and are thinned down to a thickness of about 20 to 30 nm, basically consisting of the two plasma membranes with only a minute amount of cytoplasm in-between. These areas, rarer in human lungs than in rodents, are termed the avesicular zone of the alveolar capillary endothelium. In contrast to the endothelium of conducting vessels, Weibel-Palade bodies are missing in capillary endothelial cells, thereby underscoring the structural and functional differences between alveolar and extra-alveolar endothelial cells.

Interstitium

The interstitium of the alveolar septum is for the most part extremely thin. At the thick parts of the air-blood barrier where epithelial and endothelial basement membranes are separated, one finds elastic fibers and bundles of collagen fibrils in the extracellular matrix as well as interstitial cells, mainly fibroblasts, the cells responsible for production of extracellular matrix components (Figs. 2-28 and 2-29). The precise arrangement of the connective tissue fibers will be

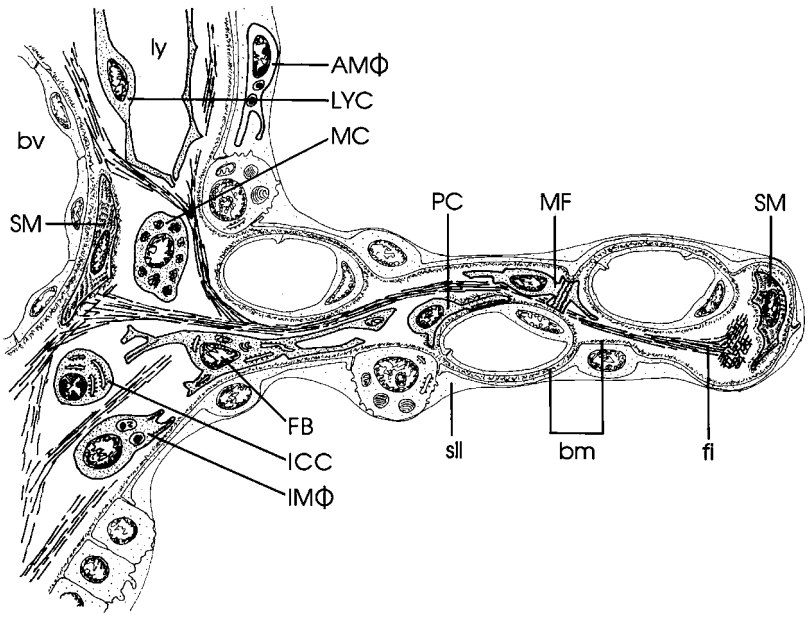


Figure 2-28 Schematic diagram of the structural organization of the alveolar interstitium. The alveolar septum extends between a free edge *(right)* and a perivascular connective tissue sleeve *(left)*, enwrapping a blood vessel (bv). Basement membranes (bm) are associated with epithelium and endothelium, and they bound the interstitial space. Fiber strands (fi) form a continuum. Interstitial cells include: fibroblasts (FB), myofibroblasts (MF), smooth muscle cells (SM), pericytes (PC), various kinds of immune competent cells (ICC), mast cells (MC), lymphatic endothelial cells (LYC), and histiocytes or interstitial macrophages (IMΦ). Alveolar macrophages (AMΦ) are submerged in the alveolar surface lining layer (sll)ly lymphatic capillary. *From Weibel ER, Crystal RG: Structural organization of the pulmonary interstitium. In: Crystal RG, West JB, Weibel ER, Barmes PJ (eds),* The Lung: Scientific Foundations, *2nd ed. New York, Lippincott-Raven, 1997, pp 685–695.*

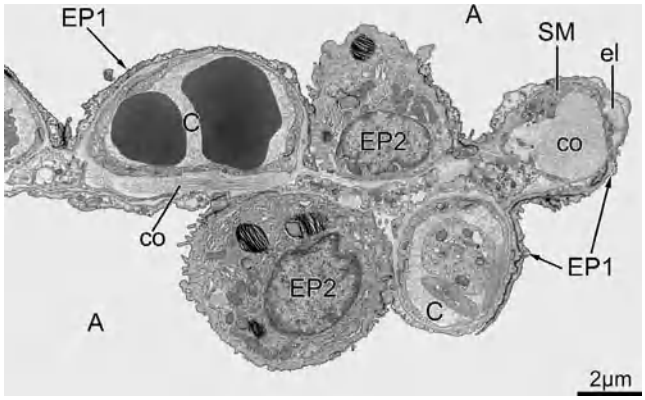


Figure 2-29 Alveolar septum with free edge (right) showing reinforced entrance ring with elastic fibers (el), collagen fibrils (co), and smooth muscle cell (SM). The two capillaries (C) are on different sides of the septum, as are the two type II cells (EP2). A = alveolar space; EP1 = type I cell. *(From Weibel ER, Gil J: Structure-function relationships at the alveolar level, in West JB, ed.: Bioengineering Aspects of the Lung. New York, Marcel Dekker, 1977, pp 1–81.)*

discussed below in relation to the mechanical properties of the lung.

Interstitial Cells

The resident interstitial cells of the alveolar septum comprise fibroblasts and contractile cells (myofibroblasts, lipofibroblasts, smooth muscle cells, and pericytes) (Fig. 2-28). Free interstitial cells are part of the defense system usually found in the juxta-alveolar connective tissue sleeves (see below) and include interstitial macrophages (histiocytes), mast cells, and under certain conditions, lymphocytes, plasma cells, and granulocytes.

Fibroblasts are a heterogeneous cell population. Many fibroblasts have notable contractile properties; therefore, they been termed myofibroblasts. Myofibroblasts contain bundles of microfilaments anchored in patches beneath the plasma membrane. These filament bundles span the entire width of the cell. At the places where the microfilament bundles are connected to the plasma membrane, attachments to the epithelial and/or endothelial basement membrane exist. Through holes in the basement membranes, myofibroblasts directly link alveolar epithelial and capillary endothelial cells.

Some contractile fibroblasts are equipped with non-membrane–bound lipid bodies, thus termed lipid interstitial cells or lipofibroblasts. These cells are more common in rodent than in human lungs and occur particularly during alveolar development and growth. Lipid bodies consist of an osmiophilic rim of amphipathic phospholipids, glycolipids, sterols and specific proteins, and a hydrophobic core of neutral lipids. In many cell types, lipid bodies represent specialized domains for the synthesis of eicosanoid mediators. Pulmonary lipofibroblasts seem to be related to the lipid-containing perisinusoidal cell (Ito cell) in the liver in that they might serve as a storage depot for retinoids. Under certain conditions, lipofibroblasts might provide fatty acid substrates for surfactant synthesis in type II cells.

The occurence of smooth muscle cells in the alveolar septa is mostly restricted to the free septal edges where they contribute to the network of alveolar entrance rings (Figs. 2-28 and 2-29). Pericytes abut alveolar capillaries (see above).

Structural Aspects of the Defense System of the Lung

The large and delicate alveolar surface is constantly challenged by inhaled microorganisms and particulate matter. Thus, normal lung function critically depends on an efficient defense system. At the alveolar level, the primary defense barrier is the alveolar lining layer. Here, alveolar macrophages are the sentinel phagocytic cells of the innate immune system, as we shall discuss below. In addition, protein components of the innate immune system, including the lung collectins SP-A and SP-D as well as a variety of other antimicrobial peptides (e.g., lysozyme, lactoferrin, defensins, cathelicidins), are present in the alveolar lining layer.

Another set of macrophages forms a second defense line just beneath the alveolar epithelium; i.e., in the interstitial space of the lung parenchyma. In the normal lung, these interstitial macrophages (histiocytes) are not found in alveolar septa; instead, they occur only in the connective tissue sleeves at the periphery and in the center of acini where septal fibers connect to the peripheral fiber system (Fig. 2-30). Thus, they are found in regions where lymphatics begin their course toward the major airways in the hilar region where lymph nodes are found. In these juxta-alveolar regions of connective tissue, we usually find the common elements of the defense system (Figs. 2-30 and 2-31). These include lymphatic vessels and several mobile cells. Interstitial macrophages are constantly being replenished by blood monocytes migrating

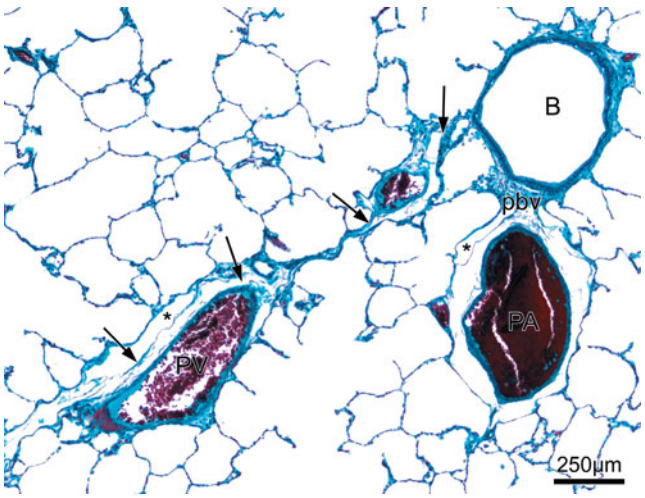


Figure 2-30 Light micrograph of human lung showing connective tissue sleeve *(arrows)* extending from the peribronchovascular space (pbv) around branch of pulmonary artery (PA) and bronchiolus (B) to pulmonary vein branch (PV). Asterisks = lymphatic.

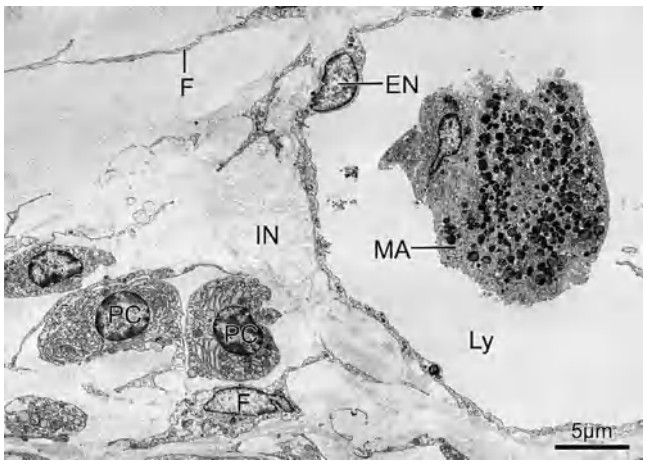


Figure 2-31 Perivascular connective tissue with lymphatic (Ly) containing a macrophage (MA) with heterogeneous population of "lysosomal" granules. Interstitium (IN) contains fibroblasts (F) and plasma cells (PC). EN = lymphatic endothelium.

into the interstitial space. Sometimes they become permanent residents in the form of storage cells for "indigestible" foreign matter, such as carbon particles and silicates. Lymphocytes are less common and are mostly present as T cells whereas B cells and natural killer cells are rare in the normal lung. Granulocytes (neutrophils, eosinophils, and basophils) are present in the human lung, but they are also very rare. Mast cells contain granules storing heparin and histamine that, in the human, show a characteristic scroll-like substructure (Fig. 2-32) as well as lipid bodies. Antigen-presenting dendritic cells possess long branched dendritic cell processes (hence, their name) and an irregular, folded nucleus. Phagolysosomes are absent. Once activated, dendritic cells migrate to lymph nodes where they induce the proliferation of antigen-specific T cells; thus, providing a link between innate and adaptive immunity. In addition to their presence within the lung parenchyma, dendritic cells are found within the tracheal and bronchial epithelium where they seem to form a network comparable to the Langerhans' cells in the epidermis. Like Langerhans' cells, airway dendritic cells are characterized by pentalaminar plate-like organelles (Birbeck granules). In the ciliated epithelium of bronchi and bronchioles diapedesis is seen; i.e., lymphocytes and other leukocytes in the process of penetrating the epithelium to reach the mucous blanket. Plasma cells occur in relatively high numbers around the acini of the seromucous glands of bronchi (Fig. 2-7); hence, it is likely that antibodies are being secreted into the mucous blanket by these glands by a process similar to that occurring in the salivary glands or in the glands of the nasal mucosa.

The third defense line is constituted by the lymph nodes, which are arranged along the major bronchi and extend to subsegmental bronchi about 5 mm in diameter (Fig. 2-33). The most peripheral lymph nodes are tiny, a mere 1 to 2 mm in diameter; but closer to the hilum they become larger, reaching 5 to 10 mm in diameter in the region of the tracheal bifurcation and along the trachea. The lymph nodes

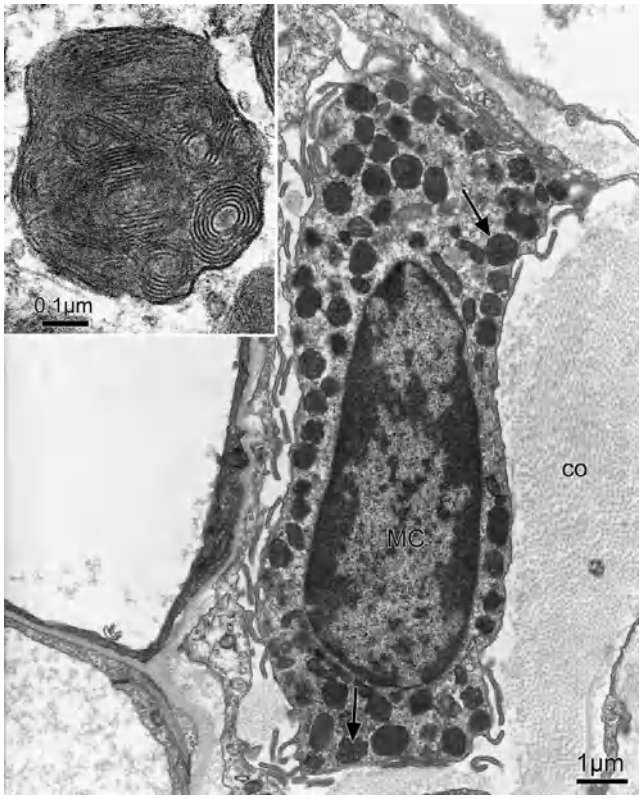


Figure 2-32 Mast cell from human lung containing granules (arrows) with scroll-like substructure. *Inset*. Scroll-like substructure of mast cell granule at higher magnification. co = collagen fibrils. *(From Weibel ER: Lung cell biology, in Fishman A, Fisher AB (eds): Handbook of Physiology. Section 3: The Respiratory System. Bethesda, MD: American Physiological Society, 1985, vol 1, pp 47–91.)*

from adult human lungs often appear gray or even black because of deposition in the medullary cords of large numbers of macrophages loaded with carbon pigment. This material entered the lung via the airways, primarily as smoke, soot, or coal dust; depending on the size of the particles, they were either deposited on the surface of conducting airways or reached the alveoli. The further down the deposition, the greater the likelihood that this material cannot be eliminated while in the airways, i.e., within the mucous blanket. The only exit from the lung parenchyma then is via the lymphatics, but this exit ultimately leads to the blood, a circumstance that is obviously to be avoided. Filtering the lymph in lymph nodes and providing a depository in the medullary cords protects the blood and hence the entire organism from dissemination of indigestible foreign matter and also, in most instances, of infective agents.

Thus, the lymphatic "circulation" in the lung plays an important defense role. It is unidirectional: It begins as interstitial fluid that seeps from the capillaries and is efficiently drained along the connective tissue fibers toward those connective tissue sleeves in the center and at the periphery of acini where lymph capillaries begin. From there, lymphatic vessels, endowed with valves and an irregular smooth-muscle wall,

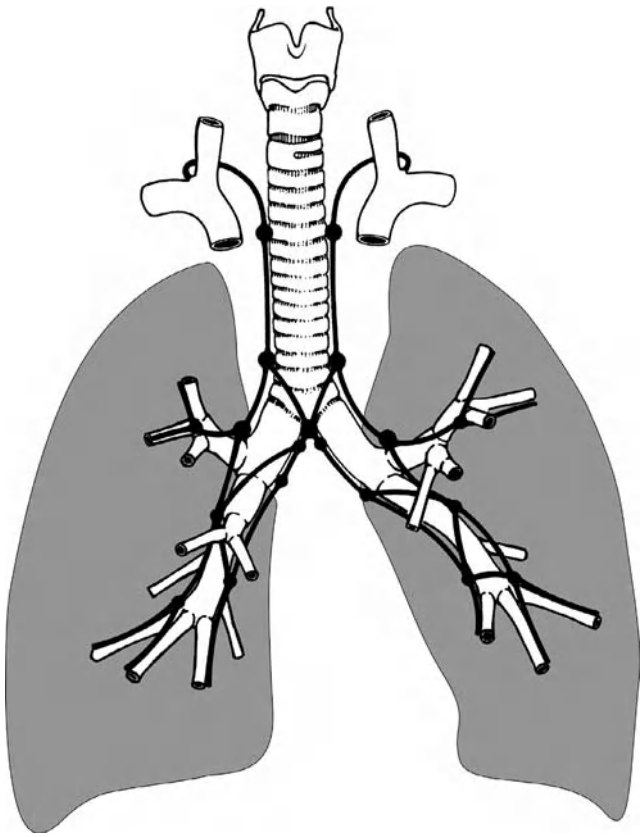


Figure 2-33 Schematic diagram of distribution of lymph nodes and main lymphatic channels along bronchial tree.

course in septal structures, in the pleura, and peribronchial and perivascular sheaths toward the hilar region (Fig. 2-33). Lymph nodes are intercalated in the course of the lymphatics, which lead the lymph toward the tracheal bifurcation and then along the trachea into the right and left mediastinal lymph channels. The right channel drains into the right subclavian vein; the left, together with the thoracic duct, into the left subclavian vein. Because of the many anastomoses connecting parallel lymphatics, a particular lymph node receives lymph from various lung regions, but the closest regions tend to predominate.

Alveolar Macrophages

Lung macrophages can be differentiated into several populations according to the compartment they are found in: intravascular, interstitial, airway, and alveolar macrophages. Of these, the alveolar macrophages, the cell population of the

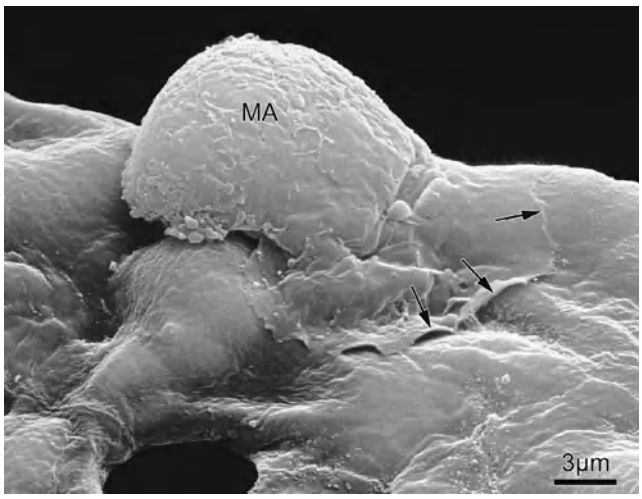


Figure 2-34 Alveolar macrophage (MA) seen sitting on epithelial surface of human lung. Note cytoplasmic lamella *(arrows)* which represents the advancing edge of the cell.

surface lining layer, are of particular importance. They are free cells, endowed with a high phagocytic capacity, which are transiently attached to the surface of the alveolar epithelium by pseudopodia and can crawl over this surface by ameboid movement (Fig. 2-34). Occasionally, alveolar macrophages can be observed during the passage through an interalveolar pore of Kohn. However, they are submerged beneath the surface film of phospholipids (Fig. 2-35) and, therefore, are part of the surface lining layer of alveoli, more specifically of its hypophase. Alveolar macrophages exert their phagocytic activity within the surface lining layer (Fig. 2-25). Hence, it is not surprising that their vacuoles contain large amounts of ingested surfactant material, in part even tubular myelin. The importance of alveolar macrophages for surfactant removal is underscored by the acquired form of pulmonary alveolar proteinosis, where a defect in surfactant catabolism by alveolar macrophages caused by autoantibodies against granulocyte/macrophage colony-stimulating factor (GM-CSF) leads to an accumulation of surfactant material in the alveoli.

Alveolar macrophages are derived from monocytes—indirectly, therefore, from bone marrow cells—and probably reach the alveoli in two steps: first, by settling in the pulmonary interstitial tissue, and second, by migration from the interstitial tissue into the alveoli where they constitute a partly self-reproducing cell population. Their removal seems to involve two different pathways: (1) some of the macrophages undoubtedly move up the bronchial tree in the mucous

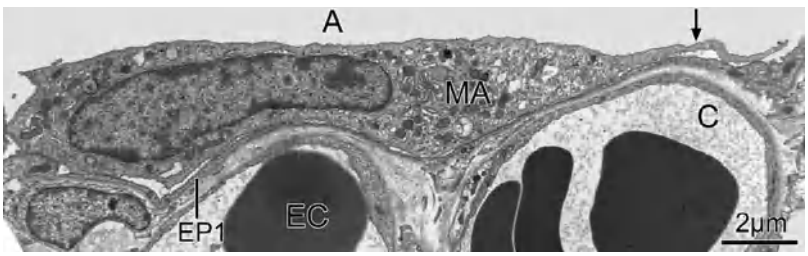


Figure 2-35 Alveolar macrophage (MA) fixed in its natural position of "flat" attachment to the alveolar epithelium. Arrow points to advancing cytoplasmic leaflet.

blanket and eventually appear in the sputum (heart failure cells, dust cells); and (2) others possibly return into the interstitial space. In the normal lung, however, the second path seems to occur exclusively in those alveoli that abut on the connective tissue sleeves around larger vessels and conducting airways or on interacinar septa; i.e., where the lymphatic capillaries are located. A preferred location appears to be in the respiratory bronchioles at the entrance into the acinus or in the center of the acinus, where one often finds congregations of dust-laden macrophages; this may be at the origin of centroacinar damages observed in smokers, which lead to progressive emphysema. In these places, macrophages either settle as carbon pigment-loaded histiocytes, or they leave the lung parenchyma via lymphatics (Fig. 2-31) to settle in the lymph nodes. The way in which macrophages and/or their ingested material are transferred from the alveolar surface to the interstitial space is still unknown.

FUNCTIONAL DESIGN OF THE LUNG

Design of the Branching Airway Tree

The entrance to the lung's airways is the trachea (Fig. 2-3), a single tube; the gas-exchange elements where air and blood are brought into close contact are contained in several million units. Between entrance and periphery lies a meticulously designed system of branching airways that serve to conduct the inspired air into those peripheral channels that carry alveoli in their walls and can thus contribute to the exchange of gases between air and blood (Fig. 2-5).

In the mammalian and human lung the airways are built as dichotomous trees. This is the result of lung morphogenesis where the end bud of each airway tube gives rise to two daughter branches. In the human lung this goes on for 23 generations, on average, and, since the number of branches doubles with each generation, there are 2^{23} or about 8 million end branches, generally called alveolar sacs. This is an average value; in reality the number of branching generations needed to reach the alveolar sacs is quite variable, ranging from about 18 to 30. This variability results from the fact that the airways form a space-filling tree (Fig. 2-3) whose endings must be homogeneously distributed in space and reach into every corner and into every gap in the available space, determined by the form of the chest cavity into which the lung develops. Some spaces are filled rapidly and the airways cannot continue to divide, whereas in other places more branches are needed to fill the space.

This branching process is accompanied by growth in length and diameter of the airway segments, the tubes between the branching nodes. The length of the tubes is adjusted to cover the distances needed to fill the space homogeneously with endings, whereas the diameter is, grossly speaking, made proportional to the volume of peripheral lung that is supplied by this branch.

Fig. 2-36 shows a portion of a cast of the airway tree from a human lung. It is evident that the airways branch

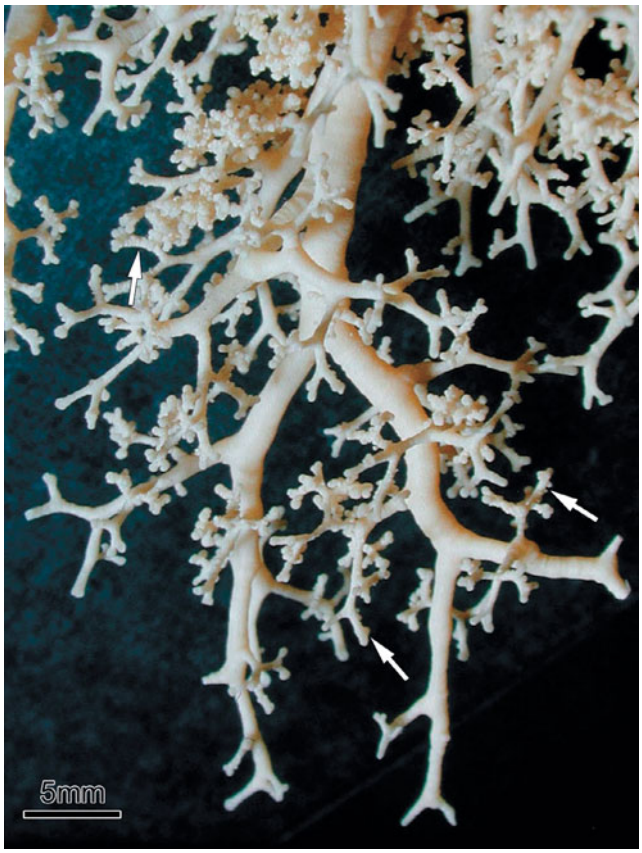


Figure 2-36 Peripheral portion of cast of human airway tree reaching out to the transitional bronchioles and some respiratory bronchioles *(arrows)*.

by dichotomy and that the length and the diameter of the tubes become gradually reduced with each generation. At first sight, the airway branching seems quite regular, but there is a certain degree of asymmetry in the sense that the two daughter branches differ in length and diameter; in animal lungs asymmetry is more pronounced than in human lungs.

Despite asymmetric branching some general rules govern the progression of dimensions along the tree. The diameter of daughter branches is smaller than that of the parent in the sense that the diameter reflects the volume of peripheral lung it supplies with air: larger airways serve larger lung units, smaller airways smaller units. The progression of airway diameters follows the law of Hess (1917) and Murray (1926) that, in a dichotomous tree, the diameters of the daughter branches, d_1 and d_2, are related to the parent branch as:

$$d_0^{\,3} = d_1^{\,3} + d_2^{\,3}$$

a law that predicts optimization of the airway diameters for convective air flow, providing lowest resistance for lowest dead space.

For a symmetric tree in which $d_1 = d_2$ this becomes:

$$d_1 = d_0 \cdot 2^{-1/3}$$

which means that the airway diameter becomes reduced by a factor of cube root of 1/2 or about 0.79 with each

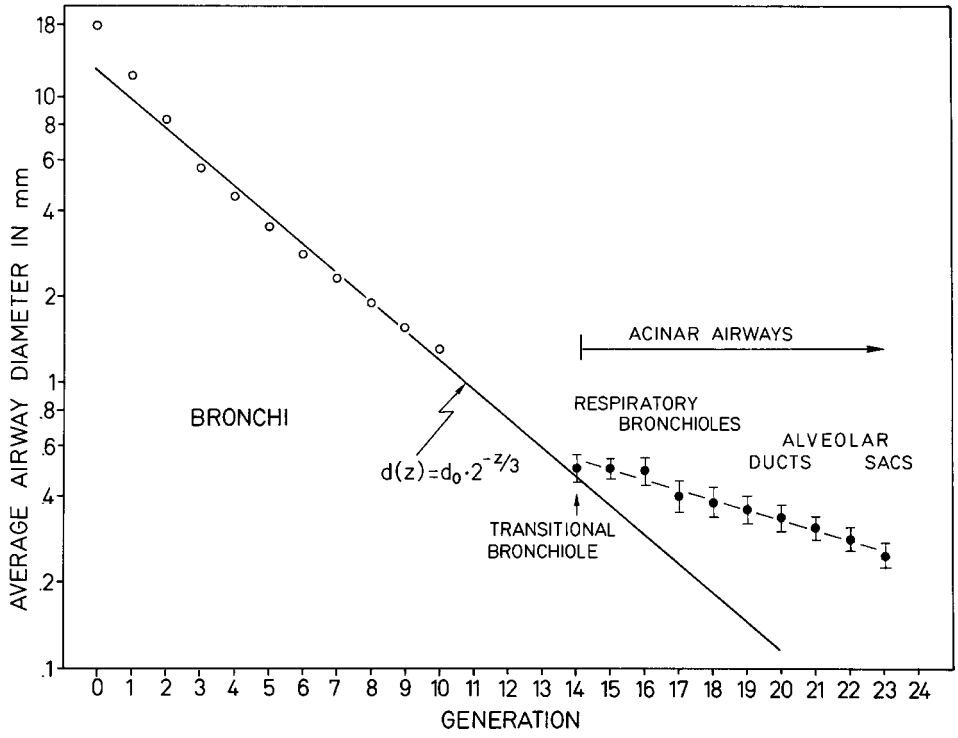


Figure 2-37 Average diameter of airways in human lung plotted by generations of regularized dichotomous branching. *(From Haefeli-Bleuer B, Weibel ER: Morphometry of the human pulmonary acinus. Anat Rec 220:401–414, 1988.)*

generation. Considering the progression of airway dimensions along the tree this law should apply to all successive generations so that we predict the average diameter in generation z to be:

$$d(z) = d_0 \cdot 2^{-z/3}$$

Fig. 2-37 shows that this is approximately the case for the first 14 generations of conducting airways.

However, a closer look at the airways of the human lung shows that this is only approximately correct. It appears that the smaller bronchioles (beyond generation 10) are provided with some safety factor in that the diameter is reduced by a factor of 0.83 rather than the physically optimal 0.79. This allows regulation of airway cross-section by contraction of the bronchiolar muscle sleeve without unduly increasing flow resistance which is very low in small airways (Fig. 2-38). Design optimalization is limited in favor of physiological robustness.

This symmetric airway model reflects the typical pathway along the airway tree. It has been very useful in modeling the basic rules governing the distribution of air flow as well as the deposition of particles entering the lung. However, it disregards the effects of asymmetric branching. It is possible to construct models that take into account irregularities in branching, for example by considering the number of airways of a given diameter, d_μ, that exist in each generation, and the length of the bronchial pathway that intervenes between the larynx and particular airways (Fig. 2-39).

An alternative approach is to regard the airways as a system of tubes converging from the periphery, the acinus,

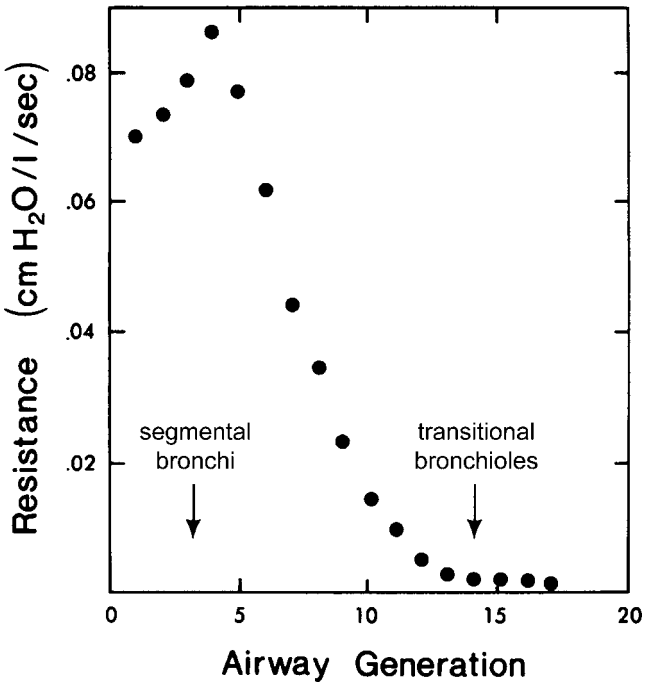


Figure 2-38 Airway resistance to mass air flow is located mostly in the conducting airways and falls rapidly toward the periphery. *(Redrawn after Pedley TJ et al. The prediction of pressure drop and variation of resistance within the human bronchial airways. Respir Physiol 9:387–405, 1970, with permission.)*

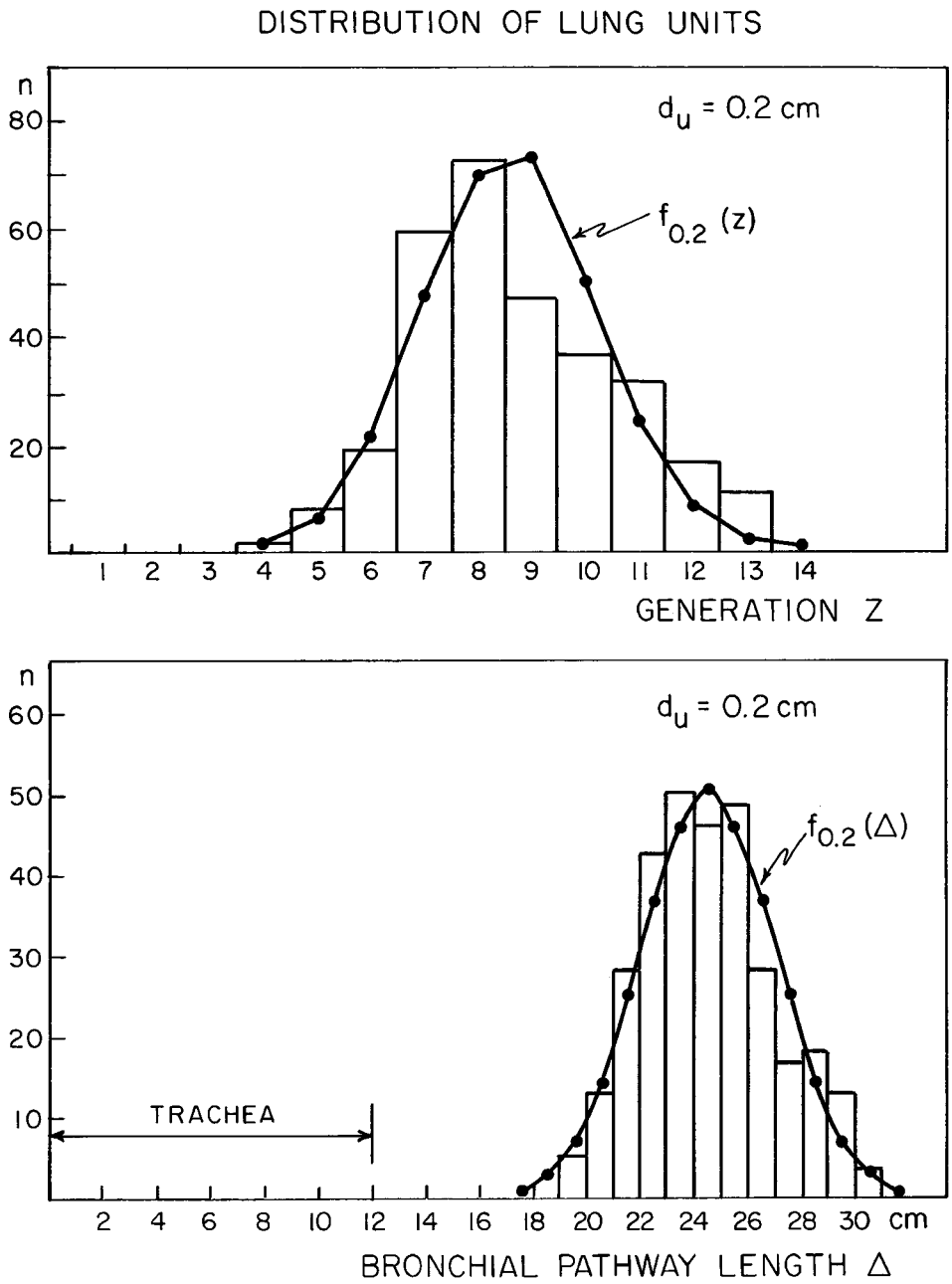


Figure 2-39 Distribution of airways of diameter $d_\mu = 2$ mm with respect to (A) generations of branching and (B) bronchial pathway lengths. *(From Weibel ER: Morphometry of the Human Lung. Heidelberg, Springer-Verlag, 1963.)*

toward the center, the trachea. By using an ascending ordering system that is employed in analyzing rivers (Strahler system), branches are grouped into orders according to the sequence of convergence, beginning with the smallest most peripheral branches, designated as order l. This ordering pattern is particularly well adapted to a system of irregular dichotomy because the size of branches in one order varies less than with the generations-down model. This approach does not really account for the asymmetry of branching, however; it rather represents an attempt at extracting average data with less variability in each order. The degree of asymmetric branching is reflected in the branching ratio determined as the ratio of the number of branches in order μ to that in order $\mu + 1$. Remarkably, the progression of diameters through the various orders is again roughly proportional to the cube root of the branching ratio. Hence, from a functional point of view both models yield comparable results.

The general conclusion drawn from this type of analysis is that the diameters of the conducting airways are such as to assure optimal conditions for airflow but relaxing physical optimality conditions in the interest of physiological robustness; the airways of the lung are thus well designed. The total volume of the conducting airways down to generation 14 (the anatomic dead space) is about 150 mL; it is rapidly flushed by simple gas flow in the course of inhaling 500 mL of fresh air during quiet inspiration. Therefore, for the larger airways,

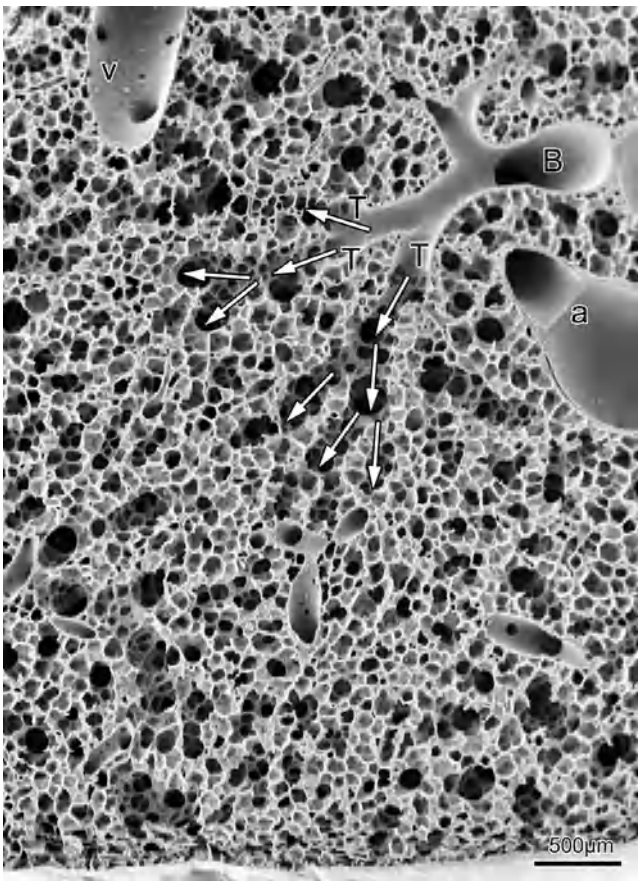


Figure 2-40 Scanning electron micrograph of lung shows branching of small peripheral bronchiole (B) into transitional bronchioles (T), from where the airways continue into respiratory bronchioles and alveolar ducts (arrows). Note the location of the pulmonary artery (a) and vein (v) as well as visceral pleura (bottom).

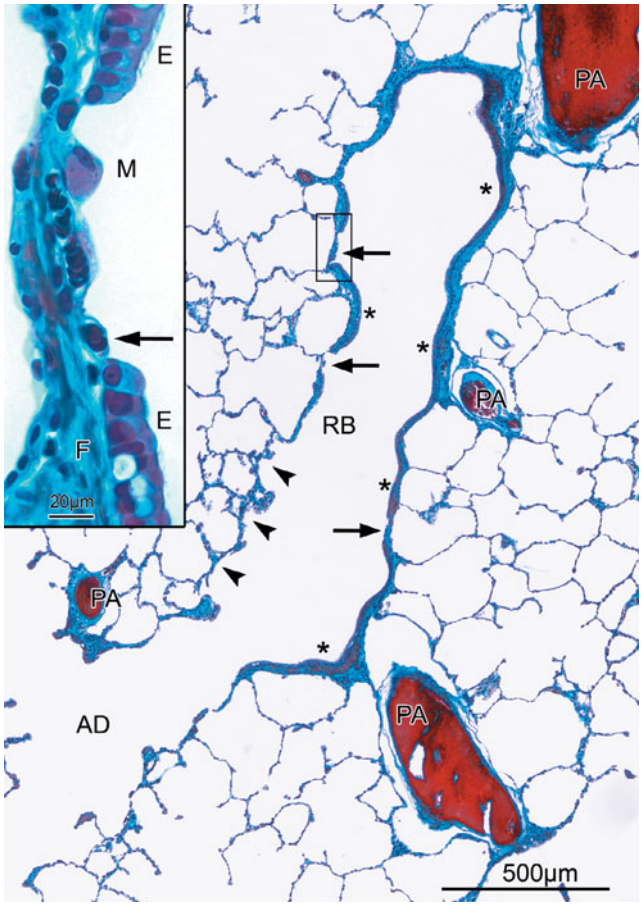


Figure 2-41 Respiratory bronchiole (RB) from human lung cut along its axis toward the transition to alveolar ducts (AD). Note lining by cuboidal airway epithelium *(asterisks)* and the occurrence of respiratory patches *(arrows)* before alveoli proper *(arrowheads)* appear. PA marks branches of pulmonary artery. Inset: Higher magnification of one of the respiratory patches in the wall of the respiratory bronchiole with capillaries *(arrow)* and alveolar macrophage (M). The cuboidal epithelium (E) with cilia is replaced by thin squamous epithelium of alveolar type 1 cell. Note thick fibrous layer (F) with smooth muscle cells.

optimization for flow and its distribution to peripheral units are essential for good design.

These are the characteristics of the proximal airways built as smooth-walled tubes to distribute convective air flow into the lung. This design ends more or less abruptly when the airways reach lung parenchyma, the complex of alveoli that are arranged around peripheral airways (Fig. 2-40). The airway tree is thus subdivided into two major functional zones (Fig. 2-5): the first about 14 to 16 generations, on average, are designed as conducting airways where air flow is by convection; this is followed by about eight generations of acinar airways where an axial channel, called alveolar duct, is enwrapped by a sleeve of alveoli with gas exchange tissue on their surface.

In the human lung the transition is not abrupt. At some point the smooth bronchiolar wall becomes interrupted by one or two alveoli (Fig. 2-41). This so-called transitional bronchiole (Fig. 2-5) marks the entrance into an acinus. It is followed by some three generations of respiratory bronchioles where an increasing fraction of the wall surface is occupied by alveoli, until the alveolar ducts are reached where the central air duct is completely surrounded by alveoli (Fig. 2-42).

These acinar airways continue to branch by dichotomy. Their length and diameter decrease with each generation, but the slope does not follow the law of reduction by the cube root of 1/2; the diameters of respiratory bronchioles and alveolar ducts change very little with each generation. Does this arrangement imply less than an optimal design? On the contrary, the cube-root-of-1/2 law relates to optimizing mass flow of a liquid or air. In the most peripheral airways, mass airflow is only part of the means of transporting O_2 toward the air-blood barrier: Since the airways are blind-ending tubes and since a sizable amount of residual air remains in the lung periphery after expiration, O_2 molecules must move into the residual air by diffusion (Fig. 2-43). However, diffusion of O_2 in the gas phase is best served by establishing as large an interface as possible between residual air and the fresh air that flows in from the trachea. In fact, since the airway diameter remains nearly unchanged, the total airway cross section nearly doubles with each generation beyond generation 14.

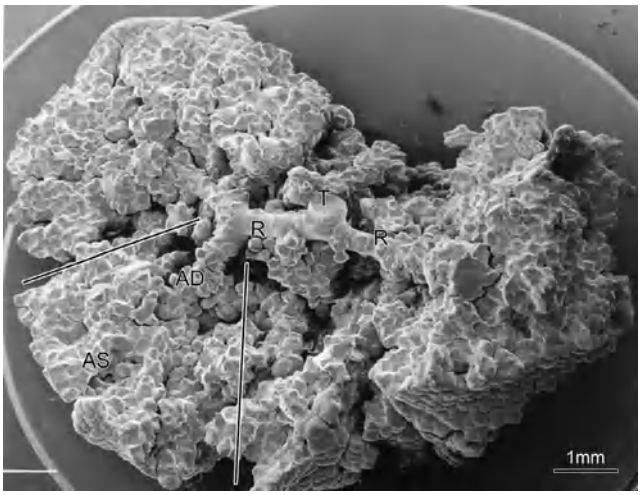


Figure 2-42 Scanning electron micrograph of a complete acinus from a silicon rubber cast of a human lung partly dissected to show transitional (T) and respiratory (R) bronchioles as well as alveolar ducts (AD) and alveolar sacs (AS). Lines mark approximate boundary of 1/8 subacinus. *(From Haefeli-Bleuer B, Weibel ER: Morphometry of the human pulmonary acinus. Anat Rec 220:401–414, 1988.)*

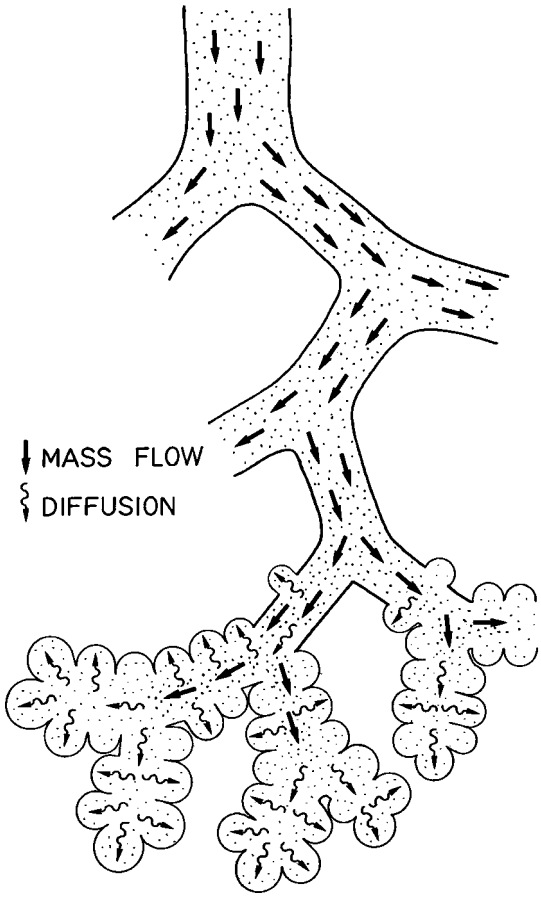


Figure 2-43 Oxygen molecules reach alveoli by combined mass airflow and molecular diffusion, the importance of diffusion increasing toward the periphery.

The dimensions of the airway tree influence the ventilatory flow of air in a number of ways. First of all, airflow velocity falls along the airway tree because the total cross-sectional area of the airways increases with every generation (Fig. 2-44); whereas the cross-sectional area of the trachea is about 2.5 cm^2, that of the 1024 airways in the 10th generation taken together is 13 cm^2, and as we approach the acinar airways, the total cross section reaches 300 cm^2. However, since the same air volume flows through all generations, the flow velocity falls by more than 100-fold from the trachea to the acini: at rest, the mean flow velocity on inspiration is about

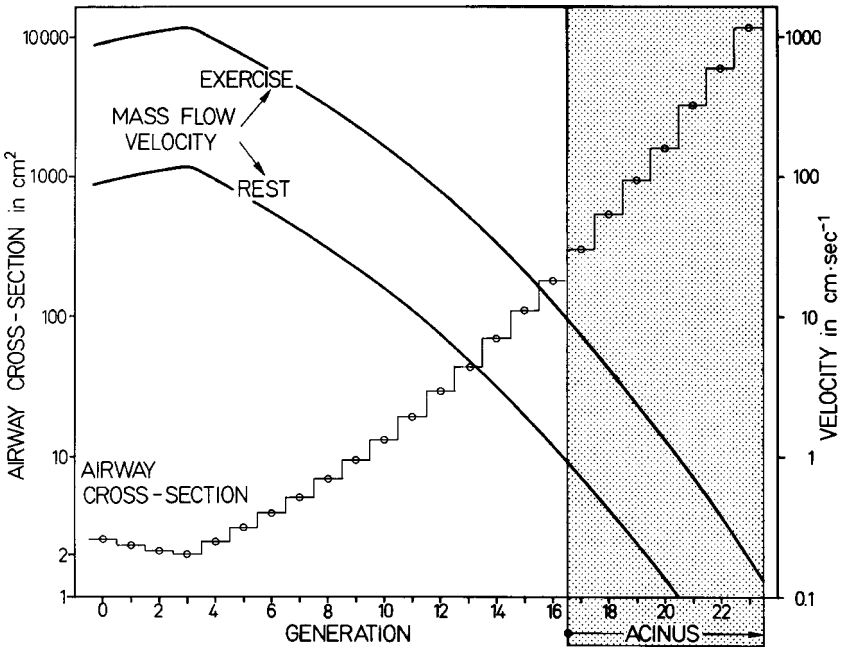


Figure 2-44 As total airway cross-section increases with the generations of airway branching, the mass flow velocity of inspired air decreases rapidly, falling below the molecular velocity of O_2 diffusion in air as we enter the acinus (see Fig. 2-66). *(From Weibel ER: The Pathway for Oxygen. Cambridge, MA, Harvard University Press, 1984.)*

1 m · s^{-1} in the trachea and less than 1 cm · s^{-1} in the first-order respiratory bronchioles. In exercise, the flow velocities are up to 10 times greater, in proportion to the increased ventilation. This is discussed further when considering the relative importance of convection and diffusion in bringing O_2 to the alveolar surface for gas exchange.

The size of airways also determines the resistance to airflow. However, the overall resistance is rather small; it is given by the reciprocal of the ratio of ventilatory airflow to the pressure difference between the mouth and alveoli, which is normally no greater than about 1 cmH_2O (mbar) or less than 1 mmHg. It is large enough, however, to potentially affect the distribution of ventilation to the many gas-exchange units. Because, in laminar flow, the resistance is inversely proportional to d^4 the distribution of air flow depends on a delicate balance of the size of parallel airway tracts. Even a slight narrowing of one of the two daughter branches at a branchpoint will cause disproportionate air flow to the other branch and thus result in ventilation inhomogeneity.

Since the diameter of airways decreases as they branch (Fig. 2-37), one would suspect that their resistance increases toward the periphery. Apparently this is not the case, as the major pressure drop along the airways occurs in medium-sized bronchi; because the airway diameter decreases with a factor larger than the optimal 0.79 resistance becomes very low in the small bronchioles (Fig. 2-38). This is further accentuated by the fact that the thin-walled bronchioles become widened as the lung expands on inspiration because they are subject to the tissue tensions in the coarse fiber system of the lung. Therefore, airway resistance is seen to fall as lung volume increases. When this effect of tissue tension is disturbed, as in emphysema, some small bronchioles may collapse. This causes ventilation of the peripheral lung units to become highly uneven.

This biophysical way of looking at the significance of the progression of airway dimensions has recently been complemented by the alternative notion that the airway and vascular trees could be determined by the laws of fractal geometry. Fractal trees are formed by repeating the branching pattern from one generation to the next: If the proportion between parent and daughter branches remain the same this is called self-similar branching. In a dichotomous tree the diameter is ideally reduced by a factor of $2^{-1/Df}$ where D_f is the fractal dimension. Since the airway tree is nearly space-filling $D_f \sim 3$, which means that the Hess-Murray law also follows from fractal geometry as a rule of optimal design, but because the reduction factor is somewhat larger than $2^{-1/3}$ it follows that the actual fractal dimension of the airway tree is a bit larger than 3; this is possible because the tree is "cut off" at the entrance to the acini and the "space" becomes filled with alveoli.

Design of the Vascular Tree

In many ways, the course and pattern of dimensional changes in the pulmonary blood vessels resemble those of the airways. Fig. 2-3 shows that the pulmonary arteries follow the airways closely, out to the smallest branches; together they form the axis of lung parenchymal units of varying order: acinus, lobule, segment, lobe. As indicated, the veins are differently disposed, lying in the boundary between two or three adjacent units (see Figs 2-30 and 2-45).

The diameter of each pulmonary artery branch also approximates closely that of the accompanying bronchus (Fig. 2-45*A*). Therefore, it is evident that the diameter law presented above for airways must also hold for the first 10 to 16 generations of pulmonary arteries (Fig. 2-37). However, the pulmonary arteries divide more frequently than the airways; very often, small branches leave the artery at right angles and supply blood to the parenchymal units adjacent to the bronchus (Fig. 2-45*B*). From a count of precapillaries, it seems that the pulmonary arteries divide, on the average, over 28 generations, as compared with 23 for the airways. The diameter of these terminal vessels is about 20 to 50 μm; if this range is plotted onto an extension of the graph of Fig. 2-37 to generation 28, it falls on the curve that is obtained by extrapolation from the major branches:

$$d(z) = d_0 \cdot 2^{-z/3}$$

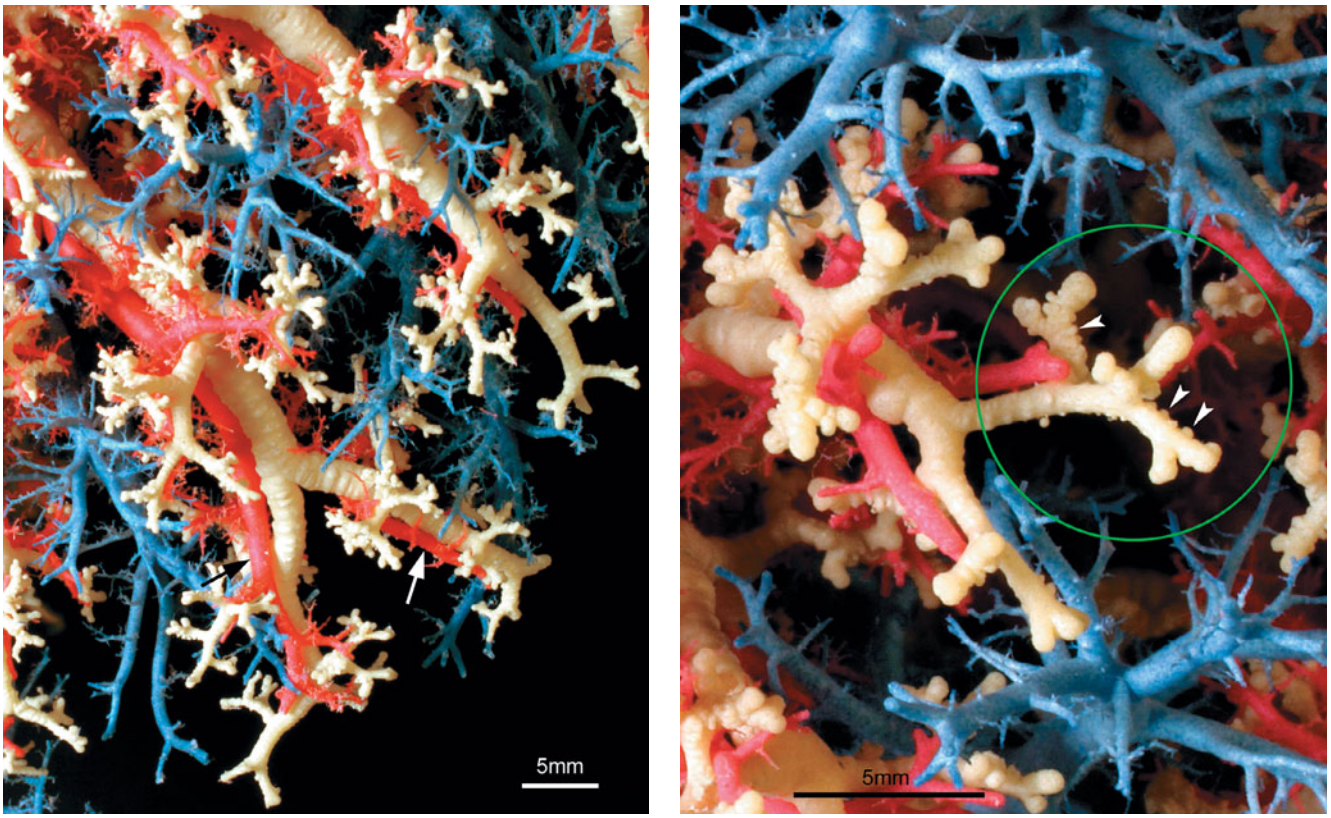
This suggests that the pulmonary arteries abide to the cube-root-of-1/2 law from beginning to end. Evidently, the blood is transported to the capillary bed by mass flow only. Therefore, there is no reason to deviate from this fundamental law of design, which minimizes the loss of energy caused by blood flow.

In a recent thorough analysis of the pulmonary vascular trees conceived as fractal structures it has been shown that the fractal dimension of both arteries and veins is 2.71, thus somewhat less than 3. The diameter reduction factor is therefore slightly smaller than cube-root-of-1/2, and the diameters follow the regression:

$$d(z) = d_0 \cdot 2^{-z/2.71}$$

Therefore, in contrast to the airways, the resistance to blood flow increases along the the pulmonary arteries and is highest in the most peripheral branches or arterioles. The resistance profile of the pulmonary arteries is thus the same as in the systemic circulation.

The alveolar capillary network of the lung is very different from that of the systemic circulation. Whereas in muscle, for example, long capillaries are found to be joined in a loose network, the capillaries of the alveolar walls form dense meshworks made of very short segments (Fig. 2-46). The meshes are so dense that some people believe blood flows through the alveolar walls like a sheet rather than through a system of interconnected tubes. In this sheet-flow concept, the sheet is bounded by two flat membranes, the air-blood barrier, connected by numerous "posts." When blood flows through this sheet, it is not channeled in a given direction but has freedom to move in a tortuous way between the posts. Although this concept oversimplifies the actual structural conditions, it does provide a useful description of the pattern of blood flow through the alveolar walls and explains why blood flow is not interrupted when some parts of the capillary bed become



A *B*

Figure 2-45 Casts of airways and blood vessels of human lung. (*A*) shows how the pulmonary artery *(red)* closely follows the airways *(yellow)* to the periphery, whereas the pulmonary vein branches *(blue)* lie between the units. Note that the diameter of the pulmonary arteries is similar to that of the accompanying airway, but becomes relatively smaller toward the periphery *(arrow);* small supernumerary arteries take off at right angles. (*B*) Higher power view of group of acini (circle), corresponding about to a secondary lobule, shows how artery penetrates into center of gas exchange unit with veins collecting the blood around the periphery. Arrowheads point to alveolar pouches on transitional and respiratory bronchioles.

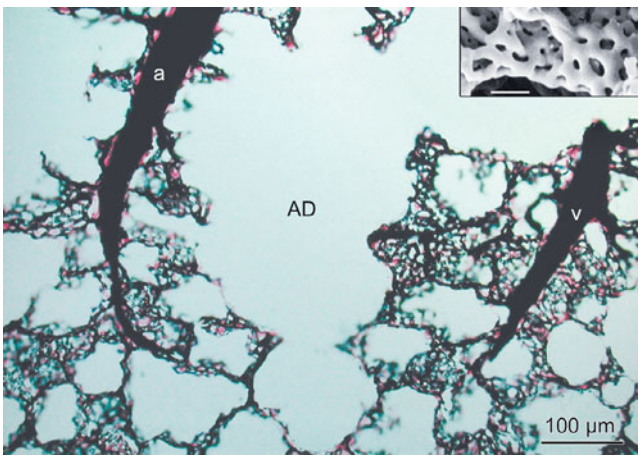


Figure 2-46 Alveolar capillary network demonstrated with gold-labeling of blood plasma in a physiologically perfused preparation of a rabbit lung. The dense capillary network spans between end branches of pulmonary artery (a) and vein (v) and extend through many alveolar septa around alveolar duct (AD). *Inset:* Plastic cast shows the dense meshes of the network. Scale bar = 20 µm. *(Inset courtesy of P. Burri.)*

squashed flat at high inflation levels (see Fig. 2-58); the capillaries that remain open in the corners are simply some channels of this broad sheet. Furthermore, it is important to note that the capillary network or sheet is continuous through many alveolar walls (Fig. 2-46), probably at least throughout the entire acinus, if not for greater distances. Consequently, it is not possible to isolate microvascular units. One finds, rather, that arterial end branches simply feed into this broad sheet at more or less even distances and that the veins drain these sheets in a similar pattern. However, now we must remember that the arteries reach the acinus along the airways, whereas the veins are in a peripheral location (Fig. 2-45). In principle, therefore, blood flows through the acinar capillary sheet from the center to the periphery of the acinar gas exchange unit.

Design of Pulmonary Parenchyma

Alveoli and Capillaries

The airspaces and blood vessels of lung parenchyma are designed to facilitate gas exchange between air and blood. To this end a very large area of contact between air and blood

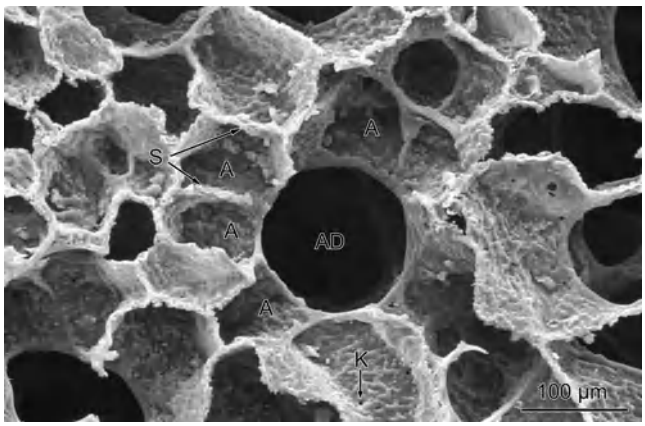


Figure 2-47 Scanning electron micrograph of human lung parenchyma. Alveolar ducts (AD) are surrounded by alveoli (A), which are separated by thin septa (S). K = interalveolar pore of Kohn.

must be established; for the human lung it is sometimes compared with the area of a tennis court in size. Furthermore, the tissue barrier separating air and blood must be kept as thin as possible—it is found to be about 50 times thinner than a sheet of airmail stationery. This is important, because less than 1 s is available for loading O_2 onto the erythrocytes as they flow through the lung's gas exchange region.

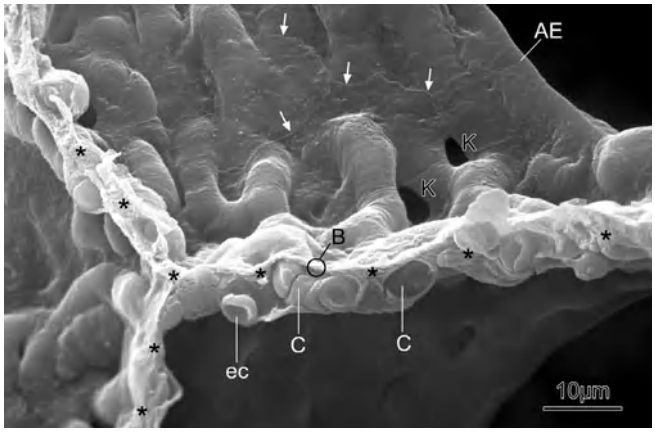
The first design feature to this end is the formation of alveoli in the walls of all airways within the acinus—i.e., in the gas-exchange units beginning with a transitional bronchiole (see above) (Fig. 2-40). In the human lung, one estimates that there are about 30,000 acini and 400 million alveoli, so that each of the gas-exchange units contains some 13,000 alveoli, on average, connected to about seven to nine generations of acinar airways, respiratory bronchioles, and alveolar ducts.

The alveoli are so densely packed that they occupy the entire surface of alveolar ducts; they are separated from each other by delicate alveolar septa that contain the capillary network (Fig. 2-47). About half the space of the septum is taken up by blood, which is thus exposed to the air in two adjacent alveoli (Fig. 2-48*A*). Although the barrier separating air and blood is extremely thin, we find the capillaries to be provided with a complete endothelial lining, as the alveolar surface of the septum is lined by an epithelium. We have seen above that these two cell linings are very much attenuated over the greatest part of the surface.

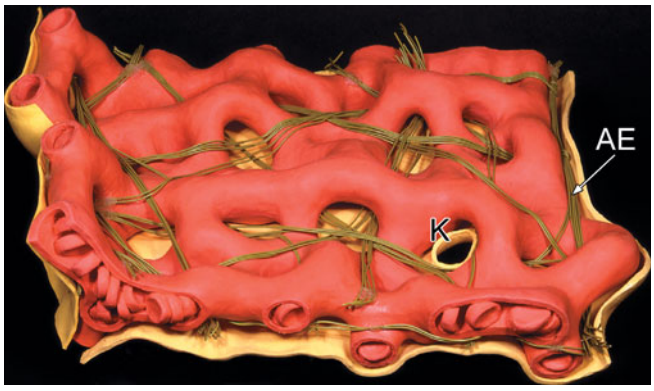
To make the barrier very thin, the interstitial structures must also be reduced to the minimum required (Fig. 2-49). The septal interstitium contains very few cells, mostly slim fibroblast with long extensions; these contain fine bundles of contractile filaments that serve an as yet unknown mechanical function. The septal interstitium usually does not contain cells of the defense system or lymphatics.

Internal Support of Parenchymal Structures: The Pulmonary Fiber Continuum

This extraordinary reduction of the tissue mass in the alveolar septa inevitably introduces a number of major problems. How is it possible to secure the mechanical integrity of the system if we consider that several forces act on the septal tissue with a tendency to disrupt it? The thin barrier must not only withstand the distending pressure of the capillary blood due both to hemodynamic forces and gravity, particularly in the lower lung zones, but must also keep the capillary bed expanded over a very large surface—a task that is made difficult because surface forces that act on the complex alveolar



A



B

Figure 2-48 In the alveolar wall, shown in (*A*) in a scanning electron micrograph from a human lung, the capillary blood (C) with its erythrocytes (ec) is separated from the air by a very thin tissue barrier (*B*). Short arrows mark intercellular junctions of alveolar epithelium that course towards interalveolar pores of Kohn (K). The model (*B*) shows the capillary network *(red)* to be interwoven with the meshwork of septal fibers *(green),* the course of which is marked by asterisks in (*A*). The epithelial lining *(yellow)* that crosses the septum at interalveolar pores (K) is removed on the upper surface of the septum to show the capillary. The septal fibers are anchored on the strong fiber bundle marking the free edge of the septum or the alveolar entrance ring (AE). *(From Weibel ER: The Pathway for Oxygen. Cambridge, MA, Harvard University Press, 1984.)*

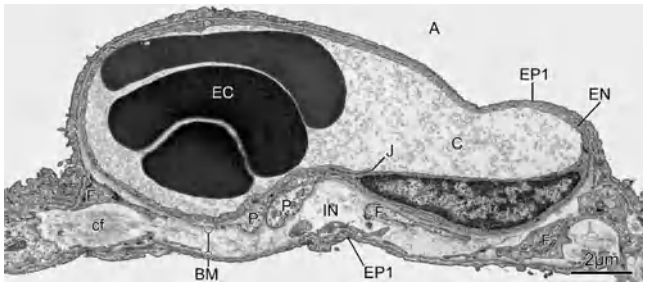


Figure 2-49 Alveolar septum from human lung lined by type I epithelium (EP1) with capillary lined by endothelial cell (EN) that is associated with processes of pericytes (P). Substantial interstitial space (IN) with collagen and elastic fibers (cf) and fibroblasts (F) occurs on one side only, whereas minimal air-blood barrier is formed on other side by fusion of basement membranes (BM) of endothelium and epithelium.

surface would tend to collapse alveoli and capillaries (see the following). This requires a very subtle, economical design of the fibrous support system.

The problem of supporting the capillaries on connective tissue fibers with as little tissue as possible has been solved ingeniously: we find that the fiber network is interlaced with the capillary network. Fig. 2-48*B* shows that when the fibers are taut, the capillaries weave from one side of the septum to the other. This arrangement has a threefold advantage: (1) it allows the capillaries to be supported unit by unit directly on the fiber strands without the need of additional "binders;" (2) it causes the capillaries to become spread out on the alveolar surface when the fibers are stretched; and (3) it optimizes the gas-exchange conditions by limiting the presence of fibers—which must interfere with O_2 flow—to half the capillary surface. The thin section of a capillary shown in Fig. 2-49 reveals that an interstitial space with fibers and fibroblasts exists on only one side of the capillary, whereas on the other the two lining cells, endothelium and epithelium, become closely joined with only a single common basement membrane interposed. Therefore, over half the surface of the capillary blood is separated from the air merely by a minimal tissue barrier made of epithelial and endothelial cytoplasmic sheets with their basement membranes fused leaving no interstitial space that could enlarge with interstitial pulmonary edema (Fig. 2-17).

The principal structural "backbone" of the lung is a continuous system of fibers anchored at the hilum and put under tension by the negative intrapleural pressure that tugs on the visceral pleura. The general construction principle follows from the formation of the mesenchymal sheath of the airway units in the developing lung; as the airway tree grows, its branches remain separated by layers of mesenchyme within which blood vessels form. When fiber networks develop within this mesenchyme, they enwrap all airway units and extend from the hilum right to the visceral pleura. The pulmonary fiber system hence forms a three-dimensional fibrous continuum that is structured by the airway system and is closely related to the blood vessels. By virtue of the design of this fibrous continuum, the lung becomes, in fact, subdivided

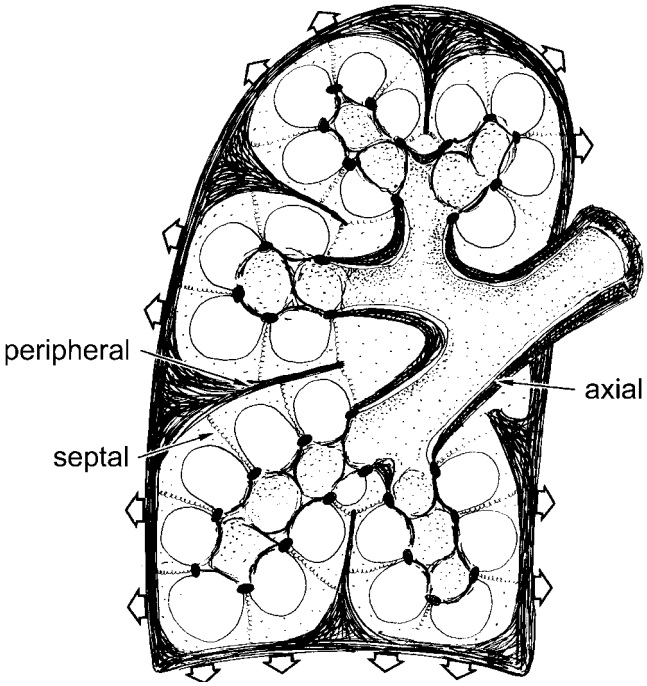


Figure 2-50 The major connective fiber tracts of the lung are divided into axial fibers along the airways and peripheral fibers connected to the pleura. They are connected by septal fibers in the alveolar walls. *(From Weibel ER, Gil J: Structure-function relationships at the alveolar level, in West JB, ed.: Bioengineering Aspects of the Lung. New York, Marcel Dekker, 1977, pp 1–81.)*

into millions of little bellows that are connected to the airway tree, as represented schematically in Fig. 2-50; these structures expand with expansion of the chest because the tension exerted on the visceral pleura by the negative intrapleural pressure becomes transmitted to the bellows' walls through that fiber system.

To try to put some order into this fiber system, we can first single out two major components that can be identified easily (Fig. 2-50). First we find that all airways—from the main-stem bronchus that enters the lung at the hilum out to the terminal bronchioles and beyond—are enwrapped by a strong sheath of fibers. These fibers constitute the axial fiber system; they form the "bark" of the tree whose roots are at the hilum and whose branches penetrate deep into lung parenchyma, following the course of the airways. A second major fiber system is related to the visceral pleura, which is made of strong fiber bags enwrapping all lobes. We then find connective tissue septa penetrating from the visceral pleura into lung parenchyma, separating units of the airway tree. We call these fibers the peripheral fiber system because they mark the boundaries between the units of respiratory lung tissue.

The peripheral fiber system subdivides the lung into a number of units that are not simple to define because they form a continuous hierarchy in accordance with the pattern of airway tree branching. However, as we have seen, two such units appear to be natural: the lobes, which are demarcated by a more or less complete lining by visceral pleura with a serosal

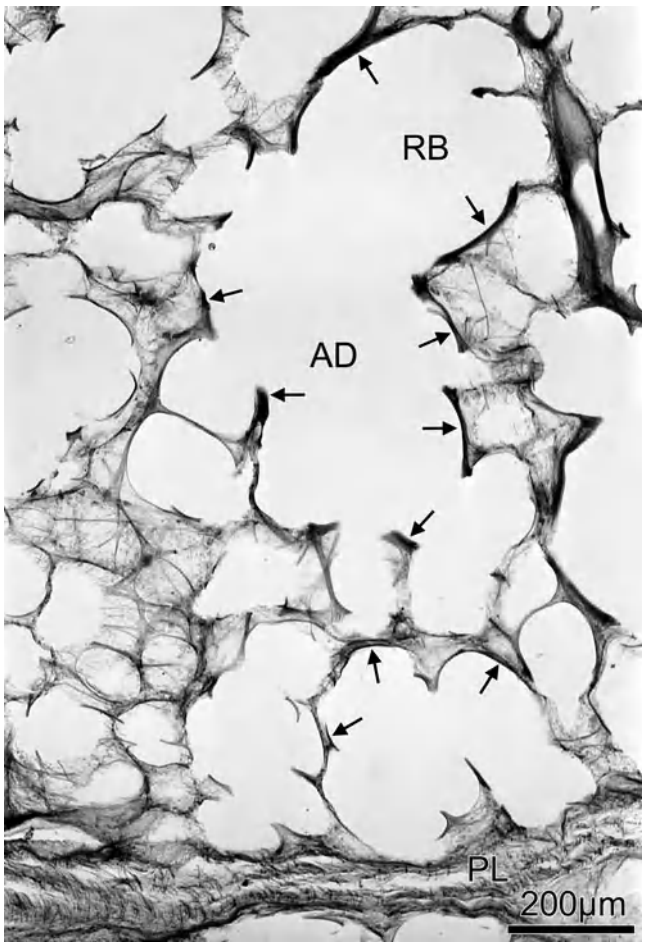


Figure 2-51 Connective tissue stain reveals the strong fiber rings (arrows) that demarcate the alveolar ducts (AD) and respiratory bronchioles (RB). *(From Weibel ER: The Pathway for Oxygen. Cambridge, MA, Harvard University Press, 1984.)*

cleft interposed (Fig. 2-1); and the acinus, the parenchymal unit in which all airways participate in gas exchange.

The acinus is the functional unit of the pulmonary parenchyma. The airway that leads into the acinus, the transitional bronchiole, continues branching within the acinus for about 6 to 10 additional generations (Figs. 2-5 and 2-40). These intra-acinar airways, called respiratory bronchioles and alveolar ducts, also carry in their wall relatively strong fibers of the axial fiber system, which extend to the end of the duct system. However, since the walls of intra-acinar air ducts are densely settled with alveoli, these fibers are reduced to a kind of delicate network whose meshes encircle the alveolar mouths, generally called alveolar entrance rings (Figs. 2-47 and 2-51). These fiber rings are associated with some smooth muscle cells (Fig. 2-29), and they serve as a scaffold for a network of finer fibers that spread within the alveolar septa (Figs. 2-48B and 2-51). However, now we must note that in a fiber system there may be no loose ends. Accordingly, the septal fiber system must be anchored at both ends—on the network of axial fibers around the alveolar ducts, and on extensions of the peripheral fibers that penetrate into the acinus from interlobular septa. Thus, the fiber system of the lung becomes a continuum that spans the entire space of the lung, from the hilus to the visceral pleura (Fig. 2-50). It is put under varying tension as the pleura is expanded by the chest wall and diaphragm.

The continuous nature of a well-ordered fiber system is an essential design feature of the lung. This becomes evident in emphysema. When some fibers are disrupted, they cannot be kept under tension. They retract and larger airspaces form as the fiber system is rearranged near the damage. Small foci of emphysema form in most lungs in the course of time.

The fiber system serves mainly as a mechanical support for the blood vessels, with which it is intimately associated in an orderly fashion. The pulmonary artery branches in parallel with the airway tree, but it is not related to the axial fiber system. Like the pulmonary veins the pulmonary arteries are associated with those parts of the peripheral fiber system that form an adventitial sheath on the larger vessels of both types and also form a boundary sheath on the surface of bronchi where alveolar complexes touch on the bronchial wall. Therefore, it is justified to characterize the connective tissue surrounding bronchi and pulmonary arteries as a peribronchovascular space, which houses the lymphatics as well as the systemic bronchial arteries and their branches. In fact, this space is continuous with the septal connective tissue that enwraps the pulmonary veins (Fig. 2-30) and is continuous with the visceral pleura. However, whereas the arteries penetrate into the acinus, the veins remain at the periphery and are thus located between the airway units (Fig. 2-45). In the alveolar septa, the capillary network spreads out as a broad sheet of vessels whose paths are continuous throughout the system of interconnected alveolar septa (Fig. 2-46). We have seen that these capillaries are intimately related to the septal fiber system (Fig. 2-48*B*).

Parenchymal Mechanics and Tissue Design

As in all connective tissue, the fibers of the lung are composed of collagen and elastic fibers. The collagen fibers are bundles of fibrils bound together by proteoglycans; they are practically inextensible (less than 2 percent) and have a very high tensile strength; they rupture at loads of 50 to 70 dyn/cm^{-2}, which means that a collagen fiber of 1-mm diameter can support a weight of over 500 g. In contrast, elastic fibers have a much lower tensile strength but a high extensibility. They can be stretched to about 130 percent of their relaxed length before rupturing.

In the fiber system of lung parenchyma, collagen and elastic fibers occur in a volume ratio of about 2.5:1, whereas this ratio is 10:1 for the visceral pleura. In a relaxed state, one finds the collagen fibers to be longer than the accompanying elastic fibers, so that they appear wavy. Because of the association between "rubberlike" elastic and "twinelike" collagen fibers, the connective tissue strands behave like an elastic band. They are easy to stretch up to the point where the collagen fibers are taut, but from there on they resist stretching very strongly.

The elastic properties of the lung's fiber system can be studied by filling the airways with fluid so as to eliminate the effects of surface tension. This reveals that the lung's fiber system has a high compliance until high levels of inflation are reached, and that the retractive or recoil force generated by the fiber system amounts to no more than a few millibars at physiological inflation levels. The actual recoil force in the air-filled lung, reflected by the negative pressure in the pleural space, is appreciably higher, but this is caused by surface tension rather than the retractive force of the fibers.

Surface tension arises at any gas-liquid interface because the cohesive forces between the molecules of the liquid are much stronger than those between the liquid and gas. As a result, the liquid surface tends to become as small as possible. A curved surface, such as that of a bubble, generates a pressure that is proportional to the curvature and the surface tension coefficient γ. The general formula of Gibbs relates this pressure, P_s, to the mean curvature $\overline{K}$:

$$P_s = 2\gamma \cdot \overline{K}$$

In a sphere, the curvature is simply the reciprocal of the radius r (Laplace's law):

$$P_s = \frac{2\gamma}{r}$$

The most critical effect of surface tension is that it endangers stability of the air space, because a set of connected "bubbles," the alveoli, is inherently unstable: The small ones should contract and the large ones expand. Since the 400 million alveoli are all connected with each other through the airways, the lung is inherently unstable: Why do the alveoli not all collapse and empty into one large bubble? There are two principal reasons.

The first reason is one of tissue structure. The alveoli are not simply soap bubbles in a froth. Rather, their walls contain an intricate fiber system, as we have seen. Thus, when an alveolus tends to shrink, the fibers in the walls of adjoining alveoli are stretched, and this prevents the alveolus from collapsing altogether. It is said that alveoli are mechanically interdependent and this stabilizes them.

The second reason is related to the fact that the alveolar surface is not simply water exposed to air but is lined by surfactant (Figs. 2-25 and 2-52), which has peculiar properties in that its surface tension coefficient γ is variable. From a large volume of evidence, it is now established that surface tension falls as the alveolar surface becomes smaller, and that it rises when the surface expands. Because of this feature, which is due to the phospholipoprotein nature of alveolar surfactant (see above), alveoli do not behave like soap bubbles whose surface tension remains constant. When an alveolus begins to shrink, the surface tension of its lining layer falls and the retractive force generated at the surface is reduced or even abolished. Combined with interdependence, this property of surfactant allows the complex of alveoli to remain stable.

Which of the two factors for stabilizing lung structure is now the most important: interdependence or surfactant properties? It turns out that both are essential. If one depletes

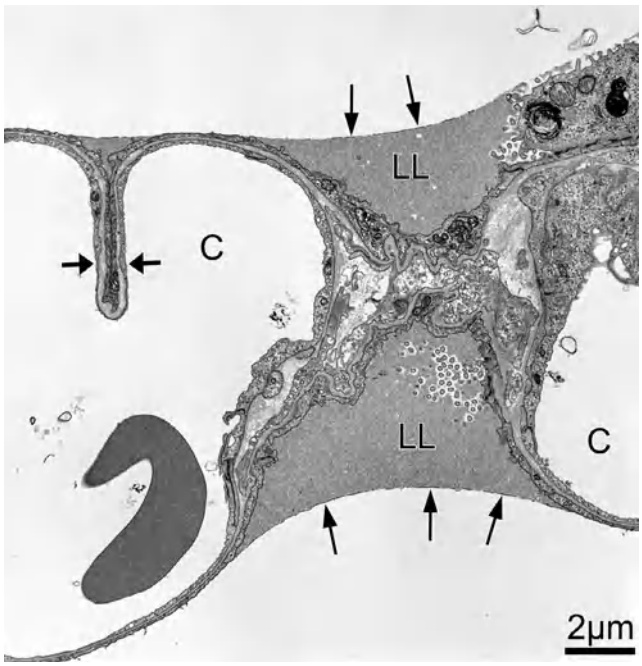


Figure 2-52 Alveolar septum of human lung fixed by perfusion through blood vessels shows alveolar lining layer (LL) in crevices between capillaries (C) topped by surfactant film that appears as a fine black line (arrows). Note the type II cell with lamellar bodies and the fold in thin tissue barrier (bold arrows). *(From Weibel ER: Looking into the lung: What can it tell us? Am J Roentgenol 133:1021–1031, 1979, with permission.)*

the lung of its surfactant lining by washing with a detergent, the pressure-volume curve changes dramatically (Fig. 2-53). On deflation, lung volume falls rapidly. If we look at samples from lungs fixed at the same volume (60 percent total lung capacity) but derived from either normal or detergent-rinsed lungs, we find that surfactant depletion causes the alveoli to collapse (Fig. 2-54). However, this causes the alveolar ducts to enlarge, stretching the strong fiber nets at the mouths of the collapsed alveoli. The ducts do not collapse because of interdependence between adjacent units.

In the normal air-filled lung, surfactant properties and interdependence owing to fiber tension both contribute to stabilizing the complex of alveoli and alveolar ducts. To understand this, let us examine Fig. 2-55, which shows a highly simplified diagram of a parenchymal unit. Interdependence is established by the continuum of axial, septal, and peripheral fibers. Surface tension exerts an inward pull in the hollow alveoli, where curvature is negative. However, over the free edge of the alveolar septa, along the outline of the duct, the surface tension must push outward because there the curvature is positive. The latter force must be rather strong, because the radius of curvature is very small on the septal edge; but this force is counteracted by the strong fiber strands, usually provided with some smooth muscle cells, that we find in the free edge of the alveolar septum (Figs. 2-29, 2-47, and 2-51). Thus, interdependence is an important factor in preventing the complex hollow of the lung, where negative and positive curvatures coexist, from collapsing. However, its capacity to

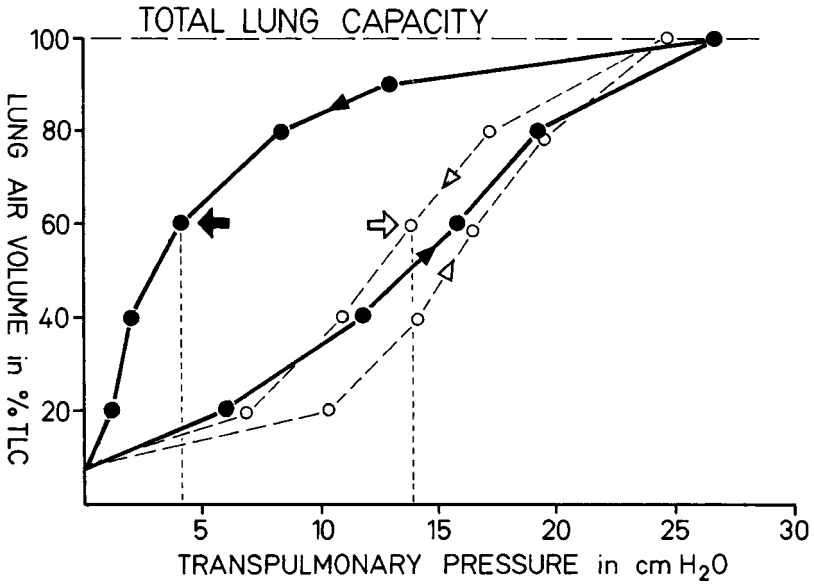
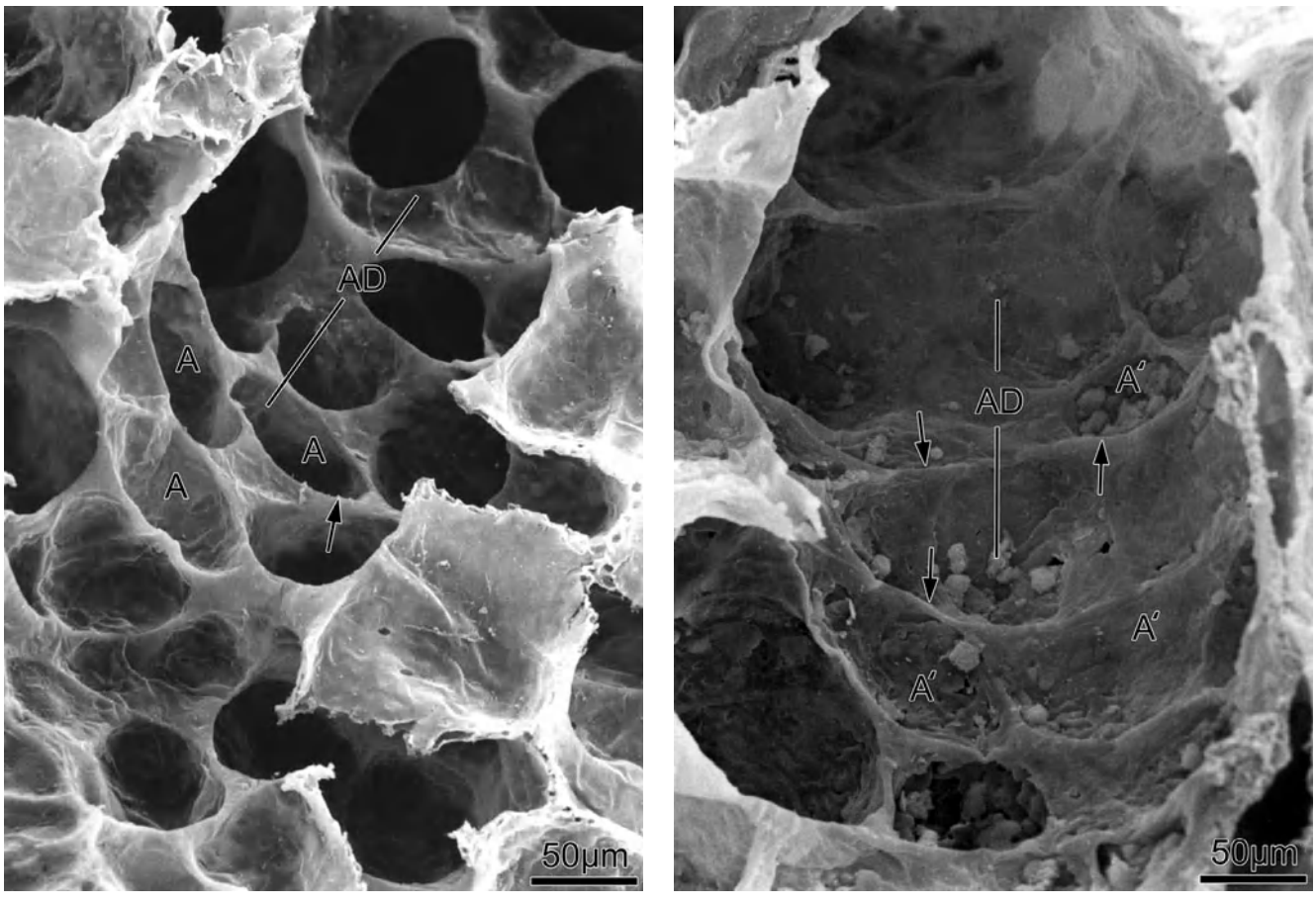


Figure 2-53 Comparison of pressure-volume curve of a normal air-filled rabbit lung with that of a surfactant depleted lung *(broken line)*. The arrows indicate the points at which the lungs shown in Fig. 2-54 have been fixed by vascular perfusion. *(From Weibel ER: The Pathway for Oxygen. Cambridge, MA, Harvard University Press, 1984.)*



A *B*

Figure 2-54 Scanning electron micrographs of normal air-filled (*A*) and surfactant-depleted (*B*) rabbit lungs fixed at 60 percent TLC on the deflation curve (Fig. 53) show alveoli to be open (A) in (*A*), collapsed (A') in (*B*). The alveolar duct (AD) is widened in the surfactant depleted lung, resulting in a stretching of the fiber strands around the alveolar mouths *(arrows). (From Wilson TA, Bachofen H: A model for mechanical structure of the alveolar duct. J Appl Physiol 52:1064–1070, 1982.)*

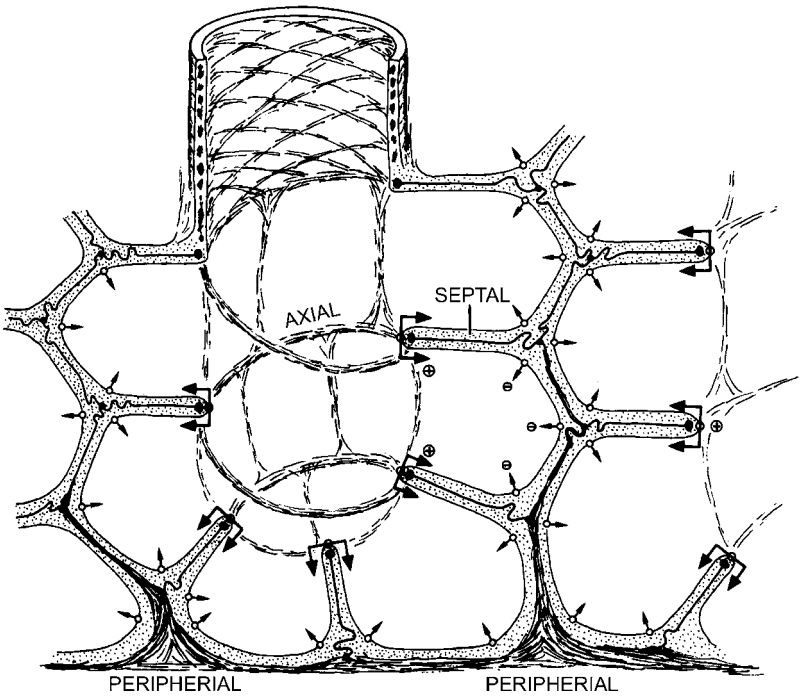


Figure 2-55 Model of the disposition of axial, septal, and peripheral fibers in an acinus showing the effect of surface forces (arrows). *(From Weibel ER: The Pathway for Oxygen. Cambridge, MA, Harvard University Press, 1984.)*

do so is limited and requires low surface tensions, particularly on deflation when the fibers tend to slack. If surface tension becomes too high, the lung's foamlike structure will partly collapse in spite of fiber interdependence (Fig. 2-54).

Micromechanics of the Alveolar Septum

We must finally consider the mechanical factors that shape the alveolar septum in the air-filled lung. As we have seen, the alveolar septum is made of a single capillary network that is interlaced with fibers (Fig. 2-48). When the fibers are stretched, the capillaries bulge alternatingly to one side or the other, and this causes pits and crevices to occur in the meshes of the capillary network.

This irregular surface is to some extent evened out by the presence of an extracellular layer of lining fluid, which is rather thin over the capillaries but forms little pools in the intercapillary pits (Fig. 2-52). This lining consists of an aqueous layer of variable thickness, called the hypophase, and surfactant, which forms a film on the surface of the hypophase. The hypophase seems to contain considerable amounts of reserve surfactant material, which occurs in a characteristic configuration called tubular myelin (Figs. 2-25 and 2-26).

In the alveolar septum, the tissue structures are extremely delicate, as we have seen. Therefore, its configuration is not exclusively determined by structural features but results from the molding effect of various forces that must be kept in balance. Fig. 2-56 shows how the three principal mechanical forces—tissue tension, surface tension, and capillary distending pressure—interact in the septum. The fibers of the alveolar septum are under a tension whose magnitude depends on the level of lung inflation. This tends to straighten out the fibers, so that a force (pressure) normal to the fiber axis results, which is responsible for shifting the capillaries to one side of the septum or the other (Figs. 2-48*B* and 2-56). The walls of the capillaries are exposed to the luminal pressure, which is the result of blood pressure in pulmonary arteries and veins but also depends on gravity, for one finds wider capillaries at the bottom of the lung than at the top. If this distending pressure acts homogeneously over the circumference of the capillary, it will push against the fibers on one side but will cause the thin barrier on the opposite side to bulge outward. This effect is to some extent counteracted by surface tension, which exerts a force normal to the surface (Fig. 2-56). This force depends on two factors: Its direction

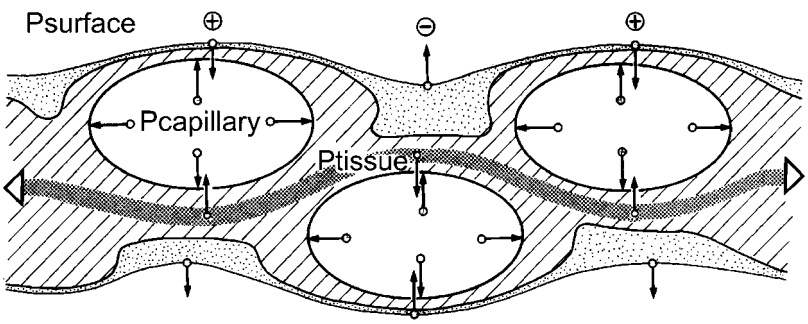


Figure 2-56 Model showing the micromechanical forces of surface tension, tissue tension, and capillary distending pressure that shape the alveolar septum. *(From Weibel ER: The Pathway for Oxygen. Cambridge, MA, Harvard University Press, 1984.)*

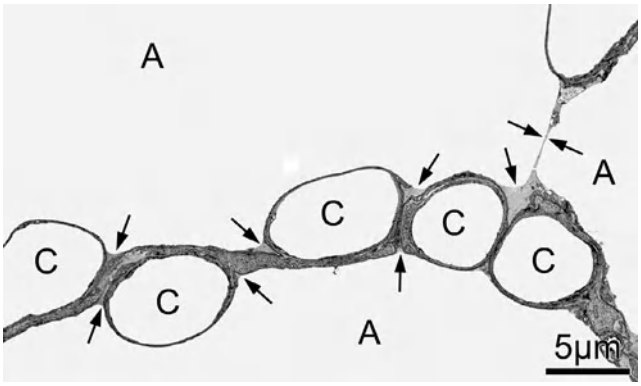


Figure 2-57 Alveolar septum of air-filled rabbit lung perfusion-fixed at 60 percent TLC shows empty capillaries (*C*), which bulge toward the alveolar air space (*A*). Note pools of surface lining layer in the crevices between capillaries *(arrows)* and film spanning across alveolar pore *(double arrows). (From Gil J et al. Alveolar volume-surface area relation in air- and saline-filled lungs fixed by vascular perfusion. J Appl Physiol 52:990-1001, 1979, with permission.)*

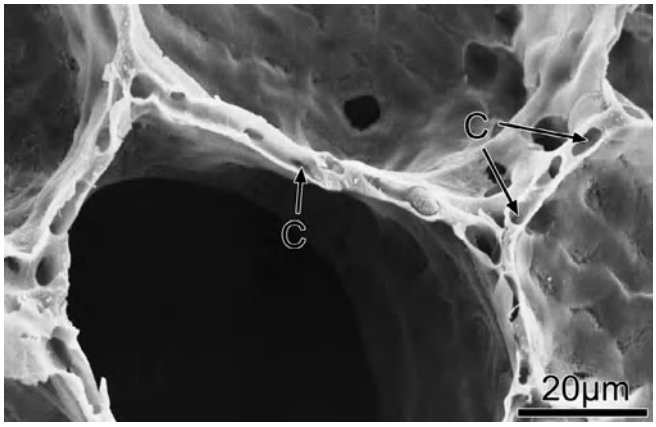
depends on the orientation of curvature, acting toward the alveolar space over concave regions (negative curvature) and toward the tissue over convexities (positive curvature); and its magnitude depends on the degree of curvature and on the value of the surface tension coefficient γ.

The alveolar septum achieves a stable configuration when all these interacting forces are in balance. Combined forces tend to squash the capillary flat; this happens at high levels of lung inflation when the fibers are under high tension and the surface tension coefficient of surfactant reaches its highest value because of expansion of the surface. On deflation, the fibers are relaxed and surface tension falls drastically. The capillary distending pressure now exceeds both the tissue and the surface forces, with the result that the slack fibers are bent, weaving through the capillary network, whereas the capillaries bulge slightly toward the airspace. Surface tension is apparently so low as to permit a considerable degree of surface "crumpling" to persist (Fig. 2-57).

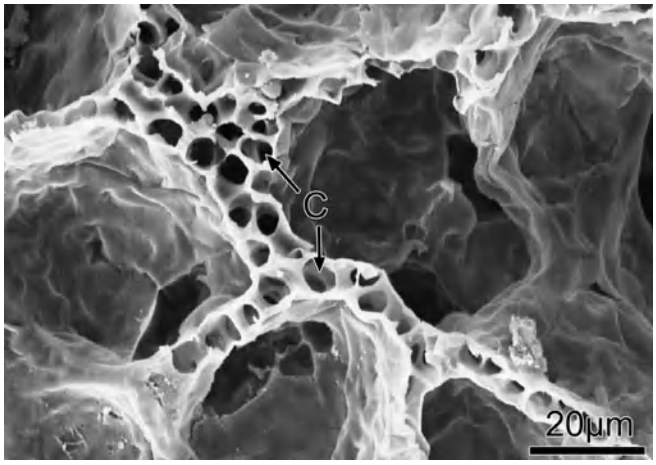
The importance of the balance between the forces that act on the septum is also shown in Fig. 2-58. The specimen of panel B was fixed under zone 3 perfusion conditions and all the capillaries are wide, partly bulging toward the airspace, as in Fig. 2-57. This is different in panel A, which was fixed under zone 2 conditions: In the flat part of the septum, the capillaries are squashed flat, because the surface and tissue forces now exceed the vascular distending pressure. However, it is interesting that the capillaries remain wide in the corners where three septa come together. The distribution of surface forces causes the internal pressure to be lower in the region of these corners, as we can see intuitively from Fig. 2-55.

The Lung as Gas Exchanger

The structures discussed so far are designed to ultimately serve the lung's main function, gas exchange between air and blood, in relation to the body's varying O_2 needs. These are set by the energetic demands of the cells and their mitochondria when these produce ATP by oxidative phosphorylation to allow the cells to do work. This process requires a flow of O_2 to be maintained from the lung to the cells, as will be discussed below. It proceeds along the respiratory system through various steps: into the lung by ventilation, to the blood by diffusion, through the circulation by blood flow, from the blood capillaries by diffusion to the cells and mitochondria, where it disappears in the process of oxidative phosphorylation. A number of basic features characterize this system: (1) under steady-state conditions the O_2 flow rate, $\dot{V}_{O_2}$, is the same at all levels, i.e., O_2 uptake in the lung is equal to O_2 consumption in the tissues; (2) the basic driving force for O_2 flow through the system is a cascade of O_2 partial pressure which falls from



A



B

Figure 2-58 Scanning electron micrographs of alveolar walls of rabbit lungs fixed under (*A*) zone 2 and (*B*) zone 3 conditions of perfusion. Note that capillaries (*C*) are wide in zone 3 and slit-like in zone 2, except for "corner capillaries," which are wide in either case. (*From Bachofen H et al: Morphometric estimates of diffusing capacity in lungs fixed under zone II and zone III conditions. Respir Physiol 52:41–52, 1983, with permission.*)

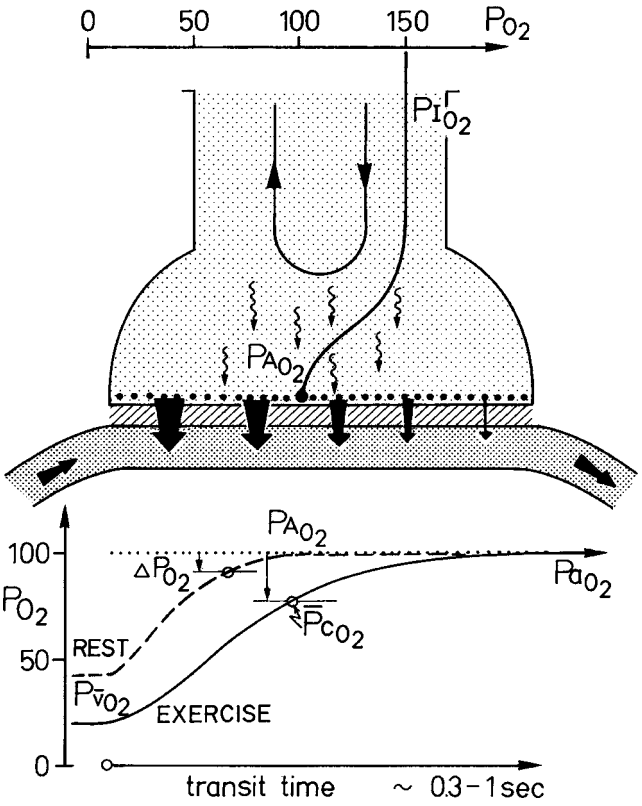


Figure 2-59 Model of gas exchange showing gradual rise of capillary PO_2 (PCO_2) as blood flows through capillary until it approaches alveolar PO_2 (PAO_2). *(From Weibel ER: The Pathway for Oxygen. Cambridge, MA, Harvard University Press, 1984.)*

inspired P_{O_2} down to near zero in the mitochondria; (3) the O_2 flow rate at each step is the product of a partial pressure difference and a conductance which is related to structural and functional properties of the organs participating in O_2 transfer. It can, for example, be shown that the O_2 flow rate into the O_2-consuming step in the cells is directly related to the amount transfer: the lung, the heart, the capillaries, and the mitochondria that perform oxidative phosphorylation.

With respect to gas exchange in the lung (Fig. 2-59), the O_2 flow rate is determined by the Bohr equation:

$$\dot{V}_{O_2} = (P_{A_{O_2}} - P\bar{c}_{O_2}) \cdot D_{L_{O_2}}$$

where

$P_{A_{O_2}} = P_{O_2}$ in alveoli,
$P\bar{c}_{O_2}$ = the mean P_{O_2} in pulmonary capillaries, and
$D_{L_{O_2}}$ = the pulmonary diffusing capacity or the lung's O_2 conductance

The important point is now that all parameters to the right of this equation may be significantly affected by design features. We will see that $D_{L_{O_2}}$ is largely determined by the surface area and the thickness of the air-blood barrier. The O_2 partial pressure difference is established by ventilation and perfusion of the gas exchange units, and this may be affected by the design of the airway and vascular trees, particularly in the acinus.

The Pulmonary Diffusing Capacity

In the above equation, $D_{L_{O_2}}$ is the total conductance of the gas exchanger for O_2 diffusion from the alveolar air into the capillary erythrocytes until it is bound to hemoglobin. It can be estimated physiologically if we can measure O_2 uptake $\dot{V}_{O_2}$ and estimate the effective P_{O_2} difference between alveolar air and capillary blood, not a trivial undertaking as the change in capillary P_{O_2} as O_2 is being taken up must be integrated (Fig. 2-59). On the other hand the conductance is a physical characteristic. Therefore, it should be possible to calculate a theoretical value of $D_{L_{O_2}}$ from the physical properties of the gas exchanger, its dimensions and material properties. In order to do that we must consider the geometry of the structures involved, alveoli, tissue barrier, and capillary blood, in setting up a physical model of $D_{L_{O_2}}$. In a first step, we can break the process into two steps (Fig. 2-60): (1) O_2 flow across the barrier or what has been called the membrane conductance $D_{M_{O_2}}$; and (2) O_2 binding to hemoglobin in the red blood cells or the conductance of capillary blood $D_{e_{O_2}}$. These two conductances are in series. Accordingly their overall effect on O_2 flow is obtained by adding their resistances or the

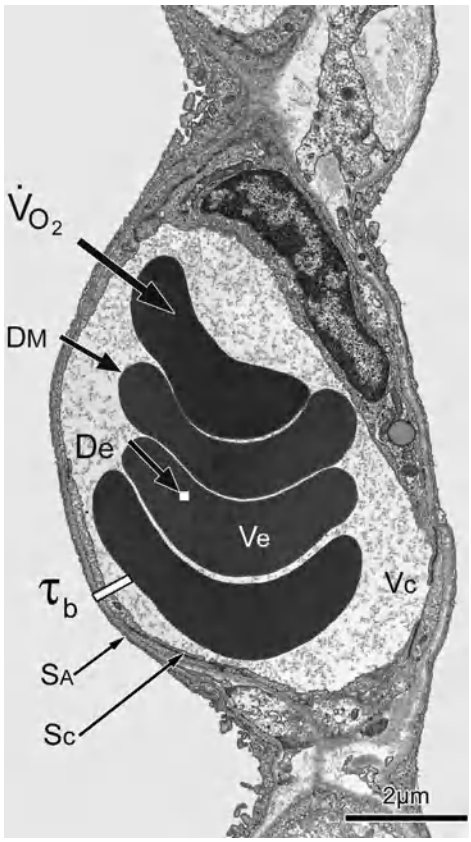


Figure 2-60 Morphometric model for calculating diffusion capacity, DL. Its two components are: (1) the membrane conductance DM, which extends from the alveolar surface (SA) to the nearest erythrocyte membrane traversing the tissue barrier, the capillary surface Sc, and the plasma layer over the distance τ_b; and (2) the conductance of the erythrocyte interior, De, that depends on the capillary and the erythrocyte volume, Vc and Ve. (See text.)

reciprocal of the conductance:

$$1/D_{L_{O_2}} = 1/D_{M_{O_2}} + 1/De_{O_2}$$

The two conductances $D_{M_{O_2}}$ and De_{O_2} are of very different nature. $D_{M_{O_2}}$ is the conductance of a diffusion barrier that offers "passive" resistance to diffusion and thus depends essentially on the material properties of the barrier, estimated by a diffusion coefficient K, and on the dimensions of the barrier: The larger the surface area S and the thinner the barrier thickness τ the greater $D_{M_{O_2}}$, according to the formula $D_{M_{O_2}} = K \cdot S/\tau$. In contrast, De_{O_2} is related to a more complex process that involves, besides diffusion, the binding of O_2 to hemoglobin, which is a non-linear process.

The Membrane Conductance ($D_{M_{O_2}}$)

The structural characteristics of the membrane conductor are seen in Fig. 2-60. It is made of the two layers that separate air in alveoli from the erythrocytes in the capillary: the tissue barrier and the layer of blood plasma. In addition, an alveolar lining layer of varying thickness spreads over the epithelial surface. Even though these layers have distinct characteristics; in effect they act as a single diffusion barrier.

As discussed earlier in this chapter, the tissue barrier is a complex structure. Its two bounding surfaces are formed by independent cell layers, epithelium and endothelium, and they are related to two independent functional spaces, alveoli and capillaries. The two surfaces are not perfectly matched, and the thickness of the barrier varies considerably (Fig. 2-60). Over about half the surface the tissue barrier shows minimal thickness compatible with an intact structure: The thin cytoplasmic leaflets of type I epithelial cells are joined to the thin extensions of endothelial cells by the fused basement membranes leaving no interstitial space. In this region we also find the surface lining layer to be very thin. Over the other half the barrier is thicker because of the occurrence of supporting connective tissue fibers (Fig. 2-49) and the presence of cell bodies of epithelial and endothelial cells as well as fibroblasts, and the lining layer can form deeper pools (Fig. 2-52).

The plasma layer shows even greater variation in its thickness and distribution. Since erythrocytes are of about the same dimension as the capillaries, the plasma layer that separates them from the endothelium can be vanishingly thin where the red cell nearly touches the wall. However, erythrocytes are corpuscular particles and there are "plugs" of plasma of varying size that separate them in the direction of blood flow. Also their distortable disc shape causes the plasma layer between erythrocyte and capillary surface to be quite variable. Furthermore, occasional leukocytes function like plasma plugs in regard to O_2 diffusion to the red cells. Therefore, the diffusion distance from the capillary wall to the red cell membrane can vary from a few nm to several μm.

Strictly speaking, these two layers of the barrier offer O_2 diffusion different resistances so their conductances should be calculated separately. However, this distinction does not appear to be important under normal conditions. Indeed, it is more reasonable to treat them as a single barrier. For one, the flow velocity of the plasma layer is much lower than the diffusion of O_2 so that plasma is quasi-static with respect to diffusion. Furthermore, under normal conditions the surface areas of alveoli, capillaries, and erythrocytes do not differ much, and the diffusion coefficients of tissue and plasma are also quite similar. Therefore, we prefer now to estimate the membrane diffusing capacity by considering O_2 diffusion from the alveolar surface to the erythrocyte membrane as:

$$D_{M_{O_2}} = K_b \cdot S(b)/\tau_{hb} = K_b \cdot (S(A) + S(c))/2 \cdot \tau_{hb}$$

where K_b is Krogh's permeation coefficient estimated at $3.3 \cdot 10^{-8} cm^2 \cdot min^{-1} \cdot mmHg^{-1}$, τ_{hb} is the harmonic mean distance from the alveolar surface to the nearest erythrocyte membrane, and S(b) is the surface area of the barrier that we estimate as the mean of the alveolar and capillary surface areas, S(A) and S(c), respectively, the two most robust measures of the area of air-blood contact. These parameters can be estimated on sections of properly sampled lung tissue by stereological methods.

We should also mention that the presence of a surface lining layer in the living lung may modify the geometry of the barrier as we see it on electron micrographs with the consequence that both the barrier thickness and the alveolar surface are reduced to a similar degree because some thicker parts of the barrier become shifted beneath the surfactant pools (Fig. 2-52). Therefore, the effect on the estimate of $D_{L_{O_2}}$ is negligible.

Erythrocyte Conductance (De_{O_2})

As mentioned, the erythrocyte conductance is of a different nature in that it involves two coupled events: diffusion of molecular oxygen and oxyhemoglobin within the red blood cell as well as the chemical reaction of O_2 with hemoglobin. A way out of this is to obtain an empirical estimate of the rate at which O_2 is bound to whole blood, θ_{O_2}, and to express the erythrocyte conductance De_{O_2} as:

$$De_{O_2} = \theta_{O_2} Vc$$

where Vc is the total capillary blood volume, which can again be estimated on sections by stereologic methods.

The coefficient θ_{O_2} is estimated in vitro on whole blood, but this is difficult because of the effect of variable unstirred layers around the red cells. In addition, θ_{O_2} depends on the hematocrit or hemoglobin concentration, and it is not a constant as it falls with increasing O_2-hemoglobin saturation; recent studies have shown that, as blood moves through alveolar capillaries, θ_{O_2} falls gradually from about 4 to 1 mL O_2 mL^{-1}, $torr^{-1}$ so that the correct value can only be found after Bohr integration of capillary P_{O_2}. For normal human lungs and a hemoglobin content of 15 g/100 ml of blood, a value $\theta_{O_2} = 1.8\,mL\,O_2 \cdot mL^{-1}$, $torr^{-1}$ is a reasonable estimate, but if the actual hemoglobin concentration [Hb] varies a corrected value can be obtained by multiplying this standard value with a factor c = [Hb]/15.

Table 2-4

Morphometric Estimate of $D_{L_{O_2}}$ for Young, Healthy Adult Humans of 70-kg Body Weight, Measuring 175 cm in Height*

Morphometric data (mean ± 1 SE)			
Total lung volume (60% TLC)	4340	±285	ml
Alveolar surface area	130	±12	m^2
Capillary surface area	115	±12	m^2
Capillary volume	194	±30	ml
Air–blood tissue barrier thickness			
Arithmetic mean	2.2	±0.2	μm
Harmonic mean	0.62	±0.04	μm
Total barrier harmonic mean thickness	1.11	±0.1	μm
Diffusing capacity (ml/min/mmHg)			
Membrane	$D_{M_{O_2}}$	350	
Total	$D_{L_{O_2}}$	158	

** Source: Gehr P, Bachofen M, Weibel ER: The normal human lung: Ultrastructure and morphometric estimation of diffusion capacity.* Respir Physiol *32:121–140, 1978; Weibel ER: Symmorphosis. On Form and Function in Shaping Life. Cambridge, MA: Harvard University Press, 2000.*

Morphometry of the Human Lung and Diffusing Capacity

With this model in hand, we can now attempt to estimate the diffusing capacity of the human lung on the basis of morphometric data, as listed in Table 2-4. These data, obtained by electron microscopic morphometry on seven young adults, reveal the alveolar surface area to amount to 130 m^2 and the capillary surface to be about 10 percent smaller. These values are higher than those most commonly quoted in textbooks derived from light microscopic studies, which did not adequately resolve the alveolar surface texture. The harmonic mean thickness of the tissue barrier is 0.6 μm, whereas the total barrier, from alveolar to red cell surface (Fig. 2-60) measures 1.11 μm. The capillary volume is estimated at about 200 ml. With these data we calculate $D_{L_{O_2}}$ for the adult human lung to be about 150 to 200 mL $O_2 \cdot min^{-1} \cdot mmHg^{-1}$, the variation depending on the choice of θ_{O_2}.

These data also allow us to ask the question how the resistance to O_2 diffusion is distributed between the diffusion barrier and the red cells. Table 2-4 shows that the diffusion conductance of the "membrane" and that of the red cells are very similar, which means that the resistance to O_2 uptake is nearly equally divided between membrane and red cell.

These morphometric estimates of the diffusing capacity are based on model assumptions that are considered reasonable. The test of their validity must be to compare them with physiological estimates. The standard physiological value of $D_{L_{O_2}}$ of a healthy adult at rest is about 30 ml $O_2 \cdot min^{-1} \cdot mmHg^{-1}$; thus, considerably less than what we find on the basis of morphometric estimates. However, this is not a valid comparison, because, under resting conditions, we take up only one-tenth the amount of O_2 that our lungs are capable of absorbing under conditions of heavy work. There have been a number of estimates of $D_{L_{O_2}}$ in exercising humans, and these have yielded values of the order of 100 ml $O_2 \cdot min^{-1} \cdot mmHg^{-1}$. This estimate should come closer to the "true capacity" of the lung for O_2 transfer to the blood than the value obtained at rest. The fact that this is only about 50 percent lower than the morphometric estimate is not disturbing, for we do not know whether the "true diffusing capacity" is completely exploited even in heavy exercise. Inhomogeneities in the distribution of ventilation and perfusion would, for example, limit the degree to which "true" $D_{L_{O_2}}$ can be exploited. One aspect of this type of limitation is discussed in the following when we consider the effect of the acinus design on gas exchange.

To test whether the morphometric estimate of $D_{L_{O_2}}$ is reasonable we performed, some years ago, a combined physiological and morphometric estimation of pulmonary diffusing capacity on four species of canids ranging from 4 to 30 kg in body mass.

Because it is difficult to estimate mean capillary P_{O_2} reliably, most physiological measurements of the diffusing capacity use carbon monoxide (CO) as a tracer gas; CO binds to hemoglobin so avidly that, for practical purposes, the Pb_{CO} is zero, so that it suffices to measure CO uptake and alveolar CO concentration. It is also possible to revise the morphometric model of diffusing capacity to estimate the conductance for CO instead of O_2 by appropriately changing the permeability coefficients and the rate of CO binding to erythrocytes, θ_{CO}, whereas the morphometric parameters are not changed. In a study on dogs and on other canids, the calculated morphometric value of $D_{L_{CO}}$ was found to be larger than the physiological estimate by less than a factor of 1.5, thus confirming the observation made with respect to human lungs.

Therefore, we conclude that the pulmonary gas exchanger is designed with a certain amount of redundancy or excess capacity, but this is by no means unreasonable from an engineering point of view. Indeed, to design the pulmonary gas exchanger with a certain degree of redundancy may make a lot of sense. The lung forms the interface to the environment and its functional performance will thus depend on environmental conditions, such as the prevailing O_2 partial pressure, which falls as we go from sea level to higher altitudes. It has been shown that goats, whose $D_{L_{O_2}}$ is about twice as large as seemingly required, can maintain their maximal level of exercise-induced $\dot{V}_{O_2}$ even under hypoxic conditions whereas the dogs that have very small excess $D_{L_{O_2}}$ cannot. It has also been suggested that human athletes exercising at high altitude may fully exploit their $D_{L_{O_2}}$. This suggests that the apparent redundancy in $D_{L_{O_2}}$ may be a safety factor to protect the good functioning of the pulmonary gas exchanger even when environmental conditions are not optimal. Recent studies with partial pneumonectomy in dogs have shown that the

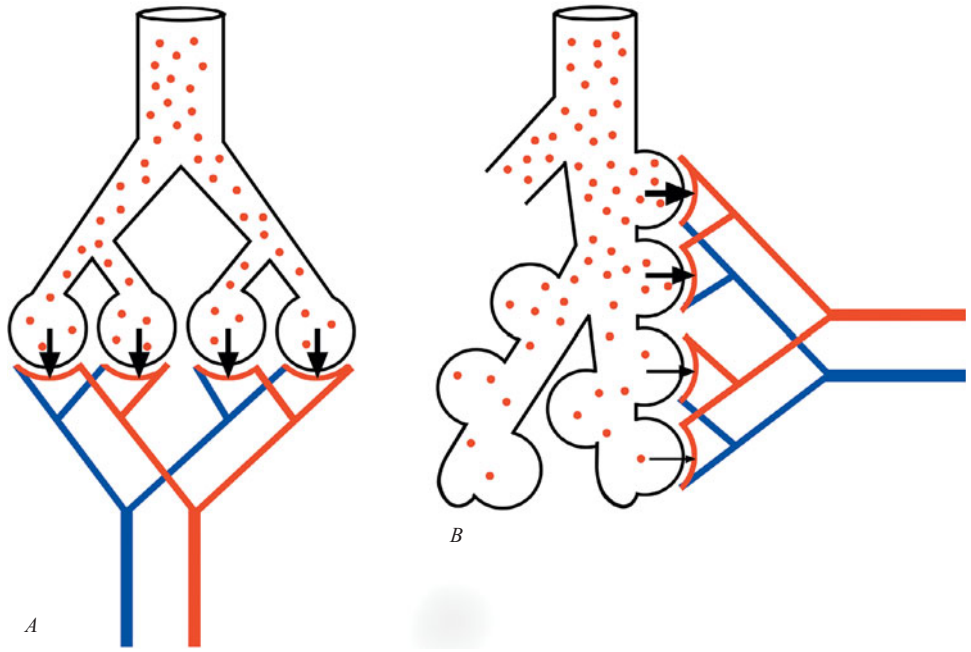


Figure 2-61 Models of ventilation-perfusion relationship in the mammalian pulmonary gas exchanger. *A*. Parallel ventilation/parallel perfusion. *B*. Serial ventilation/parallel perfusion. *(From Sapoval B, Filoche M, Weibel ER: Smaller is better, but not too small: A physical scale for the design of the mammalian pulmonary acinus. Proc Natl Acad Sci USA 99:10411–10416, 2002.)*

lung can achieve 85 percent of its maximal O_2 uptake even when 40 percent of lung tissue is removed after left pneumonectomy, making use of some of this reserve capacity; but when right pneumonectomy removes 60 percent of lung tissue, adequate function can be achieved only after compensatory growth of the residual lung tissue to restore diffusing capacity.

Design of the Acinus and Gas Exchange

The preceding section considered the overall size of the gas exchanger of the entire lung to compare it with the global performance of this organ. In reality, the surface the size of a tennis court is subdivided into some 400 million gas exchange units. These are individually perfused with blood because they correspond to the unit capillary network that spans between pulmonary arteriole and venule (Fig. 2-46). The diameter of such a disk-shaped unit is about 500 μm and has a surface area that corresponds approximately to that of an alveolus, even though alveoli and capillary unit are not congruent as the latter spans over several alveoli and each alveolus is in contact with several capillary units.

These gas exchange units are arranged along the terminal generations of the airway tree that form the pulmonary acinus (Fig. 2-61*B*). Note that this arrangement of gas exchange units to the airway system differs from the common representation of the alveolar-capillary unit as a terminal "bubble" (Fig. 2-61*A*). This has functional consequences because ventilation of alveoli occurs in two steps: (1) upon inspiration oxygen-rich air flows through the airways into the acinus carrying along O_2; (2) in the peripheral airways flow velocity slows down because the airway cross-section increases, and O_2 now moves toward the periphery by diffusion in the air phase, driven by the P_{O_2} gradient that becomes established as O_2 is absorbed at the alveolar surface (Fig. 2-62). Thus, in the peripheral airways diffusion along the airways is combined with diffusive permeation of O_2 into the alveoli and across the tissue barrier to the blood, the actual process of gas exchange. Whereas all capillary network units are individually perfused with venous blood the alveoli are not independent in terms of their O_2 supply, which depends on their location along the airway tree. Therefore, the design of the acinus has significant effects on the gas exchange conditions.

The Acinar Airway System Connected to the Gas Exchanger

In a systematic study of human lungs the mean volume of acini was found to be 187 mm^3 with a standard deviation of 79 mm^3. The branching pattern for an average size human acinus is shown in Fig. 2-63. The segment lengths have been drawn to scale and the terminal clusters of alveoli of the alveolar sacs are marked by a dot. This acinus has been subdivided into eight subacini whose substems are located in the third generation of acinar airways. The acinus shown in Fig. 2-42 in a scanning electron micrograph of a cast is comparable in size and structure. This shows that the transitional bronchiole is followed by two or three generations of respiratory bronchioles, where there are only a few alveoli. In contrast, the alveolar ducts that follow are completely and

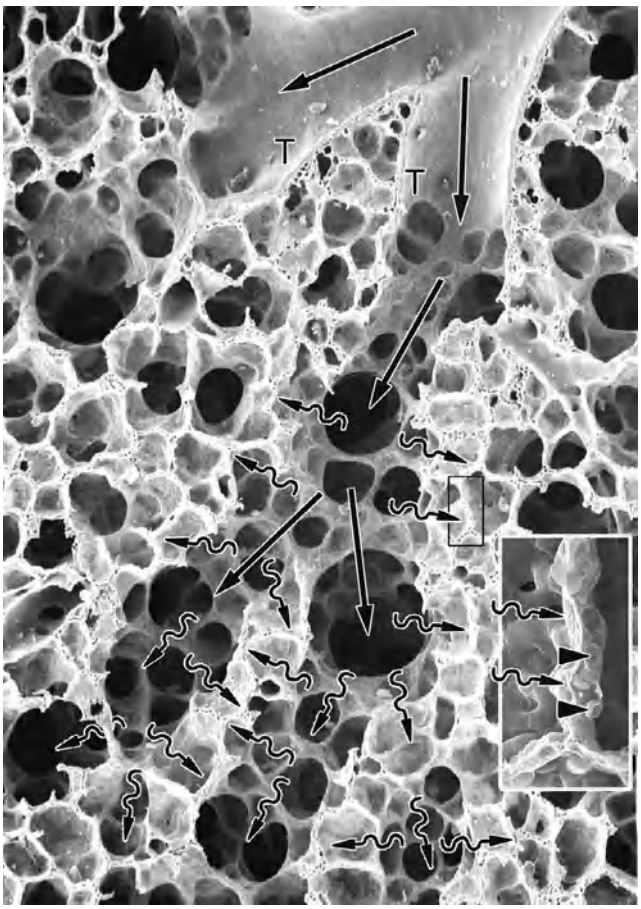


Figure 2-62 Central part of the acinar airways beginning with transitional bronchiole (T) and leading into the branched alveolar ducts. On inspiration air flows in by convection *(straight arrows),* but as flow velocity falls diffusion of O_2 *(wiggly arrows)* becomes the dominant mechanism for bringing O_2 to the gas exchange surface. All along acinar airways O_2 is absorbed by the capillary blood in the septa *(inset, arrowheads).*

densely lined with alveoli (Fig. 2-64). These are the airways of the 1/8 subacinus (Fig. 2-63), a unit that is of functional significance, as we shall see. The intra-acinar airways branch by irregular dichotomy; terminal sacs are located in generations 6 to 11 so that the intraacinar airways branch over an average of 8 generations (Fig. 2-5).

The morphometry of the intra-acinar airways of the human lung shows a number of characteristic traits. The inner diameter (d_{in}) that characterizes the cross section of the duct tube decreases from about 490 μm at the transitional bronchiole to 270 μm in the last generations. When this is plotted onto the graph relating airway diameter to generations of branching (Fig. 2-37), we note that this diameter falls less steeply than the cube-root-of-1/2 law we have observed for conducting airways. This is a significant finding in terms of the ventilation of alveoli by O_2 diffusion.

An important morphometric characteristic of acinar airways is the total path length for O_2 diffusion from the entrance at the transitional bronchiole to the terminal cluster of alveoli at the alveolar sac (Fig. 2-5). This path length is

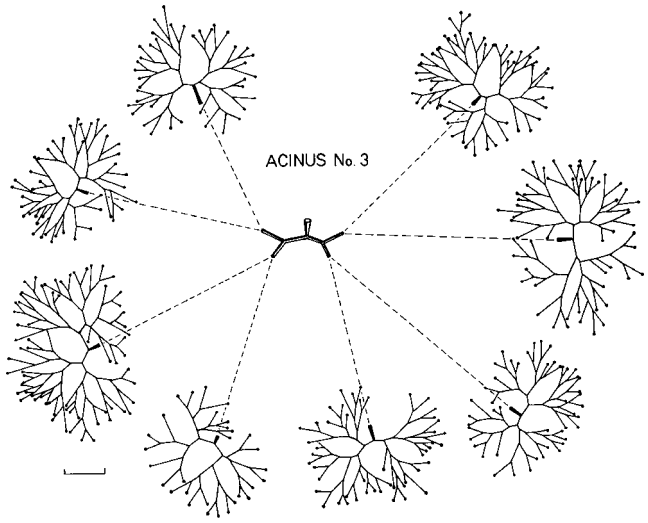


Figure 2-63 Graphic representation of branching pattern of acinar airways in one human acinus of 183 mm^3 volume with the segment lengths drawn to scale. The airways are separated at the third generation thus displaying the branching pattern within each 1/8 subacinus. *(From Haefeli-Bleuer B, Weibel ER: Morphometry of the human pulmonary acinus. Anat Rec 220:401–414, 1988.)*

determined by two factors: the number of generations and the segment length. The length of alveolar ducts gradually decreases from 1330 to 640 μm in the peripheral generations, the alveolar sacs being a little bit longer. Since the number of branching generations varies somewhat, we can expect the path length to vary even within one acinus. In the human lung, the average longitudinal path length measures 8.3 ± 1.4 mm (Fig. 2-65). Because of the decreasing length of acinar ducts 3.4 mm of this total path length are for the first three generations of respiratory bronchioles, whereas the path length of alveolar ducts and sacs comprised in the 1/8 subacinus (Fig. 2-64) averages 4.7 ± 0.88 mm.

Typical Path Model of Human Acinus

In view of assessing the effect of these structural features on the functional performance of the pulmonary gas exchanger we can attempt to develop what we may call a typical path model for an average human acinus (Fig. 2-65; Table 2-5). Such an acinus has a volume of 0.187 cm^3. Its airways branch over an average of eight generations in order to reach the terminal alveolar sacs. With each generation the number of branches doubles to end with some 256 terminal alveolar sacs in each acinus (Fig. 2-63). Locating the transitional bronchiole ($z' = 0$) in generation 14 (Fig. 2-5) the terminal air sacs are in generation 23 of the typical path airway tree. From the estimates of the lengths and inner diameters of the airway segments we can derive overall parameters of functional significance, such as the total airway cross-section per generation, $A_d(z')$, which is a determinant of air flow velocity (Fig. 2-66). Finally, we can also estimate the distribution of alveolar surface area to the different generations in proportion to the duct surface $S_d(z')$, but adjusting for the fact that only

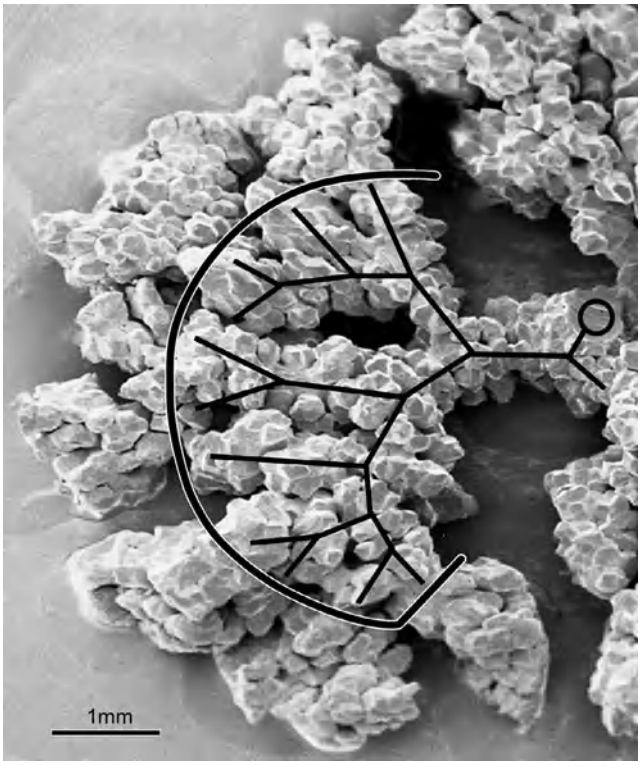


Figure 2-64 Airways of 1/8 subacinus of human lung beginning with generation 18 alveolar duct *(circle)*. The silicon rubber cast has been spread out to show the course of the subsequent branchings. The curved line marks the approximate boundary to the last generation to show that this generation of alveolar sacs (see Fig. 2-5) comprises over half the gas exchange area of the acinus.

part of this surface is associated with alveoli in the respiratory bronchioles (generations $z' = 1–3$). For an estimated alveolar surface of 130 m^2 in the human lung (Table 2-4), there would be about 54 cm^2 of gas exchange surface per average acinus. It is seen that half this gas exchange surface is in the

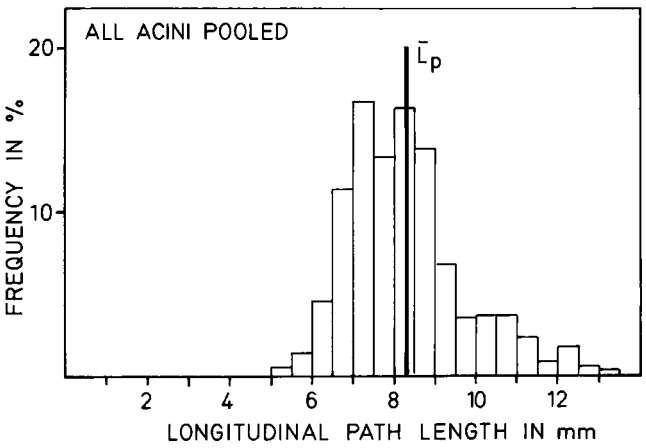


Figure 2-65 Frequency distribution of longitudinal path length from the transitional bronchiole to the alveolar sacs in the human lung. *(From Haefeli-Bleuer B, Weibel ER: Morphometry of the human pulmonary acinus. Anat Rec 220:401–414, 1988.)*

last generation (see also Fig. 2-64). A final check of this model is that the path length from the entrance into the transitional bronchiole to the end of the alveolar sacs is 8.4 mm, which agrees well with the mean path length estimated in the human acini.

Implications of Acinar Design for Gas Exchange Function: The Phenomenon of Diffusion Screening

The gas exchange in the pulmonary acinus involves several physicochemical phenomena that occur within the complex acinar geometry described in the preceding. As mentioned, in the distal regions of the lung, oxygen is transported toward the alveolar membrane both by convection and molecular diffusion. Oxygen then diffuses through the tissue membrane into the blood, where it is bound by hemoglobin. Several physical parameters govern oxygen uptake at the acinar level, such as air flow velocity, diffusion coefficient of oxygen in air, alveolar membrane permeability, blood hemoglobin content, and its reaction rate with oxygen. Conversely, carbon dioxide is discharged from the blood to the alveolar gas through diffusion across the membrane. It then diffuses backwards along the airways to the zone, where convection becomes dominant, and is lastly expelled from the lung. In all these processes, the morphology of the system plays an essential role.

Since oxygen uptake into the blood is driven by the O_2 partial pressure at the alveolar surface we must ask whether this driving force is the same throughout the acinus or whether there could be differences between its central and peripheral parts. Some earlier studies had shown that concentration gradients may exist as a consequence of efficient capture of oxygen by hemoglobin. More recently, we have come to realize that such gradients are strongly influenced by the finite permeability of the membrane that plays a dominant role in the effective properties of the acinus as the gas exchange unit. This is related to a phenomenon known as *diffusional screening*, which means that O_2 molecules entering the diffusion unit have a larger probability to hit the surface of the alveolar membrane near the entrance than in the more distal regions. If the membrane permeability is large, O_2 molecules are absorbed at the very first hits. As a consequence, O_2 is absorbed into the blood in the first parts of the acinar pathway so that the gas exchange units in the deeper part of the acinus would not receive any O_2. These regions would then be of no use: They are *screened*. Blood perfusing these regions would not be oxygenated and would thus appear as a shunt. In contrast, if the permeability is small, molecules will be absorbed only after many collisions with the wall. They then have a fair chance to reach the deeper regions and the entire acinar surface can be effective for gas exchange.

To put this into the perspective of structure-function relations this process is related to the balance between two conductances: a diffusion conductance Y_{cross} for O_2 to *cross* the barrier from alveolar air to capillary blood, and a diffusion conductance Y_{reach} for O_2 to *reach* the surface through

Table 2-5

Typical Path Model of Human Acinus

Generation		Segments			Dimensions per Generation			Path Length
Airways z	Acinus z′	N(z′)	1 mm	d_{in} mm	$A_d(z')$ mm^2	$V_d(z')$ mm^3	$S_{aiv}(z')$ mm^2	$L_p(z')$ mm
15	0	1	1.4	0.50	0.20	0.32	7	1.4
16	1	2	1.33	0.50	0.39	0.52	23	2.73
17	2	4	1.12	0.49	0.75	0.84	67	3.85
18	3	8	0.93	0.40	1.00	0.93	129	4.78
19	4	16	0.83	0.38	1.81	1.50	219	5.61
20	5	32	0.70	0.36	3.26	2.28	349	6.31
21	6	64	0.70	0.34	5.81	4.07	661	7.01
22	7	128	0.70	0.31	9.11	6.38	1204	7.71
23	8	256	0.70	0.29	16.9	13.47	2720	8.41

Source: Weibel ER, Sapoval B, Filoche M: Design of peripheral airways for efficient gas exchange. Respir Physiol Neurobiol *148:3–21, 2005.*

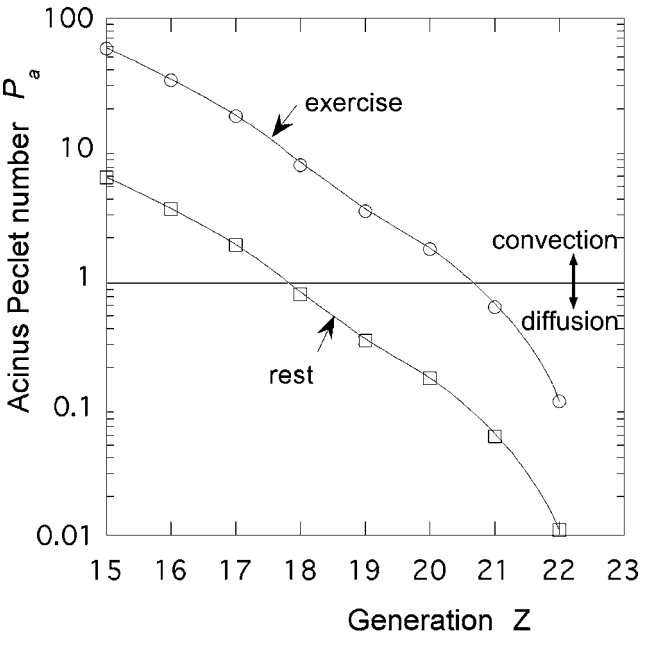


Figure 2-66 In the human acinus the Peclet number, reflecting the relation between convective flow velocity and diffusion velocity of O_2, falls as the airway cross-section increases. Below 1 diffusion becomes the dominant mechanism of alveolar ventilation. This transition point is about in generation 18 at rest and extends out to generation 21 in heavy exercise. *(From Weibel ER, Sapoval B, Filoche M: Design of peripheral airways for efficient gas exchange. Respir Physiol Neurobiol 148:3–21, 2005.)*

the air spaces. Both these conductances are determined by the product of: (a) a physical parameter (the permeability coefficient for O_2 in tissue, and the diffusion coefficient for O_2 in air, respectively); and (b) a morphometric parameter (the gas exchange surface, and the distance along the acinar airways, respectively). The physical coefficients are given quantities, except that the tissue permeability is also affected by the thickness of the tissue barrier, a parameter that varies very little between species. On the other hand, the size and surface of the acinus can be varied during evolution and growth to adjust the two conductances. We can predict that the design of the acinus is optimized if Y_{cross} and Y_{reach} are about equal as this means that both the gas exchange surface and the acinar air volume, or the diffusion distance, are matched. If Y_{cross} were much smaller than Y_{reach} the low permeability of the gas exchanger would need to be compensated by a larger gas exchange surface, and this would inevitably entail a larger volume of the acinus to accommodate the surface and by that a longer diffusion distance.

The morphometric study of acini in various mammalian species revealed that the size of the acini is such that $Y_{cross} \sim Y_{reach}$ so that their morphology seems to be at least partially adapted to minimize the effects of screening. Note that the problem of screening occurs in that part of the acinus where O_2 moves to the surface by diffusion only (Fig. 2-62), in what is called the diffusion cell. The transition between convection and diffusion is determined by the Peclet number (Fig. 2-66), essentially the ratio between air flow and

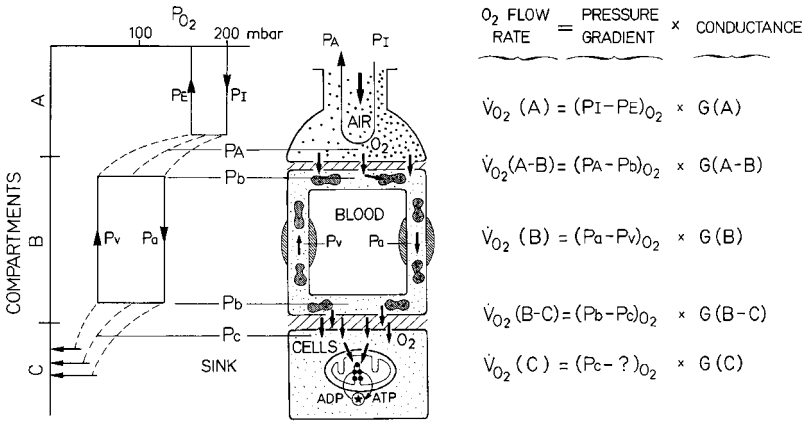


Figure 2-67 Model of the respiratory system from the lung to the cells. Oxygen flow is driven through the system by a cascade of Po_2 ranging from inspired P_{IO_2} to near zero at the mitochondria. At each level the flow rate is determined by a partial pressure difference and a conductance. *(Modified after Weibel ER, Taylor CR: Design of the mammalian respiratory system: I–IX. Respir Physiol 44:1–164, 1981.)*

diffusion velocities: diffusion is more effective than convection when the Peclet number is smaller than 1. In the human lung, under resting conditions, this transition occurs in generation 18 and that is the entrance to the 1/8 subacinus (Fig. 2-63); accordingly the diffusion cell corresponds to the 1/8 subacinus. In exercise, where O_2 consumption as well as ventilation is increased, convective transport of O_2 is effective out to generation 21 (Fig. 2-66). So in exercise there are only two to three generations of acinar airways that act as diffusion cell, but that is still highly significant because these generations accommodate 75 percent of the gas exchange surface (Fig. 2-64 and Table 2-5).

Note that what has been discussed so far relates essentially to about half the respiratory cycle, namely, inspiration when fresh O_2-rich air is actively brought into the acinus. During expiration things are in a way reversed: CO_2 that has diffused from the blood into the acinar air now dilutes O_2 and the convection-diffusion front is moved toward the bronchi. For this reason, the effective duty cycle of the gas exchange system is smaller than 1, particularly under the conditions of high O_2 uptake rate in exercise. This must be considered when modeling gas exchange.

One important aspect of this discussion must also be noted. The fact that the gas exchange units are serially arranged along the acinar airways calls for a modification of the prevailing notion of lung models. In these the gas exchange units are commonly arranged at the end of a system of branched tubes, allowing for ventilation-perfusion variation between the parallel units (Fig. 2-61*A*). That is not a correct representation. We should rather consider a model where the gas exchange units are serially arranged along the ventilation pathway but perfused as parallel units (Fig. 2-61*B*). This has serious consequences because it introduces a degree of inherent ventilation-perfusion inequality that results from the fact that O_2 is absorbed all along the acinar pathway with the result that the P_{O_2} in acinar air is gradually falling along the path. As a consequence, the P_{O_2} is lower in the most peripheral acinar airways so that blood perfusing these peripheral capillaries will be oxygenated to a lower degree than that perfusing more central units. What we measure as arterial P_{O_2} is the average of the P_{O_2} in the blood leaving all the parallel perfusion units.

The Lung as Part of the Pathway for Oxygen

The lung's main function, gas exchange between air and blood, serves the body's varying O_2 needs as they are set by the energetic demands of the cells and their mitochondria when these produce ATP by oxidative phosphorylation to allow the cells to do work. This process requires a flow of O_2 to be maintained from the lung to the cells. It proceeds along the respiratory system through various steps (Fig. 2-67): into the lung by ventilation, to the blood by diffusion, through the circulation by blood flow, and from the blood capillaries by diffusion to the cells and mitochondria, where it disappears in the process of oxidative phosphorylation. A number of basic features characterize this system: (1) under steady-state conditions the O_2 flow rate, $\dot{V}_{O_2}$, is the same at all levels, i.e., O_2 uptake in the lung is equal to O_2 consumption in the tissues; (2) the basic driving force for O_2 flow through the system is a cascade of O_2 partial pressures, which fall from inspired P_{O_2} down to near zero around the mitochondria; (3) the O_2 flow rate at each step is the product of an O_2 partial pressure difference and a conductance G, which is related to structural and functional properties of the organs participating in O_2 transfer. In the preceding section we have seen that the principal design features of the lung that determine one of these conductances, the pulmonary diffusing capacity, are sized to just yield a conductance that allows the O_2 uptake required to satisfy the demands of the whole body cell system at work, with a small margin of safety under normal conditions. Therefore, the lung appears designed to serve the body's needs efficiently and economically. The question we may now ask is whether the other parts of the respiratory system, from the heart to the mitochondria are also designed for economic functional performance.

Let us first look at the overall functional performance of the system. We first note that O_2 consumption is highly variable, increasing by about a factor of 10 between resting conditions and heavy exercise when 90 percent of the O_2 is consumed in the locomotor muscles. Fig. 2-68 shows that the oxygen consumption in muscle is proportional to the energy output, measured for example as running speed, and that it reaches a limit $\dot{V}_{O_2max}$; beyond this the running speed can still be increased, but the additional energy required by the higher

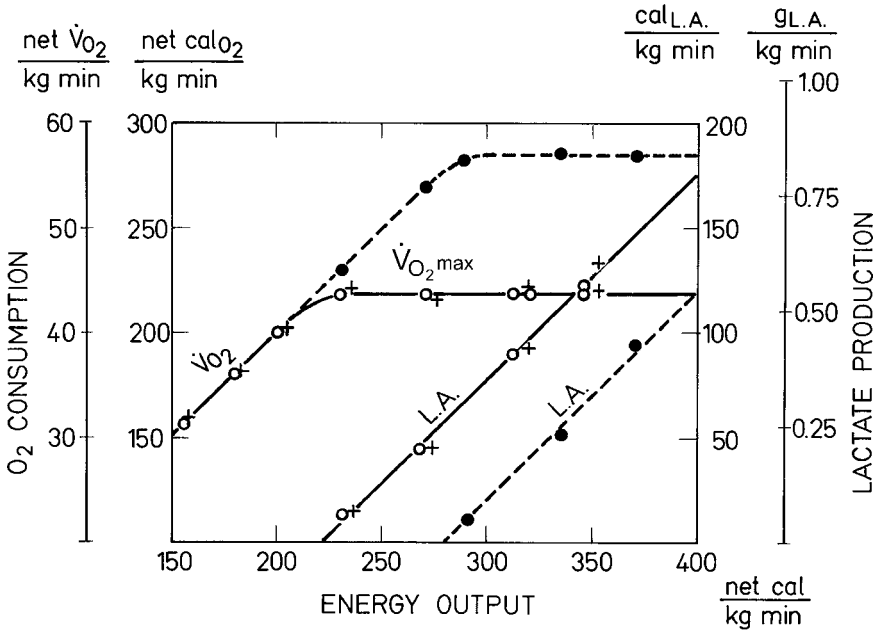


Figure 2-68 Rate of O_2 consumption (left ordinate) and lactic acid production (ordinate at right) in exercise are plotted as a function of the work intensity and, therefore, of the energy requirement (abscissa). Oxygen consumption increases linearly up to a point corresponding to an energy requirement of 220 cal/kg min^{-1}; If work is pushed beyond that there is no further increase in O_2 consumption ($VO_{2\,max}$ is reached) but glycolysis now generates the required energy resulting in an increase in lactic acid production. The broken lines refer to athletes (middle- and long-distance runners) whose maximum oxygen consumption is higher; the line of the lactic acid for these subjects is correspondingly shifted to the right. *(From Margaria R et al: Kinetics and mechanism of oxygen debt contraction in man. J Appl Physiol 18:371–377, 1963.)*

speed is then supplied through glycolysis or anaerobic ATP production with the result that lactic acid concentration in the blood gradually increases. It is now interesting to note that $\dot{V}_{O_2max}$ is a characteristic of the work capacity of an individual: well-trained athletes reach their $\dot{V}_{O_2max}$ at a higher running speed and a higher level of oxygen consumption, and lactic acid concentration in the blood also begins to increases at the higher performance levels corresponding to $\dot{V}_{O_2max}$ (Fig. 2-68).

One may now raise the question whether this variable limitation of oxidative metabolism is a result of variable functional constraints affecting the regulation of metabolic rate and circulatory transport, or whether it could be set by variations in design constraints characterizing the structural components of the pathway, one possible candidate being the pulmonary diffusing capacity. The answer to this question depends on an integrated study of structure and function of the respiratory system. For this we need a quantitative model of the oxygen pathway that identifies all the functional variables and the design parameters at the four levels of the system: the lung, circulation of blood with the heart, capillaries, and mitochondria (Table 2-6). This model is a further development of the one shown in Fig. 2-67 in the sense that, at each level, the equation describing oxygen flow rate sorts out the parameters of functional regulation and those of structural design; these are distinguished in the following sense: Functional variables are regulated according to need with short time constants (seconds), whereas structural design parameters are genetically determined static elements that can be adjusted to a certain extent, for example, by training, but with time constants of weeks to months.

Thus, design variables set the capacity of the system because they are determined by structures whose quantitative properties cannot be adjusted at short notice. If the system were designed according to the principle of symmorphosis we would predict that the design variables are adjusted to $\dot{V}_{O_2max}$ at all levels from the lung to the mitochondria.

The experimental test of this hypothesis requires the integrated measurement of $\dot{V}_{O_2max}$, of the relevant functional parameters, and of all the design parameters, which must then be correlated on the basis of the model of Table 2-6. This cannot be easily done in the human so that is where we can learn from studies in comparative physiology. We know that $\dot{V}_{O_2max}$ is highly variable among mammals. For one, some species such as dogs, horses or pronghorn antelopes have a much higher level of $\dot{V}_{O_2max}$ than "normal" species of the same size such as goats or cows; this is called adaptive variation. On the other hand body size matters so that small animals have a higher metabolic rate per unit body mass than large species, which is called allometric variation. These are genetically determined variations, the result of evolution and selection by fitness, in contrast to the changes in overall work capacity and $\dot{V}_{O_2max}$ induced by exercise training in human athletes, which are epigenetic variations. In all these cases we can ask how and to what extent the structural design parameters are adjusted to meet the different requirements for O_2 to cover the energetic need at the limit of the aerobic work capacity. If there is a bottleneck, then there will be one and only one parameter whose variation is perfectly matched to the variation in the limit of O_2 flow, $\dot{V}_{O_2max}$, whereas all the parameters that are over-designed would appear in haphazard relations to the flow limit. On the other hand, if the limiting resistances are distributed all steps would have to be matched to the varying $\dot{V}_{O_2max}$. If we take the bold view that the organisms are economically designed we would predict that the structural parameters at all levels should be sized to the maximal total O_2 flow requirement with no unnecessary excess capacity because that would be a waste. We have called this design principle symmorphosis, meaning that there should be no more structure built into the system than required to serve the functional needs.

Table 2-6

Model of Structure-Function Relations in Pathway for Oxygen Separating Functional and Structural Parameters in the Equations Defining O_2 Flow Rate through Four Levels

	Function	**Design**	
$\dot{V}_{O_2}$ (lung)	$= (P_{A_{O_2}} - Pb_{O_2})\,\{t_c, \theta_{O_2}\}$	$D_{L_{O_2}}\,\{S(A), S(c), V(c), \tau_{hb}\}$	(1)
$\dot{V}_{O_2}$ (heart)	$= (\sigma_a \cdot Pa_{O_2} - \sigma_{\bar{v}} \cdot P\bar{v}_{O_2}) \cdot f_H$	$Vs\,\{V(LV)\} \cdot V_V(ec)$	(2)
$\dot{V}_{O_2}$ (caps)	$= (Pb_{O_2} - Pc_{O_2})\{t_c, \theta_{O_2}\}$	$D_{T_{O_2}}\{S(c), V(c), V_V(ec), \delta(c,mi)\}$	(3)
$\dot{V}_{O_2}$ (mito)	$= \dot{v}_{O_2}\,\{\dot{m}_{ATP}\}$	$V(mi)\,\{S_V(im,mi)\}$	(4)

The O_2 flow rate $\dot{V}_{O_2}$ is expressed as the product of functional and design parameters; parameters that affect the factors are shown in italics and placed in breaces {.}. The functional parameters include: O_2 partial pressures [P_{O_2}], coefficients of "hematocrit-specific" O_2 capacitance [σ] which depend on O_2-hemoglobin dissociation O_2 binding rate [θ], heart frequency [f_H], capillary transit time [t_c], and mitochondrial O_2 consumption rate as function of ATP flux [$\dot{v}_{O_2}$ {$\dot{m}_{ATP}$}]. Design parameters include: diffusion conductances [D] of lung and tissue gas exchangers that depend on alveolar and capillary exchange surface areas [S(A), S(c)], capillary volumes [V(c)], hematocrit [V_V(ec)], harmonic mean barrier thickness [τ_{hb}], capillary-mitochondrial diffusion distance [δ(c,mi)], and mitochondrial volume [V(mi)] with inner membrane surface density [S_V(im,mi)].

Source: Weibel ER: Symmorphosis. On Form and Function in Shaping Life. Cambridge, MA: Harvard University Press, 2000.

Testing the Hypothesis of Symmorphosis

In order to test such a hypothesis we can first compare mammals that greatly differ in terms of their maximal O_2 consumption. The first type of this variation is found in comparing normal with athletic species, such as dogs with goats or horses with steers. It has been found that such athletic animals can achieve a $\dot{V}_{O_2max}$ that is about 2.5 times higher than that of normal species of the same size. This is much more than what human athletes can achieve. The relevant morphometric data on such species are shown in Table 2-7 for three species pairs. If we go through the respiratory system, beginning at the bottom with the mitochondria, we note that their total volume in the locomotor muscles is also 2.5 times greater in the athletic species with the result that, at $\dot{V}_{O_2max}$, the unit volume of mitochondria consumes the same amount of oxygen in all these six species, namely about 5 ml O_2 per minute and ml mitochonndria. In the next level up, the muscle capillaries, we note that the capillary volume is only 1.7 times greater in the athletic species. However we note that in the athletes the hematocrit, i.e., the concentration of erythrocytes in the blood, is larger so that as a result the capillary erythrocyte volume, the product of capillary volume with hematocrit, is 2.44 times greater, thus well matched to the mitochondrial O_2 demands. Note that this is what counts because oxygen is delivered exclusively from the capillary red blood cells. When we look at the determinants of total blood flow the heart is the central element. We notice that athletic species have larger hearts resulting in a larger stroke volume Vs, but that the maximal heart frequency is not different between the species pairs so that cardiac output is determined by the stroke volume. This is only 1.7 times greater in the athletic species. However, note that, here again, the hematocrit plays an important role as it determines the amount of O_2 that can be transported to the capillaries. If we calculate the cardiac erythrocyte output $\dot{Q}$ (ec) we find that it is again 2.4 times greater in the athletic species. Thus the design parameters of the internal steps of the O_2 transport cascade are quantitatively adjusted to the needs for O_2 flow under limiting conditions. Thus, it appears that the resistance to O_2 flow is distributed to all levels.

When we then consider the design of the pulmonary gas exchanger we note that the O_2 diffusing capacity of the lung of athletic species is only 1.7 times greater than that of normal species. Considering that we found that the human lung may have some excess capacity by about a factor of 1.5, this may signify that normal sedentary species such as goats or cows have a greater excess capacity than athletic species. Indeed, this can be shown to be the case in two ways: (1) when one calculates the progression of O_2 loading on capillary blood (Bohr integration, Fig. 2-59) one finds that dogs reach saturation just before the blood leaves that capillaries into arterial blood, whereas the goats have some 30 percent reserve capacity; (2) when goats are run on a treadmill while breathing hypoxic air one finds that they can maintain their $\dot{V}_{O_2max}$; in contrast, dogs cannot run at their established $\dot{V}_{O_2max}$ under such conditions. We concluded from this observation that athletic species have designed a lung to match the requirements for maximal O_2 uptake with no excess capacity while normal sedentary species apparently allow for a certain safety margin which allows them to perform well also under unfavorable hypoxic conditions. If this is now applied to our observations on the human lung this may mean that the excess capacity of the normal lung may just be sufficient to allow athletes to increase their $\dot{V}_{O_2max}$ by training by a factor 1.5, just about what they can achieve (Fig. 2-67).

One has also found that highly trained athletes do not tolerate heavy exercise at very high altitudes as they cannot achieve O_2 saturation of their arterial blood. Thus, it seems

Table 2-7

Comparison of Morphometric and Physiologic Parameters of Muscle Mitochondria and Capillaries, and of Heart, Blood and Lung with Variation of $\dot{V}_{O_2}$ max in Three Pairs of Athletic and Sedentary Species

		Mitochandria	Blood	Capillaries		Heart			Lung
Design Function	**$\dot{V}_{O_2}$max/M_b ml · min^{-1} · kg^{-1}**	**V(mt)/Mb ml · kg^{-1}**	**V_v(ec)**	**V(c)/Mb ml · kg^{-1}**	**V(ec)/Mb ml · kg^{-1}**	**f_H min^{-1}**	**V_S/M_b ml · kg^{-1}**	**$\dot{Q}$(ec)/Mb ml · min^{-1} · kg^{-1}**	**$D_{L_{O_2}}$/Mb ml · min^{-1} · mmHg^{-1}kg^{-1}**
25–30 kg									
Dog	137.4	40.6	0.50	8.2	4.10	274	3.17	434.3	424.8
Goat	57.0	13.8	0.30	4.5	1.35	268	2.07	166.4	288.0
D/G	2.4	2.9	1.68*	1.8*	3.0	1.02*	1.53*	2.61	1.48*
150 kg									
Pony	88.8	19.5	0.42	5.1	2.14	215	2.50	225.7	284.4
Calf	36.6	9.2	0.31	3.2	0.99	213	1.78	117.5	180.0
P/C	2.4	2.13	1.35*	1.6*	2.16	1.02*	1.40*	1.92	1.57*
450 kg									
Horse	133.8	30.0	0.55	8.3	4.57	202	3.11	345.5	388.9
Steer	51.0	11.6	0.40	5.3	2.12	216	1.52	131.3	194.4
H/S	2.6	2.6	1.4*	0.94*	2.16	2.1*	2.0*	2.63	2.0*
Ath/Sed†	2.5	2.5	1.5*	1.7*	2.44	1.0*	1.7*	2.39	1.7*

Data per unit body mass.
** These ratios are significantly different from that for V_{O_2} max.*
† This line presents overall ratios for athletic/sedentary species.
Source: Weibel ER, Taylor CR, Hoppeler H: The concept of symmorphosis: A testable hypothesis of structure-function relationship. Proc Natl Acad Sci USA *88:10357–10361, 1991.*

that the pulmonary gas exchanger is now the limiting factor for O_2 transfer to the working muscles. The reason for this is that the lung of the adult cannot enlarge its gas exchange surfaces to match the increased demands of trained muscles. So an athlete must make do with the lung she or he has developed during growth. This contrasts with the changes induced by exercise training in muscle with an increase in mitochondria and capillaries, and in the heart by enlargement of the ventricles, all well matched to the maximal O_2 demands. Therefore, it is fortunate—and perhaps a sign of good design—that the lung is designed with some excess diffusing capacity to allow the lower, internal, levels of the respiratory system to exploit their capacity to adapt to increased energetic needs.

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3

The Respiratory Muscles

Marc Decramer

The respiratory muscles constitute a complex pump system. Several muscles comprise this system, represented schematically in Fig. 3-1. Breathing under all circumstances requires a coordinated contraction of different respiratory muscles. The most important inspiratory muscle is the diaphragm. The conditions under which this respiratory muscle system weakens and eventually will fail are addressed in other chapters (see Chapters 93, 94, and 147). This chapter focuses on structural and functional properties of the respiratory muscles, respiratory muscle action, and respiration muscle interaction.

STRUCTURAL AND FUNCTIONAL PROPERTIES OF RESPIRATORY MUSCLES

The respiratory muscles are skeletal muscles, and, in essence, their structural and functional properties are within the range of other skeletal muscles located in the limbs. Adaptations to their specific function, however, make them distinctly different from other skeletal muscles in a number of respects. First, limb muscles are essentially designed to produce movements, and hence, primarily work against inertial loads. Respiratory muscles mainly have to overcome resistive and elastic loads. Second, peripheral muscles contract rhythmically during movements, while respiratory muscles contract rhythmically and continuously, and they are the only skeletal muscles on which life depends. These vital muscles thus have to be well equipped to sustain continuous rhythmic contraction. These adaptations include high fatigue resistance, high oxidative capacity, greater capillary density, and greater maximal blood flow, and they depend upon structural and functional properties of the muscles.

Structural Properties

Structural properties of muscles in general, and respiratory muscles in particular, depend upon fiber types present in the muscle, morphological characteristics of the fibers, and motor unit organization.

Fiber Types

Skeletal muscles are composed of several motor units, each with hundreds of muscle fibers. Three types of muscle fibers are usually present. They are distinguished on the basis of the myofibrillar myosin adenosine triphosphatase (ATPase) activity and its pH dependence. Alternatively, the muscle fibers

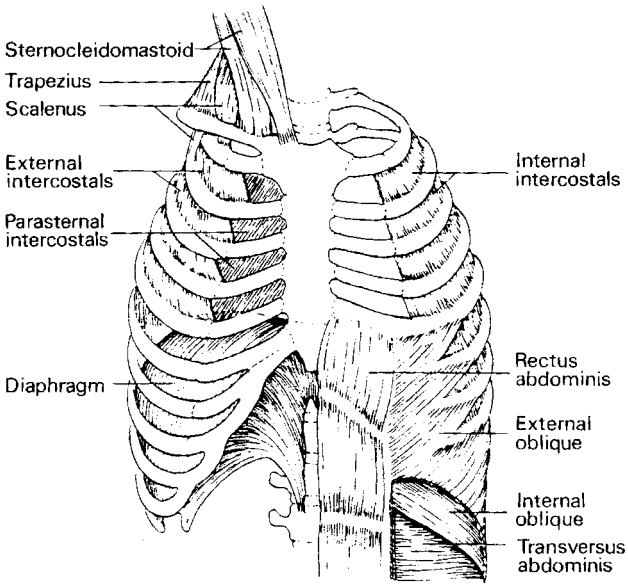

Figure 3-1 Idealized diaphragm of the respiratory muscles.

may be distinguished through myosin heavy chain gene expression. Type I fibers, or slow oxidative fibers, have a slow contraction profile but are high in endurance and rich in oxidative enzymes. Type II fibers are fast-twitch fibers that develop tension rapidly. They either are fatigue resistant or glycolytic oxidative (IIa), or fatigable or glycolytic (IIb). Type II fibers develop greater forces than do type I fibers. Muscles primarily composed of type I fibers have high endurance capacity, whereas those primarily composed of type IIb fibers are designed to develop high forces but have low endurance capacity. Type IIa fibers are intermediate and combine relatively high force development with relatively long endurance. In general, type I fibers have the smallest cross-sectional area, and type IIb fibers tend to have the largest.

Type IIb fibers were further distinguished from the histochemically different type IIx fibers by means of myosin electrophoresis and histochemistry. The respiratory muscles are mixed muscles containing both fast-twitch and slow-twitch fibers. The human diaphragm contains about 55 ± 5 percent type I fibers, 21 ± 6 percent type IIa fibers, and 23 ± 3 percent type IIb fibers. All respiratory muscles (i.e., intercostal muscles, abdominal muscles, sternomastoids, and diaphragm) contain at least 60 percent highly oxidative fibers. No data are available on the scalenes. The respiratory muscles thus seem to be generally well equipped to sustain continuous rhythmic contraction.

Morphological Characteristics of the Fibers

The respiratory muscles consist of muscle bundles oriented in a parallel fashion. These bundles consist of hundreds of muscle fibers, each of which in turn consists of hundreds of myofibrils. These myofibrils are made up of hundreds of sarcomeres arranged in series, each sarcomere consisting of a number of myosin (thick filaments) and twice the number of actin (thin) filaments. The capacity of the muscle to produce forces depends upon the number of myofibrils in parallel, since the forces developed by all these myofibrils are additive, whereas the displacement and velocity of shortening depend upon the number of sarcomeres in series. Indeed, the displacements of these sarcomeres arranged in series are additive.

The density of mitochondria in each of the three fiber types tends to be greater than in the same fiber types in limb muscles. In addition, in humans, the diaphragm is composed of about 80 percent oxidative fibers compared with 36 to 46 percent in the limb muscles of untrained men. As a consequence, the volume density of mitochondria in the diaphragm is twofold greater than in the limb muscles. Therefore, the oxygen uptake capacity of the diaphragm is considerably greater than that of limb muscles because of the high oxidative fiber content and the greater mitochondrial density. Moreover, the maximal blood flow also considerably exceeds that of limb muscles because of the greater capillary density, which is about twice the capillary density in the limb muscle. The diaphragm is thus well equipped to sustain rhythmic contraction at rest through its type I and IIa fibers: the type IIa fibers permit additional recruitment in power and rate during exercise, and the few type IIb fibers permit high power outputs necessary for sneezing and coughing.

Motor Unit Organization

Muscle fibers are organized in motor units. The muscle fibers within a given motor unit are broadly dispersed throughout a region of the diaphragm. Dispersion occurs both horizontally across the surface of the diaphragm and vertically with fibers at different depths. There are three types of motor units in the respiratory muscles: fast-fatiguable (FF), fast-fatigue resistant (FR), and slow (S). Motor units composed of fast fibers are large and develop forces in the range of 110 mN. These, however, are considerably smaller than in limb muscles. Motor units composed of slow fibers are smaller and develop forces in the range of 30 to 60 mN. The recruitment pattern of the diaphragm follows the size principle, the smallest motor units being recruited first.

Functional Properties

Functional properties of muscles are generally described in terms of force-length relationships, time-dependent characteristics of the twitch, force-frequency, force-velocity, and power-frequency relationships.

The force-length characteristics of the diaphragm are in essence similar to other muscles. Maximal tension is generated at the optimal length. Three aspects of the force-length curve of the diaphragm are potentially relevant to clinical medicine. First, with hyperinflation, the diaphragm shortens and its capacity to generate force is concomitantly reduced. Second, when hyperinflation occurs chronically, adaptation occurs in the muscle. This adaptation consists of drop out of sarcomeres such that muscle shortening is then accommodated by a reduced number of sarcomeres rather than

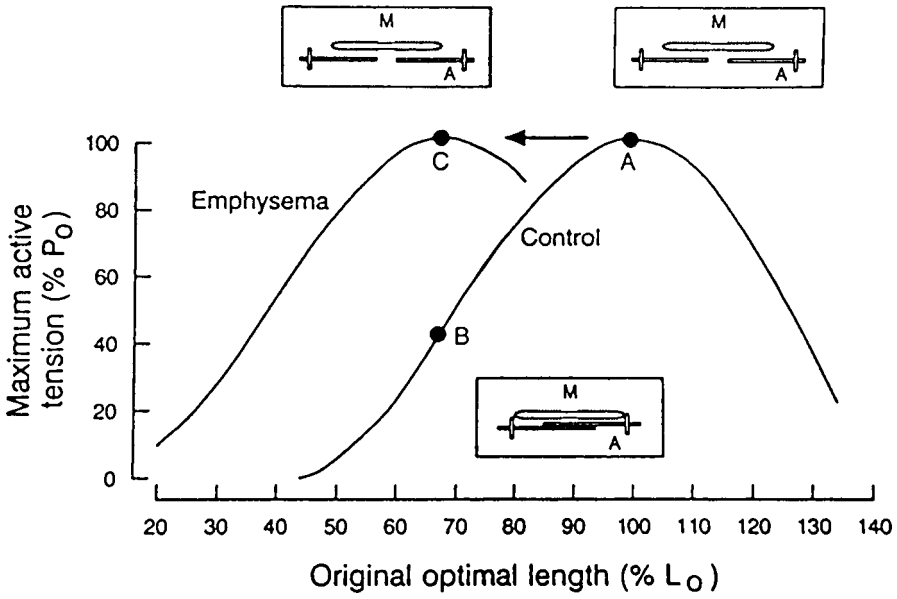

Figure 3-2 Diaphragmatic length–tension curve in normal hamsters and hamsters with elastase-induced emphysema. Tension is expressed as a percentage of maximum tetanic tension, P_O, and length is expressed as a percentage of original optimal length, P_O. The degree of filament overlap among actin (A) and myosin (M) filaments in control (A), acute (B), and chronic hyperinflation (C) is shown. Note that due to sarcomere adaptation in chronic hyperinflation, the degree of filament overlap is the same at a considerably shorter length. *(From Farkas G: Functional characteristics of the respiratory muscles.* Sem Respir Med *12:247–257, 1991, with permission.)*

alterations in filament overlap within the sarcomeres. As a consequence, the force-generating capacity is restored, at least in part, at foreshortened length. This adaptation is summarized in Fig. 3-2. The consequences of this adaptation to patients with hyperinflation are discussed below. Third, although less-than-optimal filament overlap is the primary reason for a reduction in force with muscle shortening, calcium deactivation due to T-tubular failure also plays a role. This is potentially significant for treatment, since inotropic agents restore T-tubular function in foreshortened muscle. Accordingly, inotropic agents exert much greater effects on foreshortened diaphragm than on diaphragm placed at its optimal length. This concept opens up new perspectives for respiratory muscle pharmacotherapy in patients with severe hyperinflation. The length-tension curves of other respiratory muscles and their adaptation to hyperinflation have not been systematically studied.

A particularly interesting question is the relationship between the in situ operational length of the respiratory muscles and the optimal length in vitro. For the diaphragm, the length at functional residual capacity (FRC) comes close to the optimal length. The length changes undergone by the diaphragm over the vital capacity range are large, 30 to 40 percent. These length changes are considerably smaller for the parasternal intercostals, the scalenes, and the sternocleidomastoids. For the parasternal intercostals, the length at FRC is clearly longer than optimal in supine dogs, so that with hyperinflation, the parasternal intercostals move toward their optimal length. Recent experiments, however, indicate that the fall in pleural pressure caused by stimulation of the parasternal intercostals in dogs is reduced with increasing lung volume. This discrepancy was shown to result from changes in orientation and motion of ribs with hyperinflation. The scalenes and sternocleidomastoids appear to operate on the ascending limb of their length-tension curves in supine dogs. How hyperinflation in patients affects the force-generating capacity of these muscles remains unclear. According to a recent analysis, the changes in length during passive inflation are proportional to the mechanical advantage of a particular respiratory muscle. In keeping with this analysis, the mechanical advantage of the diaphragm would be considerably greater than the mechanical advantage of other inspiratory muscles (see below).

The force developed by a muscle increases with increasing frequency of stimulation. The increase in force is considerably steeper for a slow muscle in which fusion occurs at lower frequency because of the longer relaxation time than for a fast muscle. The diaphragm is intermediate, so that at in vivo stimulation frequencies (10 to 30 Hz), a fused tetanic contraction occurs. Particularly interesting is the effect of acute shortening on the force-frequency curve. Since acute shortening is associated with a downward shift of the force-frequency curve, the detrimental effect of acute shortening on the force-generating capacity of the diaphragm appears to be twofold. With muscle shortening there is a clear reduction in maximal tetanic force. However, the decrease in force at submaximal stimulation frequencies is disproportionately greater (Fig. 3-3).

The force-velocity curve of the diaphragm is shown in Fig. 3-4. With increasing loads, the velocity of contraction is reduced. The velocity of contraction is a direct function of myosin ATPase activity, and, hence, the force-velocity curve is primarily determined by the muscle fiber composition. The diaphragm is intermediate between the force-velocity curve of a fast and a slow muscle (Fig. 3-4). The production of airflow into the lungs requires power output by the respiratory muscles. Power may be calculated as the product of the values of velocity and force according to the force-velocity relationship (Fig. 3-4). Instantaneous peak power occurs at 30 percent of maximal force and at 30 percent of maximal velocity. The frequency-isometric force relationship, frequency-shortening force, and frequency-power relationships show a

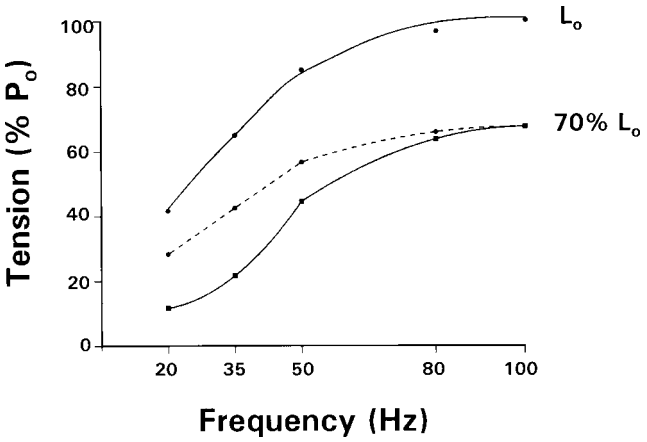

Figure 3-3 Force-frequency curve of human diaphragm at L_O and 70 percent L_O. Force is expressed as a percentage of maximal tetanic tension, P_O, and frequency is expressed in Hz. Dashed line is the predicted line at 70 percent L_O, whereas the solid line is the observed line. The predicted line is based on the assumption that a 30 percent change in length produces a 35 percent drop in force at all stimulation frequencies, as is observed for maximal tetanic force. Note that the decrease in force at lower stimulation frequencies is considerably greater than theoretically predicted. *(Modified from Farkas G: Functional characteristics of the respiratory muscles.* Sem Respir Med *12:247–257, 1991, with permission.)*

similar dependency of force and power upon frequency of stimulation.

Fatigue also affects profoundly the force-length, force-frequency, force-velocity, and power-frequency characteristics of the diaphragm. The effects of fatigue on functional properties of the respiratory muscles are discussed in Chapters 93, 94, and 147. The factors determining the development of respiratory muscle fatigue are also discussed in these chapters.

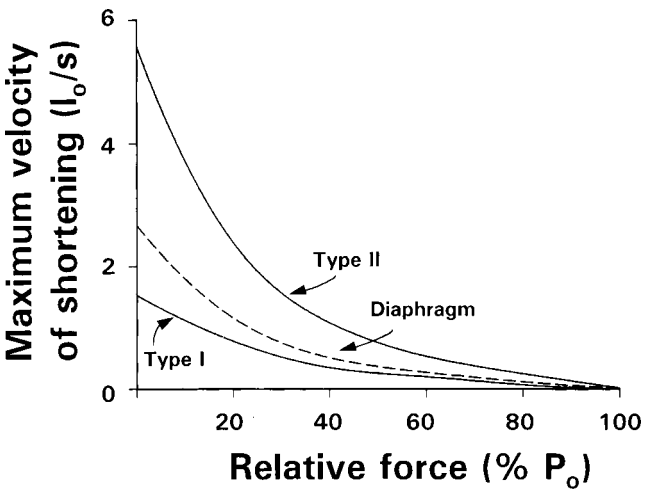

Figure 3-4 Force-velocity curve of human diaphragm (dashed line), which is intermediate between the force-velocity curve of a typical slow muscle (type I) and a typical fast muscle (type II). Maximum velocity is expressed in optimal length, l_O, per second and relative force is expressed as a percentage of maximum tetanic force, P_O.

ACTIONS OF RESPIRATORY MUSCLES

The Diaphragm

The diaphragm is the most important inspiratory muscle. It consists of two distinct parts, the costal and crural parts, which have separate actions on the rib cage, separate segmental motor innervations, and a different embryological origin. In respiratory activities, however, the diaphragm frequently operates as a functional unit, and in the following its action is described as such. Diaphragmatic action is schematically represented in Fig. 3-5. Diaphragmatic contraction increases chest wall dimensions because of three distinct reasons. First, diaphragmatic descent increases the craniocaudal dimensions of the thorax. Diaphragmatic descent is tightly coupled to outward motion of the free abdominal wall.

Second, diaphragmatic contraction increases the dimensions of the lower rib cage because of the increase in abdominal pressure that it causes. This increase in abdominal pressure acts through the zone of apposition (i.e., the zone in which the diaphragm is immediately apposed to the rib cage) to expand the lower rib cage. This action is the appositional component of diaphragmatic action (Fig. 3-5). The magnitude of the appositional component is determined by the magnitude of the zone of apposition, about 25 to 30 percent of the total internal surface area of the rib cage at FRC in standing humans, and by the magnitude of the increase in abdominal pressure caused by diaphragmatic contraction.

Third, diaphragmatic contraction further increases lower rib cage dimensions because of its insertions into the lower rib cage. The diaphragmatic fibers are oriented axially, and their contraction causes pull on the lower rib cage in an axial direction, leading to cephalad motion and outward

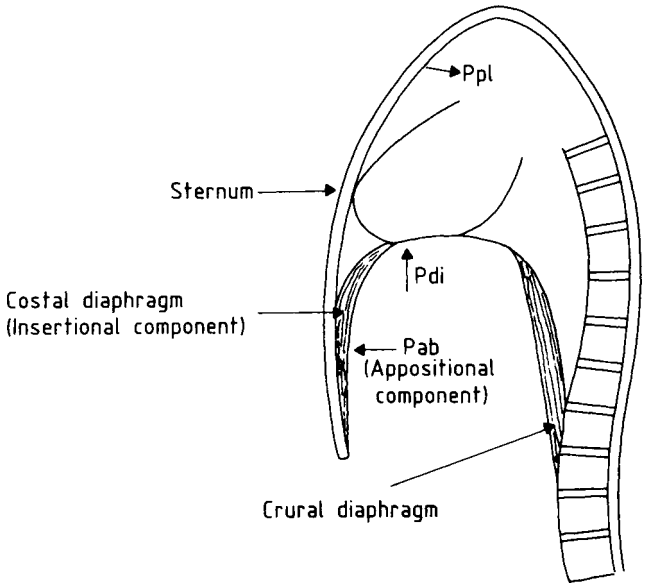

Figure 3-5 Diagram illustrating diaphragmatic action. Lateral view of the thorax. Ppl = pleural pressure, Pab = abdominal pressure. Costal and crural diaphragm are shown. See text for further explanation.

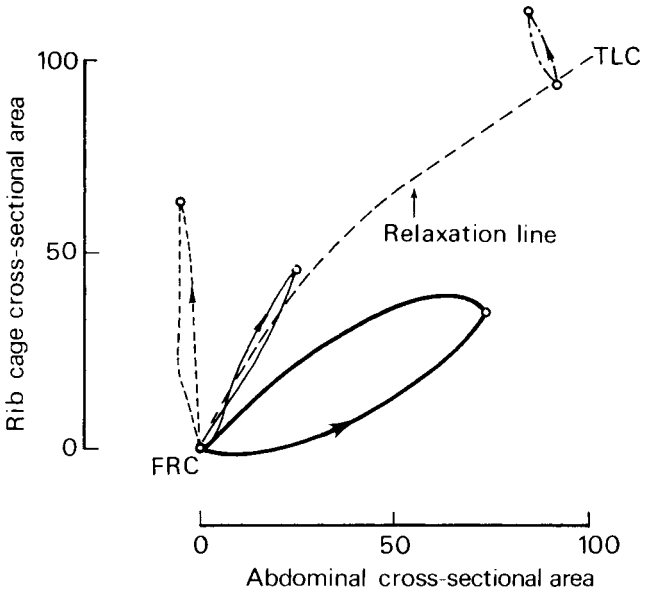

Figure 3-6 Konno-Mead diagram illustrating chest wall motion during quiet breathing (thin loop), diaphragmatic pacing or quiet breathing in tetraplegic patient (thick loop), breathing with diaphragm paralysis (dash loop), and breathing at severely elevated end-expiratory volume (dash-dot loop). Rib cage and abdominal cross-sectional areas are expressed as a percentage of inspiratory capacity. Dashed line is the relaxation line.

rotation of the lower rib and hence, to lower rib cage expansion. This is the *insertional component* of diaphragmatic contraction (Fig. 3-5).

Two points regarding diaphragmatic action are worth further mention. Diaphragmatic contraction also decreases pleural pressure, which causes a reduction in upper rib cage dimensions and hence, an expiratory effect on the lower rib cage. The latter reduction in upper rib cage dimensions is also clearly observed during diaphragmatic contraction or pacing in high quadriplegics, in whom all inspiratory muscles, except for sternocleidomastoids, are paralyzed. The pattern of chest wall motion in quadriplegics is shown in Fig. 3-6. The displacement observed in quadriplegics suggests that diaphragmatic contraction alone cannot be responsible for the pattern of chest wall motion observed during quiet breathing (see below) and, hence, that other muscles assist the diaphragm in moving the chest wall during quiet breathing.

The Intercostal Muscles

The functional anatomy of intercostal muscles is schematically represented in Fig. 3-7. Between the chondral portions of the ribs only one layer of intercostal muscles, the parasternal intercostals, is present. Between the osseous portions of the ribs, two layers are present. The outermost layer runs obliquely downward and forward and is called the *external intercostal*. The innermost layer runs obliquely downward and backward and is called the *internal intercostal* (Fig. 3-7, left panel). Note that the internal intercostals and parasternal intercostals have the same fiber orientation. Dorsally only an external intercostal is present. At its outside runs a fusiform muscle between the transverse processus of the vertebra and the angle of the lower rib. This muscle is called the levator costae (Fig. 3-7, right panel).

The parasternal portion of the intercostal musculature, the "parasternals," is consistently active during quiet breathing both in animal and human subjects, and is the most important inspiratory portion of the intercostal musculature. The parasternal intercostals have the greatest mechanical advantage, and their contraction produces about 60 percent of the cephalad motion of the rib during inspiration. Within the parasternal intercostals, the medial fibers have a greater mechanical advantage and are activated more consistently and before the middle and lateral fibers.

The action as well as the respiratory role of the interosseus intercostals remain the subject of a longstanding debate. The most commonly accepted view on intercostal muscle action is based on a theory of intercostal muscle fiber orientation and rib geometry. This theory states that the external intercostals are inspiratory in action, and the external intercostals are expiratory in action. Numerous experiments do not fit with this theory, although a finite element analysis largely confirmed these actions. It is commonly believed that the interosseus intercostals constitute a reserve system that may be recruited with increased ventilatory load. The external

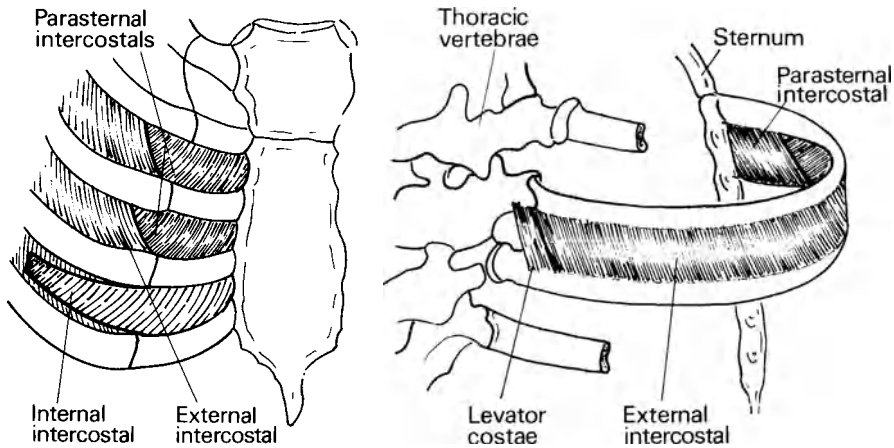

Figure 3-7 Diagram of the functional anatomy of the intercostal muscles, at their anterior (left) and posterior (right) aspects. Notice the parasternal, internal, and external intercostals, and the levator costae.

intercostals are recruited predominantly during inspiration, primarily in the upper interspaces, whereas the internal intercostals are recruited predominantly during expiration primarily in the lower interspaces. In a recent analysis Wilson et al. demonstrated by the application of the reciprocity theorem of Maxwell, that the external intercostals in the dorsal portion of the costal interspaces have a large inspiratory mechanical advantage. This advantage decreases in the ventral and caudal direction such that in the ventral portion of the caudal interspaces it is reversed in an expiratory mechanical advantage. Conversely, the internal intercostals in the caudal interspaces have a large expiratory mechanical advantage, but this advantage decreases in the cranial and ventral direction. Because of this pattern of topographic distribution the pattern of neural activation is crucial for the function of these muscles. This pattern was shown to match the pattern of distribution of mechanical advantage, such that the external intercostals have an inspiratory function and the internal intercostals have an expiratory function.

Without question, the levator costae has an inspiratory action on the rib. It is frequently activated even during quiet inspiration in supine dogs. The levator costae's contribution to inspiratory motion of the ribs during quiet breathing, however, appears substantially smaller than that of the parasternal intercostals. This contribution may further increase when the inspiratory motion of the ribs is appreciably increased.

The Scalenes

The scalenes run between the transverse process of the five lower cervical vertebrae and the upper margin of the first (scalenus anterior) and second (scalenus medius and posterior) ribs. The action of these muscles is to raise the first two ribs. The orientation of their axis in the neck causes upward motion of these ribs ("pump handle" motion). Moreover, the scalenes are consistently active during quiet breathing in normal individuals and contribute to chest wall expansion. They may be very important in the case of spinal cord injury. When the injury is below C_4-C_8, the scalenes' function is entirely or partially preserved, and they contribute importantly to upper rib cage motion in these patients.

The Sternocleidomastoids

The sternocleidomastoids run between the mastoid processes of the temporal bone and the manubrium sterni and medial portion of the clavicle. In humans, these muscles are electrically silent during quiet breathing, but they may be recruited with increased ventilatory load. These muscles are particularly important in high quadriplegics in whom they preserve their function because they are innervated by the 11th cranial nerve and spinal nerves C_1-C_2. Through training the sternocleidomastoids may develop severe hypertrophy and contribute to several hours of ventilator independence in these patients. They also may be recruited in patients with poliomyelitis and diaphragmatic dysfunction. These muscles are thought to be important in moving the upper rib cage in patients with chronic obstructive pulmonary disease (COPD), even though a clinical experimental study failed to demonstrate consistent activity in these muscles in these patients.

The Shoulder Girdle and Neck Muscles

Several shoulder girdle and neck muscles may contribute to inspiration under particular circumstances. Most of these muscles run from the rib cage to an extrathoracic extension. When the rib cage is fixed in the lean-forward position—a position commonly employed by patients with COPD—these muscles contribute to expansion of the rib cage during inspiration. Muscles that may contribute to inspiration include the trapezius, latissimus dorsi, pectoralis major and minor, erector spinae, teres major, serratus anterior, platysma, mylohyoid, and sternohyoid. Since these muscles commonly contribute to inspiration in patients with severe airflow obstruction, using these muscles for other activities, such as hair combing, may considerably increase dyspnea in these patients.

The Clavicular Head of Pectoralis Major

The clavicular head of the pectoralis major runs laterally and caudally from the medial half of the clavicle and manubrium sterni to the humerus. If the arms are fixed and braced, contraction causes downward motion of the ribs and sternum, increase in pleural pressure and, hence, expiration. Simultaneously, the lower rib cage and the abdomen move outward. Tetraplegics use this expiratory action when all other expiratory muscles are paralyzed. Training increases pectoralis strength and increases expiratory reserve volume in these patients.

The Triangularis Sterni

The triangularis sterni is the most important expiratory muscle of the rib cage. The muscle runs at the inside of the thorax between the inner aspect of the sternum and inner aspect of the five lower ribs (Fig. 3-8), and its action is to lower the ribs relative to the sternum and thus to cause expiration. The triangularis sterni is electrically silent in humans breathing quietly, but it is recruited during speech, laughing, or expiration below FRC. Its recruitment threshold is low, lower than the recruitment threshold of most other expiratory muscles.

The Abdominal Muscles

The abdominal muscles are composed of four different muscle layers (Fig. 3-1). Ventrally, a muscular sheet runs between the lower costal cartilages and the sternum and the pubis, the rectus abdominis. This muscle is enclosed in a sheath formed by the aponeuroses of the other three muscles. Laterally, an oblique muscle runs obliquely downward and forward between the lower eight ribs and the iliac crest, inguinal ligament, and linea alba medially, the external oblique. At the inner surface of this muscle lies the internal oblique with a

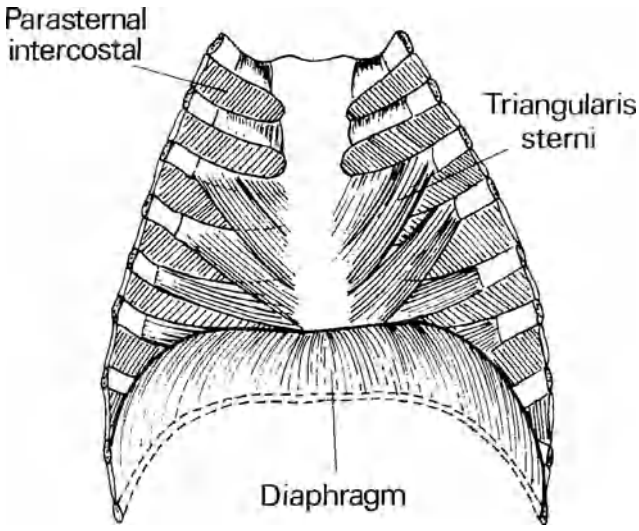

Figure 3-8 Diagram illustrating the functional anatomy of the triangularis sterni. View from inside of the thorax.

fiber orientation, which is 90 degrees perpendicular to the external oblique. These muscles are homologous to the external and internal intercostals. The innermost layer is the transversus abdominis, a circular muscular sheet surrounding the abdomen, with a fiber orientation that is parallel to the ribs. The transversus abdominis originates from the inner surface of the lower six ribs, where it interdigitates with the costal insertions of the diaphragm. It runs from this origin and the lumbar fascia, iliac crest, and inguinal ligament, circumferentially around the abdominal visceral mass to terminate ventrally in the rectus sheet. These muscles all have an expiratory action, by virtue of the inward pull of the abdomen they cause and of the insertions they have in the rib cage. In addition, however, rib cage expansion may occur with contraction of some of these muscles through the increase in abdominal pressure accompanying their contraction.

The abdominal muscles are electrically silent during quiet breathing. Usually, however, tonic activity is present in the abdominal muscles in upright position, particularly in the upper segments. During inspiratory loading, CO_2-induced hyperventilation, exercise, and forced expiration, these muscles are recruited. The transversus abdominis appears to have the lowest recruitment threshold.

RESPIRATORY MUSCLE INTERACTION

Respiratory Muscle Interaction during Quiet Breathing

Respiratory muscle interaction is traditionally studied by means of a Konno-Mead diagram, relating rib cage diameter or cross-sectional area to abdominal diameter or cross-sectional area (Fig. 3-6). First, this relationship is determined in the absence of muscle contraction, during a relaxed expiration, yielding a relaxation line. During quiet breathing in the upright position, the chest wall moves along this relaxation line, which means that proportional expansion of rib cage and abdomen is occurring. In the supine position, abdominal movement is proportionally greater than rib cage movement. Since isolated diaphragmatic contraction in quadriplegics causes abdominal movement without rib cage motion or even inward movement of the upper rib cage (upper rib cage paradox), diaphragmatic contraction alone cannot be responsible for the pattern of motion occurring during quiet breathing (Fig. 3-6). Therefore, this motion requires concomitant contraction of other muscles (i.e., the parasternal intercostals and scalenes). These muscles actively contribute to chest wall motion and cause upper rib cage expansion, whereas diaphragmatic contraction alone would cause upper rib cage paradox. During quiet breathing, the diaphragm probably contributes about 60 to 70 percent of the tidal volume, and the parasternal intercostals and scalenes contribute the rest.

PHYSIOLOGICAL CONDITIONS AFFECTING RESPIRATORY MUSCLE INTERACTION

Respiratory muscle interaction present during quiet breathing and the chest wall motion resulting from it may be altered in a number of circumstances in which ventilatory load is increased. During speech, laughing, and forced expiration, expiratory muscles are recruited. The expiratory muscles with the lowest recruitment threshold appear to be the triangularis sterni, running between the sternum and lower ribs at the inside of the thorax and transversus abdominis, the innermost layer of the abdominal muscles. Recruitment of these expiratory muscles may add significantly to inspiratory work; relaxation of these muscles just prior to the onset of inspiration contributes substantially to inspiration. Major recruitment of expiratory muscles occurs during exercise, inspiratory resistive loading, CO_2-induced hyperventilation, and anesthesia.

PATHOLOGICAL CONDITIONS AFFECTING RESPIRATORY MUSCLE INTERACTION

Respiratory muscle interaction is further profoundly affected by a number of pathological conditions. Hyperinflation is a functional abnormality of lung diseases in which airflow obstruction or loss of elastic recoil are features. Hyperinflation may be particularly severe in patients with COPD, in whom the FRC often exceeds predicted total lung capacity (TLC) (see below).

An overwhelming amount of evidence shows that hyperinflation reduces the diaphragmatic effectiveness as a pressure generator and reduces diaphragm contribution to chest wall motion. The contribution of the intercostal muscles and scalenes is likely to be increased, such that chest wall motion

becomes exclusively or predominantly rib cage motion (Fig. 3-6). The ineffectiveness of the diaphragm may result from diaphragmatic shortening, geometrical alterations, alterations in diaphragm-rib cage interaction, alteration in mechanical arrangements among the costal and crural parts of the diaphragm, reduction in the zone of apposition, and so on. Among these, diaphragmatic shortening appears to be the most important. Indeed, with inflation from FRC to TLC, the diaphragm shortens about 30 to 40 percent, which is expected to reduce significantly its pressure-generating capacity. Several studies indicate that diaphragmatic geometry is not affected significantly by hyperinflation. The appositional component of diaphragmatic action is reduced substantially due to a reduction in the zone of apposition. The insertional component is affected so that diaphragmatic contraction causes inward retraction of the lower rib cage. This may be noticed clinically in patients with severe hyperinflation. The mechanical arrangement between the costal and crural parts of the diaphragm changes from a parallel arrangement at FRC to a series arrangement at TLC. This is likely to further compromise the pressure-generating capacity of the diaphragm independently of its force-length characteristics.

It should be emphasized, however, that the above pertains to acute hyperinflation. In chronic hyperinflation, the diaphragm adapts to the chronically foreshortened state by dropping out of sarcomeres. As a consequence, the filament overlap within each sarcomere is restored toward optimal overlap. This adaptation is shown in Fig. 3-2. It should be noticed, however, that this adaptation only partially restores diaphragmatic function. First, because part of the reduction in force with shortening is due to compression of the T-tubular system, blocking exit-electrolyte flow and impeding excitation-contraction coupling. Whether adaptations in T-tubular function also occur with chronic foreshortening remains to be investigated. Second, sarcomere adaptation adapts only to the loss in diaphragmatic function associated with diaphragmatic shortening and not to the loss in function due to geometrical alterations, alterations in diaphragm-rib cage interaction, changes in mechanical arrangement among different parts of the diaphragm, or loss of zone of apposition. Third, although sarcomere adaptation restores the force-generating capacity of a foreshortened diaphragm, it reduces the number of sarcomeres in series. Consequently, sarcomere adaptation compromises the capacity of the diaphragm to undergo changes in length and, hence, its capacity to produce volume changes, presumably its most important function.

Interventions aimed at reducing hyperinflation such as lung volume reduction surgery (LVRS) and lung transplantation improve diaphragmatic function. The effects of LVRS are primarily due to an increase in the zone of apposition, lengthening of the diaphragm and improved neuromechanical coupling. To what extent complete sarcomere adaptation is present in patients with COPD and extreme hyperinflation is not clear from the clinical studies with LVRS. After lung transplantation the radius of curvature and the zone of apposition of the diaphragm are also restored. This is primarily due to mediastinal displacement toward the graft.

Expiratory muscle recruitment is frequently observed in COPD patients with severe airflow obstruction. The transversus abdominis appears to be frequently recruited. Expiratory muscle recruitment may contribute to the intrinsic positive end-expiratory pressure ($PEEP_i$) that is frequently observed in these patients. $PEEP_i$ is primarily caused by impaired pulmonary mechanics and consequent dynamic hyperinflation. The functional significance of this expiratory muscle activation is poorly understood. Indeed, in severe airflow obstruction, expiratory flow limitation is frequently present. In the presence of expiratory flow limitation, recruitment of expiratory muscles no longer contributes to expiratory flow.

In patients with pulmonary disease in general and COPD in particular, several factors may contribute to generalized muscle weakness, in which the respiratory muscles partake. These include hypoxemia and hypercapnia, malnutrition, cardiac failure, corticosteroid treatment, infection, electrolyte disturbances, and inactivity with consequent disuse atrophy. A recent study demonstrated that COPD exacerbations contributed to the development of this muscle weakness. Of particular importance appears to be treatment with corticosteroids in repetitive bursts, which is often inadvertently administered to COPD patients. Typically this myopathy causes a myopathic pattern on muscle biopsy instead of selective type IIb fiber atrophy as is commonly believed.

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4

The Genetic, Molecular, and Cellular Basis of Lung Development

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The branching pattern in the lung is extremely reproducible from one person to another, suggesting a tight temporal-spatial genetic control of the branching process. This chapter focuses on the growth factors, produced either by the epithelium or the mesenchyme, that play a key role in controlling branch formation, proximal-distal cytodifferentiation as well as folding and expansion of the alveolar gas diffusion surface.

OVERVIEW OF LUNG DEVELOPMENT AND BRANCHING MORPHOGENESIS

The human lung arises at 4 to 5 weeks gestation, while the mouse lung arises at embryonic day E9.5 (Fig. 4-1). In both species the lung arises from the ventral foregut, as the laryngotracheal groove, just anterior to the developing stomach. The primordia of the trachea and the two lung buds consist of an epithelial layer of endoderm surrounded by splanchnic (lateral plate) mesoderm. The trachea is separated from the esophagus by means of lateral, posterior to anterior longitudinal septation of the foregut, while the more distal parts of the lung develop from two lateral bronchial buds that form at the posterior end of the trachea. Initially the primary bronchial buds undergo repetitive outgrowth and branch at invariant positions. However, they develop asymmetrically; therefore, in the mouse the right bud gives rise to four lobes (cranial, medial, caudal, and accessory), whereas the left bud gives rise to only one lobe. In humans, the left lung is trilobed, while the right lung is bilobed. The number of secondary buds on the left and right sides varies among species and is regulated by the pathways that control left-right asymmetry. As lung morphogenesis continues, branching is observed at the tip of each duct, which is driven by reciprocal interactions between the distal mesenchyme and endoderm. Lobation and lobulation of the lungs, as well as the first 16 of 23 airway generations in normal humans, is stereotypic and invariant, which implies the presence of a hard-wired, genetic program that controls early embryonic lung branching morphogenesis. The latter seven generations of lower airway branching and onward into the folding and expansion phase of the alveolar surface are nonstereotypic, but nevertheless follow a recognizable, proximal-distal fractal pattern that is repeated automatically at least 50 million times. The lung morphogenetic program thus drives the formation of an alveolar gas diffusion surface 1 μ thick by 70 m^2 in surface area in humans that is perfectly matched to the alveolar capillary and lymphatic vasculature. This huge gas exchange surface area is packed into the chest in a highly spatially efficient manner, and is supplied by a circulation capable of delivering 25 L/min of blood at maximal exercise.

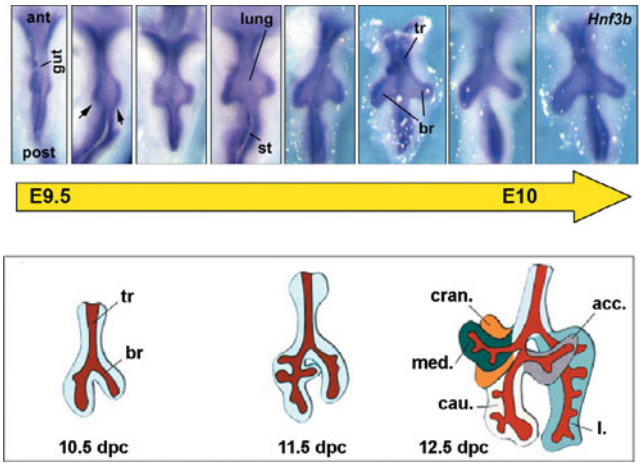

Figure 4-1 Mouse lung branching morphogenesis illustrated by *Hnf3β* expression. Mouse lung development starts at E9.5 with the emergence of two primary buds from the ventral foregut At E10.5, the lung comprises a trachea (tr) and two bronchi (br), arising from the esophagus (oe). Abbreviations; (ant) anterior, (post) posterior, (st) stomach, (cran) carnail lobe, (med) medial lobe, (cau) caudal lobe, (acc) accessory lobe.

Histologically, lung development has been divided into four stages. Following the establishment of the trachea and primary buds, development of the respiratory tree transits through four stages (Fig. 4-2): (1) pseudoglandular stage (E9.5–16.5 in mouse), characterized by the development of the bronchial and respiratory tree and a relatively undifferentiated distal endoderm and vascularization begins; (2) canalicular stage (E16.5–17.5), when the distal endoderm begins to form terminal sacs; (3) saccular stage (E17.5–P5),

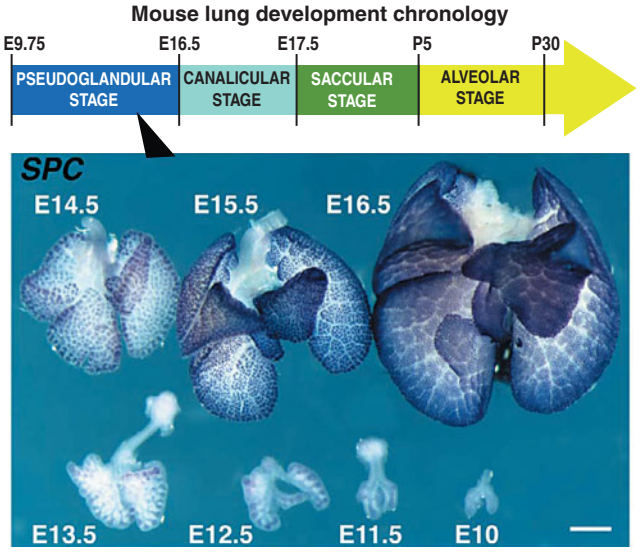

Figure 4-2 Stages of lung development. Histologically, lung development is divided into four stages in mouse; pseudoglandular (E9.5–16.5), canalicular (E16.5–17.5), saccular (E17.5–P5), and alveolar stages (P5–P30). Herein the development of the mouse bronchial and respiratory tree during the pseudoglandular stage is illustrated by *SP-C-lacZ* expression.

characterized by thinning of the mesenchyme, increase in the number of terminal sacs, and vascularization and differentiation of the endoderm into type I and type II cells; (4) alveolar stage (P5–P30), when the terminal sacs develop into mature alveolar ducts and alveoli. Unlike in the mouse, the alveolarization of the human lung begins before birth.

The larynx and trachea are genetically distinguishable from the distal airways. The mechanisms responsible for the initial specification of the lung primordia are not yet fully known. However, several genes have been shown to play a role in the very early development of the trachea and primary lung buds after initial specification.

Null mutation of *Hnf3β* results in failure of closure of the primitive foregut; thus, no laryngotracheal bud can form. Hnf3β functions as a survival factor for the endoderm and regulates *Sp-B* transcription.

Retinoic acid deficiency in mice has long been associated with total agenesis of the lungs, in association with other complex anomalies. Embryos double homozygous for null mutations in the genes encoding RARα and RARα2 are among the few known causes of complete laryngo-tracheo-pulmonary agenesis in mice. RA functions at several stages of lung development. *Raldh2* is a critical enzyme in the RA synthetic pathway that is expressed extensively in the foregut around the time of lung bud formation and subsequently in the lung mesenchyme during the pseudoglandular stage. Moreover, embryos transgenic for a RARE-lacZ reporter gene show that signaling through RA receptors is active in the lung from E10 up to at least E14, with the maximum activity shifting from the mesenchyme and endoderm to the pleura. Exogenous RA added to lung organ cultures results in proximalization of the endoderm. Recently, it has been shown that retinoic acid induces *Fgf10* expression in the mesoderm subjacent to the site of origin of the laryngotracheal groove. Blockade of RAR signaling in E9 foregut cultures not only blocks the local expression of *Fgf10* at this restricted site, but also disrupts expression of *Ttf1* and *Sp-C* in the floor of the primitive pharynx. Thus, retinoic acid signaling may connect formation of the laryngo-tracheal groove with activation of *Fgf10*–dependent bronchial morphogenesis.

Another of the earliest indications of the site of primary bud formation is the expression of *Bmp4* in two patches of the ventral foregut mesoderm.

The gene encoding the homeodomain protein TTF1 (Nkx2.1, c-ebp1) is expressed in the foregut endoderm and is required for the development of the thyroid, thymus, and lung. In $Ttf1^{-/-}$ embryos the trachea and esophagus do not separate and there are only very small or grossly cystic lung buds that do not express *Bmp4* in the endoderm.

The signaling factor Sonic Hedgehog (Shh) is expressed in the ventral foregut endoderm and throughout the endoderm of the primary buds and early respiratory tree, with the highest levels in the most distal tips. By contrast, the gene encoding the patched receptor (*Ptc*) for SHH is expressed in the adjacent mesoderm. In $Shh^{-/-}$ embryos, the trachea and primary buds fail to separate from the esophagus, resulting in a condition similar to the human birth defect

tracheo-esophageal fistula. The primary buds remain as small sacs and do not grow out or branch. Abnormal tracheal and bud morphogenesis is also seen in $Gli2^{-/-}$, $Gli3^{-/-}$, and $Gli2^{-/-}/Gli3^{+/-}$ compound mutants, probably reflecting a function for Gli proteins in the SHH signaling pathway in the foregut mesoderm.

Haploinsufficiency of *Foxf1*, which is itself a SHH target, causes esophageal atresia and tracheo-esophageal fistula. Spatial expression of SHH plays a key role in determining correct patterning of the tracheal cartilages, since peripheral misexpression of *Shh* under the control of the *Sp-C* promoter fails to rescue tracheal cartilage morphogenesis on the *Shh* null background.

FGF 10 signaling is absolutely required for lung morphogenesis distal to the carina. Embryos mutant or defective in signaling for either *Fgf10* or its cognate receptor *Fgfr2IIIb* survive to birth and develop a dysplastic trachea and primary bronchi, but no respiratory tree distal to this. The similarity of these phenotypes reflects the very localized expression of *Fgf10* in the distal mesoderm around the early lung buds and *Fgfr2IIIb* in the endoderm.

Hoxa3 and *5* also play key roles in specifying the larynx and trachea. In *Hoxa-5*$^{-/-}$ mice, tracheal occlusion and respiratory distress are associated with a marked decrease in surfactant protein production, together with altered gene expression in the pulmonary epithelium. Since *Hoxa-5* expression is restricted to the lung mesenchyme, the null mutant phenotype strongly supports the inference that *Hoxa-5* expression is necessary for induction of epithelial gene expression by the underlying mesenchyme.

Gata-6 is required for the differentiation of visceral endoderm. Thereafter, GATA-6 controls the differentiation of the alveolar type II cells and the expression of *Sp-C* and *Sp-A*.

Further evidence for distinctly separate embryonic cell lineages that form the trachea and proximal bronchi versus the peripheral lung was provided by tetracycline-driven *Sp-C-Cre* recombination, which activated lineage marker expression within the peripheral lung but not the trachea, upper bronchi or gastrointestinal tract. Non-overlapping cell lineages of conducting airways (trachea and bronchi), as distinct from those of peripheral airways (bronchioles, acini, and alveoli), were established well before formation of the definitive lung buds at E9–9.5.

GROWTH FACTOR SIGNALING DURING LUNG DEVELOPMENT

Fibroblast growth factor expression and signaling are required for distal lung morphogenesis and instruct directional growth of the epithelial buds.

Many FGFs have been implicated in multiple aspects of vertebrate development. FGF 1, 2, 7, 9, 10 and 18 play overlapping, yet distinct roles in the lung. *Fgfr1, 2,* and *3* encode two receptor isoforms (termed IIIb or IIIc) that are generated by alternative splicing; each binds a specific repertoire of FGF ligands. FGFR2-IIIb (FGFR2b) is found mainly in epithelia and binds four known ligands (FGF1, FGF3, FGF7, and FGF10), which are primarily expressed in mesenchymal cells. The expression of the FGFR2-IIIc (FGFR2c) isoform is restricted to lung mesenchyme and is known to bind to six ligands (FGF1, FGF2, FGF4, FGF6, FGF8, and FGF9).

Overexpression of a dominant negative form of *Fgfr2* in the embryonic lung under the control of the *Sp-C* promoter first clarified the role of Fgfr2-IIIb during embryogenesis. Embryos transgenic for this truncated receptor without a kinase domain, died at birth due to severe pulmonary aplasia. Only the trachea and two elongated primary bronchi developed. Overexpression of a soluble dominant negative receptor, consisting of the extracellular domain of Fgfr2 led to an even more severe reduction in branching morphogenesis and confirmed these results. While mice null for the *Fgfr2* gene die early during embryogenesis, mutant embryos defective in signaling for *Fgfr2IIIB* die at birth of the same severe pulmonary hypoplasia phenotype. They develop a trachea and primary bronchi, but no distal respiratory tree. On the other hand, FGFR3 and FGFR4 rather have a postnatal role, as double mutant mice for $Fgfr3^{-/-}$ and $Fgfr4^{-/-}$ die after birth due to defects in alveogenesis.

The broad domain of expression of Fgfr2-IIIb throughout the epithelium during the early stages of lung development suggests that the ligand controlling branching would be expressed in a more restricted way in the distal mesenchyme. Moreover, the ligand must be expressed in the distal mesenchyme from the start of lung development at E9.5. The FGFR2-IIIb isoform is able to bind several members of the FGF family: FGF1, FGF3, FGF7, and FGF10. However, FGF1, FGF7, and FGF10 are all three expressed in the lung.

FGF10 activity has been associated with instructive mesenchymal-epithelial interactions, such as those that occur during branching morphogenesis. In the developing lung, *Fgf10* is expressed focally in distal mesenchyme adjacent to stereotypically determined branching sites (Fig. 4-3). High levels of *Fgf10* expression are detected in the mesenchymal cells, some distance from the epithelium at the focal sites adjacent to the places where secondary branches later emerge. Moreover, its dynamic pattern of expression and ability to

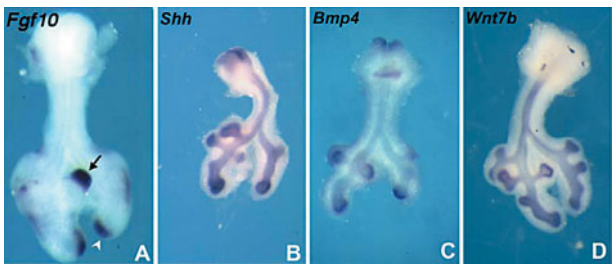

Figure 4-3 Gene expression in early mouse lung between E11.5 and E12. *A. Fgf10* is expressed in the distal mesenchyme at sites of budding (arrows). *B. Shh* is expressed throughout the epithelium. Note that its expression is up-regulated at sites of budding. *C. Bmp4* is expressed at high levels in the distal epithelium. *D.* Lung at E12, *Wnt7b* is expressed in the distal epithelium.

induce epithelial expansion and budding in organ cultures have led to the hypothesis that FGF10 governs the directional outgrowth of lung buds during branching morphogenesis. However, an equally important factor in determining the specificity of the FGF signaling response may be the presence or absence of key downstream intermediate genes. For example, the tyrosine protein phosphatase Shp2 is present in embryonic lung branch tips and plays a key role in determining when and where branching occurs. Shp2 also is essential for FGF signal transduction.

FGF7 is expressed in the mesenchyme surrounding the epithelium from E14 onwards. However, this late and broad expression rules out a role in directing the first round of branching. FGF7 function has been tested in vitro and in vivo. Isolated pulmonary endoderm cultured in Matrigel, in the presence of FGF7, does not form a bud, but a cystlike structure. Moreover, embryos overexpressing *Fgf7* under the control of the *Sp-C* promoter in the distal epithelium present a phenotype resembling pulmonary cystadenoma. This malformation is characterized by expansion of the distal parts of the branches because of the overproliferation of the epithelium and disturbances in the exchange of fluids. FGF7 is regarded to be a growth factor controlling the proliferation and differentiation of the epithelium. However, the function of FGF7 clearly can be compensated for by other factors because the $Fgf7^{-/-}$ mice do not present severe pulmonary defects.

FGF1 is expressed starting from E13.5 in the mesenchyme and the distal epithelium, while afterward its expression is restricted to the epithelium. Like FGF7, FGF18 appears to play a role in mediating postnatal lung. In in vitro culture, isolated endoderm ramifies after treatment with FGF1. Nevertheless, the chemotactic effect of FGF1 on the epithelium is less marked compared to FGF10.

Regulated expression of Heparan sulfate (HS) at sites of budding, with distinct patterns of HS sulfation in the epithelial-associated basement membrane and mesenchyme, influences lung pattern formation by mechanisms that include regulation of FGF10 protein distribution and binding to its epithelial receptor. Decreased HS sulfation results in a reduced binding for FGF10; hence, FGF10 diffuses following a rapidly changing gradient of HS from low O-sulfated HS in the mesenchyme where FGF10 is highly expressed to the epithelium with more highly sulfated HS in its basement membrane. The epithelium functions in this way as an effective FGF10 sink by effectively competing with the weaker binding sites in the mesenchyme. Sulfated domains of HS moieties can dictate specificity of FGF-FGFR binding. Without O-sulfated HS, lung epithelial cultures only survive when treated with FGF7 and not FGF10, both of which are FGFR2B ligands. FGF7 is less sensitive to regulation by HS, and heparan sulfation is suggested as a mechanism that prevents widespread activation of FGFR2B signaling in FGF-dependent branching structures.

Furthermore, FGF10 has been shown to trigger chemotaxis and proliferation on the adjacent epithelium. This results in directional growth of the primary lung buds. The chemotaxis response of the lung endoderm to FGF10 involves the coordinated movement of an entire epithelial tip, containing hundreds of cells, toward an FGF10 source. How this population of cells monitors the FGF gradient and which receptors trigger this effect remains unknown. Consistent with these observations, mice deficient for *Fgf10* show multiple organ defects including lung agenesis.

FGF10 also controls the differentiation of the epithelium by inducing *Surfactant protein C (SP-C)* expression and up-regulating the expression of *Bmp4*, a known regulator of lung epithelial differentiation.

In vitro binding assays have shown that FGF10 acts mostly through FGFR1b and FGFR2b. While there is good evidence that FGF10 acts through FGFR2b in vivo, there are as yet no conclusive data involving FGFR1b (or any other receptor) in vivo. The biologic activities mediated through these two epithelial receptors are likely to be different as FGF7 (acting mostly through FGFR2b) exhibits a different activity compared with FGF10.

FGF10 is the main ligand for FGFRIIIb during the embryonic phase of development, as evidenced by the remarkable similarity of phenotypes exhibited by embryos in which these genes have been inactivated. Mice deficient for *Fgfr2IIIB* or *Fgf10* show agenesis and dysgenesis of multiple organs, including the lungs, indicating that signaling through this receptor is critical for mesenchymal-epithelial interactions during early organogenesis. This idea is supported by the recent finding that prenatally induced misexpression of a dominant negative FGFR2b, to abrogate FGF signaling, results in a hypoplastic, emphysematous lung phenotype. In contrast, induced abrogation of FGF signaling postnatally did not produce any recognizable phenotype.

Another FGF, *Fgf9* is expressed in epithelium and mesothelium until E12.5 but is thereafter restricted to the mesothelium, a thin serous membrane enveloping the lung. The mesothelium is composed of a monolayer of flat cells of mesodermal origin. The *Fgf9* expressed in the mesothelium acts as a proliferative growth factor on the underlying mesenchyme, mostly through the receptor FGFR2-IIIC.

Fgf18 is expressed abundantly in the lung. $Fgf18^{-/-}$ mice show defects in alveogenesis but epithelial differentiation per se appears normal.

POSITIONING AND REGULATION OF FGF10 EXPRESSION IN THE LUNG BUD

Positioning and induction of the lung bud are determined through localized expression and action of FGF10. How the expression domain of *Fgf10* is controlled is still not fully understood. In the chick embryo, *Fgf10* expression in the lung is under the control of TBX4, a transcription factor of the T-box family. Ectopic TBX4 induced ectopic bud formation in the esophagus by activating the expression of *Fgf10*. Ectopic TBX4 or FGF10 then also induced ectopic expression of TTF1 which is a specific marker for the lung endoderm.

Conversely, interference with TBX4 function resulted in repression of *Fgf10* expression and failure of lung bud formation. Hox genes are also involved in defining the *Fgf10* expression domain. *Fgf10* expression is localized around the anterior border of the Hoxb-6 expression domain. *Hoxb-6* and *EphA4* exhibit a mutually exclusive expression profile whose boundaries demarcate the *Fgf10* expression domain at the prospective primary bronchus position.

Sprouty family members function as inducible negative regulators of FGF signaling in lung development. FGF10 induces the expression of its own antagonist, *Sprouty2 (Spry2)*, in the distal epithelium. *mSpry2* is localized to the distal tips of the embryonic lung epithelial branches and is down-regulated at sites of new bud formation.

On the other hand, *mSpry4* is predominantly expressed throughout the distal mesenchyme of the embryonic lung and its expression is induced by FGF acting on the mesenchyme.

Abrogation of *mSpry2* expression in cultured lungs using antisense oligonucleotides stimulates murine lung branching morphogenesis and up-regulated expression of specific lung epithelial maturation/differentiation markers. Conversely, targeted overexpression of *Spry2* in peripheral lung epithelium either under the control of the *SP*-C promoter or by intratracheal microinjection of an adenovirus containing the *mSpry2* cDNA, results in a lower level of branching, smaller lungs with a particular dysplastic appearance along the edges of the lobes and a decrease in epithelial cell proliferation.

In *Drosophila,* in vitro coprecipitation studies show that Spry binds to Gap1 and Drk (a Grb2 ortholog), resulting in inhibition of the Ras-MAPK pathway. Upon further investigation of the mechanism by which mSPRY2 negatively regulates FGF10 in mouse lung epithelial cells (MLE15), it was recently determined that mSPRY2 differentially binds to FGF downstream effector complexes that also contain Shp2, Spry2, Grb2, Sos, and Ras.

Shp2 is essential for FGF signal transduction. Shp2 is spatio-temporally expressed in embryonic lung branch tips and plays a key role in determining when and where branching occurs. Thus, localized expression of Shp2 may play a key role in specifying when and where FGF signals shall be transduced in the lung epithelium and thus may determine the spatio-temporal patterning of airway branches.

Spry is not only found downstream in the FGFR pathway, but also appears to be an inhibitor of other tyrosine kinase signaling pathways such as EGF and Torso. It is also interesting to note that overexpression of *Spry* in chick limb buds results in a reduction in limb bud outgrowth that is consistent with a decrease in FGF signaling. This suggests a possible coregulatory relationship between FGF signaling and Spry during development. In further support of this model, *Spry4* inhibits branching of endothelial cells as well as sprouting of small vessels in cultured mouse embryos. Endothelial cell proliferation and differentiation in response to FGF and VEGF are also inhibited by *mSpry4*, which acts by repressing ERK activation. Thus, *Spry4* may negatively regulate angiogenesis.

Sonic hedgehog (*Shh*) is essential for tracheoesophageal septation as well as distal branching and modulates *Fgf10* expression.

Shh is expressed throughout the endoderm with highest levels at the most distal tips. By contrast, the gene encoding the patched receptor (*Ptc*) for SHH, is expressed mostly in the adjacent mesoderm. In $Shh^{-/-}$ embryos, the trachea and primary buds fail to separate from the esophagus. The primary buds also remain as small sacs and do not grow out or branch. However, proximo-distal differentiation of the endoderm is preserved in the *Shh* null mutant, at least as far as expression of *Sp-C* and *Clara cell protein 10* are concerned.

The expression of the SHH receptor, *Ptc*, is decreased in the absence of *Shh,* as are the *Gli1* and *Gli3* transcriptional factors. *Fgf10* expression, which is highly spatially restricted in wild-type, is up-regulated and widespread in the mesenchyme in contact with the epithelium of the *Shh* null mutant mouse lung. On the other hand, overexpression of *Shh* in the mouse lung epithelium using a transgenic approach results in severe alveolar hypoplasia and a significant increase in interstitial tissue, together with reduced *Fgf10* expression. Thus, *Shh* signaling to the mesenchyme negatively regulates *Fgf10* expression, and the resulting misregulation of *Fgf10* in *Shh* mutant lungs most likely accounts for the observed failure of secondary branching. Conversely, local suppression of SHH signaling by the induction of *Shh*-binding proteins such as *Ptc* and *Hip* in the mesenchyme at branch tips may serve to facilitate FGF signaling locally where branch outgrowth is stereotypically programmed to take place. Thus, temporospatial restriction of *Fgf10* expression by SHH appears to be essential to initiate and maintain branching of lung.

Bone morphogenetic protein 4 (*BMP4*) controls proliferation, branching, and proximal-distal differentiation of the lung epithelium. *Bmp4* expression is first detected in the ventral mesenchyme of the developing lung when the primordial lung buds are emerging from the foregut. This mesenchymal expression is maintained until E13.5. Expression of *Bmp4* is also detected in the distal endoderm of the developing lung bud. Overexpression of *Bmp4*, driven by the Sp-C promoter in the distal endoderm of transgenic mice, causes abnormal lung morphogenesis, with cystic terminal sacs and inhibition of epithelial proliferation. *Bmp4* is induced at the tip of the growing lung buds in response to mesenchymal Fgf10. In isolated E11.5 mouse lung endoderm cultured in Matrigel, addition of exogenous BMP4 prevented further budding, in response to FGF10, therefore ensuring a single extending bud, rather than a cluster of buds.

Based on these results, BMP4 was postulated to mediate localized suppression of epithelial proliferation, thus providing a negative modulatory influence on FGF signaling to mediate arrest of branch extension and hence to set up branch points. However, two groups have now shown that BMP4 added at physiologic concentrations to intact embryonic lung explant cultures, thus in the presence of mesenchyme, is actually a potent stimulator of branching. Moreover, the effects of BMP4 are in turn negatively modulated by the BMP binding proteins Gremlin and Noggin.

Abrogation of Gremlin function results in septation defects of the lung airway epithelium, resulting in decreased numbers of differentiated alveoli in *Grem1*-deficient newborn mice. *Sp-C* promoter-driven over expression of either the BMP antagonist *Xnoggin* or a dominant negative *Alk6* BMP receptor to block BMP signaling, results in severely reduced distal epithelial cell phenotypes and increased proximal cell phenotypes in the lungs of transgenic mice. It thus seems unlikely that BMP4 signaling merely serves to inhibit epithelial proliferation, particularly since BMP4 specific Smads are also expressed in the mesenchyme away from the epithelium at certain developmental stages. However, the exact roles of BMP4 in early mouse lung development remain controversial.

Several additional *Bmps*, including *Bmp3, 5 and 7*, are expressed during embryonic lung development. The expression of *Bmp5* and *Bmp7* has been detected in the mesenchyme and the endoderm of the developing embryonic lung respectively, while *Bmp4* expression is restricted to the distal epithelial cells and adjacent mesenchyme.

Wnt signaling controls epithelial and mesenchymal differentiation and plays an important role in lung branching.

The Wnt growth factor family in the mouse, is comprised of 19 different secreted ligands that interact with 10 known seven transmembrane receptors of the Frizzled (Fz) gene family and either one of two single-span transmembrane proteins, low-density-lipoprotein-receptor–related proteins (LRP-5 and LRP-6). Historically, Wnt proteins have been grouped into two classes, canonical and noncanonical. Canonical Wnts bind to frizzled receptors, inhibiting glycogen-synthase kinase-3β (GSK-3β)–mediated phosphorylation of β-catenin. Hypophosphorylated β-catenin accumulates in the cytoplasm, after which it translocates to the nucleus, where it heterodimerizes with members of the TCF/LEF transcription factor family to activate the transcription of TCF/LEF target genes. Noncanonical Wnts activate other Wnt signaling pathways, such as the planar-cell-polarity (PCP)–like pathway that guides cell movements during gastrulation. Activation of Non-canonical pathway, can antagonize the canonical pathway intracellularly. Secreted Wnt antagonists can be divided into two functional classes, the secreted Frizzled-related protein (sFRP) class and the Dickkopf class. Members of the sFRP class bind directly to Wnts, thereby altering their ability to bind to the Wnt receptor complex, while members of the Dickkopf class inhibit Wnt signaling by binding to the LRP5/LRP6 component of the Wnt receptor complex. In addition to LRP5/6, DKK1 interacts with the high-affinity DKK1 co-receptors Kremen1 (Krm1) or Kremen2 (Krm2), which functionally cooperate with Dkk1 to block Wnt/beta-catenin signaling. DKK1, DKK3, and DKK4 act as inhibitors of canonical Wnt signaling, while DKK2 can function both as an inhibitor in the presence of Kremen2 or as an activator in its absence.

Between E10.5 and 17.5, β-catenin is localized in the cytoplasm and often also in the nucleus of the pulmonary epithelium and adjacent mesenchyme. Wnt ligands, Fz receptors, and the Tcf/Lef1 transcription factors are expressed during early lung development. In the early mouse lung (at E12.5), different Wnts have been reported to be expressed in the developing lung (*Wnt2, Wnt2b, Wnt5a, Wnt7b,* and *Wnt11*). Fully expressed mostly in the distal mesenchyme, *Wnt2b* is expressed in the distal mesenchyme between the epithelial branches, *Wnt7b* is expressed in the lung epithelium with a more intense expression distally, *Wnt2a* is highly expressed in the distal mesenchyme, and *Wnt5a* shows a low expression in the mesenchyme and epithelium and is highest around the trachea and pharynx. *Tcf1* (T-cell factor1), *Lef1* (lymphoid enhancer factor 1), *sFrp1* (secreted Frizzled-related protein 1), and *sFRP2* are highly expressed in the mesenchyme adjacent to the pulmonary epithelium. *Tcf3* is highly expressed at the apical side of the pulmonary epithelium, while *Tcf4* and *sFrp4* are detected in both the epithelium and adjacent mesenchyme. *Fz8* is highly expressed throughout the epithelium, while *Fz2, 3, 6,* and *7* are expressed both in the epithelium and mesenchyme. These expression patterns suggest that Wnt signaling can originate from the epithelium and mesenchyme and can target both tissues in an autocrine and/or paracrine fashion. TOPGAL or BATGAL mice, which harbor a β-*galactosidase* gene under the control of a LEF/TCF and β-catenin–inducible promoter, reveal that from E10.5 until E12.5, canonical Wnt signaling occurs throughout the epithelium and in the mesenchyme adjacent to the proximal airways where the bronchial smooth muscle cells (SMC) arise. From E13.5 TOPGAL activity is no longer present in the mesenchyme and the activity in the epithelium is reduced distally concomitant with the onset of *Dkk1* expression in the distal epithelium.

Conditional inactivation of the β-catenin gene in the epithelium of the developing mouse lung leads to neonatal death resulting from severe lung defects. Branching of secondary bronchi is altered and the number of small peripheral alveolar ducts and terminal saccules is markedly reduced. In addition, the epithelium fails to undergo proper distal differentiation, lacking the expression of pro–*SP-C* protein and vascular endothelial growth factor A *(VegfA)*, the latter correlating with a reduction in alveolar capillaries. So far, inactivation of only two WNT ligands has resulted in lung defects. The inactivation of *Wnt2a* did not show a lung phenotype, probably due to compensatory effects from other Wnts such as *Wnt2b* and *Wnt11* normally expressed in epithelial cells of the lung periphery. $Wnt7b^{-/-}$ mice exhibit perinatal death due to respiratory failure. Defects were observed in proliferation of the lung mesenchyme resulting in lung hypoplasia. In addition, $Wnt7b^{-/-}$ embryos and newborn mice exhibit severe defects in the smooth muscle component of the major pulmonary vessels, with increased apoptosis of the vascular smooth muscle cells (VSMCs), resulting in rupture of the major blood vessels and hemorrhages in the lungs after birth. *Wnt5a* is expressed at high levels in the distal lung mesenchyme. $Wnt5a^{-/-}$ mice die perinatally from lung defects including truncation of the trachea, overexpansion of the peripheral airways, and delayed lung maturation. Absence of WNT5a activity in the mutant lungs leads to increased cell proliferation and up-regulation of the expression

of *Fgf10*, *Bmp4*, *Shh,* and *Ptc*. On the other hand, hyperactive Wnt signaling changes the developmental potential of embryonic lung endoderm to express markers of gut endoderm differentiation.

VEGF isoforms induce vasculogenesis, angiogenesis, and lymphoangiogenesis during lung development. Vascularization must perfectly match epithelial morphogenesis to ensure optimal gas exchange. Several VEGF isoforms are expressed in the developing epithelium, whereas their cognate receptors are expressed in and direct the emergence of developing vascular and lymphatic capillary networks within the mesenchyme. It is possible that VEGF signaling may lie downstream of FGF signaling, since in vivo abrogation of FGF signaling severely affects both epithelial and endothelial morphogenesis. Vasculogenesis is initiated as soon as the lung evaginates from the foregut. VEGF is a critical growth factor during embryonic lung development. The loss of even a single allele of *Vegf* leads to embryonic lethality between days E9.5 and E10.5 in the mouse. VEGF is diffusely distributed in pulmonary epithelial and mesenchymal cells and is involved in controlling endothelial proliferation and the maintenance of vascular structure. VEGF is localized in the basement membrane of epithelial cells.

Both humans and mice have three different VEGF isoforms. VEGF-120, VEGF-164, and VEGF-188 are all expressed in mice during development, but VEGF-164 isoform is the most highly expressed and active during embryogenesis. VEGF signals through the cognate receptors FLK-1 (fetal liver kinase-1 or VEGFR2) and FLT-1 (fetal liver tyrosinase-1 or VEGFR1). VEGF signaling is responsible for the differentiation of embryonic mesenchymal cells into endothelial cells. Interactions between the epithelium and mesenchyme contribute to lung neovascularization, which is crucial in normal lung formation. In fact, epithelial cells of the airways are positive for VEGF, particularly at the budding regions of the distal airway. Also, lung mesenchyme cultured alone in the absence of epithelium degenerates significantly and only a few*Flk-1*–positive cells are maintained. *Vegf* misexpressing transgenic mice, where the *Vegf* transgene is under the control of the *SP-C* promoter, show gross abnormalities in lung morphogenesis that are associated with a decrease in acinar tubules and mesenchyme. VEGF-treated human lung explants show an increase of cellular proliferation in the distal airway epithelial cells with an up-regulation of the mRNA expression of *Sp-A* and *Sp-C* but not *Sp-B*.

VEGF also has been demonstrated to play a role in maintaining alveolar structure. Lungs from newborn mice treated with antibodies to FLT-1 are reduced in size and display significant immaturity with a less complex alveolar pattern. In contrast, the accumulation of VEGF in the alveoli appears to make transgenic VEGF mice more resistant to injury by hyperoxia. VEGF is a target of hypoxia-inducible transcription factor-2α (HIF-2α). *Hif-2α* deficient newborn mice die from respiratory distress syndrome. In *Hif-2α* null mice the expression of VEGF is dramatically reduced in alveolar epithelial type II cells. Additionally we have recently observed that addition of VEGF to early mouse embryonic lung explants markedly stimulates epithelial as well as vascular morphogenesis. Thus we speculate that VEGF signaling plays an important role in matching the epithelial-capillary interface during lung morphogenesis.

VEGF-C and VEGF-D are two additional members of the VEGF family. These factors have a restricted expression pattern, with high levels mainly in lung tissues. VEGF-C and -D stimulate lymphoangiogenesis through their cognate receptor VEGFR-3. Signaling via VEGFR-3 has been shown to be sufficient for lymphoangiogenesis through null mutation. Finally, VEGF-C also interacts with VEGFR-2, and therefore is able to induce angiogenesis in vivo.

PROXIMAL-DISTAL DIFFERENTIATION OF THE LUNG ENDODERM

Epithelial cell lineages are arranged in a distinct proximodistal pattern in the airways. The larynx is lined with squamous epithelium and the upper airways are lined with ciliated columnar cells that express the forkhead gene *Hfh4* and mucus-secreting cells. The lower airways are lined with Clara cells, which secrete a protein called Clara cell 10 kD protein, or CC10. The alveoli are lined with alveolar type I and II epithelial cells (AEC 1 and 2). In the adult lung the type I cells lie in close apposition to the capillaries of the alveoli, whereas the type II cells tend to be positioned in the corners of the alveoli. Type II cells (AEC2) have the potential to transdifferentiate into type I cells (AEC1). AEC2 cells are characterized by their expression of the gene for surfactant protein C (*Sp-C*) and are responsible for the synthesis of the lipoprotein complex termed pulmonary surfactant. AEC1 cells comprise the gas diffusion surface and express a limited number of specific markers, including aquaporin 5 and T1α. Within the AEC2 population lies a specific subpopulation of cells with progenitor characteristics such as relatively high resistance to oxygen, high levels of telomerase expression, and lack of e-cadherin expression. These cells may perform developmental and reparative functions to maintain the alveolar surface. Pulmonary neuroendocrine (PNE) cells are the first airway epithelial cells to form an identifiable subpopulation at around E15 in mouse. PNE cells are situated in small crests or foci and are surrounded by other epithelial cells in the upper airways. PNE cells secrete peptides such as bombesin and calcitonin gene-related peptide, but their precise function is unknown. They also express high levels of *Delta1* (Dlt1), encoding a surface ligand for Notch that may function in determining cell fate. PNE cells are completely lacking in mice null mutant for the forkhead family transcriptional factor *Mash1*. The airway epithelial cells uniformly express *Fgfr2* and *Hnf3*α (*Foxa1*) and β (*Foxa2*). The epithelial and mesenchymal cells at the very tips of the extending branches and buds have a specific pattern of gene transcription, related to intercellular signaling pathways. Genes expressed at high levels in the epithelium at the tips include *Shh, Bmp4, Wnt7b, Fgfr4,* and *c-Fos*. By contrast, the mesenchyme around the tips expresses high levels of *Fgf10, Ptc,* and *Pod1*. Thus, the distal tips are thought to be

organizing centers that contain airway epithelial progenitor cells. These centers also play key roles in regulation of both the epithelial-mesenchymal interactions that drive branching morphogenesis, as well as the proximal-distal patterning of the lung epithelium.

FORMATION OF A FUNCTIONAL RESPIRATORY UNIT (ALVEOLUS)

The alveolar stage involves the formation and maturation of the alveoli. It involves the formation of primary and secondary septa that subdivide the terminal respiratory saccules into multiple alveoli. The interstitial mesenchyme layer of each septum is initially quite substantial and contains a double capillary network that is not in very tight contact with the endodermal cells. As postnatal development in the mouse continues, the number of interstitial cells declines and the AEC 1 cells become very closely apposed to the single capillary endothelial cell network. In the mature lung the tips of the septa contain smooth muscle cells, which produce bundles of elastin fibers that are important for alveogenesis. Several gene knockouts have resulted in failure of alveogenesis. In *Elastin*$^{-/-}$ mice perinatal development of fewer distal air sacs that are dilated, with attenuated tissue septa, resulting in an emphysematous phenotype. In *Pdgfa*$^{-/-}$ mice the smooth muscle cells and elastin fibers are absent and septa fail to form, leading to postnatal death. During the pseudoglandular stage the growth factor, PDGF-A, is expressed by the distal epithelial cells and the receptor, PDGFR-A, by the surrounding mesenchyme cells, from which the smooth muscle cells derive. Finally, inactivation of both *Fgfr3* and *Fgfr4* results in a postnatal lethal pulmonary phenotype in which excess elastin is laid down and alveoli fail to form.

TOWARD AN INTEGRATED MODEL OF LUNG BRANCHING MORPHOGENESIS

As outlined earlier, different growth factors expressed either in the epithelium or mesenchyme are regulating the branching process. These factors are inducing cell proliferation, apoptosis and cell differentiation. The goal of this section is to integrate seemingly disparate data concerning the regulation of the branching process into a coherent overview (Figs. 4-4 and 4-5).

The complete cycle of budding consists of three phases: bud initiation, bud outgrowth, and growth arrest. During the initiation phase, FGF10 is so far the key molecule, and is expressed specifically in the mesenchyme adjacent to the forming epithelial buds. FGF10 expressed in the distal mesenchyme acts on the epithelium mostly through FGFR2-IIIb and promotes cell proliferation. However, in bud initiation, FGF10 also triggers chemotaxis of the epithelium (via a receptor that is not yet characterized) by modulating cell-cell and cell-extracellular matrix interactions to facilitate or

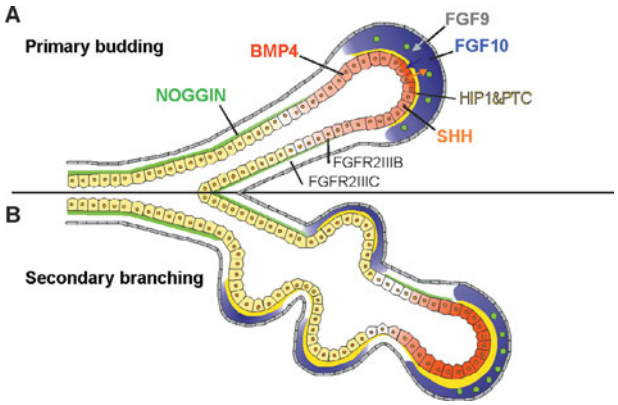

Figure 4-4 Integrated model of budding. *A.* The two primary buds initially elongate. FGF10 (blue), expressed in the distal mesenchyme, acts on the endoderm, through the FGFR2IIIB receptor isoform, to promote its proliferation (blue arrow). SHH (orange dots) is expressed in the epithelium and is up-regulated at the distal tips of the primary buds (darker orange dots). In response to FGF10 signaling, *Bmp4* (red) and *Sprouty2* expression are building up in the endoderm. Because *Fgf10* expression at the sites of future bud formation precedes *Bmp4* up-regulation and *Sprouty2* induction, lung bud outgrowth will occur before *Bmp4* and SPROUTY2 reach a critical concentration sufficient to inhibit FGF10. NOGGIN (a *Bmp4* inhibitor; green dots) is expressed in the distal mesenchyme in response to *Bmp4* signaling and at higher levels in the proximal mesenchyme near the proximal epithelium. The mesothelial layer expresses FGF9 and acts as a proliferative factor on the mesenchyme through receptor FGFR2IIIC (gray arrow). *B.* Secondary bud formation also is induced by localized FGF10 (blue) expression in the mesenchyme corresponding to the future sites of secondary bud formation. Epithelial expression of SHH might be instrumental in restricting *Fgf10* expression to the sites of secondary bud formation by inhibiting *Fgf10* expression. SHH (orange dots) is up-regulated in the epithelium of the secondary buds after the activation of *Fgf10*. However, SHH signaling to the mesenchyme transcriptionally activates *Hedgehog-interacting protein 1* (*Hip1*) and *Patched 1* (*Ptch1*) (yellow), repressors of SHH signaling, to down-regulate the SHH pathway at sites of bud formation. As a result, *Fgf10* expression gets only effectively inhibited at the inter-bud regions. As outgrowth proceeds, the expression of *Bmp4* (red) increases in the distal endoderm, which prevents FGF10 from inducing further budding from the growing lung bud. As a result, a single extending bud, rather than a cluster of buds, is generated. In response to lateral *Fgf10* expression, a new lateral, secondary bud is initiated. The mechanism by which a new *Fgf10* expression domain is initiated is unknown.

promote cell migration. On the other hand, SHH secreted by the distal epithelium induces cell proliferation in the mesenchyme through PTC and GLI. This coordinated process thus allows directional outgrowth of the buds toward the localized domain of *Fgf10* expression, until a negative feedback loop mediated by inducible negative regulators such as Spry blocks FGF signaling and hence bud outgrowth. Interestingly, the positive regulators of *Shh* and *Fgf10* expression are still unknown. For example, factors like the WNTs (*Wnt7b* is expressed in the epithelium), could positively regulate *Fgf10* expression.

During the growth arrest phase, SHH in the epithelium negatively regulates *Fgf10* expression in the mesenchyme. The

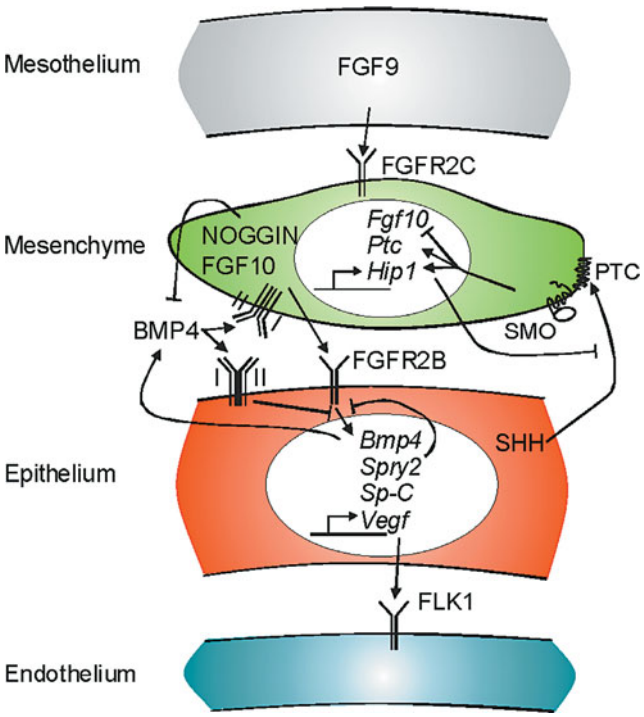

Figure 4-5 Signal integration in lung morphogenesis: mesothelial-mesenchymal-epithelial-endothelial crosstalk within the morphogenetic center at each branch tip. FGF9 is secreted by the mesothelium and activates its cognate receptor FGFR2C in the mesenchyme. Mesenchymal FGFR2C activation in turn modulates expression of *Fgf10, Ptc*, and *Hip1*. FGF10 is in turn secreted by the mesenchyme and activates its cognate receptor FGFR2B on the epithelium. This in turn modulates the epithelial expression of *Bmp4, Spry2, Sp-C,* and *Vegf*. Meanwhile, SHH is secreted by the epithelium and diffuses to the mesenchyme, where it activates its cognate receptor Ptc. SHH signaling through Ptc in turn releases SMO, which translocates to the mesenchymal nucleus, where it negatively modulates *Fgf10* and positively modulates *Ptc* and *Hip1*. HIP1 in turn negatively modulates SHH. NOGGIN is a soluble inhibitor of *Bmp4* activity, which is secreted from the mesenchyme. *Bmp4* is secreted from the epithelium and activates its cognate receptors on both the epithelium and mesenchyme. SP-C is a marker of epithelial cell differentiation down the alveolar epithelial cell lineage. VEGF in turn is secreted by the epithelium and activates cognate receptors on the endothelium of the blood and lymphatic vasculature. The net result of this complex signal integration determines the stereotypy and automaticity of branch events. WNT signaling is not depicted in this diagram, but was recently shown to be negatively modulated by Dickkopf and to determine where fibronectin matrix is laid down. This is important in determining the temporospatial location of branching events.

SHH cognate receptor, patched (PTC), exerts a negative effect on SHH signaling both through the release of the transcriptional repressor Smoothened (SMO) and the induction of the Hedgehog interacting protein (HIP). The precise nature of the inhibition of FGF10 expression is unclear, and more experiments will have to be done to determine if the inhibition is directly promoted by SHH and at what threshold level the effect is elicited. In parallel, FGF10 up-regulates *Bmp4* and *Sprouty2* expression in the epithelium, which in turn can inhibit epithelial cell proliferation and chemotaxis. In general, TGFβ family peptides exert an overriding inhibitory effect on lung epithelial cell proliferation and hence negatively regulate lung morphogenesis. However, *Bmp4* appears to exert a complex negative or positive regulatory influence, depending on whether mesenchymal signaling is intact. Wnt signaling also has emerged as exerting a critical influence on matrix fibronectin deposition and hence the specification of branch points.

Endothelium is present close to the respiratory epithelium from the earliest stage of lung morphogenesis. VEGF signaling arising from the epithelium signals to VEGF receptors on the endothelium so that morphogenesis of the epithelium and endothelium can be finely coordinated.

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5

Development and Growth of the Lung

Johannes C. Schittny • Peter H. Burri

OVERVIEW

The lung is designed to provide a large internal surface area in which the inspired air and capillary blood get in intimate contact to each other and thus allow for an efficient exchange of gases. This goal is achieved by a sequence of distinct but overlapping developmental processes (Fig. 5-1; Table 5-1). Organogenesis (embryonic stage) starts with a ventral outpouching of the foregut giving rise to the left and right lung buds. The following development of the airways and gas exchange structures is based on two different mechanisms. Starting from the lung buds, a continuous process of branching and growth into the surrounding mesenchyme preforms the whole conducting airway tree and probably also parts of the respiratory airways (branching morphogenesis). Most of this process takes place during the pseudoglandular stage. The tremendous increase of the gas exchange surface area in late fetal and postnatal lung development is brought about by a process of repetitive airspace septation leading to the formation of alveoli (stage of alveolarization). The canalicular and saccular stages may be considered as intermediate stages between both developmental principles. In the canalicular stage the first air-blood barriers are formed and surfactant production starts. During the saccular stage the switch from branching to septation occurs.

Following bulk alveolarization, which in humans occurs mainly after birth, the interalveolar septa and their capillary networks are remodeled to optimize gas exchange during the stage of microvascular maturation. At this point lung development is viewed as finished; it is followed by normal growth of the organ. However, we assume today that some form of late alveolarization at a slow rate may exist. Relative to lung development, the time point of birth varies greatly among mammalian species. In humans, birth occurs early in the alveolar stage.

The staging of lung development as described traditionally is highly descriptive. It is based on light microscopical observations of morphologic changes in the developing lung (Figs. 5-1 and 5-2). Large overlaps exist between subsequent stages for two reasons. First, lung development proceeds metachronically from the proximal to the peripheral portions of the airway tree. Second, some developmental steps and maturation processes defining the stages may run in parallel in neighboring areas. The beginning of pulmonary development is relatively well defined by the first appearance of the future trachea and the lung buds in the region of the foregut. There is no such clear limit, however, as to when it ends during childhood. Thus, lung development slowly blends into lung growth and it boils down to a question of sophisticated definitions when development ends and growth starts.

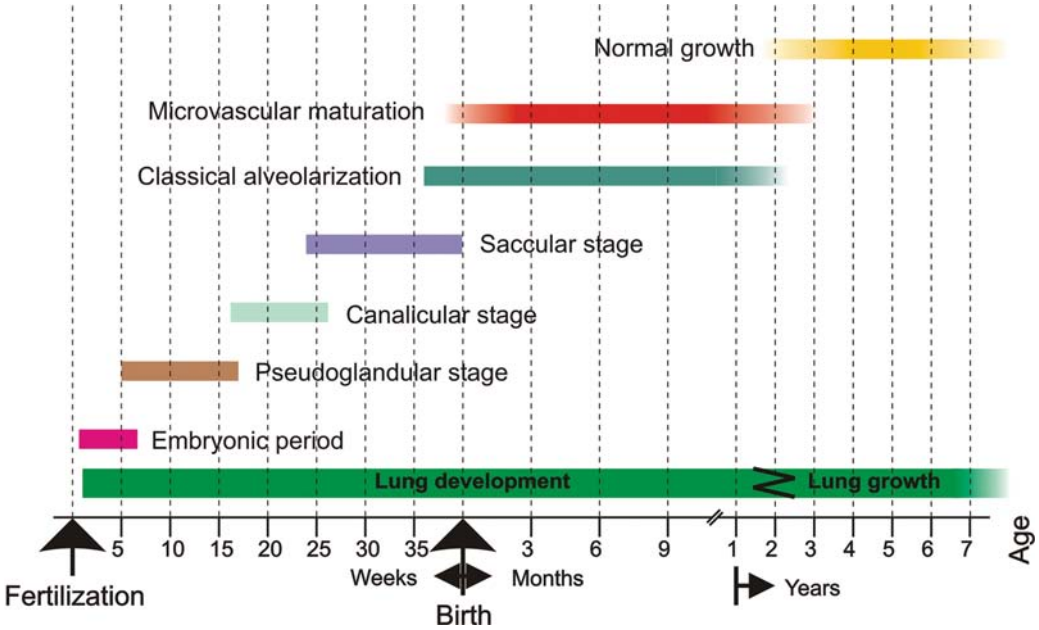


Figure 5-1 Stages of human lung development and their timing. Note overlapping between stages, particularly between the alveolar stage and the stage of microvascular maturation. Open-ended bars indicate uncertainty of the exact timing. The embryonic period is not a period specific for lung development. *(Based on Zeltner TB, Burri PH: The postnatal development and growth of the human lung. II. Morphology.* Respir Physiol *67:269–282, 1987.)*

PRENATAL LUNG DEVELOPMENT—EMBRYONIC PERIOD

Organogenesis (Weeks 4–7)

Following fertilization, the germ cells soon segregate into a cluster of trophoblastic cells to which a few embryoblastic cells adhere. The trophoblastic cells may be viewed as the future placenta, whereas the embryoblastic cells, after differentiation into the three germ layers, will form the human embryo.

Lung Anlage

The organs of the body are laid down by differentiation from the germ layers during the so-called embryonic period, which encompasses the first 7 weeks after fertilization. The lung anlage appears at day 26 as two ventral buds of the foregut at the caudal end of the laryngotracheal sulci (Figs. 5-3 and 5-4; Table 5-1). It will give rise to the left and right lung. Both buds elongate, grow into the surrounding mesenchyme, and form the left and right main bronchi (day 32) (Figs. 5-3 and 5-4). The terminal ends of the growing bronchial tree start a repetitive process of growth and mainly dichotomous branching. By day E37 the future conducting airways are preformed to the lobar, by day E41 to the segmental, and by day E48 to the subsegmental bronchi (Figs. 5-3 and 5-4). An early stage of a budding mouse lung is illustrated in Fig. 5-4.

Epithelial-Mesenchymal Interactions

As is evident from the preceding description, the high columnar epithelium of the tubular sprouts is of endodermal origin, whereas the mesenchyme is derived from the third germ layer, the mesoderm. This double origin of the lung tissues is important: many processes of lung development are dependent on the interaction between epithelium and mesenchyme. Classical transplantation experiments have shown that a cross-talk between the endodermal epithelium and the mesodermal mesenchyme is needed for the control of branching morphogenesis and cytodifferentiation, e.g., after removal of the mesenchyme at the growing tip further branching of the epithelial tubules is prevented. But when the mesenchyme of the growing tip is transplanted next to the prospective trachea, an abnormal outgrowth of bronchial branches is observed in this region.

During the last decade some of the mechanisms involved have been deciphered. Briefly, the epithelium of the growing terminal bud differs from the more proximal epithelium and the epithelium of the forming cleft, which represents the depression between the two buds. The proliferation rate is significantly elevated at the growing tip as compared to the epithelium directly proximal to it and to the one of the cleft. The basement membranes are also different. Although nidogen-1 (also known as entactin-1), collagen IV, and fibronectin are absent in the basement membrane at the growing end buds, tenascin-C is present and the latter takes part in the control of the number of branches.

In addition, a large set of factors which are secreted into the mesenchyme contribute significantly to the epithelial-mesenchymal cross-talk. These factors that are produced in both the epithelium and mesenchyme have a strong influence on the behavior of the epithelium. They include transcription factors like TTF-1, Gli2, and Gli3; as well as growth factors like FGF-10, TGF-β, BMP-4, SHH, EGF, and VEGF. No growth

Table 5-1

Stages of Lung Development and Their Time Scale

Period	Stage	Duration	Characteristics
Embryonic	Embryonic	Rabbit: n.d.–E18 Sheep: E17–E30 **Human: E26–E49 (4–7 Weeks)** Mouse: E9.5–E12 Rat: E11–E13	Start of organogenesis; formation of major airways
Fetal	Pseudoglandular	Rabbit: E18–E24 Sheep: E30–E85 **Human: E35–E119 (5–17 weeks)** Mouse: E12–E16.5 Rat: E13–E18.5	Formation of bronchial tree and large parts of prospective respiratory parenchyma; birth of the acinus
	Canalicular	Rabbit: E23–E27 Sheep: E80–E120 **Human: E112–E182 (16–26 Weeks)** Mouse: E16.5–E17.5 Rat: E18.5–E20	Completion of conducting airways; epithelial differentiation; first airblood barrier; appearance of surfactant
	Saccular or terminal sac	Rabbit: E27–E30 Sheep: E110–E140 **Human: E168–E266 (24 weeks-term)** Mouse: E17.5–P4 Rat: E21–P4	Expansion of airspaces
Postnatal	Alveolar	Rabbit: E30–term (E31) Sheep: E120–term (E145) **Human: E252 (36 weeks preterm): 1–2 years** Mouse: P4–P14 Rat: P4–P14	Alveolarization by formation of secondary septa (septation)
	Microvascular maturation	Rabbit: unknown Sheep: unknown **Human: 0–3 years** Mouse: P14–P21 Rat: P14–P21	Remodeling and maturation of intervaleolar septa and of the capillary bed
	Normal growth	Rabbit: Birth–adulthood Sheep: Birth–adulthood **Human: 2nd year–adulthood** Mouse: 4 weeks–adulthood Rat: 4 weeks–adulthood	Normal growth of the lungs

The described duration of the stages represents the time where the bulk of a particular developmental alteration takes place. Stages are overlapping, in particular the alveolar stage and the stage of microvascular maturation. In addition, regional differences are common, especially between central and peripheral regions. Litter size and nutrition also have an influence on the exact timing of development. E = embryonic day (days post-coitum); n.d. = not determined; P = postnatal day.

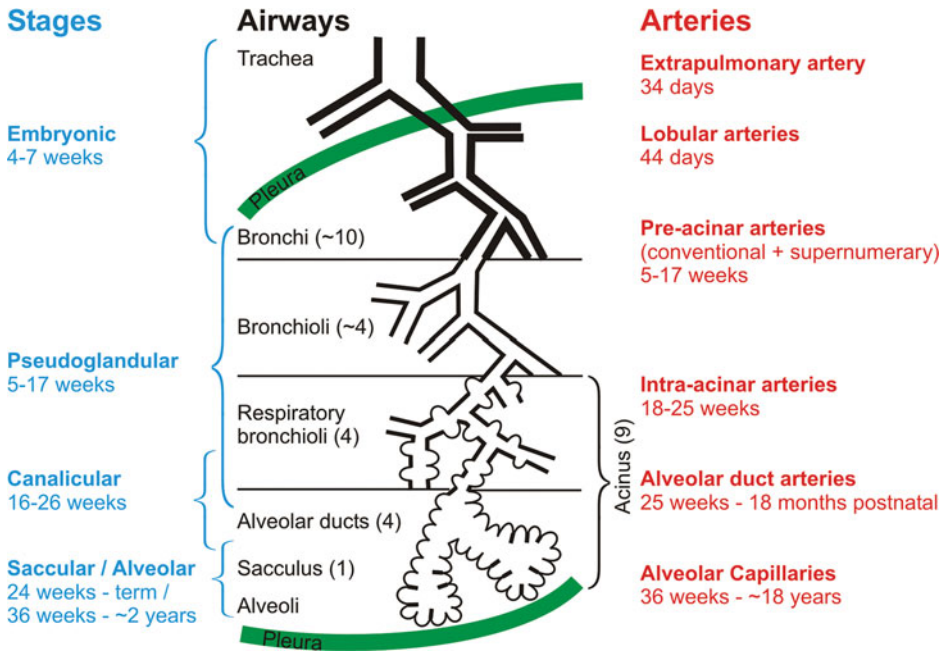


Figure 5-2 Development of the airways and arteries. The stages of lung development (blue) are correlated to the development of the bronchial tree (black) and the arteries (red). An average value of the generations formed by each category of airways is given in parentheses. On average an airway of the human lung ends after 23 generations in an alveolar saccule. In reality this number ranges from about 18 to 30. In the lung pathways are of varying lengths, partly due to space constraints in the thoracic cage. Pre-acinar arteries start as a capillary plexus surrounding the growing lung buds (vasculogenesis). Intra-acinar arteries grow by angiogenesis. *(Based on Hislop A: Developmental biology of the pulmonary circulation. Paediatr Respir Rev 6:35–43, 2005.)*

factor is able to function without its receptor. Therefore, receptors like FGFRs, EGFR, and "patched" are not of minor importance. Also involved are extracellular matrix proteins such as collagens, elastin, fibrillin, laminin-isoforms, nidogen, tenascin-C, as well as their receptors such as dystroglycan and some integrins.

During later stages of prenatal and postnatal lung development, and even in the adult lung, the interplay between differentiating pneumocytes, mesodermally derived interstitial cells, and extracellular matrix continues to be decisive for cell maturation and cell function regulation.

Development of Esophagus and Trachea

The laryngotracheal sulci of the lateral wall of the foregut are deepening and joining in parallel to the appearance of the first airway divisions. As a result the foregut is divided into the prospective trachea and the esophagus by the esophagotracheal septum (Fig. 5-3). The formation of the trachea appears to be independent of the formation of the lung buds. Because FGF10 null mice develop a trachea, but no lung buds, we must assume that trachea formation is independent of the formation of the lung buds. Toward the end of the embryonic period mesenchymal cells surrounding the prospective trachea condense focally and differentiate into cartilage precursors. Proximally, embryonic cartilage is found at the end of week 7. Cartilage formation moves distally along the future airways. Cartilage is commonly found in main bronchi around week 10 and in segmental bronchi in week 12 of gestation. However, cartilage formation continues almost until the end of the canalicular stage until it reaches its completion around the smallest bronchi (week 25). In animal studies and in the human lung, Sparrow and co-workers have demonstrated in beautiful confocal laser scanning microscopic studies that, as the primitive airways and vessels grow and divide,

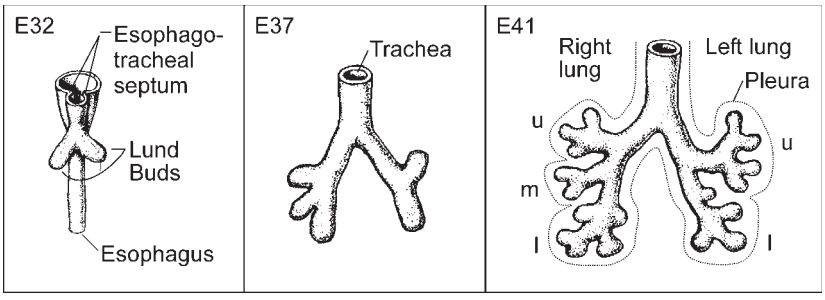
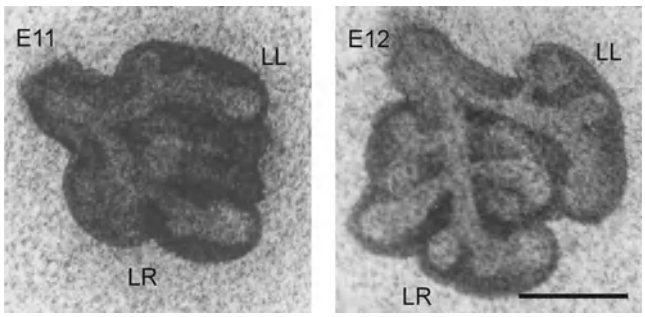


Figure 5-3 Early development of the human lung. Starting at day 26 post-coitum (pc) the anlage of the two lungs is formed by outpouchings of the foregut. The prospective trachea forms by a distal-to-proximal segregation. The lung anlage gives rise to the prospective main bronchi of the lungs at day E32 (*A*). Continuous branching results in the formation of the lobar bronchi at day E37 (*B*) and later at day E41 of the segmental bronchi (*C*). U, upper lobe; m, middle lobe; l, lower lobe. *(Modified from Sadler TW: Langman's Medical Embryology, 6th ed. Baltimore, Williams & Wilkins, 1990.)*



A *B*

Figure 5-4 Lung organogenesis. Freshly explanted mouse lung is shown at days E11.5 (*A*) and E12.5 (*B*) Toward the end of the embryonic period (E11.5/*A*) the visceral pleura and main bronchi of the lung lobes are formed. In mice the right lung consists of four lobes (cranial, middle, caudal, and accessory) and the left lung of only one. At the beginning of the pseudoglandular stage (E12.5/*B*) the lungs are already subdivided into definitive lobes. As seen in both lungs, the branching pattern of the bronchial tree is not dichotomous, but monopodial in mice. LL, left lung; LR, right lung. Bar = 0.5 mm.

they are already accompanied and enwrapped by a network of neural tissue comprising ganglia and nerve fibers.

Pleura and Formation of Lobes

The growing lung buds expand in caudolateral direction into the coelomic cavity. This rather narrow space consists of two canals located at each side of the foregut. They are called pericardioperitoneal canals and will be gradually filled by the growing lungs. During week 5 the pleuropericardial folds separate the pleural cavities from the pericardial cavity. These folds originate along the lateral body wall, elongate into the space between the heart and the developing lungs, and finally meet and fuse with the foregut mesenchyme. Caudally a pair of horizontal pleuroperitoneal membranes starts growing from the posterior body wall. They meet and fuse with the posterior edge of the septum transversum (weeks 5–7) and close the pleural cavities. The visceral pleura has formed by the splanchnic mesoderm, which covers the outside of the lung. The parietal pleura has formed by the somatic mesoderm layer covering the inner surface of the body wall.

As early as the visceral pleura has formed invaginations of the pleura start to separate the lobar bronchi and give rise to the lobar fissure and the lung lobes (Fig. 5-4). Little is known about the mechanisms involved. It appears, however, that the basement membrane of the visceral pleura plays a role, because mice lacking the nidogen-binding domain of the laminin-γ1-chain or the laminin-α5-chain show defective lobar septation and visceral pleura basement membrane formation.

At around 7 weeks, the period of organogenesis can be considered to merge imperceptibly with the period proper of lung development.

Vasculogenesis of the Pulmonary Circulation

In the adult lung, the pulmonary arteries are found in close proximity to the branches of the airways and they distribute

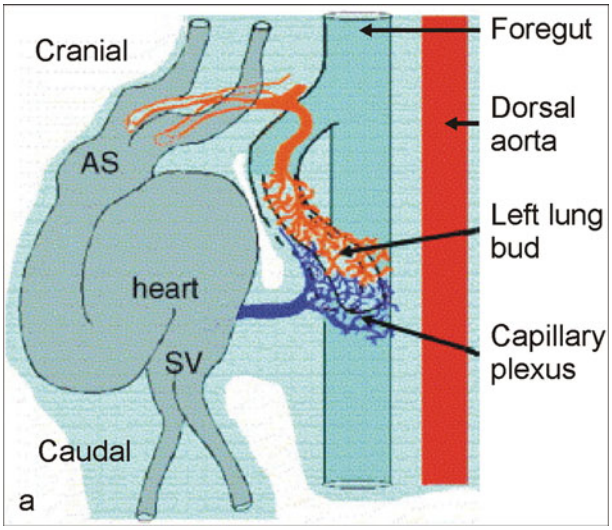


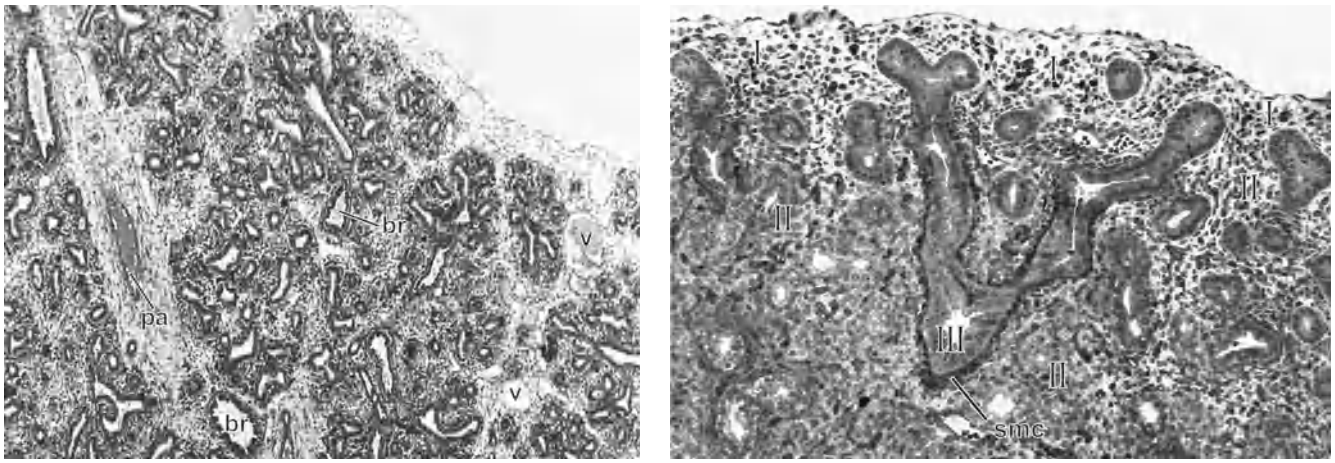
Figure 5-5 Formation of the circulation of the lung buds. *A*. Reconstruction of human embryonic lung at day 34 of gestation with completed circulation between the aortic sac (AS), through a capillary bed surrounding the single left and right lung buds and returning to the sinus venosus (SV). *(Reconstruction by Sue Hall from Hall SM, Hislop AA, Haworth SG: Origin, differentiation, and maturation of human pulmonary veins. Am J Respir Cell Mol Biol 26:333–340, 2002.)*

the blood to the alveolar capillary bed. The pulmonary veins are independent of the bronchial tree. They are found roughly in the middle between the pairs of bronchi and arteries. They maintain a similar number of branches and return the blood from the capillary bed to the heart. The close proximity of the circulation and the airways suggests that their development is linked to each other.

The mesenchyme surrounding the lung buds contains a number of cells staining positively for markers of endothelial cells. By day 34 of gestation each prospective main bronchus possesses a capillary network that connects cranially to the aortic sac and caudally to the left atrium (Fig. 5-5). After establishment of these connections there is evidence of circulating blood cells. Apparently, the earliest pulmonary vessels form by vasculogenesis—a process in which vessels form de novo due to a differentiation of mesenchymal cells. The newly formed endothelial cells are connecting to each other to form first capillary tubes. These capillaries coalesce to form small blood vessels alongside the airways. During branching of the future airways a new plexus forms as a halo around each newly formed bud. Each plexus adds to the peripheral circulation and extends the arteries and veins. Thus there is sustained addition of the newly formed tubules to the existing vessels and the airways act as a template for the development of blood vessels.

PRENATAL LUNG DEVELOPMENT—FETAL PERIOD (WEEK 5–TERM)

This period lasts till birth and comprises three phases of development, the names of which are derived from the changing



A *B*

Figure 5-6 Morphology of pseudoglandular stage of lung development in human and rat. *A*. Human fetal lung, gestational age about 15 weeks. Bright bands of loose mesenchyme containing veins (v) indicate subdivision of lung into segments and lobules. Denser mesenchyme surrounds the tubular sprouts. *B*. Subpleural region of rat lung, gestational day 18.5. Zone I (I) is characterized by a loose arrangement of mesenchymal cells immediately below the pleura. In zone II (II) epithelial tubes are enwrapped by a more densely packed network of interstitial cells. The zone I to II boundary is the site of formation, growth, and differentiation of the gas exchange region. The future conducting airways are located in zone III (III), which is characterized by epithelial tubes with an outer layer of smooth muscle cell precursors (smc). Pa, pulmonary artery; br, bronchus; light microscopical image, 65 × (*A*), 150 × (*B*).

morphology of the prospective gas exchange tissue: pseudoglandular, canalicular, and terminal sac (or saccular).

Pseudoglandular Stage (Weeks 5–17)

From the fifth week to the 17th week, the developing lung shows the characteristics of a tubular gland, giving rise to the name for this stage (Fig. 5-6). Until the end of this stage, the tubular tree preforms, through growth and branching, all the conductive airways down to their last generations—i.e., the future terminal bronchioles. Therefore, this stage has often been referred to as the stage of conductive airway formation. Although Boyden claimed that the transition to the next stage was marked by the first appearance of the pulmonary acinus (which means that the prospective lung parenchyma appears at the periphery of the developing lung), the amount of future gas exchange tissue present during and at the end of the pseudoglandular stage has been severely underestimated. Already in the early 1980s, Ten Have–Opbroek had demonstrated by immunohistochemical techniques that epithelial cells at the periphery of the airway tree in the pseudoglandular stage had to be considered precursors of the later alveolar epithelium. In morphologic and morphometric studies of fetal rat lungs, we found that half of the parenchymal epithelial cell mass in the saccular stage before birth was already present in the late pseudoglandular stage. Furthermore, Kitaoka and co-workers concluded from counts of the number of end segments in human lungs in the pseudoglandular and canalicular stages that all the airway divisions down to the level of alveolar ducts were present toward the end of the pseudoglandular stage. For these reasons, the view that the pseudoglandular stage is almost exclusively the stage of conducting airway development can be maintained no longer.

Although the appearance of the acinar structures apparently provides a well-defined morphologic characteristic for the transition to the next stage of development, a precise estimate of gestational age cannot be made from it. Differentiation usually proceeds centrifugally, and the speed of growth varies during a developmental period, with acceleration toward the end of a stage. Furthermore, animal studies have demonstrated that upper lobes develop faster than lower lobes. If the time differences in development observed between lobes in rabbits are transposed to the human lung, the differences in lobar development could amount up to 2 weeks in view of the much longer gestation period. Such differences, however, have never been assessed. Recently it was postulated that human lung development proceeded in a relatively homogeneous manner.

Epithelial and Smooth Muscle Cell Differentiation

During the pseudoglandular stage, the airway tubes are proximally lined by a very high columnar epithelium (Figs. 5-6 and 5-7 *D*). The height of the cells decreases continuously toward the periphery, to reach a cuboidal shape in the terminal branches. The epithelium of the terminal buds maintain their cuboidal undifferentiated state until branching is completed. Mitotic figures are frequent. The cytoplasmic organellar machinery looks relatively simple: mitochondria, many free ribosomes and a little rough endoplasmic reticulum, some lipid droplets, and large patches of glycogen. Remarkably, the epithelial barrier appears to be tight from the early stages of development. In freeze-fracture preparations, the morphology of the junctional complexes does not differ during development to full term; conversely, gap junctions are present early in gestation and disappear during the canalicular stage as the

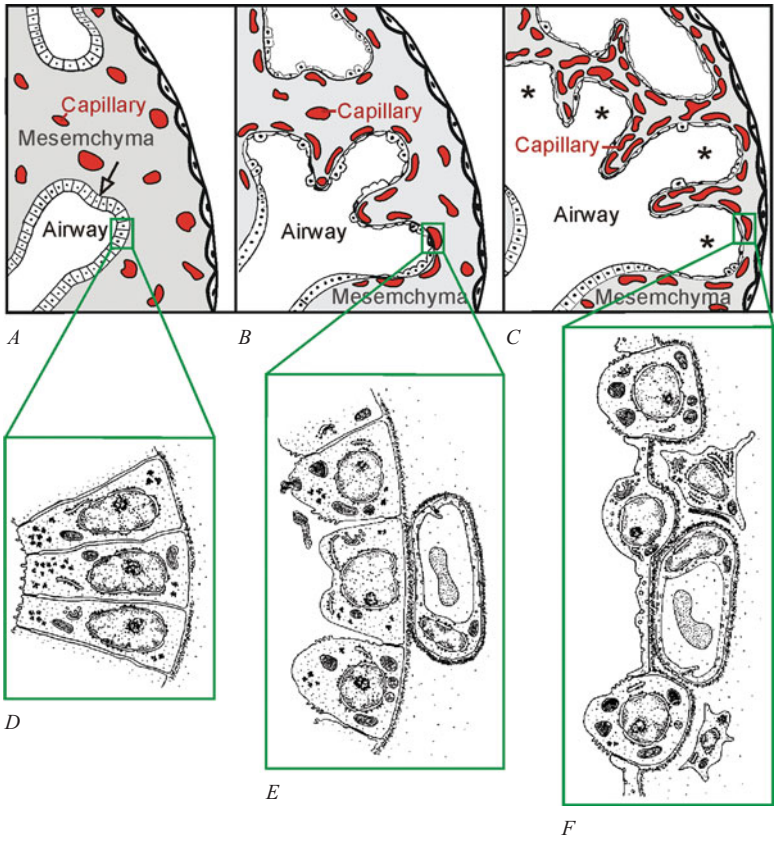


Figure 5-7 Changes in lung parenchymal morphology in the pseudoglandular, canalicular, and saccular stages. *A*. During the pseudoglandular stage, the epithelial tubules branch constantly and penetrate into the surrounding mesenchyme (open arrow, branching point). A loose three-dimensional capillary network is located in the mesenchyme. *B*. The canalicular stage is characterized by: (1) a widening of the future airways; (2) a differentiation of the tall columnar epithelial cells of the pseudoglandular stage (*D*) into prospective lining and secretory cells (type I and II epithelial cells, e + f); (3) a multiplication of the capillaries and their first close contacts to the epithelium; and (4) the formation of first air-blood barriers (e → f). *C*. Throughout the saccular stage the mesenchyme condenses to form thick inter-airway septa that contain a capillary layer on either side of the septum. The widened terminal ends of the bronchial tree are recognized as saccules (asterisks) *(A to C modified from Caduff JH, Fischer LC, Burri PH: Scanning electron microscopic study of the developing microvasculature in the postnatal rat lung. Anat Rec 216:154–164, 1986; D and E from Burri PH, Weibel ER: Ultrastructure and morphometry of the developing lung, in Hodson WA (ed).* Development of the Lung. *New York, Dekker, 215–268, 1977.)*

epithelial cells differentiate. Therefore, it may be that electrical coupling between cells plays a role in cellular differentiation.

The first ciliated, goblet, and basal cells appear in the central airways. Mucous glands and goblet cells appear almost simultaneously in the airway epithelium. They develop from solid epithelial sprouts that invade the mesenchyme underneath the epithelium. At around weeks 12 to 13, mucous glands are found in bronchi; at week 14, mucus formation can be detected in the trachea.

A continuous layer of contractile α-smooth muscle actin positive cells surrounds the larger future airways in the proximal part of the bronchial tree. These cells are defined as smooth muscle cell precursors, because morphologically they are not yet fully differentiated. The layer of smooth muscle cell precursors becomes step by step discontinuous in the more distal parts and ends in front of the terminal buds. Until birth these contractile cells perform spontaneous contractions, which start centrally and travel like a peristaltic wave into the periphery. The resulting wave of intrabronchial liquid pushes liquid into the terminal buds and extends them rhythmically. It was postulated that branching is stimulated by this mechanical signal via mechanical transduction.

Arteries and Veins

During the pseudoglandular stage, the vascular system develops along with the bronchial tree, so that by the end of this stage, all the preacinar vessels, arteries, and veins, are laid down in the characteristic pattern of the adult lung. However, the number of generations in the arterial tree is greater than in the airway system: On average, there are more than 28 generations in the arterial tree versus 23 in the airways. In addition to the conventional arteries that follow the bronchi and bronchioles, there are other branches (i.e., "supernumerary" arteries), which often split off at right angles. Usually these branches are smaller vessels that irrigate the "recurrent" gas exchange tissue adjacent to the conducting airways.

The veins follow different pathways. They run mainly interaxially in mesenchymal septa of the lung segments and subsegments. Verbeken et al. showed that as a general rule venous branches systematically follow the connective tissue septa that extend into the plane between each generation of airway branching. In the central areas the large venous branches join the arteries and airways to reach the hilum.

The generations of the three pulmonary trees—future airways, arteries and veins—develop in parallel. According to current estimations approximately five-sixths of the number of generations is laid down at the end of the pseudoglandular stage. However, due to the exponential growth by mostly dichotomous branching (2^n) the total numbers behave quite differently. In a first approximation the total number of branches, the total length, and the total volume of the airways, arteries, and veins doubles with every additional generation.

Zones of Lung Development

Based on morphologic observation during rat lung development Burri and Moschopulos established a concept of zonal

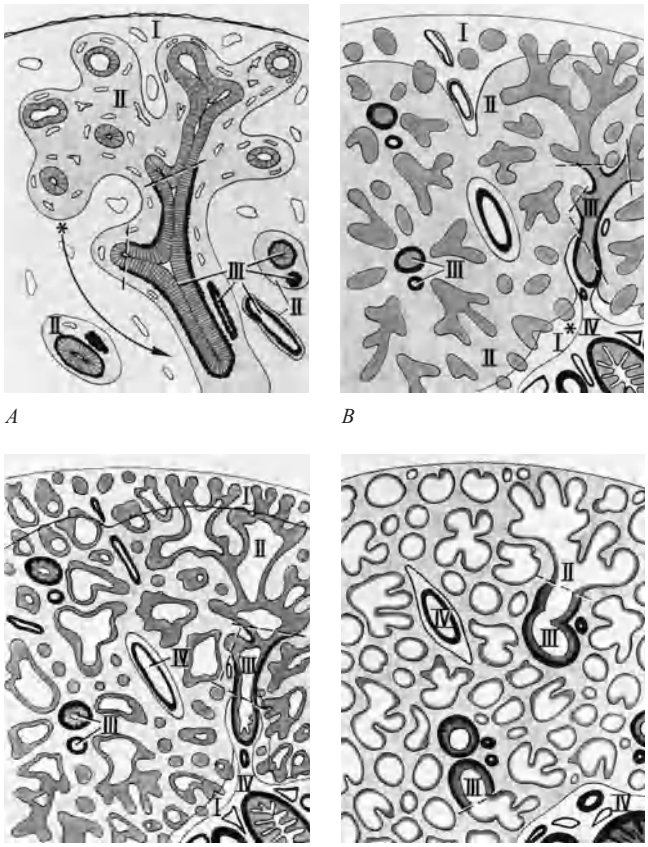


Figure 5-8 Schematic illustration of Zone concept. *A*. Early pseudoglandular stage: Zone I is made from a loose network of mesenchymal cells and capillaries into which the airway tubules of zone II penetrate. Zone III contains the prospective conducting airways and vessels. The conducting structures have no adventitial layer yet. No Zone IV is present. *B*. Late pseudoglandular stage. All four zones have now developed. The peripheral tubules reach into zone I, which represents a layer of almost constant thickness despite lung volume increase. This means that it represents a kind of cambial or germinal layer for airway growth. Due to the recurrent growth of zone II (asterisk and arrow in *A*), zone I areas have reached the cuffs of airways and vessels. Part of airways and vessels of earlier zone III are now enwrapped by an adventitial layer and have therefore muted to zone IV. *C*. Canalicular stage: Airspaces of zones II and III have widened, while the airway buds in zone I retain a cuboidal epithelium. *D*. Saccular stage. Zone I has now disappeared; there is no more budding. The lumina of airspaces and airways are wide. (*From Burri PH, Moschopulos M: Structural analysis of fetal rat lung development.* Anat Rec *1992; 234:399–418.)*

development. Zone I is defined as a superficial mantle around the lobes and the future acini. It consists of primitive mesenchymal cells and represents a zone of growth and branching of the epithelial tubules. Zone I disappears at the beginning of the saccular stage when branching is completed. Zone II is mainly a zone of differentiation. In electron micrographs its interstitium stains intensely due to a dense population of dark cells. Zones III and IV contain the elements of the airway tree and vascular system, zone IV corresponds to the most proximal generations with an adventitial layer. For all differentiation processes a centrifugal directionality is manifested (Figs. 5-6 and 5-8), the most differentiated cells being in the first branching generations, whereas cellular multiplication is at work in the periphery.

Besides helping to understand developmental processes the zone concept is also interesting in terms of molecular aspects, e.g., many factors that are expressed in zone I contribute to the epithelial-mesenchymal interaction during branching (e.g., FGF-10, Gils, Sprouty4). In zone II the expression of hepatocyte nuclear factor/forkhead homologue 4 was observed.

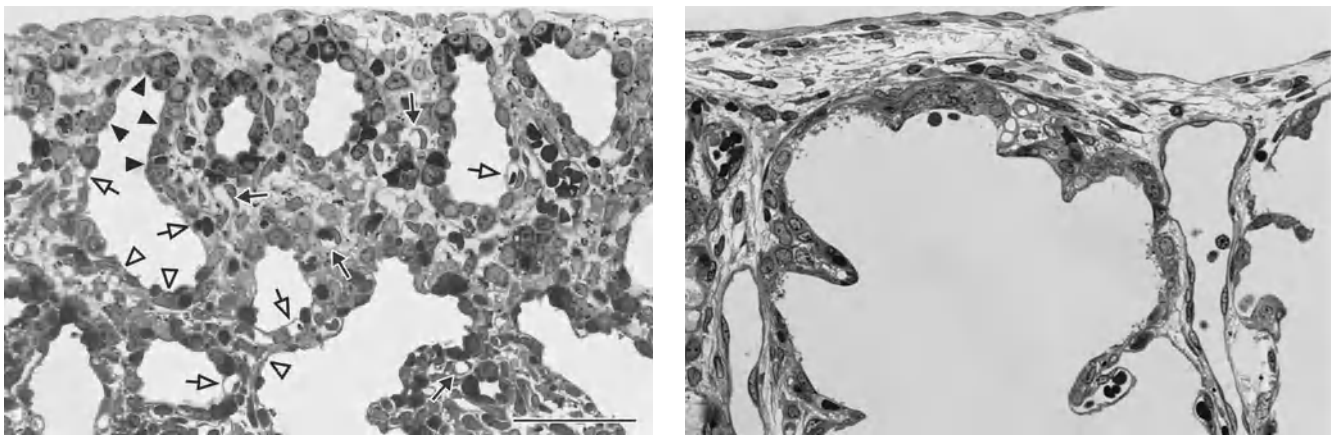
Canalicular Stage (Weeks 16–26)

The canalicular stage comprises important steps in the development of the fetal lung. The lung morphology changes dramatically, owing primarily to: (1) the differentiation of the pulmonary epithelium and formation of the typical air-blood barrier; (2) the beginning of surfactant synthesis and secretion; and (3) the "canalization" of the lung parenchyma by capillaries. The latter process gave this stage its name. These alterations have most important functional consequences: At the end of the canalicular stage, the lung has reached a state of development in which gas exchange is possible in principle. Before these developmental steps, a prematurely born infant has no chance to survive. However, clinical experience unfortunately shows that survival is by no means assured at the end of the canalicular stage.

At the beginning of this stage, the future gas exchange region of the lung can be distinguished from the conductive tubules of the airway tree. Boyden has characterized this step as "birth of the acinus." The early acini are composed of several very short generations of tubules arranged in clusters and taking origin from the actual last segment of the conducting airways, a prospective terminal bronchiole. The acinar borders can be recognized because of rarefaction of the mesenchyme (Figs. 5-6 and 5-8). In subsequent weeks, the distal segments of the airways grow in length and widen at the expense of the mesenchymal mass.

Epithelial Differentiation: Formation of the Air-Blood Barrier

To achieve an operational air-blood barrier, epithelial differentiation and capillary proliferation are needed during this



A *B*

Figure 5-9 Formation of the air-blood barrier. *A*. Early canalicular stage, rat lung. Although the most terminal part of the airway tree still contains a cuboidal, glycogen-rich epithelium (closed arrowhead), the epithelium of the more proximal parts begins to flatten out (open arrowhead) to form thin air-blood barriers. During the latter process capillaries, which are located inside the mesenchyme (closed arrow) "move" toward the epithelium (open arrow). *B*. The periphery of the gas-exchange region in human lung aged 26 days postnatal. There are still remnants of the cuboidal epithelium (closed arrowhead) present at the uttermost periphery at the beginning of alveolarization. It demonstrates the large overlap among the different phases of lung development. Light microscopical image, 175 × (*A*), 320 × (*B*).

stage. The cuboidal glycogen-rich epithelium of the bronchial tree differentiates into two types of epithelial cells: (1) type II epithelial cells, which start to produce surfactant; and (2) type I epithelial cells, which reduce their height and develop sheet-like extensions that cover most of the internal surface of the parenchyma. In addition, the type I cells contribute to the formation of the first thin air-blood barriers (Figs. 5-7*B*, 5-7*E*, and 5-9). The lung parenchyma becomes "canalized" by capillaries, resulting in a dense capillarization of the primitive interstitium. Distal of the conductive zone the future airways not only grow in length, but also widen, causing a reduction of the mesenchymal volume (Fig. 5-7*B*). In rats this reduction includes a peak of programmed cell death (apoptosis). The cellular death indicates that the condensation of the mesenchyme includes a reduction of the number of cells.

During the pseudoglandular stage the capillaries form a loose three-dimensional network inside the mesenchyme (Fig. 5-7*A*). During the canalicular stage a strong angiogenesis of the (micro)-vasculature takes place and the capillaries come into close contact to the epithelial tubules, forming a pericanalicular network (Fig. 5-7*B*). In the regions in which the epithelium has been thinned, the capillaries form the air-blood barrier by an intimate contact to the squamous cells (Figs. 5-7*E* and 5-9*A*). The epithelial and endothelial cells are only separated by one fused basement membrane that possesses one central lamina densa and two laminae lucidae. The mechanism by which the air-blood barrier forms is currently only poorly understood. It is likely that the interaction between the mesodermally derived endothelium and the endodermally derived epithelium takes part in this developmental step. This hypothesis is supported by a transgenic mouse, in which the sequence coding for the nidogen-binding site (γ1III4, within the laminin-γ1-chain) was selectively deleted by gene targeting. In these mice the basement membranes are disrupted or missing in large parts of the air-blood barriers. As a result epithelial and endothelial cells do not form close contacts. The mice die neonatally due to a failure of the gas exchange in the lungs.

During the canalicular stage the type II epithelial cells start to accumulate lamellar bodies containing components of surfactant. Soon afterward the type II cells actively secret surface active material, which appears in the lung liquid. In contrast to most species, in which surfactant appears late in gestation (at about 80–85 percent of total duration of gestation), in the human fetus small amounts are already present at weeks 22 to 24 (approximately 60 percent of gestation). Before the lungs fully mature surfactant appears to be unevenly distributed. The surfactant appears to be more abundant in apical than basal regions. The clinical observation that in some premature born infants the development of hyaline membrane disease is more pronounced in basal than apical parts of the lung may be explained by this uneven appearance of surfactant.

Type II cells are also the progenitor cells of the type I cell population in adult lungs, as could be demonstrated during repair of the damaged alveolar epithelium. Therefore, it is not surprising that a few small lamellated bodies have been found in the cytoplasm of immature epithelial cells *before* they started to differentiate into type I and II cells. In cytokinetic experiments using tritiated thymidine, it has been shown that during lung development, early type II cells (or, more precisely, cells resembling type II cells) also represented the stem cells of the type I and II pulmonary epithelium. Recently, it has been shown in adult mice that circulating bone marrow cells may also be recruited to the lung. At the uttermost periphery of the airspaces, the cuboidal cells of the epithelium remain undifferentiated until after birth (Fig. 5-9*B*).

Saccular (or Terminal Sac) Stage (Weeks 24–38)

This stage lasts from about week 24 almost to term. At the beginning of this stage, the peripheral airways form typical clusters of widened airspaces termed saccules or terminal sacs. By widening and lengthening of all airspace generations distal to the terminal bronchioles, and probably also by the addition of the last generations of airspaces (Fig. 5-2), the future gas exchange region expands massively.

Each new generation of this pathway is originally formed as a blind-ending saccule. As soon as it divides distally, however, it is no longer a saccule, but an open-ended channel. As is discussed in the section on postnatal development, the morphology of all these channels and saccules undergoes change until the formation of the alveoli is completed in the postnatal period. Therefore, these structures have been designated as transitory ducts and transitory saccules or, more generally, as transitory airways or airspaces, because their morphology changes further until alveoli are formed.

Also at this stage, within the mesenchyme, one or two populations of fibroblastic cells have differentiated. Not only are these cells responsible for the deposition of extracellular matrix and fibers but also, by way of interactions with the epithelial cover, they presumably play a role in epithelial differentiation and the control of surfactant secretion. Owing to the expansion of the lumina of the peripheral airspaces in the foregoing and the present stage, the proportion of interstitial tissue within the inter-airspace septa has decreased.

During the canalicular stage the capillary network had formed a capillary layer around each future airway. Due to the expansion of the future airways, the surfaces of the airways approach each other and a capillary double layer is thus formed inside the inter-saccular septa (Fig. 5-7*C*). The inter-saccular and inter-ductular septa are still relatively thick and their interstitium is highly cellular. Because its content in collagen is low, the fetal lung is delicate and fragile: Under mechanical stress it ruptures much more rapidly than the adult organ.

Finally, in anticipation of the next stage, during which the alveoli will be formed, the interstitial cells start to produce elastic fibers along the inter-ductular and inter-saccular walls. Elastin is found first in extracellular bays of large fibroblastic cells rich in organelles. The deposits later extend throughout the septal walls of the parenchyma, from the peribronchial and perivascular sheaths to the pleural sac.

Arteries and Veins

Keeping pace with the intense growth of the gas exchange region during this stage, the vascular tree grows in length and diameter and adds new generations. Measurements on arteriograms by Hislop and Reid have shown that arterial diameter is practically constant at a given distance from the end of the arterial pathway. This is true irrespective of age, either fetal or postnatal. Therefore, for example, a vessel of a given size will supply a large portion of a lobe in an early fetal lung, but only an acinus in a child's lung. In late fetal life, the wall structure of arteries is similar to that of adult lungs. Proximal arteries are elastic, with many elastic lamellae strutted to each other by smooth-muscle cells that are arranged obliquely between the elastic sheets. Smaller arterial vessels show a transitional structure, the muscular component becoming increasingly prominent at the expense of the elastic component. Finally, the muscle layer of the media becomes irregular and assumes a spiral configuration. This configuration explains the "partly muscular" arteries seen in histological sections. Unfortunately, there are no strict relationships between vessel diameter, size of the region supplied, and character of the wall structure; these relationships may differ from one pathway to the other. Intrapulmonary veins are practically devoid of smooth-muscle cells until the end of the canalicular period. In the following weeks, however, a thin muscle layer is formed that, at birth, extends down to vessels of about 100 μm diameter.

Time of Birth

Comparing different species the time point of birth as determined relative to lung development correlates with the activity of the newborn. So far the marsupial quokka wallaby *(Setonix brachyurus)* represents the mammal possessing the most immature lung at birth. These animals are born in the canalicular stage. As insessorial mammals, rats and mice are born during their saccular stage. While human babies are born in the early alveolar stage, precocial mammals such as sheep are born during late alveolar stage (Table 5-1).

POSTNATAL LUNG DEVELOPMENT

At birth the replacement of lung liquid by air and the onset of respiration represents a major caesura in pulmonary development. However, the change from the amniotic into the atmospheric environment is more a functionally than a structurally relevant step. At this time, the complete set of airway generations seems to be present; however, the most peripheral ones are still relatively short. The pulmonary parenchyma consists of several generations of transitory ducts and, as the last generation on each pathway, the transitory saccules. At birth, these structures are on the way to being transformed into alveolar ducts and sacs, respectively, by the process of alveolarization. Although reports indicate that in humans the formation of alveoli starts during late intrauterine life, the alveolar stage of lung development is discussed in this section because most alveoli (more than 85 percent) are formed after birth.

Alveolar Stage (Week 36 to 1–2 Years)

For ethical and technical reasons, many of the general laws and mechanisms involved in the formation of the alveoli and maturation of the alveolar septa have been derived from animal studies. Therefore, the following description of the postnatal lung development is based on experimental findings mainly obtained in the rat lung. Subsequent morphologic and morphometric investigations of human lungs have confirmed

that the postnatal developmental processes do not differ in structural essentials; but, as expected, the timing is different between different species.

At the end of the saccular stage the rat lung goes though a short phase of expansion without any alteration of the parenchymal complexity. The distal airways consist of smooth-walled channels and saccules corresponding to transitory ducts and definitive terminal saccules, respectively. The septa of the saccular parenchyma are thick and contain a double capillary network. They have been called *primary septa* because they represent the basis for the formation of new septa, the secondary septa involved in alveolarization. In many species, among them mice, rats, and humans, alveolarization can be visualized nicely by light and scanning electron microscopy (Fig. 5-10). We have termed this fast and highly visible formation of alveoli during the alveolar stage "bulk alveolarization," to distinguish it from an eventual process of late alveolarization that is much more difficult to detect.

Septation: Alveolarization

The alveoli are formed by lifting off of new tissue ridges from the existing primary septa. In light microscopic sections this process produces a large number of small buds appearing along the primary septa (Figs. 5-10*B* and 5-11*B*). In three dimensions these buds correspond to low ridges representing newly forming septa (Figs. 5-10*D* and 5-12). Soon these low ridges increase in height and subdivide the airspaces into smaller units, the alveoli (Figs. 5-10*D* and 5-11*C*).

It has been proposed that the combination of the three components—myofibroblasts, elastic fibers, and collagen fibrils—provides the critical driving force for septation (Fig. 5-11). Inside to preexisting septa (primary septa) PDGF–receptor-positive smooth muscle cell precursors proliferate and move to the locations in which the new septa will be formed. These cells produce a network of mainly elastic fibers, but also interstitial collagens. During lifting off of the new ridges the contractile cells as well as the fibrous network stay at the tip of the newly forming septa. As indicated by the mechanical stress sensitive expression of tenascin-C at the septal tip this network is supposed to take up mechanical forces.

The alveolar smooth muscle cells or myofibroblasts are required for septation. Alveolarization does not occur in PDGF-A–deficient mice, because these cells do not appear at their normal position and do not deposit the network of elastic fibers. However, it is not known whether these cells are only required for the production of elastic fibers, or whether they exert tractive forces in addition. This question could not be answered by the investigation of elastin null mice, because they do not enter the alveolar stage due to early death.

Folding of Capillary Network

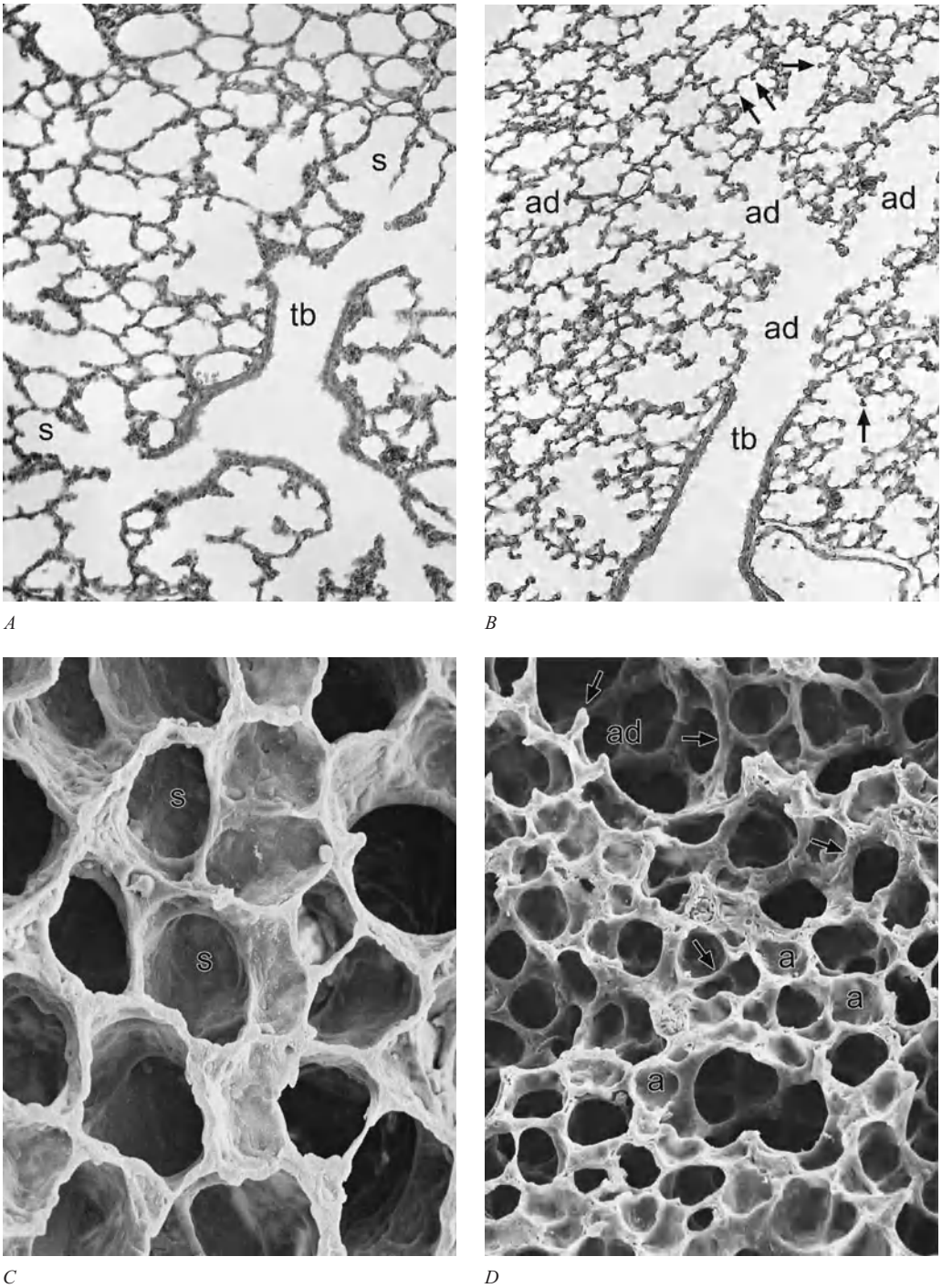
The described network consisting of the smooth muscle cells, elastic fibers, and collagen fibrils is connected to the capillary layer underlying the septal surface. At the locations in which the new ridge will be formed, the capillary layer of the preexisting septum is pulled into the new septum. It gives rise to the double capillary networks within the secondary septa (Fig. 5-11). Wherever lifting off occurs, both types of septa, primary and secondary, now contain two capillary layers, one on each side of a central layer of interstitium. Such thick septa are called "immature" or "primitive" septa to distinguish them from the thin mature septa of adult lungs that contain only a single capillary network. Septation goes along with a tremendous increase in airspace surface area. It is evident that the capillary network has to keep pace with it. If not, septal budding could not occur or forming secondary septa would be devoid of capillaries. This hypothesis was tested by the application of antiangiogenic drugs during the alveolar stage. After a treatment of rats with fumagillin, thalidomide, or Su-5416, respectively, a decrease of the alveolarization by up to 22 percent was observed. In parallel, the pulmonary arterial density decreased by up to 36 percent. This finding emphasizes the importance of vascular growth in the process of alveolarization.

Quantitative Aspects

Morphologic investigations supported by quantitative stereologic analyses have led to the following picture of alveolar formation. Due to the formation of the alveoli, the complexity and also the alveolar surface area are increasing. In simple isotropic growth (expansion of airspaces in proportion to the increase in lung volume), the surface area is expected to increase to the two-thirds power of lung volume. However, in rats the lung volume increases to the power of 1.6. Of interest is that the rapid increase in alveolar surface area is paralleled by changes at the subcellular level in type II cells. The total mass of lamellated bodies is augmented in proportion to the increase in gas exchange surface area; so that lamellar body volume divided by total surface area remains almost unchanged. Interestingly, this means that, if secreted, the lamellar bodies could cover the entire respiratory surface with a film of surfactant that is constant in thickness.

Cell Proliferation

Shortly before and also during the onset of septal formation, DNA synthesis is increased in cells located preferentially in the region of the forming crests. Autoradiographic studies with H_3-thymidine showed that DNA synthesis was high first in the mesodermally derived cells, such as the interstitial and endothelial cells. A few days later (at the age of 1 week), type II cells exhibited the highest activity in DNA synthesis. Within 1 hour after the thymidine injection, not a single type I cell could be labeled, clearly indicating that type I cells are unable to divide. If type I cell labeling could be detected in some experiments, it was always with some delay, which allowed for the differentiation of labeled type II cells into type I cells. At the age of 2 weeks, all labeling indices were back to low levels. Nonetheless, alveolar surface area continued to increase at a high rate during the third week. The morphometric data indicate that this further gain in surface area was obtained by restructuring of the available tissue mass rather than by further proliferative activity.



A *B*

C *D*

Figure 5-10 Alveolarization of rat lung as seen by light microscopy (a + b) and scanning electron microscopy (c + d). *A*. On postnatal day 1, the terminal bronchioles (tb) open into a smooth walled channel dividing into several saccules(s). *B*. On postnatal day 21, the terminal bronchiole (tb) opens now into several generations of alveolar ducts (ad) surrounded by alveoli. Secondary septa have subdivided the channels and saccules (arrows). *C*. As seen by scanning electron microscopy, the lung parenchyma is made of smoothly lined saccules at postnatal day 1. By the formation of the secondary septa (arrows) the smooth walled channels and saccules of panel a have been transformed into alveolar ducts (ad) and alveolar sacs, respectively (postnatal day 21). Both structures are lined with alveoli (a). Light microscopical images, 32 × (a + b), scanning electron microscopical images 460 × (c + d).

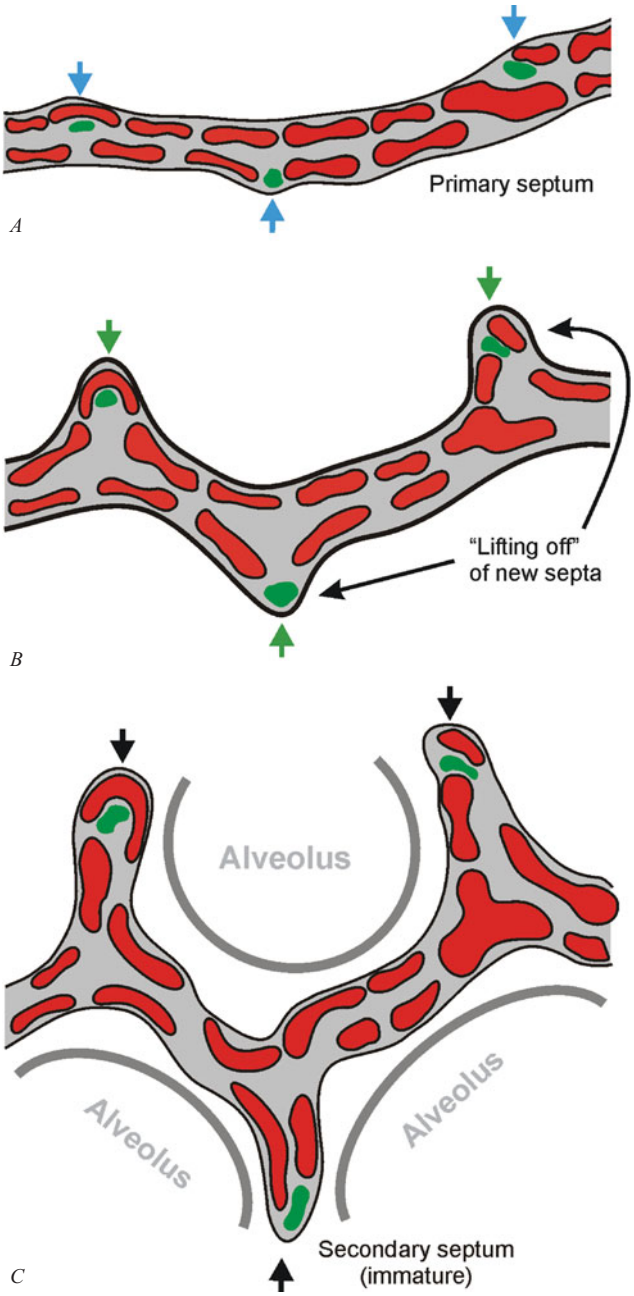


Figure 5-11 Formation of secondary septa/alveolarization. A saccular (or primary) septum contains a double-layered capillary network, where every capillary layer appears as a perforated sheet in sections. Smooth muscle cell precursors, elastic fibers, and collagen fibrils (green spots) accumulate in immature septa at sites where new septa (or secondary septa) will be formed (blue arrows, *A*). Secondary septa are formed by up folding (green arrows) of one of the two capillary layers (red, *B*). As a result, newly formed secondary septa (black arrows) subdivide preexisting airspaces and new alveoli are born (*C*). At this stage, all septa present are immature, showing two capillary layers (= primitive septa). *(Modified from Burri PH: Structural aspects of pre- and postnatal development and growth of the lung, in McDonald J (ed).* Growth and development of the lung. *New York, Dekker, 1997, pp 1–35.)*

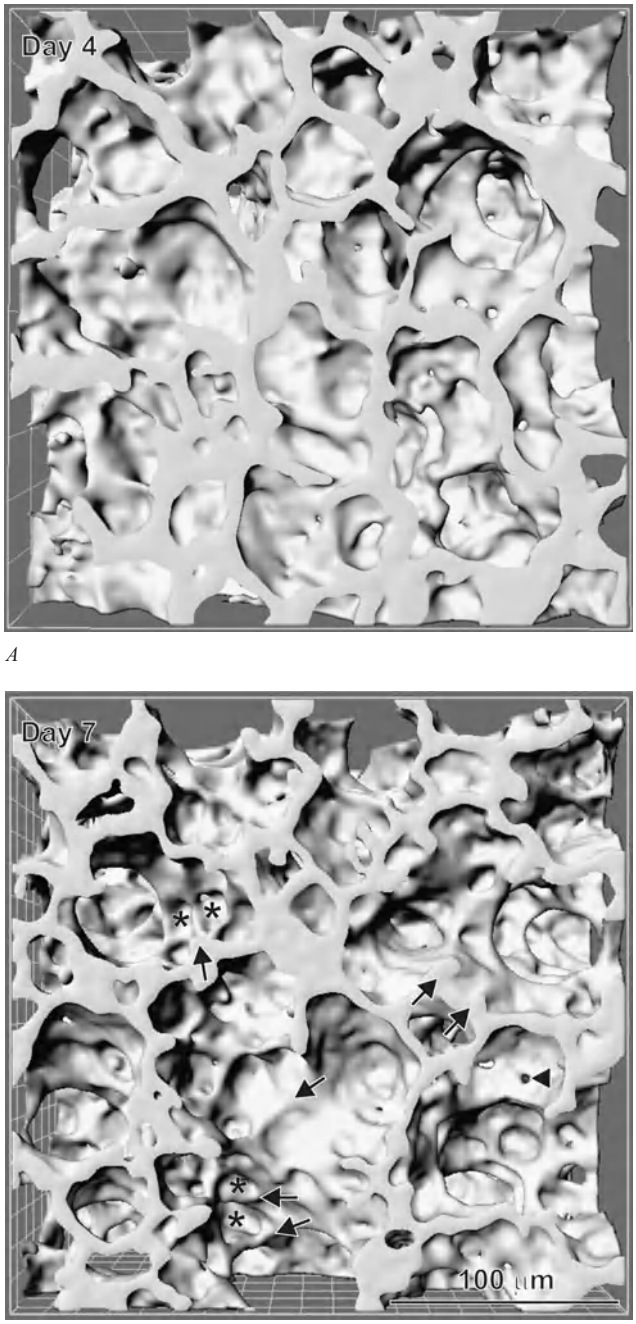


Figure 5-12 Visualization of alveolarization by x-ray tomographic microscopy. Mouse lungs were 3D-visualized by synchrotron radiation x-ray tomographic microscopy just before (postnatal day 4, *A*) and after the beginning of alveolarization (postnatal day 7, *B*). *A*. At the end of the saccular stage large terminal airspaces (saccules) were observed. *B*. Newly formed septa (arrow), which are surrounding newly forming alveoli (asterisk), are visible 3 days later during alveolarization.

Microvascular Maturation Stage (Birth to 2–3 Years)

The essence of this stage is the restructuring of the double capillary networks in the parenchymal septa to the mature aspect with a single capillary system (Figs. 5-13 and 5-14). It is assumed that the latter structure bears functional advantages over the former. Mammalian species with an immature pulmonary microvascular system at birth are mostly of the altricial type, whereas the precocial species such as the sheep are born with mature septa.

The beginning and ending of microvascular maturation are very difficult to access. Septal restructuring is a complex mechanism closely related with growth. In addition, a large overlap with the stage of alveolarization exists. As shown in Fig. 5-15, reporting morphometric measurements of the state of maturity, the rat lung shows already some maturation of the alveolar septa at postnatal day 10, where only one-third of the bulk alveolarization is completed.

Capillary Fusion and Differential Growth

Ultrastructural and morphometric studies in the rat have revealed that the approximation of the two capillary layers was induced by a decrease in the absolute mass of the intercalated septal interstitium. In the third postnatal week the interstitial tissue volume decreased by 27 percent, despite a lung volume increase of 25 percent. The two capillary layers come to lie closer to each other, contact each other, and finally merge their lumina. This happens focally, but in numerous places. However, focal capillary fusions alone would not allow to transform rapidly and extensively the appearance of the interalveolar walls. We proposed that the merged areas were expanded by preferential growth, a process well known in embryology. In summary, microvascular maturation is the result of multiple focal fusions between the two capillary layers combined with preferential growth of the fused areas. By these means large areas of the lung parenchyma can gain the mature aspect within a short period of time.

Programmed Cell Death

In rats the maturation of the alveolar septa does not only lead to a reduction of the absolute mass of the interstitial tissue, but also to a decline of the absolute number of fibroblasts (10–20 percent) and of epithelial cells (greater than 10 percent). We asked how the number of the cells may be reduced and observed that the surplus of fibroblasts is eliminated by classical apoptosis toward the end of microvascular maturation (third postnatal week in rats). Apoptosis is morphologically defined by a typical pattern of structural changes of the dying cells, including the fragmentation of the cell into membrane-enclosed vesicles (apoptotic bodies). Although this happens in the septal myofibroblast population, programmed cell death eliminates the surplus of epithelial cells—mainly type II cells—without the appearance of apoptotic bodies. Most likely alveolar macrophages phagocytose the apoptotic epithelial cells in an early stage of programmed cell death before apoptotic bodies are formed. This peak of cell death disappeared in rats after a short neonatal treatment with glucocorticoids—showing the long-lasting effect of such a treatment.

During microvascular maturation the cell proliferation index stays low. The discrepancy between the rapid growth in surface area and lack of cell proliferation could be explained by an expansion of the type I epithelial cells, meaning that surface area covered by each individual type I epithelial cell enlarges. Because the type II epithelial cells cover only less than 10 percent of the alveolar surface, a reduction of these cells is only important for the production of surfactant and a reduction of the epithelial stem cells. Apparently, a surplus of type II cells exists toward the end of the stage of microvascular maturation. Most likely only type II cells which do not serve as stem cells for the forming of type I cells are removed.

Interalveolar Pores (Pores of Kohn)

Interestingly, the formation of pores of Kohn is closely related to the process of septal thinning. Pores of Kohn represent rounded openings in the interalveolar walls with diameters of a few to several microns. Their frequency varies greatly among species. In the human lung they are not present in the newborn and they appear during postnatal development and growth. Local thinning of the alveolar septa facilitates trans-septal contact of the epithelial cells. The formation of junctional complexes is followed by the reorganization of the cell-cell contacts and retraction of epithelial cells. Finally, the latter leads to the formation of pores. The contacts may be formed by type I-type I and type II-type I cell contacts (for details, see Fig. 5-16). Due to the cuboidal shape of the type II cells the type II-type I contacts contribute more frequently to the formation of a pore than type I-type I cell contacts.

In mice a first peak of pore formation is manifest during the stage of microvascular maturation (third postnatal week). A second peak was observed during the 6th to 10th postnatal week. Because septal thinning continues with further aging of the lung, interalveolar pores may also be formed later, perhaps even up to an older age.

The pores may serve as interalveolar exchange of alveolar liquid, surfactant components, and macrophages. They are filled with surfactant under normal physiological conditions. Tubular myelin may be stored in the pores without increasing the gas diffusion pathway thickness of the active gas exchange surface itself. It is unlikely that interalveolar pores are used for collateral ventilation of alveoli during normal breathing.

In the human lung microvascular maturation starts very early, partly in parallel to alveolarization. At the age of 1 year, large parts of the lung possess already mature septa, but most likely the process goes on till the age of 2 to 3 years. Based on these morphological characteristics we can consider the lung of a 3-year-old child to represent a miniaturized version of the adult one.

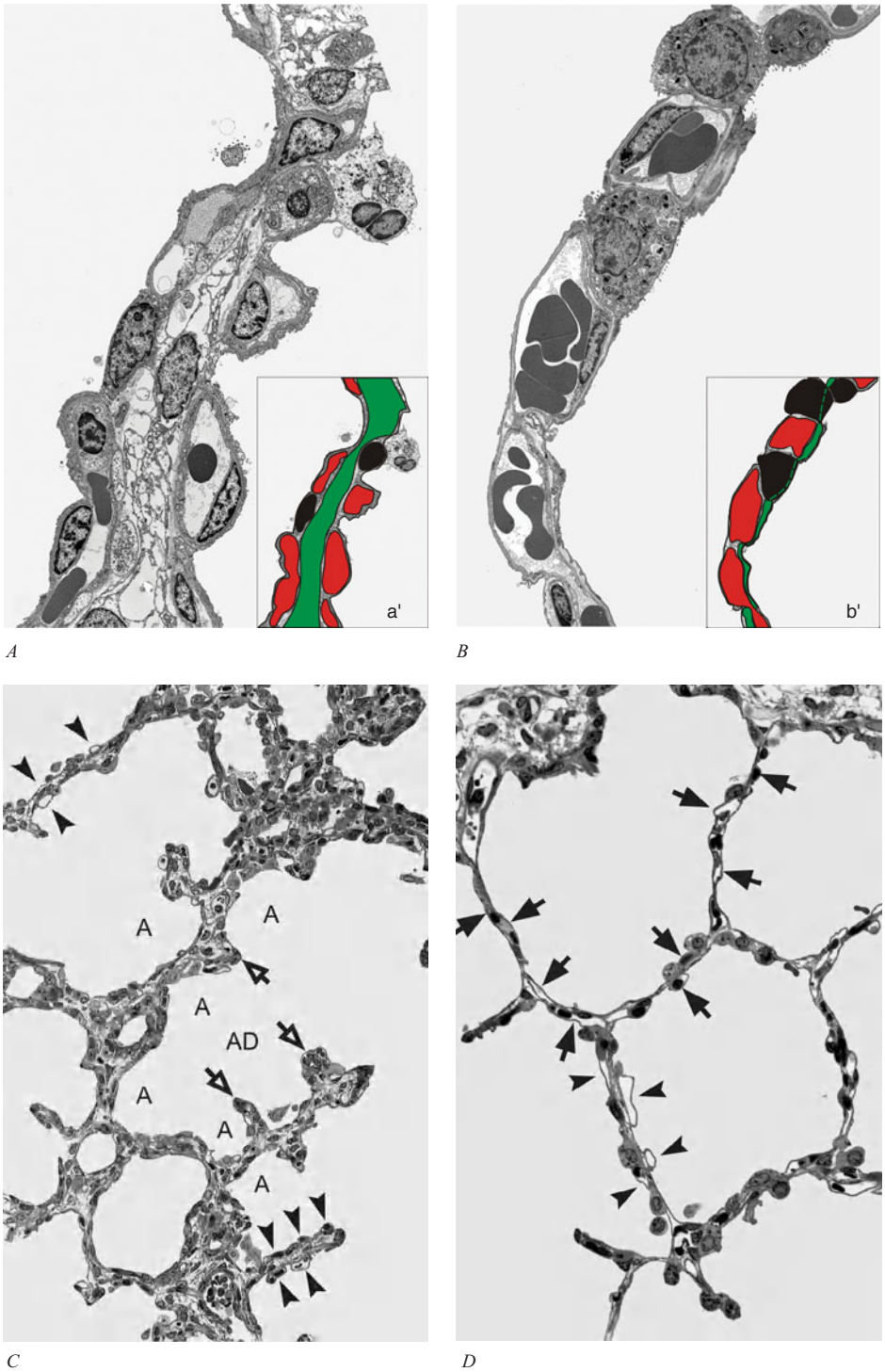
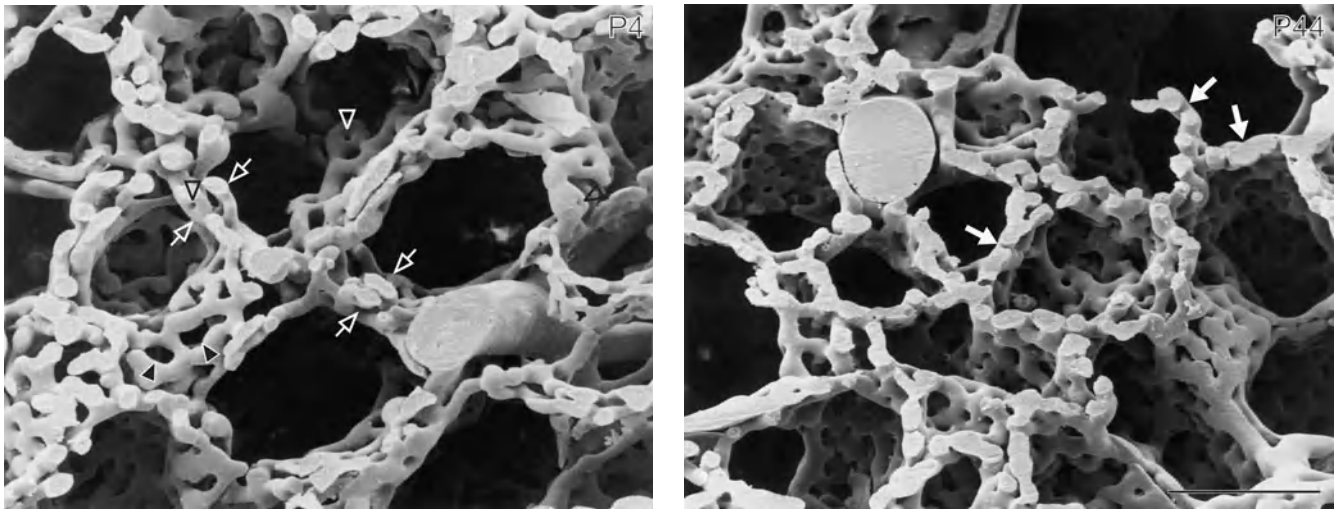


Figure 5-13 Septal maturation during the phase of microvascular maturation. Immature septa contain a double-layered capillary network in which each alveolar surface is served by its own capillary layer. The two capillary layers are separated by a central sheet of interstitial tissue (*A*, electron micrograph of a human lung aged 26 days, 1540×; a′, schematic drawing, capillaries are drawn in red, interstitial tissue in green). Upon maturation the connective tissue layer (green) condenses and thins out so that the two capillary layers merge. The result is a septum where the connective tissue skeleton of the alveolar septum is interwoven with a now single layered capillary network (red/*B*, electron micrograph of an adult human lung, 1540×; b′, schematic drawing). Panels *(C)* and *(D)* show the same development in an overview (light micrographs of human lungs, aged $3^1/_2$ weeks, 250× *(C)* and 5.8 months, 360× *(D)*. *C*. During alveolarization thick immature septa are present that contain a double-layered capillary network (arrowheads) and that are capable to form new secondary septa (open arrows). *D*. During the maturation of the alveolar septa the capillary layers fuse to a single-layered capillary network (closed arrows) that appears alternately on either side of the septum. In some places, immature septa containing a double capillary network are still present (arrowheads).



A *B*

Figure 5-14 Microvascular maturation observed in vascular casts of rat lungs. Scanning electron micrographs of vascular casts (Mercox) of rat lungs are shown at postnatal days 4 *(A)* and 44 *(B)*. The immature septa contain a double capillary network (open arrow, *A*). During maturation the capillaries rearrange and form in most parts of the septa one central single layered capillary network (closed arrows, *B*). The lung capillary networks grow mainly by intussusceptive growth. Slender transcapillary posts (holes less than 2 μm in diameter, open arrowhead, *A*) are introduced into the capillaries and grow out to capillary meshes (closed arrowhead, *A*). Bar, 50 μm. *(From Burri PH: Lung development and pulmonary angiogenesis, in Gaultier C, Bourbon J, Post M (eds).* Lung Disease. *New York, Oxford University Press, 1999, pp 122–151.)*

GROWTH OF THE LUNG

Transition from Development to Growth

Morphometric data obtained from the lungs of seven children aged between 26 days and 5 years and complemented with data from eight adult lungs allow us to distinguish two phases of lung growth. The first phase (from birth to about 18 months) corresponds to the period of ongoing lung development (alveolarization and microvascular maturation) and is therefore characterized by major shifts in the quantitative parameters of the parenchymal compartments. The parameters in close relationship with O_2 transport, the airspace and capillary volumes, grow faster than lung volume, mainly at the expense of the parenchymal tissue mass. The fact that capillary blood volume increases massively during the phase of microvascular maturation is an indication that capillary restructuring is associated with intense capillary growth.

In the second phase (from $1^1/_2$ years until body growth stops), the lung grows in a more proportionate fashion. The lung volume increases to the power of 1 to body weight, and the pulmonary compartments augment linearly with lung volume. Most important, the surface area for gas exchange and the morphometrically determined pulmonary diffusion capacity increase both to the power of 1 to body mass.

Lung Parenchyma: Late Alveolarization

As discussed, the stage of alveolarization represents a very distinct and visible period of lung development with its ongoing bulk alveolarization. It corresponds to a period of intense septation accompanied by a marked increase in gas exchange surface area. The question arises whether alveoli are formed once and for ever or further alveoli are added later at a slower pace and in a much less obtrusive manner during the period of so-called normal growth between the age of three and young adult age. This latter assumption implies that growth of existing structures is complemented by the formation of new interalveolar walls. The question can be important, because of some clinical implications. Acute lung injuries and acute respiratory distress syndromes are common causes of morbidity and mortality in intensive care units. Irrespective of the initial cause of the lung injury, both diseases are characterized by a diffuse damage of the lung parenchyma, which includes a reduction of the diffusion capacity and may lead to a loss of alveolar septa. If the lung were able to produce new alveoli all along childhood, this could favor a late recovery from various forms of structural damage. Furthermore, steroids are widely used during the treatment of lung diseases such as asthma and wheezing illnesses or other diseases such as inflammatory bowel diseases. Retinoids are used for the treatment of psoriasis and severe acne. Both drugs are known to alter the lung structure when given neonatally or during the phase of bulk alveolarization. It is evident that these drugs could have negative side effects on the lung in children and adolescents if alveolar formation is still active.

The reports about the end point of alveolarization in humans are conflicting and have been much debated in the past. So far the limitations of alveolar counting techniques,

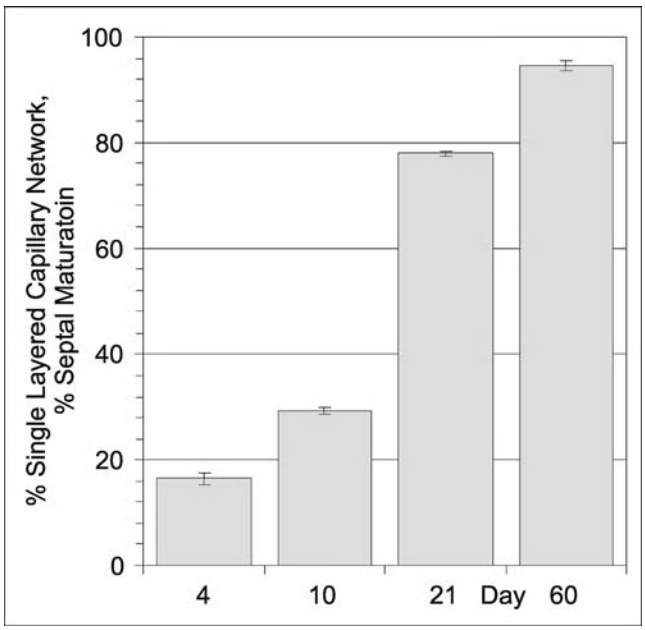


Figure 5-15 Maturation of the alveolar microvasculature. Intersection counting was used to determine the percentage of double- (immature) and single- (mature) layered capillary networks of the inter-airway septa of rat lungs. A basic level of single-layered networks was observed at the end of the saccular stage (day 4). Some maturation of the capillary network is already seen during the phase of alveolarization (day10), which demonstrates the large overlap between alveolarization and microvascular maturation. However, at the end of the phase of microvascular maturation 20 percent of the capillary networks are still immature. Standard deviations are given as error bars. *(From Roth-Kleiner M, Berger TM, Tarek MR, et al: Neonatal dexamethasone induces premature microvascular maturation of the alveolar capfl lary network.* Dev Dyn *233:1261–1271, 2005.)*

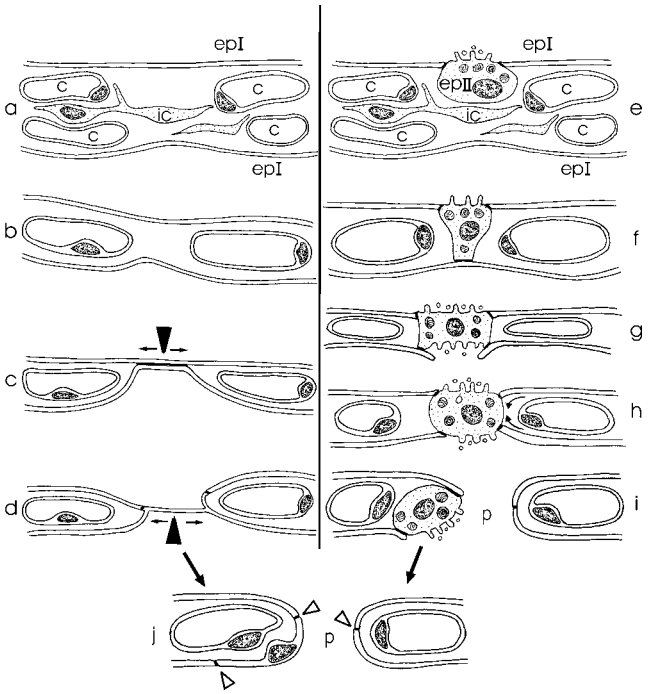


Figure 5-16 Formation of interalveolar pores of Kohn. Interalveolar pores start to form after maturation of the septum (a → b, f). Pores may be formed with (f–i) or without (b–d) the involvement of type II epithelial cells. *A*. Immature interalveolar septum with double capillary network. *B*. Cross section of a part of an interalveolar septum covered by type I epithelial cells (ep I) and containing two capillaries. *C*. Due to a thinning of the septum in the region of a capillary mesh, the connective tissue disappears in a spot like area and permits a contact between the type I cells resting on both surfaces of the septum. After rupture (arrowhead) the cell margins withdraw (arrows) and only one leaflet of one of the type I cells remains. *D*. The same process happens again (arrowhead and arrows) resulting in the formation of an interalveolar pore (i). *E*. Type II epithelial cells may also be involved in the formation of interalveolar pores. In a first step a type II cell makes a contact to a type I cell resting on the opposite side of the septum. *F*. The type II cell becomes also integrated into the epithelium opposite of its original side. *G*. In parallel to the retraction of the type II cell the two leaflets of the type I cells move toward each other. *H*. While forming the type I cell-cell junction the type II cell retracts completely and gives rise to a new pore. *I*. Finally, the type II cell is shifted along the septum and thus leaves the immediate vicinity of the pore. Alternatively, it may stay there or differentiate into a type I cell. Cellular junction running all around the pore (open arrowhead). c, capillary; ep I, type I epithelial cells; ep II, type II epithelial cells; ic, interstitial cell; p, pore. *(Based on Weiss M, Burri PH: Formation of interalveolar pores in the rat lung.* Anat Rec *244:481–489, 1996.)*

genetic and environmental induced variations on lung growth, and statistical constraints have not permitted collection of enough representative age-dependent data. Early studies have postulated an increase in alveolar number up to the age of 20 years. Successively this age has been brought down to about 11 or 8 years and then even to 2 years.

There is evidence that additional alveoli are formed in rats after the early phase of bulk alveolarization is completed. It has been postulated that this kind of later formation of alveoli takes place by means other than septation. Subpleural areas have been found to be preferred sites for the late addition of new alveoli. It was also estimated that in normal growth the number of alveoli increased by a factor of 2 after completion of bulk alveolar formation.

In view of these observations we may question the classical mechanisms of alveolar formation described in the preceding. Does the morphologic concept of alveolarization need to be revised or complemented? Are there other mechanisms of septation, in particular during so-called "late alveolarization"? Can the genetic program of lung development be delayed or even reverted under certain conditions? Or does the original concept of capillary up-folding still hold? Even in late alveolarization?

With the following considerations we would like to shed some light on these questions.

1. Disseminated interalveolar septa with an immature aspect can be found even in adult lungs. They could represent sites of focal alveolar formation (Fig. 5-13 *D*).
2. In a study in which rats were treated neonatally with high doses of glucocorticoids early, the authors observed a focal premature microvascular maturation

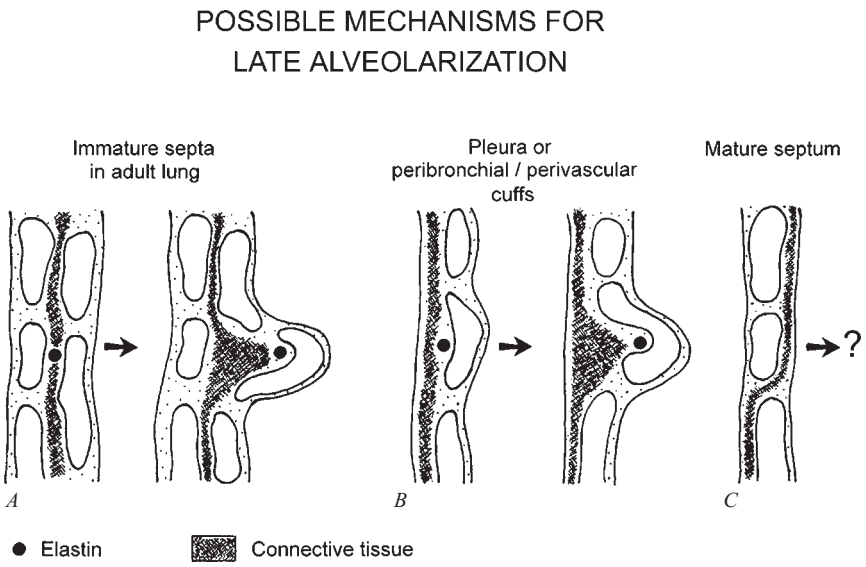


Figure 5-17 Possible mechanisms of late alveolar formation. *A*. Classical mode with lifting off of a capillary network in an immature type septum. Immature septa are still found dispersed in adult lungs. *B*. Classical mode applied in the uttermost lung periphery. *C*. Yet undefined angiogenic mechanism of capillary duplication occurring in mature septa (authors' unpublished observations). *(From Burri PH. Structural aspects of postnatal lung development – alveolar formation and growth*. Biol Neonate *89:313–322, 2006, with permission.)*

(27 percent mature single-layered capillary networks in treated rats versus 16 percent ones in controls), transient septal thinning, and transient inhibition of alveolarization. Following the withdrawal of the drug, the induced structural changes were readily compensated. By postnatal days 36 and 60 the lungs had almost completely recovered from the early insult. This suggests a high plasticity of alveolarization.

3. In the lung periphery, i.e., underneath the pleura and around the adventitial layer of the bronchi and blood vessels, the capillary network involved in gas exchange rests on a sheet of connective tissue. In these regions the capillary layer can be folded up in a manner resembling closely the classical mode of alveolarization (Figs. 5-7*C*, 5-17, and 5-18). For geometrical reasons the lung periphery makes up a high proportion of the total lung volume, especially in smaller lungs. In an adult rat lung a subpleural tissue mantle of 2-mm thickness represents almost 50 percent of the parenchymal lung volume. Therefore, the subdivision of peripheral airspaces can be very effective in increasing alveolar number.
4. There is recent evidence that capillary up-foldings can even be formed in mature rat septa thanks to local duplications of the capillary network at the base of the fold. This has been demonstrated in casts of rat lungs using synchrotron radiation x-ray tomographic microscopy allowing a 360-degree inspection of the critical sites (Schittny, unpublished data).

Conducting Airways

Unlike the lung parenchyma, the structure of the conducting airways is largely mature at birth—except perhaps for the terminal bronchioles, part of which may transform into respiratory bronchioles, as described by Boyden. Whereas the branching pattern does not change with age, it is not clear whether the bronchial tree grows proportionately after birth. In one study, the relationship between diameter and relative distance from the hilum was found to remain almost constant with age. In another analysis, this was true only after the age of 1 year, whereas during the first year of life, the larger bronchi showed a faster growth rate than the smaller conducting airways. Detailed studies of the airway epithelium of hamsters and rhesus monkeys indicate that the airway lining is largely mature at birth. Although there is some postnatal functional maturation, most developmental changes occur before birth.

Arteries and Veins

During fetal life, blood flow through the lung is limited to between 10 and 15 percent of the cardiac output. Clearly, the most important vascular event accompanying the onset of air breathing is the closure of the ductus arteriosus and the shunting of the entire cardiac output through the lung.

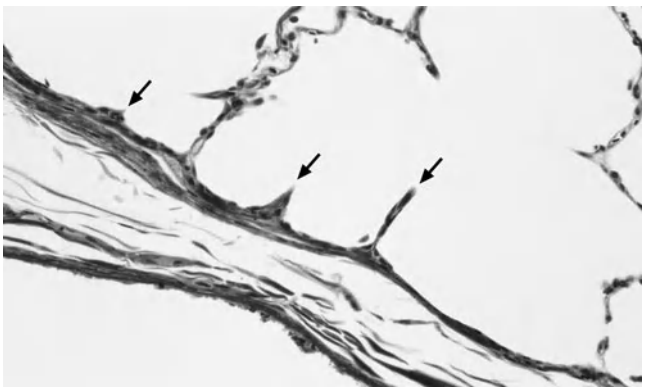


Figure 5-18 Subpleural region of human lung. Pleural interalveolar septa of varying heights. Arrows point to hypothetical sites of late alveolarization. Light micrograph, 320×. (*From Burri PH: Structural aspects of postnatal lung development–-alveolar formation and growth*. Biol Neonate *89:313–322, 2006, with permission.)*

The ductus arteriosus, first obstructed by muscular contraction, is anatomically closed within a few weeks by the fibrotic organization of an intravascular clot. The ligamentum arteriosum represents the tombstone of this important prenatal structure.

After birth, the wall thickness of pulmonary arteries decreases relative to their diameter. In small vessels (up to 200 μm in diameter), this decrease occurs very rapidly. It was assumed that it was due to a fall in smooth muscle tone. A study performed in pigs, however, related the vascular dilatation more to a concurrent extensive rearrangement and shape change of the vascular smooth muscle cells than a change in muscle tone. A similar adaptation has been noted in the small arteries of the human lung, with the structural remodeling being most rapid during the first month of life. In the larger arteries in humans, the thinning of the wall occurs less abruptly: The transformation is achieved by structural adaptations and therefore takes several months. After 1 year of age, the central pulmonary arteries no longer change their relative wall thickness appreciably; instead, they grow more or less proportionally.

Although the central vessels that accompany the conductive airways do not multiply after birth, the situation is completely different for the peripheral vessels. During the first 1 or 2 years of life, intra-acinar arteries undergo intense development and growth as they follow the extension of the peripheral airspaces. The number of small vessels therefore increases both absolutely and relatively. The relative increase

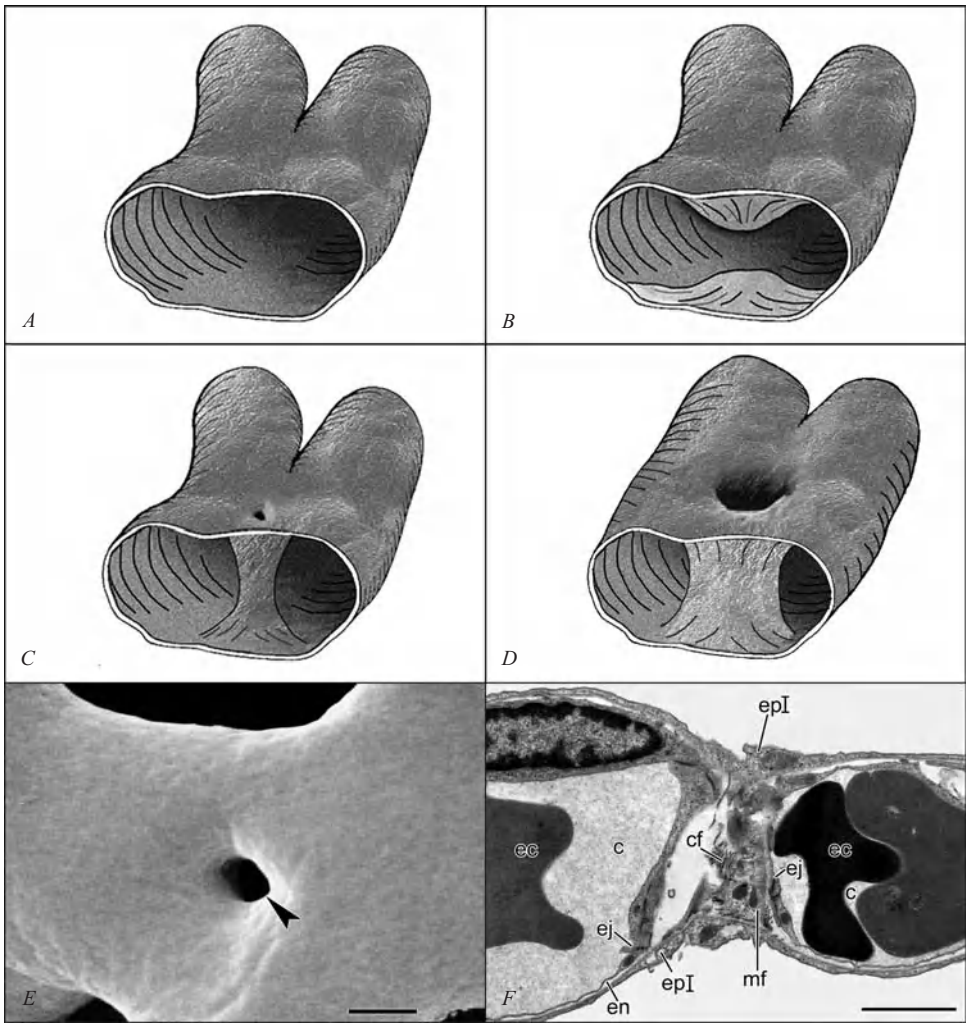


Figure 5-19 Intussusceptive capillary growth. *A–C.* During intussusceptive capillary growth the number of segments, the surface area, and the volume of an existing capillary network increases by the insertion of new transluminal tissue pillars. *D.* After formation, the pillar enlarges to form a new mesh. *E.* A Mercox cast of the alveolar microvasculature. Pillars appear as tiny holes, often in the range of 1.5 μm in diameter (scanning electron micrograph, ×5850, bar 2 μm). *F.* A longitudinal section of a transcapillary tissue pillar. The pillar structure exhibits a central axis formed by the cytoplasmic extension of a myofibroblast (mf) with actin filaments, and some collagen fibrils (cf); c, capillary; ec, erythrocyte; ej, endothelial cell junctions; en, endothelial cell; epI, type I cell (electron micrograph, ×9400, bar 2 μm). *(Panels A–D are based on Kurz H, Burri PH, Djonov VG: Angiogenesis and vascular remodeling by intussusception: From form to function.* News Physiol Sci *18:65–70, 2003.)*

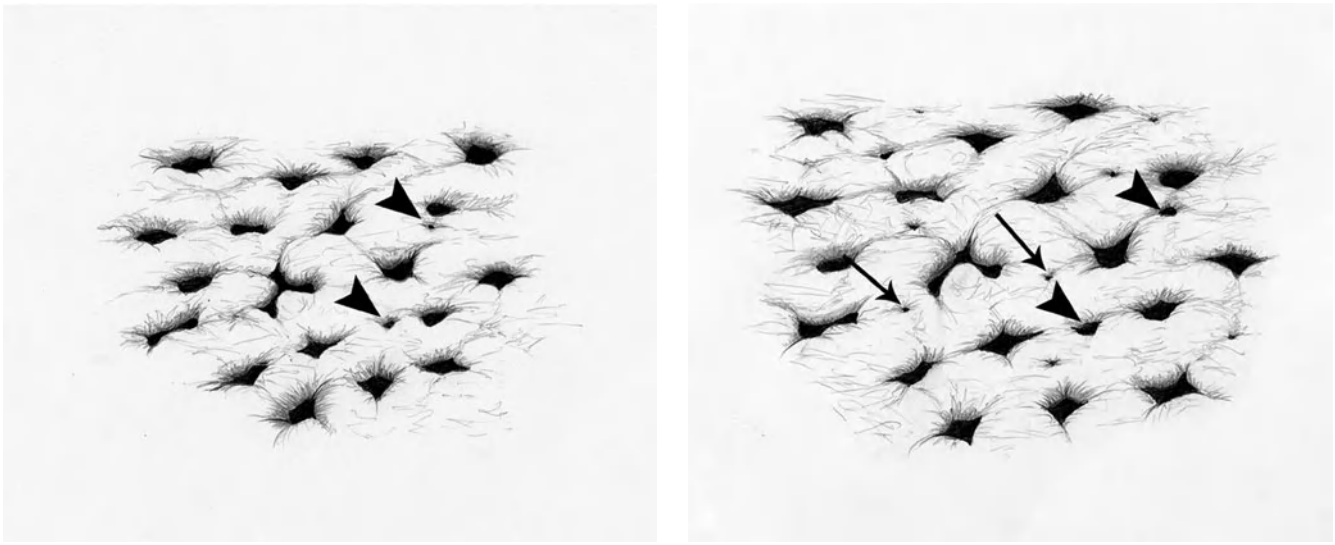
implies that their number augments per unit area of lung section. From the age of 5 years on, the relative number decreases again, reflecting the enlargement of the alveoli. The newly formed vessels are thin walled and are partly muscular or non-muscular, because muscle formation lags behind the increase in diameter. Gradually, muscularization then proceeds toward the periphery, a process that continues into adulthood.

Veins have a smaller amount of smooth muscle than do arteries. However, in principle, the same observations apply to veins as well as arterial development and growth.

Growth of the Lung Microvasculature

Interestingly, both in rats and humans, lung volume was found to increase about 23 times between birth and young adulthood. In both species lung microvasculature grows even more: The capillary volume increases by a factor of 35, whereas the capillary surface area augments about 20 times. Furthermore, scanning electron microscopy of microvascular casts reveals that the capillary meshwork in the interalveolar walls remains at the same high density, which means that all along growth the capillary system expands through the addition of new capillary segments, i.e. by angiogenesis. Angiogenesis is defined as the formation of new vascular segments from preexisting vessels. The classical concept for the expansion of the capillary networks in growing organs was vascular sprouting. Sprouting angiogenesis is characterized by a number of typical steps: local vasodilatation, increased vascular permeability, proteolytic degradation of basal laminas, proliferation and migration of endothelial cells, and formation of a solid sprout, which then is reorganized into a tubule. Finally, the new tubule connects to a neighboring vessel.

While we were investigating the capillary maturation in lung development by studying vascular casts in the scanning electron microscope, one of us (Burri) observed numerous tiny holes sometimes less than 1.5 µm in diameter (Fig. 5-19*E*). We hypothesized that these holes could represent newly formed intercapillary meshes (or "baby meshes"). By repetitive insertion of such tiny meshes, which then would grow and expand to normal-sized capillary meshes, the network would increase in surface area and gain in complexity (Fig. 5-20). Although this concept was first based on observations of casts alone, it was clear that matching structures had to be found in interalveolar walls at the ultrastructural level. The holes in the cast should correspond to some form of tissue pillars traversing the capillary lumina. By electron microscopic investigation of serial sections through the interalveolar septa, we demonstrated indeed the presence of tissue pillars of adequate diameters (Fig. 5-19*F*). The analysis of their ultrastructure allowed us to derive a plausible mechanism for their formation. As depicted in Fig. 19*A–D*, the classical formation of a transcapillary tissue pillar is a four-step process: (1) formation of symmetrical or asymmetrical protrusions from opposite parts of the capillary (Fig. 5-19*B*), which join and create a zone of inter-endothelial cell contact; (2) following reorganization of the inter-endothelial cell junctions the contact zone is centrally perforated: a transcapillary pillar of tissue is formed (Fig. 5-19*C*); (3) invasion of the pillar core by cell processes of pericytes and myofibroblasts, thus stabilizing the pillar structure (Fig. 5-19*F*); (4)



A *B*

Figure 5-20 Drawing of intussusceptive microvascular growth of a capillary layer. While the alveolar capillary networks are growing, the size of the capillary meshes stays quite constant. To achieve this, pillars are inserted into the capillaries (arrows) by intussusceptive angiogenesis. *A–B*. Two schematic drawings of consecutive stages of intussusceptive capillary growth. While newly formed pillars are growing in size (arrowheads in *A* and *B*), additional pillars are inserted into existing capillaries (arrows in *B*). Notice the larger surface covered by the capillary network in *(B)* than in *(A)*. The schematic drawing is based on scanning electron micrographs of vascular casts. *(From Burri PH, Hlushchuk R, Djonov V: Intussusceptive angiogenesis: Its emergence, its characteristics, and its significance.* Dev Dyn *231:474–488, 2004.)*

the pillar grows in diameter (Fig. 5-19 *D*) and finally becomes a normal-sized intercapillary tissue mesh.

We termed this new process of capillary growth intussusceptive microvascular growth (IMG). In histology, the term is commonly used to describe the growth of cartilage, which also grows within itself. Intussusception means "addition of new, but similar elements of formative material among those already present." Since its discovery in 1986, IMG has been well documented in numerous species and various organ systems. In tumor growth, IMG appears to play an important role besides sprouting angiogenesis and may be responsible for the failure of some antiangiogenic treatments targeting sprouting vessels.

This new "non-sprouting" intussusceptive angiogenesis has some advantages over the sprouting form: It is fast (hours versus days); it is not based on cell divisions in a first step; it is less leaky than sprouting; and it is efficient, because it happens while the blood is circulating through the vessel. However, it cannot bridge vascular gaps, such as cuts of the skin or scars.

Recent work has emphasized the significance of the intussusception process in demonstrating that besides capillary growth it was involved in the de novo formation of vascular trees and optimizing vascular branching geometry, and vascular pruning (for review, see Burri and Djonov).

Dimensions of the Adult Lung

Table 5-2 summarizes the relevant data for a "standard" adult human lung. In a direct comparison of quantitative data of adult and newborn lungs, it is manifest that lung structure is far from representing a tissue framework of stable composition. So, with age, the volume density (volume per lung volume) of interalveolar septa decreases, the volume density of the airspace increases, and, within the interalveolar walls, the volume fraction of the blood vessels increases at the expense of the tissue volume. Although the arithmetic mean thickness of the air-blood tissue interface (calculated by dividing total tissue mass by the alveolar surface area) falls from around 5 μm at birth to 2.5 μm in the adult, the functionally more relevant harmonic mean thickness of the air-blood tissue barrier, a measure of the average effective diffusion distance, remains largely unaffected by the structural alterations of postnatal development.

Despite the lung undergoing extensive structural remodeling during development and growth, the gas exchange surface areas of airspaces and capillaries increase linearly with body weight. This fact illustrates that the implemented structural alterations are always well balanced to constantly meet the O_2 needs of the organism throughout lung development.

Table 5-2

Dimensions of the Human Lung Based on Morphometry

Lung volume, l	4.3 ± 0.3
Volume of compartments	
Parenchyma, l	3.9 ± 0.3
Parenchymal tissue, ml	298 ± 36
Parenchymal capillaries, ml	213 ± 31
Surface areas	
Airspace, M2	143 ± 12
Capillary, m2	126 ± 12
Body weight, kg	74 ± 4

Values represent mean values ± standard errors of eight human lungs. Source: Data from Crapo JD, et al: Cell numbers and cell characteristics of the normal human lung. Am Rev Respir Dis *126:332–337, 1982; Gehr P, Bachoten M, Weibel ER: The normal human lung. Ultrastructure and morphometric estimation of diffusion capacity.* Respir Physiol *32:121–140, 1978.*

ACKNOWLEDGMENTS

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6

Cellular and Molecular Mechanisms Regulating Airway Smooth Muscle Physiology and Pharmacology

Reynold A. Panettieri, Jr.

Evidence suggests that airway smooth muscle, the most important cell modulating bronchomotor tone, plays an important immunomodulatory role in the orchestration and perpetuation of airway inflammation. The signaling pathways that modulate leukocyte function may be disparate from those found in resident effector cells such as airway smooth muscle, fibroblasts, and epithelial cells. Further investigation and understanding of the pivotal signaling pathways that modulate airway smooth muscle cell shortening, secretion of chemokines/cytokines, and expression of cell adhesion molecules may offer new therapeutic approaches to the treatment of asthma.

Traditionally, airway smooth muscle (ASM) in asthma was perceived as a purely contractile tissue, but new evidence challenges this concept. ASM cells play an important role, not only in regulating bronchomotor tone, but also in the perpetuation of airway inflammation and the remodeling of the airways. This chapter discusses excitation-contraction coupling and the newly identified functions of ASM cells: the synthetic function of ASM cells, defined as the ability to secrete immunomodulatory cytokines and chemokines and express surface receptors that are important for cell adhesion and leukocyte activation as summarized in Fig. 6-1. Pharmacologic approaches to modify the synthetic function of ASM

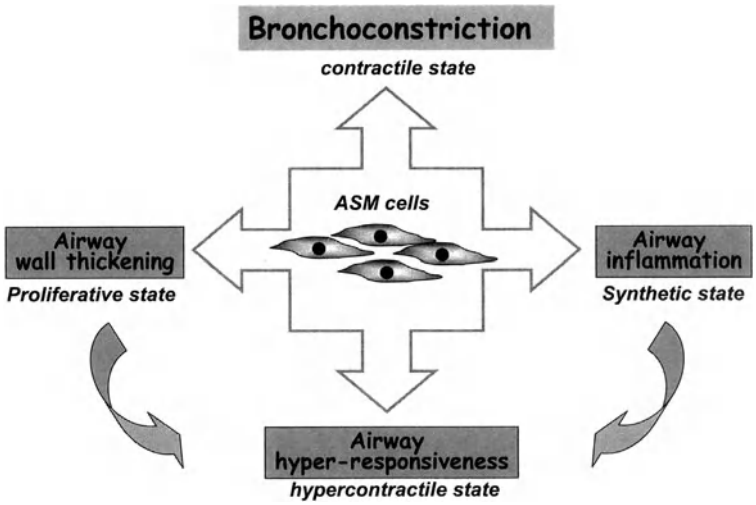

Figure 6-1 Proposed model for the pathological roles of airway smooth muscle (ASM) in lung diseases. The primary function of ASM is to regulate the bronchomotor tone in response to contractile agonists. ASM responsiveness is influenced by a variety of internal factors (contractile proteins, cell hyperplasia) and external stimuli (mechanical forces, extracellular matrix, nerves). In chronic airway diseases where there is an imbalance between these factors, ASM activity will likely be impaired. The degree of bronchoconstriction could be exacerbated by an increase in ASM mass that augments the degree of the airway wall narrowing. Structural changes that alter the forces imposed on ASM or inflammatory agents that alter the intrinsic properties of the ASM may induce airway hyperresponsiveness. By the ability of ASM to secrete a variety of pro-inflammatory mediators, ASM also may regulate airway inflammation, which in turn can affect both contractile and proliferative phenotypes. *(Used with permission from Amrani Y, Panettieri RA: Airway smooth muscle: Contraction and beyond. Int J Biochem Cell Biol 35:272, 2003.)*

cells and how altered synthetic function may contribute to airway remodeling also are discussed.

ASTHMA AND AIRWAY SMOOTH MUSCLE SHORTENING

Asthma is characterized by a nonspecific bronchial hyperresponsiveness (BHR) and is defined as excessive narrowing of airways in response to a variety of contractile agonists. Elucidating the molecular mechanisms that induce and/or maintain BHR will undoubtedly provide insight for the design of new treatments for chronic airway diseases. Evidence suggests that shortening of ASM in response to G protein–coupled receptor (GPCR) stimulation regulates airway caliber and bronchomotor tone. ASM shortening then is initiated by increases in cytosolic Ca^{2+} concentrations and the subsequent activation of the contractile apparatus, including the phosphorylation of myosin light chain (MLC) 20. A variety of stimuli such as inflammatory cytokines, pollutants, mechanical strain, and some therapeutic agents prime the ASM to become "nonspecifically" hyperresponsive to contractile agonists. Allergens and some, but not all, cytokines promote ASM responsiveness to contractile agonists. Tumor necrosis factor α (TNFα) and interleukin (IL)-13 enhance murine ASM contractile responses to carbachol without affecting changes in receptor affinity, suggesting modulation of ASM responsiveness at a site downstream from receptor activation. Repeated allergen challenge also may alter expression of different contractile proteins and increase ASM contractility. Changes in the mechanical properties of ASM (i.e., cytoskeleton reorganization) increase ASM contractile responsiveness by prolonging ASM shortening or inducing sustained mechanical strain. The precise molecular mechanisms defining such augmented ASM contractility remain unknown.

Calcium Signaling: A Potential Target for Modulators of ASM Responsiveness

Because of the central role of Ca^{2+} in regulating ASM contractile function, many investigators have focused on Ca^{2+} regulatory mechanisms in ASM. Using cultured human tracheal or bronchial smooth muscle cells as in vitro models of ASM responsiveness, GPCR-associated signaling in ASM can be modulated by a variety of inflammatory stimuli. Cytokines, such as TNFα, augment agonist-induced ASM contractility by enhancing, in a nonspecific manner, agonist-evoked Ca^{2+} transients to bradykinin and carbachol. Similarly, ASM cells derived from hyperresponsive inbred rats have augmented bradykinin-induced Ca^{2+} responses when compared with ASM cells derived from normoresponsive rats. IL-13, an important mediator in allergic asthma, also nonspecifically increased Ca^{2+} responses to contractile agonists. Together, these data suggest that "pro-asthmatic" cytokines, in a nonspecific manner, modulate GPCR-associated Ca^{2+} responses in ASM—a mechanism likely to affect ASM contractility (Fig. 6-2).

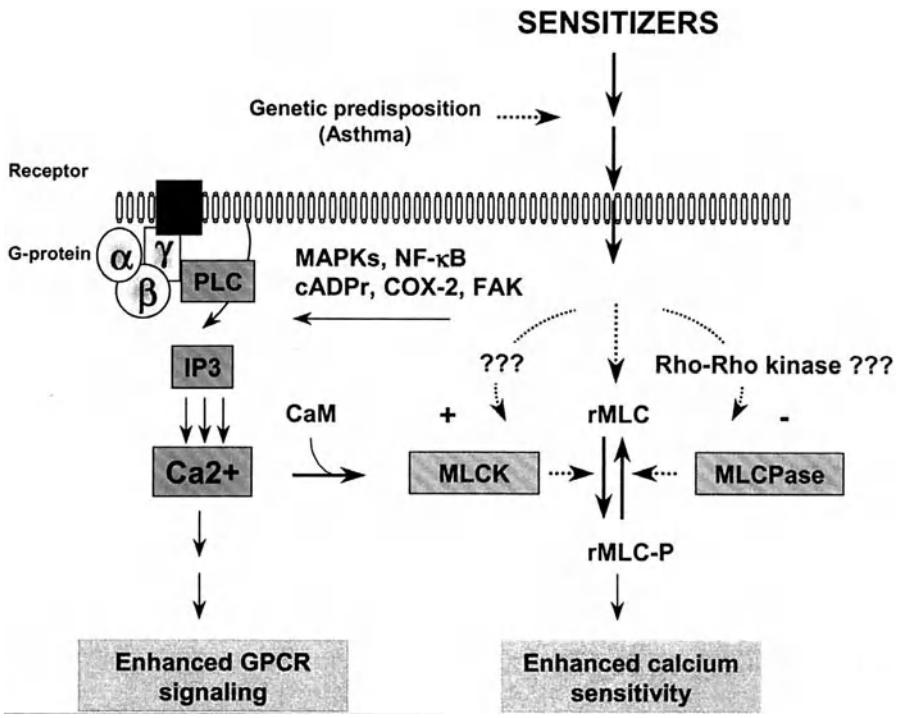

Figure 6-2 Hypothetical model of the potential intracellular mechanisms involved in the modulation of ASM hyperresponsiveness in asthma. In chronic asthma, ASM is exposed to a variety of sensitizers, defined as conditions that increase ASM contractile responses to agonists, such as allergen, inflammatory cytokines and proteins, activated T lymphocytes, therapeutic agents, and pollutants. Based on current evidence, sensitizers may act in concert to modulate ASM reactivity by activating two major intracellular pathways. Some cytokines may increase ASM contraction by enhancing G protein–coupled receptor (GPCR)–associated calcium (Ca^{2+}) responses, an effect that was shown to be regulated by multiple different signaling pathways, such as mitogen-activated protein kinases (MAPKs), nuclear factor-κB (NF-κB), cyclic ADP-ribose (cADPr), and the focal adhesion kinase (FAK). This may occur via the Rho-Rho kinase pathway, which has been shown to enhance the level of myosin light chain (MLC) phosphorylation by inhibiting the activity of MLC phosphatase (MLCPase). Increases in cyclooxygenase (COX)-2 and phospholipase (PL)A_2 expression or activity have also been found to be involved in the modulation of GPCR-associated Ca^{2+} responses. Sensitizers such as other cytokines also may enhance ASM contraction by increasing the sensitivity of the contractile apparatus to Ca^{2+}, which increases the amount of force produced for a given cytosolic concentration of Ca^{2+}. Many studies showed the important role of Rho-Rho kinase pathways, which inhibit the activity of MLCPase and increase MLC phosphorylation. Increases in MLC kinase (MLCK) content or activity, as reported in human sensitized ASM, also may play a potential role in increasing ASM contractile activity; however, the underlying mechanisms are as yet unknown. CaM, calmodulin; IP_3, inositol-1,4,5-trisphosphate; rMLC, regulatory light chains of myosin II. P, phosphorylation. *(Used with permission from Amrani Y, Panettieri RA Jr: Modulation of calcium homeostasis as a mechanism for altering smooth muscle responsiveness in asthma. Curr Opin Allergy Clin Immunol 2:39, 2002.)*

Potential Molecular Mechanisms Underlying ASM Hyperresponsiveness: Increased RhoA/Rho Kinase Pathway Activation

Differences in ASM contractility observed among different mouse strains (e.g., C3H/HeJ, Balb/C, and A/J) may involve mechanisms that are independent of agonist-induced Ca^{2+} responses and, instead, involve modulation of Ca^{2+} sensitivity of the contractile apparatus. A possible mechanism for such effects involves the small monomeric G protein Rho, which can augment ASM contractility by increasing levels of MLC phosphorylation via Rho-activated kinase-dependent suppression of MLC phosphatase as shown in Fig. 6-2. Activation of RhoA and Rho-activated kinase by a variety of stimuli, including cytokines, sphingolipids, and mechanical stress, is associated with the development of BHR. Conceivably, abnormal RhoA activity and/or expression may dramatically alter ASM contractility, not only via Ca^{2+} sensitization but also through increased expression of Rho-dependent contractile proteins.

Persistent Activation of β_2-Adrenergic Receptors

Despite the utility of β-agonists in treating acute bronchoconstriction in asthma, persistent activation of β_2-adrenergic receptors can alter BHR by increasing ASM responsiveness to contractile agonists. Overexpression of β_2-adrenergic receptors in ASM enhances agonist-induced bronchoconstrictive responses both in vivo and in vitro. Conversely, ASM from β_2-adrenoceptor–deficient mice showed reduced

agonist-induced inositol phosphate turnover and isometric force. Together, these data suggest that $G\alpha_q$-coupled receptors and $G\alpha_i$-coupled receptors in ASM are functionally linked, possibly leading to increased expression of phospholipase C-β by β_2-adrenergic receptor activation. Such observations might provide a plausible explanation for the findings that chronic use of β-agonists can worsen asthma control.

Emerging evidence shows that changes in ASM contractile properties play an important role in the development of BHR associated with chronic airway diseases such as asthma. In vitro studies support the concept that a variety of conditions including physical stimuli (e.g., repeated exposure or long-term stimulation) or chemical stimuli (e.g., cytokines) augment the contractile force generated by ASM by acting on multiple key pathways. These pathways include aberrant activation of contractile and relaxant receptors, an altered function of Ca^{2+} regulatory signaling molecules, and a reorganization of the cytoskeletal apparatus. Understanding the signaling pathways involved in excitation-contraction coupling and contractile protein expression and function in ASM therefore may offer potentially new targets for the treatment of bronchial hyperresponsiveness.

AIRWAY SMOOTH MUSCLE HYPERTROPHY AND HYPERPLASIA

Accumulating evidence suggests that asthma may develop into a progressive and irreversible disease. Subjects with asthma have a greater decline in pulmonary function as compared with normal subjects and may manifest persistent airways hyperresponsiveness even after prolonged corticosteroid therapy. Furthermore, morphometric studies in subjects with asthma have revealed structural remodeling in the airways, with reports of airway wall thickening observed at postmortem as compared with that obtained from subjects without asthma. Collectively, the term airway remodeling now refers to increases in ASM mass as well as submucosal fibrosis, airway epithelial desquamation and vascular alterations. Because increased airway wall thickening decreases airway caliber, airway remodeling may enhance airway narrowing seen in asthmatics. Although numerous cell types contribute to airway remodeling, current evidence, using sophisticated modeling techniques, suggests that the increase in ASM mass has the greatest impact on airway narrowing in asthma.

Increases in ASM mass observed in the bronchi of subjects with chronic severe asthma appear to be due to increases in cell number (hyperplasia) and increases in cellular size (hypertrophy). Although hypertrophy of ASM may play an important role in airway remodeling, regulation of ASM hyperplasia is considered an attractive therapeutic target for the potential treatment of airway remodeling and irreversible airflow obstruction in subjects with asthma, as shown in Fig. 6-3.

Despite considerable efforts in the discovery of new anti-inflammatory and bronchodilator agents, the development of anti-remodeling drugs remains in its infancy. Further, specific biomarkers that are readily accessible to investigators that would quantitate ASM hyperplasia remain elusive and, as such, the discovery of drugs to specifically treat airway remodeling remains problematic. Over the past decade, researchers have utilized cell culture techniques to elucidate the cellular and molecular mechanisms underlying ASM cell proliferation and identify the critical cell cycle events that regulate ASM cell growth. Further, new animal models that appear to mimic airway remodeling occurring in human asthma have been used in hopes of designing therapies to prevent or abrogate airway remodeling.

Mediators of Airway Smooth Muscle Proliferation In Vitro

Many inflammatory mediators are found in bronchoalveolar lavage fluid (BALF) from asthmatic airways, and some induce ASM proliferation in vitro. To date, mitogenic or co-mitogenic stimuli include: growth factors, such as epidermal growth factor (EGF), insulin-like growth factors, platelet-derived growth factor (PDGF) isoforms BB and AB and basic fibroblast growth factor; plasma- or inflammatory cell-derived mediators, such as lysosomal hydrolases (β-hexosaminidase and β-glucuronidase), α-thrombin, tryptase, lysophosphatidic acid, and sphingosine 1-phosphate (S1P); and contractile agonists, such as histamine, endothelin-1, substance P, phenylephrine, serotonin, thromboxane A_2, and leukotriene D_4 (LTD_4). Collectively, data suggest that some, but not all, agonists that activate GPCRs alone promote human ASM cell proliferation. However, any contractile agonist that increases cytosolic calcium appears to augment growth factor-induced human ASM mitogenesis.

Although the cytokines interleukin-1β (IL-1β), IL-6, and tumor necrosis factor α (TNFα) are also increased in BALF of subjects with asthma, whether these cytokines stimulate ASM proliferation in vitro remains controversial. IL-1β and IL-6 induced hyperplasia and hypertrophy of cultured guinea pig ASM cells; however, others have shown that IL-1β and IL-6 are not mitogenic for human ASM cells. TNFα has no immediate mitogenic effect on human ASM cells; however, the proliferative effect of TNFα on human ASM cells appears to be biphasic in which low concentrations of TNFα are pro-mitogenic, while at higher concentrations the mitogenic effect is abolished. This biphasic effect of TNFα may be due to cytokine-induced cyclooxygenase 2-dependent prostanoid production or autocrine secretion of interferon β that is growth inhibitory. Cyclooxygenase products, such as prostaglandin E_2, inhibit DNA synthesis. Therefore, cytokine-induced proliferative responses in ASM may be greater under conditions of cyclooxygenase inhibition, in which the expression of growth inhibitory prostanoids, such as prostaglandin E_2, is limited.

ASM proliferation also can be stimulated by mechanisms apart from exposure to soluble mediators. Mechanical stimuli, such as the acute compressive stress of the airway during bronchospasm, induce ASM DNA synthesis. ASM

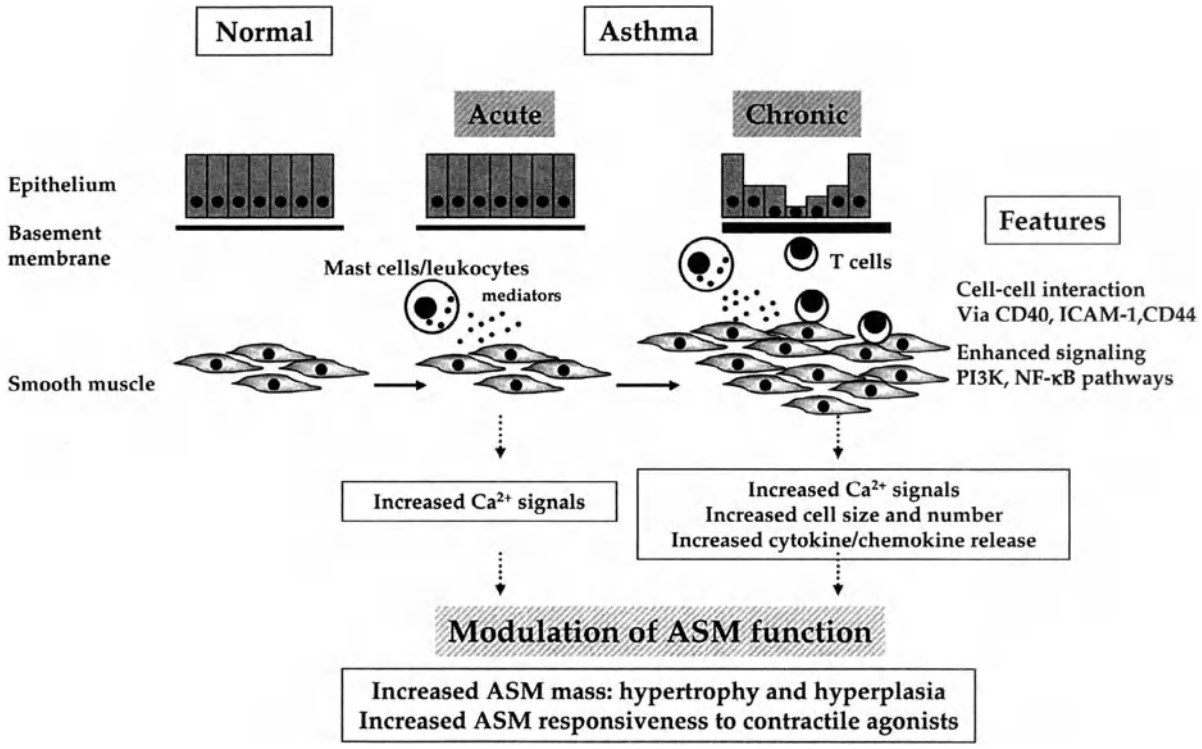

Figure 6-3 Factors affecting ASM function in acute and chronic state of asthma. During acute inflammation, a variety of mediators, such as cytokines, can modulate ASM contractile function by enhancing calcium signaling to agonists. These mediators regulate the recruitment and activation of eosinophils and T lymphocytes in the airway mucosa, a characteristic histopathological feature of the chronic disease. The persistence of airway inflammation via the production of cytokines and chemokines by both inflammatory as well as structural cells has the potential to directly stimulate ASM proliferation or as a result of T cell-ASM interaction mediated by cell surface expression of various CAM proteins such as ICAM-1, CD40 and CD44. Enhanced activation of phosphatidylinositol 3-kinase (PI3K) or the transcription factor NF-κB in ASM also may stimulate mitogenic and synthetic functions. *(Used with permission from Ammit AJ, Panettieri RA Jr: Airway smooth muscle cell hyperplasia: A therapeutic target in airway remodeling in asthma? Prog Cell Cycle Res 5:49, 2003.)*

proliferation also can be regulated by leukocyte-smooth muscle cell interactions, through cell adhesion molecules (CAM), such as ICAM-1 and VCAM-1. Deposition of extracellular matrix (ECM) proteins in the airways, a characteristic feature of airway remodeling in asthma, modulates mitogen-induced ASM growth. ECM proteins collagen I, III, V, fibronectin, tenascin, hyaluronan, versican, and laminin α2/β2 surround ASM and are increased in asthmatic airways as compared with that from healthy subjects. Fibronectin and collagen I increase human ASM cell mitogenesis in response to PDGF-BB or α-thrombin, whereas laminin inhibits proliferation. Furthermore, ECM proteins may be responsible for the low rates of apoptosis observed in ASM cells. The constitutive expression of ECM proteins by human ASM cells can be enhanced by exposure to asthmatic sera. Taken together, these studies suggest an additional cellular source for ECM deposition in asthmatic airways, apart from myofibroblasts, and implicate a novel mechanism in which ASM cells may modulate autocrine proliferative responses.

New evidence suggests that ASM from subjects with asthma may have an intrinsically different pattern of proliferation, compared with that from subjects without asthma. Cultured ASM from subjects with asthma proliferated at a faster rate and in greater numbers than the nonasthmatic controls. This was supported by flow cytometric analysis, whereby the proportion of cells from asthmatics in the G_2 + M phase was approximately twice that observed in the nonasthmatics. Further experiments are warranted to elucidate the underlying mechanism and confirm these observations.

Signal Transduction Pathways That Regulate the Cell Cycle in Airway Smooth Muscle In Vitro

Diverse stimuli, including growth factors, plasma- or inflammatory cell-derived mediators, contractile agonists and cytokines, induce ASM proliferation in vitro. These soluble ASM mitogens act via different receptor-operated mechanisms. While growth factors induce ASM cell mitogenesis by activating receptors with intrinsic protein tyrosine kinase (RTK) activity, contractile agonists released from inflammatory cells mediate their effects via activation of GPCRs. Cytokines signal through cell surface glycoprotein receptors that function as oligomeric complexes consisting of typically two to four receptor chains, coupled to Src family nonreceptor tyrosine kinases, such as lyn.

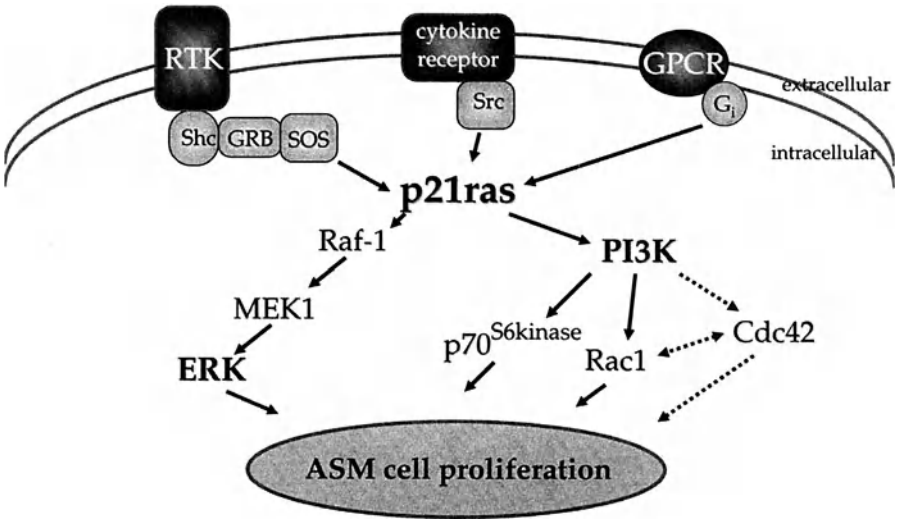

Figure 6-4 Schematic representation of signal transduction mechanisms that regulate ASM proliferation. ASM mitogens act via RTKs, cytokine receptors, or G protein–coupled receptors (GPCRs), to activate the small GTPase p21ras. p21ras Proteins then interact with downstream effectors, Raf-1 and phosphatidylinositol 3-kinase (PI3K). Raf-1 activates MEK1, which then phosphorylates extracellular signal–regulated kinase (ERK). PI3K activates downstream effectors, $p70^{S6k}$ or members of the Rho family GTPases, Rac1, and Cdc42 [although whether Cdc42 acts upstream of Rac1, or cross-talk exists is unknown at present (as indicated by the dashed lines)]. ERK, PI3K, and the downstream effectors of PI3K regulate cell cycle proteins; thus, the ERK and PI3K pathways are considered to be two major independent signaling pathways regulating ASM cell growth. *(Used with permission from Ammit AJ, Panettieri RA Jr: Invited review: the circle of life: cell cycle regulation in airway smooth muscle. J Appl Physiol 91:1431, 2001.)*

Despite disparate receptor-operated mechanisms, recent evidence suggests that the small guanidine triphosphatase (GTPase), p21ras, acts as a point of convergence for diverse extracellular signal-stimulated pathways in ASM cells, as shown in Fig. 6-4. Interestingly, synergy occurs between RTK and GPCRs that promotes human ASM mitogenesis and p21ras activation. In their GTP-bound active state, p21ras proteins interact with downstream effectors, namely, Raf-1 and phosphatidylinositol 3-kinase (PI3K). By recruiting Raf-1, a 74-kD cytoplasmic serine/threonine kinase, to the plasma membrane, GTP-bound p21ras activates the extracellular signal-regulated kinase (ERK) pathway, although Raf-1–independent signaling to ERK also has been described. p21ras Also binds and activates PI3K by using specific regions termed switch I (Asp^{30}–Asp^{38}) and switch II (Gly^{60}–Glu^{76}). Although alternative pathways exist (e.g., protein kinase C–dependent pathways or reactive oxygen–dependent pathways), ERK and PI3K activation appears to be the dominant signal transduction pathway for RTK-, GPCR-, or cytokine-stimulated growth of ASM cells.

Inhibition of Airway Smooth Muscle Proliferation In Vitro

Many of the widely used therapies for the control of asthma symptoms have been examined for their ability to inhibit ASM cell proliferation in vitro. Although a systematic study of the relative efficacies has not been performed, in vitro evidence provides useful data to suggest that anti-asthma drugs may, in part, reduce airway remodeling in vivo. Furthermore, these studies provide useful clues in the design of future therapeutic agents to treat this aspect of asthma.

Corticosteroids are the most widely used therapy for the control of airway inflammation in asthma. In human ASM cells, the corticosteroids dexamethasone and fluticasone propionate arrest ASM cells in the G1 phase of the cell cycle. Corticosteroids reduced thrombin-stimulated increases in cyclin D1 protein and mRNA levels, and attenuated pRb phosphorylation via a pathway either downstream or parallel to the MAPK pathway. Interestingly, corticosteroids may not be effective in inhibiting ASM cell mitogenesis in response to receptor tyrosine kinase–activating mitogens.

β_2-Agonists activate the β_2-adrenergic receptor G_s-adenylyl cyclase pathway to elevate 3′:5′ cyclic adenosine monophosphate (cAMP) in ASM cells. Apart from having potent and rapid effects on the alleviation of bronchospasm, cAMP, presumably through the activation of cAMP-dependent protein kinase, has significant effects on mitogen-induced ASM cell proliferation. Both albuterol and fenoterol inhibit mitogen-induced proliferation of human ASM cells. cAMP can be hydrolyzed within cells by phosphodiesterases (PDEs), a family of enzymes containing at least seven isoenzymes. PDE inhibitors also elevate intracellular cAMP concentration and inhibit cell proliferation. Mitogen-induced ASM cells were attenuated with siguazodan and rolipram, specific inhibitors of type 3 and 4 PDE, the two most important PDE isoenzymes for the control of intracellular cAMP concentration in ASM cells. The effect of cAMP on cell proliferation was via cAMP-mediated transcriptional activation, whereby the effects of forskolin, an

activator of adenylate cyclase, inhibited DNA synthesis and cyclin D1 expression, and induced cAMP response element-binding protein (CREB) phosphorylation and DNA binding in ASM. By increasing cAMP in ASM cells, forskolin suppressed cyclin D1 gene expression via phosphorylation and transactivation of CREB, suggesting that the effect of cAMP on cyclin D1 gene expression is via *cis*-repression of the cyclin D1 promoter. Furthermore, β_2-adrenergic receptor agonists, and other cAMP-elevating agents, also may induce G1 arrest by post-transcriptionally inhibiting cyclin D1 protein levels by action on a proteasome-dependent degradation pathway.

Other approaches aimed at abrogating ASM cell proliferation focus on the inhibition of contractile agonist receptor activation. Cysteinyl leukotrienes (CysLT), such as LTD_4, markedly augment proliferation induced by mitogens, such as EGF and thrombin in human ASM cells. Interestingly, there exists selectivity with regard to the inhibition of the CysLT receptors and the augmentation of ASM mitogenesis. Pranlukast and pobilukast, but not zafirlukast, inhibited LTD_4-augmented EGF-induced human ASM cell mitogenesis. Additional studies are needed to define the precise mechanism by which these antagonists block LTD_4-induced ASM cell growth. Further elucidation of the signaling and transcriptional targets for the inhibition of cell cycle progression by corticosteroids, β_2-agonists, PDE inhibitors, and CysLT receptor antagonists may suggest new uses for traditional asthma therapies. In addition to these existing anti-asthma drugs, heparin, IL-4, nitric oxide, and atrial natriuretic peptide also have been shown to have potent inhibitory effects on mitogen-induced ASM proliferation. Interestingly, inhibiting the secretion of matrix metalloproteinase-2 from ASM cells reduces ASM hyperplasia. Further, the combination of multiple agents may be conducive to limiting airway remodeling in asthma.

CHEMOKINE AND CYTOKINE RELEASE BY AIRWAY SMOOTH MUSCLE CELLS

The production of pro-inflammatory mediators by trafficking leukocytes has a profound influence on ASM cells. Exposure of ASM to cytokines or growth factors alters contractility and calcium homeostasis and induces smooth muscle cell hypertrophy and hyperplasia. New evidence suggests that ASM cells also can secrete a number of cytokines and chemoattractants. In bronchial biopsies of subjects with mild asthma, ASM constitutively expresses RANTES, a C-C chemokine; in vitro, RANTES secretion is induced by TNFα and interferon (IFN) γ. Similarly, the C-X-C chemokine IL-8 also is secreted by ASM in response to TNFα, IL-1β, and bradykinin. Other chemokines that are secreted by ASM cells include eotaxin, an eosinophil chemoattractant, and monocyte chemotactic protein (MCP)-1, MCP-2, MCP-3 as shown in Fig. 6-1.

IL-6, a pleiotropic cytokine, induces smooth muscle cell hyperplasia, but also modulates B- and T-cell proliferation and immunoglobulin secretion. IL-6 secretion by ASM cells is inducible by multiple stimuli, including IL-1β, TNFα, TGF-β, and sphingosine-1-phosphate. Interestingly, transgenic expression of IL-6 in the murine lung evokes a peribronchiolar inflammatory infiltrate but promotes airway *hypo*responsiveness, suggesting an intriguing role for IL-6 in controlling local inflammation and regulating airway reactivity and consistent with the known ability of IL-6 to inhibit TNFα and IL-1β secretion. ASM cells also may play a role in promoting both the recruitment and survival of eosinophils by secretion of GM-CSF and IL-5. Finally, additional cytokines that are secreted by human ASM cells include IL-1β, IFNβ, and other IL-6 family cytokines, such as leukemia inhibitory factor and IL-11, which are secreted following exposure of ASM cells to viral particles.

Receptors Involved in Cell Adhesion and Lymphocyte Activation

Cell adhesion molecules (CAMs) mediate leukocyte-endothelial cell interactions regulating cell recruitment and homing. The expression and activation of a cascade of CAMs that include selectins, integrins, and members of the immunoglobulin superfamily, as well as the local production of chemoattractants, leads to leukocyte adhesion and transmigration into lymph nodes and sites of inflammation involving nonlymphoid tissues. The mechanisms that regulate extravasation of leukocytes from the circulation during the establishment of a local inflammatory response are rapidly being delineated. Less defined are the subsequent interactions of the infiltrating leukocytes with other cell types in the bronchial submucosa or with the ECM, which may be important for sustaining the inflammatory response.

In addition to mediating leukocyte extravasation and transendothelial migration, CAMs promote submucosal or subendothelial contact with cellular and ECM components and serve as co-stimulatory molecules in the activation of leukocytes. New evidence suggests that CAMs mediate inflammatory cell–stromal cell interactions that may contribute to airway inflammation. ASM cells express ICAM-1 and VCAM-1, which are inducible by a wide range of inflammatory mediators. In contrast, contractile agonists such as bradykinin and histamine have little effect on ASM CAM expression. ASM cells also constitutively express CD44, the primary receptor of the matrix protein hyaluronan. Activated T lymphocytes adhere via LFA-1 and VLA-4 to cytokine-induced ICAM-1 and VCAM-1 on cultured human ASM cells. Moreover, an integrin-independent component of lymphocyte-smooth muscle cell adhesion appears to be mediated by CD44-hyaluronan interactions.

CAMs can function as accessory molecules for leukocyte activation. However, whether CAMs expressed on smooth muscle serve this function remains controversial. ASM cells do express major histocompatibility complex (MHC) class II and CD40 following stimulation with IFNγ. Recent studies also suggest that human ASM cells express low levels of CD80 (B7.1) and CD86 (B7.2). The physiological relevance of these findings remains unknown since ASM

cells cannot present alloantigen to CD4 T cells, despite the expression of MHC class II and co-stimulatory molecules.

However, functionally adhesion of stimulated CD4 T cells can induce smooth muscle cell DNA synthesis. This appears to require direct cell-cell contact and is not mimicked by treatment of the cells with T-cell conditioned medium. In addition, ligation of CD40, a co-stimulatory molecule up-regulated by IFNγ, increases intracellular calcium as well as IL-6 secretion; engagement of VCAM-1 on ASM cells activates PI3K and augments growth factor–induced ASM cell proliferation. In addition, ASM cells express Fas in vivo. In vitro, expression of Fas is up-regulated by TNFα and, importantly, crosslinking of Fas induces smooth muscle cell apoptosis. These studies highlight the finding that direct interactions between leukocytes and smooth muscle cells via immune receptors such as CD40 and Fas or adhesion receptors such as ICAM-1 and VCAM-1 contribute to the modulation of the local milieu, resulting in smooth muscle cell activation and growth.

Other Immunomodulatory Proteins

Increased amounts of exhaled nitric oxide (NO) have been detected in subjects with asthma. NO selectively suppresses the Th1 subset of helper T cells, suggesting that increased levels of NO may lead to the predominantly Th2 type response associated with asthma. NO synthase has been demonstrated in cultured ASM, and NO inhibits growth factor–induced ASM cell proliferation. In contrast, there is only indirect evidence that ASM cells produce NO in situ. ASM cells also produce large amounts of prostaglandin (PG) E_2 and, to a lesser extent, other prostanoids, following stimulation with pro-inflammatory cytokines. Although PGE_2 is a potent bronchodilator, it also has significant immunologic effects. For example, PGE_2 can decrease expression of CD23 (FcγRII), which has been shown to be expressed on human ASM cells and may have a role as a negative regulator of airway inflammation and hyperresponsiveness. PGE_2 inhibits cytokine-induced secretion of GM-CSF in vitro and allergen-induced release of PGD_2 in subjects with asthma. In contrast, PGE_2 also primes dendritic cells toward a Th2-promoting capacity and synergizes with IL-4 to induce IgE synthesis. Thus, the roles of ASM-derived NO and PGE_2 need to be further defined, as both molecules may have beneficial and deleterious effects in the airway.

ASM cells express receptors for the cysteinyl leukotrienes, LTC_4, LTD_4, and LTE_4. Expression of the CysLT1 receptor is increased by exposure to IFNγ and increases in LTD_4-mediated force generation in cultured ASM cells. The association between CysLT receptor expression and contractility may explain the increase in airway hyperresponsiveness following viral infection that induces a Th1-predominant environment. This finding suggests that leukotriene receptor antagonists may have a therapeutic role in viral-induced airway inflammation. Finally, receptors for the complement-derived anaphylatoxin peptides C3a and C5a also have been described on ASM cells. These peptides may play an important role in the pathogenesis of asthma by altering airway hyperresponsiveness, rather than airway inflammation.

Table 6-1

Immunomodulatory Proteins Expressed by Human ASM Cells

Cytokines	Chemokines	CAMs	Other
IL-1β	IL-8	ICAM-1	CD40
IL-5	RANTES	VCAM-1	Fas
IL-6	MCP-1,-2,-3	CD44	HLA-DR
IL-8	Eotaxin	LFA-1	FcγRII
IL-11	GM-CSF	$\alpha_9\beta_1$	FcγRIII
LIF		$\alpha_5\beta_1$	NO
IFNβ		α_v, α_6 subunits	PGE_2 CysLT receptors C3a/C5a receptors MMP/TIMP VEGF

ASM cells provide a rich source of cytokines and chemokines, and under certain conditions can express a wide variety of adhesion receptors, co-stimulatory molecules, and other immunomodulatory proteins (Table 6-1). Taken together, these data support the potential role of ASM cells not only in perpetuating airway inflammation, but also in leukocyte activation.

Airway Smooth Muscle as a Target for Anti-Inflammatory Therapy

Given the evidence that ASM cells secrete and express immunomodulatory proteins, investigators are now studying the cellular and molecular processes that regulate ASM synthetic function and examining the role of steroids and β-agonists in modulating cytokine-induced synthetic responses.

One of the most effective medications to date for controlling airway inflammation in asthma has been inhaled corticosteroids. Despite their use for over 25 years, the precise mechanisms by which steroids improve lung function in asthma remain unclear. Current evidence suggests that chemokine and cytokine secretion induced by inflammatory mediators is inhibited by dexamethasone in human ASM cells. Cytokine-induced secretion of RANTES, MCP, eotaxin, GM-CSF, and IL-6 is also abrogated by corticosteroids. Corticosteroid and $[cAMP]_i$ mobilizing agents can act additively to inhibit chemokine and cytokine secretion.

NF-κB is another transcriptional factor mediating chronic inflammatory responses in asthma, rheumatoid

arthritis, psoriasis, and inflammatory bowel disease. Interestingly, dexamethasone had little effect on TNFα- or IL-1β–induced NF-κB activation in human ASM cells. Furthermore, cytokine-induced ICAM-1 expression in ASM cells, which is completely dependent on NF-κB activation, was not affected by dexamethasone, and IL-6 secretion is only partially affected. In contrast, IL-1β–induced cyclooxygenase-2 expression was abrogated. Thus, the anti-inflammatory effects of steroids in asthma may not be due solely to modulation of cytokine-induced NF-κB activation and are likely regulated by myriad pathways such as AP-1 or other transcription factors.

Effects of $[cAMP]_i$ Mobilizing Agents on Cytokine-Induced Synthetic Responses

In asthma, β-agonists such as isoproterenol, albuterol, salmeterol, and formoterol are therapeutic agents that promote bronchodilation by stimulating receptors coupled to Gs, which in turn activates adenylyl cyclase, increases $[cAMP]_i$ and stimulates cAMP-dependent protein kinase (A-kinase) in ASM. $[cAMP]_i$ mobilizing agents in ASM cells also modulate cytokine-induced synthetic function. In TNFα-stimulated ASM cells, both eotaxin and RANTES expression are effectively inhibited by isoproterenol, PGE_2, dibutyl-$[cAMP]_i$, or the PDE inhibitors rolipram and cilomilast. TNFα-induced IL-8 secretion also was inhibited by the combination of $[cAMP]_i$ mobilizing agents and corticosteroids. Similarly, sphingosine-1-phosphate, which activates a Gs protein–coupled receptor and increases $[cAMP]_i$, abrogated TNFα-induced RANTES secretion in ASM cells.

In contrast to the effects of $[cAMP]_i$ on chemokine secretion, pharmacologic agents that increase $[cAMP]_i$ markedly stimulate secretion of IL-6 in human ASM cells. Whether the secreted IL-6 modulates ASM cell function in an autocrine manner or alters leukocyte function in the submucosa remains unknown. However, since the overexpression of IL-6 decreases acetylcholine responsiveness in transgenic mice, the role of IL-6 in asthma may be that of an anti-inflammatory signal in some compartments of the airway. Increases in cAMP also decrease secretion of GM-CSF by ASM cells. Cyclooxygenase inhibitors also reduce PGE_2 and enhance cytokine-induced secretion of GM-CSF, while PDE type IV inhibitors reduce GM-CSF secretion in vitro and antigen-induced BHR in an animal model. Taken together, current evidence suggests that some, but not all, pro-inflammatory functions in ASM cells are inhibited by $[cAMP]_i$ mobilizing agents.

AIRWAY SMOOTH MUSCLE CELLS AND EXTRACELLULAR MATRIX

The importance of airway remodeling in chronic severe asthma has been appreciated only recently. ASM cells, by producing ECM components and matrix-modifying enzymes, may contribute to this process. ASM cells may produce endogenous growth factors that modulate ECM secretion. TGF-β is secreted from ASM cells and inhibits mitogen-induced ASM growth but induces smooth muscle cell synthesis of hyaluronan and collagen. In turn, ECM proteins bind growth factors and may serve as an accessible reservoir of mitogens.

ECM proteins are critical for maintaining the structure and function of the airways. The composition of the ECM is tightly controlled and involves a dynamic process of matrix deposition and degradation. In inflammatory processes such as asthma, this balance is disturbed, resulting not only in an abnormal amount of matrix deposition, but also in an altered composition of matrix components. ASM cells secrete a wide variety of matrix proteins, including fibronectin, collagen, hyaluronan, laminin, and versican. In asthma, there is an increase in hyaluronan, fibronectin, tenascin, versican, laminin, and collagen types 1, 3, and 5. In vitro, serum from asthmatic patients increases smooth muscle cell release of fibronectin, laminin, perlecan, and chondroitin sulfate. In addition, fibronectin and collagen type I enhance smooth muscle cell proliferation in response to PDGF, whereas laminin reduced mitogen-induced proliferation. However, treatment of cells with corticosteroids had no effect on the production of matrix proteins by ASM cells, which is consistent with clinical studies showing that inhaled corticosteroids had minimal effect on altering ECM composition in airways of subjects with asthma. These data support the finding that while corticosteroids are effective at inhibiting inflammation, newer therapies are needed to prevent and/or reverse airway fibrosis seen in asthma.

The derangement in matrix components seen in asthma likely is multifactorial. Not only is there increased matrix deposition, but there is also an imbalance between matrix-degrading enzymes and inhibitors of these proteases. One class of proteins that has been intensively studied is the matrix metalloproteinase (MMP) family. MMP-1 expression is elevated in the smooth muscle cells of subjects with asthma, and LTD_4 increases expression of MMP-1, which acts to degrade insulin-like growth factor binding protein, a growth inhibitor. TNFα induces the release of MMP-9, which can degrade matrix but also plays a critical role in cleaving latent TGF-β to its active form. Progelatinase A (MMP-2) is constitutively released by ASM cells, but remains inactive because of high levels of tissue inhibitor of metalloproteinases (TIMP)-2 on the cell membrane. In contrast, TIMP-1 is secreted in large amounts into the conditioned media of ASM cells. Membrane type 1 MMP is also found on ASM; this proteinase can activate MMP-2 and has been shown to cleave CD44 from the cell surface and promote cell migration. Clearly, ASM cells play an active role in modifying their environment. Further studies will be necessary to understand the interaction among ECM, MMPs, and TIMPs in the development of airway remodeling.

SUMMARY

The biology of ASM is complex and fascinating. The myriad pathways regulating cell shortening, growth, and

proliferation, combined with the emerging role of ASM as a modulator of inflammation, provide a rich area of investigation. Unfortunately, virtually all work in this area has been performed in vitro, and in vivo correlation is needed. Future studies will focus on mechanisms regulating both acute inflammation and the chronic repair processes leading to airway remodeling.

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7

Pulmonary Surfactant System and Alveolar Homeostasis

Jeffrey A. Whitsett • Ann D. Horowitz

Pulmonary surfactant, a complex mixture of phospholipids and proteins, creates a unique interface, separating alveolar gas and liquids at the alveolar cell surface, reducing surface tension, and maintaining lung volumes at end expiration. Reduction of the surface tension at the air-liquid interface is a requirement for respiratory function following birth. Deficiency of pulmonary surfactant causes respiratory failure in premature infants, or infantile respiratory distress syndrome (IRDS). The adequacy of pulmonary surfactant is maintained by unique and highly regulated systems mediating the synthesis, secretion, reuptake, reutilization, and catabolism of surfactant. Loss of pulmonary surfactant later in life occurs in the adult respiratory distress syndrome (ARDS), a significant cause of morbidity and mortality following infection, shock, or trauma. Mutations in genes regulating surfactant homeostasis, including SFTPB, SFTPC, and ABCA3 cause lethal acute and chronic lung disease in newborn infants, children, and adults. This chapter reviews the biology of the surfactant system and its implications for the pathogenesis and treatment of respiratory disease in premature infants and adults. Recent reviews of this topic are suggested.

PHYSICAL FORCES AT THE AIR-LIQUID INTERFACE

In 1929, Van Neergard recognized the critical role of surface tension as a "retractile force" in the lung, observing the marked difference in inflation pressures required to inflate the air- versus water-filled lung. Avery and Mead associated the lack of a lipid-rich material in the lungs of infants dying from IRDS with alveolar collapse and respiratory failure. In the absence of pulmonary surfactant, molecular forces at the air-liquid interface create a region of high surface tension because intermolecular forces between water molecules are unopposed at the air-liquid interface, and an area of high retractile force at the surface is created. Forces of 70 dynes/cm^2 are generated at the air-water interface at 37°C; if unopposed in the alveolus, such forces lead to alveolar collapse and respiratory failure. A surface film composed of multi-layered sheets of phospholipids creates a distinct phase separating air and liquid, reducing surface tension to nearly zero and maintaining residual lung volume at end expiration. Complex

interactions between surfactant phospholipids and proteins are required to maintain surfactant activity throughout life.

COMPOSITION OF PULMONARY SURFACTANT

Pulmonary surfactant isolated by lung lavage consists of highly heterogeneous forms of phospholipid-protein aggregates of distinct sizes, structural characteristics, and composition. Tubular myelin is the most abundant form of alveolar phospholipid and consists of large, relatively dense aggregates (termed large aggregate surfactant) composed of phospholipids and surfactant proteins. Tubular myelin is a highly organized form of surfactant phospholipid, forming square tubular arrays, as in Fig. 7-1. Tubular myelin is surface-active and likely represents an extracellular pool of surfactant lipids that move to the air-liquid interface to form the monolayer or multi-layered sheets that reduce surface tension in the alveolus (Fig. 7-2). Large lamellated structures of composition similar to that of tubular myelin are also seen within the alveolus and likely represent newly secreted lamellar bodies that unravel and form tubular myelin in the airspace. The phospholipid composition of lamellar bodies, the intracellular storage form of surfactant, tubular myelin, and lamellated forms present in the alveolus are virtually identical. Smaller, less dense particles (small aggregates) are also present within the alveolar space, representing remnants or catabolic forms of surfactant that are relatively inactive and destined for uptake, reutilization, or catabolism by type II epithelial cells and catabolism by alveolar macrophages.

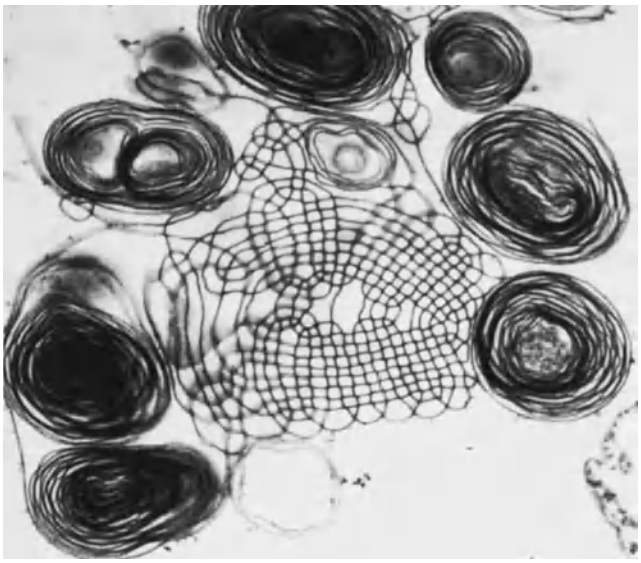

Figure 7-1 Tubular myelin. Tubular myelin is produced after secretion of lamellar bodies into the airspace by a process dependent upon surfactant proteins A and B, phospholipids, and extracellular calcium. Tubular myelin is a relatively dense, highly organized form of phospholipid present in the alveolar subphase. Phospholipid molecules move from the tubular myelin to monolayer and multilayer sheets, reducing surface tension at the air-liquid interface. Tubular myelin is not required for surfactant function or metabolism and may play a role in host defense function against pulmonary pathogens. (Bar = 1 μm.) *(Figure courtesy of Dr. Stephen Young: Randall SH, Young SL: Structure of alveolar epithelial cells and the surface layer during development, in Polin RA, Fox WW, Abman S (eds), Fetal and Neonatal Physiology, 3rd edition. Philadelphia, WB Saunders, 2004, p 1034).*

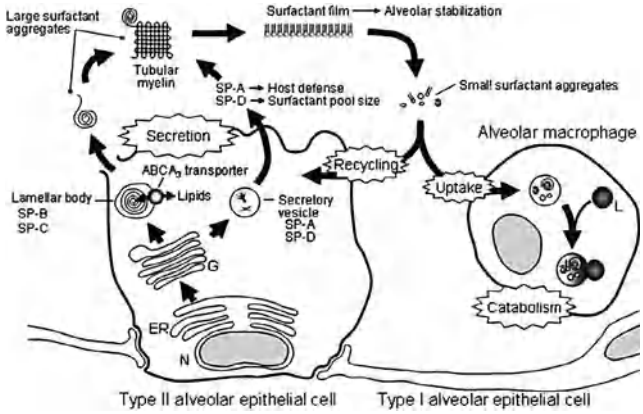

Figure 7-2 Life cycle of pulmonary surfactant. SP-B and SP-C are synthesized, proteolytically processed, and packaged with phospholipids in lamellar bodies and secreted by type II alveolar epithelial cells into the airspace. ABCA3 is present in the limiting membrane of the lamellar bodies, where it is likely to regulate lipid transport from which lipid/protein films are formed at the air-liquid interface. Used surfactant lipids are released from the film as small vesicles, which are taken up and recycled or degraded by type II cells. Alveolar macrophages also take up and degrade surfactant lipids and proteins in a process that requires GM-CSF signaling. *(Figure kindly provided by Dr. Bruce Trapnell: Whitsett JA, Wert SE, Trapnell BC: Genetic disorders influencing lung formation and function at birth. Hum Mol Genet 13:R207, 2004.)*

Surfactant Phospholipids and Proteins

The composition of surfactant phospholipids is similar in all of the structural forms of surfactant isolated from mammalian lung, generally representing 80 to 90 percent of the mass of pulmonary surfactant. In the adult lung, phosphatidylcholine (70 to 80 percent) and phosphatidylglycerol (10 percent) are the most abundant phospholipid constituents. Lesser amounts of phosphatidylserine, phosphatidylethanolamine, sphingomyelin, neutral lipids, and glycolipids are also detected in surfactant. The lung content of surfactant phospholipids increases markedly with advancing gestation. Surfactant is secreted into the amniotic fluid, and total phospholipid, dipalmitoylphosphatidylcholine (DPPC), or increased lecithin to sphingomyelin (L/S) ratio correlate with postnatal respiratory function. These tests are widely used to predict pulmonary maturity prior to the birth of preterm infants. Proteins represent approximately 5 to 15 percent of the mass of pulmonary surfactant and include serum proteins and proteins that are produced by respiratory epithelial cells. Four surfactant proteins—SP-A, SP-B, SP-C, and SP-D—named in the order of discovery, are produced

by respiratory epithelial cells, each playing specific roles in surfactant homeostasis or host defense.

Surfactant is uniquely enriched in disaturated DPPC. The saturated C16 acyl chains pack densely at an air-liquid interface, reducing tension at the surface. However, such dense and stable packing of DPPC occurs at a phase transition of 41°C, far above physiological temperatures. Thus, at 37°C, pure DPPC maintains a semicrystalline or gel phase that is incapable of moving rapidly with the expansion and contraction of the alveolus during the respiratory cycle. The capability of DPPC pulmonary surfactant to move rapidly to the alveolar interface at 37°C and to maintain low surface tension during dynamic compression is conferred by the surfactant-associated proteins SP-B and SP-C.

Structure and Function of Surfactant Proteins

Four distinct proteins have been isolated from surfactant obtained by lung lavage. Their cDNAs, genes, and structures have been identified and are well characterized. These surfactant proteins are expressed in a lung epithelial cell–selective manner and are secreted into the airspace, where they influence the structure, metabolism, and function of surfactant. Two classes of proteins have been distinguished on the basis of their structures. SP-A and SP-D are relatively abundant, hydrophilic, structurally related proteins that are members of the calcium-dependent lectin family of proteins that share collagenous domains (Fig. 7-3). These molecules have little or weak "surfactant"-like qualities, but are able to bind complex carbohydrates, lipids, and glycolipids, including those on the surface of bacteria, viruses, fungi, and other lung pathogens. They act as opsonins, activate alveolar macrophages, and play important roles in host defense in the lung. In contrast, SP-B and SP-C are small, hydrophobic proteins that play critical roles in enhancing the rate of spreading and stability of surfactant phospholipids (Fig. 7-4). SP-B and SP-C are the protein components of the animal-derived surfactant replacement preparations used for the treatment of IRDS.

Surfactant Protein-C

Surfactant protein-C (SP-C) is encoded by a single gene (SFTPC), located on human chromosome 8. SP-C mRNA is expressed exclusively in type II epithelial cells in the lung and is translated to produce a 22-kD precursor that is palmitoylated and proteolytically processed to form the active, hydrophobic peptide of 33 to 35 amino acids. SP-C enhances the surface-active properties of lipid mixtures by lowering surface tension and enhancing adsorption rate of a lipid film at the air-water interface. SP-C and SP-B reduce surface tension of a lipid film to near zero, and they increase lung compliance in premature animals. SP-C is palmitoylated on cysteine residues near the NH_2 terminus. The surface activity of depalmitoylated SP-C is somewhat less than that of palmitoylated SP-C, and the palmitoyl groups may be required for a posttranslational modification of the SP-C precursor. The carboxy-terminal

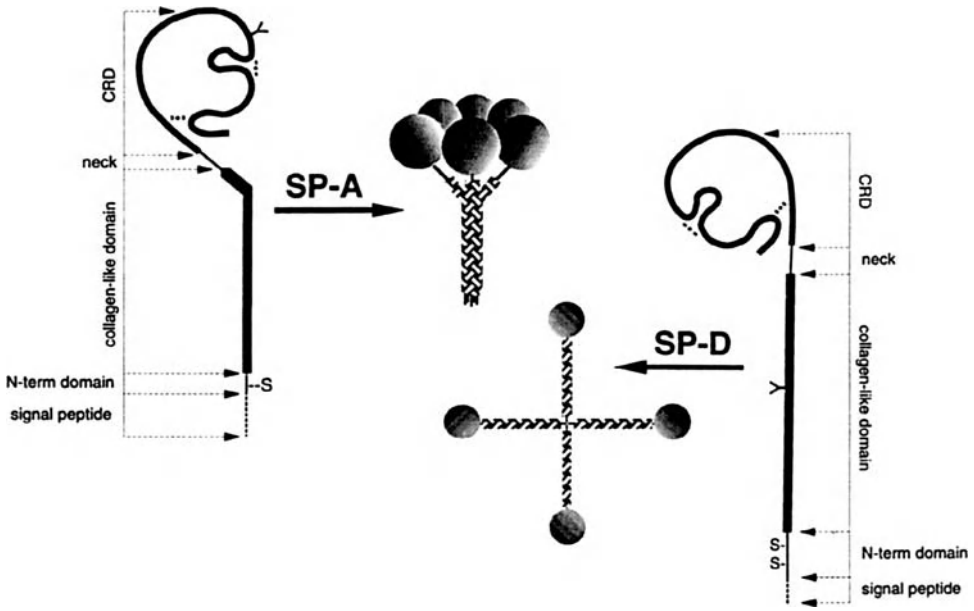

Figure 7-3 Pulmonary collectins: surfactant proteins A and D. Surfactant protein A is produced from a preproprotein that is proteolytically processed by the removal of the signal peptide and glycoslated (Y). SP-A consists of a carboxy-terminal globular, lectin-like domain (CRD) (thin line) and a more rigid, collagen-like domain (dark line) comprising the amino terminal region. Sulfhydryl-dependent interactions between SP-A monomers result in the organization of SP-A into hexamers that further associate to form the larger oligomers present in the alveolar space. SP-D is closely related to SP-A and is also a member of the calcium-dependent family of lectins. SP-D contains a C-terminal globular lectin domain (thin line) that is linked to a larger, NH_2-terminal, collagen-like domain. SP-D forms tetramers and higher-ordered multimers that are relatively weakly associated with surfactant lipids. Human SP-A is encoded by two (*SFTPA*) genes that are located within a single *SFTPD* gene on human chromosome 10.

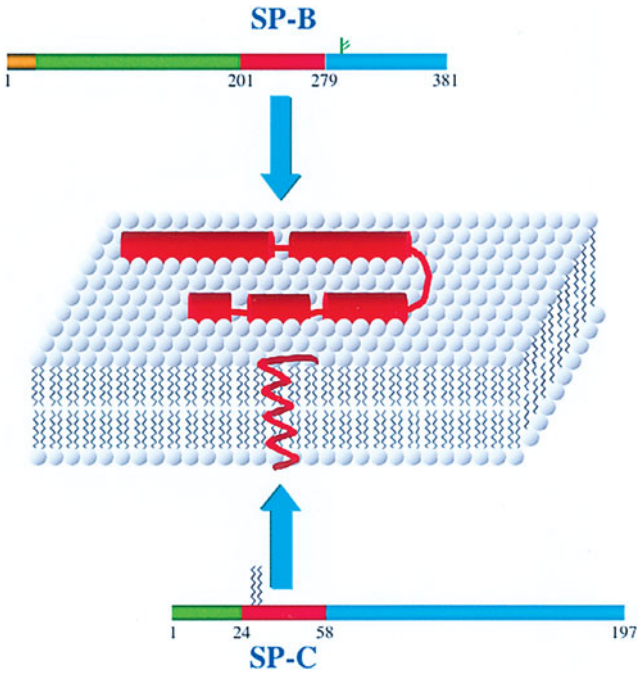

Figure 7-4 Hydrophobic surfactant proteins SP-B and SP-C. The active SP-B peptide is produced by proteolytic processing of pre-proSP-B protein consisting of 381 amino acids. The active 79–amino acid, SP-B peptide interacts with phospholipid head groups, altering the stability of phospholipid films and enhancing their rate of spreading at the air-liquid interface. SP-C is generated by proteolytic processing of a 197–amino acid preproprotein to form the 32– to 34–amino acid active hydrophobic peptide that inserts deeply into the acyl chains of lipid bilayers, disrupting acyl group packing and enhancing mobility of phospholipids at the membrane surface. *(Courtesy of Dr. Timothy Weaver, Cincinnati Children's Hospital Medical Center.)*

two-thirds of SP-C is generally in an α-helical conformation, but depalmitoylation reduces the α-helical content of native SP-C. A form of depalmitoylated SP-C that forms a very stable dimer with a high β-sheet content has also been identified. Although the orientation of the palmitoyl groups in a lipid environment is not currently known, they are likely, due to their hydrophobicity, to hold the amino-terminal region of SP-C in close contact with lipids.

In a lipid bilayer, the orientation of the α-helical segment of SP-C is closely parallel with the lipid acyl chains, implying a transbilayer orientation (Fig. 7-4). In a surface monolayer, SP-C has a preferential orientation parallel to the interface, as observed by circular dichroism of monolayer films. The positive charges near the NH_2 terminus of SP-C may promote in the binding of phospholipid vesicles to the monolayer—a step required for insertion of phospholipids into the monolayer. Blocking of the positively charged residues arginine and lysine with phenylglyoxal produced a modified SP-C, which had lost the ability to enhance binding of lipid vesicles to the monolayer and did not catalyze insertion of lipids into the monolayer. SP-C forms aggregates in DPPC/DPPG (dipalmitoylphosphatidylglycerol) mixtures below the phase transition temperature of the bulk lipid, as observed by fluorescence energy transfer among SP-C molecules labeled with fluorescent probes. SP-C also affects the size and shape of lipid vesicles. It disrupts vesicular structure, causing the formation of larger vesicles and discoid particles.

Function of SP-C In Vivo

Deletion of SP-C in transgenic mice perturbs surfactant function and causes severe interstitial lung disease. While SP-$C^{-/-}$ mice survive after birth, the mice develop airspace abnormalities, pulmonary inflammation, and abnormal lipid accumulations in alveolar macrophages, and epithelial and stromal cells. While surfactant properties are only modestly perturbed, severe and progressive remodeling, emphysema, and fibrosis occur in these mice. Severity of pulmonary disorder related to SP-C deficiency in mice is strongly influenced by genetic strain, age, and injury, indicating that the disorder is influenced by both genetic and environmental factors. The finding that SP-$C^{-/-}$ mice develop an interstitial pulmonary disorder is consistent with findings in humans, wherein SP-C mutations cause severe acute, and chronic lung disease.

Mutations in SFTPC Cause Severe Interstitial Lung Disease in Humans

Mutations in SFTPC represent a rare cause of acute and chronic lung disease in humans. SFTPC mutations are generally inherited as an autosomal-dominant gene that has been causally linked to acute respiratory disease in newborn infants and chronic interstitial lung disease in infants, children, and adults. Most mutations result in the intracellular accumulation of misfolded proSP-C protein, which also results in the lack of synthesis of the active SP-C peptide. Various forms of interstitial lung disease have been associated with the disease, including acute respiratory distress (RDS), chronic pneumonitis of infancy (CPI), non-specific interstitial pneumonitis (NSIP), and other forms of idiopathic pulmonary fibrosis (IPF) (Fig. 7-5). The lung histopathology associated with SFTPC mutations is likely dependent upon age, duration and severity of the disease, treatment, and both genetic and environmental factors. Definitive diagnosis is made by identification of mutations in the SFTPC gene. As seen in the mouse model (SP-$C^{-/-}$ mice), the onset and severity of pulmonary disease in humans is highly variable, even in the same kindreds, indicating that genetic and environmental factors strongly influence the disorder. At present, there is no effective therapy for SP-C–related disease. Lung transplantation has been successfully used to treat hereditary SFTPC deficiency.

In summary, SP-C is likely to be present in both phospholipid monolayers and bilayers. Insertion of SP-C into the phospholipid membranes disrupts acyl group packing; positive charges near the NH_2 terminus and located near the surface of the phospholipids may enhance insertion of phospholipid molecules into surfactant films. Mutations in SFTPC are a rare cause of acute and chronic interstitial lung disease

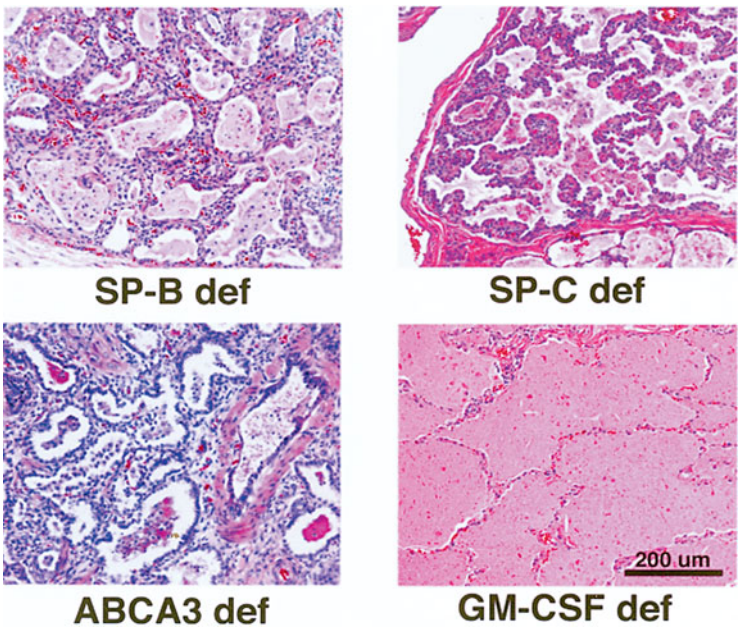

Figure 7-5 Pulmonary histopathology associated with disorders of surfactant homeostasis. Pathologic findings in neonates with mutations in SFTPB, SFTPC, and ABCA3 are consistent with childhood interstitial pneumonitis (CIP) or desquamating interstitial pneumonitis (DIP). Severe alveolar remodeling, alveolar loss, macrophage infiltration, varying degrees of alveolar proteinosis, and stromal thickening are observed. In contrast, autoantibodies against GM-CSF are associated with pulmonary alveolar proteinosis (PAP) in which surfactant lipids and proteins accumulate in the alveolus. Alveolar structure is generally well maintained in PAP. *(Figures courtesy of Dr. Susan Wert: Whitsett JA, Wert SE, Trapnell BC: Genetic disorders influencing lung formation and function at birth. Hum Mol Genet 13:R207, 2004.)*

that are generally inherited as an autosomal dominant mutation, resulting in the production of misfolded mutant proteins that accumulate within type II alveolar cells causing cell and lung injury.

Surfactant Protein-B

Surfactant protein-B (SP-B) is a hydrophobic 8.8-kD protein produced from a single gene (SFTPB) located on human chromosome 2 (Fig. 7-4). The SP-B mRNA is expressed in bronchioles and type II alveolar cells and is translated to produce a 40- to 42-kD precursor that is proteolytically processed to form the active 79-amino acid peptide found in surfactant. In combination with lipids, SP-B reconstitutes most of the surface activity of natural lung surfactant. SP-B contains two regions (Trp_9-Pro_{23}) and (Ile_{56}-Pro_{67}), predicted to form amphipathic α-helices. Almost 50 percent of the protein is in an α-helical conformation, with approximately 20 percent β-sheet and 16 percent turns, as determined by Fourier transform infrared spectroscopy (FTIR). SP-B contains three intramolecular disulfide bonds that confine the amphipathic helices of SP-B in an antiparallel configuration. Cys 48 is free to form an intermolecular disulfide bond, stabilizing the SP-B dimer. Dimers and higher multimers of SP-B, which are probably stabilized by noncovalent interactions, are found in pulmonary surfactant.

SP-B is tightly associated with surfactant phospholipids in the alveolus and lamellar bodies of type II epithelial cells. The positively charged amino acid residues of SP-B selectively interact with the negatively charged phospholipid DPPG, as determined by a variety of physical techniques. In a mixed DPPC/DPPG monolayer, SP-B is believed to purify the DPPC monolayer by removal of DPPG in a complex with SP-B. SP-B increases order in the lipid head group region with little effect on order in the membrane interior. The ability to order the lipid head group region is located in the amino- and carboxy-terminal regions of SP-B (1–20) and (53–78), which contain the predicted amphipathic helices. Synthetic peptides that contain these two regions have surface-tension lowering activity similar to that of native SP-B.

SP-B enhances the insertion of phospholipid vesicles into a preformed DPPC/DPPG monolayer, particularly in the presence of divalent cations. SP-B causes lipids in solution to form discoid particles often appearing as stacks or sheets. Together with SP-A, lipids, and Ca^{2+}, SP-B reconstitutes the characteristic structures of tubular myelin, both multilamellar aggregates and material with a square lattice configuration.

SP-B Is Required for Survival after Birth

Deletion of the gene encoding SP-B in mice causes acute respiratory failure at birth, related to surfactant dysfunction. Likewise, conditional deletion of the gene in adult mice causes acute respiratory distress associated with alveolar capillary leak and surfactant deficiency. SP-B deficiency is associated with failure to form lamellar bodies, accumulation of abnormal multivesicular bodies within the type II cells, and misprocessing of proSP-C by alveolar type II cells. Extracellularly, tubular myelin is absent and surfactant activity is deficient, demonstrating that SP-B plays a critical role in surfactant homeostasis.

Hereditary SP-B Deficiency Causes Respiratory Failure at Birth

Homozygous SP-B–deficient infants and mice die of respiratory failure following birth. While lung morphogenesis proceeds normally in SP-B deficient mice in utero, the lack of SP-B causes atelectasis and respiratory failure in the immediate postnatal period. More than 75 infants with SP-B deficiency have now been identified. SP-B deficiency is inherited as an

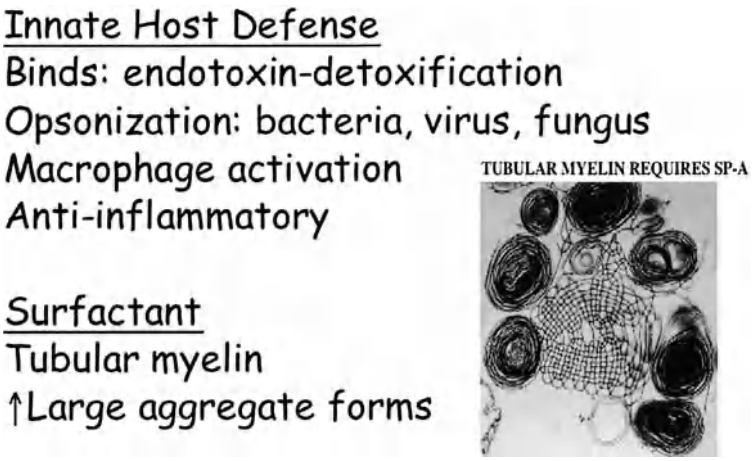

Figure 7-6 Functions of surfactant protein A.

autosomal-recessive mutation in the SFTPB gene, generally presenting in full-term infants with IRDS. The disorder is refractory to surfactant replacement therapy and is generally lethal within the first several months of life. Several infants have undergone lung transplantation. In humans as in mice, SP-B deficiency disrupts the formation of lamellar bodies and tubular myelin, and interferes with the routing of proSP-C. Thus, SP-B–deficient patients and mice lack active SP-B and SP-C proteins in the alveolus; proSP-C accumulates in the airspace, causing a proteinosis-like syndrome. The disorder is generally termed desquamating interstitial pneumonitis depending on age and supportive therapy (Fig. 7-5). The definitive diagnosis is made by identification of the mutations by nucleotide sequence analysis. In most affected infants, SP-B is lacking in bronchoalveolar lavage fluid and the abnormal proSP-C peptide accumulates in the alveoli, findings that can be verified by immunohistochemistry, aiding in the diagnosis of the disorder. Patients with SP-B deficiency do not respond to surfactant replacement and generally succumb from chronic respiratory failure in infancy in spite of intensive care.

ABCA3 Mutations: A Genetic Cause of Respiratory Failure at Birth

ABCA3 is a large, membrane-spanning protein that is present in the limiting membrane of lamellar bodies in type II alveolar epithelial cells. Mutations in the *ABCA3* gene were identified as a cause of severe lung disease in full-term infants. *ABCA3*-related lung disease is inherited as an autosomal recessive gene. A large number of distinct mutations in *ABCA3* have been associated with acute respiratory distress in full-term infants. Generally, affected infants present within the first days of life, and are refractory to conventional therapies, resulting in respiratory failure and death in the first months of life. Pathological findings associated with ABCA3 mutations include proteinosis, cuboidal epithelial cell hyperplasia, interstitial thickening, loss of normal alveolar structure, and features of desquamating interstitial pneumonitis (DIP) (Fig. 7-5). Respiratory failure is not responsive to surfactant replacement, and the only known treatment has been lung transplantation. ABCA3 is a member of the ATP-dependent, Walker domain containing proteins that comprise a family of membrane-associated transport proteins that includes the cystic fibrosis transmembrane conductance regulator (CFTR). ABCA3 homologues mediate lipid transport across membranes. The diagnosis of ABCA3-related lung disease is confirmed by nucleotide sequencing of the gene in infants and children with refractory pulmonary disease. Electronmicroscopy of lung tissue from patients with ABCA3 mutations demonstrates the presence of small, atypical lamellar bodies in alveolar type II epithelial cells and the absence of tubular myelin in the airways, indicating an abnormality in intracellular and extracellular lipid homeostasis.

The Pulmonary Collectins (SP-A and SP-D)

Surfactant Protein A (SP-A)

SP-A is an abundant hydrophilic 26-kD (monomer) glycoprotein that functions in the host defense, and regulation of surfactant lipid structure (Figs. 7-3 and 7-6). SP-A mRNA is expressed in bronchiolar and alveolar type II cells in the lung, being translated from two genes (SFTPA) located on chromosome 10 in the human. In the absence of SP-C and SP-B, SP-A enhances formation of a surface lipid film in the presence of divalent ions, although SP-A is much less effective than the hydrophobic surfactant proteins SP-B and SP-C. SP-A modestly enhances surface activity of lipid films containing SP-C and SP-B. The amino-terminal third of SP-A is arranged in a collagen-like triple helix, while a carboxy-terminal region bears homology to mammalian lectins and serum mannose-binding lectin (MBL). Protein-protein interactions among SP-A molecules mediated by the collagen-like domain and an intermolecular disulfide bond at Cys 9 are necessary for the aggregation of lipids by SP-A. Binding and uptake of SP-A by type II epithelial cells is mediated by a specific, saturable cell-surface receptors; however, the precise nature of SP-A receptors and their intracellular functions remain unclear. The noncollagenous C-terminal domain of SP-A binds to isolated type II cells, suggesting that the receptor-binding site is in the C-terminal region of SP-A. SP-A increases the association of lipids with type II cells but does not appear to increase internalization of lipid, as monitored by uptake of fluorescent

Table 7-1

Surfactant Protein D: Function

Innate host defense	Binds: endotoxin Opsonization: bacteria, virus (RSV, influenza) Macrophage activation Anti-inflammatory
Surfactant	Regulates surfactant lipid pools Influences large/small aggregate surfactant
Regulation of oxidants	SP-D protects from oxidant injury

lipid probes. Deletion of the SP-A gene (Sftpa) in mice does not alter survival or lung function after birth. While tubular myelin is absent, surfactant function, uptake, and secretion are not influenced by deletion of SP-A. SP-A$^{-/-}$ mice are highly susceptible to lung infection by bacterial, viral, and fungal pathogens, indicating that SP-A plays a primary role in innate host defense of the lung.

Surfactant Protein-D

Surfactant protein-D (Table 7-1) is a collagenous Ca^{2+}-dependent carbohydrate-binding protein that is structurally related to SP-A and other C-type lectins (Figs. 7-3). SP-D is encoded by a single gene (SFTPD) located near the SFTPA gene on human chromosome 10. SP-D is synthesized by alveolar type II epithelial cells and is found in the endoplasmic reticulum and Golgi of Clara cells, but it is also expressed in many other tissues. SP-D forms large oligomers that bind carbohydrates and glycolipids on the surface of bacteria, fungi, and viruses. The interaction of SP-D microbial pathogens is Ca^{2+} and carbohydrate dependent. In contrast to surfactant proteins SP-A, SP-B, and SP-C, SP-D is not strongly associated with surfactant lipids in the alveolus but plays an important role in determining surfactant structure and homeostasis.

Function of SP-D In Vivo

Deletion of SP-D in mice has provided insight into its important role in surfactant and alveolar homeostasis. *Sftpd*$^{-/-}$ mice survive after birth, but develop severe pulmonary disease associated with macrophage activation, airspace enlargement, and lipid accumulation. SP-D regulates alveolar pools of large and small aggregate surfactant, influencing surfactant particle size and its uptake by type II epithelial cells. Infiltration with lipid-laden macrophages, and the induction of synthesis of metalloproteinases 2, 9, and 12 by alveolar macrophages, may contribute to the spontaneous airspace remodeling seen in the *Sftpd*$^{-/-}$ mice. *Sftpd*$^{-/-}$ mice are highly susceptible to pulmonary infections and inflammation associated with a viral (respiratory syncytial and influenza virus) and bacterial endotoxin exposure, indicating that SP-D plays a critical role in innate host defense of the lung. SP-D binds bacterial, fungal, and viral pathogens, enhancing their opsonization and their killing by alveolar macrophages. Thus, SP-D plays an important role in the regulation of surfactant lipid homeostasis, innate host defense of the lung, and prevention of inflammation and alveolar remodeling.

RECYCLING AND CATABOLISM OF SURFACTANT LIPIDS AND PROTEINS

Pulmonary surfactant is taken up rapidly in the lung, and much of the lipid is reutilized (Fig. 7-2). Measurements of the efficiency of recycling of phosphatidylcholine (PC) in adult

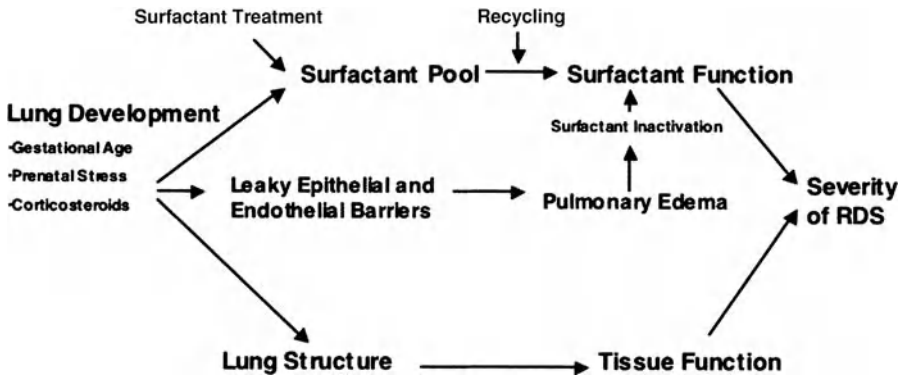

Figure 7-7 Factors influencing the pathogenesis of idiopathic respiratory distress syndrome (IRDS). The pathogenesis of IRDS is multifactional. Immaturity of the alveolar type II cells results in decreased surfactant pools. Lung collapse and injury are caused by surfactant deficiency. Alveolar damage causes leakage of serum proteins and edema, which inactivate surfactant, increasing the severity of respiratory distress. Surfactant treatment reduces surface tension, restores phospholipid pool sizes, and improves alveolar-capillary leak to maintain surfactant function. *(Courtesy of Dr. Alan Jobe).*

rabbit lungs range between 23 and 85 percent, with approximately 10 percent of the alveolar pool of 10 to 15 mg/kg total body weight being recycled every hour. In neonatal rabbits, 94 percent of the PC is reutilized, with a turnover time of the alveolar PC of 10 h. Some 30 to 50 percent of intratracheally injected ^{3}H-PC is sequestered from the alveolar space within a few minutes after instillation and cannot be removed by lavage. After intratracheal administration, labeled lipid appears in type II cells and alveolar macrophages, but is not found in type I cells, indicating that the type II cells actively take up surfactant lipids from the alveolus for recycling or catabolism. Isolated epithelial type II alveolar cells internalize ^{3}H-PC and resecrete the internalized material or degrade it with reincorporation into other lipids. Isolated type II cells endocytose SP-C and SP-B. SP-A also binds to type II cells and is endocytosed by a receptor-mediated mechanism.

Pulmonary surfactant as isolated from lavage fluid exists in several forms that can be fractionated based on density. In vivo labeling indicates that phospholipid is initially secreted in the heaviest forms, followed by conversion into distinct heavy and light forms. The most dense or ultraheavy form contains lamellar bodies and tubular myelin. The heavy forms of tubular myelin are also referred to as large aggregates (LA). A light form, or small aggregates, is comprised of small unilamellar vesicles. Unlike the other two forms, the light form has little surface activity in vitro and is ineffective in enhancing lung compliance in preterm animals. Small aggregate surfactant is inactive, being depleted of SP-A, SP-B, and SP-C, and their lipid composition is similar to that of large aggregates. SP-A and SP-D play important roles in the maintenance of large aggregate surfactant structure. Cycling surfactant by expansion and contraction of surface film in vitro converts lipids from large to small aggregates that are likely remnants destined for catabolism or recycling.

REGULATION OF SURFACTANT PRODUCTION

The synthesis of pulmonary surfactant is subject to precise regulatory controls both during development and postnatally. Surfactant phospholipid synthesis increases markedly in late gestation and is enhanced by a variety of hormones, including glucocorticoids in the fetal lung. Lung phospholipid content increases in the latter two-thirds of gestation in preparation for respiratory adaptation at birth. Prenatal glucocorticoids are routinely used to induce lung maturation and surfactant synthesis in infants at risk for preterm delivery. Glucocorticoids reduce the risk of IRDS and enhance the efficacy of surfactant replacement therapy after birth. Like surfactant phospholipids, the surfactant proteins are highly regulated, increasing in the latter two-thirds of gestation in the mammalian species studied. Expression of surfactant proteins is regulated in complex ways by a variety of hormonal agents. The levels of surfactant protein mRNA increase in the perinatal period in association with increased surfactant synthesis and secretion required for postnatal respiratory adaptation. Expression of the surfactant proteins is regulated at both transcriptional and posttranscriptional levels, maintaining steady-state protein concentrations within tight constraints in the adult lung. Surfactant production is, in general, enhanced by glucocorticoids, epidermal growth factor (EGF), and cyclic adenosine monophosphate (cAMP) but inhibited by tumor necrosis factor-alpha (TNF-α), transforming growth factor-beta (TGF-β) and insulin, depending on experimental conditions. Transcriptional control of the surfactant genes is modulated by interactions with nuclear transcription proteins including thyroid transcription factor-1 (TTF-1), members of the HNF-3 family (Foxa1 and Foxa2), retinoic acid receptors (RARs), and associated co-activators. Surfactant proteins A, B, and D are expressed in bronchiolar and alveolar type II cells, while SP-C is expressed exclusively in type II epithelial cells. Transcriptional and posttranscriptional mechanisms influence the synthesis of surfactant proteins and lipids, regulating surfactant concentrations in the airspace during development and repair.

Critical Role of GM-CSF Signaling in the Catabolism of Surfactant

While less than 10 to 15 percent of surfactant lipids is cleared by catabolism by alveolar macrophages, this pathway is critical in controlling steady-state surfactant concentrations in vivo. Granulocyte-macrophage colony-stimulating factor (GM-CSF) and GM-CSF receptor (common ß-chain) are required for normal surfactant catabolism in the mouse. Surfactant protein and lipid clearance is decreased in GM-CSF$^{-/-}$ and GM-receptor deficient mice in which severe pulmonary alveolar proteinosis is associated with failure to clear surfactant proteins and phospholipids. Therefore, GM-CSF signaling is required for normal clearance and catabolism of surfactant by alveolar macrophages. Recent clinical studies demonstrate that idiopathic pulmonary alveolar proteinosis (PAP) in adults is caused by autoantibodies against GM-CSF. Similar abnormalities in surfactant homeostasis, alveolar macrophage morphology and function are observed in mice lacking GM-CSF signaling and in patients with PAP (see Chapter 79). Administration of GM-CSF, both systemically and intratracheally, has been utilized for connection of the surfactant accumulations in the mouse and in clinical studies in patients with PAP.

SURFACTANT HOMEOSTASIS AND REPLACEMENT IN INFANTILE RESPIRATORY DISTRESS SYNDROME

IRDS is associated with prematurity, the risk increasing as gestational age decreases. In addition to the morphologic immaturity of the respiratory tract, lung phospholipid content and surfactant secretion are decreased in preterm infants. While functional surfactant can be isolated from infants with

IRDS, surfactant pool sizes are markedly decreased in the preterm compared to the term infant, and the surface activity of surfactant from infants with IRDS is decreased. Alveolar-capillary leak of serum proteins, including albumin, causes inactivation of surfactant. Decreased alveolar surfactant activity associated with pulmonary immaturity causes atelectasis, alveolar collapse, and hypoxemia, characteristic of IRDS in the preterm infant. A schematic representing factors influencing the pathogenesis of IRDS is provided by Fig. 7-7.

Supplemental oxygen and ventilatory therapy are used to treat IRDS. However, during the last two decades, widespread use of exogenous surfactant has markedly ameliorated the morbidity and mortality associated with this common disease of preterm infants. Exogenous surfactants—in the form of synthetic mixtures of phospholipids and extracts of lung or surfactant containing surfactant proteins B, C, and phospholipids—have been used extensively for prevention and therapy of RDS in newborn infants. Surfactant replacements with preparations containing surfactant proteins B and C act rapidly, increasing lung volumes and compliance, and decreasing the requirements for positive-pressure ventilation and oxygen. Morbidity and mortality from IRDS have been markedly reduced since the application of surfactant replacement to preterm neonates, decreasing barotrauma, pneumothorax, and mortality from the disorder. Surfactant replacement is given intratracheally, resulting in improved lung function and oxygenation. Synthetic surfactants lacking surfactant proteins improve lung function in a delayed manner, but treatment with both synthetic and protein-containing surfactant has been highly effective in decreasing morbidity and mortality from IRDS in clinical studies and is now standard treatment for IRDS. The effectiveness of surfactant therapy is likely related both to the immediate surface tension–reducing properties and the reuptake and reutilization of the exogenous surfactant particles by the respiratory epithelium. Following preterm birth, production of endogenous surfactant lipids and proteins by the respiratory epithelium is rapidly induced; therefore, surfactant replacement is primarily utilized in the first few days following birth. Surfactant replacement has been used successfully in the treatment of meconium aspiration and pneumonia in neonates.

SURFACTANT IN ADULT RESPIRATORY DISTRESS SYNDROME

Adult respiratory distress syndrome occurs in association with trauma, sepsis, long bone fractures, thermal burns, and injury to the lung from aspiration of gastric contents, pneumonia, and inhalation of toxic gases (see Chapter 59). The prognosis in ARDS patients remains poor, with approximately 30 to 50 percent mortality in most studies. In ARDS, increased permeability of the microvasculature permits leakage of protein and fluid into the lung, inactivating surfactant. Epithelial cell injury may also contribute to surfactant deficiency in ARDS. Various nonsurfactant proteins and lipids present in elevated concentrations in the lung in ARDS have been implicated in reducing surface activity of pulmonary surfactant; these include immunoglobulins, albumin, fibrinogen, fatty acids, lyso-phosphatidylcholine, and C-reactive protein. The mechanisms causing the decrease in surfactant activity in ARDS include competition of the proteins for the air-liquid interface, sequestration and dilution of surfactant in non–surface-active particles, and inhibition of surfactant protein and lipid synthesis and secretion. Alterations in surfactant composition occur during ARDS and may precede the development of respiratory failure. Lavage phospholipid, SP-A, and SP-B are decreased, and the minimum surface tension of surfactant tested in vitro is increased in patients at risk for ARDS. In ARDS, total phospholipid, phosphatidylcholine, phosphatidylglycerol, and surfactant proteins SP-A and SP-B are decreased and the ratio of small to large aggregates is significantly increased compared with that in non-ARDS patients. Thus, ARDS leads to both a deficiency in pulmonary surfactant constituents and inhibition of the activity of the remaining surfactant. ARDS and related syndromes are associated with protein leak into alveolar space and inactivation of surfactant function. While surfactant has been effective in ARDS syndromes in laboratory experiments, to date, clinical studies have not supported the routine use of surfactant replacement for RDS in adult patients.

INHIBITION OF SURFACTANT ACTIVITY

Phospholipases A_2 and C and their products, fatty acids, lysoPC, and dipalmitin inhibit surface activity in vitro. These molecules may be released or produced during lung injury. Inhibitory effects of oleic acid may be related to its miscibility with phospholipids, disrupting the interfacial surfactant film, rather than by competition for the interface. The inhibition by PAF, lysoPC, and oleic acid is not reversible, suggesting that their direct interaction with surfactant lipids disrupts lipid organization at the interface. However, not all fatty acids are inhibitory. Additional palmitic acid improves surfactant function of surfactant preparations used for therapy of IRDS. The surface activity of pulmonary surfactant is readily destroyed by phospholipase A_2 or phospholipase C. In injured lungs, inhibition of surface activity by fatty acids and proteins may be additive, since they appear to inhibit surfactant activity by different mechanisms.

Oxygen therapy, used routinely for ARDS and IRDS, may influence surfactant homeostasis and function in the alveolus. The rate of synthesis of surfactant lipids and clearance of radiolabeled surfactant extracts decreased in rabbits exposed to 100% O_2 for 64 h. In contrast, exposure of adult rats to 85% O_2 increased expression of surfactant proteins SP-A, SP-B, and SP-C, and phospholipids. Oxidants are also released locally in the lung by activated immune cells. Activated alveolar macrophages secrete NO and superoxide, which can then react to form peroxynitrite. Peroxynitrite in combination

with Fe^{3+} EDTA inhibited the surface activity of surfactant by damaging lipids or the surfactant proteins.

Edema fluid leaks into the airspace in both ARDS and IRDS. Edema fluid obtained from hyperoxia-exposed rabbits contains serum proteins capable of inhibiting surface activity of surfactant extracts, as evaluated in the pulsating bubble apparatus. Thus, edema fluid may interfere with surfactant therapy, although the concentration dependence of the inhibition suggests that increased doses of surfactant may aid in overcoming the inhibitory effects of edema fluid.

Plasma Proteins Inactivate Pulmonary Surfactant

Serum albumin, globulin, and fibrinogen reduce the rate of adsorption, increase the minimum surface tension of the surfactant film, and reduce the hysteresis area between compression and expansion curves in vitro. The mechanism by which plasma proteins inhibit the activity of pulmonary surfactant is likely to be one of competition for the interface, because higher surfactant lipid concentrations overcome albumin inhibition even at high albumin concentrations. Inhibition by C-reactive protein, fibrinogen, and other plasma proteins is reversible. Addition of SP-A and organic surfactant extracts reverses inhibition caused by soluble proteins but not by lysoPC. Both SP-C and SP-B increase the ability of a phospholipid mixture to resist inhibition of surface activity by plasma proteins. SP-B is more effective than SP-C at resisting inhibition by fibrinogen. The best resistance to surfactant inhibition by serum protein was observed when both SP-C and SP-B were present.

REDUCTION OF SURFACTANT SYNTHESIS

In addition to the inactivation of pulmonary surfactant by proteins and lipids in edema fluid, a reduction of synthesis of surfactant may contribute to the decreased surfactant activity in ARDS. *Escherichia coli* endotoxin-inhibited surfactant synthesis in lung organ cultures. Synthesis of surfactant proteins is also influenced by inflammatory responses following lung injury or infection. TNF-α decreased de novo synthesis of SP-A, SP-B, and SP-C mRNA, and caused respiratory distress and decreased SP-C mRNA when administered intratracheally to the mouse. TGF-β1, produced during lung injury, decreased the expression of SP-A and SP-C in vitro. Thus, sepsis or lung injury may reduce both the synthesis and functions of surfactant lipids and proteins.

CONCLUSIONS

Pulmonary surfactant is required for airbreathing after birth and for protection of the lung from microbial pathogens. Surfactant homeostasis requires the integrated functions of surfactant proteins and lipids to reduce surface tension in the alveolus. Decreased production or inactivation of pulmonary surfactant has been associated with both IRDS and ARDS. Mutations in genes mediating surfactant protein synthesis (SFTPB and SFTPC) are rare genetic causes of severe acute and chronic lung disease. Likewise, mutations in ABCA3, a lamellar body–associated transport protein, blocks lipid packaging into the lamellar body, and is associated with fatal pulmonary disease in newborn infants and chronic interstitial lung disease in older individuals. Surfactant production and activity are inhibited following injury and alveolar capillary leak. Surfactant function may be further impaired by dilution caused by pulmonary edema and the action of phospholipases. Conversion of active, large aggregate forms of surfactant, to inactive, small aggregate forms that are depleted of the surfactant proteins is accelerated in the injured lung. Surface activity of the remaining surfactant is reduced further by competition with plasma proteins for the air-water interface. Surfactant deficiency and inactivation accompanying RDS in infants can be overcome by treatment with exogenous surfactant. Surfactant therapy for IRDS in premature infants has been highly successful, reducing morbidity and mortality from pulmonary disease. While in early phases of study, therapy with exogenous surfactant preparations containing the surfactant proteins SP-C and SP-B may also be useful in treatment of other lung disorders associated with disruption of surfactant homeostasis.

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8

Transport Function of Airway Epithelia and Submucosal Glands

Paul B. McCray, Jr. • Michael J. Welsh

Secretion and solute transport by epithelial cells that line the airways and comprise the submucosal glands play key roles in the biology of the normal lung. Moreover, abnormalities in airway epithelial and submucosal gland function contribute to the pathogenesis and pathophysiology of several inherited and acquired diseases. Two major functions of these cells are the production and modification of airway surface liquid (ASL) and the secretion of a number of factors that contribute to host defenses. The active transport of electrolytes by surface cells regulates the volume and composition of airway fluid. The specialized cells of submucosal glands also contribute to the secretion of airway surface fluid and are a major producer of macromolecules, including mucins. Together the products and function of these epithelia generate a local host defense system that protects the lungs from inhaled organisms and particulate material.

This chapter describes the function of the surface epithelia and the submucosal glands and their roles in host defense. Despite progress, significant gaps in knowledge persist; these are also noted.

BIOLOGY OF EPITHELIA COVERING THE AIRWAY SURFACE

Morphologic Features Related to Function

Although morphologic aspects of airway epithelia are covered in another chapter, two morphologic features required for transepithelial transport of solute and water are worth considering. First, the epithelial cells are joined at their apical surface by tight junctions. The tight junctions and sheet of epithelial cells form a continuous barrier to solute and water movement. Yet, despite their name, tight junctions do not constitute an impermeable barrier; they have selective permeabilities to ions and other solutes. Thus, solutes can move

across the epithelium through two pathways: between the cells through the tight junctions (the paracellular pathway) or through the epithelial cells (the cellular pathway). Second, epithelial cells are polar; the apical membrane, which faces the mucosal surface, is different from the basolateral membrane, which faces the submucosal or interstitial space. The morphologic differences between the two membranes are paralleled by biochemical and functional differences. Hormone receptors and ion transporters are segregated to one or the other of the two cell membranes. These morphologic features allow the epithelium to serve as a barrier separating the luminal compartment from the interstitial compartment, modify the composition of those compartments by net vectoral transport of electrolytes and macromolecules, and selectively respond to signals from either compartment.

Proximal airway epithelium is a pseudostratified, columnar epithelium composed predominantly of ciliated cells, goblet cells, nonciliated cells, and basal cells. The distal airway epithelia contain mostly ciliated and nonciliated bronchiolar (Clara) cells. In the proximal airway epithelium, studies with intracellular microelectrodes suggest that ciliated surface cells play an important role in both sodium (Na^+) and chloride (Cl^-) transport. Transepithelial electrical resistance (Rt, a measure of the ionic permeability of the epithelium) ranges from 150 to 1000 $\Omega \times cm^2$ in proximal airways and decreases in more distal airways.

In Vivo Studies of Electrolyte Transport

Electrolyte transport by human airway epithelia has been studied in vivo by measuring the voltage across the epithelium (Vt, mucosal surface referenced to interstitial surface). Most frequently this has been done across the nasal epithelium, but qualitatively similar measurements have been made in the large intrapulmonary airways. As shown by the example in Fig. 8-1, Vt across normal human airway epithelia in vivo is in the range of –5 to –20 mV. Because Vt equals the product of Rt and electrical current, knowledge obtained from in vivo Vt measurements is limited in scope; such studies do not assess quantitative aspects of transport, they provide only minimal insight into the cellular and molecular mechanisms involved, and they do not measure electrically silent transport. Nevertheless, important clues have been obtained from measurements of Vt in the presence of various agents perfused onto the epithelial surface. Figure 8-1 shows that when the apical surface is perfused with a solution containing amiloride, which blocks Na^+ channels, Vt decreases. This finding demonstrates the presence of electrogenic Na^+ transport, although it does not determine the magnitude. If the apical surface is then perfused with a solution containing a low Cl^- concentration and an agonist such as terbutaline, which increases cellular levels of adenosine 3′,5′-cyclic phosphate (cAMP), Vt hyperpolarizes. This result, plus the finding that Vt does not hyperpolarize in people with cystic fibrosis (CF) (Fig. 8-1*B*), indicates that the apical membrane contains Cl^- channels, which as described below are CF transmembrane conductance regulator (CFTR) Cl^- channels. Finally, if

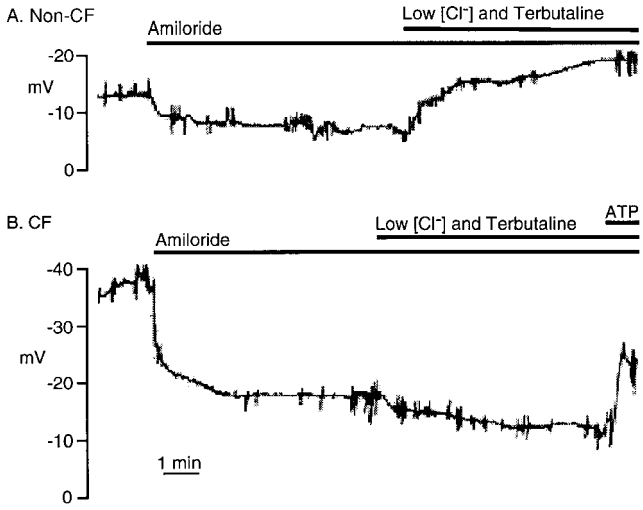

Figure 8-1 Examples of transepithelial voltage (Vt) measured in vivo across the airway epithelium of the nasal mucosa. Amiloride, a solution containing a low Cl^- concentration plus terbutaline, and ATP were present during times indicated by the bars. Top trace *(A)* was from a normal person; bottom trace *(B)* was from a person with cystic fibrosis. (Provided by Dr. Joseph Zabner and Jan Launspach.)

the apical surface is perfused with adenosine 5′-triphosphate (ATP) or another nucleotide in the presence of low Cl^- concentration, Vt transiently hyperpolarizes, indicating the presence of another type of Cl^- channel in the apical membrane. This is particularly prominent in CF epithelia that lack CFTR Cl^- channels.

Thus, measurements of Vt in vivo provide valuable qualitative information about the airways. As a result, they are used frequently to assess airway function in disease states and as an assay to test the effect of potential therapeutic agents.

In Vitro Studies of Airway Epithelia

In vitro studies have increased understanding of mechanisms of electrolyte transport. Although studies from many species have contributed to knowledge of airway biology, here we focus on human airway epithelia. The ability to culture human airway epithelial cells was an important advance for many studies of the airways. Primary cultures of human airway epithelia can be grown on permeable filter supports, often at the air-liquid interface, so that they differentiate, generate a ciliated surface, develop tight junctions, and form distinct apical and basolateral membranes. To study electrolyte transport, cultured epithelia or native epithelia can be mounted in Ussing chambers in which the apical and basolateral compartments are separated. Vt can be measured and controlled (clamped) to desired values. The transepithelial electrical resistance can be determined by measuring the change in Vt that results from an applied current pulse. The short-circuit current (Isc) is measured when Vt is clamped at 0 mV and both sides of the epithelium are bathed with identical solutions. Under these conditions, the Isc is equal to the sum of all active, electrogenic, transepithelial transport.

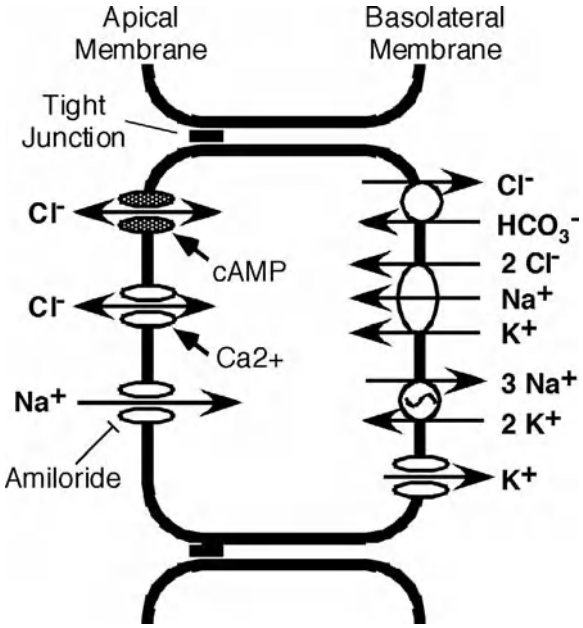

Figure 8-2 Cellular and molecular mechanism of electrolyte transport by airway epithelia. Note that cAMP-dependent and Ca^{2+}-dependent Cl^- secretion and amiloride-sensitive Na^+ absorption appear to occur in the same cell type. The CFTR Cl^- channel, which is defective in cystic fibrosis, is indicated by shading; all other channels, transporters, and pumps are indicated by open symbols.

Cellular and Molecular Mechanisms of Electrolyte Transport

The cellular and molecular mechanisms of transepithelial transport are depicted graphically in Fig. 8-2. Although the magnitude and contribution of specific processes to net transport vary depending on the airway region and experimental conditions, the cellular mechanisms appear similar throughout the airways. As described below, several aspects also apply to the function of submucosal gland epithelia. When the epithelium is studied in vitro, the Isc is accounted for by the absorption of Na^+ from the mucosal to the submucosal surface and anion secretion in the opposite direction. In human epithelia, electrogenic absorption of Na^+ makes a greater contribution to Isc than does anion secretion. In fact, definite identification of Cl^- secretion in human airway epithelia often requires inhibition of Na^+ absorption and opening of Cl^- channels.

The main features of the model for Na^+ transport (Fig. 8-2) include: (1) Na^+ enters the cell through apical membrane epithelial Na^+ channels (ENaC). ENaC channels are inhibited by apical amiloride. Entry is a passive process, with Na^+ flowing down favorable concentration (the intracellular Na^+ concentration is lower than the extracellular concentration) and electrical (intracellular voltage is negative relative to the apical side of the membrane) gradients. (2) Na^+ then exits across the basolateral membrane via the Na^+-K^+-ATPase. This enzyme powers transepithelial transport by using energy from ATP hydrolysis to pump Na^+ out of the cell, thereby maintaining a low intracellular Na^+ concentration. The Na^+-K^+-ATPase also accumulates K^+ inside the cell. (3) K^+ exits passively through basolateral membrane K^+ channels. The basolateral K^+ conductance and the K^+ concentration gradient (high intracellular and low extracellular K^+ concentrations) hyperpolarize the cell, providing part of the driving force for Na^+ entry at the apical membrane.

Under short-circuit conditions in the presence of amiloride, the epithelium can secrete Cl^- or HCO_3^-. The mechanisms for Cl^- secretion (Fig. 8-2) are: (1) Cl^- enters across the basolateral membrane via an electrically neutral cotransport process, coupled to Na^+ and K^+. Entry of Na^+ down its electrochemical gradient provides the driving force for accumulation of Cl^- at a concentration above electrochemical equilibrium. (2) Cl^- exits passively through apical membrane Cl^- channels, moving down a favorable electrochemical gradient. Regulation of the apical Cl^- permeability controls, in part, the rate of transepithelial Cl^- transport. There are at least two types of apical Cl^- channels: CFTR Cl^- channels, which are regulated by phosphorylation by cAMP-dependent protein kinase, and Cl^- channels that are activated by an increase in the cytosolic concentration of free Ca^{2+} $[Ca^{2+}]_c$. The molecular identity of the Cl^- channels controlled by $[Ca^{2+}]_c$ are not yet known. (3) Na^+ that enters the cell at the basolateral membrane coupled to Cl^- exits across the basolateral membrane via the Na^+-K^+-ATPase. (4) K^+ that enters coupled to Cl^- and on the Na^+-K^+-ATPase exits passively through basolateral membrane K^+ channels. When the epithelium is studied in an Ussing chamber under open-circuit conditions (i.e., when Vt is not clamped), often little net Cl^- transport is measured, and Cl^- absorption can occur.

The mechanisms for HCO_3^- and Cl^- secretion are similar except that HCO_3^- enters through a basolateral Cl^-:HCO_3^- exchanger before exiting through CFTR. How epithelia vary and control the proportions of Cl^- and HCO_3^- transport are not well understood. The basolateral membrane also contains a small Cl^- conductance of uncertain molecular identity. These channels may serve as a pathway for anion absorption and may influence the proportion of Cl^- and HCO_3^- secretion.

The CFTR Cl^- Channel

Because the gene for CFTR is mutated in patients with CF, the CFTR Cl^- channel has been studied extensively. CFTR is a member of a protein family named ATP-binding cassette (ABC) transporters. CFTR sits in the apical membrane and within intracellular vesicles beneath the apical membrane. Although epithelia lining the pulmonary airways express little CFTR, the Cl^- channel function (and its absence in CF) is easily measured. This is so because ion channels are very efficient, with an ability to transport 10^6 to 10^7 ions per second. Thus only a relatively few molecules of CFTR are sufficient to support transepithelial Cl^- transport.

As shown in Fig. 8-3, CFTR contains at least five domains: two membrane-spanning domains (MSDs), each composed of six transmembrane segments; an R domain, which contains several consensus phosphorylation

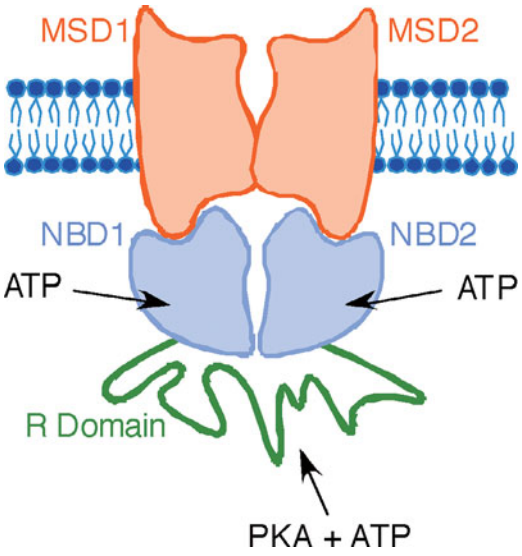

Figure 8-3 Model showing the proposed domain structure of CFTR. *MSD* refers to the membrane spanning domains, *NBD* refers to the nucleotide-binding domains, and *PKA* refers to cAMP-dependent protein kinase. The NBDs and R domain are on the cytosolic side of the membrane.

sequences; and two nucleotide-binding domains (NBDs), which interact with ATP. Each of the different domains contributes to the protein's function. The MSDs combine to form the channel pore and determine anion selectivity. The R domain controls channel activity. The balance of kinase (especially cAMP-dependent protein kinase) and phosphatase activity determines the state of R domain phosphorylation. When the R domain is phosphorylated, the channel can open. Regulation by phosphorylation seems complex because the R domain contains several sites that are phosphorylated, and we do not yet understand how individual phosphorylation sites interact to determine overall activity.

The NBDs also control channel activity. ATP binding and enzymatic activity, either adenylate kinase ($ATP + AMP \leftrightarrows ADP + ADP$) or ATPase ($ATP + H_2O \rightarrow ADP + P_i$), gate the channel. It appears that nucleotide-dependent dimerization of the two NBDs is a central feature of gating. The combination of electrophysiological, biochemical, and structural investigations of the NBDs is providing rapid progress in understanding how this interesting molecule works and how mutations disrupt its function in CF.

Regulation of Electrolyte Transport

A variety of neurohumoral and pharmacologic agents regulate the rate of transepithelial electrolyte transport by the airway epithelia. Extracellular signals regulate two main second messengers: cAMP and $[Ca^{2+}]_c$. An increase in levels of cAMP activates cAMP-dependent protein kinase, which phosphorylates and thereby activates CFTR Cl^- channels, basolateral $Na^+/K^+/Cl^-$ co-transporters, and probably some basolateral K^+ channels. An increase in $[Ca^{2+}]_c$ appears to activate a population of apical Cl^- channels and some basolateral K^+ channels. An increase in $[Ca^{2+}]_c$ and diacylglycerol also may activate protein kinase C, which can modulate the activity of CFTR and several transporters. Most agents that regulate transport tend to stimulate transepithelial Cl^- transport; less is known about how Na^+ transport is regulated. Under some conditions cAMP may stimulate Na^+ absorption, and an increase in $[Ca^{2+}]_c$ may inhibit transport. As in a variety of other Na^+-absorbing epithelia, aldosterone also may regulate Na^+ absorption, although the effect appears to be variable.

A number of hormones, neurotransmitters, and autocoids regulate the intracellular levels of cAMP. The epithelia contain receptors for and respond to β-adrenergic agonists, prostaglandins, adenosine, and vasoactive intestinal peptide. The level of $[Ca^{2+}]_c$ is controlled by bradykinin, substance P, leukotrienes, and nucleotides, such as ATP. Extracellular nucleotides are of particular interest, because they interact with receptors on the apical surface of the epithelium, and by activating Ca^{2+}-activated Cl^- channels they stimulate transepithelial Cl^- transport through a pathway other than the CFTR Cl^- channel.

Effect of Electrolyte Transport on Fluid Transport and Ion Concentrations

Despite much progress in understanding cellular and molecular mechanisms, there is a persistent paucity of knowledge about the integrated physiology of the airways. Liquid transport has been studied in cultured human airway epithelial cells. Active Na^+ absorption drives liquid absorption under baseline conditions. Adding amiloride and agonists that increase cellular levels of cAMP stimulate liquid secretion. The ASL depth is estimated at 5 to 15 μm, thus predicting that 500 to 1500 nl of ASL over each cm^2. While the measured rates of transepithelial liquid transport indicate that the epithelium can secrete or absorb several times this volume over a 24-h period, those studies suffer from the limitation that of necessity they have often been performed with the mucosal surface covered by a comparatively large volume of fluid or following liquid addition. As a result, the effects on net transport of surface forces and the composition of the ASL may not have been apparent.

Current knowledge of the composition and the regulation of ASL is inadequate, and major controversies persist in the literature. Uncertainty and apparently conflicting data result in large part from the small volumes, inaccessibility of the respiratory tract fluid, a variety of model systems, potential species differences, and diverse assay procedures. The uncertainty is compounded by variable results obtained in CF models. Most but not all studies suggest that ASL has a NaCl concentration less than that of serum. However, because the epithelium is very water permeable, the forces that maintain osmotic balance are uncertain. Much more work is needed to learn how fluid composition varies in different airway regions, how it is modified by specific electrolyte transport processes, how liquid flow between airway regions affects volume and composition, and how evaporation changes composition.

BIOLOGY OF AIRWAY SUBMUCOSAL GLANDS

Development

Human submucosal gland development is a prenatal event, beginning at 10 to 12 weeks of gestation. From then until about 25 weeks of gestation, glands appear first in the trachea, then outward to the cartilaginous bronchi. Gland formation is completed before birth and involves budding morphogenesis and migration of surface epithelial cells into the submucosa and formation of a progressively more complex system of branching ducts and tubules. The area and complexity of glands continue to increase postnatally. Recent evidence suggests that more than one surface epithelial cell type serves as a progenitor in the formation of submucosal glands, and expression of the transcription factor Lef1 is required for gland development. Whereas gland hyperplasia may occur with disease states such as chronic bronchitis and CF, the total number of glands appears to be established before birth with little change in number postnatally. It is estimated that 4000 glands are present in the adult human trachea.

Structure and Cell Types

Submucosal glands are complex tubuloacinar structures reflecting the diverse functions of the gland. The cell volume of submucosal glands is approximately 40 times greater than that of the secretory (goblet) cells of the surface epithelium. The glands are predominantly located in the submucosal tissue between cartilage plates in trachea and bronchi and are normally absent from the bronchiolar region. In the adult trachea, submucosal glands occur at a frequency of about $1/mm^2$. As shown in Fig. 8-4, each gland has four anatomic regions. A narrow ciliated duct is lined by ciliated epithelia in continuity with the surface epithelium. The ciliated duct epithelia are morphologically similar to ciliated cells of the surface epithelium. A wider collecting duct is lined by cells containing numerous mitochondria that stain positive with eosin and other poorly characterized cells. Mucous tubules and acini consist of cells rich in acidic glycoconjugates and stain positive with PAS and Alcian blue. Serous tubules and acini are composed of serous cells containing neutral glycoconjugates and are located distal to mucous tubules. Serous cells are also PAS positive but do not stain with Alcian blue. Mucous and serous cells also can be differentiated by specific patterns of staining with several lectins. Multiple branches of mucous and serous tubules occur from each collecting duct, terminating in a variable number of acini. The mucous and serous cells are the main epithelial components of the submucosal gland. In addition to these cells, contractile myoepithelial cells surround the acini and secretory tubules of glands and may be important in the short-term responses of glands, causing the ejection of secreted mucus and fluid from ducts and tubules.

Submucosal Gland Physiology

The functions of submucosal glands appear to be twofold: (1) the secretion of fluid and electrolytes, which contributes to the periciliary fluid layer and hydration of mucus; and (2) the secretion of macromolecules, including mucins and proteins that contribute to host defenses in the airways. The viscous secretions of mucous cells are rich in high-molecular-weight glycoconjugates. In contrast, the secretions of serous cells are less viscous. The thinner secretions of the distally oriented serous cells probably serve to hydrate and mobilize the thicker secretory products of mucous cells. Submucosal glands are richly innervated by postganglionic fibers from both the sympathetic and parasympathetic nervous systems. These fibers release norepinephrine and acetylcholine and produce neuropeptides such as substance P, calcitonin gene-related peptide (CGRP), and vasoactive intestinal peptide (VIP).

Electrolyte Transport in Submucosal Glands

The cellular mechanisms of ion transport in human submucosal glands are under investigation, and some data come from animal studies. Similar to the surface epithelium, the movement of water across submucosal gland epithelia is osmotically coupled to the net direction of active electrolyte transport. Both secretory and absorptive pathways for electrolyte movement are distributed in a polarized fashion in gland epithelia (Fig. 8-2). Serous cells express CFTR at the apical membrane, and the level of expression is greater than the surface epithelium. Submucosal glands also express ENaC in both ductal and acinar epithelia. The Isc of mixed seromucous cell cultures is inhibited by ouabain on the basolateral

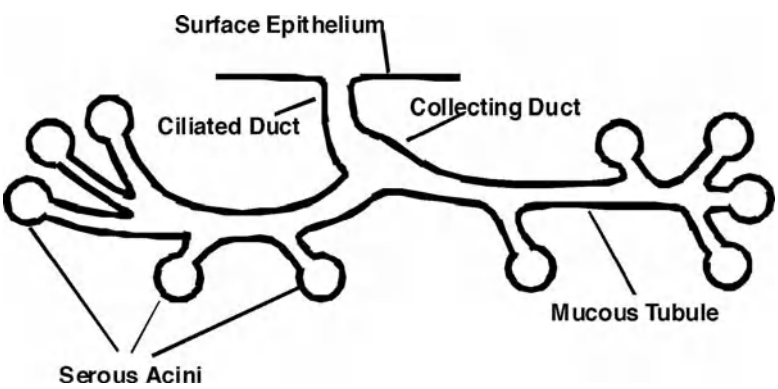

Figure 8-4 Model of submucosal gland from human trachea. The anatomic regions shown include ciliated duct, collecting duct, mucous tubules, and serous acini. See text for details.

membrane, indicating the presence of Na^+/K^+-ATPase. Thus, the pathways for ion movement across gland epithelia bear great similarity to those of the surface cells.

Advances in the isolation and culture of human serous and mucous cells from submucosal glands have brought new insights into submucosal gland physiology. The serous cells of the submucosal gland contribute greatly to the secretion of electrolytes and airway surface fluid. Unlike the surface epithelia, which exhibit absorptive transport properties in the resting state, the serous cells are predominantly Cl^- secretory. Serous gland epithelia exhibit cAMP-activated Cl^- secretion consistent with CFTR function. The Cl^- secretory capacity and CFTR protein expression of serous cells is greater than the mucous cells; thus, the serous cell is probably the predominant source of fluid secreted by submucosal glands. Cl^- secretion is induced by agents that increase $[Ca^{2+}]c$, indicating that, like the surface epithelium, submucosal glands express Ca^{2+}-activated Cl^- channels. When applied to the apical membrane of isolated human submucosal glands, cell preparation amiloride inhibits the Isc, suggesting that in addition to secreting Cl^-, the cells of the gland can modify the volume and composition of secretions by absorbing Na^+.

Electrolyte transport across submucosal gland epithelia is regulated by several secretagogues, including cholinergic agonists, adrenergic agents, bradykinin, and neuropeptides. In contrast to the surface epithelium, cholinergic pathways and agents that increase intracellular Ca^{2+}, rather than β-adrenergic pathways, are the major stimuli for Cl^- secretion in gland epithelia. This information comes from several sources, including receptor autoradiography, receptor binding assays, and in vitro physiology studies. A list of neurohumoral agents regulating Cl^- secretion in submucosal glands is listed in Table 8-1.

Table 8-1

Neurohumoral Regulation of Submucosal Gland Cl^- Secretion

	Target Cell Type	
Agent	**Mucous**	**Serous**
Methacholine	−	++
Histamine	−	+
α Adrenergic	+	+
β Adrenergic	+	++
Bradykinin	+	+
Substance P	+	+

A negative sign (−) indicates no demonstrated effect, and a plus sign (+) indicates stimulation of Cl^- secretion.

Table 8-2

Macromolecular Products of Submucosal Glands

Product	**Cell of Origin**	**Proposed Function**
Mucins	Mucous	Component of mucus blanket
Glycoconjugates	Mucous, serous	Component of mucus blanket
Lysozyme	Serous	Antimicrobial
Lactoferrin	Serous	Antimicrobial
Secretory component	Serous	Antimicrobial
Antileukoproteinase	Serous	Antimicrobial
Peroxidase	Serous	Antimicrobial
Proline-rich proteins	Serous	Antimicrobial
Antimicrobial peptides (β-defensins, LL37)	Mucous, serous	Antimicrobial

Note: The macromolecular products of submucosal glands, the cell of origin (mucous, serous, or both) and proposed function are listed. Note that glycoconjugates are a product of both cell types. Many of the products exhibit antimicrobial properties. See text for details.

Secretion of Macromolecules and Proteins

In addition to the transport of fluid and electrolytes, submucosal glands are the major source of airway mucins and secrete several protein products listed in Table 8-2. Histochemical stains demonstrate that both the serous and mucous cells of the glands produce glycoproteins. Mucous cells contain predominantly acidic glycoconjugates, identified as large, electron neutral granules, whereas serous cells contain neutral, more heavily sulfated glycoconjugates in smaller, electron-dense granules. Although both mucous and serous cells express mRNAs for mucin genes, mucin production is restricted to the mucous cells. The control of secretion by mucous cells is complex. Cholinergic stimuli cause degranulation of both mucous and serous cells. Neuropeptides, including substance P and VIP, also regulate the secretion of macromolecules. In addition to cholinergic, adrenergic, and neuropeptide-mediated secretion, several neural reflexes are associated with mucus secretion. These include cough due to irritation of the airways, hypoxia, and gastric distention.

Inflammatory mediators such as those associated with infections or allergic reactions can stimulate mucus secretion. These include histamine from mast cells, prostaglandins A_2, D_2 and $F_{2\alpha}$, and leukotrienes C_4 and D_4.

Macromolecular Products of Submucosal Glands

Submucosal glands play an important part in lung host defenses by contributing to mucociliary function and secreting products with antimicrobial activity. The fluid and electrolyte secretions produced predominantly by the serous cells of glands are in part responsible for the maintenance of the periciliary fluid layer on airway surface cells. These secretions also hydrate mucins secreted by mucous cells and thus are important for the production of the gel layer. Thus, submucosal gland products are key components of the mucociliary clearance system in the airways and support this first line of defense for handling inhaled infectious and noninfectious particulate matter.

The serous cells of glands elaborate a number of products that constitute additional host defense mechanisms in the airways. These factors act in a broad-spectrum fashion, in some cases exerting antimicrobial effects against bacteria, fungi, and viruses. The cationic, bacteriolytic protein lysozyme is a specific product of the serous cell and is found in measurable quantities in airway secretions. Lactoferrin is found in airway secretions and is distributed in submucosal glands in a pattern similar to lysozyme. It is a cationic, iron-binding protein, which may act by inhibiting growth of iron-requiring bacteria. The serous cells also produce the secretory component of IgA, which is required for the translocation of IgA from the basolateral to apical membrane, where it is released. A low-molecular-weight cationic proteinase inhibitor termed anti-leukoprotease or secretory leukocyte proteinase inhibitor (SLPI) is also produced by serous cells and comprises most of the antineutrophil proteinase activity produced in the airways. Additional products of serous cells with antimicrobial properties include peroxidase and proline-rich proteins. Antimicrobial peptides, including β-defensins and cathelicidins, are also secreted by human submucosal gland cells. It is likely that these multiple components of the nonspecific mucosal immune system act synergistically to prevent infection of the lung from a variety of inhaled or aspirated pathogens.

INTEGRATED PHYSIOLOGY AND HOST DEFENSE FUNCTIONS

Although much has been learned about the specific molecules involved in electrolyte transport and the function of the epithelium on the airway surface and submucosal glands, there is a continuing lack of knowledge about the integrated physiology of the airways. An important function of the airways is in local host defense, protecting the lung from inhaled microorganisms, particulate material, and toxins. Here we describe some aspects of the integrated physiology of the airways, but we also note deficiencies in current knowledge.

Mucociliary Clearance

An important function of airway secretions is in mucociliary clearance. Mucociliary clearance is a pulmonary defense mechanism that serves to remove inhaled particulate material from the lung. Effective clearance requires both ciliary activity and respiratory tract fluid. Cilia cover much of the airway surface, and their coordinated beating provides the mechanical force that propels particulate material toward the larynx. The cilia are immersed in a periciliary fluid layer, or sol phase of the fluid, that is about 5 μm thick. The periciliary fluid is covered by a mucous or gel layer, 5 to 10 μm thick, which exists as a discontinuous blanket, i.e., as islands of mucus. The viscoelastic mucus traps and carries inhaled material, whereas the watery periciliary fluid allows the cilia to move freely, with only the tops of the cilia contacting the overlying mucus and propelling it toward the mouth. The quantity and composition of the periciliary fluid, and perhaps hydration of the mucus, are controlled by the electrolyte transport properties of the cells of the surface and submucosal gland epithelia.

Antibacterial Activity at the Airway Surface

Airway surface liquid contains a rich variety of molecules that kill bacteria. The antimicrobials include lysozyme, lactoferrin, β-defensins, LL-37, SLPI, phospholipase A2, and secreted IgA. These molecules are secreted by the submucosal glands and to a lesser extent by the surface airway epithelium. Airway epithelia also generate nitrous oxide and reactive oxygen species that possess antimicrobial activity. The ASL factors kill bacteria rapidly; they show broad-spectrum activity; they kill some fungi and inactivate some enveloped viruses; and in contrast to pharmaceutical antibiotics, resistance does not develop. Antimicrobial activity in the ASL may be a first line of defense that protects the lung from microorganisms deposited on the airway surface after inhalation and aspiration. This process explains, in part, the ability of the airways to maintain a sterile intrapulmonary environment. Furthermore, the epithelial cells express an array of pattern recognition receptors, including Toll-like receptors that facilitate identification of microbes and elicit responses such as induction of antimicrobials or cytokines. Most endogenous antimicrobials show increased activity when the salt concentration falls, suggesting that interventions that lower ASL salt concentration might enhance host defense against infection. In addition, the beneficial properties of endogenous antimicrobials, especially the lack of resistance, recommend them for development as novel therapeutics.

Phagocytic Cells and Repair

In addition to mucociliary clearance and antibacterial activity, a second line of defense involves the recruitment of

phagocytic cells such as neutrophils and macrophages to the airway surface. By releasing a variety of cytokines and inflammatory molecules, the epithelium mediates the inflammatory response to inhaled bacteria and other pathogens. This topic is covered in depth elsewhere in this book. Airway epithelia also possess the repair mechanisms needed following disruption. These include several growth factors including epithelial growth factor (EGF). In some cases, growth factor ligands are present on the apical surface, physically segregated from their receptors on the basolateral membrane. This arrangement provides a simple system that is primed for activation the instant epithelial integrity is compromised. Such a design could be vital to rapid restoration of barrier function and protection of the organism following a mechanical or toxic wound that disrupts the epithelium. With injury, fibroblasts and interstitial cells also secrete a variety of molecules that remodel the epithelium. Of course, the processes that mediate development and repair also may be important in the pathophysiology of airway diseases involving abnormal proliferation and remodeling, including smoking-associated bronchitis, CF, and asthma.

Insights into Airway Biology from Disease States

Clues about the integrated function and biology of the airways have come from study of several disease states and the development of animal models in which specific genes have been disrupted. We discuss these only briefly here; they are discussed in greater depth in subsequent chapters.

Ciliary activity is disrupted in ciliary dyskinesia syndromes. As a result, mucociliary activity is impaired. Patients often develop chronic infections of the middle ear, sinuses, and airways, which may advance to bronchiectasis. This observation underscores the important role of mucociliary clearance as a defense mechanism in humans.

In CF, the gene encoding CFTR is mutated. The resulting loss of CFTR Cl^- channels leads to chronic respiratory tract infections. This observation supports a central role for electrolyte transport in the normal biology and host defense of the airways. However, the mechanism by which loss of CFTR predisposes to infection remains controversial, and perhaps several factors contribute. Disruption of epithelial salt transport may increase ASL salt concentrations, thereby impairing bacterial killing by ASL antimicrobials. It has been suggested that abnormal amounts or composition of the respiratory tract fluid might make mucociliary clearance less efficient. Disruption of CFTR function in submucosal gland epithelia might increase the viscosity of mucus. Loss of CFTR may reduce HCO_3^- secretion, producing a more acidic ASL. Alterations in the composition of airway surface fluid also may affect the normal hydration of mucus. Loss of CFTR also has been proposed to alter the inflammatory and/or immune response of the airway to bacterial challenge.

Diseases that alter Na^+ absorption also can provide clues about the role of this process in airway biology. In Liddle's syndrome, gain-of-function mutations in the ENaC Na^+ channel increase the rate of amiloride-sensitive Na^+ absorption. In contrast, in pseudohypoaldosteronism, loss-of-function mutations in the ENaC Na^+ channel decrease the rate of Na^+ absorption. Patients with Liddle's syndrome are not reported to have evidence of airway disease, whereas patients with pseudohypoaldosteronism develop airway disease that shows some similarity to CF. If, as expected, the gain or loss of ENaC function in the airways is similar to what has been reported in the kidney of patients with these diseases, then these observations suggest that a reduced capacity for salt absorption would impair airway host defense mechanisms, much as was suggested for the loss of CFTR Cl^- channels in CF. Studies in mice overexpressing ENaC suggest that increased Na^+ absorption may generate changes similar to those observed in CF.

The genes for the CFTR Cl^- channel and the ENaC Na^+ channel also have been disrupted in mice. Unfortunately, these models have not faithfully reproduced the human disease. Mice lacking CFTR do not develop chronic airway disease; it has been speculated that this may be because mice have quantitatively more Ca^{2+}-activated Cl^- current in the airways than humans. Mice lacking subunits of ENaC Na^+ channels die of respiratory distress because of a failure to clear fluid from the lungs after birth. While this established the important role of electrolyte transport in airway function, it did not produce an animal with disease that accurately mimics human disease. Future interventions may be of greater value, and a comparison of disease in mice and humans may yield additional clues as to the biology of the airways.

The appreciation that abnormalities in airway and submucosal gland function play central roles in the pathogenesis and pathophysiology of some inherited and acquired diseases has increased interest and focused research in this area. Future studies in this field should continue to increase our understanding of how airway surface fluid and its secretory products contribute to lung health and are altered in disease states.

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CHAPTER 9

Pulmonary Mechanics

Murray D. Altose

For venous blood to be properly arterialized, the distribution of air and blood within the lung is automatically matched in order to ensure effective gas exchange across alveolar-capillary membranes. Arterialization comprises a series of interrelated processes that begin with the mechanical performance of the ventilatory apparatus—i.e., the lungs and chest wall, including the rib cage, diaphragm, and abdominal wall. Although the function of each component of the lung and of the chest bellows can be deranged by injury or disease, the design of the ventilatory apparatus provides for considerable reserve. As a result, mechanical derangements are usually quite severe by the time clinical symptoms appear or arterial blood-gas levels become abnormal.

Depending on the nature of the underlying disorder, assessment of the mechanical properties of the ventilatory apparatus provides several different types of information. In some instances, characterization of the mechanical abnormality provides insight into pathogenesis and affords a quantitative measure of severity. In others, once the nature of the mechanical disorder is understood, the mystery surrounding a life-threatening disorder in gas exchange may be dispelled. Finally, certain breathing patterns make sense only if the mechanical performance of the chest bellows is taken into account.

During breathing, the lungs and chest wall operate in unison. The lungs fill the chest cavity so that the visceral pleura are in contact with the parietal pleura of the chest wall. The two pleural surfaces are separated by only a thin liquid film, which provides the bond holding the lungs and chest wall together.

At the end of a normal exhalation, the respiratory muscles are at rest. The pressure along the entire tracheobronchial

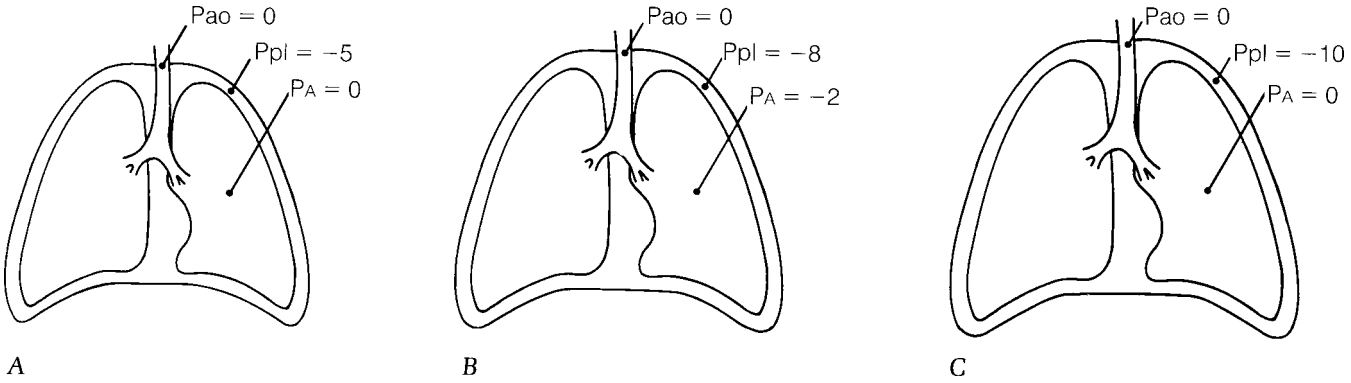

Figure 9-1 Respiratory pressures during a breathing cycle. Ppl = pleural pressure; PA = pressure in the alveoli; Pao = pressure at the airway opening. *A*. End expiration. *B*. During inspiration. *C*. End inspiration.

tree from the airway opening to the alveoli is equal to atmospheric pressure. The tendency of the lung is to deflate, however, and lung elastic recoil is directed centripetally. This is counterbalanced by the elastic recoil of the chest wall, which is directed centrifugally to favor an increase in volume. These opposing forces generate a subatmospheric pleural pressure of about –5 cmH_2O (Fig. 9-1*A*). The tendency for the lung to recoil inward and for the chest wall to recoil outward is illustrated by the observation that when the chest is opened at autopsy, the lungs collapse and the thorax expands.

Although it is conventional to consider pleural pressure as a single, mean value that reflects mechanical events within the entire ventilatory apparatus, this is clearly an oversimplification on several accounts: (1) pleural pressure is not directly determinable because normally there is only a potential space between the visceral and parietal pleura; (2) on conceptual grounds, distinctions exist between surface and liquid pleural pressures; (3) pleural pressures are not uniform over the surface of the lungs, being strongly affected by gravity; and (4) transmission of pleural pressures at the surface to alveoli located at different depths and loci with the lungs depends on the structural interplay among supporting structures in the alveolar walls (interdependence), which resists any inclination of individual alveoli or even a lobule to collapse. Nonetheless, the concept of mean pleural pressure, as generally used in considerations of respiratory system mechanics, has proved to be of great practical value.

The contraction of the muscles of inspiration produces the forces that permit the flow of gas along the tracheobronchial tree and the expansion of the lungs and chest. The movement of air into the lungs requires a pressure difference between the airway opening and the alveoli sufficient to overcome the resistance to airflow of the tracheobronchial tree. Also, a pressure difference across the alveolar walls (between the alveoli and pleural space) must be generated to overcome elastic recoil and inflate the lungs. During spontaneous breathing, the action of the inspiratory muscles causes an increase in the outward recoil of the chest wall. As a result, the pleural pressure becomes more subatmospheric. This pressure change is transmitted to the interior of the lungs, so alveolar pressure also becomes subatmospheric (Fig. 9-1*B*). In contrast, during artificial ventilation with a positive-pressure breathing machine, a supra-atmospheric pressure applied at the inlet to the airways creates the proper pressure gradient between the airway opening and alveoli for airflow.

Expansion of alveoli depends on the achievement of an appropriate distending pressure across alveolar walls. This distending pressure or transpulmonary pressure is the difference between alveolar (PA) and pleural (Ppl) pressures. As shown in Fig. 9-1*A*, the transpulmonary pressure at end-expiration (PA – Ppl) is 5 cmH_2O. At the end of inspiration (Fig. 9-1*C*), *the transpulmonary distending pressure is higher and the lungs contain more air.*

The energy used during inspiration to overcome the elastic resistance of the lungs is stored. Expiration occurs when these forces are released. When the inspiratory muscles relax, the recoil of the lungs causes the alveolar pressure to exceed the pressure at the mouth, and air flows out of the lungs. Although expiration during quiet breathing is passive, the expiratory muscles are engaged at high levels of ventilation to assist the movement of air out of the lungs.

LUNG VOLUMES

The lung volumes and capacities (Table 9-1) are also considered elsewhere in this book (see Appendix B). The end-expiratory position of the lungs, functional residual capacity (FRC), is the major reference point for the volume subdivisions of the lung. This position is set by the opposing recoil forces of the lung and chest wall when the respiratory muscles are at rest.

Total lung capacity (TLC), the total volume of air contained in the lungs after a maximal inhalation, is determined by the balance between the force-generating capacity of the inspiratory muscles and the opposing elastic recoil forces of the lung and chest wall. Weakness of the muscles of inspiration or increased stiffness of the lung reduces TLC. Loss of retractive forces exerted by the lung, as in emphysema, enlarges TLC.

Residual volume (RV), the volume of air remaining in the lungs after a complete exhalation, is set by the balance between the actions of the expiratory muscle and the recoil

Table 9-1

Lung Volumes and Subdivisions

The *functional residual capacity* (FRC) is the volume of air that remains in the lungs at the end of a normal expiration.

The *tidal volume* (TV) is the volume of air that is drawn into the lungs during inspiration from the end-expiratory position (and also leaves the lungs passively during expiration in the course of quiet breathing).

The *expiratory reserve volume* (ERV) is the maximum volume of air that can be forcibly exhaled after a quiet expiration has been completed (i.e., from the end-expiratory position).

The *residual volume* (RV) is the volume of air that remains in the lungs after a maximal expiratory effort.

The *inspiratory capacity* (IC) is the maximum volume of air that can be inhaled from the end-expiratory position. It consists of two subdivisions: tidal volume and the *inspiratory reserve volume* (IRV).

The *total lung capacity* (TLC) is the total volume of air contained in the lungs at the end of a maximum inspiration.

The *vital capacity* (VC) is the volume of air that is exhaled by a maximum expiration after a maximum inspiration.

forces of the lung, which act to decrease lung volume, and the outward recoil forces of the chest wall, which favor lung expansion. In middle-aged and older people, closure of airways at low lung volumes, with air trapping in the lung, is an important determinant of residual volume.

STATIC MECHANICAL PROPERTIES OF THE RESPIRATORY SYSTEM

To assess the elastic properties of the ventilatory apparatus, it is expedient to evaluate the elastic properties of the lungs and chest separately.

ELASTIC PROPERTIES OF THE LUNGS (PULMONARY COMPLIANCE)

The change in transpulmonary pressure required to effect a given change in the volume of air in the lungs is a measure

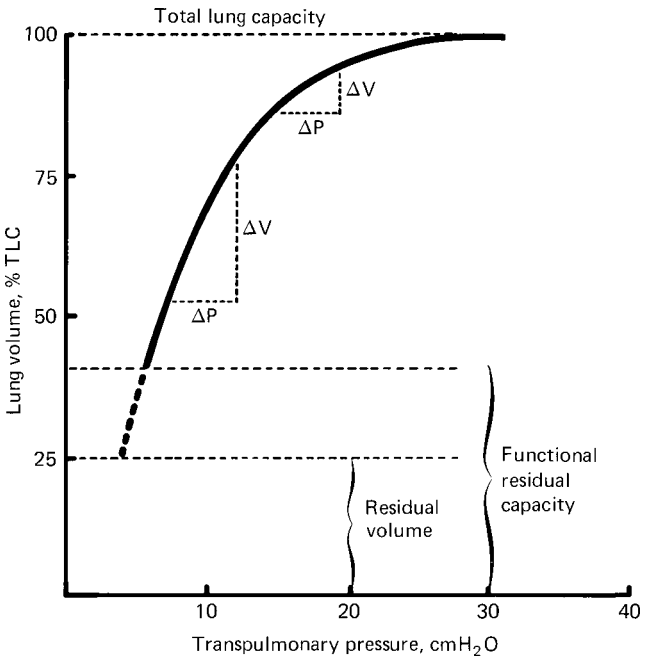

Figure 9-2 Pressure-volume curve of the lung. The static elastic recoil pressure of the lung is approximately 5 cmH_2O at FRC and 30 cmH_2O at TLC. The compliance of the lung ($\Delta V/\Delta P$) is greater at low lung volumes than at high lung volumes.

of the distensibility, or compliance, of the lungs. Pulmonary compliance is calculated as the ratio of the change in lung volume to the change in transpulmonary pressure—i.e.,

$$C = \frac{\Delta V_L}{\Delta(P_A - Pp1)}$$

where

C = lung compliance
$\Delta(P_A - P_P1)$ = change in transpulmonary pressure
ΔV_L = change in lung colume

Compliance denotes distensibility, the ease of stretch or inflation. The inverse of compliance (i.e., elastance) refers to the stiffness or the tendency to resist distortion and to return to the original configuration when the distorting force is removed.

In practice, pulmonary compliance is determined by relating the changes in transpulmonary pressures to the changes in lung volume in the course of an expiration after a maximal inspiration (i.e., starting from total lung capacity).

The pressure-volume characteristics of the lung are nonlinear. As lung volume increases, the elastic elements approach their limits of distensibility, and a given change in transpulmonary pressure produces smaller and smaller increases in lung volume. Thus, the compliance of the lung is least at high lung volumes and greatest as the residual volume is approached (Fig. 9-2). Elastic recoil forces favoring collapse of the lung can be demonstrated throughout the range of the vital capacity, even at low lung volumes approaching the residual volume. If the opposing forces of the chest wall on the lungs are eliminated—for instance, by removing the lungs from the thorax or by opening the chest—the lung collapses

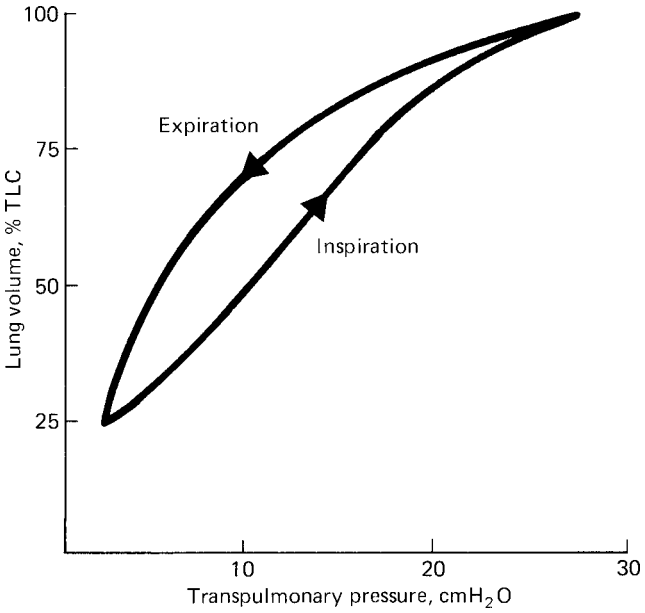

Figure 9-3 Pressure-volume curves of the lung during inspiration and expiration.

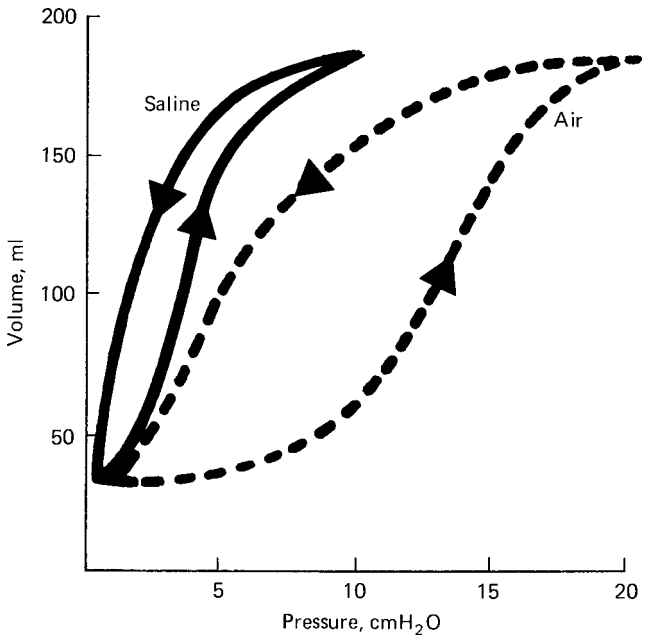

Figure 9-4 Comparison of pressure-volume relationships of air-filled and saline-filled excised lungs. Arrows directed upward indicate inflation; those directed downward indicate deflation. Since saline eliminates surface forces at the liquid-air interface without affecting tissue elasticity, the difference in pressure between the two curves, at any lung volume, is that required to overcome surface forces. To maintain a small lung volume, a large proportion of the pressure is used to overcome surface forces. In contrast, at high lung volumes a greater fraction of the pressure is used to overcome tissue elasticity.

to a near airless state. A minimal volume of air does remain in the lungs because of closure of small airways resulting in the trapping of air in more distal air spaces.

If static measurements of transpulmonary pressure are made during lung inflation rather than deflation, the pressure-volume curve has a different configuration (Fig. 9-3). This indicates that the elastic recoil of the lung depends not only on the lung volume at which the determination is made but also on the "volume history" of the lung.

Hysteresis

Differences in the pathways of the pressure-volume curve during inspiration (when force is applied) and expiration (when force is withdrawn) are designated as hysteresis, which is a property of all elastic structures. In the lungs, it is due to the surface forces and the properties of the surface material lining the alveolar walls and also to the elastic properties of the tissues. An additional factor relates to the closure of small airways at low lung volumes. Once these airways close, the lung units that they serve will not expand during inspiration until a critical opening pressure has been exceeded; only then will the closed units inflate. Recruitment of additional lung units as increasing transpulmonary pressure expands the lungs from low lung volume contributes to the hysteresis of the pressure-volume curve.

The elastic behavior of the lung depends on two factors: the physical properties of the lung tissue, per se, and the surface tension of the film lining of the alveolar walls.

Surface Forces

The interior surfaces of the alveoli are lined by a thin liquid layer of osmophilic material. The surface tension at the air-liquid interface of the alveoli, in addition to the elastic properties of the parenchyma, contributes importantly to the elastic recoil of the lungs and acts to decrease lung compliance. The cohesive forces between the molecules of the liquid lining of the alveoli are stronger than those between the film and alveolar gas, thereby causing the film to shrink to its smallest surface area. The behavior of this surface film has been examined in experimental animals by comparison of pressure-volume relationships of air-filled lungs with those of saline-filled lungs; saline eliminates the liquid-air interface without affecting elastic properties of the tissue. A lung distended with saline requires a lower transpulmonary pressure to maintain a given lung volume than a lung that is inflated with air. Also, hysteresis is less in the saline-filled lung. The greater hysteresis in the air-filled lung is explained by the surface tension of the film lining the alveoli, which is higher during inflation as the film expands than it is during deflation as the film is compressed (Fig. 9-4).

By considering the alveolus to be a sphere, Laplace's law can be applied. Laplace's law states that the pressure inside a spherical structure—e.g., the alveolus—is directly proportional to the tension in the wall and inversely proportional to the radius of curvature:

$$\text{Alveolar pressure} = \frac{2T}{r}$$

where

T = tension (dyn/cm)
r = radius

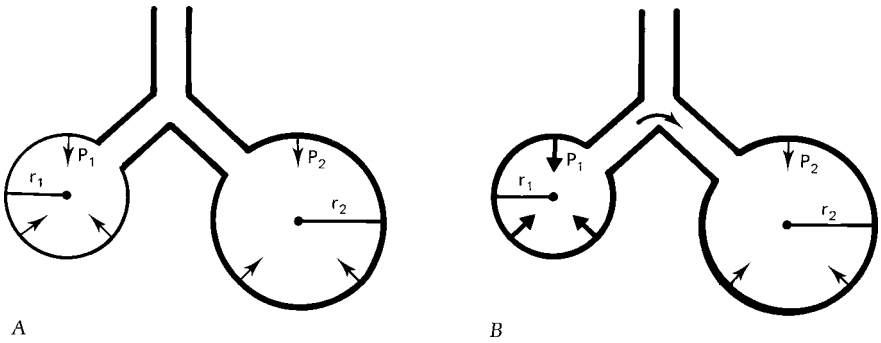

Figure 9-5 The effects of surfactant in maintaining alveolar stability. *A*. Surfactant lowers the tension (T) of the alveolar walls at low lung volumes. Consequently, the transpulmonary pressure (P) of large and small communicating airspaces is the same. $r_1 < r_2, T_1 < T_2, P_1 \leftarrow P_2$. *B*. Without surfactant, the surface tension remains constant as lung volume changes, and the recoil pressure of small airspaces exceeds that of larger ones. As a result, small alveoli tend to empty into larger ones. $r_1 < r_2, T_1 = T_2, P_1 > P_2$.

Abolition of the liquid-air interface by the instillation of saline into the alveolar spaces eliminates surface forces, thereby reducing the transpulmonary pressure required to maintain a given lung volume.

The surface tension of the alveolar walls depends on the lung volume: surface tension is higher at large lung volumes and lower at small lung volumes. These variations in surface tension with lung volume are due to the surface film, surfactant. The superficial layer of the film facing the alveolar air is made up of surface-active phospholipids, notably dipalmitoyl lecithin. The deeper layer termed the hypophase consists of surface-active phospholipids linked to protein. Surfactant is generated by type II alveolar cells and undergoes a continuous cycle of formation, removal, and replenishment.

Surfactant serves several important functions. The surface tension of surfactant is inherently low and decreases even further at low lung volumes when the surface area of the film is reduced. The minimization of surface forces, particularly at low lung volumes, minimizes the adherence of the walls of distal airways that tend to close at low lung volumes and increases the compliance of the lung and decreases the work required to inflate the lungs during the next breath. The automatic adjustment of surface tension as lung volume changes also promotes stability of alveoli at low lung volumes; if the surface tension were to remain constant instead of changing with lung volume, the transpulmonary pressure required to keep an alveolus open would increase as the radius of curvature diminished with decreasing lung volume. Therefore, small alveoli would empty into the larger ones with which they communicate, and atelectasis would be a regular occurrence (Fig. 9-5).

Interdependence and Collateral Ventilation

The low surface tension of surfactant is not the most important determinant of alveolar stability. In reality, the alveoli form a froth rather than individual bubbles. The walls of each alveolus are shared in common with those of adjacent alveoli so that contiguous air spaces attached by their connective tissue framework are tethered to one another and are not free to move independently. The tendency of any one alveolus to collapse is opposed by the traction exerted by the surrounding alveoli. This mechanical interdependence of adjacent air spaces resists the collapse of individual alveoli and serves as a stabilizing influence and ensures uniform inflation.

Even when a distal airway is completely obstructed, the alveoli served by the airway can still be ventilated through collateral channels between alveoli (pores of Kohn) and from bronchioles to alveoli (canals of Lambert). This collateral ventilation also prevents alveolar collapse and enhances the uniformity of ventilation, particularly in patients with lung disease.

Physical Properties of Lung Tissue

A number of different tissue components contribute to lung elasticity. The pleura, the intralobular septa, peripheral airway smooth-muscle tone, and pulmonary vasomotor tone, as well as the tissues of the alveolar walls, play a role in shaping lung elastic recoil.

The major connective-tissue elements of the alveolar walls are the collagen and elastin fibers. Elastin fibers in the alveolar walls and surrounding the bronchioles and pulmonary capillaries have a low tensile strength but can be stretched to over twice their resting length. Elastin fibers are thought to bear most of the stress in the lung at low volumes. Collagen fibers have high tensile strength but are poorly extensible and probably act to limit expansion at high lung volumes. Like a stretched nylon stocking, expansion of the lungs appears to entail an unfolding and geometric rearrangement of the fibers and only slight elongation of individual fibers.

As a result of alterations in the elastin and collagen fibers in the lung, the distensibility of the lungs (measured as compliance) increases with age. This is part of the normal aging process. Pulmonary compliance is also increased by the destruction of alveolar walls and the enlargement of alveolar spaces that characterize pulmonary emphysema. In contrast, the distensibility of the lungs is reduced by pulmonary fibrosis, which stiffens its interstitial tissues.

Elastic Properties of the Thorax

The elastic recoil of the chest wall is such that if it were unopposed by the lungs, the chest would enlarge to approximately 70 percent of total lung capacity. This position represents its equilibrium or resting position. In this position (when the respiratory muscles are completely relaxed), the pressure difference across the chest wall—i.e., the difference between pleural pressure and the pressure at the surface of the chest—is zero. If the chest were forced to enlarge further by an increasingly positive pleural pressure or by the application of subatmospheric pressure at the body surface, it would, like the

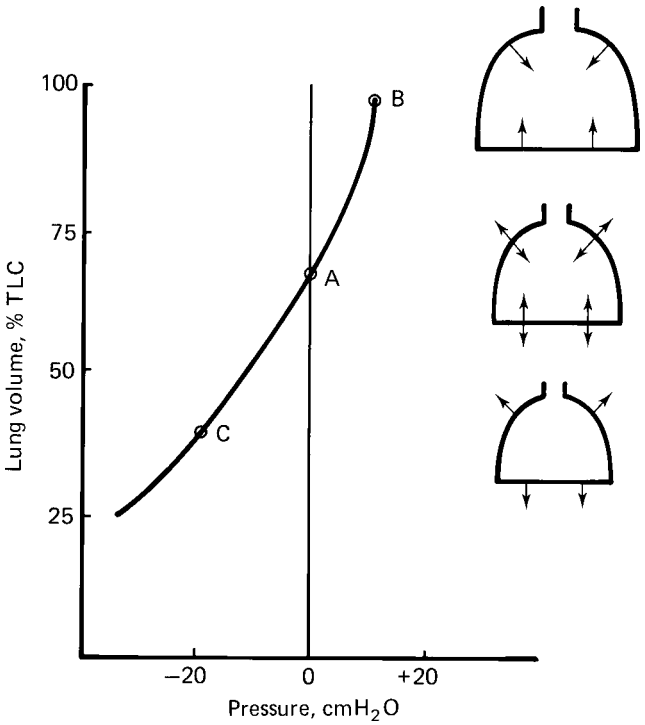

Figure 9-6 Pressure-volume relationships of the isolated chest wall. The equilibrium position of the chest wall (*A*), unopposed by the lungs, is approximately 70 percent of the total lung capacity. In this position, the pressure difference across the chest wall is zero. At larger volumes (*B*), there is inward recoil of the chest wall; at volumes below the equilibrium position (*C*), the recoil of the chest wall is directed outward, favoring expansion.

lung, recoil inward, resisting expansion and favoring return to its equilibrium position. Conversely, at volumes less than 70 percent of total lung capacity, the recoil of the chest is opposite that of the lung and is directed outward (Fig. 9-6). The chest wall can also be represented as a two-compartment system consisting of the rib cage and the abdomen, and volume changes can be partitioned between the two compartments. Changing from the upright to the supine position at a constant overall lung volume produces a shift in volume from the abdominal to the rib cage compartment. The compliance of the rib cage is similar in the supine and upright positions, but the compliance of the abdominal compartment—particularly at high volumes—is greater in the supine position.

The elastic recoil properties of the chest wall play an important role in determining the subdivisions of lung volume. They may be seriously deranged by disorders affecting the chest wall, such as marked obesity, kyphoscoliosis, and ankylosing spondylitis.

Elastic Properties of the Respiratory System as a Whole

If we consider the lung and the chest wall to operate mechanically in series, the elastic recoil pressure of the total respiratory system (Prs) can be calculated as the algebraic sum of the pressures exerted by the elastic recoil of the lung (transpulmonary pressure) and the elastic recoil of the chest wall.

Since the elastic recoil of the lung is determined (under static conditions of arrested airflow) as the difference between alveolar pressure (P_A) and pleural pressure (Ppl)—i.e., P_A – Ppl—and the elastic recoil of the chest wall is determined (while the respiratory muscles are completely at rest) as the difference between pleural pressure and the pressure at the external surface of the chest (Pbs)—i.e., Ppl – Pbs, the elastic recoil of the entire respiratory system can be expressed as the sum of the two:

$$Prs = (P_A - Ppl) + (Ppl - Pbs) = P_A - Pbs$$

Thus, a measure of the elastic recoil of the respiratory system is supplied by the alveolar pressure, provided that the respiratory muscles are completely at rest and the pressure of the body surface is at atmospheric levels. In the absence of airflow into or out of the lung and when the glottis is open, alveolar pressure corresponds to the pressure at the mouth.

Relaxation Pressure-Volume Curve

The elastic properties of the entire respiratory system can be determined from the relaxation pressure-volume curve (Fig. 9-7). Functional residual capacity represents the equilibrium position of the lung-chest wall system while the

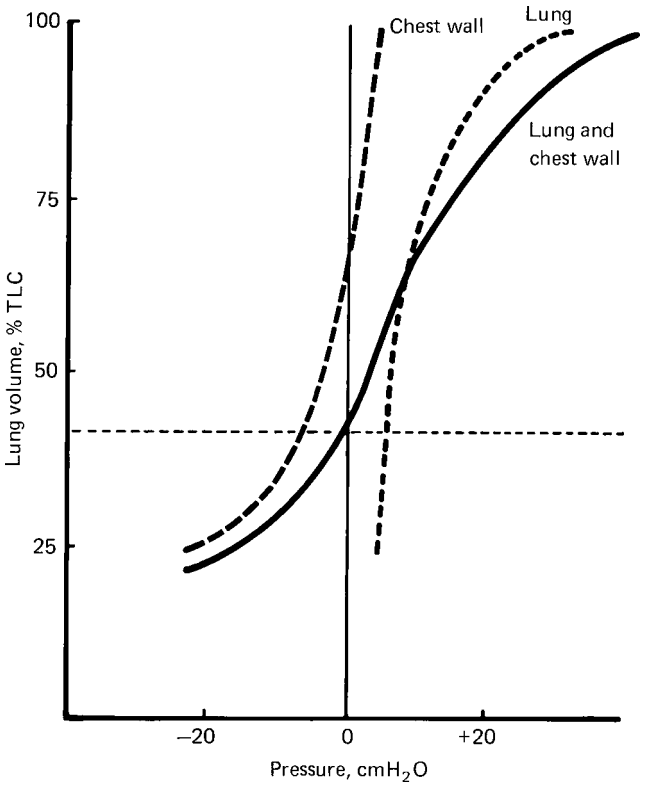

Figure 9-7 Relaxation pressure-volume curves. The elastic recoil pressures of the total respiratory system in the algebraic sum of the recoil pressures of the lung and chest wall are equal but opposite. Since the net recoil pressure is zero, the respiratory system is in a position of equilibrium.

respiratory muscles are relaxed. At this point, the opposing recoils of the lung and chest wall are of equal magnitude, and the recoil pressure of the entire respiratory system is zero. With increases in lung volume above functional residual capacity, the recoil pressure of the entire system becomes positive, owing to the combination of an increase in centripetal elastic recoil of the lungs and a decrease in the centrifugal recoil of the chest wall. The net effect favors a decrease in lung volume, and lung volume can be maintained with the airway open to the atmosphere only by the action of the inspiratory muscles. As lung volume exceeds 75 percent of total lung capacity, the recoil of the chest wall also becomes centripetal and the recoil pressure of the chest wall adds to the inward forces acting to diminish lung volume. Total lung capacity represents the lung volume at which the inward passive elastic recoil pressure of the respiratory system reaches the maximum force that can be generated by the inspiratory muscles.

At lung volumes below functional residual capacity, when the centrifugal recoil of the chest wall exceeds the reduced centripetal recoil of the lungs, the relaxation pressure is negative and this net effect favors an increase in lung volume. Lung volumes below functional residual capacity are achieved and maintained by the muscles of expiration.

A switch from the sitting to the supine position decreases functional residual capacity because of the effects of gravity. In the upright position, gravity pulls the abdominal contents away from the chest wall. In contrast, in the supine position, the push of the abdominal contents against the diaphragm decreases the centrifugal recoil of the chest wall. The chest wall pressure-volume curve—and, consequently, the pressure-volume curve of the entire respiratory system—is displaced to the right.

DYNAMIC MECHANICAL PROPERTIES OF THE RESPIRATORY SYSTEM

The total nonelastic resistance of the lungs consists of the resistance of the airways to airflow (airway resistance), defined in terms of the driving pressure and the resulting rate of airflow, and the frictional resistance of the lung tissues to displacement during breathing (tissue resistance). Normally, tissue resistance makes up only 10 to 20 percent of the total pulmonary nonelastic resistance, but in diseases of the pulmonary parenchyma, it may increase considerably.

Airway Resistance

A large fraction of the resistance to airflow is in the upper respiratory tract, including the nose, mouth, pharynx, larynx, and trachea. During nasal breathing, the nose constitutes up to 50 percent of total airway resistance. During quiet mouth breathing, the mouth, pharynx, larynx, and trachea constitute 20 to 30 percent of the airway resistance; but they account for up to 50 percent of the total airway resistance when minute ventilation increases—during vigorous exercise, for example. Most of the remainder of airway resistance is in medium-sized lobar, segmental, and subsegmental bronchi up to about the seventh generation of airways. Additional branching distally causes a progressive increase in the number of airways in any generation. While the caliber of individual airways in daughter branches compared to the parent branch is reduced, the total cross-sectional area of all of the airways in a given generation increases tremendously with successive generation along the tracheobronchial tree. Consequently, in the normal lung, the small peripheral airways, particularly those less than 2 mm in diameter, constitute only about 10 to 20 percent of the total airway resistance.

Airway Caliber

The airways, like the pulmonary parenchyma, exhibit elasticity and can be compressed or distended. Therefore, the diameter of an airway varies with the transmural pressure applied to that airway—i.e., the difference between the pressure within the airway and the pressure surrounding the airway. The pressure surrounding intrathoracic airways approximates pleural pressure, since these airways are tethered to the parenchymal tissue and are exposed to the expansive forces that are active in overcoming the elastic recoil of the lung.

As the lung volume increases, the elastic recoil forces of the lung increase; the traction applied to the walls of the intrathoracic airways also increases, widening the airways and decreasing their resistance to airflow. Conversely, at low lung volumes, the transmural airway pressure is lower and airway resistance increases. If the elastic recoil of the lung is reduced—by destruction of alveolar walls in pulmonary emphysema, for instance—the transmural airway pressure at any given lung volume decreases correspondingly; the airways are narrower and airway resistance is greater even though there is no disease of the airways per se.

The effects of a change in transmural pressure on airway caliber depend on the compliance of the airways—which, in turn, is determined by their structural support. The trachea, for example, is almost completely surrounded by cartilaginous rings, which tend to prevent complete collapse even when the transmural pressure is negative. The bronchi are less well supported by incomplete cartilaginous rings and plates, whereas the bronchioles lack cartilaginous support. All airways can be stiffened, albeit to different degrees, by contraction of smooth muscle in their walls.

In patients with airway disease, mucosal edema, hypertrophy and hyperplasia of mucous glands, increased elaboration of mucus, and hypertrophy of smooth muscle further compromise airway caliber and increase airway resistance.

The innervation of airway smooth muscle also has an important effect on airway caliber. Parasympathetic stimulation originating from the vagus nerve causes airway smooth muscle contraction and airway narrowing. Conversely, sympathetic stimulation with the release of the post-ganglionic neurotransmitter, norepinephrine, results in airway smooth muscle relaxation and airway dilatation.

Pressure-Flow Relationships: Theoretical Considerations

In the lungs, pressure-flow relationships are extremely complicated because the airways consist of a system of irregular branching tubes that are neither rigid nor perfectly circular. For purposes of simplification, pressure-flow relationships in rigid tubes are generally regarded as a model for those in the airways.

The driving pressure that produces flow of air into and out of the lung must suffice to overcome friction and to accelerate the air. Acceleration in the lungs is of two types: local (i.e., changes in the rate of airflow with time when flow is initiated) and convective (i.e., acceleration of molecules of air over distance while flow is constant). The driving pressure required for convective acceleration is proportional to the gas density and to the square of the flow rate. It is important during expiration because, as air moves downstream from the alveoli toward the airway opening, the total cross-sectional airway diameter decreases; therefore, molecules of air must accelerate through the converging channels even though the overall flow rate remains unchanged. Also, the driving pressure that produces high expiratory flow rates at large lung volume serves for convective acceleration rather than for overcoming friction.

The driving pressure required to overcome friction depends on the rate and the pattern of airflow. Two major patterns of airflow warrant special consideration: laminar and turbulent. Laminar flow is characterized by streamlines that parallel the sides of the tube and are capable of sliding over one another. Also, because the streamlines at the center of the tube move faster than those closest to the walls, the flow profile is parabolic (Fig. 9-8). The pressure-flow characteristics of laminar flow depend on the length (l) and the radius (r) of the tube and the viscosity of the gas (n) according to Poiseuille's equation:

$$\Delta P = \frac{\dot{V} 8 n l}{\pi r^4}$$

where

ΔP = the driving pressure (pressure drop between the beginning and the end of the tube)
$\dot{V}$ = the flow rate that the driving pressure produces
r = the radius of the tube

The critical importance of tube radius in determining the driving pressure for a given flow is apparent in the above equation. If the radius of the tube is halved, the pressure that is required to maintain a given flow rate must be increased 16-fold. Laminar flow patterns occur only in small peripheral airways, where, because of the enormous overall cross-sectional area, flow through the individual airways is exceedingly slow.

Turbulent flow occurs at high flow rates and is characterized by a complete disorganization of streamlines, so that the molecules of gas move laterally, collide with each other, and change velocities. Under these circumstances, pressure-flow relationships change. In contrast to laminar flow, the rate

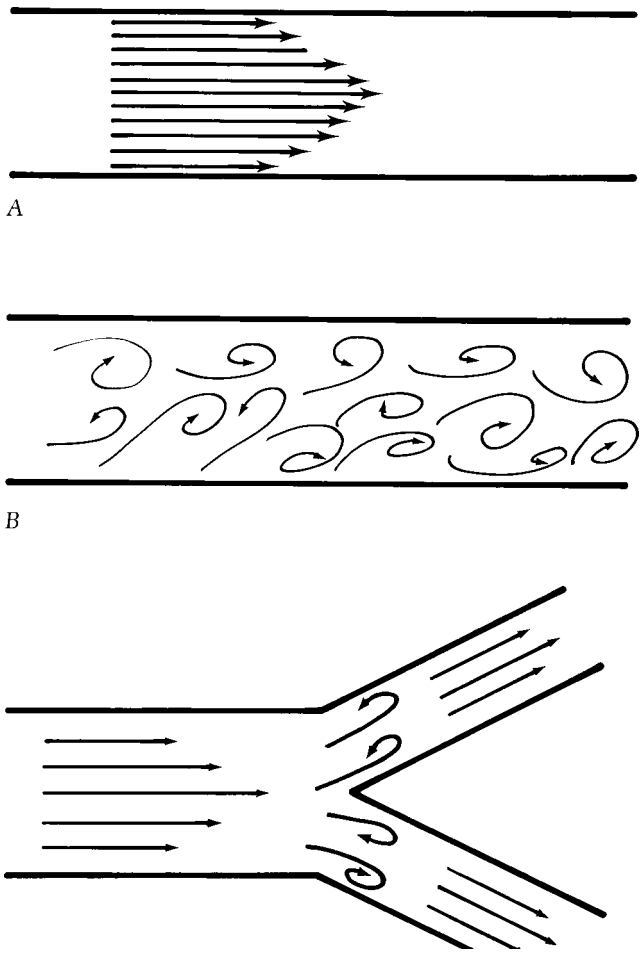

Figure 9-8 Patterns of airflow. *A*. Laminar flow. *B*. Turbulent flow. *C*. Transition flow.

of turbulent airflow is no longer proportional to the driving pressure. Instead, the driving pressure to produce a given rate of airflow is proportional to the square of flow and is dependent on gas density. Turbulent flow occurs regularly in the trachea.

At lower flow rates during expiration—particularly at branches in the tracheobronchial tree, where flow in two separate tubes comes together into a single channel—the parabolic profile of laminar flow becomes blunted, the streamlines separate from the walls of the tube, and minor eddy formation develops. This is referred to as a mixed, or transitional, flow pattern. In a mixed pattern of airflow, the driving pressure for a given flow depends on both the viscosity and the density of the gas.

Whether airflow is laminar or turbulent is predictable from the Reynolds number (Re), a dimensionless number that depends on the average velocity ($\bar{v}$), the density of the gas (ρ), the viscosity of the gas (η), and the diameter of the tube (D), so that

$$Re = \frac{\bar{v} D \rho}{\eta}$$

In straight, smooth, rigid tubes, turbulence occurs when the Reynolds number exceeds 2000. Therefore, turbulence is most apt to occur when the average velocity is high, gas density is high, gas viscosity is low, and the tube diameter is large. Since most of the resistance to airflow in the normal lung is in large airways, where resistance is density dependent, breathing a mixture of 80 percent helium and 20 percent oxygen (a mixture that is 64 percent less dense than air) increases airflow at a given driving pressure and substantially decreases airway resistance.

Calculation of Airflow Resistance

The driving pressure along the tracheobronchial tree—i.e., the difference between alveolar pressure and the pressure at the airway opening (mouth) that is required to produce a given rate of airflow into the lungs—provides a measure of the flow resistance of the airways, according to the equation

$$\text{Raw} = \frac{P_A - \text{Pao}}{\dot{V}}$$

where

$\dot{V}$ = airflow (L/s)
P_A = alveolar pressure (cmH_2O)
Pao = airway-opening pressure (cmH_2O)
Raw = airway resistance (cmH_2O/L/s)

Flow-Volume Relationships

Considerable insight into the flow-resistive properties of the airways can be obtained from the relationship between airflow and lung volume during maximal expiratory and inspiratory maneuvers. In practice, a person inhales maximally to total lung capacity; then exhales as forcefully, rapidly, and completely as possible to residual volume; and then returns to total lung capacity by a rapid, forceful inhalation (Fig. 9-9). During the maximal expiration, the rate of airflow peaks at a lung volume that is close to the total lung capacity; as the lung volume decreases and intrathoracic airways narrow, airway resistance increases, and the rate of airflow decreases progressively.

During the maximal inspiration, the pattern of airflow is different: Because of the markedly negative pleural pressure and large transmural airway pressure, the bronchi are wide, and their calibers increase further as lung volume increases. Consequently, inspiratory flow becomes high while the lung volume is still low and remains high over much of the vital capacity, even though the force generated by the inspiratory muscles decreases as they shorten.

A family of flow-volume loops is produced by repeating full expiratory and inspiratory maneuvers over the entire range of the vital capacity using different levels of effort (Fig. 9-10). The greater the effort exerted during inspiration, the greater is the rate of airflow over the entire range—i.e., from residual volume to total lung capacity. Similarly, during expiration, the rate of airflow increases progressively with increasing effort at large lung volumes close to total lung capacity. At intermediate and low lung volumes, the rate of expiratory airflow reaches a maximum while the effort expended is only moderate; thereafter, airflow does not increase further despite increasing expiratory efforts.

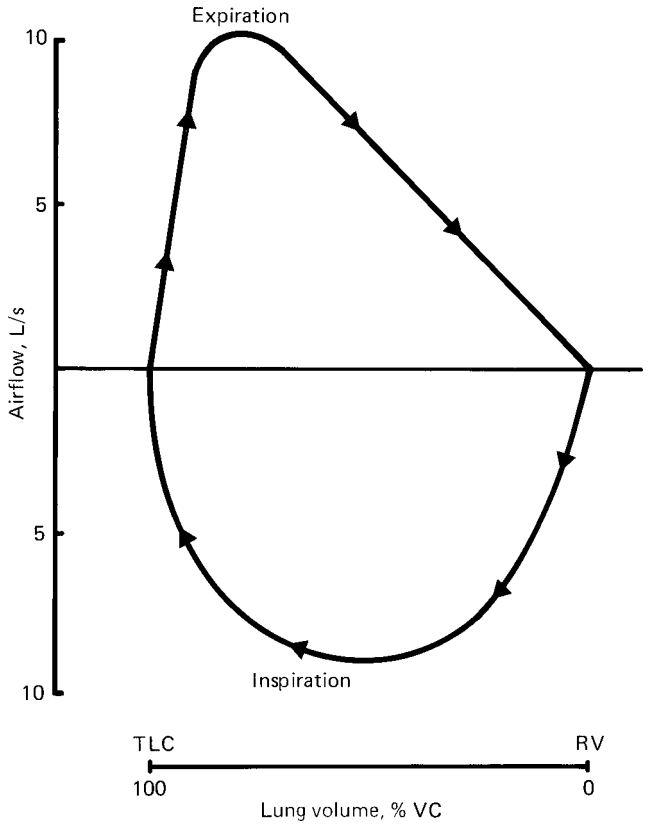

Figure 9-9 Maximal expiratory and inspiratory flow-volume loop.

Isovolume Pressure-Flow Curves

Separation of the effects of increasing effort from those of changes in lung volume on the rate of airflow during expiration can be accomplished by using isovolume pressure-flow curves (Fig. 9-11). During repeated expiratory maneuvers performed with varying degrees of effort, simultaneous measurements are made of airflow rate, lung volumes, and pleural pressure. For each lung volume the rate of airflow is plotted against the pleural pressure, an index of the degree of effort.

As expiratory effort is increased at any given lung volume, the pleural pressure increases toward, and then exceeds, atmospheric pressure; correspondingly, the rate of airflow increases. At lung volumes greater than 75 percent of the vital capacity, airflow increases progressively as pleural pressure increases; it is considered to be effort dependent. In contrast, at lung volumes below 75 percent of the vital capacity, the rate of airflow levels off as the pleural pressure exceeds atmospheric pressure and becomes fixed at a maximum level. Thereafter, further increases in effort, and in pleural pressure, effect no further increase in the rate of airflow; at these lower

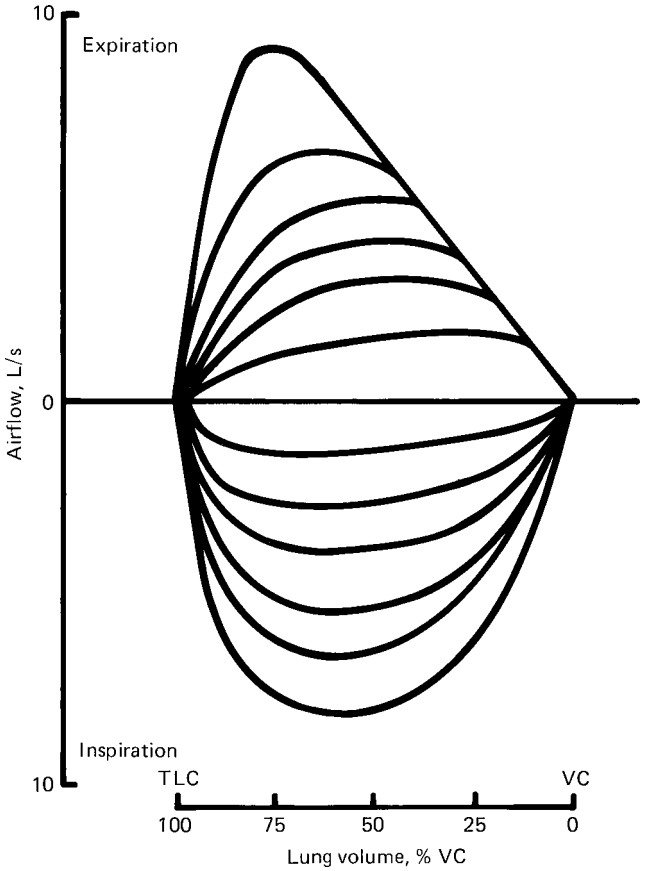

Figure 9-10 Series of flow-volume loops constructed from complete inspiratory and expiratory maneuvers repeated at different levels of effort.

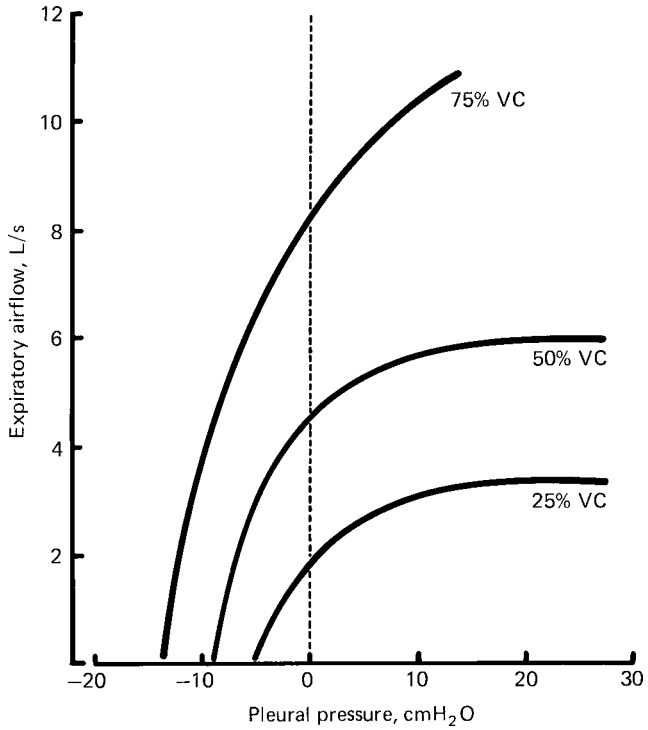

Figure 9-11 Isovolumetric pressure-flow curves. At lung volumes greater than 75 percent of the vital capacity, airflow is effort dependent; i.e., airflow increases progressively with increasing effort. At lower lung volumes, airflow is effort independent; i.e., airflow becomes fixed at a maximum level and does not increase despite further increases in effort.

lung volumes, airflow is considered to be effort independent. Since the rate of airflow remains constant despite increasing driving pressure, it follows that the resistance to airflow must be increasing in direct proportion to the increase in driving pressure. This increase in resistance is attributed to compression and narrowing of large intrathoracic airways.

Equal Pressure Point Theory: Dynamic Compression of Airways

To illustrate the mechanisms that normally limit airflow during a maximal expiratory maneuver, it is useful to consider a model of the lung where the alveoli are represented by an elastic sac and the intrathoracic airways by a compressible tube, both enclosed within a pleural space (Fig. 9-12).

At a given lung volume, when there is no airflow (as during breath holding with the glottis open), pleural pressure is subatmospheric, counterbalancing the elastic recoil pressure of the lung. The alveolar pressure (PA), which is the sum of the recoil pressure of the lung and pleural pressure (Ppl), is zero (Fig. 9-12*A*). Since airflow has ceased, the pressure along the entire airway is also atmospheric.

At the same lung volume during a quiet expiration, pleural pressure is less subatmospheric. Since lung volume and the elastic recoil pressure of the lung are unchanged, alveolar pressure is now positive with respect to atmospheric pressure; airflow occurs. The alveolar pressure is gradually dissipated along the airway in overcoming resistance so that the pressure at the airway opening (Pao) is zero. All along the airway, however, the airway pressure exceeds pleural pressure and the transmural pressure is positive; the airways remain open, and flow continues (Fig. 9-12*B*).

A forceful expiration raises pleural pressure above atmospheric pressure and further increases alveolar pressure (Fig. 9-12*C*). Airway pressure again falls progressively from the alveolus toward the airway opening. But at some point along the airway—the equal pressure point—the drop in airway pressure is equal to the recoil pressure of the lung; intraluminal pressure and the pressure surrounding the airways are equal and the same as pleural pressure. Downstream (i.e., toward the airway opening) the transmural pressure is negative, because the intraluminal airway pressure is less than pleural pressure; the airways are subjected to dynamic compression.

The equal pressure point divides the airways into two components arranged in series: an upstream segment, from the alveoli to the equal pressure point, and a downstream segment, from the equal pressure point to the airway opening. With increasing expiratory effort as the pleural pressure becomes more and more positive with respect to atmospheric pressure, the equal pressure point moves upstream. Once maximum expiratory flow is achieved, the position of the

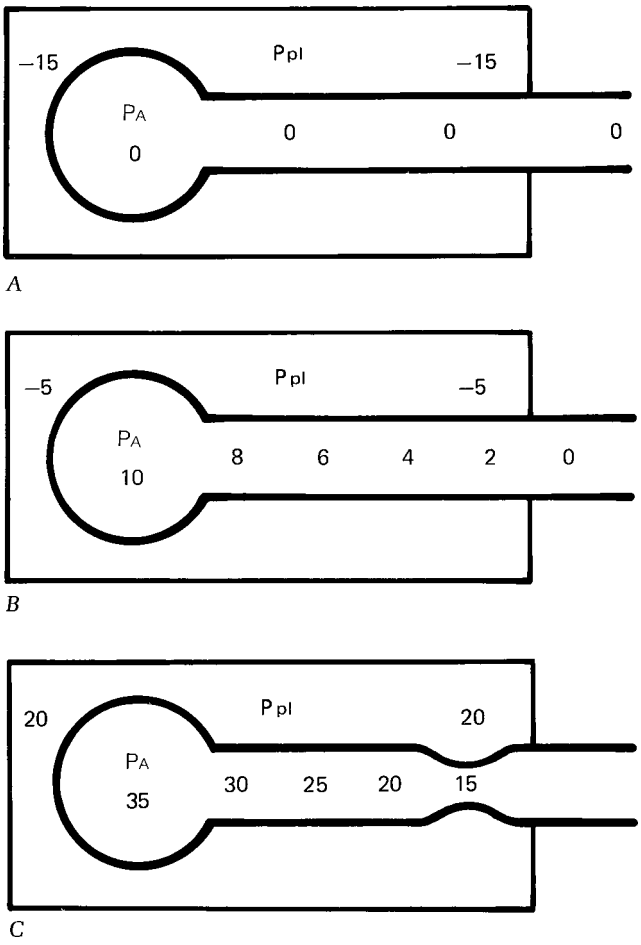

Figure 9-12 Schema of the distribution of pleural, alveolar, and airway pressures at rest and during expiration, illustrating the equal pressure point concept. *A*. End-expiration. *B*. Quiet expiration. *C*. Forced expiration.

equal pressure point becomes fixed in the region of the lobar or segmental bronchi. Further increase in pleural pressure by increasing expiratory force simply produces more compression of the downstream segment without affecting airflow through the upstream segment.

The driving pressure of the upstream segment—i.e., the pressure drop along the airways of that segment—is equal to the elastic recoil of the lung. The maximum rate of airflow during forced expiration ($\dot{V}max$) can be expressed in terms of the elastic recoil pressure of the lung (P_L) and the resistance of the upstream segment (Rus), as follows:

$$\dot{V}\,\text{max} = \frac{P_L}{\text{Rus}}$$

Measurements of the rate of airflow during force expiration form the basis of many tests used to assess the flow-resistive properties of the lung. It is evident, however, that the maximum rate of expiratory airflow depends on many factors: The lung volume at which airflow is determined, the force of expiration (particularly at high lung volumes—i.e., above 75 percent of vital capacity), the elastic recoil pressure of the lung, the cross-sectional area of large airways, the collapsibility of large intrathoracic airways, and the resistance of small peripheral airways.

Wave Speed Limitation Theory

An alternative explanation for airflow limitation during forced expiration is based on principles of wave speed theory. The wave speed theory proposes that flow is limited by the velocity of propagation of pressure waves along the wall of the tube. The velocity of propagation (v) varies proportionally with the cross-sectional area of the tube (A) and the elastance of the tube walls (dP/dA). At a site where the linear velocity of gas molecules equals the velocity of propagation of pressure waves, a choke point develops, preventing further increases in flow rate. Where choke points occur in the tracheobronchial tree depends on the lung volume: at large lung volumes, a choke point is situated in the vicinity of the lower trachea; at lower lung volumes, choke points develop more upstream along the bronchial tree. Extension of the neck exerts longitudinal tension and stiffens the trachea, increases wave velocity, and increases maximum expiratory flow rates at large lung volumes.

MECHANICAL DETERMINANTS OF REGIONAL VENTILATION

The lung is not homogeneous, and the mechanical properties of all airways in a given generation and of all alveoli are not the same. This results in important nonuniformities of regional ventilation.

Pleural pressure in the upright person is more subatmospheric at the apex than at the base of the lung, because of the effects of gravity and the weight of the lung. Pleural pressure topography and regional lung expansion are also determined by the shape of the chest wall and by the forces required for the lung to conform to the thoracic gravity shape. The rate of increase in pleural pressure from top to bottom is approximately 0.25 cmH_2O per centimeter of vertical distance. Consequently, the transpulmonary pressure—i.e., alveolar pressure minus pleural pressure—is greater at the top than at the bottom of the lung. Therefore, at most lung volumes, the alveoli at the lung apexes are larger (more expanded) than those at the lung bases (Fig. 9-13).

Because of regional variations in lung compliance, ventilation is not uniform, even in the normal lung. With the use of external scanners after the inhalation of a radioactive gas, such as ^{133}Xe, it has been demonstrated that within the range of normal tidal volume, lung units are better ventilated, and ventilation per alveolus is greater, at the bottom than at the top of the lung.

At low lung volumes (i.e., near the residual volume), pleural pressure at the bottom of the lung actually exceeds airway pressure and leads to closure of peripheral airways (Fig. 9-13). During a breath taken from residual volume, air

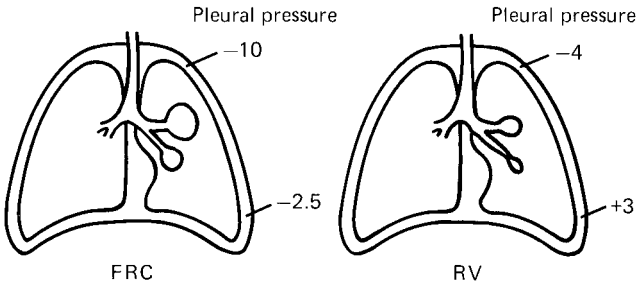

Figure 9-13 Pleural pressure gradients in the upright lung at FRC *(left)* and at RV *(right)*. The effect of the gradient on alveolar volumes is shown for each case.

that enters the lungs first is preferentially distributed to the lung apexes.

The distribution of ventilation within the lungs and the volume at which airways at the lung bases begin to close can be assessed by the single-breath N_2 washout test. This test requires a maximum expiration into an N_2 meter after a maximal inspiration of pure O_2 from residual volume; the changing concentration of nitrogen is plotted against expired lung volume (Fig. 9-14). Because the inspiration starts at the residual volume, the initial portion of the breath containing dead-space gas, rich in nitrogen, is distributed to alveoli in the upper lung zones. The rest of the breath, which contains only O_2, goes preferentially to lower lung zones. Consequently, the concentration of nitrogen is lower in the alveoli at the lung bases than in the alveoli at the apexes of the lungs.

During expiration, the initial portion of the breath consists of O_2 remaining in the large airways; it contains no N_2 (phase I). As alveolar gas containing N_2 begins to be washed out, the concentration of N_2 in the expired air rises to reach a plateau. The portion of the curve where the concentration of N_2 rises steeply is phase II. The plateau is phase III. Phase III depends on the uniformity of the distribution of ventilation in the lung. If gas enters and leaves alveoli throughout the lung

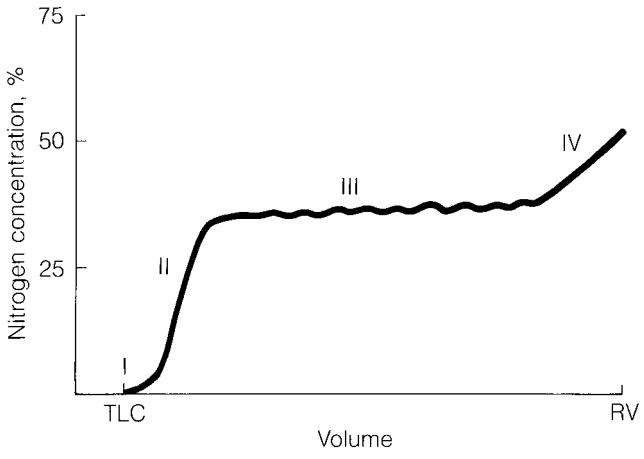

Figure 9-14 Tracing of expired nitrogen concentration during a slow expiration from TLC to RV after a full inspiration of pure O_2. The four phases are indicated.

synchronously and equally, phase III is flat. But when the distribution of ventilation is nonuniform, so that gases coming from different alveoli have different N_2 concentration, phase III slopes upward.

At low lung volumes, airways at the lung bases close; only alveoli at the top of the lung continue to empty. Since the concentration of N_2 in the alveoli of upper lung zones is higher than in the alveoli at the lung bases, the slope of the N_2-volume curve increases abruptly, marking the start of phase IV. The volume, above residual volume, at which phase IV begins is the closing volume.

Dynamic Compliance of the Lungs

The relationship between changes in volume and changes in pleural pressure during a normal breathing cycle is shown in Fig. 9-15. Airflow momentarily ceases at the end of expiration (A) and at the end of inspiration (C); the change in pleural pressure between these two points reflects the increasing elastic recoil of the lung as the volume of air in the lungs increases. The slope of the line connecting the end-expiratory and end-inspiratory points (AEC in the figure) on a pressure-volume loop provides a measure of the dynamic compliance of the lungs.

In normal persons, dynamic compliance closely approximates inspiratory static lung compliance and remains essentially unchanged even when breathing frequency is

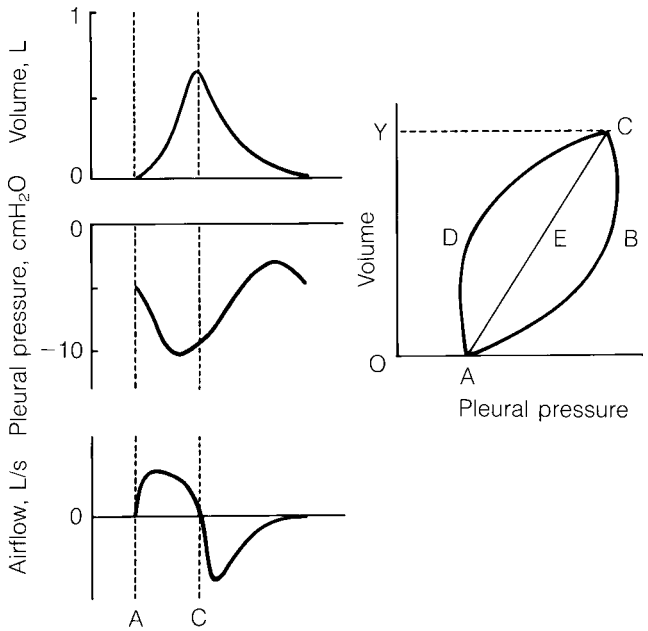

Figure 9-15 Individual tracings of tidal volume, pleural pressure, and airflow, taken simultaneously during a single complete breath, are shown on the left. The relationship between volume and pleural pressure is illustrated by the dynamic pressure-volume loop on the right. Dynamic compliance is determined as the slope of the line AEC. The work of breathing during inspiration to overcome the elastic forces of the lung is represented by the area of the trapezoid OAECY, and the work required to overcome nonelastic forces is represented by the area of the loop ABCEA.

increased up to 60 breaths per min. This indicates that lung units that are parallel with each other normally fill and empty uniformly and synchronously, even when airflow is high and the change in lung volume is rapid. The rate of filling and emptying of a lung unit depends on its time constant—i.e., the product of its resistance and compliance. In order for the distribution of ventilation in parallel lung units to be independent of the rate of airflow, the resistance and compliance of these units must be matched so that the time constants of individual units throughout the lungs are approximately the same. The time constants of lung units distal to airways 2 mm in diameter are approximately 0.01 s, and fourfold differences in time constants are necessary to cause dynamic compliance to become frequency dependent.

Patchy narrowing of small peripheral airways produces regional differences in time constants. At low breathing frequencies, when the rate of airflow is low, ventilation is fairly evenly distributed. As the breathing frequency increases, however, ventilation tends to be distributed to areas that offer the least resistance to airflow. Therefore, lung units fed by narrowed airways receive proportionally less ventilation than do areas of the lung where the airways remain normal; the change in pleural pressure required to effect the same change in overall lung volume increases. As a result, the dynamic compliance falls.

Measurements of frequency dependence of dynamic compliance are time-consuming and technically difficult, but this test has proved useful in the diagnosis of obstruction in small peripheral airways when results of other conventional tests of lung mechanics are still within normal limits.

WORK AND ENERGY COST OF BREATHING

During breathing, the respiratory muscles work to overcome the elastic, flow-resistive, and inertial forces of the lungs and chest wall. The elastic work of breathing is done to overcome the elastic recoil of the lungs and chest wall; the resistive work is done in overcoming the resistance of airways and tissues. The mechanical work of breathing can be determined by relating the pressure exerted across the respiratory system to the resulting change in volume, since the product of pressure (P) and volume (V) has the dimension of work, according to the equation

$$\text{work} = \int P\,dV$$

Records of pleural pressure and lung volume changes during spontaneous breathing can be used to measure the work of breathing; the work of breathing performed on the lungs can be determined from the area of dynamic pressure-volume loop (Fig. 9-15) and fractionated into its elastic and resistive components. During inspiration, the work done to overcome the elastic forces of the lung is determined from the area of the trapezoid OAECY (Fig. 9-15). The area of the loop ABCEA is the work in overcoming nonelastic forces during inspiration, and the area of the loop OABCY is the total work of breathing during inspiration.

Expiration during quiet breathing is passive, since the elastic recoil of the lung suffices to overcome the expiratory airflow resistance. Some of the stored elastic energy is also used to overcome inspiratory muscle activity that persists into the expiratory phase of breathing. At high levels of ventilation and when airway resistance is increased, additional mechanical work during expiration is required to overcome nonelastic forces. Under these circumstances, the pleural pressure exceeds atmospheric pressure, and the loop AECDA extends beyond the confines of the trapezoid OAECY.

Work of Breathing

The work of breathing at any given level of ventilation depends on the pattern of breathing. Large tidal volumes increase the elastic work of breathing, whereas rapid breathing frequencies increase the work against flow-resistive forces. During quiet breathing and during exercise, people tend to adjust tidal volume and breathing frequency at values that minimize the force and the work of breathing. Similar adjustments are also seen in patients with pulmonary disorders: Patients with pulmonary fibrosis, which is characterized by an increased elastic work of breathing, tend to breathe shallowly and rapidly; those with airway obstruction and increased nonelastic work of breathing usually breathe more deeply and slowly.

The work done on the chest wall during breathing is calculated by subtracting the work performed on the lung from the total mechanical work of breathing. The total mechanical work of breathing cannot be readily measured during spontaneous breathing because the respiratory muscles that perform the work also make up part of the resistance offered by the chest wall. But the total mechanical work can be determined during artificial ventilation by using either intermittent positive airway pressure or negative pressure applied to the chest, provided that the respiratory muscles are completely at rest. For this determination, the change in lung volume is related to the pressure difference across the respiratory system—i.e., differential pressure between the mouth and the body surface. Disturbances of the chest wall, such as kyphoscoliosis and obesity, usually increase the work of breathing severalfold.

Oxygen Cost of Breathing

In order to perform their work, the respiratory muscles require O_2. The O_2 cost of breathing, which reflects the energy requirements of the respiratory muscles, provides an indirect measure of the work of breathing. The O_2 cost of breathing is assessed by determining the total O_2 consumption of the body at rest and at an increased level of ventilation produced by voluntary hyperventilation or CO_2 breathing. Provided there are no other factors acting to increase O_2 consumption, the added O_2 uptake is attributed to the metabolism of the respiratory muscles.

The O_2 cost of breathing in normal subjects is approximately 1 ml/L of ventilation and constitutes less than 5 percent of the total O_2 consumption. At high levels of ventilation, however, the O_2 cost of breathing becomes progressively greater. There is a dramatic increase in the O_2 cost of breathing at high levels of ventilation in some diseases of the lung, such as pneumonia, pulmonary fibrosis, and emphysema, and in disorders of the chest wall, such as obesity and kyphoscoliosis. The increase in the energy requirement of the respiratory muscles during increased ventilation, concomitant with a decrease in O_2 supply secondary to arterial hypoxemia, probably produces muscle fatigue, thereby limiting the amount of exertion that these patients can sustain.

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10

Control of Ventilation

Neil S. Cherniack

We breathe by the coordinated action of thoracic and upper airway muscles. Principal among these is the diaphragm, which generates negative pressure in the chest, inflating the lung. Expiration in quiet breathing occurs passively by relaxation of the inspiratory muscles except during its first portion where the diaphragm, by briefly continuing its activity, brakes the release of air from the lungs. In deep or rapid breathing the abdominal and other expiratory muscles augment the expulsion of air.

To regulate the action of these muscles, the respiratory control system uses signals from chemical sensors that measure P_{O_2} and P_{CO_2} and mechanoreceptors, which monitor lung and respiratory muscle movements to match the level of ventilation to the metabolic demand. These signals are fed back to rhythm generators, neurons located in the rostral medulla that cause the respiratory muscles to contract, setting the tidal volume and frequency of breathing.

A number of other factors influence the level and pattern of breathing besides oxygen and carbon dioxide (Fig. 10-1). Of major importance is the sleep-wake cycle. In conscious humans, cortical projections to the rhythm generators and, more directly, to the respiratory motor neurons cannot only override automatic control for short periods of time but even more important provide the mechanism that allows excitatory stimuli from within and without the body to maintain ventilation even at very low levels of P_{CO_2}. This drive, known as the wakefulness drive, adds to the chemical drive arising from increases in carbon dioxide and by hypoxia (Fig. 10-2).

The breathing pattern is also affected by afferent information provided principally by receptors in the lung monitoring its deformation. In addition, movement of each of the respiratory muscles is monitored by mechanoreceptors to ensure that central commands to the muscle are executed.

MAJOR AFFERENT SYSTEMS

Peripheral Chemoreceptors

The carotid bodies are the major peripheral chemoreceptors. The aortic bodies are less important. Indeed in humans ventilation does not increase with hypoxia when carotid bodies

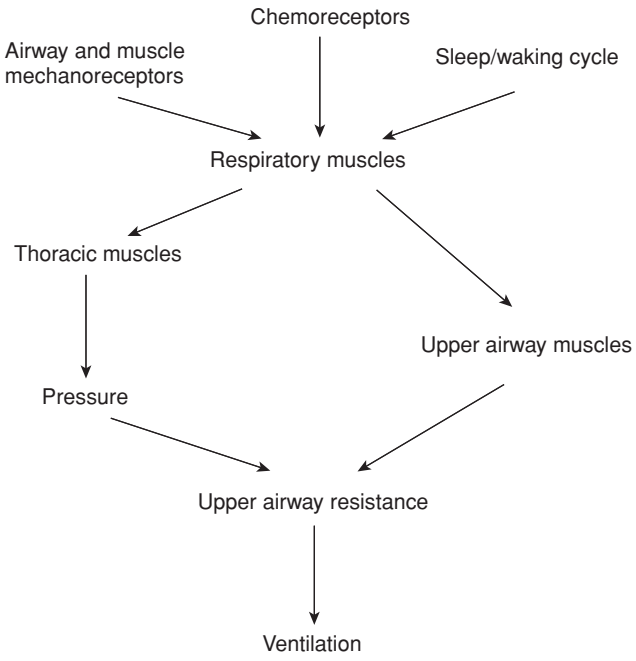

Figure 10-1 Factors controlling airway and thoracic muscles.

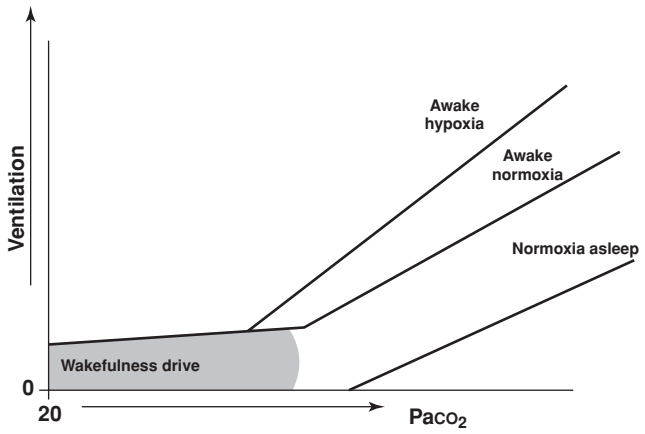

Figure 10-2 Ventilation response to hypercapnia while awake under normoxic and under constant hypoxic conditions. Not shown when the response to CO_2 is examined under more severe hypoxia the slope of the response line becomes steeper. The effect of sleep on normoxic CO_2 response is shown. Shaded area indicates approximate level of wakefulness drive. Note that apnea readily occurs with hyperventilation during sleep but is more difficult awake because of wakefulness drive.

are nonfunctioning. During normal quiet breathing of ambient air the carotid bodies contribute about 15 percent of the ventilatory drive. They also account for about 30 percent of the ventilatory response to hypercapnia. The carotid bodies are located at the bifurcations of the common carotid arteries in the neck. They are supplied by blood from a branch of the external carotid artery, while their venous drainage is to the internal jugular. They have an enormous blood flow for their small mass (of the order of 10 mg in humans). Because of the large blood flow, the arteriovenous difference for oxygen is extremely small (0.2 to 0.5 ml per 100 ml). This large blood flow, coupled with the low extraction of oxygen, makes the carotid body relatively insensitive to variations in oxygen delivery (O_2 content times blood flow). Instead, carotid bodies respond primarily to changes in oxygen tension.

At a constant P_{CO_2}, a hyperbolic relationship exists between carotid body discharge and P_{O_2}, whereas at a constant P_{O_2}, the relationship between activity and P_{CO_2} is linear (Fig. 10-3). The interaction of the two signals is such that the carotid body becomes more sensitive to P_{CO_2}, as hypoxia becomes more severe (see Fig. 10-3). Most, but not all, studies indicate that the receptors are sensitive to the rate of change of P_{CO_2}. The rate sensitivity of the receptors, and their rapid

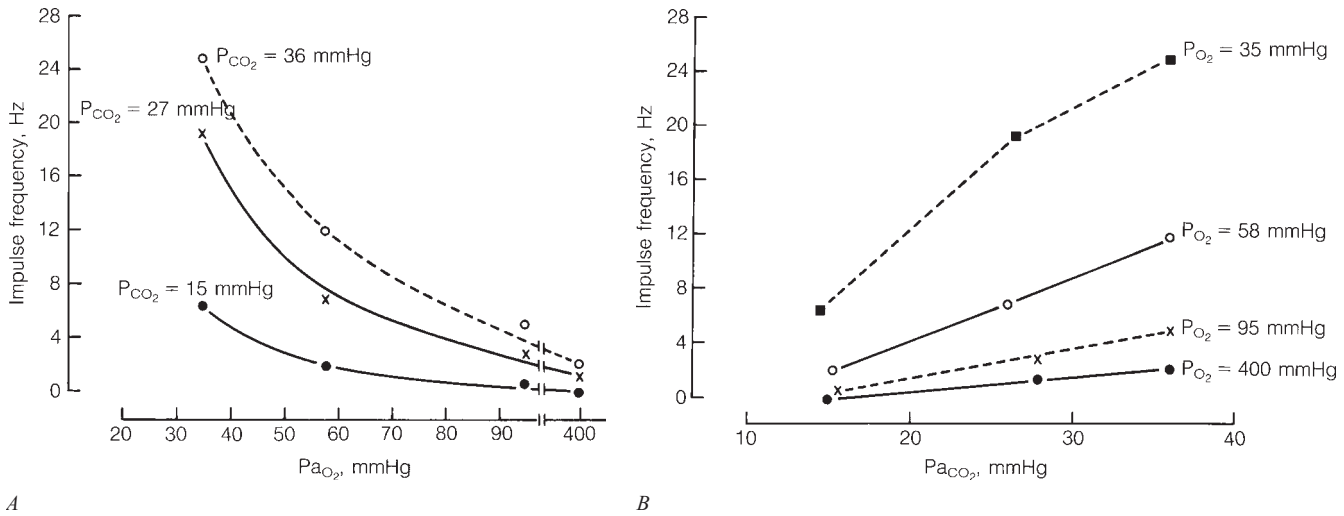

Figure 10-3 *A.* Relationship between carotid body afferent activity (single fiber) and P_{O_2} (at different levels of P_{CO_2}). *B.* Relationship between single-fiber carotid body afferent activity and P_{CO_2} at different levels of P_{O_2}. *(These data are redrawn from Lahiri S, deLaney RG:* Respir Physiol *24:249–266, 1975.)*

response to changes in P_{CO_2} and P_{O_2}, enable the carotid body to follow respiratory-related oscillations in arterial blood-gas tensions.

The afferent signals from the carotid body are relayed in fibers in the glossopharyngeal nerve to the nucleus tractus solitarius. There is also efferent innervation via sympathetic nerves and via the glossopharyngeal nerve. Stimulation of the sympathetic nervous system leads to an increase in carotid body discharge, an effect that is probably due to local changes in blood flow within the organ. In contrast, increased activity of the efferent glossopharyngeal pathway through the release of nitric oxide inhibits chemoreceptor discharge. Thus, the system allows adjustment of the sensitivity (gain) of the carotid body and the range of carotid body operations.

The majority of the afferent fibers terminate on glomus cells (i.e., the type I cells that constitute 60 to 80 percent of the specific cell types of the carotid body). The type I cells contain rough endoplasmic reticulum, aggregates of ribosomes, a well-developed Golgi apparatus, and dense core vesicles. The glomus cells are arranged in groups (glomerules), and each group is surrounded by the second main cell type of the carotid body (i.e., the sheath, or type II cell). Type II cells do not appear to be innervated, nor do they contain the dense core vesicles of the type I glomus cell.

Type I cells contain catecholamines (dopamine, norepinephrine, and epinephrine) in their dense core vesicles. Of these, dopamine is the principal one (60 to 90 percent of the total catecholamine present). The carotid bodies can take up circulating catecholamines and their precursors and can synthesize catecholamines from tyrosine. Hypoxia increases the levels of dopamine, but we do not know if dopamine is an essential neurotransmitter or, as seems more likely, it modulates the chemoreceptor process. Exogenously administered dopamine depresses chemoreceptor discharge. Other potential neurotransmitters such as 5-hydroxy-tryptamine (serotonin), acetylcholine, and neuropeptide such as substance P, vasoactive intestinal polypeptide (VIP), met- and leuenkephalin are present in the carotid body. The role of these substances in the transduction process is also unknown. Recent data indicate that both carbon monoxide (CO) and nitric oxide (NO) inhibit carotid body activity. NO formation from arginine is catalyzed by the enzyme nitric oxide synthesis, which is found in the carotid body, mainly in nerve fibers. Inhibition of NO synthase increases carotid body activity both in vivo and in vitro. Because NO synthase, which forms NO in vivo, is itself inhibited by hypoxia, the decrease in NO formation may contribute to hypoxic stimulation of the carotid body. Heme-oxygenase 2 (HO-2), which catalyzes CO production, is also found in type I cells. Metalloprotoporphyrins that inhibit HO-2 enhance carotid body discharge.

It is agreed that the type I cells contain the O_2 sensing mechanism. There are two not necessarily conflicting ideas on how hypoxia excites type I cells: One idea is that hypoxia acts at the cell membrane, decreasing the conductance in oxygen sensitive potassium channels, thus leading to cell depolarization. This in turn leads to a calcium influx and the release of neurotransmitters. The other, the so-called metabolic hypothesis, is that hypoxia interferes with respiratory energy production in type I cells, and that in turn triggers increased chemoreceptor discharge. Cytochrome A_3 according to this idea is the biochemical substance responsible for O_2 sensitivity. Reactive oxygen species that vary with oxygen level seem to be involved in oxygen sensing process.

Other tissues and organs besides the carotid body respond to long-term hypoxia with increases in the formation of enzymes that participate in anaerobic metabolism and the formation of substances such as erythropoietin, which enlarges red cell mass through the action of the transcription factor, hypoxia-inducible factor (HIF1-alpha). This is constantly produced normally but degraded by the enzyme proline hydroxylase. It accumulates during hypoxia, which inhibits proline hydroxylase.

Neurons near the ventral surface of the medulla containing the enzyme HO-2 that breaks down hemoglobin to biliverdin and CO may also be involved in hypoxic sensing and when stimulated, lead to increases in blood pressure. The importance of these central hypoxia receptors is unclear.

Central Chemoreceptors for Carbon Dioxide and Hydrogen Ion

Central chemoreceptors in the brain stem account for 70 percent of the response to hypercapnia. There is appreciable evidence that chemosensitive cells near the rostral ventral medullary surface play a significant role in mediating this response. Using tissue slices and cell cultures it has been demonstrated that neurons at other sites also respond to local changes in acidity or CO_2 by depolarization and increased activity. The current view is that neurons, which respond to acidity include besides the ventral medullary surface, rostral aspects of the ventral respiratory group, dorsal motor nucleus of the vagus, nucleus of the respiratory tract, locus ceruleus, medial raphe, pre-Boetzinger complex, and fastigial nucleus of the cerebellum. In addition, cells that respond to increases in CO_2 by increasing respiratory frequency have been observed in spinal cord and in a brain stem spinal cord preparation isolated from newborn rats.

Chemoreceptors in any single location are reported to account for only 20 to 25 percent of the total ventilatory response to breathing 7 percent CO_2 with the contribution depending on sleep-wake state. Interpretation of these results is complicated because even well-defined interventions can produce reactions in distant areas that are indirectly excitatory or inhibitory to breathing. Also CO_2, and the changes in hydrogen ion it produces, have diverse effects on many systems besides respiration as, for example, the autonomic nervous system, sleep-wake processes and metabolism.

The specific stimulus for the central chemoreceptors continues to be a subject of debate. The prevailing theory is that the stimulus is uniquely related to hydrogen ion concentration at the receptor site. However, a given decrease in pH produced by CO_2 inhalation has more marked effects on respiration than does the same decrease produced by

metabolic acidosis, suggesting that CO_2 may, per se, have an additional stimulatory action.

Cells that respond to CO_2 or acidity have no special morphological features. And several different neurotransmitters such as acetylcholine, glutamate, and serotonin may participate in central chemoreception.

A number of different molecular mechanisms have been considered to account for central chemosensitivity. It may be that chemosensitive cells, unlike nonchemosensitive cells, cannot rapidly restore internal pH after being challenged by changes in CO_2. On the other hand, many nonchemosensitive cells can. Another idea is that central chemoreceptors contain pH sensitive potassium channels that are inhibited by acidosis leading to depolarization.

Pulmonary Mechanoreceptors

Complementing the information from the chemoreceptors are afferent systems that provide information via mechanoreceptors about the state of the lungs and the respiratory muscles. There are several receptor types within the lung: stretch receptors, rapidly adapting (irritant) receptors both in the airways *(juxtacapillary*, or *J receptors)* in pulmonary interstitium and *bronchial C receptors* but the respiratory muscles are provided by muscle spindles and tendon organs, which will be discussed later. The intercostals and abdominal muscles are relatively richly innervated with both muscle spindles and tendon organs, whereas the diaphragm is relatively poor in muscle spindles.

The *pulmonary stretch receptors* are situated within the smooth muscle of the airways, mainly in the more proximal ones. They show a slowly adapting response to inflation of the lung (Fig. 10-4A). The rate of inflation (dynamic response) also affects firing rate.

The *rapidly adapting receptors* (also called, *irritant receptors* and *deflation* or *collapse receptors*) are also found mainly in the larger airways; indirect evidence indicates that they are situated in the epithelium and submucosa. The firing rate of these receptors depends strongly on the rate of airflow and occurs mainly during inflation (Fig. 10-4B); also, decreases in compliance during inflation lead to increased firing of the receptor. The rapidly adapting receptor may also be responsible for the generation of intermittent sighs without which pulmonary compliance decreases progressively.

Originally identified by their rapidly adapting response to lung inflation (see Fig. 10-4B), these receptors have since become known as irritant receptors since they respond to a variety of chemical irritants (e.g., ammonia, cigarette smoke, ether vapor, and inert dust particles). This was thought to elicit a defense reflex; i.e., coughing, laryngeal constriction, airway narrowing, and increased production of respiratory tract mucus.

Both the rapidly adapting receptors, since they are quite sensitive to histamine, which is secreted in asthmatic attacks, and a group of nonmyelinated afferent endings in the bronchi, the bronchial C receptors, may be important mediators of reflex bronchoconstriction in asthma. The latter are also stimulated by phenyldiguanide and capsaicin; as well as by a variety of pulmonary autocoids released in asthma and inflammatory disease [i.e., bradykinin, serotonin, prostaglandins (PGF_{2a}, PGE_2, PGI_2), prostacyclin] and inhaled irritants such as sulfur dioxide. Activation of these receptors produces reflex tachypnea, increased tracheobronchial secretion, and bronchoconstriction. The low baseline firing of the receptors may contribute to normal bronchomotor tone.

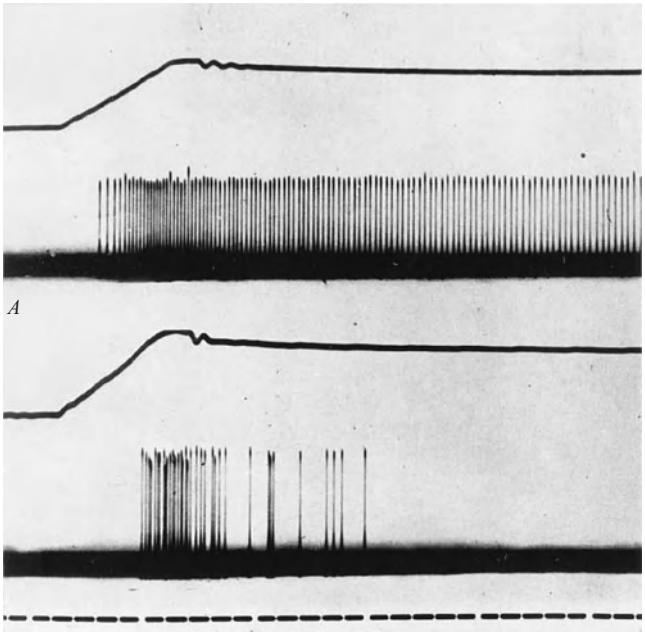

Figure 10-4 Response characteristics of the two major mechanoreceptors in the airways. *A*. A response of pulmonary stretch receptor. This shows the slowly adapting nature of the response and the continued discharge of the receptor during maintained inflation of the lung. *B*. Response of the rapidly adapting ("irritant") receptor, which fires largely during the period while the lung is being inflated and then adapts. *(Reproduced with permission from Knowlton GC, Larabee MG:* Am J Physiol *147:100–114, 1946.)*

Nonmyelinated afferent endings in the pulmonary interstitium (i.e., the juxtacapillary or J receptors) also respond to chemicals such as phenyldiguanide and capsaicin but show only weak stimulation in response to histamine and virtually no response to bradykinin. The reflex effects of stimulation of J receptors are different from those of bronchial C fibers. Stimulation of J receptors produces the pulmonary chemoreflex, a triad of apnea, bradycardia, and hypotension. Less intense but more sustained stimulation elicits tachypnea rather than apnea. The cardiac depressor effects are due to both cardiac slowing and a fall in right ventricular stroke volume. Although some cardiac depression also occurs after stimulation of bronchial C receptors, the depression is modest compared with that for J receptors.

Stimulation of J receptors additionally inhibits motor neurons of the spinal cord by a central reflex mechanism; the motoneurons that innervate the respiratory muscles and those involved in monosynaptic and polysynaptic spinal

reflexes are affected by this inhibition. This component of the reflex response, which has been called the *J reflex*, suggested that these receptors function to limit exercise by inhibiting motor neuron discharge whenever alveolar-capillary interstitial pressure increases as the result of interstitial deformation (e.g., by an increase in interstitial water). At present, the role of the J receptors in exercise can only be regarded as unsettled.

CENTRAL NEURAL MECHANISMS

Of the various ideas of the neural mechanisms that might produce rhythmic behavior, the most widely held is that respiratory rhythmicity is a property of the synaptic interactions between the various types of inspiratory and expiratory neurons in the brain stem. The central pattern generator is believed to be located in the ventral medulla. A three-part rhythm is produced consisting of: inspiration, postinspiration (phase 1, expiration), and late expiration (phase 2, expiration). Identification of these phases is based on the different mechanical effects of each (lung inflation, passive expiration with braking of expiratory air flow, and active expiration, respectively).

During inspiration, inspiratory neurons in the medulla that are premotor to the phrenic and intercostal motor nuclei display an augmenting discharge. Intracellular recordings from such neurons reveal that they receive increasing excitatory postsynaptic activity throughout inspiration. This activity is due, in part, to these neurons re-exciting each other but more than that, to an excitatory input, that they receive from an unidentified source.

At the end of inspiration, discharge from these inspiratory neurons is extinguished by an inhibitory activity from other neurons. Certain afferent inputs, such as the pulmonary stretch receptor, affect the duration of the respiratory phases. Increased activity of pulmonary stretch receptors shortens inspiratory duration. As a result, the larger the tidal volume, the shorter the duration of inspiration.

The end of inspiration is followed by a period of postinspiratory activity on the part of certain inspiratory neurons. During this period of declining activity, the inspiratory neurons receive both excitatory and inhibitory postsynaptic potentials. This neural activity is associated with active braking of airflow at the beginning of expiration. The duration of this postinspiratory phase of the respiratory cycle seems to be an important determinant of total duration of expiration.

Succeeding the postinspiratory phase of the respiratory cycle is a period during which the expiratory muscles may undergo active contraction. In this phase of the cycle, inspiratory bulbospinal neurons receive inhibitory postsynaptic potentials in an augmenting pattern.

Although the duration of expiration, like inspiration, can be set by intrinsic brain stem mechanisms, normally it is modulated by afferent inputs. Throughout expiration, there is a decreasing inhibition of the following inspiration. Thus, early in expiration larger stimuli (e.g., pulmonary deflations) are needed to trigger the onset of inspiration than later in expiration. Activity of the pulmonary stretch receptors prolongs expiration (i.e., the Hering-Breuer expiratory promoting reflex).

For many years the respiratory pattern generator has been studied in vivo in adult and neonatal animals relying mainly on electrophysiological techniques of intracellular and extracellular recordings. These studies failed to localize the pattern generator but revealed an array of neurons with differing activity patterns in relation to the respiratory cycle. In reduced preparations as in slices of neonatal rodent medulla, the respiratory pattern generator has been localized anatomically to the pre-Boetzinger complex in the rostral ventral medulla. The pattern generator seems to have a similar location in the adult animal as shown by the interruption of the respiratory pattern in studies in which this complex is ablated.

In immature beings pacemakers rather than mutually inhibiting circuits seem to produce the respiratory rhythm but their importance in the adult is questionable. Both inspiratory and expiratory pacemakers have been identified. Some believe that even in adults there are conditional pacemaker neurons imbedded within the oscillating network that produces the rhythm. Pacemaker neurons may depend on persistent sodium current or calcium-dependent currents for their spontaneous bursts of activity. The respiratory rhythm generated, whether or not it is produced by pacemaker neurons, is formed and shaped through the interactions of groups of premotor, motor, and sensory neurons.

COORDINATION OF THE ACTIVITY OF THE RESPIRATORY MUSCLES

The coordinated activity of the muscles that insert upon the thoracic cage not only brings air to the alveoli but also prevents the waste of energy that could be caused by chest wall distortion during breathing.

The pharyngeal channels, which air must traverse before arriving at the lungs, have flexible walls and contain valve-like mobile structures that can be displaced to obstruct the airways by the negative and positive swings in pressure that occur during normal breathing. The rigidity and configuration of these channels and their patency depend on the activity of the laryngeal and pharyngeal muscles, which have a respiratory modulation that increases as breathing is stimulated.

Thoracic Muscles

During quiet breathing the diaphragm is the muscle mainly responsible for the tidal excursions of air. As the diaphragm contracts, it presses on the abdominal contents, which are primarily fluid, to push the abdominal wall outward. At the same time, through its insertions on the lower ribs, the diaphragm elevates the costal margins and expands the chest cavity. Even the small transthoracic pressure changes that occur during

breathing are sufficient to distort the chest wall. Acting alone, the diaphragm would use energy not only to overcome the resistance of the airways and the stiffness of the chest wall, but also to distort the ribs. Contraction of the parasternal intercostal muscles, and perhaps the scalene muscles, prevents this distortion.

The postinspiratory activity of the inspiratory muscles may help to improve the efficiency of gas exchange and, in infants (in whom the chest wall is extremely pliable), may help to preserve the functional residual capacity by preventing too much air from leaving the lungs during the expiratory period.

The diaphragm itself does not behave as if it were a single muscle. The costal portion of the diaphragm is supplied mainly by the upper cervical roots, which make up the phrenic nerve, whereas the crural portion of the diaphragm receives its innervation mainly through the lower phrenic roots. Isolated contraction of the crural diaphragm causes primarily expansion of the abdomen, whereas contraction of the costal portion, in addition to causing movement of the abdominal wall, enlarges the rib cage. The crural diaphragm may also act as a part of the sphincter mechanism for the lower esophagus; its contraction compresses the sphincter.

The phrenic motor neurons themselves have been divided into early firing units, the activity of which begins at the very onset of inspiration, and late firing units, which commence their activity much later in inspiration. As respiration increases, the frequency of firing of both the early and late units increases; in addition, more and larger motor units are recruited according to a "size principle." Phrenic neurons supplying larger motor units (which contain more fibers) are recruited later than are neurons that innervate smaller units. Also, as ventilation increases, the intercostal muscles come into play, the upper intercostals becoming active first and then the lower intercostals. The expiratory muscles begin to contract at higher levels of ventilation. At high levels of ventilation, the "accessory" muscles of respiration, such as the sternocleidomastoid, the hyoid muscle, and muscles attaching to the spine, also contribute to breathing.

Spindles, length/tension receptors in the muscles, increase the strength of muscular contraction via a spinal reflex when their movement is hindered. Spindles however are scarce in the diaphragm. Tendon organs in the diaphragm and intercostals prevent excessively powerful contractions.

The diaphragm, like other skeletal muscles, has less ability to produce force as the velocity of contraction and the degree of shortening increase. The ability of the respiratory system to increase tidal volume is preserved by at least three mechanisms: (1) Motor output to the diaphragm grows greater; (2) as air flow accelerates, reflex mechanisms (possibly from rapidly adapting receptors) further increase motor output; and (3) the recruitment of more muscles helps curtail the load on the diaphragm.

When skeletal muscles are made to contract forcibly over long periods, they tire (i.e., are unable to generate as much pressure). The diaphragm can also become fatigued when it is obliged to develop large pressure changes because of either sustained respiratory stimulation or chronic mechanical impairment of the lungs. Fatigue leads to decreasing tidal volume and, ultimately, to CO_2 retention. Diaphragm fatigue can result from interference with cellular contractile mechanisms but can also be central in origin. Afferent signals from the diaphragm, originating from unspecified receptors that project to the brain via the phrenic nerves, may signal impending fatigue and enable motor output to diminish, thereby preventing irreversible damage to the muscle itself.

Upper Airway Muscles

The muscles of the upper airways also serve an important respiratory function. Contraction of the posterior cricoarytenoid muscle during inspiration to open the laryngeal aperture, an important site of airway resistance, increases the efficiency of energy used by the thoracic muscles during breathing. Changes in the laryngeal aperture are thus synchronized with breathing. When respiratory drive is increased, as during exercise or acute hypercapnia, the magnitude of this effect increases.

In addition to the larynx, activity of the cranial nerves that innervate muscles of the upper airways, such as the alae nasi (nasal dilator), genioglossus (protrussor muscle of the tongue), and muscles inserting on the hyoid, varies with the breathing cycle. During inspiration these muscles contract, dilating the upper airway passages and overcoming the negative intraluminal pressures produced by shortening of the thoracic muscles. This inspiratory activity may be of particular importance during sleep when the alignment of gravitational forces favors occlusion of the upper airways. Inspiratory activity of the upper airways also begins slightly before the onset of activity of the chest wall muscles. This difference in time of onset within a breath may also help to prevent airway obstruction.

The upper airway muscles seem to be more susceptible to the inspiratory inhibiting action of pulmonary stretch receptor input than are the muscles of the chest wall. The reduction in stretch receptor stimulation that occurs during airway occlusion increases the inspiratory activity of the upper airway muscles far more than that of either diaphragm or intercostal muscles. This heightening of discharge helps to dilate the upper airways and prevent obstruction during breathing.

INTEGRATED RESPONSES OF THE CONTROL SYSTEM

Response to Exercise

There are several phases to the exercise response: an initial rapid response, believed to be neurally mediated; followed by a slower exponential response that plateaus; and in severe exercise by a further increase due to the accumulation of lactic acid when oxygen consumption exceeds the anaerobic threshold and lactic acid accumulates in the blood. During exercise

there appears to be an additional stimulus to breathing which increases ventilation sufficiently so that there is little change in P_{CO_2} despite the rise in metabolic rate. The origins of this stimulus remain unclear. Proposed sources have included signals arising from the cortex (so-called feed forward control), temperature increases, afferent signals arising as a result of muscle contraction, accumulation of catecholamines, and increases in potassium in the venous blood.

The importance of the carotid body in the ventilatory response to exercise is disputed. Most but not all, studies indicate that the carotid body is sensitive to the rate of change of P_{CO_2}. The rate sensitivity of the receptors, and their rapid response to changes in P_{CO_2} and P_{O_2}, enable the carotid body to follow respiratory-related oscillations in arterial blood-gas tensions. Since the magnitude of oscillations in arterial P_{CO_2} is directly related to metabolic CO_2 production, it has been proposed that this oscillatory signal helps in the coupling of metabolic production of CO_2 and ventilation that occurs during exercise. This postulate has been the subject of much study, but experimental results have been conflicting.

Chemoreceptors in the mixed venous blood where oxygen levels decrease with increases in metabolic rate would allow measurement of changes in metabolism; but there has been little experimental support for this idea. However, recent studies in mutant mice with hemoglobin that has subnormal affinity for oxygen, has suggested that tissue levels of P_{O_2} might be sensed and initiate systemic responses.

Adaptations to Altitude and Chronic Continuous and Intermittent Hypoxia

Acute exposure to decreased barometric pressure with a resulting reduction in the partial pressure of oxygen produces an immediate boost in ventilation mediated through the peripheral chemoreceptors. With continued exposure, ventilation, in humans, continues to increase for several days resulting in a gradual decrease in arterial P_{CO_2}. There is also an increase in CO_2 sensitivity. This process, called acclimatization, is followed by the slow return of ventilation when the acclimatized individual returns to sea level. These slow processes occur mainly via changes in peripheral chemoreceptor activity rather than from the central effects of hypoxia. Similar changes in response occur with exposure to chronic hypoxia at sea level even if the exposure is intermittent rather than continuous.

Brief but repeated episodes of hypoxia for an hour or more produces augmented ventilation even when normoxia is restored, a phenomenon called long-term facilitation. This does not occur after sustained hypoxia of equal duration. This enhancement occurs in animals lacking intact carotid bodies and seems to depend largely on changes in serotonin and on brain-derived growth factors within the central nervous system. However, the carotid body when intact may contribute to the increase.

Sustained hypoxia after about 6 min has a depressive effect on the brain, limiting its response to further hypoxia. This is caused by increases in cerebral blood flow, which lower levels of brain P_{CO_2}, and by a direct depressive effect on the brain. This hypoxic depression spreads rostrally to caudally in the brain. Hypoxic depression may be the result of slowed removal of inhibitory neurotransmitters like GABA during hypoxia caused perhaps by the buildup of lactic acid in the brain.

The actions of hypoxia on the systemic circulation may also modify breathing. While the direct effect of hypoxia on the systemic blood vessels is dilating, hypoxia activates the sympathetic nervous system and produces a compensatory vasoconstriction. The inability of children with familial dysautonomia to tolerate hypoxia seems to be caused by failure of systemic blood vessels to constrict and maintain blood pressure.

Adaptation to Metabolic Acid-Base Disturbances

Lowered blood bicarbonate levels, which reduce arterial pH, increase ventilation and cause hypocapnia. For example, hyperventilation is a feature of diabetic ketoacidosis and renal failure. Conversely, repeated vomiting elevates blood bicarbonate levels and raises arterial pH, frequently causes hypoventilation and hypercapnia helping to restore pH.

Although reductions in P_{CO_2} invariably accompany metabolic acidosis, P_{CO_2} does not always rise in response to metabolic alkalosis. For example, it is widely held that blood alkalosis produced by K depletion does not elicit hypoventilation, presumably as a result of the intracellular acidosis that seems to accompany K loss. Also, in hypoxic, hypercapnic patients, complete compensation for metabolic alkalosis is limited by the hypoxia that accompanies hypoventilation.

Like the ventilatory response to altitude, the compensatory responses to chronic metabolic disturbance occur over hours and days rather than immediately. Because of this time course, it seems likely that central, as well as peripheral, chemoreceptors contribute to the ventilatory compensation, though the relative role of each remains to be determined. Acidosis either leaves ventilatory responses to inhaled CO_2 unaltered or causes them to increase; ventilatory responses tend to decrease with metabolic alkalosis.

Responses to External Mechanical Loads and Bronchoconstriction

The respiratory control system can also adjust so as to maintain ventilation in the face of mechanical impediments to breathing such as bronchoconstriction.

Several factors act to maintain ventilation. First are factors intrinsic to the respiratory muscles. The force that the muscle develops for a fixed electrical input depends on the length of the muscle (the force-length relationship). As the muscle shortens, less force is developed. The force also depends on the velocity of shortening (force-velocity relationship), with less force being developed as the velocity of shortening increases. With mechanical impediments (loading),

both the magnitude and the velocity of shortening tend to decrease.

In addition, there are reflex effects. At the spinal level, less shortening of the inspiratory muscles increases the signal from muscle spindles that, in turn, augments contraction of these muscles. During loading, afferent information from pulmonary mechanoreceptors also changes. Since tidal volume is depressed, inspiratory duration tends to be prolonged (Hering-Breuer inspiratory terminating reflex). In humans this mechanism is of little importance in compensating for mechanical loads.

Loads elicit a conscious response that increases neuromuscular output even in the face of a constant chemical drive. The magnitude of the increase is related to the severity of the mechanical load. This aspect of load compensation is abolished by anesthesia. The intensity of this load-compensating mechanism is variable. It is reduced in patients with chronic obstructive lung disease.

When loads are so severe that hypoventilation ensues, the resulting changes in arterial blood-gas tensions (increase in P_{CO_2}, reduction in P_{O_2}) act to sustain ventilation. The magnitude of this component of the response depends on the sensitivity of the peripheral and central chemoreflexes.

Major differences exist between the neural responses to bronchoconstriction and external loading. In particular, inspiratory muscle activity increases during bronchoconstriction even in anesthetized animals. During bronchoconstriction, rapidly adapting receptors can be stimulated by the mechanical changes in the airways and by substances such as histamine and bradykinin that are released in the lungs in asthma-induced bronchoconstriction.

Bronchoconstriction causes reflex changes in respiratory timing so that breathing frequency increases. Expiratory duration shortens more than inspiratory duration; within expiration, larger changes take place in the second phase of the expiratory part of the cycle.

Sleep

On the basis of EEG criteria, sleep has been divided into rapid eye movement (REM) and non-REM (NREM) sleep. REM sleep (the stage in which dreaming tends to occur) usually follows NREM (quiet sleep) states in which EEG frequencies are slower. REM sleep is characterized by the occurrence of a desynchronized EEG and periods of rapid eye movements. It is also accompanied by inhibition of motor neurons, which leads to a profound loss of muscle tone that affects the diaphragm less than other respiratory muscles. Even healthy people have occasional periods of apnea during sleep usually in the lighter forms of NREM sleep and in REM sleep.

In both REM and NREM sleep, ventilatory responses to hypoxia and hypercapnia are reduced. The normoxic and hypoxic CO_2 response curves are shifted to the right (see Fig. 10-2). Changes in lung mechanics occurring during sleep (increased upper airway resistance and decreased compliance) may contribute to depressed ventilatory responses.

Responses to mechanoreceptor stimulation are also altered by sleep. For example, the compensatory response in motor activity, which occurs during wakefulness when the airway is obstructed, is reduced or eliminated during sleep.

Airway obstruction during sleep usually terminates with arousal. Arousability varies during sleep with periods of increased arousability occurring particularly during NREM sleep.

PATHOPHYSIOLOGY: DISORDERS OF THE REGULATION OF BREATHING

Reduced Chemoreceptor Function

The importance of chemoreceptors stimulation in wakefulness and sleep may differ. Individuals with no apparent response to carbon dioxide or hypoxia may have normal blood gases while awake at rest and even during exercise. However, ventilation above the anaerobic threshold in intense exercise is subnormal in individuals lacking CO_2 sensitivity. Inadequate carotid body function in the newborn or decreased central chemosensitivity may contribute to the sudden infant death syndrome. Depressed responses to carbon dioxide may lead to persistent carbon dioxide retention in patients with thoracic diseases.

Persons who congenitally lack or have poor chemosensitivity to both hypercapnia and hypoxia (so-called Ondine's curse) suffer from inadequate ventilation during sleep. The hypoventilation is believed to be caused by maldevelopment of neural crest cells and is often associated with Hirschsprung's disease in which varying lengths of the colon are aganglionic. Patients may have a family history of the disorder that is associated with several different gene mutations especially of the PHOX2B gene, the receptor tyrosine kinase, the RET gene and endothelin1 and 3 genes, and brain derived neurotrophic factor.

Abnormalities of Respiratory Rhythm

Rapid breathing without an increase in tidal volume, i.e., tachypnea, occurs with temperature elevations and pulmonary fibrosis. Apneustic breathing occurs with lesions of the pons and is characterized by prolonged inspiratory duration.

Apnea is probably the most frequent and striking abnormality in respiratory rhythm. In Biot's breathing, a rare form of respiratory rhythm abnormality, tidal volumes of fixed amplitude are separated by periods of apnea. Apneas are observed most often in premature infants but can occur in healthy adults, especially during sleep, and can be isolated events or can be recurrent. Apneas sometimes produce severe hypoxia and hypercapnia; they may cause clinically significant cardiac arrhythmias; or have long-lasting effects such as pulmonary hypertension.

Several different mechanisms can potentially produce random central apneas. These include: (1) reduced excitation of chemoreceptors as a consequence of hypocapnia and hyperoxia; (2) loss of nonspecific respiratory excitatory stimulation (noise, light, tactile stimuli in the absence of adequate

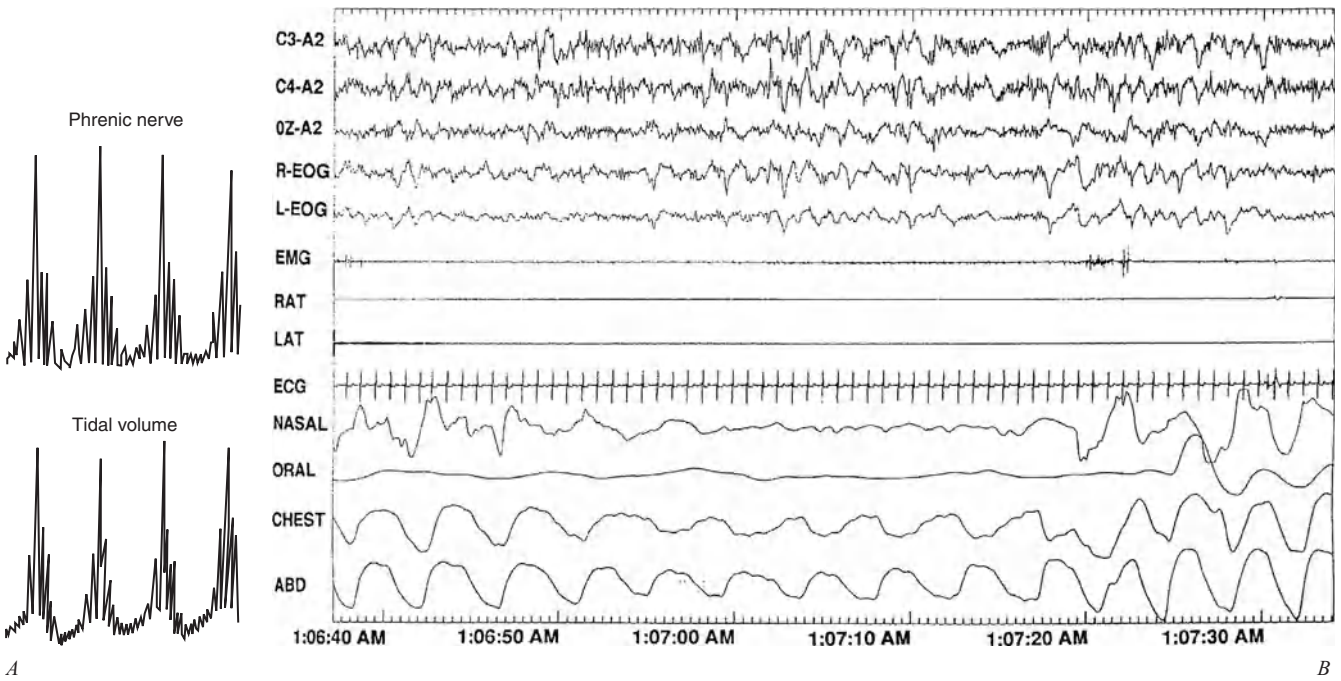

Figure 10-5 *A*. Shows Cheyne-Stokes respiration produced experimentally in a cat by increasing controller gain through a servo-respirator. Note the oscillating pattern of both tidal volume and phrenic nerve activity. *B*. Example of obstructive apnea. The top three tracings (C3-A2, C4-A2, 0Z-A2) are EEG, the next two (R-EOG, L-EOG) for eye movements, then chin EMG, right and left anterior tibialis EMG (RAT, LAT) ECG, nasal and oral airflow and finally chest and abdominal motion. The tracing shows a long episode of no airflow (apnea) but continued movement of chest and abdomen. During the apnea, chest and abdominal motion is paradoxical due to the obstruction; i.e., abdomen moves out while chest wall moves in). The apnea is terminated by an arousal with a burst of EMG activity and sudden increase in airflow as the upper airway is suddenly opened.

chemical drives); and (3) active suppression of breathing by respiratory inhibitory reflexes arising from the cardiovascular system, the lung and chest wall, or via somatic and visceral afferents. For example, excitation of receptors located in the upper airway can, via the superior laryngeal nerve, trigger an apnea. Stimulation of J receptors in the lungs by inhaled irritants may produce temporary apnea.

Recurrent apneas may appear as part of a pattern of grossly irregular ataxic breathing. Patients with this kind of breathing usually have functional or actual structural medullary damage. The breathing disturbance results from a kind of sputtering of damaged respiratory neuronal circuits. Breathing responds poorly to stimulants, and patients with this disorder tend to hypoventilate.

In other types of abnormalities, such as Cheyne-Stokes breathing and many sleep apneas, apneas occur more predictably. Apneas may be separated by periods of gradually increasing and decreasing breathing, as in Cheyne-Stokes breathing.

Sleep Apnea

Apneas occur occasionally during sleep in healthy humans; but in those who have the sleep apnea syndrome, apneas or near-apneas (hypopneas) are frequent and prolonged, so that much of the night is spent hypoxemic. They are often sleepy during the day and may have elevated levels of arterial P_{CO_2} and pulmonary artery pressure. Sleep apnea occurs most frequently in premature infants, adult males, and postmenopausal women.

Apneas can be central (absent respiratory movements) or obstructive (due to blockage of the upper airway). Heightened CO_2 sensitivity and hypocapnia during sleep have been implicated in the induction of recurrent central apneas during sleep. Sometimes these occur with a regular waxing and waning of ventilation resembling Cheyne-Stokes respiration.

Obstructive apneas are associated with obesity, snoring, and anatomical narrowing of the upper airway passages. Arousal terminates the periods of obstructive apnea, which occur more frequently in individuals with narrowed airway passages. Poor response of the upper airway muscles to carbon dioxide and or hypoxia in addition to the anatomic factors that narrow the upper airway predispose to the occurrence of obstructive apneas during sleep.

Cheyne-Stokes Respiration

Cheyne-Stokes breathing is one form of periodic breathing characterized by a cyclic rise and fall in ventilation with recurrent periods of apnea or near apnea. It was first observed in patients with cardiac or central nervous system disease, but it has since been reported in seemingly normal humans. The appearance of Cheyne-Stokes breathing can be triggered by the administration of sedatives and opiates and is more common during sleep. The period of the oscillations in ventilation in Cheyne-Stokes breathing is related to the circulation time

measured from the lung to a systemic artery. Cycle length increases when circulation time is prolonged. Arterial blood P_{CO_2} is highest during the phase of rapid breathing and arterial P_{O_2} is then at its minimum, but alveolar gas tensions cycle in the opposite way. Changes in the level of alertness occur coincidentally with the respiratory oscillations. Arousal tends to occur during the hyperpneic phase along with an increase in cerebral blood flow. The EEG shows greater fast-wave activity. The pupils dilate, and muscle tone is increased. The sensorium seems more depressed during apnea, the pupils are constricted, and muscle tone is diminished. Cerebral blood flow is often less during apnea, and there is a higher percentage of slow-wave activity in the EEG.

Cheyne-Stokes breathing has not been consistently produced in animals by lesions in the central nervous system, but it has been shown to follow manipulations that are likely to produce unstable feedback control of breathing.

Instability in the Feedback Control of Breathing as a Cause of Recurrent Apneas

Instability in feedback control can affect the regularity of breathing and produce a periodic increase and decrease in ventilation with apneas as in Cheyne-Stokes respiration. Although biologic control systems are much more complex than physical ones, design principles are similar, and some abnormalities in breathing resemble disturbances occurring in systems used to control machines. Ideally, biological control systems minimize the effects of disturbances and rapidly restore steady-state conditions to prevent wide swings in the internal conditions and to operate with minimal use of energy, but it may not be possible to meet these objectives simultaneously. Fluctuations in arterial blood-gas tensions can arise if the system is excessively stressed or from destruction of key components in the control system, which render it insensitive; less obviously, they may also occur if control is too rigorous.

Like physical control systems, the feedback system that regulates P_{O_2} and P_{CO_2} can be considered to consist of a controller and controlled elements linked by feedback loops as shown diagrammatically in Fig. 10-6. In this system the controller consists of the mechanoreceptors as well as the chemoreceptors and neurons in the brain. The mechanoreceptors and chemoreceptors communicate with the respiratory pattern generator, which produces the signal that drives the respiratory muscles and allows the lungs to be ventilated. The controlled system consists of these respiratory muscles, the lungs and the O_2 and CO_2 chemically bound and physically dissolve in the body (the gas stores). Changes in ventilation alter the amount of CO_2 and O_2 stored in the lung, blood, and tissues and so adjust the level of P_{CO_2} and O_2. Information on gas tension is transmitted to the sensors by the circulation. The bulbopontine neurons sense the difference between the input from the chemosensors and desired reference value levels and readjust the output to the respiratory muscles to reduce the discrepancy. State of alertness and sleep alter reference values.

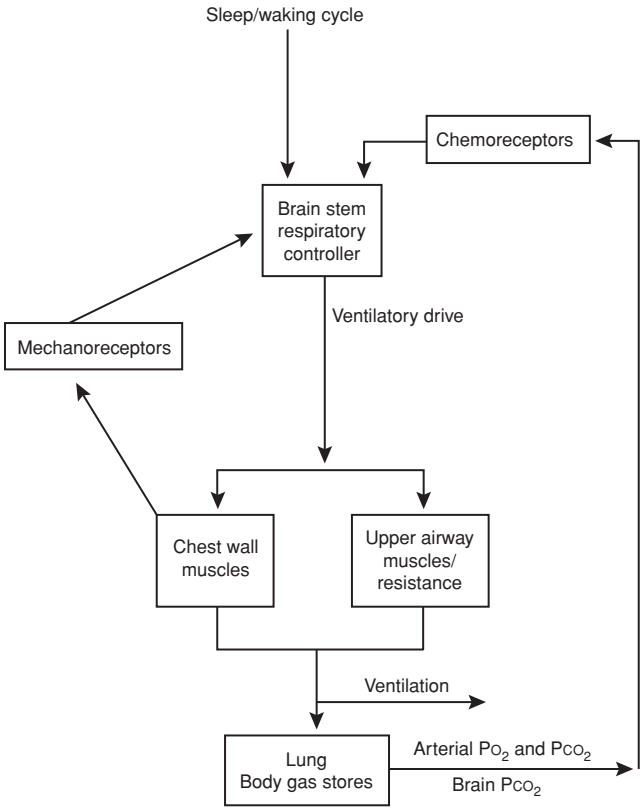

Figure 10-6 Diagram of respiratory control system showing feedback from chemo- and mechanoreceptors. See text.

Cyclic changes in both the rate of breathing and tidal volume can be produced by instability in the respiratory control system operation. Common mechanisms that produce instability include transport delays (increased circulation time such as occurs in heart failure) and increased loop gain (caused by greater controller sensitivity or changes in the operating point that allow the controller to exert a larger effect of the controlled system). This might occur in patients with a stroke.

In linear control systems, the occurrence of instability and the characteristics of the cyclic changes can be predicted by graphical techniques, for example, by the Bode and Nyquist diagrams. However, the respiratory control system behaves nonlinearly, and the prediction of the effects of specific alterations in system components usually requires the use of mathematical models. Although they differ somewhat in details, models of the respiratory system show that unstable operations can occur with alterations in the activity of the components of the system or can be triggered by disturbances that are well within the range of physiological possibility.

Dyspnea (Shortness of Breath)

Normally breathing is not noticeable, but respiratory movements and forces are perceptible and when sufficiently intense, result in symptoms of shortness of breath. Patients with lung disease may complain of dyspnea even at rest. Since

dyspnea itself can become an incapacitating symptom, considerable attention has been given to its etiology.

Earlier experiments used breathholding as a model for the investigation of dyspnea. These studies showed that hypercapnia and hypoxia decrease breath-holding times, supporting the idea that increased levels of chemical drive promote dyspnea; conversely, increased lung volume lengthened breath-holding time because it slows these chemical changes.

Combined blockade of the phrenic and vagus nerves extends the time apnea can be voluntarily maintained, leading to the idea that signals from respiratory muscles are an important contributor to the sense of dyspnea.

Dyspnea also seems to be related to the effort (motor command) used during breathing, expressed as a percentage of its maximum. Thus, dyspnea increases as the pressures required for tidal breathing grow greater or the maximal inspiratory pressure decreases (e.g., as by paresis, disease, or respiratory muscle fatigue).

Recent studies suggest that there may be two forms of dyspnea; one a sense of air hunger as occurs in breathholding and the second a sense of excessive effort as occurs during breathing against a resistance. It has been proposed that the two types are produced by different mechanisms with different anatomical pathways and this idea is supported by PET scanning studies in humans. Cognitive factors, and probably affective factors which determine the relative pleasantness of a sensation as well as sensory intensity, affect the level of dyspnea. The dyspnea experienced during CO_2 breathing may be mediated through the limbic system.

It is of interest in connection with dyspnea that subjects who fail to increase their ventilation with CO_2 inhalation also have long breath-holding times and fail to experience dyspnea, but do feel dyspneic during exercise. This is one argument for there being two types of dyspnea.

Dyspnea may have a useful purpose as a warning device. Patients who have experienced a nearly fatal asthmatic attack requiring mechanical ventilation often have depressed sensations of dyspnea when exercising or when breathing on resistive loads.

SUGGESTED READING

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11

Ventilation, Pulmonary Blood Flow, and Ventilation-Perfusion Relationships

Peter D. Wagner

This chapter and that succeeding it together share responsibility for presenting the physiological basis of normal pulmonary gas exchange. Gas exchange occurs by an integrated series of gas transport steps between the environmental air we breathe and the Hb molecule of the red cells passing through the pulmonary capillaries. These transport steps are of two types—diffusive and convective, and a number of conceptually separate diffusive as well as convective processes interact to accomplish the gas exchange mission. This is true both for gases that are taken up from the environment into the blood (i.e., O_2 and occasional toxic gases or volatile anesthetics) and for gases that are eliminated from the body (i.e., CO_2 and volatile anesthetic agents).

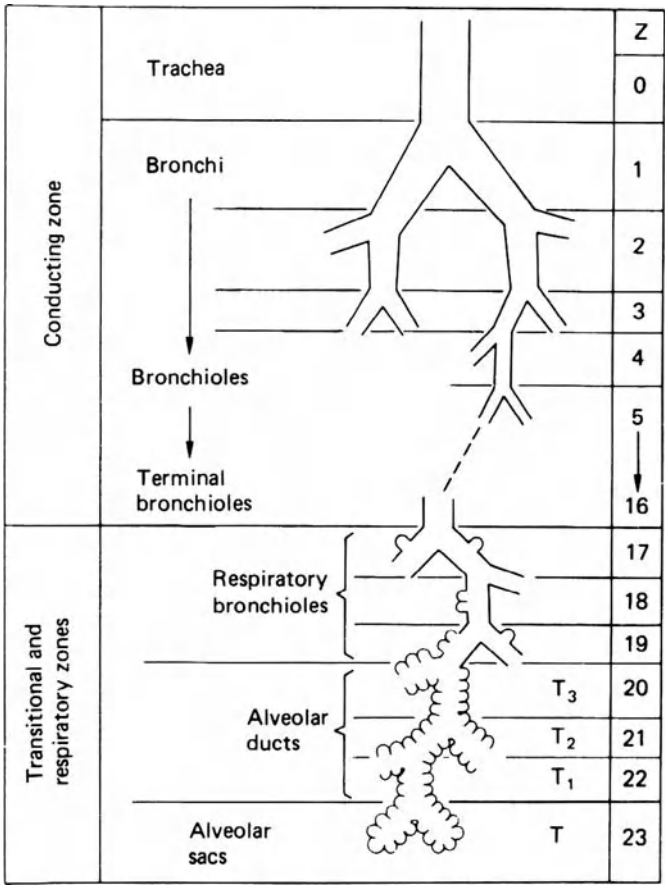
This chapter deals principally with the convective processes and the following chapter with those involving diffusion. However, since the two types of process occur simultaneously they are closely linked.

BASIC OUTLINE OF THE GAS EXCHANGE PATHWAY

This section dwells on O_2, being the gas of principal physiological interest. However, the pathway components are of course identical for all gases and furthermore do not depend on whether the gas is being taken up (O_2) or eliminated (CO_2). On the other hand, distinct quantitative differences in the uptake or elimination patterns of different gases exist, but those are readily explained by differences in their fundamental physical or chemical properties, and not by transport pathway differences.

To understand the gas transport pathway, one must first appreciate the anatomy of the lungs, laid out in detail in Chapter 2. The salient functional features are presented in Fig. 11-1.

The chest wall (rib cage and diaphragm) contain muscles that on contraction expand the volume of the chest cavity and thus reduce the intrathoracic pressure of the pleural space, expanding the lungs with air drawn in via the mouth and nose. Although there is but a single air passage in the neck (i.e., the trachea), this soon branches into right and left main bronchi. These also divide many times, essentially dichotomously. There are some 16 such orders of branching of these bronchi, resulting in a structure that resembles an inverted deciduous tree without its leaves in winter. With each successive branch the airways become shorter and narrower, but ever greater in number, usually doubling at each branching. Thus, although the cross-sectional area of any one airway becomes smaller with each branching, the greater number of airways more than makes up for loss of individual cross sectional area such that the sum of cross-sectional areas of all airways of a given generation rises essentially exponentially with each branching (Fig. 11-2). The total volume of gas in these 16 conducting airway generations is called the



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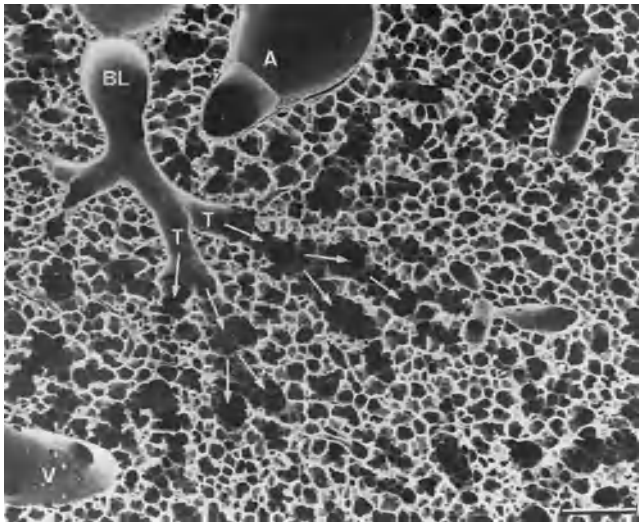

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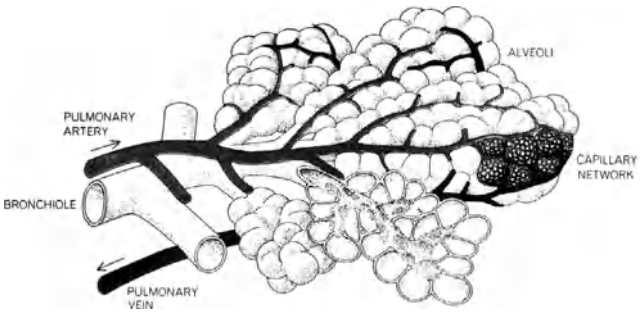

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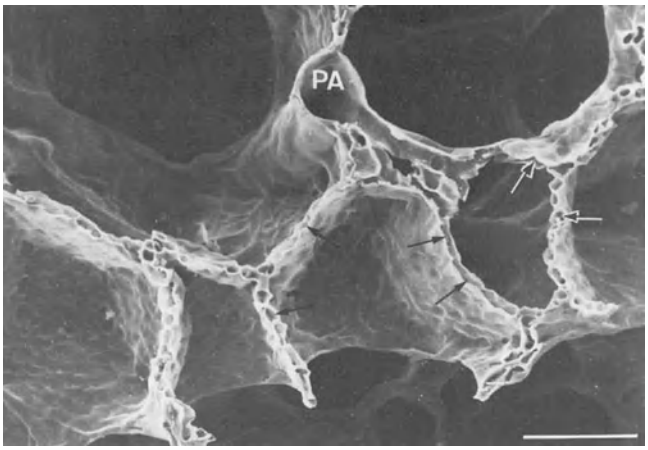

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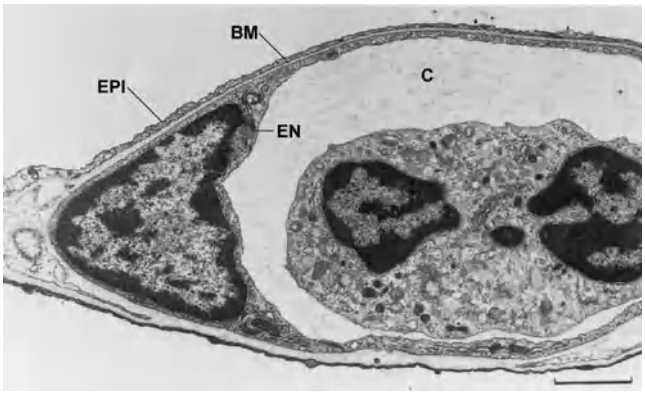

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Figure 11-1 Principal anatomical features of the lung related to gas exchange. *A*. The organization of branching airways, mirrored by a photograph (*B*) of a lung slice showing terminal (T) and respiratory (BL) bronchioles, pulmonary artery (A), pulmonary vein (V), and the alveolar parenchyma *C*. The capillaries are wrapped around alveoli. *D*. A scanning electron micrograph indicating the rich capillary networks in the alveolar walls (PL = pulmonary artery). *E*. A transmission electron micrograph showing the capillaries (*C*) and the three layers of the blood-gas barrier (BM = basement membrane; EN = endothelium; EPI = epithelium). *(Panels A, B, D and E are reproduced from Weibel ER:* The Pathway for Oxygen. *Cambridge, MA, Harvard University Press, 1984, with permission.)*

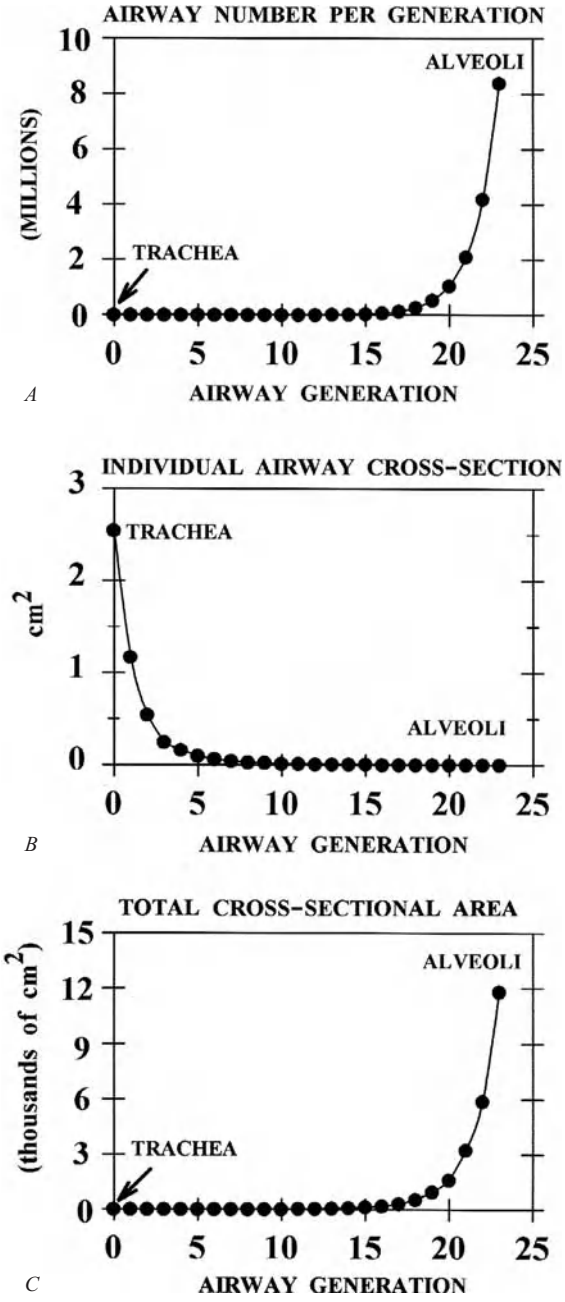

Figure 11-2 Relationship between number (*A*) and cross-sectional area (*B*) of the airways at a given generation. Note that total airway cross-sectional area (*C*) increases extremely rapidly beyond approximate airway generation 15, which is the beginning of the respiratory zone for gas exchange.

anatomic or conducting airway dead space, and approximates 1 ml per pound of body weight. After these 16 or so successive branches, the tubular, purely conducting airways begin to show alveolar units in their wall (generation 17 to 19 or so) and these finally give way to fully alveolated structures (in succession: alveolar ducts, alveolar sacs, and alveoli). There are some 300 million alveoli, each about 300 μm in diameter. They are blind structures so that ventilation has to be accomplished by a tidal, in-and-out process (rather than a flow-through process as for pulmonary blood flow). The alveoli can be seen in Fig. 11-1 from a different perspective. For gas exchange to occur, O_2 must be moved from the mouth all the way to the alveoli—it is only within alveoli that gas exchange occurs.

Each alveolus is densely covered in a capillary network, seen from various perspectives in Fig. 11-1. This network is closely applied to the alveolar gas space as Fig. 11-1 shows, with on average only about 1/2 μm of cellular and interstitial tissue between the blood inside the capillary and the alveolar gas outside. The capillary network is fed by the pulmonary arterial tree, which branches alongside the airways in a very similar pattern as the airways. The capillaries then drain into venules that join to form larger and larger vessels, eventually becoming the pulmonary veins that drain oxygenated blood into the left atrium. This coalescence of venous vessels forms a similar branching tree to the pulmonary arteries and airways, but in reverse. The right ventricle is responsible for unidirectional pumping of blood through this vascular system.

The gas exchange pathway from the lips to the left atrium is highly complex structurally, and understanding how gases pass along the pathway requires following the events an O_2 molecule must participate in between the lips and the left atrium.

1. The first step is inspiration of air into the trachea via mouth and nose. Accomplished by inspiratory chest wall muscle contraction, which reduces intrathoracic pressure, this step is convective (like water flowing from a region of high to low pressure along a garden hose). All the respired air must pass the trachea, but at the first branch point some air goes to the right lung, the rest to the left. At each successive branch point, similar mass-conserving distribution of air must occur between the daughter branches of each parent pathway. Remembering that there are some 23 total branchings from the mouth to the 300 million alveoli, there is a very real risk of quite uneven distribution of that inspired air among those alveoli. The principal determinants of how air is distributed at branch points (i.e., between daughter branches) are the mechanical properties of the respiratory system: the compliance (elastic properties), the resistance, and the inertial properties. These concepts are more fully treated in Chapter 9.
2. During normal resting inspiration, flow is laminar in most of the airways. Thus inspired gas develops a parabolic profile due to higher molecular velocities in the center than periphery of the airway (Fig. 11-3). The parabolic "tongue" of inspired gas in Fig. 11-3 moves down an airway, while around the tongue is gas remaining from the previous expiration. The tongue therefore has O_2 at a concentration of 21 percent and essentially no CO_2. The gas around the tongue, having undergone gas exchange during the preceding breath, has about 14 percent O_2 and 5 percent CO_2. Consequently, during forward motion of this tongue toward the alveoli, O_2 will diffuse from

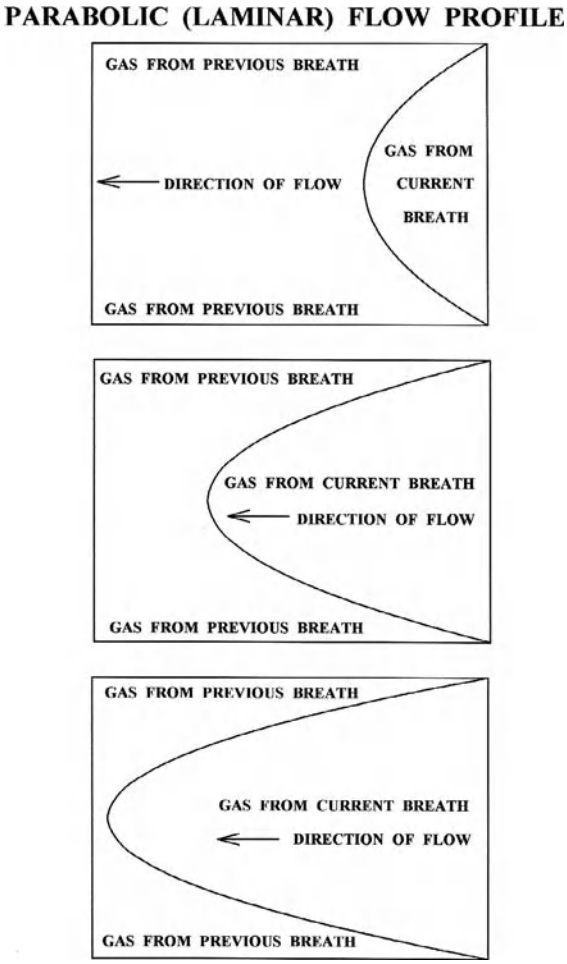

Figure 11-3 The parabolic profile of laminar flow. The three panels indicate sequential points in time during a single inspiration proceeding from right to left. Because the gas remaining from the previous breath has a low oxygen concentration and high CO_2 concentration relative to that of the inspired gas in the current breath, there is diffusive exchange between the parabolic tongue and surrounding gas (Taylor dispersion).

the tongue to its surrounding gas while CO_2 will diffuse in the opposite direction. This is called *Taylor dispersion*, and it reduces the forward transport of O_2 produced by the onward convective movement of the tongue. This effect however is considered quite small and is generally not of significance to overall gas exchange.

Note that if inspiration occurs at high rates as in exercise, such laminar flow may not occur in the larger airways—it may be turbulent and then Taylor dispersion is essentially noncontributory, as the turbulent mixing evens gas concentrations across the airway lumen.

3. Figure 11-2C shows the exponential increase in airway cross-sectional surface area as one proceeds deeper and deeper into the lungs. The significance of this curve is that since the mass flow rate of inspired gas is the same at every generation (because the airways are simply a conducting system), the forward velocity of O_2 molecules falls (since flow rate is the product of velocity and cross-sectional area). As it happens, by about generations 17 to 19, where the alveoli are just beginning to appear, this forward velocity has become so low that passage of O_2 from here on out to the alveoli is heavily dependent on simple gaseous diffusion, not just on continuing convective flow.
4. If alveoli are not equally ventilated with gas (and equally perfused with blood), their alveolar O_2 concentration will differ, as explained later in this chapter. Because adjacent alveoli are so physically close, there can be considerable diffusion of O_2 between such alveoli when their O_2 levels are different. This passive process tends to reduce concentration differences between these alveoli. However, although it can be detected experimentally, it is of probably minor clinical significance. Step 3 (and to some extent step 4) are responsible for most of the alveolar gas mixing that must occur for gas exchange to take place; that is, the mixing of each breath of newly inspired gas with alveolar gas still present from prior breaths.
5. The heart acts as a massaging pump to further enhance gas mixing into the alveolar gas spaces. Alternate filling and emptying of the cardiac chambers, respectively, facilitates exhaling and inhaling of airway gas into those alveoli physically close to the heart, but has little effect on more distant alveoli. Although a well-known and easily demonstrated phenomenon, this so-called cardiogenic mixing is probably also of minimal physiological impact for gas exchange.
6. Once the dominant convective and diffusive gas transport steps have brought O_2 from the lips to the alveolar gas spaces, O_2 physically dissolves in the tissues separating alveolar gas from capillary blood, the blood-gas barrier (see Fig. 11-1). O_2 then moves by diffusion through the blood-gas barrier and into the plasma. Over 98 percent of these O_2 molecules diffuse further, i.e., into the red cell interior, and then bind rapidly to hemoglobin. The remaining 2 percent or so remain physically dissolved in the plasma and red cell water.

   This transport process from alveolar gas to hemoglobin is accomplished passively by simple diffusion. No convective forces or active transport processes are involved. The diffusion process is discussed more fully in the next chapter. In normal lungs at rest, this process is very rapid and causes no O_2 transport limitation.
7. Finally, the red cells are transported convectively by cardiac pumping action out of the pulmonary capillaries and into the pulmonary veins and then to the left atrium, and left ventricle, finally reaching the various body tissues.

POTENTIAL DISRUPTION OF THE GAS TRANSPORT PATHWAY

If all the above elements of the transport pathway were functionally perfect, the partial pressure of O_2 (and other gases) would be identical in the gas of all 300 million alveoli and equal to that in systemic arterial blood. The system comes close to perfection in health, but there is never complete equivalence of alveolar and arterial pressures, even in healthy young, normal people. Aging further leads to a progressive impairment of the pathway with arterial P_{O_2} falling from 95 to 100 mmHg at age 20, to 75 to 80 mmHg at approximately age 80. However, alveolar P_{O_2} tends to be invariant with age. Thus, the difference between alveolar and arterial P_{O_2} steadily increases from about 5 to 10 mmHg to about 20 to 25 mmHg over this age range. Pulmonary diseases such as asthma, emphysema, bronchitis, fibrosis, pneumonia, and many others can greatly disrupt gas transport to the point of causing death from insufficient tissue O_2 supply.

Consequently, it is essential to have a good understanding of the O_2 transport pathway and what may affect it even in health, in order to appreciate the problems seen in pulmonary diseases.

A traditional view of how to consider abnormalities of the transport pathway has evolved over the years and is very useful as a framework for discussion. It is based upon the end result of gas exchange—the arterial P_{O_2}—and listing the reasons why this variable can fall below normal values.

Four principal potential mechanisms of failure of the O_2 transport pathway can lead to a reduced arterial P_{O_2} (i.e., arterial hypoxemia):

1. Hypoventilation
2. Diffusion limitation
3. Shunt
4. Ventilation-perfusion ($\dot{V}_A/\dot{Q}$) inequality

These are the so-called "intrapulmonary" factors that directly cause hypoxemia. Modulating "extrapulmonary" factors are also important. These include changes in inspired O_2 concentration, total cardiac output, overall metabolic rate, and Hb concentration.

The four "intrapulmonary" factors are now defined and discussed.

Hypoventilation

Normal levels of ventilation produce a tightly regulated arterial P_{CO_2} at 40 ± 2 mmHg in normal subjects with several control systems in place to ensure this. However, if overall ventilation is reduced for any reason, alveolar P_{CO_2} ($P_{A_{CO_2}}$), and, therefore, arterial P_{CO_2}, must rise to maintain constant elimination of metabolically produced CO_2. Reciprocally, alveolar P_{O_2} ($P_{A_{O_2}}$), and hence, arterial P_{O_2}, will fall (and by relatively similar amounts as P_{CO_2} will rise). The alveolar gas equation quantitatively relates Pa_{O_2} and Pa_{CO_2}, and is used to calculate how much $P_{A_{O_2}}$ will change for a change in $P_{A_{CO_2}}$:

$$P_{A_{O_2}} = P_{I_{O_2}} - \frac{P_{A_{CO_2}}}{R} + P_{A_{CO_2}} \cdot F_{I_{O_2}} \cdot \frac{(1 - R)}{R} \qquad (1)$$

$P_{I_{O_2}}$ and $F_{I_{O_2}}$ are inspired O_2 partial pressure and fractional concentration, respectively, and R is the respiratory exchange ratio.

Hypoventilation represents a failure of step 1 of the gas transport pathway (see above) and can occur for several reasons: (1) The control centers in the nervous system that regulate ventilation could malfunction due to trauma, diseases, drugs, or anesthetics; (2) there could be neuronal or neuromuscular dysfunction of the nerves supplying the chest wall muscles of respiration; (3) the chest wall muscles could be fatigued, damaged, or paralyzed; or (4) the airways or chest wall could be disrupted from trauma or other mechanical derangement such as compression, or in the case of airways, obstruction.

Conceptually, this type of problem is usually thought of as a whole-lung issue, usually with obvious causes, and can be reversed by recognizing the cause and taking appropriate reparative or ventilatory supportive steps.

Diffusion Limitation

Whereas diffusive transport plays a recognizable, if small role, within the airways and alveolar gas (see above), the concept of diffusive limitation affecting arterial P_{O_2} is more usually associated with transport step 6 above—diffusion of O_2 from alveolar gas into the capillary and red cell.

This topic is specifically the focus of the following chapter and is not dealt with here. Indeed, the ensuing discussion of other factors sets aside diffusion limitation of O_2 transport for the sake of simplicity and assumes that the diffusive exchange of O_2 (and CO_2) between alveolar gas and capillary blood proceeds to completion within a single red cell's passage through the pulmonary microcirculation. This is reasonable under most conditions.

Shunt

A shunt is a blood pathway that does not allow any contact between alveolar gas and red cells, so that no gas exchange occurs in the affected region. Consequently, blood passes through a shunt maintaining a mixed venous blood composition. When this blood reaches pulmonary veins, the left atrium and eventually arterial blood, it mixes with other blood that has undergone alveolar gas exchange. The result is a fall in arterial P_{O_2} and potentially an increase in arterial P_{CO_2}. (Arterial P_{CO_2} may not increase if the patient raises his or her level of ventilation, but hypoxemia will persist.)

Classical pathophysiological scenarios giving rise to shunts are: (1) pulmonary edema, which fills alveoli with fluid, thereby abolishing their ventilation and any gas exchange; (2) alveolar filling with cellular and microorganismal debris as in pneumonia, with the same result as in edema;

(3) collapse of a region of lung due to pneumothorax, gas absorption distal to a fully obstructed airway, or to external compression; (4) rarely, the presence of abnormal arteriovenous vascular channels in the lungs, which can occur in hepatic cirrhosis, for example; and (5) direct right-to-left vascular communications at the level of the heart or great (extrapulmonary) blood vessels.

Ventilation-Perfusion ($\dot{V}_A/\dot{Q}$) Inequality

The exquisite and complex branching architecture of the airways and of the blood vessels makes the lungs very susceptible to the potential problem of nonuniform distribution of alveolar ventilation and of pulmonary blood flow. Whenever alveoli are ventilated at less than average rates; for example, if their feeding airways become partially obstructed for any reason, the ratio of ventilation to blood flow ($\dot{V}_A/\dot{Q}$ ratio) will fall. In certain other conditions, lung regions may suffer a reduction in local blood flow rather than ventilation, so that the $\dot{V}_A/\dot{Q}$ ratio rises above the average value in those areas.

Whenever there is a range of $\dot{V}_A/\dot{Q}$ ratios in a lung such that the $\dot{V}_A/\dot{Q}$ ratio is not identical everywhere, it is said that $\dot{V}_A/\dot{Q}$ inequality exists. The pathological cause of $\dot{V}_A/\dot{Q}$ inequality does not matter, nor whether the problem originates in the airways or blood vessels. The principal concept is that, compared with a lung having the same total alveolar ventilation and blood flow, a lung that has $\dot{V}_A/\dot{Q}$ inequality will exchange (all) gases in an inefficient manner. The result is hypoxemia and, potentially, hypercapnia (raised arterial P_{CO_2}). A large section of this chapter presents the physiological reasons for this effect of $\dot{V}_A/\dot{Q}$ inequality.

Understanding of $\dot{V}_A/\dot{Q}$ inequality can be demanding, but no matter what its pathological origins, the concepts are similar. $\dot{V}_A/\dot{Q}$ inequality can occur at many different scales. Not uncommonly, it can manifest on a large scale as differences between the right and left lungs. Classic examples of this include unilateral atelectasis, pneumothorax, pulmonary embolus, or pneumonia. All these are relatively common phenomena that can lead to severe gas exchange disturbances. At the other end of the scale, there can be $\dot{V}_A/\dot{Q}$ ratio differences between essentially adjacent alveoli. However, research has shown that small groups of contiguous alveoli can maintain functional homogeneity of $\dot{V}_A/\dot{Q}$ ratios via rapid gas diffusion rates, possibly augmented by collateral ventilation and blood flow. It is likely that all alveoli distal to individual respiratory (or perhaps terminal) bronchioles can retain functional homogeneity for gas exchange through these mechanisms.

In between these two extremes of scale, vascular or airway obstruction at all levels will produce $\dot{V}_A/\dot{Q}$ inequality that, depending on how widespread it is, causes hypoxemia and potentially hypercapnia.

Even the young normal lung is usually subject to $\dot{V}_A/\dot{Q}$ inequality, which explains the 5- to 10-mmHg P_{O_2} difference between alveolar gas and arterial blood generally observed in healthy young subjects. There are several mechanisms for the existence of such $\dot{V}_A/\dot{Q}$ inequality.

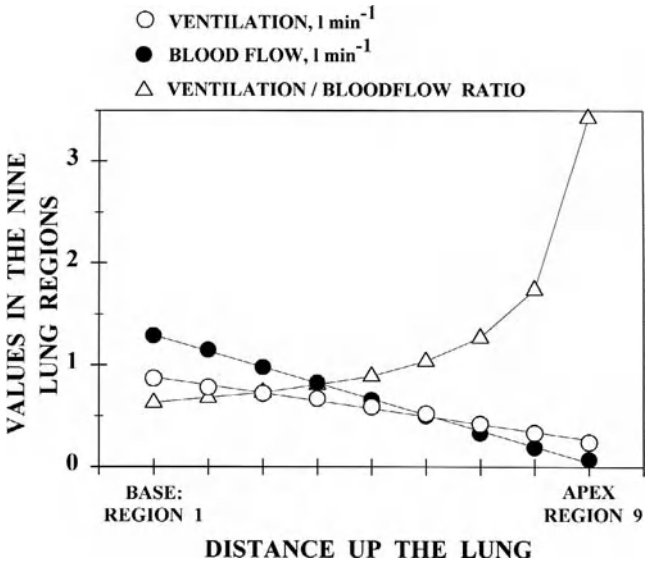

Figure 11-4 Topographical relationships between ventilation and blood flow as a function of distance up and down the upright lung (divided into nine contiguous regions). Although both ventilation and blood flow are higher at the base than at the apex, the ventilation-perfusion ratio ($\dot{V}_A/\dot{Q}$) rises exponentially from the bottom to the top of the lung. *(Adapted from West JB:* Ventilation/Blood Flow and Gas Exchange. *Oxford, Blackwell Scientific, 1990.)*

Gravity-Based Inequality

Ventilation and, even more so, blood flow, are unevenly distributed in a manner systematically influenced by gravity. This is due to the weight of the lungs and the blood in the blood vessels, respectively. Thus, dependent lung regions receive far more blood flow than nondependent regions, a finding that is independent of body position in concept. It turns out that the gravitational gradient in blood flow considerably exceeds that of ventilation. As a result, the nondependent lung regions are of *higher* than average $\dot{V}_A/\dot{Q}$ ratio, and the dependent regions are of *lower* than average $\dot{V}_A/\dot{Q}$ ratio. Average $\dot{V}_A/\dot{Q}$ ratio is about 1.0, because total alveolar ventilation and blood flow are similar. At the apex of the upright human lung, the $\dot{V}_A/\dot{Q}$ ratio is about 3; at the base it is about 0.6, fivefold lower. There is a smooth gradation between the two extremes, as depicted in Fig. 11-4. This large-scale apex-to-base gradient in $\dot{V}_A/\dot{Q}$ ratios does not produce more than about a 4-mmHg drop in arterial P_{O_2} (compared with expectations in the absence of this phenomenon); this results in a 4-mmHg alveolar-arterial P_{O_2} difference.

Fractally Based $\dot{V}_A/\dot{Q}$ Inequality

The branching airway and blood vessel structure of the lung constitutes a fractal system that is innately susceptible to $\dot{V}_A/\dot{Q}$ inequality independent of gravity. With some 23 sequential orders of branching, very small random inequalities in gas or blood flow distribution repeated at each branch point of the system can rapidly escalate into very significant degrees of nonuniform ventilation or blood flow. To illustrate, consider a branching system of just 16 dichotomous sequences—at each

of the 16 branch points, air is *not* precisely split 50/50 between each daughter pair. Rather, suppose a 49 percent/51 percent split—a nonuniform effect of trivial proportions at any one airway branch. The most poorly ventilated regions (receiving 49 percent of the split at every one of the 16 branchings) end up with only about half as much ventilation as the best ventilated regions that receive 51 percent of the split at each branch.

Unless the fractal structure somehow distributes both ventilation and blood flow in a correlated manner to preserve $\dot{V}_A/\dot{Q}$ ratios (even as $\dot{V}_A$ and $\dot{Q}$ individually vary), significant hypoxemia could result. Understanding the consequences of the fractal nature of the lung is a topic of much current interest. It appears that there must be correlation of $\dot{V}_A$ with $\dot{Q}$ since the large potential for fractally based hypoxemia is not generally realized.

Longitudinally Based Inequality

As airways and blood vessels progressively narrow with each branch point, resistance to gas and blood flow increases. Not all alveoli receive gas or blood from airways that have gone through the exact same number of branchings. Hence, some alveoli will be more and some less distant from the mouth. Such simple principles suggest the possibility of reduced $\dot{V}_A$ and/or $\dot{Q}$ of those alveoli further from the mouth compared with more proximal alveoli; therefore, the chance of a central to peripheral, or longitudinal, gradient in ventilation and blood flow. Although not universally observed, there is a fair amount of evidence that such inequality exists, but its contribution to gas exchange is hard to establish. To the extent that similar physical principles apply to both gas and blood flow in the present context, one can theorize that more distant alveoli have both less ventilation and blood flow, so again there is a natural tendency to preserve the $\dot{V}_A/\dot{Q}$ ratio between central and peripheral regions.

Anatomically Based Inequality

Another potential reason for nonuniform gas or blood flow distribution is intrinsic anatomical differences among lung regions. Perhaps the best example is in the dog and horse, in which the dorsal regions of the lower lobes often can be shown to have an unduly high share of total pulmonary perfusion independent of body position in relation to gravity. This tendency, presumably based on the overall branching architectural differences between or within lobes, becomes important in concept when patients are moved from one body position to another, to best understand consequent changes in gas exchange.

Collateral Ventilation and Blood Flow

To this point, a picture has been painted of a branching architecture that has no lateral connections between either adjacent airways or blood vessels at any level of branching. Such lateral connections can exist at several airway levels, from large airways down to alveoli. This is a species-dependent phenomenon, so that while the pig has little or no such collateral pathway structures, the dog has extensive collateral ventilatory channels. Humans are somewhere between these extremes.

Whatever the evolutionary pressure for collateral channel development, the ability to move gas around obstructions in airways by the use of collateral channels appears to be a useful property of human lungs. This is because total airway obstruction in the absence of collateral channels often leads to rapid alveolar gas absorption into the blood from the alveoli distal to the obstructed airway; this in turn leads to atelectasis and therefore vascular shunts and hypoxemia. Remarkably, chronic human lung diseases typified by airway obstruction—chronic obstructive pulmonary disease (COPD), asthma—produce $\dot{V}_A/\dot{Q}$ inequality due to presence of poorly ventilated areas, but only uncommonly lead to true shunts. The likely explanation for the paucity of shunts in COPD and asthma is the existence of collateral ventilation.

Therefore, collateral ventilation in humans appears to be a naturally occurring structural phenomenon that can counteract the gas exchange consequences of diseases to some extent.

Collateral perfusion also must occur in the alveolar capillary network. This is deduced simply from the richly interconnecting microvascular network that has the potential to allow blood to flow easily around microvascular obstructions into adjacent vessels. Just how much collateral blood flow potential exists at a larger scale is not clear, being difficult to study. However, well-documented connections occur between the bronchial and pulmonary circulations, creating a different kind of collateral circulatory network. The importance of this connection is evident when the pulmonary artery is either absent or embolized. Then, the bronchial circulation expands considerably and can support function of the affected lung regions in the long term.

Reactive Vasoconstriction and Bronchoconstriction

The distribution of ventilation or blood flow in the lung can be modified by vasoreactive or bronchoreactive functional changes that appear to be triggered by changes in alveolar gas composition. The best-documented phenomenon is that of hypoxic pulmonary vasoconstriction. Here, in response to local alveolar hypoxia produced by locally reduced ventilation, local pulmonary arterial constriction reduces blood flow in the hypoxic region. Whether this system developed to counteract disease or cope with intrauterine life and the abrupt transition to air-breathing is arguable, although most people favor the latter explanation.

Irrespective of the reason, the effect of hypoxic vasoconstriction is to help return the local ratio of ventilation to blood flow toward normal. This automatic effect (mediated by O_2-sensitive potassium channels in pulmonary arterial smooth muscle cells) is rarely able to fully restore $\dot{V}_A/\dot{Q}$ ratios to normal, but even partial improvements in $\dot{V}_A/\dot{Q}$ ratio facilitate gas exchange significantly. The negative aspect of hypoxic vasoconstriction is a rise in pulmonary vascular resistance. If this

is substantial and protracted over time, pulmonary arterial hypertension can develop, eventually leading to right heart failure. However, factors other than hypoxic vasoconstriction are generally present also, such as microvascular destruction and alveolar distortion, and these may be more important to heart failure than hypoxia per se. However, hypoxic vasoconstriction has provided a rationale for enriched O_2 therapy in patients with chronic disease to reduce the severity or delay the progression of pulmonary hypertension.

To a much less obvious extent, a counterpart to hypoxic vasoconstriction occurs in the airways known as hypocapnic bronchoconstriction. Here, especially when pulmonary embolism occurs, the $\dot{V}_A/\dot{Q}$ ratio in the embolized area rises due to loss of blood flow from vascular obstruction. This increase in $\dot{V}_A/\dot{Q}$ ratio leads to a lower local P_{CO_2} (see below), which causes bronchoconstriction in the local area. This reduces local ventilation and thus tends to normalize the local $\dot{V}_A/\dot{Q}$ ratio. Radioactive tracer ventilation scans may show evidence of this as a modest reduction in the ventilation of embolized regions.

The $\dot{V}_A/\dot{Q}$ Ratio and Gas Exchange

To this point, much space has been given to the concepts underlying the distribution of ventilation ($\dot{V}_A$), blood flow ($\dot{Q}$), and hence, their ratio, $\dot{V}_A/\dot{Q}$. The reason for this lies in the importance of $\dot{V}_A/\dot{Q}$ ratios to the basic function of the lung—to exchange O_2 and CO_2 between the blood and the air. $\dot{V}_A/\dot{Q}$ inequality, no matter what its physiological basis or pathological cause, interferes with gas exchange and causes hypoxemia and sometimes hypercapnia.

The following section explains the relationship of $\dot{V}_A/\dot{Q}$ inequality to gas exchange. The subject is complex and must be considered at several "concentric" levels. To start, consider how the $\dot{V}_A/\dot{Q}$ ratio in a small local lung region controls local P_{O_2}, P_{CO_2}, and therefore how much O_2 and CO_2 are exchanged in that region. This isolated approach requires some key assumptions at first. Removing the restrictions of these assumptions is the next "concentric" step in understanding $\dot{V}_A/\dot{Q}$ relationships. A final outer shell of modifying factors that can further affect gas exchange forms a third level of the analysis.

The $\dot{V}_A/\dot{Q}$ Ratio of a Small Homogeneous Unit of Lung and Gas Exchange

How the $\dot{V}_A/\dot{Q}$ ratio determines gas exchange is best explained by considering the flux of O_2 from the environment into and out of the alveolus with each breath as well as from the alveolar gas into the capillary blood. Equations that describe these processes and follow the fundamental principle of mass conservation must be used. Original descriptions of these appeared more than 50 years ago. Figure 11-5 provides a model of the lung and specifies the ventilation ($\dot{V}_A$) and blood flow ($\dot{Q}$) of this unit together with the key locations of the relevant O_2 levels. It can be used to consider a small homogeneous unit of lung.

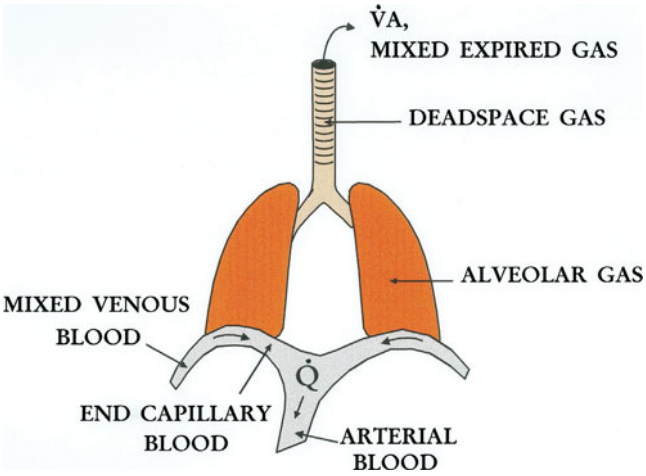

Figure 11-5 Conceptual model of the lungs indicating main sites in which oxygen and carbon dioxide partial pressures are different, together with the principal convective processes accomplishing gas exchange, ventilation ($\dot{V}_A$) and blood flow ($\dot{Q}$).

Convention has long considered ventilation over a period of time as a constant in spite of the tidal nature of breathing. In fact this is a very reasonable approximation that has stood the test of time. Similarly, blood flow is considered constant, and this too has proved reasonable. Therefore, if $\dot{V}_A$ and $\dot{Q}$ are considered as alveolar minute ventilation and blood flow of a small homogeneous unit, respectively, the following simple mass conservation equations can be written for O_2:

$$\dot{V}_{O_2} = \dot{V}_I \times F_{I_{O_2}} - \dot{V}_A \times F_{A_{O_2}} \qquad (2)$$

and

$$\dot{V}_{O_2} = \dot{Q} \times Cc'_{O_2} - \dot{Q} \times C\bar{v}_{O_2} \qquad (3)$$

In these equations, $\dot{V}_{O_2}$ is amount of O_2 transferred from the environment into the blood per unit time and, given the assumption of steady-state conditions, this equals metabolic rate when summed over all such units in the lungs. $\dot{V}_I$ and $\dot{V}_A$ are the inspired and expired volumes of gas respired per minute (less that amount remaining in the conducting airways), respectively. As anticipated, $\dot{V}_I$ and $\dot{V}_A$ are close to being identical, otherwise the lungs would blow up or collapse in a short period of time. However, $\dot{V}_I$ does not generally equal $\dot{V}_A$ because slightly more O_2 is consumed per minute than CO_2 produces (i.e., the respiratory quotient is, in general, not 1.0). Thus, $\dot{V}_A = \dot{V}_I - \dot{V}_{O_2} + \dot{V}_{CO_2}$. Mostly, the inequality of $\dot{V}_I$ and $\dot{V}_A$ can be ignored because the difference is only about 1 percent. If $\dot{V}_I$ is 6 L/min and $\dot{V}_{O_2}$ is 300 ml/min with $\dot{V}_{CO_2}$ at 240 ml/min, $\dot{V}_A = 5.94$ L/min. Although this small difference is not ignored in research applications, it can be for the present purposes, so that $\dot{V}_I$ is replaced by $\dot{V}_A$ in Eq. (1), simplifying the analysis below. In Eq. 1, $F_{I_{O_2}}$ and $F_{A_{O_2}}$ are the fractional concentrations (F) of O_2 in inspired (I) and exhaled alveolar (A) gas, respectively, from the small unit of Fig. 11-5. In Eq. (3), Cc'_{O_2} and $C\bar{v}_{O_2}$ are the O_2 concentrations (C) in the oxygenated end capillary blood leaving (c') and the deoxygenated blood entering ($\bar{v}$)

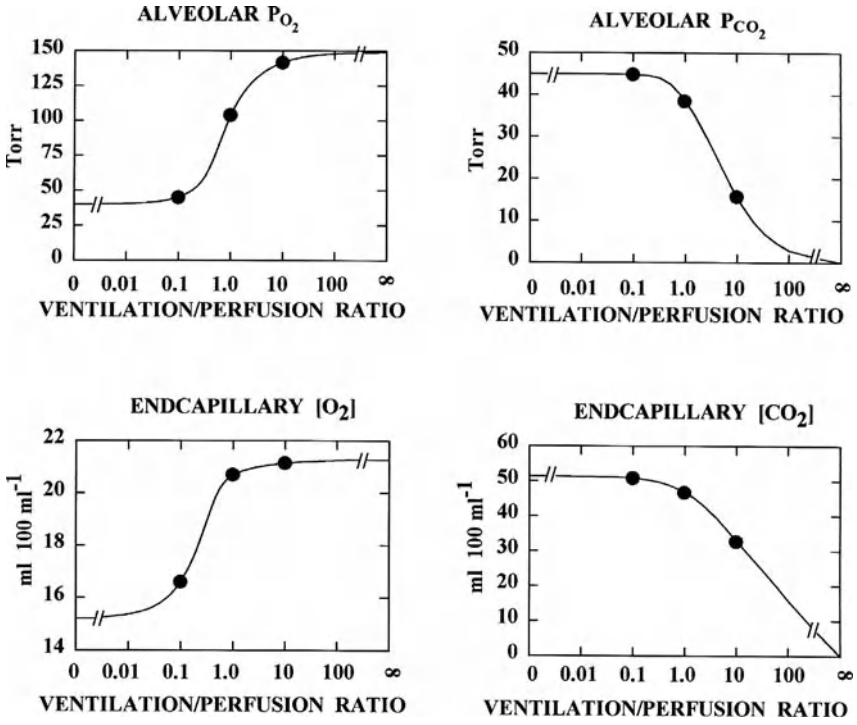

Figure 11-6 Calculated relationships between alveolar P_{O_2} and P_{CO_2} and the ventilation-perfusion ratio (top panels) and their corresponding end-capillary blood concentrations (lower panels). The three solid circles in each case represent values for ventilation-perfusion ratios of 0.1, 1.0, and 10. (See text for further details.)

the vasculature, respectively. The abbreviation c′ stands for end capillary blood; $\bar{v}$ for mixed venous (pulmonary arterial) blood.

Since Eq. (1) and (2) both describe the same O_2 flux rate ($\dot{V}_{O_2}$), they may be set equal to each other:

$$\dot{V}_A[F_{I_{O_2}} - FA_{O_2}] = \dot{Q}[Cc'_{O_2} - C\bar{v}_{O_2}] \qquad (4)$$

and rearranged so that:

$$\dot{V}_A/\dot{Q} = [Cc'_{O_2} - C\bar{v}_{O_2}]/[F_{I_{O_2}} - FA_{O_2}] \qquad (5)$$

It should further be noted that because diffusion equilibration of O_2 transfer across the alveolar-capillary membrane is assumed to be complete, alveolar P_{O_2} and end-capillary P_{O_2} are identical. Hence, the relationship between FA_{O_2} and Cc'_{O_2} is uniquely dictated by the O_2-Hb dissociation curve such that knowing FA_{O_2} allows us to determine directly Cc'_{O_2} (or vice versa).

Equation (5) is very revealing and explains directly the role of the $\dot{V}_A/\dot{Q}$ ratio in governing alveolar gas exchange. This equation states that for a *given* set of what may be called boundary conditions (i.e., composition of inspired gas and mixed venous blood, represented here by $F_{I_{O_2}}$ and $C\bar{v}_{O_2}$, respectively, and for a known O_2-Hb dissociation curve), alveolar (and, thus, end capillary) P_{O_2} is *uniquely* determined by the ratio of alveolar ventilation ($\dot{V}_A$) to blood flow ($\dot{Q}$).

Under the given assumptions, summarized as: (1) continuous and constant ventilation and blood flow; (2) steady-state conditions; (3) diffusion equilibration of alveolar-capillary exchange; and (4) equality of inspired and expired ventilation, equations identical in construct to Eq. (5) can be written for any gas being exchanged by the lung.

For CO_2, this produces Eq. (6):

$$\dot{V}_A/\dot{Q} = [C\bar{v}C_{O_2} - Cc'C_{O_2}]/[FA_{CO_2} - F_{I_{CO_2}}] \qquad (6)$$

The order of bracketed terms on the right is reversed to maintain positive numbers, since CO_2 is being eliminated from the blood. Of course, $F_{I_{CO_2}}$ is almost always zero and thus drops out of the equation.

Unfortunately, neither Eq. (5) nor (6) is amenable to simple quantitative solutions, because of the complexity of the O_2 and CO_2 dissociation curves. However, the equations are readily explored by appropriate computerized numerical analyses. Using such programs, one can explore the relationship between $\dot{V}_A/\dot{Q}$ ratio and alveolar P_{O_2} and P_{CO_2}, and this is done in Fig. 11-6. These relationships are important because they indicate what degrees of $\dot{V}_A/\dot{Q}$ abnormality are required to affect gas exchange for both O_2 and CO_2. The four panels of Fig. 11-6 show alveolar P_{O_2} and P_{CO_2} as well as end-capillary O_2 and CO_2 concentrations. The latter better reflect total gas exchange as a function of $\dot{V}_A/\dot{Q}$ ratio. Specific conditions for Fig. 11-6 are such that mixed venous blood P_{O_2} is 40 mmHg and P_{CO_2} 45 mmHg, normal resting values. Also, inspired gas is room air, and [Hb] is 15 gm dl^{-1}. In each panel, the three solid circles are positioned at the normal $\dot{V}_A/\dot{Q}$ ratio (of about 1.0) and at $\dot{V}_A/\dot{Q}$ ratios 10 times greater and less. All four relationships are highly nonlinear. Focusing on the two lower panels, it is evident for O_2 that a 10-fold reduction in $\dot{V}_A/\dot{Q}$ greatly reduces local O_2 transport, whereas a 10-fold increase barely improves it. Furthermore, as $\dot{V}_A/\dot{Q}$ falls even lower than 0.1, there is little further loss in O_2 transport. However, there is little protection against a fall in $\dot{V}_A/\dot{Q}$ below 1.0, the curve is very steep below a $\dot{V}_A/\dot{Q}$ of 1.0, as the lower left panel shows. For CO_2, the curves

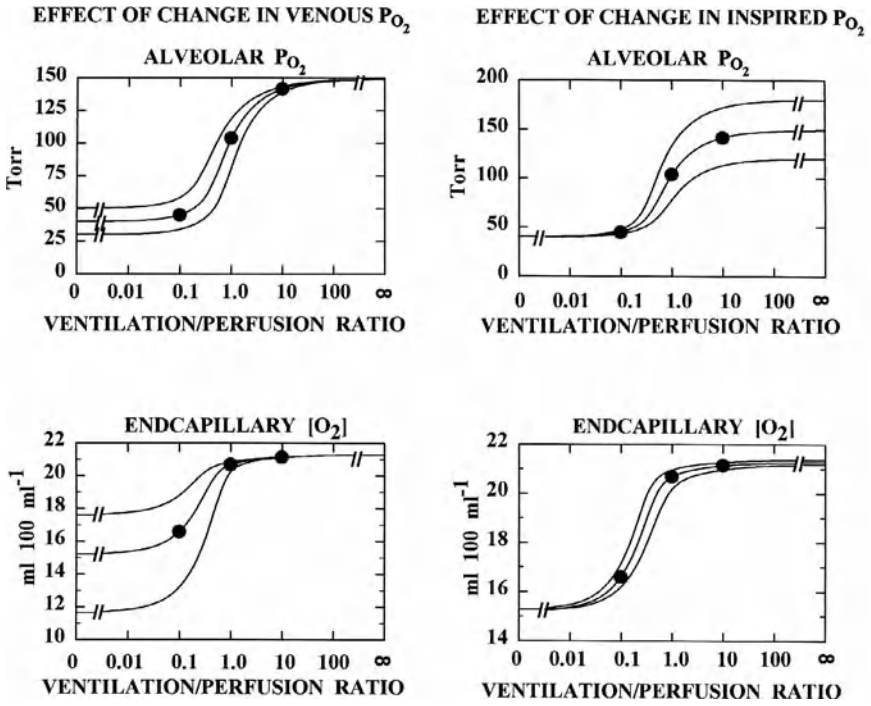

Figure 11-7 Effects of changes in mixed venous P_{O_2} (left panels) or inspired P_{O_2} (right panels) on alveolar P_{O_2} and associated end-capillary oxygen concentrations. Note that changes in venous P_{O_2} mostly affect values associated with low ventilation-perfusion ratios, whereas changes in inspired P_{O_2} affect units throughout the $\dot{V}_A/\dot{Q}$ range, especially those with medium to high $\dot{V}_A/\dot{Q}$ ratios.

are opposite in slope (P_{CO_2} falls as $\dot{V}_A/\dot{Q}$ increases). However, unlike the case for O_2, there is little difference between a $\dot{V}_A/\dot{Q}$ of 1.0 and a 10-fold reduction, whereas an increase in $\dot{V}_A/\dot{Q}$ considerably reduces alveolar P_{CO_2} and end-capillary CO_2 concentration. The reason for the differences between O_2 and CO_2 lies mainly in the slopes of their dissociation curves: That for CO_2 is about 10-fold greater than that for O_2. It has been shown that the higher the slope of the dissociation curve (or equivalently for an anesthetic gas, its solubility) the more it is sensitive to areas of high $\dot{V}_A/\dot{Q}$. The lower the slope or solubility, the more the gas is affected by areas of low $\dot{V}_A/\dot{Q}$. Consequently, areas of low $\dot{V}_A/\dot{Q}$ predictably cause more reduction in arterial P_{O_2} than increase in arterial P_{CO_2}. Although Fig. 11-6 is true strictly only for the stated "boundary" conditions (i.e., mixed venous blood and inspired gas composition), the principles hold even for different such conditions, as shown in Fig. 11-7 for O_2. The left panels illustrate how changes in mixed venous P_{O_2} alone affect alveolar P_{O_2} and end-capillary $[O_2]$ via Eq. (4). The right panels correspondingly show how change in inspired P_{O_2} affects O_2. Venous P_{O_2} is selected at 30, 40, and 50 mmHg, and inspired P_{O_2} is chosen to be 120, 150, and 180 mmHg. Changes in venous P_{O_2} dramatically affect P_{O_2} and $[O_2]$ in unventilated and poorly ventilated regions as well as regions approaching normal, but have no real effect on high $\dot{V}_A/\dot{Q}$ alveoli. Altering inspired P_{O_2} (but not venous) has the converse effect if P_{O_2} is examined (top right panel), but, because of the nonlinear shape of the O_2-Hb dissociation curve, effects on $[O_2]$ are minimal in high $\dot{V}_A/\dot{Q}$ areas, small in very low $\dot{V}_A/\dot{Q}$ areas, and more significant between $\dot{V}_A/\dot{Q}$ ratios of 0.1 and 1.0 (bottom right panel). This figure shows how the inspired and mixed venous "boundary conditions" alter the magnitude (but not basic patterns) of alveolar gas exchange.

If one returns to the normal boundary conditions ($P\bar{v}_{O_2} = 40$ mmHg, $P_{I_{O_2}} = 150$ mmHg), one can explore the consequences of $\dot{V}_A/\dot{Q}$ inequality on gas exchange. In reality, the complex structure of the lungs defies a simple analysis but conceptually even a two-compartment model is an invaluable aid to understanding this difficult area.

Figure 11-8 shows such a simple two-compartment model in three configurations: (1) each compartment equally ventilated and perfused such that there is no $\dot{V}_A/\dot{Q}$ inequality; (2) the left compartment hypoventilated due to airway obstruction, causing $\dot{V}_A/\dot{Q}$ inequality; and (3) the

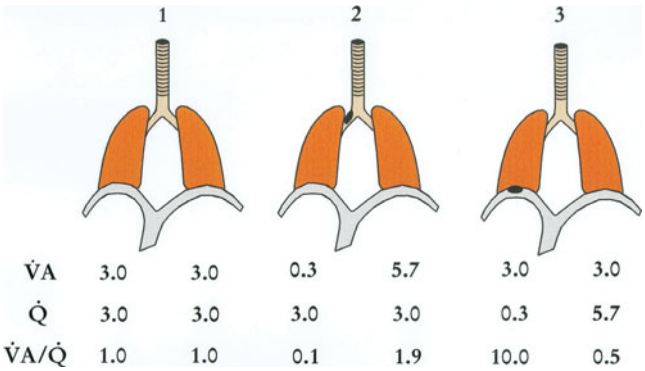

Figure 11-8 Three two-compartment models of ventilation-perfusion relationships. Model 1 represents an ideal lung without ventilation-perfusion mismatch. Model 2 represents a lung in which one compartment has a 90 percent reduction in its alveolar ventilation due to airway obstruction, and Model 3 is a lung in which one compartment has a 90 percent reduction in capillary blood flow due to vascular obstruction. Ventilation, blood flow, and ventilation-perfusion ratio of each compartment are indicated. Total ventilation and total blood flow remain the same among the three models. (See text for further details.)

Table 11-1

O_2 and CO_2 Calculations for the Models of Figure 11-8

	Normal		Airways Obstruction Model		Vascular Obstruction Model	
	Left	**Right**	**Left**	**Right**	**Left**	**Right**
$P_{A_{O_2}}$, Pc'_{O_2}, mmHg	103.0	103.0	45.0	120.0	142.0	77.0
$P_{A_{CO_2}}$, Pc'_{CO_2}, mmHg	38.8	38.8	44.9	32.5	15.5	42.7
Cc'_{O_2}, ml/dl^{-1}	20.7	20.7	16.7	20.9	21.1	20.1
$Cc'C_{O_2}$, ml/dl^{-1}	46.9	46.9	50.8	43.9	32.5	48.8
Ca_{O2}, ml/dl^{-1}	20.7		18.8		20.1	
Ca_{CO_2}, ml/dl^{-1}	46.9		47.5		48.0	
Pa_{O_2}, mmHg	103.0		55.0		77.0	
Pa_{CO_2}, mmHg	38.8		39.0		40.9	
$P\bar{A}_{O_2}$, mmHg	103.0		118.0		110.0	
$P\bar{A}_{CO_2}$, mmHg	38.8		33.7		29.2	
Total O_2 exchange, ml/min	328.0		212 (65%)		294 (90%)	
Total CO_2 exchange, ml/min	270.0		234 (87%)		203 (75%)	
$P\bar{A}_{O_2} - PaO_2$, mmHg	0.0		63.0		33.0	
$Pa_{CO_2} - P\bar{A}_{CO_2}$, mmHg	0.0		5.0		11.7	

left compartment hypoperfused from vascular obstruction. Table 11-1 shows the corresponding O_2 and CO_2 calculations for each compartment. Specific assumptions common to all three models are: (1) the mixed venous P_{O_2} remains at 40 mmHg; inspired P_{O_2} is constant at 150 mmHg; total alveolar ventilation summed over both compartments is constant as is total blood flow, both taken to be 6 L/min; [Hb] is constant at 15 g dl. Further, airways obstruction reduces L-hand compartmental ventilation from 3.0 to 0.3 L/min, redistributing the balance to the R-hand compartment. Vascular obstruction is of the same order as the right panel of the figure shows. Note that for *both* obstructive models, one compartment has developed a $\dot{V}_A/\dot{Q}$ ratio less than average and the other a $\dot{V}_A/\dot{Q}$ ratio greater than average, irrespective of the location of the obstruction.

Using the curves of Fig. 11-6, for $P\bar{v}_{O_2} = 40$ mmHg and $P_{I_{O_2}} = 150$ mmHg, $P\bar{v}_{CO_2} = 45$ mmHg and $P_{I_{CO_2}} = 0$ mmHg, alveolar P_{O_2} and P_{CO_2} are listed for each compartment of Fig. 11-8 in Table 11-1.

In Table 11-1, alveolar diffusion equilibration is assumed to be complete such that alveolar P_{O_2} ($P_{A_{O_2}}$) equals end capillary P_{O_2} (Pc'_{O_2}); the same holds for P_{CO_2}. In each obstructive model, the low $\dot{V}_A/\dot{Q}$ compartment has a lower-than-average P_{O_2} and higher-than-average P_{CO_2}, as Fig. 11-6 dictates. The converse is seen for the compartment of high $\dot{V}_A/\dot{Q}$ ratio. Corresponding end capillary O_2 and CO_2 concentrations are also listed in Table 11-1.

The question is what will the mixed arterial blood and mixed expired gas O_2 and CO_2 levels change to as a result of obstruction of one compartment, and how will this affect the ability of the total system to exchange O_2 and CO_2? To answer these questions one applies simple mixing equations to the two individual compartments (left [L] and right [R]):

For O_2:

$$P\bar{A}_{O_2} = (P_{A_{O_{2L}}} \times \dot{V}_{A_L} + P_{A_{O_{2R}}} \times \dot{V}_{A_R})/(\dot{V}_{A_L} + \dot{V}_{A_R})$$
$$Ca_{O_2} = (Cc'_{O_{2L}} \times \dot{Q}_L + Cc'_{O_{2R}} \times \dot{Q}_R)/(\dot{Q}_L + \dot{Q}_R) \quad (7)$$

For CO_2, identical equations apply. These mixing equations conserve mass and use the principle that the two gas or blood streams combine in a manner proportional to their relative ventilation and blood flow, respectively. Table 11-1 lists the results of these calculations, giving mixed alveolar partial pressure ($P\bar{A}_{O_2}$, $P\bar{A}_{CO_2}$) and mixed arterial concentrations (Ca_{O_2}, Ca_{CO_2}). From the blood gas concentration, corresponding arterial partial pressures (Pa_{O_2}, Pa_{CO_2}) are read directly off the O_2 and CO_2 dissociation curves. Finally, whole-lung computations of O_2 and CO_2 exchange rates (ml/min^{-1}) are determined using relevant equations and the mixed alveolar or arterial data, respectively, and the mixed alveolar to arterial partial pressure differences expressed for each gas.

The results are very instructive. Both obstructive models result in hypoxemia and slight hypercapnia, but the effects on arterial P_{O_2} and on the alveolar-arterial P_{O_2} difference greatly exceed those for CO_2 due to both shape and slope differences between the dissociation curves of the two gases. Airways obstruction produces *more* hypoxemia but *less* hypercapnia than the identical degree of vascular obstruction. This reflects the 10-fold greater dissociation curve slope of CO_2 compared to O_2, rendering O_2 relatively more susceptible to the lower $\dot{V}A/\dot{Q}$ areas seen in the airway obstruction model (0.1 vs. 0.5) (Fig. 11-8) and CO_2 relatively more susceptible to the higher $\dot{V}A/\dot{Q}$ areas of vascular obstruction (10.0 vs. 1.9) (see Fig. 11-8) as Fig. 11-6 would predict.

Both models have impaired overall O_2 and CO_2 exchange (recall that venous blood, inspired gas, total ventilation, and blood flow were all considered fixed and identical for all three models) as a result of the development of $\dot{V}A/\dot{Q}$ mismatch. In keeping with the differential sensitivity of O_2 and CO_2 to regions of low and high $\dot{V}A/\dot{Q}$, as discussed above, total O_2 transport is diminished to a greater extent in the airway obstruction model than in the vascular obstruction model (see Table 11-1). The converse is true for CO_2, also shown in Table 11-1.

The principal effects of $\dot{V}A/\dot{Q}$ inequality as they apply to O_2 and CO_2 exchange may thus be listed: $\dot{V}A/\dot{Q}$ inequality:

1. Affects both gases, no matter what the pathological basis of the inequality
2. Causes arterial hypoxemia and hypercapnia
3. Causes usually more severe hypoxemia than hypercapnia
4. Affects O_2 more than CO_2 when very low $\dot{V}A/\dot{Q}$ regions develop
5. Affects CO_2 more than O_2 when very high $\dot{V}A/\dot{Q}$ regions develop
6. Impairs total O_2 and CO_2 exchange by the lung
7. Creates alveolar-arterial differences for both gases

Compensation for Effects of $\dot{V}_A/\dot{Q}$ Mismatch

The preceding analysis shows that if no changes in total ventilation, blood flow, mixed venous blood, or inspired gas composition occur, O_2 and CO_2 transfer across the lung is compromised. This is not viable in the steady state: The lungs must find a way to restore total O_2 and CO_2 transfer to levels equal to metabolic use of O_2 and production of CO_2. This leads to the next concentric level of consideration of $\dot{V}A/\dot{Q}$ inequality referred to at the start of this section.

What compensatory mechanisms exist to achieve restoration of O_2 and CO_2 transfer, assuming that the initial pathophysiological insults have persisted unchanged? The same models as in Fig. 11-8 and Table 11-1 are used.

CHANGES IN MIXED VENOUS BLOOD The only possible short-term compensatory changes are in mixed venous blood, total ventilation, and cardiac output. (Hb change in response to tissue hypoxia requires days to weeks to develop and then is by no means always observed; changing inspired P_{O_2} is not usually an option until the patient seeks medical attention.) To reduce complexity, changes in venous blood alone are addressed first.

If it is assumed that there is no limit to how much O_2 can be extracted from the arterial blood by the peripheral tissues, it is evident that $\dot{V}A/\dot{Q}$ inequality will passively lead to a reduced venous P_{O_2} and increased venous P_{CO_2}. This is deduced simply from the hypoxemia and hypercapnia initially produced by the $\dot{V}A/\dot{Q}$ insult, together with the need to extract the same amount of O_2 from (and add CO_2 to) each ml of blood perfusing the tissues as before the $\dot{V}A/\dot{Q}$ insult developed.

If venous P_{O_2} falls (and P_{CO_2} rises), Fig. 11-7 indicates that alveolar P_{O_2} will fall in each $\dot{V}A/\dot{Q}$ compartment (as will P_{CO_2} rise). Thus, a circle of events is set so that if a single red cell were followed around the circulation, at each passage through the lungs and then tissues, P_{O_2} would fall progressively with each circuit of the body.

Although not intuitively obvious, this reduction in both arterial and venous P_{O_2} will not "bottom out" at zero (or in the case of CO_2 rise toward infinity) unless the $\dot{V}A/\dot{Q}$ insult was fatally overwhelming in the first place. Both arterial and venous P_{O_2} restabilize at new lower values (P_{CO_2} values will be higher) than were present immediately after the $\dot{V}A/\dot{Q}$ insult developed. In so doing, $\dot{V}_{O_2}$ and $\dot{V}_{CO_2}$ are restored to normal values.

To explore this quantitatively, we continue on with the models of Fig. 11-8 and Table 11-1 to show just what changes in venous and arterial P_{O_2} and P_{CO_2} must occur as a result of this process in order to restore pulmonary O_2 and CO_2 exchange to normal. The values are shown in Table 11-2. For the airways obstruction model, the passive blood gas changes are greater for O_2 than CO_2, consonant with the greater initial decrement in O_2 exchange caused by airways obstruction in the first place. For the vascular obstruction model, the effects are more marked for CO_2, for corresponding reasons. To restore $\dot{V}_{O_2}$ and $\dot{V}_{CO_2}$ in the airways obstruction model, hypoxemia is now more severe, but hypercapnia is mild. However, with vascular obstruction, hypoxemia remains mild, while hypercapnia is severe. In both cases, the lung is meeting the original healthy requirement of transferring 328 and 270 ml/min of O_2 and CO_2, respectively.

The speed of passive venous blood composition changes is very rapid, taking place in seconds to minutes as the blood moves continuously around the vascular system

Table 11-2

Gas Exchange Effects of Passive Changes in Mixed Venous Blood-Gas Values Required to Restore $\dot{V}_{O_2}$ and $\dot{V}_{CO_2}$ to Normal in the Models of Figure 11-8

	Airways Obstruction Model		Vascular Obstruction Model	
	Before Change	After Change	Before Change	After Change
$P\bar{v}_{O_2}$, mmHg	40.0	30.4	40.0	39.5
$P\bar{v}_{CO_2}$, mmHg	45.0	50.7	45.0	62.4
Pa_{O_2}, mmHg	55	46	77	67
Pa_{CO_2}, mmHg	39.0	44.5	40.9	55.6
$\dot{V}_{O_2}$, ml/min	212.0	328 (normal)	294.0	328.0
$\dot{V}_{CO_2}$, ml/min	234.0	270 (normal)	203.0	270.0

between lungs and tissues. The principal effects of the changes can be summarized as follows:

1. Following development of $\dot{V}A/\dot{Q}$ mismatch, and a fall in $\dot{V}_{O_2}$ and $\dot{V}_{CO_2}$ at the lungs, mixed venous P_{O_2} will fall and mixed venous P_{CO_2} will rise to restore pulmonary $\dot{V}_{O_2}$ and $\dot{V}_{CO_2}$ to equal the original metabolic requirements for O_2 and CO_2 transport.
2. As a result, there will always be a further fall in arterial P_{O_2} and rise in arterial P_{CO_2}, compared with conditions prior to mixed venous blood changes.
3. When the $\dot{V}A/\dot{Q}$ insult primarily involves development of extremely low $\dot{V}A/\dot{Q}$ areas, those effects are more marked for O_2 than for CO_2.
4. When the $\dot{V}A/\dot{Q}$ insult primarily consists of high $\dot{V}A/\dot{Q}$ areas, CO_2 is affected more than O_2.

CHANGES IN TOTAL VENTILATION When either low or high $\dot{V}A/\dot{Q}$ areas develop and the mixed venous and arterial adjustments occur as described, there is hypoxemia and hypercapnia. Either or both may well stimulate an immediate increase in total ventilation, which will alleviate to some extent both the hypoxemia and hypercapnia. Fig. 11-9 shows for the same two examples used above how increases in alveolar ventilation (distributed in the same proportions as in each of the two $\dot{V}A/\dot{Q}$ models of Fig. 11-8) variably improve arterial P_{O_2} and P_{CO_2}. In the low $\dot{V}A/\dot{Q}$ (airways obstruction) model, a 50 percent increase in total alveolar ventilation from the normal value of 6 L/min^{-1} to 9 L/min^{-1} drops arterial P_{CO_2} to almost 30 mmHg, well below the normal standard value of 40 mmHg. Arterial P_{O_2}, however, is not affected at all. This is because even a 50 percent increase in ventilation of the very poorly ventilated unit fails to significantly increase

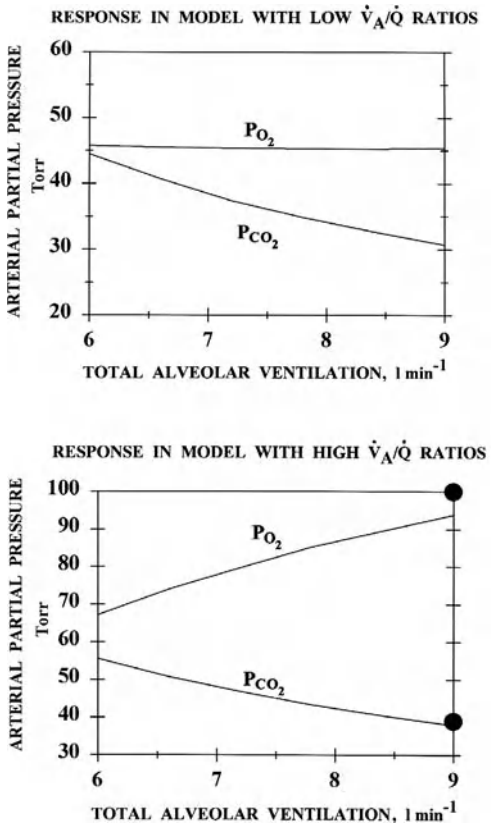

Figure 11-9 Effect of increasing alveolar ventilation on arterial P_{O_2} and P_{CO_2} in the two models with ventilation-perfusion inequalities in Fig. 11-8. The top panel is that for Model 2, and the bottom panel is that for Model 3. Increasing ventilation is ineffective in restoring arterial P_{O_2} in the low $\dot{V}A/\dot{Q}$ model 2, but much more effective in the high $\dot{V}A/\dot{Q}$ model 3. Both models respond in terms of P_{CO_2}. The filled circles in the lower panel indicate arterial P_{O_2} and P_{CO_2} for a lung with normal alveolar ventilation and no $\dot{V}A/\dot{Q}$ inhomogeneity.

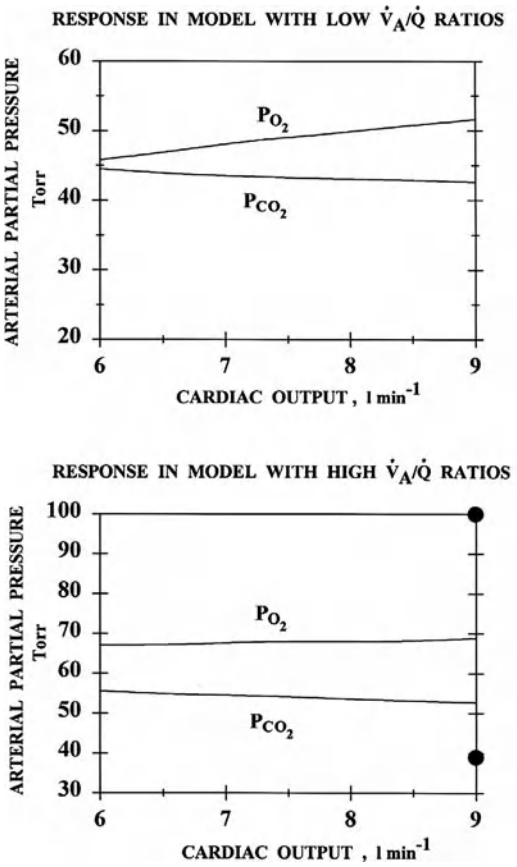

Figure 11-10 Effects of increases in cardiac output on arterial P_{O_2} and P_{CO_2} in Models 2 and 3 of Fig. 11-8. Cardiac output produces a significant rise in P_{O_2} in the presence of regions of very low ventilation-perfusion ratio (top panel) but has little influence in the presence of higher ventilation-perfusion ratios (bottom panel). P_{CO_2} is affected only minimally in either case. The filled circles in the lower panel indicate arterial P_{O_2} and P_{CO_2} for a lung with normal alveolar ventilation and no $\dot{V}_A/\dot{Q}$ inhomogeneity.

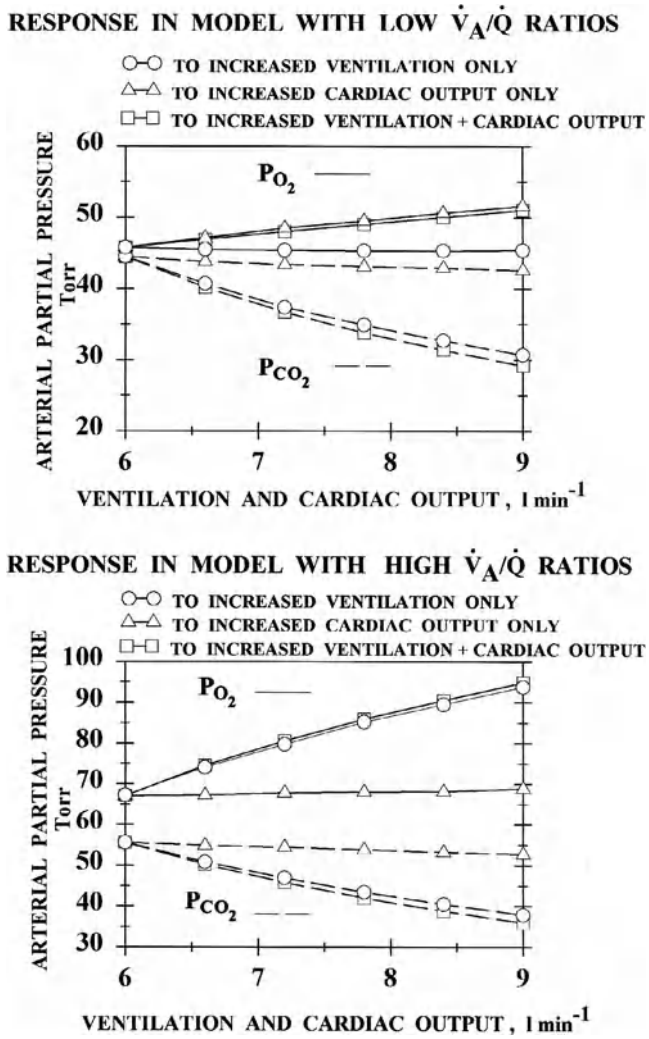

Figure 11-11 Responses to simultaneous increases in ventilation and cardiac output (compared to responses to individual increases as shown in Figs. 11-9 and 11-10). Simultaneous increases do not provide for significantly more improvement than with either alone. o-o = response to increased ventilation only; Δ-Δ = response to increased cardiac output only; □-□ = response to simultaneously increased ventilation and cardiac output.

end-capillary P_{O_2} of that unit (see Fig. 11-6), whereas in the better ventilated unit of that model, Hb in the end-capillary blood was already virtually fully saturated before the increase in ventilation.

For the model with vascular obstruction, a 50 percent increase in alveolar ventilation returns both P_{O_2} and P_{CO_2} to near-normal values (see Fig. 11-9, lower panel). The difference in the two model responses to ventilation reflects the original $\dot{V}_A/\dot{Q}$ ratios of the two compartments; that is, where they lie on the curves of Fig. 11-6.

CHANGES IN CARDIAC OUTPUT One final compensatory adjustment is possible—an increase in cardiac output. Adrenergic stimulation by arterial hypoxemia can raise cardiac output by 50 percent or more, and this also tends to improve arterial blood gases by raising mixed venous P_{O_2} (and lowering mixed venous P_{CO_2}). Fig. 11-10 shows the effects on arterial P_{O_2} and P_{CO_2} of such increases, as done for ventilation in Fig. 11-9, again assuming that the relative distribution of blood flow remains unaltered between the two compartments as total blood flow is increased. For a lung with airways obstruction causing very low $\dot{V}_A/\dot{Q}$ regions (upper panel), an increase in cardiac output significantly improves arterial oxygenation—more so than does the same relative increase in ventilation. However, arterial P_{CO_2} is only slightly improved. In stark contrast, increases in cardiac output barely alter arterial P_{O_2} and P_{CO_2} in the high $\dot{V}_A/\dot{Q}$ ratio model (see Fig. 11-9), especially when it is recalled how effective an increase in ventilation is in restoring arterial P_{O_2} and P_{CO_2}.

When both ventilation and cardiac output are simultaneously increased, there is no real synergistic effect (Fig. 11-11): P_{O_2} and P_{CO_2} are improved as predicted from the individual changes (i.e., as shown above in Figs. 11-9 and 11-10).

In all the calculations depicted in Figs. 11-9 to 11-11, the two-compartment models are exchanging the necessary

amounts of O_2 and CO_2 to sustain normal metabolism. Depending on the ventilatory and cardiovascular responses to the original insult causing $\dot{V}_A/\dot{Q}$ mismatch and the fundamental pattern of $\dot{V}_A/\dot{Q}$ mismatch (i.e., the preponderance of low and/or high $\dot{V}_A/\dot{Q}$ areas), it is possible to observe hypercapnia, normocapnia, or hypocapnia. However, it is very uncommon for arterial P_{O_2} to be fully normalized by the compensatory mechanisms, and the observed degree of hypoxemia can be extremely variable. As an important clinical corollary, it becomes difficult to establish the severity of the $\dot{V}_A/\dot{Q}$ insult per se when the extent of compensating mechanisms cannot be easily established, since these two aspects are so intertwined in their resulting effect on gas exchange.

ASSESSMENT OF VENTILATION-PERFUSION INEQUALITY

Whereas the preceding discussion highlights the complexity of how $\dot{V}_A/\dot{Q}$ inequality impairs gas exchange, there is a need for methods to assess the extent of such mismatch in the clinical setting. The *multiple inert gas elimination technique* was developed expressly for this purpose. Although the technique provides the necessary descriptions of the extent and pattern of inequality, it remains a complex technique that is not well-suited to routine clinical use. Several traditional quantifying indices of $\dot{V}_A/\dot{Q}$ mismatch remain useful on a daily basis. They all make use of O_2 and CO_2 as indicator gases:

The first is the alveolar-arterial P_{O_2} difference, $P_{AO_2} - Pa_{O_2}$. This is the difference between alveolar P_{O_2} (P_{AO_2}, calculated from the alveolar gas equation presented below) and the measured arterial P_{O_2} (Pa_{O_2}). The $P_{AO_2} - Pa_{O_2}$ is therefore given by:

$$P_{I_{O_2}} - P_{CO_2}/R + P_{CO_2} \times F_{I_{O_2}} \times (1 - R)/R - Pa_{O_2} \quad (8)$$

Use of this equation requires knowledge of inspired P_{O_2} and $[O_2]$, the respiratory exchange ratio R, and the ideal alveolar P_{CO_2}, which is that P_{CO_2} would be observed in alveolar gas of a homogeneous lung having the R value of the patient's actual lung at the time. Three problems arise with the application of this equation. First, the result is very dependent on $P_{I_{O_2}}$ even when the amount of $\dot{V}_A/\dot{Q}$ inequality does not change as $P_{I_{O_2}}$ is varied. Second, the value of R is generally not known and must be assumed. Third, in some cases, the usual substitution for the ideal alveolar P_{CO_2}, the measured arterial P_{CO_2}, leads to a systematic error because arterial P_{CO_2} can be significantly higher than the ideal alveolar value. However, $P_{AO_2} - Pa_{O_2}$ remains a useful index of $\dot{V}_A/\dot{Q}$ inequality providing these limitations are kept in mind.

The second index is simply the ratio of arterial P_{O_2} to $F_{I_{O_2}}$, which in a perfectly normal lung is virtually insensitive to $P_{I_{O_2}}$, a major advantage. However, even that is an oversimplification, because this ratio may not be as constant as hoped for depending on the pattern of $\dot{V}_A/\dot{Q}$ inequality present.

A third index is venous admixture ($\dot{Q}_S/\dot{Q}_T$) or, equivalently, physiological shunt. This is a parameter that expresses what magnitude shunt would have to be present in a particular case to explain a patient's arterial P_{O_2} if that shunt were the sole cause of hypoxemia. The formula is:

$$\text{percent } \dot{Q}_S/\dot{Q}_T = 100 \times [Cc'_{O_2} - Ca_{O_2}]/[Cc'_{O_2} - C\bar{v}_{O_2}] \quad (9)$$

where

Cc'_{O_2} = the calculated end capillary $[O_2]$ of blood perfusing a hypothetical alveolus exchanging gas at the overall respiratory exchange ratio of the patient's actual lungs

Ca_{O_2} is arterial and $C\bar{v}_{O_2}$ mixed venous $[O_2]$, respectively. This parameter, working in the O_2 concentration domain (rather than the partial pressure domain of the $P_{AO_2} - Pa_{O_2}$), better reflects the degree of gas exchange defect but requires knowledge of the ideal alveolar conditions to calculate Cc'_{O_2}, as well as [Hb]. It also is sensitive to $P_{I_{O_2}}$ in that when $\dot{V}_A/\dot{Q}$ inequality is present, its contribution to $\dot{Q}_S/\dot{Q}_T$ diminishes progressively as $P_{I_{O_2}}$ is raised. However, the most limiting aspect of this parameter is the need to know the value of $C\bar{v}_{O_2}$, reflecting mixed venous blood. If this must be assumed rather than measured, the value of $\dot{Q}_S/\dot{Q}_T$ will be only as good as the assumption, which may be extremely misleading if changes in $C\bar{v}_{O_2}$ in fact occur but are not accounted for in the $\dot{Q}_S/\dot{Q}_T$ calculation.

Finally, using the arterial and mixed expired partial pressures of CO_2 (Pa_{CO_2}, $P\bar{E}_{CO_2}$, respectively), a very similar calculation to $\dot{Q}_S/\dot{Q}_T$ can be performed to compute the percentage of total ventilation that is wasted on nongas exchanging (dead space) areas of the lungs. As for $\dot{Q}_S/\dot{Q}_T$, the calculation determines the magnitude of the dead space that would have to be present to dilute the arterial P_{CO_2} down to the mixed expired level if that dead space were the only abnormality in ventilation. Expressed as dead space (V_D)/tidal volume (V_T) percentage:

$$\text{percent } V_D/V_T = 100 \times [Pa_{CO_2} - P\bar{E}_{CO_2}/[Pa_{CO_2}] \quad (10)$$

This parameter is independent of $P_{I_{O_2}}$, but is weakened by the fact that the normal airway conducting volume is included in the computed result. Thus, it may be difficult to separate how much the V_D/V_T value represents this normal anatomic dead space as opposed to reflecting $\dot{V}_A/\dot{Q}$ inequality among the alveoli. This problem is amplified because normally V_D/V_T is very dependent on the size of the tidal volume even if the dead space volume itself is essentially constant. Thus, for a dead space volume of 150 ml and a tidal volume of 500 ml, V_D/V_T is 30 percent, but if tidal volume were to drop to 400 ml, V_D/V_T would become 38 percent, not because $\dot{V}_A/\dot{Q}$ inequality has developed, but simply because smaller breaths are being taken.

In summary, no index of $\dot{V}_A/\dot{Q}$ inequality is without potentially significant limitations, both quantitative and qualitative. However, if these limitations are recognized and the

data interpreted accordingly, they still remain very useful indices of clinical gas exchange function.

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12

Diffusion, Chemical Reactions, and Diffusing Capacity

Robert A. Klocke

Uptake of oxygen and excretion of carbon dioxide require rapid, efficient exchange in the lung. The quantities of exchanged gases are staggering. For example, an 1800-calorie diet requires absorption of 375 L of oxygen per day, as well as excretion of a slightly smaller volume of carbon dioxide. Because blood remains in the pulmonary capillary bed for a limited time, the process of exchange must be accomplished in less than 1 s at rest and one-half that time during exercise. This rapid, high-volume exchange occurs efficiently despite numerous interacting processes of diffusion and chemical reaction that occur in the lung. The rates of these processes not only are affected by intrinsic characteristics of blood, but also are determined by a host of other factors, including inspired oxygen fraction, alveolar gas tensions, cardiac output, and metabolic activity. The ease of exchange of respiratory gases belies the complexity of the overall process.

DIFFUSION

Gases diffuse from a higher to a lower partial pressure, not necessarily from a higher to a lower concentration. This fact is especially pertinent when a gas diffuses between two phases, as occurs when O_2 and CO_2 are exchanged between alveolar gas and blood. For example, dissolved CO_2 diffuses down a partial pressure gradient from blood (46 mmHg) into the alveolus (40 mmHg), even though its actual concentration (millimoles of molecular CO_2 per liter of gas or blood) is greater in alveolar gas (2.5) than it is in venous blood (1.4).

Influence of Physical Properties

The concentration (C) of a gas (x) dissolved in fluid depends upon its partial pressure (P) and solubility (α)

$$C_x = \alpha_x P_x \qquad (1)$$

Gas diffusion occurs down a partial pressure gradient, but the quantity of gas transported is critically dependent on its solubility in the medium in which diffusion occurs. Hence, the rate ($\dot{V}_x$) of a gas (x) crossing the alveolar-capillary membrane at any instant in time (t) is

$$\dot{V}_x(t) = \frac{Ak_x\alpha_x[P_{A_x}(t) - P_{cap_x}(t)]}{h} \qquad (2)$$

where

A and h = the surface area and thickness of the membrane

k_x and α_x = the diffusion and solubility coefficients of the gas in the membrane

$[P_{A_x}(t) - P_{cap_x}(t)]$ = the partial-pressure gradient between alveolar and capillary blood at time (t)

The diffusion coefficient (k_x) of a gas in the alveolar-capillary membrane is largely a function of the size of the gas molecule, which is inversely proportional to the square root of its molecular weight (MW). Oxygen (MW 32) has a slightly greater diffusion coefficient than carbon dioxide (MW 44) in the alveolar membrane. However, the solubility of CO_2 in water, the major component of tissue composing the membrane, is 20-fold greater than the solubility of O_2. This difference far outweighs the effect of the slightly smaller size of the oxygen molecule. Thus, CO_2 transfer across the alveolar membrane is approximately 20 times greater than O_2 transfer when both gases diffuse under the same partial-pressure gradient. As a result, a much greater P_{O_2} gradient across the membrane is required to maintain O_2 transfer equal to that of CO_2.

The rate of diffusion is affected by the viscosity of the medium through which the diffusion occurs. Diffusion of a gas in air occurs at a rate that is four orders of magnitude greater than diffusion in water. Diffusion coefficients in tissues are only moderately less than those in water, since most tissues are composed primarily of water. The interior of the erythrocyte is an exception to this general rule. As a consequence of the high concentration of hemoglobin inside the red cell, the viscosity of the cell contents is substantially greater than that of water. This greater viscosity reduces the diffusion coefficient for oxygen to one-third of its aqueous coefficient. The combination of increased viscosity and the large size of the hemoglobin molecules decreases the diffusion coefficient of hemoglobin within the red cell to less than 10 percent of its diffusion coefficient in a dilute aqueous solution. As a result, significant diffusion gradients are thought to exist within the red cell even though the distance between the cell membrane and the innermost portion of the cell is only a few microns.

Effect of Different Capacitances

The alveolar-capillary membrane is the only barrier to diffusion of gases between the alveoli and the capillaries. The rate of approach to diffusion equilibrium of a gas in the lung is dependent on the capacitances of the gas in the alveoli and blood relative to its solubility in the alveolar-capillary membrane. Normal ventilation of alveoli results in a large reservoir of oxygen with a pressure of ~100 mmHg to promote diffusive transfer across the alveolar-capillary membrane. The ability of hemoglobin to bind O_2 increases the oxygen capacity of blood by two orders of magnitude compared with that of the alveolar-capillary membrane. This large capacitance for oxygen in blood requires substantial oxygen transfer across the membrane to reach diffusion equilibrium. Because the solubility of oxygen in the membrane is small relative to the large capacitances in alveolar gas and blood, oxygen exchange across the membrane requires 0.3 to 0.4 s to reach equilibrium. Fortunately, this delay in reaching equilibrium is less than the average of 0.5 to 1.0 s that blood remains in the pulmonary capillary bed.

In contrast to oxygen, the solubility of carbon dioxide in the membrane is sufficiently great compared to the capacitances of CO_2 in blood and alveoli to permit rapid equilibration of CO_2 across the alveolar-capillary membrane. As discussed below, CO_2 exchange requires a finite time for completion, but this delay is the result of the time needed to complete chemical and transport processes in blood, and is not the result of impairment of diffusion across the alveolar-capillary membrane.

Gases transported in blood only in dissolved form are exchanged almost instantaneously across the alveolar-capillary membrane. As long as gas solubilities in the membrane and blood are similar, diffusion equilibrium between alveolar contents and blood is reached within 0.01 s because the normal alveolar-capillary membrane is extremely thin (median thickness of 0.3 μm). Only gases such as oxygen or carbon monoxide that have large alveolar and blood capacitances and reduced solubility in the alveolar-capillary membrane will require a finite time to reach diffusive equilibrium.

CHEMICAL REACTIONS OF GASES

Transport of respiratory gases entails numerous chemical reactions with components of the blood. Like diffusive transport of oxygen, these chemical reactions are not instantaneous and require finite periods of time to reach completion. It is commonly thought that diffusion provides the greatest time-dependent impediment to gas exchange, but in actuality, chemical processes, especially those occurring in combination with diffusion or other chemical reactions, are more likely to slow rates of exchange.

Oxygen and Carbon Monoxide

From a stoichiometric viewpoint, the binding of O_2 to each of the four heme moieties of the hemoglobin tetrameter is described by four successive steps, each with a separate association and dissociation rate constant. If the four heme rings acted independently, these constants would be the same for each heme ring and the resulting dissociation curve would have a hyperbolic shape. However, binding of oxygen to one of the heme rings affects the affinity for O_2 of the remaining heme moieties of the tetrameric molecule, leading to the familiar sigmoid shape of the oxygen dissociation curve (see Chapter 13).

Reactions of oxygen and hemoglobin during capillary transit are further complicated by the rate of oxygen diffusion through the viscous interior of the red cell. The chemical reactions of oxygen and hemoglobin occur quite rapidly in dilute hemoglobin solutions but proceed more

slowly in red cell suspensions. Because of the large size of the hemoglobin molecule and increased viscosity of the red cell contents, hemoglobin remains relatively immobile. As the red cell enters the pulmonary capillary, oxygen molecules bind to reduced hemoglobin molecules just inside the erythrocyte membrane. As these hemoglobin molecules become saturated, subsequent oxygen molecules entering the red cell must diffuse more deeply into the interior of the cell to reach reduced hemoglobin molecules. This combination of diffusion and chemical reaction causes oxygen uptake to occur as an "advancing front" that proceeds at a rate that is an order of magnitude slower than O_2 uptake in well-mixed, dilute hemoglobin solution. This combined process is complex and not easily described from a theoretical standpoint. As a result, the rate of oxygen uptake by hemoglobin contained in red cells is described by a single overall descriptive rate constant, θ_{O_2}, which incorporates all the processes into a single phenomenological value. θ_{O_2} varies with oxygen saturation, pH, and hemoglobin type. The same approach is used to describe carbon monoxide uptake in blood. The rate at which CO replaces bound O_2 in blood with a normal hemoglobin concentration is described by the constant θ_{CO}.

The rates of O_2 and CO uptake by erythrocyte suspensions are determined in vitro and assumed to be representative of the rates of gas exchange in vivo. However, measurements of these rate constants in red cell suspensions in vitro may be affected adversely by methodologic artifacts. The actual rates of combination of O_2 and CO with red cells in vivo have not been measured and this lack of data leads to uncertainties in our understanding of exchange of the two gases in the lung.

Carbon Dioxide

CO_2 is transported in blood as dissolved molecular CO_2, bicarbonate ion, and carbamate ion. The latter is a salt of a carbamic acid formed by reaction of CO_2 with certain amino groups on the hemoglobin molecule. The relation between the partial pressure of CO_2 and the total content of CO_2 in all forms is described by the CO_2 dissociation curve of blood (see Chapter 13). Because CO_2 is more soluble than O_2 in the alveolar-capillary membrane, it has been assumed that CO_2 exchange occurs much more rapidly than O_2 exchange. However, only dissolved CO_2 can cross the alveolar capillary membrane, and conversion of bicarbonate and carbamate to dissolved CO_2 limits the rate of CO_2 exchange. As indicated in Fig. 12-1*A*, when a bolus of dissolved CO_2 is injected into an isolated lung perfused with saline buffer, CO_2 is instantaneously exchanged similar to the inert gas acetylene. In contrast, when a bicarbonate bolus is injected into the same preparation (Fig. 12-1*B*), CO_2 exchange lags behind acetylene excretion because a finite period of time is required to convert bicarbonate into dissolved CO_2 that can cross the alveolar-capillary membrane.

Dissolved CO_2 is excreted immediately as blood enters the pulmonary capillary bed, but constitutes only 8 percent of the total quantity of CO_2 exchanged during capillary transit. The majority (79 percent) of excreted CO_2 enters the capillary bed as bicarbonate ion. As dissolved CO_2 leaves capillary blood, the equilibrium between bicarbonate ion and CO_2 is disturbed, leading to further production of CO_2.

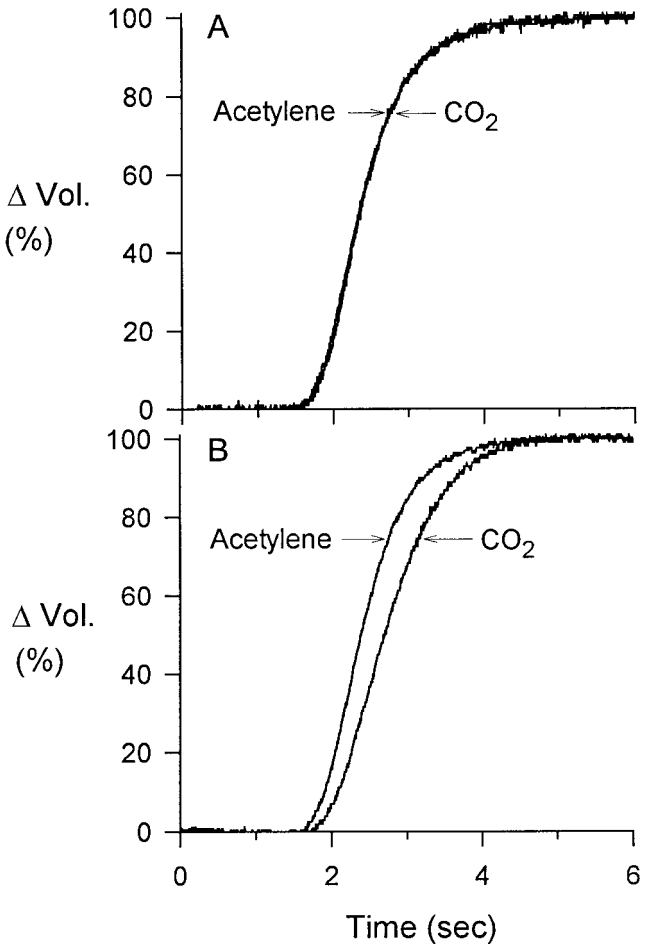

Figure 12-1 Rate of acetylene and CO_2 excretion after bolus injections into the pulmonary artery of isolated lungs perfused with buffer. Volume changes are normalized to facilitate comparison. *A.* The excretion of both acetylene and CO_2 proceed at the same rate after injections of buffer containing either dissolved CO_2 or acetylene. *B.* The excretion of CO_2 lags behind that of acetylene after injection of buffer containing bicarbonate ion. In this example, the mean time of CO_2 excretion lags 0.312 s behind that of acetylene. This slower excretion of CO_2 is caused by the time required to convert bicarbonate to CO_2 with catalysis in this experiment provided by carbonic anhydrase localized to the capillary endothelium. *(Based on data of Schunemann HJ, Klocke RA: Influence of CO_2kinetics on pulmonary carbon dioxide exchange. J Appl Physiol 74:715, 1993. Reproduced with permission from Klocke RA. Carbon dioxide transport, in, Crystal RG, West JB, Weibel ER, et al (eds), The Lung: Scientific Foundation, 2nd ed. New York, Lippincott, Williams & Wilkins; 1997, p 1633.)*

$$HCO_3^- + H^+ \rightarrow H_2CO_3 \xrightarrow{CA} CO_2 + H_2O \qquad (3)$$

Bicarbonate ion combines with hydrogen ion extremely rapidly to form carbonic acid (H_2CO_3). The natural rate of dehydration of carbonic acid to CO_2 and water is a slow process, but is catalyzed by a factor of 10,000 to 16,000 by the large concentration of carbonic anhydrase (CA) inside the

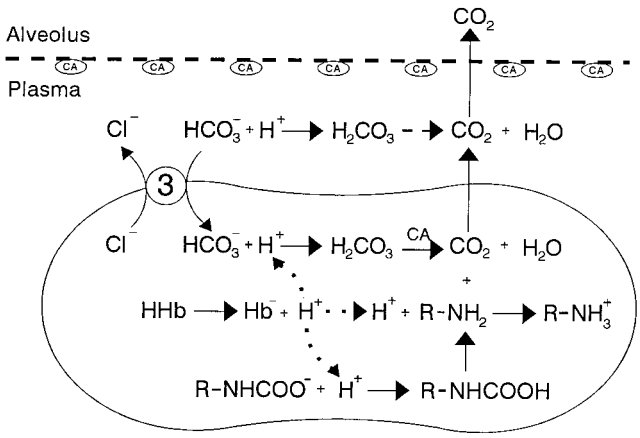

Figure 12-2 Pathways of CO_2 transport and exchange in the lung. CA = carbonic anhydrase within the erythrocyte or localized to the capillary endothelium; dashed arrow indicates that the production of CO_2 from plasma bicarbonate proceeds more slowly than the same reaction inside the erythrocyte; dotted arrows indicate that hemoglobin provides protons that partake in these reactions; R-NH_2 = amino groups of hemoglobin molecule that bind CO_2 to form carbamate compounds, R-NHCOOH; 3 = band 3 anion exchange protein in the cell membrane, which facilitates exchange of bicarbonate and chloride ions across the membrane. *(Reproduced with permission from Klocke RA. Carbon dioxide transport. In: Crystal RG, West JB, Weibel ER, et al (eds), The Lung: Scientific Foundation, 2nd ed. New York, Lippincott, Williams & Wilkins, 1997, p 1633.)*

erythrocyte (Fig. 12-2). The substantial buffering capacity of hemoglobin provides the hydrogen ions required for this reaction and intracellular pH changes minimally. This rapid conversion of bicarbonate to CO_2 depletes the concentration of intracellular bicarbonate after a short time (0.1 s), slowing the production of CO_2.

As intracellular concentration of bicarbonate decreases, plasma bicarbonate enters the cell in exchange for intracellular chloride (Fig. 12-2). Bicarbonate-chloride movement across the erythrocyte membrane occurs in an electrically neutral, one-for-one exchange that is facilitated by a carrier, termed band 3 protein, present in the erythrocyte membrane. Despite the presence of approximately 1 million carrier sites with an extremely rapid turnover number (50,000 ions per second) in the cell membrane of each erythrocyte, bicarbonate-chloride exchange has a half-time of 0.1 s and requires 0.4 to 0.5 s to reach completion. Computational models suggest that in some circumstances the time required for the combined processes of dehydration of carbonic acid and transmembrane ionic exchange is sufficiently long that CO_2 exchange is not quite completed prior to blood leaving the pulmonary capillary. Even in the worst case, the degree of disequilibrium is small and a minimal increase in ventilation can easily compensate for a slight impairment of CO_2 exchange.

Approximately one-half of the total quantity of CO_2 excreted in the lung entered the pulmonary capillaries as plasma bicarbonate, but before being excreted first had to enter the erythrocyte to be converted into dissolved CO_2 under the influence of intracellular carbonic anhydrase. A small amount of plasma bicarbonate is converted into CO_2 without entering the erythrocyte. Carbonic anhydrase is localized on the interior surface of the pulmonary capillary in sufficient concentration to catalyze the dehydration reaction by a factor of 100 to 150. Mathematical models of CO_2 exchange indicate that this relatively small catalytic activity, together with plasma buffering power that is substantially less than that of hemoglobin, result in relatively little production of CO_2 from bicarbonate within the plasma.

Besides exchange of dissolved CO_2 and bicarbonate, a modest amount of CO_2 excretion (13 percent) results from release of CO_2 bound to hemoglobin as carbamate (Fig. 12-2). This exchange is facilitated by the alteration of the molecular conformation of hemoglobin that accompanies oxygenation. This pathway accounts for a portion of the Haldane effect, the change in the CO_2 dissociation curve that results from oxygenation of blood (see Chapter 13).

Carbon dioxide transport processes may not quite reach equilibrium in the pulmonary capillary bed because of the time required to complete chemical reactions and ionic exchanges. However, CO_2 itself crosses the alveolar-capillary membrane as rapidly as an inert gas, and the diffusing capacity for CO_2 is so great that to date it has not been possible to measure it accurately.

DIFFUSING CAPACITY

The pulmonary diffusing capacity (D_L) of a gas provides an estimate of its rate of transfer from the alveoli into capillary blood. Initially it was thought that only diffusion of gas across the membrane limited exchange, as described by Eq. (2). This is the case for inert gases and, as noted above, equilibrium of these gases is achieved rapidly even in disease. However, transfer of gases that combine with hemoglobin may be limited both by diffusion across the alveolar membrane and by the rate of reactions in blood. The only gases that have measurable diffusing capacities are those with low solubility in the pulmonary membrane and high capacitance in blood. These gases include oxygen (O_2), carbon monoxide (CO), and nitric oxide (NO).

Diffusing Capacity for Oxygen ($D_{L_{O_2}}$)

The diffusing capacity is calculated as the volume of gas absorbed by pulmonary blood per unit time ($\dot{V}$) divided by the pressure gradient between alveolar gas (P_A) and capillary blood (P_{cap}).

For oxygen,

$$D_{L_{O_2}} = \frac{\dot{V}_{O_2}}{P_{A_{O_2}} - P_{cap_{O_2}}} \qquad (4)$$

Measurement of $D_{L_{O_2}}$ is difficult because, in addition to diffusion, O_2 transfer may be limited by other mechanisms, such as ventilation-perfusion mismatching and shunting

(see Chapter 13). The measurement is further complicated by a changing capillary P_{O_2} during capillary transit that cannot be accurately determined. These difficulties have led clinicians and investigators to abandon attempts to measure.

Diffusing Capacity for Carbon Monoxide ($D_{L_{CO}}$)

Carbon monoxide provides an excellent alternative to measuring diffusing capacity because CO normally is present in minimal amounts in blood and binds to hemoglobin in the same manner as O_2. Because capillary P_{CO} is so low in usual circumstances, it can be assumed to be negligible and $D_{L_{CO}}$ is calculated by dividing CO uptake ($\dot{V}_{CO}$) by alveolar P_{CO}. However, CO uptake is limited both by diffusion across the alveolar-capillary membrane and by chemical reaction of CO with intracellular hemoglobin. As described by Roughton and Forster, $D_{L_{CO}}$ is comprised of two elements

$$\frac{1}{D_{L_{CO}}} = \frac{1}{Dm_{CO}} + \frac{1}{\theta_{CO} V_c} \qquad (5)$$

where

Dm_{CO} = the diffusing capacity of the alveolar-capillary membrane for CO
θ_{CO} = the rate of displacement of O_2 from intracellular hemoglobin by CO
V_c = the volume of blood in the pulmonary capillary bed

Because O_2 and CO compete for binding sites on hemoglobin, CO binding is inhibited by increases in P_{O_2}. Thus, $D_{L_{CO}}$ and θ_{CO} vary inversely with P_{O_2}. Using known in vitro values of θ_{CO} and two measurements of $D_{L_{CO}}$ at normal and elevated inspired O_2 concentrations, Eq. (5) can be solved to provide values of both Dm_{CO} and V_c. Calculation of the diffusing capacity is based on the assumption that the lung is homogeneous, i.e., all portions of the lung have the same relative ventilation, perfusion, alveolar volume, and diffusing capacity.

Diffusing Capacity for Nitric Oxide ($D_{L_{NO}}$)

Nitric oxide binds to hemoglobin at the same site as O_2 and CO, but the rate of NO binding is much more rapid. It is estimated that NO binding in red cells occurs more than two orders of magnitude faster than CO binding ($\theta_{NO} \gg \theta_{CO}$). Thus, the time required for binding of NO to intracellular hemoglobin, analogous to the $1/\theta_{CO}V_c$ term in Eq. (5), should approach zero and contribute little to the measured value of $D_{L_{NO}}$. As a result, $D_{L_{NO}}$ is assumed to be equal to Dm_{NO}. This conclusion is supported by the lack of effect of changes in inspired O_2 concentration on $D_{L_{NO}}$. In contrast, $D_{L_{CO}}$ is markedly sensitive to such changes because the θ_{CO} is diminished by competition with O_2. Measurements of D_L with CO and NO in the same subjects demonstrate that $D_{L_{NO}}$ is 4.1 to 5.2 times greater than $D_{L_{CO}}$ (Fig. 12-3*A*).

Key assumptions in the measurement of $D_{L_{NO}}$ are that NO binds negligibly to receptors in lung parenchyma other than hemoglobin and that NO has no major physiological effects during the measurements. Measurements with different breath-hold times and inspired NO concentrations yield constant values of $D_{L_{NO}}$, supporting the validity of these assumptions. Recent work indicates that NO is produced in the lung and nasal sinuses, but these concentrations of NO are well below the NO concentrations used in the measurement of $D_{L_{NO}}$ and it is unlikely that this NO production causes errors in measurement. Since NO is highly reactive with oxygen, requires special equipment for analysis, and has potential cardiovascular effects, measurements of $D_{L_{NO}}$ are confined to research settings.

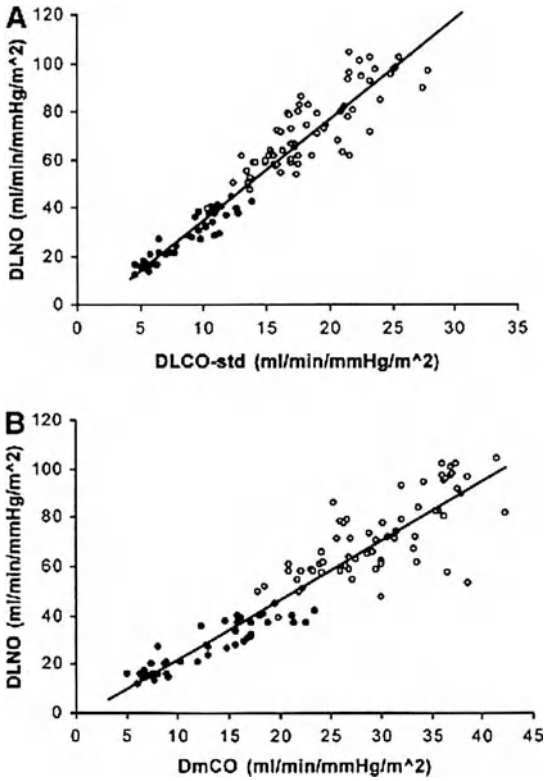

Figure 12-3 The relationships between (A) $D_{L_{NO}}$ and $D_{L_{CO}}$ and (B) between $D_{L_{NO}}$ and Dm_{CO} are similar for patients (closed circles) and normal subjects (open symbols) normalized by body surface area (m^2). $D_{L_{CO}}$ was standardized to hemoglobin concentration of 14.6 g/dl and alveolar O_2 tension of 120 mmHg. Regression lines through the pooled data are (A) $D_{L_{NO}} = 4.16\ D_{L_{CO}} - 6.82$, $r^2 = 0.918$ and (B) $D_{L_{NO}} = 2.42\ Dm_{CO} - 1.87$, $r^2 = 0.865$. *(Reproduced with permission from Phansalkar AR, Hanson CM, Shakir AR, et al: Nitric oxide diffusing capacity and alveolar microvascular recruitment in sarcoidosis. Am J Respir Crit Care Med 169:1034, 2004.)*

Methods for Measuring the Diffusing Capacity

Several different techniques are used to measure the carbon monoxide diffusing capacity. In clinical settings the single breath method is utilized almost exclusively. The steady-state and rebreathing methods of determining $D_{L_{CO}}$ are employed primarily in research. The steady-state method usually is performed in subjects who are exercising, thereby limiting its clinical application in patients with restricted ability

to exercise. The rebreathing methodology requires rapid-responding gas analyzers and has technical requirements beyond those available in most clinical laboratories.

Single-Breath Method

With the single-breath technique the subject exhales to residual volume, inhales a maximal breath of 0.3 percent CO and a tracer gas (usually 10 percent helium) in air, holds the breath for approximately 10 s, and then exhales maximally. After sufficient expiration to clear the dead space, a gas sample is collected to estimate final alveolar CO and helium fractions. After inspiration, the alveolar partial pressure of CO falls exponentially as CO enters the capillary blood. The volume of CO absorbed in the lungs can be calculated from the volume of inspired gas and the initial and final concentrations of CO in alveolar gas. The rate of CO uptake during the breath-hold varies as a function of the alveolar $P_{A_{CO}}$, which falls throughout the breath-hold. Capillary CO pressure is assumed to be equal to zero. The single-breath diffusing capacity is calculated by

$$D_{L_{CO}} = \frac{60\ V_A}{t_{bh}(P_B - 47)} \cdot \ln \frac{F_{A_{CO\ initial}}}{F_{A_{CO\ final}}} \qquad (6)$$

where

60 = the number of seconds per minute
V_A = the alveolar volume of gas (ml_{STPD}) present in the lung at the start of the breath-hold
t_{bh} = the duration of the breath-hold (seconds)
P_B = the barometric pressure (mmHg)
$F_{A_{CO}}$ = the alveolar fraction of carbon monoxide at the initial and final times of the breath-holding period

The insoluble inert gas, usually helium, included in the inspired volume is diluted in the alveolar volume but is not absorbed in capillary blood. V_A is calculated from the dilution of the inert gas and the inspired volume (V_I)

$$V_A = V_I \frac{F_{I_{He}}}{F_{A_{He}}} \qquad (7)$$

where

$F_{I_{He}}$ and $F_{A_{He}}$ = the inspired and alveolar helium concentrations

The alveolar fraction of He and the final alveolar CO fraction are obtained by measuring CO and He concentrations in the expired alveolar gas sample. The initial alveolar CO fraction is calculated from the dilution of the inspired CO in the volume of gas present in the lung during the breath-hold,

$$F_{A_{CO\ initial}} = F_{I_{CO}} \frac{V_I}{V_A} \qquad (8)$$

where

$F_{I_{CO}}$ = the inspired CO fraction

The single-breath method requires some degree of patient cooperation to perform the necessary respiratory maneuvers. A patient with reduced lung volume may not have a vital capacity large enough to clear the dead space and provide a sufficient sample for analysis of alveolar gas concentrations. The ability to hold the breath for 10 s also limits applicability to some patients. Finally, this method can be employed only in the resting state since few patients can breath-hold during exercise. Despite these limitations, the single-breath $D_{L_{CO}}$ is the most practical and widely used method for measuring $D_{L_{CO}}$.

Measurement of Dm and V_c

Using values of θ_{CO} measured in vitro and values of $D_{L_{CO}}$ determined with different inspired O_2 concentrations, Eq. (5) can be solved for the membrane diffusing capacity (Dm_{CO}) and capillary blood volume (V_c). However, there is considerable uncertainty regarding values of θ, the rate of red cell uptake of gases that bind to hemoglobin. Most in vitro measurements of θ have utilized rapid reaction techniques that are flawed due to unstirred layers of fluid surrounding the red cells. This artifact is greater the more rapidly that the gas reacts with hemoglobin ($NO > O_2 > CO$). Furthermore, the rate of gas uptake by erythrocytes is influenced by the ability of the red cells to be deformed during passage through the pulmonary capillaries, a factor not present during in vitro measurements of θ. Mathematical models suggest that the rate of uptake of gases also depends on erythrocyte orientation and spacing within capillaries. Since the characteristics of erythrocyte transit in the capillary bed have not been defined, extrapolation of in vitro measurements to the in vivo situation introduces an element of uncertainty. Despite these reservations, solution of Eq. (5) using values of θ_{CO} determined in vitro yields values of Dm_{CO} and V_c that agree with independent estimates of these variables.

Several research groups have investigated the use of NO to determine the role of diffusion across the alveolar-capillary membrane in gas exchange. As noted previously, it is likely that the reaction of NO with hemoglobin contained in erythrocytes is so rapid that the only resistance to NO uptake is diffusion across the alveolar-capillary membrane. Thus, since $D_{L_{NO}}$ is equal to Dm_{NO}, the value of Dm_{CO} can be calculated from the relative solubilities and diffusion coefficients of NO and CO. The diffusion coefficients of the both gases are similar, but the aqueous solubility of NO is approximately twice that of CO. Therefore, Dm_{CO} is approximately one half of the value of $D_{L_{NO}}$ (Fig. 12-3*B*). This approach to estimation of Dm_{CO} has yielded results similar to determinations of Dm_{CO} using two levels of inspired oxygen and in vitro values of θ_{CO} as originally described by Roughton and Forester. These similar values of Dm_{CO} were obtained during simultaneous measurements of both CO and NO uptake, thereby insuring that experimental conditions were identical for both gases. Most recent measurements indicate that Dm_{CO} under resting conditions is 75 to 100 ml/min/mmHg in men. Values in women are slightly lower due to smaller lung volumes, but data in women are sparse.

Calculation of pulmonary capillary blood volume (V_c) from measurements of $D_{L_{CO}}$ is dependent upon the value of

θ_{CO} chosen for the computation. Using in vitro data for θ_{CO} yields values at rest of 75 to 100 ml for men and slightly less for women. V_c measured by the CO method is dependent upon the quantity of hemoglobin present in the capillary bed in addition to the actual capillary volume. Calculation of V_c assumes a normal hemoglobin concentration in capillary blood and variation in this parameter affects the $\theta_{CO}V_c$ component of D_{LCO}.

Dm and V_c have been estimated from morphometric data obtained from excised, fixed canine lungs. Calculations of D_{LCO} using these post-mortem morphometric values and in vitro values of θ_{CO} have yielded estimates of D_{LCO} that are much greater than measurements of D_{LCO} under resting conditions in the same intact animal. This discrepancy arises because morphometric measurements are obtained in maximally inflated lungs. The morphometric estimates reflect a fully recruited alveolar surface area and capillary blood volume, a circumstance seen during maximal oxygen uptake during exercise. When D_{LCO} calculated from morphometric data is compared to D_{LCO} measured in intact animals under conditions of maximum exercise, there is good agreement between the two estimates.

Factors Influencing Diffusing Capacity

The CO diffusing capacity originally was thought to reflect the resistance of the alveolar-capillary membrane to transfer of CO from the alveoli to capillary blood. The classic work of Roughton and Forster elucidated the influence of chemical reactions on transfer of CO. D_{LCO} may be a measure of decreased gas transfer caused by abnormal diffusion, but also can reflect reduction in hemoglobin concentration, nonuniform distribution of physiological properties throughout the lung, loss of lung tissue, or artifacts in measurement. Since multiple factors in addition to diffusion can affect D_{LCO}, in Europe this test is termed the CO transfer factor, rather than the CO diffusing capacity.

Hemoglobin Concentration

Capillary blood volume (V_c) is a prime variable in the diffusing capacity; its importance is due to the quantity of hemoglobin available to combine with CO within the capillary bed. The calculated value of V_c can be reduced directly by diseases that decrease capillary volume, but also can vary with the concentration of hemoglobin in blood. For this reason, the predicted D_{LCO} is corrected for alterations in hemoglobin concentration. For adult males and adolescents

$$\text{Predicted } D_{LCO} \text{ (Corrected)} = \text{Predicted } D_{LCO}(1.7\,\text{Hb}/(10.22 + \text{Hb})) \quad (9)$$

where

$$\text{Hb} = \text{hemoglobin concentration expressed in g/dL}$$

For adult women and children less than age 15, the factor of 10.22 in Eq. (9) is replaced by a factor of 9.38.

Alveolar Partial Pressure of Oxygen

As indicated previously, θ_{CO} depends on P_{O_2}, and increased alveolar P_{O_2} will reduce measured D_{LCO}. Therefore, D_{LCO} will be lowered if patients receive supplemental oxygen during the measurement. Conversely, reduced alveolar P_{O_2} will lead to an increment in measured D_{LCO}. This has led to the suggestion to apply a correction to D_{LCO} if the measurement was made with an altered inspired oxygen fraction or at altitude. Even when alveolar P_{O_2} is kept at a sea level value during the measurement, lifelong residents of a community located 10,000 feet above sea level have slightly greater diffusing capacities than sea-level residents. Short-term residence (6 weeks) at altitude does not cause an increase in D_{LCO}. Even after reacclimation to sea level, beagles raised at altitude still have slightly greater diffusing capacities than beagles raised at sea level. However, adult dogs taken to altitude for 3 years do not exhibit an increased D_{LCO}, suggesting that residence at altitude during growth is the basis for the increased D_{LCO}.

Body Position

D_{LCO} is 5 to 15 percent greater in the supine position than in the erect position. Blood volume shifts from the lower trunk and legs to the lungs in the supine position. Most of the increase in D_{LCO} appears to be due to a 13 to 27 percent increase in V_c accompanying the fluid shift. However, there is also a minimal increase in Dm_{CO} in the supine position. The effect of posture on D_{LCO} decreases with age, but the reasons underlying this observation remain unknown.

Exercise

D_{LCO} can increase as much as twofold during exercise. This increase is attributed to proportionally equal increases in both D_M and V_c. Both alveolar-capillary surface area and capillary volume are recruited by the increase in cardiac output that accompanies exercise. The transit time through the capillary bed decreases, but not to the same degree as would be predicted in a vascular bed with fixed resistance. The potential reduction in transit time is partially offset by recruitment and distention of the pulmonary capillary bed. Values of Dm_{CO} during exercise are essentially the same when calculated by either the Roughton-Forster method or from simultaneous measurements of D_{LCO} and D_{LNO}. Similar agreement is observed with values of V_c measured using both methods.

Theoretically, D_{LCO} must have a maximum that cannot be exceeded when the entire pulmonary capillary bed and alveolar surface have been recruited. This should lead to a plateau in measured D_{LCO} even though the level of exercise continues to increase. This has never been observed in humans. Using a unique animal preparation of conscious greyhounds exercising on a treadmill, Carlin and coworkers could not demonstrate a plateau in D_{LCO} with increasing exercise even though oxygen uptake reached a level of approximately 120 ml/kg/min. This level of O_2 uptake is almost twice that seen in highly trained humans. Thus, it seems unlikely that the diffusing capacity in humans reaches a plateau during maximal exercise, but this does not rule out the possibility

that gas exchange is limited by diffusion in this circumstance. Disequilibrium may occur before maximum recruitment of the diffusing capacity because capillary transit time may be less than the time required for O_2 exchange to be completed. Indirect evidence in humans suggests that blood may leave the capillary bed without attaining complete equilibrium between alveolar P_{O_2} and capillary P_{O_2} during maximal exercise at sea level.

Measurements of D_{LCO} after exercise have led to the interesting observation that D_{LCO} decreases by approximately 10 to 15 percent after strenuous exercise of any type. This decrement persists for at least 6 h but returns by 24 h to the level present before the exercise. The mechanism underlying this phenomenon has not been elucidated. Interestingly, despite the reduction in D_{LCO}, a second bout of exercise is not associated with decrements in blood oxygenation or maximal oxygen uptake compared to values obtained in the first period of exercise. Thus, it is uncertain if the reduction in D_{LCO} following exercise has physiological importance.

Alveolar Volume

D_{LCO} decreases with reduction in alveolar volume due to accompanying decreases in Dm_{CO} and V_c. This occurs with an inadequate inspiration to total lung capacity in persons with normal lungs, or with maximal inspiration in patients whose total lung capacities have been reduced by disease. In an effort to correct for alterations in alveolar volume rather than a true loss of diffusing capacity, some clinicians and investigators normalize D_{LCO} by dividing the observed D_{LCO} by the alveolar volume present during the measurement. This ratio of D_{LCO}/V_A will be a useful index only if two assumptions are valid. First, there must be an approximately linear relation between D_{LCO} and V_A. This assumption appears to be reasonable at lung volumes greater than 50 percent of total lung capacity, but not at lower lung volumes. Second, the relation between D_{LCO} and V_A must be directly proportional (i.e., a graph of D_{LCO} versus V_A must pass through the origin of the graph). This clearly is not the case. Multiple investigators have demonstrated that D_{LCO}/V_A is not constant in normal persons and varies as alveolar volume changes. Although frequently used, the D_{LCO}/V_A ratio alone does not provide a valid index of the effect of changes in alveolar volume.

Non-uniform Distribution of Physiological Properties

Calculations of D_{LCO}, regardless of the method used to make the measurement, implicitly assume that the lung is completely uniform with regard to ventilation, volume, perfusion, and diffusive properties. This requires that each alveolus possesses the same relationship between all these physiological properties—an assumption that is not completely valid even in normal, healthy persons. The most important factor determining CO uptake is the relationship of local diffusing capacity to local blood flow, the ratio of D_{LCO}/Q. In addition, computational models indicate that factors such as the alteration of shape or uneven distribution of erythrocytes during capillary transit will diminish gas exchange. Non-uniform distribution of these important physiological variables throughout the lung produces a decrease in diffusing capacity and, by analogy, a reduced ability to transfer oxygen from the inspired air to capillary blood. Transfer is further complicated by the nonlinear nature of the processes involved. For example, the oxygen dissociation curve of hemoglobin has a sigmoid shape and a change in alveolar P_{O_2} may have a large or a minimal effect on the quantity of O_2 exchanged depending on the absolute value of the P_{O_2}. Disruptions of these complex relationships among physiological parameters have variable effects on O_2 transfer. The contributions of individual pathophysiological deviations cannot be assessed by a global measurement such as the diffusing capacity. Thus, D_{LCO} provides a means of assessing overall oxygen transport but does not indicate specific defects in gas exchange.

Technical Considerations

Measurements of D_{LCO} have greater variation than spirometric observations such as the forced vital capacity (FVC) or forced expiratory volume in one second ($FEV_{1.0}$). Criteria for acceptable measurements of D_{LCO} have been based upon relative or absolute differences between repeated measurements. The American Thoracic Society/European Respiratory Society (ATS/ERS) consensus statement recommends reporting the average of two measurements, both of which agree within 3.0 ml/min/mmHg or within 10 percent of the higher measured value. Punjabi et al. reported that an absolute difference of 2.5 ml/min/mmHg between duplicate measurements could be achieved in 96 percent of patients. This criterion was deemed more reasonable than a percentage variation because it remained constant over a wide range of measured values in contrast to a changing percentage criterion. The strength of this study is in its size (over 6000 patients) and its performance during routine pulmonary testing in a clinical setting. A drawback to its universal application is that more than two determinations of D_{LCO} were required in one-half of patients to meet this criterion of acceptability.

The time of the breath-holding maneuver in the single-breath method requires patient cooperation. Because of non-uniform distribution of physiological variables, CO uptake does not occur in a strictly exponential fashion even in healthy persons. As a result, measured D_{LCO} decreases slightly with prolonged breath-hold in normal subjects. This decrement can be substantially greater in patients. The empirical breath-holding time of 10 s was chosen as a practical compromise to permit measurable CO uptake but still be feasible for patients to perform. Many laboratories set a breath-hold range of 9 to 11 s as acceptable, although the ATS/ERS consensus report accepts a range of 8 to 12 s.

Patients with lung disease often cannot perform rapid respiratory maneuvers mandated by the single-breath D_{LCO} measurement. Slower flow rates prolong the time required for inspiration and expiration. As a result, instantaneous, uniform mixing of alveolar contents assumed in the calculation

of D_{LCO} is not achieved. A series of three equations, rather than a single equation, more accurately describes conditions during CO uptake in this circumstance and minimizes errors. However, the calculations are more complex and may not be available in some automated, commercial equipment.

Most laboratories request that patients refrain from smoking for variable periods of time prior to measurement of D_{LCO} to avoid accumulation of CO in blood. Significant elevation of carboxyhemoglobin reduces measured D_{LCO} in two ways. First, the presence of carboxyhemoglobin produces a functional anemia, lessening the capacity of hemoglobin to bind O_2 or CO. This reduces the $\theta_{CO}V_c$ component of D_{LCO}. Second, calculation of D_{LCO} assumes that the back pressure of CO in the capillary is zero, and the gradient for CO transfer is equal to P_{ACO}. The presence of carboxyhemoglobin in blood produces an actual alveolar-capillary P_{CO} gradient less than that assumed in the calculation, thereby leading to a lower calculated value of D_{LCO}. Graham and colleagues measured the effect of experimental elevation of carboxyhemoglobin in normal individuals. Values of D_{LCO} obtained with the usual single breath calculation decreased approximately 1.5 percent from the true value for each 1.0 percent elevation of carboxyhemoglobin. Although algorithms are available to correct observed D_{LCO} for carboxyhemoglobin effects, it is preferable to make the measurement without a significant elevation of carboxyhemoglobin. Twelve hours of abstinence from smoking is advisable in patients who smoke extensively because carboxyhemoglobin levels as great as 6 to 12 percent are observed immediately following tobacco usage.

Controversies in Interpretation of D_{LCO}

As noted previously, D_{LCO} is affected by a number of circumstances. Alveolar P_{O_2} and body position do not present significant problems since a standard inspired P_{O_2} and the sitting position are utilized during measurements in most clinical laboratories. Equations to correct for alterations of alveolar P_{O_2} are available if needed. Empirical equations also can adjust the predicted value of D_{LCO} to compensate for anemia or polycythemia.

Variability in cardiac output and the alveolar volume present during the measurement provide more significant problems. The increases in D_{LCO} observed during exercise are the result of large increases in cardiac output. Clinical measurements of D_{LCO} are accomplished under resting conditions, minimizing but not obviating, variability in cardiac output. In addition, disease can alter the distribution of blood flow in the lung in patterns that do not match the distribution of diffusive properties. Unfortunately, measurements of pulmonary blood flow and its distribution are not measured conveniently in clinical laboratories. As a result, the effect of cardiac output on D_{LCO} may not be appreciated in routine determinations. The only practical alternative is to minimize conditions that might alter pulmonary blood flow.

Reduction in alveolar volume by disease processes is the largest potential source of error in interpreting D_{LCO}. Correction for the effect of altered alveolar volume has been attempted by reporting the ratio of D_{LCO}/V_A. However, this attempt to normalize measurements by alveolar volume leads to errors because D_{LCO}/V_A does not remain constant as alveolar volume changes. Stam and colleagues reported values of D_{LCO} and D_{LCO}/V_A obtained at different alveolar volumes in normal subjects. They recommend setting predicted values of D_{LCO} or D_{LCO}/V_A for patients with reduced alveolar volumes equal to values in normal subjects measured at the same reduced alveolar volume. This assumes that disease processes that reduce alveolar volume in patients produce the same changes in D_{LCO} as voluntary reduction in alveolar volume in normal subjects. In a subsequent report, they demonstrated this to be the case in patients with normal lung function tested prior to, during, and after undergoing treatment with bleomycin for malignancies. In these patients, the linear relationship of D_{LCO}/V_A measured at different alveolar volumes shifted downward in parallel fashion as bleomycin produced lung injury. This finding supports the adjustment of predicted values on the basis of reduced alveolar volumes in normal subjects since the slope of the D_{LCO}/V_A ratio in relation to V_A was the same before and after lung injury. These data were obtained by measuring D_{LCO} at a variety of alveolar volumes prior to and after the pulmonary insult, a situation that is rarely possible. Recent data obtained in patients with sarcoidosis also support the concept of using predicted values obtained at lower lung volumes in normal subjects. However, other reports in different clinical conditions suggest that some diseases may not affect D_{LCO} in the same manner as voluntary changes in normal subjects. These uncertainties have led to substantial controversy regarding the value of the ratio D_{LCO}/V_A. Final judgment will require collection of extensive data in a variety of disease states. Regardless of the outcome of this controversy, it is apparent that if D_{LCO}/V_A is to be used in the interpretation of measurements of D_{LCO}, there must be some adjustment of predicted values of D_{LCO}/V_A to reflect reductions in alveolar volume. Use of D_{LCO}/V_A alone as a correction for changes in alveolar volume will lead to errors in interpretation of the diffusing capacity.

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13

Blood-Gas Transport

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OXYGEN TRANSPORT

The circulatory system provides special mechanisms in order to deliver the large quantities of oxygen required by the peripheral tissues. The major factor is the presence of hemoglobin in blood. Reversible binding of O_2 greatly enhances the effective solubility of O_2 in blood compared with that in other body fluids. In addition to quantitative transport requirements, O_2 must be delivered at a pressure sufficient to allow for its diffusion to the intracellular mitochondria where it is utilized.

Oxygen Equilibrium Curve

The relationship between content and pressure for gases dissolved in blood is linear (Henry's law). Inert gases (e.g., nitrogen and argon) are carried only in the dissolved form in blood. Oxygen differs from inert gases because of its binding with hemoglobin. Four O_2 molecules can bind with each hemoglobin molecule but produce complex interactions that occur among the four heme moieties. Binding of an O_2 molecule to one heme site affects the affinity for ligands at other heme sites on the molecule. This results in an S-shaped content-pressure relationship, the *O_2 equilibrium curve* (also called the *O_2 dissociation curve*) of blood. This relationship also can be normalized to account for varying blood hemoglobin concentration by expressing O_2 content as a fraction of the maximum quantity of O_2 that can be bound to hemoglobin (percent saturation) as shown in Fig. 13-1. The physiological portion of the curve includes the partial pressures and contents normally seen in arterial blood and in the venous effluent of various organs under resting (Fig. 13-2) and exercising conditions. The flatness of the curve in the arterial range is an advantage because decrements in arterial P_{O_2} (as might be caused by lung disease or excursions to altitude) will still allow for a relatively normal arterial O_2 content as long as arterial P_{O_2} remains greater to or equal to 60 mmHg. Because of the steep nature of the equilibrium curve below 50 mmHg, increased O_2 extraction can be achieved with only a relatively modest decrease in partial pressure of oxygen. Thus, large quantities of O_2 can be released and blood P_{O_2} remains sufficiently high to support diffusion of O_2 into metabolizing tissues. The normal mixed venous O_2 content at rest is 4 to 5 ml/100 ml less than arterial content, providing substantial reserve for oxygen consumption during increased metabolic activity or decreased blood flow (Fig 13-2). However, the O_2 contents of venous blood leaving some organs, such as the heart, are substantially less than the mixed venous value and increased oxygen requirements are largely met through increasing blood flow to the organ. During exercise or in pathological circumstances, the arterial-mixed venous O_2 content difference may increase substantially to meet tissue oxygen requirements.

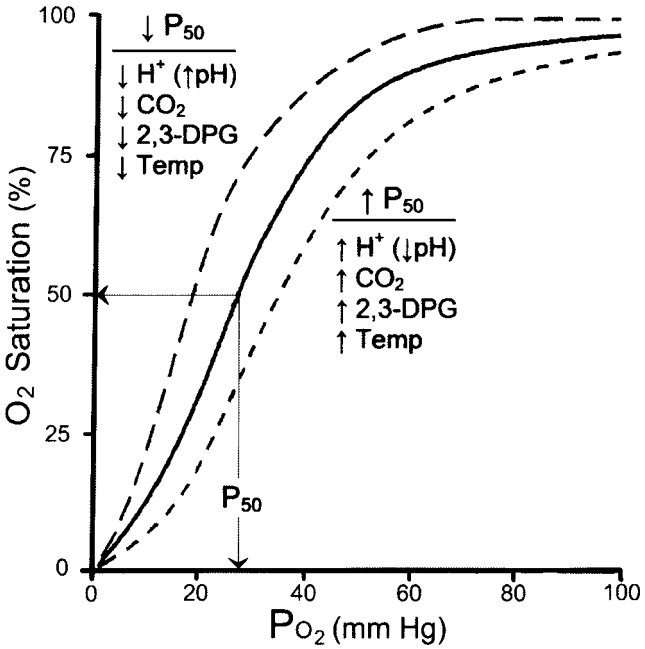

Figure 13-1 The oxygen equilibrium curve of human blood. The normal curve (solid line) has a P_{50} (P_{O_2} at 50 percent saturation) of 27 mmHg. The curve of fetal blood with increased oxygen affinity (decreased P_{50} of 19 mmHg) is indicated by the line with the long dashes. A curve with decreased oxygen affinity (increased P_{50} of 34 mmHg) as seen in severe anemia is indicated by the line with short dashes. The factors that decrease or increase P_{50} are shown to the left and right, respectively, of the equilibrium curves.

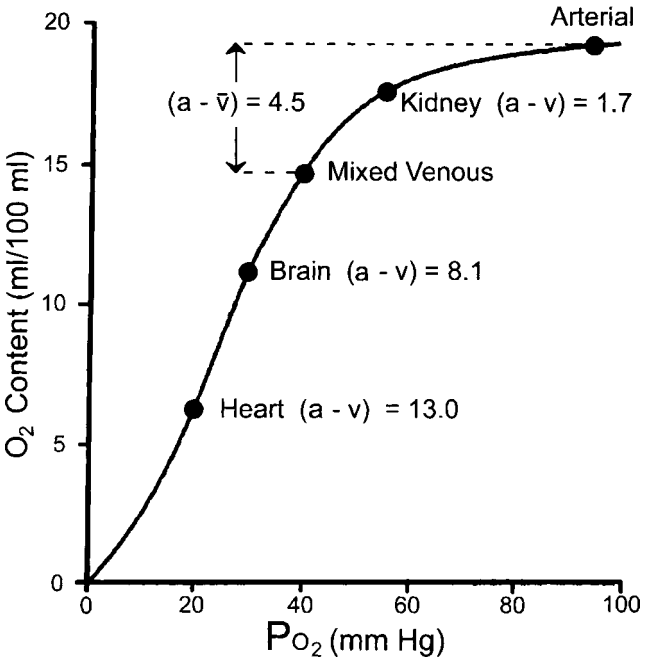

Figure 13-2 The normal oxygen equilibrium curve expressed in terms of O_2 content (ml/100 ml). The arterial-mixed venous ($a-\bar{v}$) content difference under resting conditions is indicated for the body as a whole. Differing (a-v) content differences for several organs are shown to emphasize the differing quantities of oxygen extracted by organs. In contrast to the kidney, the heart normally extracts large quantities of oxygen and little oxygen reserve in blood is available for changing conditions of metabolism or perfusion.

Oxygen Affinity

The relative affinity of hemoglobin for oxygen, and the position of the O_2 equilibrium curve can change under a variety of different physiological conditions. However, the sigmoid shape of the curve remains unchanged and the curve is either compressed or stretched along the P_{O_2} axis. The magnitude of change in O_2 affinity is indicated by the change in P_{50}, i.e., the oxygen partial pressure needed to achieve 50 percent saturation of hemoglobin. The curve to the left of the normal curve in Fig. 13-1 has a P_{50} of 19 mmHg, indicating that the O_2 affinity is high since the P_{O_2} required to half-saturate blood is less than normal (27 mmHg). Shifts of the equilibrium curve can be physiologically important—a left shift permits greater O_2 binding, an important factor in O_2 uptake in the fetus in utero or in normal lungs at altitude. However, an increased affinity (lower P_{50}) may impair tissue O_2 delivery since greater binding can limit O_2 release in the periphery. A shift of the curve to the right may enhance O_2 delivery to tissues because oxygen can be delivered while maintaining a higher-than-normal P_{O_2}, thereby promoting diffusion from the capillaries to the cells. Shifts in the curve in either direction are mediated by substances (carbon dioxide, hydrogen ions, and 2,3-diphosphoglycerate) that bind to hemoglobin and affect the affinity of hemoglobin for oxygen, even though they bind at different sites than O_2 molecules. Changes in temperature also can affect oxygen affinity, but the narrow temperature range seen in most clinical circumstances does not have much effect on the P_{50}. All these factors are additive in their effects on the position of the O_2 equilibrium curve (Fig. 13-1).

Bohr Effect

An increase in plasma (and therefore intracellular) hydrogen ion concentration [H^+] displaces the equilibrium curve to the right. Originally, the shift in the curve was attributed entirely to a change in pH, whether mediated by the addition of fixed acid or a change in P_{CO_2}. However, CO_2 does have a direct effect on O_2 affinity in addition to that associated with a change in pH. This direct effect results from binding of CO_2 to the hemoglobin molecule, but is small compared with the H^+ effect. A shift of the curve produced by a fixed acid, such as lactic acid, is less than the shift caused by CO_2 with the same change in pH.

The Bohr effect assists O_2 exchange to a small extent. In the tissues, addition of CO_2 to blood shifts the O_2 equilibrium curve to the right, releasing O_2 bound to hemoglobin. In the lungs, as the equilibrium curve returns to its normal position with excretion of CO_2, O_2 binding is enhanced. However, it has been calculated that the Bohr effect accounts for only 2 percent of total O_2 uptake at rest, less than assumed previously, because of the small pH changes that occur between arterial and venous blood.

2,3-Diphosphoglycerate

The human erythrocyte contains large quantities of 2,3-diphosphoglycerate (DPG), an organic phosphate that binds

to hemoglobin and affects O_2 affinity. Two mechanisms are involved: (1) DPG binds more readily to reduced hemoglobin than to oxyhemoglobin, tending to "hold" the molecule in the reduced configuration; and (2) at body pH DPG has four negative charges and reduces intraerythrocytic pH by the Donnan effect since this large, negatively charged molecule does not cross the cell membrane. This reduction in intracellular pH causes a decrease in affinity through the Bohr mechanism.

An increased concentration of DPG is a compensatory mechanism in some pathological states characterized by reduced O_2 transport. The shift of the O_2 dissociation curve to the right facilitates O_2 delivery, maintaining tissue oxygenation despite a reduction in the absolute quantity of O_2 delivered to peripheral tissues.

Blood stored in acid solution is deficient in DPG, leading to questions concerning its efficacy after transfusion in O_2 delivery. Fortunately, normal levels of DPG are regenerated in transfused cells within a day after transfusion. In the intervening period, O_2 exchange continues to take place even though efficiency may be somewhat reduced.

Abnormal Hemoglobins

Most abnormal hemoglobins per se have normal equilibrium curves despite differences in amino acid sequences. Although shifts of the equilibrium curve to the right are common in hemoglobinopathies, this alteration is usually due to other factors, such as increased DPG concentration or mean corpuscular hemoglobin concentration. However, a few mutant hemoglobins are exceptions to this rule and exhibit altered O_2 affinity.

Carbon Monoxide

Carbon monoxide (CO) poisoning is the most serious toxicological problem in the United States. Annually, it accounts for 40,000 hospital visits or admissions and 5000 deaths. One-half of the former and 90 percent of the latter events are intentional in origin. CO has an affinity for hemoglobin 200 to 250 times that of oxygen. Both CO and O_2 compete for the same ferrous binding sites on the heme components of hemoglobin. Although small quantities of CO are produced in the body by the breakdown of heme proteins, CO is important clinically only when it contaminates inspired air (as caused by cigarette smoke or automobile exhaust). The adverse effects of CO poisoning are twofold: (1) binding of CO to hemoglobin interferes with oxygen binding and produces a functional anemia; and (2) binding of CO to hemoglobin also increases the affinity of hemoglobin for oxygen, thereby shifting the oxygen equilibrium curve to the left. This increased affinity hinders the release of oxygen in the tissues. The combined effect of these two mechanisms produces a greater deficit in the ability to exchange O_2 than the loss of comparable O_2 carrying capacity in anemia.

Severe CO poisoning can be treated by increasing inspired oxygen concentration and, to a lesser extent, by increasing ventilation. The half-time of CO clearance from the body is 4 to 5 h, but inspiration of 100 percent O_2 reduces the half-time to less than 1 h by increasing the O_2 competition with CO for binding sites on hemoglobin. Inhalation of 5 percent CO_2 in O_2 has been used to treat CO poisoning. Although it was once postulated that CO_2 has a specific effect on CO release from hemoglobin, it has now been demonstrated that the faster elimination of CO while breathing a CO_2-O_2 mixture is the result of the hyperventilation produced by CO_2 inhalation. If patients treated with CO_2-O_2 mixtures cannot increase ventilation sufficiently to avoid respiratory acidosis during CO_2 inhalation, this treatment can be dangerous. For this reason, the treatment of choice for CO poisoning is inhalation of 100 percent O_2.

Studies of the benefit of hyperbaric oxygenation in treatment of CO poisoning have produced equivocal results because of problems with methodology and small sample size. A recent study by Weaver and colleagues has produced encouraging results supporting treatment with 100 percent oxygen at 2 to 3 atmospheres pressure for three 2 to $2^1/_2$ hour periods delivered over the first 24 hours after reaching a hyperbaric facility. In this study, cognitive impairment was significantly lower (25 percent vs. 46 percent) at 6 weeks and one year (18 percent vs. 33 percent) after CO exposure in those patients treated with hyperbaric oxygenation as compared with control subjects. Delayed neurological sequelae, especially cognitive dysfunction, are the most serious complications of CO toxicity in survivors. Although further study is required to confirm the value of hyperbaric oxygen therapy, many experts currently recommend its use, if available, for pregnant individuals who have had 20 percent of hemoglobin sites bound by CO (COHb) or non-pregnant patients who have experienced 40 percent COHb levels or have lost consciousness.

In the past there has been considerable controversy regarding the impact of low-level CO exposure, but recent studies have suggested that 5 percent COHb can impair exercise performance in healthy individuals. Patients with cardiac disease may have adverse effects associated with COHb levels as low as 6 percent. Further investigation is required to better define the effects of low concentrations of CO in the atmosphere.

CARBON DIOXIDE TRANSPORT

Carbon dioxide (CO_2) is produced principally by aerobic metabolism, but also is generated in the buffering of hydrogen ions by intracellular and extracellular bicarbonate ions (HCO_3^-). Bicarbonate stores are utilized to buffer organic acids, such as lactic acid and ketoacids, generated by anaerobic metabolism, starvation, and uncontrolled diabetes. CO_2 produced by these mechanisms in tissues diffuses into capillary blood and is carried in chemical combination and physical solution to the lungs where it is eliminated in the expired ventilation (see Chapter 12). As is the case with the transport of O_2 by blood, most CO_2 is not carried as the gas itself, but rather in several chemical forms directly or indirectly dependent

on hemoglobin. CO_2 is not an acid but forms carbonic acid in combination with water and needs to be eliminated continuously by the lungs to avoid acidosis. Body acid-base status is maintained by a balance between excretion of CO_2 in the lungs and renal regulation of body HCO_3^- stores.

Carbon Dioxide Equilibrium Curve

The relationship between blood content and partial pressure is considerably different for CO_2 compared with O_2. The total quantity of CO_2 contained in arterial blood is more than twice that of O_2 despite the generally lower CO_2 partial pressures that are involved. Because the slope of the CO_2 equilibrium curve is quite steep, CO_2 partial pressures in arterial and venous blood normally range between 40 and 50 mmHg in contrast to large arterial-venous differences in blood P_{O_2}. The entire CO_2 curve is curvilinear, but over the range encountered under normal conditions the content-pressure relationship is nearly linear (Fig. 13-3). This characteristic helps maintain efficiency of CO_2 exchange when mismatching of ventilation to blood flow occurs in the lungs. Despite the 20-fold greater solubility of CO_2 compared with oxygen, there still must be transport of CO_2 in blood in other than simple physical solution if CO_2 transport is to be maintained without large increases in cardiac output and/or venous P_{CO_2}. The total content of CO_2, i.e., the vertical axis of the CO_2 equilibrium curve, is the sum of three forms: dissolved CO_2, bicarbonate ion and carbamate compounds (see Chapter 12).

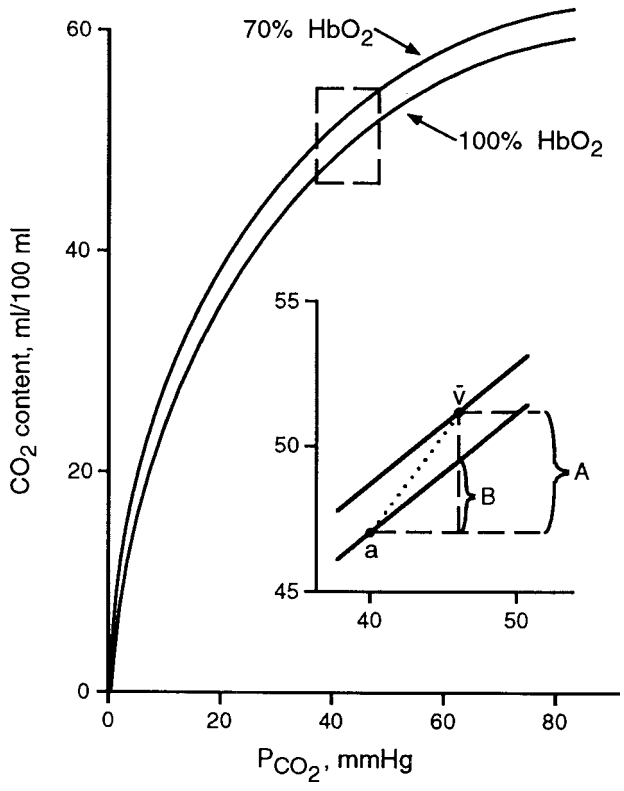

Figure 13-3 The carbon dioxide equilibrium curves of completely oxygenated (100 percent HbO_2) and partially oxygenated (70 percent HbO_2) human blood. The inset shows the enhancement of pulmonary CO_2 exchange by the Haldane effect. Mixed venous ($\bar{v}$) and arterial (a) points are shown. The CO_2 exchange resulting from the Haldane effect is the difference between the total ($\bar{v}$-a) difference *(A)* and the exchange that would occur without the Haldane effect *(B)*.

Dissolved Carbon Dioxide

Approximately 5 percent of total CO_2 content is transported in physical solution in plasma and red cell water. This dissolved form is critical for CO_2 transport because only molecular CO_2 can rapidly cross cell membranes to be excreted in the lungs. The partial pressure of carbon dioxide, P_{CO_2}, is directly proportional to the quantity of dissolved CO_2. It is indirectly related to CO_2 content through the equilibrium curve.

Bicarbonate

Under the influence of the enzyme carbonic anhydrase (CA) contained within the cytosol of the erythrocyte, approximately 80 to 90 percent of CO_2 entering blood from the tissues is rapidly converted into bicarbonate ion (HCO_3^-) inside the red cell

$$CO_2 + H_2O \overset{CA}{\leftrightarrow} H_2CO_3 \leftrightarrow H^+ + HCO_3^- \qquad (1)$$

Catalysis of this otherwise very slow reaction permits rapid interconversion between CO_2 and HCO_3 so that large quantities of CO_2 can be absorbed by blood in tissues and transported to the lungs. Although the isoenzyme CA I is present in high concentration in erythrocytes, its activity in limited by intracellular chloride ion. Another isoenzyme, CA II, is present in only one-sixth the concentration of CA I within red cells, but CA II is not inhibited by chloride ion and has intrinsic activity sevenfold greater than CA I. CA II is responsible for almost all the catalysis of the CO_2-bicarbonate reaction in vivo. Hydrogen ions generated by the conversion of CO_2 to HCO_3^- must be buffered to prevent large changes in pH and limitation of CO_2 uptake. In blood, this is accomplished by proton binding to hemoglobin, enhanced to a significant degree by the simultaneous off-loading of oxygen (the Haldane effect; see below).

A rate-limiting build-up of bicarbonate in the red cell as CO_2 enters blood is avoided by one-for-one electrically neutral exchange across the red cell membrane of intracellular bicarbonate for plasma chloride. The latter exchange is mediated by an integral membrane glycoprotein, band 3 protein (also known as AE1, i.e., anion exchanger 1). It has been postulated that exchange is facilitated by binding of CA II, but not CA I, to a specific carboxyl-terminal site on the anion exchanger. The efficacy of CO_2 exchange would be enhanced since bound CA II provides local substrate for transport of HCO_3^- out of the red cell in peripheral tissues and conversion of HCO_3^- entering the cell to CO_2 in the lung. The close association of these two proteins would avoid limitation of HCO_3^- exchange as a result of impaired diffusion of bicarbonate ions through the viscous interior of the erythrocyte.

Further evidence is needed to support possible binding of CA II to the exchanger.

Carbamates

Less than 10 percent of CO_2 binds directly to terminal α-amino groups of hemoglobin as carbamate compounds. Because reduced hemoglobin binds more CO_2 than the oxygenated protein, more CO_2 can be carried in venous blood at any given P_{CO_2} than in oxygenated arterial blood. The physiological importance of this process would be twice as great except that binding of DPG to hemoglobin limits carbamate formation. However, changes in carbamate concentration still account for 10 to 15 percent of the difference between arterial and venous CO_2 contents during normal gas exchange.

Haldane Effect

Oxygenated blood at any P_{CO_2} has a lower CO_2 content than reduced blood at the same partial pressure. This difference, illustrated in Fig. 13-3, is known as the *Haldane effect*. The effect of oxygenation on CO_2 transport is analogous to the Bohr effect, but has far greater physiological importance. Deoxygenation of hemoglobin permits greater binding of H^+ since reduced hemoglobin is a weaker acid (stronger base) than oxyhemoglobin. In peripheral blood, hydrogen ions formed by the conversion of CO_2 to HCO_3^- are buffered by binding to hemoglobin. As a result of this proton binding, at any P_{CO_2} more HCO_3^- is present in blood and total CO_2 content is greater when hemoglobin is reduced. As mentioned previously, direct CO_2 binding to hemoglobin as carbamate compounds is also facilitated in deoxygenated blood, increasing the total CO_2 content in deoxygenated as compared with oxygenated blood. At normal H^+ and DPG concentrations, approximately 40 percent of the Haldane effect is the result of direct binding of CO_2; the remainder is the result of H^+ binding to hemoglobin. The relative contribution of carbamate compounds to the Haldane effect is inversely proportional to the combined effect of H^+ and DPG, increasing as their concentrations decrease, and conversely decreasing as $[H^+]$ and [DPG] become greater.

The physiological importance of the Haldane effect is illustrated in the inset in Fig. 13-3. The change in CO_2 content between normal arterial and mixed venous CO_2 partial pressures in oxygenated blood is indicated by bracket B on the right side of the inset. However, under physiological circumstances, the CO_2 equilibrium curve shifts from the position of the partially oxygenated curve to that of fully oxygenated blood. Thus, as is shown by bracket A on the right side of the inset, the shift from one curve to the other produces a greater change in blood CO_2 content between arterial and mixed venous partial pressures. As a result, changes in venous pH and P_{CO_2} are minimized despite transport of large amounts of CO_2.

Quantitatively, the Haldane effect has a much larger effect on gas transport under physiological circumstances than does the Bohr effect. Under resting normoxic conditions, the Bohr effect is responsible for only a few percent of O_2 uptake in the lung and 10 to 15 percent in the systemic capillaries. Binding of oxygen to hemoglobin alters both binding of CO_2 directly as carbamate compounds and the overall pK (buffering capacity) of hemoglobin. The first effect accounts for virtually all the contribution of carbamate compounds to CO_2 transfer between tissues and the lungs. The remainder derives from the reduced buffering capacity of hemoglobin as it is fully oxygenated. Model calculations and in vitro data suggest that the Haldane effect accounts for 40 to 50 percent of total CO_2 exchange under normal conditions. Either cardiac output or the difference between arterial and venous (and therefore tissue) P_{CO_2} would have to increase by a similar percentage if the Haldane effect were not operative to aid in transport of CO_2.

Kinetic Aspects of CO_2 Exchange

It is conventionally taught that CO_2 equilibration reaches completion very quickly during capillary gas exchange because diffusion exchange of CO_2 occurs 20 times more rapidly than O_2. If CO_2 transport by blood were accomplished solely as dissolved CO_2, this would be correct. However, chemical reactions and exchange rates involved in CO_2 transport occur far more slowly than diffusion of CO_2 across membranes (Table 13-1). These individual rates provided in the table are less than the usual transit times of blood through the pulmonary capillaries. However, when more than one reaction occurs in series, the approach to equilibrium is substantially slower than the individual rates of single processes. Although controversy persists regarding the true magnitude and

Table 13-1

Rates of CO_2 and O_2 Exchange Processes

Process	Time to 90% Completion (S)
Diffusion of CO_2	0.001–0.003
Carbamate-CO_2 binding/release*	0.250–0.300
Chloride-bicarbonate exchange	0.400–0.500
Bohr/Haldane effects	0.250
CO_2 hydration/HCO_3^- dehydration	
Uncatalyzed	40.0
Catalyzed by carbonic anhydrase	0.005
Uptake of O_2 by red cells	0.050–0.100

** This value reflects the predominant rate-limiting effect of O_2 uptake by red cells, because all the carbamate-CO_2 contribution is O_2 exchange-dependent.*

physiological significance of failure to reach end-capillary CO_2 equilibrium, it is becoming increasingly clear that CO_2 exchange cannot be considered fully complete in the duration of normal capillary transit times.

The uncatalyzed rates of CO_2 hydration and HCO_3^- dehydration are exceedingly slow but are accelerated sufficiently by carbonic anhydrase. The degree of catalysis by carbonic anhydrase is so great that more than 99 percent inhibition is necessary before CO_2 hydration becomes a limiting factor in CO_2 exchange. The rate of red cell anion exchange, on which significant CO_2 exchange depends, may be rate-limiting even at rest in normal individuals. As capillary transit times decrease, the potential exists for significant CO_2 disequilibrium between arterial blood and alveolar gas and between peripheral tissues and venous blood. Drugs interfering with either carbonic anhydrase (acetazolamide, methazolamide) or red cell anion exchange (high-dose salicylate or loop diuretic therapy) may cause end-capillary CO_2 disequilibrium. Since the Haldane effect plays a large role in CO_2 exchange and is dependent upon prior completion of O_2 exchange, delay in O_2 exchange magnifies any delay in reaching CO_2 equilibrium.

The physiological consequences of any in vivo CO_2 end-capillary disequilibrium at rest in a healthy person are minimal. P_{CO_2} gradients between blood and tissues or between blood and the alveoli are fairly small (4 to 8 mmHg), and a lack of equilibration that would raise P_{CO_2} can be countered easily by slight increases in ventilation and/or cardiac output. At rest lung CO_2 equilibration is about 97 percent complete, which would lead to less than a 1 mmHg difference between arterial and alveolar P_{CO_2}. With maximal exercise, equilibration likely is more impaired and the arterial-alveolar P_{CO_2} difference is larger. However, if normal ventilatory and cardiac responses are limited, and/or parenchymal lung disease exists, then significant CO_2 retention possibly could develop. It should also be noted that with severe $\dot{V}_A/\dot{Q}$ mismatching or shunting, significant arterial-alveolar P_{CO_2} differences can occur which have been ascribed to these factors alone and not to end-capillary CO_2 disequilibrium.

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14

Acid-Base Balance

Stanley Goldfarb • Kumar Sharma

Regulation of $[H^+]$ is of crucial importance for maintenance of normal cellular functions. The normal $[H^+]$ is maintained at about 40 neq/L. When there is even a small change in the $[H^+]$, intracellular proteins gain or lose H^+ ions resulting in alterations in charge distribution, which may affect molecular structure and protein function. The hydrogen ion concentration in bodily fluids is largely regulated by the ratio of the concentrations of carbon dioxide and bicarbonate. This is predicated upon the relationship demonstrated in the Henderson-Hasselbalch equation:

$$pH = pKa + \frac{[HCO_3^-]}{0.03\,P_{CO_2}} \qquad (1)$$

where

$pH = -\log[H^+]$ (the H^+ concentration measured in moles per liter)

$pKa = 6.10$

Whereas the lungs are responsible for modulating arterial P_{CO_2}, the kidneys are primarily responsible for modulating the concentration of bicarbonate in plasma. In concert these organs maintain a stable extracellular acid-base milieu that is readily assessed by measuring arterial pH.

The normal internal environment is maintained within narrow limits: The arterial blood pH is kept remarkably close to 7.40, the bicarbonate concentration is maintained around 24.5 mEq/L, and the P_{CO_2} is maintained at about 40 mmHg. Deviations of the pH with accompanying changes in the P_{CO_2} and $[HCO_3^-]$ result in the four major categories, as denoted in Table 14-1. Metabolic acidosis is characterized by acidemia (pH less than 7.35) that is due to a reduced plasma $[HCO_3^-]$. Metabolic alkalosis is characterized by an alkalemia (pH greater than 7.45) that results from an elevation in the plasma $[HCO_3^-]$. Respiratory acidosis is due to hypoventilation, resulting in a net increase in P_{CO_2} (hypercapnia) and a concomitant fall in pH. Respiratory alkalosis is due to primary hyperventilation leading to a fall in P_{CO_2} (hypocapnia) and a rise in pH.

In this chapter, we first review the basic physiological roles that the kidneys and lungs play in maintaining acid-base

Table 14-1

Patterns of P_{CO_2} and HCO_3 Changes in Acid-Base Disorders

Primary Disturbance	Initial Abnormality	Compensatory Response	Expected Compensation
Metabolic acidosis	Decreased pH, decreased $[HCO_3^-]$	Decreased P_{CO_2}	$P_{CO_2} = 1.5 \times [HCO_3^-] + 8 \pm 2$ (Winter's formula)
Metabolic alkalosis	Increased pH, increased $[HCO_3^-]$	Increased P_{CO_2}	P_{CO_2} increases 0.6 mmHg per mEq/L rise in $[HCO_3^-]$
Respiratory acidosis	Decreased pH, increased P_{CO_2}	Increased $[HCO_3^-]$	Acute: $[HCO_3^-]$ increases 1 mEq/L per 10 mmHg rise in P_{CO_2} Chronic: $[HCO_3^-]$ increases 3.5 mEq/L per 10 mmHg rise in P_{CO_2}
Respiratory alkalosis	Increased pH, increased P_{CO_2}	Decreased $[HCO_3^-]$	Acute: $[HCO_3^-]$ falls 2 mEq/L per 10 mmHg fall in P_{CO_2} Chronic: $[HCO_3^-]$ falls 5 mEq/L per 10 mmHg fall in P_{CO_2}

balance and then discuss their adaptation in primary acid-base disorders. The following section then focuses on clinical application of physiological concepts in analyzing acid-base problems as encountered by the clinician.

BASIC PHYSIOLOGY OF THE ROLE OF THE KIDNEY IN ACID-BASE BALANCE

Normal metabolism generates large quantities of volatile acid (CO_2) and nonvolatile acid daily. The complete metabolism of carbohydrates and fats generates 15,000 mmol of CO_2 daily. This leads to acid generation as the CO_2 combines with H_2O to form carbonic acid (H_2CO_3). As the volatile fraction is excreted by the lungs during respiration, acid accumulation does not occur. The nonvolatile or "fixed" fraction is produced at a rate of 1 mEq/kg per day. The major source of the nonvolatile acid fraction is the oxidation of sulfur-containing proteins from the diet to sulfuric acid. If this amount of nonvolatile acid is not excreted, life-threatening metabolic acidosis ensues. Therefore, for a normal individual to maintain acid-base balance, 50 to 100 mEq of nonvolatile acid must be excreted daily by the kidneys.

The addition of 50 to 100 mEq of acid requires initial buffering before it can be excreted. Whole-body buffering capacity is composed of interacting buffer systems: the bicarbonate and nonbicarbonate buffers (Buf^-), consisting primarily of hemoglobin, proteins, and phosphates. The sum of the buffer anions $[HCO_3^-]$ and $[Buf^-]$ is the total buffer base and defines total-body buffering capacity. Since all body buffer systems are in equilibrium, a change in the serum $[HCO_3^-]$ reflects concurrent changes in the other body buffer systems. The importance of bicarbonate in buffering is due to its relationship with CO_2. As H^+ are buffered by HCO_3^-, there is a decrease in the $[HCO_3^-]$ and a concurrent increase in the dissolved $[CO_2]$. As the $[CO_2]$ can be excreted by the lungs to maintain a constant $[CO_2]$, this substantially increases the buffering capacity of bicarbonate. Since the kidney plays a major role in controlling the $[HCO_3^-]$ and $[HCO_3^-]$ is easily measured in serum, the HCO_3^- anion is a useful parameter to evaluate the renal response to an acid load.

The H^+ ions released from the dissociation of sulfuric acid are titrated by blood bicarbonate and nonbicarbonate buffers.

$$\begin{aligned} H_2SO_4 + 2NaHCO_3 &\rightarrow Na_2SO_4 + 2H_2CO_3 \\ &\rightarrow 2H_2O + CO_2 \end{aligned} \qquad (2)$$

Although the added H^+ is excreted via CO_2 elimination by the lungs, this occurs at the cost of depletion of $[HCO_3^-]$. In order to *replenish* the consumed base, bicarbonate is reabsorbed by the kidneys and returned to the blood. This process does not accomplish the replacement of consumed base, since continuous metabolic production of acid will ultimately decrease the available base present. The process of renal *regeneration* of base requires the urinary excretion of acid or H^+ ions in the absence of any urinary bicarbonate. For every H^+ ion excreted, bicarbonate is returned to the body. If there is any bicarbonate in the urine, there will be a net gain of H^+. Therefore, the kidney has two major functions in this context: (a) reabsorption of all the filtered bicarbonate—this takes place primarily in the proximal tubule; and (b) the base consumed by metabolism must be generated in the process of urinary acid excretion. This takes place in the distal

portions of the nephron, distal collecting tubule, and collecting ducts.

BICARBONATE RECLAMATION

The proximal tubule is responsible for reclaiming 70 to 90 percent of the filtered bicarbonate. This may occur either by direct bicarbonate absorption at the proximal tubule or via proton secretion into the lumen of the tubule. The latter mechanism appears to be the predominant pathway. Protons generated from intracellular water are secreted into the tubular lumen via a Na^+/H^+ antiporter, where they can then combine with filtered bicarbonate to form carbonic acid. The carbonic acid is dehydrated by carbonic anhydrase in the brush border of the proximal tubular epithelium to form CO_2 and H_2O. The CO_2 diffuses into the cell and combines with hydronium ion (OH^-) to form bicarbonate (via intracellular carbonic anhydrase). The bicarbonate is transported in the basolateral direction back into the blood via a Na^+/HCO_3^- cotransporter (Fig. 14-1). It is important to understand that this process reclaims filtered bicarbonate but does not result in a net gain of bicarbonate. At the end of the proximal tubule there is a lowering of the luminal pH from 7.26 to 6.70, and the bicarbonate concentration is lowered from 24 to 8 mEq/L. The fluid delivered to the distal tubule is essentially the same with respect to pH and bicarbonate concentration as that which leaves the proximal tubule. The reclamation of the remaining bicarbonate occurs in the thick ascending limb and the outer medullary collecting tubule. At the collecting tubule, H^+ secretion occurs primarily by an H^+-ATPase pump at the luminal membrane and bicarbonate entry to the blood is via a Cl^-/HCO_3^- exchanger at the basolateral membrane.

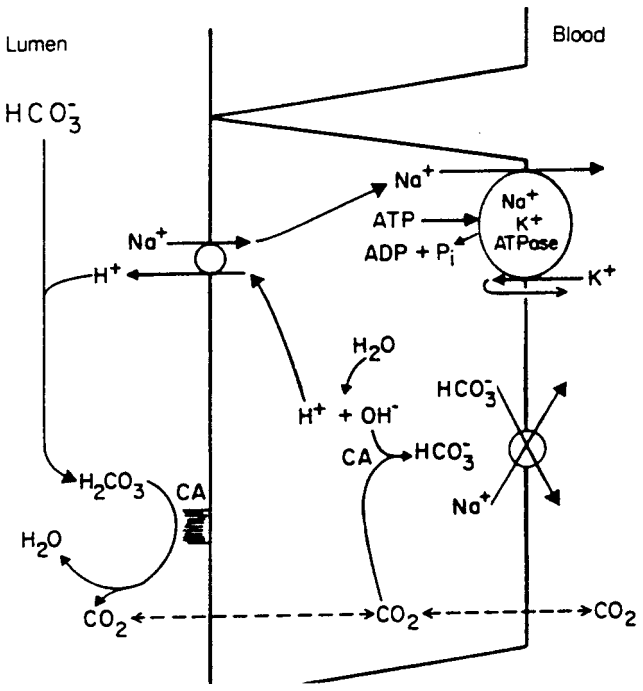

Figure 14-1 Schematic representation of proximal tubular reclamation of filtered bicarbonate. In the lumen, filtered bicarbonate reacts with secreted H^+, generating carbonic acid, which is dehydrated by carbonic anhydrase (CA), located on the brush border. The cell secretes H^+ by a process that exchanges H^+ for filtered Na^+. The source of secreted H^+ is water, which in turn generates OH^- and subsequently bicarbonate because of the presence of intracellular CA. Bicarbonate exits the basolateral side of the cell linked in some fashion with Na^+; sodium is also actively pumped out of the cell.

The crucial role of carbonic anhydrase is demonstrated by the fact that carbonic anhydrase inhibitors (i.e. acetazolamide) result in bicarbonate wasting and the generation and maintenance of metabolic acidosis. The most physiologically important regulators of reclamation of bicarbonate are the pH, the P_{CO_2} and the extracellular volume status of the patient. In states of acidosis, there is enhanced luminal Na^+/H^+ exchange that may be mediated by an increase in intracellular H^+ ions and the number of new exchangers as well as increased activity of the Na^+/HCO_3^- cotransporter at the basolateral membrane. Elevation of the P_{CO_2} will promote higher proximal tubular concentration of CO_2 and lead to intracellular acidosis, giving rise to further secretion of H^+ ions and reclamation of bicarbonate. If there is volume depletion, there will be avid Na^+ reabsorption at the proximal tubule in exchange for H^+ and thus greater reabsorption of bicarbonate. Other factors that are important include the luminal bicarbonate concentration, tubular flow rate, and serum potassium.

NET RENAL ACID EXCRETION

Net excretion of acid occurs primarily in the distal nephron and is largely mediated by the active secretory pumps, H^+-K^+ ATPase and H^+-ATPase. The latter appears to be linked in some way to Cl^- reabsorption to preserve electroneutrality. By definition, to produce net H^+ excretion the secreted H^+ will have to be excreted in processes that do not consume bicarbonate.

To achieve net secretion of protons in the luminal fluid of the distal nephron requires association of the protons with urinary buffers other than bicarbonate. Although secreted protons lower the urinary pH to 4.5 resulting in a 3-pH unit differential from arterial pH (a thousandfold increase in H^+ concentration), the quantity of acid excreted as free H^+ is trivial. For example, daily excretion of 2 L of urine with a pH of 5 would result in excretion of only 0.02 mEq of dissociated H^+ ions in contrast to the 50 to 100 mEq of H^+ generated each day from dietary sources. The nonbicarbonate buffers present in the urine that carry out the role of net acid excretion are the titratable buffers, primarily phosphate, which accounts for 40 percent of net acid excretion, and ammonia, which accounts for the remainder.

The ability of phosphate to act as proton acceptor in the urine is based on its pKa of 6.8. As the urine pH is lowered below the pKa of 6.8, there is conversion of HPO_4^- to

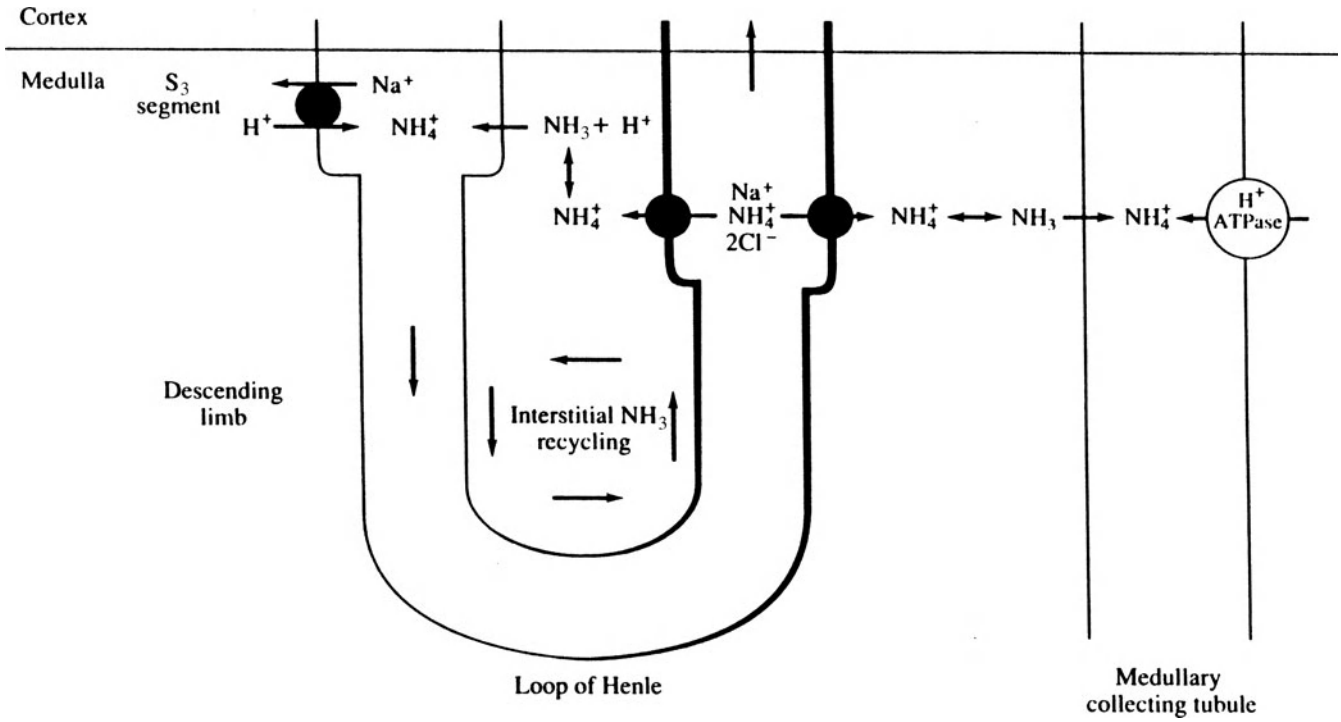

Figure 14-2 Schematic representation of ammonia recycling within the renal medulla. Although NH_4^+ production occurs predominantly in the proximal tubule, most of the NH_4^+ is then reabsorbed in the thick ascending limb, apparently by substitution for K^+ on the Na^+-K^+-$2Cl^-$ carrier in the luminal membrane. Partial dissociation into NH_3 and H^+ then occurs in the less acid tubular cell. The NH_3 diffuses into the medullary interstitium, where it reaches relatively high concentrations; it then diffuses back into those segments that have the lowest pH and therefore have the most favorable gradient: The S_3 segment of the late proximal tubule and, more important, the medullary collecting tubule, where the secreted NH_3 is trapped as NH_4^+ and then excreted. *(From Rose B: Clinical Physiology of Acid-Base and Electrolyte Disorders, 4th ed. New York, McGraw-Hill, 1994, with permission.)*

H_2PO_4. This transfer continues until the urine pH reaches 5.5, at which point almost all the phosphate present is in the associated form, H_2PO_4. Other components of this system are uric acid (pKa = 5.75) and creatinine (pKa = 4.97). Although the titratable buffers account for a sizable fraction of net basal acid excretion, they cannot increase in amount to enhance acid excretion in settings of acid loading.

However, the rate of ammonium ($NH4^+$) production and excretion can be varied according to physiological needs. Ammonia (NH_3) combines with H^+ to form ammonium, which is trapped in the collecting tubule lumen and excreted in the urine. The pKa for this reaction is 9.0. The majority of ammonia is synthesized in the proximal tubular cell by the enzymatic breakdown of glutamine. Glutamine is actively taken up by the proximal tubule at the apical and basolateral membranes and transported to mitochondria. Deamidation by glutaminase forms ammonium and glutamate. The latter is further metabolized by glutamate dehydrogenase to form ammonium and α-ketoglutarate. Metabolism of α-ketoglutarate to bicarbonate in the liver leads to return of bicarbonate to the systemic circulation (Fig. 14-2).

The ammonium that is formed is transported into the proximal tubular lumen via the Na^+-H^+ antiporter, working in this case as a Na^+-NH_4^+ antiporter. The ammonium is then reabsorbed in the thick ascending limb by substitution of NH_4^+ for K^+ on the Na^+-K^+-$2Cl^-$ carrier. The intracellular ammonium in the thick ascending limb cell is then dissociated into ammonia and H^+. The ammonia accumulates in the medullary interstitium and is finally secreted into the lumen of the medullary collecting tubule. At this site, due to the low lumen pH (4.5 to 5), the ammonia accepts a H^+ and is trapped in the lumen and excreted in the urine as NH_4Cl.

The importance of the ammonia system is that it can be regulated by the systemic acid-base state. An acid load initially leads to an increase in ammonium excretion within 2 h due to formation of more acid urine, which enhances ammonia diffusion into the lumen at the collecting duct. After 5 to 6 days there is maximal NH_4^+ excretion due to increased glutamine uptake and enhanced activity of phosphate-dependent glutaminase and glutamate dehydrogenase to produce more ammonium in the proximal tubule. This is presumably mediated by intracellular acidosis of the proximal tubular cell. The net effect is that NH_4^+ excretion can increase from about 30 mEq per day to as much as 300 mEq per day in severe metabolic acidosis. The plasma potassium is an important regulator of ammonia synthesis as hyperkalemia results in a transcellular influx of K^+ in exchange for H^+, resulting in lowering of the intracellular H^+ concentration, thus causing intracellular alkalosis with consequent inhibition of ammonia synthesis. Hypokalemia would have the opposite effect. Urinary acidification is also very important, since an inability to lower urinary pH results in a reduction in NH_3 trapping in

the collecting duct lumen and a subsequent inhibition of the degree of ammonium formation. Inadequate acidification of the urine also inhibits H_2PO_4 formation.

RESPIRATORY CONTRIBUTION TO ACID-BASE BALANCE

The major roles of the lungs in acid-base balance are to excrete the CO_2 produced daily by aerobic metabolism and compensate for primary metabolic acid-base disturbances by altering the rate and depth of ventilation. The CO_2 generated by the tissues diffuses into the plasma, at the peripheral capillaries, and is present in the blood in three compartments. Part of the CO_2 remains in the gas phase, but the amount is limited by the solubility coefficient of CO_2 (0.03 mM/mmHg). CO_2 may also react with amino groups of proteins and form carbamino compounds. The majority of the CO_2 is carried within red blood cells. The red cells contain carbonic anhydrase, which hydrates the CO_2 and thus forms carbonic acid which dissociates to H^+ and HCO_3^-. The protons are buffered by hemoglobin, which has an increased affinity for H^+ at the low oxygen tension present in the peripheral capillaries and venous blood. The bicarbonate produced in the red cell leaves the cell in exchange for chloride. This chloride shift is a characteristic response to elevation of CO_2 in the blood, resulting in an acute elevation of bicarbonate in exchange for a drop in serum chloride. When the blood enters the pulmonary circulation, the enhanced oxygenation of hemoglobin promotes release of bound H^+. The H^+ and HCO_3^-, via carbonic anhydrase, combine to reform CO_2, which passively diffuses from the blood into the pulmonary interstitium where the CO_2 tension is very low. Subsequently CO_2 is lost into the alveolar space.

The rate of minute ventilation is controlled by two sets of chemoreceptors: those in the respiratory center in the brain stem and those in the carotid and aortic bodies located at the bifurcation of the carotid arteries and in the aortic arch, respectively. The central chemoreceptors are stimulated by an increase in the P_{CO_2} or by metabolic acidosis, both of which appear to be sensed by a fall in the pH of the surrounding cerebral interstitial fluid. The peripheral chemoreceptors are primarily stimulated by hypoxemia, although they may also respond to acidemia. The level of alveolar or effective ventilation varies in accord with the total minute ventilation. The level of total ventilation changes as a function of metabolic demand. Under normal circumstances, P_{CO_2} is well controlled between 38 and 42 mmHg according to the relationship:

$$P_{CO_2} = \frac{\dot{V}_{CO_2}}{\dot{V}_A} \qquad (3)$$

where

$\dot{V}_{CO_2}$ = CO_2 production (reflecting metabolic rate)
$\dot{V}_A$ = alveolar ventilation (reflecting CO_2 clearance)

Under basal conditions the volatile acid production or CO_2 that is metabolically generated is completely eliminated by the lungs. The mechanism of the central stimulation of respiration in response to an elevated CO_2 is a topic of intense debate and will not be focused upon in this section. However, intracranial adjustments to pH have been consistently observed and have interesting parallels to the effects of acidosis on the proximal tubular cell in the kidney. Increased concentrations of CO_2 in the cerebrospinal fluid (CSF) result in intracellular acidosis, an increase in CSF bicarbonate concentration, and an equimolar reduction in CSF chloride concentration. As brain cells increase their bicarbonate concentration, there is increased buffering, and intracellular brain pH is returned toward normal. The major group of cells within the central nervous system (CNS) responsible for acid-base regulation are the glial cells and the cells of the choroid plexus. These cells contain carbonic anhydrase which converts intracellular CO_2 H_2O to H^+ and HCO_3^-. The H^+ is exchanged for Na^+ on the blood side, allowing the intracellular pH to increase. The administration of acetazolamide into the cerebral ventricles blocks the expected increase in CSF bicarbonate in response to hypercapnia. In addition to changes in bicarbonate concentration in the CSF in response to hypercapnia, there are also changes in the levels of ammonia. Brain and CSF ammonia increase in hypercapnia; ammonia acts to enhance H^+ buffering, thereby preventing a fall in the bicarbonate concentration.

ACUTE AND CHRONIC ADAPTATION TO RESPIRATORY ACIDOSIS

Figure 14-3 depicts the acute steady-state relationships among P_{CO_2} plasma bicarbonate concentration, and plasma hydrogen concentration during graded degrees of acute hypercapnia. These observations were obtained by sequentially exposing unanesthetized normal human volunteers to increasing concentrations of inspired carbon dioxide in a large environmental chamber. Increasing degrees of hypercapnia are associated with a curvilinear rise in plasma bicarbonate concentration, with higher levels of P_{CO_2}, resulting in lesser incremental changes in bicarbonate concentration. This acute rise in bicarbonate is largely due to the chloride shift as described above. As a result of the modest increment in bicarbonate, the average rise in plasma $[H^+]$ is limited to 0.75 neq/L per mmHg rise in P_{CO_2} rather than the 1 neq/mmHg rise that would have occurred if the plasma bicarbonate concentration did not change.

The quantitative aspects of the adaptive response to acute hypercapnia are influenced markedly by the baseline acid-base status. Acute hypercapnia induces a larger increment in both plasma bicarbonate and H^+ ion concentrations in animals with preexisting hypobicarbonatemia (whether from metabolic acidosis or from chronic respiratory alkalosis) than in animals with preexisting hyperbicarbonatemia (whether from metabolic alkalosis or from chronic respiratory acidosis). This points out that the factor controlling the amount of bicarbonate generated from an acute rise in P_{CO_2} is not only the initial pH but also the initial bicarbonate

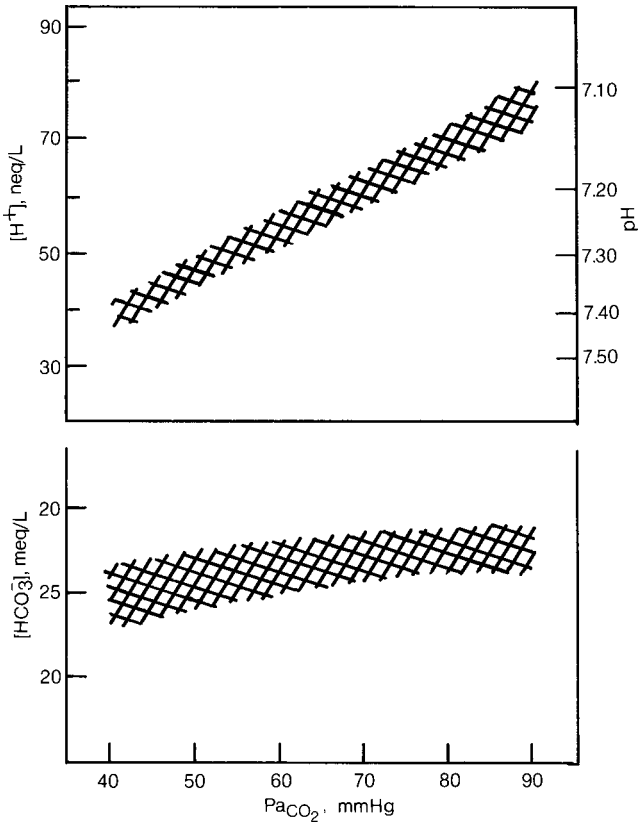

Figure 14-3 Ninety-five percent confidence bands for plasma hydrogen ion and bicarbonate concentrations during acute hypercapnia in normal humans. *(From Brackett NC Jr, Cohen JJ, Schwartz WB: Carbon dioxide titration curve of normal man: Effect of increasing degrees of acute hypercapnia on acid-base equfl ibrium. N Engl J Med 272:6, 1965, with permission.)*

concentration. Although the rise in bicarbonate in response to hypercapnia limits the fall in pH acutely, to excrete the gain of H^+ produced from the rise in P_{CO_2} requires renal compensatory mechanisms.

During the initial period of respiratory acidosis, renal compensation takes about 3 to 5 days, during which time there is enhanced reabsorption of proximal tubular bicarbonate, enhanced secretion of H^+, and increased ammonia production. These processes will lead to an increase of the serum bicarbonate concentration and a rise in the systemic pH toward normal. However, when steady state is achieved and a stable P_{CO_2} is present, there is no longer an increase in ammonia production: As filtered bicarbonate is increased, there is enhanced proximal secretion of H^+ and a normalization of intracellular pH, removing the stimulus for ammonia synthesis.

RENAL ADAPTATION TO RESPIRATORY ALKALOSIS

The adaptive responses to respiratory alkalosis occur in two distinct steps, in close analogy with respiratory acidosis. Hypocapnia reduces the carbonic acid concentration and causes a prompt fall in H^+. Acutely this alkalemia is ameliorated by a secondary, adaptive reduction in plasma bicarbonate concentration that stems principally from titration of nonbicarbonate body buffers. During protracted hypocapnia, renal adaptive mechanisms yield a further and larger secondary reduction in plasma bicarbonate that results in still greater amelioration of the alkalemia.

In acute uncomplicated respiratory alkalosis the plasma bicarbonate concentration falls by approximately 0.2 mEq/L for each mmHg reduction in P_{CO_2}; thus a reduction in plasma bicarbonate of 3 to 4 mEq/L occurs within minutes after P_{CO_2} is lowered to 20 to 25 mmHg. The resulting change in plasma H^+ concentration is approximately 0.75 mEq/L for each mmHg fall in P_{CO_2}, similar to the relationship between P_{CO_2} and H^+ in acute hypercapnia.

When hypocapnia persists beyond the acute phase, the additional decrement in plasma bicarbonate concentration is a consequence of renal adaptive responses and reflects a dampening of hydrogen ion secretion by the renal tubule. As a result, a transient suppression of net acid excretion occurs, largely manifested by a fall in ammonium excretion and an increase in net bicarbonate excretion. These changes lead, in turn, to a positive hydrogen ion balance and a reduction in the body's bicarbonate stores. Persistence of the resulting hypobicarbonatemia is explained by the continued inhibition of tubular hydrogen ion secretion and suppression of bicarbonate reabsorption.

The adaptive retention of acid during chronic hypocapnia is normally accompanied by a loss of sodium into the urine; the resultant decrease in the extracellular volume promotes chloride retention and the typical hyperchloremia of chronic respiratory alkalosis. Upon reaching a new steady state, the net excretion of acid returns to control levels, and the altered anionic concentration of the extracellular fluid (ECF), namely hypobicarbonatemia and hyperchloremia, is maintained by a reduced bicarbonate reabsorption and enhanced chloride reabsorption. On average, the combined effect of cell buffers and renal compensation results in a new steady state in which the plasma HCO_3^- concentration falls approximately 4 mEq/L for each 10 mmHg reduction in the P_{CO_2}. The renal adaptation to persistent hypocapnia appears to be mediated by some direct effect of P_{CO_2} itself, not the systemic pH. In animals in which plasma bicarbonate was reduced by HCl loading prior to adaptation to sustained hypocapnia, the renal response to a primary reduction in P_{CO_2} was the same as in normal individuals, even though the net effect of this adaptation was an overt fall in pH.

RESPIRATORY ADJUSTMENT TO METABOLIC ACIDOSIS

Metabolic acidosis stimulates both central and peripheral chemoreceptors to increase alveolar ventilation and decrease P_{CO_2} to limit the fall in pH. Although peripheral chemoreceptors appear to play a role, in animal experiments the same

degree of respiratory compensation occurs with intact and with ablated peripheral chemoreceptors. The increase in ventilation begins within 1 to 2 h and reaches its maximal level at 12 to 24 h. The stereotype is Kussmaul's breathing in acute diabetic ketoacidosis, in which tidal volume is characteristically large with minute ventilation increasing by as much as 35 L. On average, studies in otherwise normal patients with metabolic acidosis reveal that the P_{CO_2} will fall 1.2 mmHg for every 1.0 mEq/L reduction in plasma HCO_3^- down to a minimum P_{CO_2} of 10 to 15 mmHg.

On the other hand, failure to mount the expected ventilatory response to metabolic acidosis is an important indicator of respiratory decompensation. Subashini and coworkers in a study of 140 critically ill trauma patients with metabolic acidosis applied the traditional formula derived from patients with chronic metabolic acidosis. Those whose Pa_{CO_2} exceeded the predicted Pa_{CO_2} by 2 mmHg or more were 4.2 times more likely to be intubated and compensation status was an independent predictor of intubation as early as 60 minutes after episodes of significant hypotension.

RESPIRATORY ADJUSTMENT TO METABOLIC ALKALOSIS

The development of metabolic alkalosis is sensed by the respiratory chemoreceptors resulting in a decline in alveolar ventilation and an elevation of the P_{CO_2}. On average, the P_{CO_2} rises 0.7 mmHg for every 1.0 mEq/L increment in the plasma HCO_3^- concentration. Values significantly different from the predicted value represent superimposed respiratory acidosis or alkalosis. However, it is unclear whether this response significantly protects the pH from rising. In experimental animals, the rise in P_{CO_2} in metabolic alkalosis increases net H^+ excretion leading to an increase in the HCO_3^- concentration. The effect after several days is that the arterial pH is the same as it would have been if there had been no respiratory compensation.

Ventilation may be strongly affected by influences other than acid-base balance. Among these influences are body temperature, increases in circulating catecholamines, changes in cerebral blood flow, changes in systemic blood pressure, and changes in metabolic activities of different organs (e.g., liver), as well as the physiological state of the lung itself. Perhaps for teleological reasons, the defense of chronic metabolic acid-base imbalances by ventilatory compensation is not of major importance.

ALTERNATIVE CONCEPTS OF ACID-BASE BALANCE

The preceding discussion has tacitly assumed that the systemic pH is the final control that affects the renal and respiratory response to an acid-base disorder; however, this issue is certainly not settled. The proximal tubular cell of the kidney can often have effects that are more predictably based on the P_{CO_2} rather than the arterial pH. If P_{CO_2} is elevated, the proximal tubular cells acts to secrete protons and reabsorb bicarbonate whether or not there is systemic alkalosis or acidosis. This may be explained if an elevation in P_{CO_2} results in intracellular acidosis and the cell is responding appropriately to its internal milieu. Similarly, in the central control of respiration, it is controversial as to whether it is CSF pH, interstitial pH, P_{CO_2}, or the bicarbonate concentration that stimulates compensatory changes in ventilation.

In addition to the preceding observations, it is also known that changes in salt and water balance may affect acid-base status. For example, Schwartz's group found that a low dietary sodium chloride intake in dogs with a stable amount of water intake results in hypoventilation, increased P_{CO_2}, and increased HCO_3^- concentration. Studies in dogs have demonstrated that increasing dietary NaCl with a fixed water intake increases the acidity of body fluids, whereas decreasing the NaCl in diet with a fixed water intake decreases the acidity of body fluids.

An alternative view to understanding acid-base disorders and the regulatory response of the lungs and kidneys is offered by the theories initially proposed by Stewart. Based on physicochemistry, Stewart emphasized the important principle that H^+ and HCO_3^- as well as the acidic and anionic forms of weak acids are actually dependent variables in a solution. The three independent variables, P_{CO_2}, the strong ion difference, and the total weak anion concentration, can be manipulated externally and serve to determine the concentration of the dependent variables, H^+ and HCO_3^-. The major components of the weak anions in plasma are the albumin and inorganic phosphate concentrations. The strong ion difference (SID) is the difference between the sums of all strong cations and all strong anions:

$$\begin{aligned} SID = ([Na^+] + [K^+][Ca^{2+}][Mg^{2+}])([Cl^-] \\ + [\text{other strong anions (lactate}^-)]) \end{aligned} \quad (4)$$

This equation is based on the principles of: (a) electroneutrality; (b) dissociation equilibria of all incompletely dissociated substances; and (c) conservation of mass. This concept appears to better explain the basis for renal and ventilatory response in a variety of states that also affect acid-base balance. Practically, it is observed that the plasma SID is primarily regulated by the kidneys, whereas the P_{CO_2} is regulated by alveolar ventilation. The weak anion concentration is generally not regulated and often may be assumed to be stable.

This concept has primarily been used by investigators in relation to the study of central regulation of ventilation. As albumin and other proteins are not present in the CSF, it is the SID and P_{CO_2} that determine the concentration of weakly dissociating electrolytes, H^+, OH^-, and HCO_3^-. In analyzing various acid-base disturbances, it appears that the change in CSF SID can predict the concentration of CSF bicarbonate.

In evaluating acid-base balance in many species, note that there is a consistent inverse relationship between the pH and body temperature, whereas the CO_2 content remains stable. To explain this relationship, Reeves and his coworkers provided evidence that the imidazole ring structure of histidine is responsible for the pH-temperature relationship. This is because imidazole has a pKa in the physiological range (7), is relatively ubiquitous, and has enthalpy of ionization (7 kcal/mol). To integrate acid-base regulation with receptor function and control of respiration, Reeves and Rahn have proposed the hypothesis that it is not the arterial or intracellular pH that is being regulated per se but rather the constancy of the fractional dissociation of the imidazole moiety of histidine contained in proteins throughout the body. α-imidazole is defined as the ratio of the absolute amount of unprotonated imidazole (Im) to total imidazole (HIm + Im):

$$\alpha \text{ imidazole} = \frac{\text{Im}}{\text{HIm} + \text{Im}} \qquad (5)$$

α-Imidazole regulation (alphastat regulation) would have the effect of maintaining cellular protein charge states and enzymatic functions constant. It would also maintain the OH^-/H^+ ratio constant in all compartments. There is also evidence that alphastat regulation directly influences ventilatory status. For example, application of an imidazole blocker to the chemosensitive area of the medulla in cats blocked increases in ventilation caused by local application of acid. Thus, changes in P_{CO_2}, reflecting alveolar ventilation, may be determined by alphastat regulation, which maintains the OH^-/H^+ ratio constant in membranes of the cells in the chemosensitive areas of the medulla.

The difficulty with using these concepts lies in the practical measurement of the relevant molecules. For example, although the imidazole moiety of histidine is considered the most important of the intracellular buffers, its pKa and enthalpy of ionization may vary widely due to the influence of the local configuration of molecules into which they are incorporated. Thus, even in lower animals such as fish under different temperatures, calculations based on the alphastat model do not accurately predict the acid-base disturbance, since the pKa and enthalpy of ionization vary with temperature and are difficult to measure.

Similarly, measurement of the plasma SID is problematic and is often replaced by the "SID effective," which is roughly equal to the bicarbonate concentration plus albumin and inorganic phosphate. Calculation of the anion gap—$[Na^+] - [Cl^-] - [HCO_3^-]$—accounts for the roles of the strong ions Na^+ and Cl^- as well as bicarbonate but does not account for the role of inorganic phosphate or plasma proteins. Although the bicarbonate concentration may not be strictly speaking an independent variable, the anion gap calculation does indicate the quantity of unmeasured anions and hence is an indirect measure of the strong ion difference. If one considers the impact of serum proteins and inorganic phosphate in the unmeasured anion pool, the anion gap gives a very useful parameter in evaluating acid-base disturbances. As will be described in more detail in the following section, the use of the anion gap is still the most clinically useful tool to determine the contribution of different metabolic etiologies of metabolic acidosis.

APPROACH TO THE PATIENT WITH AN ACID-BASE DISTURBANCE

In this section, we examine the diagnostic approach to disorders of acid-base balance with a particular emphasis on the ventilatory response and its role in mitigating or exacerbating acid-base disorders. We will also review the approach to the patient with complex acid base disorders.

Analysis of Clinical Information

Table 14-1 summarizes the pattern of abnormality of arterial blood acid-base parameters in the four classic acid-base disorders. It also indicates the physiological or compensatory response induced in pulmonary or renal function in response to the initial disturbance.

Base Excess and Base Deficit Notations

Base excess and *base deficit* are terms applied to an analytical method for determination of the appropriateness of responses to disorders of acid-base metabolism. The base excess or deficit is determined by measuring blood pH against ambient P_{CO_2} and against a P_{CO_2} of 40 mmHg. If the calculated HCO_3^- is below 25 when the P_{CO_2} is 40 mmHg and the original pH is low, a base deficit is indicated. The magnitude of the deficit is expressed as the number of mEq of bicarbonate needed to restore the serum bicarbonate to 25 mEq/L at a P_{CO_2} of 40 mmHg compared with that at the ambient P_{CO_2}. The use of notations for base excess and deficit has been debated in the medical literature. This notation is favored in the evaluation of acid-base status in the operating room because acute changes in P_{CO_2} and in HCO_3^- can be simply evaluated by this approach. However, this notation can be misleading in chronic respiratory alkalosis or acidosis, since the patient with chronic respiratory alkalosis will be categorized as suffering from a base deficit because of the low serum bicarbonate induced as compensation for the reduced P_{CO_2}. In fact, a "base deficit" is a normal physiological response to the chronic reduction in P_{CO_2}. Unfortunately, lack of familiarity with the complete analytical paradigm used for this analysis of acid-base disorders has led some to focus on the designations "base deficit" and "base excess" as guides to bicarbonate or acid therapy in chronic respiratory disorders. In addition, discrepancies among the buffering characteristics of plasma, blood, and whole body have also been cited as potential weaknesses in a system for assessing acid-base disorders, which relies on in vitro CO_2 titration methods. Therefore, we recommend that the physiological evaluation of the patient be the mode of analysis of acid-base disorders rather than an emphasis on derived formulae.

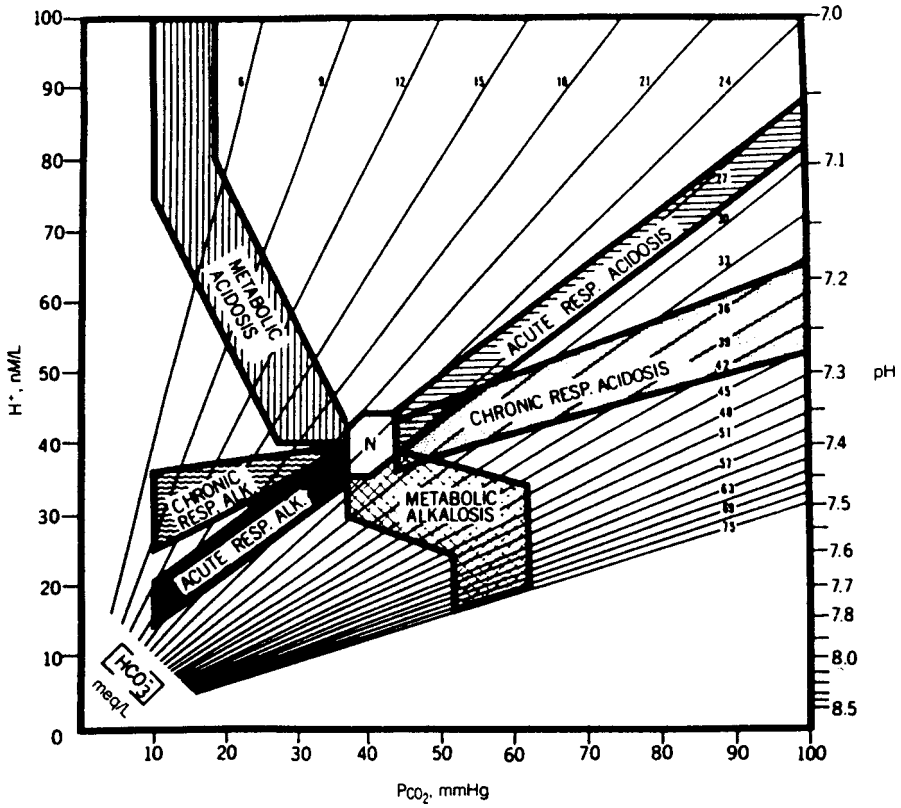

Figure 14-4 Acid-base map showing the normal range (N) and the confidence bands for acute or chronic respiratory and metabolic acid-base disturbances. The ordinates are the partial pressure of CO_2 and the hydrogen-ion activity given in nmol/L and pH units. Isopleths for bicarbonate concentration, in milliequivalents per liter, are also shown. *(From Goldberg M, Green SB, Moss ML, et al: Computer-based instruction and diagnosis of acid-base disorders. A systematic approach. JAMA 223:269, 1973, with permission.)*

Use of Nomograms

As indicated, the body buffers and the kidneys respond in a predictable fashion to a change in P_{CO_2}, whereas ventilatory response to changes in $[HCO_3^-]$ is also predictable. Also, the resulting changes in bicarbonate and pH are time dependent so that a larger change occurs in several days than in the first hours. The confidence bands for changes in P_{CO_2} or HCO_3^- in response to primary disturbances are shown in Fig. 14-4. Any deviation can be interpreted as a reflection of processes other than a compensatory response. For example, in a patient with chronic obstructive airways disease, other factors affecting the acid-base status are the concentration of potassium in the plasma, the size of extracellular fluid volume, chloride depletion, diuretics, renal hypoperfusion, and coexisting renal disease. The special case of posthypercapneic alkalosis is discussed in the next section.

In evaluating an acid-base disorder, the history and physical examination are invaluable in focusing attention on potential pathological processes. The composition of blood, with respect to serum electrolytes and blood gases, is then examined for consistency with the clinical impressions. However, in using the acid-base map (Fig. 14-4), remember that the map is based on data from individuals who had a single disorder. Therefore, the map does not take into account the possibility of multiple disorders. For example, in a patient with chronic obstructive airways disease whose sputum has turned purulent and who develops nausea and vomiting, the possibility arises of coexistent metabolic alkalosis and acute respiratory acidosis. However, ill-advised application of the arterial blood-gas values from this patient (e.g., pH = 7.25 and P_{CO_2} = 75 mmHg) to the acid-base map would lead to the erroneous conclusion that a chronic respiratory acidosis is present. Thus, the clinician needs to integrate laboratory data with clinical assessments to properly analyze clinical disorders of acid-base balance.

Approach to the Patient with Metabolic Acidosis

An increase in the H+ concentration of the extracellular fluid will result in a series of predictable responses that allow the clinician to ascertain the appropriateness of organized homeostatic responses to the perturbation. The pathophysiological basis for the initiation of metabolic acidosis and homeostatic responses in the defense of systemic pH have been defined above in descriptions of the buffering of newly introduced acid [see Eq. (1)] and in the demonstration of the normal confidence band for the ventilatory response to metabolic acidosis as detailed in the acid-base nomogram (Fig. 14-4).

An essential clinical distinction in the pathogenesis of metabolic acidosis is whether the production of the acidosis is rapid or slow. If the etiology of the metabolic acidosis is merely the continued ingestion of a diet that generates a variety of fixed acids such as H_2SO_4 [see Eq. (2)] from the metabolism of methionine residues, then the serum HCO_3^- will fall slowly, as only that fraction of the 50 to 100 mEq of H^+ generated from diet that is not excreted would be added to the body fluids each day. However, if the addition occurs because of an acute increase in the acid load such as may occur with lactic acidosis, the kidney capacity can be rapidly overwhelmed,

Table 14-2

Causes of Metabolic Acidosis (Common)

Failure to generate new bicarbonate to replace that consumed in buffering dietary acid load
- Diminished NH_4^+ production and excretion
  - Reduced renal mass
  - Chronic hyperkalemia
  - Chronic aldosterone deficiency
- Decreased H^+ ion secretion (primary)
  - Distal renal tubular acidosis
- Increased H^+ ion production
  - Lactic acidosis
  - Ketoacidosis
  - Toxic ingestion
- Bicarbonate or equivalent losses from body fluids
  - Renal-proximal RTA, carbonic anhydrase inhibitors
  - GI-diarrhea, villous adenoma, fistula

and serum bicarbonate may fall precipitously. See Table 14-2 for the common causes of metabolic acidosis.

Utility of the Anion Gap

As seen in Eq. (6), the buffering of mineral acids will result in the production of the salt of the acid, NaA.

$$NaHCO_3 + HA \; NaA + H_2CO_3^- + H^+ \; CO_2 + H_2O + NaA \tag{6}$$

If the kidney is able to excrete this salt or, in the case of the production of the salts of organic acids such as lactic acid, if the liver can metabolize the anion to HCO_3^-, then there will be no accumulation of the anion in the extracellular fluid. Typically, anions associated with strong organic acids are not measured with routine electrolyte determinations and contribute to the so-called anion gap. Determination of the plasma anion gap is primarily used in the differential diagnosis of metabolic acidosis. However, the anion gap also changes in other conditions, a finding that may be of diagnostic importance.

The plasma anion gap (AG) is calculated from the following formula based on routine laboratory determination:

$$AG = (\text{cations}) - (\text{anions})$$

Since Na^+ is the primary measured cation and Cl^- and HCO_3^- are the primary measured anions,

$$AG = [Na^+] - ([Cl^-] + [HCO_3^-]) \tag{7}$$

and normal $= 12 \pm 2$ mEq/L.

An increase in the anion gap can be produced by an increase in unmeasured anions or by a reduction in unmeasured cations. Hypokalemia, hypocalcemia, or hypomagnesemia can only raise the anion gap by a few mEq/L, since these ions can only deviate from normal by an mEq/L or less and maintain a physiological condition. The predominant extracellular unmeasured anion is actually albumin with many negative charge sites per molecule. Hence, a mild elevation in the anion gap can occur in conditions in which the albumin concentration or the charge characteristics of albumin are altered, for example, in metabolic alkalosis. In that instance, a number of factors may contribute to the increment, including a rise in the plasma albumin concentration due to extracellular volume depletion and contraction of plasma constituents, an increase in the number of negative charges per albumin molecule induced by the rise in extracellular pH titrating protons off the albumin molecule, and a tendency for systemic alkalemia to induce an increase in lactate production. This latter response serves a homeostatically beneficial function.

In forms of metabolic acidosis in which there is buffering of excess hydrochloric acid by extracellular bicarbonate, then,

$$HCl + NaHCO_3 \; NaCl + H_2CO_3CO_2 + H_2O \tag{8}$$

Bicarbonate is replaced on an equimolar basis by chloride, and there is no change in the anion gap; this disorder is also called a *hyperchloremic acidosis* because of the rise in the plasma chloride concentration. Both diarrhea and type 2 (proximal) renal tubular acidosis can lead to the loss of $NaHCO_3$. The kidneys compensate by retaining NaCl in an attempt to preserve volume, with the net effect being an mEq-for-mEq exchange of chloride for bicarbonate.

If the retained acid is not HCl but an organic acid whose anion is not routinely measured such as lactic acid, then the increase in the unmeasured lactate anion will raise the anion gap. It is important to emphasize that the acidosis is due to the retained proton; the anion is irrelevant to the change in acid-base status or systemic pH but is important as a diagnostic tool. The major causes of a high anion gap metabolic acidosis include those listed in Table 14-2 under disorders of increased H^+ production. Although renal failure produces an acidosis because of failure of H^+ excretion and bicarbonate production, most patients with severe renal failure retain both hydrogen and anions, such as sulfate, phosphate, and urate, and hence demonstrate a high anion gap.

The diagnostic utility of a high anion gap is greatest when the anion gap is above 20 mEq/L; in this setting, renal failure, lactic acidosis, or evidence of a toxic ingestion will almost always be present. When the anion gap is less than 20 mEq/L, identifying the anions which contribute to the mild elevation10 often is impossible.

Urine Anion Gap

Estimation of the urinary ammonia content may be a useful clue to the etiology of metabolic acidosis, as the value will increase in diseases in which kidney function affecting acid-base balance is completely intact but in which bicarbonate is lost from the body fluids. The calculation of the urinary anion gap is shown in Eq. (9):

$$\text{Urine anion gap} = (\text{Urine}[Na^+] + \text{Urine}[K^+]) - \text{Urine}[Cl^-] \tag{9}$$

The usual value will be negative, between –25 and –50 mEq/L, as the ammonium content of the urine is typically in this range, and ammonium accounts for the apparent discrepancy between the level of cations and anions in the urine. In states of metabolic acidosis due to diarrhea or to chronic acid ingestion, the value will be greater than 50 mEq/L as ammonium production is stimulated.

In three conditions, the urine anion gap will be very low or even positive in the face of metabolic acidosis. In all forms of renal insufficiency, ammonia production by the kidney will be deficient and significantly contribute to a reduced urinary anion gap and metabolic acidosis. In type I distal RTA, inability to maintain a steep gradient for protons in the distal tubular lumen and in the collecting duct results in a deficiency in ammonia trapping in the luminal fluid and therefore a decreased excretory rate for ammonia. This in turn leads to metabolic acidosis, a low ammonia excretion, and an abnormally low urinary anion gap. Type IV RTA, a condition in which hyperkalemia and mild renal insufficiency are found, hyperkalemia suppresses renal ammonia production, and a low urinary anion gap is found.

In any condition associated with hypokalemia, increased intracellular proton accumulation (which results from the exchange of cellular potassium for extracellular protons) will lead to an exaggerated ammonia production in the kidney. Hence, the use of the anion gap in the urine will be particularly useful to differentiate classic type I RTA from hypokalemia and acidosis due to diarrhea. The former will show a very low urine anion gap. Typically, a careful history will elicit the crucial information, and measurement of the urine anion gap will be confirmatory.

Clinical Assessment of Metabolic Acidosis

In approaching a patient with metabolic acidosis, the clinician should first assess the history and clinical circumstances. For example, patients with renal failure or uncontrolled diabetes may be presumed to have a metabolic acidosis until disproved by laboratory analysis. The next step is to evaluate the serum electrolytes to determine the level of the serum HCO_3^- and the presence of a anion gap of greater than 12 ± 2 mEq/L. If both are present, then one must consider the possibility of a metabolic acidosis secondary to increased acid production as listed in Table 14-2. If the HCO_3^- is reduced but the serum anion gap is normal, then one is dealing with either a respiratory alkalosis or a metabolic acidosis due to reduced renal capacity to generate replacement HCO_3^- to compensate for that lost as a result of decreased acid excretion or increased HCO_3^- loss.

At this point arterial blood gases should be assessed to determine the pH and ventilatory response. Finding a low pH establishes the diagnosis of metabolic acidosis. Reference to the acid-base nomogram (Fig. 14-4) will verify whether the clinical response is consistent with a simple metabolic acidosis with a normal ventilatory response or whether some other disturbance in ventilation is present.

Table 14-3

Causes of Metabolic Alkalosis

Gastrointestinal hydrogen loss
Removal of gastric secretions
Renal hydrogen loss
Primary mineralocorticoid excess
Loop or thiazide diuretics
Posthypercapneic alkalosis
Intracellular shift of hydrogen
Hypokalemia
Alkali administration
Contraction alkalosis

Metabolic Alkalosis

Two separate processes are involved in metabolic alkalosis: an excess load of base that is generated either endogenously or exogenously (Table 14-3) and maintenance of an abnormally high concentration of bicarbonate in the plasma. During hypercapnia, the load of base is the result of renal compensation and de novo bicarbonate generation; in posthypercapneic alkalosis, the key abnormality is maintaining the bicarbonate level in plasma at inordinately high levels, as discussed below.

Generation of Metabolic Alkalosis

Causes of metabolic alkalosis are predominantly events that remove H^+ ions from the body but also include circumstances in which excess base is added to the body fluids. Hydrogen loss can occur from the gastrointestinal tract or in the urine. Each mEq of hydrogen lost generates 1 mEq of bicarbonate, as the source of hydrogen ions in cells that produce and secrete protons is:

$$H_2O \; H^+ + OH^- + OH^- + CO_2 \; HCO_3^- \qquad (10)$$

When vomiting or tube drainage prevents stomach acid from reaching the duodenum and combining with HCO_3^- released from pancreatic secretions, the net balance of bicarbonate in body fluids becomes positive, and serum HCO_3^- begins to rise.

Increased renal acid losses may result from enhanced distal hydrogen secretion. Aldosterone acts both by directly stimulating the secretory H^+-ATPase pump and, via the stimulation of sodium reabsorption, by making the lumen more electronegative, thereby favoring hydrogen ion secretion. Increased distal nephron delivery and reabsorption of sodium further stimulates hydrogen ion secretion as the accompanying anion is less avidly reabsorbed than is sodium, and the lumen of the distal nephron becomes more negatively charged. Excess secretion of mineralocorticoids can lead to metabolic alkalosis by this pathway. In patients treated with loop-active or thiazide diuretics, enhanced distal delivery of sodium and increased secretion of aldosterone are usually present, thereby enhancing renal bicarbonate production as

a result of enhanced hydrogen ion secretion. This pattern commonly leads to the development of metabolic alkalosis.

Chronic respiratory acidosis leads to a secondary increase in renal hydrogen secretion, as the subsequent rise in the plasma bicarbonate concentration will restore the pH toward normal as a compensatory response. If the patient undergoes a therapeutic maneuver such as rapid lowering of the P_{CO_2} by mechanical ventilation, a posthypercapneic form of metabolic alkalosis will ensue as the patient is left with an elevated plasma bicarbonate concentration.

Hypokalemia is a frequent finding in patients with metabolic alkalosis and may not only be the consequence of some of the disorders that lead to the initiation of metabolic alkalosis but may also actually induce an alkalotic tendency. Gastric drainage, diuretics, and mineralocorticoid excess all induce potassium as well as hydrogen losses through the gastrointestinal tract and kidney, respectively. Hypokalemia also induces a transcellular shift in which potassium is exchanged in an electroneutral fashion for hydrogen ions in the extracellular fluid. This exchange directly raises the extracellular pH, lowers the intracellular pH, and mitigates the hypokalemia. Intracellular acidosis in renal tubular cells promotes hydrogen secretion and therefore bicarbonate reabsorption (see above).

Administering large amounts of alkali does not maintain metabolic alkalosis in normal individuals because of rapid urinary excretion, but it may induce the initiation stage of metabolic alkalosis if factors are active to sustain a high rate of renal HCO_3^- reabsorption. A form of metabolic alkalosis termed *contraction alkalosis* occurs when there is loss of relatively large volumes of bicarbonate-free fluid. Administration of a loop diuretic to induce rapid fluid removal in a markedly edematous patient is the most common cause of a contraction alkalosis. The plasma bicarbonate concentration rises in this setting because there is contraction of the extracellular volume around a relatively constant quantity of extracellular bicarbonate. The degree to which this occurs is in part minimized by intracellular buffering, as the release of hydrogen ions from cells buffers lowers the plasma bicarbonate concentration toward the baseline value. Even this form of alkalosis is probably critically dependent on increases in renal bicarbonate production for its manifestation, since the diuretics promote excess renal hydrogen ion secretion as noted above.

Maintenance Phase of Metabolic Alkalosis

Maintenance of metabolic alkalosis requires an increase in the reabsorption of bicarbonate by the renal tubule. Four factors are known to be important in the maintenance phase of metabolic alkalosis: extracellular volume depletion, chloride depletion, hypokalemia, and mineralocorticoid excess.

A reduction in extracellular fluid volume and possibly a fall in the glomerular filtration rate secondary to extracellular volume depletion are major stimuli for increasing the proximal reabsorption of bicarbonate. The enhanced proximal tubular bicarbonate reabsorption is likely the most important factor. This reabsorption is stimulated by the extracellular volume depletion that is a frequent accompaniment of metabolic alkalosis. Enhanced proximal tubular reabsorption of sodium ions is a major factor in the enhanced rate of proton secretion, a key factor in the proximal tubular reabsorptive pathway for bicarbonate. Enhanced activity of the sodium-proton exchanger in the luminal membrane of the proximal tubule is an important component of the transport system.

In addition, an important role is played by the distal nephron in maintaining metabolic alkalosis by way of the secondary phenomena of chloride depletion, extracellular volume depletion, and hypokalemia. Cells of the cortical collecting tubule can either reabsorb or secrete bicarbonate depending on homeostatic requirements. For example, during excess bicarbonate ingestion, the secretory process predominates, and excess bicarbonate is lost into the urine. Chloride depletion enhances the bicarbonate reabsorptive pathway by reducing chloride availability at an anion exchange site on the luminal membrane of the type A intercalated cell. This exchange process normally allows bicarbonate entry into the urine in exchange for chloride absorption. Chloride depletion thus blocks bicarbonate loss.

Hypokalemia acts to stimulate bicarbonate reabsorption through several mechanisms. First, loss of potassium from the extracellular fluid leads to a shift of protons into the cell as potassium leaves the cell. Hence, intracellular pH falls, driving enhanced tubular bicarbonate reabsorption. Also, severe potassium depletion produces a defect in tubular fluid chloride reabsorption, thus mimicking a chloride depletion state. Finally, excess mineralocorticoid hormone, either as a result of primary overproduction or due to a variety of secondary hyperreninemic states, stimulates H^+ secretion in the cortical collecting tubule and thereby stimulates increased renal tubular bicarbonate production and helps maintain metabolic alkalosis.

Typically, all four components coexist in patients with metabolic alkalosis secondary to vomiting or gastric drainage following gastric intubation. If any of the factors is present in a patient with metabolic alkalosis, therapy will be only partially successful until all the factors have been eliminated.

Depression of ventilation in metabolic alkalosis is a normal physiological response to the elevation in serum bicarbonate but is difficult to assess clinically and may not be found in many patients, as detailed above.

Posthypercapneic Metabolic Alkalosis

In response to sustained hypercapnia, the increased excretion of hydrogen ion in the urine and the increased bicarbonate generated by the acid secretory process increase the concentration of bicarbonate in the plasma as described above. During this process, the total sodium content of the body remains stable as does the extracellular fluid volume (unless there is a separate reason for a volume abnormality, such as right ventricular failure and the use of diuretics). If correction of hypercapnia occurs (e.g., through the use of mechanical ventilation without simultaneous replacement of sodium chloride), the urinary loss of sodium bicarbonate may lag for several hours

or days. This is particularly true if there is concomitant depletion of the extracellular fluid volume. This leads to an increase in the reabsorption of solute, including sodium bicarbonate, by the proximal tubule, sustaining the high bicarbonate concentration in blood. This process is similar to the maintenance phase of metabolic alkalosis described above; the other processes outlined also could pertain to this posthypercapneic state and produce a persistent metabolic alkalosis following correction of hypercapnia.

Approach to the Patient with a Mixed Acid-Base Disorder

The approach to patients with mixed acid-base disorders, that is, more than one disturbance in acid-base metabolism, is particularly challenging because no nomogram, calculation of base excess or deficit, or other formula can allow the clinician to parse the pathophysiological disorders and allow a rational therapeutic plan. Rather, it is the combination of clinical assessment, application of expected compensatory responses, assessment of the anion gap, and application of principles of physiology that together allow a successful analysis.

In order to determine the presence of a mixed or complex acid-base disorder, the clinician must follow a rigorous approach that integrates clinical observation with assessment of a variety of laboratory parameters. No single nomogram or other shortcut device will suffice. The initial step is to perform a history and physical examination to seek processes which could contribute to acid-base disorders. For example, any patient who has vomited has the potential for developing a metabolic alkalosis, and any patient with chronic renal failure surely has metabolic acidosis as an ongoing process for which compensation will be necessary. Moreover, many clinical conditions are typically characterized by the presence of more than one concurrent disorder. Patients with severe liver failure usually experience respiratory alkalosis as a consequence of hepatic encephalopathy so that any other conditions associated with abnormalities of acid-base balance that may develop in these patients will result in mixed acid-base disorders. Septic shock is associated with the mixed disorders of respiratory alkalosis and metabolic acidosis due to lactic acid production. Immediately following cardiac arrest, patients will have both a respiratory and a metabolic acidosis. Patients with renal failure who undergo gastric drainage will manifest both metabolic alkalosis and metabolic acidosis as a result of the underlying conditions. The clinician must consider these expected abnormalities in acid-base balance when addressing laboratory results.

The second step in the process is to evaluate a venous blood sample for determination of the electrolytes, blood urea nitrogen (BUN), creatinine, and other parameters indicative of liver function. Here, the evaluation of the $[HCO_3^-]$ and analysis of the anion gap is invaluable. Decrements or elevations of $[HCO_3^-]$ will point toward a disturbance in the body's buffering system. The anion gap measurement, if elevated, will clarify whether a metabolic acidosis is present, as described above. Also, analyzing the anion gap together with the venous $[HCO_3^-]$ can provide important information. Because the anions that accumulate in most forms of organic acidosis (lactic acidosis, ketoacidosis, many toxic ingestions) can be metabolized in the liver to bicarbonate through the Kreb's cycle, adding the unmeasured anion concentration to the current plasma HCO_3^- concentration indicates the level of $[HCO_3^-]$ prior to the onset of the metabolic acidosis.

APPENDIX

The following cases illustrate the clinical approach to the patient with acid-base disturbances.

Metabolic Acidosis

A 75-year-old patient presented with a 7-day history of intermittent diarrhea and a 5-lb weight loss. The rest of the history was unrevealing. Physical examination only revealed signs of volume depletion. Laboratory values were as follows:

$[BUN] = 18$ mg/dl
$[Na^+] = 138$ mEq/L
$[K^+] = 3.0$ mEq/L
$[Cl^-] = 110$ mEq/L
$[HCO_3^-] = 13$ mEq/L

At this point, the lack of an elevated anion gap (12 mEq/L) and the reduced bicarbonate concentration together suggest the possibility of either respiratory alkalosis or metabolic acidosis of the non–anion-gap variety, i.e., in which the chloride concentration has risen as bicarbonate has been utilized in buffering reactions or has been lost from body fluids. The history of diarrhea strongly suggests that a metabolic acidosis is the culprit in the disorder. The relatively low BUN supports the theory that diarrhea and not renal insufficiency is the main etiologic factor.

Arterial blood gases are then obtained:

pH = 7.24
$P_{CO_2} = 27$ mmHg
$P_{CO_2} = 100$ mmHg
$[HCO_3^-] = 13$ mEq/L

The low serum bicarbonate in association with a low arterial blood pH indicates that the patient has a metabolic acidosis. Finding that the rate of ventilation produces a P_{CO_2} of 27 is consistent with the expected P_{CO_2} of 27.5 ± 2 mmHg calculated from Winters' formula (Table 14-1). Reference to the acid-base nomogram (Fig. 14-4) reveals the graphical equivalent of this calculation as the values for pH, P_{CO_2}, and $[HCO_3^-]$ fall in the confidence band for metabolic acidosis. Other possible etiologies for this form of non–anion-gap metabolic acidosis include mild renal insufficiency, wherein the decline of GFR has not reached a level in which the unmeasured anions such as SO_4^{2-} would begin to accumulate in plasma, and the ingestion of salts such as ammonium chloride, which are

metabolized in the liver to urea and hydrochloric acid. Urinary electrolyte analysis confirms the diagnosis:

$[Na^+] = 50$ mEq/L
$[K^+] = 20$ mEq/L
$[Cl^-] = 140$ mEq/L
Urine volume = 2 L
Urinary anion gap = −70 mEq/L

The discrepancy between the sum of urine cations and anions in the negative range indicates that an unmeasured cation, in this case ammonium, is being excreted into the urine. It is the excretion of protons in association with ammonia that allows the renal excretion of the accumulated acid load and the attempted regeneration of body HCO_3^- stores. If this value were not greater than –20 to –50 mEq/L, a defect in ammonia production or excretion such as could be found in renal insufficiency or in renal tubular acidosis could be present. In this case, diarrhea is the culprit.

Metabolic Alkalosis

A 65-year-old patient experienced severe and unremitting vomiting for 4 days. He has had a history of peptic ulcer disease, but he decided to medicate himself with an antacid, which he could not keep from vomiting. There was no other significant past medical history. Physical examination showed a moderate degree of orthostatic hypotension as blood pressure fell from 100/70 mmHg supine to 90/60 mmHg when seated. The rest of the examination was not remarkable except for some abdominal tenderness.

Laboratory results revealed the following:

[BUN] = 28 mg/dl
$[Na^+] = 43$ mEq/L
$[K^+] = 3.0$ mEq/L
$[Cl^-] = 85$ mEq/L
$[HCO_3^-] = 39$ mEq/L

The elevation in HCO_3^- content is consistent with either metabolic alkalosis or chronic respiratory acidosis with renal compensation. The clinical circumstances strongly imply that metabolic alkalosis will be found, since the patient has been vomiting and therefore has been generating new alkali in the body fluids as gastric hydrochloric acid is lost. Also, the vomiting-induced deficit in extracellular fluid volume and body fluid chloride content will likely act to help sustain the metabolic alkalosis by stimulating a high rate of renal bicarbonate transport by the proximal tubule and inhibiting distal nephron bicarbonate secretion.

Arterial blood gases are then obtained:

H = 7.52
$P_{CO_2} = 46$ mmHg
$[HCO_3^-] = 36$ mEq/L

These confirm the diagnosis. Note that the hypoventilatory response is modest, probably because of the degree of hypokalemia, which tends to acidify the intracellular fluid and stimulate ventilation. Correction of this abnormality requires both replacement of fluid with sodium and chloride and adequate intake of potassium to fully restore acid-base balance to normal.

Mixed Acid-Base Disturbance

An insulin-dependent diabetic patient with several days of vomiting developed diabetic ketoacidosis. The following set of electrolytes is obtained:

$[Na^+] = 140$ mEq/L
$[K^+] = 5$ mEq/L
$[Cl^-] = 90$ mEq/L
$[HCO_3^-] = 15$ mEq/L
Anion gap = 35 mEq/L

Since the normal anion gap is 12 ± 2 mEq/L, this individual has utilized 23 mEq/L of HCO_3^- to buffer the ketoacids. If the production of ketoacids ceases and hepatic metabolism is restored through insulin administration, then 23 mEq/L of HCO_3^- could be added to body fluids. The new set of electrolytes would be:

$[Na^+] = 140$ mEq/L
$[K^+] = 5$ mEq/L
$[Cl^-] = 90$ mEq/L
$[HCO_3^-] = 38$ mEq/L
Anion gap = 12 mEq/L

By assessing the value—(anion gap increment above 12 mEq/L) + (serum $[HCO_3^-]$)—and finding a value greater than 30, one can infer that some process has previously raised the bicarbonate content above normal even if the ambient total CO_2 level is subnormal at the current moment. Hence either metabolic alkalosis or respiratory acidosis is a component process of the acid-base disorder. Conversely, finding a value less than 20 suggests that the patient had a preexistent metabolic acidosis or a respiratory alkalosis prior to the onset of the organic acidosis. Finally, the clinician may assess the alveolar-arteriolar O_2 gradient to determine the effectiveness of oxygenation as an initial assessment of respiratory intactness.

At this point the clinician is able to ascertain a tentative diagnosis and perform an arterial blood gas determination to conclude the process. Measurement of the blood gas will show whether the respiratory response to a metabolic disturbance (metabolic alkalosis or metabolic acidosis) or the metabolic (renal) response to a respiratory disturbance is as expected. The acid-base disorder could still be labeled a simple disturbance if the initial assessment of the clinical condition and the anion gap support that conclusion. Consulting the acid-base map (Fig. 14-4) will provide the expected compensatory response to each disturbance. In the case above of a patient with diabetic ketoacidosis and an initially increased [anion gap + total CO_2] concentration, the following arterial blood gases were obtained:

pH = 7.18
$P_{CO_2} = 38$ mmHg
$[HCO_3^-] = 15$ mEq/L

In pure metabolic acidosis, the ventilatory response to a $[HCO_3^-]$ lowered to 15 mEq/L would be a P_{CO_2} of 25 mmHg (Table 14-1 and Fig. 14-4). In this example, the patient shows a P_{CO_2} that is higher than the expected value of 25 for a patient with pure metabolic acidosis and a depressed HCO_3^- value of 15 mEq/L. Hence this patient demonstrates a so-called triple disturbance, metabolic acidosis (low HCO_3^-, high anion gap), a metabolic alkalosis [(HCO_3^- + anion gap increment above 12) greater than 30 mEq/L] and a respiratory acidosis (P_{CO_2} higher than expected value given the lowering of HCO_3^- level as determined from the acid-base nomogram or the formula for expected compensation). Therapy for this patient will require awareness of these various processes, since removal of a counter disturbance can induce a more severe expression of the still-present abnormality.

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15
CHAPTER

Exercise, Integration, and Adaptation

Alfred P. Fishman

Muscular exercise, such as walking, is such a regular feature of daily life that it is usually taken for granted until something goes wrong. The range of daily activity and its limits vary greatly from person to person. The range is narrower in individuals who lead sedentary lives than in those who are active. In the athlete who regularly engages in competitive sports, the physiological adjustments are of a degree and type different from those in individuals who engage in less strenuous activities. Moreover, these functional changes are generally accompanied by structural changes in the heart and lungs (see "Adaptation" below).

In recent years, normal individuals have learned that moderate and regular exercise is both healthful and personally gratifying. However, the rewards of exercise are not confined to normal subjects. More than a few days' bed rest, such as a weeklong convalescence from an acute illness, is accompanied by a decrease in strength and physical capacity. Physical inactivity also imposes a continuing threat to persons for whom freedom of motion is limited, such as those who get about in motorized wheelchairs. In these people, physical deconditioning is inevitable unless physical exercise is deliberately incorporated into their way of life. Exercise also minimizes the risk of thromboembolism from leg veins.

Over the years, studies of the integrated adjustments during exercise led to such concepts as "fixity of the internal environment," "homeostasis," and adaptation. In addition, attention has been paid to adaptive changes such as hypertrophy and hyperplasia. This introductory chapter deals with such concepts as they apply to the physiological processes of normal subjects during exercise. Viewed from this perspective, diseases of the cardiorespiratory apparatus can be considered as failures in one or more components of the integrative and compensatory responses.

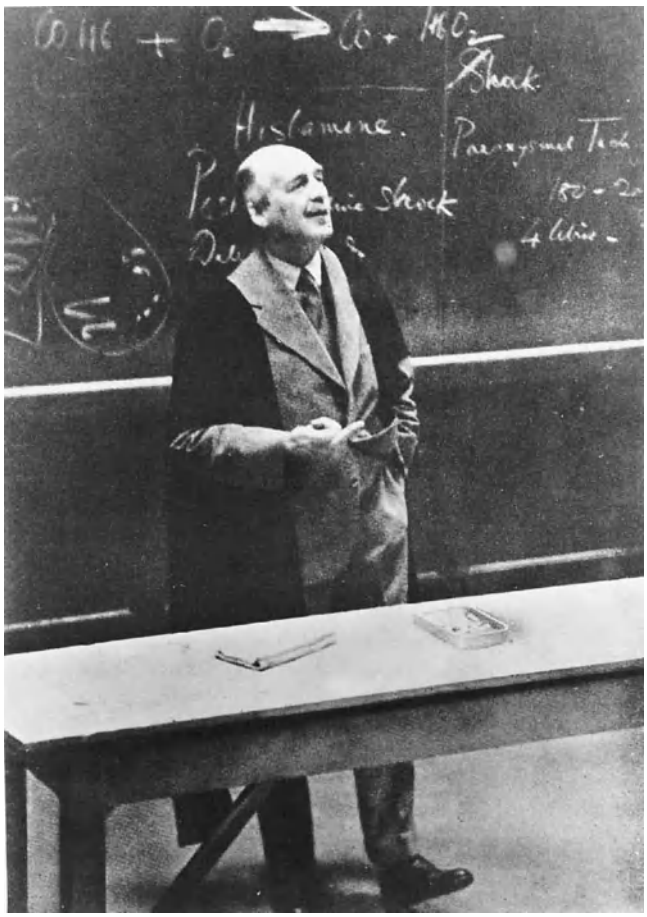

Figure 15-1 Joseph Barcroft (1872–1947) explored the integrating functions responsible for adjustments to diverse external environments, such as high altitude and fetal life. He maintained a lifelong interest in the properties of the oxygen dissociation curve and proved that oxygen entered pulmonary capillary blood by diffusion rather than by secretion.

THE INTEGRATED RESPONSE

Principles of the Integrated Response

Barcroft's classic monograph of 60 years ago, *Features in the Architecture of Physiological Function*, includes three chapters under the heading "Every Adaptation Is an Integration." One chapter deals with exercise; the other two deal with pregnancy and anoxia (i.e., hypoxia), respectively. All three are concerned with the physiological changes that make possible the successful transition from one biologic state to another (e.g., rest to exercise) (Fig. 15-1).

Barcroft's considerations of the three states led him to several generalizations about cardiorespiratory adjustments that can be paraphrased as follows: (1) after a person adjusts to a new environment or to a changed demand for oxygen, the blood gases undergo measurable changes instead of remaining constant; (2) the changes in blood gases occur in an orderly way and reverse upon return to the person's original condition or environment; and (3) the physiological adjustment is usually due to a summation or multiplication of several small changes rather than to a single major change (e.g., the cardiac output can undergo a ninefold change because of threefold variations in stroke volume and heart rate).

The Integrated Response for O_2 Uptake

The increase in energy called for by the exercising muscles has to be delivered by the heart, lungs, and blood, working as a coordinated system for the delivery of oxygen and removal of carbon dioxide. The amount of oxygen required can be quite large and impose large demands on the heart as a pump, on the transport system between the alveolar capillaries and the mitochondria, and on the ventilatory apparatus. Traditionally, the capacity to respond has been tested by progressive, steady-state exercise calibrated according to successive levels of oxygen uptake. For each level of exercise, the normal response of the cardiorespiratory apparatus has been quantified. For example, to satisfy the need for a 10-fold increase in oxygen uptake, the ventilation is expected to increase to about 20 times the resting minute volume and the cardiac output (predominantly by an increase in heart rate) to about three times the resting minute volume. These changes operate in concert with a striking redistribution of blood flow to the exercising muscles.

In 1925, Morgan and Murray, close collaborators of Barcroft and Henderson, used a four-quadrant diagram to graphically demonstrate the complex interplay in oxygen uptake by the lungs at rest (Fig. 15-2). Since then, the same type of representation has been used to depict related aspects of oxygen uptake by the lungs during steady-state exercise (Fig. 15-3). It also can be used to illustrate oxygen delivery to the exercising muscles and carbon dioxide elimination by the lungs in health and disease (Fig. 15-4).

During recent decades, the physiological parameters that make up the individual quadrants of the Morgan-Murray diagram have been extensively studied at rest and during graded exercise. For example, at consecutive levels of exercise, the cardiac output increases by a combination of an increase in heart rate and stroke volume. However, the increase in cardiac output is proportionally less than the increase in oxygen consumption. The difference between the two is made up by redistribution of the cardiac output. Thus, at the maximum rate of oxygen uptake ($\dot{V}O_{2\,max}$)—i.e., when oxygen uptake levels off despite further increases in work rate—blood flow to skeletal muscle increases from about 20 percent of the cardiac output at rest to almost 90 percent during exercise; concomitantly, the splanchnic blood flow decreases from about 25 percent of the cardiac output to about 1 percent. In addition to redistribution of the cardiac output in favor of the exercising muscles, the arteriovenous O_2 difference increases greatly; i.e., the O_2 extraction from each unit volume of perfusing blood increases. This increase in O_2 extraction is, in turn, a consequence of several physiological adjustments: an increase in the hemoglobin concentration of blood, a shift to the right of the O_2 dissociation curve due to increased release of CO_2 by the exercising muscle, and an increase in temperature of blood.

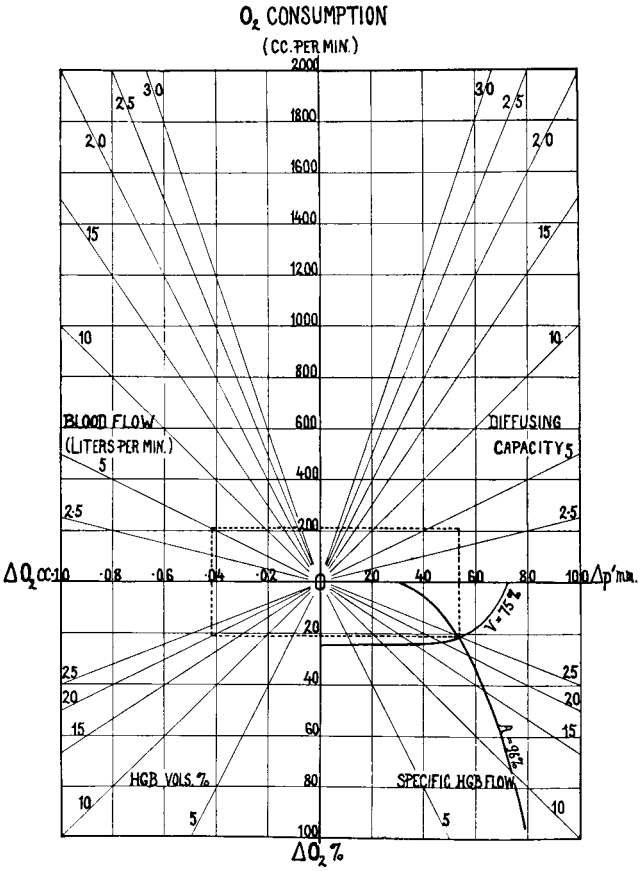

Figure 15-2 The original Morgan-Murray diagram. This diagram illustrates the linkages between physiological mechanisms at work in achieving adequate O_2 uptake by the lungs. *(From Richards DW Jr: Lawrence Joseph Henderson, in Medical Priesthoods and Other Essays. Connecticut, Connecticut Printers, 1970, p 81.)*

The circulatory component of the cardiorespiratory system imposes more of a limit on the O_2 delivery system than does the ventilation. Thus, at $\dot{V}O_2$, the cardiac output reaches almost 90 percent of the capability of the heart, whereas the ventilation is only at 65 percent of the capability of the ventilatory apparatus.

Not illustrated in graphic representations are the underlying automatic adjustments brought about by both the autonomic nervous system and local mechanisms. For example, even though muscle arteries are compressed during exercise, resulting in increased resistance to blood flow, the dramatic increase in blood flow and O_2 delivery to the exercising muscles suffices to keep pace with the increase in energy requirement. Helping to increase blood flow and O_2 delivery are vasodilation induced by the metabolic products of the exercising muscles and the modest increase in blood pressure that accompanies exercise.

Exercise Testing of the Integrated Response

Steady-state, graded exercise enables testing of the integrated response of the cardiorespiratory system, at different levels of work, in terms of power output (W) or, more conventionally, of oxygen uptake ($\dot{V}O_2$). The two are closely related. Steady state is also useful in defining the ceiling of exercise capacity in similar terms (W_{max}, $\dot{V}O_2$ max). The peak power (W_{max}) and the maximum O_2 consumption ($\dot{V}O_{2\,max}$) are among the most informative measurements obtained from a graded exercise test.

For clinical purposes, however, a standardized exercise test of the global aerobic capacity of the cardiorespiratory-muscular apparatus is often substituted for tests utilizing graded exercise. For example, in patients with chronic obstructive pulmonary disease, the 6-min walking test has been used to identify the maximum sustainable exercise. When

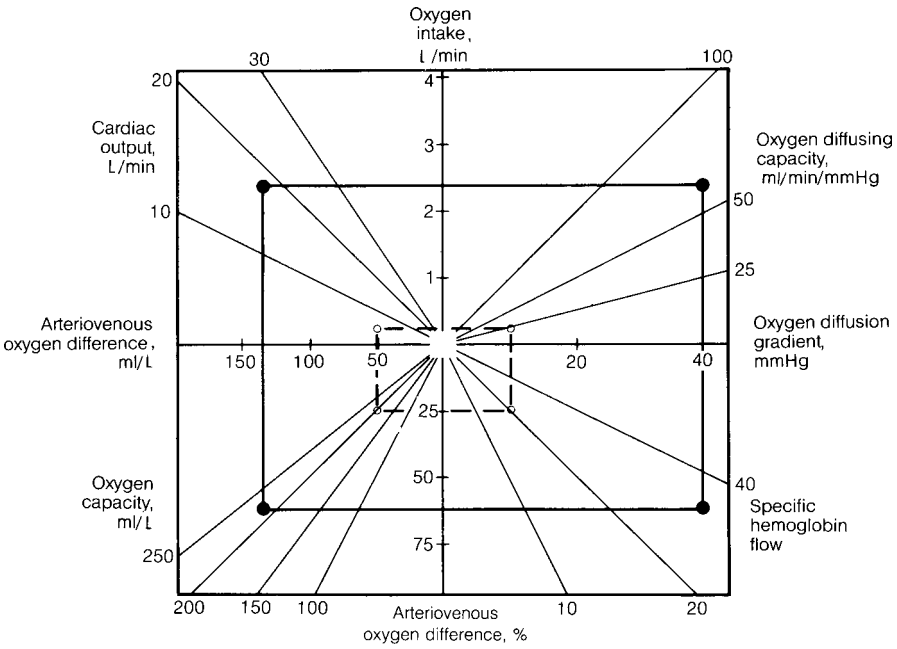

Figure 15-3 A more recent edition of the Morgan-Murray diagram, modified to show mechanisms of oxygen uptake by the lungs at rest (inner dashed rectangle) and during moderate exercise (solid rectangle). The oxygen uptake increased from 240 ml/min at rest to 2400 ml/min during exercise.

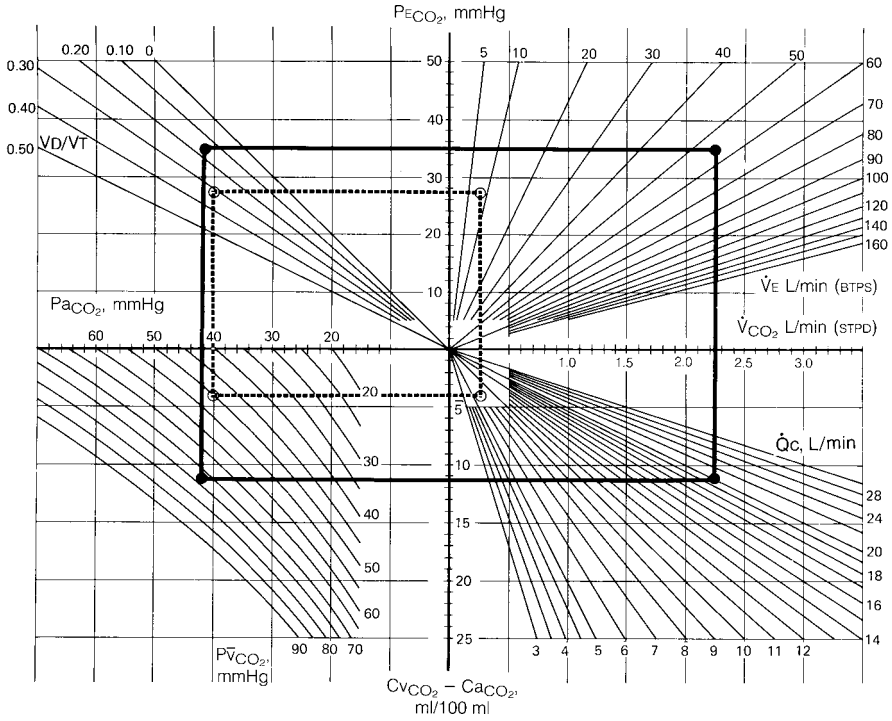

Figure 15-4 Application of the Morgan-Murray diagram to CO_2 elimination in the lungs. The inner (dashed) rectangle represents CO_2 output at a $\dot{V}O_2$ of 200 ml/min; the outer rectangle (solid line) is for a $\dot{V}O_2$ of 2250 ml/min. *(From Jones NL: Physiological basis of exercise testing, in Fishman AP (ed), Pulmonary Diseases and Disorders, 2d ed. New York, McGraw-Hill, 1988, p 235.)*

global testing is combined with specific pulmonary function tests, precise localization of the impaired structure or function can be achieved.

Anaerobic Threshold

During exercise, the rate of oxygen uptake increases predictably until a plateau is reached—i.e., the maximum oxygen uptake ($\dot{V}O_{2\,max}$). In the course of increasing exercise to the level of $\dot{V}O_{2\,max}$, as oxygen delivery to the muscles cannot keep pace with oxygen requirements, anaerobic metabolism becomes evident. As indicated in Chapter 17, at the "anaerobic threshold," serum lactate levels begin to increase when the energy requirements of exercise exceed the ability of the combined respiratory and circulatory systems to supply oxygen at a sufficiently high rate. At this juncture, ventilation increases inordinately, accompanied by decreases in blood pH and bicarbonate levels. In normal nonathletic subjects, this anaerobic threshold is reached at about 50 to 60 percent of predicted $\dot{V}O_{2\,max}$. In persons with impaired ability to transport oxygen (e.g., heart failure), this threshold occurs at a lower $\dot{V}O_2$ (expressed as a percentage of predicted $\dot{V}O_{2\,max}$).

HOMEOSTASIS AND ITS PERTURBATIONS

Homeostatic Mechanisms

For clinicians, an understanding of normal physiological processes is prerequisite for dealing with disease and with disturbances in regulatory processes. The term *homeostasis* refers to the automatic, self-regulating physiological mechanisms found especially in so-called higher animals that, after a disturbance, operate to restore the original equilibrium state of the organism. The two essential ingredients of this concept are internal stability and the integrated (coordinated) response that maintains it. Cannon (Fig. 15-5), who coined the term "homeostasis," pictured the situation in the following way: "In

Figure 15-5 Walter B. Cannon (1871–1945) incorporated the idea of stability of the internal environment into the larger concept of *homeostasis*. He appreciated the role of the autonomic nervous system in maintaining the stability of the internal environment.

Figure 15-6 Claude Bernard (1813–1878) enunciated the principle that the ability of humans and animals to function in the external environment (i.e., to maintain a "free life") is due to the stability of its internal environment (i.e., the circulating body fluids that bathe organs and tissues). *(From Fishman AP, Richards DW: Circulation of the Blood: Men and Ideas. New York, Oxford University Press, 1964.)*

Figure 15-7 Lawrence J. Henderson (1878–1942) developed seminal concepts of acid-base balance and the regulation of the neutrality of the blood based on his explorations of blood as a physicochemical system. Founder of the Fatigue Laboratory at Harvard, he created nomograms to illustrate graphically the interrelations of the major chemical constituents of the blood in normal humans and various pathological states (e.g., anemia, nephritis, diabetic acidosis).

an open system, such as our bodies represent, compounded by unstable material and subjected continually to disturbing conditions, constancy is in itself evidence that agencies are acting, or ready to act, to maintain this constancy."

Although Cannon coined the term in 1939, its roots are much older. In 1859, Claude Bernard, concerned with stability of the internal environment of the body as a prerequisite for a free and independent life in the face of a changing external environment, identified blood and lymph, the circulating body fluids, as the internal environment (Fig. 15-6). His experiments dealt with the mechanisms for ensuring this stability. The concept of blood as a critical element in the internal environment was subsequently developed by other physiologists and reached its peak of sophistication early in the twentieth century when Lawrence J. Henderson (Fig. 15-7) described the physicochemical properties and respiratory function of blood. For these classic works, Henderson drew heavily on collaborative efforts with Van Slyke's group at the Rockefeller Institute and his own group in the Fatigue Laboratory at Harvard. Henderson's monograph affords a remarkable synthesis of the composition of the blood and its biologic behavior in the transport of the respiratory gases. It deals not only with perturbations in the composition of blood in normal subjects, but also with abnormalities induced by disease (e.g., anemia, nephritis, diabetic coma).

Cannon envisaged homeostatic mechanisms as part of *The Wisdom of the Body*. His concept of homeostasis extended far beyond Bernard's ideas about the internal environment. He pictured homeostasis in the following way:

> The coordinated physiological processes which maintain most of the steady states in the organism are so complex and so peculiar to living beings—involving, as they may, the brain and nerves, the heart, lungs, kidneys, and spleen, all working cooperatively—that I have suggested a special designation for these states, *homeostasis*. The word does not imply something set and immobile, a stagnation. It means a condition—a condition which may vary, but which is relatively constant.

Restorative mechanisms per se, without intervening mechanisms to tide the body over abrupt and marked disturbances (e.g., temperature, body water, blood pressure), could not suffice to sustain the stability of the internal environment. Henderson appreciated that "the body seems to contain what may be likened to marshes or swamps into which substances may disappear and be lost to view." Aerobic metabolism illustrates the need for such "marshes." Faced with abrupt changes in ambient air or pulmonary function sufficient to elicit disease that compromises arterial hypoxemia, the body draws

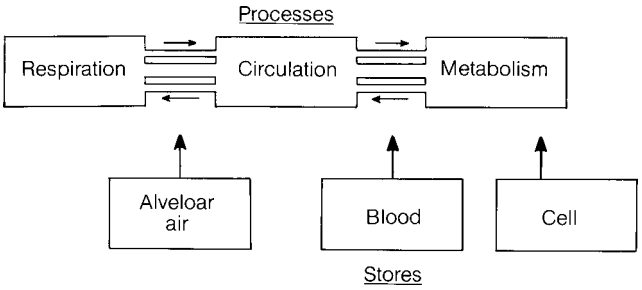

Figure 15-8 Processes and stores that maintain stable levels of P_{O_2} within cells. The alveolar air acts as a store for O_2 between ambient air and blood, serving as a tonometer of fairly stable composition. The blood, interposed between alveolar air and metabolizing tissues, has hemoglobin as the store. Within the cells are stores in the form of high-energy phosphates, dissolved O_2, myoglobin, and substrates for metabolic processes. Rearrangements in the distribution of blood by vasomotor activity determine the rate of delivery of O_2 to the different tissues. *(Modified from Weibel ER: The Pathway for Oxygen. Cambridge, MA, Harvard University Press, 1984.)*

upon oxygen-containing "swamps" to satisfy its need for oxygen. Thus, between ambient air and the mitochondrion are several distinct stores—the alveolar air, blood, and metabolizing cells. These are interposed seriatim between the processes of respiration, circulation, and metabolism (Fig. 15-8).

Disease can affect the "marshes" (stores) or the processes. With respect to the "marshes," pulmonary edema compromises oxygen uptake by replacing alveolar air with liquid; anemia limits the oxygen transport function of the blood; occlusive arterial disease can compromise oxygen delivery to the metabolizing cells. Considerations such as these prompt the idea that disease and regulatory disorders can be viewed as failure or insufficiency of normal processes and stores, components of the homeostatic system originally designed to sustain stability of the internal environment. Familiar examples of insufficiencies that compromise normal functions are arterial hypotension or abnormal hemoglobins, both of which can interfere with oxygen transport.

Homeostasis as a Feedback Process

The principles that govern man-made control systems apply equally well to the self-regulatory mechanisms of living organisms. The paradigm of a man-made control system is the regulation of temperature by means of a thermostat, which in turn is an example of a closed-loop (negative feedback) control system—one in which any deviation of the controlled output (room temperature) from the desired value automatically signals a change in input (fuel supply that generates heat) to the system in order to minimize the discrepancy between controlled output and desired output. There are two types of feedback: *negative*, which operates to the advantage of the system to minimize the original deviation in the controlled output, and *positive*, which perpetuates the deprivation, promotes instability, and runs the risk of destroying the organism unless turned off by the calling of another mechanism into play. Clearly, in a biologic system, failure of a negative-feedback system or unbridled positive feedback is capable of causing disorder or disease.

Although it is instructive to draw an analogy between man-made and living systems, it should be noted that a living system is infinitely more complex, entailing endless interplay (information transfer) among all levels in the biologic hierarchy, from cell to organ. Also, the sensory part of the regulatory apparatus is almost invariably more intricate than the effectors. Finally, the desired value ("set point") of a biologic parameter often depends on the physiological state (e.g., as dictated by the diurnal rhythm or the level of physical activity): During sleep, arterial P_{CO_2} is kept higher than during waking hours; while the subject is upright, the set point of the arterial P_{CO_2} is lower than it is while the subject is supine. Larger biologic rhythms, such as the monthly cycles in females, also are associated with different set points for the arterial P_{CO_2}.

The Bounds of Homeostatic Mechanisms

Before we consider the limitations imposed by disease, it is important to recall that the concept of homeostasis was conceived by physiologists to deal with adjustments of normal subjects to changing environments and circumstances. As a rule, considerations of homeostatic mechanisms in normal persons deal with acute or subacute adjustments. As noted above, even in normal subjects, the capacity of the cardiorespiratory-muscular system to transport, deliver, and utilize oxygen in aerobic metabolism is limited. Although compensatory mechanisms such as widening of the arteriovenous difference for oxygen can raise the ceiling, the limit, as defined by the $\dot{V}O_{2\,max}$, remains and is measurable.

A flaw or malfunction at any point in the uptake, transport, and delivery system for oxygen can lower the limit. In normal persons breathing ambient air at sea level, the weak link in the O_2 delivery system is the heart, which has only a modest capacity for increasing stroke volume. When this limitation coexists with hypoxia, as may occur at altitude, oxygen delivery (cardiac output multiplied by O_2 content) can be seriously impaired.

One special case of limitation in the aerobic capacity of the human organism under stress in a hypoxic environment has been seen in mountain climbers who have ascended to the summit of Mount Everest without supplementary oxygen. At this peak (altitude 8848 m), where the inspired P_{O_2} is about 42 mmHg, the $\dot{V}O_{2\,max}$ is at a level that barely suffices for basal metabolism. The oxygen consumption is then limited, in part, by a marked alveolar-arterial P_{O_2} gradient (attributable to diffusion limitation of O_2 uptake across the alveolar-capillary barriers) and the dependence of O_2 uptake and delivery on O_2 exchanges conducted on the steep part of the O_2 dissociation curve.

Homeostatic Malfunctioning

D. W. Richards analyzed the applicability of concepts about homeostatic mechanisms in normal individuals to patients in

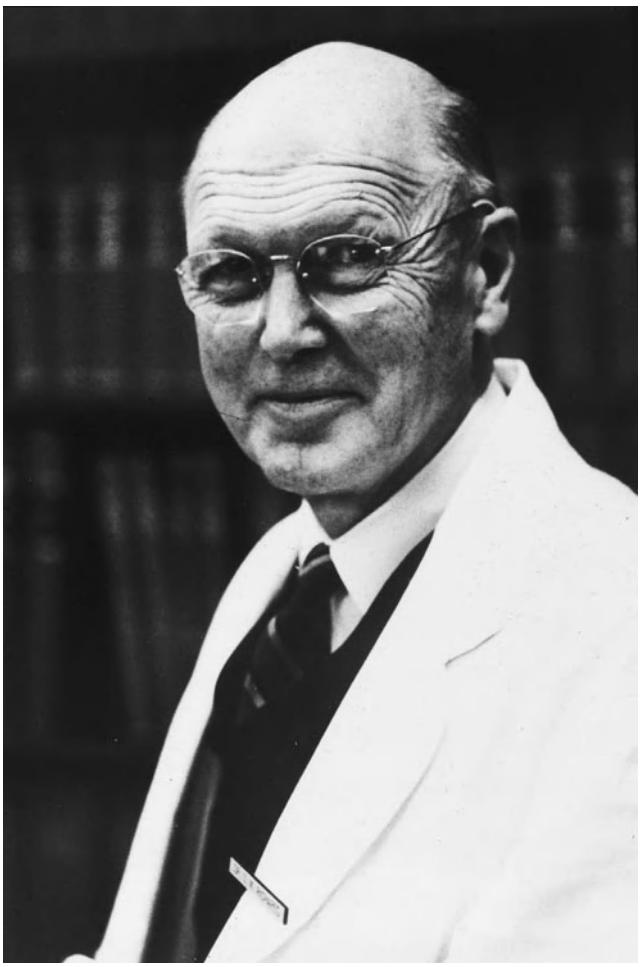

Figure 15-9 Dickinson W. Richards (1895–1973), a physician/scientist, related disturbances in homeostatic mechanisms to clinical disorders. Strongly influenced by L. J. Henderson, he shared the Nobel Prize with André Cournand and Werner Forssmann for contributing to the development of cardiac catheterization and standardization of measurements of pulmonary function.

whom the set point has been dislocated. He took into account that integrative mechanisms designed to restore the internal environment to normal levels operate within boundaries imposed by the structures and functions of the coordinating system. He recognized that diseases of the cardiorespiratory-muscular system often impose additional limits and generate distortions that may cause physiological mechanisms to undershoot or overshoot their mark or become unstable (Fig. 15-9).

Undershooting of homeostatic mechanisms is commonplace in cardiac diseases such as acute myocardial infarction, in which a low cardiac output may compromise oxygen delivery to the tissues despite other compensatory mechanisms, such as widening of the arteriovenous oxygen difference. *Overshooting* can be illustrated by renal failure in the course of the adult respiratory distress syndrome: Ischemic necrosis of the kidney can follow intense systemic homeostatic vasoconstriction to counteract systemic hypotension. *Instabilities* are exemplified by Cheyne-Stokes breathing, in which rhythmic changes in ventilation are accompanied by swings in arterial blood gas composition. These examples represent instances in which homeostatic mechanisms can miss the mark, to the detriment of the organism. In the clinical setting, well-intentioned therapeutic interventions can contribute to homeostatic malfunction. Such iatrogenic disturbances pose continuing threats in emergency or intensive care settings, in which urgency often dictates or dominates therapeutic interventions.

ADAPTATION

Adaptation signifies changes in both physiological and biochemical function and in structure that enhance performance or facilitate survival. It signifies the adjustment of an organism to its environment. In a setting in which O_2 is chronically in short supply, it entails enhancement of the O_2 delivery system coupled with redirection of metabolic activities toward sustaining oxidative functions. In doing so, it spares undue reliance on the anaerobic machinery. As a rule, adaptation is a gradual process in which anatomic changes feature prominently.

Homeostatic (physiological and biochemical) mechanisms are the first line of defense upon exposure to a threatening environment. Subsequently, structural changes come into play (e.g., muscularization of the pulmonary arteries and arterioles at altitude and right ventricular hypertrophy). When the new steady state has been achieved (i.e., when adaptation has occurred), the person at altitude can carry on the activities of daily life, including moderate exercise, about as effectively as at sea level. However, should control mechanisms, such as the sensitivity of the carotid bodies to hypoxia, fail to reset properly, maladaptation ensues. For example, Monge's disease is caused by failure to increase alveolar ventilation due to inadequate responsiveness of the carotid bodies to the hypoxic stimulus. The approach to disease in terms of malfunctioning of homeostatic and adaptive mechanisms is not confined to the cardiorespiratory-muscular system. In a similar fashion, many diseases, such as those due to hypersecretion by endocrine glands or tumors (e.g., thyrotoxicosis, Addison's disease), can be considered in terms of failure of homeostatic and adaptive mechanisms.

Adaptation may be *inherited*, as in native residents at high altitude in whom the process of natural selection, operating over the ages, has yielded a population that can exist, thrive, and reproduce in a hypoxic environment. On the other hand, adaptation may be *nonhereditary,* as in the case of the sea-level native who becomes a permanent dweller at high altitude.

Adaptation is commonly studied in people who relocate to different environments (e.g., from sea level to altitude). Upon arrival at altitude, the newcomer is tachycardic (to sustain cardiac output) and breathes rapidly. In time, these changes are succeeded by adjustments that favor O_2 uptake by

the lungs and O_2 delivery to the tissues (e.g., a left shift of the O_2 dissociation curve and increased capillary density in the muscles). Another common approach to the study of adaptation is to compare populations of animals and humans, born and raised in different environments, with respect to not only adaptive mechanisms, but also genetic influences in adaptation.

Adaptation also has been studied in people exposed to a wide variety of other chronically stressful circumstances. One large group is made up of endurance athletes who, over time, undergo biologic changes that enable them to perform optimally in competitive sports that require maximum oxygen delivery to the exercising muscles. These changes are evident both in the cardiorespiratory system and exercising muscles. The changes in the components of the cardiorespiratory system proceed at different rates: The plasma volume increases (in weeks), the pump capacity of the heart increases (in months to years), the red cell mass increases the O_2-carrying capacity of the blood (in months), the number of capillaries in skeletal muscles increases (in weeks to months), and the mitochondrial enzymes in skeletal muscle increase (in weeks).

During endurance athletic training, not only do the muscles employed in exercise undergo hypertrophy, but also the heart enlarges by combined hypertrophy and dilation, thereby raising the capacity for increasing the cardiac output. Finally, at the maximum level and intensity of the exercise, the $\dot{V}O_{2\,max}$ reaches a plateau ($\dot{V}O_{2\,max}$). Whether the heart or peripheral muscles (i.e., the mitochondria and capillaries) set the limit for maximal O_2 uptake in the endurance-trained athlete continues to be debated. However, the bulk of the evidence currently assigns the limitation to the heart rather than the number of capillaries and mitochondrial enzymes in the peripheral muscles.

Chronic respiratory disease often calls forth adaptive mechanisms that sometimes overshoot their mark. For example, polycythemia, which originates as a homeostatic response to hypoxia and serves to increase the oxygen-carrying capacity of the blood, if continued, increases the circulating blood volume. Cardiac volume and mass then increase to handle the increased circulatory load; i.e., a homeostatic mechanism has been succeeded by adaptive change in the heart. If carried to excess (the so-called "hyperexis" of D. W. Richards), venous thrombosis, on the one hand, or cardiac failure, on the other, may ensue.

Optimization and Limitation of Human Adaptation

The cardiorespiratory-muscular system operates within limits imposed by the structure and the integrated functioning of its components. The maximum oxygen uptake ($\dot{V}O_{2\,max}$) provides a measure of the limit of the capacity of this system to transport and utilize oxygen. The activities of daily life are generally conducted well below this limit. In sports, however, this ceiling is apt to be approached, usually in spurts but occasionally in sustained effort.

The capability of the cardiorespiratory-muscular system to satisfy the energy needs of the cells depends on its ability to match oxygen delivery to their aerobic needs. The system is vulnerable at many sites, particularly where respiration and circulation cross paths—i.e., in the lungs, in which O_2 is taken up from the environment and transferred across alveolar-capillary barriers into flowing blood; in the blood, which transports the oxygen to the tissues; in the tissues, in which the blood releases oxygen for diffusion into cells; and within cells, in which oxygen moves to mitochondria for oxidative phosphorylation, and which generates the high-energy organic phosphates for biologic work. Each of these sites operates within its own boundaries, which, if exceeded, could set the limit of O_2 uptake and delivery for the entire organization (i.e., the $\dot{V}O_{2\,max}$). At each site, buffer mechanisms exist: Between ambient air and the blood is the large volume of alveolar air; in the blood is the large reservoir of hemoglobin; in the muscle cells is the bank of myoglobin; and within the muscle cells are stores of high-energy phosphates. In addition to these stores, which neutralize abrupt changes in oxygen supply, compensatory mechanisms, such as an increase in heart rate to sustain oxygen delivery by increasing cardiac output are on standby alert. The autonomic nerve system plays a critical role in orchestrating the response to the call for oxygen as the energy needs increase.

In disease, adaptation to a chronic impairment may favor realignment of physiological process to compensate for a deficiency in either a component or process of the system. For example, in patients with severe kyphoscoliosis and dwarfing, a breathing pattern is adopted that minimizes the energy cost of breathing; this pattern consists of rapid frequency and small tidal volumes. However, as indicated above for homeostatic overshoot, this pattern may pay the penalty of alveolar hypoventilation, which in turn results in respiratory acidosis and arterial hypoxemia and their consequences, respiratory and cardiac failure. Thus, by adopting a respiratory pattern that minimizes the work, energy cost, and discomfort of breathing, the individual may be put at risk of losing life because of the consequences of alveolar hypoventilation.

Limitation of the adaptive potential can also vary with the disease or circumstance. For example, after lung transplantation, limitation to maximal exercise is imposed not by the heart or lungs but by abnormalities in the peripheral muscles, probably secondary to preoperative muscle disuse and atrophy.

CONCLUSIONS

Exercise is a remarkable example of the integrative and adaptive capacities of the body. Disease may impose limitations on the capacity of the body to acquire, transport, and utilize oxygen. This limitation in aerobic capacity can be tested by calibrated exercise, either graded or global, and the

malfunctioning component uncovered by a combination of clinical evaluation and pulmonary function testing.

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16

Breathing in Exercise

Brian J. Whipp • Susan A. Ward

The increased ventilatory demands imposed by muscular exercise, and the responses to them, should not be considered in isolation. The system is a component of the complex coordinated structure configured to link the atmosphere to the mitochondria through a series of linear conductances, transferring oxygen (O_2) by means of: (1) convective flow of air into the lungs; (2) diffusional exchange into the pulmonary capillary blood; (3) convective flow of arterial blood to the contracting muscle units; and (4) the final diffusive flux into the mitochondria to serve as the terminal oxidant in the electron transport chain. This is the major mechanism of the ATP generation that directly fuels the muscular contractions. However, in order to maintain the acid-base status of the fluid milieux of the contracting muscle units within the relatively narrow range that is compatible with efficient chemical-mechanical coupling, the consequently increased carbon dioxide must be cleared at an appropriate rate along the same pathway.

To preserve alveolar, and hence arterial, O_2 partial pressure (Pa_{O_2}), the O_2 extracted from the alveoli by the increased flow of more-desaturated mixed venous blood must be replenished. The lungs must also provide diluting quantities of CO_2-free (atmospheric) air to the alveoli at rates appropriate for the increased delivery rate of CO_2 by mixed venous blood so as to maintain the stability of alveolar and arterial P_{CO_2}. However, although the function of the lung is commonly defined as that of "arterializing" the mixed-venous blood (regardless of how well the gas exchange has been effected), a better definition, in this regard, might be that its function is to "alveolarize" it. This both obviates the obvious tautology in the definition and also provides a frame of reference for quantifying the effectiveness of the exchange process; this being the alveolar-to-arterial partial pressure difference for the gas of interest.

As schematized in Fig. 16-1, there are competing ventilatory demands for: (a) alveolar PO_2 ($P_{A_{O_2}}$) and P_{CO_2} ($P_{A_{CO_2}}$) regulation when the respiratory exchange ratio (R) differs from unity; and (b) arterial P_{CO_2} (Pa_{CO_2}) and pH (pHa) regulation when the exercise results in a metabolic acidosis, i.e., a reduction of Pa_{CO_2} is necessary to provide respiratory compensation that constrains the fall of pHa. In patients with lung disease, this process is further complicated by pulmonary gas exchange inefficiencies, which result in often-marked differences between alveolar (either "ideal" or "real") and arterial gas partial pressures, which further increase the regulatory demands on ventilation ($\dot{V}_E$). Although many of the integrative aspects of the control of these regulatory processes remain to be elucidated, the general *patterns* of ventilatory response are not topics of serious dispute. These response profiles, especially their dynamics, provide clues to the elements of the control processes.

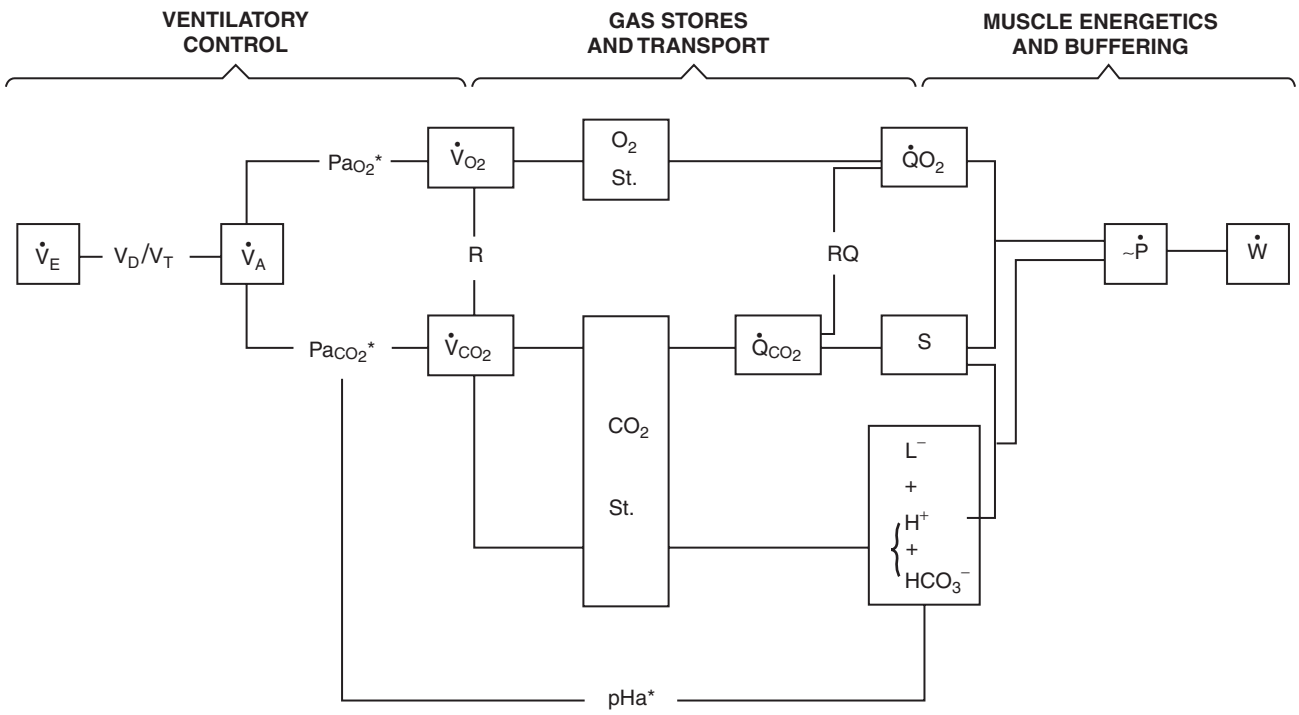

Figure 16-1 Schematic representation of physiological determinants of blood-gas and acid-base regulation in exercise. $\dot{W}$ represents the muscular power generation (i.e., work/time); ~P is the high-energy phosphate utilization rate; S is the metabolic substrate. Other symbols are standard. The regulated variables are denoted by asterisks. See text for further details. *(Reproduced with permission of Whipp BJ, Wasserman K: Blood-gas transport and acid-base, in Crystal RG, West JB (eds), The Lung: Scientific Foundations. New York, Raven Press, 1991, pp 1573–1584.)*

VENTILATORY REQUIREMENTS

We consider the primary feature of the ventilatory demands of muscular exercise to be that of arterial blood-gas and acid-base regulation; mass balance considerations therefore predominate. For example, in the steady state of moderate exercise, mean alveolar, and hence arterial, PO_2 and P_{CO_2} can be regulated at, or close to, resting levels *only if* alveolar ventilation ($\dot{V}A$) increases in *appropriate* proportion to the metabolic rate of the relevant gas. With respect to CO_2 exchange:

$$F_{A_{CO_2}} = \dot{V}_{CO_2}(STPD)/\dot{V}A(STPD) \qquad (1)$$

where

$F_{A_{CO_2}}$ = the fractional concentration of alveolar CO_2
$\dot{V}_{CO_2}$ = pulmonary CO_2 output

Note that in this equation both gas volumes are determined under the same conditions, i.e., standard temperature (0°C) and pressure (one atmosphere) dry (STPD). However, as convention has reasonably dictated that ventilatory volumes are expressed under the conditions at which they actually operate (i.e., body temperature and pressure, saturated with water vapor, BTPS), and as the partial pressure of the gas is of more interest physiologically than the concentration, then:

$$P_{A_{CO_2}} = 863 \cdot \dot{V}_{CO_2}(STPD)/\dot{V}A(BTPS) \qquad (2)$$

and

$$P_{A_{O_2}} = P_{I_{O_2}} - 863 \cdot \dot{V}_{O_2}(STPD)/\dot{V}A(BTPS) \qquad (3)$$

where

863 = the constant that corrects for these different conditions of reporting the gas volumes (at a body temperature of 37°C, saturated with water vapor) and also the transformation of fractional concentration to partial pressure
$P_{I_{O_2}}$ = inspired P_{O_2}
$\dot{V}_{O_2}$ = pulmonary O_2 uptake

However, neither $\dot{V}A$ nor the alveolar gas partial pressures in Eqs. (2) and (3) are conceptually straightforward. That is, it is difficult to validly establish a single average value for the alveolar gas tensions in a structure as complex as the lung, which has significant regional differences of alveolar ventilation-to-perfusion ($\dot{V}A/\dot{Q}$) ratios. The expedient of assigning $P_{A_{CO_2}}$ to be exactly equal to Pa_{CO_2}, as would be the case in the "ideal" lung, dispenses with this difficulty and allows $\dot{V}A$ to be computed readily from Eq. (2). However, this alveolar ventilation is figmentary. Similarly, the alveolar P_{O_2} in Eq. (3) is also that of the "ideal" lung: The "real" $P_{A_{O_2}}$ would be higher and the "real" $P_{A_{CO_2}}$ lower than the "ideal" alveolar values calculated in this manner.

Accepting these definitions, and ignoring the slight effect on P_{O_2} of the small difference between inspired ventilation ($\dot{V}I$) and $\dot{V}E$ that occurs when the respiratory exchange

ratio (R) does not equal 1, it becomes apparent from Eqs. (2) and (3) that $P_{A_{CO_2}}$ and $P_{A_{O_2}}$ can only be maintained constant during exercise if $\dot{V}_A$ changes in precise proportion to $\dot{V}_{CO_2}$ and $\dot{V}_{O_2}$, respectively. Note, however, that $\dot{V}_A$ is common to both equations, i.e.:

$$863 \cdot \dot{V}_{CO_2}/P_{A_{CO_2}} \leftarrow \dot{V}_A \rightarrow 863 \cdot \dot{V}_{O_2}/(P_{I_{O_2}} - P_{A_{O_2}}) \quad (4)$$

Therefore, alveolar ventilation cannot meet the demands of both pulmonary O_2 and CO_2 exchange under conditions in which $\dot{V}_{O_2}$ and $\dot{V}_{CO_2}$ differ. This can occur during exercise, either because of differences in substrate utilization or because of transient variations in the body gas stores. Under such conditions, $\dot{V}_E$ has been consistently demonstrated to change in closer proportion to $\dot{V}_{CO_2}$ than to $\dot{V}_{O_2}$. Pa_{CO_2} is therefore the more closely regulated variable, with alveolar and arterial P_{O_2} changing as a consequence. In normal subjects at sea level, these P_{O_2} changes only vary over the relatively flat upper region of the oxyhemoglobin dissociation curve, with little consequent effect on arterial O_2 content or saturation.

The close coupling of $\dot{V}_E$ to $\dot{V}_{CO_2}$ is perhaps most strikingly evident in their responses to a constant-load exercise of moderate intensity (Fig. 16-2, *left panel*). Following an initial $\dot{V}_E$ component (phase 1, $\phi 1$) of modest amplitude and short duration (i.e., 15–20 seconds), a more prominent slower and exponential phase 2 ($\phi 2$) component follows whose time course is very similar to but very slightly slower than that of $\dot{V}_{CO_2}$ and, interestingly, *considerably* slower than that of $\dot{V}_{O_2}$. Consequently, the rate of development of these $\phi 2$ profiles can be described by a time constant (τ), that is, the time taken to attain 63% (i.e., $(1 - 1/e) \cdot 100$) of the steady-state (or phase 3, $\phi 3$) response, or to a close approximation as 1.5 times the half-time of the response. The close matching of $\dot{V}_E$ to $\dot{V}_{CO_2}$ establishes the relative stability of Pa_{CO_2} both in the steady and transient phases of moderate exercise.

Consequently, it is more appropriate to consider the ventilatory demands of exercise using CO_2 exchange rather than O_2 exchange as the frame of reference. Note, however, that the relevant "CO_2" in this relationship is the exchange rate at the lung and *not* that of the muscle. It follows from Eq. (2) that the demands for alveolar ventilation increase as a linear function of $\dot{V}_{CO_2}$ at any "set-point" level of Pa_{CO_2}:

$$\dot{V}_A(BTPS) = 863 \cdot \dot{V}_{CO_2}(STPD)/Pa_{CO_2} \quad (5)$$

Consequently, the greater the $\dot{V}_{CO_2}$, the greater is the ventilatory requirement. However, if Pa_{CO_2} is regulated at a lower level, $\dot{V}_A$ must be appropriately higher for any given level of $\dot{V}_{CO_2}$. Nevertheless, ventilating the alveoli requires simultaneous ventilation of the dead space; i.e., the ventilatory demand is expressed through the total or minute ventilation ($\dot{V}_E$), not $\dot{V}_A$. However, as:

$$\dot{V}_A = \dot{V}_E - \dot{V}_D \quad (6)$$

or

$$\dot{V}_A = \dot{V}_E(1 - V_D/V_T) \quad (7)$$

then

$$\dot{V}_A = 863 \cdot \dot{V}_{CO_2}/Pa_{CO_2}(1 - V_D/V_T) \quad (8)$$

where

V_D/V_T = the physiological dead space fraction of the breath

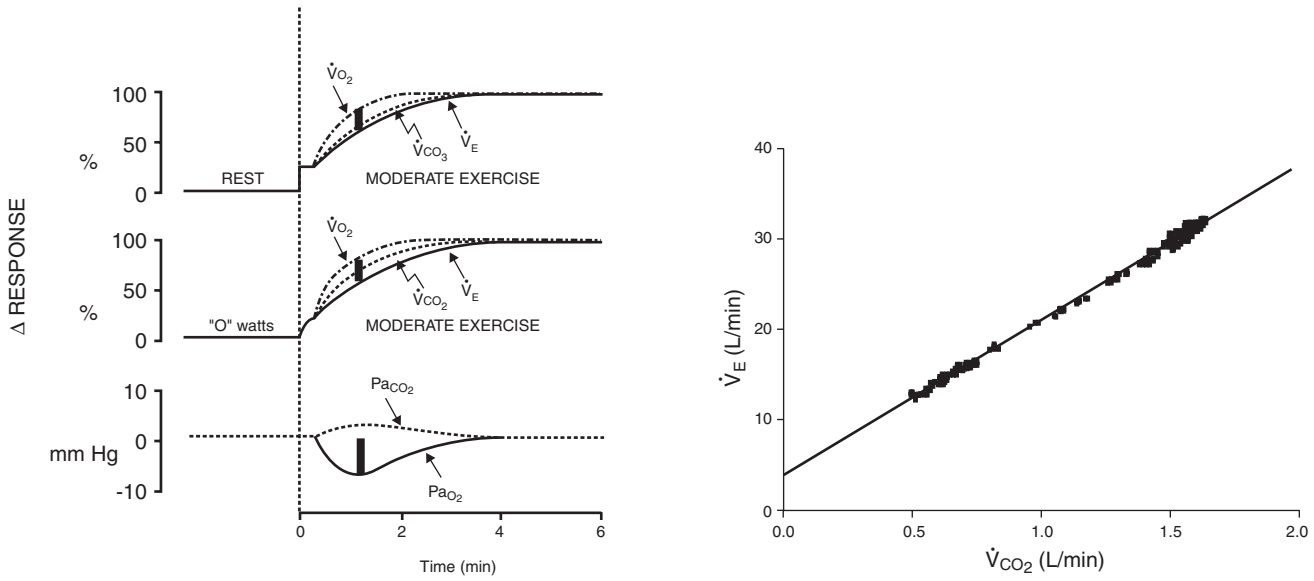

Figure 16-2 *Left.* Schematic representation of time course of O_2 uptake ($\dot{V}_{O_2}$, — · —), CO_2 output ($\dot{V}_{CO_2}$, · · · · · ·), and ventilation ($\dot{V}_E$, —) in response to a moderate work-rate step from rest *(top panel)* and unloaded pedaling *(middle panel),* with corresponding profiles of arterial P_{CO_2} (Pa_{CO_2}, · · · · · ·) and P_{O_2} (Pa_{O_2}, ———). *(Reproduced with permission of Whipp BJ, Ward SA: Int J Sports Med 1:146–159, 1981.) Right:* "Cross plot" of $\dot{V}_E$ as a function of $\dot{V}_{CO_2}$ during the on-transient of a moderate work-rate step. In both panels, note close matching of $\dot{V}_E$ to $\dot{V}_{CO_2}$.

Table 16-1

Determinants of Exercise Ventilation

	$\dot{V}_{O_2}$ (L/min)	R	$\dot{V}_{CO_2}$ (L/min)	Pa_{CO_2} (mm)	V_D/V_T	$\dot{V}_E$ (L/min)
a	1.00	0.85	0.85	40	0.2	23.0
b	1.00	0.80	0.80	60	0.5	23.0
c	1.00	0.85	0.85	50	0.2	18.3
d	1.00	1.00	1.00	30	0.5	57.6

Therefore, the ventilatory demands of exercise should be considered with respect to the three defining variables of Eq. (8):

1. The rate of pulmonary CO_2 clearance ($\dot{V}_{CO_2}$)
2. The *set-point* at which Pa_{CO_2} is regulated
3. The *physiological dead space fraction of the breath,* which represents *an* index of the *inefficiency* of pulmonary gas exchange

As shown in Table 16-1, for a range of reasonably representative values at a notional $\dot{V}_{O_2}$ of 1 L/minute, simultaneous changes in these defining variables can elicit major variations in the level of exercise $\dot{V}_E$ or potentially misleadingly similar values: a, provides a normal frame of reference; b, a subject with gas exchange abnormality (as reflected by the high V_D/V_T) and a degree of CO_2 retention, the resulting $\dot{V}_E$ being apparently normal; c, also has some CO_2 retention but, with a normal V_D/V_T, yields a relatively low $\dot{V}_E$; d, the combination of high R and V_D/V_T coupled with a low Pa_{CO_2} yields a $\dot{V}_E$ more than threefold greater than for c.

It should be noted that end-tidal P_{CO_2} ($P_{ET}CO_2$) is not a good index of either the level or pattern of change of arterial P_{CO_2}, especially during exercise; it becomes systematically greater than Pa_{CO_2} in normal subjects, by an amount that depends both on the metabolic rate and the pattern of breathing. The reason for this is that $P_{A}CO_2$ and Pa_{CO_2} fluctuate during the breathing cycle: increasing throughout expiration (chiefly as a result of continuing gas exchange, as the mixed-venous P_{CO_2} ($P\bar{v}_{CO_2}$) is greater than $P_{A}CO_2$) and decreases during inspiration. However, arterial blood is normally sampled over several respiratory cycles. Hence, the syringe value represents the mean of the Pa_{CO_2} oscillation. The end-tidal value, in contrast, is a measure of the peak of this oscillation. Consequently, $P_{ET}CO_2$ is greater than both mean $P_{A}CO_2$ and Pa_{CO_2}. As work rate (WR) and $P\bar{v}_{CO_2}$ increase, so the does the rate at which arterial and alveolar P_{CO_2} increase during exhalation, resulting in a further widening of the end-tidal to arterial P_{CO_2} difference ($P[_{ET}\text{-}a]_{CO_2}$). Naturally, when breathing frequency increases at high WRs, the shortened expiratory duration truncates the rising phase of $P_{A}CO_2$, attenuating the increase in $P[_{ET}\text{-}a]_{CO_2}$. Consequently, $P_{ET}CO_2$ should *not* be used as a direct estimator of Pa_{CO_2}, either for ventilatory control considerations or for computing the physiological dead space or cardiac output during exercise. Mean alveolar P_{CO_2}, estimated from the time average of the $P_{A}CO_2$ profile, provides a better index of Pa_{CO_2} during exercise—but only in subjects free of pulmonary disease (including pulmonary vascular disease), as maldistribution of $\dot{V}_A/\dot{Q}$ leads to mean alveolar P_{CO_2} being necessarily less and $P_{ET}CO_2$ being typically less than the arterial value.

Although arterial hypocapnia is characteristic for normal subjects during high-intensity exercise, Pa_{O_2} (at least at sea level) tends to be maintained at or close to resting levels. However, as both the ventilatory equivalent for O_2 ($\dot{V}_E/\dot{V}_{O_2}$) and "ideal" $P_{A}O_2$ increase systematically at these work rates, why does Pa_{O_2} not also increase systematically? Rather, there is a progressive widening of the alveolar-to-arterial P_{O_2} difference ($P[_{A}\text{-}a]_{O_2}$), from 5 mmHg or so at rest to as much as 40 mmHg or more in athletic subjects at high WRs.

As the topographical distributions of $\dot{V}_A$ and $\dot{Q}$ in the lung had been shown to be improved (at least for upright moderate exercise) it was assumed, seemingly reasonably, that the $\dot{V}_A/\dot{Q}$ distribution itself was also improved and that the lung exchanged gas more efficiently during exercise than at rest. Interestingly, however, the multiple inert gas technique has actually demonstrated that the dispersion of the $\dot{V}_A/\dot{Q}$ distribution is *increased* at high WRs, although with great inter-subject variability. This increased dispersion seems only sufficient to account for a relatively small component of the widening of the $P[_{A}\text{-}a]_{O_2}$. Lack of diffusion equilibrium across the alveolar-capillary membrane at these high WRs is thought to be the major contributor, even at sea level, as a result of some lung regions not having the capacity to recruit pulmonary capillary volume appropriately for the increased capillary flow. Therefore, the capillary transit time becomes insufficient for diffusion equilibrium of P_{O_2}, a mechanism exacerbated by pulmonary disease and also a major contributor to the arterial hypoxemia seen at high WRs in some highly fit subjects. However, there is also likely to be a distribution of transit times, on the basis of variations of both pulmonary-capillary lengths and diameters. Transit times longer than the critical do not further increase oxygenation; shorter ones reduce it further. Consequently, the actual hypoxemia-inducing effect begins to be manifest at WRs *less* than suggested by the *mean* transit time.

Although it has been demonstrated that intrapulmonary and intra-cardiac right-to-left shunts normally provide only a small contribution to the widened $P[_{A}\text{-}a]_{O_2}$, the reduction in mixed-venous O_2 content (especially during high-intensity exercise) affects $P[_{A}\text{-}a]_{O_2}$ more markedly for any given shunt fraction of the cardiac output ($\dot{Q}s/\dot{Q}t$) or any degree of $\dot{V}_A/\dot{Q}$ mismatch.

CO_2 Clearance

CO_2 clearance measured at the lung ($\dot{V}_{CO_2}$) only equals the CO_2 production rate in the tissues ($\dot{Q}_{CO_2}$) in the steady-state of exercise. Under these conditions R equals the metabolic

Table 16-2

Energetics of Substrate Catabolism

	RQ	$\dot{V}_{O_2}$ (L/min)	$\dot{V}_{CO_2}$ (L/min)	~P:O_2	~P:CO_2	O_2 ~:P	CO_2 ~:P
Glycogen	1.0	1.0	1.0	6.00	6.00	6.00	0.17
Palmitate	0.7	1.0	0.7	5.65	8.13	8.13	0.12
Glycogen/palmitate	1.43	1.0	1.43	1.06	0.74	0.74	1.42

Values are expressed at a particular $\dot{V}_{O_2}$ of 1L/min.

RQ. The substrates being catabolized, therefore contribute to the RQ and place fundamental demands on the pulmonary system. For example, a given rate of high-energy phosphate formation requires 6% less O_2 when carbohydrate is metabolized than when fatty acids serve as the substrate (Table 16-2). However, the carbohydrate metabolism yields 40% more CO_2 than for a typical fatty acid, leading to a greater demand for CO_2 clearance and, by extension, $\dot{V}_E$. To minimize the ventilatory demands for CO_2 clearance, fatty acids may be considered a more suitable substrate. The consequence is that alveolar and arterial PO_2 are necessarily reduced, as $\dot{V}_E$ is now low for the O_2 requirement of the task. Conversely, alveolar and arterial Po_2 are higher in subjects metabolizing carbohydrate, other things being equal.

Under non–steady-state conditions $\dot{V}_{CO_2}$ is dissociated from $\dot{Q}_{CO_2}$ as a result of transient changes in the body CO_2 stores (Figs. 16-1 and 16-2). Thus, during the on-transient of constant-load exercise, some of the metabolically produced CO_2 never reaches the lung for exchange as a result of the capacitative storage of CO_2, predominantly in the muscle. Therefore, $\dot{V}_{CO_2}$ is less than $\dot{Q}_{CO_2}$ during this phase. Because the changes in the muscle O_2 stores are trivially small with respect to those of CO_2, R *falls* transiently to reach a minimum at the point of the maximum *rate* of CO_2 storage. It subsequently rises again to equal the new metabolic steady-state RQ as the muscle P_{CO_2} stabilizes at its new and higher exercise value. As noted, although $\dot{V}_E$ during the transient is closely coupled to $\dot{V}_{CO_2}$, it changes slowly with respect to $\dot{V}_{O_2}$ (Fig. 16-2, *left*) which has a more rapid time constant. Consequently, alveolar and arterial Po_2 are reduced in the transient (Fig. 16-2, *left*). At the off-transient, the increased levels of the CO_2 stores now discharge, leading the pulmonary R to increase to levels *above* that of the metabolic RQ.

At WRs associated with a metabolic (chiefly lactate) acidosis (above the lactate threshold, θ_L), pulmonary CO_2 exchange is increased further. Additional CO_2 is produced as a result of the bicarbonate (HCO_3^-) component of the proton buffering that is formed in concert with the increased lactate at these WRs:

$$\begin{aligned} CH_3 \cdot CHOH \cdot COO^- + H^+ + NaHCO_3 \rightarrow \\ CH_3 \cdot CHOH \cdot COO \cdot Na + H_2CO_3 \\ CO_2 + H_2O \end{aligned} \qquad (9)$$

The extra CO_2 formed in these reactions is quantitatively large. For example, although the complete aerobic catabolism of one glucosyl unit of glycogen to CO_2 and H_2O yields 37 ATP molecules, its breakdown to two lactates and associated protons yields only three ATP molecules. Therefore, glycolytic flux must increase by 12.3-fold (37/3) to sustain the required ATP production rate. This leads to 24.6 mEq of lactate (2 × 12.3 mEq). Consequently, the accompanying proton production decreases [HCO_3^-] by approximately 22 mEq; i.e., HCO_3^- only accounts for 90% of this buffering. Phosphate and protein buffers provide the remainder. Of this *additional* yield of approximately 22 mM of CO_2 production, however, 6 mM replaces the CO_2 that would have been produced aerobically for this rate of ATP formation:

$$\begin{aligned} &22 \text{ mM anaerobic } CO_2 - 6 \text{ mM aerobic } CO_2 \\ &= 16 \text{ mM net } CO_2 \text{ yield} \end{aligned}$$

This represents an approximately 2.5-fold increase in $\dot{V}_{CO_2}$ – for the anaerobic component of the total $\dot{V}_{CO_2}$.

The extra *amount* of CO_2 produced under these conditions is a direct function of the *amount* of [HCO_3^-] decrease in blood and muscle compartments. Any contribution from non–HCO_3^- buffering mechanisms (e.g., phosphate and protein), although important for [H^+] regulation, does not produce extra CO_2. Consequently, the *rate* at which extra CO_2 is produced from these reactions is directly related to the *rate* at which HCO_3^- levels fall, not, it should be recognized, the *amount* of the decrease. Consequently, the more rapid the rate of rise of [lactate], the greater is the increase in $\dot{V}_{CO_2}$. This accounts for both $\dot{V}_{CO_2}$ and R (and, importantly, work rate) being appreciably higher in the period of increasing blood [lactate] during rapid-incremental exercise, compared with tests in which the WR incrementation rate is slow (Fig. 16-3).

Arterial P_{CO_2} Set-Point

Although Pa_{CO_2} is normally regulated at or near resting levels in the steady-state of moderate exercise, hyperventilation can occur transiently at exercise onset, especially in excitable subjects. This is more common in treadmill than cycle ergometry. However, as the $\dot{V}_E$ time constant ($\tau\dot{V}_E$) during the subsequent increase to the steady state is slightly longer than

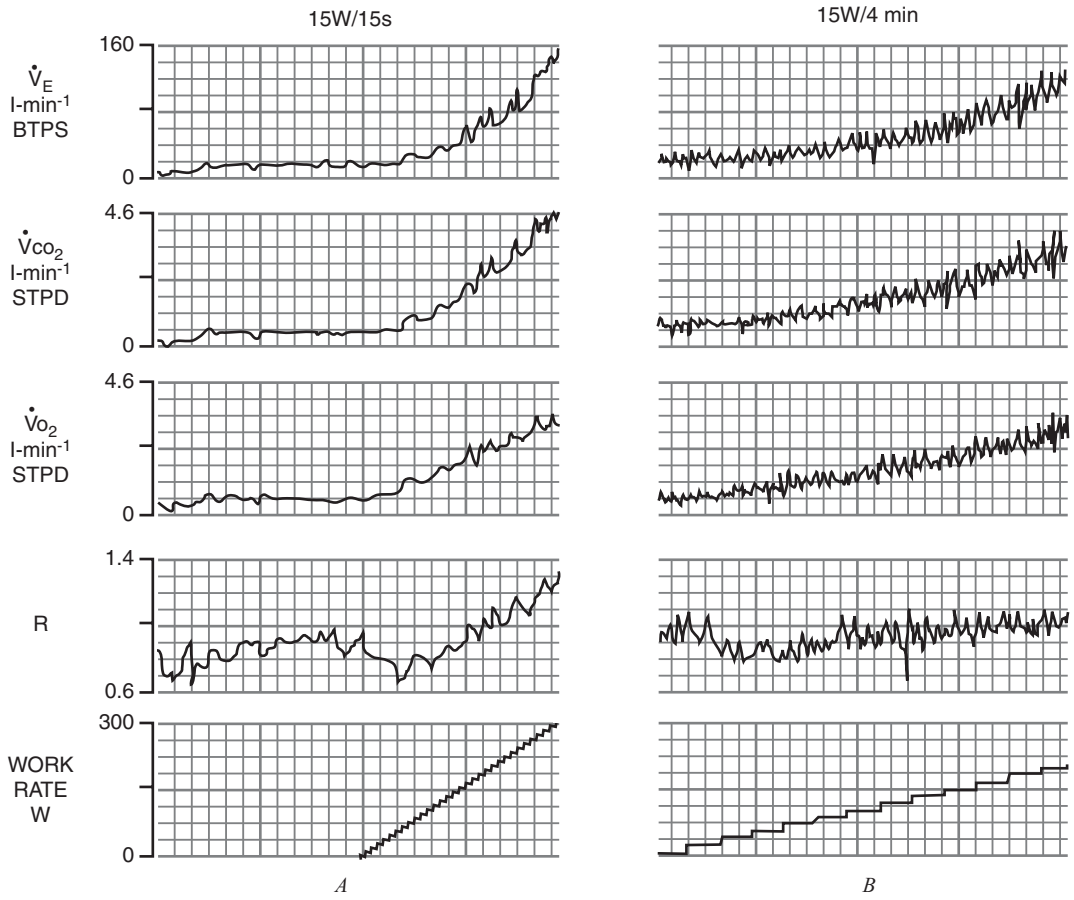

Figure 16-3 Ventilatory and pulmonary gas exchange response to a rapidly incrementing *(A)* and slowly incrementing *(B)* exercise test in the same subject, each performed to the limit of tolerance. Note that, although the peak $\dot{V}_{O_2}$ is not appreciably different in the two tests, the maximum values of $\dot{V}_E$, $\dot{V}_{CO_2}$, R, and WR are all significantly greater during the rapidly incremental test.

$\tau\dot{V}_{CO_2}$, a small and transient increase in $P_{A_{CO_2}}$ and Pa_{CO_2} is predictable and has been measured. $\tau\dot{V}_E$ seems to depend largely on the sensitivity of the subject's peripheral chemoreceptors, in humans predominantly the carotid bodies. Thus, $\tau\dot{V}_E$ is short when carotid body sensitivity is high (e.g., with hypoxia or metabolic acidemia), whereas $\tau\dot{V}_E$ is long when carotid body sensitivity is low (e.g., with hyperoxia, pharmacological suppression with dopamine or following their surgical resection) (Fig. 16-4).

Although Pa_{CO_2} appears to be a regulated variable during moderate exercise, it must be lowered by hyperventilation to constrain the fall of pHa at levels of exercise that induce a metabolic acidosis. This compensatory decrease in Pa_{CO_2} washes CO_2 out of the body stores and provides an additional source of extra CO_2 at high WRs:

$$pHa = pK' + \log\{[HCO_3^-]a/\alpha \cdot Pa_{CO_2}\} \qquad (10)$$

where

α = the CO_2 solubility coefficient that relates Pa_{CO_2} (mmHg) to CO_2 content (mM/L)

An instructive consideration of the inter-relationship among the ventilatory-related variables for pHa regulation is apparent in an alternative way of considering Eq. (10):

$$pH_a = pK' + \log\left\{([HCO_3^-]_a/25.9) \cdot (\dot{V}_E/\dot{V}_{CO_2}) \cdot (1 - V_D/V_T)\right\} \qquad (11)$$

where

$\dot{V}_E/\dot{V}_{CO_2}$ = the ventilatory equivalent for CO_2

Physiological Dead Space

The total requirement for dead space ventilation must, of course, take account of both the anatomical and alveolar dead space volumes. In healthy subjects at rest, the alveolar dead space is small and reflects, in large part, the relative underperfusion of apical alveoli. However, during exercise, the increased pulmonary artery pressure leads to a more even perfusion throughout the lung, tending to reduce the alveolar dead space. Furthermore, as the end-inspiratory expansion of the conducting airways during exercise is small compared

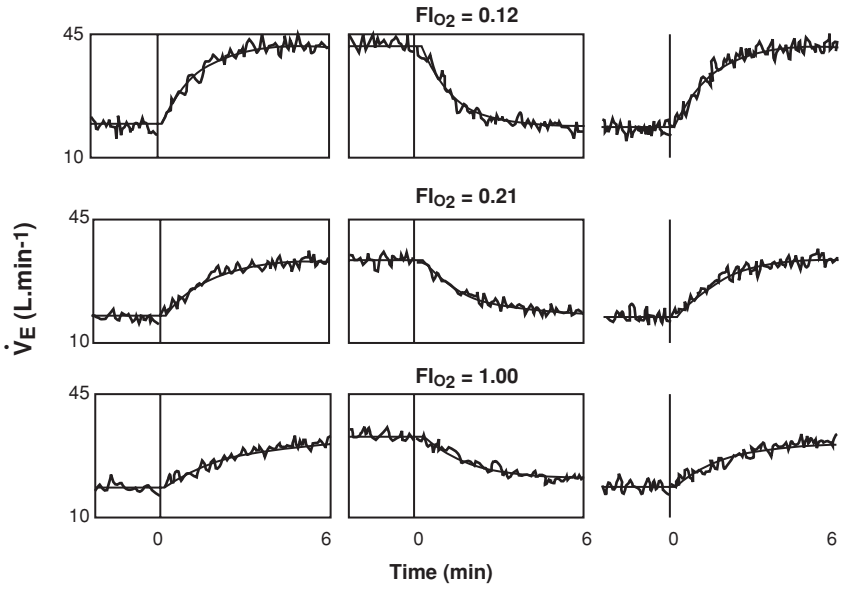

Figure 16-4 Influence of inhaled O_2 fraction (FI_{O_2} = 0.12, 0.21, and 1.00) on the time course of the phase 2 $\dot{V}_E$ response to moderate constant-load cycling (90 W) from unloaded pedaling, for a single subject. *Left panel.* On-transient responses, with the best-fit monoexponential superimposed. *Center panel.* Off-transient responses, with the best-fit monoexponential superimposed. *Right panel.* Off-transient responses (reversed) superimposed on the corresponding on-transient responses. Note that these superimposed responses are effectively indistinguishable. *(Reproduced with permission of Whipp BJ, Ward SA: Pulmonary Physiology and Pathophysiology of Exercise. New York, Dekker, 1991, pp 271–307.)*

with that of the total lung volume increase, V_D/V_T falls despite the absolute value of the dead space increasing.

Ventilation typically increases linearly with respect to $\dot{V}_{CO_2}$ over a wide WR range (Figs. 16-2 and 16-5, *right*):

$$\dot{V}_E = m \times \dot{V}_{CO_2} + c \qquad (12)$$

where

- m = the slope that has a value of approximately 25 in healthy young subjects (when $\dot{V}_E$ and $\dot{V}_{CO_2}$ are reported in L/minute)
- c = the $\dot{V}_E$-intercept, which has a value of approximately 3–5 L/minute

Therefore, it is important to recognize that the $\dot{V}_E - \dot{V}_{CO_2}$ slope alone is *not* the decisive variable with respect to Pa_{CO_2} and pHa regulation, as is apparent from Eq. (11) and also from Eq. (8), which can be rearranged as:

$$Pa_{CO_2} = 863/(\dot{V}_E/\dot{V}_{CO_2}) \cdot (1 - V_D/V_T) \qquad (13)$$

Note that two compound variables dictate the regulation, but *only* two! Therefore, $\dot{V}_E/\dot{V}_{CO_2}$ and V_D/V_T must change in a closely related pattern for Pa_{CO_2} to be regulated (Fig. 16-6); that is, the normal decrease in V_D/V_T must be closely matched by the decrease in $\dot{V}_E/\dot{V}_{CO_2}$ for Pa_{CO_2} to be regulated (Fig. 16-6*A*). Although $\dot{V}_E/\dot{V}_{CO_2}$ also typically decreases during exercise in patients with airflow limitation (Fig. 16-6*B*), it neither falls to the normal level nor is there the secondary

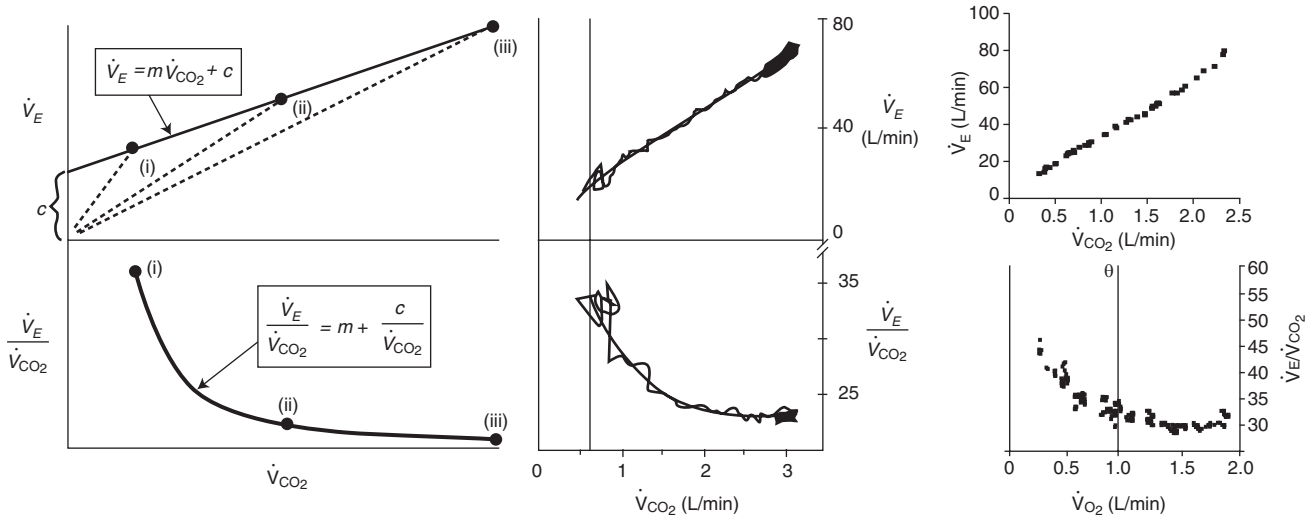

Figure 16-5 *Left.* Schematized responses of $\dot{V}_E$ and $\dot{V}_E/\dot{V}_{CO_2}$ as a function of $\dot{V}_{CO_2}$ for square-wave exercise. The dashed lines represent $\dot{V}_E/\dot{V}_{CO_2}$ isopleths at three progressively higher levels of $\dot{V}_{CO_2}$ *(below). Center and right.* As for the left panel, but showing actual responses in a representative subject during square-wave and incremental exercise. *(Modified with permission of Whipp BJ, Ward SA: J Exp Biol 100:175–193, 1982.)*

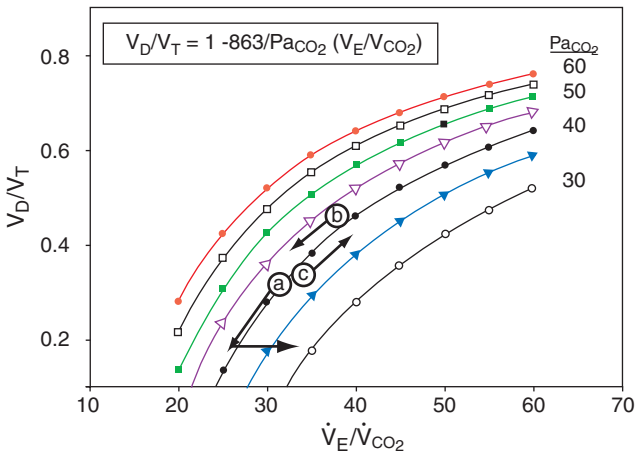

Figure 16-6 Schematic to illustrate the interaction between physiological dead space fraction of the breath (V_D/V_T) and ventilatory equivalent for CO_2 ($\dot{V}_E/\dot{V}_{CO_2}$) as determinants of Pa_{CO_2}. To maintain isocapnia on going from rest to moderate exercise, the decrease in $\dot{V}_E/\dot{V}_{CO_2}$ must be appropriate for the fall in V_D/V_T *(normal subject, a)*. As there is little further change in V_D/V_T during high-intensity exercise, the compensatory hyperventilation is brought about by $\dot{V}_E/\dot{V}_{CO_2}$ now increasing from its reduced level; this increase is commonly not seen in subjects with airflow limitation (e.g., *b*). When V_D/V_T actually increases, Pa_{CO_2} is maintained only if $\dot{V}_E/\dot{V}_{CO_2}$ increases appropriately (e.g., *c*). See text for further consideration.

increase in $\dot{V}_E/\dot{V}_{CO_2}$ that normally occurs at high WRs (or one that is markedly attenuated). The ventilatory impairment constrains the response. The consequence is typically a modest uncompensated metabolic acidosis at maximum exercise. Similarly, the relatively sudden increase in V_D/V_T associated with the opening of a right-to-left shunt in many patients with pulmonary hypertension requires an appropriate increase in $\dot{V}_E/\dot{V}_{CO_2}$ for Pa_{CO_2} to be regulated (Fig. 16-6*C*).

Consequently, as shown in Eqs. (12) and (13) and Fig. 16-6, it is the ventilatory equivalent for CO_2 that is the crucial CO_2-linked variable with respect to Pa_{CO_2} and pHa regulation and *not* the slope of the linear $\dot{V}_E$-$\dot{V}_{CO_2}$ relationship per se. Furthermore, it is the profile of the hyperbolic decrease in V_D/V_T, consequent to the linear increase in V_D as a function of V_T (Fig. 16-5) that determines the hyperbolic decline in $\dot{V}_E/\dot{V}_{CO_2}$ over the region for which Pa_{CO_2} remains regulated, with control mechanisms that remain poorly understood.

End-expiratory lung volume (EELV) plays an important role in the ventilatory response to exercise, especially its pattern of response. The profile of EELV change during exercise is usually determined by having the subject perform a series of inspiratory capacity (IC) maneuvers during the exercise test and assuming that TLC remains unaltered. In normal subjects, EELV typically decreases by as much as 0.5 L, or more, below functional residual capacity (FRC) with increasing WR (Fig. 16-7). This not only improves the mechanical advantage of the inspiratory muscles, but also maintains a low elastic work of breathing by allowing V_T to operate over a wider "linear" range of the thoracic volume-pressure (i.e., compliance) curve (Fig. 16-7*A*). Conditions such as chronic obstructive pulmonary disease (COPD), which predispose to increased regional pulmonary-mechanical time constants, can reduce the spontaneous emptying rate to an extent that FRC is not re-attained in time for the next inhalation (Fig. 16-7*C*). EELV consequently increases (dynamic hyperinflation) with progressive increases in WR. Attempts to increase flow by further expiratory effort are typically counterproductive. The associated reduction in inspiratory capacity places increased demands on the inspiratory muscles and also reduces

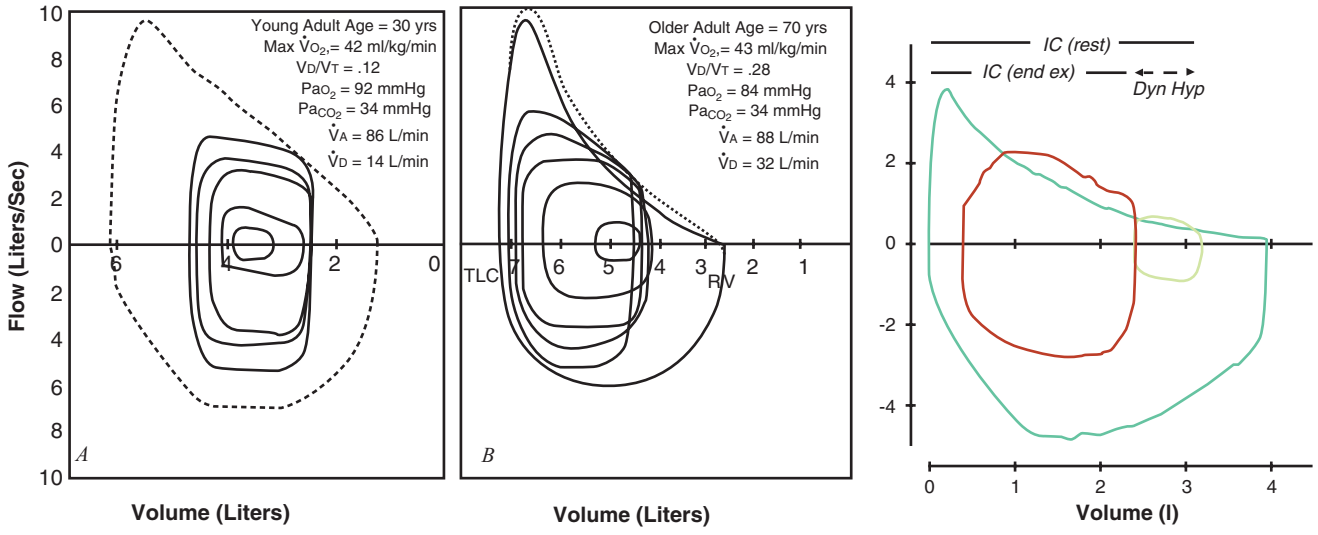

Figure 16-7 Comparison of *spontaneous* airflow-lung volume relationships at rest and during exercise with that of the *maximum* resting relationship in *(A)* a healthy "youngish" subject; *(B)* a healthy "oldish" subject; and *(C)* a patient with COPD. Note during exercise: little or no airflow limitation and a decrease in EELV in *(A)*; significant airflow limitation, an initial decrease in EELV but a subsequent increase in *(B)*; and spontaneous airflow that exceeds that achieved on the maximum maneuver and an increase in EELV in *(c)*. See text for further elaboration. (Panels A and B reproduced with permission of Johnson BD, Badr MS and Dempsey JA: Clinics in Chest Medicine 15:229–246, 1994.)

the scope for V_T increase before end-inspiratory lung volume (EILV) begins to encroach onto the flatter upper reaches of the compliance curve. In ostensibly normal elderly subjects (but with the age-related reductions of lung recoil increasing the mechanical time constant(s)), EELV has been shown to decline over the moderate WR range, but then subsequently to increase back toward, or often beyond, the resting level of FRC as the mechanical time constants become inadequate for the increased airflow demands (Fig. 16-7*B*).

VENTILATORY CONTROL

Although the postulated mechanisms of ventilatory control during exercise continue to foment considerable debate, neurogenic, chemoreflex, and circulatory-coupled processes are considered to be contributory. The challenge is to establish a justifiable control model that not only integrates these processes, but also accounts for both the dynamic and steady-state $\dot{V}_E$ responses over the range of exercise intensities. Such a model is not yet available.

Central Neural Control

As the ventilatory and cardiovascular responses to dynamic muscular exercise are initiated with little or no discernible delay, they are considered to result from neurogenic mechanisms of both central and peripheral origin.

Central Command

The cortical somatomotor command that triggers locomotion has been proposed also to influence brain stem respiratory (and cardiovascular) control centers. This has been termed "central command" of ventilatory responses, which is roughly equivalent to the magnitude of the "central command" to locomotion. Proponents of central command argue that feedback control via humoral mediation (or related to muscle contraction) need only be modest to provide a $\dot{V}_E$ response that is appropriate for the metabolic demands of the exercise.

The descending motor influences on the medullary ventilatory integrating regions include: (1) direct "irradiation" of the cortical somatomotor drive; and (2) subcortical projections from hypothalamic regions, such as the paraventricular locomotor region of the hypothalamus and the fields of Forel, and mesencephalic locomotor regions. Evidence that supports central neurogenesis derives from animal studies in which discrete focal CNS stimulation is used to activate descending central command pathways to ventilatory control regions; and also experiments in humans that attempt to dissociate the magnitude of central command from its subsequent motor outcome. For example, in conscious rats running on a treadmill, *c*-fos labeling has been used to identify activity in the hypothalamic and mesencephalic locomotor regions as well as medullary regions involved in cardiorespiratory integration. Furthermore, evidence of motor cortical involvement in the exercise hyperpnea has been provided in humans using positron emission tomography (PET) to estimate regional cerebral blood flow (indicative of regional neuronal activation). Thus, significant increases in the superomedial primary motor cortical activity (i.e., spatially consistent with the motor cortical leg region) have been demonstrated during leg exercise but not recovery. In contrast, although the activity of the superolateral primary cortical areas also increased during exercise, the activity remained during recovery. As these superolateral regions previously have been demonstrated to be associated with volitional activation of the respiratory muscles, it was concluded that this provided evidence in humans for a feed-forward component of the exercise hyperpnea, of motor cortical origin.

However, evidence from animal studies suggests that the cerebral cortex is not the sole origin of this control component. Spontaneous locomotion can be elicited in decorticate animals that is associated with prompt respiratory and cardiovascular responses. Focal stimulation (electrical or chemical) of the hypothalamic paraventricular locomotor region or the H2 field of Forel leads to locomotor activity accompanied by rapid hyperpnea, tachycardia, and arterial hypertension. Furthermore, efferent neural connections have been demonstrated from these hypothalamic sites to medullary sites of cardiovascular and respiratory control, such as the nucleus of the solitary tract (NTS), nucleus ambiguus, and dorsal vagal nucleus.

These evoked responses are essentially unaffected by muscle paralysis; hence, they appear not to depend on actual muscular contraction and increased metabolic rate. Although neural projections from the NTS to hypothalamic locomotor regions have been demonstrated (i.e., consistent with central command modulation by respiratory-related neuronal feedback), it is still not clear to what extent the hypothalamus is involved in the normal exercise hyperpnea. For example, the normal exercise $\dot{V}_E$ profile has been reported to be abolished by hypothalamic lesioning, as was also the case for the "fictive" locomotory model. However, removal of hypothalamic influences had no clear effect in other studies. Furthermore, no evidence of increased neuronal activity in these hypothalamic motor regions was found during exercise in conscious humans using PET, despite evidence of increased cortical respiratory motor activity. These hypothalamically induced $\dot{V}_E$ responses are also typically accompanied by a rapid and usually marked hypocapnia. This is not normally characteristic of humans during moderate exercise, although it does appear to be the case for many, but not all, conscious experimental animals.

Procedures designed to augment or diminish the central command for a task have also been used to characterize its role in the exercise hyperpnea. For example, selective stimulation of muscle spindles by means of high-frequency vibration applied to a contracting muscle in humans has been shown to reduce the central command required to maintain a given contractile force (i.e., the reflex facilitation of motor neurons to the exercised muscle takes over a component of force generation from central command), with the $\dot{V}_E$ response being

less than under control conditions. Similarly, stimulating an antagonist muscle led to an exaggerated $\dot{V}_E$ response. This is thought to be a consequence of the greater effort now required to sustain the force.

Other evidence seems inconsistent with the view that central command subserves the dominant component controlling $\dot{V}_E$ during exercise. Thus, the magnitude of the $\phi 1$ $\dot{V}_E$ response to exercise is not a simple function of the number of motor units recruited to generate the muscle force or of the magnitude of the central command required for their recruitment. Neither is it systematically altered over a wide range of imposed WRs. Also, when the WR increment is imposed from a background of light exercise (Fig. 16-2, *left*), the $\phi 1$ hyperpnea develops more slowly and is smaller. The initial hyperpnea is also slow when subjects initiate rest-to-work transitions in the supine position. Supporters of the central command hypothesis do not explain how body position per se would so markedly reduce this component of control. Therefore, although neurogenesis seems beyond serious challenge as the mechanism mediating the $\phi 1$ hyperpnea, the nature and functional organization of the signals themselves remain to be elucidated.

The results of sinusoidal exercise are also instructive in this regard. When WR is "forced" sinusoidally over a range of increasing input frequencies, the $\dot{V}_E$ response amplitude decreases as a close linear function of the decrease in $\dot{V}_{CO_2}$ amplitude, both in humans (Fig. 16-8) and conscious sheep. Importantly, the relationship extrapolates to the origin at high frequencies. Therefore, the ventilatory control system cannot keep up with the amplitude demands of the task at high forcing frequencies: A rapid neurogenic mechanism should! Consequently, the central command, which continues to drive the force-generating muscle units over the same WR amplitude range, either subserves a trivially small role in the exercise hyperpnea under these non–steady-state condition or these mechanisms themselves exhibit slow neural dynamics—but somehow closely proportional to those of $\dot{V}_{CO_2}$.

A servo-assisted positive-pressure ventilator has been used as a means of dissociating a subject's intrinsic ventilatory drive from the motor task. That is, the applied pressure is carefully synchronized with the respiratory cycle to take over a proportion of the normal inspiratory flow. Were the $\dot{V}_E$ to be dictated wholly by the central command, then the subject's intrinsic ventilatory drive would be expected to remain unchanged despite the external proportional-flow assistance to ventilation. Consequently, overall $\dot{V}_E$ would be expected to increase, resulting in a sustained hypocapnia. This is *not* the case, however (Fig. 16-9). Rather, a proportional compensatory reduction in the intrinsic ventilatory drive results.

Finally, if central command was a major and obligatory component of the exercise hyperpnea, then one would expect an attenuated $\dot{V}_E$ response when exercise is performed in the absence of central command. However, in subjects with clinically complete spinal cord transection, with exercise induced by direct electrical stimulation of the quadriceps muscles, both the magnitude and time course of the $\dot{V}_E$ response have been shown to be essentially normal with respect to $\dot{V}_{CO_2}$, albeit over a restricted range of metabolic response. These observations argue against a major obligatory involvement of central command in ventilatory control during moderate exercise. Rather, they reinforce the notion of redundancy of ventilatory control mechanisms during exercise.

Short-Term Potentiation

Eldridge and his associates have demonstrated that exercise activates a slowly developing neurogenic drive to ventilation in the cat, short-term potentiation or reverberation. The hyperpneic response to the abrupt cessation of afferent activity from sources such as limb muscle afferents, carotid bodies, and ventral medullary surface results in a slowly decaying exponential decrement of $\dot{V}_E$. A similarly slow decrement of $\dot{V}_E$ also can be demonstrated in humans following the abrupt cessation of volitional isocapnic hyperventilation. However, the onset of the ventilatory response in the cat is much more rapid when the stimulus is imposed; that is, the mechanism exhibits dynamic *asymmetry*. However, the reverberatory component itself is symmetrical, as evidenced by Eldridge and Gill-Kumar's cleverly designed alternate-breath stimulation study. That is, it appears that the intrinsic symmetry of the reverberatory component is masked by a direct component at the on-transient that renders the overall response asymmetrical. The exercise hyperpnea in humans, however, exhibits symmetry of the exponential $\phi 2$ $\dot{V}_E$ responses at the onset and cessation of moderate exercise. This on-off kinetic symmetry is maintained even when the $\phi 2$ $\tau\dot{V}_E$ is varied by up to fourfold (Fig. 16-4) by altered peripheral chemoreceptor gain. To date, studies addressing this issue have not been performed in the cat.

Long-Term Potentiation

In 1993, Martin and Mitchell proposed that a component (at least) of the exercise hyperpnea may be the result of long-term modulation or potentiation (LTP) resulting from repeated exposure to activity, akin to associative motor learning. They demonstrated that goats consistently overbreathed during a standard treadmill task after they had been trained to exercise repeatedly for 2 days at that level, with an additional stimulus to breathing in the form of added dead space (0.8 L). This resulted in appreciable hypercapnia (ΔPa_{CO_2} approximately + 10 mmHg) during the exercise, in contrast to the 0.5 mmHg average decrease in Pa_{CO_2} during the initial pre-training trial (i.e., hypocapnia was *not* characteristic in these goats!) and the approximately 3 mmHg decrease during the post-training trial without the added dead space. This augmented hyperpnea during exercise as a result of the hyperpneic history resolved over a period of approximately 6 hours. As the training had no effect on the $\dot{V}_E$ response to inhaled CO_2, these authors concluded that the neural mechanisms controlling the exercise hyperpnea evidence adaptability, plasticity, or "learning," possibly involving central serotonergic mediation. Evidence consistent with LTP was subsequently reported also in humans. Thus, LTP of the exercise hyperpnea is consistent with

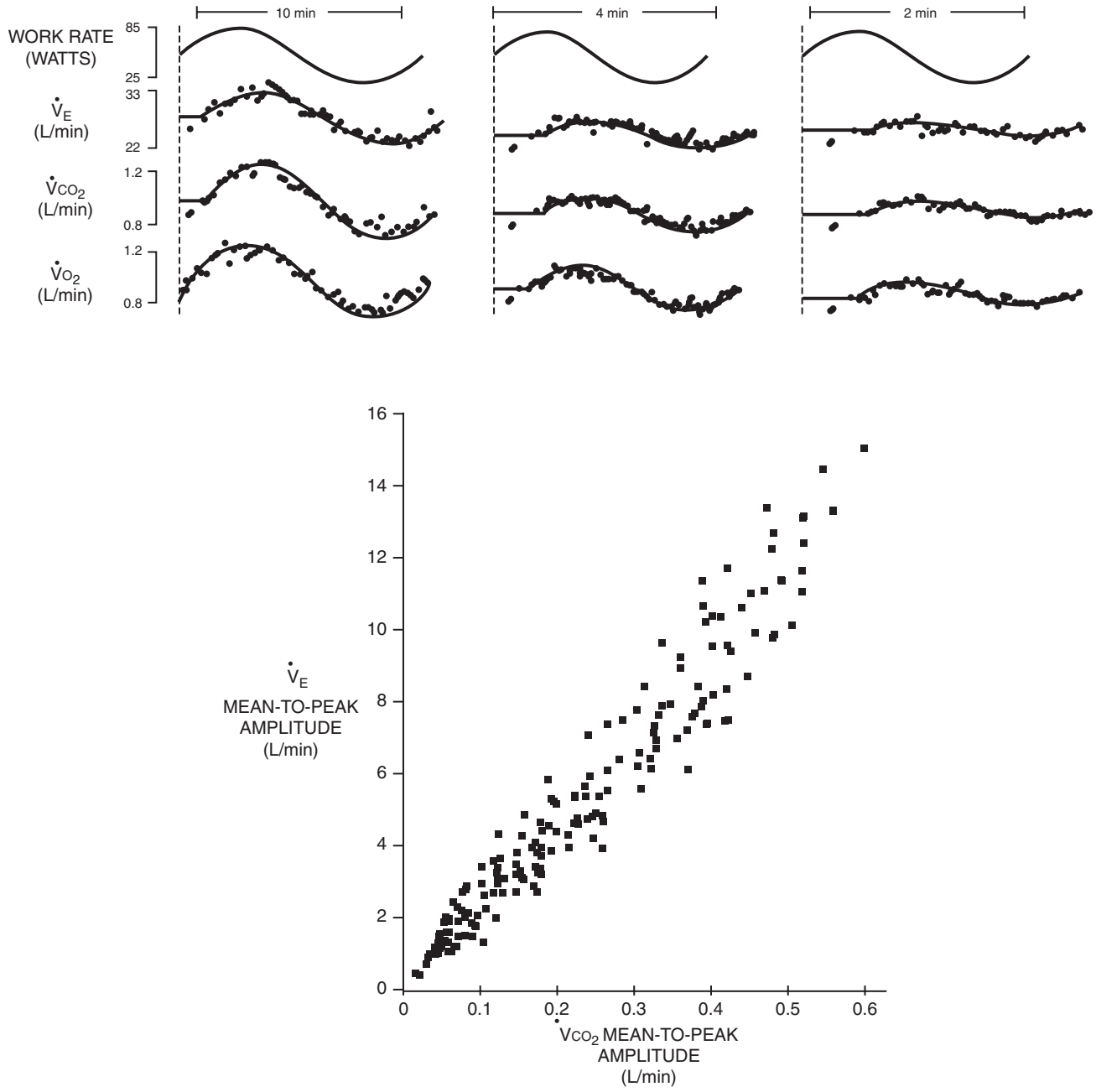

Figure 16-8 Relationship between the amplitude of $\dot{V}_E$ and $\dot{V}_{CO_2}$ in response to exercise of sinusoidally varying work rate. Note that the reduction in $\dot{V}_{CO_2}$ amplitude is matched by a proportional reduction in $\dot{V}_E$ amplitude as the forcing frequency of the work-rate sinusoid is increased, the relationship extrapolating to the origin. *(Reproduced with permission of Casaburi R, Whipp BJ, Wasserman K et al: Chest 73S:280S–283S, 1978.)*

Somjen's postulate that functionally error-free physiological control systems may operate through central nervous system control that "anticipates present and future needs on the basis of past experience."

However, evidence consistent with LTP could not be demonstrated in other studies in exercising humans. When $\dot{V}_E$ was normalized appropriately (i.e., relative to $\dot{V}_{CO_2}$) and a robust noninvasive index of Pa_{CO_2} is used (i.e., mean alveolar rather than end-tidal P_{CO_2}), the hyperpneic response following associative conditioning via external dead space was not different from control either in the exercise steady state or during the transient.

Muscle Reflex Control

There is a wide range of receptors and "free" nerve endings in skeletal muscles, the afferent projections of which have been proposed to contribute to the control of the exercise hyperpnea. For example, $\dot{V}_E$, heart rate, and arterial blood pressure all increase when the muscle contraction is induced

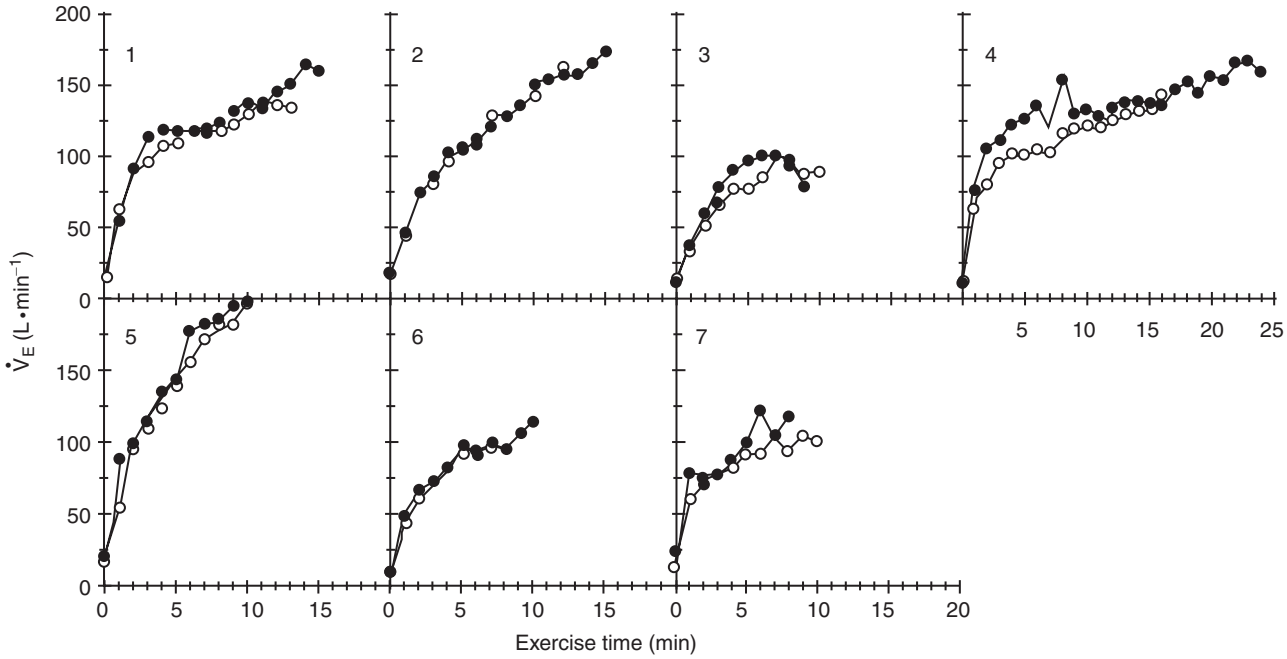

Figure 16-9 Profile of ventilatory response to high-intensity exercise in normal subjects under control conditions (○) and when the respiratory muscular demands for pressure generation were reduced by approximately one-third by means of a proportional ventilatory assist (●). *(Reproduced with permission of Krishnan B, Zintel T, McParland C et al: J Physiol (Lond) 490:537–550, 1996.)*

in experimental animals by stimulation of: (1) ventral spinal roots; (2) motor nerves; or (3) the muscles themselves. These responses are abolished by section of the dorsal spinal roots, evidence of their origin in the exercising muscles. More specifically, electrical stimulation of small-diameter group III and IV afferents (but not of the larger group I and II afferents) leads to an increase in $\dot{V}_E$, heart rate, and arterial blood pressure, which can be abolished by differential blockade of these small-diameter fibers. Other stimuli, such as local mechanical distortion and increased intramuscular pressure, also have been demonstrated to activate a sub-population of the small-diameter afferents. A second subpopulation of small-diameter afferents is responsive to humoral mediators such as intramuscular levels of potassium (K^+), lactic acid (but not lactate), bradykinin, capsaicin, and di-protonated phosphate.

However, a simple interpretation of the role of skeletal muscle metaboreception or chemoreception in the exercise hyperpnea is confounded by the consistent demonstration that when pneumatic thigh-cuffs are inflated to suprasystolic pressures at the end of exercise, the $\dot{V}_E$ response decreases *more rapidly* than normal and *not* more slowly, despite the local accumulation of exercise-induced metabolites and presumably the sustained activation of chemosensitive muscle afferents *after* the cessation of the work (Fig. 16-10). In addition, removing the influence of somatic limb afferents does not seem to impair the ventilatory response to dynamic exercise to any appreciable extent in humans—at least over the usual range of metabolic rates achieved. Furthermore, the $\dot{V}_E$ response to dynamic exercise has been shown to be essentially normal, both in normal subjects with muscle sensory blockade induced by epidural anesthesia and patients with sensory neuropathies, despite the absence of functioning afferent projections from the exercising limbs. Finally, the results of the assisted inspiration experiments described in the preceding section are relevant in this regard (Fig. 16-9). That is, the subjects' $\dot{V}_E$ was *not* significantly affected by the assist as a result of the intrinsic ventilatory drive being proportionally reduced (i.e., despite neither central command nor mechanical feedback from the exercising muscles presumably being altered). Consequently, although there appears to be little doubt that respiratory drives originate within contracting muscles, whether these represent an obligatory or necessary control component during normal volitional exercise is by no means certain.

Central Chemoreflex Control

Studying central chemoreflex function in humans is difficult owing to the inaccessibility of the receptors themselves, whose distribution is now thought to extend beyond the classical ventral medullary surface areas into higher regions of the CNS. Hyperoxic hypercapnia is commonly used to assess the "sensitivity," and in some studies, the dynamics, of the central chemoreflex; the hyperoxia is necessary to suppress peripheral chemosensitivity. However, there is no consistent evidence that central chemosensitivity is increased significantly with exercise. Patients with congenital central hypoventilation syndromes (CCHS) have impaired central chemosensitivity, with little or no $\dot{V}_E$ response in inhaled CO_2. Importantly in this regard, their $\dot{V}_E$ response to exercise was considered to be remarkably normal.

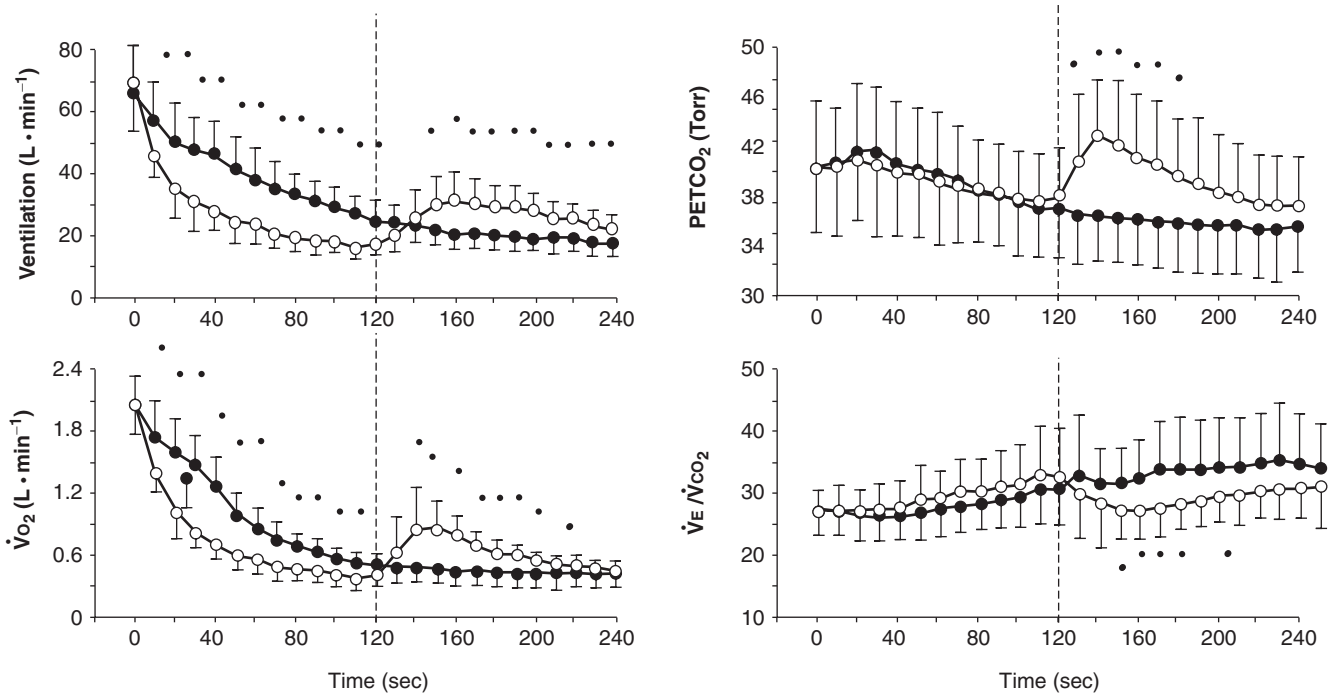

Figure 16-10 Dynamics of the ventilatory response during recovery from heavy cycle ergometer exercise in normal human subjects under control conditions (●) and when thigh cuffs were inflated to suprasystolic pressures at the cessation of exercise (○). Note ventilation decreases appreciably more rapidly with the thigh cuffs inflated. The subsequent release of the cuff pressure is marked by the dashed vertical line. *(Reproduced with permission of Haouzi P, Huszczuk A, Porszasz J et al: Respir Physiol 94:137–150, 1993.)*

The onset of the slower ϕ2 $\dot{V}_E$ response has a time delay consistent with the limb-to-lung transit time, suggestive of downstream chemoreceptor mediation. Although the ϕ1 − ϕ2 transition is prolonged with hyperoxic inspirates, it is unlikely that there is any significant involvement of the central chemoreceptors in this response, as CCHS patients demonstrate essentially normal ϕ2 $\dot{V}_E$ kinetics despite poor or absent central CO_2 chemosensitivity. However, what triggers the ϕ1 − ϕ2 transition is not known. It seems a crucial part of the puzzle.

The central chemoreceptors also appear not to play an essential role in the ϕ3 $\dot{V}_E$ control for moderate exercise. First, there is the issue of a discernible chemical stimulus: The pH of cerebrospinal fluid (CSF) remains relatively stable during the steady-state of moderate exercise. Also, despite significant increases in arterial $[K^+]$, CSF $[K^+]$ does not increase. The report that the normal $\dot{V}_E$ response to exercise in CCHS patients regulates P_{CO_2} close to resting levels (although this is often elevated in these patients) appears decisive in this regard.

Above θ_L, ventilatory compensation for the lactic acidosis results in a respiratory alkalosis in the CSF. Under these conditions, the central chemoreceptors are likely to provide *constraint* on the hyperpnea. The alkalotic CSF would not only reduce ongoing central chemoreceptor activity, but also stimulate efferent projections to the carotid chemoreceptors, which have been demonstrated to inhibit their afferent chemosensory discharge.

Interestingly, during prolonged constant-load exercise designed to produce the same degree of metabolic acidosis with markedly varying degrees of peripheral chemosensitivity, Rausch and colleagues showed a slow but systematic restoration of pHa back toward normal after its initial fall—even with hyperoxic suppression of peripheral chemosensitivity. This slow compensation might reflect a slow "leak" of H^+ ions into the CSF from blood or, possibly, a slow central chemoreflex response to the transiently elevated Pa_{CO_2} that was a consistent finding of the study. It has been suggested that this behavior may reflect, in part at least, modulation of the activity of the primary carotid-body ion channel involved in sensing changes in metabolic acidemia; possibly, a H^+ sensitive type I voltage-sensitive tandem-P-domain K^+ (TASK-I) channel.

Arterial Chemoreflex Control

It seems unlikely that the carotid bodies mediate the ϕ1 $\dot{V}_E$ response to exercise. This response is typically unaffected when hypoxic or hyperoxic gas mixtures are breathed or in subjects whose carotid bodies have been surgically resected (CBR): procedures that respectively increase, decrease and, of course, abolish carotid chemosensitivity. In contrast, the carotid bodies do appear to play a prominent role in ϕ2 $\dot{V}_E$ control. As described earlier, $\tau\dot{V}_E$ is reduced when carotid body sensitivity is increased, both in absolute terms and relative to $\dot{V}_{CO_2}$, and prolonged by procedures that reduce or

abolish carotid chemosensitivity (Fig. 16-4). Consequently, as the carotid bodies appear to modulate $\dot{V}_E$ response kinetics relative to those of $\dot{V}_{O_2}$ and $\dot{V}_{CO_2}$, they play an important role in the "tightness" with which Pa_{O_2}, Pa_{CO_2}, and pHa are regulated throughout the non–steady-state phase of exercise. For example, the faster $\dot{V}_E$ kinetics resulting from hypoxemia-increased carotid chemosensitivity reduce the magnitude of further hypoxemia during the transient.

There seems to be no dispute that the carotid bodies also provide a component of the ϕ3 $\dot{V}_E$ control, which some have termed "fine tuning." The proportional contribution of the carotid bodies to the ϕ3 hyperpnea has been estimated using the Dejours test, in which high inspired O_2 fractions are used surreptitiously to abolish abruptly any carotid body contribution to the hyperpnea. Thus, CBR subjects have no $\dot{V}_E$ decrease during the Dejours test. These tests have demonstrated that the carotid bodies normally appear to account, on average, for approximately 20% of the ϕ3 hyperpnea, although there is some concern that this may be an underestimate.

The proportional role of the various stimuli in the arterial blood during exercise, however, is unclear. Components of the oscillating CO_2-H^+ pattern, such as its amplitude and rate of change, have been proposed to provide a CO_2-linked drive to $\dot{V}_E$ in ϕ3. The carotid bodies in animals have been shown to be capable of transducing such signals into respiratory stimulation. However, whether such oscillating signals provide any significant humoral feedback for ventilatory control in exercising humans remains to be demonstrated.

The increased arterial $[K^+]$ that results from release from contracting muscle cells during exercise has been demonstrated to stimulate $\dot{V}_E$ via the carotid bodies. As K^+ does not cross the blood-brain barrier, the increased arterial $[K^+]$ apparently does not influence sites of central chemosensitivity. Consequently, the increased arterial $[K^+]$ may account for or contribute a component of the average 20% of the steady-state exercise hyperpnea mediated by the carotid bodies. However, the unaltered hyperpnea when the exercise-induced increase in $[K^+]$ is modified by propranolol infusion argues against a crucial role for $[K^+]$ as a mediator. Other known carotid-body stimuli, such as increases in the plasma levels of H^+, adenosine, osmolarity, catecholamines, temperature, and rate of change of the P_{CO_2}-H^+ oscillations also increase during exercise. These presumably also contribute to this approximately 20% of the ϕ3 hyperpnea.

It has been argued that the carotid bodies normally appear to be largely responsible for mediating the respiratory compensation for the lactic acidosis above θ_L in humans, responding to stimuli such as $[H^+]$, $[K^+]$, and catecholamines. Evidence against this view has been presented, however. Individuals deficient in the glycogenolytic enzyme myophosphorylase b (McArdle's syndrome) are constrained to exercise only at relatively low WRs as they are unable to catabolize glycogen anaerobically. These subjects have been reported to hyperventilate despite there being no metabolic acidemia at these low WRs. This suggests, to some investigators, that the compensatory hyperventilation seen in *normal* subjects above θ_L does not require a lowered pHa for its mediation. However, other mechanisms, such as apprehension, discomfort, and increased intramuscular pressure or pain can induce acute hyperventilatory *alkalosis* under some circumstances. Indeed, muscle pain is a cardinal symptom of McArdle's syndrome. Another important distinction is that respiratory alkalemia is *not* normally seen in humans performing high-intensity dynamic exercise.

In response to constant-load exercise above θ_L, the compensatory hyperventilation has been reported to be nonexistent in CBR subjects. Not only did pHa fall more for a given decrease in $[HCO_3^-]a$, but Pa_{CO_2} was higher than the corresponding control values. It has been proposed, however, that this marked reduction in the compensatory hyperventilation for the metabolic acidemia in these subjects may be a consequence of their asthmatic history rather than the absence of carotid bodies. Furthermore, despite reducing the "gain" of the carotid chemoreflex (assessed by hypoxic ventilatory responsiveness) and significantly slowing the ϕ2 $\dot{V}_E$ response to moderate constant-load exercise in humans, infused dopamine did not discernibly affect the $\dot{V}_E$ response above θ_L during ramp-incremental exercise.

In studies designed to induce a standard and more prolonged degree of metabolic acidemia during constant-load exercise (Δ standard $[HCO_3^-]$ of 5 mEq/L) in normal subjects, Rausch and associates demonstrated that hypoxia constrained the magnitude of the transient decrease in pHa, whereas hyperoxia amplified it (Fig. 16-11). However, even when carotid body chemosensitivity was suppressed by inhalation of 80% O_2, a *slow* compensatory component was still evident. Therefore, the carotid bodies in humans may be considered to play a significant, and even, dominant role in constraining pHa in response to the acute metabolic acidemia of exercise in humans. However, there are secondary—presumably central chemosensory—mechanisms that subserve a slower compensatory role. An alternative interpretation of these findings, consistent with the demonstration that $\dot{V}_E$ evidences an upward concavity at high WRs during hyperoxic incremental exercise, is that hyperoxia does not abolish peripheral chemosensitivity under these conditions. However, the absence of an early $\dot{V}_E$ response to an increased inspired CO_2 fraction in hyperoxia, both at rest or during exercise, suggests that this is not the case.

Cardio-Circulatory Reflex Control

Some investigators have proposed that a component of ventilatory control during exercise may be of cardiac or circulatory origin. Vascular distention of the heart and adjacent vasculature, for example, can elicit tachycardia and hyperpnea. Therefore, might the increased venous return of exercise contribute to the ventilatory control during exercise in humans? The relative stability of the end-tidal gas tensions and R, as a result of the close proportionality between the

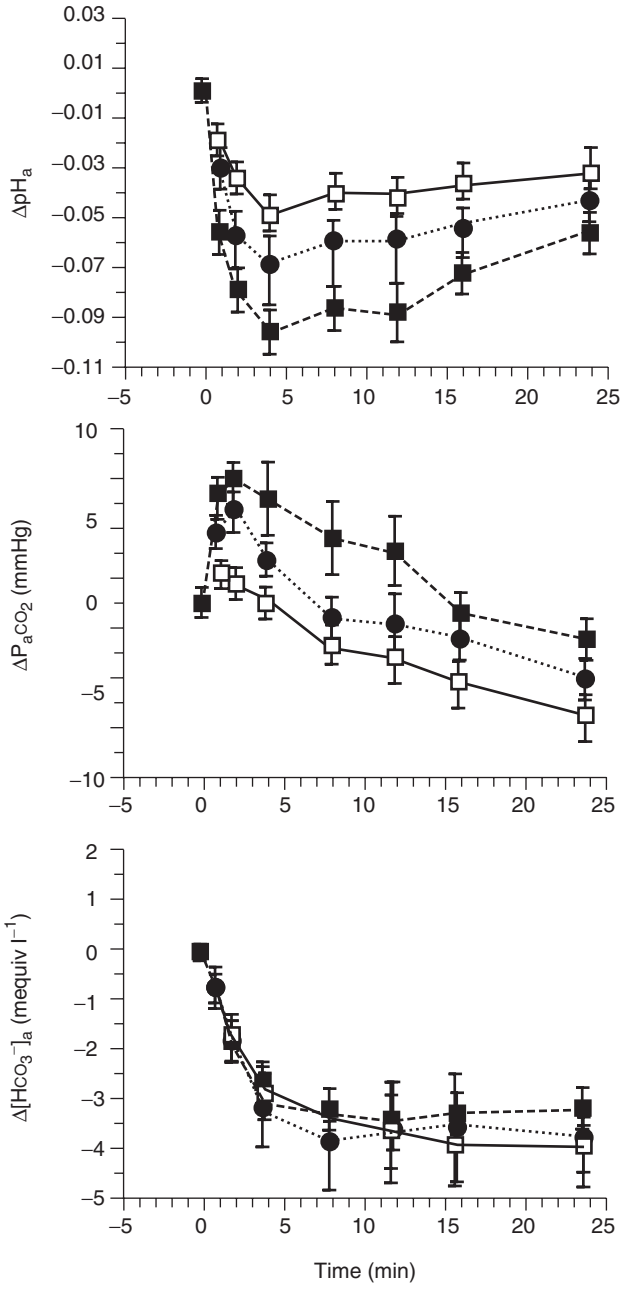

Figure 16-11 Responses of arterial pH, P_{CO_2}, and standard $[HCO_3^-]$ to suprathreshold square-wave exercise for three inspired oxygen fractions (□ = 12% O_2; ● = 21% O_2; ■ = 80% O_2), expressed as changes (Δ) from unloaded cycling. Values are means ± SEM ($n = 7$). *(Reproduced with permission of Rausch SM, Whipp BJ, Wasserman K et al: J Physiol (Lond) 444:567–578, 1991.)*

ϕ1 cardiovascular and ventilatory responses, has suggested to some investigators that there may be a component of cardiodynamic $\dot{V}_E$ control in this phase of exercise. However, evidence from several sources has questioned such a role. When the resting heart rate (and therefore cardiac output) was abruptly increased in patients with permanent demand-type pacemakers, there was no difference in the immediate $\dot{V}_E$ response amplitude compared with when heart rate was not allowed to increase, despite a clearly greater increase in $\dot{V}_{O_2}$. It is also clear that cardiac afferents do not subserve an obligatory role in the exercise hyperpnea although they can, under some circumstances, stimulate $\dot{V}_E$. Humans who have undergone cardiac transplantation and calves with an implanted pneumatically driven artificial heart have no reduction in either the magnitude or rapidity of onset of the exercise hyperpnea.

Recent studies have suggested that $\dot{V}_E$ may respond to a signal mediated by altered vascular conductance and/or tissue pressure in the exercising muscles themselves. There is evidence that some group IV muscle afferents are stimulated by venous occlusion and injection of vasodilating agents. Therefore, this proposal changes the focus of a cardio-respiratory linkage during exercise from a central circulatory control site to one more intimately related to the peripheral microvasculature and its innervation. Of course, a control link between the peripheral and pulmonary gas-exchange surfaces and breathing is intuitively attractive. However, although the mechanism itself has been clearly demonstrated, its proportional contribution to the exercise hyperpnea in humans remains to be determined.

VENTILATORY COSTS

Mechanical Costs to Respiratory Muscles

The intra-pleural pressure changes resulting from respiratory muscle contraction (P_{MUS}) serve to expand the lung and generate tracheal-bronchial airflow, with an additional small component providing lung-tissue flow and overcoming inertia. Therefore, the pressure, or power, required to overcome the total impedance of the respiratory system is given by:

$$P_{MUS} = E \cdot V + R \cdot \dot{V} + I \cdot \ddot{V} \qquad (14)$$

where

E, R, and I = the respiratory system elastance, resistance, and inertance respectively

In patients with COPD, the added cost is predominantly in the resistive component, whereas in patients with restrictive lung disease it is predominantly in the elastic component.

The relationship between $\dot{V}_E$ and respiratory muscle power during exercise is not linear. A given increment in $\dot{V}_E$ requires a larger increase in P_{MUS} at high WRs than at low WRs. Subjects who are moderately fit, however, use only 30% to 40% of their maximum available respiratory power at maximal WRs and also have a considerable breathing reserve (BR); that is, the difference between the maximum exercise $\dot{V}_E$ and that achieved volitionally during a maximal voluntary ventilation maneuver (MVV), usually measured at rest. Highly fit subjects who are able to achieve high metabolic rates and consequently high levels of $\dot{V}_E$, on the other hand, typically have a low BR at maximum exercise as the MVV is essentially unaffected by training status and fitness. A BR

that is minimal, zero, or even negative suggests a ventilatory limitation to exercise tolerance.

The mechanical cost of $\dot{V}_E$ is appreciably greater at high WRs because: (1) increased contributions from turbulence (and even inertia) when airflow is high; (2) increased elastic work of breathing, owing both to decreased lung compliance even in the tidal range (an effect ascribed to increased pulmonary blood volume) and especially as end-inspiratory lung volume reaches the poorly compliant upper region of the compliance curve at high V_Ts-the decrease in EELV, however, tends to ameliorate this effect, at least in normal subjects; and (3) the recruitment of respiratory muscles with low mechanical efficiencies at high levels of $\dot{V}_E$.

Metabolic Costs to Respiratory Muscles

These increased mechanical costs of the exercise hyperpnea require both an increased respiratory muscle work rate and respiratory muscle O_2 consumption ($\dot{Q}_{O_2}$rm). The relationship between $\dot{Q}_{O_2}$rm and $\dot{V}_E$ during exercise is not linear; rather it is concave upward, with greater increments in $\dot{Q}_{O_2}$rm being required as WR increases. Although $\dot{Q}_{O_2}$rm is small at resting levels of $\dot{V}_E$, it can be appreciable at high levels of exercise, especially in highly fit athletes. In moderately fit subjects a $\dot{Q}_{O_2}$rm of approximately 0.5 L/minute, approximately 15% of the total $\dot{V}_{O_2}$, has been reported for a $\dot{V}_E$ in excess of 120 L/minute. This is presumably even greater in athletes, who are capable of attaining appreciably higher levels of $\dot{V}_E$ at maximum exercise.

Estimation of $\dot{Q}_{O_2}$rm in humans, however, is technically difficult, as it represents such a small fraction of the whole-body $\dot{V}_{O_2}$ during exercise. A further complication results from the fact that whole-body $\dot{V}_{O_2}$ can change not solely as a result of the increased respiratory muscle work rate in tests that attempt to reproduce the exercise hyperpnea in a resting subject, but also as a result of the altered pH if Pa_{CO_2} is not maintained precisely—acute respiratory alkalosis has been shown to increase whole-body $\dot{V}_{O_2}$ by approximately 10% per 10 mmHg decrease in Pa_{CO_2}. Also, although this relationship for spontaneous breathing during exercise may be expected to be qualitatively similar to that of volitional hyperpnea at rest, there may be significant quantitative differences. The respiratory muscle recruitment patterns, their mechanical efficiencies, their operating lengths, and the metabolic cost of the $\dot{V}_E$ attained are all likely to be different.

As the respiratory muscles, like other skeletal muscles, have the potential for the O_2 demands of the task of breathing to outstrip the vascular supply mechanisms during exercise, they themselves can exercise beyond their "lactate threshold". However, the blood that flows *to* the respiratory muscles naturally cannot also flow *to* the locomotor muscles. An added inspiratory resistive load, for example, has been shown to compromise exercise $\dot{V}_{O_2}$ by this mechanism under conditions of maximum cardiac output (but not at lower levels). This is commonly (and unfortunately, in our opinion) termed "respiratory steal". The respiratory muscles "take" (they hardly "steal"!) the component of the cardiac output that is theirs by right.

SYSTEM CONSTRAINTS AND LIMITATIONS

The mechanical and metabolic costs of $\dot{V}_E$ during muscular exercise are themselves sources of *constraint* and potential *limitation* of exercise tolerance. Constraint, in this context, reflects a condition in which the $\dot{V}_E$ response is less than that of its regulatory requirement as a result of the influence of an opposing mechanism, e.g., an added resistive load. Ventilation in this case is not actually limited, as higher WRs lead to greater hyperpnea. In contrast, limitation occurs when $\dot{V}_E$ cannot increase, despite further increases in ventilatory drive. For example, maximum expiratory airflow during exercise (at a particular lung volume) becomes limited in subjects with reduced lung recoil pressure (Prec) and/or increased airways resistance (Raw), despite further increases in ventilatory drive; similarly, the achievable V_T is limited during exercise in patients with diffuse interstitial fibrosis as a result of the increased elastance.

Ventilatory Constraints

The V_T limit theoretically extends from zero to vital capacity (VC), whereas the breathing frequency extends from zero to approximately 5 Hz. Normally, however, the ventilatory system "only" operates at a V_T of approximately 50% to 60% of VC and a frequency of less than or equal to 1 Hz even during maximum exercise. The maximum airflow that can be attained, at a given lung volume, during exercise in normal subjects is that generated by a maximal forced volitional effort, i.e., that characterized by the maximum expiratory flow-volume (MEFV) relationship. At maximum exercise, the spontaneously generated expiratory flow profiles fall well below the maxima of the MEFV curve in subjects of poor or moderate fitness. However, in highly fit athletes, who are capable of generating high instantaneous airflows at their high levels of $\dot{V}_E$, these maxima may be encroached upon (Fig. 16-7).

The hypothesis that respiratory work would be minimized, at a particular level of $\dot{V}_E$, with a particular breathing frequency, is largely based on the recognition that when $\dot{V}_E$ is achieved with a high frequency and a low V_T, the flow-resistive component of the respiratory work increases. When this is accomplished with a large V_T and low breathing frequency there is an increased contribution from the elastic component of the respiratory work, as the lung volume encroaches on the flatter portion of the lung compliance curve. Exercising subjects normally seem to choose a breathing pattern at or near the optimum for minimum respiratory muscle work rate; unless, of course, this is prevented by the breathing demands of an event such as swimming.

There is likely to be turbulent constraint of airflow during exercise even in moderately fit subjects. When the inspired nitrogen is replaced by the lower-density gas helium (taking care to mask the sudden sensation of cold in the airways), there is no discernible effect when $\dot{V}_E$ is low. However, at higher levels of WR, and hence $\dot{V}_E$, replacing the nitrogen with helium, induces prompt and sustained hyperventilation. This is consistent with the removal of a constraint on $\dot{V}_E$ imposed by the turbulent component of airflow. However, the extent to which such turbulent constraint impairs the respiratory compensation for the metabolic acidemia in athletes is not clear at present.

Ventilatory Limitations

Mechanical Limitations

In moderately fit young individuals, $\dot{V}_E$ appears not to be mechanically limited during maximal exercise: (1) Such subjects can volitionally increase $\dot{V}_E$ to appreciably greater levels than those attained spontaneously at maximum exercise. (2) The ratio of maximum exercise $\dot{V}_E$ to MVV ($\dot{V}_{E_{max}}$/MVV) is relatively low (i.e., approximately 60%–70%). (3) The spontaneously generated expiratory F-V curve does not encroach on the boundaries of the MEFV curve even at maximum exercise. (4) There is also no evidence of significant respiratory muscle fatigue.

There is evidence of both ventilatory-mechanical limitation and inspiratory muscle fatigue in subjects who are more fit. For example, the spontaneous expiratory F-V curve often impacts on the envelope of the MEFV curve during maximal exercise in subjects with a maximum $\dot{V}_{O_2}$ of approximately 5 to 6 L/minute and a maximum exercise $\dot{V}_E$ of approximately 110 to 160 L/minute (i.e., 80% of MVV). Diaphragmatic fatigue has been demonstrated in such subjects both in terms of electromyographic criteria and also as reduced maximum trans-diaphragmatic pressures following exhausting exercise. Finally, there have been reports of reductions in VC, respiratory muscle strength, and endurance following exercise, but this has only been consistently observed following prolonged exercise in athletes.

In older subjects who have developed or maintained high levels of fitness, such airflow limitation has been demonstrated at lower levels of $\dot{V}_E$ during exercise (Fig. 16-7). This is predominantly caused by the age-related reduction in lung recoil reducing the maximum attainable airflow (evident as a bowing in the MEFV curve) and MVV, despite increased ventilatory demands as a result of increased V_D/V_T (Eqs (7) and (8)). However, it has been reported that even with the evidence of airflow limitation, subjects do not generate nonproductive, airway-compressive pressures that would increase respiratory work without further benefit to airflow. Rather, they generate only sufficient pleural pressures to establish the maximum flow—although this, of course, only reflects the average for the lung as a whole. There could be regions within the lung where this might occur, especially in patients with COPD.

The resting MEFV curve—and MVV—should be used with caution when deciding whether there is airflow limitation during exercise. This is because the interpretation depends on the accurate placement of the spontaneous expiratory F-V curve on the volume axis of the MEFV curve. It is more appropriate to trap an F-V display oscillographically and then perform the MEFV maneuver immediately afterward during the exercise. Furthermore, catecholamine-induced bronchodilatation can occur during exercise, which presumably accounts for the exercise MVV being greater that the resting MVV even in some normal subjects. Also, in older athletes with diminished lung recoil and airways function, and especially in patients with COPD, the maximum expiratory-*effort* F-V maneuver does not yield the optimum maximum expiratory-*flow* F-V curve.

The increased Raw and/or reduced Prec in COPD patients reduces both volume-specific maximum expiratory airflow and MVV, resulting in a reduced effective operating range for $\dot{V}_E$ during exercise. However, the ventilatory demands are typically greater than normal because V_D/V_T is high consequent to increased dispersion of $\dot{V}_A/\dot{Q}$ ratios. The ventilatory drive is also often increased consequent to arterial hypoxemia, although some patients, predominantly of the bronchitic type, can have Pa_{CO_2} levels that are higher than normal as a result of ventilatory constraint. The consequence is typically a modest uncompensated metabolic acidosis at maximum exercise.

Accordingly, during exercise, subjects with COPD commonly manifest the following:

1. Spontaneous expiratory airflows that equal or even exceed those achieved during a maximal flow-volume maneuver at a given lung volume
2. A level of $\dot{V}_E$ during maximum exercise that reaches or sometimes even exceeds the MVV determined at rest
3. An increase in end-expiratory lung volume during exercise, although this is less apparent when there is also significant inspiratory airflow impairment
4. A tendency to decrease the inspiratory duty cycle (inspiratory duration/breath duration (T_I/Ttot)) to conserve a large portion of the breath for exhalation, with T_I/Ttot falling to values as low as 0.2 in severe cases
5. Often, although not invariably, dyspnea as the cause of exercise limitation

The apparent paradox of expiratory airflow during exercise exceeding that generated during a maximal expiratory effort at rest can be explained by three factors: (1) An exercise-induced increase in circulating catecholamine concentrations can result in bronchodilatation. (2) As the fast time-constant units of the lung empty at high lung volumes during the forced expiratory maneuver from total lung capacity (TLC), the longer time-constant units empty at lower lung volumes. During the spontaneous exercise breath, the fast time-constant units now begin to empty at lung volumes that are low compared with the vital capacity breath. This results in greater

airflow at that particular generated lung volume. (3) The maximum expiratory airflow is not achieved with a maximum expiratory effort in COPD patients, especially at low lung volumes. During maximum expiratory efforts, there is typically dynamic airway compression, and even closure in some cases. This complicates appropriate "placement" of the spontaneous breath at the appropriate lung (rather than simply expired) volume with respect to the maximal maneuver.

Airflow limitation during exercise also occurs in subjects with exercise-induced asthma (EIA). Although the bronchoconstriction and reduction in forced expiratory airflow is typically manifest in the post-exercise period, it can also occur during the exercise; high-intensity exercise is a more potent causative trigger than low-intensity exercise. A bout of prior moderate exercise warm-up has been shown to ameliorate the intensity of EIA provoked by subsequent high levels of exercise. Also, many subjects with EIA can become relatively refractory to the bronchospastic effects of subsequent exercise (for a short period) after the resolution of the initial exercise-induced bronchospastic episode. However, it should be recognized that exercise-induced bronchoconstriction can also occur in subjects who do not have a history, or even recognition, of airway hyper-reactivity.

Although flow limitation at high relative WRs is most common in subjects with obstructive lung disease, it also occurs in patients with restrictive lung disease, such as diffuse interstitial fibrosis. This is because, as a result of the high lung elastance, it not only operates over such a restricted range of lung volumes, but also requires greater inspiratory muscle force development, more negative intra-pleural pressures, and greater respiratory work to produce the same inspiratory volume. Consequently, not only are the conventionally determined lung volumes reduced, but the V_T response to exercise is also typically reduced, both at a given WR and at maximum exercise. The resulting high breathing frequency and small V_T exacerbate the impaired gas exchange influence on V_D/V_T. Therefore, ventilation is typically high at a given metabolic rate. However, although V_T is relatively low during exercise, in absolute terms, in patients with restrictive lung disease, it is typically high as a fraction of the IC (measured either at rest or during exercise, as EELV does not change significantly with exercise in those with restrictive lung disease, unlike patients with COPD). Consequently, V_T/IC approaches 1.0 during heavy exercise. At maximum exercise, breathing frequency is commonly greater than 50/minute with a low, to nonexistent breathing reserve; with $\dot{V}_E$ often approximating MVV. This mechanical limitation, in addition to the effects of arterial hypoxemia, leads to dyspnea, the dominant exertional symptom in patients with restrictive lung disease.

CONCLUSIONS

Thus, although the ventilatory response to exercise is easy to measure, determining the appropriateness of its response is by no means straightforward. Its assessment should address at least four inter-related issues.

1. To what extent are the "requirements" met? This requires direct determination of the arterial blood gas and acid-base status or the use of reliable and valid estimators.
2. What is the cost of meeting these requirements? This requires an assessment of: (1) the magnitude and pattern of the $\dot{V}_E$ response used to meet the requirements; (2) by how much the alveolar and arterial gas partial pressures differ; and (3) the amount of respiratory muscle work, oxygen, and blood flow cost.
3. To what extent is the system constrained or limited? This requires determination or appropriate estimation of whether the mechanical limits of the system are achieved or closely approached. Indices of mechanical reserve, such as flow-volume and tidal volume-inspiratory capacity considerations, the maximum voluntary ventilation, breathing reserve, and even in some circumstances the maximum sustained ventilatory capacity, provide useful frames of reference.
4. How intensely is the response perceived? Useful information can be gained by the use of standardized techniques for scaling or grading the relative ease or difficulty with which the work rate or breathing is achieved.

With respect to the control of the exercise hyperpnea, we remain far from a satisfying resolution. The current congeries of mechanisms capable of stimulating ventilation under some circumstances during exercise is not sufficient. The core challenge is to establish the integrative aspects of the control that accounts for the *actual* dynamic features of the intensity-dependent responses in humans.

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17

The Lungs in Pregnancy

Daniel B. Rosenbluth • John Popovich, Jr.

The anatomic and physiological changes of pregnancy have major pulmonary and cardiovascular consequences throughout the gravid period. Physiological values and requirements, as well as normal laboratory assessment parameters, dynamically change in preparation for fetal support and parturition. An appreciation of these changes is essential to understanding the clinical cardiopulmonary manifestations of both preexisting diseases during pregnancy and cardiopulmonary diseases that may be unique to pregnancy.

ANATOMIC CHANGES OF NORMAL PREGNANCY

Respiratory and cardiac anatomy change as a process of normal pregnancy. Basic structural changes occur in the upper and lower airways, thoracic cage, and the respiratory muscles, most notably the diaphragm.

Airways

Hyperemia, friability, mucosal edema, and hypersecretion of the airway mucosa occur throughout pregnancy. These changes are most pronounced in the upper airways, especially during the third trimester, and may be aggravated by preeclampsia, upper respiratory tract infection, or allergic rhinitis. Nasal obstruction, epistaxis, sneezing episodes, and vocal changes may occur, and these may worsen when the individual lies down. Nasal and sinusoidal polyposis is often seen and tends to recur in women with each pregnancy. Common complaints include recurrent or chronic "head colds," which are often treated with over-the-counter medications for relief. Nasal obstruction may contribute to upper airway obstruction during sleep, leading to snoring and even obstructive sleep apnea.

Clinical consequences of the anatomic changes of the upper airway may include preferential mouth breathing and intolerance of nasal cannula delivery of oxygen, if required. Nasopharyngeal obstruction may make the pregnant individual poorly tolerant of the introduction of nasogastric tubes, nasal airways, or nasotracheal tubes. Small endotracheal tubes, such as 6.0 mm or less, may be advised for nasotracheal intubations.

The anatomic changes that occur in the lower airways during pregnancy have not been characterized, but some of the mucosal changes that affect the upper airways may also occur in the central portion of the airway, such as the larynx and trachea. Nonspecific complaints of airway irritation, such as irritant cough or sputum production, may be intensified during pregnancy, often in association with functional changes in airway reactivity and/or coexistent pulmonary conditions. Other more tangible symptoms and signs of lower-airway

irritation, such as hemoptysis and wheezing, should not be considered the result of normal anatomic changes associated with pregnancy, and other etiologies for these findings should be sought.

The physiological causes of nasal mucosal changes appear to be predominantly mediated by estrogens. Estrogens increase tissue hydration and edema. They also cause capillary congestion and hyperplastic and hypersecretory mucous glands.

Respiratory Muscles and the Thoracic Cage

The enlarging uterus produces upward displacement of the diaphragm. Although the diaphragm may be elevated up to 4 cm cephalad, diaphragmatic function is not impaired. The anatomic effects of the elevation of the diaphragm are offset by an increase in the anteroposterior and transverse diameters of the thoracic cage. Diminished tone and activity of the abdominal muscles also serve to counterbalance this effect of the gravid uterus. Diaphragmatic excursion during breathing may be greater in pregnancy than during the puerperium, suggesting that breathing may be more diaphragmatic than costal during pregnancy. Progressive relaxation of the ligamentous attachments of the ribs broadens the subcostal angle by approximately 50 percent (from 68 to 103 degrees). Consequently, there is a 5- to 7-cm increase in chest circumference. These parameters, with the exception of the subcostal angle, return to pre-pregnancy values after delivery.

The shortening and widening of the thoracic cavity results in upward and lateral displacement of the cardiac apex on chest radiography. Except for the appearance of smaller lung volumes and/or positional effects, such as lordotic or rotational views, no other radiographic change should be attributed to the anatomic changes of normal pregnancy.

PHYSIOLOGICAL CHANGES OF NORMAL PREGNANCY

Profound physiological changes coincide with and may be the result of the anatomic changes needed for fetal growth and childbirth. Both respiratory and cardiovascular changes ensure the delivery of necessary oxygenated blood and other nutrients required for this process.

Respiratory Physiology

The anatomic changes induced by the enlarging uterus cause serial changes in lung volumes (Fig. 17-1). During pregnancy, the expiratory reserve volume decreases by 8 to 40 percent and the residual volume by 7 to 22 percent. As a result, there is a 10 to 25 percent decrease in functional residual capacity after the fifth or sixth month of pregnancy. This decline in functional residual capacity (FRC) is more pronounced in the supine position. Due to the counterbalancing effects of widening of the lower rib cage, attenuation of the abdominal musculature, and unimpaired diaphragmatic movement, inspiratory capacity increases. Vital capacity and total lung capacity are not substantially changed in normal healthy gravidas, although total lung capacity does minimally decrease in the third trimester. Residual volume to total lung capacity ratio is low in the third trimester.

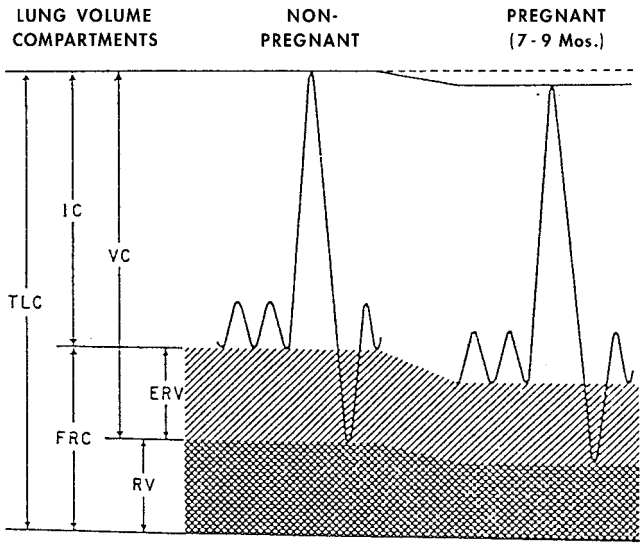

Figure 17-1 Lung volume changes associated with pregnancy. Although total lung capacity, residual volume, and expiratory reserve volume diminish, vital capacity is preserved in values similar to nonpregnant women. TLC = total lung capacity, IC = inspiratory capacity, FRC = functional residual capacity, VC = vital capacity, RV = residual volume, ERV = expiratory reserve volume. *(From Cugell DW, Frank NR, Gaensler EA, et al: Pulmonary function in pregnancy: I. Serial observations in normal women. Am Rev Tubercul Pulmon Dis 67:568, 1953.)*

In late pregnancy, airway closure may occur at a lung volume close to or greater than functional residual capacity. This phenomenon is more significant in the supine position. Increased gastric and esophageal pressure occurring in late pregnancy has been considered major factors that produce a decrease in transpulmonary pressure leading to peripheral airway collapse. An increase in lung water, resulting in a change in the elastic properties of the lungs and in the tethering small airways, may also play a role.

Tidal volume increases considerably, i.e. 30 to 35%, as a result of increased ventilatory drive. The increase in tidal volume is the predominant mechanism for the increase in minute ventilation during pregnancy, since respiratory rate either does not change appreciably or increases slightly, especially after the middle of the second trimester (Fig. 17-2*A*). Accordingly, the occurrence of tachypnea during pregnancy is an important abnormal finding that must be investigated. Maximum voluntary ventilation does not change greatly during pregnancy.

Values of FEV_1 throughout pregnancy are not significantly different from the nonpregnant condition. Nevertheless, it is not clear how pregnancy affects lower airway function. In theory, changes in maternal prostaglandin and cyclic nucleotide concentrations may affect bronchomotor tone,

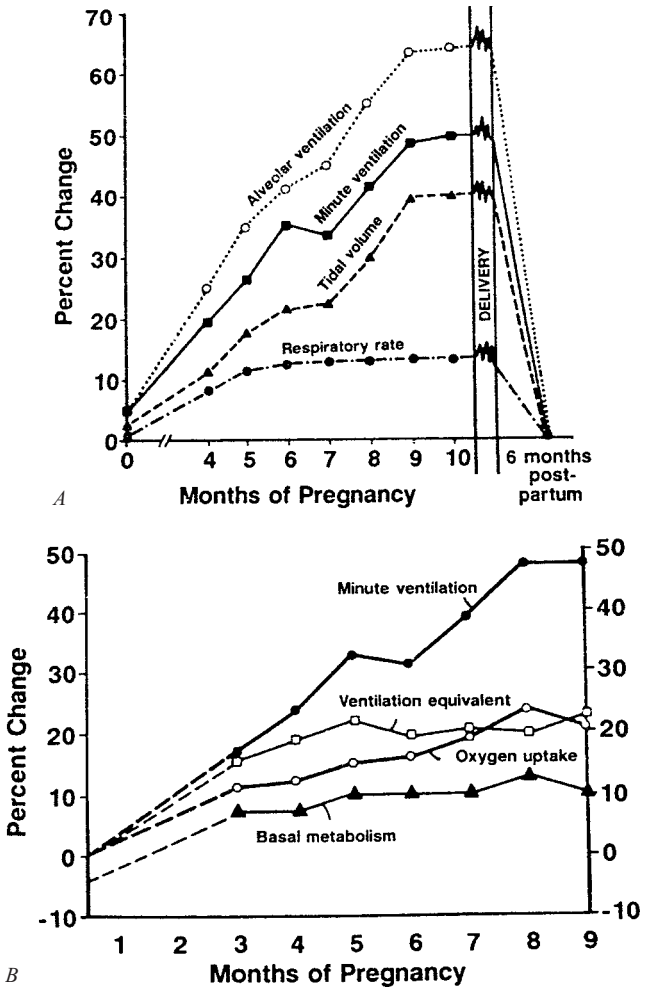

Figure 17-2 Ventilatory changes during pregnancy. *A.* The increase in minute ventilation is produced primarily by augmentation of tidal volume. This produces the significant increase in alveolar ventilation of approximately 70 percent noted at term. *(From Bonica JJ: Principles and Practice of Obstetric Analgesia and Anesthesia. Phfl adelphia, FA Davis, 1967; Cugell DW, Frank NR, Gaensler EA, et al: Pulmonary function in pregnancy: I. Serial observations in normal women. Am Rev Tubercul Pulmon Dis 67:568, 1953.) B.* Minute ventilation increases out of proportion to the increase in oxygen consumption, basal metabolism, and ventilatory equivalent. This demonstrates the physiological hyperventilation associated with pregnancy. *(From Prowse CM, Gaensler EA: Respiratory and acid-base changes during pregnancy. Anesthesiology 26:381, 1965.)*

but their effects are unclear. Progressive increases of airway conductance have been reported to occur between 6 months of pregnancy and term along with a decrease in airway resistance. However, other reports have failed to document significant changes in the function of the lower airways during pregnancy. Total pulmonary resistance, consisting of both airway and tissue resistance, is reduced by approximately 50 percent in pregnancy, most of the decrease attributable to a reduction in airways resistance. Lung compliance does not change significantly during pregnancy. Compliance of the thoracic cage decreases, as the anatomic changes in chest wall and the decrease in tone and activity of the abdominal musculature counterbalance the uterine enlargement.

In early pregnancy, the diffusing capacity is either unchanged or slightly increased. Throughout the rest of pregnancy, the diffusing capacity decreases, returning to normal or slightly lower than normal values. The relative contributions of the specific factors that affect diffusion, such as membrane diffusing capacity and pulmonary capillary blood volume, are not known.

Minute ventilation increases 20 to 50 percent before the end of the first trimester (Fig. 17-2*B*). This increase in may be explained by an increase in respiratory drive, presumably due to the effect of increased serum progesterone acting either as a direct respiratory stimulant or by increasing chemosensitivity of the respiratory center to P_{CO_2}, and an increase in the production of carbon dioxide. Carbon dioxide production and oxygen consumption increase as a result of the increase in basal metabolic rate, coupled with growth in the mass of fetal and maternal tissue and a small increase in cardiac and respiratory work. Since the increase in minute ventilation is approximately two times greater than the increase in oxygen consumption, without significant change in respiratory exchange ratio, the increased respiratory drive of pregnancy results in alveolar hyperventilation. The alveolar hyperventilation induced by altitude has been reported to be greater in pregnant women than in nongravid control subjects, again suggesting a predominant increase in respiratory drive.

Progesterone levels increase gradually during pregnancy from 25 ng/ml at 6 weeks to 150 ng/ml at 37 weeks. In normal non-pregnant women this hormone increases both the resting minute ventilation and the slope of the ventilatory response curve to changes in alveolar P_{CO_2}. Mouth occlusion pressures increase progressively during pregnancy in keeping with increasing progesterone levels. Estrogen may have an additional effect by causing an increased responsivity of the respiratory center.

The increase in minute ventilation which outpaces increases in carbon dioxide production results in a respiratory alkalosis with compensatory renal excretion of bicarbonate. As a rule, arterial P_{CO_2} falls to levels of 28 to 32 mmHg. Arterial pH is maintained in the range of 7.40 to 7.45, and plasma bicarbonate decreases to 18 to 21 mEq/L. In contrast, the acute hyperventilation during active labor and delivery superimposed on the chronic hyperventilation is not easily compensated and may produce dangerous elevations of pH, to values such as 7.6 or greater. Blunting of the increase in ventilatory drive evoked by pain and/or anxiety control can minimize this abnormality. The increase in ventilatory drive and the decrease in functional residual capacity accelerate induction and recovery from inhalational anesthesia.

Values for arterial P_{O_2} are generally greater than 100 mmHg during pregnancy. In the upright position, values for the alveolar-arterial oxygen gradient, physiological shunt, and VD/VT ratios remain similar to nonpregnant values. With the supine position, the alveolar-arterial oxygen gradient may widen, and mild arterial hypoxemia may develop, due to decrease in functional residual capacity and to increase

in closure of small airways. The decrease in functional residual capacity, the increase in closing volumes, and the increase in oxygen consumption lead to a more precipitous decline in arterial P_{O_2} in pregnant patients who are apneic or hypoventilating. Arterial P_{O_2} has been reported to decrease to 50 to 60 mmHg after 30 s of apnea during endotracheal intubation.

Exercise poses physiological challenges to the pregnant patient that may adversely affect the fetus. The oxygen reserve, which is diminished by the reduction in the functional residual capacity and the increase in oxygen consumption, may be further depleted during exercise. While some have shown that the minute ventilation is increased during exercise in pregnancy compared with nonpregnant control subjects, a recent study utilizing analysis of breath by breath gas exchange during graded exercise showed no difference in minute ventilation or maximal oxygen uptake between late gestation pregnant women and matched nonpregnant controls. Absolute oxygen consumption during exercise is primarily affected by the increase in body mass and weight that occurs with pregnancy rather than to a change in basal aerobic metabolism. During pregnancy, there is neither a significant change in the absolute oxygen cost of non–weight-bearing (e.g., cycling) exercise nor in the oxygen cost per kilogram during weight-bearing exercise.

Respiratory responses during parturition are greatly affected by stage of labor and the response to pain and anxiety. During labor, tidal volumes ranging from 350 to 2250 ml and minute ventilations from 7 to 90 L/min have been recorded. The higher values were close to the maximum voluntary ventilation and were associated with the second stage of labor, whereas the lower values were obtained in the first stage of labor while the patient was sedated. Mean alveolar P_{CO_2} measured during the contractions of uncomplicated labor in patients medicated with meperidine, nitrous oxide, and oxygen is about 32 mmHg during early labor, 24 mmHg at the end of the first stage, and 26 mmHg during the second stage. These data support the observation that the physiological hyperventilation of pregnancy that occurs during labor and delivery is independent of appreciable pain. Along with the alveolar hyperventilation, oxygen consumption during labor doubles and can even triple (e.g., to 750 ml/min) during uterine contractions. The possibility of relative hypoventilation between contractions coupled with the grave implications of fetal hypoxemia makes it reasonable to be liberal in the use of oxygen in order to keep maternal oxygen saturation at 95 percent or greater.

Sleep Disturbances

Several alterations in maternal physiology can affect breathing in pregnant women during sleep. Sleep quality is often poor. Sleep disruption can be due to leg cramps, low back pain, urinary frequency, or responsibilities relating to child care. Total sleep time and daytime sleepiness increase during the first trimester, whereas sleep time decreases and complaints of an increase in the number of nocturnal arousals increase in the third trimester. Polysomnographic studies have shown an increase in sleep latency, an increase in the amount of stage I sleep and a decrease in rapid eye movement (REM) sleep and delta sleep, as well as an increase in the number of awakenings. Although several restrictive lung factors similar to those associated with obesity are present in pregnancy, arterial oxygen saturation remains normal in pregnant women during sleep. Most sleep difficulties during pregnancy appear to relate to maintaining, rather than to initiating, sleep. The incidence of sleep-disordered breathing during pregnancy is unknown. After childbirth, most parameters of sleep quality and architecture return to pre-pregnancy values, with the possible exception of the quantity of REM sleep.

Cardiovascular Physiology

Profound changes in cardiovascular physiology occur during pregnancy (Table 17-1). Beginning around the fifth week of pregnancy and continuing into the postpartum period, cardiac output increases and peaks near term at 30 to 50 percent above normal. Multiple gestations are accompanied by greater change in cardiac output. The principal mechanisms of this change in cardiac output are increases in heart rate (maximum of 10 to 30 percent above prepartum values by week 12) and stroke volume, and a decrease (20 to 30 percent) in pulmonary and peripheral vascular resistances. Early in pregnancy the change is independent of changes in basal metabolic rate. Cardiac output is increased further by 10 to 15 percent (1 to 2 L per minute) to meet the challenges of labor and delivery. This response is principally a result of an increase in endogenous catecholamines and an increase in venous return of up to 300 to 500 ml of blood that occurs during uterine contractions. Immediately after delivery, cardiac output increases further to levels as high as 40 to 50 percent greater than values during labor, probably due to an increase in venous return and autotransfusion resulting from the contracted uterus and release of the aortocaval compression (see below) caused by the enlarged uterus. Although cardiac output remains high for the first few days after delivery, cardiac output returns to prepregnancy values over the ensuing 2 weeks.

Maternal blood volume increases progressively throughout pregnancy, beginning as early as 4 to 6 weeks of gestation and plateauing at approximately 32 to 34 weeks of gestation (Fig. 17-3). Total blood volume increases up to 35 to 50 percent above baseline (approximately 1.6 L), peaking by the third trimester. The magnitude of the increase is greater in multiparous pregnancies or multigravida mothers. The increase in blood volume provides some protection against peripartum blood loss, which averages approximately 0.6 L following uncomplicated vaginal delivery and 1.0 L following cesarean section. Plasma volume increases to a greater degree than red blood cell mass, which increases less, and more gradually, to an average increase of about 25 percent. These changes result in a decrease of hemoglobin concentration and hematocrit, producing the "physiological anemia of pregnancy." The increase in blood volume is probably determined by multiple, primarily endocrine factors, such as

Table 17-1

Central Hemodynamic Changes of Normal Pregnancy

Parameter	Nonpregnant	Pregnant*	Significance
Cardiac output, L/min	4.3 ± 0.9	6.2 ± 1.0.	$p < 0.05$
Heart rate, beats/min	71 ± 10.0	83.0 ± 10.0	$p < 0.05$
Systemic vascular resistance, (dyne/cm/s^{-5})	1,530 ± 520	1,210 ± 266	$p < 0.05$
Pulmonary vascular resistance, (dyne/cm/s^{-5})	119 ± 47.0	78 ± 22	$p < 0.05$
Colloid oncotic pressure	20.8 ± 1.0	18.0 ± 1.5	$p < 0.05$
Colloid oncotic pressure – pulmonary capillary wedge pressure (mmHg)	14.5 ± 2.5	10.5 ± 2.7	NS
Mean arterial pressure (mmHg)	86.4 ± 7.5	90.3 ± 5.8	NS
Pulmonary capillary wedge pressure, mmHg	6.3 ± 2.1	7.5 ± 1.8	NS
Central venous pressure, mmHg	3.7 ± 2.6	3.6 ± 2.5	NS
Left ventricular stroke work index, g/m/m^{-2}	41 ± 8	48 ± 6	NS

** 36–38 weeks' gestation.*

Source: Data from Clark SL, Cotton DB, Lee W, et al: Central hemodynamic assessment of normal term pregnancy. Am J Obstet Gynecol 161:1439–1442, 1989, with permission.

estrogen stimulation of aldosterone, non-renal renin, and atrial natriuretic factor. Chorionic somatomammotropin (a growth-hormone–like substance produced by the placenta), progesterone, and possibly prolactin probably stimulate the increase in red blood cell mass. Extracellular water increases by 1 to 2 L, which, in addition to inferior vena caval compression by the enlarging uterus and fetus, results in the peripheral edema that occurs in 50 to 80 percent of normal pregnancies.

Cardiac structure changes progressively during pregnancy. Left ventricular wall thickness increases by 28 percent, and left ventricular mass by 52 percent above baseline, resulting in a decrease in left ventricular compliance. Nevertheless, left atrial and left ventricular diastolic dimensions increase due to significant increases in filling volumes. Central venous pressure, pulmonary capillary wedge pressure, and left ventricular stroke work do not change significantly when compared with prepregnancy values. Although left ventricular end-diastolic and left atrial dimensions return to normal during the 2 weeks after delivery, left ventricular wall thickness does not return to normal for approximately 24 weeks.

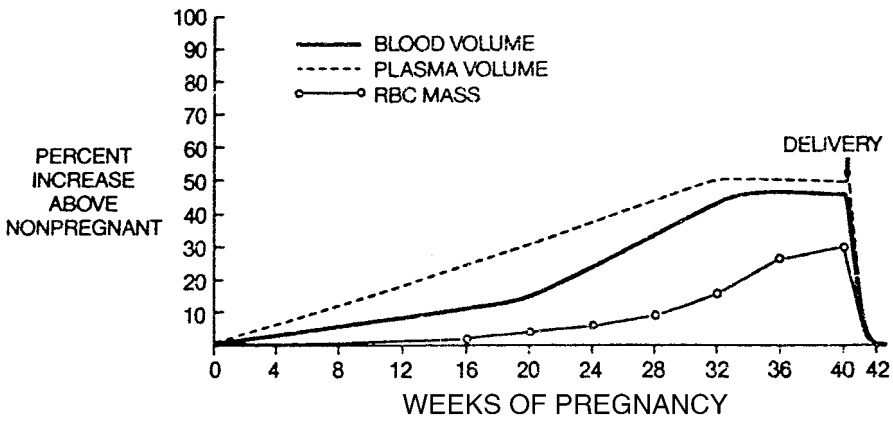

Figure 17-3 Blood volume changes during pregnancy. Plasma volume more significantly increases than red blood cell mass, especially during the first two terms. This produces the relative anemia and the hypervolemia state of pregnancy. *(From Scott AE: Anemia in pregnancy. Obstet Gynecol 1:219, 1972.)*

The changes in cardiovascular physiology during pregnancy affect maternal tolerance to preexistent cardiac disease in different ways. Thus, the increased blood volume and decreased afterload of pregnancy may cause overt heart failure in patients with stenotic lesions of heart valves or worsen right-to-left shunts in uncorrected congenital heart defects. In contrast, pregnant women with regurgitant valvular heart disease often tolerate pregnancy well.

Systemic blood pressure, especially the diastolic component, is slightly lower during pregnancy. Diastolic blood pressure reaches its nadir in the middle of the third trimester, falling by 10 to 20 percent of prepregnancy values. Subsequently, blood pressure increases to near prepregnancy levels. The mechanism for this reduction in blood pressure appears to be hormonally mediated decreases in systemic vascular resistance. Although the resultant blood pressures in the third trimester appear to be distinctly hypotensive when compared with nonpregnant patients, prenatal blood pressure records should be reviewed to ascertain the extent and the significance of the blood pressure changes associated with pregnancy, especially in patients in the second trimester. Pregnant women are susceptible to profound postural hypotension. Approximately 10 to 30 percent of women in the third trimester exhibit postural systolic hypotension. The enlarging uterus may compress surrounding vascular structures, particularly the inferior vena cava and distal aorta. The principal physiological consequence of this compression is a decrease in venous return leading to a decrease in stroke volume and cardiac output. Reflex vasovagal effects may also occur. The normal maternal compensatory response is tachycardia with vasoconstriction in the lower extremities. Care must be taken during spinal or epidural anesthesia, which causes sympathetic blockade that can prevent this normal compensatory phenomenon. Hypotension from aortocaval compression can be minimized by restoration of intravascular volume and displacement of the uterus, which is achieved by right or left lateral tilt of the pelvis.

Reductions in maternal cardiac output may have profound fetal implications. Uterine blood flow is estimated to be 10 percent of maternal cardiac output, approximately 500 ml/min. Reductions in maternal cardiac output occurring during positional changes or due to underlying heart disease may significantly impair uterine blood flow, leading to fetal distress and potential fetal loss. The low resistance nature of the uteroplacental unit makes this region highly dependent on global flow rates, and compensation by increasing vasodilation is poor when flow is impaired.

The umbilical vein supplies fetal blood, which has a P_{O_2} of 26 to 32 mmHg, an oxyhemoglobin saturation of 80 to 90 percent, a P_{CO_2} of 38 to 42 mmHg, and a pH of 7.30 to 7.35. Several factors determine the rate of transfer of oxygen across the placenta: the higher affinity of fetal hemoglobin than adult hemoglobin for oxygen, the diffusion characteristics of the placenta, and umbilical blood flow. Transfer of gas across the placenta is more limited by blood flow than diffusion. Consequently, clinical conditions that diminish maternal cardiac output and/or regional uterine blood flow, such as shock, vasoconstricting agents (epinephrine, norepinephrine, phenylephrine, or high-dose dopamine), and severe respiratory alkalosis, could have serious detrimental effects on the fetus. Likewise, any decrease in the oxygen content of maternal blood resulting from profound hypoxemia, anemia, or alterations in oxyhemoglobin saturation (carbon monoxide, severe alkalosis) could also compromise fetal health.

Dyspnea of Pregnancy

Sixty to 70 percent of normal healthy pregnant women complain of dyspnea during pregnancy even though they have no prior history of cardiopulmonary disease. These complaints commonly occur during the first and second trimester and remain stable or improve near term, suggesting that the etiology is not the mechanical burden of the enlarging uterus. Pulmonary function tests do not appear to correlate with symptomatology in this group, although one study suggested a reduction in diffusing capacity as a factor in dyspneic pregnant women. While some investigators have related the dyspnea of pregnancy to a combination of increased ventilatory drive and increased mechanical load, others have not substantiated these findings and attribute the increased dyspnea to excessive chemoreceptor sensitivity to carbon dioxide or hypoxemia.

ACUTE RESPIRATORY DISTRESS IN PREGNANCY

While preexistent cardiac and pulmonary disorders may be aggravated by pregnancy, several conditions that develop during or are specific for pregnancy need to be considered in evaluating acute respiratory distress during pregnancy. Many of these conditions, with the exception of pulmonary thromboembolic disease, pneumonia, or delivery-related pneumothorax, are attributable to the development of pulmonary edema (Table 17-2). Critical to the clinical evaluation of acute respiratory distress in pregnancy is the careful search for preexistent heart and/or lung disease, a detailed history to characterize precipitating and associated events (e.g., tocolytic therapy, aspiration, obstetrical complications), knowledge of infectious complications commonly encountered in pregnancy, and the meticulous examination of the patient and chest radiograph for findings consistent with cardiogenic failure. As a rule, causes of respiratory distress due to conditions specific to pregnancy (e.g., amniotic fluid embolism, or pulmonary edema secondary to preeclampsia or tocolytic therapy) pose little problem in clinical diagnosis. However, more complicated presentations often require invasive hemodynamic monitoring to differentiate between cardiogenic and noncardiogenic pulmonary edema. Pulmonary thromboembolism should always be strongly considered in the

Table 17-2

Differential Diagnosis of Acute Respiratory Distress in Pregnancy

Disorder	Distinguishing Features	Chest Radiograph
Venous thromboembolism	Evidence of DVT, pleuritic chest pain, positive $\dot{V}/Q$ scan, helical CT, leg dopplers, angiogram	Normal/atelectasis/effusion
Amniotic fluid embolism	Hemodynamic collapse, seizures, DIC	Normal/pulmonary edema
Pulmonary edema secondary to preeclampsia	Hypertension, proteinuria	Pulmonary edema
Tocolytic pulmonary edema	Tocolytic administration, rapid improvement	Pulmonary edema
Aspiration pneumonitis	Vomiting, reflux, fever	Focal infiltrate/pulmonary edema
Peripartum cardiomyopathy	Gradual onset, cardiac gallop	Cardiomegaly, pulmonary edema
Pneumomediastinum	Occurs during delivery, subcutaneous emphysema	Pneumomediastinum, subcutaneous air
Air embolism	Profound hypotension, cardiac murmur	Normal/pulmonary edema
Other: asthma, pneumonia, cardiac disease, ARDS	As for nonpregnant patient	As for nonpregnant patient

DVT = Deep venous thrombosis; $\dot{V}/Q$ = ventilation-perfusion; DIC = disseminated intravascular coagulopathy; ARDS = adult respiratory distress syndrome.
Source: Data from Lapinsky SE, Kruczynski K, Slutsky AS: Critical care in the pregnant patient. Am J Respir Crit Care Med 152:427–455, 1995, with permission.

absence of other explanatory conditions or as a complicating process.

RESPIRATORY DISEASES IN PREGNANCY

Asthma

Approximately 4 to 8 percent of pregnant women in the United States are asthmatic and the prevalence appears to be increasing. A recent large multicenter prospective observational study failed to show an association between asthma and preterm delivery or adverse perinatal outcomes, except for a discharge diagnosis of neonatal sepsis and an increased maternal cesarean section rate in women with moderate or severe asthma. Asthma exacerbation and hospitalization rates increased with the severity of disease. Pharmacologic management of pregnant asthmatics is quite similar to management of nonpregnant asthmatics with a stepwise approach utilizing inhaled short acting beta$_2$-agonists, inhaled corticosteroids, inhaled long acting beta$_2$-agonists, and systemic corticosteroids. Although there is little published human data, animal data suggest that leukotriene receptor antagonists are safe in pregnancy. Theophylline at recommended doses is safe in pregnancy; however, its use is associated with increased side effects. Contrary to some early reports, inhaled corticosteroids are not associated with increased risks of pregnancy-induced hypertension or preeclampsia. Oral corticosteroid use in the first trimester is associated with a small increased risk of isolated cleft lip with or without cleft palate (0.1 to 0.3 percent), and may be associated with increased risks of pregnancy-induced hypertension, preeclampsia, preterm delivery, and low birth weight. However, it is difficult to separate out the effects of the medication from the effects of severe or uncontrolled asthma. The risks of poorly controlled asthma to the mother and fetus are greater than those posed by most medications (including oral corticosteroids) used to treat asthma, so all medications should be used as indicated to maintain optimal asthma control during pregnancy.

Venous Thromboembolism

The risk of venous thrombosis during pregnancy ranges from 0.5 to 3.0 per 1000 pregnancies in those without a history of thromboembolism. Prior thromboembolic disease, smoking, prior venous thrombosis, and thrombophilias are risk factors for deep venous thrombosis or pulmonary embolism (PE) during pregnancy. The risk of venous thromboembolism

is greatest in the postpartum period. Heparin prophylaxis for women with increased risk of thromboembolism during pregnancy and in the immediate postpartum period remains controversial.

Evaluation of the pregnant woman with suspected venous thromboembolism should begin with lower extremity venous ultrasound. If negative, a ventilation-perfusion (V-P) scan or helical computed tomography (CT) scan should be performed next. While helical CT is more sensitive for the diagnosis of PE, and the average fetal radiation dose appears to be less with helical CT when compared with V-P scanning, helical CT delivers about a 40 times greater radiation dose to the breast at a time when it is proliferating. Therefore the appropriate test needs to be carefully considered in each woman. Confirmed cases of venous thromboembolism during pregnancy should be managed with unfractionated or low molecular weight heparins. Coumarin should be avoided due to the risk of embryopathy.

Pulmonary Hypertension

The cardiovascular and hemodynamic changes associated with pregnancy, anesthesia, and delivery pose a severe risk to women with primary pulmonary hypertension, Eisenmenger's syndrome, and secondary pulmonary hypertension. Studies have documented maternal mortalities in these groups from 30 to 56 percent, although most of these studies evaluated patients who did not receive current vasodilator therapy. Recent case reports have documented successful use of intravenous or inhaled epoprostenol, and sildenafil in pregnant women with pulmonary hypertension; however, their long-term effect on overall pregnancy related mortality is unknown.

Sleep-Disordered Breathing

Hormonal changes of increased estrogen resulting in hyperemia and upper airway narrowing, and increased progesterone resulting in increased respiratory drive, along with other physiologic changes of sleep (decreased FRC and respiratory system compliance) predispose to alterations in sleep during pregnancy. While snoring is increased in pregnancy, and sleep-disordered breathing may worsen during pregnancy, the incidence and prevalence of sleep-disordered breathing during pregnancy are unknown. Symptoms of sleep-disordered breathing should be reviewed with women who develop pregnancy-induced hypertension or preeclampsia, and all pregnant women with symptoms of sleep-disordered breathing should be evaluated with a polysomnogram and treated with nasal continuous positive airway pressure as indicated.

Cystic Fibrosis

As survival of individuals with cystic fibrosis continues to improve, fertility and pregnancy have become important issues for many women with the condition. Maternal and fetal outcomes are satisfactory for women with good lung function and nutritional status. Pregnancy appears to have no deleterious effect on long-term survival in women with cystic fibrosis.

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Aging of the Respiratory System

Edward J. Campbell

Even in individuals who enjoy apparently good health, there are measurable decrements in function of the respiratory system with age. These changes occur progressively as a healthy individual grows older and are most marked beyond 60 years of age. Cross-sectional studies show clear differences between elderly and young persons with regard to the structure and function of the components of the respiratory system (Table 18-1). However, caution must be exercised in ascribing observed changes to age alone, since the lungs are exposed to a lifetime of environmental stresses, including tobacco smoke, respiratory infections, air pollutants, and occupational exposures to dusts and fumes. Increasingly sedentary life-styles and decreasing fitness with age have marked effects, especially upon cardiovascular function. Longitudinal studies of "healthy" individuals followed to old age are essentially not available. Despite these caveats, age-related changes in the respiratory system clearly exist, although the magnitude of the changes attributable to aging alone may be somewhat uncertain. Where appropriate, methodological problems in the available cross-sectional studies are described.

Although age-associated changes can be measured easily by objective testing, it is important to note that the routine activities of healthy elderly persons are not limited by decreasing respiratory system function. However, whereas youthful persons have a marked excess of functional capacity over the amount required to meet metabolic needs at rest or with stress (physiological reserve), the respiratory system draws on this reserve as its function declines with age. Thus, the physiological reserve, especially for alveolar gas exchange, is reduced with aging. This leaves elderly individuals vulnerable to stresses, diseases, and injuries that are weathered much more easily in the young.

STRUCTURAL CHANGES IN THE LUNG

Studies of the aging lung have shown changes in shape, with increases in anteroposterior diameter that lead to a "rounding" of the shape of the lung. These changes are presumably

This chapter has been slightly modified from the version that appeared in the third edition of *Fishman's Pulmonary Diseases and Disorders.*

Table 18-1

Respiratory System: Functional Divisions and Changes with Aging

Functional Division	Components	Function	Change(s) with Aging
Conducting airways	All airways not involved in gas exchange (mouth to terminal bronchioles)	Gas movement between environment and alveolar space	Slight changes in size; calcification; glandular hypertrophy
Lung parenchyma	Gas-exchanging airways and vessels; connective tissue framework	Gas exchange between alveolar space and capillary blood	Enlarged terminal airspaces; ventilation/perfusion mismatching
Bellows apparatus	Chest wall and muscles of respiration	Provide mechanical forces for ventilation	Increased rigidity of chest wall; decreased respiratory muscle strength
Ventilatory control	Respiratory control center (pons and medulla); carotid and aortic bodies	Maintaining homeostasis by altering ventilation to match metabolic needs	Markedly decreased responses to hypercapnia and hypoxemia
Cardiovascular system	Heart and systemic vasculature	Blood transport and tissue exchange of respiratory gases	Decreased maximal heart rate and cardiac output; decreased responsiveness to hypoxemia

secondary to changes in the shape of the surrounding thoracic cage and are not thought to have functional consequences.

Conducting Airways

The conducting airways consist of the air passages from the mouth to the level of the respiratory bronchioles. Their volume comprises the anatomic dead space, and their geometry is a primary determinant of airway resistance. The larger cartilaginous airways show a modest increase in size with age, resulting in slight but probably functionally insignificant increases in anatomic dead space. Although calcification of cartilage in the walls of the central airways and hypertrophy of bronchial mucous glands is seen in advanced age, these and other changes in the extraparenchymal conducting airways appear to have little or no physiological significance.

Lung Parenchyma

After age 30 or 40, the respiratory bronchioles and alveolar ducts undergo progressive enlargement (Fig. 18-1). This change has been termed "ductectasia" because of the prominent finding of enlargement of alveolar ducts. The proportion of the lung made up of alveolar ducts increases, and alveolar septa become shortened, leading to a "flattened" appearance of the alveoli. With the change in geometry, the distance between alveolar walls (known to morphologists as the mean linear intercept, or MLI) increases, while the surface-to-volume ratio of the lung decreases. The age-related enlargement of the terminal respiratory units also produces a decrease in the percentage of parenchymal air contained within alveoli. The net result of these structural changes is that the alveolar surface area decreases by approximately 15 percent by age 70.

Pulmonary emphysema is also characterized by an increase in the size of terminal airspaces, an increase in MLI, and a decrease in surface area; however, destruction of alveolar septa with fusion of terminal airspaces is a defining characteristic of emphysema. There have been some reports of emphysematous lesions in aged lungs, but it is not certain that smokers were excluded from these studies. Since the fate of individual alveolar septa during the aging process has been somewhat controversial, some have referred to the histological changes in aged lungs as "senile emphysema." A National Heart, Lung, and Blood Institute Workshop on the definition of emphysema weighed the available evidence and decided not to include age-related changes in the lung parenchyma under the definition of *emphysema.* To simplify terms and avoid confusion, they recommended use of the term *aging lung* to apply to the uniform airspace enlargement that develops with increasing age.

CHANGES IN MECHANICAL PROPERTIES OF THE LUNGS

The lungs and chest wall are both elastic. The resting volume of excised lungs is smaller than that of the lungs contained

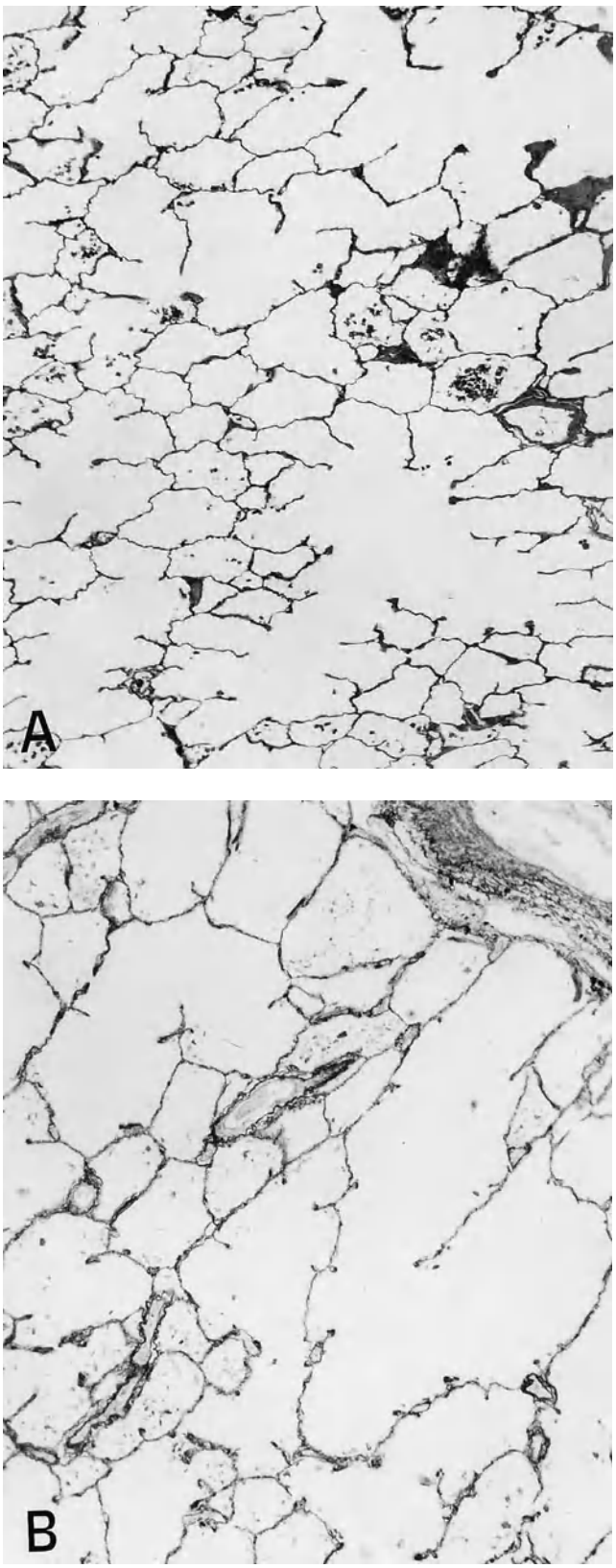

Figure 18-1 Histologic changes in the aging lung. *A*. Normal lung of a 36-year-old woman. *B*. Lung of a 93-year-old woman. In (*B*), the alveolar ducts are dilated, and shortening of interalveolar septa is observed. *(By permission of the Mayo Foundation; photomicrographs courtesy of Charles Kuhn III, M.D.)*

within an intact thoracic cage, because the lungs are held at an increased volume by the outward recoil forces of the chest wall. Thus, in the intact thoracic cage, the lungs exert an inward recoil force. The retractile force of the lungs, or "elastic recoil," can be measured during life by estimating the pleural pressure with an esophageal balloon at progressively decreasing lung volumes from total lung capacity to functional residual capacity, when the airways are open and there is no air flow. The negative pleural pressure is generated by the lungs' elastic recoil forces.

The pressure measurements may be displayed on a pressure-volume diagram (Fig. 18-2). Figure 18-2 compares, at the same volume, the elastic recoil pressures of a young man, a normal elderly adult, and a patient with emphysema. The normal elderly individual and the patient with emphysema both have a greater decrease in elastic recoil pressure than does a young person. This is reflected in the leftward shift of their pressure-volume curves. This loss of elastic recoil is the physiological hallmark of emphysema. However, emphysema is characterized by a much greater loss of elastic recoil than is caused by aging alone.

There has been some disagreement regarding the effects of aging on lung compliance (Δ volume/Δ pressure;

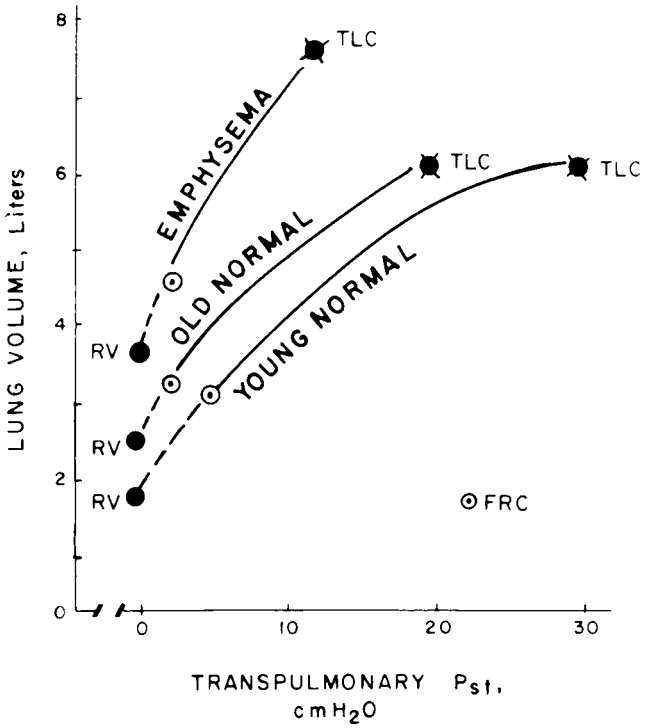

Figure 18-2 Static pressure-volume curves of the lungs. Static recoil pressure, expressed as transpulmonary pressure measured at various lung volumes, is plotted against lung volume on the ordinate. Note that at any lung volume, the recoil pressure is less in the aged individual than in the young, normal control, resulting in a pressure-volume curve that is shifted upward and to the left. For comparison, a curve for a patient with emphysema is shown. In emphysema, recoil pressures are reduced much more, and lung compliance (the slope of the pressure-volume relationship) is clearly abnormal. *(From Pride NB: Bull Eur Physiopathol Respir 10:103–108, 1974, with permission.)*

i.e., the slope of the pressure-volume relationship, Fig. 18-2). The question is whether there is a parallel leftward shift of the pressure-volume curve with aging (no change in compliance), or, instead, a steeper slope in addition to a shift (indicating an increase in compliance), as seen in emphysema. In aged individuals, the static pressure-volume curve is slightly steeper and is more concave in relation to the pressure axis. However, there is general agreement that changes in lung compliance with aging are not physiologically significant.

Two forces in the lung parenchyma are responsible for producing the elastic recoil of the lungs. The greatest part of the elastic recoil forces is provided by the surface tension at the curved air-fluid interface of the small airways and alveoli. The second retractive force is that produced when the fibrous skeleton of the lung (primarily the elastic fibers) is stretched.

Changes in Surface Forces

Most of the loss in lung recoil with age is likely to be related to the decrease in lung surface area with age. The loss of surface area that accompanies aging can be expected to reduce the area of gas-liquid interface, resulting in a decrease in the surface tension forces and, ultimately, a decrease in the total elastic recoil of the lung. Whether it is due to loss of air-liquid interface or to changes in lung structural macromolecules (see below), the reduced elastic recoil has important consequences for the function of the intraparenchymal airways and, ultimately, on alveolar gas exchange and forced expiratory flow (see "Pulmonary Function Tests," below).

Changes in Structural Macromolecules

Elastic fibers, which are composed in large part of an extremely hydrophobic, highly cross-linked, and very elastic macromolecule (elastin), form a continuous skeleton that follows the airways and pulmonary vessels and extends to a fine meshwork in the alveolar septa. These fibers are thought to contribute substantially to lung elasticity. Analysis of whole lungs has revealed that the elastin content actually increases (rather than decreases) with age. More recent evidence indicates that the increase in lung elastin with age is accounted for by an increase in pleural elastin; parenchymal elastin does not change.

Careful studies of the elastic fibers in the lung parenchyma have shown that they are remarkably stable following postnatal lung growth. Certain biochemical changes in very long-lived proteins (change of amino acids into their mirror-image structures, or racemization) provide a type of "biological clock" that permits an estimate of the time that has elapsed since the proteins were synthesized. Because of the constraints of the protein synthetic mechanisms, only L-amino acids are incorporated into newly synthesized proteins. With the passage of years at body temperature; however, there is a readily measurable accumulation of D-aspartic acid. When all of the lung proteins are examined together, minimal D-aspartic acid is found. In purified lung elastin,

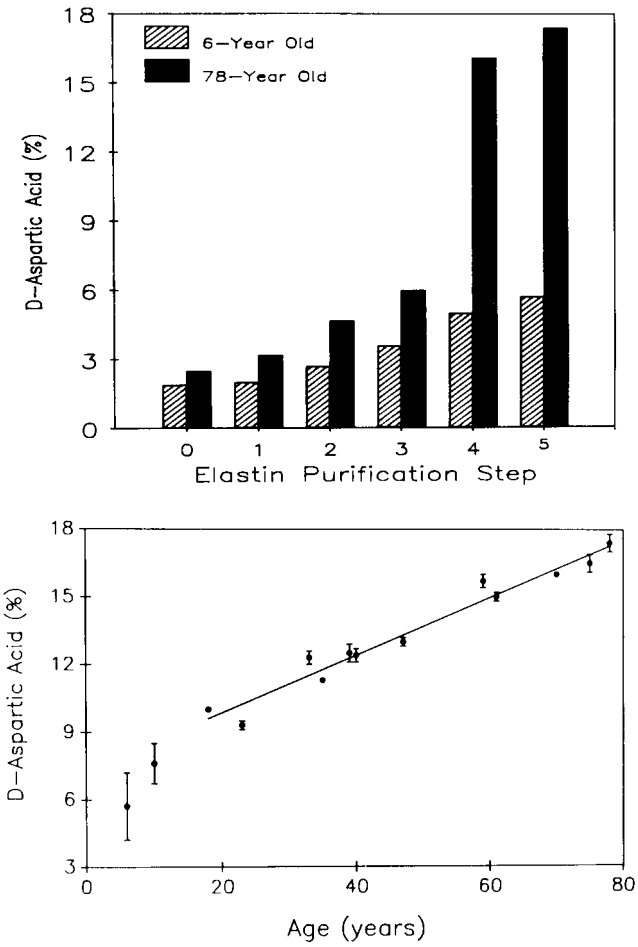

Figure 18-3 Longevity of human lung parenchymal elastin, as evidenced by in vivo racemization of aspartic acid. *Top panel.* Each pair of bars shows results from two individuals with greatly differing ages at time of death. Step 0 of elastin purification represents whole lung parenchyma, while step 5 is purified elastin. D-Aspartic acid detected in the 6-year-old specimen can be attributed to racemization that occurs during the analytical procedures, whereas the difference in prevalence of D-aspartic acid between the young and old individual has resulted from racemization in vivo. Note that results from whole-lung hydrolysates (step 0) are similar for both specimens, reflecting their composition of proteins, having predominantly rapid turnover. However, purified elastin from the oldest specimen has racemized extensively in vivo, indicating that it was synthesized many decades before death. *Bottom panel.* D-Aspartate in elastic fibers is shown as correlated with age at death. The relationship of D-aspartic acid to the age of the subject indicates that parenchymal elastin is markedly persistent after its synthesis. The data for elastin agree well with results for other very long lived proteins. *(From Shapiro SD, Endicott SK, Province MA, et al: Marked longevity of human lung parenchymal elastic fibers deduced from prevalence of D-aspartate and nuclear weapons–related radiocarbon. J Clin Invest 87:1828–1834, 1990, with permission.)*

however, there is an age-related accumulation of D-aspartic acid, indicating that lung elastin is turning over very slowly if at all (Fig. 18-3). It has also been possible to estimate lung elastin turnover by measurement of the incorporation into elastic fibers of carbon 14 (^{14}C) from atmospheric nuclear

weapons testing. For example, individuals who completed their postnatal lung growth prior to the nuclear age show no excess ^{14}C in their lung elastin, indicating absence of new elastin synthesis. In contrast, an appropriate excess of ^{14}C is found in the lung elastin of individuals whose lungs were growing in the post–weapons testing era. Modeling of the radiocarbon data indicates that the "mean carbon residence time" in elastin is 74 years.

Taken together, the amino acid racemization and radiocarbon data indicate that lung parenchymal elastin is stable over the human life span, and it appears that the elastin content of the lung parenchyma not only does not change with age, but the individual fibers persist for at least many decades. The remarkable longevity of lung elastic fibers raises the strong possibility that these connective tissue structures provide a metabolically inert scaffold for the structure of the lung. This may explain the appearance of structural abnormalities in the lung parenchyma (such as pulmonary emphysema) when the elastic fibers are injured.

Other studies of lung elastic fibers have shown changes in the location and orientation of individual fibers with age as well as changes in the cross-linking of elastin. Thus, some authors have suggested that remodeling of the lung architecture may occur without replacement of elastic fibers. In any case, at the present time, the age-related changes in connective tissue do not provide a sufficient explanation for the decrease in elastic recoil forces observed in the elderly.

Studies of lung collagen have failed to show a consistent change in its quantity during aging. Although human studies have not been done, studies in rodents and birds suggest that lung collagen fibers, like elastic fibers, are very long-lived. Finally, although some qualitative changes in collagen during aging have been described (decreases in solubility and increases in intermolecular cross-links), these appear to have no relationship to changes in lung elastic recoil.

Changes in Chest Wall

There is good evidence that the chest wall becomes more rigid with advancing age. As may be seen in Fig. 18-4, the static pressure-volume curve of the chest wall is shifted to the right and is less steep with increasing age. The articulations of the ribs with the sternum and spinal column may become calcified, and the compliance of the rib articulations decreases. The changes in rib articulations may be compounded by the development of kyphosis due to osteoporosis. The decreasing compliance of the chest wall demands greater work from the respiratory muscles. For example, in a 70-year-old person, approximately 70 percent of the total elastic work of breathing is expended on the chest wall, whereas this value is 40 percent in a 20-year-old.

Figure 18-4 also demonstrates that the compliance of the total respiratory system decreases with age because the decrease in lung elastic recoil is outweighed by the changes in the mechanical properties of the chest wall.

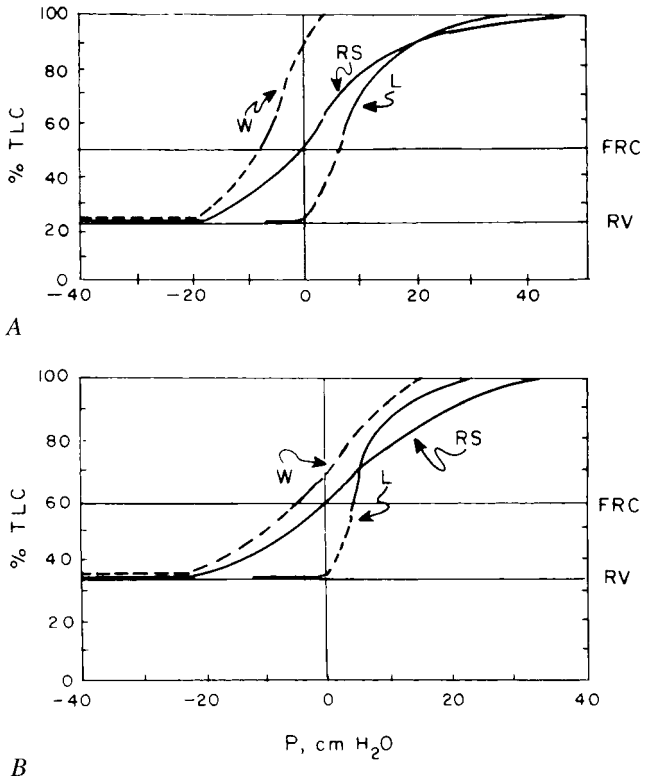

Figure 18-4 Static compliance relationships of the components of the respiratory system. (L = lungs; W = chest wall; RS = total respiratory system.) *A*. A 20-year-old man. *B*. A 60-year-old man. Note that the static compliance of the chest wall is substantially decreased (reduced slope) in the older individual, while functional residual capacity (the resting volume of the respiratory system, or the point at which the pressure gradient across the respiratory system is zero) increases. As in Fig. 18-2, it is also apparent that the static recoil pressure of the lungs is reduced in the older subject. *(Based on data from Mittman C, Edelman NH, Norris AH, et al: Relationship between chest wall and pulmonary compliance and age. J Appl Physiol 20:1211–1216, 1965; Turner JM, Mead J, Wohl ME: Elasticity of human lungs in relation to age. J Appl Physiol 25:664–671, 1968, with permission.)*

CHANGES IN MUSCLES OF RESPIRATION

Age-related changes in nonrespiratory skeletal muscle include decreased work capacity due to alterations in the efficiency of muscle energy metabolism, atrophy of motor units, and electromyographic abnormalities. Based upon lessons learned with other skeletal muscles, it appeared likely that age-related abnormalities in respiratory muscles also would be found.

An early study by Black and Hyatt appeared to confirm age-related decrements in respiratory muscle function by measuring maximal inspiratory pressure (PI_{max}) and maximal expiratory pressures (PE_{max}) in 120 normal individuals (both smokers and nonsmokers) between the ages of 20 and 70. Maximal respiratory pressures in females were 65 to 70 percent of those in males. No significant age-related changes were observed in individuals under the age of 55. Trends toward reduced maximal respiratory pressures with age were

seen in both genders and with both PI_{max} and PE_{max}. With the numbers of males studied, the change with age in PI_{max} was not statistically significant for male gender.

More recently, McElvaney and coworkers came to a different conclusion in a similar study of 104 healthy individuals over the age of 55. They found large variation in maximal respiratory pressures from individual to individual (as had Black and Hyatt), but no significant correlation with age. In contrast, in a third population of 160 healthy individuals who ranged in age from 16 to 75 years, Chen and Kuo found significant gender differences in maximal respiratory pressures as well as trends toward decrements with age for both PI_{max} and PE_{max} in both genders. The age-related change in PE_{max} in males was not statistically significant with the sample size studied. When the 40 individuals of both genders in the youngest age group (16 to 30 years) were compared with the 40 individuals in the oldest group (61 to 75 years), the decrement in PI_{max} was 32 to 36 percent, while the decrement in PE_{max} was 13 to 23 percent. Representative findings for maximal respiratory pressures in women are illustrated in Fig. 18-5.

Chen and Kuo also measured inspiratory muscle endurance against a resistive load, and found significant decrements with age. Physically active men had greater inspiratory muscle endurance than sedentary men.

In summary, it appears that when populations of healthy individuals of widely differing ages are studied, moderate age-related decrements in respiratory muscle strength and endurance can be found. These studies usually define *healthy* only by the absence of disease and do not control for physical activity. They are complicated by marked interindividual variability, and longitudinal studies have not been reported. Continuous respiratory muscle activity may have a training effect that leads to better preservation of respiratory muscle function when compared with other skeletal muscles. Finally, physical activity may have an additional training effect that enhances inspiratory muscle endurance in all age groups.

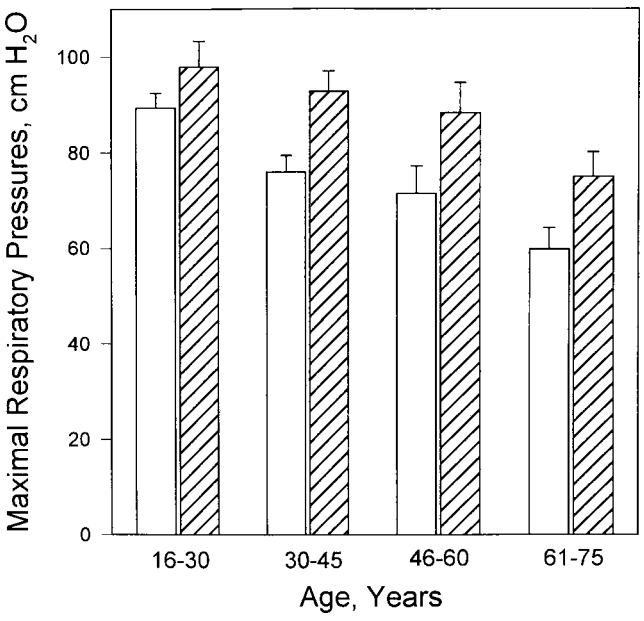

Figure 18-5 Representative variations in maximal respiratory pressures with age among women. Inspiratory and expiratory measurements were made at residual volume and total lung capacity, respectively. Maximal inspiratory pressure (*open bars*) and maximal expiratory pressure (*hatched bars*). Error bars are standard errors of the mean. Although quantitatively moderate, variations with age were statistically significant for both measurements. *(From Chen H-S, Kuo C-S: Relationship between respiratory muscle function and age, sex, and other factors. J Appl Physiol 66:943–948, 1989, with permission.)*

CONTROL OF BREATHING

In young individuals, minute ventilation is matched to metabolic demands. As a result, arterial blood gas values remain stable throughout a wide range of activities from rest to strenuous exertion, while oxygen consumption and carbon dioxide production are varying widely. Similarly, when the efficiency of gas exchange is diminished by lung disease or congestive heart failure, appropriate increases in minute ventilation minimize the resulting hypercapnia and/or hypoxemia in healthy young individuals. The ventilatory control system is described in detail in Chapter 11.

Ventilatory control mechanisms are typically tested by stressing the respiratory system, by inducing either hypoxemia or hypercapnia while monitoring ventilatory parameters (and often cardiac parameters as well). Such tests have shown striking differences between young and elderly individuals in both ventilatory and cardiac responses.

Diminished Ventilatory Response to Hypercapnia

Kronenberg and Drage compared the ventilatory responses to hypercapnia in eight young (mean age, 25.6 years) and eight elderly (mean age, 69.6 years) individuals. During the tests, the subjects were asked to rebreathe 5 percent CO_2 while their $P_{A_{O_2}}$ was held above 200 mmHg by supplemental oxygen to eliminate hypoxic ventilatory drive. Measurements were made while $P_{A_{CO_2}}$ was allowed to rise to 65 mmHg. Although there was considerable individual variation and some overlap between the groups, the elderly individuals had a significantly diminished ventilatory response to hypercapnia, measured as the slope of the relationship between ventilation and $P_{A_{CO_2}}$.

Diminished Ventilatory Response to Hypoxia

When Kronenberg and Drage measured the ventilatory response to hypoxia at constant CO_2, they found even more striking differences between the young and elderly subjects (Fig. 18-6). For example, the ventilatory response to a $P_{A_{O_2}}$ of 40 mmHg was uniformly smaller in the older subjects, and there was no overlap between the groups. The mean minute ventilation at a $P_{A_{O_2}}$ of 40 mmHg was 40.1 and 10.2 L/min in the young and old groups, respectively.

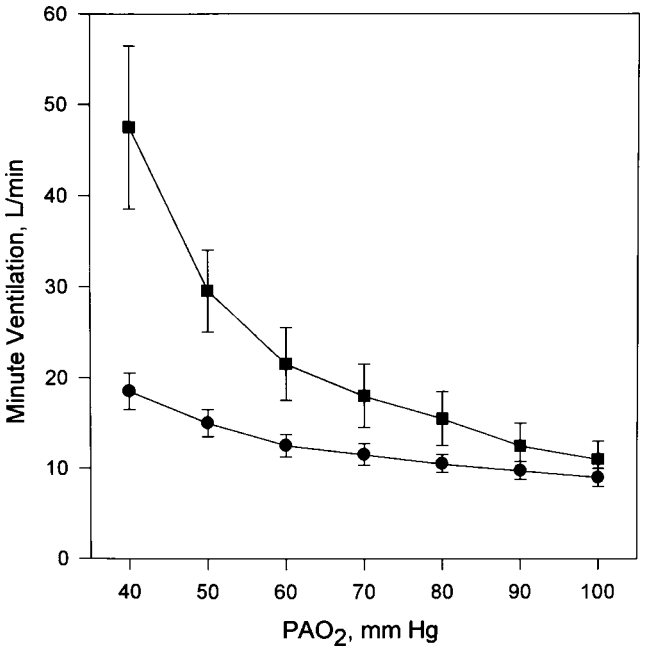

Figure 18-6 Variations with age in ventilatory responses to hypoxia. Eight normal men aged 64 to 73 (squares) and eight controls aged 22 to 30 (circles) were subjected to isocapnic progressive hypoxia by a rebreathing method. Data values are means, with standard errors of the mean shown by the error bars. Note that the ventilatory responses differ strikingly between the elderly individuals and the controls. *(From Kronenberg RS, Drage CW: Attenuation of the ventilatory and heart rate responses to hypoxia and hypercapnia with aging in normal men. J Clin Invest 53:1812–1819, 1973, with permission.)*

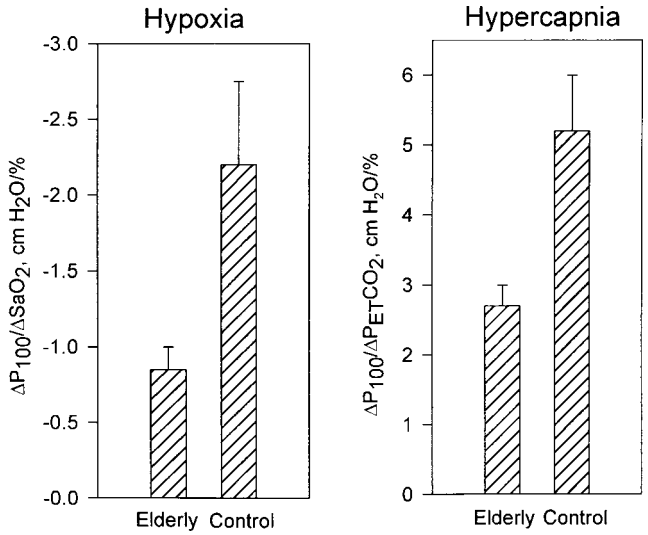

Figure 18-7 Variations with age in occlusion pressure responses to hypoxia and hypercapnia. Data shown are slopes of relationships between occlusion pressure responses and either Sao_2 or end-tidal P_{CO_2}; error bars are standard errors of the mean. Elderly individuals had significantly diminished occlusion pressures in response to both hypoxia and hypercapnia. Both differences were significant, with $p < 0.01$. *(From Peterson DD, Pack AI, Silage DA, et al: Effects of aging on the ventilatory and occlusion pressure responses to hypoxia and hypercapnia. Am Rev Respir Dis 124:387–391, 1981. with permission.)*

Diminished Occlusion Pressure Responses

Peterson and colleagues confirmed the above observations and have shown that the differences in responses of elderly subjects to both hypercapnia and hypoxia are due to a lesser increase in tidal volume while the ventilatory rate increases normally. Since this observation could be caused by differences in respiratory muscle strength or increases in chest wall stiffness, the authors also measured airway occlusion pressures, which are valuable indices of respiratory drive that are not affected by respiratory muscle strength or respiratory mechanics. The measurement (P_{100}) is the negative pressure at the mouth, measured 100 ms after the start of inspiration against an occluded airway. The occlusion pressure responses to both hypoxia and hypercapnia (Fig. 18-7) were significantly reduced in the 10 elderly subjects studied by Peterson (mean age, 73.3 years) when compared to nine young control subjects (mean age, 24.4 years). Although the elderly individuals had reduced respiratory muscle strength (mean, 24 percent lower maximal static inspiratory pressure), the differences in occlusion pressure persisted when normalized for these differences.

In summary, the reduced responsiveness in tidal volume to either hypoxemia or hypercapnia with age is apparently due to a reduced responsiveness of ventilatory drive or neural output from the respiratory center. It has not been determined whether the diminished ventilatory drive results from altered chemoreceptor function or from altered function of the respiratory center. Kronenberg and Drage favor altered receptor function based on their observation that elderly subjects responded to an alveolar oxygen tension of 40 torr with only an 11 percent increase in heart rate, whereas the young subjects responded with a 34 percent increase.

Respiratory Load Compensation and Dyspnea

Reflex compensation for a change in respiratory mechanical load (as in lung disease, changes in posture, and mouth versus nose breathing) normally serves to maintain ventilation constant during the change. Akiyama and colleagues measured responses to inspiratory flow-resistive loading in young and elderly individuals and found significant differences. In the young control group, inspiratory loading resulted in an increase in P_{100} at each level of induced hypercapnia, such that inspiratory loading did not change the ventilatory response to hypercapnia when compared with unloaded responses. In marked contrast, the P_{100} in the elderly group did not change when an inspiratory load was applied. In the absence of a compensatory change in ventilatory drive, ventilatory responses to hypercapnia were reduced during inspiratory loading in the elderly group.

At each level of P_{CO_2}, the intensity of perceived dyspnea in response to inspiratory loading was greater in the elderly than in the control group. Thus, the sensation of dyspnea was intact or enhanced in the elderly subjects, while their

compensatory responses were reduced. This suggests the possibility that elderly individuals may complain of greater dyspnea than younger individuals with similar pathophysiological deterioration.

PULMONARY CIRCULATION

Invasive physiological studies of pulmonary artery catheterization have typically been biased by including only subsets of patients whose signs and symptoms led to referral for heart catheterization and who, therefore, may not be representative of a "healthy" cohort. Further, age-related changes in the pulmonary circulation are difficult or impossible to separate from changes due to heart disease or age-related changes in cardiac function.

Ehrsam and colleagues reported a retrospective analysis of right heart catheterization studies performed in 125 asymptomatic subjects who ranged from 14 to 68 years of age. Small increases in right atrial, pulmonary artery, and pulmonary artery wedge pressures observed in the highest age group disappeared when values were adjusted for sex, weight, and height. No significant age-related changes were found in cardiac output, stroke volume, or oxygen uptake. Age explained 10 percent or less of the total variation in the hemodynamic and pressure variables when assessed by multiple regressions. During supine exercise with a bicycle ergometer, however, pulmonary artery and wedge pressures increased with age, particularly in subjects over age 45. The changes were highly significant, with age accounting for 12 to 30 percent of the total variation when assessed by multiple regressions. Finally, pulmonary artery resistance showed a highly significant increase with age, whether measured at rest or during exercise, with age contributing 12 to 27 percent to the total variation in pulmonary artery resistance. Although the cohort studied were all asymptomatic and ambulatory, it is possible that silent coronary artery disease was present in some of the subjects, and the prevalence of coronary artery disease can be expected to increase with age. Moreover, younger patients tended to be referred for evaluation of a heart murmur, whereas the older patients were referred for "pulmonary investigation" that included coin lesions, hilar lymphadenopathy, "previous pulmonary infiltrates," and smoke inhalation. Cigarette smoking history was not discussed. Thus, it is not certain that the younger and older patients were strictly comparable.

More recently, Davidson and Fee reported the results of right-heart catheterization at rest in 47 normal subjects who were free of coronary disease and had normal left ventricular systolic function. Smokers were included. The investigators found highly significant but quantitatively modest age-related increases in mean pulmonary artery pressure, pulmonary vascular resistance, and pulmonary/systemic vascular resistance ratio, but they found no age-related differences in pulmonary artery wedge pressure. The authors felt that the most likely explanation for the age-related changes in pulmonary artery pressure and pulmonary vascular resistance was a primary abnormality of the pulmonary vascular bed, but they could not exclude effects of subtle abnormalities in left ventricular function.

In summary, studies of pulmonary hemodynamics with aging are limited by retrospective design, bias in patient selection, and potential effects of smoking. Minor increases in pulmonary vascular resistance and age-related increases in pulmonary artery wedge pressure during exercise have been reported. These age-related changes may not be physiologically significant.

PULMONARY FUNCTION TESTS

Lung function and exercise capacity decline with age in concert with numerous other physiological, morphological, and biochemical changes. Descriptions of "normal" age-related changes are confounded by an increasing prevalence of disease, chronic illness, medication use, and an increasingly sedentary life-style. Further, chronological age only approximates physiological age; the two often differ significantly. Chronological age is, therefore, an imperfect measure for indexing changes with senescence. While it would be desirable to isolate the effects of "normal aging" (aging in the absence of disease), it is essentially impossible to do so. The best studies to do so are longitudinal, tracing change with time, because they avoid the obvious biases of cross-sectional studies. Longitudinal studies, however, have methodologic problems and biases of their own, the most obvious being that the healthy elderly represent a healthy survival population. If, as a group, they have better than average lung function, they would not represent the general population of elderly people well.

Lung Volumes

Figure 18-8 illustrates typical lung volume changes with aging based on cross-sectional studies. With the exception of vital capacity, the effect of aging on lung volumes is based on cross-sectional rather than longitudinal data because there are almost no longitudinal studies of static lung volumes. Total lung capacity (TLC), the volume of air in the lungs at the end of a maximal inspiration, is marked by the point at which the recoil pressure exerted by the respiratory system is exactly counterbalanced by the maximal inspiratory pressure generated by the respiratory muscles. Since both the compliance of respiratory system (lung and chest wall combined) and maximum inspiratory pressure fall with aging, TLC might also be expected to fall. However, in seven cross-sectional studies of TLC summarized by the European Coal and Steel Community, four of the studies in men and three of those in women did not find a significant age coefficient. The remaining studies found only small declines in TLC with age, on the order of −8 to −19 ml/year. When these study results were combined into average equations, no significant age coefficients were reported for either men or women. McClaran and colleagues

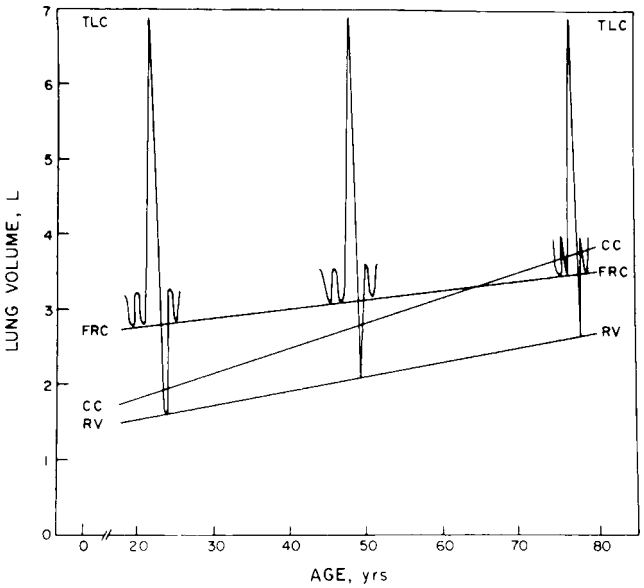

Figure 18-8 Schematic illustration of lung volume changes with age based on cross-sectional studies in seated individuals. (TLC = total lung capacity; FRC = functional residual capacity; RV = residual volume; CC = closing capacity.) Although not labeled, vital capacity (VC) is TLC minus RV. The most consistent changes are an increase in RV and a decrease in VC. *(From Peterson DD, Fishman AP: Aging of the respiratory system, in Fishman AP (ed): Update: Pulmonary Diseases and Disorders. New York, McGraw-Hill, 1992, pp 1–17, with permission.)*

measured lung volumes twice in 18 healthy, fit men. The first measurement was at a mean age of 67 and the second was 6 years later. Although average TLC fell 25 ml/year, the change was not statistically significant. The study was small and the interval was short.

In summary, current cross-sectional studies suggest that TLC either does not decline with age or declines very slowly. It is interesting to speculate on the possibility that cross-sectional studies of TLC might be confounded because they typically index TLC to both age and height. Height declines with aging, and maximum height during a life span appears to increase with successive generations. The authors believe that longitudinal studies of TLC with age are likely to show small but significant declines with age.

Both slow and forced vital capacity (FVC) decline with age, more rapidly in men than women. Average decrements in vital capacity per year vary considerably; in cross-sectional studies, declines range from 21 to 33 ml/year in men and 18 to 29 ml/year in women. Theoretically, longitudinal studies should provide better estimates of the effect of aging on lung function. Ware and colleagues, in a study containing both longitudinal and cross-sectional computations, found cross-sectional falls in FVC for men and women to be −34 and −27.8 ml/year, respectively. The longitudinal estimates were −40 ml and −31.3 ml/year, respectively. This study contradicts the generally held concept that longitudinal studies show smaller declines in FVC than cross-sectional studies. Currently, it is not certain whether longitudinal studies are all that much different from cross-sectional studies in describing declines in FVC and forced expiratory volume in 1 s (FEV_1). Longitudinal studies tend to show an acceleration in the rate of loss in FVC and FEV_1 as age advances.

Cross-sectional studies of residual volume (RV) and the RV/TLC ratio consistently show increases with age. In the young, RV, the volume of air in the lungs at the end of a maximal expiration is the volume at which the outward static recoil pressure of the respiratory system is counterbalanced by the maximal pressure exerted by the expiratory muscles. In older subjects, expiratory flow never completely reaches zero and the determination of RV is made partly by the length of time an individual can maintain expiratory effort. Other factors leading to an increased residual volume with aging include loss of lung recoil, decreased chest wall compliance, decreased expiratory muscle force, and increased small airway closure (air trapping) in dependent lung zones. Time of exhalation and increase in air trapping are probably more important than changes in lung and chest wall compliance in explaining the increase in RV with aging.

Functional residual capacity (FRC) is also determined by the balance of the elastic recoil forces of the lung and chest wall; but, in this instance, the equilibrium occurs at the end of a quiet (unforced) exhalation. Since lung recoil falls and the chest wall stiffens with age, one would expect FRC to increase. Cross-sectional studies, however, show inconsistent results, with most showing no change in FRC with aging. Studies that find an increase in FRC with aging show a small positive age coefficient on the order of 7 to 16 ml/year. McClaran's longitudinal study found FRC to increase 40 ml/year, but, again, the change was not significant. Despite the conflicting data, it is generally believed that FRC increases with aging.

Loss of lung recoil also changes the volume at which airway closure occurs. When adults exhale fully, small airways close in the region of the terminal bronchioles in dependent lung zones. The lung volume at which this closure begins is measured as closing volume or, if it is added to residual volume, closing capacity. Closing volume increases linearly with age from about 5 to 10 percent of TLC at age 20 to about 30 percent of TLC at age 70. The loss of lung elastic recoil, a possible decrease in the recoil of the intrapulmonic airways, and decreases in small airway diameter probably explain most of the change in CV.

Closing volume encroaches on tidal volume by about age 44 when subjects are supine and about age 65 when they are seated (Fig. 18-8). Airway closure during tidal breathing explains part of the decrease in arterial oxygen tension ($P_{A_{O_2}}$) observed with aging and may contribute to an aging-related increased frequency dependency of compliance.

Airflow

While essentially all expiratory flows measured during a maximum expiratory maneuver decrease with age, the declines are most evident at lower lung volumes (Fig. 18-9). Nunn and colleagues, in a study of 225 male and 228 healthy female nonsmokers, reported a modest, nonlinear decrease in peak expiratory flow (PEF) with aging (Fig. 18-10), which reached

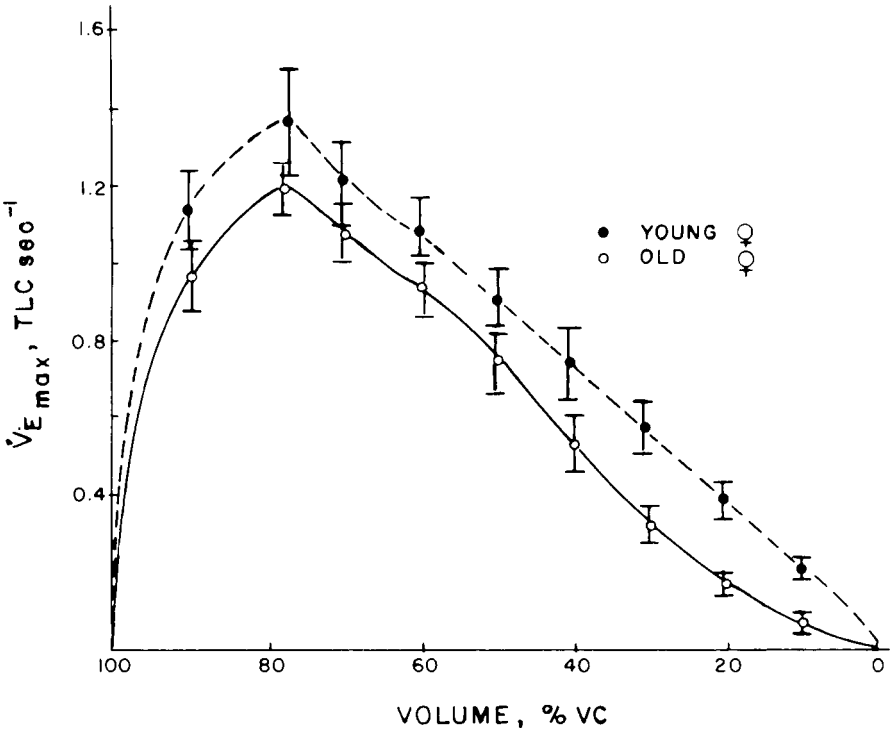

Figure 18-9 Illustrative maximal flow-volume curves for healthy "elderly" women (mean age, 63 years) and healthy young women (mean age, 25 years). Although all flows tend to be reduced with aging, the reduction in flow is most evident at lower lung volumes, where the flow-volume curve is clearly concave to the volume axis. *(From Peterson DD, Fishman AP: Aging of the respiratory system, in Fishman AP (ed): Update: Pulmonary Diseases and Disorders. New York, McGraw-Hill, 1992, pp 1–17, with permission.)*

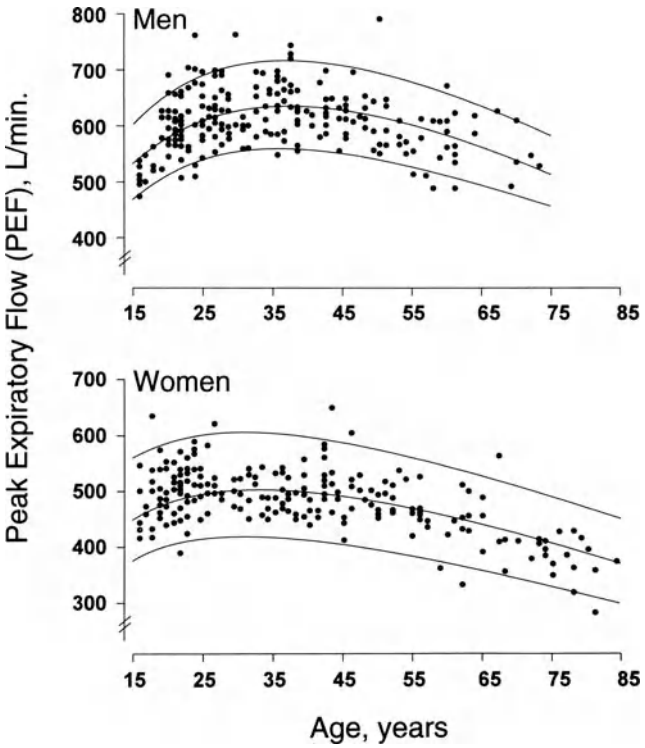

Figure 18-10 Changes in peak expiratory flow in 225 males and 228 females who were healthy nonsmokers. The center line is a regression curve representing mean data and the boundaries are 90 percent confidence intervals. *(From Nunn AJ, Gregg I: New regression equations for predicting peak expiratory flow in adults. Br Med J 298:1068–1070, 1989, with permission.)*

a high point at age 30 to 35; decline became evident at about age 45. After age 50, the average decline in men was about 4 L/min per year, about 2.5 L/min per year for women.

Figure 18-11, from Paoletti et al., illustrates changes in FEV_1 during growth, maturation, and senescence. Changes in FVC are similar. In one model of aging, FVC and FEV_1 increase progressively during the growth phase until about age 12. In the maturation phase (during adolescence) there is an acceleration of these increases. Increases in FVC and FEV_1 are seen up to about age 20 years in women and about 25 years in men; increases in lung volumes occur even after somatic growth ceases. There appears to be a plateau phase where there is little or no change in FVC or FEV_1 prior to the onset of a decline. However, Robbins and colleagues demonstrated that, while the plateau correctly represents average data, lung function is often increasing or decreasing in individuals (Fig. 18-12). Their study confirms the suspicion that the "plateau" phase represents the merging of slower maturation-related increases in FVC and FEV_1 in some subjects, with subtle decreases in others. In the decline phase, there appears to be acceleration in the rate of loss of FVC and FEV_1 as age progresses. An accelerated rate loss at older ages is, however, not found in all studies. The rate of decline in FVC and FEV_1 with age tends to be greater: (1) in men; (2) in taller individuals; (3) in individuals with larger baseline values; and (4) in individuals with increased airway reactivity.

Airways Resistance

Total airway resistance measured at FRC does not change with aging. Since upper airways increase and smaller airways decrease in size with aging, it is likely that peripheral airway

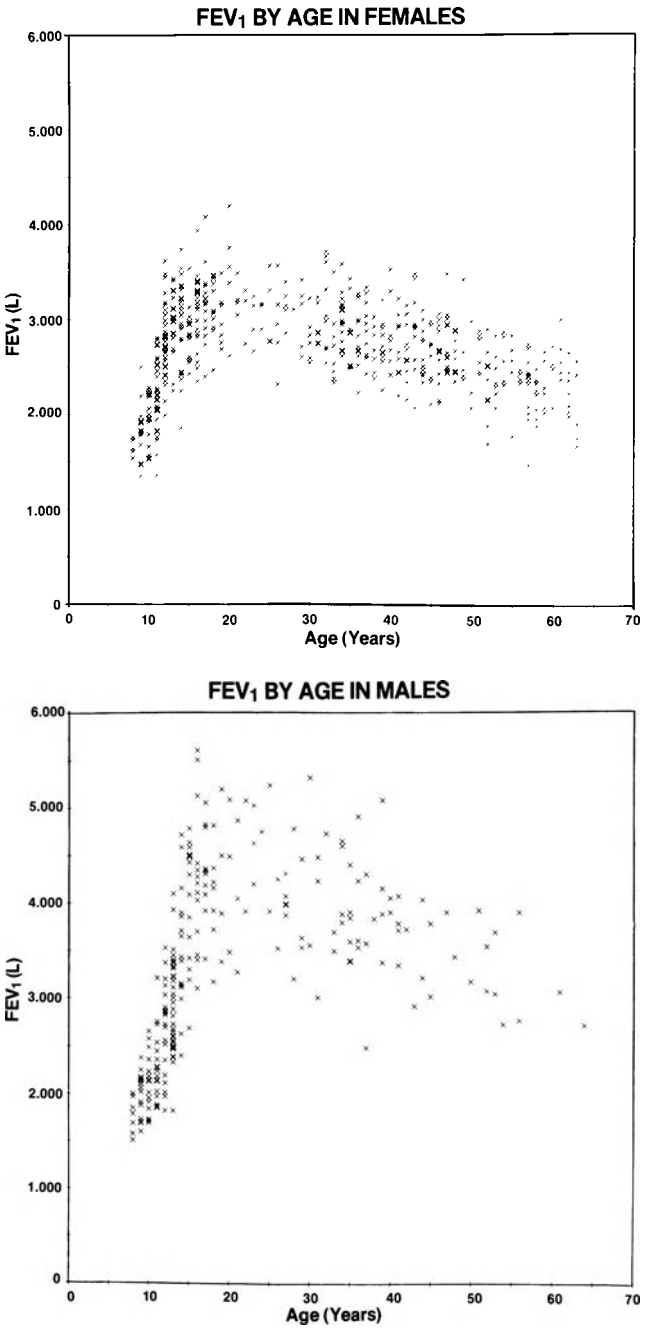

Figure 18-11 Change in FEV_1 with age from a cross-sectional study of 538 females and 263 males selected as ''normal" from a larger study of 3289 subjects. Changes in FVC are similar. *(From Paoletti P, Pistelli G, Fazzi P, et al: Reference values for vital capacity and flow-volume curves from a general population study. Bull Eur Physiopathol Respir 22:451–459, 1986, with permission.)*

resistance increases and central airway resistance decreases. That total airway resistance does not change with aging may be a function of the counterbalancing of these two opposite changes. However, since about 90 percent of total airway resistance resides in the upper airways, significant changes in peripheral airway resistance might not be readily reflected in total airway resistance. Significant increases in peripheral airway resistance with age also would be consistent with the more dramatic decreases in maximum flow observed at low lung volumes.

Gas Exchange

The carbon monoxide diffusing capacity (D_{LCO}), also known as transfer factor (T_{LCO}), declines with age. Earlier cross-sectional studies report a linear decline in D_{LCO} of about −0.2 ml CO/min per mmHg per year for men and −0.15 mL CO/min per mmHg per year for women. These declines are roughly 0.5 percent per year. In a large representative sample of U.S. adult men, Neas and Schwartz found an almost identical linear fall in D_{LCO}. In women, however, they found a nonlinear, quadratic decline in D_{LCO} with age. After age 47, the nonlinear component was not significant and the decline in D_{LCO} was identical to that in the earlier studies. The decline in D_{LCO} with age did not vary with race.

The decline in D_{LCO} with age is not explained by increased nonhomogeneity of gas distribution. Measured D_{LCO} falls as alveolar P_{O_2} increases and venous hemoglobin concentration falls. Neither alveolar P_{O_2} nor hemoglobin concentration varies enough with age to explain the aging decline in D_{LCO}. The magnitude of the decline in D_{LCO} corresponds fairly well to the magnitude of the known aging-related decrease in the internal surface area of the lung.

The components of D_{LCO} are membrane diffusing capacity (Dm) and pulmonary capillary blood volume (Vc). Both Dm and Vc decrease with age. In a cross-sectional reference value study of 54 male and 36 female healthy nonsmokers, the declines in Dm and Vc with age were found to be linear. Membrane diffusing capacity fell at about 0.6 percent per year in both men and women. Pulmonary capillary blood volume fell at about 0.3 percent per year.

Although alveolar oxygen pressure ($P_{A_{O_2}}$) remains constant with age, arterial P_{O_2} (Pa_{O_2}) decreases and the alveolar-arterial oxygen tension gradient ($P_A - a_{O_2}$) increases with aging (Fig. 18-13). The decline in Pa_{O_2} with aging is more pronounced when subjects are studied in a recumbent as contrasted with an upright position. The most likely explanation for the decline in Pa_{O_2} with aging is increased mismatching of ventilation to blood flow ($\dot{V}E/\dot{Q}$) as airway closure begins to occur during tidal breathing. Increased $\dot{V}E/\dot{Q}$) mismatching with aging is also associated with an increase in physiological dead space. Hypoventilation does not contribute to the age-related fall in Pa_{O_2}, since Pa_{CO_2} and pH do not change with age (Fig. 18-13).

EXERCISE CAPACITY

Peak $\dot{V}O_2$ ($\dot{V}O_{2\,peak}$) and maximum work capacity decrease with aging in both sedentary and active individuals. $\dot{V}O_{2\,peak}$ (L/min) increases until about age 20. Declines are evident at about age 25 in both men and women and continue at about 1 percent per year (Fig. 18-14). If one expresses $\dot{V}O_{2\,peak}$ as a function of body weight (L/kg per min), the decline is evident

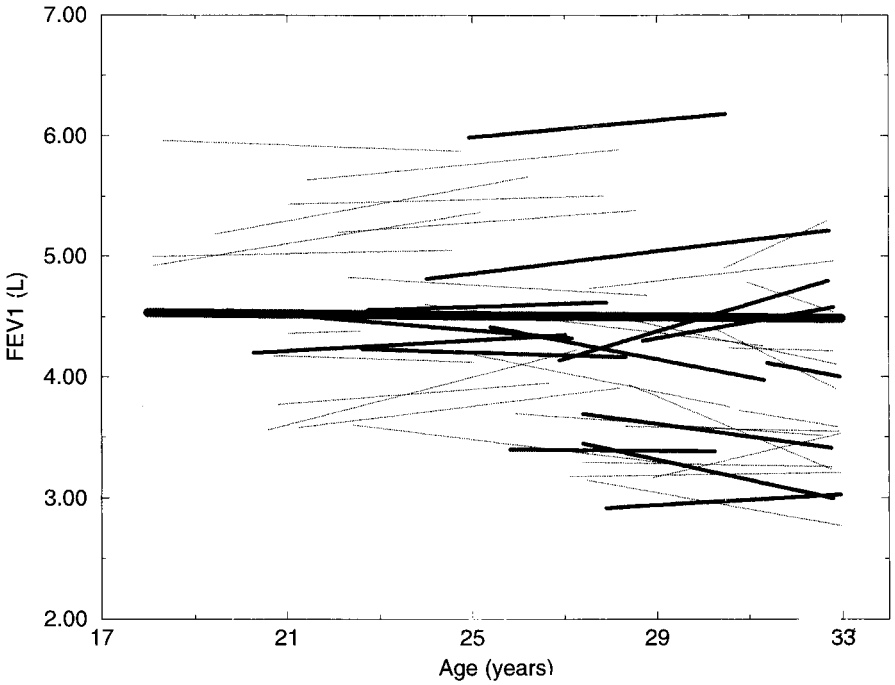

Figure 18-12 Predicted FEV_1 trajectories from 44 men based on linear regressions of longitudinal data. Nonsmokers (fine lines) and smokers (dashed lines). The heavy line is based on the entire group's data. While the group's data show no change with age, data for individuals show both increases and declines with age during this time period, when a plateau in lung function was theorized to occur. *(From Robbins DR, Enright PL, Sherrill DL: Lung function development in young adults: Is there a plateau phase? Eur Respir J 8:768–772, 1995, with permission.)*

much earlier, perhaps in the first decade of life. The magnitude of the decline in $\dot{V}O_{2\,peak}$ tends to be greater in longitudinal than in cross-sectional studies and occurs roughly twice as fast in sedentary than in physically active persons. Most but not all studies report linear declines in $\dot{V}O_{2\,peak}$ with age, even though a nonlinear decline would be expected based on the number and type of variables that affect exercise capacity.

The decline in exercise capacity with age occurs as a result of normal aging but is accelerated by life-style issues. Aging is associated with significant changes in body configuration. Specifically, there is an increase in total body weight, primarily representing an increase in fat mass, since fat-free mass (mostly muscle mass) decreases with aging. The changes are most pronounced in sedentary persons. Muscle mass decreases, with a preferential atrophy of type II muscle fibers, and is associated with a decrease in muscle capillarization and oxidative activity. Muscle strength decreases on the order of 2 percent/year from ages 20 to 70. Variables associated with loss of exercise capacity with aging are listed in Table 18-2.

While exercise capacity declines with aging, it is also clear that the ability to respond to exercise conditioning is well maintained even at very advanced ages. Elderly individuals respond to both endurance and resistive training

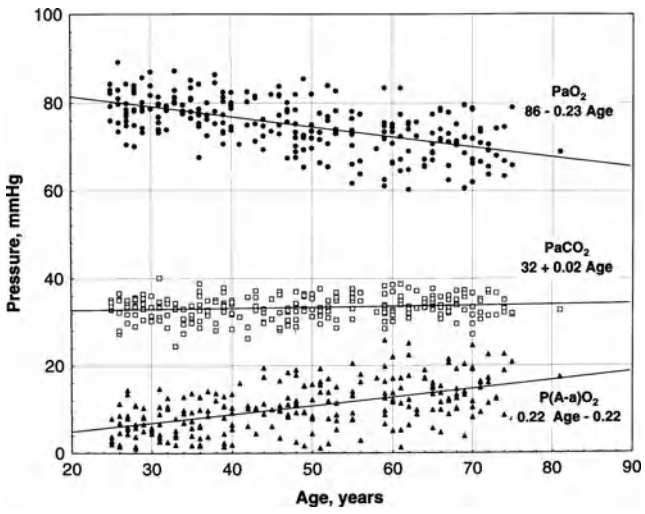

Figure 18-13 Change in Pa_{O_2}, Pa_{CO_2} and A–a gradient [$P(A–a)_{O_2}$] with age. Data were obtained from 200 healthy men and women living in Salt Lake City, UT (altitude = 1400 m). Sea level data would be similar, with a small upward shift in Pa_{O_2} and Pa_{CO_2}.

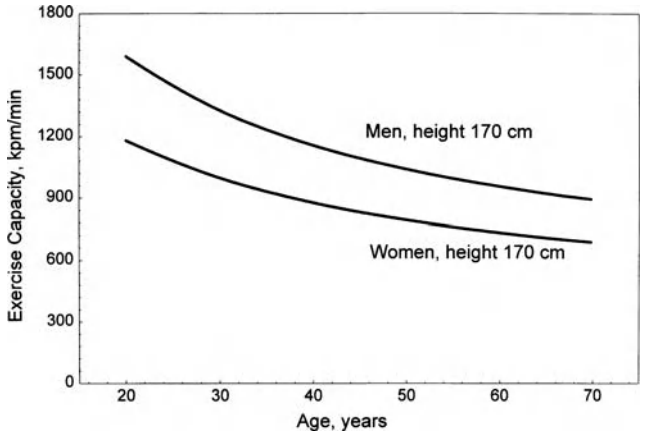

Figure 18-14 Decline in maximum exercise capacity with age. Exercise capacity declines nonlinearly with age. Maximum work capacity correlates strongly with peak oxygen uptake. *(From Jones NL, Summers E, Killian KG: Influence of age and stature on exercise capacity during incremental cycle ergometry in men and women. Am Rev Respir Dis 140:1373–1380, 1969, with permission.)*

Table 18-2

Variables Associated with a Decline in Exercise Capacity with Age

Variable	Comment
Decreased muscle mass	These changes especially affect $\dot{V}O_2$ calculated per kg of body weight
Increased fat mass	
Decreased cardiac output oxygen	As a result of the decreased cardiac output and maximal $C(a-\bar{v})O_2$, delivery and extraction are reduced; decreased cardiac output is a major contributor to the age-related decline in exercise capacity
Decreased maximal stroke volume	
Decreased maximal heart rate	
Decreased maximal $C(a-\bar{v})O_2$ difference	
Decreased maximum voluntary ventilation	
Increased ventilation at each workload	At each workload, older individuals breathe more and work harder for each breath than younger persons; however, the effect is small and contributes little to the decline in exercise capacity with aging
Increased oxygen cost of breathing	
Sedentary life-style	Life-style issues play a large role in the rate at which exercise capacity is lost with age; the good news is that, like other deconditioned groups, the elderly respond very well to exercise training
Decreased training intensity in active persons	
Decreased willingness to work to maximal level during tests	

with improvements similar in magnitude to those seen in the young. There are equivalent increases in $\dot{V}O_{2\,peak}$, muscle mass, capillarization of muscle tissue, muscle oxidative activity, and general muscle strength.

SLEEP

Sleep complaints from elderly patients present a difficult problem for the clinician, who must determine whether the complaints are related to the normal aging process, sleep hygiene issues, or the presence of pathology. Problems with sleep are widespread among elderly persons, with 25 to 40 percent complaining about sleep difficulties. There is no evidence to confirm the widely held belief that the need for sleep declines with age. However, sleep quality decreases, and the frequency of various primary sleep disorders increases. The most common age-related change in sleep pattern is a striking increase in the number of nocturnal awakenings, resulting in lower total sleep time and lower sleep efficiency (total sleep time/time in bed). Whether or not sleep latency changes with aging is equivocal. The amount of time spent in stage 1 non–rapid eye movement (NREM or light) sleep tends to increase with age. The decrease in total sleep time at night is associated with an increase in unwanted daytime naps. Disrupted sleep in the elderly is, in large part, explained by medical and psychological issues and the lack of structured physical and social activity during the day. Chronic illnesses, nocturia, medication and alcohol use, periodic leg movements, bereavement, and depression also play a role. Not surprisingly, the elderly are more likely to use sedatives or hypnotics; their use is more frequent in elderly women than in elderly men. While hypnotics and sedatives are occasionally necessary, their chronic use may contribute to sleep disruption and aggravate certain sleep disturbances, such as sleep apnea. Increased autonomic activity, increased sensitivity to external stimuli (which may increase arousals as a result of environmental factors),

decreased exposure to outdoor light, inactivity, and daytime napping also play a role in sleep disruptions in the elderly. Alterations in endogenous circadian rhythms for variables like temperature and cortisol or thyroid-stimulating hormone (TSH) levels may also contribute to sleep disruption in the elderly.

However, the neural system that regulates sleep is, like most other systems, subject to the "normal" aging process, and sleep disruption occurs in the elderly in the absence of any pathological process. The amount of stages 3 and 4 sleep (slow- or delta-wave sleep) declines with aging, although some argue that the aging decline is mostly a technical issue related to how delta-wave amplitude is defined. Changes in slow-wave sleep appear to be evident early, perhaps by 20 years of age. Arguments have been made both for and against declines in the amount of REM sleep with age. The persistent controversy about REM sleep and aging suggests that if REM sleep does change with aging, the magnitude of decline is so small that it does not overwhelm the confounding factors in studies.

Sleep disorders such as sleep apnea and restless legs syndrome, with periodic limb movements, appear to be more prevalent in older persons, and they are also more marked among nursing home residents than the independent elderly. For example, using an apnea index of five per hour as a threshold, one study found evidence of sleep apnea in 42 percent of elderly nursing home residents, in contrast to 24 percent of the independent elderly. Some argue that sleep disorders are associated with less morbidity and mortality in the elderly, but the data are inconsistent and remain inconclusive.

INTERPRETING PULMONARY FUNCTION TESTS IN THE ELDERLY

Several issues complicate the interpretation of lung function tests in the elderly. The elderly are not well represented in most reference value reports; the number of subjects usually falls off significantly after age 60. The number of subjects over age 80 is usually so small that mean values calculated from regression equations are essentially an extrapolation of the data for younger persons. This means that the average or "predicted" value may not be as representative for the elderly as it is for middle-aged persons. The fall in sample size with aging likely reflects the reduced total number of candidates for participation and the larger number of individuals who fail screening criteria. In reference value studies, individuals are screened so as to be free of symptoms and illnesses that alter lung function. These selection criteria may eliminate more older than younger candidates because of their increased prevalence of illness. Also, test quality is carefully standardized. Cognitive impairment may compromise test quality. As a result, older individuals may have more difficulty meeting test quality criteria, increasing their likelihood of exclusion and potentially increasing the variability of reference data for the elderly. In summary, the selection processes may make the older individuals who participate in reference studies less representative of the individuals who present for clinical lung function testing.

These same issues also affect the limits applied to determine whether a tested individual is within the "normal" range. Limits are often defined assuming that the distribution of data is gaussian. Although tests of this assumption are sparse, there is reason to suspect that it is more likely to fail in the elderly. Even when the "normal" range is defined using methods that avoid assumptions about data distribution, data from the elderly are often lumped with those of younger subjects. The result may be an erroneous "normal" range. These reference value issues all suggest that increased caution should be used in interpreting lung function tests in the elderly. This caution is especially important for those over age 80 and in any elderly person whose data lie near the limits of a "normal" range.

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19
CHAPTER

Pulmonary Defense Mechanisms against Infections

Herbert Y. Reynolds • Jack A. Elias

The atmosphere that we breathe is more than just "air." In reality, it is a complex mixture of ambient gases and environmental particulates to which virus- and bacteria-containing droplets can be added when respiratory secretions are coughed or sneezed out by others. Moreover, normal humans frequently aspirate secretions from the upper respiratory tract, particularly during sleep. The respiratory system must recognize and eliminate these unwanted elements in inspired air to keep pulmonary structures free of infection, yet not overreact inappropriately to every stimulus. This is accomplished by local mechanisms and innate immune defenses spaced along the entire respiratory tract to protect it. The fact that the normal lower respiratory tract is infection-free despite its constant exposure to foreign antigens and infectious agents is testimony to the efficiency of these defense mechanisms. The evolving appreciation of direct associations between aging and breakdowns of these host defenses and resultant pulmonary diseases emphasizes the need for all physicians to be familiar with these critical protective processes.

Components of the defense system are spaced along the entire respiratory tract, from the point of air intake at the nose and lips or mouth to the level of oxygen uptake at the alveolar surface. The conducting airways functionally extend from the nares down to the respiratory bronchioles and include the nasal turbinates, epiglottis, larynx, pharyngeal lymphoid tissue (Waldeyer's ring), and other anatomic barriers. Fourteen generations of dichotomous airway branching of the respiratory tree, as bronchi and bronchioles, in this segment cause the airstream flow to decelerate and deflect the particles it contains onto the mucosal surface, trapping them in airway mucus. In this location, inhaled particulates and infectious agents also interact with other locally produced proteins, such as secretory immunoglobulin A (IgA). Resulting ciliary clearance or coughing efficiently removes these particulates from the respiratory tree. Beyond the respiratory bronchioles, other noncellular host defenses remain important in protecting the alveolar units (Fig. 19-1). These defenses are in the lining material fluid of the alveoli, which contains

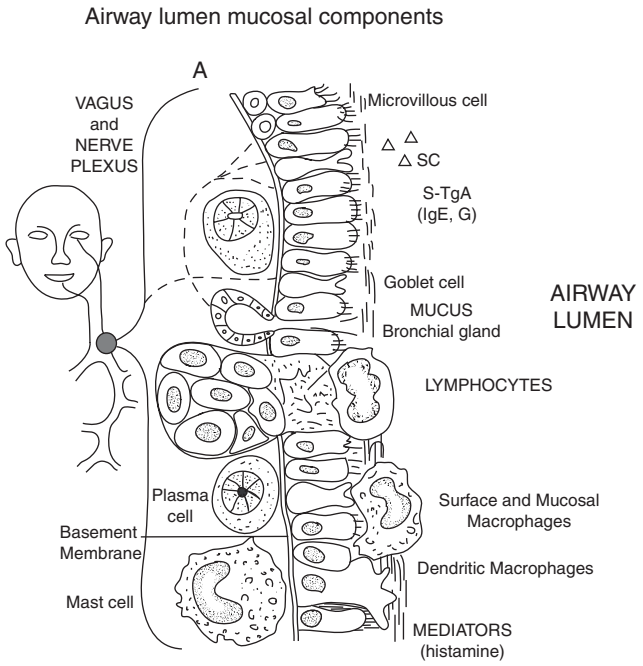

Figure 19-1 Airway lumen mucosal components. A portion of the conducting airway surface is enlarged (A) and depicts the mucosa and its submucosal structures. The pseudostratified ciliated epithelium has a covering layer of mucus (produced by goblet cells and bronchial glands) and fluid that contains various proteins, including immunoglobulins and secretory component. A few surface cells may be present, such as lymphocytes (from bronchial-associated lymphoid aggregates) and macrophages. Among the epithelial cells are absorptive microvillous brush cells and the dendritic cells, concentrated near lymphoid aggregates or in the respiratory bronchiole area, whose cellular processes interdigitate with the mucosal surface. In addition, the epithelial cells can produce proinflammatory cytokines that influence mucosal swelling and permeability. In the submucosa below the basement membrane, plasma cells and mast cells reside that secrete local immunoglobulins (such as IgA) and mediators (such as histamine). Interacting with all of these glandular and cellular networks are nerves, exerting their control through neuropeptides, and by adrenergic and cholinergic nerve fibers. A rich bronchial arterial vascular supply also exists. *(Modified from Reynolds HY: Pulmonary host defenses-state of the art. Chest 95(Suppl):223–230, 1989, with permission.)*

surfactant apoproteins and glycoproteins such as fibronectin, immunoglobulins such as IgG opsonins, and complement (properdin factor B), which are active against aerosolized, inhaled particles or microorganisms.

Alveolar macrophages are the principal phagocytic and scavenger cells on alveolar surfaces. Particulates and microbes that evade other host defense mechanisms and arrive on the alveolar surface are efficiently removed by these roaming cells. When further assistance is required, an inflammatory reaction can be initiated, which attracts polymorphonuclear neutrophils (PMNs) and other vasomediators and humoral immune elements from systemic sources.

At all levels of the respiratory tract, specific and nonspecific defense mechanisms exist to protect respiratory structures. The nonspecific mechanisms, as noted above, include the mechanical barriers, cough, mucociliary elevator, and macrophage phagocytosis, which behave similarly regardless of the inhaled particulate. They also include aspects of the innate immune response, such as the inflammation triggered by Toll-like receptors (TLR). In contrast, prior contact with a microbial agent or a sensitizing substance can induce antigen-specific cellular or humoral immune responses, activating adaptive or acquired immunity. The latter includes the production of secretory IgA antibody in the airway, which prevents mucosal adherence, and IgG opsonins that facilitate phagocytosis. Such responses help the lung deal more efficiently with these agents and substances on rechallenge in the future.

In summary, the integrated action of diverse pulmonary defense mechanisms along the respiratory tract acts to remove or neutralize microorganisms, particulates, and noxious gases that are inhaled or aspirated into respiratory structures. Many are mechanical barriers and reflex actions that are concentrated in the naso-oropharynx and along the conducting airways. There is also phagocytosis, which occurs in the alveoli and airways. These are surveillance mechanisms that function mechanically and can be activated by nonspecific (nonimmunologic) or immunogenic stimuli. In addition, several augmenting mechanisms exist that enhance the responsiveness of this defense system and make it flexible and adaptable. Crucial in this regard are the pathways of innate immunity and the ability of dendritic-type macrophages in the lung to mount antigen-specific immune responses (humoral and cellular)—adaptive immunity—and a local inflammatory reaction. This allows components in plasma and blood cells to bolster local defenses in the airways and alveoli. A more in-depth review of these innate defense mechanisms follows. Also in the "Suggested Reading" section, several reviews by the authors and others provide more details about this actively expanding topic.

SPECIALIZED REGIONAL DEFENSES

Nose and Oropharynx

Inhaled air passes through the nose or mouth back to the glottis and into the extrathoracic portion of the trachea before it enters the thorax. With nasal breathing, air is filtered and conditioned for humidity and body temperature as it flows over the nasal turbinates and mucosa of the posterior pharynx. With nasal obstruction or ventilatory requirements for exertion that exceed about 20 to 30 L/min, mouth breathing occurs. Inhaled air then may pass into the trachea without optimal filtering and climatic conditioning.

The nose provides formidable barriers to inhaled particulates. The nasal hairs help to exclude large particles, and materials greater than 10 μm in diameter that bypass the hairs impact upon the nasal mucosa. Sneezing (or blowing) then has the effect of coughing and provides high-velocity ejection from the mucosal surface. For substances that attach to the nasal mucosa, production of large quantities of watery secretions helps to wash off the surface (rhinorrhea).

Mucociliary clearance is also operant in the nasal cavity. "Downspouts" leading from the ears, lacrimal glands, and sinus cavities provide numerous points for the addition of fluid to the nasal secretions. However, these drainage systems also contain vulnerable points that are prone to blockage. The complex plumbing found in the nose works well if there is good gravitational flow and orifices stay open. If not, sinusitis, otitis media, parotid gland obstruction, and occluded tear ducts result. In some diseases, dryness of secretions (sicca syndrome) is problematic.

Several substances in nasal secretions help control bacteria or viruses. Prominent in this regard are lysozyme and immunoglobulins, especially secretory IgA (SIgA) which bathes mucosal surfaces. The nose and upper airways are contiguous immunologically with the lower airways and have been studied extensively. Nasal secretions, like those from other external or mucosal surfaces, are rich in IgA, which is synthesized locally by submucosal plasma cells. Free secretory component (SC) can also be detected in nasal wash fluid. Of the nasal immunoglobulins, SIgA is the major source of antibody, accounting for approximately 10 percent of the total protein content of nasal washings. IgG is present in smaller amounts. IgE probably is not secreted by normal, nonatopic people. Only in people with allergic rhinitis will IgE antibody be substantial. The usual specificity of IgA antibody is antiviral. After nasal immunization of normal subjects with various viral or mycoplasmal vaccines, many experimental studies have shown that appropriate neutralizing IgA antibody can be elicited. Although these antibodies are protective against homologous and live microbial challenge, the duration of protection is often brief, and the antibody titers diminish rapidly unless repeated exposure occurs.

In the oral cavity, the tongue sweeps against many surfaces during chewing and swallowing. This should make it difficult for bacteria to persist in these locations. However, bacteria adhere to buccal squamous cells, and many accumulate in crevices around teeth and gums and colonize dental plaque. Many kinds of bacteria are present: aerobes and anaerobes, spirochetes, gram-positive and gram-negative species, and some that specialize in making dental plaque and causing tooth decay. A common feature of host defense in the mouth and nose is the plentiful amount of SIgA in secretions that bathe each area. The parotid glands and probably the submandibular salivary glands secrete IgA as their principal humoral immune substance; this immunoglobulin accounts for 12 to 15 percent of the total protein in their secretions. In this fluid, albumin represents about 10 percent of the protein, but IgG is barely detectable (under 1 percent). In parotid fluid, IgA is found in monomeric and dimeric forms, and free secretory component can be detected as well. Thus, normal nasal and parotid (or salivary) secretions have about the same composition of immunoglobulins. As with the nasal immune system, it has been possible to manipulate SIgA in the mouth to produce antibodies against certain cariogenic strains of streptococci that will subsequently prevent bacterial adherence to teeth—the immune exclusion function of SIgA antibody. The importance of a vaccine approach for augmenting dental defenses has yet to be fully determined.

Host defenses in the nose and mouth serve as a reminder that the upper portion of the respiratory tract has features in common with the lower part, particularly at the mucosal surfaces. They also demonstrate that infections in the nose, sinuses, ears, teeth, and gums may have ramifications for the diagnosis or successful treatment of illness in the lower respiratory tract. As examples, aspiration of anaerobic bacteria in oral secretions or dental plaque contributes to lung abscess formation; chronic sinusitis can be present with cystic fibrosis, dyskinetic ciliary syndromes, and dysgammaglobulinemia; atopic diseases can manifest with rhinitis, sinusitis, and asthma; and control of asthma symptoms often requires vigorous treatment of concomitant sinus infection.

Conducting Airways

Bridging the upper airway (nose, oropharynx, and larynx) and the alveolar air-exchange area distal to the terminal bronchioles are the conducting airways (Fig. 19-1). Mucociliary clearance and coughing are the principal means of cleansing the mucosal surfaces of these airways. SIgA antibodies also prevent epithelial attachment of certain bacteria and viruses to the ciliated and nonciliated airway epithelial cells. The branching structure of the airways also causes airborne particulates to impact against the mucosa, enhancing the efficiency of mucociliary clearance. Bronchial-associated lymphoid aggregates are present, especially around branching points. This segment is susceptible to many diseases—e.g., epithelial cell infection with viruses or bacteria such as *Bordetella pertussis, Chlamydia pneumoniae,* or *Mycoplasma pneumoniae;* inflammation, edema, and bronchoconstriction in asthmatic syndromes; chronic infection in bronchiectasis; irritation from noxious gases; and lung cancer.

The conducting airways mucosa is coated to a depth of 5 to 100 μm with a mucous gel-aqueous sol complex viscous fluid, which has a low pH (6.6 to 6.9). This is secreted by bronchial glands, goblet cells, and Clara cells (nonciliated bronchiolar secretory cells found in the terminal bronchioles). Airway surface liquid is also derived from transepithelial acid-base flux across the bronchial epithelium. Special proteins, such as SIgA and SC, can be added locally along airways by immunoglobulin-secreting plasma cells and epithelial cells. Antimicrobial factors such as lysozyme, lactoferrin, cathelicidin, and defensins are present.

About half of the mucosal epithelial cells have beating cilia that propel secretions up the respiratory tree. Periodic coughing can assist the process. An intact mucosal lining and overlying mucous layer, containing mucin glycoproteins and proteoglycans, provide a protective barrier or blanket that prevents inhaled particulates from penetrating or sticking to the respiratory surface. This seems to be an important component of host defense. Bacteria and other infectious agents may transiently colonize the airways, but mucociliary clearance effectively removes them. Tight junctions between epithelial cells also limit the passage of macromolecules into

the submucosa, and microvillous brush cells may help clear fluid. A number of circumstances can alter these protective barriers, making this portion of the respiratory tract susceptible to disease. They include (1) malnutrition, which affects the integrity of mucosal epithelial cells and enhances bacterial adherence; (2) cigarette smoke and noxious fumes, which disrupt the anatomy of epithelial junctions and enhance the passage of airway substances into areas that are usually inaccessible; and (3) some bacteria, which elaborate proteolytic enzymes that may break down IgA, promoting selective colonization and persistence in matrix-enclosed biofilms that help avoid innate immunity and create chronic infections.

Lymphoid tissue is present along the entire respiratory tract, but the level of organization of the lymphoid tissue varies greatly. A ring of lymphoid structures are situated in the naso-oropharynx. Lymphoid nodules may occur in the mucosal surface of large and medium-sized bronchi and are particularly numerous at points of airway branching. On the airway side, these submucosal follicles are covered by a layer of flattened, nonciliated surface epithelium, which is often observed to be infiltrated with lymphocytes. These bronchial-associated lymphoid tissues (BALT) bear some resemblance to gut-associated lymphoid tissues (Peyer's patches), and are part of the body's overall mucosal-associated lymphoid network (known as MALT) that is important in mucosal immunity. Whereas BALT is easily demonstrated in some rodents and rabbits, subhuman primates and humans have decidedly less obvious amounts of this lymphoid tissue, and it may not be as relevant to airway defenses as initially thought, especially in adults.

Loosely organized collections of lymphocytes (lymphoid aggregates) are concentrated in the distal airways, especially at the bronchoalveolar junctions at the interface between the ciliated epithelial cells of the terminal bronchioles and the alveolar lining cells. These aggregates provide an opportunity for close interaction between lymphoid cells and inhaled antigens that have been deposited in the lower respiratory tract. Antigens and microbes may adhere to surface macrophages or dendritic cells imbedded in the mucosa where immune processing or elimination occurs. Bacteria such as *Pseudomonas aeruginosa* may become enmeshed in a biofilm containing their exopolysaccharides, which can interfere with macrophage or dendritic cell elimination of them and contribute to airway colonization and persistence. Also, in the vicinity of the respiratory bronchioles, lymphatic channels begin that might provide these lymphocytes with a route to draining lymph nodes (hilar nodes) where immunologic responses develop.

Respiratory Bronchioles

Anatomically, lung structure changes at the level of the respiratory bronchioles, which are inserted between the distal conducting airways and the acinar units (alveolar ducts and alveoli) of the air exchange surface. They functionally separate the upper and lower respiratory tracts. This segment can be a bottleneck or choke point for airflow, but it is the last surface to capture small airborne particulates and microbial or antigenic debris before entering the alveolar space; adaptive immune responses can begin here. Several structural changes occur: the single-layer cuboidal epithelial surface flattens and differentiates into alveolar type I cells that primarily cover the alveolar lining surface; mucus-secreting cells disappear, although goblet cells can be found in cigarette smokers; and another secretory cell type becomes prominent, the Clara cells. Pulmonary brush cells with a tuft of squat microvilli are found in this area, especially in rodent species, and may be involved with chemosensing or trapping inhaled particles and pollutants, or with regulating fluid and solute absorption. Dendritic macrophage-like cells, which may constitute 1 percent of the cells in the surface of this segment, are present to capture and process antigens. Lymphatic channels form to collect the lymphatic fluid emerging from the interalveolar interstitial spaces. The changeover from the bronchial arterial blood supplying the conducting airways to the pulmonary artery-capillary blood flow structure that surrounds the alveoli also occurs, which is necessary for aeration.

The Alveolar Spaces

Defenses in the airways (Fig. 19-2) eliminate most particles and microbes inspired into the lungs. As a result, the airways distal to the major bronchi are probably sterile in normal subjects. However, some particles of small size and special geometry can elude the airway mucosal mechanisms and reach the air-exchange surface of the alveoli. When this occurs, another set of host defense mechanisms must take over. Microbial clearance and the removal of other antigenic material from alveoli depend on cellular and humoral factors such as the lipoproteins, immunoglobulins, and complement factors in the alveolar lining fluid and phagocytic cells such as alveolar macrophages and PMNs.

Inhaled microbes are an appropriate example. If a bacterium of critical size (0.5 to 3 μm in diameter) is deposited in an alveolus, it is likely to make contact with the alveolar wall and roll along in about 0.2 μm of alveolar lining fluid, pH 6.9, which is a combination of a watery subphase with an overlying film of surfactant secreted by type II pneumocytes. In the process, a microbe encounters several substances that can inactivate it and assist in its eventual phagocytosis. These substances include a variety of soluble lipoprotein substances, IgG, complement factor (C3b), and nonimmune opsonins, such as high-molecular-weight fibronectin fragments. The lipoproteins in the form of surfactant are secreted by type II pneumocytes, and surfactant proteins A and D have opsonic effects through binding of surface carbohydrates, which promotes antibacterial activity against staphylococci and rough colony strains of some gram-negative rod bacteria. The immunoglobulins are principally of the IgG class. They account for 5 percent of the total protein in alveolar fluid, with subclasses IgG1 and IgG3 being the most important and lesser concentrations of monomeric and secretory forms of IgA being noted. These immunoglobulins can develop specific opsonic antibody activity for the bacterium. The complement components, especially properdin factor B, interact with the

bacterium and can trigger the alternative complement pathway, thereby lysing the microbe directly. One or all of these interactions can prepare the bacterium for ingestion by an alveolar macrophage. Although alveolar macrophages avidly phagocytose some inert particles, they ingest viable bacteria with considerably less enthusiasm. Coating or opsonizing the organisms will enhance phagocytosis appreciably as studied in an in vitro culture system. The nonimmune opsonins nonspecifically enhance this process. The immunoglobulins are capable of enhancing alveolar macrophage phagocytosis in an antigen-specific fashion, and the C3b complement fragment can function in concert with IgG to enhance or amplify this process.

Phagocytosis, the ingestion of particulate matter by cells, is divided into two phases: receptor attachment of the particle to the cell surface and internalization. Attachment of the particle to the surface of the phagocytic cell is essential before ingestion occurs. Although binding occurs randomly, it is greatly enhanced by opsonization of the particle by antibody (especially IgG) or a component of the complement system, C3b. Opsonin-dependent phagocytosis is mediated by receptors on the cell surface for the Fc component of the opsonizing immunoglobulin or complement. Specific receptors for the Fc portion of IgG (Fcγ) (IgG3 and IgG1 primarily) and for the third component of complement (C3b) are present on human monocytes and alveolar macrophages. Receptors for IgA are also found on alveolar macrophages.There is evidence that the number and function of these receptors can be modulated by lymphocyte-derived cytokines such as interferon-γ (IFN-γ). Ingestion of membrane-bound particles occurs via a process that is energy-dependent as the plasma membrane of the ingesting cell surrounds the bound particle, enclosing it in an endocytic vesicle. This is followed by the activation of a number of well-developed mechanisms that operate to kill internalized pathogens.

Following internalization of bacteria, the fate of alveolar macrophages is not certain. They are long-lived tissue cells that can survive at least for several months and presumably are capable of handling repeated bacterial and other microbial challenges (reusable phagocytes). Because they are mobile cells, they can migrate quickly to other alveoli through the pores of Kohn, or move to more proximal areas of the respiratory tract (to the region of the respiratory bronchioles) for elimination from the lungs by the mucociliary escalator. In addition, macrophages may gain entry into lung lymphatics at the same location and be carried to regional lymph nodes. This exit gives them access to systemic lymphoid tissue and is important in initiating cellular immune responses. Undoubtedly, macrophages are also instrumental in degrading antigenic material and presenting it in an appropriate manner to local T lymphocytes as part of innate and adaptive immunity in the lung.

Increasingly, attention is being given to the immune effector role of macrophages. The alveolar macrophage has a dual role in the respiratory tract—one as a phagocyte to dispose of debris, process foreign antigens, and kill ingested microorganisms and a second as an effector cell to initiate immune and inflammatory responses. Alveolar macrophages are usually successful in inactivating inhaled microorganisms. As a result, clinical disease and pneumonitis rarely develop after day-to-day exposures. However, if a sufficiently large bacterial inoculum reaches the lower respiratory tract, or if particularly virulent microorganisms are inhaled, the macrophage system can be overwhelmed. By the secretion of proinflammatory chemotactic factors such as the chemokine family cytokines, alveolar macrophages then recruit PMNs and other cells to the lung, and pneumonitis develops. Also, airway epithelial cells can generate proinflammatory cytokines to assist with PMN attraction.

Gram-negative rod bacteria provide an interesting example. Some complement components, particularly factor B, are present in small amounts in bronchoalveolar fluids. The bacterial endotoxin in the gram-negative rod bacteria can directly activate the alternative complement pathway—leading to the formation of C5a, which is a potent stimulus for PMN chemotaxis. Also, the inflammatory response may activate the kinin system; this results in generation of kallikrein, which has chemotactic activity, and bradykinin, which is capable of increasing vascular permeability. The latter allows for the seepage of fluid and other humoral and bioactive substances from the intravascular compartment into the alveoli. Another mechanism of inflammation emanates from the alveolar macrophage itself. Following phagocytosis of opsonized bacteria or other forms of activation, proinflammatory chemokines are synthesized and secreted by macrophages that will attract PMNs and other cells. Several substances with chemotactic activity have been found to be produced by human alveolar macrophages. These include interleukin-8 (IL-8), macrophage inflammatory protein-2 (MIP), monocyte chemoattractant protein-1 (MCP-1), tumor necrosis factor (TNF), and lipoxygenase pathway metabolites of arachidonic acid, namely leukotrienes. Leukotriene B_4 (LTB_4) is one of the most important of these.

Inflammation is the ultimate host response to contain common bacteria that reach the alveolar space. This response can be activated in several ways: (1) directly by microbes or substances such as lipopolysaccharide (endotoxin) that can activate the complement cascade, probably via the alternate complement pathway; (2) through the generation of phlogistic factors from the kallikrein and bradykinin pathways; and (3) from the effector cell function of macrophages. It is also known that other airway cells, such as epithelial cells, elsewhere in the respiratory tract, can produce chemokines like IL-8 and that this can stimulate inflammation in other sites (bronchitis).

Special interest has focused on the macrophage-secreted proinflammatory chemokines, a family of cytokines that can stimulate cellular motion (chemokinesis) and promote directed migration of different populations of responder cells (chemotaxis). These populations are primarily PMNs in the acute inflammatory responses. Lymphocytes, monocytes, and eosinophils are also recruited in the chronic phase of pneumonia, chronic inflammatory disorders such as hypersensitivity pneumonitis and sarcoidosis, and atopic and eosinophilic syndromes. Investigation has elucidated the cellular mechanisms whereby CXC chemokines activate and

initiate the migratory process of PMNs. An extensive review of the literature is summarized to say that this process involves a number of cell surface adhesion molecules, found on endothelial cells (adhesion molecule ICAM-1, L- and P-selectins and integrins) and granulocytes, that bind to one another. At sites of inflammation mediators such as IL-1, TNF, and IFN-γ induce or augment the expression of these adhesion molecules. As a result, intravascular PMNs slow down, roll along, deform, and then anchor on the endothelium. They then enter the interstitium via traversing capillary endothelial cells, which contract or pull apart to allow a gap through which PMNs pass, and plasma fluid can leak, and the cells emerge through the alveolar type I pneumocyte lining barrier into the alveoli. Microvillous brush cells may also absorb fluid or regulate ion-solute flux.

Eventually, all pneumonic responses run their course. If the host is successful in containing the infective microbes or particles that initially incited the host response, resolution usually occurs. Resolution can be passive, resulting from the removal of the initiating agent. Resolution can have an active phase as well. In the active phase, signals must go out to begin the healing and resorption phases that will restore the lung to normal respiratory function and architecture. Less is known about active resolution of inflammation. A platelet-derived substance, sphingosine 1-phosphate (S 1-p) may help restore the endothelial barrier by reducing PMN infiltration and vascular leak, as found with endotoxin injury. Moreover, cytokines such as transforming growth factor-β, IL-6, IL-10, and the IL-1 receptor antagonist released by macrophages and possibly other cells are believed to be important mediators of this process. As such, they provide a view of potential anti-inflammatory therapies of the future.

Lymphocytes in the Alveolar Space

When cells are retrieved from the alveolar surface by bronchoalveolar lavage (BAL), approximately 7 to 10 percent of the respiratory cells are lymphocytes. Some characteristics of these cells are given in Table 19-1. Two major populations of lymphoid cells are recognized, those that depend on the thymus gland for differentiation (T cells) and those that differentiate independently of the thymus in the bone marrow (B cells). The T and B lymphocytes are indistinguishable by usual morphologic criteria but can be differentiated by membrane surface markers. They are also functionally distinct, with T cells playing an important role in cell-mediated immunity and cell-mediated cytotoxicity while the B cells serve as precursors for cells that synthesize immunoglobulins and, hence, antibody molecules that are the basis of the humoral immune response.

As shown in Table 19-1, approximately 70 percent of the lymphocytes in lavage fluid are T cells and approximately 5 percent are B cells. The ratio of T to B cells in lavage fluid is roughly that of peripheral blood, although in blood more circulating B cells are usually identified (approximately 15 percent). Approximately 1 to 5 percent of lung lymphocytes seem to be able to release or secrete class-specific immunoglobulin. Enumeration of these cells has found that IgG- and IgA-secreting cells are much more numerous than IgM-producing cells. Natural killer lymphocytes make up about 5 to 8 percent of lung lymphocytes. As they do not express T-cell receptors or surface immunoglobulins for specific antigens, they can respond in an antigen-independent way to help contain viral infections and are thus important in innate immunity. With phenotypic markers, T cells can be divided into two principal groups. The CD8 cells usually have a suppressor-cytotoxic phenotype. The CD4 cells usually have a helper-inducer phenotype and thus are also called T-helper (TH) cells. In the BAL fluid from normal subjects there is a greater percentage of CD4 cells, with approximately 45 percent of the total T cells expressing this surface marker. In contrast, approximately 25 percent of lung T cells express the CD8 phenotype. In lung lavage fluid, the ratio of these subtypes of T cells is approximately 1.5 to 2:1, which is approximately the same ratio found among peripheral blood lymphocytes.

As noted, most of the T lymphocytes in the alveoli are CD4-positive. When activated, these TH cells are capable of producing regulatory cytokines that in turn modulate the function of other immune and structural cells. Recent studies suggest that there are at least two subsets of CD4 TH

Table 19-1

T-Lymphocyte Subgroups in Lung Lavage Fluid from Normal Subjects

Fluid	Cell Count $\times 10^6$	Lymphocytes (%)	T Cells (%)	CD4 (T Helper) (%)	CD8 (T Suppressor) (%)
Lung lavage*	$10 \pm 4^{\dagger}$	7 ± 1	73 ± 5	46 (35–55)	25 (18–32)
Blood				48 (40–60)	28 (22–40)

* *Cells from 300-ml lavages of six normal nonsmokers.*

† *Mean ± SEM; range observed in parentheses.*

Source: Hunninghake GW, Crystal RG: Pulmonary sarcoidosis: A disorder mediated by excess helper T-lymphocyte activity at sites of disease activity. N Engl J Med *305:429–434, 1981.*

cells, T-helper–1 (TH1) and T-helper–2 (TH2) cells. These cell populations have different functions based on the different array of cytokines that they produce. The TH1 cells secrete IFN-γ and IL-2, which activate macrophages and play a major role in cell-mediated immunity. The TH2 cells produce IL-4, IL-5, and IL-6, which stimulate B lymphocytes to produce immunoglobulins and, by their production of IL-10 and IL-13, suppress monocyte/macrophage activity and cell-mediated immune responses. Thus, TH2 cells play a particularly important role in generating tissue eosinophilia and stimulating IgE production, processes that are extremely important in atopy, allergic asthma, and other inflammatory pulmonary disorders. IL-2, formerly called T-cell growth factor (TCGF), is among the most important T-cell–regulating cytokines. It is produced by activated T cells and acts in an autocrine or paracrine fashion to stimulate TH1 cells and TH2-cell precursors. IL-2 can also activate killer T cells. A few killer lymphocytes can be identified among alveolar T cells, but these cells seem to be dormant in normal subjects until stimulated. Lastly, IL-2 can stimulate B lymphocytes to differentiate into plasma cells that synthesize various classes of immunoglobulins. This is a mechanism by which local production of immunoglobulin in the lung can occur. In all cases, the effects of IL-2 are mediated by the multimeric IL-2 receptor, a component of which is the Tac-surface ligand. The expression of the IL-2 receptor is highly regulatable, and the expression of the Tac antigen can be used as a marker of T-cell activation.

Most T cells have T-cell receptors with alpha and beta subunits (α/β T-cell receptors). In the normal lung, a lesser number of T cells have gamma and delta T-cell receptors. The function of these cells is poorly understood. They may, however, play an important role in mucosal immunity, since they are increased in atopic allergic subsets.

Alveolar macrophages and lymphocytes have the capacity to produce many cellular mediators (cytokines) that in turn affect each other as well as other inflammatory, structural, and immune effector cells. This dynamic and complex interaction is illustrated in Fig. 19-2, which reviews dendritic cell, alveolar macrophage, and lymphocyte interactions in the airways and alveolar milieu. Monocyte precursors from the blood differentiate into mature macrophages under the influence of vitamin D metabolites and undoubtedly other stimuli and become long-lived, aerobically metabolizing alveolar phagocytes. Their principal activity is to cleanse the alveolar surface and ingest debris that accumulates or microbes aerosolized into the lungs. In the process, the macrophages may become "activated" and are then capable of secreting an enormous array of enzymes and cytokines. These moieties can affect the function of resident cells of the lung such as lymphocytes or epithelial cells. In addition, the release of proinflammatory chemokines attracts PMNs, lymphocytes, monocytes, and other cells into the alveoli. Of particular note are LTB_4, IL-8, TNF-α, MIP-1α, MCP-1, and IL-1. When secreted by activated macrophages (especially in active lung forms of sarcoidosis) IL-1 may attract T lymphocytes to the lungs.

In the other direction, activated TH cells can produce several monokines that affect macrophage function. Such a substance is migration inhibition factor, which immobilizes macrophages engaged in phagocytosis. Of special interest is IFN-γ, which activates macrophages, increasing their expression of membrane receptors, which in turn enhances macrophage phagocytic uptake. IFN-γ also has other functions that promote cellular immunity. Almost mutually exclusive sets of chemokines can be induced by TH1 immune responses (IL-12 and IFN-γ) and by TH2 cells (IL-4 and IL-13) toward infectious challenges. The scheme shown in Fig. 19-3 may help to explain certain derangements found in a number of lung diseases that have excessive or deficient secretion of cytokines and feature changes in the relative proportions of macrophages and lymphocytes. Examples of

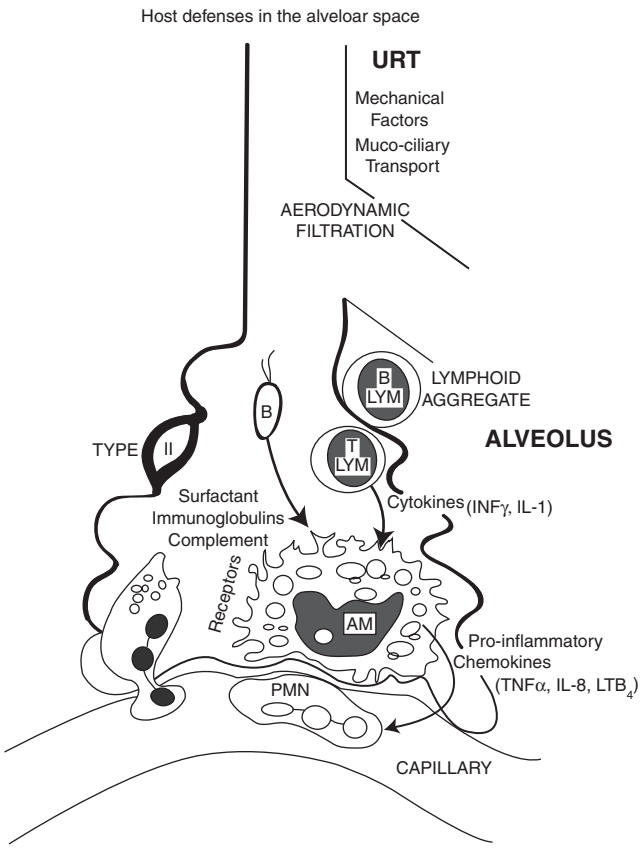

Figure 19-2 Host defenses in the alveolar space. Bacteria (B) that escape clearance mechanisms in the upper respiratory tract (URT) can reach the alveolus (represented by an enlargement of one). Most of the alveolar surface is lined by type I epithelial cells with pulmonary microvillous brush cells interspersed, and type II cells positioned in the corners that secrete surfactant. A variable amount of interstitial space separates the epithelium from the capillary endothelium where sequestered PMNs and platelets reside. A bacterium deposited in an alveolus may encounter at least three different but coordinated sets of innate immunity immunologic materials and cells that can destroy it: opsonins, both IgG and surfactant proteins A and D, or complement factors that facilitate phagocytosis or create a lysis of the microbe; activated macrophages stimulated by cytokines produced by nearby lymphocytes; and other inflammatory phagocytic cells, usually PMNs attracted into the alveolar space by proinflammatory chemokines produced locally by macrophages and epithelial cells. *(Modified from Reynolds HY: Respiratory infections may reflect deficiencies in host defense mechanisms. Dis Mon 31:1–98, 1985, with permission.)*

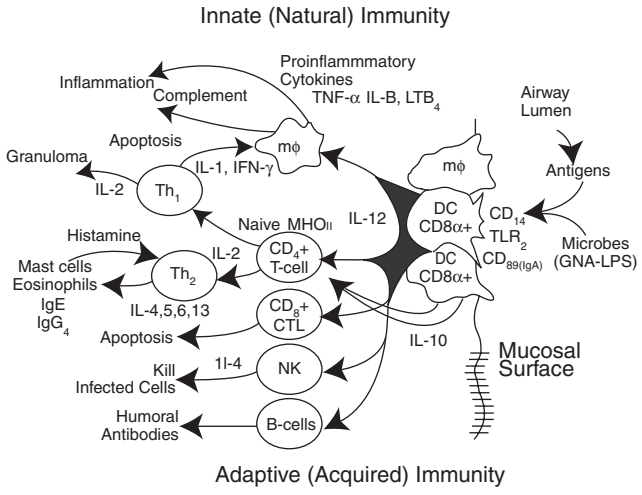

Figure 19-3 Major immunity pathways. Within the body, mucosal surfaces are positioned at initial intake and contact points to ''meet" external substances that enter with inhaled air, ingested food and liquids, or reproductive secretions. Mucosae in the nose, airways, and gastrointestinal and genital tracts must discriminate between pathogens and harmless microbes or possible toxins and essential nutrients, and then respond quickly to exclude, tolerate, or initiate immune responses.

Respiratory host defenses balance two important immune mechanisms created for dealing with airway microbes or other entering antigens: (1) an innate or quick reaction response producing inflammation as an end point (bronchitis or pneumonitis), and (2) a more deliberate approach through stimulation of lymphocytic pathways that creates a versatile and adaptive response involving specific T-cell activity and/or production of immunoglobulins (antibodies). Foreign substances or microbes or their exoproducts (lipopolysaccharide from gram-negative rod bacteria) that enter the airway lumen and adhere to the mucosa will be picked up by macrophages (M) or dendritic cells (DCs). Toll receptor recognition and attachment are important, and dealt with in a variety of ways. Phagocytic uptake and intracellular killing of bacteria might suffice, or recruitment of PMNs may be needed through secretion of proinflammatory cytokines by macrophages, creating pneumonitis for example. Later, active resolution of inflammation requires inhibition of PMN influx (suppress chemotaxis) and cellular cleanup (apoptosis). Alternatively, DCs (or macrophages) can process antigens, present these to major histocompatibility complex (MHC) compatible but naïve CD4+ cells, facilitated with the stimulatory cytokine IL-12; IL-2 produced by CD4+ T cells can direct TH1 lymphocytes to develop and proliferate. In turn, TH1 cells can produce IL-1 and IFN-γ that can stimulate macrophages for the inflammatory pathway, or induce clonal expansion of CD4+ lymphocytes that contribute to building granulomata for containment of certain microbes or particles.

Returning to the DC-antigen–presenting cell process involving the CD4 cells, another subset of DCs (or macrophages) can produce IL-10, an inhibitory cytokine that promotes the TH1 response preferentially in normal subjects and suppresses the TH2 cellular pathway. However, pending the allergic status of the host (atopy) and/or the particular antigen present, TH2 lymphocytes can be stimulated and in turn produce IL-4, 5, 6, and 13 cytokines that culminate in allergy (asthma and allergic rhinitis) with stimulation of mast cells and then eosinophils and production of reaginic antibodies (IgE, IgG 4). The TH2 immune response is also effective against certain parasites. *(From Reynolds HY: Modulating airway defenses against microbes. Curr Opin Pulm Med 8:154–165, 2002.)*

such cellular imbalances include sarcoidosis, hypersensitivity pneumonitis, and acquired immunodeficiency syndrome (AIDS).

DEFECTS IN HOST DEFENSES THAT CAN BE ASSOCIATED WITH RESPIRATORY INFECTIONS

Infection can occur everywhere along the respiratory tract—upper airways (nose, sinuses, ears, and oropharynx), conducting airways (trachea and bronchi down to the respiratory bronchioles), or the alveolar area. Although exposure to a virulent microorganism or to a large inoculum, if inhaled or aspirated into the lungs, may cause illness in a normal person, recurrent or chronic infections may point to deficiency or malfunction of a particular component of the host defense system (Table 19-2). A number of situations associated with frequent respiratory infections serve as examples. Endotracheal tubes give direct access to the lung but, in so doing, bypass the larynx and the other upper-airway protective structures. Patients with depressed consciousness or with postoperative chest or abdominal pain become infected because of their inability to cough and clear airway secretions. In addition, patients with viral infections have an increased incidence of bacterial superinfection. The cause of this association appears to be multifactorial, including the ability of these infectious agents to damage ciliated epithelial cells and diminish the clearance of airway secretions; also viruses and other microbes can infect alveolar macrophages, diminishing their bactericidal activity. In combination, these host defense defects are believed to contribute to the frequent association of influenza infection and staphylococcal superinfection.

Ultrastructural defects in the cilia located on the apical edge of the airway epithelial lining cells cause mucociliary dysfunction. As a result, the removal of mucus and respiratory secretions is depressed, and recurrent infections and bronchiectasis occur. The constellation of multiple upper and lower respiratory infections and bronchiectasis should raise the possibility of a ciliary dyskinesis syndrome. Infertility, especially in males, may be associated, and the evaluation of this problem may bring the respiratory symptoms to the physician's attention. With age, ciliary beat frequency decreases and might be a factor in greater susceptibility to lung infections in the elderly.

A variety of γ-globulin abnormalities are associated with recurrent infection. In patients with hypogammaglobulinemia, the lack of opsonic antibody can promote infections with encapsulated bacteria. Several common bacteria that colonize the airways of patients with chronic bronchitis and chronic obstructive pulmonary disease (*Streptococcus pneumoniae, Haemophilus influenzae,* and *Neisseria*) can also produce a specific IgA protease that cleaves the IgA heavy chain in its hinge region adjacent to the Fc portion. By this mechanism, these bacteria could inactivate a substantial portion

Table 19-2

Pulmonary Host Defenses

Component	Possible Impairment Defect	Related Impact or Infection
Conducting airways		
Mechanical barriers (larynx, etc.)	Bypassing barriers with an endotracheal tube or tracheostomy	Aspiration, direct aerosol of microbes into airway
Mucociliary clearance (cough)	Intrinsic structural defect in cilia; ciliotoxic infections	Stagnant secretions, coughing, bronchiectasis, sinusitis, pneumonitis
Bronchoconstriction and mucosal edema	Hyperactive airways; asthma	Poor removal of secretions; excessive secretions
Local immunoglobulin coating—secretory IgA	IgA deficiency or functional deficiency from breakdown by bacterial IgA1 proteases	Sinopulmonary infections; abnormal colonization with bacteria
Iron-containing proteins (transferrin, lactoferrin)	Iron deficiency	May not inhibit certain bacteria (*Pseudomonas, Legionella*)
Alveolar space		
Other immunoglobulin classes (opsonic IgG)	Acquired hypogammaglobulinemia; selective IgG2 and IgG4 deficiency	Sinopulmonary infections; pneumonia with encapsulated bacteria
Alternative complement pathway activation	C3 and C5 deficiency	Recurrent infection possible
Surfactant (protein)	Decreased synthesis; acute lung injury	Loss of opsonization activity; alveolar collapse (atelectasis)
Alveolar macrophages	Subtle effects from immunosuppression; cannot kill intracellular microbes	Propensity for intracellular microbes and *Legionella* infections; poor containment of *Mycobacteria* spp
Polymorphonuclear granulocytes	Absent because of immunosuppression; intrinsic defects of motility; lack of chemokine stimulus	Poor inflammatory response, associated with gram-negative bacillary infection and fungi (*Aspergillus*)
Augmenting mechanisms		
Initiation of immune responses (humoral antibody and cellular immunity)	Immunosuppression	Inadequate SIgA or IgG antibody available (more susceptible to viral, mycoplasmal, and bacterial infections)
Generation of an inflammatory response (influx of PMN granulocytes, eosinophils, lymphocytes, and fluid components)	Generally reflects status and supply of PMN granulocytes; impaired adherence to endothelium	Inadequate inflammatory response, recurrent infection

Source: Modified from Reynolds HY: Respiratory infections may reflect deficiencies in host defense mechanisms. Dis Mon *31:1–98, 1985.*

of the secretory IgA coating the conducting airways and gain better access to the ciliated epithelial cells for attachment. While this mechanism is somewhat theoretical, associations between deficiencies in IgG and recurrent infection are well documented. Particularly important are the associations between deficiencies of IgG subclasses IgG2 and IgG4, alone and in combination with IgA deficiencies and chronic inflammation and bronchiectasis. Presumably, an absence of these subclasses denies phagocytic cells potential opsonic antibody, thereby diminishing membrane receptor attachment of opsonized particles or bacteria and subsequent phagocyte ingestion. Clinically, establishing the diagnosis of an IgG deficiency is quite important because, in contrast to many other immunodeficiencies, replacement preparations of IgG are often available for these patients.

Cytotoxic antineoplastic chemotherapy and other forms of immunosuppression also compromise host defenses in a major way. A major side effect of these therapies is granulocytopenia, which prevents the mobilization of PMNs and creates a poor inflammatory reaction.

HOST DEFENSES IN THE APPROACH TO PATIENTS WITH PULMONARY DISEASE

As noted above, normal hosts can develop respiratory infections or inflammation as a result of exposure to particularly virulent agents or a large inoculum of aerosolized particulates. In others, respiratory infections are associated with obvious clinical features that compromise pulmonary defenses (Table 19-2). Occasionally, however, the physician is confronted with a relatively young person who has an unexpected number of respiratory problems that seem inappropriate. The illness can manifest as recurrent infection or poorly controlled allergic rhinitis, asthma, frequent sinusitis, recurrent nasal polyps, and/or bouts of otitis media. Because the severity of these respiratory problems may not seem great, the physician may not initially suspect that something unusual is present. The propensity for infection may not have been obvious in childhood but became apparent as the patient reached adolescence or adulthood. Although genetic defects usually are manifested in infancy, minor forms of host deficiency, creating antibody deficiency diseases, may not be recognized until later in life. Cystic fibrosis (adult onset), selective absence of IgG subclass immunoglobulins, structural ciliary defects, and IgA deficiency are the principal diseases that should be considered in this differential diagnosis. Recurrent sinopulmonary infections are an important clue to all these syndromes.

The physician should be prepared to examine such a patient thoroughly. A detailed history will immediately provide important information about affected siblings, infertility, or a striking change in respiratory health that makes an acquired abnormality likely. Preliminary screening tests are a complete blood count and quantitative serum immunoglobulins, and perhaps pulmonary function tests, even if the chest radiograph is normal in appearance; also indicated may be microbial cultures of respiratory secretions and analysis of the electrolytes contained in a sample of sweat or nasal potential difference measurements. Mucoid strains of *Pseudomonas aeruginosa* and elevated sweat chloride values can be noted in cystic fibrosis. Other useful secondary-level screening tests are quantitation of subclasses of IgG; secretory IgA as sampled in parotid fluid or nasal wash samples; subtyping of blood lymphocytes; measurement of antibody responses to protein and/or polysaccharide antigens; search for genetic mutations of the cystic fibrosis transmembrane conductance regulator (CFTR); assessment of ciliary clearance with an aerosolized, isotopic tracer; nasal mucosal biopsy for electron-microscopic ultrastructural analysis of cilia; sperm motility in males of appropriate age; and documentation of bronchiectasis by high-resolution computed tomographic scans of the chest. A thorough evaluation by an otolaryngologist is also often helpful because of the recurrent sinusitis, otitis media, and nasal polyps that might be present.

Alternatively, certain forms of pneumonia point to possible deficiencies in lung cells such as alveolar macrophages, lymphocytes, or PMNs. As opsonization of certain encapsulated bacteria is necessary for optimal phagocytosis by macrophages and PMNs, the lack of appropriate IgG antibodies against pneumococci, *Haemophilus* species, *Klebsiella pneumoniae,* and staphylococci may contribute to infections with these common bacteria. However, other causes of pneumonia may reflect abnormal lymphocyte function and cell-mediated immunity. Infection with *Legionella* bacteria is an example. After an infection with *L. pneumophila,* the host develops specific IgM and IgG serum antibodies. These antibodies, in the presence of complement, do not create a lytic state that is sufficient to kill the bacteria. However, they do behave as opsonins to ensure that the *Legionella* organisms can attach and be ingested by various phagocytic cells, including PMNs, blood monocytes, and alveolar macrophages. Once inside the phagocytes, *Legionella* multiply and eventually can kill and disrupt the host cells. When alveolar macrophages are activated with IFN-γ these stimulated phagocytes will inhibit the growth of the bacteria. This may be the result of the ability of IFN-γ to down-regulate the transferrin receptors on these cells, thereby limiting the accumulation of intracellular iron which is an essential metabolite for *Legionella.* Support for this concept comes from experiments with an experimental *Legionella* pulmonary infection rat model, in which administration of intratracheal IFN-γ reduced intrapulmonary replication of the bacteria, improving host defenses.

Another example of defects at the level of the lymphocyte is AIDS, in which the human host is infected with human immunodeficiency virus (HIV) that destroys CD4 TH lymphocytes. These patients experience recurrent respiratory infections with diverse organisms, including viruses (cytomegalovirus or herpes simplex), *Pneumocystis carinii, Mycobacterium tuberculosis, M. avium-intracellulare,* fungi such as *Cryptococcus* species, and *Toxoplasma gondii* and *Legionella.* These infectious agents have a common feature of residing in macrophages or similar cells as facultative intracellular organisms. One reason why a patient with AIDS has trouble with this group of infections relates to the relative imbalance of lymphocytes found in the alveoli, as sampled by BAL of the lung. Normal values for T lymphocytes have been given in Table 19-1. From subjects with AIDS, the recoverable alveolar lymphocytes reflect a decrease in the CD4 TH cells from HIV infection, offset by an increase in the suppressor-cytotoxic species of T lymphocytes. Although alveolar macrophages normally exist in an environment where they can be activated sufficiently to kill or control microbes of this sort, the CD4 deficiency in lungs of patients with AIDS compromises this activation process. This causes an impressive defect in cell-mediated immunity and the ability of macrophages to contain or kill organisms such as *Pneumocystis* or mycobacterial species.

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20

Lymphocyte- and Macrophage-Mediated Inflammation in the Lung

Frederic F. Little • Kevin C. Wilson • Jeffrey S. Berman • David M. Center

The lung receives a flow of foreign infectious and noninfectious antigens on the tide of airflow. Like the gut, genitourinary tract, and skin, the lung is one of the interfaces of the sterile body with the environment. The lung immune defense system and inflammatory mechanisms are poised to deal with this role. This chapter considers the inflammatory and immune roles of two key cells of hematopoietic origin, the lung lymphocyte and the lung macrophage.

While these two cell types interact extensively and might even be considered codependent in many situations, they represent two very different arms of the inflammatory response. The macrophage, as a phagocytic cell, is of ancient phylogenetic lineage. It is the sentinel of the innate immune system. As such, it is not antigen specific, but it is triggered by many inflammatory stimuli through both specific and pattern recognition receptors. Lymphocytes are present only in vertebrates and represent a significant refinement in the inflammatory response by the ability to recognize specific antigens and discriminate between self and non-self.

Macrophages or macrophage-associated dendritic cells (DCs) are required for optimal presentation of antigens to lymphocytes, and for optimal lymphocyte activation and cytokine production. Conversely, macrophage microbicidal function and release of arachidonate and oxygen metabolites is influenced by cytokines produced by activated T lymphocytes and phagocytosis is markedly enhanced by antibodies produced by B lymphocytes. The cooperation between these two cell types represents a cornerstone of lung defense against noninfectious antigen challenge or microbial infection. Another chapter deals with acute lung inflammation mediated by neutrophilic leukocytes. This chapter presents a brief overview of the macrophage and lymphocytes in the human lung, their function and interactions, and a synthesis of their role in lung inflammation and disease.

We will assume a basic knowledge of immunology. However, an explanation of the terminology used in this chapter is appropriate. Many surface receptors expressed by immunologic cells have had multiple names based on different functions. In the past 30 years these terms have been grouped together in a series of standardized "clusters of differentiation" (CD) for the purpose of standard nomenclature. A list of the CD markers referred to in this chapter, other names used for them, and their putative functions are included in Table 20-1.

Table 20-1

Cluster of Differentiation (CD) Antigens and Surface Molecules

Name/CD Designation	Function
CD1	Accessory molecule for antigen presentation on APCs
Sheep RBC receptor/CD2	Accessory molecule for T lymphocyte activation, adhesion receptor (ligand LFA-3)
T3/CD3	Signaling subunit of TCR
αβ TCR	T cell receptor for antigen
γδ TCR	Alternate form of the T-cell receptor for antigen
CD4	T-cell coreceptor (ligand MHC class II); marker for helper/inducer cells
CD8	T-cell coreceptor (ligand MHC class I); marker for cytotoxic cells
CD11a,b,c	α chains of the β2 integrin; CD11a (LFA-1); CD11b (Mac-1/CR3); CD11c (CR4)
CD14	Macrophage receptor for lipopolysaccharide
CD18	β_2 integrin chain
CD25	p55 IL-2 receptor; T-cell activation antigen (Tac)
HLA-DR	Class II MHC; expressed on APC's; activation antigen for T cells
CD28	Accessory molecule for T-lymphocyte activation (ligands B7-1, B7-2, and CTLA-4)
CD29	Common beta chain of the β_1 integrins
VLA-1-6/CD49a-f	Adhesion molecules; α-chains of the β_1 integrins (ligands ECM proteins)
VLA-4/α4β1 integrin	Adhesion molecule (ligand VCAM expressed on endothelium, fibronectin)
α4β7 integrin	Adhesion molecule (ligand VCAM, fibronectin)
HML-1/αEβ7 integrin	Adhesion molecule (ligand epithelial cell carbohydrate antigen)
ICAM-1/CD54	Cell adhesion molecule for cell-cell interaction (ligand LFA-1/CD11a/CD18)
B7-1, B7-2/CD80	Accessory molecule for T-cell activation; ligand CD28
CD95/Fas	Receptor for Fas ligand, induction of apoptosis
VCAM/CD106	Adhesion molecule expressed on activated endothelium (ligand α4 integrins)
CCR3	Chemokine receptor (CKR) for CCL11/eotaxin
CCR4	CKR for CCL17/TARC (thymus and activation-regulated chemokine)
CCR5	CKR for CCL4
CCR7	CKR for CCL21/SLC (secondary lymphoid-tissue chemokine)/TCA-4 (T-cell activation-4)

Notes: Abbreviations: CD = cluster of differentiation; RBC = red blood cell; TCR = T-cell receptor; VLA = very late activation antigen; LFA = lymphocyte function–associated antigen; APC = antigen presenting cells; MHC = major histocompatibility complex antigen; CR = complement receptor; ECM = extracellular matrix; ICAM = intercellular adhesion molecule; VCAM = vascular cell adhesion molecule; CCR = chemokine CC type receptor; CCL = chemokine CC–type ligand.

LYMPHOCYTES IN THE LUNG

In the normal lung lymphocytes are distributed in one of four compartments (Fig. 20-1). The compartments include lymphocytes at the epithelial surface (LES), including those in the bronchoalveolar space; lymphocytes associated with the epithelium in lymphoid aggregates (also known as bronchus-associated lymphoid tissue; BALT); interstitial and intraepithelial lymphocytes (IL); and an intravascular pool. The presence of BALT in normal human lung is controversial; it is clear that BALT is present in the setting of infection and possibly with chronic airway inflammation. Each compartment has a distinct phenotypic and functional repertoire. It is not yet clear whether there is a sequential influx of lymphocytes from the blood/intravascular pool to interstitium or BALT and finally to the epithelial surface, or whether lymphocytes are destined to reside in one or another of these pools from the time of maturation and/or activation. The absence of afferent lymphatics to the lung dictates that the intravascular pool is the original source of lymphocytes destined to one of the pulmonary compartments. The exact nature of influx and turnover of normal lung lymphocyte populations is not clear; however, the identification of organ and lung specific homing chemotactic cytokines (chemokines) with selective distribution of their cognate receptors raises the possibility that the origins of the populations of each compartment are distinct, and for inter-compartmental trafficking to occur there must be site-specific signals that alter the chemotactic receptor repertoire in situ.

Lymphocytes at the Epithelial Surface

Lymphocytes at the epithelial surface (LES) and intraepithelial lymphocytes are best studied as lymphocytes from the bronchoalveolar space that are easily recovered from the lung using bronchoalveolar lavage (BAL). In normal non-smoking individuals, lymphocytes make up only about 5 to 15 percent of the 10^5 cells found per milliliter of BAL fluid; lymphocyte numbers may increase dramatically during an inflammatory response. LES differ markedly from blood lymphocytes suggesting either a selection bias or organ specific maturation process that occurs between blood and lung (Table 20-2). Approximately 70 percent of LES are T cells; the CD4/CD8 ratio of T cells is approximately the same as in the blood, although with a larger scatter among individuals. Over 70 percent of BAL T cells are of the previously activated memory type as determined by expression of a low molecular weight form of the leukocyte common antigen CD45 (CD45RO); and many have been chronically activated as shown by expression of the $\alpha 1 \beta 1$ integrin. The balance of BAL T-cells are naïve, based on their expression of one of the chemokine receptors CCR7, which identifies cells that have not come into contact with their cognate antigen. LES are more likely than blood T cells to express the activation antigen HLA-DR, and CD8+ (cytotoxic/suppressor) LES are more likely to express

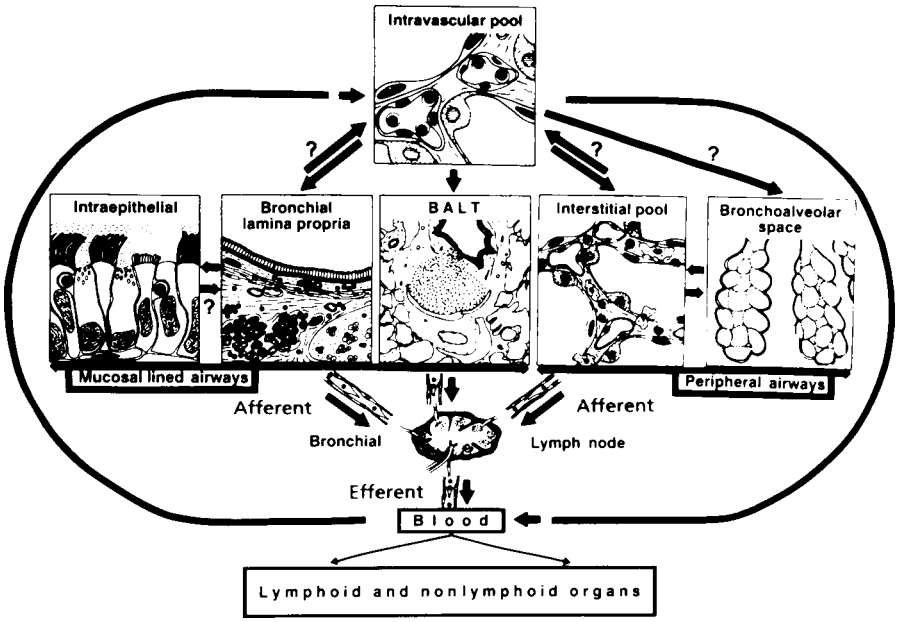

Figure 20-1 Lymphocytes are found in the lung in distinct sites. These include lymphocytes at the epithelial surface (including those at the bronchoalveolar surface); the interstitial and intraepithelial lymphocytes, bronchus-associated lymphoid tissue (BALT), which are centers of airway antibody production; and an intravascular pool. Lymphocytes travel from lymph nodes to blood and into lung via interaction with lung endothelial cells. Hypothesized trafficking from one pulmonary compartment to another is indicated by arrows. Some lymphocytes from these various compartments may be able to exit the lung back to lymph nodes, and others become effete and die. For further explanation see text. *(Reproduced from Pabst R: The immune system of the respiratory tract, in Busse W, Holgate ST (eds), Asthma and Rhinitis. Cambridge, MA, Blackwell Scientific, 1994, pp 415–425, with permission.)*

Table 20-2

Characteristics of Lung Lymphocytes*

Location	Number	Cell Type	Comments
Epithelial surface	10^4/ml BAL; Approx 10^8 total	CD4/CD8 ratio = blood 70% T cells >90% memory cells 40% express $\alpha_E\beta 7$ integrin (70% of CD8+) Memory CTL NK phenotype present, decreased function	Specialized for interaction with epithelial cells. First line of defense?
BALT	? If present in normal human lung	B cells in center T cells scattered in center and surrounding follicle	Local antigen sampling and antibody production
Interstitium	10^7/gm lung tissue Approx 6×10^9 total	CD4/CD8 ratio < blood >90% memory T cells Bulk of NK activity	With intravascular, equal to total blood lymphocyte pool
Intravascular	?Characteristics in human	?	Possible mobilizeable cells poised for lung entry

Note: Abbreviations: ELF = epithelial lining fluid; BAL = bronchoalveolar lavage; CD = cluster of differentiation; CTL = cytotoxic T lymphocyte; BALT = bronchus-associated lymphoid tissue.

**For a review, see Ainslie MP, McNulty CA, Huynh T, et al. Characterisation of adhesion receptors mediating lymphocyte adhesion to bronchial endothelium provides evidence for a distinct lung homing pathway. Thorax 57:1054–1059, 2002.*

markers associated with cytotoxic cell function. An unusual population of memory cytotoxic cells that lack the accessory molecule CD28 has also been described in normal LES. In rodent lung the majority of T cells express the gamma-delta T-cell receptor, and account for up to 20 percent of resident (whole lung) pulmonary T cells in normal mice; a percentage that is markedly upregulated with infection. By contrast, the vast majority of human T cells at the epithelial surface are alpha-beta+. The function of the small population of gamma-delta LES T cells in humans remains unknown, but functional similarities to homologous mouse cells suggest that their primary role is in regulating the primary immune response. There are a variable number of natural killer (NK) (including NK-T) cells in this compartment as might be expected in an area of microbial and antigen assault. However, the bulk of NK activity in the lung is found in the interstitial population. B cells are also present in the LES population derived by BAL. They have been documented to produce antibodies of all types, with their primary role being to provide mucosal immunity through the secretion of IgA. It is unknown whether there are selected B cell populations among LES.

The source and fate of these T and B cells are unknown. It seems reasonable to hypothesize that epithelial surface T cells (and other lung T cells) emerge from the circulation, perhaps proliferate locally and differentiate further while in the lung, and then die or recirculate. Appearance of labeled blood T cells in LES has been documented in animals, as has the reverse. The predominant memory phenotype of epithelial surface and interstitial T cells strongly suggests that such differentiation occurs before entry into the lung.

Many LES adhere to and interact with airway epithelial cells through the expression of a unique adhesion molecule (HML-1/αeβ7 integrin). This integrin is expressed on 40 percent of LES (60 percent of CD8+ cells are HML-1+ while fewer CD4+ cells express it) and on intestinal lymphocytes, but only rarely on blood or lung interstitial lymphocytes. It is likely that local influences, such as epithelial derived cytokines like transforming growth factor beta-1 (TGFβ1), result in the expression of this molecule on LES. Epithelial cells are directly stimulated by bacteria to release specific chemokines and cytokines [e.g., IL-8, MIP2α (CXCL2), MIP3α (CCL20), IL-7, IL-15] depending on the organism and pathogenicity. These ligands can bind surface chemokine and cytokine receptors on adjacent LES, suggesting that these cells are not necessarily effete or dying cells that are present in the airway only to be cleared by the mucociliary escalator and expectorated. Rather, they include a specialized lymphocyte population involved in the surveillance of the airway and interaction with epithelial cells. The possibility that LES reenter the interstitium and lymphoid tissue has been confirmed experimentally in the rat. In addition to their interaction with airway epithelial cells, LES directly interact with mucosal DCs, whose phenotype

directs further T-cell phenotype evolution (see Lymphocyte Activation in the Lung, below).

LES can be stimulated to proliferate, produce cytokines and antibodies, and perform cytolytic functions. However, they are in general hyporeactive in proliferative or antibody responses to antigen or mitogens when compared with blood T cells or even when memory T cells in lung interstitium. The reason for this is not known, but may relate to immunosuppressive influences in the airways, including alveolar macrophages (AM), local production of TGFβ1, the immunosuppressive activity of pulmonary surfactant lipids or proteins, and the possible presence of other immunomodulatory cytokines such as IL-10 and IL-16.

Bronchus Associated Lymphoid Tissue

BALT is the term applied to localized subepithelial collections of lymphocytes in the airways, and is a secondary lymphoid tissue analogous to other types of mucosa-associated lymphoid tissue. BALT is present in normal rodent airway and increases in amount with age. Current evidence suggests these structures are uncommon or absent in adult humans but are present in childhood and may appear and proliferate in response to infection or chronic inflammation. These data suggest that antigen, infection-induced cytokine production, or some other stimulus is required for the development of these lymphoid aggregates in humans, perhaps through the development of "high" venular endothelium (HEV, characteristic of lymphoid tissues) which facilitates lymphocyte exit from the post capillary venule.

BALT is similar to gut associated lymphoid tissue (GALT; e.g., Peyer's patches) in appearance, association with epithelium and a blood vessel; presence of specialized cuboidal or (HEV) characteristic of lymphoid tissues; and a specialized thinned overlying epithelium facilitating antigen entry from the bronchial lumen and exit of lymphocytes and lymphocyte products. Immunohistochemistry has revealed a preponderance of B cells staining with IgM, IgG, and IgA, with a scattering (approximately 20 percent) of T cells, especially CD4+ helper cells within and surrounding the aggregate. BALT lacks organized germinal centers found in other secondary lymphoid tissue. The resemblance of BALT to GALT, as well as the similarity of lymphocyte recirculation patterns from lung and gut associated lymphoid tissue, has suggested to some authors that these structures represent a common mucosal immune system. In this paradigm, recirculating blood lymphocytes exit into these structures, which provide an efficient exposure to antigens sampled from the environment. Activated memory cells are then a source of local antibody production, and they may disperse through the circulation to other mucosal sites to provide dissemination of immunologic memory.

Despite observations that have been made in rodents, several issues continue to limit what we can infer about BALT function in humans: its near absence in normal human airways and limited presence in experimental animals, primarily observed in pathogen-free colonies.

Interstitial Lymphocytes

Lymphocytes are rarely seen in histologic sections of normal human lung, and there are no established techniques to study these cells as an exclusive, pure population. However, several investigators have prepared lymphocytes from human lungs extensively washed to remove airway surface cells using minced tissue and enzymatic digestion. The resulting population of pulmonary infiltrating lymphocytes in normal humans appears to be distinct from lymphocytes recovered from normal BAL. Specifically, approximately 20×10^6 mononuclear cells were found per gram of wet lung tissue; of these 70 percent were lymphocytes, of which 90 percent were CD2+ T lymphocytes. There was enrichment for memory T cells similar to that seen in LES, but the CD4/CD8 ratio among interstitial lymphocyte (IL) T cells was lower than that seen in blood or LES. Memory T lymphocytes from the interstitial compartment can be stimulated to produce cytokines, and proliferate in response to IL-2 despite a decreased proliferative response to mitogens. Most if not all NK activity in the lung has been localized to the interstitial compartment. The exact origin, fate, and function of interstitial lymphocytes are not known.

Intravascular Lymphocytes

The presence of this lymphocyte pool has been convincingly shown in animals, especially the pig. Experimental data include lung perfusion studies showing the continued slow elution of lymphocytes from lung following elimination of red blood cells. The presence of an intravascular lymphocyte pool in humans has not been directly confirmed. However, labeled lymphocytes injected into humans are "held up" in the lung whether injected intravenously or intra-arterially. These data confirm the more recently detected presence of homing receptors on the surface of lymphocytes that match cognate organ specific chemokine expression. Therefore, this phenomenon likely represents margination of lymphocytes in capillaries due to adhesion molecule interactions. Complete phenotypic characterization of this pool in the human is unknown, as is the size and role of this pool in populating interstitial or epithelial lymphocytes.

Lymphocyte Recruitment to the Lung

Lymphocytes are recruited to extravascular sites through a complex process involving adhesion to endothelial cells (EC), release from adhesion, transendothelial migration, interaction with cellular matrix, and response to locally produced chemoattractants. This sequential process is characterized by an initial capture step that is mediated by selectins and integrins, followed by arrest/activation mediated by chemokine and cytokine receptors and other integrins. The role of chemokines has emerged as central to the regulation of tissue-specific lymphocyte homing and retention. These are low-molecular-weight proteins that share a cysteine repeat motif (e.g., C-C or C-X-C), near the N-terminus. As a class, these proteins have cationic charge, and therefore bind

heparin. Chemokine function is mediated through cognate seven transmembrane-spanning receptors. There is significant promiscuity between chemokine receptors and their ligands, such that any specific chemokine may have several ligands and vice versa. Because of their physicochemical properties, the chemokines may bind to heparinlike regions of endothelial cell membrane receptors, preventing dilution of locally produced chemoattractant signal by blood flow and facilitating concentration gradients, a phenomenon known as haptotaxis. The chemokines have been shown to enhance both adhesion to endothelial cells and endothelial transmigration of multiple leukocyte types including T-cell subsets and monocytes. Recently the chemokines have also been found to act as accessory growth factors for T lymphocytes. While CXCL15 (lungkine) appears to be selectively expressed in mouse lung, there does not appear to be a unique human lung specific lymphocyte directed chemokine profile. However, certain chemokines (see below) are preferentially expressed in Th2- and Th1-type immune responses in the lung.

The interaction of adhesion molecules expressed on blood T cells with complementary adhesion molecules on EC is the critical first step to T-cell emigration from the blood. This step is closely regulated at the level of expression of adhesion molecules by T cells at different stages of development, and by transiently increased adhesion molecule function following T-cell activation. Similarly, expression of adhesion molecules by EC may be increased markedly by organ site and location, or proinflammatory cytokines, especially tumor necrosis factor (TNF)-α, IL-1, and interferon-γ (IFN). Treatment of EC with these cytokines markedly alters the adhesiveness of EC for leukocytes, including certain subsets of T cells. The result of such EC activation by local production of cytokines or other factors is that the exit of T cells from the blood is not random, but rather is restricted to sites such as lymphoid tissues, mucosal sites, or tissue sites of inflammation.

The specific events involved in T-cell transendothelial migration have been dissected at the cellular level, while their characterization in human lung is incomplete. T lymphocytes first appear to "roll" along the endothelium, an interaction that requires loose adhesion via T-cell $\alpha 4\beta 1$ integrin/endothelial VCAM-1 and P-selectin/PSGL-1. A signal is required to produce formal "capture" via other integrin molecules, particularly lymphocyte LFA-1 ($\alpha L\beta 2$ integrin) interaction with ICAM-1 or other ligands on endothelium. This latter signal enhances the avidity of integrins for ligand, strengthening adhesion. Other interactions, including decay of integrin affinity, homotypic interaction of T cell and endothelial PECAM (CD31) at endothelial cell junctions, and release of matrix-degrading enzymes, permit release of firm adhesion and T-cell migration into matrix. Preliminary evidence in TH2 cell migration suggests that this step is mediated by T-cell CCR3/endothelial CCL11 and CCR4/CCL17, respectively.

T cells are constantly recirculating from blood to tissue and back, with an average half-life in the blood of only about 18 h. In addition, the sites of migration in vivo appear to be quite different for naïve/virgin cells, as opposed to previously activated memory cells. Due to high level of CCR7 expression, naïve cells preferentially traffic to lymphoid tissue where they are likely to encounter antigen, while memory cells traffic to non-lymphoid tissues such as skin or lung.

The normal lung vasculature may have unique properties that facilitate the retention of circulating lymphocytes. Whether injected intravenously or intra-arterially, labeled lymphocytes are held up in the lung disproportionately in comparison with other organs. Thus, this is not just a "first-pass" clearance effect from capillary passage. Several investigators have found that antibodies to adhesion molecules, particularly lymphocyte function–associated antigen (LFA)-1, decrease lymphocyte retention in the lung. However, capillary size may determine trapping of activated cells since cytoskeletal changes occurring coincident with activation reduce cellular deformability; this has been shown to be a significant force in the lung trapping of activated neutrophils and monocytes. Lymphocytes also become larger, and lose deformability with activation, but the role of this process in lung retention of lymphocytes is not yet defined.

Lymphocyte chemoattractants represent another step in the regulation of the exit of adherent or trapped T cells from the capillary circulation. As noted earlier, varied T-cell chemoattractants have been described that are relevant to the lung, many of which also alter the growth and activation of T cells. A partial listing of known chemoattractants may be found in Table 20-3. In lung diseases multiple T-cell chemoattractants have been found in BAL or tissue specimens, including the chemotactic growth factors IL-2, IL-16, insulin-like growth factor I, the C-X-C chemokine IL-8 (CXCL8), and the C-C chemokines macrophage chemotactic protein (MCP)-1 (CCL2), RANTES (CCL5), and macrophage inflammatory protein (MIP)-1α (CCL3). IL-2 is presumed to be of lymphocyte origin while IGF-1 and IL-16 have multiple potential cellular sources, including T cells, eosinophils, and epithelial cells. The chemokines likewise have multiple cellular origins, including macrophages, endothelial cells, and epithelial cells. It also has been noted that CXCL9, 10, and 11 appear to be important in Th1 responses in the lung, but their expression may relate more to induction by gamma interferon rather than a lung-related phenomenon.

Lymphocyte Function in the Lung

Lymphocytes in the lung serve four major functions: (1) antibody production; (2) cytotoxic activity, including lysis of virally infected cells, cells which have bound antibody, and tumor cells; (3) cytokine production; and (4) immune tolerance. These functions are summarized in Table 20-4.

Antibody production in the lung by B lymphocytes serves to bind antigen and facilitate inactivation of bioactive material and phagocytosis by macrophages. Mucosal IgA is of particular interest in its active transepithelial transport to the bronchial lumen. Antibody production by lung B cells has been extensively studied in mouse lung. Following challenge,

Table 20-3

Lymphocyte Chemoattractants*

Interleukins	**Activation Stimuli**
IL-1	Antibody to T-cell receptor (T cells)
IL-2	Anti-surface immunoglobulin (B cells)
IL-6	Phorbol esters
IL-10	
IL-15	
IL-16	
Chemokine Chemoattractants	**Growth Factors**
CXCL8/IL-8	Insulin
CCL5/RANTES	IGF-1
CCL3/MIP1-α, CCL4/MIP-1β	TGFβ1
CCL2/MCP-1, CCL8/MCP-2, CCL7/MCP-3	
CXCL10/IP-10	
CL11/eotaxin	
Matrix Proteins	**Miscellaneous Chemoattractants**
Laminin	Lysophosphatidylcholine
Fibronectin	fMLP, mycobacterial lipoarabinomannan
Amyloid protein AA	Casein/denatured protein

Note: Abbreviations: IL = interleukin; RANTES = regulated activated normal T cells expressed, secreted; MIP = macrophage inflammatory protein; MCP = monocyte chemotactic peptide; IGF = insulin-like growth factor; TGF = transforming growth factor.

**Not a complete listing. For reviews see Barnes PJ, Cosio MG: Characterization of T lymphocytes in chronic obstructive pulmonary disease.* PLoS Medicine *1:e20, 2004, Kallinich T, Schmidt S, Hamelmann E, et al: Chemokine-receptor expression on T cells in lung compartments of challenged asthmatic patients. Clin Exp Allergy 35:26–33, 2005; Pober JS: Warner-Lambut/Parke-Davis award lecture. Cytokine-mediated activation of vascular endothelium. Physiology and Pathology. Am J Pathol 133:426–433, 1988.*

antigen is removed to regional lymph nodes by motile phagocytic cells (macrophages and DCs) where optimal activation of T and B cells occurs. Activated cells relocate into the circulation and migrate into the lung at areas of inflammation and local antibody production results. Re-challenge with antigen results in a more rapid local response derived from resident memory cells. While the duration of pulmonary memory lymphocytes is unknown, systemic B lymphocytes can persist for over 100 days in the absence of antigen, as is the case with memory CD4+ and CD8+ T cells.

The lung contains multiple types of cytotoxic cells, including NK cells (not antigen restricted), antigen-restricted cytotoxic cells, and cells exhibiting antibody-dependent cytotoxicity. One unusual aspect of lung cytotoxic cells is the preeminence of CD3+ cytotoxic T cells with NK activity (non-antigen receptor-mediated killing of tumor cell targets). This is in contradistinction to the blood, where the majority of cells expressing NK activity are CD3–. NK activity is found in the interstitial compartment of lung T cells; NK cells are phenotypically present among LES, but have been found to be functionally impotent.

Cytokine production by lung helper T cells (TH) has emerged as a major focus of investigation in lung inflammation. In contrast to antibody production by B cells, T cells produce cytokines. A broad range of cytokines have been documented to be produced by lung T cells in inflammatory disease (Table 20-4). In general, the complexion of the inflammatory response correlates with the cytokines produced by T cells, suggesting that T cells orchestrate many inflammatory responses.

Activated T-helper (TH) cells produce a distinct spectrum of cytokines. The repertoire of a single T cell to produce cytokines appears to be limited and stereotyped, depending on the circumstances of activation. According to data accumulated in mice, virgin T cells produce mainly IL-2 in response to activation. After proliferation and switch to memory cell phenotype, T cells produce one of two major clusters of cytokines, either TH1 (interferon gamma, IL-2) or TH2 (IL-4, IL-5, IL-10, IL-13), and share mutually exclusive transcriptional programs, regulated by the transcription factors T-bet and GATA-3, respectively. In humans this distinction between phenotypes has not been as predictable as in the mouse, and IL-10 may be produced by either TH1 or TH2 cells. These two phenotypes roughly conform to polarized expressions of cell-mediated immune responses: granuloma formation with activation of mononuclear phagocytes and production of opsonizing IgG2 antibody (TH1); or optimal antibody response including IgE formation, often with associated eosinophilia (TH2).

Certain immune responses are dominated by either a TH1 or TH2 response, while others are mixed. For example, in human asthma T cells producing TH2, cytokines predominate, but IFN-γ–producing cells are found in the airways suggesting a mixed response. In contrast, granulomas at sites of tuberculin reactions in skin show evidence for production of IFN-γ and IL-2 but not IL-4. In leprosy or leishmaniasis, an ineffective host reaction is associated with a TH2 response, and an effective granulomatous response is associated with a TH1 response; treatment of ineffective responses to leishmania with IFN-γ has been reported to increase the efficacy of chemotherapy. In sarcoidosis, airway and granuloma cells, particularly activated CD4+ (HLA-DR+) T cells, have been found to produce both IL-2 and IFN-γ, suggesting the predominance of a TH1 response. There is considerable cross regulation of TH1 and TH2 subsets even after commitment to production of these cytokines, leading to the general concept that the character of an immune response as well as its termination may depend on the sequential predominance of TH1 or TH2 responses. Indeed, the functional distinction

Table 20-4

Function of Lung Lymphocyte Subpopulations*

Cell Type	Function	Secreted Products
TH1 cell	Antiviral and antifungal defense, granuloma formation, CMI, Graft rejection	IL-2, IFN-γ, IL-3, IL-6, IL-12, IL-16, GM-CSF, TGFβ1
TH2 cell	Allergic inflammation, antiparasite defense	IL-2, IL-4, IL-5, IL-9, IL-10, IL-3, IL-13, IL-16, GM-CSF, TGFβ1
TCTL	Antigen-restricted lysis of viral- or mycobacteria-infected macrophages or epithelia; lysis of fungi, tumor cells	TH1 cytokines, perforin, IL-4
T reg cell (various phenotypes)	Peripheral tolerance Maintenance of immature DC	IL-10, TGF-β1
NK cell	Non-antigen–restricted lysis of tumor cells	IL-2
B cell	Antibody production	IgM, IgG subtypes, IgE, IgA, IL-10

Note: Abbreviations used: TH1 = T-helper type 1; TH2 = T-helper type 2; CTL = cytotoxic T lymphocyte; NK = natural killer cell; IL- = interleukin-; CMI = cell-mediated immunity; GM-CSF = granulocyte-macrophage colony stimulating factor; TGFb1 = transforming growth factor beta 1; DC = dendritic cell.

Source: Ainslie MP, McNulty CA, Huynh T, et al: Characterisation of adhesion receptors mediating lymphocyte adhesion to bronchial endothelium provides evidence for a distinct lung homing pathway. Thorax *57:1054–1059, 2002, Kim CH, Rott L, Kunkel E, et al.: Rules of chemokine receptor association with T cell polarization in vivo. J Clin Invest 108:1331–1339, 2001.*

**Not a complete listing. Listed are cytokines or other products produced under in vitro conditions or documented in lung disease.*

between TH1 and TH2 cells is less distinct in humans than it is in the mouse.

The role of T cells (and T-regulatory cells in particular) in mediating mucosal tolerance is directly related to their interaction with mucosal DCs. The mechanism of action of Treg cells is incompletely understood and the phenotypic classification of these cells is evolving. The majority of studies examining the regulatory potential of T cells in inflammatory lung disease have been in ex vivo manipulation, depletion, and adoptive transfer experiments in the mouse. The evidence for intraparenchymal (i.e., mucosal or interstitial) Treg cells is not direct, but their requirement for maintenance of peripheral tolerance in the lung and the systemic inducibility of tolerance to inhaled antigen provide the basis for their speculated presence in the epithelium. In addition, intratracheal treatment of mice with the immunomodulatory cytokine IL-16 elicits an expansion of lung CD4+CD25+ T cells.

Lymphocyte Activation in the Lung

T lymphocytes are designed to require specific (antigenic) signals for activation, restricting their involvement in inflammation to situations in which antigen overwhelms the mucociliary escalator and macrophage and neutrophil defenses. Lymphocytes are activated following engagement of an antigen receptor of remarkably fine specificity. This receptor is unique to a given lymphocyte clone, and is generated by recombination of gene segments in the antibody (for B cells) or T-cell receptor genes. B-cell receptors consist of single membrane-spanning antibody molecules of the same specificity as the B cell, whereas T-cell receptors consist of a heterodimeric receptor (dimers of alpha and beta or gamma and delta chains). The T-cell receptor is highly antigen specific and has structural homology to the immunoglobulin molecule. Lymphocytes are activated by cross-linking of membrane antibody by antigen (B cells) or engagement of the antigen receptor by antigen bound to major histocompatibility complex (MHC) molecules on the surface of so-called antigen presenting cells (APC) also known as accessory cells. APC provide many "accessories" for T-cell activation, including: (1) a source of MHC molecules to which antigen can bind; (2) internalization and "processing" of antigen, including protease digestion into antigenic fragments; (3) multiple cell adhesion molecules that bind to complementary adhesion molecules on T cells and serve to strengthen T cell–accessory cell interactions and transduce activation signals required for optimal lymphocyte activation; and (4) production of cytokines that amplify activation, including IL-1.

APC in the lung includes pulmonary macrophages of all varieties; however, DCs and Langerhans' cells are most efficient in this function (see below). These cells express important "accessory" cell adhesion molecules important to accessory cell function, including ICAM-1, LFA-2, LFA-3, and the CD28 ligands B7-1, B7-2, and CTLA-4. Other cells that

Table 20-5

Function of Lung Macrophage Populations

Cell Type	Phagocyosis	Microbial Killing	AG Presentation	Cytokine Production
Alveolar macrophage	+ + ++	+ + ++	+/− (suppression)	+ + ++
Interstitial macrophage	++	++	++	++
Dendritic cell	+	+	+ + ++	++
Langerhans cell	++	+	+ + ++	++
Blood monocyte	++	++	+ + +	+ + +

Source: Erle DJ, Brown T, Christian D, et al: Lung epithelial lining fluid T cell subsets defined by distinct patterns of beta 7 and beta 1 integrin expression. Am J Respir Cell Mol Biol 10:237–244, 1994; Ford WL, Simmonds SJ: The tempo of lymphocyte recirculation from blood to lymph in the rat. Cell Tissue Kinet 5:175–189, 1972; Johnston RB Jr: Current concepts: Immunology. Monocytes and macrophages. N Engl J Med 318:747–752, 1988.

may be induced to express Class II MHC molecules may also act as weak accessory cells. Such cells include local B cells, epithelial cells, smooth muscle cells, and fibroblasts. Uncommitted naïve T cells require intense accessory cell interaction in order to be activated by antigen, while previously activated (memory) T cells require less accessory cell input and might be influenced by interaction with such weak accessory cells. Due to naïve CCR7+ T cells' inability to cross post-capillary venules, most lung T cells are memory cells, which suggests that the relatively weak lung accessory cells may indeed play a role in T-cell activation in the lung inflammatory response (Table 20-5).

As discussed earlier, the lung has proved to contain major immunosuppressive elements that may serve to prevent inappropriate or excessive T-cell activation in an area of the body characterized by constant antigen exposure. These influences include surfactant lipids, which have been shown to inhibit T-cell activation, proliferation, and cytokine production; basal production (perhaps by epithelial cells) of the potent immunosuppressive cytokine TGF-β1; and an inhibitory effect of alveolar macrophages. These inhibitory effects may be moderated, reduced, or increased in various disease states. The role of dendritic cell phenotype and degree of maturation in directing activation versus tolerance in T cells is emerging as a key determining step in pulmonary T-cell differentiation. DCs can be broadly described as activating or tolerogenic; this distinction appears to be related to the maturity of the dendritic cell and functionally to the presence of costimulatory molecules on the cell surface (e.g., CD80, CD86, CD40). Typically, DCs process inhaled antigen and migrate to draining lymph nodes to present antigen to naïve T cells. (The role of BALT in this process is unknown, see earlier discussion.) Thereafter, the nature and concentration of processed antigen determines the fate of cognate T-cells: TH1, TH2, or Treg. Presumably, TH cells that have encountered Ag in secondary lymphoid tissue acquire cell surface markers that direct homing and permit post-capillary emigration to lung interstitium and epithelium, either as regulatory or effector cells. There is evidence that the communication between DC and T cells is not exclusively toward T cells; differentiated T cells communicate with local DC via cytokines and cell surface markers to alter DC phenotype. This phenomenon has been described in a mouse diabetes model, and proposed in murine allergic airway inflammation. In light of the emerging central role of DCs in immunologic lung disease and growing knowledge of their plasticity, future directions will likely approach modulating DC phenotype and function as targets for therapy.

Lymphocyte Clearance and Death in the Lung

The means by which lymphocytes exit the lung or are cleared during homeostasis or following an inflammatory response is largely unknown. It is not known how long memory T or B cells reside in the lung in any of the compartments, nor is the extent of lymphocyte exit from the lung via lymph to nodes or to the circulation. However, it is clear from studies in the mouse that programmed cell death, or apoptosis, is involved in the termination of antigen-induced inflammatory responses. In lymphocytes, this energy requiring form of cell death leading to the fragmentation of the nucleus and DNA may result from one of three events: (1) "neglect" or absence of stimulation; (2) stimulation out of context, or without the appropriate second signals (e.g., CD28 or matrix interactions); or (3) signaling via Fas (CD95) engagement with Fas ligand. Such regulation of cell death appears to be critically important for the termination of an immune response once antigen has been cleared, preventing the accumulation of activated lymphocytes.

MACROPHAGES IN THE LUNG

Macrophages reside in many organs. However, they are especially prominent in the lung and perform many functions.

Macrophages ingest inhaled particles or antigens and are then removed on the mucociliary escalator. They also serve as "professional" antigen presenting cells, traveling to regional lymph nodes where they sensitize T and B lymphocytes. Lung macrophages release a variety of cytokines and biologically active arachidonate metabolites that influence the function of nearby cells, including T cells, B cells, endothelial cells, and fibroblasts. Finally, macrophages ingest microorganisms and, when stimulated, kill them using a variety of means, including toxic oxygen metabolites and nitric oxide.

Macrophages or macrophage-like cells are found in several lung compartments, including the epithelial lining fluid, interstitium, epithelium, and intravascular compartment. These cells have varying functional repertoires and are typically categorized as alveolar macrophages, interstitial macrophages, DCs, Langerhans' cells, blood monocytes, or blood macrophages, respectively. Each of these cell types, their recruitment, and their activation will be discussed.

Macrophage Types

Alveolar Macrophages

Derivation of AMs from blood monocytes was initially suggested by an experiment in which the quantity of AM declined 20 to 30 days after bone marrow ablation despite in situ proliferation and increased cell stability. It has since been established that AM derive from blood monocytes and that differentiation is regulated by the tissue microenvironment. The molecular details of differentiation from blood monocyte to AM remain largely unknown.

If quantity implies importance, then one would surmise that AMs play an essential role in the lung's defense against foreign invaders. Found in airspaces throughout the lung, it is estimated that macrophages make up 90 percent of cells found in the alveolar spaces of both smokers and nonsmokers. The absolute quantity of AM, however, is approximately fourfold greater in smokers than nonsmokers. The increased quantity of alveolar macrophages in smokers is likely due to both recruitment of blood monocytes from the bone marrow and their differentiation into alveolar macrophages. In one study, alveolar macrophages were exposed to ambient particles and their supernatant collected. The supernatant promoted transit of monocytes through the bone marrow and their release into the circulation. Analysis of the supernatant revealed large amounts of inflammatory mediators including granulocyte-macrophage colony-stimulating factor (GM-CSF), macrophage colony-stimulating factor (M-CSF), macrophage inflammatory protein (MIP)-1beta (CCL4), monocyte chemotactic protein (MCP)-1 (CCL2), interleukin (IL)-6, and ICAM-1. Many of these mediators are known to increase monocyte turnover in the bone marrow and enhance their recruitment into peripheral tissues.

AMs have a diverse repertoire of functions. Importantly, AMs are the first line of defense against inhaled antigens and pathogens. As such, they have well-developed phagocytic activity that is enhanced when activated by opsonization or inflammatory signals (e.g., IFN-γ). Activated AMs release more inflammatory mediators and have superior microbial killing than their unstimulated counterparts. It is impossible to accurately assess the phagocytic and microbicidal capabilities of AM compared with other lung macrophages because many of the accessible AM may have been depleted of a portion of their functional capabilities due to previous activation. In general, smaller AM are more efficient at phagocytosis and microbial killing than large AM. The smaller AM may represent younger, recently emigrated phagocytes and the larger AM may represent previously activated AM.

AM release a variety of inflammatory mediators including arachidonate products, cytokines, and enzymes (Table 20-6). These mediators impact extracellular matrix, fibrin deposition, and the function of leukocytes and lung cells at sites of inflammation. Many also play key roles in the pathogenesis of lung diseases. As an example, IFN-γ inducible protein 10 (IP-10; CXCL10), monokine induced by IFN-γ (Mig; CXCL9), and IFN-inducible T-cell α chemoattractant (I-TAC; CXCL11) are released by alveolar macrophages and stimulate the release of matrix metalloproteinases −9 and −12 in emphysema.

Table 20-6

Cytokines and Other Bioactive Substances Released from Lung Macrophages*

Arachidonate Metabolites	**Cytokines**	
Thromboxane A_2	IL-1	
PGE_2, D_2, $F_{2\alpha}$	IL-1RA	IL-10
LTB_4	IL-6	IL-12
5-HETE	TNF-α	IL-15
	IFN-α/β	MIF
Reactive Oxygen Metabolites	**Nitric Oxide**	
Superoxide anion (O_2^-)	Constitutive	
H_2O_2	Inducible?	
hydroxyl radical (OH^-)		
Enzymes		
Metalloproteases		
Elastase		
Procoagulant activity		

** Not a complete listing. Abbreviations: Tx = thromboxane; PG = prostaglandin; LT = leukotriene; HETE = hydroxy tetraenoic acid; MIF = macrophage migration inhibitory factor; IL- = interleukin; TNF = tumor necrosis factor; IFN = interferon; MIF = migration inhibition factor.*

Source: Curtis JL, Kaltreider HB: Characterization of bronchoalveolar lymphocytes during a specific antibody-forming cell response in the lungs of mice. Am Rev Respir Dis 139:393–400, 1989; Johnston RB Jr: Current concepts: Immunology. Monocytes and macrophages. N Engl J Med 318:747–752, 1988; Kremlev SG, Umstead TM, Phelps DS: Effects of surfactant protein A and surfactant lipids on lymphocyte proliferation in vitro. Am J Physiol 267:L357–L364, 1994

A wide array of receptors is expressed by AMs, of which most mediate AM activation, migration, or phagocytosis. Perhaps most important are the toll-like receptors that are pattern recognition receptors for microbial cell walls lipids, DNA repeats, and other components of infectious agents. They provide the recognition function of the innate immune system that links to CD14 and subsequent inflammatory cytokine release (e.g., IL-1, IL-6, TNFα secretion). These cytokines are essential in controlling infection with intracellular organisms such as *Mycobacterium tuberculosis*. For example, AMs express toll-like receptor-2, which, when activated, induces killing of intracellular *Mycobacterium tuberculosis*. MARCO is a scavenger receptor expressed by AMs that facilitates phagocytosis of unopsonized particles. In the absence of MARCO, pulmonary infection and inflammation are markedly increased. Other receptors expressed by AMs include chemokine receptors, cytokine receptors, Fc receptors that recognize opsonizing antibodies, complement receptors that facilitate phagocytosis, lectin receptors, bacterial endotoxin (CD14) receptors, and mannose receptors (Table 20-7).

Under certain circumstances, AMs function as antigen-presenting cells and facilitate memory T lymphocyte activation. This ability is enhanced in disease states such as HIV, transplant graft rejection, and sarcoidosis. In alternative situations, AM may impact the immunologic synapse to suppress T-lymphocyte activation. This supposition is corroborated by one animal model in which AM depletion enhanced lymphocyte activation, suggesting that AMs can suppress T-lymphocyte activation in normal lung homeostasis.

Interstitial Macrophages

Interstitial macrophages are a population of macrophages found in the interstitium of the lung instead of the airway lumen. They may be precursors of AMs in transit from the vasculature to the air spaces. Little is known about human interstitial macrophages because they are not readily accessible for study.

Dendritic Cells and Langerhans' Cells

DCs are potent APCs that reside within airway epithelium. Like alveolar macrophages, they likely originate in the bone marrow, travel via the blood (0.5 percent of blood mononuclear cells are DCs), then translocate into tissue. Although chemokines and other factors like IL-16 that are chemotactic for DCs have been identified, the precise stimulus for translocation of lung DCs is unknown. DCs are most numerous in large airway epithelium and decrease in quantity as the airways become smaller. Histologic sections along the long axis of airways have revealed a meshwork of DC processes ideal for antigen sampling and interaction with T cells. A similar meshwork is found in BALT in the mouse. It is unknown whether DCs proliferate in the lung.

DCs are highly mobile and travel from the airway to regional lymph nodes, where they interact with lymphocytes. DCs are tenfold to 100-fold more potent than monocytes at presenting antigens to naïve T lymphocytes. DCs express cell surface proteins that are essential for antigen presentation and lymphocyte activation, including MHC, cell-cell adhesion molecules (e.g., ICAM/CD54, LFA-3/CD58, and β1 and β2 integrins), CD4, and the CD28 ligands. Specialized DCs with distinctive infoldings of the plasma membrane called Langerhans' cells also exist in the lung, especially

Table 20-7

Ligands Recognized by Alveolar Macrophage Receptors*

Immunoglobulins (Fe Receptors)	**Complement Receptors for**
$IgG1$, $IgG2_a$ (murine)	C3b, iC3b, C4b, C3d, C5a
IgG2b, IgG3 (murine)	
IgG1, IgG3 monomers (human)	
IgE, IgA (murine, human)	
Protein, Cytokine, and Matrix Receptors	**Lipoprotein Receptors for**
Fibronectin R	Low-density lipoprotein
Fibrin R	Beta-very-low-density lipoprotein
Lactoferrin R, transferrin R	
GM-CSF R	
IFN-γ R, IL-2 R, IL-4 R, IL-1 R, IL-1RA	
Insulin	
Chemotactic factor receptors	
Other Receptors and Adhesion Molecules	**Lectin Receptors for**
Class II MHC (HLA-DR, -DP, -DQ)	α-Linked galactose residues
CD4	N-acetylgalactosamine residues
β_2 Integrins (CD18; CD11a, b, c)	N-acetyl galactosamine residues
β_1 Integrins (CD29; CD49a,b,c,e,f)	α-Linked fucose residues
CD54 (ICAM-1)	N-acetylneuraminic acid residues
CD14 (lipopolysaccharide receptor)	Mannose residues (mannose receptor)

* *Not a complete listing.*

Note: Abbreviations: Ig = immunoglobulin; Fc = complement binding fragment of immunoglobulin; IL = interleukin; IFN = interferon, GM-CSF = granulocyte-macrophage colony stimulating factor; MHC = major histocompatibility complex antigen; R = receptor; RA = receptor antagonist; CD = cluster of differentiation.

Source: Curtis JL, Kaltreider HB: Characterization of bronchoalveolar lymphocytes during a specific antibody-forming cell response in the lungs of mice. Am Rev Respir Dis 139:393–400, 1989; Johnston RB Jr: Current concepts: Immunology. Monocytes and macrophages. N Engl J Med 318:747–752, 1988.

those of smokers. Like DCs, Langerhans' cells are potent antigen-presenting cells but are less efficient at phagocytosis, microbial killing, and cytokine secretion compared with macrophages.

The importance of DCs to the pathogenesis of lung diseases was highlighted by a murine model in which CD11+ DC depletion during an allergen trial resulted in abrogation of the characteristics of an asthmatic response eosinophilic inflammation, goblet cell hyperplasia, and bronchial reactivity. Their role with T-cell education in the lung was discussed earlier.

Blood Monocytes and Intravascular Macrophages

As discussed above, blood monocytes are likely the precursors of both lung macrophages (alveolar and interstitial) and intravascular macrophages, with differentiation being directed by the microenvironment. This is supported by the observation that blood monocytes can be induced in vitro to express receptors characteristic of AM over a period of days if cultured in the correct microenvironment. The average monocyte spends 1 to 3 days in the circulation and then exits the circulation to differentiate into a macrophage. During inflammation, translocation from blood to tissue increases.

Intravascular macrophages are found within the vasculature of the lung. They are located in postcapillary venules, strongly adherent, and face the flow of blood. Like interstitial macrophages, these cells are not readily accessible and, therefore, are difficult to study. They are presumed to act as intravascular inflammatory sentinels, ingesting antigens and releasing mediators in response to inflammatory stimuli that reach the lung via the blood.

Recruitment of Monocytes and Macrophages

Monocytes are motile cells that adhere to endothelial cells and then migrate with extraordinary efficiency. Monocyte adherence to endothelial cells is promoted by the monocyte "rolling" along vascular walls to increase the likelihood that its β2 integrins (αLβ2, αMβ2, and 4β1) will bind the endothelial cell selectins. Following adhesion, translocation into the lung parenchyma occurs. Once the monocytes have entered the tissue, they differentiate into interstitial macrophages and continue to migrate via their β1 integrins. Both differentiation and migration are influenced by local tissue-specific factors including chemokines, cytokines, matrix components, complement fragments, antigens, and interactions with other cells.

Monocytes respond to a variety of chemotactic influences including complement fragments (e.g., C5a), bacterial peptide f-MLP, leukotriene B4, and the chemokines CCL2, CCL3, CCL4 and CXCL8 (IL-8). The importance of chemokines for monocyte migration is illustrated by a study that investigated the impact of CCR2 (the receptor for CCL2; MCP-1) deletion in a murine model of pulmonary granulomatous inflammation. Following deletion, there was marked decrease in granuloma size and a dramatic decrease in the level of interferon gamma in draining lymph nodes. These findings suggest that CCL2 is vital for monocyte/macrophage migration to sites of inflammation.

Motility of AMs and DCs has also been studied. When labeled DCs and AMs are introduced into the airways, DCs but not AMs are readily found in draining lymph nodes, suggesting that DCs are far more motile than AMs. DC migration is likely chemokine-mediated. In one set of experiments, interleukin-13 (IL-13) and IFNγ were administered intranasally, resulting in increased numbers of DCs accumulating in draining lymph nodes, similar to the experiment previously described. Compared with untreated mice, the treated mice had more expression of chemokines, including CCL5, CCL2, and CCL7 (MCP-3). In addition, chemokine receptor expression was increased including CCR2, CCR5, and CCR10.

Activation of Lung Macrophages

A major feature of tissue macrophages is its ability to be "activated." Activation of macrophages is a key event in the inflammatory cascade in the lung and defines a functional state characterized by extrusion of pseudopodia and an increase in cell size and membrane ruffling. Examples of stimuli that interact with receptors on the macrophage's surface to induce activation include antigen-antibody complexes (via the macrophage's Fc receptors), complement fragments (via the macrophage's complement receptors), and cytokines (e.g., interferon-γ). When activated, macrophage phagocytosis, receptor expression, and production of toxic oxygen metabolites are markedly enhanced. The activated macrophage is a secretory cell, releasing cytokines, toxic oxygen metabolites, and enzymes. Finally, antigen presentation is optimized in activated macrophages but increased expression of class II MHC.

Activated macrophages are prominent in many lung diseases. While it is unclear whether macrophage activation is a cause or result of lung disease, it is probably both. As an example, in emphysema, macrophage activation is initiated by cigarette smoke exposure and results in the release of inflammatory mediators and by products that are toxic to lung parenchyma. These inflammatory mediators, in turn, activate additional macrophages, establishing a vicious cycle of macrophage activation and parenchymal lung destruction.

LYMPHOCYTE-MACROPHAGE INTERACTIONS IN THE LUNG

The interactions between lymphocytes and macrophages, and their effects on lung inflammatory cells and lung inflammation are summarized in Fig. 20-2. Lung macrophages and lymphocytes each perform important functions and influence the differentiation and function of a large variety of cells.

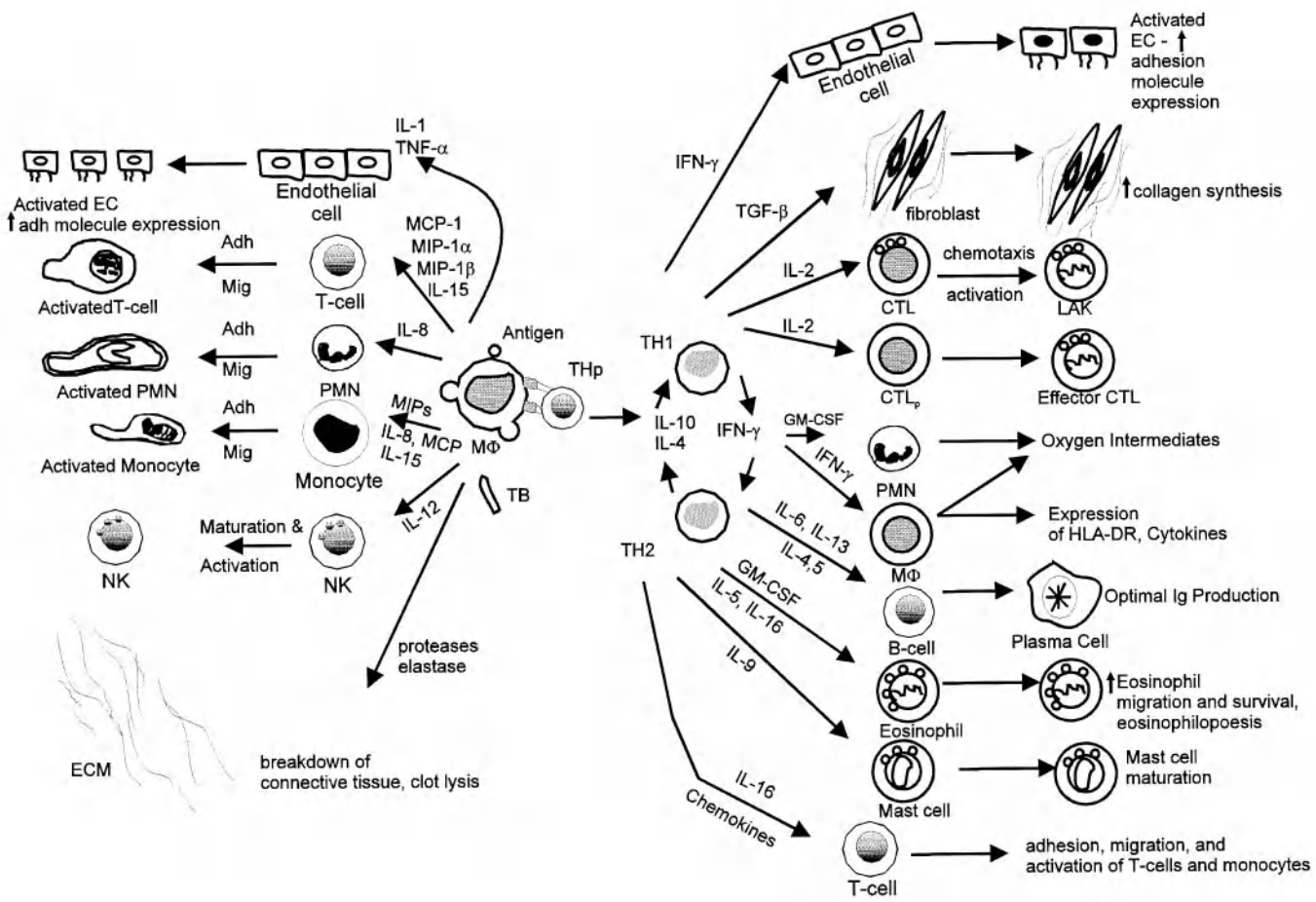

Figure 20-2 Lymphocyte and macrophage interactions in lung inflammation. Lymphocytes and macrophages interact directly and indirectly to influence lung inflammation. These interactions are complex, as illustrated by this diagram, which contains a necessarily incomplete sampling of these processes. Lymphocytes and macrophages interact directly in the process of lymphocyte activation; macrophages also are immunosuppressive in some circumstances. Activated T lymphocytes express a broad range of cytokines that interact with a variety of effector cells; B lymphocytes produce antibodies. T lymphocytes also may interact with infected epithelial or phagocytic cells or with tumor cells to effect cell lysis. Macrophages similarly produce a large number of cytokines that alter the functions of a variety of cells. Macrophages also release arachidonate metabolites, reactive oxygen species, nitric oxides, and a large number of proteases that alter the function of surrounding cells, kill invading microorganisms, and degrade matrix proteins. See text for further explanation. *(Adapted from Agostini C, Chilosi M, Zambello R, et al: Pulmonary immune cells in health and disease: Lymphocytes. Eur Respir J 6:1378–1401, 1993, with permission.)*

Lung macrophages and lymphocytes also interact via direct cell-cell contact during T-cell activation and are greatly codependent.

AM and related cells are the initial sentinels of the innate immune response, phagocytosing and eliminating invading antigens and microbes. After interaction with microbial invaders, and especially in conditions of overwhelming invasion, lung macrophage activation via toll-like receptors and CD14 and other receptors (Table 20-7) results in the release of inflammatory mediators that activate adhesion molecule expression on endothelial cells, and promote the migration and activation of blood leukocytes including polymorphonuclear leukocytes (PMNs), monocytes, lymphocytes, and eosinophils (left half of Fig. 20-2). Rapid induction of selectin molecules stored in Weibel-Palade bodies of endothelium results in the rolling adhesion of neutrophils and monocytes. Migration of these leukocytes may be rapidly modulated by rapid release of arachidonate products such as LTB4, bacterial products themselves such as the peptide f-MLP, complement fragments, and chemokines. More time is required for optimal expression of adhesion molecules that enhance lymphocyte entry, especially VCAM and expression of the chemokine chemoattractant cytokines. One exception is the release within hours of IL-16 from epithelium or resident T cells in response to mast cell–derived histamine.

Interaction of resident or infiltrating T cells with antigen-presenting cells (mainly DC, Langerhans' cells, and

monocytes) results in optimal T-cell activation with resultant production of cytokines that act upon a variety of cytokine-receptor bearing cells (right half of Fig. 20-2). This results in the activation of endothelium, optimal B-cell production of antibody, generation of cytotoxic effector T cells, and (depending on the nature of the cytokines produced) a delayed-type hypersensitivity or granulomatous (TH1-cytokine) or allergic (TH2-cytokine) immune response. Fibrosis or repair also may be influenced by the production of neutral proteases by AM, or the elaboration of the fibrogenic cytokine TGFβ1 by T cells or other cells depending upon the TH skewing. Of particular interest for the future are the ways the lung macrophage–lymphocyte inflammatory access is "turned off." The networks responsible for control of inflammation to prevent lung damage are likely to be as complex as those that initiate the inflammatory responses in infectious and noninfectious lung diseases.

Overall, the mammalian lung is uniquely poised to protect the sterile environment of the lower respiratory tract and its essential gas exchange units through the presence of a complex network of monocyte/macrophage and lymphocytes selectively sequestered in various anatomic compartments. Together they coordinate early innate responses to microbial infection and subsequent specific acquired immune responses (e.g., to viruses) that have evolved to protect the organ. Of particular interest in certain noninfectious or autoimmune lung diseases is the similarity of inflammatory responses to those in response to infections in which the consequences are deleterious rather than beneficial. Thus, understanding ways to control lung innate and acquired immune responses will be essential in developing appropriate therapies for inflammatory lung diseases. Unfortunately, the converse is also true. Individuals treated with antibodies to TNFα to control the inflammation of rheumatoid arthritis or inflammatory bowel disease are at risk for reactivating latent *Mycobacterium tuberculosis* infections, an infectious disease clearly controlled by early innate and late acquired immunity. More detailed understanding of these processes, how to regulate them quantitatively, and how to replace essential elements is clearly needed to adjust the balance in individuals whose immune systems are compromised or in those whose immune systems are overwhelmed by infection or self-antigens.

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Mast Cells and Eosinophils

Edward S. Schulman • Peter H. S. Sporn

For more than a century physicians have noted a clear connection between mast cell (MC) activation and the subsequent appearance of eosinophils both within the circulation and in tissues. Only recently, however, have basic insights been gained into the mechanisms of this cellular collusion. In keeping with this association, human mast cells and eosinophils are considered together in this chapter.

Mast cells and eosinophils were discovered in the 1870s by the same observer, Paul Ehrlich. He noted that some cells stained in a peculiar fashion when incubated with standard aniline dyes such as toluidine blue and alcian blue. He used the term *metachromasie* or *metachromasia* to describe the peculiar color modifications that occurred and the term *Mastzellen,* meaning "well fed" or "fattened" in German, to describe what we now call MC. Interestingly, this latter term is now known to be a misnomer, since mast cell cytoplasmic granules are not phagocytosized but rather synthesized during cell growth and again during regranulation. Ehrlich also noted that some cells stained intensely when incubated with the acidic dye eosin. As a result, these cells were called *eosinophils.* Studies of these two cell types, over the ensuing years, have provided great insight into their roles in biology. They have also highlighted the differences that exist in these cells among different species and their heterogeneity even within a single species and even within single organs.

MAST CELLS

The capacity of strategically localized human MC to rapidly release a panoply of powerful chemical mediators makes this cell a unique member of the body's immune response network. Although most frequently discussed in the context of hypersensitivity immune responses, MC are also known to participate in normal physiological processes including gastric acid secretion, angiogenesis, and lipid clearance. Increasing evidence supports a role in the innate immune response, especially serving bacterial defense. Mast cells also participate in nonallergic pathophysiological processes such as inflammatory bowel disease, arthritis, scleroderma, tumors, interstitial pulmonary fibrosis, angiogenesis, and atherosclerosis. Over the years, basophils have been confused with MC in a number of contexts. This confusion is due, in part, to a number of similarities between the cells, including the shared expression of FcRI (high-affinity receptor for Fc fragment of IgE), release of preformed histamine, and metachromatic staining. However, MC are mononuclear cells and are almost exclusively localized to tissues. In contrast, basophils are circulating polymorphonuclear cells that are found occasionally in tissue reactions, including the late-phase allergic response. In addition, significant differences in the two

cell populations exist in cell lineage, ultrastructure, mediator release biochemistry, mediator profiles, pharmacology, and surface antigenicity.

Anatomic Localization

Mast cells are present in all organs but are particularly abundant in the nose, skin, gastrointestinal tract, and lung. They reside primarily near blood vessels, within the adventitia of arteries, and also near lymph vessels and nerves. Estimated concentrations of human lung MC (HLMC) range from 500 to 4000 mm^{-3}. In nonasthmatics, HLMC localize to submucosal connective tissues and not epithelium or smooth muscle. Though data in asthmatics are conflicting as to whether numbers are increased vs. nonasthmatics, MC localize to three critical sites: bronchial epithelium, airway mucous glands, and within smooth muscle. Mediator release from the small numbers of HLMC within the epithelium may subserve initial antigen recognition and also be strategically placed to respond to nonantigenic signals, including hyperosmolarity, as well as "endogenous" mediators, including extracellular adenosine and adenosine 5′ monophosphate (ATP). In the case of aeroallergens, permeabilization resulting from epithelial mast cell mediators enhances further antigen penetration to deeper airway smooth muscles and mucous glands, which in turn, promotes bronchoconstriction and mucous secretion, respectively. The finding of HLMC within the smooth muscle layer appears to be a common finding in asthmatics. It is an uncommon finding in nonasthmatics and in patients with eosinophilic bronchitis. In the lung periphery, abundant MCs reside within small airways and in the alveolar septa, within a few microns of the alveolar lumen. The small numbers of MC in bronchoalveolar lavage (BAL) fluid ($\leq$0.1 percent of all cells) likely result from epithelial shedding.

Origins of Mast Cells

Mast cells are believed to be derived from the multipotential hematopoietic stem cell. Tryptase-negative mast cell–colony-forming cells leave the marrow and circulate with a surface phenotype that is CD (cluster of differentiation) 34+, c-kit (CD117)+, LY−, CD14−, and CD17−. The progenitors home in a tissue-specific manner where they undergo differentiation, maturation, and synthesis of granule proteases in response to microenvironmental factors, including chemokines from fibroblasts, endothelial cells, airway smooth muscle cells, and possibly T cells. The microenvironmental factor most critical in chemotaxis, differentiation, adhesion, proliferation, maturation and survival is stem cell factor (SCF or c-kit ligand), the ligand for the c-kit tyrosine kinase receptor. This receptor is expressed on the MC surface throughout its life span.

Mast Cell Heterogeneity

Striking differences in the morphology, T-cell dependence, resident proteoglycans, and responsiveness to secretagogues and drugs have been described in human MC. The ontogeny of this heterogeneity, as well as the differing roles these MC play in physiology and disease remain speculative.

The most commonly recognized system for classifying human MC is based on the expression of protease profiles as determined by immunohistochemical staining using monoclonal antibodies. According to this system, the serine proteinase tryptase (T) is expressed in virtually all human MC, and a subset, predominantly in the submucosa of the gut and in the skin, also express chymase (C) and multiple other proteases. Those that express tryptase alone are classified as the MC_T type, and those with additional proteases, as the MC_{TC} type. Because significant numbers of both types can be found in the same organ (e.g., lung), tissue location alone cannot dictate the protease type. In the lung, only 8 to 35 percent of MC are MC_{TC}, 1 percent are MC_C, and the remainder are MC_T. The protease system does follow some rules of distribution and function. MC_T are preferentially localized at mucosal surfaces, within airway smooth muscle, in areas of T-cell infiltration and are reduced in immunodeficiency syndromes. The MC_{TC} phenotype does not appear immune related. As detected by immunohistochemical staining, the MC_{TC} subtype more selectively expresses interleukin (IL)-4 (85 percent MC_{TC} vs. 15 percent MCT). IL-5 and IL-6 are almost exclusively restricted to the MCT subtype.

HLMC diameters vary between 8 and 18 μm with the majority being 12 to 15 μm. Histamine contents of 2.5 pg to 10.0 pg/MC vary directly with cell diameter. HLMC densities vary from 1.053 g/ml to 1.123 g/ml with the majority (67 percent) between 1.077 and 1.088 g/ml. These diameter and density-based subtypes also are distinct with respect to mediator content and function. MC location also subserves function: Airway and parenchymal MC differ in their releasibility. At the ultrastructural level, marked heterogeneity has been described (see Morphology). Last, at least two types of proteoglycans are present in HLMC: chondroitin sulfates, predominantly chondroitin sulfate E, and heparin. HLMC are both positive and negative for the heparin-sensitive dye berberine sulfate, whereas stomach MCs synthesize exclusively chondroitin sulfate E and not heparin.

Morphology

All MC are mononuclear cells with heterogeneous cytoplasmic granules (Fig. 21-1). A variety of granule-filling patterns occur within individual cells: scrolls, crystals, particles (the least seen in pure form), and combinations (mixed). The appearance of individual patterns can be influenced by cross section. Granules are outlined by a perigranular membrane. Cell membranes are outlined by short, narrow surface folds.

Morphology of Degranulation and Regranulation

Following IgE-mediated (anaphylactic) activation, granules swell and their perigranular membranes fuse to form canaliculi that open through multiple pores to the cell exterior. Within 20 min of activation, granular matrix materials solubilize within these intracytoplasmic channels and

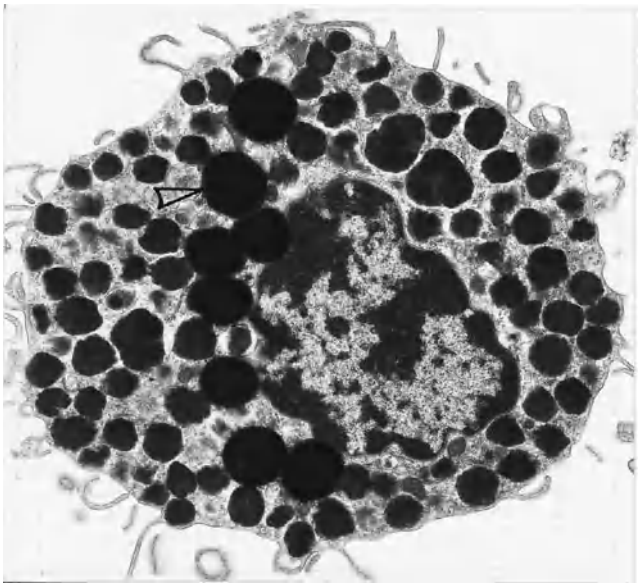

Figure 21-1 Ultrastructure of the human lung mast cell after purification. The mast cell is a mononuclear cell packed with multiple dense cytoplasmic granules that vary in size and shape. Eight electron-dense lipid bodies (open arrow) are bunched near the nucleus (× 15,000). *(Reproduced with permission from Dvorak AM: Recovery of human lung mast cells from anaphylactic degranulation utilizes a mixture of conservation and synthetic mechanisms, in Galli SJ, Austen KF (eds),* Mast Cell and Basophil Differentiation and Function in Health and Disease. *New York, Raven, 1989, p 124.)*

empty. In HLMC, only rarely is extrusion of nonsolubilized granules observed. Lipid bodies, which are electron-dense nonmembrane-bound organelles, remain adjacent to these channels. They appear to serve as repositories of arachidonic acid and occasionally release lipid into the degranulation channels. In vivo, a process termed "piecemeal degranulation" is more frequently observed than anaphylactic degranulation. This process involves the budding of small vesicles from granule membranes and their movement to the cell surface. Piecemeal degranulation may be more typical of the ongoing MC release observed in chronic asthma.

Depending on the extent to which an individual cell has degranulated, one of two predominant types of regranulation are observed individually or in combination. In partially degranulated cells, the channel (formerly perigranular) membranes are reutilized, and regranulation events resemble degranulation in reverse. In cells with more complete degranulation, the channel membranes are placed in continuity with the plasma membrane and externalized. This results in the appearance of elongated, activated cell surface folds. These excessive folds can be internalized or shed. Shedding results in cells that are initially small (7 μm), but then enter a rapidly expanding recovery cycle to produce a fully mature cell.

Activation

Immunological activation of MC is the mechanism most studied. It results from antigen cross-linking of antigen-specific cell surface IgE molecules and subsequent aggregation of the high-affinity receptors (FcεRI) to which they are attached. Receptor dimerization is the minimum cross-linkage requirement for IgE-mediated activation. In vitro, immunological activation can be achieved using antibodies directed against human IgE or the FcεRI-receptor itself. The mechanism(s) involved in chronic HLMC activation characteristic of asthma are not known but likely may reflect low-level allergen activation. Recent evidence contends that monomeric IgE alone, in the absence of antigen, can also induce prolonged mediator release.

Non–IgE-mediated release triggers of MC are also well characterized. In general, the profile of agents that degranulate MC from human intestine and synovium is similar to that of HLMC but different from skin MC. These non–IgE-mediated secretagogues include ionophores, hyperosmolar stimuli, and "histamine-releasing activities" derived from human alveolar macrophages. The purified anaphylatoxin C5a, an active trigger of human basophils and dermal MC, is generally inactive in HLMC, although CD88, the receptor for C5, has been reported in the MC_{TC}. Consistent degranulators of dermal but not HLMC include substance P, morphine, polyamines such as 48/80, and SCF. Even within lung compartments, responsiveness to triggers may vary. Compound 48/80 is reported to degranulate BAL MC, whereas those from lung parenchyma are minimally responsive. To date, neuropeptides have been shown to be inactive in degranulating HLMC. Last, expression in both mouse MC and human progenitor–derived MC of several innate pattern recognition receptors, including the Toll-like receptor-2 (TLR2) and TLR4, has been reported. The expression of TLR and effects on activation of HLMC are as yet poorly defined.

Modulators of Activation

Although not acting as direct release triggers, a number of endogenous chemicals in the MC microenvironment can influence activation. Extracellular ATP and its breakdown product, adenosine, are potent modulators of HLMC degranulation, although neither directly activates HLMC in vitro. In asthmatics, aerosolized adenosine induces bronchoconstriction, an effect not observed in other groups of pulmonary patients or normals. The ability of antihistamines to inhibit this response has directly implicated activation of allergically primed airway MC by adenosine. Components of the local connective tissue matrix such as fibronectin also modulate MC reactivity.

Biochemical Analysis of HLMC Activation

Elegant studies defining the biochemical events following IgE-mediated activation have been performed in rodent MC or cell lines. Evaluations of similarities and differences in HLMC activation await future investigations. Two receptors for IgE have been identified. The high affinity IgE receptor (FcεRI) on MC and basophils is expressed in a tetrameric form ($\alpha\beta\gamma 2$) and on antigen presenting cells is present in a trimeric form ($\alpha\gamma 2$). The Fc fragment of IgE binds to the α-chain of FcεRI. Expression of the β-chain amplifies signaling. A low-affinity

IgE receptor (FcεRII; CD23) is present on B cells but not on MC or basophils. Serum IgE levels correlate with basophil expression of FcεRI, likely indicating a role for IgE in stabilizing the FcεRI on the cell surface. As noted above, receptor dimerization is the minimum cross-linkage requirement for antigen-mediated allergen activation through the FcεRI. Following receptor aggregation, multiple signal transduction pathways are activated. Since FcεRI possesses no inherent tyrosine kinase activity, critical to the sequential activation are two tyrosine kinases, lyn which is associated with the β chain and syk. Lyn binds to the β chain associated immunoreceptor tyrosine-based activation motifs (ITAMs), which are phosphorylated after FcεRI aggregation. For degranulation to proceed, syk then binds to the γ-chains–linked ITAM, which are also phosphorylated after receptor aggregation. The lyn-syk driven pathway directly or indirectly stimulates tyrosine phosphorylation of several adapter proteins, including the transmembrane adaptor molecule linker for activation of T cells (LAT) among others. Also activated are phospholipase C-γ1 and PLC-γ2. In this context, at 2 minutes following FceRI aggregation, extracellular calcium influx occurs, which is a prerequisite for degranulation to proceed over the next 5 to 20 min. Other "early-phase" granule-associated and lipid mediators (e.g., arachidonate metabolites) are also released over 20 min. Over the ensuing 1 to 24 h, mRNAs for select cytokines are generated followed by their protein synthesis and release.

Chemical Mediators

The clinical expression of MC–mediated responses may reflect the individual mediators or in certain instances, the interplay of the multiple mediators these cells release (Table 21-1). The temporal sequence of their release appears critical to the development of both the early and late phase responses after antigen challenge (Fig. 21-2). Certain mediators are virtually unique to MC (e.g., tryptase, chymase, heparin), and others are shared with one or more other cells (e.g., histamine, leukotriene (LT) C_4, and IL-5).

Mediators released within minutes after activation are divided into preformed, or secretory, granule-associated mediators (e.g., histamine) and non-preformed, or newly synthesized mediators (e.g., lipids). It is now known that tumor necrosis factor alpha (TNFα) may be both preformed and newly synthesized. Other cytokine mediators, including IL-5 and IL-13, are only detected over hours and may be critical to the evolution of the "late-phase" response.

Table 21-1

Human Mast Cell and Eosinophil Mediators

	Mast Cells	Eosinophils
Granule-associated (performed) mediators	Histamine Heparin Chondroitin-sulfate E TNFα	MBP ECP EDN EPO CLC protein
Enzymes	Tryptase Chymase Cathepsin-G Elastase Carboxypeptidase-A	EPO CLC protein Collagenase MMP-9 Indoleamine 2,3-dioxygenase
Acid hydrolases	β-hexosaminidase β-glucuronidase Arylsulfatase	β-glucuronidase Arylsulfatase B
Lipid mediators (nonpreformed)	PGD_2 LTC_4 LTB_4 PAF Thromboxane-A_2	LTC_4 15-HETE 5-oxo-ETE PAF
Cytokines	IL-4, IL-5, IL-13 IL-6, IL-8 TNFα TGF-β bFGF	IL-1α, IL-2, IL-3, IL-4, IL-5, IL-6, IL-8, IL-10, IL-12, IL-13, IL-16, IL-17 GM-CSF TNFα TGF-α TGF-β SCF NGF PDGF VEGF
Chemokines		RANTES MIP-1α MCP-4 Eotaxin
Reactive oxygen products	None detected	$O2^-$, H_2O_2, OH· HOBr, HOCI

Preformed Mediators

Histamine

Histamine measurements have served as a classic marker of MC-mediated events. The pleiotrophic effects of histamine are mediated through the differential expression, regulation, and distinct intracellular signals evoked by four distinct receptors, H1, H2, H3, and H4. The actual role of histamine in asthma remains less clear, although levels in bronchoalveolar lavage fluid are many-fold higher in asthmatics, and plasma levels rise three- to fivefold following airway antigen challenge. Most histamine-induced allergic repiratory reactions are mediated via the H1 histamine receptor subclass, producing enhancement of vascular permeability, mucous production, initiation of neurogenic reflexes, and bronchial smooth muscle contraction. The reasons for the marginal value of the H1 receptor-blocking drugs in asthma may be due to high local tissue concentrations of histamine that exceed the inhibitory capacity of these agents and/or the redundancy of histamine actions with the multiple other mediators that are released.

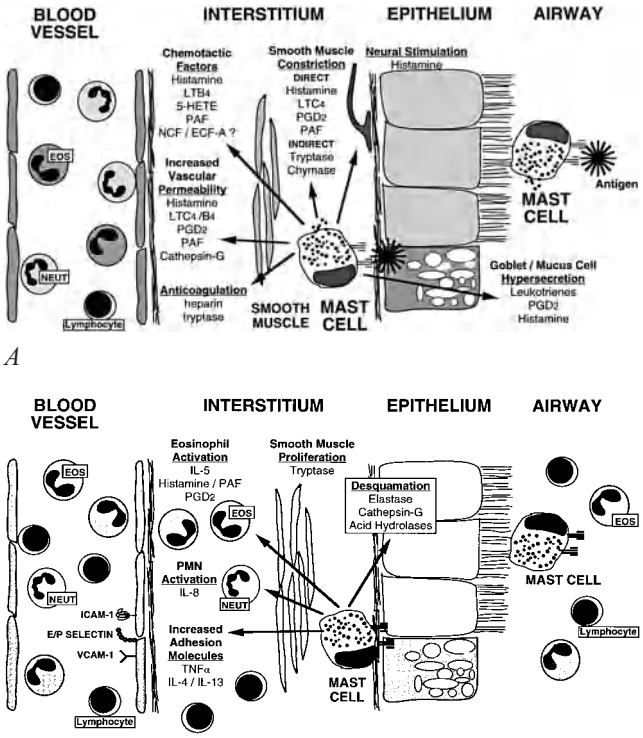

Figure 21-2 Effects of mast cell mediators in the early- and late-phase responses following airway allergen challenge. *A.* Early phase: Mediators are released within minutes following antigen cross-linking of allergen-specific IgE on the cell surface. Mechanisms of the initial airflow obstruction that persists for 30 to 60 min include smooth muscle constriction, edema formation due to increased vascular permeability, nerve stimulation, and mucus hypersecretion from both goblet cells and submucosal glands. *B.* Late phase. Within hours, the effects of newly synthesized and released cytokine mediators along with delayed effects of early-phase mediators produce recurrent airway obstruction. Mast cell mediators and cytokines can increase the expression of adhesion molecules on endothelial cells, both recruit and activate leukocytes (particularly eosinophils), contribute to epithelial desquamation, and stimulate smooth muscle proliferation.

Proteoglycans

Mast cell proteoglycans serve as the major determinant for the metachromatic tinctorial properties of the cell and form the granule backbone to which other preformed mediators, including histamine and neutral proteases, are bound. HLMC synthesize heparin and chondroitin sulfate E proteoglycans in roughly a 2:1 ratio. In humans, heparin appears to be unique to MC. In addition to anticoagulant activity, heparin possesses both anti-inflammatory and immunoregulatory properties. Heparin may limit allergic responses in the skin, nose and lung and exert protective effects on exercise-induced asthma. The inhibitory effects may be related to the extracellular binding and inhibition of multiple mediators, including histamine and cytokines.

Chemotactic Factors

Within hours of MC activation, airway inflammation (the late-phase response) at the tissue level is characterized by the infiltration of leukocytes. This response is principally eosinophilic but also contains neutrophils and, over time, lymphocytes. Chemotactic mediators may be derived directly from MC and/or other cells through secondary stimulation. Early-phase MC-derived eosinophilic chemotactic activities include leukotriene B_4 (LTB_4), platelet activating factor, and histamine. HLMC robustly express IL-8, which along with LTB4, attracts neutrophils. A high-molecular-weight (750 kDa) chemotactic factor for neutrophils (NCF-A) can measured in the blood of sensitive asthmatics following antigen, may actually represent a small MC-derived lipid (e.g., LTB_4) bound to a high-molecular-weight carrier. Mast cells are responsive to chemokines released from other cells. Airway smooth muscle secretes a number of chemotactic factors including CXCL9, -10 and -11 that can serve as ligands for CXCR3 expressed by HLMC.

Proteases

Large quantities of neutral proteases are contained within MC and constitute the predominant protein component of the secretory granule. The proteases include tryptase, chymase, cathepsin-G, carboxypeptidase A, and elastase.

Tryptase is the predominant neutral protease of the MC granule. It is a tetramer that is stabilized by its association with proteoglycan. The concentration of tryptase in pulmonary MC is 11 pg/MC. Since the concentrations of tryptase in circulating basophils (α tryptase, see below) are negligible, responses characterized by the presence of histamine but not tryptase at the reaction site or in the circulation implicate mediation by basophils and not MC. Two forms of tryptase (α and β) have been identified. The α tryptase is constitutively secreted in an inactive form and reflects systemic MC burden. The active β form is packaged in the secretory granule and acutely rises in anaphylactic reactions. Postulated roles for tryptase in pathophysiology remain to be established. Described actions include the degradation of the neuropeptide vasoactive intestinal peptide (VIP), mitogenic effects on smooth muscle and epithelial cells, and inactivation of procoagulant proteins.

Chymase is associated with heparin in a manner similar to tryptase. The role of chymase in asthma and other disorders is not clearly defined. Chymase may play a role in tissue remodeling. Substrates include angiotensin I, converting it to the angiotensin II, VIP (inactivates), substance P, bradykinin, and kallidin (inactivates). Other activities include activation of matrix metalloprotease and stimulation of tissue neutrophilia and eosinophilia.

Cathepsin G is a neutral protease with chymotryptic specificities. The concentration of cathepsin-G in HLMC is roughly 100 to 700 ng/10^6 cells. An elastase released from HLMC appears to be identical to human neutrophil elastase. A measurement of 40 to 170 ng/106 cells assumes all HLMC contain this enzyme, although it may be localized to a HLMC subset. Among carboxypeptidases, the MC carboxypeptidase A, a metalloexopeptidase, is unique. Granule-associated acid hydrolases include β-hexosaminidase, β-glucuronidase, and arylsulfatase.

Nonpreformed Mediators

Arachidonic acid metabolites are generated within minutes of MC activation and play a crucial role in the early phases of the asthmatic response. Cyclooxygenase metabolism in MC generates large quantities of prostaglandin (PG) D_2 and a small quantity of thromboxane A_2. PGD_2 is the most potent bronchoconstrictor of the cyclooxygenase metabolites. Additional actions of PGD2 include induction of chemotaxis in eosinophils, basophils, and TH2 cells; increase in capillary permeability and vasodilation. Although all tissue MC generate PGD2, not all generate significant quantities of 5-lipoxygenase products (e.g., lung > skin). The major 5-lipoxygenase pathway products of HLMC are LTC_4, and LTB_4, with lesser quantities of 5-HETE. In IgE-mediated human lung challenges, MCs constitute the major source of released LTC_4.

Platelet activating factor *(PAF)* is an early phase phospholipid bronchoconstrictor that consists of a family of molecules. In contrast to the other lipid mediators, MCs appear to retain PAF intracellularly or demonstrate rapid reuptake of any that may be released.

HLMC synthesize and release TH2-type cytokines, including IL-5, and -13, which are felt to be central to the evolution of the late-phase response. Additional multifunctional cytokines, including IL-3, -6, -8, transforming growth factor beta (TGFβ), basic fibroblast growth factor (bFGF) and TNFα, are also synthesized by HLMC. In general, cytokine protein products are released over a 1- to 24-h period following allergic activation. Interleukin-4, a cytokine that virtually defines TH2 immunity, is immunolocalized to HLMC, which are rich in surface IL-4 receptors. However, generation of IL-4 mRNA and protein release has been reported by some, but not all, investigators. TNFα, stored preformed within MC granules is in a unique position to exert diverse host defense effects in allergy and innate immunity. Recent studies suggest that increased expression of TNFα within HLMC may play a role in asthmatic airway inflammation and correlates with asthma severity.

Amphiregulin, a member of the epidermal growth factor family, is secreted following FcεRI-mediated activation. Its effects include increasing mucin gene expression, which may contribute to the epithelial cell metaplasia and mucous hypersecretion of asthma.

Pharmacologic Modulation of Mast Cell Function

Only a limited number of pharmacologic agents have been tested in vitro on HLMC activation-secretion. In general, these agents have been tested on human parenchymal MC rather than those in bronchi or resident in BAL. The common classes of antiallergic and/or antiasthmatic drugs used in clinical practice have received most evaluation. To date, the β-agonist pharmacologic agents, as typified by fenoterol and salmeterol, are reported to be among the most potent global inhibitors of HLMC mediator release with concentrations that inhibit histamine release by 50 percent (IC_{50}) of $\leq 10^{-8}$M. Less effective inhibitors include the theophylline-like phosphodiesterase inhibitor isobutylmethylxanthine ($IC_{50} = 0.5$ mM) and PGE_2 ($IC_{50} = 10^{-5}$M). Although widely touted as "MC stabilizers," disodium cromoglycate and nedocromil sodium poorly inhibit purified HLMC histamine release. Inhibition of BAL MC activation by these agents is reportedly more striking.

The effects of glucocorticosteroids on MC are diverse, including both stimulatory and inhibitory effects on the transcription of select genes. Release of early-phase mediators (e.g., histamine, LTC_4) in vitro and acute airway responses in vivo are unaffected by short pretreatment (up to 24 h) with these drugs. In contrast, IgE-mediated generation of TH2-type late-phase cytokine mRNA and protein (e.g., IL-5, -13) are suppressed ($IC_{50} = 10^{-8}$ to 10^{-9}M).

FK-506, a macrolide that binds to a specific binding protein, inhibits HLMC mediator release at low concentrations (0.1 to 300 nM). Cyclosporin A, which binds to cyclophilin, and auranofin, an orally absorbable gold compound, both inhibit HLMC mediator release.

Specific inhibitors of leukotriene generation include direct 5-lipoxygenase enzyme inhibitors, such as A-60477 (Zileuton), and indirect inhibitors, such as MK-886, which bind to a protein termed *5-lipoxygenase activating protein* (FLAP). Interestingly, PGD_2 release is markedly enhanced by FLAP inhibiton. This phenomenon has been termed a *reverse shunt effect.* Generally, 5-lipoxygenase pathway inhibitors do not affect HLMC histamine release. Cyclooxygenase-1 inhibition plays a critical role in a certain subset of "aspirin-sensitive" asthmatic patients (see below). Agents such as indomethacin potently inhibit HLMC PGD_2 generation ($IC_{50} = 5.5 \times 10^{-10}$M) while producing significant enhancement of LTC_4 release.

Mast Cells in Pulmonary Disease

Mast cells have been implicated in a variety of pulmonary disorders based, to a great extent, on their presence in increased numbers and/or percentages in diseased tissues and the recovery of increased concentrations of MC-derived mediators, particularly histamine, in BAL fluid. Implicated pulmonary disorders include asthma, idiopathic pulmonary fibrosis, sarcoidosis, extrinsic allergic alveolitis, and chronic bronchitis.

Asthma

At baseline, even very mild asthmatics show evidence of MC degranulation in bronchial mucosa and increased histamine content in BAL. Analysis of BAL in allergen-challenged atopic subjects and asthmatics demonstrates increased release of histamine, tryptase, and PGD_2. Increased numbers of lumenal MC are also noted and correlate with mediator content, airflow obstruction, and bronchial hyperresponsiveness. In general, asthmatic MCs exhibit ultrastructural evidence of degranulation. In nonfatal asthma, there is a significant increase of MC within airway smooth muscle and mucosal gland stroma. Multiple redundant MC mediators likely contribute

to increased mucous gland secretion and smooth muscle constriction. Following chronic corticosteroid treatment, allergic reactions are diminished in association with depletion of MC in both the epithelium and submucosa.

Although much attention has been given to IgE-mediated mechanisms of asthmatic airway activation, it is likely that multiple other MC-triggering mechanisms operate under a variety of immunologic and environmental conditions. One mechanism proposed for exercise-induced asthma (EIA) relates to airway cooling and the generation of hyperosmolarity on the airway surface leading to MC degranulation.

Up to 10 to 20 percent of asthmatics are intolerant of aspirin and other nonstructurally related nonsteroidal anti-inflammatory drugs (NSAIDs). The potential role for MC in this disorder remains controversial. Support for MC involvement includes the demonstration of a neutrophil chemotactic activity following challenge and that indomethacin pretreatment of human airway tissues results in increased LTC_4 generation following IgE-mediated stimulation.

Fibrosis

The cellular composition of diffuse fibrotic reactions includes striking increases in MC numbers. Mast cells synthesize and release important mediators of fibrosis, including TGFβ and hFGF. The hypothesis that MC and their mediators are critical to the development of fibrotic reactions is supported by animal models in which MC hyperplasia has been a constant finding in pulmonary fibrosis induced by bleomycin, ionizing radiation, and asbestos. Bronchial remodeling with subepithelial fibrosis is also a prominent feature of the asthmatic airway. It is not clear whether MC proliferation and activation drive and/or are secondary to the fibrotic process. The latter mechanism could be effected through fibroblast generation of SCF, producing MC proliferation, chemotaxis, and inhibition of apoptosis.

EOSINOPHILS

While eosinophils are considered leukocytes, in actuality, like MC, they reside primarily in the tissues. Indeed, the ratio of tissue to blood eosinophils is estimated to be 100:1 or greater. Under normal circumstances, the major resident population of eosinophils is in the lamina propria of the gastrointestinal tract. Eosinophils are also present in the thymus, as well as the uterus and developing mammary gland in females. In the absence of disease, very few eosinophils are found in the lung. On the other hand, large numbers of eosinophils traffic to the lungs and other tissues in the setting of allergic diseases, helminthic parasite infections and certain other pathological states.

Eosinophil Development

Eosinophils develop in the bone marrow from hematopoietic stem cell precursors. The immediate eosinophil precursor is a common eosinophil-basophil progenitor. Specific differentiation to the eosinophil lineage involves coordinated expression of the transcription factors, GATA-1, PU.1, and C/EBP. Among these, GATA-1 plays a central role, since GATA-1–deficient mice completely lack eosinophils, without loss of other hematopoietic lineages. The cytokines, interleukin-3 (IL-3), granulocyte-macrophage/colony-stimulating factor (GM-CSF) and interleukin-5 (IL-5) stimulate growth and differentiation of eosinophils in the bone marrow. IL-5, the only one of these that is eosinophil-specific, plays an essential role in stimulating bone marrow production of eosinophils and triggering their release into the circulation. IL-5 is produced by lymphocytes and endothelial cells in the bone marrow, as well as by lymphocytes and parenchymal cells in the lung and other tissues. The importance of IL-5 in eosinophil production is demonstrated by the fact that transgenic mice overexpressing IL-5 develop profound blood and tissue eosinophilia. On the other hand, IL-5 knockout mice have markedly reduced numbers of eosinophils at baseline, and fail to develop eosinophilia in response to allergen sensitization and challenge. These and other findings provided the impetus for development of therapeutic anti-IL-5 monoclonal antibodies, which have been studied in asthma, as discussed below.

Morphology and Structure

The mature human eosinophil has a diameter of 12 to 17 μm, slightly larger than the neutrophil. The nucleus is usually bilobed, and the cytoplasm contains characteristic granules that stain yellow-pink with eosin. The distinctive features of eosinophil granules can be seen clearly by electron microscopy (Fig. 21-3). Primary granules, which appear during the promyelocytic stage of development, are round, membrane-limited structures that contain Charcot-Leyden crystal (CLC) protein. Secondary or specific granules appear later during eosinophil differentiation. These are more numerous and appear as oval or elongated membrane-bound structures with a dense crystalline core and less dense matrix. The secondary granule core contains major basic protein, while other granule proteins are in the matrix. Lipid bodies are non–membrane-bound, lipid-rich organelles that localize arachidonic acid-metabolizing enzymes and serve as sites of eicosanoid synthesis.

Granule Proteins

Eosinophils contain a number of cationic granule proteins that have toxic effects on parasitic helminths and RNA viruses, as well as on host cells. In addition, a variety of other proteins, including enzymes and cytokines, are stored in and released from eosinophil granules. Major basic protein (MBP), a highly basic protein that accounts for more than half of eosinophil granule protein mass, is found in the crystalline core of specific granules. MBP is synthesized as a preproprotein, which is cleaved to a 13.8-kD highly cationic molecule during eosinophil maturation. The pro-peptide, which is

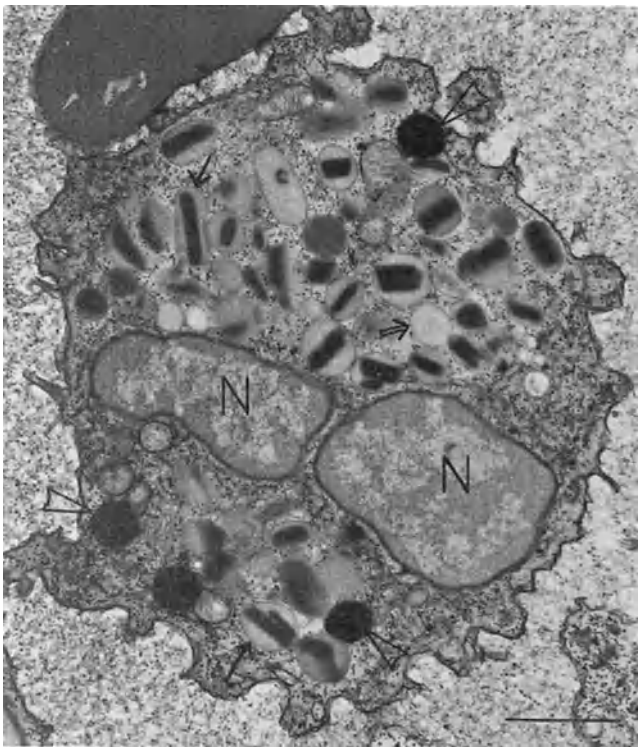

Figure 21-3 Ultrastructure of a mature human blood eosinophil. The bilobed nucleus (N), specific granules (closed arrows), primary granules (open arrow), lipid bodies (open arrowheads), mitochondria, and irregular surface processes are seen. Dark cytoplasmic particles represent glycogen. *(Reproduced with permission from Dvorak AM, Ackerman SJ, Weller PF: Subcellular morphology and biochemistry of eosinophils, in Harris JR (ed),* Blood Cell Biochemistry 2, Megakaryocytes, Platelets, Macrophages, and Eosinophils. *New York, Plenum Press, 1991, p 239.)*

anionic, is thought to protect the developing eosinophil from the toxic effects of the highly cationic mature MBP. Low levels of MBP are expressed in basophils, consistent with their close lineage relationship to eosinophils. MBP is directly toxic to larvae of *Schistosoma mansoni*, *Trichinella spiralis*, and other helminths, supporting a role in host defense against parasites. Several lines of evidence have suggested that MBP could be an important mediator of asthma. MBP inhibits ciliary function and is toxic to bronchial epithelial cells. When administered to the airways of monkeys, MBP caused transient bronchoconstriction followed by persistent bronchial hyperresponsiveness. In addition, MBP was shown to bind to and inhibit M2 muscarinic receptors, increasing vagally mediated bronchoconstriction in guinea pigs. Despite these observations, a critical role for MBP in asthma pathophysiology was thrown into doubt by a recent report that mice deficient in MPB showed no attenuation of airway histopathological changes or airway hyperreactivity in an allergen-induced asthma model.

Eosinophil cationic protein (ECP) and eosinophil-derived neurotoxin (EDN) are both highly basic proteins found in the matrix of specific granules. ECP and EDN are homologous proteins (67 percent amino acid sequence identity), the result of gene duplication, that are also similar to human pancreatic ribonuclease (RNase) A. Indeed, both ECP and EDN are active RNases, with the ability to inactivate RNA viruses, such as respiratory syncytial virus (RSV). EDN was initially described as a neurotoxin that causes severe damage to myelinated neurons, a property possessed by ECP, as well. This activity may account for the neurological abnormalities seen in patients with hypereosinophilic syndrome and CSF eosinophilia. Like MBP, ECP and EDN are both helminthotoxic. Levels of ECP are elevated in blood, bronchoalveolar lavage fluid, and sputum in patients with asthma, and have been found to correlate with disease activity. For this reason, ECP levels in blood or sputum are often monitored in asthma clinical trials as a means of assessing response to treatment.

Eosinophil peroxidase (EPO) is another highly basic protein found in the matrix of specific granules. EPO is a unique peroxidase, expressed only in eosinophils. In the presence of H_2O_2, EPO oxidizes halide ions to form highly reactive hypohalous acids. Bromide is the preferred substrate, leading to hypobromous acid (HOBr), an extremely potent oxidant that damages DNA and other critical cellular targets. EPO plus H_2O_2 and halide ions can kill multiple parasites, bacteria, mycobacteria, and also MC and tumor cells. The potential role of EPO in asthma has been explored in mice with targeted deletion of the EPO gene. In this study, despite a marked reduction in bromo-oxidation of lung proteins, EPO deficiency did not result in any attenuation of allergen-induced airway inflammation or bronchial hyper-responsiveness.

CLC protein localizes to the primary eosinophil granule, and is also expressed in basophils. CLC protein belongs to the galactose-binding lectin family (galectins). Also known as galectin-10, CLC protein avidly binds the sugar mannose. CLC protein also possesses weak lysophospholipase activity. Thus, it may protect cells from potentially toxic lysophospholipids generated at sites of inflammation, or it may degrade surfactant lysophosholipids and contribute to atelectasis. The true role of CLC protein remains to be determined.

Eosinophils also contain within their granules various other enzymes, including β-glucuronidase, arylsulfatase B, and matrix metalloproteinase-9 (MMP-9), as well as preformed cytokines and chemokines, that all can be released in regulated fashion, as discussed further below.

Chemical Mediators

Lipid Mediators

Upon stimulation, eosinophils produce large quantities of the 5-lipoxygenase–derived eicosanoid, LTC_4. Synthesis of LTC_4 in eosinophils occurs in cytoplasmic lipid bodies and at the nuclear membrane. Following secretion, LTC_4 is converted extracellularly to LTD_4 and LTE_4. These cysteinyl leukotrienes act through $cysLT_1$ and $cysLT_2$ receptors to cause bronchoconstriction, stimulate mucus secretion, promote synthesis of Th2 cytokines, and contribute to airway remodeling. The ability to block these effects underlies the beneficial actions of cysLT receptor antagonists and leukotriene synthesis

inhibitors in asthma. Other biologically active lipids produced in substantial quantities by eosinophils include 15-HETE, 5-oxo-ETE, and platelet-activating factor (PAF). However, the roles of these products in asthma and other eosinophil-associated diseases remain unclear.

Cytokines and Chemokines

Classically, eosinophils were considered as terminal effector cells of inflammatory responses, acting by secretion of granule proteins and the acute release of other mediators. More recently, however, it has been recognized that eosinophils synthesize an array of cytokines and chemokines, equipping them to participate in immunoregulation. The major cytokines and chemokines known to be expressed in eosinophils are listed in Table 21-1. Interestingly, a number of these factors have autocrine or paracrine effects on eosinophils themselves. For instance, IL-3, GM-CSF, and IL-5, which may be produced by various cells in the lung and other tissues, and by eosinophils themselves, inhibit apoptosis and enhance eosinophil survival. In another example, IL-16, a product of eosinophils and other cells, triggers rapid eosinophil release of RANTES, which generates autocrine signals that augment release of LTC_4 and IL-4. A number of cytokines and chemokines synthesized eosinophils are stored within granules. When cells are stimulated, these preformed cytokines are released by a regulated process involving piecemeal degranulation, which is described further below.

Eosinophil-derived cytokines likely contribute to regulation of inflammatory responses in eosinophil-associated diseases and may drive specific pathophysiological responses. For example, elaboration of Th2 cytokines would be expected to amplify allergic responses, and may be important in host defense against parasites and in pulmonary fibrosis. TGF-α released by eosinophils is a potent stimulus for synthesis of mucins by airway epithelial cells, which contributes to asthma and other eosinophilic airway diseases. Also, there is accumulating evidence linking eosinophil-derived TGF-β with airway remodeling in asthma and with pulmonary fibrosis. However, a clearer understanding of the roles of eosinophil cytokines in human diseases must await clinical studies with pharmacologic agents designed to target specific cytokines or cytokine receptors.

Reactive Oxygen Metabolites

Like neutrophils, eosinophils synthesize superoxide anion (O_2^-) and H_2O_2 through the action of NADPH oxidase. Notably, NADPH oxidase components are more highly expressed and more readily activated in eosinophils than neutrophils, endowing stimulated eosinophils with a greater capacity to produce O_2^- and H_2O_2. As discussed previously, eosinophils produce HOBr through the action of EPO on bromide and H_2O_2. In a reaction involving HOCl and O_2^-, EPO also catalyzes formation of hydroxyl radical ($OH^\cdot$), the most reactive of all oxygen metabolites. As noted, EPO-derived oxidants kill parasites and other microorganisms, and thus may be important for host defense. By contrast, EPO appears not to play a key role in allergic airway disease in mice. The importance of eosinophil-derived oxidants in human health and disease is at present uncertain, and requires further study.

Eosinophil Recruitment

Current knowledge about the mechanisms of eosinophil recruitment into tissues is based largely on studies of asthma and allergic diseases, but these mechanisms may operate in other eosinophilic disorders as well. The initial step in eosinophil recruitment involves *priming*, which converts the resting cell to an adhesive, migratory and activation-sensitive phenotype. Priming likely results from exposure to IL-3, IL-5, and GM-CSF in the circulation, particularly in allergic individuals, in whom these cytokines are elevated. TNF-α and eotaxin may prime eosinophils as well. Once primed, eosinophils make contact with the blood vessel wall and undergo *rolling*, mediated by E- and P-selectins on endothelial cells, which can be up-regulated by IL-1 and TNF-α, and L-selectin that is constitutively expressed on the eosinophil. Rolling can activate eosinophil integrins, which mediate tight adhesion through high-affinity binding to endothelial cell adhesion molecules. The eosinophil integrins, VLA-4 (α4β1 or CD49d/CD29) and CD11b/CD18, and their respective endothelial counterligands VCAM-1 and ICAM-1, comprise the most important binding pairs responsible for firm adhesion to the vessel wall. IL-4 and IL-13 increase VCAM-1 expression on endothelial cells. Since its binding partner, VLA-4, is expressed on eosinophils, but not neutrophils, this represents a mechanism for selective eosinophil recruitment to sites of allergic inflammation. Integrin-mediated firm adhesion is followed by diapedesis, or transmigration across the endothelium. Eosinophils are further activated by endothelial transmigration, which also increases their ability to survive. Based on in vitro studies, eosinophils can probably survive in tissues for 2 weeks or longer.

Upon entering tissue, eosinophils shift from β_1- to β_2-integrin–dominated interactions under the influence of chemokines such as eotaxin-2, and migrate along chemoattractant gradients. Multiple factors are known to be chemotactic for eosinophils, including PAF, LTB_4, complement factors C3a and C5a, GM-CSF, IL-3, IL-5, IL-16, and the chemokines RANTES, MIP-1α, MCP-3, IL-8, eotaxin, eotaxin-2, and eotaxin-3. Among these, IL-5 and the eotaxins are the most highly selective for eosinophils. For this reason, they have been considered as potential therapeutic targets, and clinical trials of monoclonal antibodies directed against IL-5 in patients with asthma have recently been reported. The results of these studies are discussed below.

Eosinophil Activation and Degranulation

The priming process required for eosinophil recruitment also represents the initial phase of eosinophil activation. IL-5 is probably the most important cytokine for priming of eosinophils in vivo. IL-5 binds to heterodimeric receptors on the eosinophil surface, consisting of a ligand-specific α

chain and common β chain that is also used in the receptors for IL-3 and GM-CSF. Binding of IL-5 to its receptor triggers a variety of intracellular signaling cascades, which enhance multiple eosinophil functions, including the response to chemotactic factors, integrin-mediated adhesion, agonist-stimulated LTC_4 and superoxide generation, phagocytosis, and helminthotoxic activity. IL-3 and GM-CSF are capable of enhancing these functions, as well. As noted earlier, IL-5, IL-3, and GM-CSF also enhance eosinophil survival. The effects of all three cytokines are antagonized by glucocorticoids, which also induce eosinophil apoptosis. Other factors that have been shown to prime eosinophils include TNF-α, nucleotides such as ATP, and chemokines such as eotaxin and RANTES.

Priming of eosinophils in the circulation is enhanced in patients with asthma and hypereosinophilic states, resulting in greater functional responses when blood eosinophils from such individuals are studied in vitro, in comparison to cells from normal controls. In vivo priming has also been demonstrated in eosinophils obtained by bronchoalveolar lavage following antigen instillation into the lungs of allergic subjects (segmental allergen challenge).

Eosinophils express a panoply of surface receptors that can mediate cell activation. These include receptors for immunoglobulins (IgA, IgG, and IgE), complement components (C3a and C5a), eicosanoids (LTB_4, cysteinyl leukotrienes, and PGD_2) and PAF, and numerous cytokines and chemokines. Priming can up-regulate cell surface expression of specific receptors, and may induce new expression of receptors not normally present on resting eosinophils, e.g., the high-affinity IgE receptor FcεRII (CD23). Ligand binding to many of these receptors triggers responses that include degranulation, lipid mediator synthesis, and generation of reactive oxygen species. Various ligands activate distinct signaling cascades within the cell, resulting in stimulus-specific differential activation of eosinophil effector functions.

As in MC, the principal mode by which granule-associated proteins are released from human eosinophils is piecemeal degranulation. This process involves secretion of specific granule contents in discrete packets, without granule-to-granule or granule-to-plasma membrane fusion. An eosinophil undergoing piecemeal degranulation in vitro is illustrated in Fig. 21-4. Electron microscopic studies reveal that piecemeal degranulation is associated with the development of complex vesiculotubular networks within emptying granules. Recent data indicate that intracellular cytokine receptors within granules and secretory vesicles play a key role in transporting and guiding selective secretion of their cognate cytokines. Regulation of these events also involves SNARE family transport docking and vesicle fusion proteins. These mechanisms allow for stimulus-specific, selective, and sequential release of cationic granule proteins, such as MBP and multiple stored cytokines and chemokines.

Besides piecemeal degranulation, the secretion of whole granules, referred to as compound exocytosis, has been described. This process also involves SNARE docking and fusion proteins. Finally, cytolytic degranulation is a term used to account for the presence of cell-free eosinophil granules seen in tissue in certain eosinophilic diseases. Whether this is a regulated process or the result of eosinophil necrosis at sites of inflammation is not known.

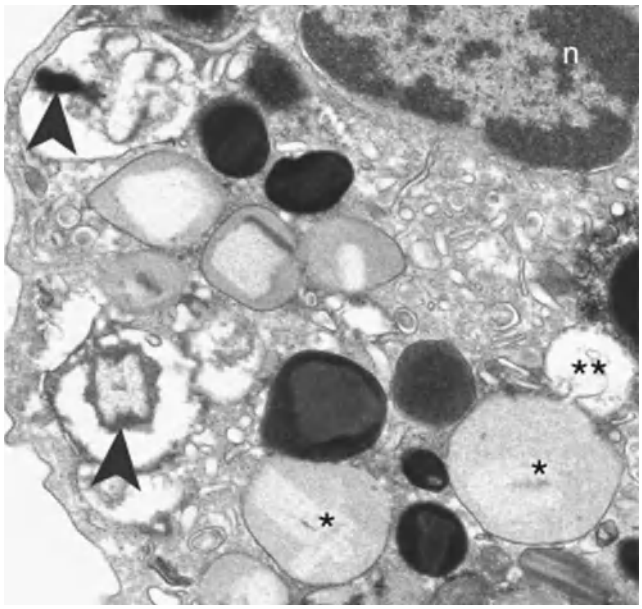

Figure 21-4 Ultrastructure of a human blood eosinophil activated in vitro with eotaxin. Specific granules undergoing piecemeal degranulation exhibit lucent areas in their cores, matrices, or both. Granules with residual cores (arrowheads), reduced internal electron density (*) and membrane empty chambers (**) are shown. *(Reproduced with permission from Melo RCN, Perez SAC, Spencer LA, et al.: Intragranular vesiculotubular compartments are involved in piecemeal degranulation by activated human eosinophils. Traffic 6:866-879, 2005.)*

Mast Cell--Eosinophil Interactions

Since shortly after their discovery, it has been recognized that MC and eosinophils home to many of the same tissues, particularly in the setting of allergic and other inflammatory conditions. Not surprisingly, therefore, researchers have identified a variety of cooperative interactions between the two cell types. For example, the eosinophil granule proteins MBP and ECP can trigger histamine, PGD_2, and cytokine release from human MC. Eosinophils also produce important MC survival and activation factors, such as SCF and nerve growth factor (NGF). Conversely, MC-derived TNF-α induces eosinophil GM-CSF release and autocrine survival enhancement, while MC tryptase induces eosinophil IL-6 and IL-8 secretion. Also, the MC mediators histamine and PGD_2 have been shown to augment synthesis of LTC_4 in human eosinophils. Not all MC-eosinophil interactions are proinflammatory, however, as it has recently been reported that MC tryptase can cleave and inactivate the eosinophil chemokines eotaxin and RANTES. Thus, MC and eosinophils communicate bidirectionally in complex ways that may amplify or potentially modulate the inflammatory response.

Eosinophils and Host Defense

Many years ago, histopathological evidence of eosinophils surrounding dying helminths in tissue biopsy specimens led to the hypothesis that eosinophils play a role in the immune response to multicellular parasites. Subsequently, it was demonstrated that, in the presence of antibodies or complement, eosinophils can kill parasites in vitro, as can purified eosinophil granule proteins. Further support of a role for eosinophils in host defense against helminths came from epidemiological studies that correlated high eosinophil counts with resistance to post-treatment reinfection with *Schistosoma* spp. in humans. Moreover, some recent studies of experimental helminth infections in mice depleted of eosinophils by IL-5 neutralization or gene targeting have indicated that IL-5 and eosinophils are important for protective immunity against a variety of parasites, although the results are not all consistent. Other recent studies of mice deficient in eotaxin or CCR3 (the receptor for eotaxin and related chemokines) have also demonstrated that eosinophils are important for clearance of parasites in vivo. Thus, while some uncertainty remains, substantial evidence supports the concept that eosinophils have a role in protective immunity against helminths and participate in their elimination.

As noted earlier, human ECP and EDN are both RNases, and can inactivate RSV in vitro. Mouse eosinophils also express RNases with the ability to inactivate murine pneumonia virus, a major pathogen in rodents that is closely related to RSV. These observations suggest a role for eosinophils in defense against infection with RNA viruses. In vivo viral infection studies utilizing animals in which eosinophils are pharmacologically or genetically manipulated are needed to further our understanding of this important area.

Recent investigations have demonstrated that eosinophils can process antigen, express major histocompatibility complex II (MHC-II) and co-stimulatory molecules, and function as antigen-presenting cells. Eosinophils within the airway lumen can migrate to regional lymph nodes where they stimulate antigen-specific T-cell proliferation. In addition, eosinophils metabolize tryptophan via the enzyme indoleamine 2,3-dioxygenase to kynurenines, which contribute to Th2 skewing of immune responses by promoting selective apoptosis of Th1 cells. The degree to which these eosinophil immunoregulatory functions contribute to host defense and allergic or hypersensitivity responses is currently unknown.

Eosinophil–Disease Associations

Peripheral blood eosinophilia and eosinophilic lung inflammation are common in a variety of pulmonary conditions, including those listed in Table 21-2. The clinical manifestations and treatment of these disorders are discussed in detail elsewhere in this textbook.

Among eosinophilic lung diseases, asthma is by far the most common and most well studied. Over the years, much evidence has accumulated supporting a key role for eosinophils in asthma pathogenesis. This includes findings that eosinophils and their specific products (e.g., ECP) increase in the airway lumen and airway wall during spontaneous exacerbations and following experimental allergen challenge. Sputum eosinophil numbers and ECP levels also correlate with asthma severity. Eosinophil mediators, including MBP and other granule proteins, induce characteristic features of asthma, such as epithelial damage and bronchial hyperreactivity. When asthma improves, either spontaneously or in response to treatment, eosinophils and their products decline. Corticosteroids, the most effective therapy for asthma, have potent anti-eosinophil effects. Finally, a treatment strategy directed specifically at reducing sputum eosinophils resulted in significantly better asthma control than treatment based on standard asthma guidelines. Despite this large body of evidence, the importance of eosinophils was thrown into question by the finding that treatment of mild asthmatics with an anti–IL-5 monoclonal antibody reduced blood and sputum eosinophils markedly, but did not alter bronchial hyperresponsiveness. However, it was subsequently shown that the anti–IL-5 monoclonal antibody used only depleted eosinophils in bronchial tissue by about 50 percent, indicating that neutralization of IL-5 alone may be insufficient to eliminate eosinophils from the airway. This notwithstanding, the IL-5 antibody did reduce deposition of extracellular matrix proteins in the airways, confirming both a role for eosinophils in airway remodeling and a therapeutic benefit of anti-IL-5 treatment in asthma. Additional new evidence supporting a critical role for eosinophils in allergic airway disease comes from animal studies in which the eosinophil lineage was selectively eliminated using two different genetic strategies. These important studies showed

Table 21-2

Eosinophilic Lung Diseases
Asthma
Allergic bronchopulmonary aspergillosis/mycosis
Allergic angiitis and granulomatosis (Churg-Strauss syndrome)
Simple pulmonary eosinophilia
Chronic eosinophilic pneumonia
Acute eosinophilic pneumonia
Helminthic infections
Drug hypersensitivity reactions
Hypereosinophilic syndrome

that eosinophils were required for airway mucus accumulation, bronchial hyperreactivity, and peribronchiolar collagen deposition in an allergen-induced asthma model in the mouse.

Hypereosinophilic syndrome (HES) is a rare disorder characterized by persistent blood eosinophilia (>1500/μl for at least 6 months) and eosinophil-induced organ damage or dysfunction, without evidence for other known eosinophilic disorders. Pulmonary involvement is seen in 50 percent of cases. Corticosteroids are the first line of treatment for HES. A subset of HES patients bears a fusion gene, *FIP1L1-PGDFRA*, which produces a constitutively active tyrosine kinase that drives eosinophil hyperproliferation. The tyrosine kinase inhibitor, imatinib mesylate (Gleevec®), is useful in treatment of these patients. Others with HES have been reported to respond to anti–IL-5 monoclonal antibodies.

In addition to the disorders listed in Table 21-2, eosinophils may play a role in the pathogenesis of several pulmonary diseases not normally thought of as eosinophilic in origin. Among these is idiopathic pulmonary fibrosis, in which elevated numbers of eosinophils in BAL fluid have been associated with a poor prognosis. This is consistent with in vitro and animal data demonstrating the ability of eosinophils to promote tissue fibrosis. Another example is cystic fibrosis, in which increased levels of cationic eosinophil granule proteins correlate with worse pulmonary function, presumably due to toxic effects of these proteins on lung cells.

Pharmacologic Modulation of Eosinophils

Corticosteroids have been the mainstay of pharmacotherapy for eosinophilic disorders for many years. Corticosteroids induce apoptosis of eosinophils, both directly and by inhibiting formation of the pro-survival cytokines, IL-5, IL-3, and GM-CSF. This leads to rapid reductions of circulating and tissue eosinophils and clinical improvement in the majority of treated patients. Leukotriene receptor antagonists and the anti-IgE monoclonal antibody omalizumab are two other classes of drugs used to treat asthma and allergic diseases that have been shown to reduce circulating eosinophil counts and cause eosinophil apoptosis. Of course, none of the foregoing classes of drugs are specific for eosinophils, so the degree to which their anti-eosinophil activities contribute to their beneficial effects is uncertain. Specific anti-eosinophil therapeutics, such as the anti-IL-5 monoclonal antibodies discussed above, remain investigational at the time of this writing. Other specifically eosinophil-directed agents in development include monoclonal antibodies and small molecule inhibitors of the integrin VLA-4, the selectins, and the chemokine receptor CCR3.

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22

Antibody-Mediated Lung Defenses and Humoral Immunodeficiency

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Immunoglobulin (Ig) plays a key role in both respiratory tract host defense and the pathogenesis of respiratory disease. These unique protein products of B lymphocytes are composed of a highly variable amino acid sequence at the amino terminal end of the molecule that conforms to a broad array of antigens; and a highly conserved carboxy terminus that interacts with other components of the immune system to effect antigen clearance from the body. For that reason, appropriate Ig responses participate in clearance of antigens from the lung and minimize injury responses that are caused by antigen deposition in that tissue. In contrast, inadequate, or inappropriate, Ig responses can allow or even cause life-threatening lung injury. This chapter reviews the development of B cells, which are the cells with the unique capacity to produce antibody; how antibody responses to antigen are generated; some of the physical and functional characteristics of Ig; unique features of pulmonary antibody immunity; and humoral immunodeficiency syndromes relevant to the lung.

OVERVIEW OF B LYMPHOCYTE BIOLOGY

Definition of Antibody

Ig is a member of the Ig superfamily of adhesive proteins. Ig heavy-chain and light-chain genes are present in all cells; however, Ig genes are only expressed in B cells, because only in B cells do the genes undergo a series of structural rearrangements that permit expression of their gene products. B lymphocytes express Ig both as integral cell membrane receptors and as secreted proteins. Production and secretion of Ig by B cells in response to antigen is the hallmark of a humoral immune response. Antibodies are Ig that bind specifically

to stimulating antigen. In vivo antibody production normally results from the combined activation of a number of B-lymphocyte clones that respond and produce antibodies to different antigenic determinants, or epitopes, on the same antigen.

Development of B Lymphocytes in the Bone Marrow

B lymphocytes, like all other circulating leukocytes, derive from a pool of blood-forming stem cells in hematopoietic tissues. Embryonically, committed hematopoietic progenitor cells destined to give rise to B lymphocytes are first detectable at 9 weeks of gestation in the developing liver of humans, deriving from stem cells that first appear in the periaortic splanchnopleure surrounding the heart. B-lymphocyte progenitor cells undergo a temporal migration and subsequently appear in the developing spleen and bone marrow. B-lymphocyte production in postnatal humans resides in the bone marrow and requires continual renewal from hematopoietic stem cells throughout life to maintain immunocompetence. In the marrow, the tempo of B-lymphocyte production is regulated by cytokines produced by hemopoietic stromal cells and extramedullary cytokines that circulate through the marrow spaces. B-cell precursors are retained in the bone marrow in part via the CXCR4 chemokine receptor and the chemokine CXCL12.

The steps involved in the differentiation and commitment of stem cells to form B lymphocytes can be characterized based on the progressive rearrangements of immunoglobulin genes and associated expression of immunoglobulin molecules that occur. Immunoglobulin molecules expressed after differentiation of B cells are made up of two identical protein heavy chains and two identical protein light chains (Igκ or Igλ) that are encoded by separable gene families. Immunoglobulin heavy-chain genes reside on chromosome 14 and immunoglobulin light chains are derived from either the Igκ-locus on chromosome 2 or the Igλ locus on chromosome 22. The unique expression of either κ or λ gene products by an individual B lymphocyte is genetically regulated and known as light chain isotype allelic exclusion.

The initial stages of differentiation of B lymphocytes occur independently of antigen in the bone marrow (Table 22-1). Ig heavy-chain and Ig light-chain transcription in B lymphocytes requires somatic recombination and repair of the germline genetic material that encodes immunoglobulin prior to protein transcription. The variable domain of the heavy chain is encoded in three sets of genes, the variable (V), diversity (D), and junctional (J) genes, which must be physically rearranged to result in expression of Ig heavy-chain protein. Similarly, the variable region of the Ig light-chain protein is encoded in two sets of genes, the V and J genes, which are likewise rearranged to allow transcription of functional

Table 22-1

Overview of B Cell Development*+

	Stem Cell	Early Pro-B Cell	Large Pre-B Cell	Immature B Cell	Mature B Cell	Activated B Cell/ Centrocyte	Plasma Cell
Antigen dependence	I	I	I	D	D	D	D
Location	BM	BM	BM	BM + SLT	BM + SLT	SLT	SLT + BM + periphery
Heavy-chain genes	germline	D-J rearrangement	VDJ rearranged	VDJ rearranged	VDJ rearranged, μ + δ Fc	VDJ rearranged, isotype switch, somatic hypermutation	VDJ rearranged, Isotype switched, secreted forms
Light-chain genes	germline	germline	germline	VJ rearranged	VJ rearranged	VJ rearranged, somatic hypermutation	VJ rearranged, somatic hypermutation
Ig production	none	none	cytoplasmic μ membrane μ	membrane IgM (κ/λ)	membrane IgM, IgD	membrane + secreted (low rate), various isotypes	secreted (high rate), various isotypes

**I-independent; D-dependent; BM-bone marrow; SLT-secondary lymphoid tissue; Ig-immunoglobulin.*

+Adapted from references: Parham P: The Immune System. New York, Garland Science, 2005 and Shearer WT, Fleisher WA: The immune system: an overview, in Adkinson NF, Yunginger JW, Busse WW, Bochner BS, Holgate ST, Simons FER (eds), Middleton's Allergy: Principles and Practice, *Philadelphia, Mosby, 2003.*

protein. The rearrangement of DNA to join V, D, and J heavy-chain exons and V and J light-chain genes (or exons) also results in elimination of unused V, D, and J sequences and noncoding stretches of DNA or introns. The many possible variable regions resulting from these random rearrangements confer a broad range of potential antigen specificities to the mature Ig molecules. Additional diversity results from introduction of additional nucleotides (P and N nucleotides) at the junctions between gene segments during the process of recombination.

Ig V-region genes are located 5′ of constant regions. After successful recombination, rearranged VDJ or VJ variable regions are transcribed in a unit that also includes the constant region of Ig. The constant regions on the nucleotide sequence remain separated from VDJ and VJ segments in the primary transcript of RNA and formation of a mature mRNA transcript requires removal of this noncoding RNA by post-transcriptional RNA processing in the cell. Newly formed B cells are capable of expressing mature mRNA transcripts for both IgM and IgD. This is accomplished by producing a single primary RNA transcript containing both μ and δ constant regions. This initial primary mRNA for immunoglobulin heavy chain is then processed to remove intervening sequences and exons for the entire coding sequence of either μ or δ constant regions. Newly formed B cells initially produce only mature IgM transcripts; however, within 24 hours, coexpression of IgD occurs on individual B cells by this mechanism. Contact with bone marrow stromal cells plays a key role in stimulating B lymphocytes with successful Ig gene rearrangements to survive and divide. Marrow stromal cells produce a set of cytokines that affect the tempo of B lymphocyte production, including interleukin-7 (IL-7), c*kit*-ligand (or stem-cell factor), insulinlike growth factor-1 (IGF-1), and FLT-ligand. IL-7 is the primary proliferative cytokine for developing lymphocyte precursors, and c*kit*-ligand, IGF-1, and FLT-ligand potentiate the effect of IL-7 on these cells. Absence of specific receptors for these cytokines or failure to express B linease specific intracellular signaling molecules like B-cell–specific tyrosine kinase *Btk*, which are activated by cytokine exposure may result in failure of stem cell differentiation into the B-lymphocyte pathway, or failure to appropriately produce (or respond to) IL-7, c*kit*-ligand, or IGF-1 and lead to humoral immunodeficiency.

The process of Ig gene rearrangement is random and generates B cells producing immunoprotective antibodies as well as potentially harmful self-reactive cells and cells without protective value. These B cells must be inactivated or removed. In the bone marrow, immature B cells expressing surface IgM that is self-reactive to cell surface components are removed by induction of programmed cell death, or apoptosis (clonal deletion), and immature B cells expressing IgM that binds soluble self-antigens are rendered unresponsive (clonal inactivation; anergy). B lymphocytes without protective value that are not stimulated by cognate antigen within 1 week die by apoptosis. Anergic B lymphocytes are unable to be stimulated in the periphery, and thus are also rapidly eliminated by apoptosis.

B-Cell Differentiation and Antibody Responses in Secondary Lymphoid Tissues

Newly formed B cells expressing IgM on their cell surfaces exit the marrow and circulate through peripheral secondary lymphoid tissues, such as spleen, lymph nodes, or mucosa-associated lymphoid tissues. Migration to secondary lymphoid tissues is in part mediated by production of the chemokines CCL19, CCL21, and CXCL13 by these tissues. Recirculation of B cells to secondary lymphoid tissues throughout the body increases the chance that relevant B-cell responses are generated wherever foreign antigen penetrates into the body. Unless stimulated in these secondary lymphoid tissues by cognate antigen, recirculating newly formed B cells have a limited life span of only a few weeks. B lymphocytes encountering appropriate antigen in peripheral lymphoid tissues during the responsive period after expression of surface IgM are activated, enlarge, and prepare to enter the cell cycle. However, these activated B cells require additional signals for continued response and cell division.

Most antigens, including proteins, are thymus dependent. To mount antibody responses to thymus dependent antigens, B cells require help from antigen-specific T cells in secondary lymphoid tissues such as lymph nodes. T cells can be activated to provide B-cell help in two ways. Antigen can be presented to T cells in lymph nodes antigen presenting cells (APCs) such as dendritic cells that carry antigen from tissues to draining lymph nodes. Alternatively, B cells serve as APCs, presenting antigen directly to T cells. In either case, antigen is presented in the form of antigen-derived peptides bound to cell surface proteins encoded by major histocompatibility complex (MHC) class II genes. The specific interactions between peptide:MHC class II complexes on an APC and antigen-specific TCRs on a $CD4^+$ T cell trigger the T cell to make membrane and secreted molecules that drive B-cell proliferation and differentiation. One such T-cell surface molecule is CD40-L, which is a member of the TNF family. CD40-L binding to CD40 on the B-cell surface results in intracellular signaling necessary for B cells to enter the cell cycle. This interaction is essential for B-cell responses to thymus dependent antigens, as demonstrated by the effect of absent CD40L function in the X-linked hyper-IgM syndrome. Thus, regardless of the type of APC stimulating T cells, direct contact between T cells and B cells is necessary for effective T-cell help. Interactions between B and T cells also stimulate T cells to secrete a variety of B-cell stimulatory cytokines, such as IL-2, IL-4, IL-5, and IL-6.

During an antibody-mediated immune response, individual B cells alter the isotype of antibody that is produced via a process termed isotype switching, e.g., cells producing IgM and/or IgD switch to producing IgE or one of the IgG or IgA subclasses. Isotype switching involves translocation of the V_HDJ_H gene to a position immediately 5′ to one of the constant gene regions coding for heavy-chain isotypes other than IgM or IgD; 5′ to each heavy chain constant region gene (except the *δ* gene) lie repetitive DNA sequences called *switch regions*. Switching occurs by recombination between the switch

regions, with deletion of intervening DNA and requires the presence of an inducible enzyme, activation-induced cytidine deaminase (AID). In addition to being needed for isotype switching, AID also increases the diversity of antibody V regions through a process termed *somatic hypermutation*. AID deaminates cytosine to uracil in expressed Ig genes. Subsequent DNA repair results in point mutations. Isotype switching occurs during B-cell proliferation and does not occur in nondividing plasma cells. Ability of the same heavy-chain variable gene segment to become associated with different heavy-chain constant gene segments provides a mechanism for use of a single antigen-binding specificity by different Ig heavy-chain classes. No isotype switching occurs in light chains.

Isotype switching is regulated by T lymphocytes and T-cell–derived cytokines. T cells affect isotype switching in B cells both through cell surface interactions, such as those between CD40-L on T cells and CD40 on B cells, and by secreting cytokines. Cytokines alone are not sufficient to induce isotype switching in proliferating B cells but must act in concert with B-cell activators such as LPS, antigen-receptor cross-linkers, or activated T cells. Cytokines appear to act by selectively inducing transcriptional activation of the constant heavy (C_H) genes that encode the Ig class that is subsequently induced. C_H gene activation, in turn, makes switch regions accessible to switch recombinases and induces the enzyme AID. Different cytokines can preferentially induce switching to specific isotypes. For example, in humans, IL-4 and IL-13 are able to promote isotype switching and production of IgE and IgG4; IL-10 may act as switch factor for IgG1 and IgG3 production; gamma-interferon (IFN-γ) supports IgG2 production; and transforming growth factor-beta (TGF-β) induces IgA production.

Because of their differing patterns of cytokine secretion, polarization of the CD4+ T cells providing B-cell help into T-helper 1 (Th1) and T-helper 2 (Th2) phenotypes has a profound impact on isotype switching. For example, Th2 polarization, associated with prominent production of IL-4 and and IL-13, favors class switching to IgE and IgG4. Th1 polarization, associated with IFN-γ production, antagonizes this effect. Because dendritic cells play a key role in regulating Th1/Th2 polarization, they are also important in determining patterns of isotype switching in vivo. Similarly, because NK cells (through secretion of IFN-γ) and NKT cells, eosinophils, and mast cells (through secretion of IL-4) regulate the function of dendritic cells, they also likely play an important role.

Successsful stimulation of B cells by antigen in the secondary lymphoid tissues can lead to several possible outcomes. Some of the activated B cells in lymph nodes and spleen can proliferate and differentiate directly into low-affinity IgM producing plasma cells. Plasma cells are efficient producers and secretors of antibody. Antibody secretion is the result of alternative splicing of the heavy-chain mRNA resulting in expression of a hydrophilic carboxy terminus, rather than the hydrophobic carboxy terminus of membrane-bound immunoglobulin. Other activated B cells migrate into a primary lymphoid follicle to form a germinal center. The chemokine receptor CXCR5 plays an important role in this process. Within the germinal center, somatic hypermutation of variable regions leads to affinity maturation, or the selection of B cells with surface immunoglobulins having the highest affinities for antigen. Both class switching (described above) and somatic hypermutation require the B lymphocyte specific enzyme AID (described above).

Cells that survive the process of affinity maturation can migrate to other sites in the secondary lymphoid tissue and bone marrow and complete their differentiation into plasma cells. Alternatively, they can develop into memory B cells. Memory B cells are long lived. They recirculate through the body in a fashion similar to naive B cells, but require only intermittent stimulation for survival and are much more easily activated by antigen to differentiate into plasma cells and engage in secondary antibody responses that develop more quickly and are stronger than primary antibody responses. Thus, memory B cells can provide enhanced protective immunity when an antigen is re-encountered.

MARGINAL ZONE AND B1 B CELLS

In addition to the conventional "B2" B cells described in the preceding, based on work in rodents, two other populations of B cells are also recognized. Marginal zone B cells and B1 B cells are thought to play important roles in generating antibody responses to T-independent antigens. These are generally nonprotein antigens such as polysaccharides. T-cell involvement is not absolutely required for antibody responses to these antigens.

Marginal zone B cells arise from immature B cells that migrate to the spleen but differentiate differently than conventional B cells. Differentiation into marginal zone B cells is proposed to result from the combination of weak B-cell receptor activation and other signals. This cell population localizes to the marginal zone of the spleen adjacent to B-cell follicles. In humans, marginal zone B cells have been considered particularly important for antibody responses to T-independent type 2 multivalent antigens such as pneumococcal, meningococcal, and *H. influenzae* capsular polysaccharides because the spleen is required for these responses. In addition to splenectomy, age less than 2 years (when the marginal zone is immature and poorly organized in humans) is associated with poor antibody responses to these antigens.

Much of what is known about B1 B-cell subpopulations comes from studies of the immune system of mice. B1 B cells appear to be produced during embryonic development in the fetal liver and omentum and are subsequently maintained throughout life as replicating cells primarily in the peritoneal and pleural cavities, where they are the major B-cell population. In the mouse, B1 B cells express a unique cell surface protein, CD5, but CD5 is not required for their development or function. However, in the past, B1 B cells often were referred to as CD5+ B cells. B1 B cells express little or no IgD. The variable regions of antibodies produced by B1 B cells are less diverse than those of conventional B cells. They tend to produce low affinity antibodies to nonprotein

antigens such as polysaccharides. B1 B cells also appear to play an important role in producing "natural antibodies" that arise spontaneously without prior infection or defined immune exposure (such as hemagglutinins).

IMMUNOGLOBULIN STRUCTURE AND FUNCTION

Immunoglobulins are expressed in five unique heavy-chain isotypes encoded in the immunoglobulin heavy-chain gene complex. Each heavy-chain isotype or class has unique structure and properties (Table 22-2). The basic structure of immunoglobulin is a protein complex composed of two identical immunoglobulin heavy chains and two identical immunoglobulin light chains held together by intrachain disulfide bonds. An immunoglobulin monomer has an approximate molecular weight of 160,000 kD. This immunoglobulin monomer has two antibody binding sites, composed of the amino terminal ends of both heavy and light chains, and a single carboxy-terminal Fc region. (The name derives from the historical observation that it could be crystallized.) By binding to Fc receptors on cells, Ig can confer antigen specificity and can modulate cell function through either activation or inhibition. The Fc region of Ig is also able to interact with other immune system components, such as complement.

IgM

Immunoglobulin M is the first immunoglobulin isotype expressed on newly formed B cells and is expressed as both a cell surface protein and a circulating immunoglobulin making up approximately 10 percent of total plasma Ig. Circulating IgM is a pentamer of IgM molecules, polymerized by a unique B-cell–derived J-chain protein. The approximate molecular weight of pentameric IgM is 960,000.

IgM is the most effective complement-fixing immunoglobulin class and the 10 antigen binding sites on the pentameric form make it a good agglutinating antibody. It is the first antibody to be produced in an immune response. IgM is well suited to bind to and eliminate particulate antigens and microorganisms from the intravascular compartment.

IgD

Immunoglobulin D is expressed primarily as a cell surface receptor, making up less than 1 percent of total plasma immunoglobulin. Although IgD is thought to function in B cell signaling and activation, its unique function remains unknown.

Table 22-2

Structural and Functional Characteristics of Human Immunoglobulin Classes*

	IgM	IgD	IgG1	IgG2	IgG3	IgG4	IgA1	IgA2	IgE
Heavy Chain	μ	δ	γ1	γ2	γ3	γ4	α1	α2	ε
Molecular Wt. (kDa)	970+	184	146	146	165	146	160**	160**	188
Serum Level (mg/ml)	0.5–1.5	0–0.4	5–12	2–6	0.5–1.0	0.2–1.0	0.5–2.0	0–0.2	0–0.002
Half life (days)	10	3	21	20	7	21	6	6	2
Complement Fixation++	+++	–	++	+	+++	–	+/–	+/–	–
FcR Binding++	–	–	+++	+/–	+++	+/–	+	+	+++
Relevant Fc Receptor	–	–	FcγRI, FcγRII, FcγRIII	FcγRI, FcγRII, FcγRIII	FcγRI, FcγRII, FcγRIII	FcγRI, FcγRII, FcγRIII	FcαR	FcαR	FcεRI FcεRII

** Data compiled from references: Li JT: Immunoglobulin structure and function, in Adkinson NF, Yunginger JW, Busse WW, Bochner BS, Holgate ST, Simons FER (eds),* Middleton's Allergy Principles and Practice, *Philadelphia, Mosby, 2003 and Parham P:* The Immune System. *New York, Garland Science, 2005.*

+ Pentameric form.

*** Monomeric form.*

++ Relative importance.

IgG

Immunoglobulin G is the major circulating plasma immunoglobulin class, making up some 70 to 75 percent of total detectable circulating antibody. IgG is also expressed as a cell membrane immunoglobulin, primarily on memory cells. Circulating IgG is found as a monomer of approximately 150,000 molecular weight and in humans can be subdivided into four subclasses each with a unique heavy-chain structure (serum concentrations of IgG1 > IgG2 > IgG3 and IgG4).

Considerable functional differences exist among the four subclasses. For example, differing antigenic stimuli induce differing IgG subclass responses. In general, polysaccharide antigens evoke a predominantly IgG2 response systemically, whereas protein antigens induce IgG1 and IgG3 responses. IgG4 responses appear to evolve with chronic antigen exposure. The subclasses also differ in their ability to fix complement with IgG1 and IgG3 > IgG2 in this respect. IgG4 does not fix complement.

IgG subclasses also differ with regard to ability to bind Fcγ-receptors (FcγRs). Types of FcγRs include FcγRI; FcγRII-A, B1, and B2; and FcγRIII. These receptors are found on many cell types, including neutrophils, monocytes, macrophages (including alveolar macrophages), eosinophils, platelets, NK cells, and other lymphocytes. By binding to Fc receptors, IgG can mediate a number of functions including phagocytosis, endocytosis, antibody-dependent cell cytoxicity, inflammatory cell activation, and release of inflammatory cell mediators. FcγRIII binds IgG1 and IgG3 with equal strength. For the other FcγRs, IgG1 binds most strongly, IgG3 and IgG4 bind with intermediate strength, and IgG2 binds most weakly. FcγRI is the only FcγR capable of binding monomeric IgG with high affinity. It is expressed mainly on mononuclear phagocytes. FcγRIII can also bind monomeric IgG but with moderate affinity. It plays an important role in antibody-dependent cell cytotoxicity mediated by NK cells. FcγRII receptors bind monomeric IgG poorly but do bind IgG in aggregates or immune complexes. FcγRII-B1 and B2 are inhibitory receptors that help control the activation of naïve B cells, mast cells, macrophages, and neutrophils. Their cytoplasmic tails contain immunoreceptor tyrosine-based inhibition motifs (ITIMs), which mediate this inhibitory activity.

Another type of Fc receptor is termed the neonatal Fc receptor (FcRn) or the Brambell receptor (FcRB). FcRn has two roles, to protect IgG from catabolism and engage in IgG transport. In humans, it likely plays an important role in antenatal transport of IgG from mother to young. FcRn is expressed in several human epithelial tissues, including lung, kidney, and intestine. FcRn-mediated transport of IgG across rat alveolar epithelial cell monolayers is fivefold greater in the apical-basal than in the basal-apical direction. Transport via this receptor may be relevant to the human respiratory tract, given that a fusion protein consisting of erythropoietin and the Fc domain of IgG1 administered by aerosol was better able to penetrate the lungs of non-human primates and reach the circulation than was native erythropoietin.

IgA

Humans produce more IgA than any other immunoglobulin class. The major role of IgA is mucosal immunity. Although IgA is a major constituent of external secretions, it constitutes only about 20 percent of plasma immunoglobulin. In humans, 88 percent of circulating IgA is in monomeric form with the remainder in polymeric form. Dimeric IgA polymerized by J chain is the predominant IgA polymer. As compared to circulating IgA, which is mostly monomeric and derived from bone marrow B cells, most IgA in secretions is dimeric, associated with J chain, and derived from mucosal B cells. Two subclasses of IgA exist—IgA1 and IgA2. Circulating IgA and IgA in secretions differ in IgA subclass composition, with the IgA2 subclass constituting a lesser proportion (about 20 percent) of circulating IgA and a greater proportion (approaching 50 percent) of IgA in secretions. Thus, IgA2 may be particularly important for mucosal immunity, especially in view of its resistance to bacterial proteases specific to the hinge region of IgA1 produced by certain pathologic strains of *Streptococcus pneumoniae, Haemophilus influenzae, Neisseria gonorrheae,* and *Neisseria meningitidis.*

Polymeric IgA is actively secreted onto mucosal surfaces by epithelial cells, which express a polymeric immunoglobulin receptor (pIg-R) on their basolateral surfaces (Fig. 22-1). After binding of polymeric IgA to the pIg-R, the IgA-pIg-R complex is endocytosed into intracellular vesicles that transport the complex to the apical (luminal) surface of the epithelial cell. The complex is cleaved with release of the polymeric IgA onto the mucosal surface by exocytosis, still bound to a cleavage fragment of the pIg-R known as secretory component (SC). Polymeric IgA bound to secretory component is termed secretory IgA (sIgA). Binding of secretory component probably prolongs IgA half-life by increasing resistance to proteolysis. sIgA on the mucosal surface is mostly derived from locally produced, not plasma-derived, IgA.

Mucosa-associated lymphoepithelial tissue (MALT), where precursors of IgA-producing cells are generated in response to antigen and T-cell regulation, is a key site for mucosal IgA production. These lymphoid tissues—which include Peyer's patches and other gut-associated lymphoid tissue (GALT), bronchus-associated lymphoid tissue (BALT), and nasal-associated lymphoid tissues (NALT) like the palatine and nasophyaryngeal tonsils—are covered by specialized epithelium facilitating uptake and processing of antigen from the mucosal lumen. They are also supplied with high endothelial venules (HEVs) facilitating entry of circulating lymphocytes from the vasculature.

Factors in MALT such as T cells and cytokines promote development of antigen-specific B cells committed to IgA production. These cells leave MALT and recirculate to mucosal surfaces, where they are subjected to further immunoregulatory signals, causing both local proliferation and terminal differentiation to IgA plasma cells. MALT has been considered

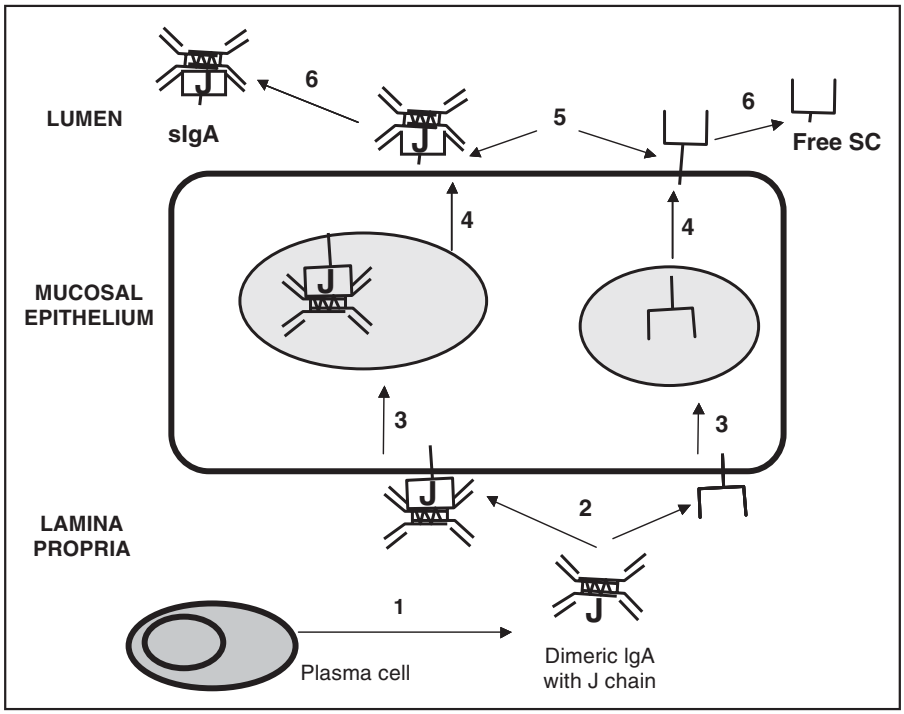

Figure 22-1 Active secretion of secretory IgA (SIgA) and free secretory component (SC) onto mucosal surfaces via the polymeric immunoglobulin receptor (pIgR). An epithelial cell is depicted with the apical surface at the top and basolateral surface at the bottom. *1.* Dimeric IgA (dIgA) is produced by plasma cells in the lamina propria. *2.* Some pIgR molecules on the basolateral surface of the epithelial cell bind dIgA (left) and others do not (right). *3.* The dIgA-pIgR complex (left) and unbound pIgR (right) are packaged into transcytotic vesicles. *4.* Vesicles are transported to the apical epithelial surface. *5.* The extracellular, ligand-binding portion of pIgR is proteolytically cleaved. *6.* SIgA, consisting of dIgA bound to the cleaved, extracellular fragment of pIgR, is released onto the mucosal surface (left); free SC, or the unbound extracellular fragment of pIgR, is also released (right). Diagram is adapted from Kantele A: [Mucosa: The first specific immune defense system in the body]. *Duodecim* 108:2088–2096, 1992. Reproduced with permission from: Pal K: *Regulation of Polymeric Immunoglobulin Receptor by Reovirus Intestinal Epithelial Cells*. Morgantown, WV, West Virginia University (doctoral thesis), 2006.

a key component of the common mucosal immune system, as immunocytes generated in MALT are capable of migrating to distant mucosal surfaces and producing IgA at these sites. For example, immunocytes generated in GALT can migrate to breast and secrete IgA into breast milk. However, recent studies have shown fundamental differences in the patterns of cell adhesion molecules involved in migration of cells to GALT and BALT. Binding of lymphocytes to HEV from BALT is dependent on lymphocyte expression of the integrin $\alpha_4\beta_1$ and HEV expression of VCAM-1. In contrast, binding of lymphocytes to HEV from GALT is dependent on lymphocyte expression of $\alpha_4\beta_7$ and HEV expression of MAdCAM-1. These findings suggest a mechanism for differing migratory patterns of cells generated by respiratory mucosal immune responses from that of cells generated by mucosal immune responses in the gut.

IgA is less able to induce inflammation via Fc interactions than IgM or IgG. One of IgA's key functions is immune exclusion and/or neutralization of bound antigens (Fig. 22-2). An Fc receptor for IgA, FcαR1 (CD89), is expressed on monocytes, macrophages, neutrophils, and eosinophils. It binds monomeric IgA and promotes phagocytosis and killing of IgA-opsonized bacteria.

IgE

Immunoglobulin E (IgE) constitutes only a minuscule fraction of the total antibody in human serum. However, the biologic effects of IgE are not mediated by free antibody, but rather by IgE bound to cell surface receptors. The high-affinity receptor for IgE (FcεRI) binds IgE via its Fc portion and is expressed constitutively by mast cells and basophils and by eosinophils after activation by cytokines. IgE bound to FcεRI is responsible for immediate hypersensitivity reactions such as occur in asthma and allergic rhinitis. Cross-linking of cell surface IgE bound to FcεRI by multivalent antigen triggers degranulation of mast cells and basophils, resulting in rapid release of stored mediators such as histamine. IgE cross-linking also leads to synthesis and secretion of cytokines that subsequently attract and activate inflammatory cells, leading to the "late-phase response." On eosinophils, FcεRI can mediate IgE-dependent killing of parasites.

IgE also binds to a low-affinity receptor, FcεRII (CD23). Unlike other Fc receptors, FcεRII is not a member of the immunoglobulin superfamily. It is found on a broad range of cell types including B cells, activated T cells, monocyte-macrophages (including alveolar macrophages), eosinophils,

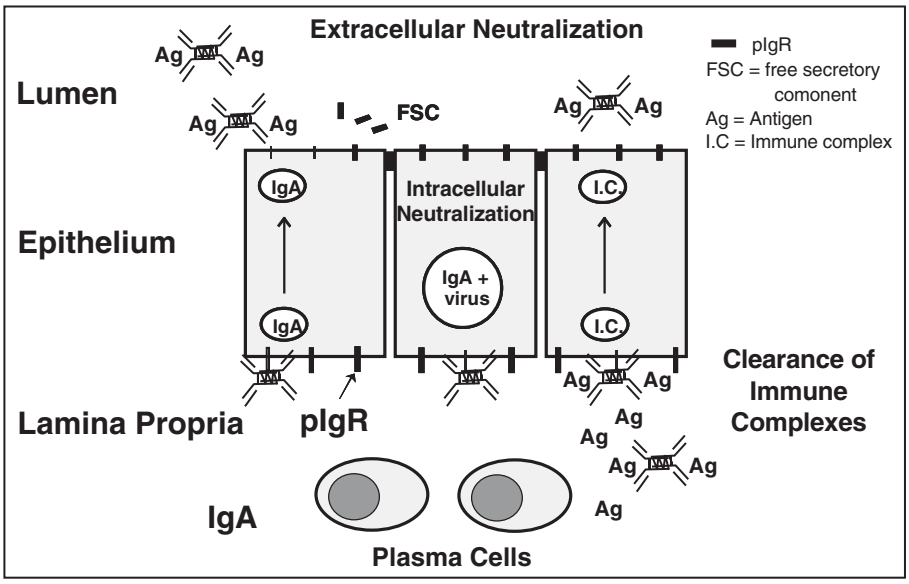

Figure 22-2 Neutralization and removal of antigen by polymeric IgA in both intracellular and extracellular compartments of the mucosa. Epithelial cells are depicted with apical surfaces at the top and basal surfaces at the bottom. *Left cell:* Secretory IgA is secreted into the mucosal lumen, where it binds to microbial pathogens and either neutralizes them or excludes them from the mucosa by preventing them from binding to the mucosal epithelium. *Middle cell:* During transcytosis, the dimeric IgA (dIgA)-polymeric immunoglobulin receptor (pIgR) complex is able to bind and neutralize intracellular pathogens. *Right cell:* Active transport via pIgR removes dIgA-antigen immune complexes from the lamina propria and secretes them into the mucosal lumen. *Diagram is adapted from: Mazanec MB, Nedrud JG, Kaetzel CS, et al.: A three-tiered view of the role of IgA in mucosal defense.* Immunol Today *14:430–435, 1993. Reproduced with permission from Pal K:* Regulation of Polymeric Immunoglobulin Receptor by Reovirus Intestinal Epithelial Cells. Morgantown, WV, West Virginia University (doctoral thesis), 2006.

platelets, follicular dendritic cells, and thymic epithelial cells. FcεRII also has important immunoregulatory functions both with and without IgE binding. Binding of IgE to FcεRII on B cells inhibits IgE synthesis. Murine antigen–induced airways inflammation is negatively regulated by FcεRII and is exacerbated in its absence. Thus, IgE and its receptors mediate a broad range of biologic activities.

ORIGINS AND FATE OF RESPIRATORY TRACT IMMUNOGLOBULINS

There are several sources for respiratory tract Ig. Passive transudation (diffusion) from the vascular compartment across lung tissue is an important source. The rate of transudation is dependent on several factors, including plasma Ig concentration, "resistance" to diffusion, and effective Ig size. Transudation rate may be elevated during increased permeability states such as inflammation.

Another source of respiratory tract Ig is local production by B cells within lung tissue. By far the most active site for Ig production is the bronchial mucosa, although under certain conditions, Ig production also can be demonstrated in other compartments of the lung, such as the parenchymal interstitium and within the airways. After synthesis, Ig reaches airways lumina by either passive diffusion across epithelial barriers or, in the case of polymeric IgA and IgM, by active transport through epithelial cells via the pIg-R.

Assessment as to whether Ig in respiratory secretions are serum derived or locally produced has often been performed by standardizing Ig concentrations to proteins that are purely serum-derived, such as albumin. Using this approach, similar Ig/albumin ratios at both sites are interpreted as evidence for passive transudation of Ig from blood to lung. Increased Ig/albumin ratio in respiratory secretion relative to blood is interpreted as evidence for local antibody production (although active transport of Ig also could result in this finding). A limitation to this approach is that Ig are larger than albumin, so the lung is less permeable to Ig. For this reason, use of Ig/albumin ratios to standardize data may lead to overestimation of Ig proportion derived from serum.

Relative to production, far less is known about the fate of respiratory tract Ig. It is likely that inflammatory conditions associated with increased epithelial permeability and the presence of endogenous and bacterial proteases increase Ig clearance and contribute to pathology.

ANTIGEN-SPECIFIC PULMONARY ANTIBODY RESPONSES

Pulmonary antibody responses have been evaluated in a number of animal species using models based on instillation of antigen into the lower respiratory tract. In general, exposure of the lung to low doses of antigen is not sufficient to induce a primary antibody response, even after repeated antigen

exposures. These low doses of antigen appear to be cleared by nonspecific defense mechanisms, such as mucociliary clearance and nonspecific phagocytosis. Induction of an antibody response requires a dose of antigen sufficient to overwhelm nonspecific clearance mechanisms and induce pulmonary inflammation, leading to translocation of antigen from the lung to the draining lung-associated lymph node (LALN). Dendritic cells play an important role in antigen uptake, transport, and presentation in the LALN. LALN are the primary site for induction of an antibody response to intralobar antigen. Antibody-forming cells (AFCs) generated in LALN are then released into efferent lymphatics and blood. AFC reach the lung parenchyma from blood. Nonspecific pulmonary inflammation promotes recruitment of AFC from blood to lung, regardless of antigen specificity or lymph node of origin. Findings in humans are consistent with this sequence of events.

In addition to recruiting AFC to the lung, localized antigen exposure leads to recruitment and/or production of immune memory cells only in the immunized lung lobe. These cells are able to function locally and manifest their presence in several ways. First, they confer the ability on immunized and challenged lung to mount AFC and antibody responses to far lower doses of antigen than can induce these responses in previously unimmunized lung lobes. Second, after local challenge with a given dose of antigen, they allow previously immunized and challenged lung lobes to mount AFC responses of markedly greater magnitude than occur after antigen instillation in previously unimmunized lobes. Finally, in the dog model, B cells recruited to and/or produced in the lung interstitium are able to produce antibody for years after localized immunization and challenge. Thus, primary antibody responses induced in the lung by intrapulmonary deposition of antigen are mediated by B cells recruited from regional lymph nodes via the circulation. Subsequent local antigen exposure can result in antibody responses that are compartmentalized within the lung and mediated by memory cells recruited to and/or produced in the pulmonary interstitium.

Recent work in mice has shown that BALT is also a site in which T-cell, B-cell, and antibody responses to antigen can be generated. Mice lacking spleens, lymph nodes, and Peyer's patches formed inducible BALT (iBALT) in response to infection with intranasal influenza virus. iBALT contained structures necessary to mount immune responses, including B-cell follicles centered around networks of follicular dendritic cells and interfollicular regions containing dendritic cells and T cells. iBALT was also equipped with HEV, a key structure through which immune cells migrate from the circulation. iBALT was the site of vigorous T- and B-cell responses to influenza, including specific IgG responses. These responses were protective and cleared infection. Thus, iBALT is an inducible lymphoid tissue that can generate local pulmonary immune responses independently of conventional draining LALN. iBALT may represent an adaptive local pulmonary response to antigen overload, such as in COPD, in which progression of COPD is strongly associated with percentage of airways with lymphoid aggregates containing follicles.

IMMUNOGLOBULIN MEASUREMENT IN THE HUMAN LUNG

Immunoglobulins are prominent protein constituents of normal respiratory secretions, with IgG, IgM, and IgA accounting for approximately 20 percent of total protein in bronchoalveolar lavage (BAL) fluids. IgG and IgA are the Ig present in greatest concentrations, with the relative content of IgA progressively decreasing and IgG progressively increasing as one moves from oral cavity to alveolus. In canines, saliva IgA concentrations exceed IgG concentrations, whereas in tracheal and bronchial washings IgG concentrations exceed those of IgA (with higher proportions of IgA in the more proximal tracheal washings). Similarly, in humans the ratio (by weight) of IgG to IgA in nasal washings has been reported at about 1:3 as compared to 2.5:1 in lung lavage obtained via a bronchography catheter. Thus, the relative contribution of IgA to respiratory tract host defense appears greater proximally than distally; the reverse is true for IgG.

Because of ease of sample collection, most measurements of Ig levels in the human lung have been performed using BAL fluid. Bronchoalveolar lavage samples both conducting airways and the alveolar surface. Levels of IgG, IgM, and IgA have been reported in a large multicenter study that used a standardized BAL technique to collect samples. In 76 never-smokers, mean BAL IgG, IgA, and IgM concentrations were 5.9, 6.2, and 0.2 μg/ml, respectively. Current smoking significantly increased mean BAL IgG and IgM concentrations to 10.2 and 0.23 μg/ml, respectively (62 subjects studied). Mean BAL IgA concentrations were unaffected by smoking (5.9 μg/ml).

Data were also presented for serum and BAL Ig/albumin ratios for all 184 subjects studied (including an ex-smoker group). Mean IgG/albumin and IgM/albumin ratios were significantly lower in BAL than in serum, suggesting that these Ig were largely serum derived. In contrast, mean IgA/albumin ratios documented were significantly greater in BAL than in serum, suggesting that a significant proportion of BAL IgA was locally produced.

Respiratory Tract IgA

As noted, BAL data support local production and active secretion of total IgA into the human respiratory tract. The various forms of IgA also have been evaluated in human BAL. With regard to relative proportions of monomeric and polymeric forms, approximately 84 percent of BAL IgA is polymeric sIgA. With regard to IgA subclass levels, IgA2 constitutes 10 to 20 percent of total IgA in blood and about 30 percent of total IgA in BAL. Free secretory component also can be recovered by BAL. SC recovery ranges from less than 25 to 500 μg per BAL. Of interest is that SC recovery is markedly decreased in about 20 percent of smokers, perhaps as a result of epithelial dysfunction.

Immunohistologic studies have documented sites of IgA production and secretion in the human lung.

IgA-producing plasma cells are most abundant in the glands and lamina propria of the major bronchi but also are found in small bronchi, bronchioles, and alveolar septa. The proportion of IgA plasma cells producing IgA2 is somewhat greater in bronchial mucosa (26 to 33 percent) than in bone marrow or peripheral lymph node (10 to 20 percent), but less than in large bowel mucosa (about 60 percent). As staining for SC is also most intense in the bronchial glands (in glandular epithelial cells), bronchial glands appear to be particularly important sites for production and transepithelial secretion of IgA. SC and IgA associated with J chain also have been demonstrated in bronchiolar nonciliated epithelium and type II alveolar cells, so IgA production and secretion also appears to occur at other sites, including the lower respiratory tract.

Respiratory Tract IgG

As noted, respiratory tract IgG is serum derived to a far greater extent than is IgA. However, some variation in the level of local production has been noted among the IgG subclasses. All IgG subclasses have been identified in human BAL. In healthy nonsmokers, the various subclasses constitute the following percentages of BAL IgG: IgG1, 65 percent; IgG2, 28 percent; IgG3, 1.8 percent; and IgG4, 1.3 percent. Based on albumin ratios, IgG1 and IgG2 appear to reach the airways lumen primarily by passive transudation, IgG4 originates to a significant degree from local antibody production, and demonstrable local IgG3 production occurs only in some individuals. Smoking is associated with increased levels of IgG1 in both serum and lavage and evidence for increased local production of IgG3 (based on BAL and serum IgG3/albumin ratios).

Using immunostaining techniques, IgG-producing cells have been identified in human bronchial mucosa and are present in relatively greater proportions than at other mucosal surfaces, such as the intestine. Unlike IgA-producing cells, IgG-producing cells in bronchial mucosa do not localize to glandular areas.

In contrast to IgA, whose main role is immune exclusion, the main role of respiratory tract IgG appears to be immune elimination of foreign antigens penetrating the respiratory mucosal barrier. Immune elimination is facilitated by interactions with Fc receptors on inflammatory cells such as neutrophils, monocytes, macrophages, and NK cells, as well as interactions with soluble factors such as the complement system.

Respiratory Tract IgE

IgE appears to be locally produced in the human respiratory tract. In healthy nonsmokers, mean BAL IgE concentrations have been reported to be 9.1 ng/ml, with mean IgE/albumin ratios significantly greater in BAL than in serum, suggesting local IgE production. Healthy smokers' mean BAL IgE concentrations appeared elevated at 14.0 ng/ml, but the study lacked sufficient power to document statistical significance. Based on albumin ratios, IgE production also appeared to be occurring in the lungs of smokers.

IgE bound to histamine-containing cells can also be identified in the human lung by BAL. Over 95 percent of such cells obtained during the late-phase response to segmental challenge with antigen are basophils.

PATHOLOGY INDUCED BY RESPIRATORY TRACT IMMUNOGLOBULIN

The Gell and Coombs classification system is dated, but still useful. It classifies immune-mediated tissue injury into four types. Types I to III are antibody mediated and type IV is cell mediated. Type I, or allergic, responses are mediated by IgE. Types II and III responses are usually mediated by IgG or IgM, with activation of either complement-mediated or phagocytic effector mechanisms. Type II responses are the result of antibodies directed against cell surface– or matrix-associated antigen. Type III responses are directed against soluble antigens with tissue damage caused by responses to immune complexes. All three types of tissue injury can occur in the lungs and respiratory tract.

A common pulmonary disease associated with type I injury is atopic asthma, in which IgE plays a prominent role. An example of a disease causing type II injury is Goodpasture's syndrome in which autoantibodies against basement membrane collagen type IV activate complement and recruit inflammatory cells, leading to necrotizing hemhorragic interstitial pneumonitis. Type III injury mediated by immune complexes may contribute to the pathogenesis of hypersensitivity pneumonitis.

Elevated BAL Ig levels are noted in a variety of pulmonary diseases, including interstitial diseases such as hypersensitivity pneumonitis, idiopathic pulmonary fibrosis, and sarcoidosis as well as acquired immunodeficiency syndrome (AIDS). It is often unclear whether increased Ig levels are of pathogenic importance or simply a marker of some other underlying disease process. For example, BAL IgG2/IgG1 ratio of greater than 1 in lung allograft BAL fluid has been proposed as a biomarker to assess for underlying Th1 (and IFN-γ)-mediated lung allograft rejection after lung transplantation.

HUMORAL IMMUNODEFICIENCY AND THE LUNG

The respiratory tract is profoundly affected by systemic humoral immunodeficiency. Patients with defects in the B-lymphocyte (humoral) system have a tendency to develop sinopulmonary infections such as otitis media, sinusitis, bronchitis, and pneumonia as well as complications of recurrent bacteremia such as sepsis or meningitis. Encapsulated bacteria such as *S. pneumoniae, H. influenzae,* and *N. meningitidis* or, less commonly, gram-negative bacteria are often

the etiologic organisms. Recurrent infection often leads to chronic disease such as bronchiectasis as well as respiratory dysfunction.

Humoral immune deficiencies can vary from a complete failure of B-cell development, such as Bruton's agammaglobulinemia, to relatively mild conditions, such as selective IgG subclass deficiency. A number of molecular defects associated with B-cell deficiency have been described. These B-cell deficiencies are characterized by either a decreased ability to produce all or some immunoglobulin classes or a diminished ability to make an antigen-specific antibody response. Failure of antibody function results in recurrent infection and is the primary indication for antibody replacement with intravenous immunoglobulin. Almost all of the original descriptions of primary B-cell deficiencies were in children. However, over the last decade, people 18 years of age and older constituted an increasing percentage of those identified with primary immunodeficiency diseases.

Bruton's Agammaglobulinemia

Bruton's agammaglobulinemia or X-linked hypogammaglobulinemia was the first immunodeficiency disease described. It is an X-linked disorder caused by a wide variety of mutations in the gene of the B-cell–specific tyrosine kinase *Btk*. In this disorder, affected infants are relatively infection free for the first 6 to 9 months of life as a result of transplacental IgG. They then develop recurrent chronic middle ear, sinus, and pulmonary infections. Sepsis, meningitis, septic arthritis, osteomyelitis, pyoderma, and encephalitis may occur also. Gastrointestinal infections and malabsorption may develop. Occasionally, viruses such as echoviruses have caused a progressive, fatal neurological infection in these patients. Prior to antibiotics and immunoglobulin replacement, few patients survived past infancy.

IgG levels are usually below 200 mg/dl, and IgM, IgA, IgD, and IgE levels are extremely low or absent. There is a complete inability to make antigen-specific antibody to protein and polysaccharide antigens after stimulation. Pre-B cells are present in the bone marrow, but B lymphocytes bearing surface immunoglobulin are almost completely absent from the circulation. Lymph nodes without germinal centers and hypoplastic adenoids and tonsils are found due to the lack of B cells. Immunity involving T lymphocytes is completely intact.

Prior to diagnosis, multiple or recurrent pulmonary infections may occur because of *S. pneumoniae, H. influenzae, N. meningitidis,* and *Staphylococcus aureus.* This leads to the development of bronchiectasis. Even after diagnosis and the institution of antibody replacement with intravenous immunoglobulin (IVIG), chronic sinopulmonary disease may continue and worsen due to the inability to replace mucosal IgA. Delay in diagnosis and treatment with IVIG results in severe chronic pulmonary disease. In one study, approximately 75 percent of patients over 20 years of age had chronic lung disease, either obstructive disease or mixed obstructive and restrictive disease. Most of these older patients had received intramuscular immunoglobulin, which results in lower serum IgG levels. High doses of IVIG in the range of 400 mg/kg given every 3 weeks, leading to serum trough IgG levels of around 500 mg/dl, are associated with decreased infections, especially pneumonias. With early diagnosis and appropriate treatment, many of these patients now reach adulthood.

Common Variable Immunodeficiency

Common variable immunodeficiency (CVID) presents with hypogammaglobulinemia, decreased antigen-specific antibody function and increased recurrent infections. Patients with CVID are heterogeneous. Although most cases are sporadic and of unknown etiology, several different genetic defects have been reported as capable of causing this disorder. Unlike X-linked agammaglobulinemia, some ability to develop a functional antibody response is present. In addition, tonsils, adenoids, and lymph nodes are usually enlarged and splenomegaly is generally present. Cellular immune defects, such as a decreased CD4/CD8 ratio may be present. CVID generally has a later onset than Bruton's agammaglobulinemia and occurs in either sex. There is a marked predisposition to autoimmune disease, malignancy, and gastrointestinal malabsorption. The gastrointestinal manifestations of CVID are variable and tend to mimic known diseases, such as celiac sprue, pernicious anemia, and inflammatory bowel disease. There is a high prevalence of inflammatory, malignant, and infectious gastrointestinal disorders in patients with CVID.

Patients with CVID tend to develop chronic and recurrent otitis media, sinusitis, and pneumonia due to *S. pneumoniae, H. influenzae,* and *S. aureus.* Recurrent pulmonary infections with *Mycoplasma pneumoniae* are frequently seen. Due to the cellular immunologic abnormalities observed in these patients, infections with fungi, mycobacteria, and *Pneumocystis carinii* are possible. Bronchiectasis and pulmonary compromise are common sequelae in these patients. Of 47 patients with CVID, 42 patients had respiratory complications, 32 had bronchiectasis, seven had asthma, nine had recurrent chest infections without concomitant evidence of structural lung damage, and two granulomatous lung disease. There was a median 4-year delay between the first symptoms of the disease and diagnosis. Many of the patients were followed for chronic lung disease for a period of years before their underlying immune abnormalities were discovered.

Patients with common variable immune deficiency exhibit a variety of immune abnormalities; IgG levels are generally below 300 mg/dl. IgA and IgM levels are usually low. Antibody responses to specific antigens such as tetanus toxoid, pneumococcal vaccine, or the neoantigen bacteriophage øX 174 are diminished or absent. Peripheral B-cell numbers are usually normal but may be decreased. Lymphocytes do not differentiate into immunoglobulin-producing plasma cells in vivo and in vitro. B-cell activators such as pokeweed mitogen are also incapable of stimulating immunoglobulin production. Standard in vitro proliferation assays for mitogens and

antigens are abnormal in about 50 percent of patients with CVID. Thus, CVID is felt to result from an arrest in the terminal differentiation of B cells that prevents them from evolving into normal Ig-producing cells. This can either be secondary to defects in T-cell help or due to intrinsic defects in the B cell itself.

The most important aspect of therapy for patients with CVID is antibody replacement with intravenous immunoglobulin. Most patients are started on a dose of 400 mg/kg given once per month and show considerable improvement on these doses. Those patients with increased frequency of infection usually have the dose increased or the interval between doses decreased. There is evidence that patients with CVID and chronic lung disease respond to considerably higher doses of IVIG, in the range of 600 to 800 mg/kg. Chronic pulmonary infections may require long-term treatment with oral broad-spectrum antibiotics in addition to IVIG. Those patients with evidence of T-cell dysfunction are at risk of developing a wider variety of pulmonary infections, and appropriate investigations for *P. carinii,* mycobacteria, viruses, and fungi should be instituted in those patients when appropriate.

IgA Deficiency

IgA deficiency is a relatively common disorder, with the prevalence estimated to be between 1/300 to 1/2000. It is usually defined as an IgA level of less than 5 mg/dl, which is 1 to 3 percent of the normal age-adjusted levels. There is an increased incidence of IgA deficiency in first-degree relatives as well as evidence that it occurs more commonly in relatives of patients with common variable immunodeficiency.

The ability to produce Ig isotypes other than IgA is usually intact, as is the ability to produce antigen-specific antibody. Occasionally, IgA deficiency is associated with a deficiency of one or more IgG subclasses. When this happens, inability to make antigen-specific antibody may occur.

Infections of the sinopulmonary tract and gastrointestinal tract are usually due to encapsulated bacterial organisms rather than opportunistic infections. These infections are similar to CVID but with a greatly decreased frequency and severity. Patients with extremely low IgA levels combined with IgG subclass deficiencies tend to have more severe infections. Although recurrent pneumonias, bronchiectasis, chronic obstructive lung disease, and chronic bronchitis all have been described in patients with IgA deficiency, these clearly do not occur as often as in disorders associated with antigen-specific antibody deficiencies. IgE-mediated allergy is strongly associated with IgA deficiency, and allergic asthma occurs frequently in these patients. The asthma in these patients can be quite severe and difficult to manage. Gastrointestinal problems are also similar to CVID, with an increased risk of giardiasis, nodular lymphoid hyperplasia, and celiac disease. Malignancies, especially B-cell lymphoma, occur at a higher rate in IgA-deficient patients.

For patients with selective IgA deficiency, there is no specific therapy. Rapid identification of bacterial infections and prompt antibiotic therapy is usually all that is required. Prophylactic antibiotics may be of value in those patients with recurrent bronchitis or sinusitis. Asthma in these patients can be treated in the usual manner, although they are often resistant to therapy, and aggressive use of inhaled steroids and oral corticosteroids may be required. Those patients with both IgA deficiency and IgG subclass deficiency with a functional antibody defect can be cautiously treated with IVIG. Immunoglobulin replacement is complicated in these patients because of the possibility of IgA-deficient patients making anti-IgA antibodies capable of causing an anaphylactic reaction. Use of an IgA-depleted IVIG in these patients may be helpful in decreasing these reactions. For the same reasons, anaphylactic reactions to blood transfusions may occur, and anti-IgA antibody titers should be checked prior to the administration of any blood product. If anti-IgA antibody is detected, the red blood cells should be washed with saline to remove IgA.

IgG Subclass Deficiency

Clinical presentation of the IgG subclass deficiencies depends upon the subclass or subclasses involved. Measurement of serum concentrations of antibodies to specific bacterial antigens, such as *Haemophilus influenzae* type B, *pneumococcus*, *tetanus,* and *diphtheria* must be used in conjunction with IgG subclass levels to identify individuals at increased risk of infection and actual immune deficiency. Deficiency of IgG1 is associated with lifelong increased susceptibility to pyogenic infection and progressive deteriorating lung disease. It is commonly linked with deficiency of IgG2 and IgG3 and many consider it to be a form of CVID, particularly if the total IgG level is low. Most patients with IgG2 deficiency have normal total IgG levels and even elevated IgG1 and IgG3 levels. These patients tend to have difficulty making antibody to polysaccharide antigens. They tend to have infections with encapsulated organisms and will develop sinusitis, otitis media, and pneumonias leading to chronic lung disease or recurrent meningitis. IgG2 subclass deficiency may be associated with IgA deficiency, and these patients tend to have more severe lung disease than those with either deficiency alone. Patients with IgG3 deficiency tend to develop recurrent respiratory infections, and some have been reported with chronic lung disease. Defining IgG4 deficiency is problematic since 20 to 30 percent of the general population, have levels that are undetectable using standard techniques. Patients defined as absolutely IgG4-deficient using the most sensitive techniques (less than 0.005 mg/dl) have been reported with recurrent pulmonary infections and bronchiectasis.

It is important to realize that individuals exist who are completely healthy yet have one or more IgG subclasses missing. Before a diagnosis of IgG subclass deficiency is made, a thorough evaluation of the patient's ability to make a specific antibody response to tetanus toxoid and the pneumococcal vaccine must be pursued. Response to IVIG is good in those patients with a defect in specific antibody production.

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CHAPTER 23

Cytokines and Chemokines in Lung Inflammation and Injury

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The cascade of events that dictate the initiation, maintenance, and resolution of pulmonary inflammation are usually the consequence of the host responding to direct and indirect insults. Infection, trauma, ischemia/reperfusion injury, and autoimmune disease are examples of clinically important insults that produce lung injury associated with inflammatory cell infiltration. These inflammatory responses involve coordinated interactions of specific signals that dictate the evolution of the inflammatory process. The signals, which are generated as the inflammatory response evolves, serve as important communication networks between the different cellular components of the local response. A variety of mediators are involved in the coordination of these networks. These include nucleotides, reactive oxygen and nitrogen intermediates, lipids, peptides, and polypeptides. This latter group of inflammatory agents comprises a large number of mediators collectively identified as *cytokines*. These polypeptide mediators are known to play key roles in a spectrum of pulmonary diseases.

Cytokines are soluble, hormonelike proteins produced by a variety of cells. It is now clear that the cellular source and biologic targets of these polypeptides are not restricted to cells of the immune system, since endothelial cells, stromal cells, and epithelial cells are all capable of both producing and responding to a number of different cytokines. An area of increasing importance in cytokine biology is the ability of nonimmune cells to participate as effector cells in the perpetuation of an inflammatory response by producing cytokines. This is particularly true in the lung, as pulmonary epithelial cells and stromal cells produce both proinflammatory and immunoregulatory cytokines under specific conditions.

Cytokines have a wide range of concentration-dependent physiological activities, but they are most distinguished for their activities associated with inflammation, immune reactivity, tissue injury, and potential loss of organ function. The broad scope of biologic activities of cytokines is fundamental to their ability to participate in various aspects of inflammation. For example, specific cytokines are known to initiate inflammation via the activities of early response cytokines, such as interleukin-1 (IL-1) and tumor necrosis factor (TNF), regulate inflammation through the effects of interleukin-10, and repair tissue injury through the activities of transforming growth factor-beta. These mediators are only representative of the many cytokines that participate in different facets of the evolving pulmonary response.

EARLY-RESPONSE CYTOKINES AND THE INITIATION OF PULMONARY INFLAMMATION

Cytokines are important communication links to initiate, maintain, and resolve the inflammatory response. The cytokines that are involved in the innate immune response of the lung are not constitutively expressed, and must be called into play by specific signals that alert the host to invading microorganisms or early triggering events. Evolution has provided the mammalian host with two major forms of host defense: the innate and the adaptive immune responses. The innate defense is the gatekeeper for immediate host defense against invading microorganisms and has been predetermined to recognize microorganism-associated molecular patterns. The adaptive immune response is naïve, delayed in development, and depends on two classes of specialized lymphocytes, T and B cells, which respond to antigen presentation by professional antigen-presenting cells (i.e., dendritic cells).

Microorganisms express highly conserved molecular patterns that are unique and distinguish themselves from the host. The host has evolved specific pattern recognition receptors to detect these pathogen-associated molecules. The mammalian Toll-like receptors (TLR) are important signaling receptors in innate host defense, and have evolved from the *Drosophila* Toll gene. Both toll and mammalian TLRs share similar signal-transduction pathways that ultimately involve the nuclear factor-κB (NF-κB) family of transcriptional factors. NF-κB plays an important role in the transactivation of a number of cytokines that are involved in the innate immune response and development of pulmonary inflammation.

While TLRs and the innate immune response are necessary to sense and initiate the host response to microorganism molecular patterns, cytokines are necessary for the full development of the innate host defense and the promotion of acute pulmonary inflammation. Early response cytokines are cytokines that are activated initially after TLR signal coupling. Two of the most important early response cytokines in innate immunity and acute pulmonary inflammation are IL-1 and TNFα. Almost all cells in the body possess functional receptor for IL-1 and TNF, suggesting that these cytokines are important in local and systemic cell communication.

Interleukin-1 Family of Cytokines

The interleukin-1 family of cytokines consists of two agonists, IL-1α and IL-1β, and one antagonist, interleukin-1 receptor antagonist (IL-1Ra). These two forms of IL-1 are distinguished by whether they are found predominantly membrane associated (IL-1α) or secreted (IL-1β). IL-1Ra is the only known naturally occurring cytokine with specific antagonistic activity. IL-1Ra acts as a pure antagonist of either IL-1α or IL-1β and can attenuate a variety of IL-1 actions, which may play a role in the resolution of the pulmonary inflammatory cascade.

IL-1 and IL-1Ra have been implicated in the pathogenesis of a variety of lung diseases, including bronchial asthma, acute respiratory distress syndrome (ARDS), panbronchiolitis, and pulmonary fibrosis. In ARDS, low levels of the anti-inflammatory cytokines, IL-10 and IL-1Ra, in the BAL of patients with early disease correlated with a poor prognosis. Intratracheal injection of LPS, IL-1, or TNF has similar effects with an intra-alveolar inflammatory response composed predominantly of neutrophils, followed later by mononuclear cells. In addition, LPS is capable of inducing both TNF and IL-1 gene expression in the lung, which is important for its effect in amplifying the inflammatory response. In contrast, IL-1ra reduces the inflammatory response to LPS in the lungs.

Chronic imbalance between IL-1β and IL-1ra may result in the propagation of an overexuberant reparative and fibrotic phase. Inhibition of IL-1–dependent collagenases may manifest as a lack of reabsorption of excessive collagen, and the failure to repair the matrix. IL-1ra levels from lung tissue homogenates of patients with idiopathic pulmonary fibrosis (IPF) may directly correlate with mortality. Similarly, IL-1ra is elevated in lung transplant patients with obliterative bronchiolitis and correlates with the development of obliterative bronchiolitis. Further support for the role of IL-1ra in the development of fibrosis is seen in the report of a polymorphism in the IL-1Ra gene that is associated with increased risk of development of IPF.

Tumor Necrosis Factor-alpha

Tumor necrosis factor (TNF) is produced primarily by monocytes/macrophages, and has many overlapping biologic activities with IL-1. Elevated levels of TNF have been implicated in the pathogenesis of a number of disease states, including septic shock/sepsis syndrome, ARDS, hepatic ischemia/reperfusion injury, graft vs. host disease, and heart, kidney, liver, and lung allograft rejection. TNF exhibits a variety of inflammatory effects, including induction of neutrophil- and mononuclear cell–endothelial cell adhesion and transendothelial migration; enhancement of a procoagulant environment; and acting as an early response cytokine in the promotion of a cytokine cascade.

Although the pathogenesis of septic shock and the development of acute lung injury are multifactorial, the role of TNF and IL-1 in mediating septic shock and ARDS has been clearly demonstrated. Serum levels of both TNF and IL-1 correlate with mortality in meningococcal septicemia. The ratio of TNF to IL-10 in BAL fluid is significantly higher in ARDS patients than at-risk patients. Administration of TNF to animals induces similar pathophysiological effects to either endotoxin or infusion of live gram-negative bacteria. Based on these studies, there was considerable enthusiasm for the inhibition of TNF in sepsis. However, inhibition of TNF in humans with sepsis has been disappointing, although there may be subgroups of patients that derive benefit.

TNF has an important role in the development of pulmonary fibrosis. (For further discussion of pulmonary fibrosis, see Chapter 26.) TNF levels are paralleled by the increase in the gene expression of TGF-β and precede the gene expression of both types I and III procollagen in the murine bleomycin model. Inhibition of the biologic effect of TNF attenuates fibrosis in animal models. In mice, transgenic expression of TNF in the lungs leads to a predominant lymphocytic alveolitis and the pathology of the lung demonstrates a continuum of inflammation to fibrosis demonstrating many features of UIP (usual interstitial pneumonia). These studies support the notion that TNF may be an important cytokine in the pathogenesis of pulmonary fibrosis; however, its role may be variable in different situations.

TYPE I AND TYPE II CYTOKINES

Type I (Th_1) cytokines, which include IFN-γ, IL-2, and IL-12, appear to be involved in cell-mediated immunity associated with autoimmune disorders and allograft rejection. Type II (Th_2) cytokines, which include IL-4, IL-5, IL-10, and IL-13, are predominantly involved in mediating allergic inflammation and chronic fibroproliferative disorders, such as asthma, atopic dermatitis, IPF, and systemic sclerosis. Therefore, it is reasonable to define certain diseases in terms of the predominant cytokine profile that is present (i.e., type I or II cytokine type) (Fig 23-1).

IFN-γ is a pivotal type I cytokine in regulating both the innate and adaptive immune responses. IFN-γ induces the expression of interferon-inducible CXC chemokines and CC chemokines from a variety of cells, and indirectly amplifies the recruitment of additional leukocytes to a site of innate host response. The recruitment of mononuclear cells expressing the CXC chemokine receptor, CXCR3, especially Th1 cells, leads to further amplification of the local expression of IFN-γ. In contrast, IFN-γ suppresses a number of ELR^+ CXC chemokines from a variety of cells. The suppression of ELR^+ CXC chemokines by IFN-γ and the induction of interferon-inducible CXC and CC chemokines may be an important mechanism for switching from a predominant neutrophil to mononuclear cell infiltration, allowing the transition from innate to adaptive immunity.

The cytokine profile of the inflammatory response determines the disease phenotype responsible for either resolution or progression to end-stage fibrosis (Fig 23-1). IFN-γ has profound suppressive effects on the production of extracellular matrix proteins, such as collagen and fibronectin, although it does not have a direct effect on collagen gene expression. IFN-γ is also a potent modulator of a major matrix-degrading metalloproteinase, stromelysin-1, inhibiting or activating expression differently in different cell types. It up-regulates gene expression of stromelysin-1 by human fibroblasts. Whether this in vitro observation applies in vivo is unclear, as IL-12 attenuates bleomycin induced pulmonary fibrosis via induction of IFN-γ.

Pulmonary expression of the type II cytokine, IL-4, in transgenic mice leads to little or no fibrosis, suggesting a disparity between the in vitro and in vivo effects. Similarly, IL-4 depletion studies and studies with IL-4 –/– mice fail to demonstrate an indispensable role for IL-4 in models of type II–mediated inflammation and fibrosis. Many of the fibroblast activation properties of IL-4 are shared by IL-13, which has similar biologic properties to IL-4, and has been implicated in the pathogenesis of fibroproliferative disorders. The phenotype of transgenic mice expressing IL-13 demonstrates airway epithelial cell hypertrophy, mucus cell metaplasia, and subepithelial airway fibrosis. Similarly, IL-13 has been shown to induce fibrosis by selectively stimulating production and activation of TGF-β. Furthermore, IL-13 can promote fibrosis through the elaboration of CCL5. In a model of *Schistosomiasis*-induced liver fibrosis, IL-13 can promote fibrosis by a mechanism that is independent of TGF-β.

Lung tissue in patients with IPF has been examined for type I and 2 cytokines, and the presence of type II cytokines predominated over the expression of IFN-γ. In further support of an imbalance of the presence of type II cytokines as compared with IFN-γ, is the finding that IFN-γ levels are inversely related to the levels of type III procollagen in the BALF of IPF patients. The levels of IFN-γ were especially correlated with patients that demonstrate progression of their pulmonary fibrosis by evidence of further deterioration of their pulmonary function. Further support for this notion comes from a recently completed phase 3 trial of IFN-γ in patients with IPF, which suggested an improvement in survival in patients treated with IFN-γ. These findings suggest that the persistent imbalance in the expression of type I and II cytokines in the lung may be a mechanism for the progression of pulmonary fibrosis.

IL-10 is a type II cytokine that inhibits a variety of innate and adaptive immune activities. IL-10 inhibits a number of proinflammatory cytokines that include IFN-γ, IL-1, TNF, IL-12, and CXC and CC chemokines. While the exogenous administration of IL-10 may protect the lung from injury in response to either LPS or immune-complex deposition, IL-10 can be detrimental to the host under conditions of microorganism invasion. The role of IL-10 in pulmonary fibrosis is controversial, with experimental data pointing to both anti-inflammatory and profibrotic activity.

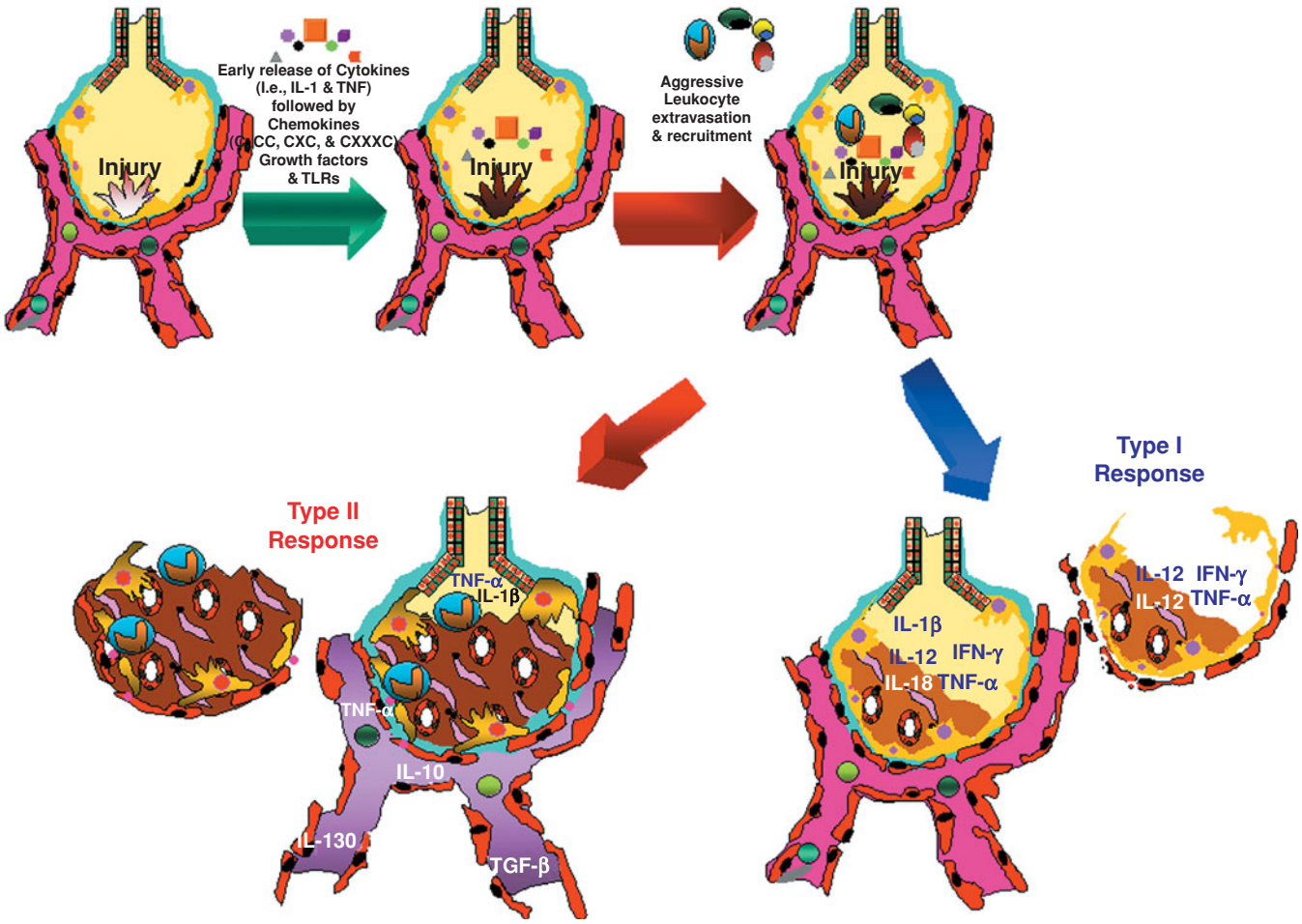

Figure 23-1 The inflammatory response to lung injury. The cytokine profile that is secreted by inflammatory cells during lung injury determines the ultimate outcome following injury. Polarization of the inflammatory response toward a type I response is associated with resolution of lung injury or infection. In contrast chronic infections (e.g., tuberculosis) and chronic inflammatory diseases (e.g., idiopathic pulmonary fibrosis) are associated with a type II profile.

FIBROTIC CYTOKINES

Transforming Growth Factor-beta

Mammalian transforming growth factor-beta (TGF-β) belongs to a superfamily of genes and exists as three closely homologous (72 to 80 percent) dimeric isoforms: TGF-β_1, TGF-β_2, and TGF-β_3. Although the three isoforms of TGF-β appear to have overlapping biologic activity, the predominant isoform of TGF-β is TGF-β_1. There are three TGF-β receptors and signal transduction to the nucleus is via the Smad group of proteins. Smad 1, 2, 3, 4, 5, 8, and 9 are activating signals, whereas Smad 6 and 7 are inhibitory signals of TGF-β_1 signaling.

TGF-β is produced by a variety of cells, including platelets, neutrophils, eosinophils, mononuclear leukocytes, fibroblasts, and endothelial cells. TGF-β is a pleiotropic cytokine that can modulate inflammatory and immune responses, and orchestrate fibrosis and tissue repair. TGF-β is a potent chemoattractant for monocytes and macrophages, and can activate these cells to express IL-1, TNF, PDGF, and itself (TGF-β_1). TGF-β is a potent immunosuppressive agent that inhibits IL-1–dependent lymphocyte proliferation.

TGF-β is chemotactic for fibroblasts and can indirectly induce their proliferation via the expression and autocrine and paracrine activity of PDGF-B. TGF-β is perhaps the most potent and efficacious promoter of extracellular matrix production–inducing gene expression and protein production of many of the constituents of extracellular matrix. Furthermore, it inhibits the generation of metalloproteinases and augments the expression of tissue inhibitors of metalloproteinases (TIMP).

Transient overexpression of active TGF-β_1 results in prolonged and severe interstitial and pleural fibrosis. Transfer of TNF-α or GM-CSF to rat lung induces pulmonary fibrosis, due in part to induction of TGF-β_x. Furthermore, transient expression of IL-1β using an adenoviral vector can lead to progressive fibrosis that is associated with a sustained increase in levels of TGF-β_1. Smad 3 –/– mice developed less fibrosis in response to bleomycin compared with wild-type controls. In contrast, IL-7 down-regulates TGF-β production and inhibits

bleomycin-induced pulmonary fibrosis, and this is mediated via Smad 7 signaling.

In IPF, increased expression of TGF-β has been found in bronchiolar epithelial cells, epithelial cells of honeycomb cysts, and hyperplastic type II pneumocytes. BALF from patients with IPF induces apoptosis in cultured bronchiolar epithelial cells, and this effect is attenuated using anti TGF-β_1 antibodies. In the bleomycin model, in vivo administration of TGF-β_1 enhanced Fas-mediated epithelial cell apoptosis and lung injury. While polymorphisms in the TGF-β gene do not predispose to the development of IPF, there is an increased rate of progression in patients with the presence of a proline residue at codon 10 of the TGF-β gene. These studies support the contention that TGF-β is an important mediator of human pulmonary fibrosis.

Connective Tissue Growth Factor

Connective tissue growth factor (CTGF) is a member of the structurally related CCN (ctgf/cyr61/nov) gene family, which contains six genes: CTGF, cyr61, nov, elm1, cop1, and WISP-3. CTGF I is produced by vascular smooth muscle cells, fibroblasts, endothelial cells, and epithelial cells, and is activated by a number of factors, particularly TGF-β. CTGF has in vitro activities that include fibroblast proliferation, fibroplasia, and extracellular matrix production. Furthermore, its presence has been documented in skin lesions of systemic sclerosis, keloids, scar tissue, and eosinophilic fasciitis and in BALF from patients with IPF and sarcoidosis. Transient overexpression of CTGF in a rat model leads to a moderate but reversible pulmonary fibrosis that is associated with increased levels of TIMP-1. Overexpression of TGF-β leads to a concomitant increase in CTGF and TIMP-1, suggesting that CTGF may be a co-factor for the development of fibrosis. CTGF may be responsible for some of the downstream actions of TGF-β and is a potential therapeutic target for the treatment of interstitial lung disease.

CHEMOTACTIC CYTOKINES AND THE INFLAMMATORY RESPONSE

The salient feature of inflammation is leukocyte infiltration. These recruited leukocytes contribute to the pathogenesis of chronic inflammation and promote fibrosis via the elaboration of a variety of cytokines. Maintenance of leukocyte recruitment during inflammation requires the expression of cell-surface adhesion molecules, and the production of chemotactic molecules, such as chemokines. The chemokines can be divided into four families—CXC, CC, C, and CXXXC—which behave as potent chemotactic factors for neutrophils, eosinophils, basophils, monocytes, mast cells, dendritic cells, NK cells, and T and B lymphocytes (Table 23-1). There is approximately 20 percent to 40 percent homology between the members of the four chemokine families. Chemokines are produced by an array of cells, including monocytes, alveolar macrophages, neutrophils, platelets, eosinophils, mast cells, T- and B-lymphocytes, NK cells, and various structural cells, including keratinocytes, mesangial cells, epithelial cells, hepatocytes, fibroblasts, smooth muscle cells, mesothelial cells, and endothelial cells. Production of chemokines by both immune and nonimmune cells supports the contention that these cytokines may play a pivotal role in orchestrating chronic inflammation.

CXC Chemokines

CXC chemokines can be further divided into two groups on the basis of a structure/function domain consisting of the presence or absence of three amino acid residues (Glu-Leu-Arg; ELR motif) that precede the first cysteine amino acid residue in the primary structure of these cytokines. ELR^+CXC chemokines are chemoattractants for neutrophils and act as potent angiogenic factors. In contrast, ELR^-CXC chemokines are highly induced by interferons, are chemoattractants for mononuclear cells, and are potent inhibitors of angiogenesis (Table 23-2).

CXC Chemokine Receptors

Chemokine activities are mediated through G-protein–coupled receptors. Seven CXC chemokine receptors have been identified (Table 23-3). The ELR+ chemokines bind to CXCR1 and CXCR2 receptors, which are found on neutrophils, T-lymphocytes, monocytes/macrophages, eosinophils, basophils, keratinocytes and mast cells, and endothelial cells. CXCR3 is the receptor for CXCL9, CXCL10, and CXCL11, and is expressed on activated T-lymphocytes. CXCR3 is also expressed on HUMVEC in a cell cycle–dependent fashion. CXCR4 is the specific receptor for CXCL12 and is the cofactor for lymphotropic HIV-1. In contrast to CXCR3, CXCR4 appears to be expressed on resting T-lymphocytes. Two other chemokine receptors have been identified that bind chemokines without a subsequent signal-coupling event. The DARC receptor is similar to other chemokine receptors and it binds both CXC and CC chemokines without apparent signal coupling. This receptor was originally found on human erythrocytes and was thought to represent a "sink" for chemokines. The second nonsignaling chemokine receptor is the D6 receptor, which binds several CC chemokines with high affinity, including CCL2, CCL4, CCL5, and $CCL7^-$.

CXC Chemokines in Pulmonary Inflammation

CXC chemokines play a significant role in mediating neutrophil infiltration in the lung parenchyma and pleural space in response to endotoxin and bacterial challenge. CXCL8 is in the bronchoalveolar lavage of patients with community-acquired pneumonia and nosocomial pneumonia and a variety of animal models of pneumonia. In a model of *Aspergillus fumigatus* pneumonia, neutralization of TNF resulted in marked attenuation of the expression of CXCL1 and CXCL2/3 that was paralleled by a reduction in the infiltration of neutrophils and associated with increased mortality. Administration of a TNF agonist peptide to animals

Table 23-1

The Human C, CC, CXC, and CXXXC Chemokine Families of Chemotactic Cytokines

C Chemokines	
XCL1	Lymphotactin
XCL2	SCM-1β
CC Chemokines	
CCL1	I-309
CCL2	Monocyte chemotactic protein-1 (MCP-1)
CCL3	Macrophage inflammatory protein-1 alpha (MIP-1α)
CCL4	Macrophage inflammatory protein-1 beta (MIP-1β)
CCL5	Regulated on activation normal T-cell expressed and secreted (RANTES)
CCL7	Monocyte chemotactic protein-3 (MCP-3)
CCL8	Monocyte chemotactic protein-2 (MCP-2)
CCL9	Macrophage inflammatory protein-1 delta (MIP-1δ)
CCL11	Eotaxin
CCL13	Monocyte chemotactic protein-4 (MCP-4)
CCL14	HCC-1
CCL15	HCC-2
CCL16	HCC-4
CCL17	Thymus and activation-regulated chemokine (TARC)
CCL18	DC-CK-1
CCL19	Macrophage inflammatory protein-3 beta (MIP-3β)
CCL20	Macrophage inflammatory protein-3 alpha (MIP-3α)
CCL21	6Ckine
CCL22	MDC
CCL23	MPIF-1
CCL24	MPIF-2
CCL25	TECK
CCL26	Eotaxin-3
CCL27	CTACK
CXC Chemokines	
CXCL1	Growth-related oncogene alpha (GRO-α)
CXCL2	Growth-related oncogene beta (GRO-β)
CXCL3	Growth-related oncogene gamma (GRO-γ)
CXCL4	Platelet factor-4 (PF4)
CXCL5	Epithelial neutrophil–activating protein-78 (ENA-78)
CXCL6	Granulocyte chemotactic protein-2 (GCP-2)
CXCL7	Neutrophil–activating protein-2 (NAP-2)
CXCL8	Interleukin-8 (IL-8)
CXCL9	Monokine induced by interferon-γ (MIG)
CXCL10	Interferon-γ-inducible protein (IP-10)
CXCL11	Interferon-inducible T cell alpha chemoattractant (ITAC)
CXCL12	Stromal cell–derived factor-1 (SDF-1)
CXCL13	B-cell–attracting chemokine-1 (BCA-1)
CXCL14	BRAK/Bolekine
CXCL16	
CXXXC Chemokine	
CXC3CL1	Fractalkine

Table 23-2

The CXC Chemokines That Display Disparate Angiogenic Activity

CXC Chemokines containing the ELR motif	
CXCL1	Growth-related oncogene alpha (GRO-α)
CXCL2	Growth-related oncogene beta (GRO-β)
CXCL3	Growth-related oncogene gamma (GRO-γ)
CXCL5	Epithelial neutrophil activating protein-78 (ENA-78)
CXCL6	Granulocyte chemotactic protein-2 (GCP-2)
CXCL7	Neutrophil activating protein-2 (NAP-2)
CXCL8	Interleukin-8 (IL-8)
CXC Chemokines that lack the ELR motif	
CXCL4	Platelet factor-4 (PF4)
CXCL9	Monokine induced by interferon-γ (MIG)
CXCL10	Interferon-γ-inducible Protein (IP-10)
CXCL11	Interferon–inducible T-cell alpha chemoattractant (ITAC)
CXCL12	Stromal cell–derived factor-1 (SDF-1)

that had been intratracheally inoculated with *Klebsiella pneumoniae* led to markedly elevated levels of CXCL2/3 associated with increased neutrophil infiltration. Interestingly, ELR-CXC chemokines have direct antimicrobial properties. These studies have established the critical importance of CXC chemokines in acute inflammation and the innate immune response to a variety of microorganisms.

CXCL8 significantly contributed to reperfusion lung injury in a rabbit model of lung ischemia-reperfusion injury, and ventilator-induced lung injury in a murine model is associated with increased expression of CXCL1 and CXCL2

Table 23-3

The CXC Chemokine Receptors

Receptor	Ligand
CXCR1	CXCL6, CXCL8
CXCR2	CXCL1, CXCL2, CXCL3, CXCL5, CXCL6, CXCL7, CXCL8
CXCR3	CXCL9, CXCL10, CXCL11
CXCR4	CXCL12
CXCR5	CXCL13
CXCR6	CXCL16

that parallels lung injury and neutrophil recruitment. CXCR2 –/– mice were protected from ventilator-induced lung injury. These findings support the notion that ventilator-induced lung injury is secondary to stretch-induced chemokine release with a subsequent inflammatory response and neutrophil recruitment. CXCR2 –/– mice are also protected from hyperoxia-induced lung injury. In other studies, it has been demonstrated that hepatic ischemia-reperfusion injury and the generation of TNF can result in pulmonary-derived CXCL5, showing the importance of cytokine networks between the liver and lung. The production of CXCL5 in the lung was correlated with the presence of neutrophil-dependent lung injury, and passive immunization with neutralizing CXCL5 antibodies resulted in significant attenuation of lung injury.

Several studies have demonstrated that CXCL8 levels correlate with the development and mortality of ARDS. Early increases in CXCL8 in bronchoalveolar lavage fluid correlated with an increased risk of subsequent development of ARDS, and also demonstrated that alveolar macrophages were an important source of CXCL8 prior to neutrophil influx. Furthermore, there is an imbalance in the expression of ELR+ (CXCL1, CXCL5, CXCL8) as compared with ELR-CXC (CXCL10, CXCL11) chemokines from BALF of patients with ARDS as compared with controls. This imbalance correlated with angiogenic activity and both procollagen I and procollagen III levels in BALF. These findings suggest that CXC chemokines have an important role in the fibroproliferative phase of ARDS via the regulation of angiogenesis.

The Role of CXC Chemokines in Pulmonary Fibrosis

IPF is characterized by the progressive deposition of collagen within the interstitium and subsequent destruction of lung tissue. The mechanisms of cellular injury and the role of classic inflammatory cells remain unclear. While the number or proportion of neutrophils in BALF does not correlate with activity of alveolitis and has limited prognostic value, declines in BALF neutrophils typically occur among patients exhibiting favorable responses to therapy. CXCL8 is significantly elevated in IPF, as compared with either normal or sarcoidosis patients, and correlates with BALF presence of neutrophils. The alveolar macrophage is an important cellular source of CXCL8 in IPF. In addition, BALF levels of CXCL8 in IPF may correlate with a worse prognosis.

Vascular Remodeling in Pulmonary Fibrosis: The Role of CXC Chemokines

The existence of neovascularization in IPF was originally identified in 1963 by Turner-Warwick, who demonstrated that within areas of pulmonary fibrosis there was extensive neovascularization with anastomoses between the systemic and pulmonary microvasculature. Further evidence of neovascularization during the pathogenesis of pulmonary fibrosis has been demonstrated in a rat model of bleomycin-induced pulmonary fibrosis. Recently, an imbalance in the levels of angiogenic chemokines (CXCL5, CXCL8), as

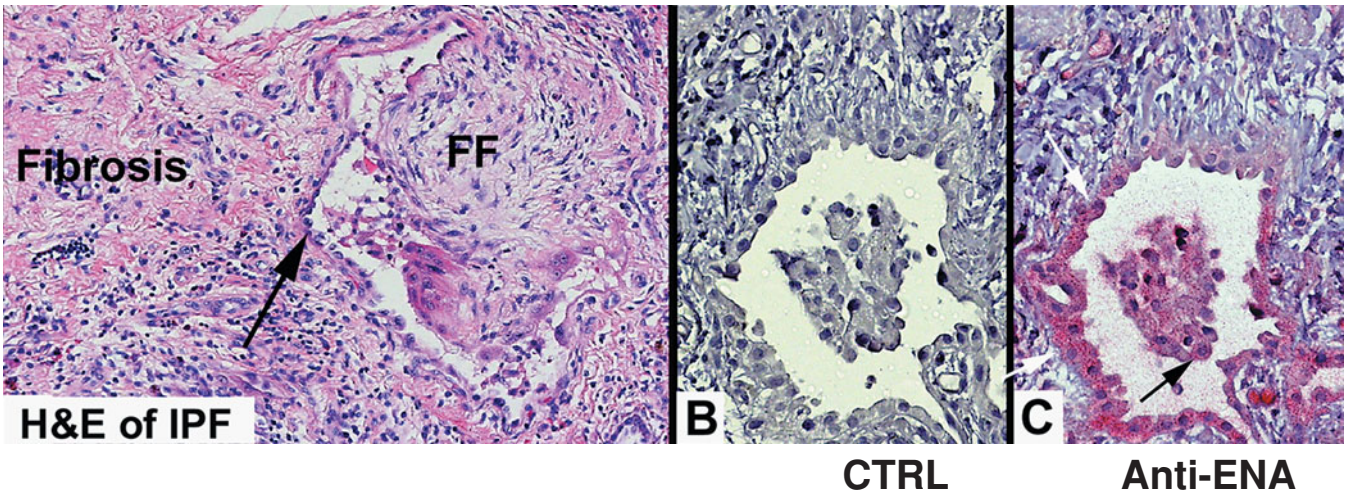

Figure 23-2 Photomicrograph showing immunolocalization of CXCL5 from idiopathic pulmonary fibrosis (IPF) lung tissue specimens. *A*. Hematoxylin and eosin stain of IPF lung tissue (×66) demonstrating a fibroblastic focus (FF) in close proximity to hyperplastic epithelium (arrow). *B*. IPF lung section (×66) stained with control antibodies demonstrating the lack of non specific staining. *C*. IPF lung section (×66) stained with anti-CXCL5 antibodies demonstrating immunolocalization to hyperplastic type II pneumocytes (white arrows) and macrophages (black arrow). *(From Keane MP, Belperio JA, Burdick MD, et al: ENA-78 is an important angiogenic factor in idiopathic pulmonary fibrosis. Am J Respir Crit Care Med 164:2239–2242, 2001.)*

compared with angiostaxic chemokines (CXCL9, CXCL10, CXCL11), favoring net angiogenesis has been demonstrated in both animal models and tissue specimens from patients with IPF (Fig. 23-2). Renzoni et al have demonstrated vascular remodeling in both IPF and fibrosing alveolitis associated with systemic sclerosis. Cosgrove et al provided further support for the concept of vascular remodeling in IPF when they demonstrated a relative absence of vessels in the fibroblastic foci of IPF. This appeared to correlate with increased expression of pigment epithelium–derived factor in the fibroblastic foci. Interestingly, they also noted significant vascularity in the areas of fibrosis around the fibroblastic foci, with numerous abnormal vessels in the regions of severe architectural distortion. These findings are similar to those of Renzoni and support the concept of regional heterogeneity of vascularity in IPF. This heterogeneity is not surprising, as usual interstitial pneumonia, which is the pathological description of IPF, is defined by its regional and temporal heterogeneity.

Furthermore, a phase II study of the administration of IFN-γ to patients with IPF demonstrated a significant upregulation of lung CXCL11 gene expression and BAL and plasma protein levels of CXCL11. These findings support the notion that vascular remodeling is a critical biologic event that supports fibroplasia and deposition of ECM in the lung during pulmonary fibrosis.

Chemokines and the Trafficking of Fibrocytes to the Lung

Fibrocytes present in the peripheral circulation were first identified in 1994, comprise a minor component of the circulating pool of leukocytes (less than 1 percent), and express a characteristic pattern of markers, including collagen (Col) I and CD45. Subsequent studies have revealed that circulating fibrocytes express chemokine receptors such as CXCR4 and CCR7 and extracellular matrix proteins, such as procollagen I and procollagen III. Fibrocytes migrate in response to CXCL12 and traffic to the lungs in a model of bleomycin-induced pulmonary fibrosis. Treatment of bleomycin-exposed animals with specific neutralizing anti-CXCL12 antibodies inhibits intrapulmonary recruitment of fibrocytes and attenuated lung fibrosis. These findings challenge the dogma that fibroblasts and myofibroblasts arise from an intrapulmonary pool of tissue fibroblasts.

The CC Chemokines

CC chemokines (Table 23-1) are chemoattractants for monocyte, T and B lymphocytes, NK cells, dendritic cells, basophils, mast cells, and eosinophils. The CC chemokines are produced by an array of cells, including monocytes, alveolar macrophages, neutrophils, platelets, eosinophils, mast cells, T cells, B cells, and NK cells, as well as structural cells such as keratinocytes, mesangial cells, epithelial cells, hepatocytes, fibroblasts, smooth muscle cells, mesothelial cells, and endothelial cells.

CC Chemokine Receptors

CC chemokine receptors are structurally homologous. Currently at least ten cellular CC chemokine receptors have been cloned, expressed, and identified to have specific ligand-binding profiles (Table 23-4). It has become increasingly recognized that chemokine receptors are differentially expressed on T cells depending on their antigenic experience and type of polarization. Chemokines and their receptors are essential components of type I– and II–mediated responses. Naïve

Table 23-4

The CC Chemokine Receptors

Receptor	Ligand
CCR1	CCL3, CCL5, CCL7, CCL14, CCL15, CCL16, CCL23
CCR2	CCL2, CCL7, CCL13
CCR3	CCL5, CCL7, CCL11, CCL11, CCL15, CCL26
CCR4	CCL17, CCL22
CCR5	CCL3, CCL4, CCL5
CCR6	CCL20
CCR7	CCL19
CCR8	CCL1
CCR9	CCL25
CCR10	CCL27

T cells express CXCR4 and CCR7 and migrate in response to CXCL12 and CCL19. CXCR3, CXCR6, and CCR5 are expressed at higher levels on type I cells than type II, whereas CCR3, CCR4, and CCR8 are more characteristic of type II cells.

CC Chemokines in Pulmonary Inflammation

The CC chemokines, CCL2, CCL3, CCL4, CCL5 have been implicated in mediating the innate host defense in animal models of *Influenza* A virus, *Paramyxovirus* pneumonia virus, *Aspergillus fumigatus*, and *Cryptococcus neoformans* pneumonias. *Cryptococcus neoformans* is acquired via the respiratory tract and is a significant cause of fatal mycosis in immunocompromised patients. CCL2 and CCL3 play important roles in the eradication of *Cryptococcus neoformans* from the lung and prevent cryptococcal meningitis. These studies support the notion that CC chemokine ligand/receptor biology plays a critical role in innate host defense and development of pulmonary inflammation that is important in eradication of microorganisms.

The host response to *Influenza* A virus is characterized by an influx of mononuclear cells into the lungs that is associated with the increased expression of CC chemokine ligands. CCR5 –/– mice displayed increased mortality related to severe pneumonitis, whereas CCR2 –/– mice were protected from the severe pneumonitis due to defective macrophage recruitment. However the delay in macrophage accumulation in CCR2 –/– mice was correlated with high pulmonary viral titers. In CCR1 –/– mice infected with *Paramyxovirus* pneumonia virus, the inflammatory response was found to be minimal, the clearance of virus from lung tissue was reduced, and mortality was markedly increased.

The effect of CC chemokines in mediating the recruitment of mononuclear cells during the innate host defense is not limited to viral infections. Mehrad and colleagues have shown that CCL3 and the recruitment of mononuclear cells play an important role in the eradication of invasive pulmonary aspergillosis. They demonstrated that in both immunocompetent and neutropenic mice CCL3 is induced in the lungs in response to intratracheal inoculation of *Aspergillus fumigatus*. Depletion of endogenous CCL3 resulted in increased mortality in neutropenic mice, which was associated with a reduced mononuclear cell infiltration and markedly decreased clearance of lung fungal burden. These findings have been confirmed by the demonstration that CCR1 –/– mice exposed to *Aspergillus fumigatus* had markedly increased mortality compared with wild-type mice. These studies indicate that CCL3 and elicitation of mononuclear cells are crucial in mediating host defense against *Aspergillus fumigatus* in the setting of neutropenia.

CC Chemokines in Pulmonary Fibrosis

Animal models, such as bleomycin-induced pulmonary fibrosis, have demonstrated the presence and contribution of CC chemokines to the pathogenesis of fibrosis. CCL2 is an important cofactor for the stimulation of fibroblast collagen production and induction of the expression of TGF-β_1. Inhibition of CCL2 or CCL3 resulted in a reduction of infiltrating cells into the lungs of bleomycin-treated animals.

Furthermore, it has been shown that CCL2 can stimulate interleukin-4 production, indicating that it might be involved in type II polarization. Neutralization of CCL2 leads to a reduction in IL-4 and an augmentation in IFN-γ production by CD4+ lymphocytes when co-cultured with fibroblasts. These findings suggest that endogenous CCL2 has an important role in the modulation of CD4+ T-cell activation during cell-cell interactions with lung fibroblasts and that these interactions may dictate the cytokine profile associated with an inflammatory response. IL-13 promotes bleomycin-induced fibrosis through the elaboration of CCL6. Both CCL17 and CCL22 and their receptor, CCR4, are significantly elevated in the bleomycin model and neutralization of CCL17 attenuates pulmonary fibrosis. Thus, chemokines may have an important role in the switch toward a profibrotic type II phenotype.

Both CCR1 and CCR2 have been shown to play an important role in the pathogenesis in the mouse model of bleomycin-induced pulmonary fibrosis. Treatment with antibodies to CCR1 leads to a reduction in both inflammatory cell infiltrates and the development of fibrosis. Similarly, CCR2 –/– mice are protected from pulmonary fibrosis in response to bleomycin. Furthermore, alveolar epithelial cells from CCR2 –/– mice suppress fibroblast proliferation more than AECs from wild-type mice. CCL2 and CCR2 have an important

role in suppression of PGE2, thereby promoting fibroproliferation. Similarly, an important role for CCR2 has been seen in murine model of obliterative bronchiolitis, in which the fibrotic response associated with this disorder was attenuated in CCR2 –/– mice. Accordingly, targeting chemokine receptors may be an efficient way to inhibit pulmonary fibrosis.

CCCL2 and CCL3 are elevated in BALF and lung tissue of ILD patients. Furthermore, pulmonary fibroblasts isolated from patients with IPF produced greater amounts of CCL3 after challenge with IL-1β, than did similarly treated normal pulmonary fibroblasts. In addition, CCL2 was produced to a greater extent in the presence of either TNF or IL-1β from isolated pulmonary fibroblasts of patients with IPF, as compared with normal controls. Moreover, pulmonary fibroblasts from IPF patients demonstrate a reduced ability to down-modulate their CCL2 expression in the presence of either PGE_2 or the glucocorticoid dexamethasone.

Choi et al described enhanced expression of the chemokines CCL7 and CCL22, in lung tissue of patients with IPF as compared with nonspecific interstitial pneumonia, and nonidiopathic interstitial pneumonia. Furthermore, they describe increased expression of CCL5 in nonspecific interstitial pneumonia as compared with usual interstitial pneumonia. Interestingly, CCL5 protein was identified in nonspecific interstitial pneumonia more prominently than usual interstitial pneumonia. This is all the more interesting as CCL5 is a major stimulus for the production of CCL7 through its interactions with CCR5. These findings raise the possibility that there is a continuum from nonspecific interstitial pneumonia to usual interstitial pneumonia with higher levels of CCL5 in nonspecific interstitial pneumonia leading to subsequent increased CCL7 expression as the disease progresses to usual interstitial pneumonia. There is considerable controversy as to whether nonspecific interstitial pneumonia is an earlier lesion of usual interstitial pneumonia. Several studies have demonstrated the presence of usual interstitial pneumonia and nonspecific interstitial pneumonia patterns in the same patients, which suggests that these are overlapping processes. The findings of Choi suggest a transition from a predominance of CCL5 to CCL7 and further support this notion. Of further interest is the previous description that CCL7 can act as a natural antagonist at the CCR5 receptor, which raises the possibility that CCL7 may play a role in regulating its own production. It is possible that fibroblasts from patients with usual interstitial pneumonia have an inherent defect that prevents CCL7 from shutting off its own production.

Recently the importance of receptor polymorphisms in various disease states has been demonstrated. CCR5 is the major receptor for CCL3, CCL4, and CCL5. Homozygosity for the CCR5Δ32 mutation has been shown to predict prolonged renal allograft survival (90 percent at 20 years), reduced risk of asthma and decreased severity of rheumatoid arthritis. In contrast, there was an increased frequency of the CCR5Δ32 allele in patients with sarcoidosis that was associated with more apparent disease and an increased need for corticosteroids. This suggests that CCR5Δ32 is associated with altered susceptibility to immunologically mediated diseases and that the balance between chemokines and their appropriately expressed receptor is necessary for the full manifestation of various diseases. Similarly, polymorphisms in the CXCR2 gene have been described in patients with systemic sclerosis both with and without evidence of interstitial lung disease, suggesting that CXCR2 may have a role in the fibrotic process.

CONCLUSIONS

Cytokine and chemokine expression often occur via an amplified cascade or network that involves cellular activation by an early-response cytokine that triggers the expression of more distal cytokines. The generation of cytokine networks is necessary for both the pathogenesis and resolution of a variety of acute and chronic lung diseases, as these mediators are fundamental to the initiation, maintenance, and final resolution of the inflammatory response. Studies that illuminate the mechanistic role of cytokines and chemokines in mediating lung inflammation are likely to lead to novel cytokine-based forms of therapies, which will significantly aid in treating enigmatic lung disease.

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Leukocyte Accumulation in Pulmonary Disease

Nicholas W. Lukacs • Peter A. Ward

Mediators produced during inflammatory/immune responses dictate the severity and intensity of pulmonary disease. The profile of inflammatory and chemotactic factors produced during acute and chronic pulmonary disease is responsible for the cell-to-cell communication that orchestrates leukocyte adhesion to vascular endothelium, extravasation, and localization of leukocytes at the site of inflammation. Recruitment of leukocyte populations into inflamed tissues is initiated by cytokine-induced expression of adhesion molecules on vascular endothelium. Endothelial adhesion molecules, which can be up-regulated primarily by tumor necrosis factor (TNFα) and interleukin-1β (IL-1β), include intracellular adhesion molecule-1 (ICAM-1), vascular cell adhesion molecule-1 (VCAM-1), as well as E- and P-selectins. These adhesion molecules play an essential role in facilitating leukocyte adhesion to the endothelium, a necessary step for leukocyte transmigration. Subsequently, leukocyte adhering to the activated vascular endothelium is followed by leukocytic migration into the inflamed tissue, directed by chemotactic molecules at the site of the inflammatory/immune response. Up-regulation of the early response cytokines is crucial for the initiation of these early events to alleviate the inciting agent whether it is infectious or noxious in nature. However, the continuous overproduction of these activating and chemotactic mediators can lead to destructive, pathological consequences. In human lung, inflammation-induced damage can be observed in multiple human diseases, including both acute and chronic inflammatory settings. In this chapter we will examine the factors, molecules, and mediators required in initiation and maintenance of pulmonary inflammatory events in both acute and chronic inflammatory conditions.

LEUKOCYTE ADHERENCE AND MIGRATION REGULATED BY ADHESION MOLECULES

The release of early response mediators leads to the up-regulation of selectins (E and P) and other adhesion molecules (ICAM-1, VCAM-1, etc.) on the surface of vascular endothelial cells within and around the site of inflammation. Selectin molecules (L, P, and E) interacting with their "counter

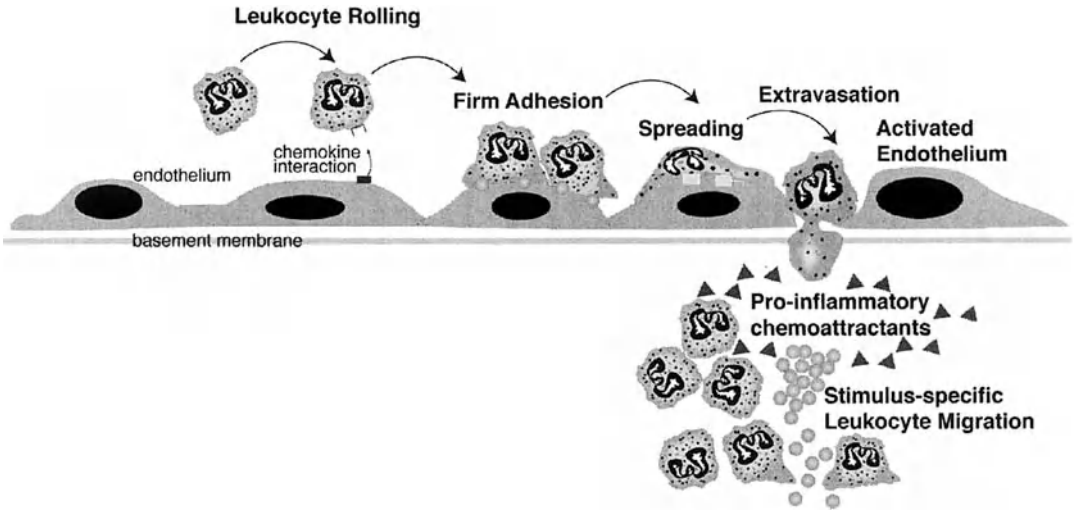

Figure 24-1 Leukocyte adhesion and extravasation into inflamed tissue.

receptors" have been shown to play a role in early adhesion events. E and P selectins are rapidly inducible and initiate rolling of leukocytes on activated endothelium through Ca^{2+}-dependent recognition of cell surface carbohydrates of the sialyl Lewis X family and related oligosaccharides that may be expressed on glycoproteins or glycolipids. L-selectin on lymphocytes, originally referred to as the "lymphocyte homing receptor", has been associated with adhesion of lymphocytes to high endothelial venules (HEV) of lymph nodes. Initial and rapid expression of selectin molecules function to slow the flow of leukocytes in the vascular compartment and allow transient adherence to "counter receptors" expressed on activated vascular endothelium. Normally, adhesion molecules or their "counter receptors" are tightly regulated, while inappropriate or excessive and prolonged expression contributes to inflammatory disorders. The currently held concept is that the rapid expression of selectin molecules facilitates the reversible binding resulting in "rolling" of leukocytes along the activated vascular endothelial surface. This rolling allows the leukocytes to be slowed from circulatory flow, permitting development of firm adhesion to endothelial cell expressed adhesion molecules (VCAM-1 and ICAM-1) at the site of inflammation. These interactions are outlined in Figure 24-1.

The expression of endothelial adhesion molecules leads to a sequence of adherence- promoting events whereby leukocytes ultimately bind firmly to the vascular endothelium via β-integrin receptors on leukocyte surfaces. Although the mechanism is not entirely clear it appears that, at least in the case of β_2 integrins, a change in affinity occurs (at least in CD11a/CD18, LFA-1) during cell activation events, which allows an increased avidity of adhesion-promoting molecules. The change of affinity can be mediated, at least in part, by the interaction of the rolling leukocytes with endothelial cell bound chemokines that can bind to glycosylaminoglycans (GAGs) or are expressed on the surface of the endothelial cell. The β1α4 integrins (VLA-4), expressed primarily on mononuclear cells and eosinophils, have been shown to bind to VCAM-1, while β2-integrins (CD11/CD18), expressed on all leukocytes, bind in varying degrees to intracellular adhesion molecules-1,2,3 (ICAM-1,2,3), the first of which is highly expressed on endothelial cells. These two families of adhesion molecules are able to facilitate leukocyte binding to the activated endothelium and can further dictate the type of leukocytes that bind and extravasate into the inflamed tissue. For example, while neutrophils rely on CD11/CD18 binding to ICAM-1, eosinophils depend upon VLA-4/VCAM-1 interactions to firmly adhere to the endothelial cell wall. Once firmly adherent, leukocytes may then enter the tissue following chemotactic gradients through a series of detachment/readherence events typified by the polar expression of integrins specific for the adhesion molecules on the surface of mesenchymal-derived cells.

Cell-to-cell communication during inflammatory events is mediated by cytokines that mediate, maintain, and regulate the inflammatory responses and dictate the intensity of the reaction. The early response cytokines IL-1 and TNFα appear to play a pivotal role in the induction of inflammatory responses through the initiation of cytokine cascades. The exuberant production of IL-1 and TNFα may lead to multisystem injury and systemic complications, as exemplified in septic shock syndromes. As previously indicated, IL-1 and TNFα initially up-regulate the selectin (E-selectin) and adhesion molecules (ICAM-1, VCAM-1) needed for the first step of leukocyte extravasation into tissue. In addition, IL-1 and TNFα up-regulate other inflammatory cytokines (e.g., IL-6) involved in the chemotactic responses of leukocytes into inflamed tissue. Interestingly, the type of cytokine can dictate the nature of the inflammatory response based upon the adhesion molecule that it induces. For example, while TNF and IL-1 are critical for up-regulation of ICAM-1, which allows neutrophil and monocyte adhesion, IL-4 produced during allergic responses preferentially up-regulates VCAM-1, which mediates eosinophil adhesion. Thus, the inflammatory/immune cytokine environment of the lung can help to tailor the initiation and adhesion of a particular leukocyte

recruitment profile. The production of one of a number of classes of chemotactic factors is required for the movement of leukocytes from the vascular compartment to the interstitium of the lung. We will next describe and characterize the function of chemotactic mediators that are expressed in the lung during specific disease conditions.

CHEMOATTRACTANT MOLECULES DURING LUNG RESPONSE

Complement---An Expande d Role in Acute and Chronic Immunity

The initiation of the complement cascade can be accomplished via multiple mechanisms, including antibody-antigen complexes, bacterial products, and toxins (Fig. 24-2). Of the complement activation products, fragments from C3 and C5 have the most profound effects on the inflammatory response. The split products of C3, C3a and C3b, generated by C3 convertase (as well as further products [iC3b, C3d, C3g]) have important activating roles in the inflammatory pathway. C3a is an anaphylatoxin that induces the activation of mast cells/basophils and appears to have direct and indirect effects on vascular permeability. C3b acts as a potent opsonizing component; it binds to bacteria and allows accelerated phagocytosis and clearance of pathogens via its receptor on neutrophils and macrophages, Mac-1 (CD11b/CD18). The split products of C5, C5a, and C5b can subsequently be induced through the sequential participation of C3b and C5 convertase. Similar to C3a, but much more potent, C5a is an anaphylatoxin, which activates mast cell and basophil degranulation as well as neutrophils and induces immediate changes in vascular permeability. In addition, C5a stimulates smooth muscle contraction and has neutrophil chemotactic and activating characteristics that promote directed migration of these leukocytes toward a concentration gradient. Furthermore, C5a stimulates neutrophil oxidative metabolism, granule discharge, and adhesiveness to vascular endothelium. C5a can directly stimulate endothelial cells in a G protein receptor-dependent fashion (C5aR), to cause signal transduction events resulting in increased intracellular Ca^{2+}, induction of superoxide (O_2^-), and expression of P-selectin. C3a lacks these latter activities. Accordingly, C5a has the ability to stimulate both leukocyte as well as endothelial cells. Altogether, these functions of C3 and C5 split products suggest that they are potent inflammatory mediators.

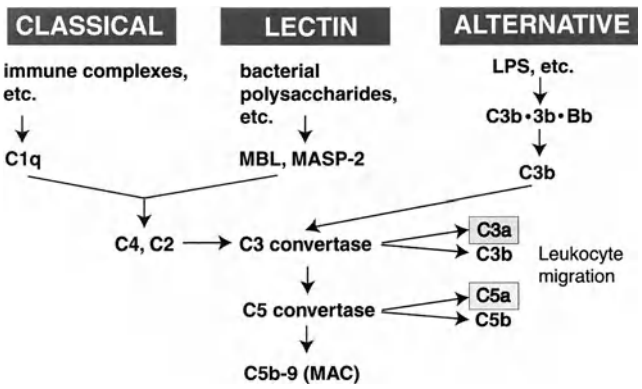

Figure 24-2 Activation pathways for complement cascade.

Elevated complement component levels have been described with several pulmonary diseases, including sarcoidosis, idiopathic pulmonary fibrosis (IPF), acute respiratory distress syndrome (ARDS), and chronic obstructive pulmonary disease (COPD). Bronchoalveolar lavage fluid (BALF) samples from sarcoid and patients with IPF demonstrate a significant increase in complement component C2/CH50 ratio when compared to BALF analysis from normal individuals, suggesting the presence of complement pathway activation within the lung. In trauma patients at risk for ARDS, an increased ratio of BALF C3a to plasma C3a has been associated with development of ARDS, suggesting substantial complement activation locally within the lung. Using animal models of acute pulmonary disease related to sepsis, blocking C5a or C5aR has been demonstrated to prevent severe pulmonary consequences and long-term disease, suggesting a potential therapeutic strategy to blocking C5a activation. Interestingly, a major source of complement component C3 within the lung has been identified as type II epithelial cells with synthesis being induced by several mechanisms, including IL-4 activation. In addition to being activated by IL-4, recent data have begun to outline the differential role that C3a and C5a have on induction of immune responses. These complement components are able to direct the development of immune responses during the initiation of immune responses by regulating IL-12 production. Specifically, C3a appears to drive IL-12 production that then favors type 1 immune responses, while C5a down-regulates IL-12 and allows IL-4–mediated type 2 immune responses to be induced. This scenario may be especially important during sensitization to various antigens in determining the extent and severity of the pulmonary immune response. However, these two complement activation products maintain their ability to be potent recruitment factors when generated during an established allergic/immune response and will promote additional leukocyte recruitment and activation. Although increased levels of complement components, which likely amplify the inflammation and injury within the lung, can accompany pulmonary diseases, it is not clear whether these components have causative or potentiating effects in end-stage lung disease. Thus, conclusions of the role of C3a and C5a should be viewed cautiously in relationship to chronic inflammatory diseases of the lung, while targeting these molecules during pulmonary inflammatory disease continues to be a controversial topic.

The receptors for C3a and C5a have been a source of intense research over the past several years and have led to the resurgence of interest in potentially blocking specific responses during pulmonary disease. The distribution of these receptors depicts their broad role in innate and acquired immune responses as both C3aR and C5aR can be found on

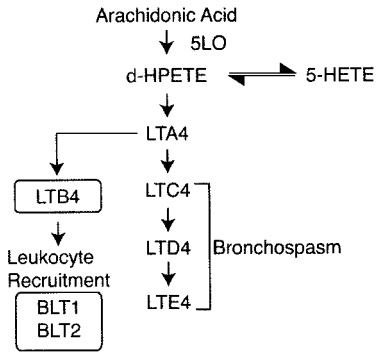

Figure 24-3 Arachidonic acid metabolism for leukotriene biosynthesis.

alveolar macrophages, dendritic cells (DCs) and mast cells, and in sentinel cell populations in the lung that provide important cues for the immediate and prolonged determination of effective immune responses. In particular, activation of these cell populations has been assessed for the differential activation consequences of C3a and C5a. At the same time the expression of C5aR on neutrophils allows an immediate and efficient migration into the lung and activation at the site of inflammation. C5aR is also displayed on cells involved in chronic immune responses, such eosinophils recruited during allergic responses. Thus, the activation of the complement system likely has potent effects on both acute inflammatory responses as well as chronic inflammation that can lead to long-term pulmonary dysfunction. Interestingly, recent findings have described an additional C5a receptor, C5L2, which binds C5a extremely efficiently, but has no linkage to G protein and therefore conveys no activation pathways for inflammation. Research examining the possible implications of this second receptor for modulating C5a-mediated responses by competitively binding up C5a during inflammatory responses is the subject of focus from several laboratories.

Arachidonic Acid and Lung Responses

The enzymatic processing of arachidonic acid (AA) produces a number of lipid mediators that have long been known to be associated with acute and chronic inflammatory responses in the lung. Phospholipase A2 degradation of AA-containing phospholipids lead to the breakdown into PAF-derivative and free AA that can be immediately processed by 5-LO into 5-HPETE and further processed by 5-LO into leukotriene A4 (Fig. 24-3). 5-HPETE can alternatively be processed into 5-HETE by peroxidase. Leukotriene A4 can be further processed into LTB4 by LTA4 hydrolase or LTC4 by LTC4 hydrolase, followed by continued processing of LTC4 into LTD4 and finally LTE4. These latter metabolites, C4, D4, and E4, are known as the cysteinyl leukotrienes and provide an important stimulus for airway reactivity and decreased lung function during large airways disease, such as asthma. In fact, targeting the cysteinyl leukotrienes has provided significant relief to particular subsets of asthmatics.

Of these AA metabolites, PAF and LTB4 have been best characterized for their chemotactic activity promoting migration of leukocytes into sites of inflammation. These mediators were originally identified as potent neutrophil chemoattractants and associated with acute inflammation-induced airway damage. PAF has a broad range of specificity in its ability to induce leukocyte chemotaxis, since it induces the recruitment of not only neutrophils, but also of monocytes, lymphocytes, and eosinophils. During allergic diseases, PAF may have a particular role in augmentation of eosinophil responses. Although PAF is a relatively weak eosinophil chemotactic factor compared to LTB4 or RANTES, PAF does have activating effects on eosinophils, inducing superoxide production, and release of ECP as well as eosinophil peroxidase release. As with all of the eosinophil chemotactic factors, IL-5 enhances the ability of PAF to induce eosinophil chemotaxis. In addition, PAF also appears to have a significant application for augmenting and directly stimulating cytokine production from leukocyte populations. PAF dose dependently stimulates the production of IL-1, but not TNFα, in monocyte and macrophage cultures. PAF-primed neutrophils and monocytes have demonstrated increased superoxide production, elastase release, and endothelial cell lysis in response to phorbol ester or bacterial-derived f-met-leu-phe (fMLP). Not only does PAF have an effect on phagocytic cells, it also can augment T-lymphocyte–derived cytokine production. The actions of PAF on endothelial cells indicate that PAF has a direct role in up-regulation of selectin and adhesion molecules and can induce the release of superoxide anion. Instillation of PAF into human, monkey, or guinea pig airways induces an immediate LTC4-independent bronchoconstrictor response, suggesting a possible role in development of pathophysiology in asthmatic responses. In addition, even the earliest publications identified that PAF airway instillation resulted in an accumulation of leukocytes, including macrophages, neutrophils and eosinophils, accompanied by significant epithelial cell degeneration. Overall, these studies indicate that the signals provided by PAF are not only chemotactic but can also participate in the augmentation of the immune/inflammatory pathway. However, over the years a number of PAF- specific inhibitors have been developed that have not been effective for blocking or attenuating inflammatory responses in the lung.

While leukotrienes in general have broad effects on inflammatory responses, LTB4 is one of the most potent neutrophil chemotactic molecules known and induces superoxide production. However, LTB4 can also act to recruit other leukocyte populations, such as monocytes and eosinophils. In eosinophil chemotactic assays, LTB4 is more potent than PAF in the activation and degranulation of eosinophils. LTB4 has been found in many disease states, including psoriasis, bacterial peritonitis, inflammatory bowel disease, and asthma. LTB4 is rapidly synthesized by phagocytic cells (polymorphonuclear cells [PMNs] and macrophages) after stimulation with bacterial LPS or fMLP. More recently, the LTB4 receptor, BLT1, has been implicated in preferential recruitment of Th2 type T lymphocytes during allergic pulmonary

responses. This receptor has also been implicated in recruitment of T lymphocytes that mediate lung rejection and obliterative bronchiolitis using rodent models. Thus, LTB4 and BLT1 are now being considered targets for therapy in chronic immune responses in the lung compared to their traditional role as a potent neutrophil chemoattractant in acute lung injury.

Chemokines and Immune Cell Migration

Chemokines and their receptors have been primarily divided into two main families based upon their sequence homology and the position of the first two cysteine residues, C-x-C (α) and C-C (β) (Table 24-1). There are two minor families—the C and Cx3C families—each with a single member. Much of our understanding of chemokines has centered upon their role in mediating leukocyte recruitment to the site of inflammation or specifically directing recirculation of leukocytes during homeostasis. Interestingly, results have indicated that many of these family members also have diverse roles in the activation and differentiation of various immune and nonimmune cell populations. While the fact that the chemokine family contains so many members creates confusion of function, the promiscuous binding relationship between multiple members with a single receptor as well as a specific receptor able to bind multiple chemokines contributes considerably to our relative lack of understanding of the biology of the family. In particular, it is often difficult to understand how such a vast number of chemotactic molecules, several being produced at any one time, could coordinate inflammatory responses. Accordingly, studies demonstrate that it may be the overall profile of chemokines that are produced that dictates the inflammatory cell response that accumulates at a site of injury or infection. This latter aspect can be best displayed during acute inflammatory responses, such as in bacterial infections, when the cellular infiltrate is primarily neutrophilic and it is the production of CxCR binding chemokines that mediate this process. Likewise, when more insidious pathogens are present and acute inflammatory mechanisms cannot control the infectious process, immune cytokines, such as interferon (IFN) and IL-4, tend to drive the production of chemokines that allow the mononuclear cells, macrophage, and lymphocytes to be elicited to the site of infection and allow a more sophisticated immune response to develop for clearance of the pathogen. Thus, although there are numerous chemokines being produced during any single response, the overall profile of the response may be directed to recruitment of cells that are most appropriate to deal with the particular stimuli.

In addition to coordinating a response based upon the profile of chemokines being produced, the differential expression of chemokine receptors can also predict what cell populations may migrate into an inflamed lung. The C-x-C family of chemokines has six receptors described to date, C-x-CR1 to C-x-CR6. In general, the C-x-CR1 and R2 appear to be primarily displayed on neutrophils, whereas C-x-CR3 and R4 are displayed on mononuclear cells. This pattern follows the specificity and chemoattractant function of the specific ligands for these receptors as the ELR-containing C-x-C chemokines bind to C-x-CR1 and 2, whereas the non–ELR-containing chemokines bind to C-x-CR3 and SDF binds to C-x-CR4. A fifth C-x-C receptor has been recently identified with specificity for B lymphocytes (BLR1) and appears to have specificity for primarily those cells, while a sixth receptor has been identified that binds a single ligand. This latter receptor has not been well characterized in pulmonary diseases, but has recently been associated with T-cell alveolitis in sarcoidosis.

The CC chemokine receptors have also expanded over the past several years. There are now at least 10 different receptors and their ligand specificity has not completely been identified. The newer receptors of this family (CCR6 through CCR10) have been less well characterized compared to the first five receptors. The first receptor, CCR1, was shown to bind CCL3, CCL4, CCL5, and appears to be expressed on most leukocytes. CCR2 was originally shown to bind CCL2 (MCP-1), and subsequently appears to bind all of the CCL2 family members (CCL2, 7, 8, 12, and 13). CCR3 is highly expressed on eosinophils, is associated with allergic responses, and binds CCL5, CCL7, CCL11, CCL4, CCL24, and CCL26. All of these latter chemokines that bind to CCR3 have been implicated in eosinophil accumulation during allergic responses, such as asthma. CCR4 appears to bind two chemokines, CCL17 and CCL22, and has been linked to both acute and disease conditions. Perhaps the best-characterized receptor is CCR5 due to its use as a coreceptor for human immunodeficiency virus (HIV) infectivity. This receptor binds CCL3, CCL4, and CCL5, and when ligated with these chemokines, can inhibit HIV infectivity in vitro. The CCR6 and CCR7 were initially identified as having a predominant function as homeostatic chemokines providing a function for recirculation of inactivated leukocytes, especially naïve lymphocytes and DCs. However, more recent evidence suggest that these receptors are found on a whole host of leukocyte populations, including memory T cells, suggesting that their function is more extensively involved in the development of chronic disease and long-term immune function. Although the research community has made great strides in our understanding of the role of chemokines and their receptors, we still do not fully understand their diverse functional properties during homeostatic and inflammatory responses.

Chemokines regulate migration of leukocytes in three distinct phases of the response. Initially, chemokine binding to its receptor at the endothelial border allows leukocytes rolling along selectin molecules to activate their β-integrins for firm adhesion to the activated endothelial cells. This initial conformational change is usually mediated by chemokines either bound to the GAGs on the endothelial wall or by membrane-anchored Cx3CL1 (fractalkine) or CxCL16. Both of the latter chemokines are displayed on the surface of cells anchored by an adhesion molecule-like stalk with a transmembrane domain and a cytoplasmic tail. The chemotactic region of this molecule can be cleaved off and still

Table 24-1

Chemokines and Their Receptors

Chemokine	Former Designation	Known Receptor(s)
CC Chemokine Ligands		
CCL1	TCA3/I-309	CCR8
CCL2	MCP-1	CCR2
CCL3	MIP-1α	CCR1, CCR5
CCL4	MIP-1β, HC21	CCR5, CCR8
CCL5	RANTES	CCR1,CCR3,CCR5
CCL6	C10	CCR1 (?)
CCL7	MCP-3, MARC	CCR1,CCR2,CCR3
CCL8	MCP-2	CCR2,CCR3
CCL9	MIP-1γ	CCR1
CCL11	Eotaxin	CCR3
CCL12	MCP-5	CCR2
CCL13	MCP-4,CKβ10	CCR2,CCR3
CCL14	HCC-1	CCR1
CCL15	HCC-2,MIP-5,MIP-id	CCR1
CCL16	HCC-4,LEC,NCC-4	CCR1
CCL17	TARC	CCR4
CCL18	PARC, MIP-4	?
CCL19	MIP-3β,ELC,exodus-3	CCR7
CCL20	MIP-3α,LARC,Exodus-1	CCR6
CCL21	SLC,6Ckine,Exodus-2,TCA4	CCR7
CCL22	MDC,ABCD-1	CCR4
CCL23	MPIF, CKβ8	CCR1
CCL24	Eotaxin-2,CKβ6,MPIF-2	CCR3
CCL25	TECK	CCR9
CCL26	Eotaxin-3	CCR3
CCL27	CTACK,ILC,Eskine	CCR10
CCL28	none	CCR10
CxC Chemokine Ligand		
CxCL1	GROα,MGSA-α	CxCR2
CxCL2	GROβ,MGSA-β	CxCR2
CxCL3	GROγ,MGSA-γ	CxCR2
CxCL4	PF4	?
CxCL5	LIX	CxCR1,CxCR2
CxCL6	ENA-78, GCP-2	CxCR1,CxCR2
CxCL7	NAP-2	CxCR2
CxCL8	IL-8	CxCR1,CxCR2
CxCL9	MIG	CxCR3
CxCL10	IP-10	CxCR3
CxCL11	ITAC	CxCR3
CxCL12	SDF-1	CxCR4
CxCL13	BCL	CxCR5
CxCL14	BRAK	?
CxCL15	Lungkine	?
CxCL16	none	CxCR6
Cx3C Chemokine Ligand		
Cx3CL	Fractalkine, Neurotactin	Cx3CR

remains active in its soluble form. Once activated by whatever form of chemokine on the endothelium the β-integrins permit the leukocyte to stop, firmly adhere, and allow cytoplasmic spreading. The second phase of migration, movement from the vascular wall into the tissue can be mediated by chemokine gradients maximized at the source of inflammatory stimuli. Once at the site of highest concentration, the cells can then be further activated by the chemokines for effector functions, such as CxCL8-mediated neutrophil degranulation. Thus, it is likely that multiple chemokines could be involved in the process of migrating leukocytes along with other chemotactic molecules, such as C5a or LTB4.

G PROTEIN--COUPLED RECEPTOR-MEDIATED REQUIREMENT FOR MIGRATION

Binding of chemoattractants to specific cell surface receptors on leukocyte populations can initiate directed leukocyte chemotaxis toward the site of inflammation, as well as a number of other biologic events. The chemoattractant receptors appear to all be coupled to protein G_i-mediated pathways (Fig. 24-4). Traditionally, monitoring the hydrolysis of polyphosphoinositides to initiate Ca^{2+} mobilization and cellular activation has been a key end point. However, more information suggests that different subunits of the G protein signaling pathway are involved in Ca^{2+} mobilization and cellular migration, with the alpha subunit inducing Ca^{2+} flux and beta/gamma subunits together responsible for chemotaxis. There appear to be critical signal pathways that are activated and determine chemotactic movement of cells through the beta/gamma subunits (Fig. 24-4). The subunits of heterotrimeric G proteins are known to activate PI3K, MAPKp38, and FAK signaling pathways. While a number of other pathways such as ERK can often be initiated, the essential activation of the ERK1, two pathways required for migration of leukocytes in response to chemoattractants, is not clear. Of these different pathways, PI3K activation has been the most thoroughly studied after a chemotactic signal and acts at the apex of the activation scheme. PI3K activation generates phosphatidylinositols (Ptdlns) species, especially Ptdlns (3,4,5)P_3 (PIP3), which are enzymatically modified by a series of kinases and phosphatases to regulate chemotaxis. The characteristic of a PI3K-mediated chemotactic response via the P110 subunits α, β, γ, which complex with one of seven known adapter molecules, is its sensitivity to pertussis toxin which inhibits the G_i protein–mediated activation of PI3K and blocks cellular migration. Although all three P110 subunits of PI3K may be involved in chemotaxis, the P110γ subunit has been the focus of much of the research in this area and several in-depth reviews have been written. Evidence of the importance of PI3K for chemotaxis can be found in studies using cells deficient in PI3K P110γ as well as in localization studies that have identified activated P110γ

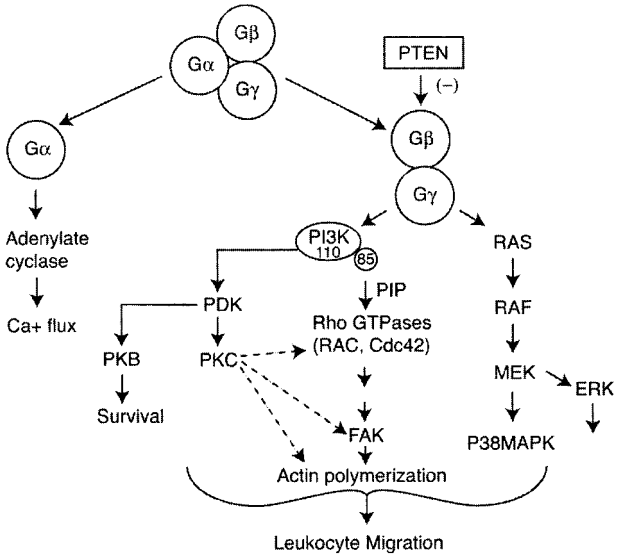

Figure 24-4 G protein–coupled chemoattractant receptor signal transduction pathways.

at the leading edge of migrating cells. Once activated, PI3K appears to couple with the p85 adaptor protein to mediate activation of other important pathways, including activation of rac, rho, and Cdc42 GTPases that subsequently activate actin polymerization pathways. The PI3K-induced responses can be actively regulated by PTEN (phosphatase and tensin homology deleted on chromosome 10 protein) processes. Interestingly, while PI3K appears to be localized to the leading edge during migration, PTEN is found in the trailing edge and is excluded from the leading edge via mechanisms related to GTPase-associated amplification of PIP3 activation. Thus, polarization of PI3K and PTEN in migrating cells is actively achieved by chemoattractant-induced G_i protein–coupled signaling.

Several groups have documented that the tyrosine phosphatase SHP-2 positively regulates cell adhesion and migration by modulating the tyrosine phosphorylation of FAK. It has been proposed that FAK may participate in the regulation of chemotaxis by modulating the turnover of focal adhesions. FAK has been shown to associate with SHP-2 in immune complexes and this association has been shown to increase the tyrosine phosphorylation of FAK, suggesting that SHP-2 may play a role in the activation FAK. Additionally, the protein tyrosine phosphatase PTEN has also been shown to negatively modulate FAK and FAK functions. Together, these studies suggest a mechanism in which chemokine receptors could stimulate the activation of SHP-2 and FAK in order to induce cell migration. Overall, the requirement of multiple parallel signaling pathways to be activated for cellular movement allows better fidelity and control of the migration of leukocytes via G protein–coupled receptors. While these signaling cascades continue to be better defined, there is a paucity of information regarding the differential regulation of migratory signals to control leukocyte recruitment.

PROGRESSION OF LEUKOCYTE MIGRATION DURING PULMONARY INFLAMMATION

The primary function of the immune system is for protection of the host from invading pathogens. Instigating the proper leukocyte populations to migrate into the lung for clearance of a specific pathogen is paramount for efficient clearance of pathogen and preservation of lung function. This process can be regulated based upon the level and type of chemoattractant that is produced. Each type of chemoattractant has a specific and important role for immediate and rapid induction of leukocyte migration or prolonged and more stable recruitment of leukocyte subsets. Unfortunately, the most insidious disease phenotypes in the lung are a result of inappropriate and chronic recruitment of leukocytes that damage the airways and can lead to organ dysfunction. By examining specific types of pulmonary insults, infectious and noninfectious, patterns of mediator involvement emerge that dictate the profile of leukocytes recruited for specialized function. It is this inflammatory response that needs to be controlled for regulation of the long-term effects of lung damage. Our understanding of pulmonary disease has been better defined by examining the differential aspects of infectious and noninfectious lung inflammation.

Bacterial Infection and Sepsis

The early response to infectious organisms is most important when dealing with bacterial infections that can be battled by preventing colonization and by quickly eliminating the inciting agents. This is especially important since bacteria, once established, can proliferate at an expedited rate that outpaces our ability to clear the bacteria. Subsequently, large numbers of bacterial expansion can provide a systemic response leading to sepsis, which is ultimately characterized by multi-organ involvement and often leads to severe pulmonary disease, such as ARDS. The first process that is initiated in this case is the activation of the complement system which quickly responds by the generation of C3a and C5a and provides a quick and effective chemoattractive mechanism for the recruitment of PMNs and monocytes. This early wave of leukocytes is often sufficient for the removal of the invading pathogens. In a parallel process of de novo synthesis, continued persistence of the bacteria quickly leads to LTB4 to be sequentially released from granulocyte stores, such as C3a/C5a-induced mast cell degranulation, or an induced production from macrophages. LTB4 release effectively maintains the inflammatory influx of PMNs for the disposal of the infectious bacteria. As these initial chemoattractant factors are being produced resident and migrating macrophage populations begin producing early response cytokines, IL-1 and TNF, which activate both adhesion molecule expression and chemokines, such as IL-8, that promote continued influx of PMNs. Thus, a well-coordinated and multifaceted series of chemoattractants are produced to promote the most effective acute inflammatory response to control the bacterial infection. In addition to recruiting the leukocyte migration, these chemoattractants activate PMNs and macrophages to promote enhanced phagocytosis and killing.

Although during most bacterial infections the inflammatory response can be controlled and localized, during certain situations of catastrophic injury or severe bacterial contamination/colonization the response can spiral out of control. This is clearly the situation in septic shock where overproduction of activating and chemotactic molecules leads to an intense influx and activation of PMNs and monocyte/macrophages. This often-devastating response has an especially harsh impact on the lung where the edematous and inflammatory response can quickly overwhelm the pulmonary airspace. ARDS is one of the most common disorders encountered in the intensive care unit in septic patients. ARDS can be described as an overwhelming inflammatory response characterized by a mediator "storm" produced that can only be clinically managed and not controlled. Since the failure of anti-TNFα therapy, researchers have turned to downstream chemotactic mediators, which have been successfully targeted in animal models. In particular, the primary strategy has been to target the neutrophil influx and activation. Inhibition of the complement system (either by complement depletion or infusion of sCR1, the soluble complement receptor) has significantly reduced neutrophil recruitment, adherence, and degranulation, thus blocking release of destructive proteases and oxygen radicals in animal models. More recently, use of antibodies to target C5a or C5aR have proved extremely efficacious in several models of sepsis and indicate striking effects on recovery of lung function. These latter studies have re-ignited the idea that by blocking this early and persistent mediator throughout the septic and ARDS responses an attenuated disease process could be attained.

The blockade of other important systems has also led to some successes in animal models. In studies utilizing blocking antibodies to selectin and adhesion molecules an attenuation of neutrophil accumulation can be attained, however, severe pulmonary effects cannot be modulated suggesting a more complex disease pattern. This likely stems from the unique pulmonary vasculature that does not require adhesion molecule-mediated events for neutrophils to transmigrate into the alveolar space. Although early attempts to target LTB4 and other lipid mediators were seen as a feasible option, blocking these mediators in animal models of sepsis has made little progress.

The continuous production of CxC chemokines during sepsis has been identified as a direct correlative factor for the severity of disease and a predictor of whether a septic patient will progress to developing ARDS. The high levels of CxC chemokines related to severe bacterial infections, such as with COPD and cystic fibrosis patients, have also provided convincing data for understanding their function in disease progression. Thus, targeting these molecules during severe bacterial infections and septic responses may have a beneficial effect on survival. In fact, blocking IL-8 homologues or their receptor in mouse studies of pulmonary bacterial

infections appear to have one of the most impressive effects on pulmonary disease through the reduction of neutrophil accumulation and activation. The activation of CxCL8 (IL-8) and other neutrophil-associated chemokines are quickly induced by TLR4 activation through LPS that up-regulates NF-κB activation and initiates high levels of CxCL8 to be produced from resident and infiltrating macrophages. In addition, the production of TNF and IL-1 from macrophages subsequently causes high levels of CxCL8 and other neutrophil-active chemokines to be produced from the structural cells of the lung. Thus, infecting bacteria provide both direct and indirect stimulation of chemokines that greatly exacerbate the disease process. Although clinical trials to block these chemokines have not been initiated in bacterial pulmonary diseases or in septic patients, there continues to be a great deal of interest for targeting these molecules in the lung.

Viral Clearance

While bacterial infections continue to provide clinical challenges, recent data suggest that many long-term pulmonary problems in otherwise healthy individuals are likely initiated by viral infections. This may be especially the case in developed countries where antibiotic therapy is pervasive and bacterial infections controllable. The clinical data appear clear that one of the common features of most pulmonary viral infections is the early and intense production of chemokines. The viruses that have been ascribed to producing chemokines upon infection of target cells include rhinovirus (RV), adenovirus, influenza virus, respiratory syncytial virus (RSV), as well as parainfluenza and severe acute respiratory syndrome (SARS). The one characteristic that these viruses have is an often intense inflammatory response that initiates damage in the lungs of susceptible patients. Those most at risk usually have underlying pulmonary diseases, such as asthma, COPD, or are transplant recipients, premature infants, and so forth, and suffer the most severe disease from the initiation of the antiviral inflammatory responses. Unlike bacterial infections the recruitment of neutrophils has little effect on the virus itself and only serves to promote pulmonary damage in the lung. Thus, in many patients with underlying pulmonary disease the side effects of virus-induced inflammation can be devastating.

The initiation of the earliest events in viral responses is the recognition of one of many types of viral nucleic acids, double- and single-stranded RNA or DNA, by immune cell-associated proteins that recognize pattern-associated molecular patterns (PAMPs). The best characterized of the innate receptors are toll-like receptors that can quickly initiate an effective innate immune response by activation of several mediator pathways and initiate the production of chemotactic factors for recruitment of the proper immune cell types. One of the clearest activation events is via MyD88 adapter protein pathways that are initiated with all TLRs but TLR3, which recognizes dsRNA. Importantly, antiviral TLR7 and TLR8 that recognize ssRNA and TLR9 that recognizes unmethylated CpG motifs found in bacteria and DNA viruses potentially promote a common set of mediators (Fig. 24-5). These TLRs, through MyD88-mediated pathways, activate NF-κB and allow a number of chemokines to be produced, such as CxCL8 and CCL2. In addition to the NF-κB–mediated chemokine production, an alternative activation pathway via IRF7 can also be initiated for the production of a number of other chemokines including CCL3, CCL5, and CxCL10 via a type I IFN-mediated pathway. These important chemokines together allow the accumulation of specific leukocyte populations associated with effective viral clearance, including natural killer (NK) cells and CD4 T cells as well as CD8 cytotoxic T-cell populations. MyD88-mediated pathways are also initiated by most IL-1R family responses, including IL-1β and IL-18. In addition to the MyD88-mediated pathway of activation another adapter, TICAM-1 (TRIF), which is the only adapter known to be used by TLR3, also initiates a specific subset of chemokines due to the activation of IRF-3. In particular, those same chemokines induced by IRF7, CCL5, and CxCL10 are also induced by this pathway along with type I IFN production. Thus, these pathways likely synergize to create multiple activation sources for a whole array of chemokines. For example, a negative strand RNA virus such as influenza will go through both an ssRNA and dsRNA

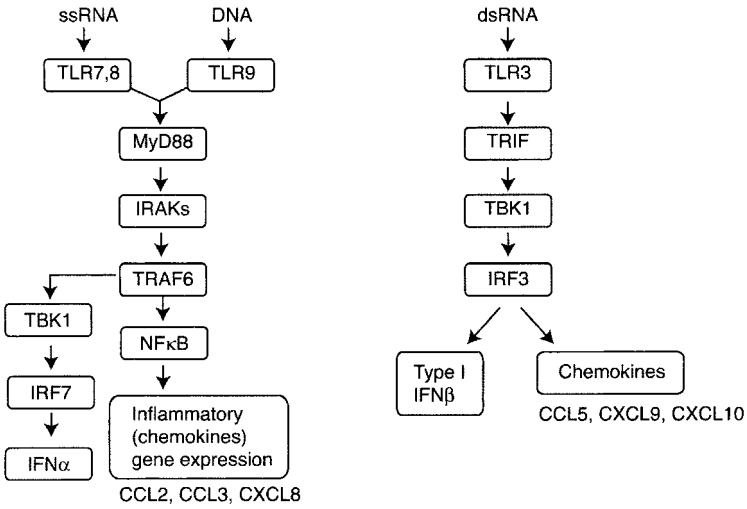

Figure 24-5 TLR activation by viral pattern-associated molecular patterns (PAMPs) lead to inflammatory chemokine production.

stage and would therefore induce both a TLR3 → TICAM-1 → IRF3 pathway and TLR7,8 → MyD88 → NF-κB or IRF7 pathway. Thus, a broad profile of chemokines to recruit multiple cell types would be produced both for the benefit and to the detriment of the lung, depending upon the success of the clearance mechanisms. Although these TLRs have been primarily subscribed to promote immune cell function, many of the studies outlining these processes have been performed on structural cells. Several studies have now outlined that viral responses themselves can up-regulate TLR expression on airway epithelial cells and other structural cells of the lung. Thus, one must consider that epithelial cells, which are usually the primary target for infection, would be the initial source of chemokines due to their expression of TLRs and may provide a significant source of chemokines initially needed for clearance of virus, but can also lead to tissue damage if overactivated. Future studies designed to focus on the differential role of TLR activation in acute and chronic pulmonary disease should highlight these differences.

Asthma

Asthmatic inflammation is one area that has attracted a great deal of attention and funding from both private and public organizations. The early immune responses in allergic asthma stem from immunoglobulin E (IgE)-mediated mast cell degranulation and release of chemotactic mediators, such as LTB4 and chemokines. The release of these factors quickly causes the recruitment of granulocytes and mononuclear cells that continue to respond to the allergen by production of type 2 cytokines, IL-4, IL-5, and IL-13. The initiation of this Th2-type environment promotes the production of a characteristic set of chemokines that has been associated with severe asthmatic responses, including CCL11, CCL2, CCL7, CCL17, CCL22, as well as several others. The receptors for these chemokines, CCR3 and CCR4, have been long implicated in the disease process due to their expression on eosinophils and Th2 cells, respectively. Thus, the immune environment created by the immune response dictates the chemotactic molecules that are produced. Although our understanding of how severe asthma develops and progresses has become more focused on inflammation, a number of issues still remain. It appears, for example, that viral exacerbation of asthma promotes the most severe disease phenotypes and initiates crisis events leading to emergency room visits. As indicated previously, this may be due to the activation of a distinctly different set of chemotactic mediators that, together with those induced by the allergen response itself, promote a very intense and diverse set of responses that appear to persist for long periods of time. The lack of resolution of these infectious stimuli in the asthmatic lung, perhaps due to the Th2 environment, likely leads to the chronic phenotype and remodeling of the airway that is associated with the most severe conditions. In addition to enhancing recruitment of cell populations associated with asthma, eosinophils, and CD4+ T cells, additional cell populations are also recruited in an attempt to take care of the viral responses, including CD8+ T cells. It has now been recognized that the CD8+ T cell is associated with the most intense and severe asthmatic disease phenotypes. Thus, the severity of asthmatic disease may not be due to a single set or class of chemoattractants, but rather to the overproduction of several different mediators leading to the recruitment and activation of a number of leukocyte subsets that are not characteristic to allergen or virus responses alone.

CONCLUSIONS

The chemotactic migration of leukocytes during inflammatory/immune reactions in lung requires multiple steps and participation by many chemotactic factors. The use of specific chemoattractants during various phases of disease progression can dictate not only the type of cell to be recruited, but also the outcome on the tissue cells in the area of disease. In the lung, the overproduction or incorrect profile of chemoattractants can cause damaging processes that lead to severe and chronic disease and dysfunction. The specific inhibition of particular chemoattractant molecules during inflammatory events may provide beneficial therapeutic outcomes although it is likely that during any inflammatory response multiple mediators are involved and the inhibition of a single chemoattractant molecule may not offer complete control of the response.

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25

Oxidative and Nitrosative Lung Injury

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Lung injury can present with differing signs and symptom complexes that emanate from a variety of etiologies. However, whether it is the adult respiratory distress syndrome (ARDS) or other forms of lung injury, inflammatory stimuli giving rise to the generation of reactive oxygen species (ROS) and reactive oxygen-nitrogen species (RONS) contribute to lung pathophysiology. Generation of RONS not only initiates injury, but amplifies inflammatory pathways ultimately culminating in enhanced tissue damage, in this case, in the lung. Thus, precursor cell activation leads to the formation of RONS, which perpetuate a vicious cycle of inflammatory cell recruitment and production of cytotoxic mediators that culminates in injury to the alveolar capillary endothelium, epithelium, and connective tissue—all of which are important in maintaining lung integrity. Clinically, the net result will generally be dyspnea, tachypnea, and arterial hypoxemia due to respiratory failure, and may require intubation and mechanical ventilation. While many patients manifest predominantly respiratory signs and symptoms, systemic inflammation fueled in part by RONS can involve extrapulmonary vital organ systems, many times leading to the development of the multiple organ dysfunction syndrome (MODS) and death.

FORMATION OF OXIDATIVE AND NITROSATIVE SPECIES

Reactive Oxygen Species

Most forms of lung injury involve oxidative injury via the liberation of ROS from the reduction of molecular oxygen. ROS implicated in pulmonary pathophysiology include superoxide radicals ($\cdot O_2^-$), hydrogen peroxide (H_2O_2), hydroxyl radical (OH^-), and hypochlorous acid (HOCl) (Fig. 25-1). Superoxide anion generation has been demonstrated from a variety of biologic sources. An important enzymatic source of superoxide is nicotinamide adenine dinucleotide phosphate (NADPH) oxidase which catalyzes a one-electron reduction of molecular oxygen to form $\cdot O_2^-$. NADPH oxidase is an

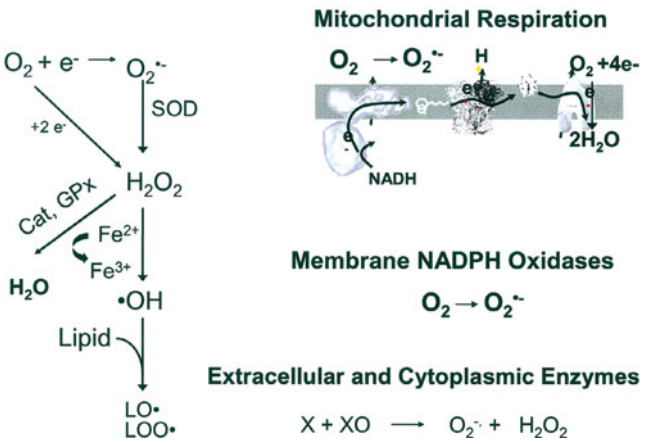

Figure 25-1 Generation of reactive oxygen intermediates by the incomplete reduction of oxygen in the mitochondria, cytoplasm, and cell membrane and extracellular space. O_2 = oxygen; $\cdot O_2^-$ = superoxide radical; H_2O_2 = hydrogen peroxide; $\cdot OH$ = hydroxyl radical; SOD = superoxide dismutase; Cat, GPx = catalase and glutathione peroxidase; LO·, ·LOO = lipid peroxides; X, XO = xanthine and xanthine oxidase, respectively; NADH = nicotinamide adenine dinucleotide; NADPH = nicotinamide adenine dinucleotide phosphate.

enzyme complex derived after the activation of phagocytes by microorganisms or their products that includes lipopolysaccharide (LPS), tumor necrosis factor (TNF), and interleukin (IL)-8. NADPH oxidase is vital for yielding ROS in phagocytic cells that inhabit the lung (e.g., macrophages and polymorphonuclear cells) where these species play a role in host defense mechanisms, targeting killing and removal of invading microorganisms. However, RONS (see later) are also implicated in the pathogenesis of both pulmonary- and nonpulmonary-based diseases which typically are also associated with inflammation. It is not surprising then that a variety of systems are present to prevent or limit oxidative tissue injury. In this context, and specific for superoxide, are superoxide dismutases (SOD) that catalyze the conversion (dismutation) of two moles of $\cdot O_2^-$ to H_2O_2, which is subsequently converted to water by catalase and glutathione peroxidase (Fig. 25-1). Copper (Cu)/zinc (Zn) SODs (CuZn) are present in the cytosol, while manganese (Mn) SOD is found in the mitochondria. An extracellular form of SOD (ECSOD) has also been identified and may play an important role not only in converting extracellular $\cdot O_2^-$ to hydrogen peroxide but also in controlling blood pressure by modulating the reaction of $\cdot O_2^-$ with nitric oxide (NO). In newborns ECSOD exists both intracellularly and extracellularly and plays an important role in intracellular antioxidant defenses. These enzymes possess a very high reaction constant that allows for the rapid dismutation of $\cdot O_2^-$ to H_2O_2.

Additional sources of superoxide include xanthine oxidase, nitric oxide synthase (under conditions that lead to uncoupling of electron transfer; discussed later), and components of the mitochondrial electron transport chain (Fig. 25-1). Xanthine oxidase (XO) catalyzes the oxidation of xanthine (or hypoxanthine) by molecular oxygen to form uric acid and $\cdot O_2^-$. Xanthine dehydrogenase (present in the liver) converts xanthine (or hypoxanthine) to uric acid without forming partially reduced forms of molecular oxygen. During ischemia and the subsequent reperfusion phases, xanthine dehydrogenase is reduced to XO, which may be released into the circulation, and is known to bind to pulmonary endothelial cells, thus acting as an intense focus for the production of ROS. Similarly, mitochondrial generation of superoxide also has been documented, and although precise function for this process remains unclear, roles in cell signaling and regulation of cell death have been proposed.

PRODUCTION OF NITRIC OXIDE AND REACTIVE NITROGEN SPECIES

Nitric oxide synthases (NOS) catalyze the formation of ·NO and L-citrulline from L-arginine, and oxygen via a 5-electron redox reaction that also involves cofactors including NADPH, flavin adenine dinucleotide (FAD), and tetrahydrobiopterin. Various forms of NOS have been identified: NOS-1 or neuronal NOS (nNOS), NOS-2 or inducible NOS (iNOS), and NOS-3 or endothelial NOS (eNOS). nNOS and eNOS are expressed constitutively, and their activity is regulated largely by changes in intracellular Ca^{2+} concentration. Although previous studies claimed that iNOS was not expressed constitutively, more recent findings show expression of iNOS in both inflammatory and lung cells of humans and mice under baseline conditions with significant up-regulation of mRNA, protein, and activity following exposure to cytokines and LPS. A form of NOS also has been identified in the mitochondria and may play an important role in regulating mitochondria function.

RONS refer to a variety of nitrogen-containing molecules that are typically derived via nitric oxide (·NO) reactions. RONS implicated in pulmonary pathology include peroxynitrite ($ONOO^-$), nitrogen dioxide (NO_2), and nitroxyl (HNO) which can be formed via NO reactions, as discussed later in the chapter, but also through environmental exposure and inhalation (Fig. 25-2). Peroxynitrite is formed by the rapid reaction of NO with superoxide and when protonated (addition of H^+), will decompose into nitrogen dioxide (NO_2) and hydroxyl radicals (·OH) as well as nitrate (NO_3^-). These species may then interact with each other as well as with oxygen, forming higher oxides of nitrogen which may oxidize thiols, nitrate aromatic amino acids (most notably tyrosines), nitrosate, and glutathionylate cysteines and oxidize a variety of amino acids including methionine and cysteines (Table 25-1). Myeloperoxidase (MPO), present in pulmonary neutrophils and secreted during their activation, catalyzes the production of nitrating, oxidizing, and chlorinating species from H_2O_2, chloride and nitrite (Fig. 25-2). Currently, there is considerable controversy as to the source and origin of nitrating intermediates in vivo, with some studies showing that MPO knockout mice (but not iNOS knockout mice, or mice-depleted of inflammatory cells) exhibit significantly less nitration following exposure to pathogens as well oxidant gases.

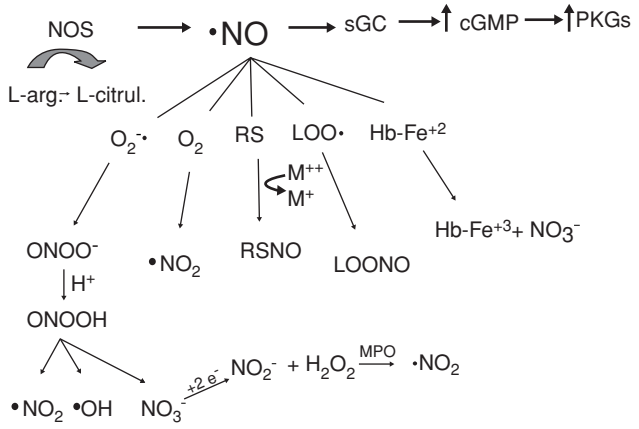

Figure 25-2 Generation of reactive nitrogen species. Nitric oxide synthases (NOS) catalyze the formation of nitric oxide (·NO) and L-citrulline from L-arginine. NO either binds to the heme center of soluble guanylate cyclase (sGC) leading to increased production of cyclic guanosine monophosphate (cGMP) and activation of cGMP-dependent protein kinases (PKGs), binds to oxygenated hemoglobin (Hb-Fe^{+2}) to form nitrate (NO_3^-), or interacts with superoxide ($\cdot O_2^-$), molecular oxygen (O_2), thiols (RS), or lipid peroxides (LOO·) to form various intermediates. $ONOO^-$, ONOOH = peroxynitrite and peroxynitrous acid, respectively, $\cdot NO_2$ = nitrogen dioxide, RSNO = nitrosothiols; LOONO = nitrated unsaturated fatty acids; ·OH = hydroxyl radicals, NO_2^- = nitrite; MPO = myeloperoxidase; M = metal.

As shown in Fig. 25-2, nitrite (NO_2^-) may serve as a substrate for nitrotyrosine formation via reactions with peroxidases. More recently, nitrite has emerged as playing a key role in supporting NO formation during hypoxemia and tissue ischemia and in this context is shown to protect against reperfusion injury. Moreover, nitrite reactions in vivo also lead to diverse NO-dependent protein adducts including S-nitrosothiols and C-/N-nitrosamines, underscoring the rich biochemical interplay between distinct RNS and ROS. The therapeutic potential for this inorganic anion in replenishing NO during low oxygen states has also been demonstrated in the lung, with inhalation of nitrite-reversing pulmonary hypertension analogous to inhaled NO. A key difference between nitrite and NO however is the lack of rebound hypertension upon withdrawing inhaled nitrite.

Reactive Oxygen-Nitrogen Species as Signaling Molecules

Formation of RONS is related to the inflammatory environment within the lung at a particular point in time, which has the potential to generate noxious concentrations of products detrimental to lung function. Production of ·NO in the lung serves as an important regulator of local functions, including airway tone, pulmonary vascular tone, mucin secretion, ciliary function, and ion channel activity. The role of ·NO is extremely complex, and probably depends ultimately on its concentration, timing of production during injury, and association with other biomolecules and proteins and formation of specific redox congeners. In the latter context, in addition to the RNS discussed previously, relatively stable NO adducts including S-nitrosothiols are important and discussed later.

Activation of Cyclic Guanosine Monophosphate (cGMP)-dependent Protein Kinase

NO binds to the heme group of soluble guanylate cyclase (sGC) leading to an increase in cGMP levels. Many effects of cyclic guanosine monophosphate (cGMP) are mediated by various isoforms of cGMP-dependent protein kinase (PKG) which phosphorylate various substrate proteins, thereby reducing intracellular Ca^{+2} and causing smooth muscle relaxation. ·NO-mediated increases in cGMP levels also decrease platelet aggregation and adhesion of neutrophils to endothelial cells, thus reducing oxidant load. At lower concentrations, RONS function as signaling molecules (Table 25-1) regulating fundamental cellular activities such as cell growth and adaptation responses, while at higher concentrations they can induce significant cellular injury, apoptosis, and death.

Activation of Nuclear Factor-κB

Nuclear factor-κB (NF-κB), a transcriptional regulating protein, is among the most important transcription factors responsive to ROS during inflammation and oxidant stress. NF-κB is one member of a ubiquitously expressed family of *Rel*-related transcription factors. These are a family of structurally related eukaryotic transcription factors that are involved in the control of a vast array of processes, including immune and inflammatory responses, growth, development, and apoptosis. The production of ROS, cytokines, or other inflammatory stimuli can activate NF-κB and induce gene expression, eliciting a response generally observed to be proinflammatory in nature. Specifically, various signals such as ROS/RNS, cytokines, or inflammatory stimuli converge to activate the inhibitory-κB kinase (ILK) complex via the upstream NF-κB–inducing kinase (NICK). The ILK-α/ILK-β complex then phosphorylates inhibitory-κB (I-κB) at two N-terminal serines that signal its ubiquitination and destruction by the ^{26}S proteasome system. NF-κB can then enter the nucleus and bind specific κB-promoter sequences to activate gene expression. Various studies have reported activation of NF-κB in alveolar macrophages from patients suffering from ARDS.

Intracellular Ca^{+2}, Protein Kinase C, and Mitogen-activated Protein Kinase

Evidence also indicates that ROS lead to increases in intracellular calcium concentrations which correlate with endothelial permeability. Some observations suggest that Ca^{2+} influx occurs through membrane Ca^{2+} channels that are regulated by ·OH generation; however, this remains controversial due to differing effects depending on cell lines. Myosin light chain kinase phosphorylation also increases when endothelial cells are treated with H_2O_2, suggesting that endothelial contraction

Table 25-1

Actions of Reactive Nitrogen Species

Immunoglobulins (Fe Receptors)	**Complement Receptors for**
Signal Transduction	
	Vessel relaxation
Activation of cGMP/PKG	Bronchodilation
	Modification of ion channel function
	Inhibition of platelet aggregation
cGMP-independent	Activation of NF-κB; MAPK
S-thiolation	NMDA, PKC, adenylate cyclase,
S-nitrosation	complex I, cardiac ryanodine receptor, L-type calcium channels, GPx + others, Caspase-3, p21ras, CFTR
Interactions/modifications	
Binding to heme protein metal centers	Inhibition of protein and DNA synthesis
	Inhibition of mitochondria respiration and ATP production
	Increased methemoglobin levels
	Deactivation of NOS
	Enzyme inhibition (lipooxygenase, cyclooxygenase; ribonucleotide reductase)
Post-translational modifications	
Nitration	Proteins: ceruloplasmin; SP-A; transferrin; albumin, α1-protease inhibitor; actin; α1 - antichymotrypsin; MnSOD β-chain fibrinogen
	Lipids
Oxidation/Deamination	Lipids, sulfhydryls, DNA base

Abbreviations: NF-κB, nuclear factor = κB; MAPK, mitogen-activated protein kinase; NMDA; PKC, protein kinase C; GPx, glutathione peroxidase; CFTR, cystic fibrosis transmembrane conductance regulator; ATP, adenosine triphosphate; NOS, nitric oxide synthases; SP-A, Surfactant protein-A; Mn SOD, manganese superoxide dismutases.

may play an essential role in oxidant-induced endothelial barrier dysfunction. It appears that an important fundamental requirement for vascular endothelial permeability is the activation of endothelial contraction.

Additional signaling molecules such as protein kinase C (PKC), mitogen-activated protein kinase (MAPK), tyrosine kinases, and Rho GTPases appear vital in mediating endothelial barrier dysfunction. PKC (a family of serine/threonine protein kinases consisting of at least 12 isoforms) is activated in response to oxidants and increases endothelial permeability. In guinea pig lungs pretreated with H-7 (a nonspecific PKC inhibitor acting on the catalytic site of the enzyme), there was no increase of the pulmonary capillary filtration coefficient in response to perfusion of H_2O_2. Increases in pulmonary microvascular permeability were accompanied by reorganization of actin cytoskeleton, a process inhibited by PKC inhibitors. The exact mechanism(s) of the role PKC plays in endothelial barrier function is complex but appears due to activation of ROS and probably involves only a few select PKC isoforms. The MAPK pathway is activated by ROS and is an important mediator of cellular responses to oxidant stress. The ERK (extracellular signal-regulated kinases), JNK (c-JUN NH_2-terminal kinase), and p38 cascades all contain the same series of three kinases. A (MEK) MAPK/ERK kinase phosphorylates and activates an MAPK, and then MEK phosphorylates and activates an MAPK. Various ROS, most notably H_2O_2, have been demonstrated to mediate endothelial injury via stimulation of ERK pathways. This H_2O_2-mediated action was inhibited by PD-98059, an ERK (MEK) inhibitor. Furthermore, both ROS and RNS induce a variety of actions that are potentially detrimental and include abnormal cell differentiation/proliferation, apoptosis, and DNA damage, with the ERK pathway implicated as playing the predominant role.

There also appears to be an emerging role for tyrosine-mediated phosphorylation of functional proteins resulting in increased endothelial cell permeability. Focal adhesion kinase (FAK) is a nonreceptor kinase involved in regulating structure and function of focal adhesions, which are critical for maintaining endothelial integrity via cell-cell and cell-matrix interactions. Tyrosine phosphorylation of FAK has been associated with alterations in the actin cytoskeleton network and relocation of focal adhesion-associated proteins, actions potentially precipitating pulmonary edema formation.

Adhesion Molecules

In addition to inducing changes in endothelial cell conformation and integrity, ROS have been shown to promote cellular and molecular events that result in enhanced aggregation and adhesion of leukocytes to endothelium. Prominent inflammatory participants emanating from these investigations include intercellular adhesion molecule-1 (ICAM-1) and selectins (a family of transmembrane molecules, expressed on the surface of leukocytes and activated endothelial cells involved at enhancing leukocyte-endothelial interactions). Investigations in diverse models implementing a variety of oxidant-generating systems (hypoxanthine/xanthine oxidase, H_2O_2, prolonged hyperoxia) have demonstrated consistent increases in ICAM-1 and P-selectin expression in the vascular endothelium, which promote leukocyte adhesion. Interestingly, expression of these biomolecules is not uniform throughout the vasculature. For example, following exposure of isolated lungs to normobaric hyperoxia, P-selectin expression was augmented in the arterioles, while ICAM-1 expression was induced in the pulmonary venules and capillaries.

Post-translational Modifications

The generation of oxidants has been documented under a variety of clinical conditions in a number of studies. Unfortunately, direct evidence implicating oxidants as pathological contributors in diseases such as acute lung injury (ALI) and ARDS is very difficult to find. Unequivocal measurements of ROS in biologic tissues and fluids are nearly always unsuccessful, both because the biologic half-life of these molecules is in the range of nanoseconds to milliseconds, and because concentrations may vary dramatically within the time course of a particular disease state. On the other hand, relatively stable byproducts of these species, such as hydrogen peroxide, nitrite and nitrate as well as long-lived products of reactions of RNS/ROS with tissues and specific proteins are routinely detected in exhaled breath, alveolar lavage, plasma, urine, and autopsy or biopsy specimens.

Higher oxides of NO (such as NO_2, N_2O_3, etc.) induce the formation of *S*-nitrosothiols from cysteine residues in the reaction called *S*-nitrosylation. This reaction has been determined to modify the activity of a large number of proteins involved in cellular regulatory mechanisms in a reversible fashion and has been the subject of numerous reviews.

$ONOO^-$ can oxidize thiols and lipoproteins, and damages both DNA and the mitochondrial electron transport chain. Equally important, $ONOO^-$ nitrates phenolics, including tyrosine residues in proteins. 3-Nitrotyrosine residues, which are the products of the addition of a nitrogroup (NO_2) to the other position of the OH group of tyrosine, are stable end products of RONS-mediated reactions. Thus, they represent "footprints" of RNS activity that can be detected by immunohistochemistry, enzyme-linked immunoabsorbent assay, high-pressure liquid chromatography, or mass spectrometry. In vitro, proteins can be nitrated by either $ONOO^-$ per se or by reactive intermediates formed by peroxidase (e.g., MPO) catalyzed reactions of reactive species (H_2O_2, Cl^-, and $\cdot NO_2^-$) liberated from activated neutrophils. A number of studies have provided evidence that nitration reactions occur in vivo during inflammatory processes.

FUNCTIONAL CONSEQUENCES OF PROTEIN NITRATION IN VITRO

Surfactant Protein-A

Protein nitration and oxidation by ROS and RNS in vitro have been associated with the diminished function of a variety of crucial proteins. Considerable levels of protein-associated nitrotyrosine (~400–500 pmol/mg protein), as well as nitrated surfactant protein-A (SP-A) were present in pulmonary edema fluid from patients with either ALI/ARDS or hydrostatic pulmonary edema, and in bronchoalveolar lavage fluid (BALF) of patients with ARDS (Fig. 25-3). In vitro studies have indicated that nitrated SP-A loses its ability to enhance the adherence of *Pneumocystis carinii* to rat alveolar macrophages. Thus, nitration of SP-A may be one factor responsible for the increased susceptibility of patients with ARDS to nosocomial infections. The use of inhaled NO in patients with ARDS was shown to increase both 3-nitrotyrosine and 3-chlorotyrosine (an index of neutrophil activation) concentrations compared to similar patients that did not receive inhaled NO.

Histone Deacetylases

A study by Ito et al demonstrates the complex interplay that exists between ROS and RNS, and their potential contributions to the pathogenesis of disease. Histone deacetylases (HDAC) are important enzyme systems that protect DNA after cell activation in order to minimize DNA vulnerability. Reduction in HDAC activity is thought to be one factor that may aggravate inflammation. In this study, IL-1β stimulated BEAS-2B cells were exposed to H_2O_2 and peroxynitrite for 2 h. Interestingly, HDAC-2 was significantly nitrated at 0.5 h after stimulation, and nitration was maximum at 4 h (Fig. 25-4). Additionally, HDAC-2 activity was observed to be directly regulated by $ONOO^-$ as demonstrated by enhanced nitrotyrosine formation in the presence of SIN-1 (an $ONOO^-$ generator). Lastly, SIN-1 significantly decreased IL-1β–induced HDAC-2 activity. These findings support the notion, at least in vitro, that ROS/RNS-enhanced IL-1β–induced inflammatory cytokine release is a consequence of reduced HDAC activity due to tyrosine nitration.

Current In Vivo Evidence Implicating Reactive Nitrogen Species and Reactive Oxygen Species as Contributors to Lung Injury

Toxicity from oxygen-nitrogen metabolites released by stimulated neutrophils, macrophages, and other cells has been proposed as one of the significant mechanisms of lung injury.

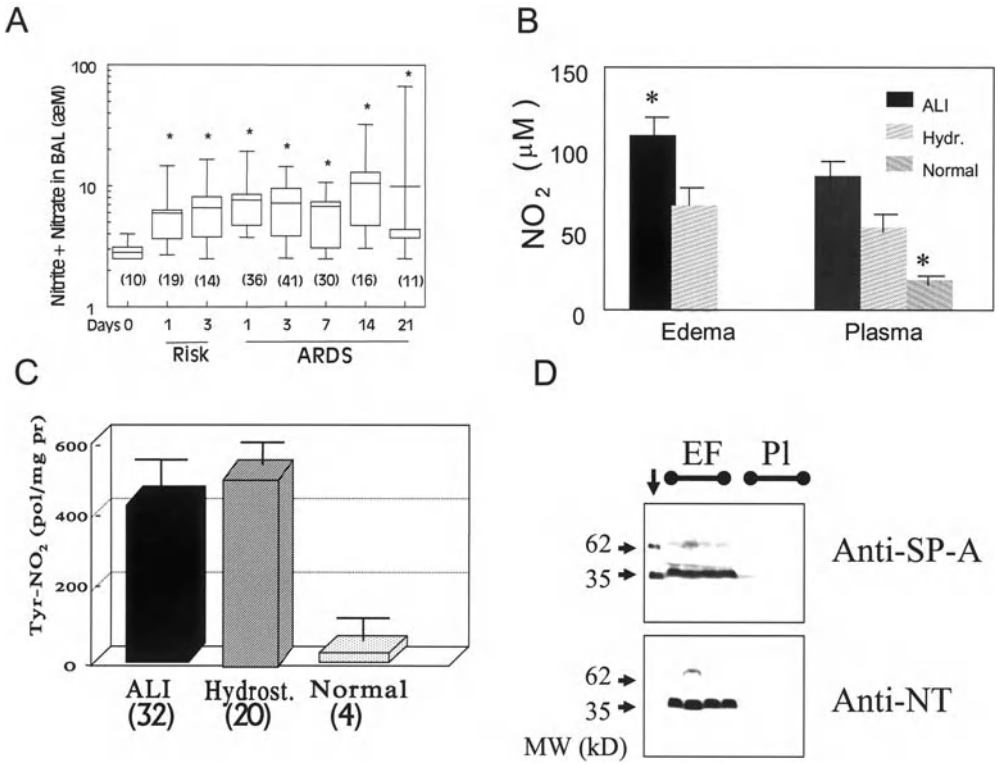

Figure 25-3 Evidence for increased levels of reactive oxygen-nitrogen intermediates and nitrated proteins in the bronchoalveolar lavage fluid (BALF), edema fluid (EF), and plasma (Pl) of patients with acute respiratory distress syndrome (ARDS) and hydrostatic pulmonary edema. *A*. Nitrate and nitrite concentration in BALF from normal volunteers (NL), patients at-risk for ARDS (RISK), and patients with established ARDS (ARDS) studied at sequential times. The horizontal axis shows the patient group and the day on which the BAL was performed. (n) = number of subjects in each group. The data are presented as box plots showing the 10th, 25th, 75th, and 90th percentiles and the median. (*) $p \leq 0.005$ vs. normal subjects. (*From Sittipunt C, Steinberg KP, Ruzinski JT, et al: Nitric oxide and nitrotyrosine in the lungs of patients with acute respiratory distress syndrome. Am J Respir Crit Care Med 163:503–510, 2001.*) *B*. Nitrate and nitrite in pulmonary edema fluid and plasma samples from acute lung injury (ALI), hydrostatic edema patients (Hydr.), and normal volunteers. Numbers in parenthesis are sample numbers. Values are means ± SEM. (*From Zhu S, Ware LB, Geiser T, et al: Increased levels of nitrate and surfactant protein A nitration in the pulmonary edema fluid of patients with acute lung injury. Am J Respir Crit Care Med 163:166–172, 2001.*) *C*. Levels of nitrated proteins (measured by enzyme-linked immunosorbent assay) in the plasma of patients with acute lung injury (ALI), hydrostatic edema (Hydrost.), and normal volunteers (Normal). Values are means ± SEM (n = number of patients or volunteers). (*Data adapted from Zhu S, Ware LB, Geiser T, et al: Increased levels of nitrate and surfactant protein A nitration in the pulmonary edema fluid of patients with acute lung injury. Am J Respir Crit Care Med 163:166–172, 2001.*) *D*. Nitration of surfactant protein A (SP-A) in pulmonary edema fluid samples from ALI/ARDS patients. SP-A was immunoprecipitated from edema fluid (EF) or plasma (Pl) from four patients with ALI/ARDS. Immunoprecipitated SP-A was probed with polyclonal antibodies to SP-A (anti-SP-A) or nitrotyrosine (anti-NT). Nitrated SP-A was detected in the pulmonary edema fluid but not in the plasma of all patients. Vertical arrow shows purified human SP-A from a patient with alveolar proteinosis. Notice the lack of nitration in the control sample. (*From Zhu S, Ware LB, Geiser T, et al: Increased levels of nitrate and surfactant protein A nitration in the pulmonary edema fluid of patients with acute lung injury. Am J Respir Crit Care Med 163:166–172, 2001.*)

One of the initial studies published described the effects of inflammation on α-1-proteinase inhibitor (α-1-PI), which was found to be inactivated in BALF samples from patients with ARDS. This contrasted to plasma samples from the same patients that retained more than 90 percent α-1-PI activity. The activity of α1-PI could be restored by the reducing agent, dithiothreitol, implicating oxidants generated in bronchoalveolar lavage as responsible for its loss of function. Shortly thereafter a different group measured expired fractions of hydrogen peroxide (H_2O_2), a more stable membrane-permeable and volatile oxidant. These samples were collected in patients with normal lungs undergoing elective surgery and critically ill patients suffering from acute hypoxemic respiratory failure (AHRF). Expired breath condensates of H_2O_2 were observed to be significantly greater in patients suffering from AHRF and focal pulmonary infiltrates than those without pulmonary infiltrates, indirectly implicating increased oxidation. Interestingly, H_2O_2 concentrations were greatest in patients with head injury and sepsis, whether pulmonary infiltrates were present or not. This unexpected finding suggested the participation of oxidants in sepsis and other forms of vital organ injury, such as in the brain.

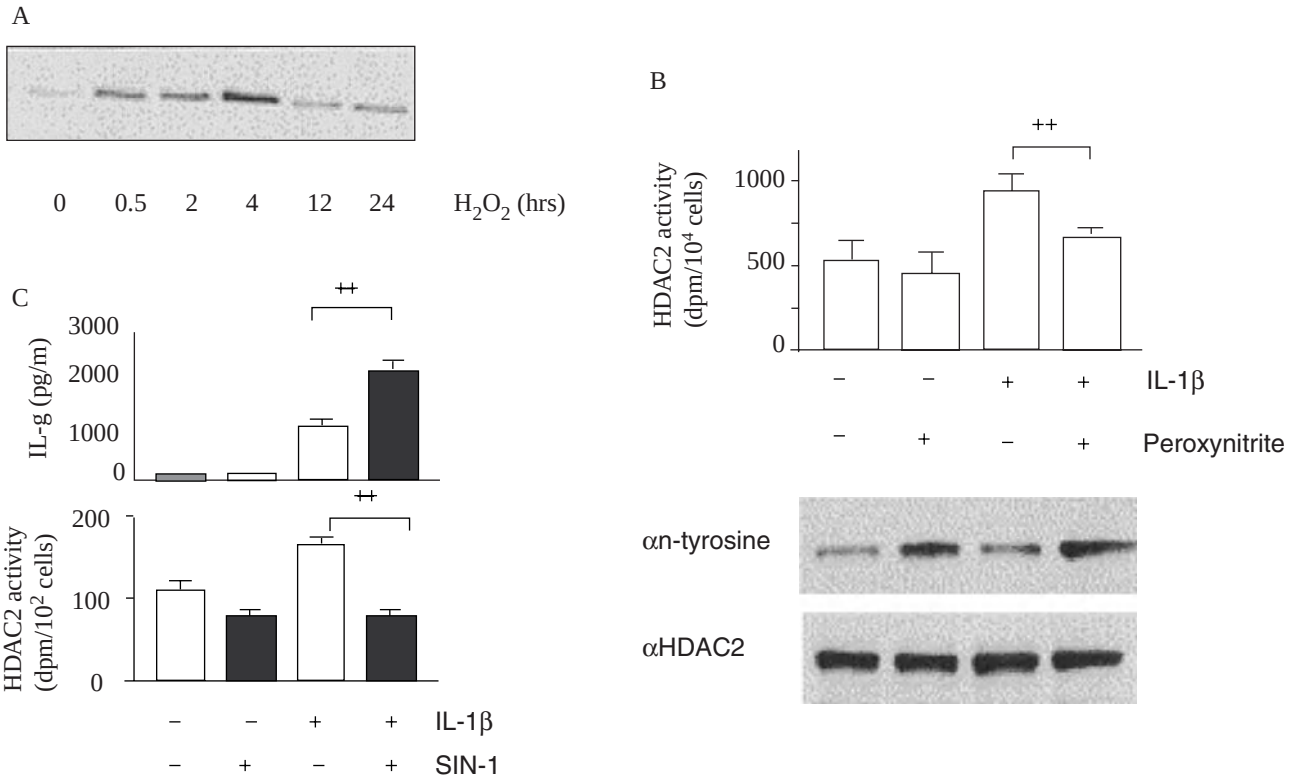

Figure 25-4 H_2O_2 and peroxynitrite induce histone deacetylase-2 (HDAC-2) tyrosine nitration and suppression of HDAC activity. *A*. Western blotting analysis of H_2O_2-induced tyrosine nitration of HDAC-2 in BEAS-2B cells. Cells were collected after the indicated time, HDAC-2 immunoprecipitated, and nitrotyrosine levels were determined. *B*. Peroxynitrite directly regulates HDAC-2 activity and nitration. Cells were stimulated with interleukin (IL)-1β (1 ng/ml) or control medium and after 1 h were collected, lysed with immunoprecipitation buffer, and immunoprecipitated with anti-HDAC-2 antibody. Peroxynitrite (500 nM) was incubated with the immunoprecipitates from IL-1β-treated or nontreated cells for 10 min at 30°C. HDAC activity assay and Western blotting for nitrotyrosine and HDAC-2 protein were performed. Results are expressed as means ± SEM (n = 3). $^{**}p < 0.01$ compared to IL-1β-stimulation. *C*. SIN-1 (500 μM) attenuates HDAC-2 immunoprecipitated HDAC-2 activity and enhanced IL-8 production. Results are expressed as means ± SEM (n = 3). $^{**}p < 0.01$ compared to IL-1β-stimulation. (*From Ito K, Hanazawa T, Tomita K, et al: Oxidative stress reduces histone deacetylase 2 activity and enhances IL-8 gene expression: Role of tyrosine nitration. Biochem Biophys Res Commun 315:240–245, 2004.*)

Further studies have continued to create a solid foundation that implicates oxidant generation as a significant contributor to inflammatory-mediated lung injury. In fact, in one of the most recent studies, levels of plasma hypoxanthine, a key cofactor that accumulates during intervals of hypoxia leading to the production of O_2^- and H_2O_2, were found to be significantly elevated in patients with ARDS. Moreover, the highest concentrations occurred in patients that did not survive, implicating oxidative damage as an influential contributor to mortality. Higher levels of nitrate and nitrite were also noted in the bronchoalveolar lavage of patients with ARDS as compared to those of healthy volunteers, as well as in the edema fluid of patients with either ARDS or cardiogenic pulmonary edema (Fig. 25-3).

Substantial evidence supports the notion that ROS and RNS are injurious to the pulmonary epithelium in a number of pathological conditions. Induction of immune complex alveolitis in rat lungs results in increased alveolar epithelial permeability, which is associated with the presence of ·NO decomposition products in the BALF. Moreover, alveolar instillation of the NOS inhibitor N(G)-monomethyl-L-arginine ameliorates ·NO production and alveolar epithelial injury. Infection with pathogens such as *Bordetella pertussis* and influenza is associated with significant increases in ·NO production. While animals infected with *B. pertussis* demonstrated a significant reduction in ·NO production with NOS inhibition, the administration of NOS inhibitors to animals exposed to influenza increased survival.

Further evidence suggesting that RONS plays a role in pulmonary inflammation is derived from studies using transgenic *Nos2*$^{-/-}$ mice. Lung injury provoked by influenza exposure or hemorrhage and resuscitation is significantly reduced in these mutant mice. Contradictory results have been reported concerning the responses of *Nos2*$^{-/-}$ mice to hyperoxia, with some investigators reporting shorter survival periods while others found that these mice survived considerably longer, indicative of a protective effect of NO in oxidant injury.

The ''Good Side of NO"

Although formation of $ONOO^-$ can result in tissue damage, NO can ameliorate tissue injury by several mechanisms. As mentioned previously NO increases steady-state levels of cGMP resulting in vasodilation, and decreased platelet and neutrophil adhesion to endothelium, thereby reducing cell-mediated inflammatory damage. Additional anti-inflammatory mechanisms include down-regulation of the NF-κB pathway. The reaction of $\cdot NO$ with $\cdot O_2^-$ reduces steady-state levels of O_2^- and limits H_2O_2 buildup, which may be especially important under conditions favoring O_2^--dependent hydroxyl radical formation. Finally, by scavenging lipid radical species, such as alkoxyl ($LO\cdot$) and peroxyl ($LOO\cdot$) radicals, NO can inhibit oxidant-induced membrane and lipoprotein oxidation and terminate chain radical propagation reactions. These reactions may be of particular importance, since NO significantly concentrates in lipophilic cellular compartments. However, species resulting from the reaction of NO with lipid peroxides may themselves have biologic activity which could be either pro- or anti-inflammatory.

Inhaled Nitric Oxide and Acute Respiratory Distress Syndrome: An Ongoing Debate

Clinically, inhaled NO initially appeared to possess ideal properties for a selective pulmonary artery vasodilator in patients suffering from ALI/ARDS. In theory, selective pulmonary vasodilation would act on the endothelial surface of the lung to produce regional vasodilation in ventilated lung units, with the net effect being improved Pa_{O2}/F_{IO2} ratios and reduced pulmonary artery pressures. Unfortunately, this ideal agent has not withstood clinical scrutiny of its efficacy when administered to patients with lung injury. In fact, a recent review of inhaled NO compared to placebo or no therapy administered to patients with AHRF concluded that inhaled NO produced only moderate improvements in oxygenation and demonstrated no reduction in patient ventilator days or mortality. However, there is agreement that oxygenation generally improves for 24 to 36 hours, which under certain clinical circumstances and combined with alternative treatment strategies, may lend itself to a multimodal approach to treatment in a particular patient with ALI/ARDS. Potential pitfalls of the recent clinical evidence using inhaled NO in the treatment of patients suffering from inflammatory-mediated lung injury include: (1) oxygenation may have very little to do with survival in patients suffering from inflammatory-mediated lung injury (only ~20 percent of patients die of refractory hypoxemia); (2) benefits may have been masked by the negative effects of ventilator-induced lung injury; (3) long-term inhalation of NO may damage the lung by increasing steady state concentrations of RNS/ROS and thus overshadow their acute physiological benefit; (4) as many intensivists expect, inhaled NO may have been applied too late after the onset of injury since most enrollment occurred up to 72 h after patients presented. Thus, at the present time, the only recognized and Food and Drug Administration (FDA)-approved application for inhaled NO is for the treatment of hypoxic respiratory failure of term and near-term newborns.

HYPERCAPNIA: AN EXAMPLE OF A RADICAL QUANDARY?

The effect of CO_2 in excess (hypercapnia) and its impact on the generation of ROS/RNS is generating increasing clinical interest. Due to the relatively higher concentration of CO_2 in plasma (1.2 mM), the majority of $ONOO^-$ generated in biologic fluids will react with CO_2 to form the nitrosoperoxycarbonate anion ($O=N-OOCO_2^-$). These species are more likely to nitrate and less likely to oxidize proteins (Fig. 25-5). CO_2 also up-regulates iNOS by an as-yet uncharacterized mechanism. Thus, hypercapnia may either protect or enhance oxidant injury. For example, hypercapnia augmented the LPS-induced injury across fetal alveolar epithelial cells in vitro and rabbit lungs in vivo. On the other hand, hypercapnia and acidosis decreased the inactivation of pulmonary surfactant by plasma proteins. Thus, the precise mechanism and consequences of hypercapnia are still unknown.

Therapies to Attenuate Reactive Nitrogen Species/Reactive Oxygen Species-Mediated Lung Injury

While the direct measurements of oxidants pose problems, monitoring of antioxidant concentrations and oxidant-antioxidant balance can also be assessed. For instance, levels of selected antioxidants, including plasma ascorbate, a major plasma antioxidant, were significantly decreased in patients with ongoing ARDS when compared to healthy controls. In addition, ubiquinol, a key lipid-soluble antioxidant residing in the membranes of the mitochondria, was significantly decreased in patients suffering from ARDS. Interestingly, α-tocopherol, another plasma antioxidant, was unchanged. In a series of separate experiments, after plasma from a healthy donor was incubated with activated polymorphonuclear cells, rapid oxidation of ascorbate was observed. The ubiquinol concentration slowly and steadily decreased over time, whereas α-tocopherol levels remained virtually unchanged. Glutathione (GSH), which is the most abundant non-protein thiol, is also an important antioxidant, especially for reducing H_2O_2 and HClO, which are produced by activated neutrophils. Recently, samples of BALF and epithelial lining fluid were analyzed for GSH in 10 patients with ARDS and found to be decreased when compared to healthy controls. In a subsequent study, N-acetylcysteine was administered to patients with ARDS and significantly improved oxygenation, pulmonary mechanics, and increased total plasma GSH concentrations. Catalase, a scavenger of H_2O_2, was found to increase in patients with sepsis with and without the eventual progression to ARDS. Interestingly, GSH peroxidase activity was unchanged when compared between control subjects, septic patients without ARDS, and septic

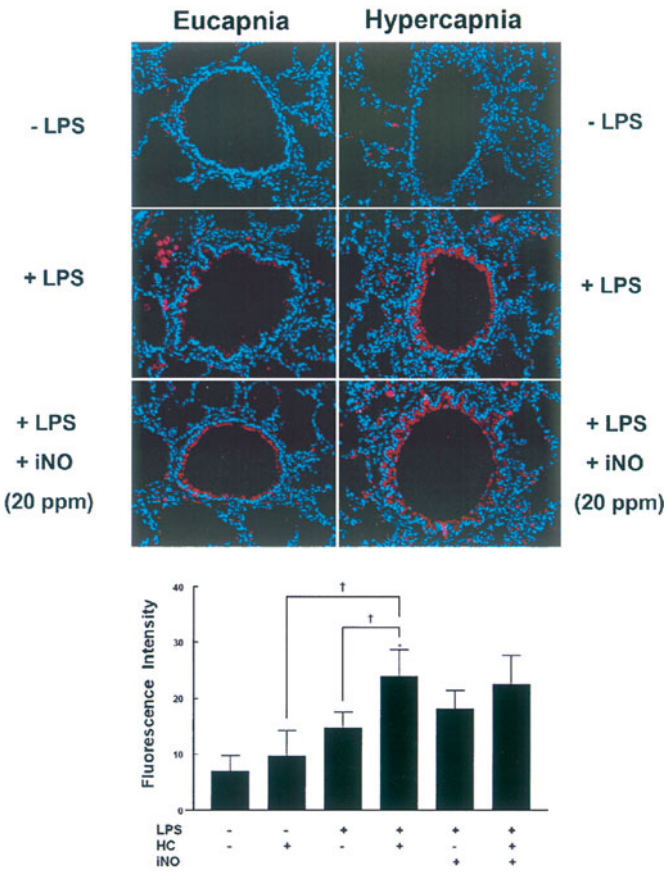

Figure 25-5 Effects of hypercapnia and inhaled nitric oxide (iNO) in distribution of bronchoalveolar lavage protein 3-nitrotyrosine (3-NT) rabbits' lungs. New Zealand white rabbits were treated with intravenous lipopolysaccharide (LPS) and ventilated under eucapnic ($Pa_{CO2} = 40$ torr) or hypercapnic ($Pa_{CO2} = 59$ torr) conditions. Formalin-fixed lung tissues were immunostained with a monoclonal antibody to nitrotyrosine. Lungs of rabbits treated with LPS and ventilated under hypercapnic conditions exhibited significantly higher nitrotyrosine levels compared to eucapnic ventilation. The formation of 3-NT significantly also increased in groups receiving inhaled nitric oxide (iNO compared with the eucapnia-alone group. *Significant difference compared with eucapnia alone, $p < 0.05$; †significant difference from the eucapnia group in the same treatment group, $p < 0.05$. (*From Lang JD, Figueroa M, Sanders KD, et al: Hypercapnia via reduced rate and tidal volume contributes to lipopolysaccharide-induced lung injury. Am J Respir Crit Care Med 171:147–157, 2005.*)

patients with ARDS. Endothelial injury as measured by ^{51}Cr release was greatest in the control group and least in patients with sepsis and ARDS. Additional studies have confirmed that in sepsis and lung injury, antioxidant responses are significantly elevated when compared to control patients.

Describing the influences of inflammation on host oxidant production and antioxidant defense mechanisms has been extremely important in our understanding of ALI/ARDS. However, treatment strategies employing antioxidants have failed to show a benefit in ARDS. Recently, 8 patients with ARDS receiving "standardized" total parenteral nutrition were compared to 17 healthy individuals on standard diets without vitamin or trace element supplementation in an attempt to assess the influence of micronutrients on the oxidative system. Plasma antioxidants and antioxidant enzyme systems were measured at baseline and days 3 and 6. In addition, the lipid peroxidation product, malondialdehyde (MDA), superoxide anion, and H_2O_2 were measured over the same time points. Plasma levels of α-tocopherol, ascorbate, β-carotene, and selenium were reduced when compared to controls. MDA was significantly increased and was observed to increase significantly over the 6-day interval. The authors concluded that in patients with ARDS, the antioxidant systems are severely compromised and there is evidence of progressive oxidant stress, as per the steady increase in MDA. Thus, administration of "standardized" total parenteral nutrition seems inadequate to compensate for the increased requirement for antioxidants in ARDS.

In a contrasting study, when patients with ARDS were entered into a prospective, multi-centered, double-blind randomized control trial comparing a specialized enteral formulation containing fish oil (eicosapentaenoic acid), borage seed oil (γ-linoleic acid), and elevated antioxidants (vitamin A, α-tocopherol, ascorbate, and β-carotene) vs. an isonitrogenous, isocaloric standard diet, beneficial anti-inflammatory effects were observed, which translated into a reduction in mechanical ventilator days, a decreased length of stay in the ICU and reduction in new organ failure. When administered over a 4- to 7-day interval, the formulation significantly increased Pa_{O2}/FI_{O2} ratio, decreased the production of neutrophils in BALF, and decreased the total cell count in the BALF. Oxidants and antioxidants per se were not directly measured, but a decrease in pulmonary inflammation with reduced neutrophil adhesion and oxidant production was observed. In a subsequent study conducted retrospectively by the same group, enteral feeding with the same formulation resulted in decreased BALF IL-8 and leukotriene B_4 levels, together with a trend toward decreased BALF total protein and neutrophils.

Albumin also has potential antioxidant ability, as a consequence of an exposed thiol group (Cys 34). Quinlan and colleagues administered 25 g of albumin solution every 8 h for a total of 9 doses to patients meeting criteria for ARDS and compared them to a placebo group. In this cohort of patients, supplementation with albumin increased total plasma albumin concentrations and decreased plasma protein carbonyls (a marker of protein oxidation). Positive correlations

were found between albumin and plasma thiol concentrations, and thiols and antioxidant capacity. This result was not observed in the placebo group. These studies are first steps in this complex area of investigation—clearly additional studies are warranted.

CONCLUSIONS

RONS, produced by the interaction of NO with partially reduced oxygen species, affect lung function and homeostasis in a variety of different ways. They act as signaling agents and play an essential role in the killing of pathogens. On the other hand, they may contribute to tissue injury by upregulating genes responsible for production of inflammatory mediators and by directly nitrating and oxidizing proteins, events known to adversely affect critical functions. A significant challenge to defining their role in lung injury results from their short biologic half-lives, lack of sensitive detection techniques, and the difficulty in deciphering the relevance of the various substrate concentrations to a particular measured response. Thus, many questions relating to the chemical, physiological, pathobiological, and clinical consequences of RONS generation remain unanswered. Therapeutic strategies, such as enhanced anti-inflammatory and antioxidant therapies are in their infancy in the clinical arena. Hence, this discussion of what is known or most likely known leads one to realize how much is not known with regard to the role of RNS/ROS in lung injury.

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26

The Pathogenesis of Pulmonary Fibrosis

Moisés Selman • Annie Pardo

Pulmonary fibrosis is the end result of a diverse group of lung disorders known as interstitial lung diseases (ILDs). In these disorders, fibrosis results from chronic damage to the lung parenchyma and it is characterized by the excessive accumulation of extracellular matrix (ECM) proteins, primarily fibrillar collagens.

Usually after lung injury, parenchymal cells regenerate and replace the necrotic or apoptotic cells. This process is associated with a controlled inflammatory response and probably a limited remodeling of the ECM. However, if the magnitude of the lung damage overwhelms the mechanisms of defense and/or if lung injury persists (i.e., drug intake, environmental exposure), or if some unknown and uncontrolled event takes place [idiopathic pulmonary fibrosis (IPF)], lung regeneration fails and parenchymal cells are substituted with abundant ECM, with the subsequent destruction of the lung architecture. Under all circumstances, development of fibrosis provokes dramatic changes in the lungs resulting in progressive and irreversible respiratory insufficiency and a terminal outcome in a relatively short period of time.

It is important to appreciate that the fibrotic remodeling in ILDs is not restricted to the interstitium—the anatomic space interposed between the alveolar epithelial and endothelial basement membranes—but also occurs in the alveolar spaces. Therefore, it would be more appropriate to refer to ILDs as diffuse parenchymal lung diseases.

PATHWAYS TO PULMONARY FIBROSIS

In most ILDs inflammation is a crucial profibrotic event that precedes the development of pulmonary fibrosis. The mechanisms of alveolitis differ from one to another ILD, but all inflammatory cell types, macrophages, lymphocytes, and polymorphonuclear cells have the potential to provoke a fibrotic reaction and several essential common cytokine networks are involved.

By contrast, it has been hypothesized recently that IPF, a devastating condition of unknown etiology, represents an inflammatory-independent, epithelial-dependent fibrotic process mirroring abnormal wound healing (Fig. 26-1). Therefore, at least two different cellular routes, *the inflammatory pathway* and *the epithelial pathway*, may lead to the development of lung fibrosis.

It is important to indicate that experimental models of lung fibrosis, typically provoked with bleomycin, and less frequently with radiation, silica, or other agents, have been useful to dissect some of the pathogenic mechanisms of the

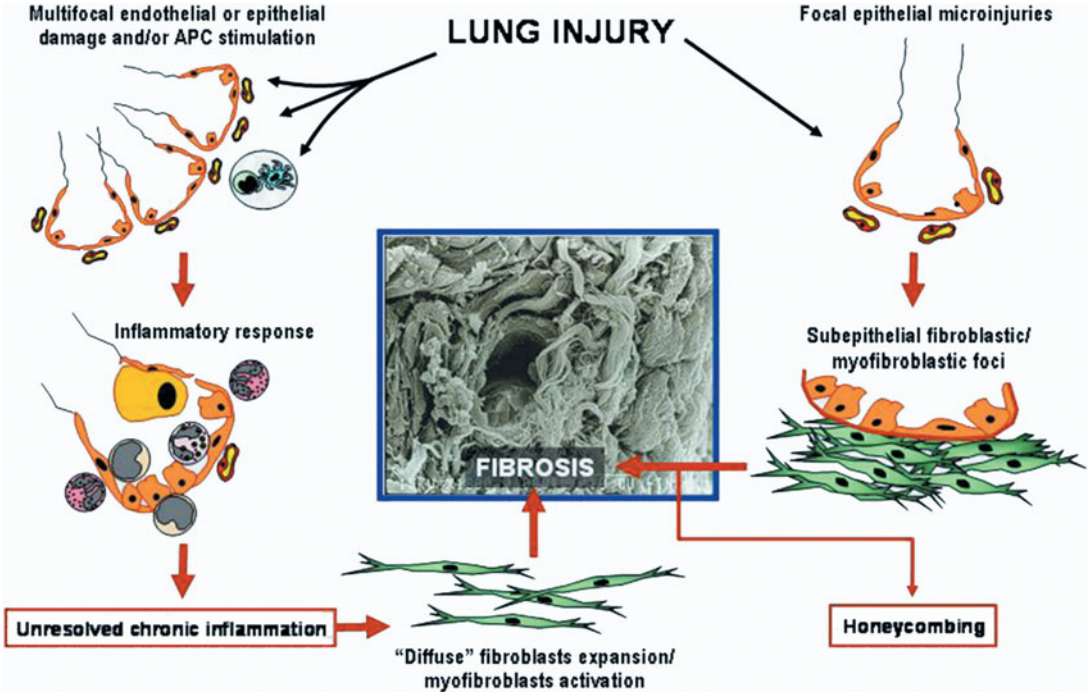

Figure 26-1 Hypothetical scheme of the two proposed pathways leading to pulmonary fibrosis. In the inflammatory pathway, a multifocal and essentially concurrent injury of known or unknown etiology provokes the up-regulation of diverse cytokines, chemokines/chemokine receptors, and adhesion molecules leading to alveolitis. Perpetuation of inflammation results in the release of cytokines/growth factors causing fibroblast migration/proliferation and differentiation to myofibroblasts. In the epithelial pathway, alveolar micro-injuries occurring over a long period of time result in dynamic alterations in the alveolar microenvironment that also promote accumulation of activated fibroblasts/myofibroblasts but mostly forming characteristic subepithelial foci. In both pathways, fibroblasts/myofibroblasts induce irreversible changes in extracellular matrix architecture resulting in an erratic remodeling of the lung parenchyma. Although honeycomb-like changes may be seen in advanced/terminal lesions of many interstitial lung diseases, it is a distinguishing feature of idiopathic pulmonary fibrosis.

inflammatory-driven pathway to fibrosis but none of them replicates human IPF.

The Inflammatory Pathway

Almost immediately after lung injury and loss of lung homeostasis, cytokines and chemokines are released from the tissue. These mediators stimulate leukocyte migration from the blood into the lung and vascular endothelial cells to express adhesion molecules on the luminal surface. The adhesive interactions of endothelial cells with their counter-receptors on leukocytes, selectins and integrins, initiate the process of leukocyte entry into injured tissues (Fig. 26-2).

Chemokines/Chemokine Receptors

Chemotactic cytokines, termed "chemokines", are involved in leukocyte chemotaxis and migration through the endothelial barrier into the injured lungs. Chemokines are a group of small molecules characterized by a distinctive pattern of conserved cysteine residues. They are classified into two major (CXC and CC) and two minor groups depending on the number and spacing of the first two conserved cysteine residues. Chemokines mediate their effects by binding G protein–coupled receptors. There is redundancy and binding promiscuity between chemokines and receptors; a single chemokine may bind to several receptors, and a single chemokine receptor may transduce signals for several chemokines. Chemokines can also influence cell survival and proliferation, and have emerged as a prominent superfamily whose importance extends far beyond their function as inflammatory mediators. Thus, the release of chemokines may exert effects not only on inflammation but also on remodeling events.

Chemokines in Inflammatory/Fibrotic Lung Disorders

A number of chemokines are up-regulated and seem to play a role in the inflammatory and/or the fibrotic response in experimental models and in human ILDs. Macrophage inflammatory protein-1α (MIP-1α/CCL3) and monocyte chemoattractant protein-1 (MCP-1/CCL2), which are chemotactic for macrophages, basophils, eosinophils, and subsets of T lymphocytes, are up-regulated in systemic sclerosis where they correlate with the presence of pulmonary fibrosis. MIP1α/CCL3, interleukin (IL)-8/CXCL8 (a chemoattractant for neutrophils), and RANTES/CCL5 (*regulated on activation, normal T cell expressed and secreted*), a potent eosinophil and lymphocyte chemoattractant, are increased in patients with sarcoidosis while CCL18/DC-CK-1, a

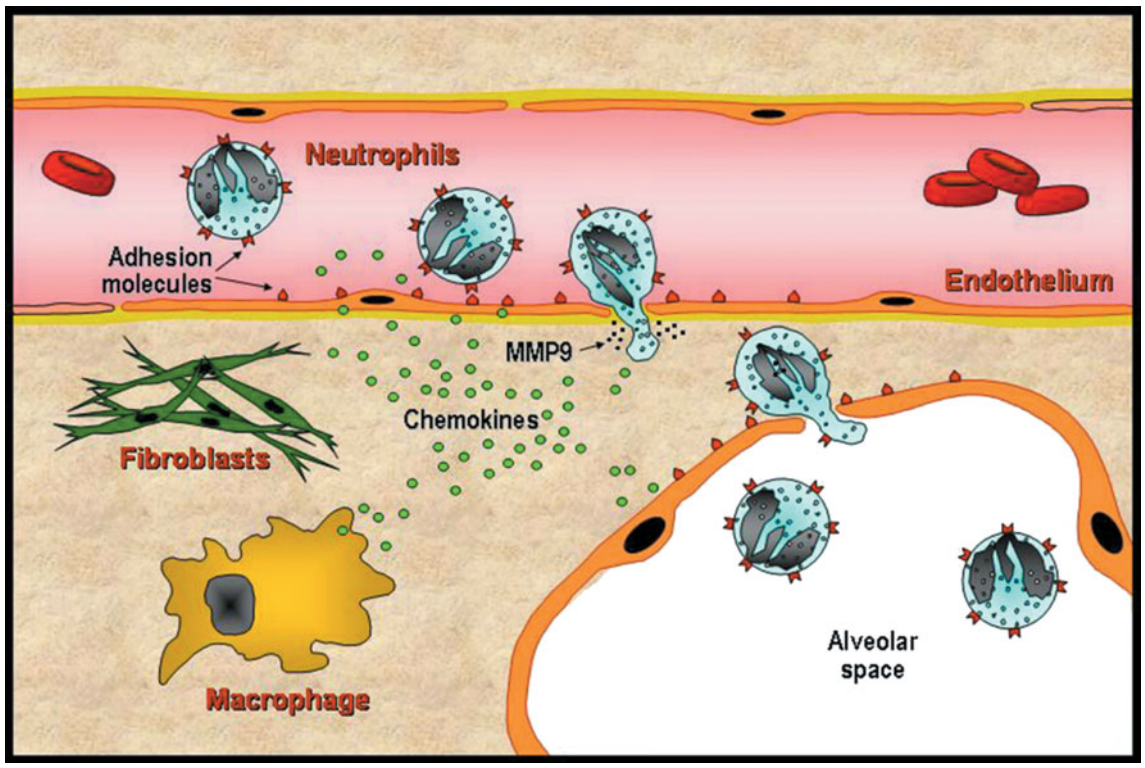

Figure 26-2 Mechanisms of leukocyte recruiting/homing into the injured lung. A multistep and coordinated process regulates leukocyte migration to the extravascular tissue. Chemokines (green dots) diffuse into the bloodstream through the junctions between endothelial cells or are internalized and transcytosed by the endothelial cells from venular walls to their luminal side where they are presented to the chemokine receptors on rolling leukocytes. The cascade of cellular responses involved in this process includes rolling of leukocytes within the vascular lumen, firm adhesion to, and migration of, leukocytes on the surface of the endothelium and subsequent transendothelial movement. This stepwise process involves interactions between specific adhesion molecules (e.g., selectins, integrins, and immune globulin superfamily molecules) and their counter-receptors. The up-regulation of some integrins and proteases (e.g., MMP-9) enhance the interaction of leukocytes with basement membrane constituents. Following transendothelial migration, leukocytes may express increased levels of integrins and proteases which might facilitate their migration through the interstitial and alveolar spaces. Transmigration induces changes in leukocyte phenotype mainly characterized by a different repertoire and distribution of the cell surface and intracellular molecules.

chemokine involved in naïve T-cell recruitment, and CXCL9 and CXCL10 which participate in polarized T-helper (Th) 1 response, are strongly up-regulated in the lung in hypersensitivity pneumonitis (HP). In systemic sclerosis the up-regulation of fractalkine/CX3CL1 and its receptor CX3CR1 cooperatively augments the recruitment of mononuclear cells into the affected tissues including lung.

In IPF, three CC chemokines, CCL2, CCL3 and CCL4, are increased in the bronchoalveolar fluid (BALF) associated with a decreased expression of cellular receptor CCR5 in lymphocytes. Furthermore, CCL2 shows a significant correlation with the severity of the disease. Since activation of CCR5 induces increased production of interferon-γ (IFN-γ), down-regulation of this receptor could result in a decrease in the levels of this strong antifibrogenic cytokine. CCL7 is also significantly increased in IPF lungs and fibroblasts compared with those in nonspecific interstitial pneumonia and respiratory bronchiolitis-ILD, suggesting that this CC chemokine may have a role in the progression of fibrosis.

Chemokines may participate in the expansion of the fibroblast population during lung fibrosis. In some experimental models, CCR2/CCL2 pathway is involved in the recruitment and activation of lung fibrocytes, a source of fibroblasts during lung injury.

Chemokines also play a role in neovascularization, a fundamental process in tissue repair after injury. Some are angiogenic (i.e., IL-8/CXCL8 and the growth-related genes alpha, beta, and gamma [GROα, GROβ, and GROγ]), while others are angiostatic (CXCL9, CXCL10, and CXCL4). It is unclear whether angiogenesis is involved in the resolution of the inflammatory process or in the progression to fibrosis. In some experimental models of lung injury, angiogenesis seems to be associated with an increased fibrotic response.

By contrast in IPF, where there is aberrant vascular remodeling, capillaries are virtually absent within the fibroblastic foci, which are thought to represent areas of active ECM synthesis and are considered to be the "leading edge" of the fibrotic response. A similar situation has been noticed

in fibrotic skin lesions where a significant reduction in the vascular density has been found in keloids when compared with surgical and hypertrophic scars. Thus, it appears that under certain pathological settings increased angiogenesis plays a profibrotic role while in others decreased angiogenesis enhances fibrosis.

In summary, chemokines play a pivotal role in the regulation of inflammation/fibrosis processes. Up-regulation/down-regulation of certain chemokines and receptors may participate in the control of the responses at least at four levels (i.e., inducing and perpetuating inflammation, altering angiogenesis, polarizing the immune response to a type 2 profibrotic reaction [see below], and recruiting bone marrow/circulating fibroblast precursors).

Leukocyte Emigration

Endothelial cells play a central role in the organization and composition of the inflammatory microenvironment. They communicate with underlying cells coordinating the traffic of leukocytes through direct communication as well as via soluble mediators released at sites of inflammation (Fig. 26-2). During leukocyte migration through the endothelial cell barrier, both leukocytes and the endothelium actively participate in the regulation of this process through bidirectional signaling. Molecular specificity in the targeting of leukocytes at sites of inflammation is tightly regulated by at least three families of cell adhesion molecules (CAMs): integrins, selectins, and the immunoglobulin gene superfamily, each structurally distinct and whose function is controlled by a diverse set of signaling pathways.

Integrins are a family of heterodimeric transmembrane glycoproteins that attach cells to ECM proteins of the basement membrane or to ligands on other cells. Integrins contain large (α) and small (ß) subunits of sizes 120 to 170 kDa and 90 to 100 kDa, respectively. Selectins are a family of transmembrane molecules, expressed on the surface of leukocytes and activated endothelial cells. Members of the immunoglobulin superfamily are expressed by the vascular endothelium acting as counter-receptors for leukocyte integrins.

Studies of CAMs in human inflammatory/fibrotic lung diseases are scanty. Intracellular adhesion molecule-1 (ICAM-1) and vascular cell adhesion molecule-1 (VCAM-1) have been found broadly distributed on the endothelium both in sarcoidosis and IPF, while ELAM-1 is mostly found in progressive sarcoidosis. Macrophages bearing the ICAM-1 antigen are present in sarcoid tissue but not in the interstitial or alveolar spaces of IPF lungs. Lymphocyte function-associated antigen-1 (LFA-1, CD11a/CD18) and very late antigen-4 (VLA-4; CD49d/CD29) are usually present on leucocytes but seem to be more highly expressed on lymphocytes in sarcoidosis. These findings suggest that the LFA-1/ICAM-1 and VLA-4/VCAM-1 pathways are involved in leukocyte migration in sarcoidosis and perhaps in IPF while in the active phases of sarcoidosis ELAM-1 is also involved.

Inflammatory Cells and Pulmonary Fibrosis

Lymphocytes

In many chronic inflammatory lung diseases evolving to fibrosis, inflammation is characterized by the influx into the lungs of immune cells. For example, a vast infiltration of T lymphocytes and macrophages, with the subsequent formation of noncaseating granulomas, characterizes sarcoidosis. Patients with this disorder typically show a lymphocytosis predominantly with activated CD4+ T cells oriented to a Th1 cell pathway (see below). The majority of these cells expresses CXCR3 and produces IFN-γ. The CXCR3 ligand IP-10 is also increased in the BALF and localizes to macrophages and epithelioid cells in the lung granulomas.

T Lymphocytes and Type 1 and Type 2 Cytokine Network in the Fibrotic Response

Key regulators in the orchestration of the immune response are the Th-cell subsets. When naïve Th cells first encounter antigen, they are induced to differentiate into one of two lineages, termed *Th1* and *Th2*.

A number of studies have shown that fibrogenesis is strongly linked with a polarized Th-cell response. In general, Th1 cytokines are mostly involved in cell-mediated immunity associated with autoimmune disorders and allograft rejection, whereas Th2 cytokines are primarily implicated in mediating allergic inflammation and importantly, chronic fibroproliferative disorders.

When an inflammatory reaction develops with a Th1 response, which is characterized by the local production of IFN-γ, the development of tissue fibrosis is attenuated. This cytokine substantially decreases fibroblast proliferation, differentiation to myofibroblasts, and ECM synthesis in vitro and reduces the lung fibrotic response in vivo. By contrast, the development of a Th2-cell response involves the secretion of at least two putative fibrogenic cytokines, IL-4 and IL-13. These interleukins activate fibroblasts, and induce the production of ECM components. Both IL-4 and IL-13 are capable of modulating the phenotype of human lung fibroblasts to myofibroblasts through a c-Jun NH2-terminal kinase-dependent pathway. In vivo experimental models have strongly supported the assumption that a Th2 reaction is related to fibrosis. Interestingly, IL-13 selectively stimulates the production of latent TGF-β1 in both transgenic mice and isolated macrophages, and it also can indirectly activate this factor by up-regulating the expression of matrix metalloproteinase-9 (MMP9) that cleaves the LAP-TGF-β1 complex. Therefore, the fibrotic reaction associated with polarized Th2 responses might involve a pathway in which IL-13–producing CD4+ Th2 cells stimulate TGF-β1 expression.

Human lung tissues of different idiopathic interstitial pneumonias (IIP) show an abnormal, heightened expression of the receptor subunits that bind IL-4 and IL-13. Specifically, IL-4Rα and IL-13Rα-2 are present in greater abundance in tissues and fibroblasts from the lungs of patients with IIP compared with normal lungs. When exposed to increasing

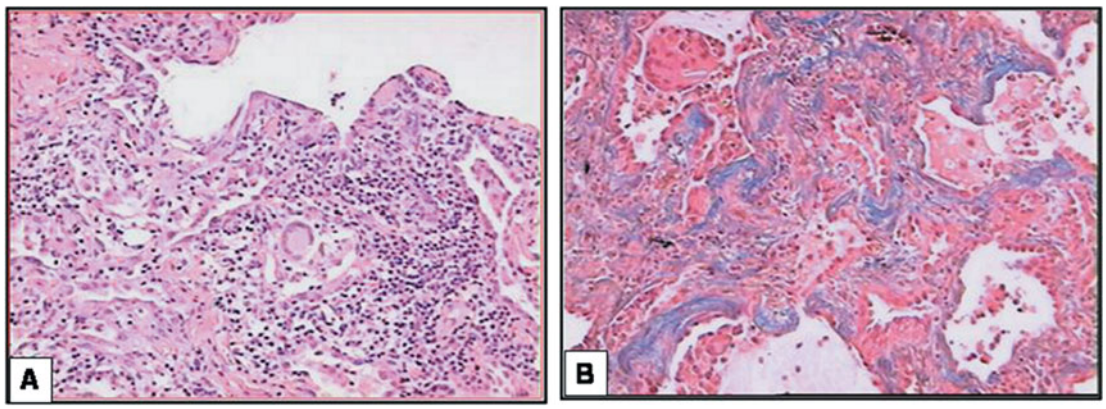

Figure 26-3 Hypersensitivity pneumonitis is an inflammatory disorder provoked by exposure to organic particles *(A)* that may progress to fibrosis *(B)*. The reasons are unknown, but may be partially related to a Th1/Th2 switch.

concentrations of a chimeric protein comprised of human IL-13 and a truncated version of *Pseudomonas exotoxin*, the proliferation of primary IPF fibroblasts was inhibited to a much greater extent compared with fibroblast lines from other lung disorders. In experimental models the intranasal administration of this chimera significantly attenuated the fibrotic response.

CD8+ T cells obtained through BAL from the majority of patients with systemic sclerosis—an autoimmune disease highly associated with pulmonary fibrosis—express IL-4 and/or IL-5 mRNA, and this type 2 dominant response is associated with a greater decline in pulmonary function. Likewise, reduced Th1 responses with decreased INF-γ production have been found in patients with ILD who subsequently showed spontaneous lung functional deterioration.

A hypothetical scenario exemplifying the Th1/Th2 role in lung inflammation/fibrosis could be drawn from HP. HP is a diffuse granulomatous lymphocytic alveolitis provoked by the exposure to a variety of organic particles, which is believed to be a predominantly Th type 1 lung disorder. While a number of patients improve or heal after therapy, around 30% progressively evolve to fibrosis even if they avoid further exposure (Fig. 26-3). The fibrotic response is accompanied by a change in the inflammatory infiltrate with an increase of Th2 lymphocytes and neutrophils loaded with MMP8 and MMP9. Therefore, it can be speculated that in this ILD, the host reaction to the organic particle or the chronicity of the disorder or some unknown event may induce a response dominated by the type 2 cytokine phenotype, whose consequence is the development of progressive fibrosis.

A non-Th1, non-Th2 effector T cell termed *follicular B-helper T* (T_{FH}) is capable of providing help for B cells in lymphoid tissues through expression of the chemokine receptor CXCR5. T_{FH} cells are a cellular subset displaying a distinct pattern of gene expression of cytokines (predominantly IL-21), chemokine receptors, and transcription factors, and recent evidence suggests that they may participate in autoimmune diseases. In a recent study of patients with HP, several genes associated with this cell subset were found to be up-regulated.

Macrophages

Alveolar macrophages are key sentinels of the lung parenchyma and play an essential role in mediating the inflammatory response. After injury, monocytes, the precursors of alveolar macrophages, are recruited readily to the lungs through a number of specific chemokines such as MCP-1/CCL2, MIP-1α/CCL3, and MIP-1β/CCL4 with the expression of the chemokine receptors (CCR1 and CCR2).

Lung macrophages are implicated in the pathogenesis of several ILDs where an increase of interstitial/alveolar macrophages is usually noticed. Surface phenotypic analysis reveals that alveolar macrophages are quite heterogeneous in ILD. In general, macrophages from patients with ILD bear adhesion receptors (CD11c, CD29, CD36, CD44, CD49e, and CD54), molecules involved in signal transduction and/or inflammation (CD13, CD45, and CD53), and other markers (CD9, CD52, CD71, and CD98). In addition, a massive monocyte influx takes place during the development of the alveolitis, as shown by the increased expression of CD14.

Acting as accessory cells, macrophages release various biologic mediators of the immune response, such as IL-1, IL-6, IL-15, and granulocyte-macrophage colony-stimulating factor (GM-CSF) that may enhance local effector cell functions. They also release proteases and oxygen radicals that contribute to amplify inflammation.

Some typical examples of ILDs where macrophages are thought to have a relevant role include diseases provoked by inhaled inorganic or organic particles and some idiopathic interstitial pneumonias, such as desquamative interstitial pneumonia and respiratory bronchiolitis associated with ILD.

Ingestion of silica provokes alveolar macrophage damage and activation with the subsequent release of reactive oxygen species, proteases, inflammatory cytokines/chemokines, and arachidonic acid metabolites. These mediators in turn recruit inflammatory cells into the alveolar wall and alveolar epithelial surface, initiating alveolitis. In sarcoidosis, activated macrophages spontaneously secrete exaggerated levels of a number of cytokines and chemokines including IL-1, TNFα, MIP-1, MCP-1, RANTES, IL-8, IL-12, and IL-18.

Macrophages also synthesize several profibrotic mediators including platelet-derived growth factor (PDGF), insulin-like growth factor-1 (IGF-1) and TGF-β a dual mediator that on one hand is a potent immunosuppressive molecule and on the other is a strong profibrotic factor. Through the secretion of these molecules to the local milieu it is thought that macrophages contribute to the development of lung fibrosis in a variety of ILDs.

Eosinophils

Eosinophils have been associated with fibrotic processes. In bleomycin-induced lung fibrosis in rats, a causal correlation between an early eosinophilic reaction and subsequent development and severity of pulmonary fibrosis has been reported. Overexpression of IL-5 in transgenic mice or by adenoviral gene transfer induced eosinophilia and increased bleomycin-induced lung fibrosis. In some types of human pulmonary fibrosis, the number of eosinophils is increased and seems to correlate with the severity of clinical symptoms and functional abnormalities.

Eosinophils stimulate a number of fibroblast activities, and hence modulate tissue remodeling through the release of their distinct granule basic proteins and an array of cytokines. Eosinophil cationic protein inhibits proteoglycan degradation while eosinophil-derived neurotoxin stimulates fibroblast proliferation. In addition, eosinophils store and release one of the most potent fibrogenic factors, TGF-β, which enhances the differentiation of fibroblasts to myofibroblasts and increases ECM accumulation through several mechanisms. Furthermore, eosinophils modulate fibroblast properties by other cytokines such as IL-4 and IL-13, which promote fibroblast functions by up-regulating matrix protein expression. Eosinophils also contain preformed matrix metalloproteinases (MMPs) such as MMP9 that is released by TNF-α stimulation and some tissue inhibitors of MMPs (i.e., tissue inhibitor of metalloproteinase-1, or TIMP1), suggesting that they can also modulate ECM formation in the lung.

Neutrophils

Persistence of neutrophils may enhance lung fibrosis to a number of injuries. In experimental lung fibrosis induced by silica or bleomycin, the increase of neutrophils and duration of tissue neutrophil activation has been correlated with chronic alveolitis progressing to fibrosis. Likewise, increased BAL neutrophils and increased levels of granulocyte colony-stimulating factor (G-CSF) and IL-8, two potent neutrophil chemotactic glycoproteins, have been found in a number of ILDs that result in fibrosis. Furthermore, neutrophil migration and activation are usually higher in patients with more aggressive and worse prognosis fibrotic lung disorders, and increased tissue neutrophils containing MMP9 (gelatinase B) and MMP8 (collagenase-2) seem to be implicated in the fibrotic reaction of patients with chronic HP. In this disorder a significant correlation between lung neutrophils and the percentage of pulmonary fibrosis has been described. Therefore, the persistence of activated tissue neutrophils may be one of the processes underlying the inflammatory-driven fibrotic response. However, neutrophils are a source of hepatocyte growth factor (HGF) in IPF lungs that could be beneficial for regeneration since HGF induces epithelial cell proliferation and inhibits apoptosis, and gene transfer of human HGF to alveolar septa suppresses bleomycin-induced lung fibrosis.

Mast Cells

Several lines of evidence suggest that mast cells may be involved in fibrotic processes. In several ILDs mast cell populations increase, expanding from small numbers in normal alveolar septa to an abundance of activated and degranulating cells that infiltrate the remodeling interstitium where they are in close apposition with fibroblasts. Mast cells can participate in polarizing T cells toward the Th2 "profibrotic" phenotype through the effects of IL-4 and IL-13. In culture, mast cells induce fibroblasts to lose contact inhibition, proliferate, and synthesize increased amounts of type I collagen. However, it is unclear whether they actively contribute to lung fibrogenesis in vivo or are merely attracted to areas of injury in a nonspecific way.

Ultimately, the temporal and spatial sequence of the inflammatory-driven fibrotic response seems to be mediated by an as yet unclear repertoire of chemokines, cytokines, and growth factors released by immune and inflammatory cells. However, the large number of mediators whose expression is increased in experimental and human fibrosis as well as their redundancy and pleiotropic effects makes it difficult to distinguish the factor(s) that play a pivotal role in fibrogenesis. The key and unsolved question is whether an up-regulated mediator is a cause or an epiphenomenon.

The Epithelial Pathway

Normally following alveolar injury, the alveolar epithelium is repaired by the proliferation of alveolar epithelial type II cells with the subsequent differentiation into new alveolar epithelial type I cells. Also, injured alveolar epithelial cells may be replaced by bone marrow and airway progenitor cells.

It has been proposed that IPF, which is by far the most aggressive fibrotic lung disorder, develops as a result of an aberrant reaction of epithelial cells to multiple cycles of alveolar injury resulting in disturbed epithelial cell function and inappropriate re-epithelialization after damage. Ordered re-epithelialization is fundamental for lung regeneration, as demonstrated, for example, in cryptogenic organizing pneumonia, usually a reversible disorder, where alveolar re-epithelialization is significantly more widespread and structured compared with IPF. The cause of epithelial cell injury is unknown. It is probable that no single mechanism initiates the disease response in the lung; rather, a combination of injuries may potentially contribute to the development of IPF. Virus, tobacco smoke, metal dust exposure, and other agents may be important sources of injury, and may trigger the disease in genetically predisposed individuals.

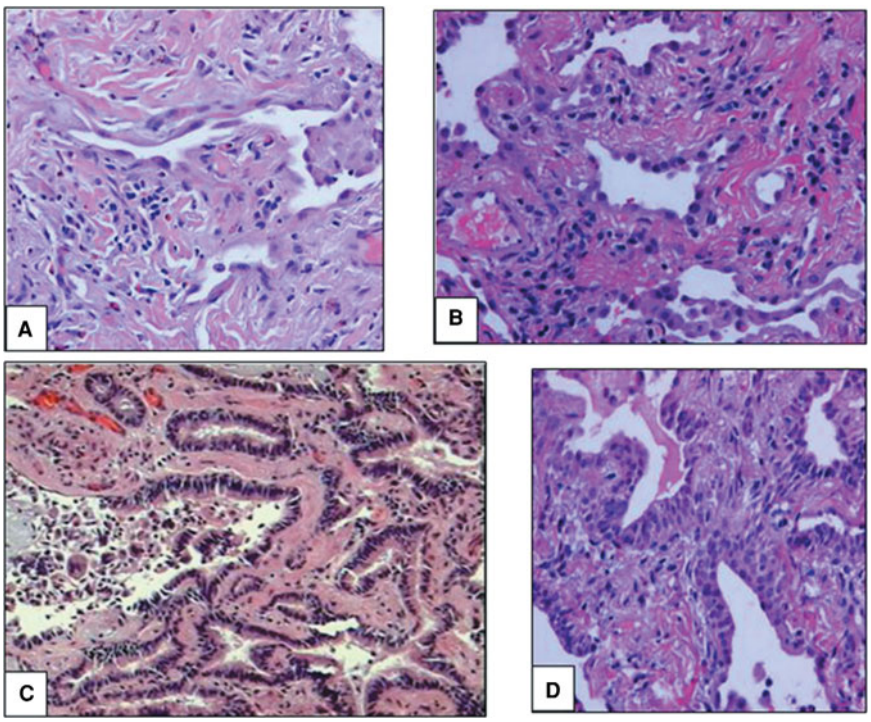

Figure 26-4 Lungs with idiopathic pulmonary fibrosis show several phenotypic changes in epithelial cells. *A.* Attenuated and flat cells may be noticed overlying fibroblastic focus. *B.* Hyperplastic cuboidal epithelial cells or a bronchiolar type of epithelium tend to line the fibrotic thickened alveolar septa. *C.* Extensive proliferation of bronchiolar epithelium (*bronchiolization*). *D.* Epithelial squamous metaplasia.

A striking disturbance in the integrity of the alveolar epithelium with presence of several altered phenotypes is a distinctive characteristic in IPF lungs (Fig. 26-4). The most conspicuous feature is represented by the presence of numerous hyperplastic and hypertrophic (cuboidal) type 2 pneumocytes. Levels of circulating KL-6, a marker of regenerating type 2 pneumocytes and indirectly a marker of the magnitude of the death of type 1 pneumocytes, are increased, and high levels seem to predict rapidly progressive IPF. Other frequent morphologic phenotypes include flattened and attenuated epithelial cells usually overlying the fibroblastic foci, bronchiolar-type epithelium lining the enlarged airspaces of honeycomb lesions (bronchiolization), and squamous metaplasia.

The reasons for, and the significance of, the epithelial changes described above are unknown, but some of them seem to be related to the putative initial insult while others are a consequence of accelerated epithelial cell proliferation/migration indicating regenerative epithelia after injury. Up-regulation of HGF and its high-affinity receptor c-Met, as well as of the recently described mediator, hepatoma-derived growth factor, may explain some of the epithelial changes. Also, alveolar epithelial cells from some patients with IPF exhibit microsatellite instability of the type 2 receptor for TGF-β that may be relevant to the epithelial proliferative responsiveness to this growth factor.

Epithelial Cell Apoptosis

In IPF, epithelial cell apoptosis is a common event and probably an essential feature. Several mechanisms appear to be implicated in this process including a fas-signaling pathway which has been found up-regulated in alveolar epithelial cells from IPF lungs, and the release by fibroblasts/myofibroblasts of angiotensin peptides which induce epithelial apoptosis. Mitochondrial-mediated apoptotic pathways are also implicated in the increased apoptotic rates of epithelial cells in IPF. Oxidant stress may also contribute to epithelial cell damage and death. H_2O_2 secreted from myofibroblasts functions as a diffusible death signal for lung epithelial cells, and oxidative modifications of DNA caused by reactive oxygen species are present in the nuclei of alveolar epithelial cells in IPF.

Epithelial Cell Expression of Profibrotic Cytokines/Growth Factors

In IPF, alveolar/bronchiolar epithelial cells are the main source of a variety of profibrotic mediators. These include PDGF, TGF-β, tumor necrosis factor α (TNFα), endothelin-1, connective tissue growth factor (CTGF), and osteopontin.

Recently, a new product of alveolar epithelial cells has been identified that may explain why fibroblastic/myofibroblastic foci in IPF lungs lack capillaries. Pigment epithelium-derived factor (PEDF), a 50-kD protein with strong angiostatic properties is highly up-regulated in IPF. PEDF, a TGF-β target gene, has been co-localized with this mediator, particularly within the fibrotic interstitium, and within the alveolar epithelium directly overlying the noncapillarized fibroblastic foci.

Alveolar epithelial cells may enhance a fibrotic response by inducing a procoagulant milieu. Alveolar damage results in transudation of plasma proteins and activation of the coagulation cascade leading to the formation of a fibrin-rich provisional matrix that needs to be degraded for appropriate repair. However, the coagulation cascade and the subsequent fibrinolytic pathway, responsible for clearing the fibrin clot, are dysregulated in lung fibrosis, including IPF. Importantly, alveolar epithelial cells seem to play a pivotal role in this pathological process. Tissue factor, the primary cellular initiator of

the coagulation protease cascade, and plasminogen activator inhibitor (PAI)-1 are strongly expressed by these cells. Moreover, tissue factor is synthesized by alveolar epithelial cells covering the affected alveolar septa and the fibroblastic foci, near where fibrin is being deposited.

Increased procoagulant activity in the lung microenvironment may enhance fibrosis in several ways, including fibrin accumulation, lack of activation of some MMPs responsible for ECM degradation, impairment of epithelial cell migration, and a thrombin-mediated increase of fibroblast activation and transition to myofibroblasts.

Injury of type II epithelial cells and fibrin deposition may also have a profound effect on the pulmonary surfactant. IPF lungs exhibit markedly impaired surfactant function and altered biochemical composition, alterations including changes in phospholipid species distribution, and pronounced modifications in the fatty acid profiles of phosphatidylcholine, phosphatidylglycerol, and phosphatidylinositol. Surfactant-associated proteins A and D also show quantitative changes. These alterations in surfactant may contribute to alveolar collapse and impairment of gas exchange.

The alveolar epithelium may also generate a Th2-like pattern in IPF lungs. For instance, while in HP and sarcoidosis—two reversible ILDs—type II alveolar epithelial cells express both IL-4 and INF-γ in IPF, yet only IL-4 is detectable. These results are consistent with a predominantly type 2 pattern of cytokine network in IPF and support a role for epithelial cells in the characteristic imbalance of profibrogenic cytokines in the distal lung of patients with this disease.

Epithelial Cells and the Loss of Antifibrotic Functions

Epithelial cells on the alveolar surface of the fibrotic microenvironment in IPF may contribute to fibrogenesis not only because they overexpress profibrotic cytokines, but also because they might not secrete mediators with inhibitory effects on fibroblasts. Under physiological conditions alveolar epithelial cells suppress fibroblast migration, proliferation, and activation, including collagen synthesis, through the action of prostaglandin E_2 (PGE_2). In IPF lungs, epithelial cell expression of both cyclooxygenase-1 (COX-1) and COX-2, responsible for PGE_2 synthesis, is significantly reduced compared with controls.

FIBROBLASTS/MYOFIBROBLASTS: THE BRIDGE BETWEEN INFLAMMATION OR EPITHELIAL ACTIVATION AND RELENTLESS FIBROSIS

Expansion of the fibroblast/myofibroblast population is a critical event in IPF that precedes the fibrotic remodeling. Fibroblasts migrate and proliferate under a number of stimuli, and myofibroblasts develop from fibroblasts in response to stimulation by TGF-β and other growth factors and cytokines (Table 26-1). It has been proposed that myofibroblast differentiation occurs in two steps. First, fibroblasts differentiate into proto-myofibroblasts, which form cytoplasmic actin-containing stress fibers that terminate in fibronexus adhesion complexes. Functionally, these cells can generate contractile force. After that, TGF-β1 and ED-A fibronectin, in the presence of mechanical stress, promotes the modulation of proto-myofibroblasts into differentiated myofibroblasts that are characterized by the de novo expression of α smooth muscle actin (αSMA) in more extensively developed stress fibers and by large fibronexus adhesion complexes. Functionally, differentiated myofibroblasts generate greater contractile force than proto-myofibroblasts, which is reflected by a higher organization of extracellular fibronectin into fibrils.

In chronic, unresolved lung inflammation or sustained epithelial activation, increased numbers of fibroblasts and myofibroblasts with excessive ECM deposition are a hallmark of the lung fibrotic response. Interestingly, while fibroblasts proliferate ubiquitously in the chronic inflammatory areas in the fibrotic reaction associated with an inflammatory-driven disease, in IPF fibroblasts usually form widely scattered subepithelial fibroblastic foci. These

Table 26-1

Cytokine/Growth Factors Involved in Fibroblast/Myofibroblast Expansion

Intrapulmonary fibroblast migration	PDGF PDGF/IL-1β,TNFα KL-6 Fibronectin NGF Tenascin-C
Fibrocyte migration	CXCL12 CCL2
Fibroblast proliferation	IGF-1 PDGF FGF-2
Differentiation to myofibroblasts	TGFβ1 ED—a splice variant of cellular fibronectin Tenascin-C N-terminal domain of CTGF PTEN (suppresses)

Abbreviations: PDGF, platelet-derived growth factor; IL-1β, interleukin-1 beta; TNFα, tumor necrosis factor alpha; KL-6, mucin-like glycoprotein; NGF, nerve growth factor; CXCL12, stromal-derived factor 1; CCL2, monocyte chemotactic protein 1; IGF-1, insulin growth factor 1; FGF-2, basic fibroblast growth factor; TGFβ1 transforming growth factor beta 1; CTGF, connective tissue growth factor; PTEN, phosphatase and tensin homologue deleted on chromosome 10.

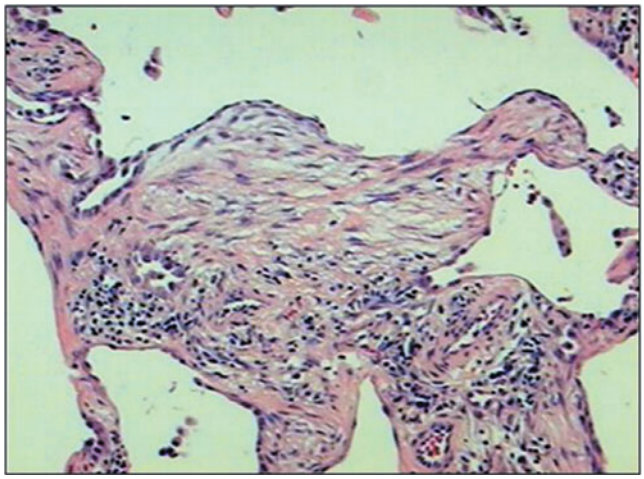

Figure 26-5 Typical subepithelial fibroblastic/myofibroblastic focus in idiopathic pulmonary fibrosis. Numerous spindle-shaped cells are arranged with their long axis parallel to the long axis of the alveolar septum.

aggregates are characterized by spindle-shaped cells within lightly staining, myxoid-appearing matrix, usually arranged with their long axis parallel to the long axis of the alveolar septa (Fig. 26-5).

The Origin of Fibroblasts: Emerging Evidence for an Extrapulmonary Source

For decades the prevailing view has been that in response to lung injury resident mesenchymal cells migrate, proliferate, and synthesize ECM. However, recent findings challenge this concept suggesting that at least part of the expanded fibroblast population has an extrapulmonary origin (Fig. 26-6). It is well known that lung fibroblasts in IPF are phenotypically and functionally heterogeneous. This heterogeneity may reflect not only activation and differentiation processes that take place in the cells but that the cells have different sites of origin.

Bone Marrow-derived Fibroblasts

Bone marrow-derived stem cells possess the unique ability to self-renew and differentiate into multiple lineages, and recent evidence suggests that these cells may participate in tissue repair/fibrosis. Thus, in one study bone marrow-chimeric mice exposed to total lung irradiation exhibited homing and proliferation of bone marrow-derived stromal cells to sites of developing organizing alveolitis/fibrosis. In this study, bone marrow cells comprised almost half of detectable cells, primarily macrophages and fibroblasts, in areas of fibrosis at the time of death. Similar results were reported in bleomycin-induced

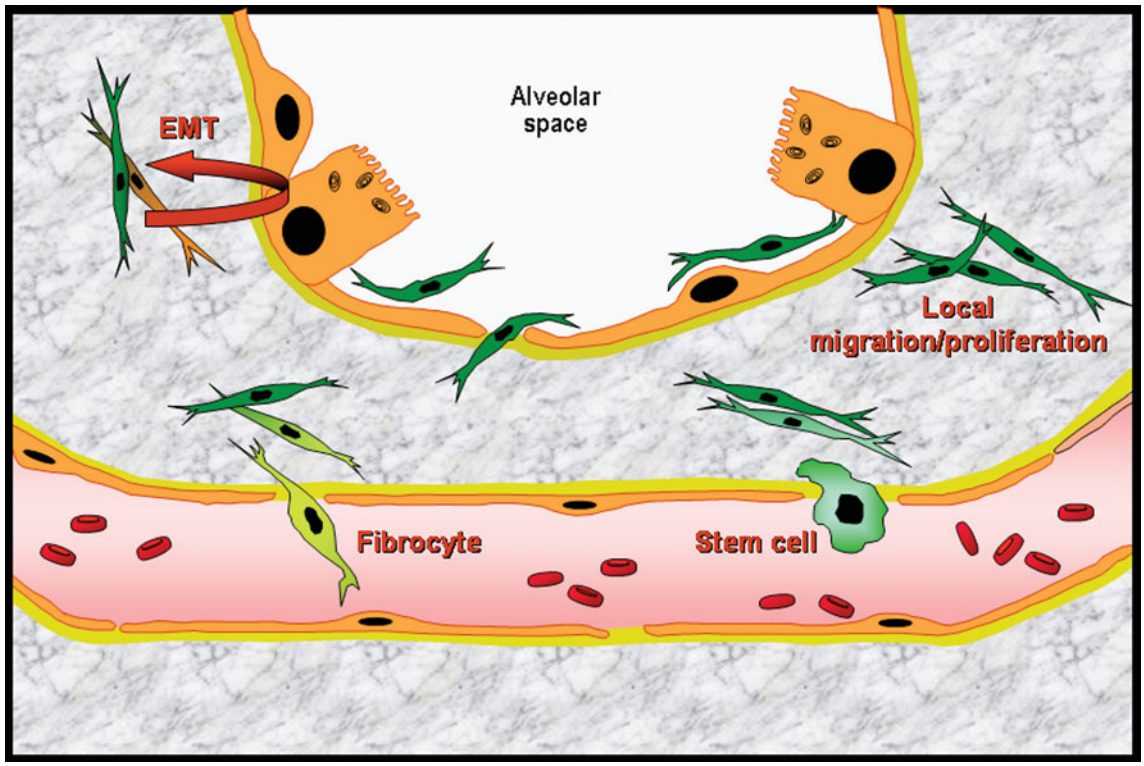

Figure 26-6 Where do fibroblasts come from in pulmonary fibrosis? Theoretically, at least four mechanisms/sources may account for the expanded fibroblast/myofibroblast population in pulmonary fibrosis. (1) Release of growth factors (e.g., PDGF, IGF-1) may induce migration/proliferation of resident mesenchymal cells. (2, 3) Signal(s) from the injured lung may reach the circulation and bone marrow to stimulate recruitment of circulating fibrocytes (e.g., CCL2, CXCL12) or bone marrow-derived stem cells. (4) Alveolar epithelial cells may transition into fibroblasts and myofibroblasts in response to TGF-β and other growth factors/cytokines. However, there is limited definitive in vivo evidence to support the contribution of these potential mechanisms/sources.

lung fibrosis in mice. Mice durably engrafted with bone marrow cells isolated from transgenic mice expressing green fluorescent protein (GFP+) and then injured with bleomycin showed a large number of GFP+ cells expressing type I collagen in fibrotic lungs.

Fibrocytes: A Distinct Mesenchymal Cell Type from Peripheral Blood May Mediate Fibrosis

Another potential extrapulmonary source of fibroblasts/myofibroblast is the circulating progenitor fibrocyte. Fibrocytes are a distinct population of blood-borne cells that display a unique cell surface phenotype and exhibit potent immunostimulatory activities. These cells comprise 0.1 to 0.5 percent of nonerythrocytic cells in peripheral blood and display an adherent, spindle-shaped morphology when cultured in vitro. Circulating fibrocytes rapidly enter sites of tissue injury, and may contribute to connective scar formation.

Indeed, there is evidence that fibrocytes may participate in tissue fibrosis. For example, allergen exposure in patients with allergic asthma induces the accumulation of fibrocyte-like cells in the bronchial mucosa that localize to areas of collagen deposition below the epithelium. Likewise, in a mouse model of allergic asthma, circulating fibrocytes were recruited into the bronchial tissue following allergen exposure and differentiated into myofibroblasts. In pulmonary fibrosis this mechanism may participate in the accumulation of fibroblasts since infiltrating fibrocytes have been demonstrated in lung tissue of mice injured by bleomycin. However, evidence in human lung fibrotic disorders is lacking.

Epithelial-Mesenchymal Transition

Epithelial-mesenchymal transition (EMT) is a central mechanism for diversifying cells during embryonic development and it may play a role in the genesis of fibroblasts during organ fibrosis in adult tissues. Epithelium in transition displays loss of cell-cell and cell-matrix attachments, new actin rearrangements, and gain of mobility. This phenotypic conversion requires the molecular reprogramming of epithelium. To date, the participation of EMT in the fibrotic response has been demonstrated mainly in progressive kidney diseases. The intracellular signaling pathways leading to initiation of EMT remain largely unknown, though recent studies have identified β-catenin and Smad3 activation of lymphoid-enhancer factor, integrin-linked kinase, small GTPases, and mitogen-activated protein kinases as key components.

EMT appears to occur in IPF and may also occur in other forms of lung fibrosis. Lung tissue from patients with IPF has revealed transitional cells lining cystic airspaces that co-express alveolar epithelial and mesenchymal markers, suggesting that alveolar epithelial cells may serve as a source of myofibroblasts in pulmonary fibrosis.

Translocation of β-catenin to the nucleus may play a role in this process since induces the expression of genes that are involved in proliferation as well as in EMT. Interestingly, accumulation of nuclear β-catenin in both epithelial cells and myofibroblasts has been reported in IPF lungs. Likewise, several genes that are implicated in the Wnt signaling pathways (Wnt1, secreted frizzled-related protein 2, and collagen type XVIII), as well as N-cadherin, a mesenchymal cadherin preferentially expressed in migratory cells, are strongly upregulated.

In summary, the origin of fibroblasts/myofibroblasts in the fibrotic lung disorders has not been fully clarified, but it appears that both intra- and extrapulmonary cells may participate.

Myofibroblast Persistence in the Active Fibrotic Site

During the resolution of normal wound healing, there is a striking decrease in cellularity, including the disappearance of myofibroblasts through apoptosis. Indeed, the finding of markers of apoptosis within myofibroblast populations in vivo has led to the speculation that fibroblast differentiation to the myofibroblast phenotype might represent a terminal pathway leading to apoptosis.

The question that arises is why this process does not seem to occur during the development of IPF. In IPF, apoptotic activity is remarkably lower in fibroblastic/myofibroblastic foci compared to the fibromyxoid lesions of cryptogenic organizing pneumonia, a reversible disease, suggesting that in IPF fibroblasts/myofibroblasts have longer survival. The reasons for this behavior have not been elucidated, but inhibition of inducible nitric oxide synthase expression and the prevention of a decline in bcl-2 expression seem to be involved. Also IGF-1 may play a role.

Extracellular Matrix Remodeling: The Role of Matrix Metalloproteinases (MMPS) and Tissue Inhibitors of Metalloproteinases (TIMPS)

The ECM plays a key role in lung architecture and homeostasis, providing much of the supporting framework necessary for the organization and communication between cells. ECM in the lung parenchyma is comprised of numerous molecules including collagens (mainly type I and III), elastin, proteoglycans, and fibronectin. Other proteins contribute to specialized components of the ECM structure, such as the epithelial and endothelial basement membranes, including laminin, entactin, and collagen IV.

Independent of etiology, lung fibrosis is associated with major alterations in both the quantity and composition of ECM. In advanced stages, the fibrotic lung contains approximately two to three times more ECM than normal, including collagens (I, III, V, VI, and VII), fibronectin, elastin, and proteoglycans. Likewise, disruption of basement membranes is often found.

ECM turnover depends on a balance between MMPs and their tissue inhibitors (TIMPs). Disturbances in the complex process of matrix metabolism (synthesis and degradation) have been linked to the aberrant remodeling characteristic of lung fibrosis.

In this context, recent work has explored the possible role of MMPs during ECM remodeling. MMPs represent a family of 24 distinct genes that are collectively capable of cleaving all components of the ECM and basement membranes, as well as many other nonmatrix substrates

including chemokines, cytokines, growth-factor receptors, CAMs, apoptotic ligands, and angiogenic factors. This plethora of MMP substrates has significantly broadened our understanding of these enzymes as proteolytic executors and regulators in various physiological and pathological states. Therefore, they participate in the regulation of multiple cellular functions including cell growth, apoptosis, angiogenesis, and inflammatory and immune responses. MMPs can be classified according to their structural domains into several subfamilies including: collagenases, gelatinases, stromelysins, matrilysins, furin-activated MMPs which include secreted and membrane bound, and other MMPs that do not appear to fall into any of these subgroups.

The regulation of MMPs is controlled at several levels including gene transcription, activation of latent enzyme, and inhibition through binding to a specific family of four proteins referred to as TIMPs 1 through 4. TIMPs differ in expression patterns, and other properties such as pro-MMP activation, cell growth-promoting activity, matrix binding, inhibition of angiogenesis, cell survival promoting activity, and induction of apoptosis.

The possible role of MMPs and TIMPs in the development of lung fibrosis has been analyzed in humans and in experimental models with some similar and some contradictory findings. In general, increases of MMP2 and/or MMP9, also known as gelatinases A and B, are usually found. MMP2 is mostly constitutively expressed with only moderate up- or down-regulation under various conditions. MMP9, however, is highly inducible and under the control of a variety of cytokines and growth factors. Gelatinase substrates include a broad assortment of molecules including ECM proteins, proteinases, proteinase inhibitors, blood clotting factors, chemokines, latent growth factors, cell surface receptors, and adhesion molecules. However, the relevance of these events in vivo is presently unclear. In IPF, MMP2 is found in alveolar and bronchiolar epithelial cells and in fibroblastic foci; MMP9 is also expressed by epithelial cells, and fibroblast type cells. Increases of MMP2 and MMP9 in lung fibrosis have been suspected to have a role in the disruption of the basement membranes, which may enhance the fibroblast invasion into the alveolar spaces, and epithelial cell apoptosis.

Another MMP that seems to play a role in lung fibrosis is MMP7, also known as matrilysin. MMP7 cleaves many substrates, including fibronectin, collagen type IV, laminin, elastin, and fibrin/fibrinogen cleavage, suggesting it has a role in cell migration and tissue remodeling. MMP7 also cleaves pro-forms of the proteases MMP2 and MMP9 leading to their activation, and ADAM28 (a disintegrin and metalloproteinase), which is highly expressed by lymphocytes. MMP7 is highly up-regulated in IPF lungs where it is expressed primarily by the abnormal epithelium. Of note, MMP7-deficient mice do not develop lung fibrosis in response to bleomycin.

Probably the main disparity between the different experimental models of pulmonary fibrosis explored so far and human IPF is related to the subfamily of collagenases (MMP1, MMP8, and MMP13) and TIMPs. In general, animal models show either no changes or a decrease in expression of collagenases (MMP13 and MMP8) with an increase of TIMP1, whereas IPF is characterized by a huge increase of MMP1 (the main interstitial collagenase) with a modest increase of TIMP1 and TIMP3.

The finding of high levels of collagenase in IPF, a fibrotic disorder where the main characteristic is the exaggerated deposition of ECM, is of course a paradox, since MMPs are mainly viewed as enzymes contributing to pathological ECM destruction. However, the location of MMPs and TIMPs in the microenvironment is critical for ECM degradation. In IPF, collagenase (MMP1) is primarily localized to reactive alveolar epithelial cells and bronchiolar epithelial cells lining honeycomb cystic spaces. It is virtually absent in the interstitial compartment where collagen is being accumulated. Lack of this enzyme in interstitial fibroblasts might explain in a simplistic way the persistence of fibrosis in IPF. Additionally, TIMP2 and TIMP3 are expressed in the fibroblastic foci in IPF.

GENETIC SUSCEPTIBILITY AND PULMONARY FIBROSIS

Numerous observations support the notion that genetic factors determine susceptibility or resistance to the development of lung fibrosis. Thus, for example, substantial variability exists in the development of lung inflammation/fibrosis among individuals similarly exposed to organic particles (i.e., HP), inorganic particles (i.e., asbestosis), or drugs (i.e., amiodarone). Similar observations have been made in experimental models of pulmonary fibrosis in mice of different strains.

Familial forms of IPF-like pulmonary fibrosis have been described, and the disorder has also been found in monozygotic twins who were separated at early age. Familial IPF may be inherited as an autosomal recessive trait or as an autosomal dominant pattern of inheritance perhaps with reduced penetrance. Genetic studies in familial lung fibrosis (that often include IPF and other forms of idiopathic interstitial pneumonias) have demonstrated an association with surfactant protein-C (SP-C) genes where two mutations resulting in protein misfolding cause type II epithelial cell damage. In other cases of familial IPF a deficiency of SP-C seems to exist which may cause abnormal shear forces in the alveoli, thereby causing mechanical injury of the respiratory epithelium. Recently, mutations in the genes encoding telomerase components were reported in familial IPF.

Also, lung fibrosis often occurs in a number of pleiotropic inherited syndromes such as Niemann-Pick disease, infantile Gaucher's disease, neurofibromatosis, tuberous sclerosis, and Hermansky-Pudlak syndrome.

Genetic Polymorphisms and Pulmonary Fibrosis

Association studies designed to explore the co-occurrence of a genetic marker and a specific disease at the population level are widely used for discovering susceptibility loci. Several gene

polymorphisms have been studied in different cohorts of IPF patients but results have shown weak associations or no associations at all. Genes analyzed so far include TNFα (–308 adenine), IL-1 receptor antagonist (+2018 thymidine), complement receptor-1 gene (GG genotype for the C5507G, exon 33), plasminogen activator inhibitor-1 (4G/5G in the promoter region), IL-12 p40 (1188 (A/C) 3′ untranslated region), IFN-γ (5644 (G/A) 3′ untranslated region), and IL-10 (G to A substitution of +43). Interestingly, severity and progression of IPF have been associated with IL-6/TNF receptor II (IL-6 intron 4G; TNF-RII 1690C) and TGF-β1 (+869 cytosine).

In some inflammatory-driven fibrosis where an autoimmune or exaggerated T-cell response is involved, associations with the major histocompatibility complex have been found. In systemic sclerosis, antitopoisomerase antibodies are associated with the carriage of human leukocyte antigen (HLA) DRB1*11 and DPB1*1301 alleles, suggesting the recognition of a specific amino-acid motif. In a different cohort, pulmonary fibrosis was associated with HLA-B*62 and HLA-Cw*0602.

In general, however, there are several problems with all of these studies. First, a significant association between an allele and a disease does not mean that the candidate gene is a causal one. Thus, a positive finding always needs confirmation in another group of subjects with different ethnic background. It is now evident that only a combined approach studying large numbers of familial and sporadic cases, all clinically well phenotyped, using multiple distinct cohorts, and genotyped according to relevant gene ontologies will be successful.

Gene-Gene Interactions

Different gene alterations involving key pathways may provoke the development of a complex disease. If IPF is primarily an epithelial/fibroblastic disorder, perhaps changes in genes involving both cells are important in the pathogenesis of the disease. In this context, it has been observed that alveolar epithelial cells from some patients with IPF exhibit microsatellite instability in the TGF-β1 type 2 receptor gene (deletion in the polyadenine tract in exon 3), and coincidentally exhibit low expression of the receptor. The putative pathogenic effect, if any, of this deletion mutation is still unclear, although hyporesponsiveness to TGF-β may induce increased expression of the cytokine and consequently promote fibrosis.

Also, lung fibroblasts isolated from IPF patients have shown a defect in the expression of COX-2, and a failure in their capacity to synthesize PGE_2 that has, among other functions, a strong antifibrogenic effect. Furthermore, mice deficient in COX-2 exhibited an enhanced fibrotic response to bleomycin. Therefore, it seems that a reduced capacity to upregulate COX-2 expression and COX-2–derived PGE_2 synthesis may lead to unopposed fibroblast proliferation and collagen synthesis and contribute to the pathogenesis of pulmonary fibrosis. A defect in PGE_2 may also contribute to a decrease in the production of HGF, another important antifibrotic mediator. Likewise, a substantial difference in the response to some cytokines between normal-derived and fibrosis-derived fibroblasts has been observed. For example, while IL-6 inhibits proliferation of normal fibroblasts it was a potent mitogen for IPF-derived fibroblasts. The switch in responsiveness seems to correspond with a shift from STAT-3–dependent signaling in normal cells to extracellular signal-regulated kinase-dependent signaling in IPF cells.

Gene-Environment Interactions

Genetic dissection of complex disorders should take into account that the risk to develop the pathological condition might be conferred jointly by the interaction of multiple genes and environmental factors. For example, IPF is more frequent in smokers, and some studies suggest associations of polymorphisms of surfactant-associated proteins with or without smoking and the occurrence of IPF. Gene-environment interactions are clearly exemplified in some ILDs of known etiology such as HP, where an increased frequency of the HLA haplotype DRB1*1305-DQB1*0301, and of TNF-2 (–308) allele significantly increase the risk of developing the disease in some cohorts exposed to organic particles, while in others it has been associated with HLA-DQw3.

CONCLUSIONS

Pulmonary fibrosis is the final common result of multiple forms of chronic lung disease, and it is characterized by a marked disruption of the lung architecture with accumulation of excess abnormal ECM resulting from both increased synthesis and decreased degradation of matrix components. A complex interplay among different lung cell types takes place during tissue fibrogenesis. In most ILDs the fibrotic response is triggered by unresolved chronic inflammation leading to the end-stage fibrotic scar. In others, primarily IPF, fibrosis is provoked by aberrant and not yet completely understood epithelial cell activation. In both pathways, a number of imbalances take place causing an excessive release of chemokines, cytokines, growth factors, eicosanoids, oxidants, and procoagulant factors in the alveolar microenvironment leading to dysregulated repair and aberrant tissue remodeling. However, there are substantial differences between the inflammatory-driven and the epithelial-driven lung fibrosis. The latter is temporally and topographically heterogeneous, and the fibroblasts/myofibroblasts usually gather together in peculiar subepithelial foci which seem to represent the sites of ongoing injury and repair. Delayed or ineffective re-epithelialization is a crucial trigger for recruiting, activating, and sustaining mesenchymal cells in these foci. Inflammatory-driven fibrotic lung disorders vary in the inflammatory composition and phenotypes and the intra-alveolar and interstitial milieu of mediators can be diverse according to the specific ILD.

Certainly, epithelial injury and activation may be observed in several ILDs, and some inflammation is usually

noticed in IPF, but their respective pathogenic roles are most likely negligible.

The cells primarily responsible for ECM production in the fibrotic lung are myofibroblasts. The origin of the expanded lung fibroblasts/myofibroblast population has not been determined but probably includes intra- and extrapulmonary sources. The putative roles of resident cells, bone-marrow stem cells, circulating fibrocytes, and EMT need to be elucidated.

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PART

III

Symptoms and Signs of Respiratory Disease

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27
CHAPTER

Approach to the Patient with Respiratory Symptoms

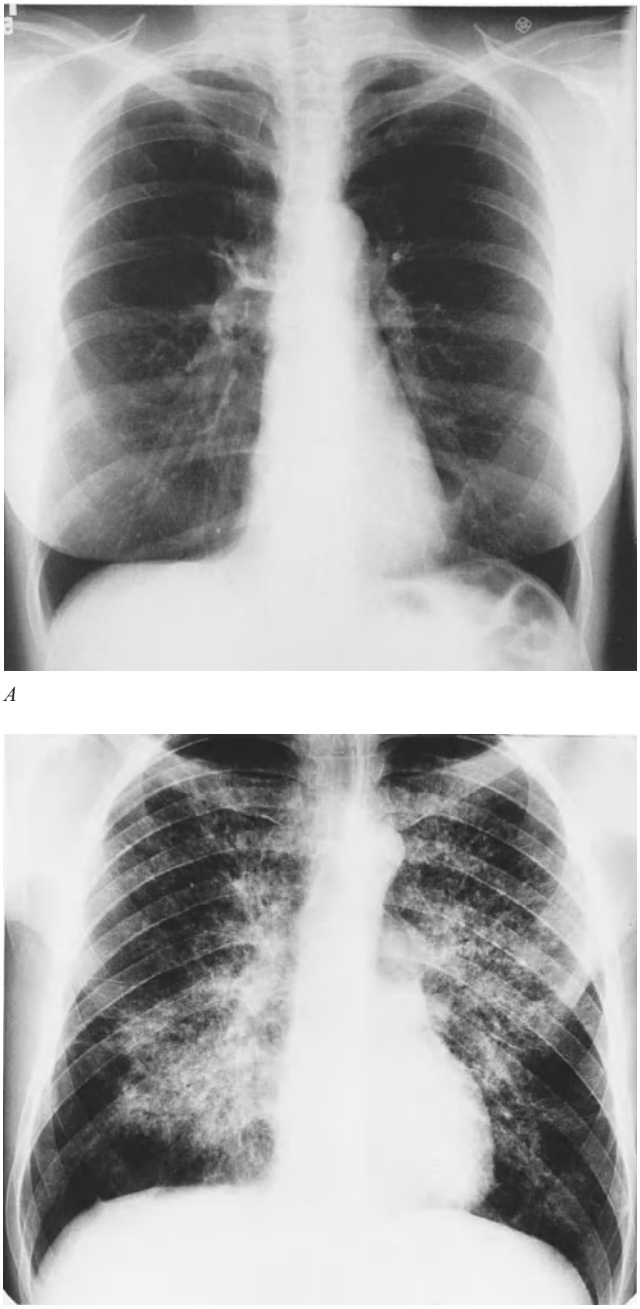
Darren B. Taichman • Alfred P. Fishman

The most common respiratory complaint for which a person seeks medical help is either shortness of breath or cough. Less frequent are hemoptysis, thoracic pain, cyanosis, and an abnormal breathing pattern. As in the case of any medical evaluation, the paramount diagnostic mainstays are the history and physical examination. The use of plain chest radiography for routine screening, once popular in the hope of uncovering silent disease amenable to therapy, has fallen into disuse and remains controversial because it has not been proven to decrease mortality, to be cost-effective, or to be worth either the inconvenience to the patient or the exposure to radiation. The use of computed tomography of the chest as a screening tool is also being debated and of unproven benefit. Chest radiography is now usually reserved for patients who have clinical manifestations of chest disease or are from families or populations known to be particularly vulnerable to chest disease. Serial chest radiographs often provide invaluable clues into the nature of chest lesions. More sophisticated diagnostic measures and interventions help to complete and supplement the clinical picture. Regardless of whether the analysis and diagnostic synthesis are accomplished in the clinician's mind or by computer-assisted mathematical modeling, the history, physical examination, and chest radiograph still remain the three-legged underpinning for diagnosis in chest medicine.

HISTORY

Even though seasoned clinicians may be adept at spotting telltale diagnostic clues, there still is no substitute for a comprehensive, penetrating medical history. This should include a detailed inventory of substances in the air that can harm the lungs. One of the most common offenders is cigarette smoking. An attempt should be made to quantify the exposure. When did it begin? When did it stop? How many cigarettes per day (expressed in number of pack-years)? Often, the workplace is the site where toxic air is inhaled. An almost forgotten exposure to a toxic inhalant 20 years ago can explain certain types of pulmonary or pleural diseases. Symptoms that appear to improve during weekends or other periods away from work may be a clue to an occupational exposure that causes a respiratory ailment. A newly installed home humidifier or an air-conditioning system that incorporates stagnant pools of water can point the way to resolving a mysterious illness. A brief residence in an area where either cryptococcosis (southwestern United States) or histoplasmosis (southern and midwestern United States) is endemic may help to clarify the nature of an illness that mimics tuberculosis. A recent visit to a South or Central American country may bring into focus a more remote possibility (e.g., South American blastomycosis) (Fig. 27-1).

The history should include a thorough evaluation of prior and current medical problems. Rheumatologic disorders such as systemic sclerosis (scleroderma) may be associated with interstitial lung disease, aspiration pneumonia due to the involvement of the esophagus, or pulmonary vascular disease. Certain malignancies often metastasize to the lung (e.g., breast or colon carcinoma), or predispose to the development of venous thromboembolism (e.g., pancreatic carcinoma). Infection with the human immunodeficiency virus (HIV) should not be overlooked since pulmonary complications are often the initial presentation of acquired immunodeficiency syndrome (AIDS). Other causes of immunodeficiency, such as a hematologic malignancy or chemotherapeutic treatment of cancer, should



A

B

Figure 27-1 Exposure in an endemic area. *A.* Clear lung fields. *B.* South American blastomycosis. *(Courtesy of Dr. Nelson Porto.)*

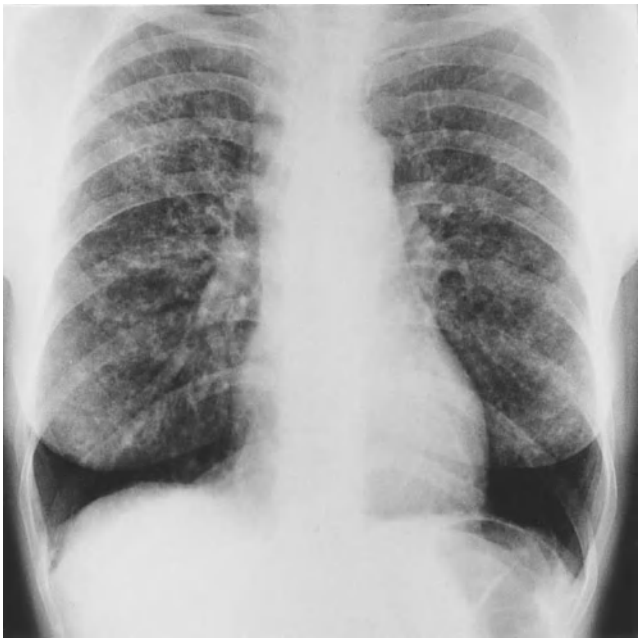


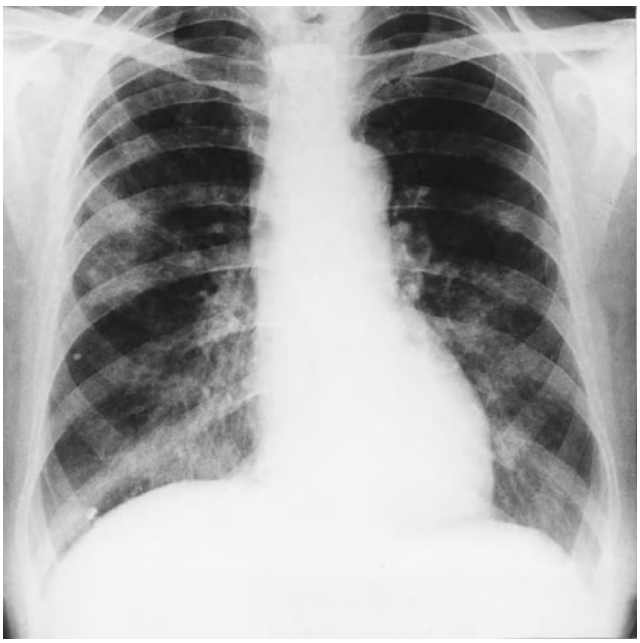
Figure 27-2 Nitrofurantoin hypersensitivity pneumonitis. The ingestion of nitrofurantoin, 50 mg qid, was accompanied by the appearance of patchy interstitial and alveolar changes throughout both lungs.

heighten suspicion of infection as the cause of respiratory symptoms.

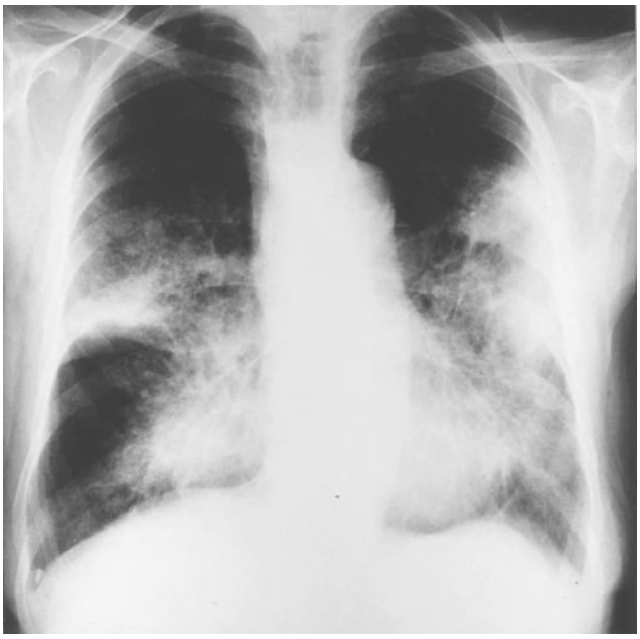
Personal habits of the patient, such as intravenous drug abuse or sexual practices, may also help to uncover the cause of an unusual pulmonary disorder. Recent treatment of a disorder with immunosuppressive agents can arouse suspicion of toxicity caused by the therapeutic agent or of pulmonary infection by organisms that are usually noninvasive.

Certain pharmacologic agents have a propensity for inflicting lung damage. Among these are bleomycin, nitrofurantoin, and methotrexate (Fig. 27-2). Beta blockers, administered as part of a cardiac regimen, can evoke bronchoconstriction. Even a common medication, such as aspirin may, on rare occasion, cause a severe pulmonary disorder (e.g., pulmonary edema).

The family history is an essential ingredient of the medical inventory. This history can be particularly helpful in uncovering heritable diseases of the lungs (e.g., cystic fibrosis, α_1-antitrypsin deficiency, alveolar microlithiasis, and hereditary telangiectasia). The unraveling of a familial history of asthma, a common disease, or of familial pulmonary arterial hypertension, a rare disease, can be much more difficult.



A



B

Figure 27-3 Chronic aspiration pneumonia. *A.* Chronic aspiration pneumonia in a 72-year-old man hospitalized for repair of hernia. Patchy infiltrates bilaterally. No pulmonary symptoms. Initiating cause was achalasia of esophagus. *B.* Eighteen months later. Persistent cough and breathlessness.

PHYSICAL EXAMINATION

Before the widespread use of chest radiography, the physical examination, along with the history, played the pivotal role in the diagnosis of pulmonary disease. The advent of chest radiography and of more sophisticated methods of imaging has tended to de-emphasize the value of the physical examination. Nonetheless, the physical examination remains a key diagnostic measure in the proper appraisal of chest disease.

General Aspects

Important clues are often available before examination of the chest. Neglected pyorrheal teeth raise the prospect of a necrotizing aspiration pneumonia. A lacerated tongue suggests that a convulsive episode may have led to aspiration (Fig. 27-3).

Pursing of the lips during expiration ("pursed lip breathing") is frequent in patients with chronic obstructive pulmonary disease (COPD). Subtle changes in consciousness or coordination may signal that metastasis has occurred to the brain from a primary carcinoma of the lung. In the patient with COPD, a clouded sensorium or a disturbed personality can signify acute CO_2 retention.

Inspection of the skin can often provide clues to diseases of the chest. Evidence to support the diagnosis of pulmonary sarcoidosis may be found in the eyes and skin. Petechiae in the skin may reflect a systemic vasculitis that also affects the vessels of the lungs. The skin lesions of neurofibromatosis type 1 (von Recklinghausen's disease) may signify that a solitary pulmonary nodule in the paraspinal region may be a neurofibroma. A minute skin abscess can turn out to be the source of multiple lung abscesses. Distinctive scars over the antecubital veins of a drug addict can help to clarify the etiology of old lesions in the lungs as well as of fresh abscesses. Erythema nodosum and erythema multiforme occasionally complicate sarcoidosis, tuberculosis, histoplasmosis, and coccidioidomycosis; on occasion, these skin lesions may be part of a drug reaction.

A variety of endocrine syndromes can accompany a carcinoma of the lung. An altered mental status may be due to hyponatremia caused by the syndrome of inappropriate antidiuretic hormone (SIADH) in a patient with a lung cancer. Clubbing of the digits may accompany various clinical disorders, including idiopathic pulmonary fibrosis, bronchiectasis, and certain carcinomas of the lung (Table 27-1). A puffy face, neck, and eyelids, coupled with dilated veins of the neck, shoulder, thorax, and upper arm (i.e., superior vena cava syndrome) may constitute the first clinical evidence of obstruction of the superior vena cava by a neoplasm of the lung. Although the causes of superior vena cava syndrome are many and diverse, at least 80 percent are attributable to a primary carcinoma of the lung (Fig. 27-4). In the patient in whom a neoplasm has evoked acute signs and symptoms of increased systemic venous pressure that progresses rapidly (e.g., to laryngeal edema), early diagnosis and prompt treatment of the neoplasm can be lifesaving. The presence of Horner's syndrome—unilateral ptosis, miosis, and anhidrosis—in a patient with a carcinoma of the lung suggests a pulmonary sulcus tumor with involvement of the ipsilateral sympathetic pathway within the thorax (Fig. 27-5).

Table 27-1

Clinical Disorders Commonly Associated with Clubbing of Digits

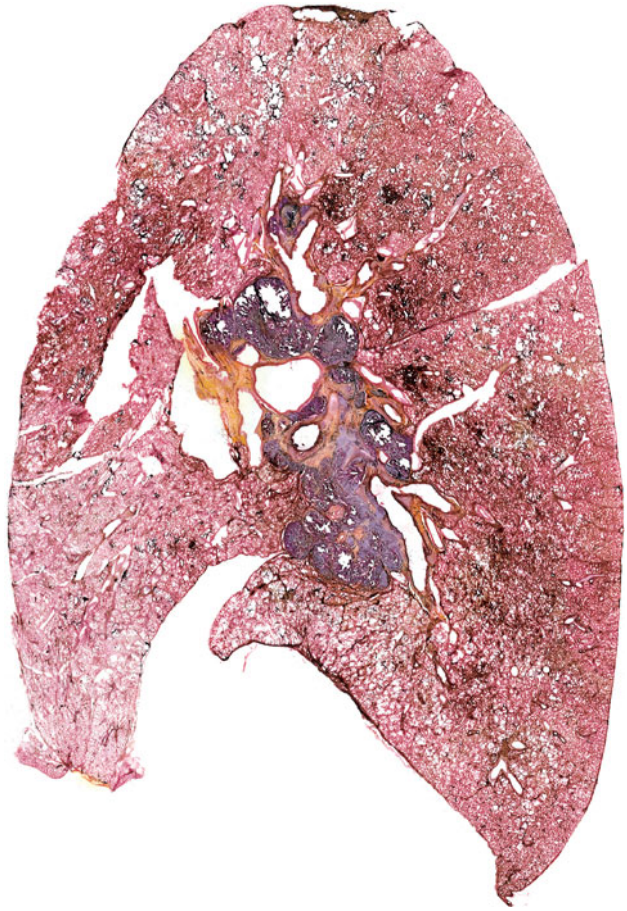
Pulmonary and thoracic
Primary lung cancer
Metastatic lung cancer
Bronchiectasis
Cystic fibrosis
Lung abscess
Pulmonary fibrosis
Pulmonary arteriovenous malformations
Empyema
Mesothelioma
Neurogenic diaphragmatic tumors
Cardiac
Congenital
Subacute bacterial endocarditis
Gastrointestinal and hepatic
Hepatic cirrhosis
Chronic ulcerative colitis
Regional enteritis (Crohn's disease)
Miscellaneous
Hemiplegia

Inspection of the Chest

Observation of the chest from the foot of the bed can be informative: a visible lag of one side of the thorax localizes a pleural effusion, pulmonary infection, or a paralyzed diaphragm. The position of the trachea with respect to the midline can be a useful clue to atelectasis of one lobe or to obstruction of a major bronchus. The respiratory pattern may be informative: patients with severe airflow obstruction often take slow, deep breaths; whereas rapid and shallow breaths are often seen with restrictive processes such as interstitial lung disease or kyphoscoliosis. Inspection of the chest and abdomen in the supine position may reveal the paradoxical inward movement of the abdomen indicative of respiratory muscle weakness (e.g., as in bilateral diaphragmatic paresis or paralysis). Thoracoabdominal discoordination during sleep raises the possibility of obstructive sleep apnea.

Palpation of the Chest

Over the years, the role of palpation in the examination of the chest has been considerably devalued. Nonetheless, palpation can provide helpful diagnostic clues as well as confirmatory evidence for other physical signs. For example, the position of



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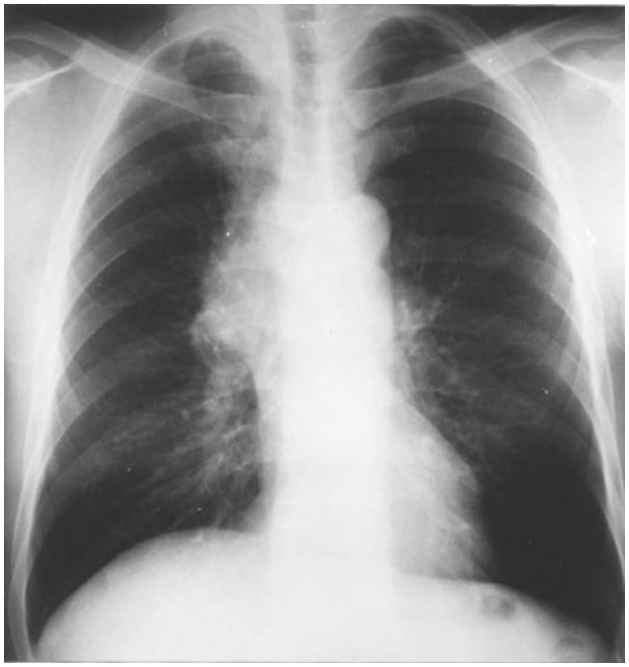

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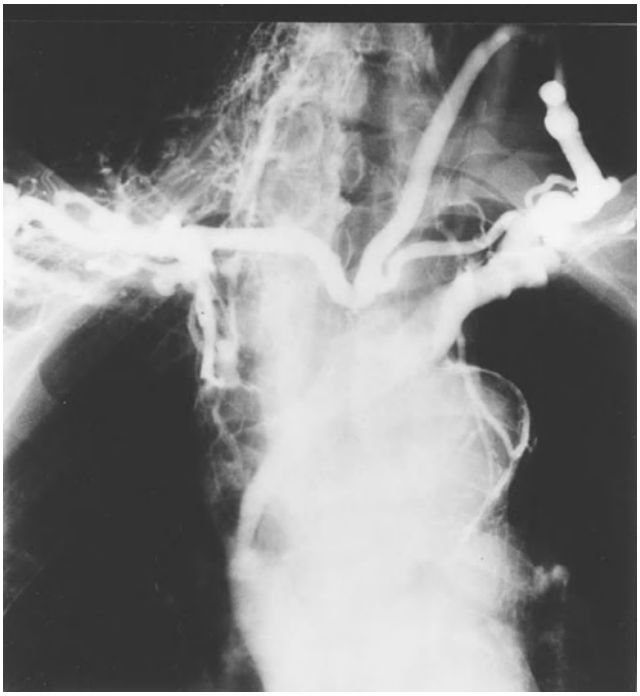


C

Figure 27-4 Local invasiveness of carcinoma of the lung. *A.* Sagittal section of the lung illustrating a carcinoma (blue) of the lung in the vicinity of the hilus. *B.* Chest radiograph showing right hilar mass. *C.* Angiogram showing obstruction and extensive collateral circulation.

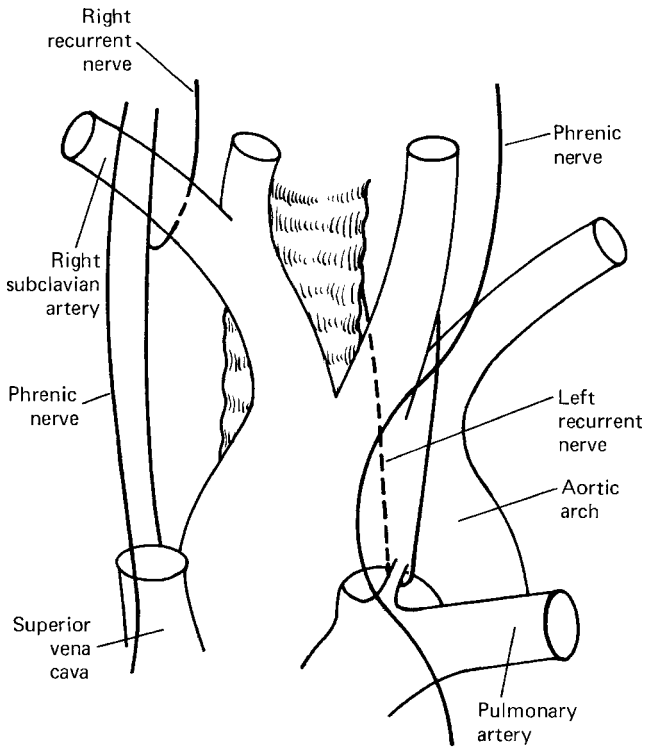


Figure 27-5 Courses of the recurrent laryngeal nerves. Invasion or compression of a nerve by a carcinoma of the lung causes paralysis of the vocal cord.

the trachea determined by palpation in the suprasternal notch can be helpful in detecting a lateral displacement of the upper mediastinum. Dislocation of the apical impulse and of cardiac dullness can be useful indices in detecting shift of the lower mediastinum. Tenderness over a rib may reflect a fracture, a metastasis, or an underlying pleuritis. Enlargement of the right ventricle can be more readily detected by palpation in the subxiphoid region than by other examination of the chest. Hoover's sign can be useful in disclosing a unilateral lag in motion of one side of the chest due to pleuritis or a pleural effusion. This sign is elicited by comparing the displacement from the midline during a patient's deep inspiration of the examiner's hands, each placed lightly over one hemithorax, with thumbs touching beneath the xiphoid at the start of the breath.

An abnormal mass or fullness palpated in the supraclavicular space may be a clue to the presence of a neoplasm or to an involved lymph node, and suggest a convenient location to obtain a biopsy for diagnosis.

Consolidation of the lung, which causes increased transmission of sound, can be detected as fremitus (i.e., as a palpable vibration) over the affected area while the patient repeats the traditional "one, two, three" as the examiner moves his/her palms systematically over the two hemithoraces. Conversely, impairment of sound transmission, as by a pleural effusion, diminishes vocal fremitus. In some instances, a pleural friction rub is palpable. Overall, the more seasoned the chest physician, the more likely is palpation to get its full due in the physical examination of the chest.

Percussion of the Chest

Percussion for physical examination has followed Auenbrugger's sounding of beer barrels to determine their fluid levels. The response to percussion is impaired whenever something other than air-filled lung lies directly beneath the chest wall. Common causes of dullness to percussion are consolidation or atelectasis of the lung, fluid in the pleural space, pleural thickening, and a large mass at the surface of the lung. Widespread hyperresonance can often be elicited in emphysema and circumscribed hyperresonance over a pneumothorax or large bulla. As a rule, a decrease in breath sounds, as over a large bulla, is more characteristic than an increase in resonance.

Auscultation of Lungs

Ever since the time of Laennec, physicians have applied the stethoscope to the chest in search of sounds of disease. Attention is focused on the intensity and quality of the sounds, as well as the presence of abnormal (often called adventitial) lung sounds.

Changes in the Intensity and Duration of Lung Sounds

The generation of lung sounds requires an ability to move air through patent airways. A global decrease in the intensity of breath sounds over the thorax or a hemithorax can be due to a variety of abnormalities: impaired movement of air due to airways disease (e.g., in emphysema), paralysis of a diaphragm, or complete obstruction of a bronchus. A decrease in audible breath sounds can also occur when the transmission of sounds to the chest wall is impaired (e.g., by a pleural effusion, pleural thickening, or a pneumothorax). A bulla gives rise to a more circumscribed diminution in breath sounds. In a patient with COPD, regional variations in breath sounds correspond to the distribution of ventilation.

An abnormal increase in intensity of breath sounds is accompanied by a change in their character (the sounds become either harsh or bronchial). The abnormal sounds are heard over consolidated, atelectatic, or compressed lung as long as the airway to the affected portion of the lung remains patent. Consolidated lung is presumed to act as an acoustic conducting medium that, unlike normal lung, does not attenuate transmission of tracheal sounds to the periphery.

Noting the duration of the inspiratory and expiratory phases of breathing can be useful. Inspiration is normally audible for a longer period, with little if any expiratory noise. A prolongation of expiration, often longer than inspiration, is found with obstructed airways.

Changes in the Transmission of Lung Sounds

Changes in voice sounds are often easier to appreciate than changes in breath sounds. Large pleural effusions, pneumothorax, and bronchial occlusion produce distant or inaudible breath sounds. Transmission of voice sounds is enhanced by consolidation, infarction, atelectasis, or compressions of lung tissue. Accompanying the increased transmission is a change in the character of the voice sounds that causes them to be higher pitched and less muffled than normal (bronchophony). When bronchophony is extreme, spoken words assume a nasal or bleating quality (egophony) and the sound "ee" is heard through the stethoscope as "ay." Egophony is most common when consolidated lung and pleural fluid coexist; sometimes it is heard over an uncomplicated lobar pneumonia or pulmonary infarction. Transmission of whispered voice sounds with abnormal clarity (whispered pectoriloquy) has the same significance as bronchophony.

Changes in the Quality of Lung Sounds

Normal breath sounds have a smooth, soft quality and are referred to as *vesicular*.

Adventitious Lung Sounds

Abnormal lung sounds have traditionally been resistant to meaningful clinical classification. The American Thoracic Society attempted to develop a rational and clinically useful classification based on acoustic analysis of tape recordings and the nomenclature introduced by Forgacs (Table 27-2). With this approach, lung sounds are categorized as continuous (wheezes, rhonchi, or stridor) or discontinuous (crackles).

Wheezes, rhonchi, and stridor are musical adventitious sounds. Wheezes originate in airways narrowed by spasm, thickening of the mucosa, or luminal obstruction. Although

Table 27-2

Classification of Common Lung Sounds

Acoustic Characteristics	American Thoracic Society Nomenclature	Common Synonyms
Discontinuous, interrupted explosive sounds; loud, low in pitch	Coarse crackle	Coarse rale
Discontinuous, interrupted explosive sounds; less loud than above and of shorter duration; higher in pitch than coarse crackles or rales	Fine crackle	Fine rale, crepitation
Continuous sounds longer than 250 ms, high-pitched; dominant frequency of 400 Hz or more, hissing sound	Wheeze	Sibilant rhonchus
Continuous sounds longer than 250 ms, low-pitched; dominant frequency about 200 Hz or less, snoring sound	Rhonchus	Sonorous rhonchus

Source: From Loudon R, Murphy RLH: Lung sounds. Am Rev Respir Dis *130:663–673, 1984.*

wheezes are more apt to occur during forced expiration, which further narrows airways, they may occur during both inspiration and expiration in asthma. Wheezes presumably originate through a combination of limitation to airflow and vibrations in the walls of the airways. Rhonchi are due to the presence of liquid or mucus in the airways; the quality and location may be readily changed by asking the patient to cough, thus moving the secretions. Stridor is predominantly inspiratory and best heard over the neck. Common causes of stridor are a foreign body in the upper intrathoracic airway or esophagus, an acquired lesion of the airway (e.g., carcinoma in adults), or a congenital lesion in children.

Crackles

Crackles are generally attributed to a rapid succession of explosive openings of small airways that closed prematurely during the previous expiration. Crackles have been subdivided according to their timing during inspiration (early or late) and by differences in their quality ("wet" or "dry"); at times they have been termed "rales". Noting differences in timing has been advocated as a way of distinguishing between possible causes (e.g., "dry" crackles in the fibrosis of interstitial lung disease vs. "wet" crackles in pulmonary edema). Unfortunately, wide variation in the interpretation of these sounds generally renders such attempts at classification of little value and often a cause of confusion. Crackles may accompany alterations in the elastic recoil of airways (emphysema), the presence of secretions (bronchitis or pneumonia), inflammation or fibrosis (interstitial lung disease) or fluid (pulmonary edema). Crackles can also be due to atelectasis, as in bedridden patients, and may clear with sequential deep breaths.

Pleural Rub

A pleural friction rub is a coarse, grating, or leathery sound that is usually heard late in inspiration and early in expiration; most often a pleural friction rub is audible low in the axilla or over the lung base posteriorly. The rub sounds close to the ear and usually is not altered by coughing.

DYSPNEA

Dyspnea is the medical term for breathlessness or shortness of breath. For the patient, dyspnea involves an experience of discomfort in breathing. It is alarming to most patients and can arouse great concern about a potential dire cause, making it one of the most frequent complaints that prompts patients to seek medical evaluation.

In the extensive medical, physiological, and psychological literature, dyspnea is used variously to designate a range of sensations from awareness of breathing on the one hand, to respiratory distress on the other. The wide range of meanings is understandable on several counts: (1) dyspnea is a subjective complaint without consistency in objective signs such as tachypnea; (2) few physicians have experienced the respiratory discomfort associated with chest disease, so that most interpretations of the complaint represent extrapolations from normal breathlessness (e.g., after strenuous exercise); (3) most experimental observations relating to dyspnea are based on the study of normal subjects or animals under artificial circumstances; and (4) most physicians apply the term loosely, based on their experience with the predominant patient population that they serve (e.g., patients with COPD or asthma). Despite this variability, in clinical medicine, the complaint of dyspnea almost invariably implies respiratory discomfort.

Because of its subjective nature, the sensation of dyspnea is an amalgam of two components. The *first* is the sensory input to the cerebral cortex, which consists of information from specialized receptors, predominantly mechanoreceptors, at various sites in the respiratory

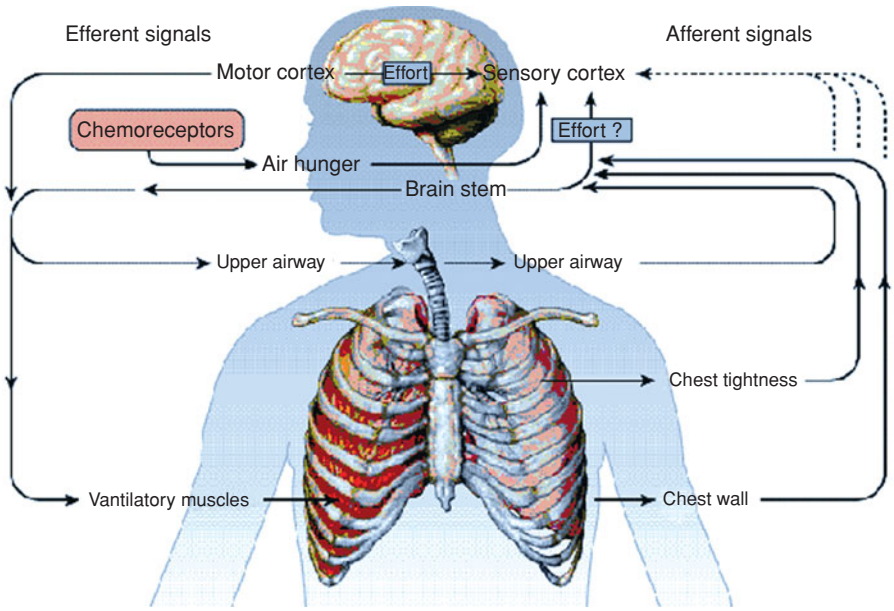


Figure 27-6 Pathways to the sensation of breathlessness. Respiratory effort is believed to originate as a signal transmitted from the motor cortex simultaneously to the sensory cortex and to the motor command to ventilatory muscles. The brain stem may also contribute to the sense of effort. The perception of air hunger is believed to arise, in part, from increased respiratory activity within the brain stem, whereas the sensation of chest tightness probably results from stimulation of vagal irritant receptors. Although afferent information from airway, lung, and chest-wall receptors most likely passes through the brain stem before reaching the sensory cortex, the dashed lines indicate uncertainty about whether some afferents bypass the brain stem and project directly to the sensory cortex. *(From Manning HL, Schwartzstein RM: Pathophysiology of dyspnea. N Engl J Med 333:1547–1553, 1995, with permission.)*

apparatus (predominantly the upper airways) and face (Fig. 27-6). The different sites of stimulation may contribute to the disparities in the sensation. Furthermore, no specific area in the central nervous system has been identified as the sensory locus for dyspnea. The input—from airways, lungs (via the vagus nerves), respiratory muscles, chest wall, and chemoreceptors—is processed at consecutive levels of the nervous system (i.e., spinal cord and supraspinal regions en route to the sensorimotor cortex). Additional sensory input, triggered by inadequate oxygen delivery or utilization, is poorly understood. The *second* component is the perception of the sensation, which rests heavily on the interpretation of information arriving at the sensorimotor cortex. The interpretation depends greatly on the psychological makeup of the person.

A variety of influences can modify the psychological component of dyspnea. During "Kussmaul breathing" (see below), "air hunger" may seem obvious to the observer, even though the patient does not feel short of breath. In contrast, patients with congestive heart failure or COPD frequently volunteer the complaint of "air hunger." Blunting of the sensorium, as by narcotics or by acute hypercapnia, can eliminate the sensation of breathlessness, even though the abnormal breathing pattern remains. Anxiety can heighten the sense of breathlessness. Indeed, anxiety can be responsible for the clinical syndrome of psychogenic dyspnea, in which the patient experiences "breathing discomfort" that eludes explanation on the basis of a somatic cause. Ill-defined sensations may accompany a full-blown hyperventilation syndrome consisting of light-headedness, tingling of the hands and feet, tachycardia, inversion of T waves on the electrocardiogram, and even syncope. Breathing discomfort at rest that decreases with activity is often seen when anxiety or other psychological issues are the cause, and is a distinctly unusual pattern for dyspnea due to a cardiopulmonary abnormality.

The quality of dyspnea can vary greatly. In normal persons, as well as in those with chest disease, dyspnea may simply signify the transition from an effortless process that is ordinarily conducted at a subconscious level to the awareness that muscular effort is being expended in breathing. The healthy athlete completing a dash experiences breathlessness that can be exhilarating rather than uncomfortable. The asthmatic often interprets breathlessness in terms of "tightness in the chest." The patient with COPD often complains of less-severe breathlessness than would be expected from the degree of airway obstruction, possibly reflecting adaptation either to the chronic obstructive airway disease or to CO_2 retention.

Patients may use different terms to describe breathing discomfort due to various causes. In some instances these descriptors may be useful in establishing a differential diagnosis and in assessing the response to therapy. Patients with asthma or myocardial ischemia often refer to "chest tightness." Patients with pulmonary edema may suffer a sensation of "air hunger" or "suffocation." Patients with COPD and hyperinflation of the chest often note an inability to take a deep, satisfying breath. Individuals who are physically out of

shape may complain of "heavy breathing." Unfortunately, no descriptor has sufficient sensitivity or specificity to be used alone in establishing the cause of a patient's dyspnea.

Clinical Presentations

Dyspnea may be acute, chronic, or paroxysmal (Table 27-3).

Table 27-3

Causes of Acute and Chronic Dyspnea*

Acute
Pulmonary edema
Asthma
Injury to chest wall and intrathoracic structures
Spontaneous pneumothorax
Pulmonary embolism
Pneumonia
Adult respiratory distress syndrome
Pleural effusion
Pulmonary hemorrhage
Chronic, progressive
Chronic obstructive pulmonary disease
Left ventricular failure
Diffuse interstitial fibrosis
Asthma
Pleural effusions
Pulmonary thromboembolic disease
Pulmonary vascular disease
Psychogenic dyspnea
Anemia, severe
Postintubation tracheal stenosis
Hypersensitivity disorders

**Many chronic processes (eg, left ventricular failure, asthma, and COPD) may have acute exacerbations.*

Acute

The usual causes of acute dyspnea in children differ from those in adults. In children, upper-airway infection (e.g., epiglottis, laryngitis, or acute laryngotracheobronchitis) is a common cause. In adults, the causes of acute dyspnea are much more varied (Table 27-3). Among the most common are an episode of acute left ventricular failure, a thromboembolic event, pneumonia, and spontaneous pneumothorax. Less common, but not unusual, is massive collapse of one lung due to inability to clear the airways of thick tenacious secretions (e.g., in chronic bronchitis or asthma) or the first attack of asthma.

Chronic (and Progressive) Dyspnea

Chronic dyspnea is almost invariably progressive. As a rule, this type of dyspnea begins with breathlessness on exertion—which, in time, progresses to dyspnea at rest. Pulmonologists encounter dyspnea in patients who have COPD; cardiologists more often deal with dyspnea in patients who are in chronic congestive heart failure. Especially in older patients, distinction between the heart and lungs in the etiology of dyspnea, or the relative contributions of each, can be difficult to establish.

Asthma is a common cause of recurrent bouts of dyspnea which are usually accompanied by cough and wheezing. Cardiac dysfunction is another cause of acute bouts of bronchospasm, especially in middle-aged or elderly persons. Another, much less frequent cause of paroxysmal wheezing and breathlessness is bronchopulmonary aspergillosis. Etiologies of asthma vary in different parts of the world; where schistosomiasis is endemic, an attack of asthma may accompany the migratory stage of schistosomiasis (i.e., larvae traversing the lungs).

Physiological Correlates of Dyspnea

Historically, attempts to understand the physiological bases of dyspnea have evolved along four separate lines: ventilatory performance, the mechanics of breathing, chemoreception, and exercise testing.

Ventilatory Performance

The earliest investigations related dyspnea to minute ventilation. Dyspnea was found to correlate with an excessive minute ventilation for the level of oxygen uptake. Most of the increase in ventilation was accounted for by an increase in respiratory rate, especially in patients with stiff lungs. In patients who continued to ventilate excessively for the level of oxygen uptake (e.g., those with chronic left ventricular failure), the sensation of breathlessness gradually diminished, suggesting adaptation to the continued stimulus.

A second ventilatory measurement that proved to correlate well with dyspnea is the maximum voluntary ventilation (MVV). MVV is decreased by diseases of the lungs, airways, or chest cage. The smaller the maximum breathing capacity, the more likely is dyspnea to occur.

A third time-honored approach to measurement is the "breathing reserve." This value is determined as the difference between the MVV and the actual minute ventilation. In principle, the sensation of breathlessness during the performance of any ventilatory task may be related to the fraction of the maximum breathing capacity that is used for force generation by the respiratory apparatus. Thus, the closer the minute ventilation is to the maximum breathing capacity, the more likely is the subject to complain of breathlessness. Indeed, when the actual level of ventilation reaches 30 to 40 percent of the maximum breathing capacity, dyspnea is inevitable. Unfortunately, the breathing reserve correlates better with the dyspnea of normal subjects during exertion than with the dyspnea of chronic bronchitis and COPD or of left ventricular failure. Thus, in COPD the minute ventilation may be a very large fraction of the MVV (greater than 50 percent) without eliciting dyspnea. In contrast, in acute left ventricular failure, a mild increase in ventilation and a nearly normal MVV may be associated with considerable breathlessness.

Mechanics of Breathing

One teleological way to regard dyspnea is as a sensation that prompts an unconscious effort to minimize the work, energy cost, or force of breathing. In this light, dyspnea protects the respiratory apparatus from overwork and inefficient operation. This approach has led to exploration of the relationships between dyspnea and the work or oxygen cost of breathing.

Work, Oxygen Cost, and Efficiency of Breathing

It has not been possible to identify a critical level for the work of breathing at which dyspnea will occur. However, a breakdown of the work of breathing into its elastic, resistive, and inertial components has helped to relate physiological disturbances to particular diseases. For example, in chronic mitral stenosis with pulmonary congestion, the elastic work is greatly increased (Fig. 27-7), whereas in obstructive airway disease, resistive work predominates. Moreover, such observations have reinforced the concept that patterns of breathing are automatically adjusted to minimize the work done by the respiratory muscles in breathing.

The relationship between ventilation and O_2 consumed by the respiratory muscles is curvilinear (Fig. 27-8). This O_2 cost of breathing can increase extraordinarily in patients with COPD or with abnormalities of the chest wall. Indeed, in patients with COPD, the quantity of O_2 delivered to the respiratory muscles during the large ventilatory effort may fail to satisfy their aerobic needs, leading to anaerobic metabolism and lactic acidosis. Although the greater the O_2 cost of breathing the greater the likelihood of dyspnea, the determination of O_2 cost provides no more useful insight into the mechanism of dyspnea than does the work of breathing. Calculation of the efficiency of breathing (i.e., the work of breathing related to energy cost) provides no further clarification.

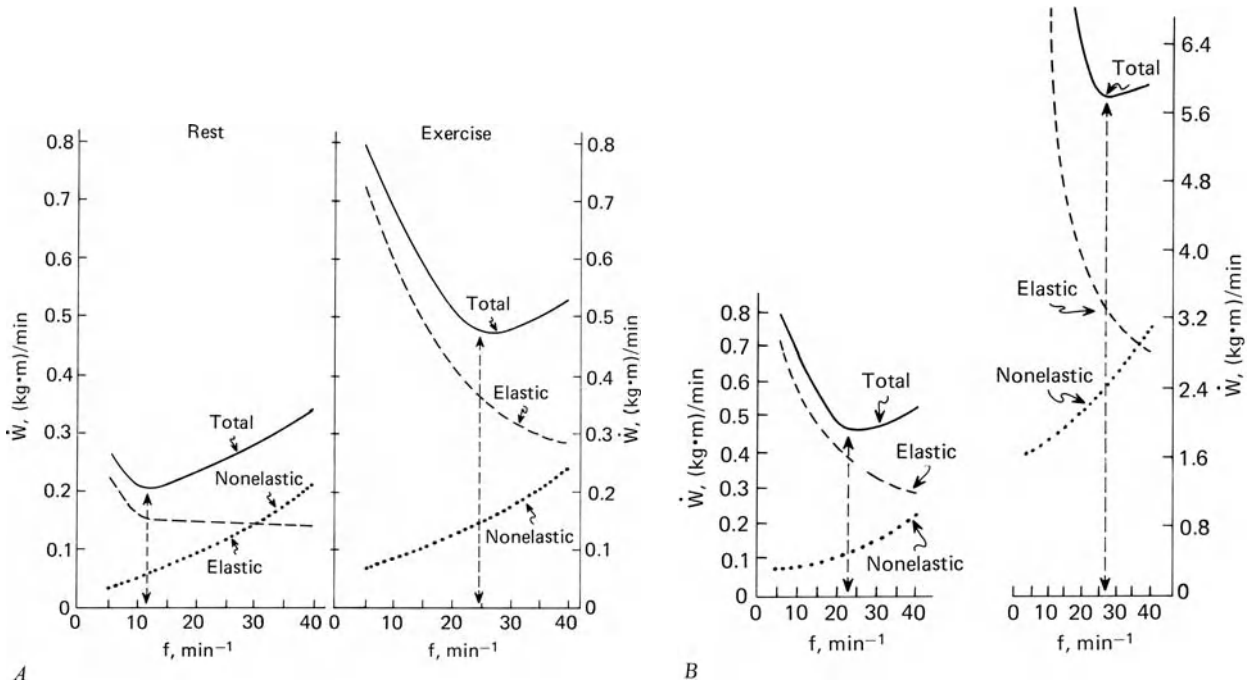


Figure 27-7 Partition of the work of breathing in pulmonary congestion and edema at rest and during exercise. *A.* Normal. The minimal work of breathing at rest was at a respiratory frequency of 12 breaths per min; during exercise, the minimal work was done at a higher frequency (25 breaths per min). *B.* Mitral stenosis. At rest, the frequency for least respiratory work was abnormally high (22 breaths per min); during exercise it increased further (to 28 breaths per min). The dashed vertical line (capped by arrowheads) in each frame indicates the respiratory frequency at which respiratory work was minimal. *(From Christie RV: Dyspnea in relation to the visco-elastic properties of the lung. Proc R Soc Med 46:381–386, 1953, with permission.)*

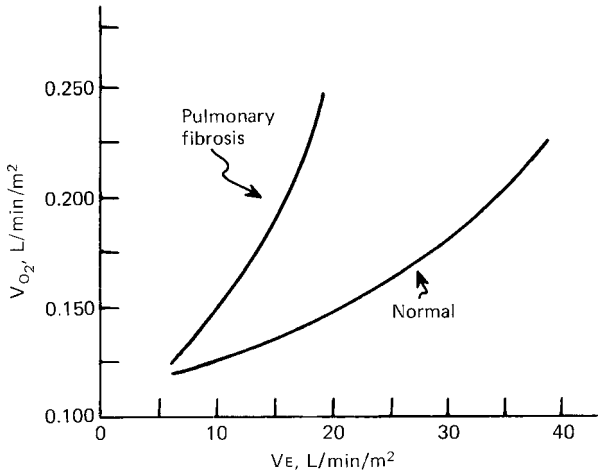


Figure 27-8 Oxygen cost of breathing in restrictive lung disease. Relationship between ventilation and O_2 consumption in pulmonary fibrosis. At each level of ventilation, the patient with pulmonary fibrosis does more work and expends more energy in breathing than does the normal subject.

Length-Tension Inappropriateness

The concept of "length-tension inappropriateness" explains dyspnea as a mismatch between the central motor command to the respiratory muscles (i.e., the motor signal emitted from the brain) and the suboptimal ("inappropriate") shortening of the respiratory muscles elicited by this command (e.g., suboptimal thoracic expansion for any level of central motor command). In essence, this concept pictures a decrease, instead of an increase, in the pressure-generating capacity of the respiratory muscles in the face of the increased need arising from the heightened respiratory drive.

Chemoreception

Chemoreceptors in the medulla respond to changes in pH and Pa_{CO_2}. Peripheral receptors in the aortic arch and carotid body also respond to alterations in Pa_{O_2}. Acute hypoxia, hypercapnia, and acidosis are the traditional stimuli for ventilation. For example, upon ascent to altitude, acute hypoxia can stimulate ventilation to the level of awareness that may progress to discomfort during exertion. The effects of these stimuli on breathing decrease if they continue unabated. In addition, side effects, such as blunting of the sensorium during chronic CO_2 retention, diminish the likelihood of dyspnea, even if the level of ventilation is increased. In patients with abnormal pulmonary mechanics, the onset of abnormalities in blood gas composition, as during exercise, can aggravate or contribute to dyspnea. In general, acute hypercapnia is a stronger stimulus for dyspnea than is acute hypoxia.

Scaling

A variety of scaling methods have been devised in the attempt to quantify dyspnea during exercise and various experimental conditions. Some, such as the Borg Category Scale (Table 27-4), use numbers and descriptive terms to depict a change in the intensity of the stimulus ("threshold stimulus detection methods"). Others rely on visual analog scales, which are straight lines, usually 10 cm long, that extend from "not breathless" at one end to "extremely breathless" at the other. The patient marks on this line the intensity of respiratory discomfort elicited by external stimuli, such as resistive loads or exercise testing. The score is measured as the length of the line between "not breathless" and the mark made by the patient. The Shortness of Breath Scale issued by the American Thoracic Society (Table 27-5) has also been used in one form or another, particularly in epidemiological studies. No single scale is applicable to all subjects or patients.

Table 27-4

Modified Borg Category Scale

Rating	Intensity of Sensation
0	Nothing at all
0.5	Very, very slight (just noticeable)
1	Very slight
2	Slight
3	Moderate
4	Somewhat severe
5	Severe
6	
7	Very severe
8	
9	Very, very severe (almost maximal)
10	Maximal

Dyspnea: Overview

In general, the sensation of dyspnea seems to be related to the intensity of afferent input from thoracic structures (especially the respiratory muscles) and from the chemoreceptors (central, peripheral, local). In patients with respiratory disease, dyspnea occurs most often when breathing is impeded, mechanics of breathing are abnormal, the lungs are stiffened, ventilatory musculature is weakened, and/or chemoreceptor input is increased.

Dyspnea in Chronic Pulmonary Disease

Two common types of pulmonary disease in which dyspnea features prominently are chronic obstructive airway disease and restrictive lung disease.

Table 27-5

American Thoracic Society Scale

Descriptions	Grade	Degree
Not troubled by shortness of breath when hurrying on the level or walking up a slight hill	0	None
Troubled by shortness of breath when hurrying on the level or walking up a slight hill	1	Mild
Walks more slowly than people of the same age on the level because of breathlessness or has to stop for breath when walking at own pace on the level	2	Moderate
Stops for breath after walking about 100 yards or after a few minutes on the level	3	Severe
Too breathless to leave the house; breathless on dressing or undressing	4	Very severe

Chronic Obstructive Pulmonary Disease (COPD)

COPD refers to a spectrum of airway diseases in which obstruction to airflow is the common denominator. Cigarette smoking is the leading cause of COPD. The outer limits of the spectrum are marked by chronic bronchitis at one end and emphysema at the other. Most patients with COPD fall into categories between those limits (i.e., they manifest mixtures of chronic bronchitis and emphysema which vary in degrees) (Fig. 27-9).

Asthma constitutes a different entity, not only in its clinical expressions but also because it is usually episodic and is often related to allergic manifestations, and generally affects younger individuals. Cystic fibrosis is another distinct entity because of its genetic basis, clinical and radiographic presentations, and nature of the airway obstruction (i.e., by inspissated mucus) and proclivity to superinfection. Dyspnea is a regular feature of each of these causes of chronic airways obstruction.

Patients with COPD suffer from disturbances in the mechanics of breathing, abnormal lung volumes, and derangements in gas exchange. The minute ventilation, which may be only slightly increased at rest, constitutes an abnormally large fraction of the maximum breathing capacity (i.e., the "breathing reserve" is low).

Abnormalities in the mechanics of breathing dominate the scene: resistance to airflow is high; the thorax assumes a hyperinflated position, placing the inspiratory muscles at mechanical disadvantage; the work of breathing is greatly increased. The O_2 cost of breathing is correspondingly high. Derangements in dead space ventilation and in alveolar-capillary gas exchange add to the afferent stimuli. As a result of the disturbances in mechanics and gas exchange, swings in pleural pressure (a measure of force applied to the lungs) are large, and a considerable muscular effort is expended in breathing; instead of the normal increase of about 1 ml of O_2 uptake per liter of ventilation per minute, the O_2 uptake increases enormously (up to 25 ml/min). Should O_2 delivery to the overworked respiratory muscles be insufficient, fatigue and exhaustion may send nervous and chemical signals of their own to the brain. Finally, if the patient accumulates excess water in the lungs, the juxtacapillary ("J") receptors provide additional sensory input to the central integrating mechanism. As noted above (see "Length-Tension Inappropriateness"), the convergence of these diverse stimuli upon the sensorimotor cortex may generate an inordinate motor command to the respiratory muscles, which cannot mobilize the thorax sufficiently to generate the pleural pressures needed for adequate ventilation.

One enigma is why some patients with COPD settle for a lower ventilation than others. For example, despite equal abnormalities in conventional pulmonary function tests, the "CO_2 retainer," with respiratory acidosis and arterial hypoxemia, often breathes less than does the non–CO_2 retainer in whom blood gas levels are near normal. One teleological explanation is that the lower ventilation in the CO_2 retainer causes less dyspnea. However, this explanation affords no insight into the physiological mechanism.

Treatment of the patient with COPD is directed at diminishing airways resistance and restoring arterial blood gases toward normal. Unfortunately, bronchodilators and corticosteroids generally exert little effect, and the basic abnormalities in the mechanics of the lungs and airways remain. Consequently, the load on the respiratory muscles is not readily alleviated by medical management. Accordingly, therapeutic interest in these disorders has turned to ways by which the performance of the respiratory muscles can be improved. These have generally taken the form of training exercises to facilitate adaptive changes and to increase both muscle strength and endurance. Exercise reconditioning in patients with COPD has been shown to diminish breathlessness, possibly owing to three interactive mechanisms: (1) increased mechanical efficiency of the exercising muscles, which decrease ventilatory requirements; (2) improved function of the respiratory muscles; and (3) increased tolerance of the "dyspneagenic" sensory input to the brain. Attempts to rest the respiratory muscles have no lasting effect on dyspnea.

Asthma

The mechanisms described above for COPD apply as well to asthma. However, these mechanisms do not account for the sensation of "tightness in the chest" or the inordinate sense of labored breathing that accompanies the breathlessness in asthma.

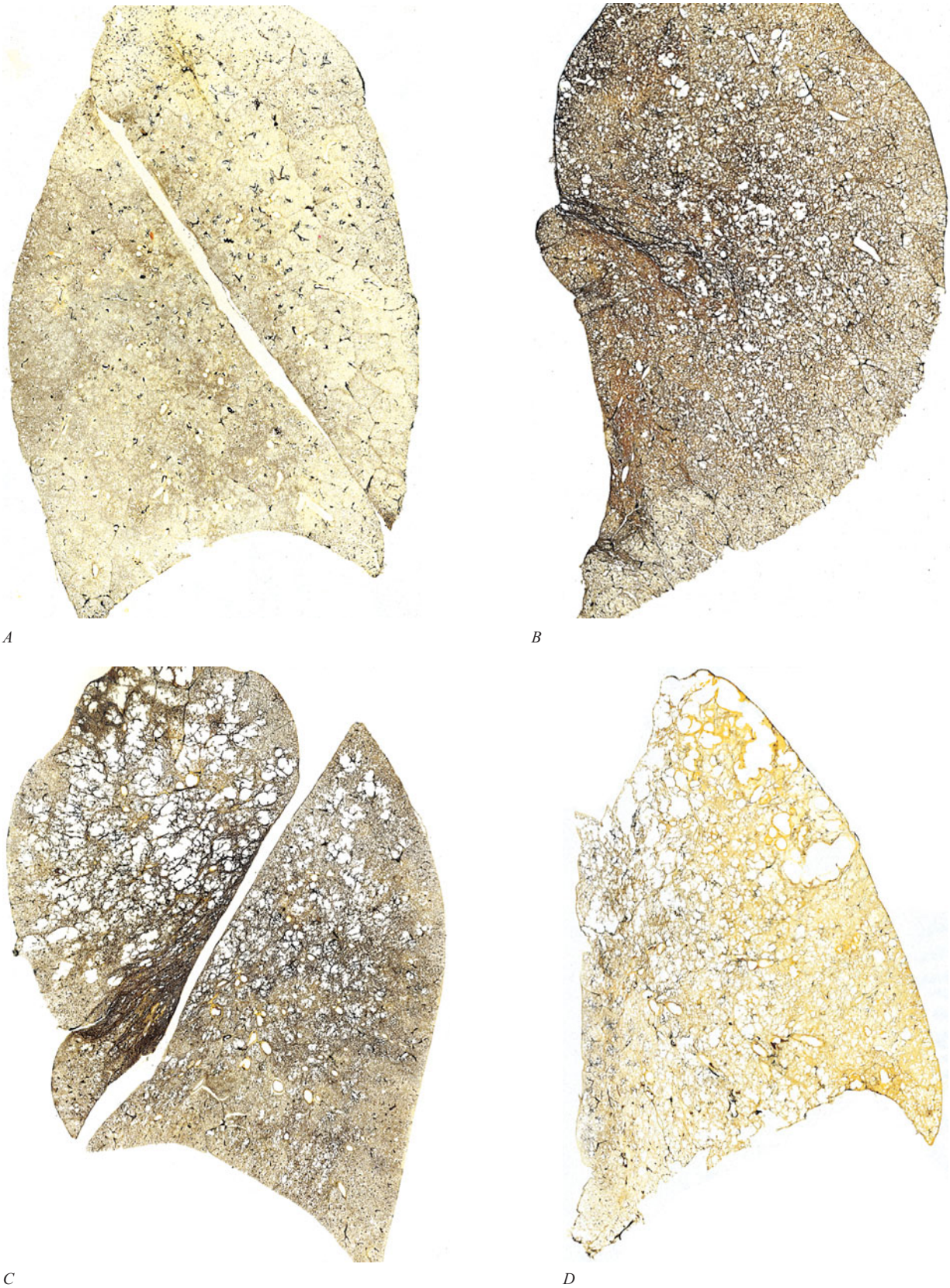


Figure 27-9 Chronic obstructive pulmonary disease (COPD). Sagittal sections showing patterns of emphysema. *A*. Normal lung from a patient who died of unrelated causes. *B*. Predominantly centrilobular emphysema. *C*. Predominantly centrilobular and panlobular emphysema. *D*. Predominantly panlobular emphysema. Centrilobular emphysema is less marked. The three patients with emphysema *(B, C, D)* also had clinical manifestations of chronic bronchitis confirmed by histological sections.

Table 27-6

Common Causes of Restrictive Lung Disease

Cause	Example
Interstitium	
Interstitial fibrosis and/or infiltration	Asbestosis
Pulmonary edema	Left ventricular failure
Pleura	
Pleural disease	Fibrothorax
Thoracic cage and abdomen	
Neuromuscular disease	Poliomyelitis
Skeletal abnormalities	Severe kyphoscoliosis
Marked obesity	Grossly overweight

Restrictive Lung Disease

Restrictive lung diseases can be due to different causes, but usually they have in common a reduction in lung volumes and diffusing capacity (Table 27-6). Diffuse interstitial disease, has many different causes and may be either acute or chronic (Table 27-7). Characteristically, in widespread interstitial disease, the diffusing capacity is low and accompanied by a considerable decrease in total lung capacity and in vital capacity accompanied by lesser decrements in functional residual capacity and residual volume. Similar findings occur in severe kyphoscoliosis or encasement of the lung by pleural thickening (Fig. 27-10). In contrast, in pulmonary vascular disease, such as idiopathic pulmonary arterial hypertension, a low diffusing capacity may be accompanied by normal lung volumes. Neuromuscular disease that affects the inspiratory muscles sufficiently to diminish maximum inspiratory pressures may only decrease the vital and total lung capacities, leaving the functional residual capacity and residual volume unaffected.

Patients with widespread pulmonary fibrosis breathe faster and maintain a higher minute ventilation than do normal subjects, both at rest and during exercise. The work and oxygen cost of ventilating the stiff lungs are increased. The maximum breathing capacity is well preserved. In these patients, dyspnea is attributable to the considerable effort by the respiratory muscles in ventilating the stiff lungs and in sustaining the high ventilatory rate. During exercise, dyspnea may become intolerable.

Dyspnea in Chronic Cardiac Disease

The mechanisms responsible for dyspnea in cardiac disease vary with the extent to which the lungs are stiffened.

Without Stiff Lungs

Dyspnea occurs in many forms of heart disease that are not associated with congestion of the lungs. Uncomplicated pulmonic stenosis is an excellent example. The symptom is probably related to an inadequate cardiac output during exercise. In tetralogy of Fallot, dyspnea is sometimes severe and often relieved by assuming a squatting position. In this and other forms of cyanotic heart disease, both dyspnea and fatigue appear during exertion when the arterial oxyhemoglobin saturation decreases appreciably below the resting level.

With Stiff Lungs

Cardiac dyspnea is associated with an increase in blood and water content of the lungs. It is a common occurrence in left ventricular failure and mitral stenosis, both of which are accompanied by increases in pulmonary venous and capillary pressures. The engorged pulmonary circulatory bed, coupled with interstitial and alveolar edema, stiffens the lungs (i.e., decreases their compliance) and stimulates the ventilation via "J" receptors. In chronic left ventricular failure, pulmonary fibrosis, consequent to long-standing interstitial edema, contributes to the stiff lungs. Edema of the tracheobronchial mucosa increases airway resistance.

As a result of the stiff lungs and increased airway resistance, the swings in pleural pressure during the respiratory cycle are large and the work and energy cost of breathing are increased. Arterial hypoxemia, generally mild, may add to the ventilatory drive. Exercise exaggerates the pulmonary congestion and edema, promotes arterial and mixed venous hypoxemia, and increases the dyspnea.

In patients with pulmonary congestion and edema, tachypnea is a regular feature at rest and increases during exercise. Although tachypnea is consistent, its degree is generally modest and probably not entirely responsible for the dyspnea. Fatigue is a common concomitant of low cardiac output and may stem from diminished O_2 delivery to the respiratory muscles, contributing to respiratory discomfort.

Orthopnea and Other Positional Forms of Breathlessness

Orthopnea signifies dyspnea in the recumbent, but not in the upright or semivertical position; it is usually relieved by two or three pillows under the head and back. Oppositely, platypnea signifies dyspnea induced by assuming the upright position and relieved by assuming the recumbent position. Platypnea can be seen when, due to gravity, increased blood flow worsens right to left shunting of blood through arteriovenous malformations at the lung bases. Orthopnea is a hallmark of pulmonary congestion that stiffens the lungs (i.e., decreases

Table 27-7

Some Types of Diffuse Interstitial Disease

Etiology	Example	Common Features
	Acute	
Infections	Miliary tuberculosis, histoplasmosis	Opportunity for exposure to organism
	Pneumocystis, cytomegalic inclusion virus, fungi	Immunosuppression
Pulmonary edema	Narcotic overdosage, nitrogen dioxide (silo-filler's disease), uremia	Distinctive history
Inhalation	Byssinosis	Monday morning asthma and fever
Aspiration	After loss of consciousness	History of alcoholism or epilepsy
Immunologic	Goodpasture's syndrome	Renal and pulmonary involvement
Carcinoma of lung	Alveolar cell carcinoma	
	Chronic	
Inhalation	Pneumoconioses	History of exposure to inorganic dust
Radiation therapy	After mastectomy	Gradual evolution after treatment
Lymphangitic spread	Carcinoma of breast, lung, stomach, pancreas	Evidence of primary carcinoma
Medications	Hexamethonium hydralazine, bleomycin, busulfan, nitrofurantoin	History, suggestive chest radiograph
Systemic disorders	Sarcoidosis, collagen, disorders, histiocytosis X, amyloidosis, tuberous sclerosis	Multi-organ involvement; biopsy
Idiopathic	Idiopathic pulmonary fibrosis	Exclusion of known causes

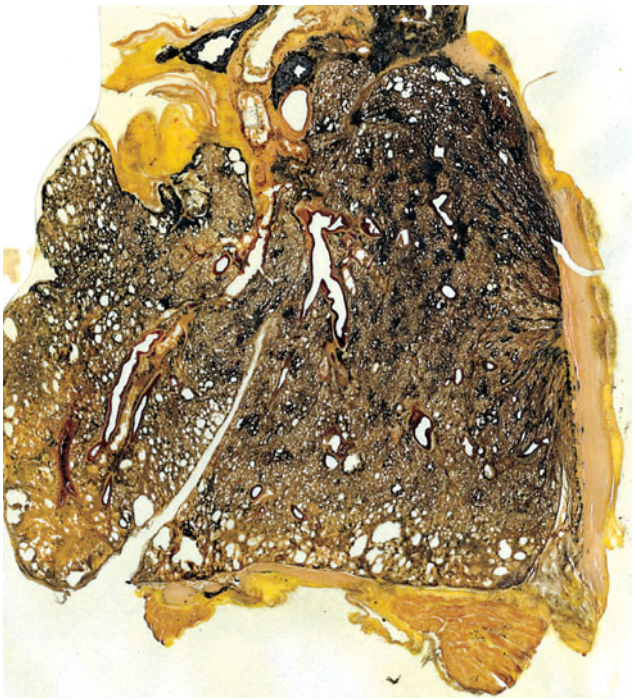
their compliance). The decrease in compliance on lying flat is attributable to the fact that more of the lung is located at or below the level of the heart. During recumbency, the swings in pleural pressure, the work of breathing, and the respiratory frequency increase. The increase in respiratory frequency appears to be automatically adjusted to minimize the work of ventilating the more rigid lungs.

Some patients with chronic lung disease or asthma are also intolerant of recumbency. In these people, the discomfort is attributed to the greater difficulty of performing vigorous movements of the chest bellows in the recumbent position.

Paroxysmal Nocturnal Dyspnea

In an episode of paroxysmal nocturnal dyspnea, the patient is aroused from sleep gasping for air and must sit up or stand to catch his or her breath; sweating may be profuse. Sometimes the patient throws a window open wide in an attempt to relieve the oppressive sensation of suffocation. The chest tends to become fixed in the position of forced inspiration. Both inspiratory and expiratory wheezes, often simulating typical asthma, are heard. In some instances, overt pulmonary edema occurs, accompanied by many inspiratory crackles. The acute pulmonary edema is rarely fatal, however, the attacks occasionally recur several times a night, forcing the patient to sleep upright in a chair.

An episode of paroxysmal nocturnal dyspnea represents precipitous failure of the left ventricle caused by the factors that produce orthopnea (see above), abetted by pulmonary hypervolemia caused by a surge in systemic venous return. Mobilization of peripheral edema from the periphery as the extremities are elevated from the



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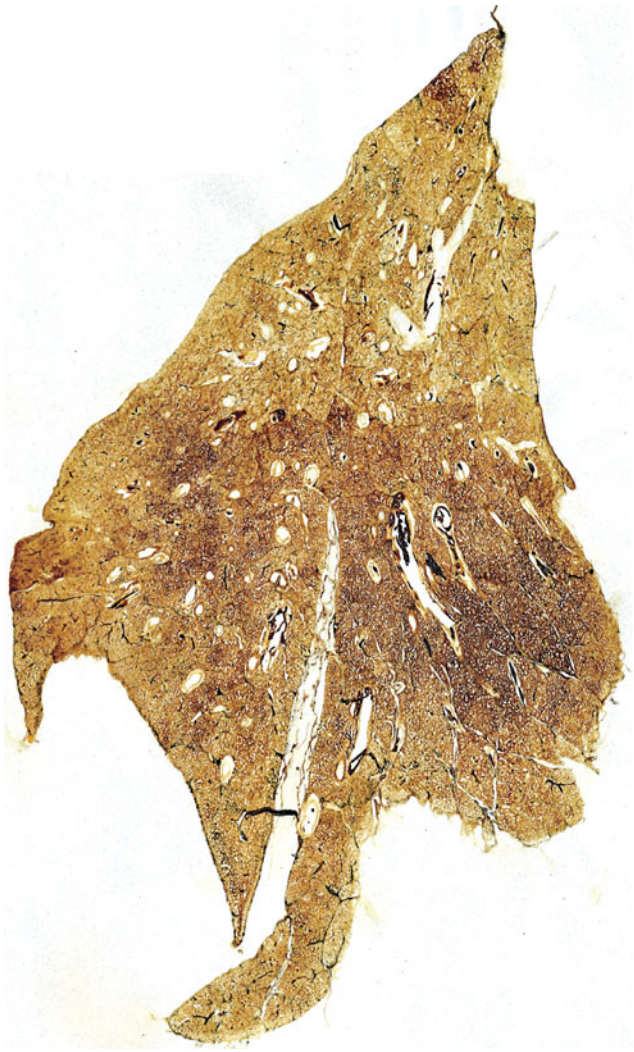


B

dependent position may contribute to the increase in systemic venous return. The acute increase in pulmonary blood volume increases pulmonary capillary pressures, thereby promoting pulmonary edema, while the surge in venous return imposes an additional burden on the left ventricle.

A variety of factors can trigger an episode of paroxysmal nocturnal dyspnea: coughing, abdominal distention, the hypercapnic phase of Cheyne-Stokes respiration, a startling noise, or anything that causes a rise in heart rate and further increases the pulmonary capillary and venous pressures. Usually the attack is terminated by assumption of the erect position and a few deep breaths. Cough, an important manifestation of pulmonary congestion, frequently occurs during the attack.

Cardiac Asthma

Asthmatic wheezes, often audible in patients with pulmonary congestion, have given rise to the term *cardiac asthma.* The wheezes are a manifestation of tracheobronchial edema and often are accompanied by overt signs of pulmonary edema. In addition to the reduction in the lumen of the airways and thickening of bronchial walls by edema, the high intrathoracic pressures which are required to overcome the obstruction during expiration tend to narrow the airways even further. The resistance to airflow is increased during both inspiration and expiration, and the compliance of the lungs is greatly reduced, reaching values as low as one-tenth of normal. Upon recovery from the acute episode of pulmonary edema, airway resistance and pulmonary compliance return toward normal unless previous episodes have left a residue of pulmonary fibrosis.

Dyspnea in Anemia

Shortness of breath during exercise or excitement is a common complaint in severe anemia (e.g., hemoglobin concentration under 6 to 7 g/dl). It is more common in acute than in chronic anemia. Often the dyspnea is associated with dizziness or faintness, and invariably the patient manifests signs of a high cardiac output and low peripheral resistance (i.e., bounding pulse, warm skin, and systolic cardiac murmurs). Although the pathogenesis of the dyspnea is not entirely clear, inadequate O_2 delivery to the respiratory muscles has been proposed.

←

Figure 27-10 Restrictive lung disease. *A.* Asbestosis with markedly thickened pleura that encases and compresses the lungs. In addition, the lungs were afflicted with diffuse interstitial fibrosis. *B.* Compressed, distorted lung in patient with kyphoscoliosis. The lungs were otherwise normal, so that in this instance restriction was imposed by the chest wall rather than by intrapulmonary or pleural disease.

Metabolic Abnormalities and Drugs

Increases in CO_2 production demand a concomitant rise in ventilation to dispose of the metabolic load, and can thus result in dyspnea. To prevent acidemia, patients with diabetic ketoacidosis may require an enormous increase in minute ventilation in order to reduce Pa_{CO_2} to even single digits. Thyrotoxicosis, fever, infection, and pregnancy can also cause an increase minute ventilation; so can drugs, such as aspirin and progesterone.

Miscellaneous Disorders

Breathlessness is not uncommon in patients with musculoskeletal disorders. The usual explanation is the heightened motor drive that is needed to activate the weakened respiratory muscles. In the intensive-care unit, inadequate ventilator settings for flow and tidal volume may fail to satisfy the intrinsic ventilatory drive of the patient, generating the sensation of breathlessness.

ABNORMAL BREATHING PATTERNS

An important clue to the nature of a clinical problem in pulmonary disease is sometimes provided by bedside observation of a patient's breathing pattern. The pertinent features are the rate, regularity, depth, and apparent effort being expended in breathing. A normal person at rest breathes about 12 to 15 times per minute, with a tidal volume of 400 to 800 ml. As a result, minute ventilation is normally greater than 5 L/minute. The pattern is quite regular except for an occasional slow, deep breath, and the respiratory movements appear effortless. In the patient with lobar pneumonia, both the rate and depth of breathing accompany the increase in body temperature.

Severe skeletal deformity, as well as massive obesity, can limit chest excursions to cause alveolar hypoventilation. Neuromuscular weakness, as in myasthenia gravis or Guillain-Barré disease, can do the same, not only by diminishing ventilatory excursions as a result of generalized weakness of the respiratory muscles but also by causing overload of respiratory muscles (e.g., residual effects of poliomyelitis). Unilateral involvement of one pleural space by pneumothorax, effusion, or fibrothorax limits excursions on the affected side. Massive chest trauma can cause flail chest.

In COPD, a slow respiratory rate and large tidal volumes are characteristic. This pattern presumably serves to minimize the work of breathing. Pursed-lip breathing, a self-induced type of positive-pressure breathing, is often part of the picture. In contrast, persons with restrictive lung disease adopt a breathing pattern that is characterized by small tidal volumes and a rapid respiratory rate, often with little apparent effort. This pattern is seen in patients with a decrease in the distensibility of the lung or chest wall or with reduction of the vital capacity from any other cause. During exercise, minute ventilation increases inordinately with respect to the level of O_2 uptake and frequency increases more than tidal volume.

Fatigue of the diaphragm and intercostal muscles, sufficient to disturb their coordinated contractions, can give rise to paradoxical breathing which heralds the onset of respiratory failure.

Cheyne-Stokes Respiration

In the fourth century B.C., in a preterminally ill person with fever, sweats, and black urine, Hippocrates described a pattern of breathing in which "the respiration throughout [was] like that of a man correcting himself, and rare and large." Presumably he had observed Cheyne-Stokes breathing, which was described more graphically by William Stokes two millennia later (in 1854) as follows:

> The symptom in question (previously described by Dr. Cheyne) consists in the occurrence of a series of inspirating, increasing to a maximum, and then declining in force and length, until a state of apparent apnea is established. In this condition the patient may remain for such a length of time as to make his attendants believe that he is dead, when a low inspiration, followed by one more decided, marks the commencement of a new ascending and descending series of inspirations.

Cheyne-Stokes breathing is characterized by alternating periods of hypoventilation and hyperventilation (Fig. 27-11). In its typical form, an apneic phase, which lasts for 15 to 60 s, is followed by a phase during which tidal volume increases with each successive breath to a peak level and then decreases in a progressive fashion to the apneic phase. At the onset of apnea, CO_2 tension in brachial or femoral arterial blood is at its lowest. As apnea persists, CO_2 tension gradually increases, and respiration is stimulated. CO_2 tension continues to increase until maximum hyperventilation is attained, after which ventilation decreases until apnea again occurs. The arterial oxyhemoglobin saturation varies in an inverse manner, being highest at the onset of apnea and lower during mid-hyperpnea. During the cycle, CO_2 tension varies by as much as 14 mmHg and oxyhemoglobin saturation by as much as 18 percent.

In patients with congestive heart failure, the respiratory oscillations are attributable to slowing of the circulation so that the blood gases reaching the respiratory centers in the brain are 180 degrees out of phase with those in pulmonary capillary blood. This mechanism has been verified experimentally by eliciting Cheyne-Stokes breathing in dogs by prolonging the circulation time from heart to brain by way of an extracorporeal circuit.

Fluctuations in mental state and electroencephalographic patterns, and evidence of nervous system dysfunctioning, may occur during Cheyne-Stokes breathing because of swings in cerebral blood flow. In neurological disorders, Cheyne-Stokes breathing can be due to supramedullary

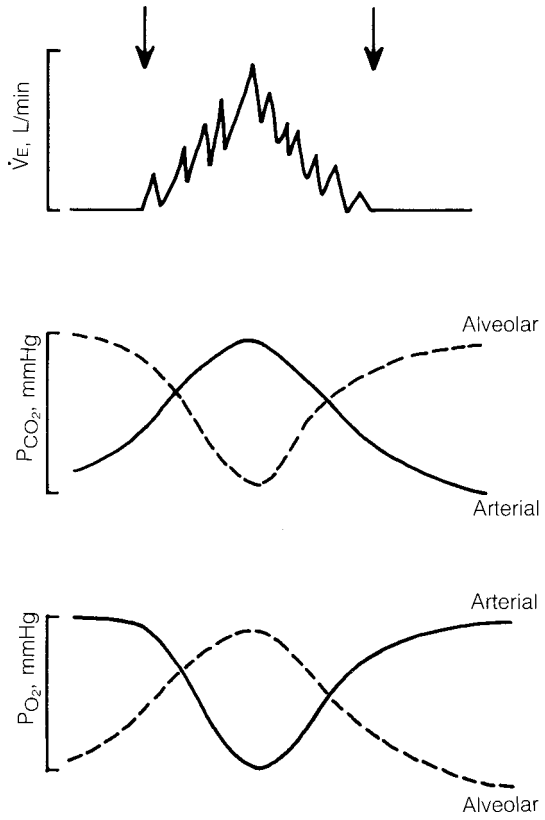


Figure 27-11 Cheyne-Stokes breathing, illustrating the relationship between the ventilation and the blood and alveolar gas tensions during the periods of apnea and hyperpnea. *(From Cherniack NS, Fishman AP: Abnormal breathing patterns. Dis Mon 3–45, 1975, with permission.)*

dysfunctions, particularly in patients who have destructive lesions in the tegmentum of the pons.

Less common than in heart failure or neurological disorders is the occurrence of Cheyne-Stokes respiration in normal infants, in healthy elderly persons, and in normal persons at high altitude. It is also seen occasionally after the administration of respiratory depressants (e.g., morphine) often accompanied by an increase in intracranial pressure, uremia, or coma. At one time, the respiratory center was believed to be depressed in Cheyne-Stokes respiration. This hypothesis has been proved to be in error, since it has been shown that the respiratory response to inhalation of CO_2 is greater than normal in individuals with Cheyne-Stokes respiration. Respiratory alkalosis is common and the arterial P_{CO_2} remains subnormal in both the apneic and hyperpneic phases.

Kussmaul Breathing

In 1874, Kussmaul described three patients with diabetic ketosis who manifested "air hunger": they were breathing with large tidal volumes and so rapidly that there was virtually no pause between breaths. In essence, they were breathing at rest as though they were exercising; breathing was accomplished with little apparent effort. Since then, this pattern of breathing has been observed in other types of severe metabolic acidoses (e.g., alcoholic ketoacidosis). The usual sequence leading to this type of breathing is renal failure with a progressive decrease in plasma bicarbonate and resultant acidosis. The "compensatory" increase in ventilation that Kussmaul described mitigates the fall in systemic pH caused by the fall in plasma bicarbonate.

Other Abnormal Patterns

Gasping respirations are characteristic of severe cerebral hypoxia. The pattern consists of irregular, quick inspirations associated with extensions of the neck and followed by a long expiratory pause. It is commonly seen in shock or in other conditions associated with severe reduction in cardiac output.

Hyperventilation is commonly seen in anxious patients without structural disease of the lungs. In some of these patients, striking deep sighs dominate the ventilatory pattern.

DIAGNOSTIC TESTING IN THE EVALUATION OF DYSPNEA

Attention to important history and physical examination findings as described in the preceding sections will help to focus the initial approach to diagnosis. In most cases, the initial diagnostic impression can be confirmed or excluded with only a few tests, and appropriate therapy instituted or the hunt for a cause continued (Table 27-8). In some instances, the response to a therapy instituted empirically on the basis of the history and physical examination findings is itself diagnostic. For example, the relief of dyspnea following the administration of diuretics given to a patient with progressive orthopnea, bilateral basilar inspiratory crackles, and a prominent third heart sound (S_3) is strong evidence of heart failure as the cause.

A plain chest radiograph is frequently useful in demonstrating changes suggestive of COPD (chest hyperinflation, bullous changes). Vascular engorgement, an enlarged cardiac silhouette, interstitial markings and pleural effusions may indicate left heart failure. Interstitial markings may also have a pattern consistent with an inflammatory or fibrotic process.

Spirometry is useful in identifying airways obstruction, at times noting a change in values following the administration of a bronchodilator. The measurement of lung volumes or the diffusing capacity may be reserved for when there is suspicion of an interstitial process or other cause of restriction (e.g., muscle weakness). Measurement of arterial oxyhemoglobin saturation both at rest and with exertion is important. While oxyhemoglobin desaturation may not itself indicate the etiology of the problem, its presence is always an important indicator of the severity of the disease and may itself warrant treatment with oxygen while the evaluation of its cause continues. An echocardiogram can be used to assess ventricular or valvular cardiac function or to estimate pulmonary arterial pressures.

Table 27-8

Common Tests in the Evaluation of Dyspnea

Test	Some Possible Abnormalities	Some Possible Diagnoses
Plain chest radiograph	Cardiac enlargement	Congestive heart failure
	Vascular enlargement	COPD
	Abnormal interstitial markings	Malignant pleural effusion
	Pleural effusions	Neoplastic disease
	Hyperinflation	Infection
	Nodules/masses	
Pulmonary function tests		
Spirometry	Obstructive ventilation defect (Decreased FEV_1/FVC ratio)	Asthma
		COPD
	Restrictive ventilatory defect	Interstitial lung disease
Diffusing capacity	Decreased	Interstitial lung disease
		Pulmonary vascular disease
	Increased	Alveolar hemorrhage
Inspiratory and expiratory maneuvers	Decreased values	Respiratory muscle weakness
Computed tomography	Abnormal interstitial markings	Interstitial lung disease
	Cystic changes	Congestive heart failure
	Lymphadenopathy	Atelectasis
	Vascular filling defects	Pulmonary embolism
	Ground-glass opacities	Neoplastic disease
Blood tests	Elevated white blood cell count	Infection
	Anemia	Anemia
	BNP	Heart failure
	Cr	Acidoses (respiratory or metabolic)
	HCO_3	
	ABG	Alkaloses (respiratory)

COPD, Chronic obstructive pulmonary disease; FEV_1/FVC, forced expiratory volume in 1s/forced vital capacity; BNP, brain natriuretic peptide; Cr, creatine; HCO_3, bicarbonate; ABG, arterial blood gas.

A complete blood count may reveal anemia or suggest an infection. Electrolytes may indicate the presence of an acidosis or renal dysfunction. Measurement of brain natriuretic peptide (BNP) has been useful in helping to exclude heart failure as an acute cause of dyspnea. Fewer than 5 percent of patients with BNP values below 50 pg/ml have heart failure as the acute cause of dyspnea.

Additional testing is usually not required unless the cause of dyspnea remains unclear following these more basic studies. Further tests often include computed tomography (CT) of the chest which may rarely reveal changes of emphysema or an interstitial process not suggested by plain radiographs or lung function testing. The CT may additionally help to better characterize an interstitial process identified on plain radiographs. Cardiopulmonary exercise testing may be helpful in differentiating between cardiac and respiratory causes of dyspnea, or in excluding a significant abnormality of either system and suggesting deconditioning as the culprit. Arterial blood gas measurements may be necessary to characterize the level of blood oxygenation or to identify hyperventilation or hypercapnia. More invasive testing, including cardiac catheterization or lung biopsy (by either bronchoscopy or surgery), is reserved for when the diagnosis remains unsettled and the results will be helpful in guiding therapy or discussions of prognosis.

COUGH

Cough is one of the most frequent causes of visits to the doctor's office. Patients are frequently anxious about the possibility of a serious malady as the cause. They may also be troubled by the complications of cough, including chest pain from intercostal muscle strain or even a fractured rib in patients with bone disease. They may be embarrassed by

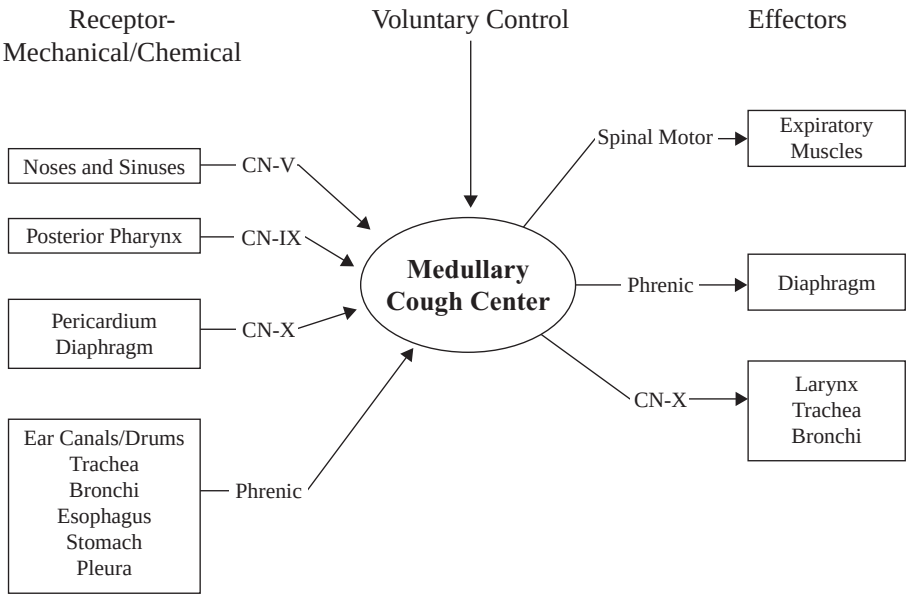


Figure 27-12 Signaling pathways in the development of cough. CN, cranial nerve. *(After Silvestri RC, Weinberger SE: Evaluation of chronic cough in adults. In Rose B (ed), UpToDate. Wellesley, MA, 2006.)*

cough-induced incontinence of the bladder or stool. Embarrassment, and even social isolation may also arise from the frequent fear of others that the patient's cough is infectious and communicable.

A cough is an explosive expiration that protects the lungs against aspiration and promotes the movement of secretions and other airway constituents upward toward the mouth. It is a critical element in the self-cleansing and protective mechanisms of the lungs—a reflex act that usually, but not invariably, arises from stimulation of the bronchial mucosa somewhere between the larynx and the second-order bronchi. On rare occasions the cause is remote: impacted cerumen in an external ear or an inflammatory process of the pleura (see "Mechanism" below) (Fig. 27-12). The stimuli that can elicit a cough are diverse: inhaled particles, mucus that has been elaborated by the lining of the airways, inflammatory exudate in airways or parenchyma, a new growth or foreign body in an airway, pressure on the external wall of the bronchus.

A cough may be voluntary, involuntary, or a combination of the two if the subject attempts to control an involuntary cough. Three categories of stimuli are commonly at work in producing an involuntary cough: mechanical, inflammatory, and psychogenic. Mechanical and chemical causes range from inhalation of irritants, such as smoke or dust, to distortions of the airways produced by pulmonary fibrosis or atelectasis. Most often, coughs are due to tracheobronchial inflammation. The cigarette smoker is particularly vulnerable to exacerbation of cough by inhaled particles and fumes because of underlying chronic pharyngitis, laryngitis, and tracheobronchitis. As a rule, cough represents organic disease. But on occasion, psychogenic influences are responsible for a dry cough that is related to anxiety. Psychogenic stress can aggravate cough due to organic causes.

The site and significance of a cough can sometimes be localized from telltale signs and symptoms (Table 27-9). For example, the cough of acute tracheitis is often associated with retrosternal "burning." Acute laryngitis is usually associated with hoarseness and sore throat as well as cough. Tuberculosis of the larynx is associated not only with painful swallowing but also with unequivocal evidence of pulmonary tuberculosis. In asthma, cough is part of a constellation of airway obstruction. Body position can influence the persistence of a cough. When the pathological process is changing, as in pneumonia or a neoplasm, the cough undergoes concomitant change, reflecting the evolution of the disorder.

Interpretation of the significance of a cough depends on the clinical company that it keeps. It has to be viewed in context: Is it acute or chronic? productive or nonproductive? How long has it lasted? What is the general condition of the patient, and what co-morbidities are present? For example, the acute onset of a hacking, nonproductive cough accompanied by coryza, sore throat, malaise, sweating, and fever generally heralds a viral upper respiratory infection. An episode of asthma may begin with cough and wheezing. In contrast, a persistent cough, even if virtually ignored by the patient, may be a harbinger of serious disease (e.g., carcinoma of the lung). In a cigarette smoker, in whom bronchi are chronically irritated, a change in the nature of the cough from nonproductive to productive may signify the onset of a serious tracheobronchial infection or pneumonia. Alternatively, a lung neoplasm may present with a dry cough that not only persists and intensifies but also gradually becomes associated with systemic manifestations (e.g., loss of weight).

The implications of dry cough are different from those of productive cough. Before a cough can be regarded as

Table 27-9

Some Causes and Characteristics of Cough

Cause	Characteristics
Sinusitis or nasopharygnitis	Cough following an upper respiratory syndrome or sinus symptoms; sensation of a need to clear the throat; postnasal drip
Acute infections of lungs	
Tracheobronchitis	Cough associated with sore throat, running nose and eyes
Lobar pneumonia	Cough often preceded by symptoms of upper respiratory infection; cough dry, painful at first; later becomes productive
Bronchopneumonia	Cough dry or productive, usually begins as acute bronchitis
Mycoplasma and viral pneumonia	Paroxysmal cough, productive of mucoid or blood-stained sputum associated with flulike syndrome
Exacerbation of chronic bronchitis	Cough productive of mucoid sputum becomes purulent
Chronic infections of lungs	
Bronchitis	Cough productive of sputum on most days for more than 3 consecutive months and for more than 2 years
	Sputum mucoid until acute exacerbation, when it becomes mucopurulent
Bronchiectasis	Cough copious, foul, purulent, often since childhood; forms layers upon standing
Tuberculosis or fungus	Persistent cough for weeks to months, often with blood-tinged sputum
Parenchymal inflammatory processes	
Interstitial fibrosis and infiltrations	Cough nonproductive, persistent, depends on origin
Smoking	Cough usually associated with injected pharynx; persistent, most marked in morning, usually only slightly productive unless succeeded by chronic bronchitis
Tumors	
Bronchogenic carcinoma	Cough nonproductive to productive for weeks to months; recurrent small hemoptysis common
Alveolar cell carcinoma	Cough similar to that with bronchogenic carcinoma except in occasional instances, when large quantities of watery, mucoid sputum are produced
Benign tumors in airways	Cough nonproductive; occasionally hemoptysis
Mediastinal tumors	Cough, often with breathlessness, caused by compression of trachea and bronchi
Aortic aneurysm	Brassy cough

(*Continued*)

Table 27-9

(*Continued*)

Cause	Characteristics
Gastrointestinal	
Gastrioesophageal reflux (GERD)	Nonproductive cough often following meals or with recumbancy; may (or may not) be accompanied by other symptoms of GERD (e.g., heartburn, a bitter oral taste, belching)
Foreign body	
Immediate, while still in upper airway	Cough associated with progressive evidence of asphyxiation
Later, when lodged in lower airway	Nonproductive cough, persistent, associated with localizing wheeze
Cardiovascular	
Left ventricular failure	Cough intensifies while supine, along with aggravation of dyspnea
Pulmonary infarction	Cough associated with hemoptysis, usually with pleural effusion
Medication-induced	
Angiotensin-converting enzyme (ACE) inhibitors	Nonproductive cough, more common in women, may occur at any time (following soon after drug initiation or with years of use)

nonproductive, the possibility should be weighed carefully that sputum has been produced but swallowed. Failure to probe deeply into this possibility once led to the notion that British and American patients suffered from different types of chronic bronchitis. Improved history taking and interviews discounted this idea.

A cough that is productive of purulent sputum is generally a reliable indication of infection in the tracheobronchial tree or lungs. When this symptom is associated with an acute illness, the characteristics of the sputum can be of considerable diagnostic help. Rust-colored sputum, which contains its distinctive coloration from the even dispersion of blood in yellow, purulent sputum was previously seen often in pneumococcal pneumonia but less so today due to the widespread use of antibiotics. The classic description of sputum in Friedlander's pneumonia is a resemblance to currant jelly; it also contains blood, but it is bright red and more translucent and viscid than the sputum of pneumococcal pneumonia. Purulent sputum with a foul odor usually indicates an anaerobic infection, commonly due to streptococci or *Bacteroides* in a lung abscess. A persistent cough that is productive of purulent sputum occurs in chronic bronchitis, bronchiectasis, and a variety of other suppurative disorders. Sputum that is mucoid can be a consequence of any long-standing bronchial irritant. Copious sputum production (bronchorrhea) may be a sign of bronchoalveolar carcinoma.

Mechanism

The cough begins with a rapid inspiration, followed, in rapid sequence, by closure of the glottis, contraction of the abdominal and thoracic expiratory muscles, abrupt increase in pleural and intrapulmonary pressures, sudden opening of the glottis, and expulsion of a burst of air from the mouth (Fig. 27-13). The high intrathoracic pressures, which often exceed 100 to 200 mmHg, increase the velocity of airflow through the airways, hastening the propulsion of the offending particles and producing the sound of a cough by setting into vibration airway secretions, the tracheobronchial walls, and the adjacent parenchyma (Fig. 27-14).

Afferent stimuli for a cough originate in irritant receptors and are conveyed centrally by the vagus, glossopharyngeal, trigeminal, and phrenic nerves (Fig. 27-12). In subjects with an idiopathic, persistent, nonproductive cough, increased sensitivity of the afferent nerves of the airways due to neuropeptides stored in them has been proposed. The vagus nerve carries impulses not only from the larynx, trachea, and bronchi but also from the pleura and stomach. Receptors in the airways are most concentrated in the larynx, diminish in density in the conducting airways, and are absent from the distal airways, enabling the pooling of secretions in the periphery. The glossopharyngeal nerve carries stimuli from the pharynx; the trigeminal nerve, from the nose and paranasal sinuses; the phrenic nerve, from the pericardium and diaphragm. The motor pathways are even more extensive,

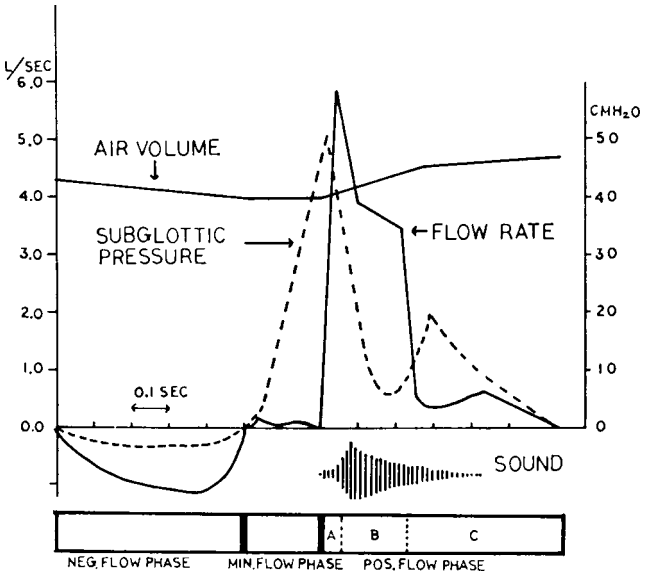
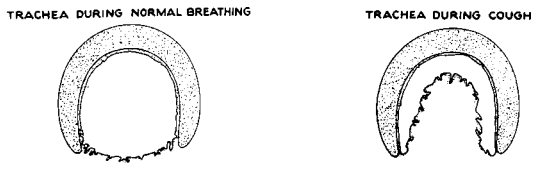


Figure 27-13 Sequence of events during a cough. Simultaneous recordings obtained during a single explosive cough by a normal subject. The three phases of a cough are identified by the boxes at the bottom of the figure. They correspond to (1) a deep initial inspiration, (2) compression of air in the lungs and airways by forceful contraction of the expiratory muscles coupled with tight closure of the glottis and opening of the larynx, and (3) sudden explosive expiration followed by narrowing of the glottis and return of the larynx to its normal inspiratory position. *(From Yanagihara, von Leiden, Werner-Kukuk: Acta Otolaryngol 61:495–510, 1965.)*

comprising not only the cranial and phrenic nerves but also the nerves to the muscles of the rib cage and the accessory muscles. Additional impulses from chemoreceptors are located in the esophagus and carried by the phrenic nerve.

The effectiveness of a cough is strongly influenced by the lung volume at which it occurs. As indicated elsewhere in this volume, cough only removes particles toward the mouth ("downstream" from the "equal pressure points"). In healthy persons at high lung volumes, the equal pressure points are located in the larger airways; they move toward the alveoli ("upstream") as lung volume decreases. A series of coughs without any intervening inspiration moves the equal pressure points even closer to the small airways, helping to clear the depths of the lungs.



Intrathoracic pressure, cm H_2O	−4	+150
Cross-sectional area, cm^2	1.5	0.25
Volume flow, L/sec	1	7
Linear velocity, cm/sec	667	28,000

Figure 27-14 Effects of tracheal narrowing during a cough. The forced expiratory effort during coughing causes invagination of the noncartilaginous part of the intrathoracic trachea by the high intrathoracic pressure. Air rushing with a high linear velocity through the exceedingly narrow trachea dislodges the material to be dispelled and propels it into the throat. *(From Comroe: Physiology of Respiration. St. Louis, Mosby-Year Book, 1965, p 122.)*

The cough reflex may be impaired by interrupting or blunting any step in the sequence. Irritant receptors can be damaged by a local destructive process (e.g., bronchiectasis), or their sensitivity can be diminished by narcotics or anesthetics.

The reflex pathways can be damaged as part of a neurological disease. Tracheostomy, which eliminates glottic closure, decreases peak intrapulmonary pressures. Contraction of the respiratory muscles can be impaired by weakness due to illness, age, or neuromuscular disease. In general, as long as the patient can achieve maximum expiratory pressures greater than about 60 cm H_2O, the peak flow will suffice to produce effective coughs.

Circulatory Consequences

The increase in intrathoracic pressure that is part of the cough mechanism exerts considerable circulatory effects. However, because the increase in intrathoracic pressure is accompanied by an equal rise in vascular (and cerebrospinal fluid) pressures, distending pressures on the vessels of the heart, lungs, and other vital organs are unaltered, so they are normally spared the ill consequences of marked swings in transmural pressures.

The increase in intrathoracic pressure is accompanied by reflex vasodilation of systemic arteries and veins. Both of these effects contribute to a decrease in cardiac output. In patients with cor pulmonale and right heart failure, cough impedes systemic venous return and may result in syncope.

Posttussive Syncope

Charcot recognized the syndrome of posttussive syncope in individuals without underlying cardiopulmonary disease 100 years ago. Originally conceived of as a form of epilepsy or a consequence of a laryngeal reflex, it is now attributed to the same circulatory consequences of raised intrathoracic pressures that coughing evokes in a normal person. However, the patient with cough syncope probably coughs more forcefully and longer than do normal persons.

The syncope usually develops within a few seconds after the onset of a paroxysm of coughing and ends quickly once the coughing has stopped. Return to consciousness is without sequelae unless the subject falls and is injured during the faint. Posttussive syncope nearly always occurs in men, probably because they generate a higher intrathoracic pressure and much more profound decrease in cardiac output than do women. It is not clear why this type of fainting occurs in the supine as well as the upright position; this occurrence suggests that the reduction in cerebral blood flow during posttussive

syncope reflects more than interference with cardiac output. The extent to which intense reflex vasodilation contributes to posttussive syncope is unclear.

Etiology

The most common causes of chronic cough (defined as lasting longer than 8 weeks) are postnasal drip (recently termed *upper airway cough syndrome*), gastroesophageal reflux disease (GERD), and asthma. In patients treated with angiotensin-converting enzyme (ACE) inhibitors, the drug is very often the cause of a chronic cough (even one developing after years of uncomplicated use). A deliberate evaluation can identify the cause in the vast majority of patients. Usually, the diagnosis is established only by the resolution of the cough following a specific intervention (Fig 27-15). For example, cough that disappears after antihistamines and inhaled nasal steroid treatment for allergic rhinitis can logically be attributed to postnasal drip. Similarly, cough may disappear after interventions for GERD (e.g., the use of H_2-blockers) or asthma (use of inhaled bronchodilators and steroids). A cough that resolves after discontinuation of an ACE inhibitor was presumably caused by the drug. Although the more common causes of chronic cough are usually benign, a chest radiograph is nonetheless warranted at the beginning of the evaluation of a chronic cough to assess for possible worrisome causes.

HEMOPTYSIS

The coughing up of blood is termed *hemoptysis*. The material and amount produced varies from mere blood streaking of expectorated sputum to massive volumes of pure blood. Massive hemoptysis has been variably defined according to the volume, but implies a life-threatening process requiring immediate evaluation and treatment.

An initial decision faced by the physician who is told that blood has been coughed up is whether to conclude that the blood is coming from the respiratory tract. Any portion of the respiratory tract can be the source of bleeding including a main bronchus, the lungs, or the nose or throat. On occasion, blood from the nose and throat is inhaled and then expectorated. As long as this possibility is kept in mind, bleeding that originates in the nose, throat, or larynx is not apt to be overlooked.

An additional consideration is distinguishing hemoptysis from hematemesis (vomited blood). Even if the blood is aspirated and then coughed up, the patient can usually tell if the blood originated in the respiratory or alimentary tract. The appearance of the bloody material also helps to distinguish between hemoptysis and hematemesis: blood that originates in the airways is usually bright red, is mixed with frothy sputum, has an alkaline pH, and contains alveolar macrophages that are laden with hemosiderin; in contrast, blood from the stomach usually is dark, has an acid pH, contains food particles, and often occurs in patients with a long history of gastric complaints.

Blood arising from the bronchial arteries is more often the source of massive hemoptysis, owing to its higher perfusion pressure than blood from the pulmonary circulation. The bronchial circulation may be the source of life-threatening bleeding, for example, in patients with bronchiectasis in whom the vessels frequently become distorted and easily ruptured.

The differential diagnosis of hemoptysis includes disorders arising within the airways and the pulmonary parenchyma. Inflammatory processes (e.g., bronchitis and bronchiectasis) and neoplasms are the most common causes of blood arising within the airways. Within the pulmonary parenchyma common causes are infections, such as tuberculosis, pneumonia, *Aspergillus*, or lung abscess. Inflammatory processes that involve the lung, such as Wegner's granulomatosis or Goodpasture's syndrome are also important causes of hemoptysis (Fig. 27-16). Bleeding may be iatrogenic, as for example, after a lung biopsy or when chemotherapy for bone marrow transplantation evokes diffuse alveolar hemorrhage. Vascular disorders, including pulmonary embolism, arteriovenous malfunctions, and mitral stenosis are also to be considered in the differential diagnosis.

The list of causes of hemoptysis is long and diverse (Table 27-10). The clinical setting is usually helpful in identifying the cause. Hemoptysis before middle age usually brings to mind infections; after 40 to 45 years of age or if there is a history of smoking, bronchogenic carcinoma heads the list. In patients left with a pulmonary cavity after pulmonary disease that has healed (e.g., tuberculosis), and in regions of the country where pulmonary fungal diseases are prevalent, a bout of hemoptysis is occasionally the first sign of the disease. In patients who have a predisposing cause, such as oral contraceptives or chronic heart failure, pulmonary embolism must be considered.

The evaluation of hemoptysis involves a careful history, physical examination, and a chest radiograph. Initial studies also include a complete blood count. The degree of anemia may influence the rapidity of further testing, and thrombocytopenia may be a contributing factor to hemoptysis. Rapid correction of anemia, thrombocytopenia, or coagulopathy with the transfusion of appropriate blood products may be required promptly depending upon the clinical status and degree of abnormality. Similarly, measurement of coagulation times are important. Studies of renal function and a urinalysis may be indicated when a systemic process which causes a pulmonary-renal syndrome is a possibility. Sputum should be zealously collected and, depending on the circumstance, microbiologic cultures and stains or cytologic examination should be performed. Depending on whether a cause is identified, and the risk factors for a serious cause of bleeding, the evaluation next involves additional studies to search for a source.

Because hunting for the cause and the source of bleeding is generally uncomfortable for the patient and often expensive, the intensity of the search depends on the circumstances. For example, rarely is a search for the bleeding site needed in a patient with acute bronchitis, pneumonia, or

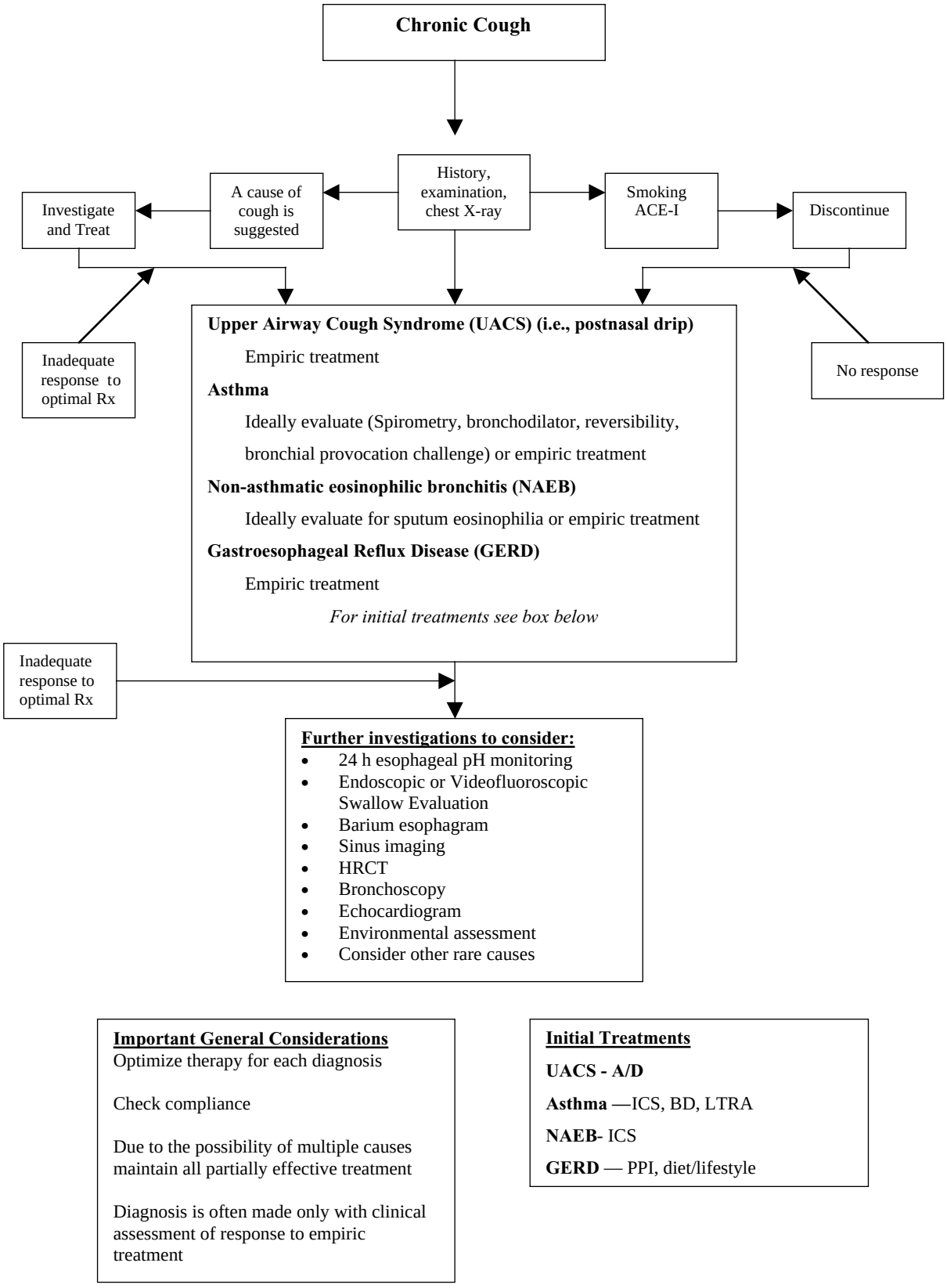
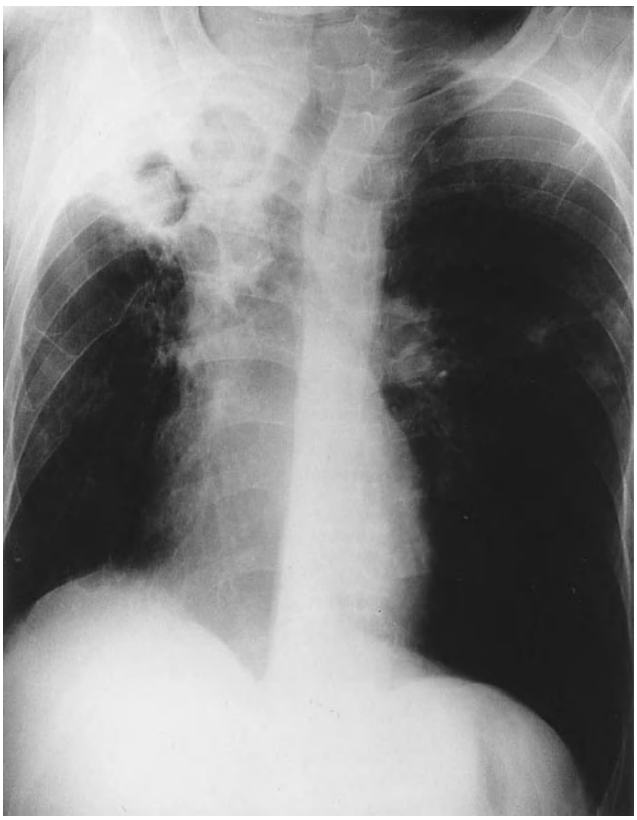


Figure 27-15 Algorithm for the evaluation of chronic cough lasting 8 weeks in adults. ACE-I = ACE inhibitor; BD = bronchodilator; LTRA = leukotrienes receptor antagonist; PPI = proton pump inhibitor; ICS = inhaled corticosteroid; A/D = antihistamine/decongestant; HRCT = high-resolution computed tomography. *(After Irwin RS, et al: Diagnosis and management of cough executive summary: ACCP evidence-based clinical practice guidelines. Chest 129(1 Suppl):1S–23S, 2006, with permission.)*



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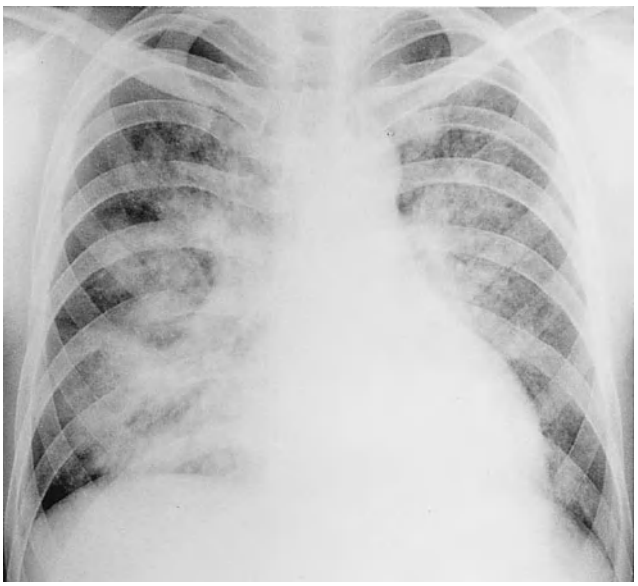

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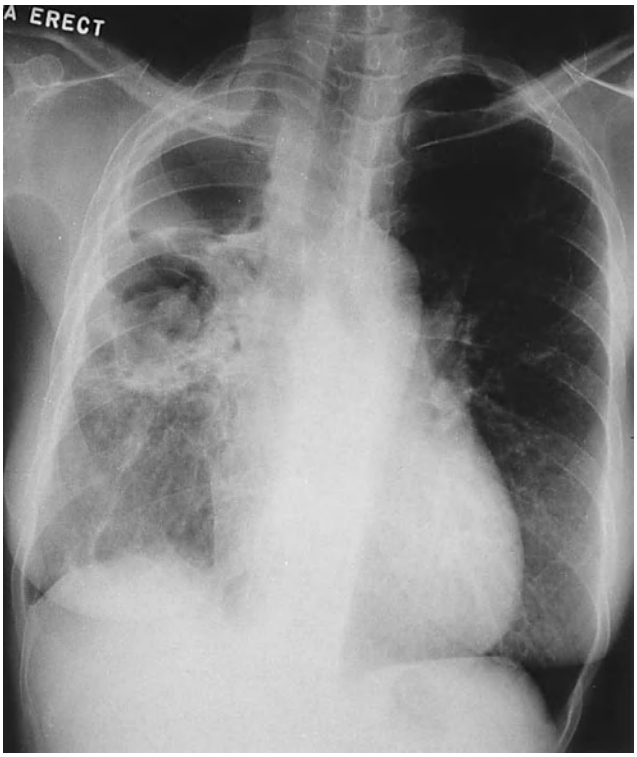


C

D

Figure 27-16 Causes of hemoptysis. *A.* Old tuberculosis cavities in right apex. They were removed surgically to control hemoptysis. *B.* Goodpasture's syndrome. *C.* Fungus ball in coal miner's pneumoconiosis. Sagittal section of lung. *(Courtesy of J. Gough.) D.* Fungus ball due to aspergillosis in old tuberculosis cavity. Recurrent hemoptysis was arrested by surgical removal of right upper lobe.

Table 27-10

Some Common Causes of Hemoptysis

Infections
Bronchitis
Tuberculosis
Fungal infections
Pneumonia
Lung abscess
Bronchiectasis
Neoplasms
Bronchogenic carcinoma
Bronchial adenoma
Cardiovascular disorders
Pulmonary infarction from thromboembolism
Mitral stenosis
Trauma
Foreign body
Hematologic/immunologic
Blood dyscrasia
Goodpasture's syndrome

bronchopulmonary suppuration. But as a rule, unless the cause is evident, a full-scale investigation is mandatory, particularly if this is not the first episode.

Patients with hemoptysis and a history of tobacco smoking, individuals who are more than 40 years of age, or those who experience hemoptysis that lasts for more than 1 week are at greater risk for a worrisome cause and warrant additional studies. A high-resolution computed tomography (HRCT) of the chest is usually the next step if the patient has no history of tobacco use or if the plain chest radiograph suggests a parenchymal abnormality, such as bronchiectasis or arteriovenous malformation. Patients with a history of tobacco use or other risk factors for a malignancy warrant fiberoptic bronchoscopy. In practice, HRCT and bronchoscopy are often complementary for visualizing abnormalities that are not apparent on plain chest radiographs. Patients with chronic bronchitis and at low risk for malignancy, or in whom the chest radiograph is normal or identifies the cause of hemoptysis (e.g., epistaxis or pneumonia) can usually be treated initially for bronchitis with follow-up appraisals to show prompt resolution of hemoptysis. However, should hemoptysis recur, further evaluation is required.

Neoplasms

Nonmassive hemoptysis is common in bronchogenic carcinoma; less frequently it is the cause of massive hemoptysis. The likelihood of a neoplastic cause of hemoptysis is greatly increased in a cigarette smoker. Usually a troublesome cough and vague chest pain precede and accompany the hemoptysis. For hemoptysis to occur, the lesion must communicate with the airways. Most often the bleeding is a consequence of ulceration caused by an expanding tumor; sometimes it is due to a pneumonic process or to an abscess in the lung behind the obstructive lesion. Hemoptysis rarely complicates metastatic tumors of the lungs, since few (primarily renal and colon carcinomas) intrude on the airways until preterminal.

Not only malignant but also benign tumors of the lung cause bleeding. The classic example is bronchial carcinoid, which often causes bleeding that is generally difficult to arrest.

Infections

Hemoptysis can accompany a severe infection anywhere from the top to the bottom of the respiratory tract. It is uncommon in the usual viral or bacterial pneumonia. Conversely, it is not uncommon in the pneumonia that complicates bronchogenic carcinoma or in the pneumonia that is caused by staphylococci, influenza virus, or *Klebsiella.*

The infecting organism determines the appearance and composition of the material that is expectorated with the blood. As indicated above, in pneumococcal lobar pneumonia, the sputum at the onset is characteristically rusty-looking, but sometimes it is faintly or grossly bloody. In staphylococcal pneumonia, the blood is mixed with pus. In *Klebsiella* pneumonia, the bloody sputum often resembles currant jelly. Brisk bleeding is common in lung abscess; the blood is mixed with copious amounts of foul-smelling pus. In lung gangrene, blood is associated with necrotic lung tissue.

Bleeding is common in bronchiectasis. Because it usually originates in a bronchial artery, bleeding is often brisk. While most episodes stop spontaneously, it tends to recur and can be life-threatening.

Fungal infections of the lungs can cause hemoptysis (Fig. 27-16). As in tuberculosis, hemoptysis is generally a consequence of a continuing necrotizing and ulcerating inflammatory process or of bronchiectasis. The most common fungal disorder associated with hemoptysis is a "fungus ball" that resides either in a healed tuberculous or bronchiectatic area or in a cystic residue of sarcoidosis. *Aspergillus* is the usual fungal agent; less often another fungus (e.g., *Mucor*) is the cause.

The most common source of hemoptysis used to be an active tuberculosis cavity. But currently tuberculous pneumonia is a more common cause of hemoptysis than is active cavitation. Despite the increasing frequency of tuberculosis, hemoptysis is uncommon because of effective antituberculous therapy. If tuberculosis is allowed to progress to the point of extensive fibrosis and causation, or becomes complicated by bronchiectasis, hemoptysis can be troublesome and persistent. Hemoptysis from a Rasmussen's aneurysm involves the erosion of a small or medium-sized pulmonary artery into an adjacent tuberculosis cavity.

The "right middle lobe syndrome" is frequently associated with hemoptysis. It is due to a partial or complete

obstruction of the right middle lobe bronchus, resulting in atelectasis and/or pneumonitis in the right middle lobe. The obstruction is more often caused by scarring and/or inflammation than by physical compression of the lumen by an enlarged lymph node. The cause is usually infectious; the infection can be tuberculosis.

In parts of the world where amebiasis is endemic, hemoptysis follows perforation into the airways of an amebic lung abscess. The sputum resembles anchovy sauce.

Cardiovascular Disorders

Pulmonary congestion and alveolar edema sometimes produce blood-tinged sputum. In chronic pulmonary congestion, secondary to left ventricular failure or to mitral valve disease, alveolar macrophages in the sputum are often laden with hemosiderin ("heart failure cells"). In severe congestion and edema, the sputum is often pink and frothy. Usually there is no difficulty in recognizing that inadequate performance of the left ventricle is the cause of the bloody sputum.

Pulmonary thromboembolism can produce hemoptysis when associated with infarction (Fig. 27-17). The hemoptysis of pulmonary infarction is usually associated with pleuritic pain and often with a small pleural effusion because of the peripheral location of the infarct.

Tight mitral stenosis is sometimes first manifested by a bout of brisk, bright-red hemoptysis that is difficult to control. The source of the bleeding is the submucosal bronchial veins, which proliferate considerably in this disorder. Massive hemoptysis due to mitral stenosis is a medical emergency and is an indication for surgical intervention to relieve the obstruction at the mitral valve.

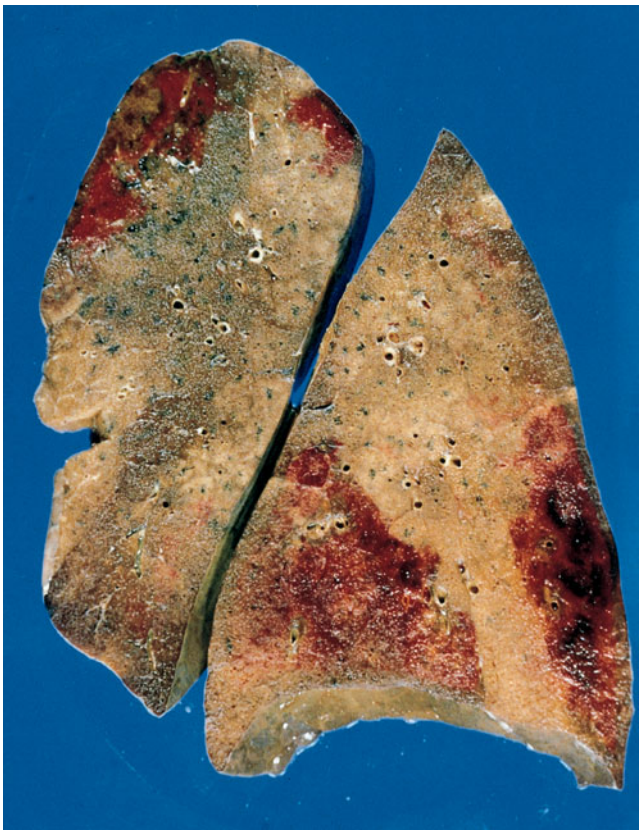


Figure 27-17 Hemorrhagic pulmonary infarcts. Several subpleural areas of infarction are clearly demarcated.

Hemoptysis from other circulatory disorders is much less common. Occasionally, an aortic aneurysm penetrates into the tracheobronchial tree, causing death by exsanguination and asphyxiation. An extraordinary event is the communication of an arteriovenous fistula with a small airway, causing bleeding that is exceedingly difficult to arrest.

Trauma

Hemoptysis follows a variety of chest injuries: puncture of a lung by a fractured rib, contusions of a lung by severe blunt trauma to the chest, and necrosis of the lining of the tracheobronchial tree by inhaled fumes or smoke. Blunt trauma from the steering wheel during an automobile collision sometimes lacerates or fractures the tracheobronchial tree. Stab or gunshot wounds often tear the lungs or airways. On occasion, mucosal lacerations in the course of severe coughing evoke hemoptysis.

After pneumonectomy or lobectomy, a large hemothorax occasionally empties into the airways. This is an alarming and ominous event. Its imminent occurrence is often heralded by the expectoration of blood-stained sputum after a paroxysm of coughing. The hemothorax must be promptly evacuated and the bronchus surgically repaired. Hemoptysis within a few weeks to months after pneumonectomy has different implications: recurrence of tumor, granulation tissue, or bronchial sutures. Prompt bronchoscopy is necessary for accurate appraisal of the situation.

Miscellaneous

Other causes of hemoptysis are listed in Table 27-10. They vary greatly in severity, urgency, and prognosis. Sometimes the cause is obscure, as in the occasional instance of hemoptysis that accompanies menstruation ("catamenial hemoptysis"). An aspirated foreign body produces bleeding by damaging the mucosa on impact; if allowed to remain in place, it sometimes causes bronchiectasis, which in turn may cause bleeding. Pulmonary calcific foci, either in the pulmonary parenchyma or in lymph nodes, sometimes cause hemoptysis by ulcerating into a bronchus.

Blood dyscrasias, notably thrombocytopenic purpura and hemophilia, and the therapeutic use of anticoagulants are occasional causes of hemoptysis. In areas where scurvy is endemic, vitamin C deficiency is a major cause.

Hemoptysis in Goodpasture's syndrome (Fig. 27-16) or in idiopathic hemosiderosis is life-threatening. This grim prospect has led to an aggressive therapeutic approach, including use of plasmapheresis and immunosuppressive agents.

Management of Massive Hemoptysis

The first priority in the care of a patient with life-threatening hemoptysis is to protect the airway and prevent asphyxiation. Intubation should be performed promptly, and consideration given to selective intubation of one lung in order to protect it from spillage of blood from the other. When the site of bleeding is known, one simple, initial bedside maneuver is to place the involved side in a dependent position in order to protect the uninvolved lung. Bronchoscopy should be performed promptly in order to identify the source. This may also allow bronchoscopic interventions such as the placement of a balloon catheter to isolate the involved segment, lavage with iced saline, or the application of topical epinephrine (1:20,000). Bronchoscopic localization may help to guide attempts at arresting the bleeding by angiographic embolization. If these modalities fail to stop the bleeding, surgical exploration may be required. Not surprisingly, emergency procedures are accompanied by a high mortality. None of the approaches has been rigorously studied and the choice is frequently dictated by the urgency, local experience, and availability of bronchoscopy.

CYANOSIS

Cyanosis refers to a bluish discoloration of the skin that is caused by increased amounts of reduced hemoglobin in the subcapillary venous plexus. The discoloration is most apparent in the lobes of the ears, the cutaneous surfaces of the lips, and the nail beds. In patients with dark skin, the mucous membranes and the retina are important sites to examine for cyanosis. Unless flow through the skin is slowed, as in heart failure, cyanosis implies arterial hypoxemia. Cyanosis does not appear in carbon monoxide poisoning or in severe anemia even though arterial O_2 content is extremely low. This is because there is an insufficient amount of reduced hemoglobin present for the cyanotic discoloration to be visible. The presence of abnormal pigments in blood, such as methemoglobin or bilirubin, complicates the detection of cyanosis.

Capillary O_2 Content

An increase in the amount of reduced hemoglobin in the capillaries of the skin, as elsewhere, results from inadequate oxygenation of arterial blood, excessive removal of O_2 from capillary blood (as when the circulation through a region is slowed by vasoconstriction or a very low cardiac output), or from a combination of the two. The concentration of reduced hemoglobin in the skin capillaries must reach about 5 g/dl before cyanosis becomes discernible. Thus, in severe pernicious anemia, in which hemoglobin concentrations are exceedingly low (on the order of 3 to 4 g/dl), although virtually all the hemoglobin can be reduced in traversing the skin capillaries, an insufficient amount of reduced hemoglobin remains to produce a visible discoloration. Oppositely, the polycythemic patient develops cyanosis at a higher arterial O_2 saturation than does the normal individual.

The combination of intense vasoconstriction and excess reduced hemoglobin is responsible for the distinctive gray or heliotrope color that is frequently seen in patients with circulatory collapse and severe pulmonary edema.

Causes of Cyanosis

Several types of cyanosis are usually identified according to the underlying mechanism. They include peripheral cyanosis, cyanosis arising from pulmonary disease, cyanosis from venous admixture, and cyanosis due to abnormal pigments in the blood.

Peripheral Cyanosis

This type is secondary to abnormally large extraction of O_2 from blood flowing through peripheral capillaries. The most common cause is a diminished cardiac output associated with peripheral vasoconstriction. Not only the hands and feet but also the tip of the nose becomes blue in severe heart failure. Indeed, in patients with intractable heart failure, necrosis occasionally develops at the tip of the nose.

Peripheral vasoconstriction per se, as in Raynaud's disease, also produces cyanosis of the nail beds.

Cyanosis in Pulmonary Disease

Patients with chronic bronchitis and emphysema characteristically manifest derangements in ventilation-perfusion relationships. In some, arterial hypoxemia results. In patients with diffuse interstitial fibrosis, normal arterial oxygenation at rest is succeeded by arterial hypoxemia, and sometimes by cyanosis, during exercise. Another cause of arterial hypoxemia is the syndrome of alveolar hypoventilation in patients with normal lungs. In any of these situations, cyanosis is intensified if heart failure supervenes and slows blood flow through the skin (i.e., decreases O_2 delivery).

Cyanosis Due to Venous Admixture

In patients with intracardiac right-to-left shunts, cyanosis arises from a mixture of venous and arterial blood. The effect of venous admixture is particularly striking if the O_2 content of mixed venous blood is inordinately low, as in some types of congenital heart disease and in severe heart failure. Often secondary polycythemia contributes to the cyanosis. On occasion, regional cyanosis is diagnostic. For example, in patent ductus arteriosus with reversal of blood flow, the lower extremities are deeply cyanotic, whereas the upper extremities are virtually normal in color.

Cyanosis Due to Abnormal Pigments in Blood

Methemoglobinemia is an occasional cause of cyanosis. Methemoglobinemic blood is chocolate brown, and spectrophotometric examination of blood reveals the characteristic pigment. Arterial blood examination discloses a normal P_{O_2}.

The cause of methemoglobinemia may be hereditary (i.e., due to the presence of hemoglobin M or a deficiency in methemoglobin reductase) or, more often, acquired (e.g.,

by exposure to chemical agents such as aniline dyes, chlorates, nitrates, and nitrites); or methemoglobinemia may result from drugs such as dapsone acetanilide, nitroglycerin, phenacetin, and primaquine. Nitrates are a common cause of methemoglobinemia. Nitrates are reduced to nitrites by bacteria in the intestinal tract. Excessive use of nitroglycerin, an organic nitrate, leads to methemoglobinemia.

In methemoglobinemia, the ferrous iron is oxidized to ferric iron, rendering the hemoglobin molecule incapable of binding O_2 or CO_2. Methemoglobin is formed continuously in the normal erythrocyte, but its level within the cell is kept low (less than 2 percent) by intracellular reductive mechanisms. High levels of methemoglobin result from hereditary abnormalities (e.g., a deficiency in methemoglobin reductase) or from exposure to drugs or chemicals that increase the rate of oxidation beyond the reductive capacity of the erythrocytes. Clinical manifestations of methemoglobinemia vary with the blood levels. Concentrations of methemoglobin between 10 and 25 percent usually cause asymptomatic cyanosis. When these levels are exceeded, dizziness, fatigue, and headache appear.

Because of the normal methemoglobin reductase and Nicotinamide adenine dinucleotide (NADH) generated during anaerobic glycolysis, treatment beyond discontinuation of an offending drug is often unnecessary unless serious manifestations occur (angina, stupor, or coma). Then methylene blue is given intravenously (1 to 2 mg/kg as a 1 percent solution) over 5 to 10 min. Cyanosis should disappear within 1 h; if not, the dose should be repeated. Larger doses of methylene blue engender the risk of aggravating the methemoglobinemia. Methylene blue should not be used in patients with glucose-6-phosphate dehydrogenase deficiency (common in certain African-American and Mediterranean populations) as it cannot be metabolized and may result in accidental toxicity.

CLUBBING

Clubbing of the digits is a classic finding in medicine that dates back to Hippocrates' awareness of the association between characteristic changes in the fingertips and empyema. Occasionally it constitutes a valuable clue to clinically unapparent disease of the lungs and pleura. Clubbing of the fingers designates the selective bulbous enlargement of the distal segments of the digits due to an increase in soft tissue (Fig. 27-18). Although most often it is painless, clubbing remains an important finding as its presence should signal an evaluation for potential serious causes.

When full-blown, clubbing is easy to recognize: (1) the nails, particularly the index finger, become abnormally curved in the longitudinal and coronal planes; (2) the hyponychial angle, viewed in profile, becomes blunted, often in conjunction with softening and sponginess of the base of the nail; and (3) the undersurface of the terminal digit becomes large and bulbous. Early stages of clubbing are subtle and generally difficult to diagnose. Clubbing often has to be distinguished from simple curvature of the nails and occasionally from chronic paronychia and Heberden's nodes. A variety of methods have been proposed for quantifying clubbing (e.g., measuring casts of the fingertips), but none has become popular.

Clubbing is generally acquired, but it may be hereditary. Acquired clubbing is seen in a wide variety of disorders, both extrathoracic and thoracic (Table 27-1).

It is important to recognize that clubbing is not caused by all forms of chronic lung disease. COPD, for example, does not cause clubbing. The presence of clubbing in a patient with COPD should alert the clinician to the possibility of a second process, commonly lung cancer. As a rule, clubbing is bilaterally symmetrical, affecting hands and feet; on occasion, local factors, such as injury of a finger or of the median nerve, may cause clubbing that is confined to a single finger. Rarely, clubbing may be confined to the digits of one hand (e.g., in an ipsilateral pulmonary sulcus tumor that has invaded the brachial plexus or following hemiplegia). In certain types of congenital heart disease, a telltale distribution of clubbing is of considerable diagnostic value. For example, in patent ductus arteriosus associated with reversal of shunt through the ductus, clubbing affects only the toes.

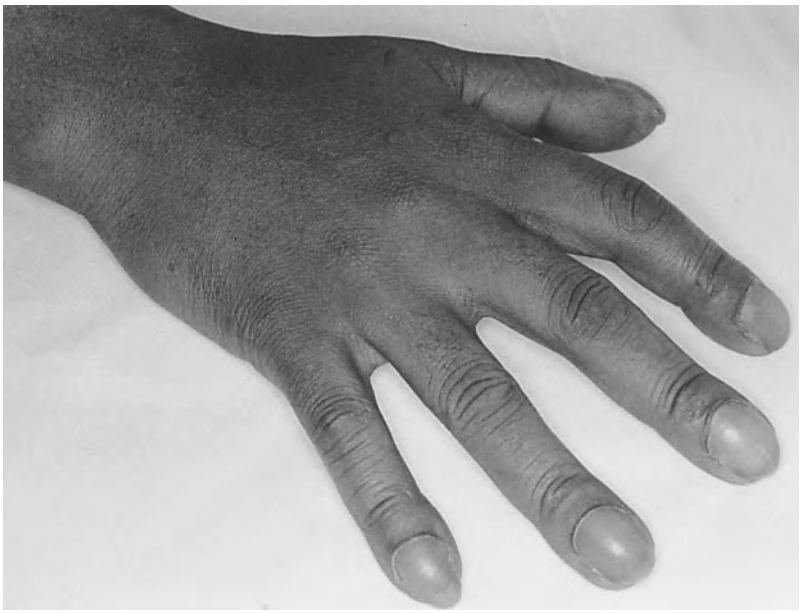
Pathogenesis

The pathogenesis of clubbing is unknown, and no suitable animal model of clubbed fingers has yet been developed, largely because so few species other than primates have fingers. A common denominator in the pathogenesis of clubbing appears to be vasodilation of vessels in the fingertip, including formation of the arteriovenous connections. As a result, hydrostatic pressures increase in the capillaries and venules, promoting the transduction of fluid into the interstitium. The reason for this preferential vasodilation is unclear. A popular notion is that a humoral substance escapes normal deactivation by pulmonary capillaries. This theory could account for clubbing in cyanotic congenital heart disease, in various pulmonary diseases in which proliferation of the bronchial circulation occurs, and in hepatic cirrhosis in which pulmonary arteriovenous anastomoses and right-to-left shunts are common. However, it is difficult to relate this theory to the high incidence of clubbing in subacute bacterial endocarditis.

At present, a single hypothesis that would account for the clubbing that occurs in such diverse disorders as subacute bacterial endocarditis, carcinoma of the lung, hemiplegia, chronic mountain sickness, and purgative abuse is not possible. Indeed, it seems likely that clubbing of the digits is a stereotyped consequence of diverse influences that have in common the capacity to induce marked digital vasodilation and interstitial edema of the soft tissue.

HYPERTROPHIC OSTEOARTHROPATHY

Occasionally, clubbing of the digits is accompanied by hypertrophic osteoarthropathy (HOA), a separate entity both



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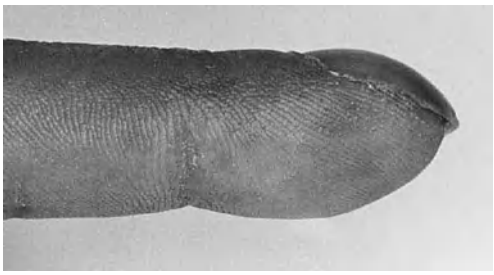

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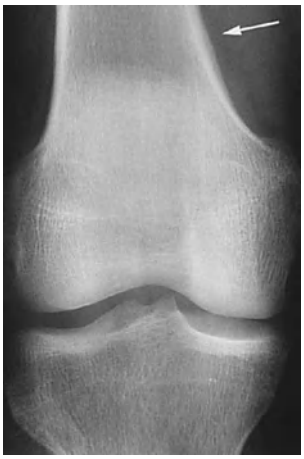

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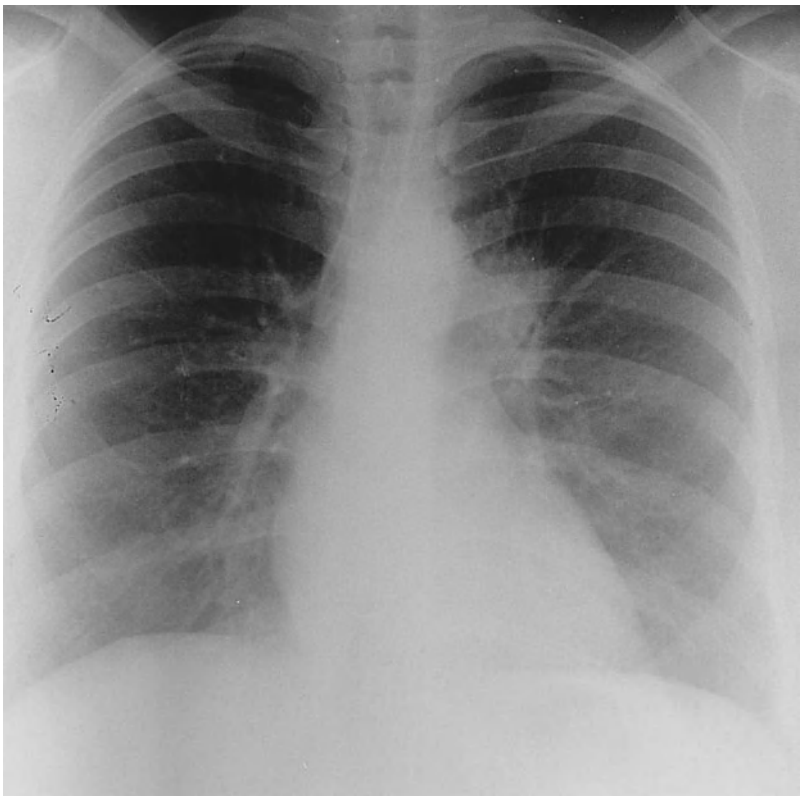

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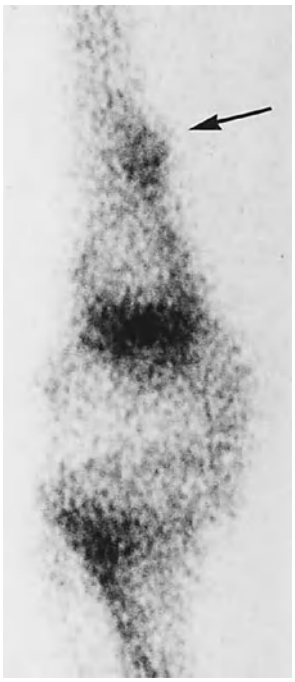


E

Figure 27-18 Clubbing of the digits and hypertrophic osteoarthropathy. A 40-year-old woman developed swelling and tingling of the fingertips in association with painful swelling of both knees. She was a heavy smoker (36 pack-years) and had an 8-month history of a dry cough. *A.* Clubbing of all fingers. *B.* Index finger. *C.* Left hilar mass that proved to be a primary adenocarcinoma of the lung. *D.* Subperiosteal formation of new bone on the medial aspect of the diaphysis of the femur. *E.* Bone scan, using ^{99m}Tc methylene diphosphonate. An abnormal accumulation of isotope is seen in the area of new bone (arrow).

clinically and radiographically. Clinically, HOA is manifested by pain and swelling of the soft tissues over the distal ends of the long and tubular bones. Radiographically, the distinctive feature of HOA is the formation of new bone beneath the periosteum of the distal diaphyses of the long bones of the extremities (Fig. 27-18).

The most common disorder associated with HOA is carcinoma of the lung. The incidence is about 5 percent and is unrelated to the cell type of the cancer, except that small-cell carcinoma is rarely implicated; a peripheral carcinoma of the lung is slightly more common than a central one. Joint symptoms precede the local signs of tumor in about one-third of the cases; the interval is sometimes as long as 2 years. Pulmonary metastases rarely cause HOA. Pulmonary tuberculosis is seldom, if ever, associated with HOA. Cystic fibrosis and idiopathic pulmonary fibrosis can be accompanied by HOA. Pregnancy can rarely be a cause of HOA, with symptoms resolving promptly with delivery.

As in the case of clubbing of the digits, theories about pathogenesis tend to focus on humoral factors generated elsewhere. However, a neurogenic theory has also been advanced on the basis of two types of observations: (1) in a few patients, vagotomy has relieved the symptoms of inoperable carcinoma of the lung and led to regression of the bony lesions; and (2) in keeping with the observations on the few patients, vagotomy in dogs is usually followed by a decrease in blood flow to the limbs. At present, neither theory has much convincing support, but both suggest future directions for exploration.

In contrast to clubbing of the digits, which is rarely painful, HOA associated with carcinoma of the lung often causes severe rheumatic symptoms. These symptoms vanish after resection of the carcinoma, even though clubbing usually remains. In patients who are treated with radiotherapy for unresectable carcinoma, pain in the vicinity of the joints usually decreases greatly and usually does not recur even if metastases develop to the lungs or elsewhere.

THORACIC PAIN

First thoughts about chest pain almost invariably turn to the pain of myocardial ischemia. However, cardiac pain is often distinguishable from other types of chest pain because of its viselike nature; its characteristic radiation to the left arm, shoulder, or neck; and its lack of relation to breathing. Extracardiac painful sensations can arise from various sites within the thorax, most often from the pleura, the lungs, and the chest wall. Pain may also be referred to the thorax as a result of GERD.

Pleuritic Pain

The most characteristic pain associated with the respiratory apparatus is pleural pain. It originates in the parietal pleura and endothoracic fascia; the visceral pleura is insensitive to pain. In contrast to the deep, oppressive substernal pain of myocardial infarction, pleuritic pain is identified by the patient as being close to the thoracic cage. It is predominantly an inspiratory pain reflecting the stretching of inflamed parietal pleura during movement of the thorax; coughing or laughing is exceedingly distressing; the patient often clutches the chest to minimize its excursion. The pain is usually local, but sometimes it spreads along the course of the intercostal nerves that supply the affected area. Irritation of the diaphragmatic pleura by an inflammatory process either below or above the diaphragm often causes ipsilateral shoulder pain when the central portion of the diaphragm is involved; sometimes the pain is referred to the abdomen when the outer diaphragmatic pleura is irritated.

As a rule, pleural pain is part of a syndrome of pleural inflammation that includes malaise and fever; an important exception to this generalization is the pleural pain of pulmonary infarction, which is often unassociated with any premonitory signs. In addition to inflammation and malignant etiologies, pleuritic pain occurs with pneumothorax.

Pulmonary Pain

A second distinctive type of respiratory chest pain accompanies a tracheitis or tracheobronchitis. The pain is searing and is most pronounced after cough. Invariably this central chest pain is associated with evidence of upper respiratory infection.

An uncommon type of chest pain is associated with pulmonary hypertension. It is usually absent at rest and appears during exertion. The pain is substernal and is invariably associated with dyspnea; it subsides promptly when exercise stops. It is often mistaken for left heart angina until the presence of pulmonary hypertension is uncovered. It may be due to right ventricular strain and ischemia.

Chest Wall Pain

Pain in the chest is a common clinical problem. It may arise from within the thorax (the heart, pericardium, lungs, pleura, chest wall) or be referred from elsewhere (e.g., from below the diaphragm). Characteristic patterns and associations may help to clarify the source of the pain.

Pleural pain is generally associated with fever or dyspnea. Most often it is abrupt in onset, unilateral, and incapacitating. As a rule, it affects the lower part of the chest, but occasionally it is referred to the shoulder or abdomen. Almost invariably, pleural pain is aggravated by deep breathing or coughing. The patient tends to splint the chest on the affected side. Tachypnea and shallow tidal volumes are a consistent pattern.

Musculoskeletal pain arising in the chest that is also aggravated by breathing may be confused with pleuritic pain. It is rarely severe and incapacitating, is often bilateral, and generally is intensified by changes in body position or flexing the thorax. The affected muscles are often tender to gentle pressure. A fractured rib is often identified as the source of pain by a history of a fall, injury, or trauma. Additional clues

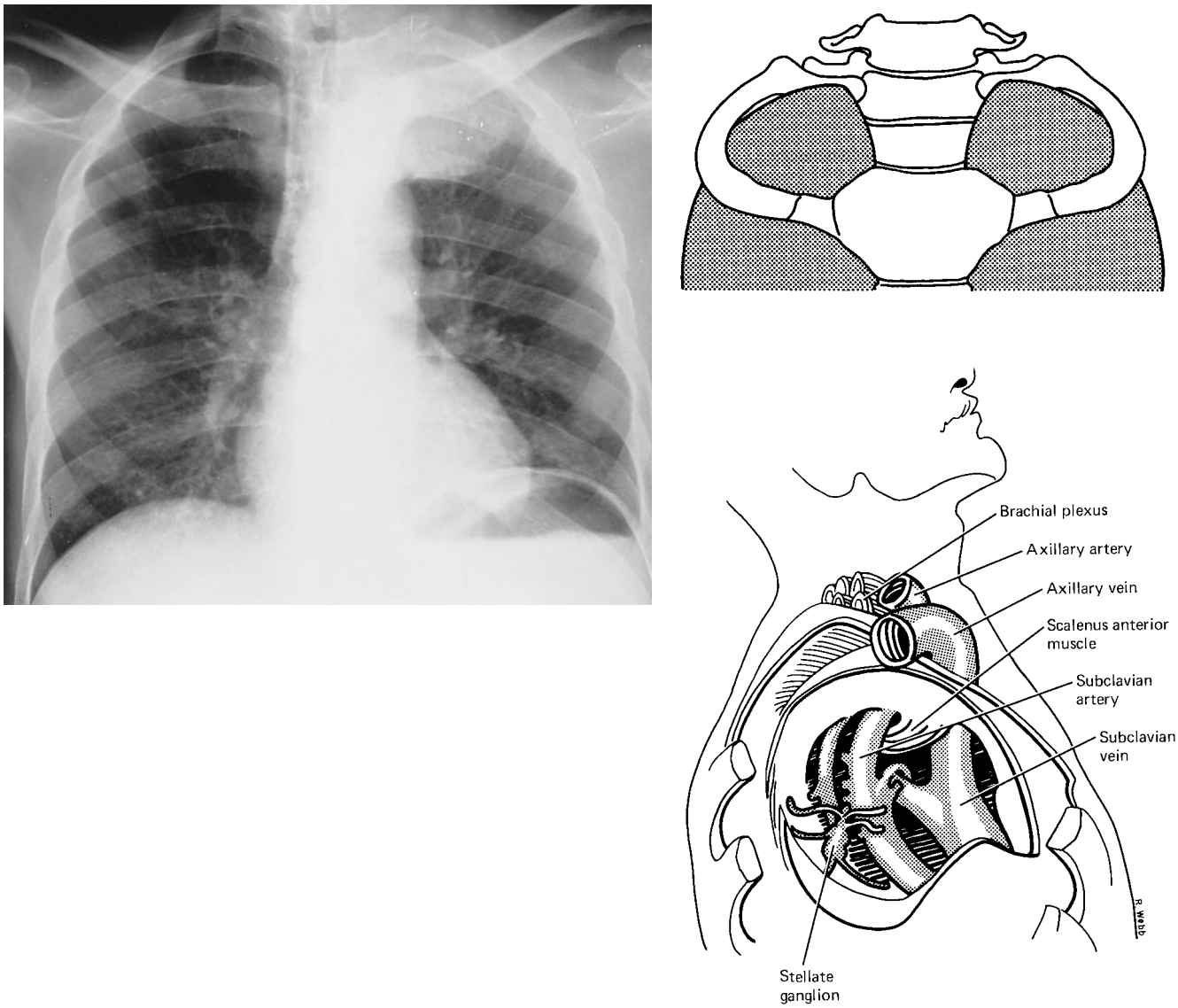


Figure 27-19 Pulmonary sulcus tumor. *A.* Chest radiograph. *B.* Relationships of apex of the lung to adjacent bony structures. *C.* Lateral view of area occupied by apex of lung, showing proximity not only to nerves of brachial plexus but also to sympathetic chain and to blood vessels. A mass that grows posteriorly and laterally can encounter sympathetic chain and bony structures; superiorly, the axillary vessels, brachial plexus, and bony structures; anteriorly, the subclavian vein and its tributaries. *(From Pernkopf: Atlas of Topographical and Applied Human Anatomy. Philadelphia, WB Saunders, 1964, p 22.)*

are point tenderness and crepitus of the affected area, reproduction of the pain upon manual compression of the chest, or radiographic evidence of the broken rib.

Pain arising from the large airways is usually burning in nature and retrosternal in location and is disturbing rather than incapacitating. It is aggravated by cough and is commonly accompanied by evidence of a bronchitis. Cold air may be intolerable.

The pain of a pulmonary sulcus tumor (Fig. 27-19) is quite distinctive. This unusual location of a carcinoma of the lung was originally described by Pancoast in 1932 as characterized by pain along the distribution of the eighth cervical and the first and second thoracic nerves, Horner's syndrome, local destruction of bone by the tumor, and atrophy of hand muscles. The chest radiograph is distinctive in showing a small, sharply defined shadow at one apex. Destruction of one or more of the upper three ribs posteriorly and of their adjacent transverse processes may also be observed.

Cardiac Pain

Attention was called above to the pain of myocardial ischemia. Another type of cardiac pain is that of pericarditis. Pericardial pain is often aggravated by deep breathing and, almost invariably, is accompanied by a telltale rub that is synchronous

with the heartbeat. The discomfort may be relieved by leaning forward.

The postcommissurotomy (postpericardiotomy) syndrome is characterized by chest pain that develops within a few days to weeks after cardiac surgery or pericardiotomy. The pain is usually sudden in onset and substernal, with radiation to the left side of the neck; often it is aggravated by deep breathing. Low-grade fever and a high sedimentation rate are regular concomitants. Chest pain can also be troublesome in patients who have undergone cardiac transplantation. The diagnosis is usually self-evident when account is taken of the antecedent history of cardiac surgery. Indeed, confusion is more apt to arise with the pain of myocardial infarction than with respiratory causes of chest pain.

Miscellaneous Pain

Other structures in the mediastinum can be the source of chest pain. Noteworthy are the types of pain arising from the esophagus (peptic esophagitis) and dissection of the aorta. Their patterns and intensity help to distinguish them from respiratory pain. Esophageal disease is typically accompanied by a burning pain, frequently after eating. Acid reflux may worsen with recumbency. Aortic dissection is often described with a sharp, tearing sensation of acute onset with radiation to the shoulder; these are often signs of impending cardiovascular collapse.

Arthritis of the cervical spine is a common cause of thoracic pain. Usually the cause is quite clear because of the characteristic distribution of the pain. Cervical spondylosis occasionally causes severe pain in the chest and arms, but it is more apt to mimic myocardial infarction than is respiratory pain. A metastatic tumor to the thoracic spine often causes bilateral symmetric pain; there is often discomfort to palpation over the affected area. Unilateral pain, along the distribution of an intercostal nerve, is characteristic of herpes zoster before the appearance of the skin eruption and is often described as an intense burning sensation.

Anxiety can produce or intensify chest pain. Usually, pain related to anxiety is accompanied by dyspnea and hyperventilation. Manifestations of vasomotor instability, such as excessive palmar sweating, flushing, and tachycardia, may accompany the complaint of chest pain due to anxiety. Rarely does the pain conform to a characteristic or consistent pattern. Anxiety also interferes with the quantification of pain originating in a somatic lesion and with its management.

FEVER

In the patient with lung disease, fever usually, but not invariably, signifies infection. When the lung disease is chronic, as in bronchitis and emphysema, a bout of acute bronchitis usually elicits only a modest fever, even though the sputum turns purulent. In contrast, an acute pneumonia of lung abscess may be associated with high fever.

The possibility that fever is due to infection lends urgency to the situation. Elsewhere in this book, the patterns of acute pulmonary infection are considered with particular attention to systemic effects, chest radiography, white blood cell count, sedimentation rate, and sputum examination. Often overlooked at the outset is miliary tuberculosis, which occasionally escapes detection on the initial chest radiograph. Favoring this diagnosis is a history of recent contact with a patient experiencing active tuberculosis, general malaise, easy fatigability, and anorexia during the previous few weeks. This insidious onset differs strikingly from the more sudden onset of acute pneumonia.

Neoplasms are also associated with fever. In certain neoplasms, such as carcinoma within a bronchus, the fever is generally a secondary effect attributable to infection distal to obstruction; necrosis within the tumor is a less common cause. In others, such as hypernephroma, fever and chills are striking, even though evidence of infection is absent. A mesothelioma of the pleura is often associated with fever. Presumably, in patients with neoplasms who have no evidence of infection, necrosis within the tumor leads to the elaboration of pyogenic substances within and around the tumor.

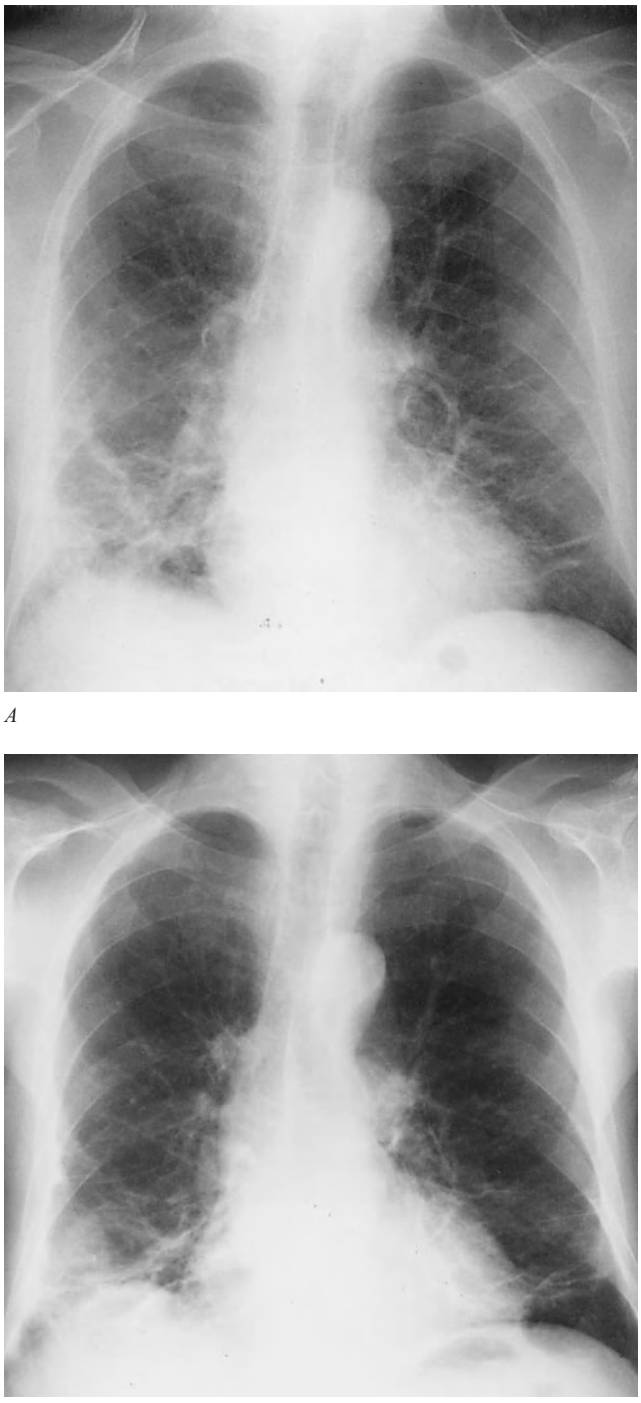
Hypersensitivity pneumonitis (extrinsic allergic alveolitis) is sometimes followed by fever as well as by pulmonary disability after exposure to the offending antigen.

In contrast to the pulmonary disorders in which fever is a characteristic feature, pulmonary sarcoidosis is uncommonly associated with fever unless there is extrapulmonary involvement, such as lymphadenopathy or erythema nodosum. Nor is pneumoconiosis associated with fever unless complicated by necrosis in the midst of conglomerate fibrosis or by superimposed tuberculosis. Among the other extensive disorders of the lungs that cause no fever (and few systemic complaints) are idiopathic pulmonary fibrosis, lymphangitic carcinomatosis, multiple pulmonary metastases, alveolar proteinosis, idiopathic pulmonary hemosiderosis, and alveolar microlithiasis.

RADIOLOGIC EVALUATION

The radiologic evaluation of the patient presenting with respiratory symptoms is dealt with in considerable detail elsewhere in this book (see Chapter 30). Over the years, the chest radiograph has become an invaluable tool, not only for diagnosis but also for following the result of treatment (Fig. 27-20) and for directing interventions. The value of routine screening films in asymptomatic subjects (e.g., as part of annual physicals or in chronic cigarette smokers to detect cancer) is still a matter of debate. The diagnostic yield of such studies has not been impressive. In contrast, the chest radiograph is an integral component of the initial evaluation of the patient with new respiratory symptoms.

In recent years, the conventional chest radiograph has been supplemented by a succession of imaging techniques, such as computed tomography, magnetic resonance imaging,



A

B

Figure 27-20 Occasional response of interstitial lung disease to corticosteroids. *A*. Interstitial lung disease in a 67-year-old man before administration of corticosteroids. Widespread interstitial lung disease, more marked on the right. The lung function tests were characteristic of severe restrictive lung disease. *B*. After corticosteroids. Pulmonary function tests improved dramatically along with clearing of the pulmonary lesions on the chest radiograph.

and positron emission tomography. Although these powerful tools are generally used as complementary techniques, they often assume primary roles (e.g., examination of the mediastinum for lymphadenopathy or invasion of the chest wall in a patient with carcinoma of the lung). As successive improvements in these techniques continue to be made, the future seems to hold even brighter prospects for these noninvasive methods.

COMMON CHRONIC PULMONARY DISEASES

The great majority of chronic pulmonary diseases that affect both lungs fall into four categories: chronic obstructive airway diseases, restrictive lung diseases, global alveolar hypoventilation, and obliterative pulmonary vascular diseases.

Chronic Obstructive Airway Disease

Obstruction of the airways generally occurs during expiration. Based on expiratory maneuvers, airway obstruction has been categorized by a wide variety of tests (see Chapter 50). But it is remarkable how much information about the obstruction can be obtained from the forced expiratory volume in 1 s (FEV_1; determined serially, before and after administration of a bronchodilator), inspection of the flow-volume loop, and arterial blood gas analyses. Preoccupation with expiration may obscure disorders characterized primarily by inspiratory obstruction. These are commonly overlooked because of failure to elicit stridor on the physical examination.

In asthma, generalized wheezing occurs during both inspiration and expiration. Except for attacks precipitated by specific antigens, two common mechanisms often precipitate an episode: a respiratory infection, usually viral rather than bacterial, and an emotional event. Between episodes, most asthmatics, even those who are symptom-free, can be shown to have heightened bronchomotor tone (Fig. 27-21). In a latent asthmatic, a brief period of hyperventilation generally suffices to induce a bout of asthma. In patients with left ventricular failure, a paroxysm of wheezing ("cardiac asthma") occasionally heralds the onset of acute pulmonary congestion and edema. The new onset of asthma in an elderly person should be carefully assessed with respect to the state of the left ventricle before vigorous bronchodilator therapy is initiated.

Restrictive Lung Disease

The diagnosis of restrictive lung disease usually begins with a complaint of dyspnea, reinforced by a telltale chest radiograph. Indeed, without abnormalities on the chest radiograph, detection of interstitial disease by pulmonary function testing is uncommon. The combination of tachypnea, the typical chest radiograph, concentric reduction in lung volumes, and the appearance of arterial hypoxemia during exercise almost invariably clinches the diagnosis; a low value for the

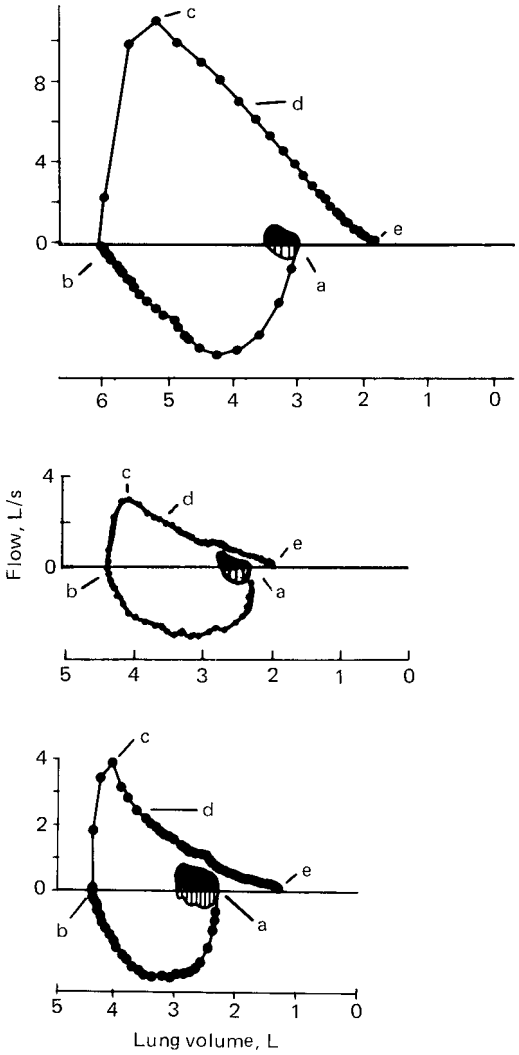
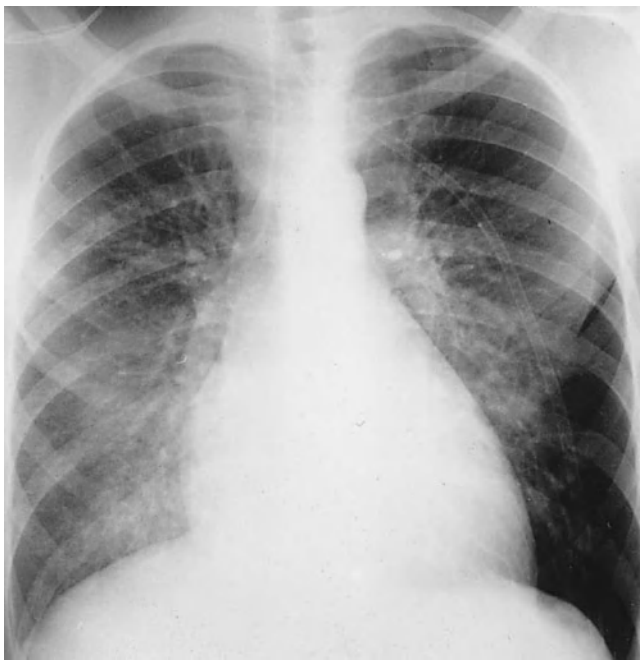


Figure 27-21 Simultaneous flow-volume curves in asthma. Top: Normal subject. Beginning at the end of a quiet expiration (a), the curves were recorded during a normal tidal breath (small, shaded loops) and during a forced expiration from peak lung inflation (b) to full expiration (e). Peak flow rates were reached at c. Expiration then continued along segment cde. In the record of the tidal breath, inspiration is hatched and expiration is solid black. The interval between each dot is 0.05 s. Center: Asthmatic subject. The vital capacity (be) is abnormally small, and flow rates along cde are diminished. Bottom: Same asthmatic subject 2 weeks after clinical recovery. Although flow rates are considerably higher than during the acute attack, the slope of segment de is still abnormally low, indicating that the resistance to airflow as lung volume decreases is still inordinately high. *(From Mellins R, Lord GP, Fishman AP: Dynamic behavior of the lung in acute asthma. Med Thorac 24:81–98, 1967, with permission.)*

diffusing capacity of the lungs is final proof and is useful in following the course of the disease. Much more troublesome is the identification of the cause (Table 27-6).

An important distinction at the outset is whether the disease is acute or chronic (Table 27-3). Some types of interstitial disease, such as asbestosis, take years to become symptomatic. Others, such as hypersensitivity pneumonitis can have a more fulminant onset.



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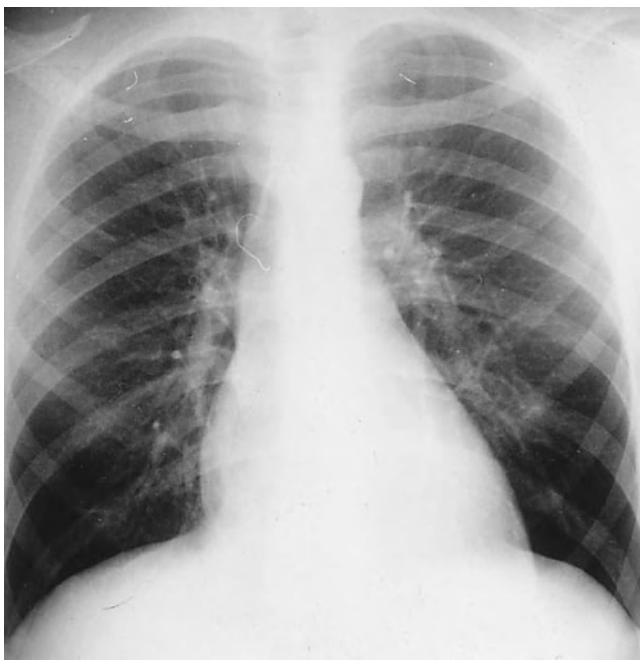
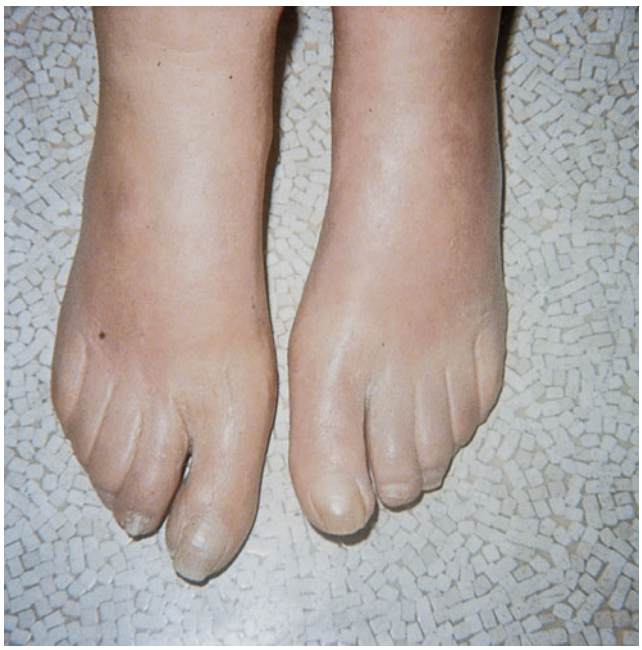


B

Figure 27-22 Interstitial edema and infection. Pneumocystis infection in an immunosuppressed patient in uremia. *A*. Bilateral interstitial and alveolar pattern and enlarged cardiac silhouette suggestive of pulmonary edema. *Pneumocystis carinii* (*Pneumocystis jiroveci*) was obtained by bronchial lavage. *B*. Three weeks later. Reduction in size of cardiac silhouette and clearing of infiltrates after marked diuresis and treatment with antibiotics.

Another way to assist in categorization is the presence of systemic complaints. Sometimes, particularly in immunosuppressed patients, distinction between interstitial infection and interstitial edema may be difficult to make (Fig. 27-22). Persistent fever suggests infection. Lung impairment by a



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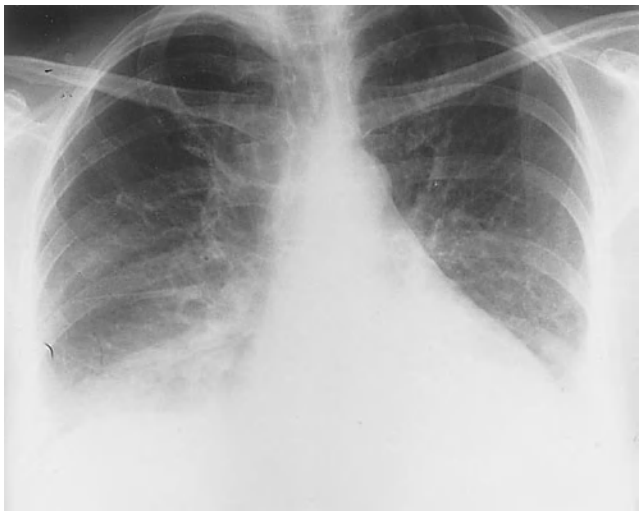

B

Figure 27-23 Scleroderma. *A*. Raynaud's phenomenon of the toes. *B* .Diffuse bilateral basilar interstitial infiltrates on chest radiograph.

systemic disease, such as scleroderma, is often suggested by telltale stigmas in extrapulmonary sites (Fig. 27-23). In some instances, the cause is self-evident. This relationship is striking in some occupational disorders (e.g., silo-filler's disease that occurs after exposure to moldy hay). Also, the chest radiograph in sarcoidosis or silicosis is sometimes so characteristic as to be virtually diagnostic (Fig. 27-24). But sometimes the cause remains enigmatic or idiopathic despite elaborate laboratory investigations, including lung biopsy.

In essence, uncovering the cause of diffuse interstitial fibrosis is often a matter of painstaking and discriminating medical detection. The flash of brilliant insight, in the tradition of Sherlock Holmes or Lord Peter Wimsey, is apt to

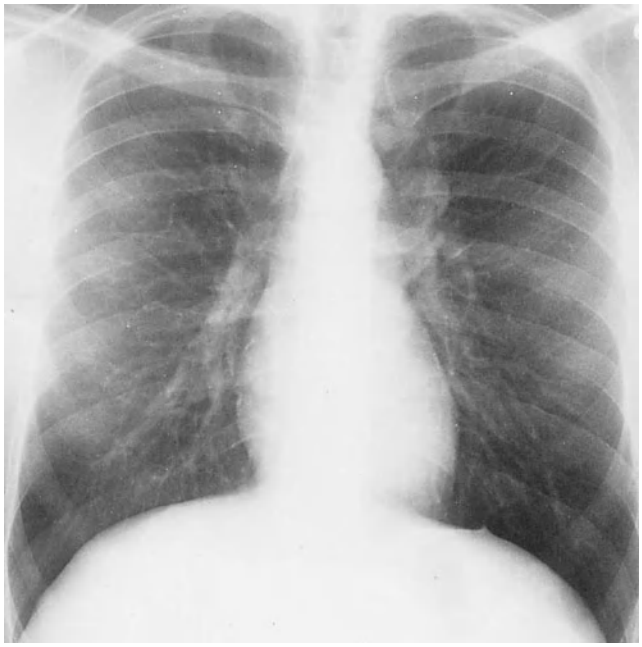

Figure 27-24 Sarcoidosis. Unilateral hilar adenopathy due to sarcoidosis in a 27-year-old asymptomatic man with left hilar adenopathy and interstitial lung disease of upper lobes. Bronchoscopic biopsy disclosed widespread noncaseating granulomas.

be less revealing about cause than is a meticulous, systematic account of lifestyle, habits, occupation, and background. The distribution and pattern of disease on the chest radiograph often provide clues to the next step in diagnosis. Sometimes the identification of abnormal constituents in sputum is diagnostically helpful (e.g., blood or blood products in the macrophages of the patient with Goodpasture's syndrome or eosinophils in the patient with a hypersensitivity disorder). In many instances, diagnosis rests on lung biopsy. Unfortunately, except in diseases such as sarcoidosis, biopsy is often deferred indefinitely, owing to a perceived lack of likely change in treatment. As a result, biopsy is usually performed at the stage of nonspecific interstitial fibrosis when scarring is so indiscriminate that neither etiology nor pathogenic mechanisms are decipherable.

As pointed out above, the physiological hallmarks of diffuse interstitial disease are those of restrictive lung disease (i.e., stiffening of the lung [low compliance] and concentric reduction in lung volumes [decrease in vital capacity, residual volume, and total lung capacity]). Accompanying the decrease in compliance is an increase in the work of breathing and a breathing pattern of rapid, shallow tidal volumes. The chest radiograph demonstrates the inability of the patient to expand fully the stiffened lungs. Dyspnea is evoked at first by mild exercise and later persists at rest.

The once-popular picture of widespread disease confined to the alveolar-capillary interstitium has been modified by the recognition that alveoli are generally implicated in the underlying process. In interstitial pulmonary edema, groups of alveoli are often flooded. In inflammatory processes, such as sarcoidosis or desquamative interstitial pneumonia, alveoli,

as well as the interstitial space, are commonly caught up in the process. In pneumonia caused by *Pneumocystis carinii (Pneumocystis jiroveci)*, the organisms are found in alveoli as well as in the interstitial spaces. Therefore, the designation of diffuse interstitial disease should not be misconstrued as being confined solely to the interstitium of the lungs, even though the term generally does identify the predominant seat of disease.

Syndromes of Alveolar Hypoventilation

The common denominator in disorders characterized by alveolar hypoventilation is an abnormally high value for arterial (and alveolar) P_{CO_2}. The most common cause is chronic bronchitis and emphysema (COPD), which produces hypercapnia by deranging ventilation-perfusion relationships. This "net" alveolar hypoventilation is conceptually different from the "generalized" alveolar hypoventilation that results from a disorder of respiratory control or of the chest bellows as occurs in kyphoscoliosis, respiratory muscle weakness, or obesity-hypoventilation. The usual manifestation of generalized alveolar hypoventilation is the combination of normal lung volumes and FEV_1, normal chest radiograph in conjunction with arterial hypoxemia, hypercapnia, and respiratory acidosis.

Obliterative Vascular Disease

Pulmonary thromboemboli usually affect large as well as small vessels. Occlusive vascular diseases, such as idiopathic pulmonary arterial hypertension, which are more confined to small ("resistance") pulmonary vessels, are much less common. More often, the pulmonary resistance vessels are caught up in the adjacent and surrounding diffuse interstitial disease. In pulmonary vascular disease that compromises the area available for gas exchange, the diffusing capacity becomes subnormal. Occlusive vascular diseases of the lung are usually recognized when the extent of the disease is sufficient to cause considerable pulmonary hypertension. The diagnosis is most often first suggested by the estimated pulmonary artery pressure in the echocardiogram. Additional testing is required to establish the cause (e.g., pulmonary function testing to rule out airways obstruction, a polysomnogram to assess possible sleep apnea); confirmation of pulmonary arterial hypertension requires right heart catheterization.

CHOOSING PULMONARY FUNCTION TESTS

In Chapter 34, pulmonary function testing is discussed in some detail. Often a combination of pulmonary function tests is needed to characterize a patient's abnormalities. Pulmonary function tests can be particularly helpful in obstructive diseases of the airways, in which chest radiographs are often normal. Some of the tests are simple; others require special facilities and personnel. For example, closing volume and closing capacity, previously popular as "sensitive" tests for obstruction of small airways, have proved to be of little clinical value. There is certainly no value to these tests once the FEV_1 is abnormal. Nonetheless, the possibility exists that such sensitive tests may be useful in special conditions (e.g., in assessing obstruction of small airways in occupational disease).

The battery of tests that is used experimentally to portray the full length and breadth of the patient's pulmonary disorder is rarely needed for clinical purposes. However, only a few physiological test patterns result from a wide variety of causes. Indeed, virtually all diffuse diseases of the lungs and airways that compromise pulmonary performance can be categorized into four distinctive patterns: (1) obstructive disease of the airways, (2) restrictive lung disease, (3) obliterative vascular disease, and (4) alveolar hypoventilation due to malfunctioning of the chest bellows or control mechanisms.

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28

Skin Disease in Patients with Pulmonary Disease

Jeffrey P. Callen

Examination of the skin can provide important clues in the diagnosis and treatment of persons with pulmonary disease. Some skin lesions either accompany pulmonary disease or complicate its treatment; occasionally, systemic diseases that affect both skin and lung first manifest themselves in the skin. In this chapter we deal briefly with processes in which there is prominence of cutaneous manifestations that might impact the care of the patient with pulmonary disease. The diagnosis and development of a differential diagnosis of cutaneous lesions is beyond the scope of this chapter and can be found in general dermatologic texts.

ATOPIC DERMATITIS

Atopy refers to a group of disorders, including asthma, allergic rhinitis, and atopic dermatitis, in which immune and pharmacologic responses are abnormal. The atopic person usually has a family history of one or more of these disorders. Atopic dermatitis is a common disorder, affecting 1 to 3 percent of the population in the United States. In 85 percent of affected subjects, the skin lesions appear before 5 years of age. The dermatitis often resolves as the patient reaches adulthood; in

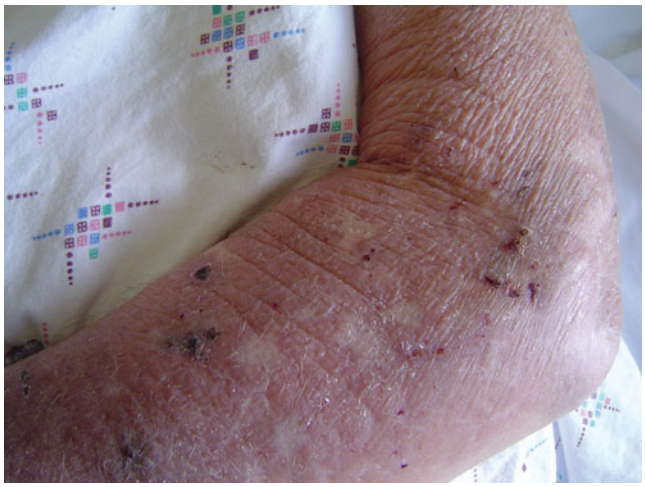


Figure 28-1 Atopic dermatitis is characterized by lichenification, excoriations and slight scale.

the adult, either the skin lesions or respiratory systems may predominate.

In infants, the skin lesions often begin as dry, erythematous plaques on the cheeks; excoriations and scaling may be prominent. In older children, the lesions localize in flexures; lichenification and excoriated papules are prominent features (Fig. 28-1). In adults, the lesions favor the hands and extremities. Atopic subjects also manifest prominent folds of the lower eyelids, periorbital hyperpigmentation with facial pallor, generalized dry skin, and white dermatographism. At any age, pruritus may be prominent and become secondarily infected, leading to bacterial impetigo within the lesions. In some patients, increased itching may be a prodrome to exacerbation of asthma.

The cause of atopic dermatitis is unknown. In all likelihood, the pathogenesis is multifactorial, probably including disordered immune regulation as a causative factor. In persons with atopic dermatitis, abnormalities in cell-mediated immunity and lymphocyte function increase the risk of disseminated viral and fungal skin lesions. The role of food or environmental antigenic challenge in flares of atopic dermatitis is unsettled, but it is known that asthma can be precipitated by such challenges.

The relationship between atopic dermatitis and lung disease is imperfect. Although hyposensitization is useful for asthma, it is either not helpful or is detrimental in atopic dermatitis.

Treatment of atopic dermatitis in adults is multifaceted. The patient should avoid irritants. Bathing can occur on a daily basis, but should be followed by the application of emollients. Patients with atopic dermatitis frequently harbor or develop infections, particularly *Staphylococcus aureus* and eradication of infection is useful in those instances. Topical therapy with corticosteroids of an appropriate strength and in an appropriate vehicle for the site on the body that is being treated is a standard form of therapy. Recently topical calcineurin inhibitors, including pimecrolimus and tacrolimus, have been used as an adjuvant or as a replacement for topical corticosteroids. Full discussions of the therapy of atopic dermatitis are available elsewhere.

COLLAGEN VASCULAR DISORDERS

Dermatomyositis

Dermatomyositis (DM) is an idiopathic inflammatory myopathy characterized by proximal, symmetrical, slowly progressive muscle weakness and characteristic cutaneous lesions. The skin lesions that are pathognomonic include a heliotrope eruption, which consists of erythematous to violaceous periorbital changes that may be accompanied by edema (Fig. 28-2). Gottron's papules are also pathognomonic for DM and consist of erythematous papules over the bony prominences on the dorsal hands (Fig. 28-3). In addition, patients might manifest a photodistributed poikiloderma

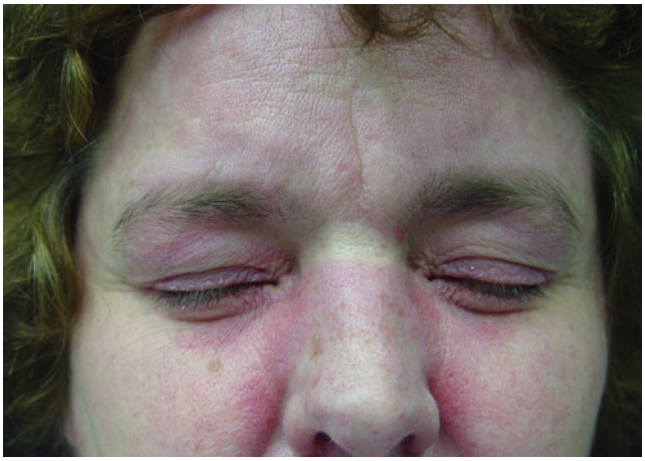


Figure 28-2 Heliotrope eruption of dermatomyositis.

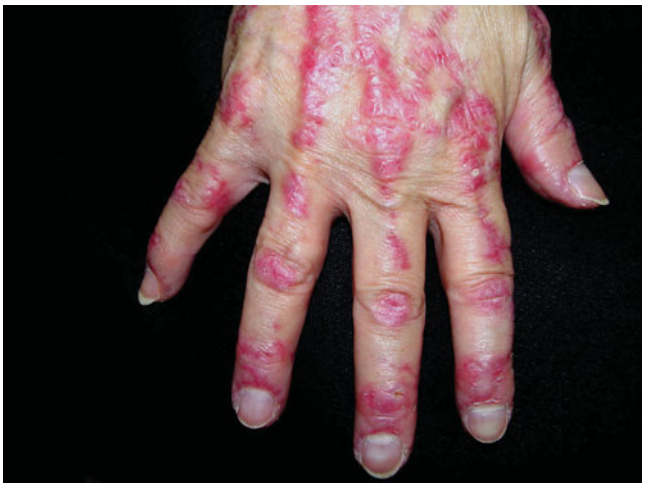


Figure 28-3 Gottron's papules in dermatomyositis: Erythematous to violaceous lesions are most prominent over the joints. In addition, this patient demonstrates cuticular and periungual changes that are frequent in dermatomyositis.

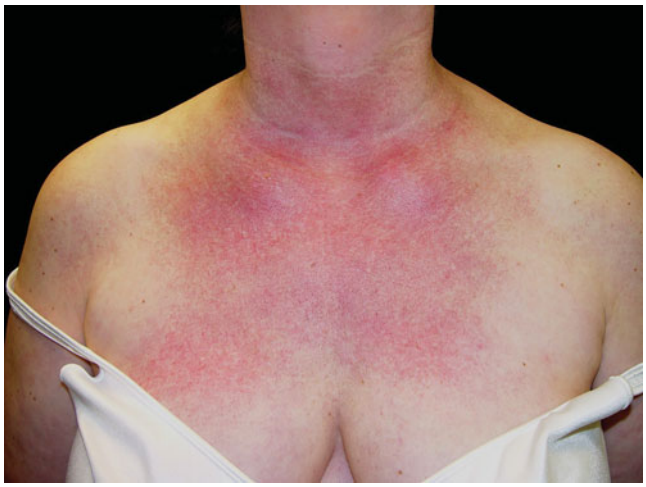


Figure 28-4 Photodistributed poikiloderma in a patient with dermatomyositis.

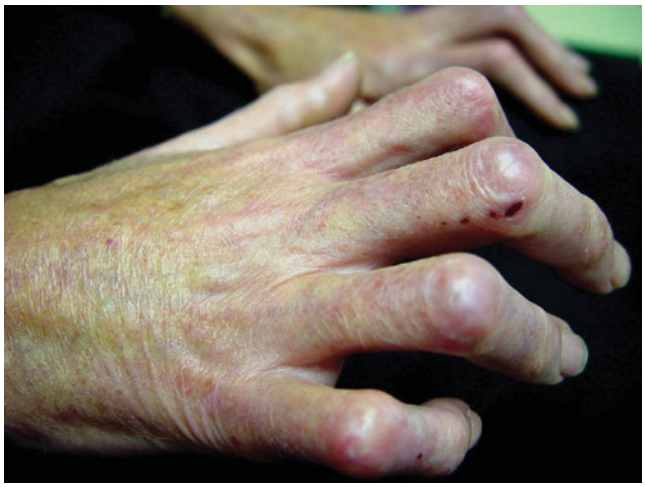


Figure 28-5 Acrosclerosis characterized by marked contractures and sclerodactyly.

(Fig. 28-4), nail fold changes, and an erythematous to violaceous scaly alopecia. Patients with dermatomyositis frequently complain of marked itching. Patients with dermatomyositis may also have other systemic manifestations, including arthritis, esophageal disease, and cardiopulmonary disease. Some patients with dermatomyositis have a malignancy. Others with the characteristic cutaneous lesions of DM are not weak and do not have an increase in muscle-derived enzymes. These patients are said to have amyopathic dermatomyositis.

Pulmonary disease occurs in dermatomyositis and polymyositis (PM) in approximately 15 to 65 percent of patients. Interstitial pneumonitis is a primary process in DM/PM. Kang et al. have demonstrated that interstitial lung disease also occurs in patients with amyopathic dermatomyositis; in this subset of patients survival is poor. Pulmonary involvement is more frequent in patients with esophageal dysfunction. Lung disease may also occur as a direct complication of the muscle disease, such as hypoventilation or aspiration in patients with dysphagia, or may be a result of treatment, such as opportunistic infections or drug-induced hypersensitivity pneumonitis. In a retrospective review of 70 patients with myositis-associated interstitial lung disease seen at the Mayo Clinic between 1990 and 1998, most presented with either symptoms of lung disease or symptoms of myositis alone; in only 15 did the involvement occur simultaneously. The lung disease was originally felt to be a pneumonitis that was antibiotic resistant. Biopsy of the lung revealed non-specific interstitial pneumonitis or diffuse alveolar damage in a majority of those who were biopsied. Only two patients had bronchiolitis obliterans organizing pneumonia (BOOP). It is unclear how many of the patients had dermatomyositis; perhaps between 8 and 12. Therapy included corticosteroids with or without an immunosuppressive agent. However, the prognosis is poorer for these patients than for unselected patients with myositis, as demonstrated by a 5-year survival of 60.4 percent. Patients with Jo-1 antibodies (19 of 50 who were tested) had roughly the same features and prognosis as those who did not have these antibodies.

Scleroderma

Scleroderma refers to hard skin. This process may be localized to the skin or may be part of a systemic disease. Localized scleroderma may occur as limited plaques of morphea, generalized morphea, deep morphea, or linear scleroderma. Despite the fact that the disease occurs primarily on the skin, in rare instances pulmonary disease in the form of interstitial pneumonitis may complicate the course of the disease.

There are two principal forms of progressive systemic sclerosis (PSS): limited scleroderma (acrosclerosis) and diffuse scleroderma. Acrosclerosis is the more common of the two, and is characterized by sclerosis of the skin of the fingers (sclerodactyly) (Fig. 28-5) and Raynaud's phenomenon (Fig. 28-6). A variant known as the CREST syndrome includes esophageal dysfunction, telangiectasia, and calcinosis. In contrast, patients with diffuse scleroderma have widespread sclerosis beyond the acral areas of sclerodactyly. The prognosis for diffuse scleroderma is much worse than for acrosclerosis. Both types of scleroderma are often preceded by Raynaud's phenomenon, diffuse arthralgias, or arthritis. The skin manifestations begin with transient, recurrent swelling of the hands and progress to tapered fingers with shiny, hidebound skin (sclerodactyly). The feet, chest, face, and scalp are often involved in the sclerotic process. In time, the skin becomes taut, leading to contractures of the large and small joints that culminate in a claw-like deformity of the hand. A variety of pigmentary disturbances may occur in scleroderma, including generalized hyperpigmentation that resembles adrenal insufficiency, focal hyperpigmentation, and hypopigmentation, and areas of perifollicular pigmentation that resemble vitiligo (Fig. 28-7). Raynaud's phenomenon leads to small pitted scars at the fingertips or frank ulceration, with or without gangrene of the fingertips, toes, knuckles, and ankles, especially the malleoli.

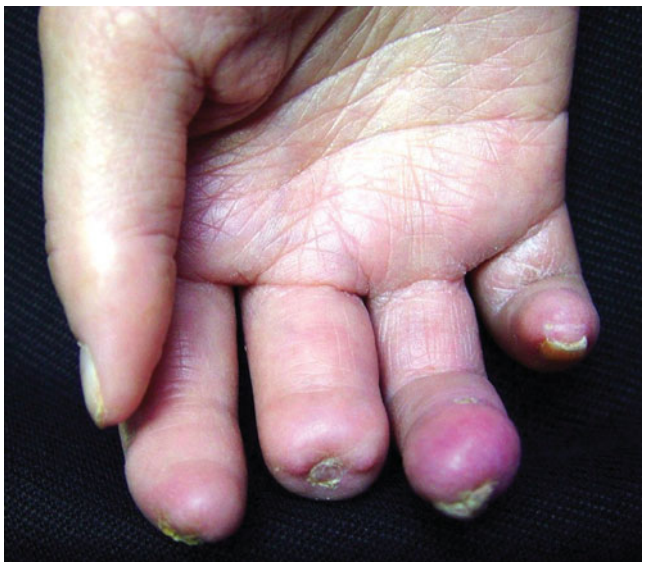


Figure 28-6 Raynaud's phenomenon in this patient was so severe that autoamputation of the distal digits occurred.

The face often undergoes distinctive changes, leading to a fixed stare and inability to wrinkle the forehead. As the facial tissues shrink, the nose becomes pinched, the cheeks sunken, the mouth narrows, and the lips thin. In diffuse scleroderma, cutaneous sclerosis, accompanied by a yellowish-brown hue, spreads from the chest to the head and extremities. Sharply delineated, broad telangiectatic macules appear on the face, buccal mucosa, lips, and hands.

PSS is associated with interstitial pneumonitis. This is more common in patients with diffuse disease than in patients with limited disease. Pulmonary hypertension has been reported to occur in patients with CREST syndrome.

Treatments for the cutaneous disease are multiple, but few have been tested in double-blind, randomized trials. Raynaud's phenomenon is treated by avoidance of exposure to cold, and with calcium channel-blocking agents such as nifedipine, angiotensin-2 receptor antagonists such as lorsartan and most recently with phosphodiesterase type 5 inhibitors such as sildenafil or tadalafil. Ulcerations from scleroderma might be treated with the endothelin receptor antagonist bosentan. Localized scleroderma (morphea) might be treated with topical application of superpotent corticosteroids or calcipotriene. Systemic therapy with methotrexate seems promising in patients with progressive skin disease, although the therapy of systemic sclerosis is beyond the scope of this chapter. Over time the sclerosis that involves the skin seems to improve naturally; therefore, studies that suggest benefit based on improvement of the cutaneous disease should be interpreted cautiously.

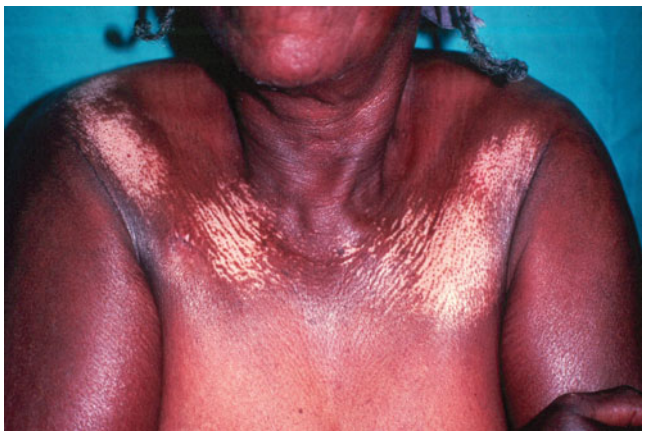


Figure 28-7 Vitiligo-like dyspigmentation associated with progressive systemic sclerosis.

INFECTIONS

Blastomycosis

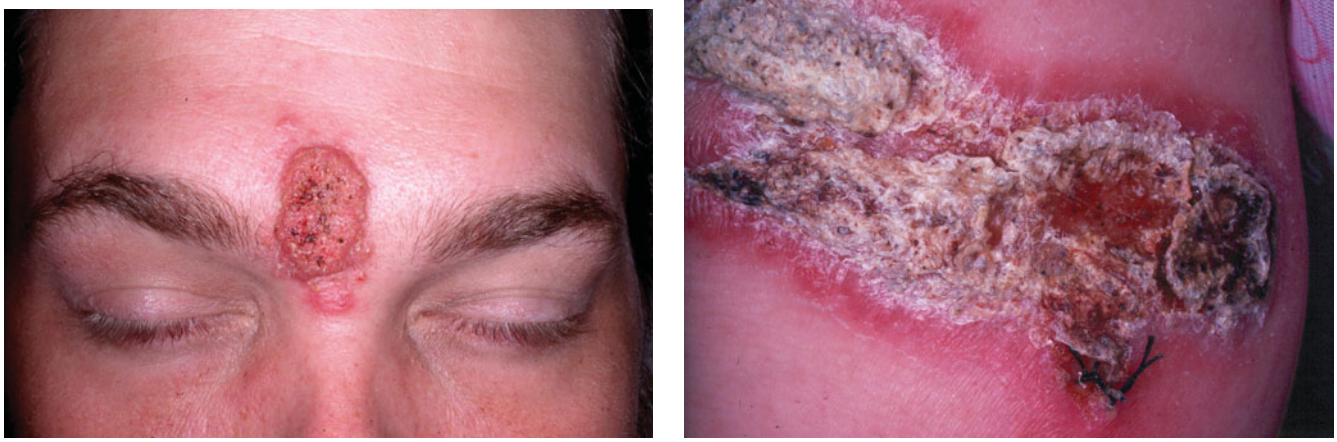
Skin lesions are as common as pulmonary lesions in patients with blastomycosis. Cutaneous disease usually represents dissemination from a pulmonary focus that is often small and may be inapparent. The typical presentation is as a solitary nodule or multiple papules or nodules on the face, wrists, hands, or feet, which subsequently ulcerate and discharge pus (Fig. 28-8). The lesions grow eccentrically at the periphery and atrophy centrally over a period of months, eventually forming an arciform or serpiginous contour with sharply elevated and verrucous borders. Miliary abscesses occur along the borders of the lesions. In addition to the cutaneous involvement, osteolytic lesions may occur in the bones. Patients with cutaneous blastomycosis should be treated with antifungal therapies such as itraconazole, fluconazole, ketoconazole, or amphotericin B.

Coccidioidomycosis

Coccidioidomycosis is usually manifest as a pulmonary infection. In its acute form, it is often associated with cutaneous symptoms; roughly 20 percent of patients develop erythema nodosum. Erythema nodosum is often accompanied by fever, arthritis, and eosinophilia. In patients with progressive pulmonary disease and eventual disseminated disease, the skin may be affected; subcutaneous granulomatous eruptions form and undergo necrosis and ulceration. After several months, the lesions tend to become verrucous. A third form is primary cutaneous disease, which occurs in farmers and laboratory workers as a chancriform lesion with sporotrichotic spread. This variant is extremely rare. Acute disease is often self-limiting and requires only symptomatic management; however, disseminated disease requires aggressive antifungal therapy and is associated with a poor prognosis.

Actinomycosis

The thoracic form of this disease presents as a pulmonary parenchymal process that sometimes forms multiple draining sinus tracts. Diagnosis is often difficult, but identification



A *B*

Figure 28-8 *A–B.* Blastomycosis: verrucous lesions on the face *(A)* and trunk *(B)*.

of sulfur granules in the draining exudates is helpful. Treatment with penicillin or tetracycline may eliminate the need for surgery.

Tuberculosis

Cutaneous involvement results from direct inoculation with the tubercle bacillus, via either the skin or mucous membranes or as a consequence of widespread organ involvement that begins in the respiratory tract.

When the tubercle is introduced via the skin or mucous membranes by a contaminated syringe or a wound in a previously unexposed host, a nodule usually develops at the site of injury. Within several weeks, the nodule evolves into a chancre, a well-circumscribed ulcer. Particularly if host defenses are impaired, these chancriform lesions, which are typically located on the extremities, develop associated regional lymphadenitis, followed by systemic dissemination of the organism.

A person who was previously infected with *M. tuberculosis* is apt to develop *tuberculosis verrucosa cutis* after receiving a cutaneous inoculation. The characteristic lesion in a sensitized person is a papule or a pustule, which becomes verrucous. On occasion, this disorder produces plaque-like lesions of the extremities consisting of verrucoid–indurated papules surrounded by an erythematous halo.

Lupus vulgaris is the most common form of cutaneous post-primary tuberculosis that follows inoculation or lymphatic or hematogenous spread of *M. tuberculosis.* Patients with this disorder typically present with reddish-brown plaques surrounded peripherally by yellowish nodules, especially on the neck or extremities. The skin lesions tend to spread centrifugally as the center becomes atrophic. Papillary growths also occur in the nasal, buccal, and conjunctival mucosa. Histologically, lupus vulgaris generally shows epithelioid tubercles with caseation necrosis. Chronic cutaneous eruptions tend to involute, leaving considerable scarring. Chemotherapy with the usual antituberculosis drugs is effective in treating these skin manifestations.

Disseminated miliary tuberculosis can result in macules, papules, or vesicles. In children, especially those who are debilitated, subcutaneous nodules or gummas appear, ulcerate, and eventually develop draining sinus tracts, especially in the extremities and trunk. *Scrofuloderma,* which occurs following the necrosis of cervical nodules, is associated with fistula and sinus tract formation in the overlying cutaneous tissues.

Tuberculids are skin lesions that are considered to represent either a hypersensitivity reaction to *M. tuberculosis* or an embolic response to atypical *Mycobacteria.* Erythema nodosum also occurs in association with primary tuberculosis.

NEOPLASTIC DISORDERS

Kaposi's Sarcoma

Early in the epidemic of HIV infection, the incidence of Kaposi's sarcoma (KS) increased. However, since the advent of HAART therapy, KS again became less common. KS can occur in any immune-suppressed individual whether the immune dysfunction is due to HIV infection, age, or iatrogenic immunosuppression in transplant recipients. Human herpesvirus-8 (HHV-8) has been identified and linked to all forms of KS. In addition, a recent report has documented that HHV-8 viremia is associated with progression on KS in both classic and endemic forms. In the elderly population, KS has an indolent course and occurs primarily on the lower extremities. At the outset, the lesions are dark-blue, purplish, or reddish papules, macules, and nodules (Fig. 28-9). After months to years, plaques evolve in association with thickening of the skin from midtibia to ankle and lymphedema. In patients with immune dysfunction, including AIDS, KS is more aggressive and is often widespread in its cutaneous manifestations.

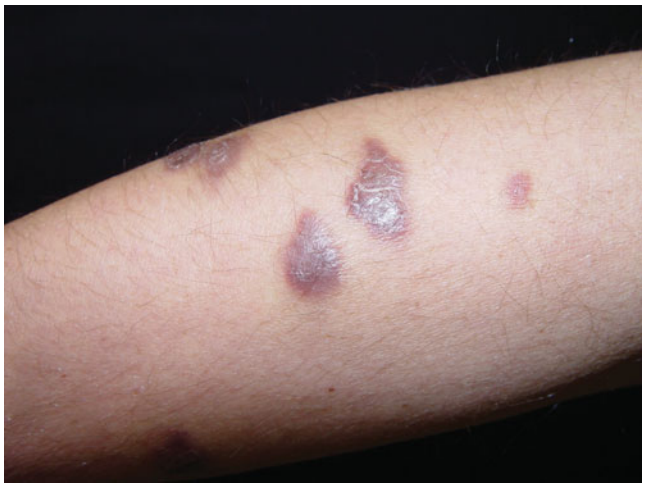


Figure 28-9 Kaposi's sarcoma in an HIV-positive patient.

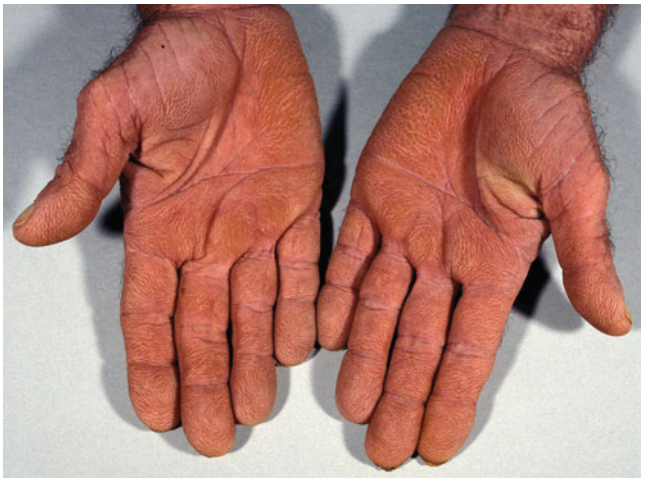


Figure 28-10 Tripe palms. *(Courtesy of Dr. Jon Dyer.)*

The respiratory tract is second only to the gastrointestinal tract in frequency of systemic involvement. Tumors may involve the larynx, trachea, bronchi, pulmonary parenchyma, and pleura. Accordingly, local manifestations of respiratory tract involvement range from hoarseness, signs of airway obstruction, cough, and hemoptysis, to dyspnea. When the parenchyma of the lung is affected, chest radiographs usually show many small nodules; occasionally, parenchymal infiltration of the lung is massive. On bronchoscopic examination, bronchial and tracheal lesions appear as small bluish nodules. Bloody pleural effusions are rare.

Treatment of KS associated with immune suppression involves correction of the dysfunction by discontinuing immunosuppressive drugs when feasible or reconstitution of immune function in the HIV-infected individual. Local therapies for skin lesions include topical application of alitretinoin gel, liquid nitrogen cryotherapy, local irradiation, intralesional interferon, systemic interferon-α2a, or systemic chemotherapy. Liposomal doxorubicin or paclitaxel infusions are reserved for patients with extensive skin disease or systemic disease.

Lung Cancer and the Skin

Several paraneoplastic syndromes may occur in patients with lung cancers. In most instances the dermatosis is not specific for lung cancer; other sites may be involved. The following are some of the more ominous manifestations of potential pulmonary malignancy.

Tripe palms is a paraneoplastic condition that is manifest as rugose thickening of the palms and occasionally the soles (Fig. 28-10). Patients often have coexistent acanthosis nigricans (AN) and sometimes the sign of Leser-Trélat. Patients with tripe palms and AN usually have adenocarcinomas of the gastrointestinal tract; however, when tripe palms occurs in the absence of AN, patients often have squamous cell carcinoma of the lung. There is no known treatment for the cutaneous changes other than removal of the tumor.

Patients with *Bazex syndrome (acrokeratosis paraneoplastica)* develop an erythematous to violaceous psoriasiform eruption primarily on acral surfaces (Fig. 28-11). The ears, nose, cheeks, hands, feet, and knees are most often affected, but the nails may become dystrophic and the palms and soles may develop a keratoderma in later stages of the disease. The disorder may develop in stages, and is associated primarily with carcinomas of the upper respiratory and digestive tracts (larynx, pharynx, trachea, bronchus, and/or upper esophagus); the malignancy is often detected concurrently. If the tumor is effectively treated the eruption may resolve, but may return with tumor recurrence. There is no known effective treatment for the cutaneous eruption, although corticosteroids and keratolytic agents have been used.

Ectopic ACTH-producing tumors cause many of the typical signs and symptoms of Cushing's syndrome. Intense hyperpigmentation, present in only 6 to 10 percent of patients with Cushing's disease, is especially common in association with ectopic ACTH production and should alert the clinician to the possibility of a hormone-secreting tumor. Although

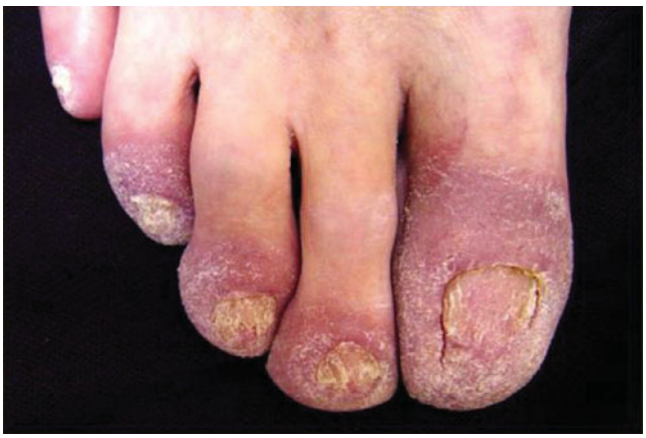


Figure 28-11 Acrokeratosis paraneoplastica (Bazex's syndrome). This patient was thought to have psoriasis prior to the diagnosis of a squamous cell carcinoma of the tonsillar pillar.

the cause of the hyperpigmentation is unclear, it may be related to tumor production of the peptide β-lipotropin, which contains within its sequence of 91 amino acids the 22–amino acid sequence of β-MSH. A myasthenia gravis–like syndrome, including profound proximal muscle weakness, may be a striking clinical feature and may reflect either underlying hypokalemia or polymyositis. Oat cell carcinoma of the lung is the tumor most often associated with ectopic ACTH production, although other malignancies have been reported.

The *carcinoid syndrome* is a second example of a hormonal syndrome associated with a nonendocrine tumor. The disorder is probably most often caused by the release of the enzyme kallikrein from tumor cells with subsequent conversion of kininogen to vasoactive kinin peptides, including bradykinin; in addition, increased blood levels of histamine may be important in the rare metastatic gastric carcinoid. The most striking cutaneous manifestations are episodes of flushing, initially lasting 10 to 30 minutes and involving only the upper half of the body; as the flush resolves, gyrate and serpiginous patterns may be noted. With successive attacks more extensive areas may be affected and the redness takes on a cyanotic quality, eventually leading to a more permanent facial cyanotic flush with associated telangiectasia, resembling rosacea. Persistent edema and erythema of the face may result in leonine facies. A pellagra-like picture, which has been noted in some patients, may be due to abnormal tryptophan metabolism. Systemic symptoms associated with the cutaneous flushing include abdominal pain with explosive watery diarrhea, shortness of breath, and hypertension.

Carcinoid tumors are usually found in the appendix or small intestine; extraintestinal carcinoid tumors may arise in the bile ducts, pancreas, stomach, ovaries, or bronchi. The carcinoid syndrome occurs primarily when an intestinal carcinoid tumor metastasizes to the liver or with extraintestinal tumors; flushing attacks can be provoked by palpation of hepatic or abdominal metastases or by alcohol ingestion, enemas, emotional stress, or sudden changes in body temperature. When the syndrome is associated with bronchial adenomas of the carcinoid variety, the flushing is more prolonged and often associated with fever, marked anxiety, disorientation, sweating, salivation, and lacrimation.

Migratory superficial thrombophlebitis and multiple deep venous thrombosis have been noted in cancer patients, especially those with tumors arising in the pancreas, lung, stomach, prostate, or hematopoietic system. The neck, chest, abdominal wall, pelvis, and limbs are most frequently affected.

Lymphomatoid Granulomatosis

The skin is the most commonly affected extrapulmonary site in lymphomatoid granulomatosis, occurring in 40 to 50 percent of patients. In 10 to 25 percent of patients, the skin lesions are the first clinical evidence of the disorder; the skin lesions precede involvement of the lungs by 2 weeks to 9 years. Because of the frequent occurrence of skin lesions, ease of biopsying the skin, and characteristic histology of these disease, careful dermatologic examination should be carried out in patients suspected of having lymphomatoid granulomatosis.

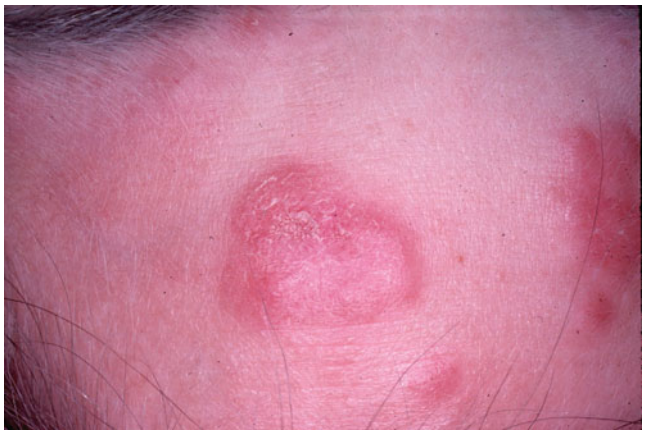


Figure 28-12 Lymphomatoid granulomatosis. This young woman developed the acute onset of multiple erythematous plaques on her face, accompanied by dyspnea and fever. She died within a month from pulmonary disease.

The characteristic cutaneous lesions in lymphomatoid granulomatosis are 1- to 4-cm erythematous-to-purplish dermal papules, or subcutaneous nodules, with or without ulceration. The lesions generally occur over the buttocks, thighs, and lower extremities (Fig. 28-12), but may occur anywhere. Healing is often accompanied by scarring and hyperpigmentation.

This histopathology of the skin lesions is similar to that of the lesions in the lungs, and is characterized by a marked angiocentric and angiodestructive lymphohistiocytic infiltrate composed predominantly of CD4-positive T cells. EBV-positive B cells are often present. This disorder is presumed to be a T-cell–rich B-cell lymphoproliferative disease.

The papules or nodules in lymphomatoid granulomatosis sometimes clear spontaneously; more often, they recur or progress. The skin lesions seem to respond to therapy with systemic corticosteroids and cyclophosphamide. Recently the use of rituximab has been associated with a favorable outcome in some patients. Localized radiation therapy has been used for some refractory skin lesions.

REACTIVE DERMATOSES

Clubbing and Hypertrophic Osteoarthropathy

Pachydermoperiostosis is a syndrome in which hypertrophic osteoarthropathy is associated with cutaneous changes of the face and extremities that are similar to those that occur in patients with acromegaly. Although this disorder is generally benign, it is occasionally associated with bronchogenic carcinoma.

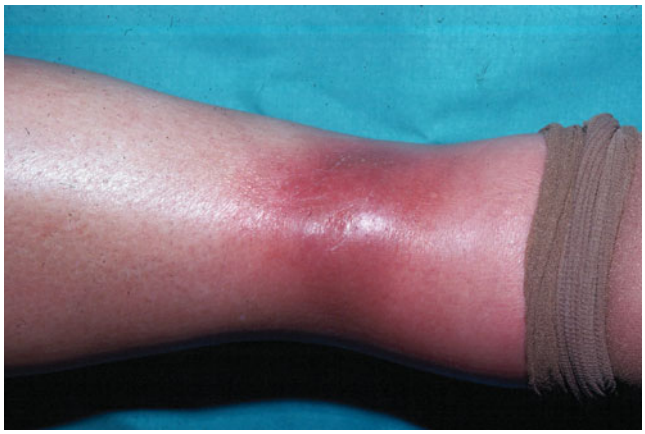


Figure 28-13 Erythema nodosum. Red tender subcutaneous nodule on the leg.

Erythema Nodosum

A relatively common process, erythema nodosum (EN) is usually acute and self-limited. The typical clinical presentation is the sudden onset of one or more, tender, erythematous nodules on the anterior legs, which are more easily palpated than visualized (Fig. 28-13). The eruption is often preceded by a prodrome of fever, malaise, and/or arthralgias. As the lesions age, they may develop an ecchymotic appearance. Over a 4- to 6-week period they eventually heal without scar formation. Ulceration of the primary process is rare. Although EN is usually an acute process, patients with chronic or recurrent disease have been described using such terms as chronic EN, EN migrans, subacute nodular migratory panniculitis (Vilanova's disease), or septal granulomatous panniculitis. Chronic or recurrent EN most commonly occurs in middle-aged women. The disease is often present for several years, and is most common on the legs.

Etiologic or associated conditions are present in about 50 percent of patients with EN. The associated conditions can be divided into three broad categories: infections, drugs, or systemic diseases (usually inflammatory disorders). The infectious agents associated with EN tend to primarily affect the respiratory or gastrointestinal tract and are most often bacterial or fungal in origin. The most common drugs are antibiotics and oral contraceptives. Pregnancy, particularly in its second trimester, is a known association, and the EN will recur with subsequent pregnancies or with the administration of oral contraceptives. EN-like lesions may occur in Behçet's disease and are accompanied by oral and genital ulcerations, pathergy, uveitis, and/or central nervous system (CNS) disease or other systemic manifestations. A specific variant of sarcoidosis associated with EN is known as Löfgren's syndrome. This is an acute, self-resolving process in which EN occurs with bilateral hilar lymphadenopathy, arthritis, and anterior uveitis. Granulomatous colitis (Crohn's disease), regional enteritis, and ulcerative colitis have been associated with EN. In patients with inflammatory bowel disease, it appears that the EN parallels the activity of the bowel disease. At least half of the cases of EN are not found to have an associated or underlying process.

The treatment of EN first involves assessment of a causative disease and its treatment. In the absence of a treatable disorder, therapy is symptomatic. Acute EN is often self-limited, thus non-toxic therapies are advised. Bed rest and leg elevation are very helpful in controlling symptoms. In patients who need to continue to be ambulatory, support stockings or tights may be helpful. Aspirin or other NSAIDs may be helpful. Sometimes, however, treatment with aspirin does not produce results prior to toxicity; therefore, oral indomethacin (25–75 mg/day) is recommended.

In patients with chronic EN or frequent recurrences, oral potassium iodide 300 to 900 mg/day has been useful in open clinical trials. When the drug is stopped or the dose is lowered the disease often relapses, only to respond again to the reinstitution of therapy. Other therapies that may be considered include oral corticosteroids, colchicine, hydroxychloroquine, or an immunosuppressive agent.

Neutrophilic Dermatoses: Sweet Syndrome and Pyoderma Gangrenosum

Sweet syndrome (Fig. 28-14) and pyoderma gangrenosum (Fig. 28-15) are distinct dermatoses, but share common associations and are often managed with similar therapies. In addition, a condition known as neutrophilic dermatosis of the dorsal hands (Fig. 28-16) often has characteristics that overlap between a superficial variant of pyoderma gangrenosum (also termed atypical pyoderma gangrenosum) and Sweet syndrome. The associated diseases include inflammatory bowel disease, rheumatoid arthritis, and myelogenous malignancy and pre-malignancy. Extracutaneous neutrophilic inflammation has been reported in multiple organs, but the most frequently reported are the lungs. The inflammatory reaction can cause infiltrates including cavitary disease. It is critical that infectious diseases be excluded with appropriate culture prior to initiating therapy with corticosteroids with or without immunosuppressive therapy.

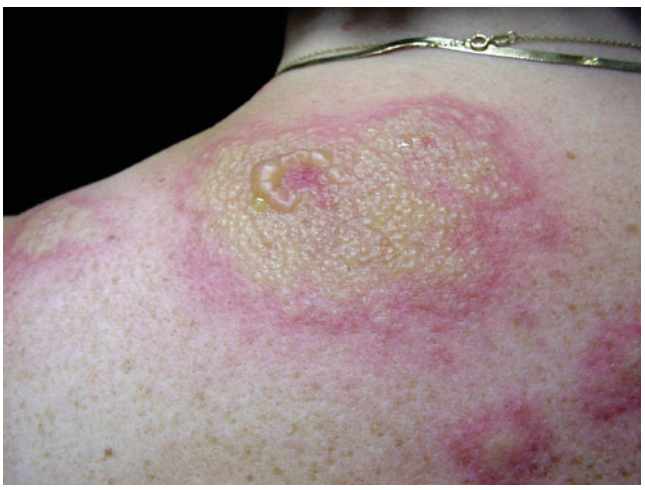


Figure 28-14 Acute febrile neutrophilic dermatosis (Sweet syndrome): erythematous plaque with what appears to be vesiculation on the surface.

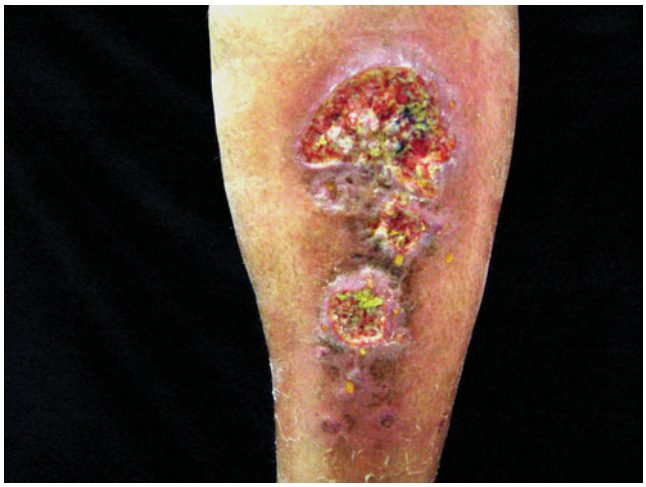


Figure 28-15 Pyoderma gangrenosum: large ulceration on the leg with a violaceous, undermined border. This patient had active Crohn's disease.

Pruritus

Pruritus is a symptom that accompanies many dermatoses, but may also accompany systemic diseases. Patients without an obvious cause for their itching require a systemic evaluation, which usually includes a chest x-ray. Causes for pruritus are not commonly found, but Hodgkin's disease and other malignancies might be uncovered during the evaluation. Effective treatment of an underlying malignancy will result in a disappearance of the pruritus.

Urticaria

Urticaria is a reactive cutaneous disease manifest by transient urticarial skin lesions. Acute urticaria is almost always due to the ingestion of a food or medication and usually subsides within several days. The presence of chronic urticaria requires a thorough evaluation and at times the pulmonary evaluation might reveal an infectious, inflammatory, or neoplastic cause for the urticaria. This happens in less than 25 percent of patients.

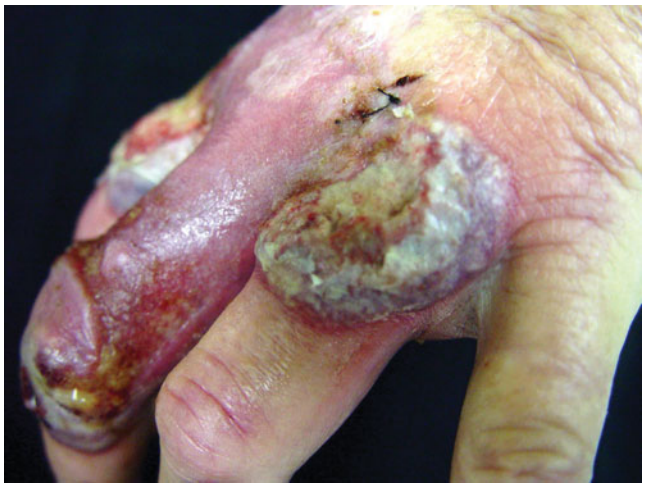


Figure 28-16 Neutrophilic dermatosis of the dorsal hands (aka atypical pyoderma gangrenosum). Such patients often have a hematologic malignancy or pre-malignant process.

Vasculitic Syndromes

Churg-Strauss Syndrome

The clinical picture of allergic rhinitis, asthma, peripheral eosinophilia, and pulmonary infiltrates concomitant with systemic vasculitis has been designated the Churg-Strauss syndrome. However, the histologic finding of necrotizing granulomas and tissue eosinophilia is not unique to this clinical syndrome. Indeed, the same histologic appearance may be seen in a wide variety of systemic diseases, including allergic granulomatosis, Wegener's granulomatosis, rheumatoid arthritis, and lymphoproliferative disease.

One or more types of skin lesions develop in 70 percent of patients with Churg-Strauss syndrome. Most common is palpable purpura of the extremities; histologically, these lesions show necrotizing vasculitis without granuloma formation. In one-third of the patients, the cutaneous lesions are nonspecific—i.e., erythematous and urticarial. In another one-third, however, the skin lesions are distinctive—i.e., tender red to violaceous, indurated nodules, measuring 0.5 to 2 cm, which develop central crusting or become infarcted. These nodules occur most often over the scalp or symmetrically over the extensor surfaces of the extremities. It is these nodules that are most likely to have the histologic picture of necrotizing granulomatous vasculitis and eosinophilic infiltration; immunofluorescence staining may show vascular deposition of fibrin and complement. The skin lesions in Churg-Strauss syndrome generally respond to systemic corticosteroids or adjuvant cytotoxic therapy.

Wegener's Granulomatosis

About 45 percent of patients with Wegener's granulomatosis have cutaneous manifestations, most often small vessel vasculitis. Occasionally, biopsy of the skin lesions reveals a granulomatous vasculitis. In addition, the presence of cutaneous disease is usually indicative of active systemic involvement; therefore, such patients should be carefully evaluated and aggressively treated.

Polyarteritis Nodosa

Patients with polyarteritis nodosa frequently have cutaneous lesions. The skin disease may represent small vessel vasculitis as in Wegener's granulomatosis or may represent medium-sized vessel involvement. In the latter case the manifestation is livedo reticularis or ulceration. Treatment of polyarteritis should include corticosteroids along with an immunosuppressive agent.

Urticarial Vasculitis

Urticarial lesions can occur in patients as a manifestation of small vessel vasculitis. McDuffie et al. first described urticarial vasculitis in four patients with recurrent attacks of erythematous urticarial and hemorrhagic skin lesions associated with synovitis and, sometimes, abdominal distress. Their patients

did not have lupus erythematosus or paraproteinemia, but did have hypocomplementemia; two had nephritis.

Urticarial lesions may also be an early clinical manifestation of lesions that become typical palpable purpura. The spectrum of urticarial vasculitis has also grown, in recent years, to include the presence of lung disease characterized by asthma or obstructive lung disease. Patients with hypocomplementemic urticarial vasculitis often have or develop obstructive pulmonary disease, whereas most patients with normal complement levels, chronic urticaria and vasculitis have little or no systemic involvement.

The burning or itching of the lesions most often irritates patients with urticarial vasculitis. The patient should be first treated with antihistamines. Histamine 1 receptor (H_1) antagonists can be combined with H_2 antagonists, but the doses required often result in drowsiness. In some cases, the use of doxepin hydrochloride, which has effects on both H_1 and H_2 receptors, is effective. Lastly, the newer, less-sedating agent, cetirizine, or non-sedating agents such as fexofenadine or loratadine, can be used during waking hours and as a soporific agent before retiring.

Patients are also often treated with corticosteroids and/or immunosuppressive agents. Although these agents are useful in controlling the cutaneous lesions, they do not seem to have any impact of the progression of pulmonary disease.

Toxic Epidermal Necrolysis

Toxic epidermal necrolysis (TEN) is one of the true dermatologic emergencies. This disorder is most often due to drug administration and develops acutely. Patients often have a prodrome followed shortly by widespread skin involvement with a superficial blistering (Fig. 28-17). Multiple mucosal surfaces are affected (Fig. 28-18). Prognosis is dependent upon the extent of the blistering, age, and the presence of co-morbid diseases. Lung involvement is unusual, but these patients often are treated in an intensive care unit or burn unit and frequently end up on a ventilator. Infections are a frequent complication and can result in death. Pulmonary infection is one of the more frequent sites. Therapy of TEN is controversial, but in the United States treatment with high-dose intravenous immune globulin (0.75 g/kg per day for 4 days) has become a "standard" therapy. The use of corticosteroids or other immunosuppressive agents is controversial. Prophylactic antibiotics are contraindicated, but prompt therapy of an identified infection should occur.

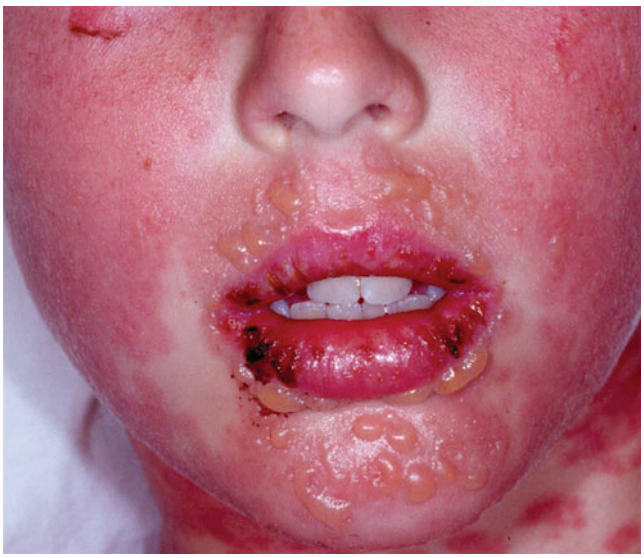


Figure 28-18 Mucosal lesions of Stevens-Johnson syndrome/toxic epidermal necrolysis.

Yellow Nail Syndrome

Thick, yellow discoloration of all 20 nails occurs in the yellow nail syndrome (Fig. 28-19). The nails are thick, but there is no onycholysis and no subungual debris, allowing clinical differentiation from onychomycosis. The nails are not clubbed and there are no underlying bony abnormalities. This disorder is almost always associated with pulmonary abnormalities, including pleural effusions, lymphoma, and sleep apnea. There is no known therapy for the nail changes in this disorder, but improvement of the associated pulmonary disease can result in improvement of the nails.

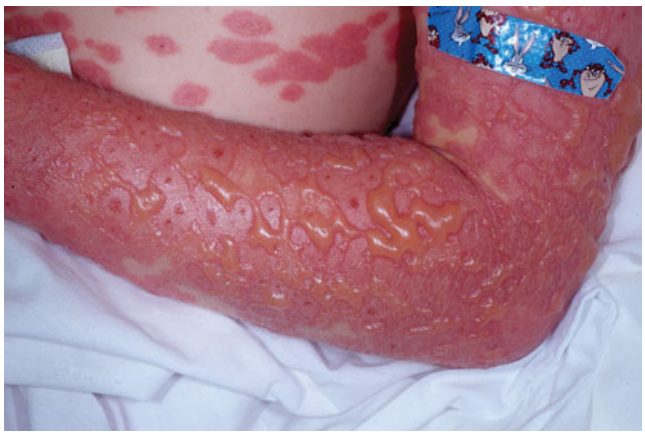


Figure 28-17 Stevens-Johnson syndrome/toxic epidermal necrolysis.

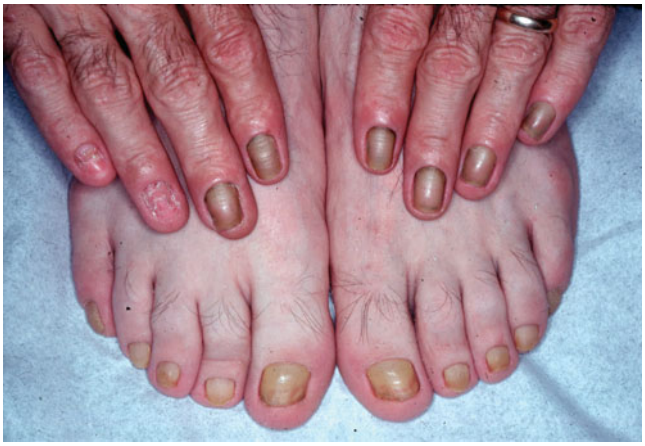


Figure 28-19 Yellow nail syndrome. All 20 nails were affected in this patient.

MISCELLANEOUS DISORDERS

Inherited Congenital and Developmental Disorders

α_1-Antitrypsin Deficiency

α_1-Antitrypsin deficiency is regularly associated with pulmonary and hepatic disease. Cutaneous manifestations may also occur in some patients with this inherited disorder and most commonly manifests as a panniculitis or rarely as a cutaneous vasculitis. Although the panniculitis is a lobular panniculitis in contrast to the septal panniculitis that is found in erythema nodosum, the clinical disease is similar except that these patients' lesions might ulcerate. Therapy with replacement of the hormone will temporarily result in control of the panniculitic lesions.

Cutis Laxa

Cutis laxa is caused by a disorder in the formation of elastin that is transmitted as a dominant hereditary trait. In children with this disorder, skinfolds of the abdomen and face are large and pendulous. The pulmonary manifestations of cutis laxa are emphysema and pulmonary artery stenosis.

Cystic Fibrosis and the Skin

Cystic fibrosis (CF) is an inherited disorder that frequently affects the lungs and results in premature death. The skin is often useful for the diagnosis of this condition, but in addition there are patients in whom skin disease is due to CF. Specifically, cutaneous vasculitis seems to be more frequent in CF patients, probably due to the frequent formation of circulating immune complexes in the CF patient. Treatment of the patient with CF with cutaneous vasculitis is similar to other patients with cutaneous vasculitis.

Ehlers-Danlos Syndrome

The most important disorder of collagen affecting the skin and lungs is Ehlers-Danlos syndrome (cutis hyperelastica), a hereditary disorder of collagen in which the skin and blood vessels are unduly elastic and fragile and the joints are hyperextensible. The skin is smooth, rubbery, and bruisable; the joints are hypermobile. Associated systemic abnormalities include megaesophagus, megacolon, dissecting aortic aneurysm, and diaphragmatic and inguinal hernias. Among the pulmonary disorders are spontaneous pneumothorax, arteriovenous fistulas, mega-trachea, and bronchial ectasia.

Birt-Hogg-Dubé Syndrome

Birt, Hogg, and Dubé described an autosomal dominant condition that was manifest by multiple facial flesh-colored papules that were characterized histologically as trichodiscomas (Fig. 28-20). These patients have been subsequently found to have frequent renal cell carcinomas, particularly oncocytomas. In addition, these patients frequently develop spontaneous pneumothorax at a young age. Although there is no known therapy for BHD patients, their recognition can lead to discovery of renal tumors prior to spread to other organs. In addition to study of the patient, family members should be examined clinically and perhaps genetically.

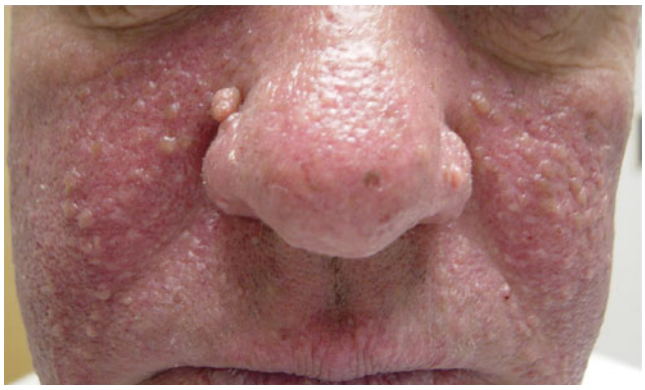


Figure 28-20 Flesh-colored central facial papules in a patient with Birt-Hogg-Dubé syndrome.

Hereditary Hemorrhagic Telangiectasia

Hereditary hemorrhagic telangiectasia (HHT), also known as Osler-Rendu-Weber syndrome, is an autosomal dominant disorder that is manifested by vascular ectasia in various organs, including the skin and mucous membranes (Fig. 28-21). HHT often is first manifest as nosebleeds. Eventually lesions affect the lips, tongue, nasal mucosa, palate, and palms. On rare occasions, patients with HHT have arteriovenous malformations of the lungs or CNS. Epistaxis, melena, and hemoptysis are common in adults. There is no known therapy for HHT at present, but if an A-V malformation is found, surgical consultation is indicated.

Nephrogenic Systemic Fibrosis

Nephrogenic systemic fibrosis is a recently recognized disorder of the skin in which a rapid onset of skin hardening (Fig. 28-22) occurs in patients with some form of renal disease. Often the onset of the fibrosis is preceded by anasarca. The cause of this disease is not known, but possibilities include vascular

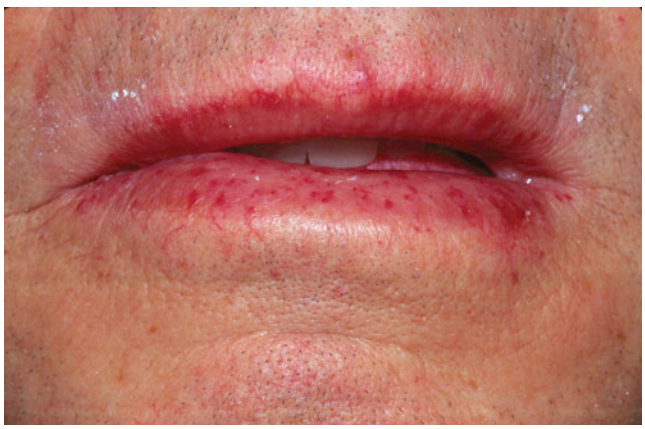


Figure 28-21 Mucosal telangiectasia in a patient with hereditary hemorrhagic telangiectasia.

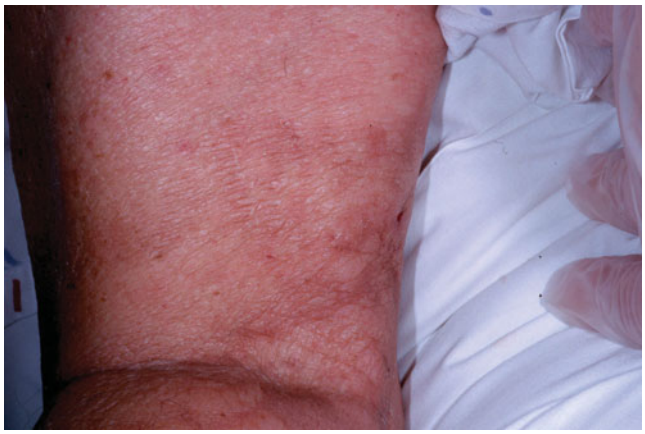


Figure 28-22 Peau 'd orange changes in a patient with nephrogenic systemic fibrosis.

thrombosis and recent surgical interventions. Recent identification of gadolinium in tissue following its use for MRI or MRA has suggested that this radiocontrast agent may be implicated in the etiology of nephrogenic systemic fibrosis. Initial descriptions of the disease focused on the cutaneous findings, but it has become evident that patients may also have systemic fibrosis, including pulmonary fibrosis. There is no known effective therapy for these patients, but with time the fibrosis does seem to lessen.

Paraneoplastic Pemphigus

Paraneoplastic pemphigus (PNP) is a severe mucocutaneous disease with a specific pattern of immunofluorescence. It is a rare vesiculobullous disorder. Patients with PNP often present with severe oral erosions and polymorphous cutaneous lesions, including targetoid lesions, bullae, and erosions (Fig. 28-23). Patients with PNP often have a lymphoproliferative disorder with a high prevalence of Castleman's disease. In addition to the mucocutaneous disease, these patients frequently have bronchiolitis obliterans. There is no therapy for PNP that is uniformly effective; however, if a coexisting tumor is removed, the disease will remit. Suggested therapies include high-dose daily corticosteroids, cyclophosphamide, and rituximab.

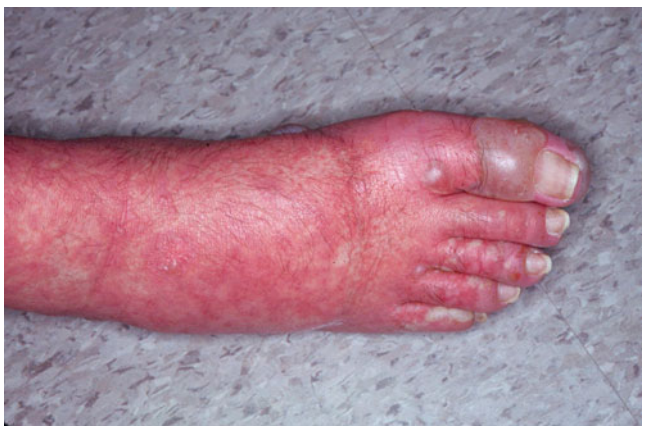


Figure 28-23 Paraneoplastic pemphigus.

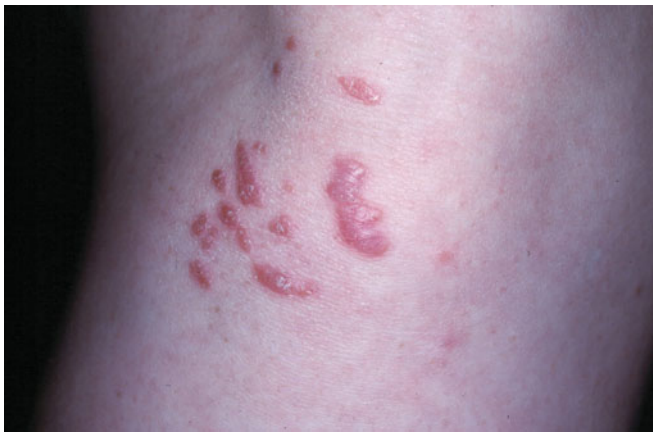
Sarcoidosis

Sarcoidosis is a multisystem disorder with protean manifestations. The pulmonary manifestations and other aspects of the disease are well covered elsewhere in this text and we focus solely on the cutaneous disease. Skin lesions occur in about 25 percent of patients with sarcoidosis and may be "histopathologically specific" or "non-specific." The most common nonspecific manifestation is erythema nodosum. Histopathologically, specific lesions are manifestations of granulomatous inflammation in the skin. Although associated with chronic disease in the past, it now appears that there are many patients with self-limiting granulomatous disease of the skin. Skin lesions are most commonly papules, plaques, or nodules. Rarely is there a great deal of surface change, and ulceration is uncommon. Several clinical variants are worth noting. Papular lesions on the knees (Fig. 28-24) are commonly associated with EN and are self-limiting. Lesions on the nasal ala (Fig. 28-25) are frequently associated with sarcoidosis of the upper respiratory tract (SURT) and a thorough otolaryngologic evaluation is indicated. Erythematous to violaceous plaques on the face are known as lupus pernio (Fig. 28-26) and residual scarring is possible. In addition, these patients tend to have accompanying chronic disease in the lungs. Finally, lesions of sarcoidosis frequently occur within scars or tattoos (Fig. 28-27). In this circumstance it may be difficult to distinguish sarcoidosis from foreign body granulomas.

Management of cutaneous sarcoidosis is often challenging. Patients with chronic disease are often treated with systemic corticosteroids, but at times these are ineffective or are associated with toxicity. Oral tetracyclines have been used in open-label studies and are at times effective. Oral hydroxychloroquine 200 to 400 mg/day (less than 6.5 mg/kg per day based on ideal body weight) has been effective for cutaneous disease in small case series, but when the therapy is discontinued the disease often relapses. Methotrexate is the most commonly reported immunosuppressive agent, although azathioprine, mycophenolate mofetil and other agents have also been utilized. With methotrexate in doses of 15 to 25 mg per week, about 80 percent of patients with cutaneous lesions respond; however, chronic therapy in sarcoidosis patients has been associated with hepatic abnormalities that limit the use of methotrexate. Anti-tumor necrosis factor-α therapy with thalidomide or biologic agents has been reported to be effective. Infliximab is regularly effective; the use of etanercept has rarely resulted in improvement and the use of adalimumab has only been reported in several individual cases.

Tuberous Sclerosis

Tuberous sclerosis is a hereditary disorder that is characterized by mental retardation, epilepsy, and skin lesions, including adenoma sebaceum, Shagreen patches, and ash leaf macules. Also seen as part of this disorder are retinal phakomas, calcification of basal ganglia, and ungual fibromas.



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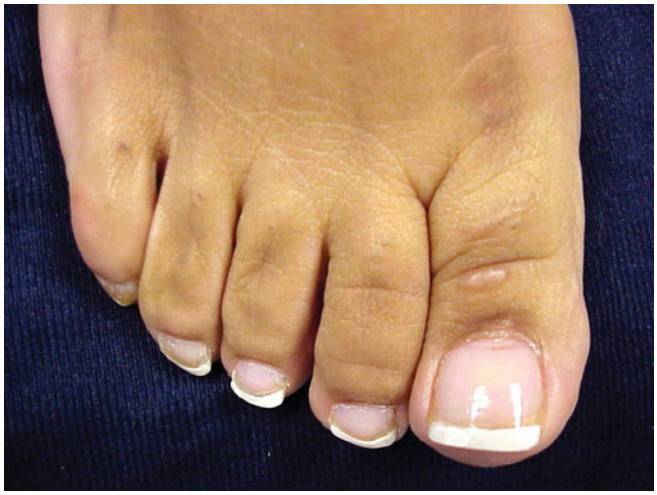

B

Figure 28-24 *A–B*. Sarcoidosis: acute onset of papular lesions *(A)* on the knees and feet *(B)* were associated with a self-limited course in these patients.

Approximately 9 percent of patients with visceral tuberous sclerosis have pulmonary manifestations; some of the pulmonary lesions are cystic and may be associated with recurrent spontaneous pneumothorax and hamartomas. Certain poorly understood diseases, such as fibrocystic pulmonary dysplasia, may represent a forme fruste of tuberous sclerosis.

TOXICITY OF MEDICATIONS

Cutaneous Toxicity from Therapies for Pulmonary Disease

Epidermal Growth Factor Receptor Inhibitors

Epidermal growth factor receptor inhibitors are now being used for the treatment of solid tumors, including lung cancers.

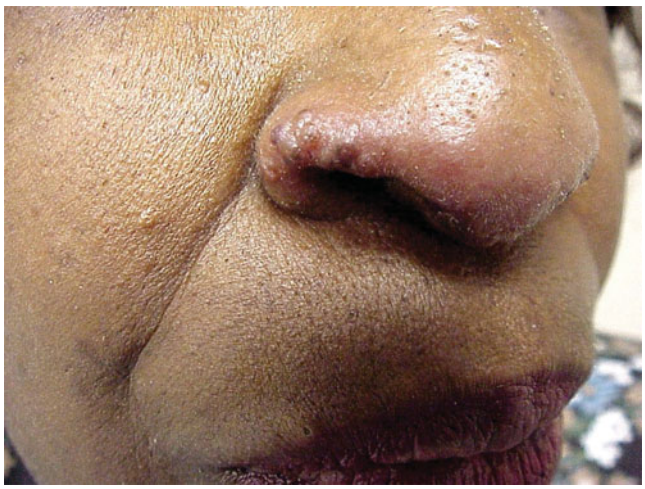

Figure 28-25 Sarcoidosis affecting the nasal ala is regularly associated with granulomatous disease in the upper respiratory tract (SURT).

These agents are regularly associated with the development of an acneiform eruption on the face. The presence and severity of this eruption appear to correlate with survival. A variety of therapies have been suggested for prevention or treatment of this eruption, including oral tetracycline, oral isotretinoin, topical corticosteroids, and topical sulfacetamide. None of these therapies has been regularly reported to be effective.

Consequences of Immunosuppressive Therapy in Lung Transplant Recipients

Patients who are organ recipients are regularly treated with corticosteroids in combination with various immunosuppressive agents. Therapy with corticosteroids has well-known dermatologic consequences, including striae, steroid-acne, and/or folliculitis, and an increased risk of superficial fungal infections. The intensity of the immunosuppression and duration of therapy are associated with increasing risk of cutaneous malignancy, specifically non-melanoma skin cancer (NMSC) and Kaposi's sarcoma. Squamous cell carcinoma is

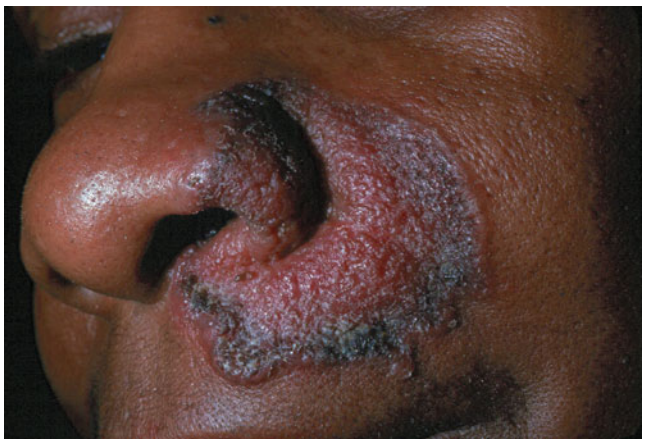

Figure 28-26 Lupus pernio (sarcoidosis).

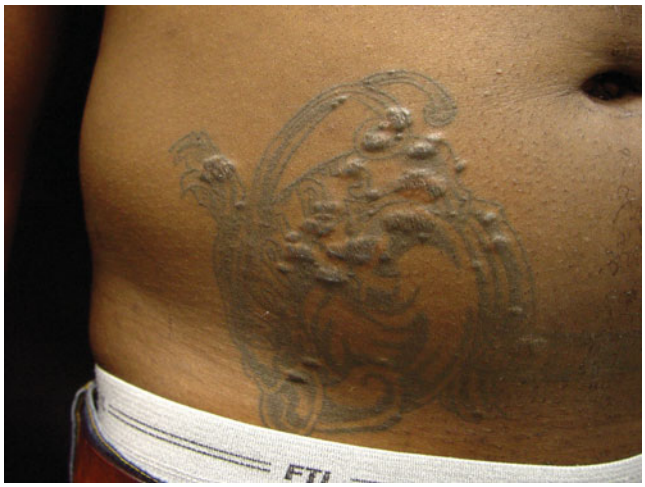

Figure 28-27 Sarcoidosis within tattoos.

overrepresented in comparison to basal cell carcinoma; in addition the tumors appear to be more aggressive in the presence of immunosuppressive therapy. Therefore, in patients who develop multiple squamous cell carcinomas immunosuppressive therapy should be less intense if possible or substitution of cyclosporin and azathioprine by other "less" toxic agents should be considered. In addition, the use of oral retinoids such as acitretin might lessen the frequency of NMSC.

Pulmonary Toxicity from Dermatologic Therapies

Methotrexate

Methotrexate is a common systemic therapy for patients with psoriasis. In addition, it is regularly used for cutaneous dermatomyositis, cutaneous sarcoidosis, and cutaneous lymphomas. Pulmonary toxicity is not common and is believed to be idiosyncratic. Most of the dermatologic use is for psoriasis vulgaris and psoriatic arthritis; fortunately, pulmonary disease appears to be quite rare in these patients. No specific monitoring is recommended.

Tumor Necrosis Factor-α Inhibitors

There are three available tumor necrosis factor (TNF) antagonists: infliximab, etanercept, and adalimumab. These therapies have revolutionized our approach to psoriasis, psoriatic arthritis, inflammatory bowel disease, and rheumatoid arthritis. All have been associated with an increased risk of infection, particularly pneumonitis. In addition, these agents may rarely cause or exacerbate cardiac failure.

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29

Pulmonary-Systemic Interactions

Alfred P. Fishman

The lungs are incorporated into the body in such a way as to serve a variety of functions other than external gas exchange. These include hemodynamic, metabolic, endocrine, and immunologic activities. Inadequacy or failure on the part of any of these functions can have serious systemic repercussions. Moreover, as part of the total body fabric, the lungs share in diverse pathological processes, such as collagen vascular diseases, and inherit susceptibility to others, such as cystic fibrosis, in which a generalized defect in ion transport across epithelial surfaces affects the liver, gastrointestinal tract, and pancreas, as well as the lungs.

Because of its strategic location between the two ventricles and as the recipient of the entire output of the right ventricle, the pulmonary circulation is uniquely situated to transmit the products of pulmonary metabolism and injury to systemic organs and tissues. Its position at the exit of the right ventricle also enables the pulmonary vascular bed to serve as a filter for particulate matter arising in the systemic venous circulation (e.g., thromboemboli). Finally, the arrangement in series of the gastrointestinal tract, liver, and lungs enables interdependence in the handling of biologically active materials that release in health (Fig. 29-1) and disease (e.g., hepatic cirrhosis, gastrointestinal disorders, and splenic dysfunctions).

The diversity of cells that constitute the pulmonary parenchyma, the vasculature, and the airways, coupled with the ready access of blood constituents to the structures in the lungs, affords great opportunity for the lungs to influence systemic organs and vice versa. For example, the endothelial cells that line the enormous expanse of pulmonary vessels can release vasodilator or vasoconstrictor substances, anticoagulants, and a wide variety of enzymes and cytokines into the circulation. Mast cells in the vicinity of the pulmonary vessels can release a variety of substances that can influence both intrapulmonary and extrapulmonary vessels and structures. Chloride-secreting cells, not only in the airways but also in other glandular structures (e.g., sweat glands, pancreas), can suffer inherited defects that disturb different kinds of bodily functions. Immunologically competent cells in the lungs that are part of natural body defenses can open the way for serious systemic infections if their guard is dropped or if environmental pollutants are overwhelming.

The large pulmonary blood flow and the brief pulmonary transit time ensure virtually instantaneous exposure to biologically active substances originating in the lungs. Among these substances are hormones (e.g., angiotensin II), mediators (e.g., nitric oxide), and neurotransmitters. Disease,

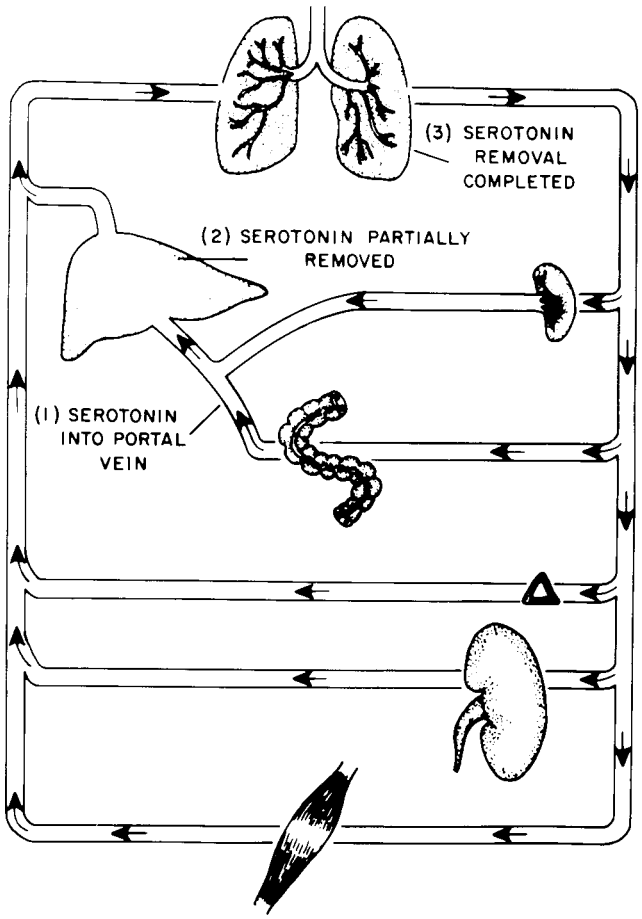


Figure 29-1 The sequential processing of serotonin.

such as pneumonia, can promote the release of inflammatory and immunologic mediators from both the resident cells and the migratory blood cells (e.g., leukocytes).

Another access route to the lungs is the bronchial circulation. This systemic blood supply can undergo remarkable proliferation in some diseases (e.g., bronchiectasis), but remain small in others (e.g., primary carcinoma of the lung). As is noted below, proliferation of the bronchial circulation often accompanies clubbing of the digits.

THE LUNG AS AN ENDOCRINE ORGAN

In addition to its roles in gas exchange and water exchange, the lung is active metabolically. The metabolic processes entail uptake, storage, and elaboration of substances, many of which (such as nitric oxide) function locally, whereas others, such as angiotensin II (Fig. 29-2), exert their effects on remote tissues and organs (i.e., they enter the bloodstream and influence systemic tissues and organs).

In addition to such chemical messengers, the lungs secrete amines and peptides, whose functions are far less well defined. These messengers are released by a system of epithelial cells (i.e., *pulmonary endocrine cells*) which are part of a widespread system that is contained within other organs as well as within the lungs. The so-called pulmonary endocrine cells have attracted the attention of clinicians more because of their potential for undergoing neoplastic transformation than because of recognizable biologic functions.

The Pulmonary Endocrine System

Pulmonary endocrine cells, or *pulmonary neuroendocrine cells*, have been found in a wide variety of species, ranging from the African lungfish to humans. These cells can be found in the respiratory epithelium from trachea to alveolar walls, where they may appear as single cells, as clusters associated with nerve terminals (*neuroepithelial bodies*), or in mounds (*tumorlets*). The typical pulmonary endocrine cell is usually argyrophilic and is characterized ultrastructurally by a dense-core vesicle surrounded by clear scant cytoplasm; within the core are granular chromatin bodies and prominent nucleoli. Histochemistry and immunochemistry have displayed a large spectrum of biologically active mediators, including serotonin, calcitonin, substance P, cholecystokinin, somatostatin, calcitonin gene-related peptide, and bombesinlike peptides. Although these substances have been identified in cells and in serum, few have yet proved to be of clinical significance, although a variety of physiological functions (i.e., vasomotor, bronchomotor, secretomotor, and inflammatory) have been attributed to them. The basal aspect of these cells is often closely related to nerve endings or nerve varicosities. Acute hypoxia has been shown to cause exocytosis of the dense-core vesicles in neuroepithelial bodies, presumably a reflection of a receptor or effector function.

Cells of the pulmonary endocrine system can give rise to neoplasms with endocrine characteristics. These endocrine tumors can be pictured as a continuum of neoplasms that range from benign to malignant (i.e., from carcinoid to small cell carcinoma). The carcinoids mark one end of the continuum: they are the more highly differentiated, and their endocrine features are the most marked. Toward the opposite end are the small cell carcinomas, which are poorly differentiated. Non–small cell carcinomas are less apt to show endocrine differentiation. In this continuum, carcinoids are generally indolent, whereas small cell carcinomas are very aggressive.

Paraneoplastic Syndromes

Pulmonary neoplasms are more commonly associated with paraneoplastic syndromes than are any other types of neoplasms. Three types of paraneoplastic syndromes illustrate the systemic effects of pulmonary neoplasms: the carcinoid syndrome, Cushing's syndrome, and the syndrome of inappropriate secretion of antidiuretic hormone (SIADH). Clubbing of the digits is considered below.

The carcinoid syndrome is attributed to the release of various mediators from the neoplasm, owing to either

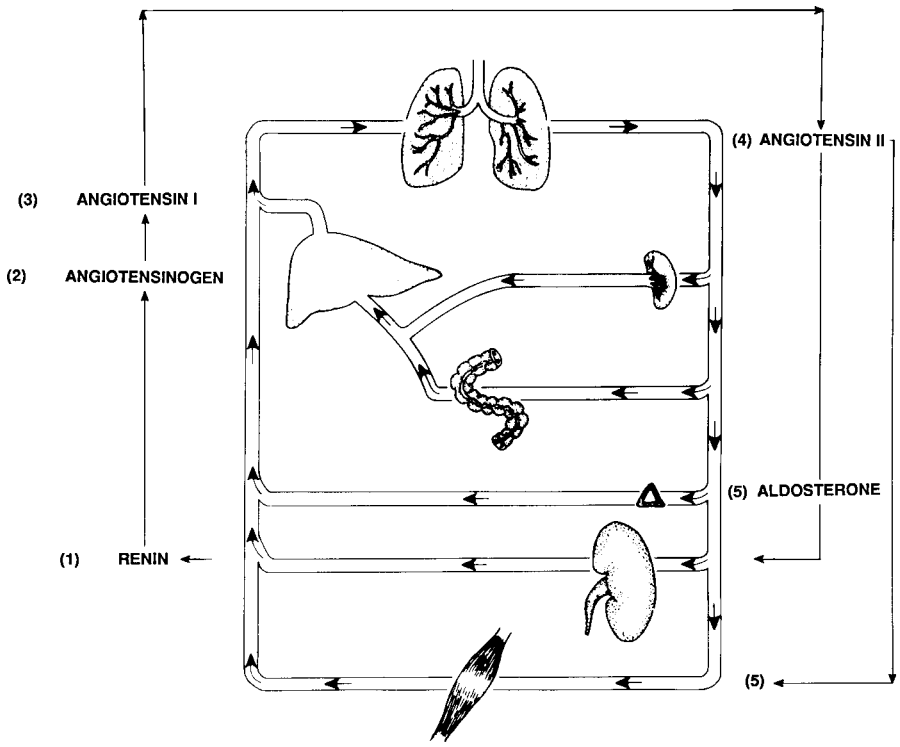


Figure 29-2 The renin-angiotensin system. The interplay among kidney, liver, and lungs results in the formation of angiotensin II. This hormone, generated in the lungs from precursors in the kidneys and blood, is active in the regulation of systemic blood pressure. It does so by way of its effects as a systemic vasoconstrictor and as a regulator of the circulating blood volume. The latter operates through the salt- and water-retaining effects of aldosterone.

a carcinoid tumor or, less often, a small cell carcinoma. Various mediators have been implicated, including serotonin, histamine kinins, and prostaglandins. The systemic effects include flushing, diarrhea, bronchospasm, and heart disease.

Cushing's syndrome is due to excessive secretion of adrenocorticotropic hormone (ACTH) or ACTH-like peptides by the neoplasm, generally a small cell carcinoma. The systemic effects are hypokalemic alkalosis, systemic hypertension, impaired carbohydrate tolerance, muscle weakness and wasting, edema, and weight loss.

SIADH generally occurs in association with pulmonary tuberculosis or bronchial carcinoma. The clinical syndrome, caused by inappropriate secretion of arginine vasopressin and antidiuretic hormone, is manifested by hyponatremia (not attributable to drugs), water retention, hyperosmolar plasma accompanied by disproportionately high hyperosmolarity of the urine, persistent natriuresis without volume depletion, and hypouricemia. These disorders may lead to altered mental state, lethargy, confusion, psychosis, or coma.

Other familiar syndromes involving pulmonary neoplasms in association with systemic effects are clubbing of the digits, gynecomastia, a variety of cutaneous disorders (e.g., acanthosis nigricans), neurological disorders (e.g., cerebellar degeneration), and autonomic disturbances (e.g., orthostatic hypotension).

PULMONARY VASCULAR ENDOTHELIUM

The lungs contain the largest expanse of endothelium in the body. This lining of the pulmonary circulation is engaged in a variety of vital functions (Table 29-1). Some, such as pulmonary vasodilation, are served by local mediators, such as nitric oxide and prostacyclin. Countering these effects are local vasoconstrictors, such as the endothelins. As noted above, other products, such as angiotensin II, exert their effects on remote functions (e.g., in the regulation of systemic blood pressure).

Endothelin (ET-1) is a powerful vasoconstrictor peptide which is synthesized by vascular endothelium. Increased circulating levels of ET-1 have been reported in pulmonary arterial hypertension. Endothelin contributes to setting pulmonary vascular tone by counterbalancing the vasodilatory effects of prostacyclin and other endothelium-derived relaxing substances. In addition to its vasoconstrictor actions, endothelin exerts a variety of other biologic effects depending on the cell type on which the receptors are found: positive inotropic and chronotropic effects on the heart, decrease in renal blood flow and filtration rate, and release of atrial natriuretic peptide (ANP). Among its deleterious effects are vasoconstriction, vascular hypertrophy, cell proliferation, fibrosis, and inflammation. ET-1 has been implicated in the

Table 29-1

The Processing of Certain Vasoactive Substances by the Lungs

Metabolized at the luminal surface
Angiotensin I
Bradykinin
Adenine nucteotides
Uptake by endothelium and then metabolized
Serotonin
Norepinephrine
Prostaglandins E and F
Released by endothelium
Lipoprotein lipase
Heparin
Prostacyclin
Kallikrein
Leukotrienes
Unaffected in traversing the lungs
Angiotensin II
Epinephrine
Dopamine
Vasopressin
Prostaglandin A
Vasoactive intestinal polypeptide
Oxytocin
The Generation of Vasoactive Substances by the Lungs
Endothelins
Nitric oxide
Prostacyclin
Hyperpolarizing factor

pathogenesis of systemic hypertension, pulmonary hypertension, and heart failure. Bosentan, a non-selective ET-1 receptor antagonist, is currently used in the treatment of pulmonary hypertension.

Nitric oxide is a highly reactive gas. It is synthesized within cells by nitric oxide synthase (NOS). The human genome contains three different genes that encode NOS, one of which, NOS-3, is found in endothelial cells. NOS is produced from arginine with the aid of molecular oxygen and nicotinamide adenine dinucleotide phosphate (NADPH). Nitric oxide acts as a vasodilator and anti-aggregator of platelets. The feasibility of direct measurements of the release of nitric oxide into expired air by vasoactive drugs has been demonstrated in both pigs and humans.

Thrombin is another interactive substance. It plays a key role in coagulant processes: on the one hand, it is procoagulant (i.e., it activates platelets, stimulates monocyte and neutrophil chemotaxis, cleaves fibrinogen, stimulates the endothelial release of tissue factors, and releases von Willebrand factor from Weibel-Palade bodies); on the other, it can serve as an anticoagulant molecule that stimulates protein C activity, promotes prostacyclin secretion, and causes the liberation of tissue plasminogen activators. Thrombin is also a potent growth factor that initiates proliferation of smooth-muscle cells at the site of injury. These diverse effects are due to the prevalence of thrombin receptors in many cell types. A variety of strategies to inhibit thrombin are being tested for therapeutic purposes: hirudin has been used to prevent the cleavage of fibrinogen and activation of thrombin receptors; peptides that act as antagonists for thrombin receptors are being tested; monoclonal and polyclonal antibodies are being developed that prevent activation of thrombin receptors; antisense oligonucleotides are being tried to block expression of thrombin receptors.

Chronic injury to the pulmonary vascular endothelium can evoke proliferation of the intima, invasion of the endothelial lining by underlying smooth muscle and adventitial cells, and accumulation of blood cells at the blood-endothelial interface. The end result is replacement of the single endothelial lining layer by occlusive heaps of endothelial, smooth-muscle connective-tissue cells (Figs. 29-3 and 29-4). How well the heaped-up endothelium preserves the functions of normal endothelial function (e.g., anticoagulation) is not clear.

The pulmonary circulation, like the systemic venous circulation, remains virtually free of atherosclerotic lesions unless pulmonary arterial blood pressures increase to hypertensive levels. Acute injury to endothelium can provide access of circulating proteins, such as fibrinogen, and blood cells to the pulmonary interstitium, thereby setting the stage for interstitial fibrosis. Aside from leakage, endothelial injury can stimulate a complex array of local reactions: circulating white blood cells and platelets are drawn to the injured site, undergo activation, and release factors that contribute to the response.

THE GUT-LIVER-LUNG AXIS

Perhaps nowhere is the principle of effluent from one organ influencing the behavior of its neighbor better illustrated than in the gut-liver-lung axis (Fig. 29-5). Misbehavior by any one of the series can seriously derange the workings of the next in line and the entire organism. For example, in liver failure, not only are noxious substances added to its effluent but also injurious substances from the gut, spleen, and other systemic organs, which are normally detoxified by the liver, gain access to the pulmonary circulation. The remote consequences of liver injury, such as clubbing of the digits in patients with liver cirrhosis, are considered below.

Dietary Pulmonary Hypertension

In 1974, the concept of *dietary pulmonary hypertension* was proposed. The idea stemmed from the ability of the drug

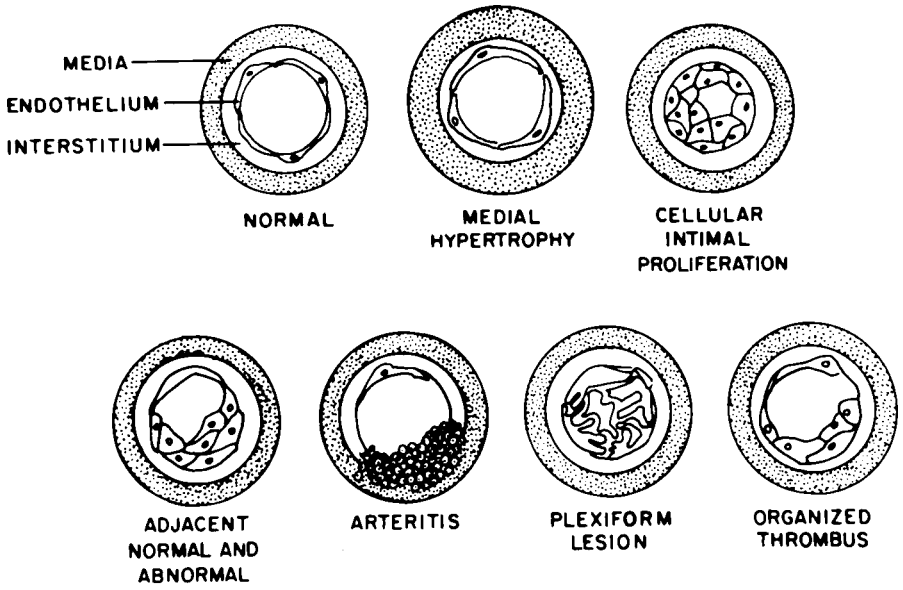


Figure 29-3 Normal and abnormal endothelium. Various endothelial abnormalities illustrating the different surfaces encountered by the perfusing blood.

aminorex in humans and the plant crotalaria in animals to elicit pulmonary hypertension. The generalization from this experience with drugs and plants taken by mouth was that other medications, foods, and herbs, taken by mouth, might injure the pulmonary circulation sufficiently to evoke pulmonary hypertension. Since then, ample evidence has accrued in support of this hypothesis (e.g., the toxic oil syndrome; fenfluramine derivatives; female "crack-cocaine" users).

The outbreak of primary pulmonary hypertension attributed to aminorex occurred in Austria, Switzerland, and Germany, and came to a close after the sale of the over-the-counter drug was stopped. Aminorex is a catechol derivative that acts by releasing norepinephrine at nerve terminals and synapses. One important lesson from the aminorex experience was that individual susceptibility was prerequisite for developing pulmonary hypertension: of the many thousands who used the drug, only a few developed the findings of primary pulmonary hypertension.

History repeated itself in April 1996, when another anorexigenic agent, dexfenfluramine, became available in drugstores throughout the United States. Its use spread widely. Dexfenfluramine exerts its pharmacologic effects by its enhancing effects on serotonin-mediated neurotransmission: it blocks serotonin reuptake, whereas its principal metabolite, dexnorfenfluramine, not only releases serotonin into synapses but also activates 5-HT_2 receptors.

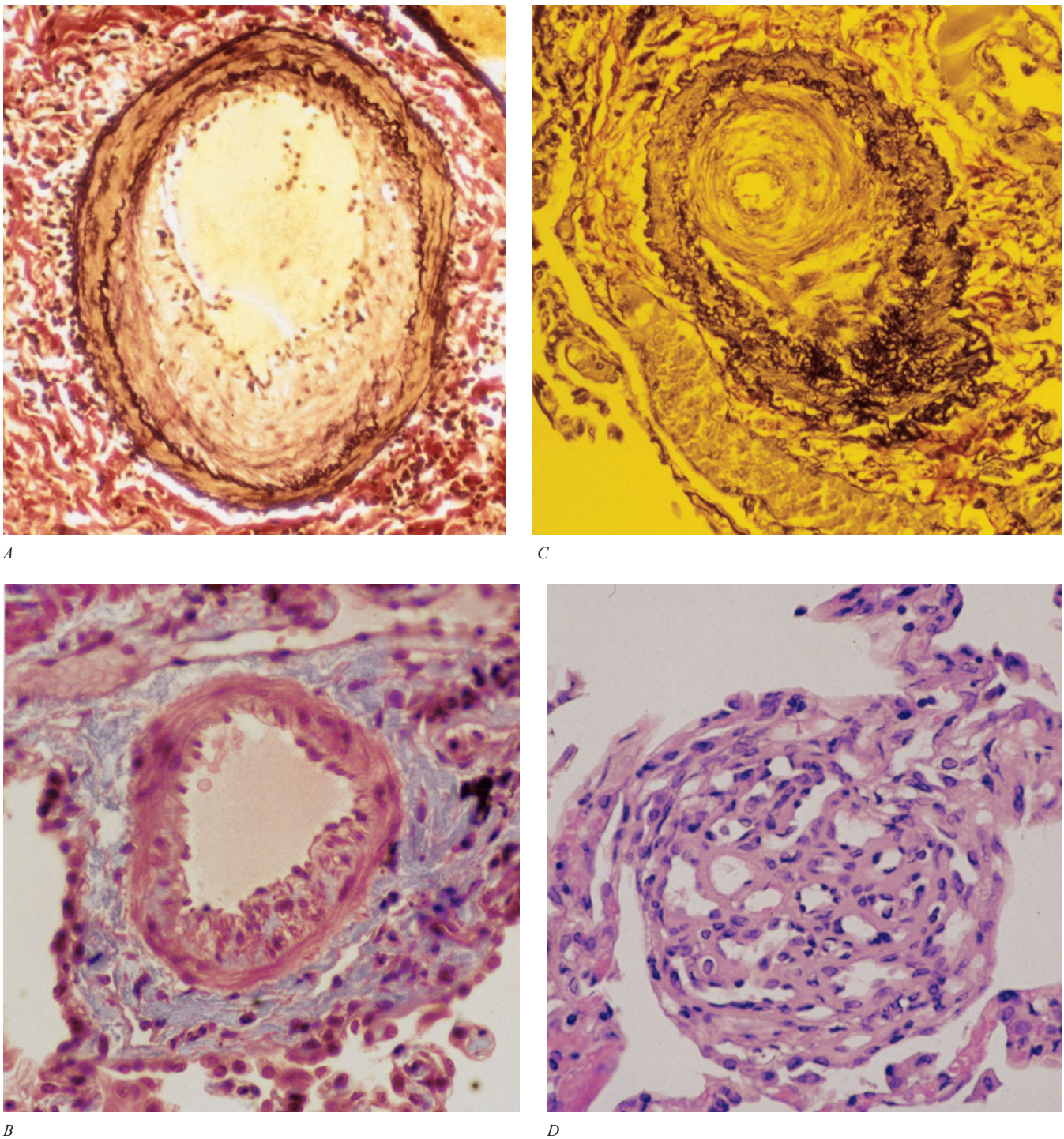
After sporadic case reports in the early 1980s of the association of pulmonary hypertension with the use of fenfluramine, Brenot and colleagues published a retrospective analysis that linked fenfluramine use with primary pulmonary hypertension. A follow-up, case-controlled study under the auspices of the Medical Research Council of Canada confirmed the higher incidence of primary pulmonary hypertension in people taking anorexigens, predominantly fenfluramine or dexfenfluramine. Moreover, the use of the anorexigen for more than a few months was associated with increased risk of primary pulmonary hypertension. Because of the widespread use of anorexigens, an outbreak of primary pulmonary hypertension seems inevitable. Indeed, a registry set up to keep track of such cases has already received reports of people in whom the use of anorexigens is associated with primary pulmonary hypertension.

Ventilation and Circulation in Liver Cirrhosis

Liver cirrhosis, and the accompanying portal hypertension, is often associated with striking changes in the pulmonary circulation. Some of these changes appear to be diametrically opposite. Thus, on the one hand the minute vessels of the lungs often show evidence of vasodilation in the pulmonary microcirculation (e.g., dilated arterioles and capillaries), whereas on the other hand the pulmonary microcirculation may be affected in obliterative vascular disease. The mechanisms at work are speculative. For example, the commonly held view that the obliterative pulmonary disease originates in pulmonary vasoconstriction, presumably because of some unknown vasoconstrictor mechanism, is unproven. Three aspects of the lung-liver relationship in liver cirrhosis have received special attention: pulmonary vasomotor control, pulmonary vasodilation, and pulmonary hypertension.

Ventilatory Responses to Hypoxia in Liver Cirrhosis

Hypoxic pulmonary vasoconstriction is blunted in patients with chronic liver disease, indicating a defect in intrinsic autonomic control. This blunting is in the face of the characteristic



A

C

B

D

Figure 29-4 Microscopic appearance of small pulmonary muscular arteries and arterioles, illustrating different degrees of intimal proliferation and vascular occlusion. Plexiform lesion is at bottom right.

high-cardiac-output state that is a feature of patients with liver cirrhosis. The mechanism responsible for both the high-output state and the blunted hypoxic pulmonary pressor response is unknown. Nitric oxide is the most recent candidate to explain the high-output state associated with liver cirrhosis.

CIRCULATORY ADAPTATIONS IN LIVER CIRRHOSIS

Mild arterial hypoxemia is found in 30 to 70 percent of patients with hepatic cirrhosis. This arterial hypoxemia is attributable to "anatomic" venous admixture (i.e., to anatomic shunts or to their equivalent; the rapid passage of unoxygenated blood past the gas-exchanging surfaces of the lungs).

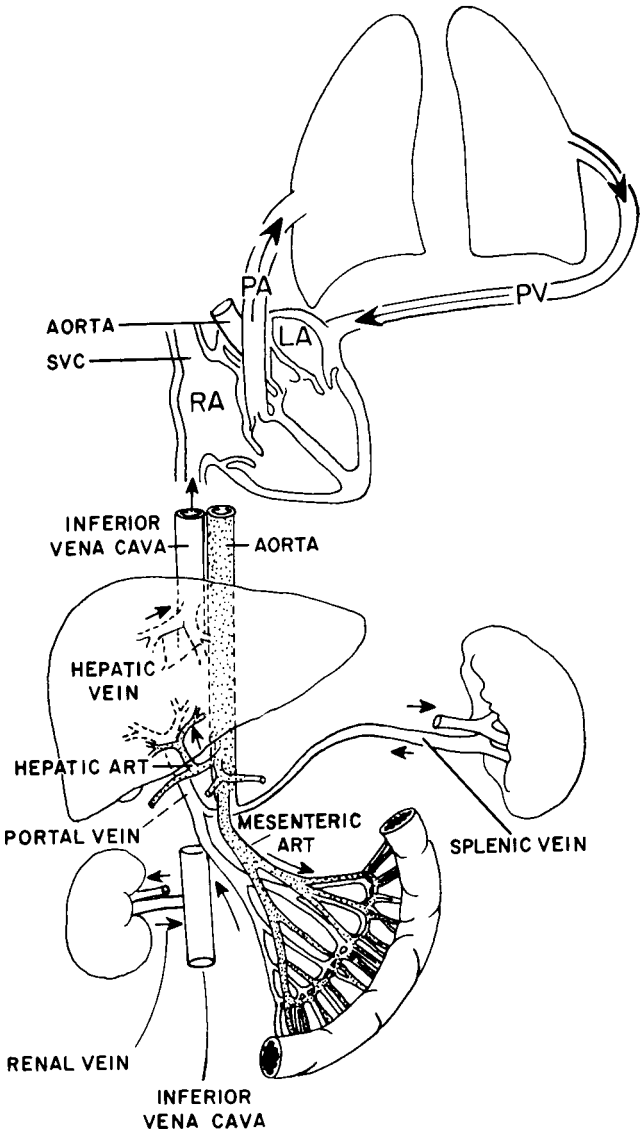


Figure 29-5 The gut-liver-lung axis.

This abbreviated transit time is, in turn, due to a combination of high-cardiac output and dilation of the pulmonary precapillaries and capillaries.

Dilatation of microvessels in liver cirrhosis is not confined to the lungs. Instead, it occurs throughout the body, including the skin and kidneys. In the fingers, it contributes to the rare occurrence of clubbing in patients with liver cirrhosis.

Inexplicably, the blood vessels on the pleural surface are more affected by dilatation than are the intrapulmonary vessels. The *spider nevi* on the pleural surface are fed by the pulmonary circulation. They are composed of short vessels, less than 1 mm in diameter, and are generally quite conspicuous. Although anatomic dilation of intrapulmonary microvessels has often been seen at autopsy, as a rule such dilatation is rare compared to that on the surface of the lung.

Portal-Pulmonary Hypertension

The association of pulmonary hypertension with liver cirrhosis has attracted considerable attention. The pulmonary hypertension is due to obliterative pulmonary vascular disease.

In the 1960s, the obliterative pulmonary vascular disease in patients with liver cirrhosis was attributed to organized pulmonary emboli that originated in thrombi in the portal vein. Since then, this possibility has largely been discounted, and it is now generally recognized that the pulmonary vascular lesions are identical with those of primary pulmonary hypertension.

The etiology of portal-pulmonary hypertension remains speculative. Among the possibilities being entertained is the prospect that vasoconstrictor substances or autoimmune substances, or other injurious agents, might start the obliterative process by injuring pulmonary vascular endothelium. The arrangement of the gut, liver, and lungs in series nurtures this hypothesis. One intriguing aspect of this proposition is why the endothelium of pulmonary resistance vessels should be extensively affected by the injury while the more extensive endothelium of the pulmonary capillary bed is spared.

SEPSIS-INDUCED MULTIPLE ORGAN FAILURE

Probably the most striking impact of the lungs on the rest of the body is exemplified by multiple-organ failure that complicates the adult respiratory distress syndrome (ARDS). Indeed, most patients who die of ARDS do so because of multiple-organ failure rather than from the lung disease. In recent years, the liver, as well as the kidneys, has been recognized to be a major determinant of the outcome of ARDS.

In its systemic effects, ARDS behaves like sepsis elsewhere in the body, overwhelming host defenses by the release into the circulation of inflammatory cytokines, such as tumor necrosis factor (TNF) and interleukin-1 (IL-1). TNF continues to be the major center of attention. Endotoxin is the most potent stimulus known for the production of TNF. Instead of acting directly to cause injury, endotoxin (or its lipopolysaccharide) prompts the formation of host factors that cause the damage. Macrophages are deeply implicated in generating these host factors. In addition to releasing injurious agents, sepsis interferes with the biologic inactivation of mediators of inflammation. Novel therapies have been directed at countering the role of TNF in the septic shock syndrome. These include anti-TNF monoclonal antibodies, soluble TNF receptors, and soluble TNF receptor-immunoglobulin G heavy-chain fusion proteins. These approaches are still under development.

Recently, attention has turned to attempts at blocking the production of nitric oxide, an endogenous vasodilator and immune modulator that may be active in inducing the systemic hypotension associated with sepsis. The target has been nitric oxide synthase (NOS), the enzyme that produces nitric

oxide. Blocking NOS affords promise not only of relieving systemic hypotension but also of favorably influencing other harmful processes that may contribute to organ failure, including direct tissue injury, myocardial depression, derangement of cellular metabolism, and release of inflammatory cytokines (e.g., TNF) from macrophages. However, the therapeutic role of inhibiting nitric oxide has not yet been settled because nitric oxide may have beneficial as well as harmful properties.

INJURY BY OXYGEN-DERIVED PRODUCTS

Mechanisms of Action

In recent years, mounting evidence has implicated oxidative injury in the pathogenesis of a wide array of biologic processes, ranging from the normal aging process to a variety of disease states, including atherosclerosis, carcinoma, and ischemia-perfusion injury. Oxidative injury has also been increasingly held responsible for diverse diseases of the lungs and airways, such as emphysema, interstitial pulmonary fibrosis, asthma, and ARDS. The relationship between cigarette smoking and the development of emphysema illustrates one pathway: oxygen-derived products, either contained in cigarette smoke or generated by activated leukocytes attracted to the lungs by smoking, oxidize the methionine residue of α_1-antitrypsin, an antiprotease, thereby inactivating it and enabling the destruction by proteases of alveolar walls (see Chapter 41). The abnormal pulmonary function that ensues exerts systemic effects by way of abnormal blood gases and mechanics of breathing, stimulation of respiratory control mechanisms, and the sensation of dyspnea. The oxidant injury may be aggravated by administration of supplementary oxygen in the form of O_2-enriched inspired air mixtures.

Sensitized asthmatics respond to an allergen by degranulation of mast cells, which causes the release of TNFα. In turn, TNFα prompts the migration of neutrophils and eosinophils to the site of the allergic reaction. At this site, the leukocytes release toxic oxygen products, which contribute importantly to the inflammatory response.

Most of the molecular oxygen entering the body is reduced sequentially to water via the respiratory chain. However, in the course of the serial reductions that are part of normal intermediary metabolism, superoxide anion (O_2^-) and hydrogen peroxide (H_2O_2) are generated as undesirable by products.

Generation of Toxic Reactive Oxygen Species

Cells that respire aerobically generate toxic reactive oxygen species. These reactive species are produced not only in the course of normal aerobic metabolism but also as by products of inflammatory reactions. The toxic reactive species known as free radicals include the superoxide anion and hydroxyl

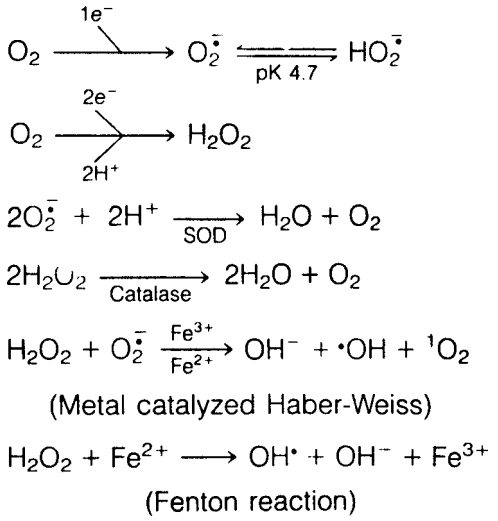


Figure 29-6 The generation of oxygen free radicals by the addition of electrons.

radicals and hydrogen peroxide (Fig. 29-6). Cellular damage is inflicted by these species on proteins, nucleic acids carbohydrates, and lipids. Damage to the lungs inflicted by free radicals (e.g., ARDS) can exert disastrous effects on systemic organs (e.g., renal failure). In turn, the cell damage causes the induction of antioxidant genes that prompt the elaboration of enzymes directed at scavenging the reactive oxygen species. Among the clinical situations in which free radicals feature prominently are reperfusion injury and the adverse immunologic responses elicited by organ transplant action.

In the lungs, reactive oxygen species from the environment can inflict damage. Oxygen toxicity, produced by breathing O_2-enriched inspired air, affords a traditional example of injury produced by O_2-derived products. Within 24 h of the start of oxygen breathing, the endothelium of the pulmonary microcirculation is damaged and becomes "leaky," enabling blood plasma to gain access to the interstitial spaces and alveoli. Along with excess fluid and serum proteins, inflammatory cells accumulate in the lungs. Should exposure to the O_2-rich inspired gas continue, the end point can be ARDS. One experimental strategy for mimicking the pathological and pathophysiological changes in the lungs induced by oxygen toxicity is the administration of endotoxin.

Another mechanism for causing oxidant injury involves nitric oxide (see Chapter 25). Nitric oxide, a mediator of signal transduction with diverse physiological functions, is categorized as a free radical because of its unpaired electron. Because of this property, it has biologically important reactivities with certain kinds of proteins, carbohydrates, and other free radicals (e.g., superoxide radicals). In its reactions with other free radicals, it can yield even more potent oxidants (e.g., peroxynitrite). Some toxic reactions, originally attributed to its chemical precursors, superoxide and nitric oxide, are now attributed to peroxynitrite. Oppositely, nitric oxide can also exert a protective action against free radicals, such as the superoxides. Thus, nitric oxide can either inflict damage or ward

it off, depending on the oxidative environment in which the reactions are taking place. An intense research effort is currently directed at unraveling the nature of reactions involving nitric oxide and peroxynitrite with proteins, lipids, carbohydrates, and gene expression in a variety of pathological processes.

The amino acid homocysteine is operative in another mechanism by which oxidative injury can damage endothelium. This mechanism is mediated primarily by autooxidation, which generates the superoxide anion radical (O_2^-) and H_2O_2 and the hydroxyl radical (OH·). Abnormally high levels of homocysteine in plasma blunt the responses of endothelium to endothelium-dependent vasodilators (e.g., nitric oxide) by way of the damage caused by products of homocysteine oxidation. The antithrombotic function of endothelium and the migration and proliferation of vascular smooth-muscle cells are also affected by high levels of homocysteine.

Two other clinical areas in which oxidant-produced injury features prominently are the inhalation or ingestion of oxidants (e.g., paraquat) and the chronic injury caused by smoking, which predisposes to low-level inflammation, pulmonary damage, and neoplasm.

GENERAL SYSTEMIC EFFECTS OF PULMONARY DISEASE

Pulmonary infections and neoplasms are notorious for the systemic effects that they can elicit (Table 29-2). Pneumonias caused by bacteria, mycoplasma, viruses, or fungi can cause a spectrum of disturbances, ranging from mild fever to bacteremia and circulatory collapse. Viral infections commonly induce leukopenia, anemia, and thrombocytopenia. Metabolic derangements are also the rule in these acute disorders; abnormal hepatic and bone marrow functions are the bases for common abnormalities (e.g., high erythrocyte sedimentation rate and leukocytosis). The span of disturbances is just as great for neoplasms, not only because they encroach on adjacent structures and functions but also because of derangements in remote bodily functions that they cause by releasing biologically active materials (Table 29-3; see also Chapter 134). The impact of pulmonary disease on the rest of the body rises exponentially when infectious organisms or neoplastic cells escape the confines of the lungs to enter the bloodstream.

Bacteremia, viruses, fungi, and other microorganisms can invade the bloodstream from the lungs. Such infections gain in virulence with increasing numbers of organisms and their products; the elderly are particularly vulnerable to the systemic effects of pulmonary infections. Among the common consequences of diseases that begin in the lungs and affect the rest of the body are fever and body wasting.

Table 29-2

General Systemic Effects of Nonrespiratory Diseases of the Lung

Disturbances in the control of body temperature (fever, chills, sweating)
Central nervous system abnormalities (euphoria, irritability, confusion, delirium)
Faintness, reduced alertness, syncope (postural hypotension, arrhythmias, decreased blood flow to the brain)
Anorexia, asthenia, cachexia
Remote organ failure

Table 29-3

Some Substances from Pulmonary Endocrine Neoplasms That Can Affect Systemic Organs and Tissues

Adrenocorticotropin
Calcitonin and calcitonin gene-related peptide
Arginine vasopressin
Growth hormone
Serotonin
Pituitary gonadotropins
Thyroid-stimulating hormone
Vasoactive intestinal polypeptide
Insulin
Parathyroid hormone
Somatostatin
Renin
Gastrin
Prolactin
Bombesinlike peptides

Fever, Chills, Sweating

There are many causes of fever. Among the most common are infections, inflammation, injury to the central nervous system, thrombosis, hematoma, vasculitis, and necrosis. Fever is generally regarded as harmful. However, fever has enhancing functions. For example, in infections, it enhances neutrophil migration and the production of antibiotic substances by neutrophils.

The body is constructed to keep internal core temperature stable at about 37.1°C (corresponding to a rectal temperature of about 37.6°C) and equipped with automatic feedback devices that minimize fluctuations in the core temperature. Regulation of the core temperature is accomplished almost entirely by neural feedback mechanisms, virtually all of which are controlled by temperature-regulating mechanisms in the hypothalamus. Fever represents an upward shift in the thermostatic set point. The automatic attempt by the body to restore body temperature to normal includes cutaneous vasodilatation, sweating, decreased chemical thermogenesis, and a widespread decrease in muscle tone due to reflex inhibition of the *primary motor center for shivering*.

Chills are a response to an abrupt disparity between the set point of the thermostat in the hypothalamus and the temperature of the blood. Certain substances, notably pyrogens and products of tissue destruction (see next paragraph), can suddenly raise the hypothalamic set point without raising body temperature. Until the body temperature catches up, mechanisms to raise it are turned on, and the subject feels cold and experiences chills—even while the body temperature is increasing to match the hypothalamus set point: the cold sensation is a consequence of cutaneous vasoconstriction, whereas shivering causes the "shakes." When the body temperature reaches the higher set point, chills cease and the subject feels neither cold nor hot. Until the factor responsible for increasing the set point stops, the febrile state is maintained by the usual mechanisms. Precipitous discontinuance of the initiating factor results in widespread cutaneous dilatation and flushing and intense sweating (i.e., "the crisis").

Pyrogens feature prominently in causing clinical fevers. They do so, directly or indirectly, by raising the thermostatic set point in the hypothalamus. Particularly effective in this regard are endotoxins produced by gram-negative bacteria. Leukocytes and macrophages act as intermediaries in this process: these phagocytic cells, after digesting the bacterial products, release leukocyte or endogenous pyrogen, which, in minute amounts, stimulates the hypothalamus to raise its set point; prostaglandin E_1 is presumably the intermediary within the cells of the hypothalamus that effects the febrile response. Blockage of prostaglandin formation, as by aspirin, can prevent or reduce the febrile response.

Chills, fever, and sweating are familiar manifestations of the syndrome of pneumococcal pneumonia and its complications. Some infecting organisms tend to be associated with distinctive diurnal fever patterns. Although these patterns were once regarded as diagnostic clues to the etiological agent, not much clinical attention is now paid to patterns, although the peaks and valleys in the fever curves can suggest clues to origin, and undue persistence of fever may signal a complication.

Body Wasting

Progressive infection or the growth of a neoplasm often elicits anorexia, weight loss, and cachexia. Cachexia is characterized by an inexorable loss of weight that is inordinate for the degree of anorexia and the decrease in food intake. Both adipose tissue and muscle mass are depleted; death usually is the end result of progressive depletion of lean body tissue.

Anorexia and underlying metabolic abnormalities appear to be at work in the pathogenesis of cachexia. Anorexia regularly accompanies weight loss. Although the initiating mechanism for anorexia seems to relate to the infection or neoplasm, in time other mechanisms supervene. Among these are depression, continued immobilization, and comorbid conditions. Appetite suppression is often aggravated further by medications. Attempts to reverse cachexia by nutritional supplements are rarely successful.

Key factors in the production of cachexia fall into three categories: (1) metabolic products of the pathogen or neoplasm; (2) catabolic hormones and a lipid-mobilizing factor (LMF) produced by neoplasms that acts to cause breakdown of adipose tissue; and (3) cytokines, such as TNFα and interleukin-6 (IL-6), which seem to affect adipose tissue by inhibiting lipoprotein lipase. TNFα plays a pivotal role. It is produced by macrophages, monocytes, and T cells, and its toxic effects are exceedingly diverse: it is a pyrogen, directly damages endothelium, can suppress adipose-specific enzymes, and is a mediator of the inflammatory process.

Since the 1994 discovery of leptin, a hormone active in the control of body weight, interest in starvation has taken a new turn. Leptin is a hormone produced by the obesity gene (*ob*), manufactured by adipocytes, and delivered to receptors in the hypothalamus (arcuate nucleus and paraventricular nucleus). Leptin functions as a lipostat: when fat stores increase, adipocytes produce leptin, which tells the brain to decrease appetite and increase activity.

Leptin exerts its effects via a complex interplay that involves neuropeptide Y and the melanocortins, a family of peptides. Decreased leptin levels work through neuropeptide Y to deal with the stresses of starvation; high levels may work through melanocortins to resist overweight. One feature of starvation is altered endocrine activity (e.g., decreased production of thyroid and sex hormones and increased production of adrenal stress hormones). Low levels of leptin elicit starvation-induced changes in endocrine function. The components of the hormone-neuropeptide system and their interplay in the control of body weight are currently under intense investigation. Most studies have been conducted in the rat, however, and their implications for human disorders, such as starvation, are incompletely understood.

Some success in reversing cachexia has been accomplished by the use of two groups of agents: those that stimulate

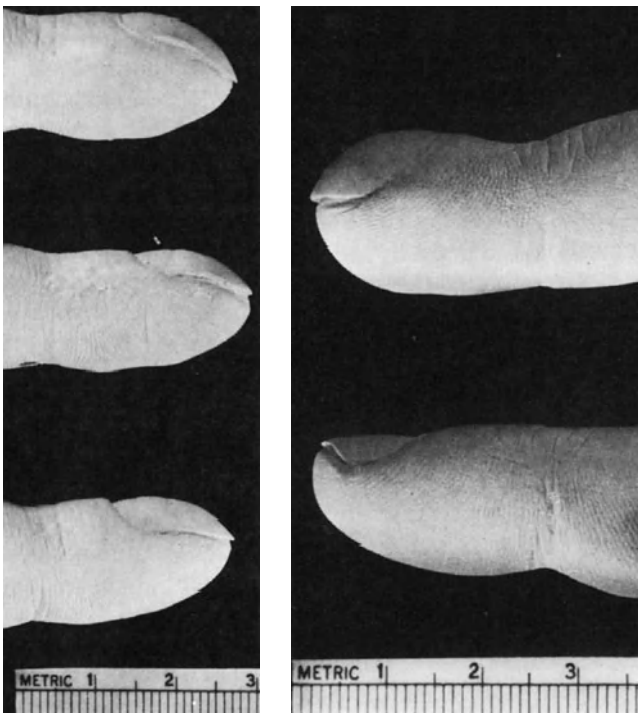
intake of food (e.g., megestrol acetate, which can also stimulate tumor growth) and those that inhibit LMF (e.g., eicosapentaenoic acid).

SPECIFIC SYSTEMIC EFFECTS OF PULMONARY DISEASE

Certain systemic manifestations, although not unique to pulmonary disease, occur often enough to warrant special mention. Among these is clubbing of the digits.

Clubbing of the Digits and Hypertrophic Osteoarthropathy

The characteristic and preferential bulbous enlargement of the distal segment of the digits (Fig. 29-7) and the distinctive bony lesions of secondary hypertrophic osteoarthropathy are generally explained in terms of humoral mediators that cause selective vasodilatation of the digital precapillary vessels. As is noted in Chapter 108, this explanation seems to suffice in certain disorders (e.g., the clubbing of the digits and the hypertrophic osteoarthropathy that accompany carcinoma of the lungs) but not in others (e.g., subacute bacterial endocarditis). One other intriguing aspect of clubbing is its association both with chronic bronchiectasis, in which the adjacent collateral circulation of the lungs undergoes remarkable proliferation, and with carcinoma of the lung, in which the collateral blood supply is modest.



A *B*

Figure 29-7 Casts of clubbed fingers. *A*. The second right finger of an 18-year-old woman with tetralogy of Fallot before and after surgery. *Upper:* Preoperatively, showing marked clubbing. *Middle:* Two months later, showing partial reversal of changes. *Lower:* Regression of the clubbing. *B*. The third right finger of a 40-year-old woman with digital clubbing *(above)*, compared with that of a normal 36-year-old woman *(below)*. *(Mellins RB, Fishman AP: Digital casts for the study of clubbing of the fingers. Circulation 33:143–145, 1966.)*

CONCLUSIONS

Once the metabolic functions of the lungs were fully appreciated, it became evident that interplay between the lungs and systemic tissues and organs was part of normal body functioning and that more than nervous connections is operative. This interplay became even more evident in clinical syndromes that involved the transport by the circulation (and possibly lymph) of products of inflammation from one part of the body to the other. Syndromes such as the hepatorenal syndrome and organ failure in ARDS underscored the interplay. Others, such as coexistent portal and pulmonary hypertension, remain enigmas to be resolved. With these insights came the realization that understanding of the interplay between the lungs and other organs is still in its infancy.

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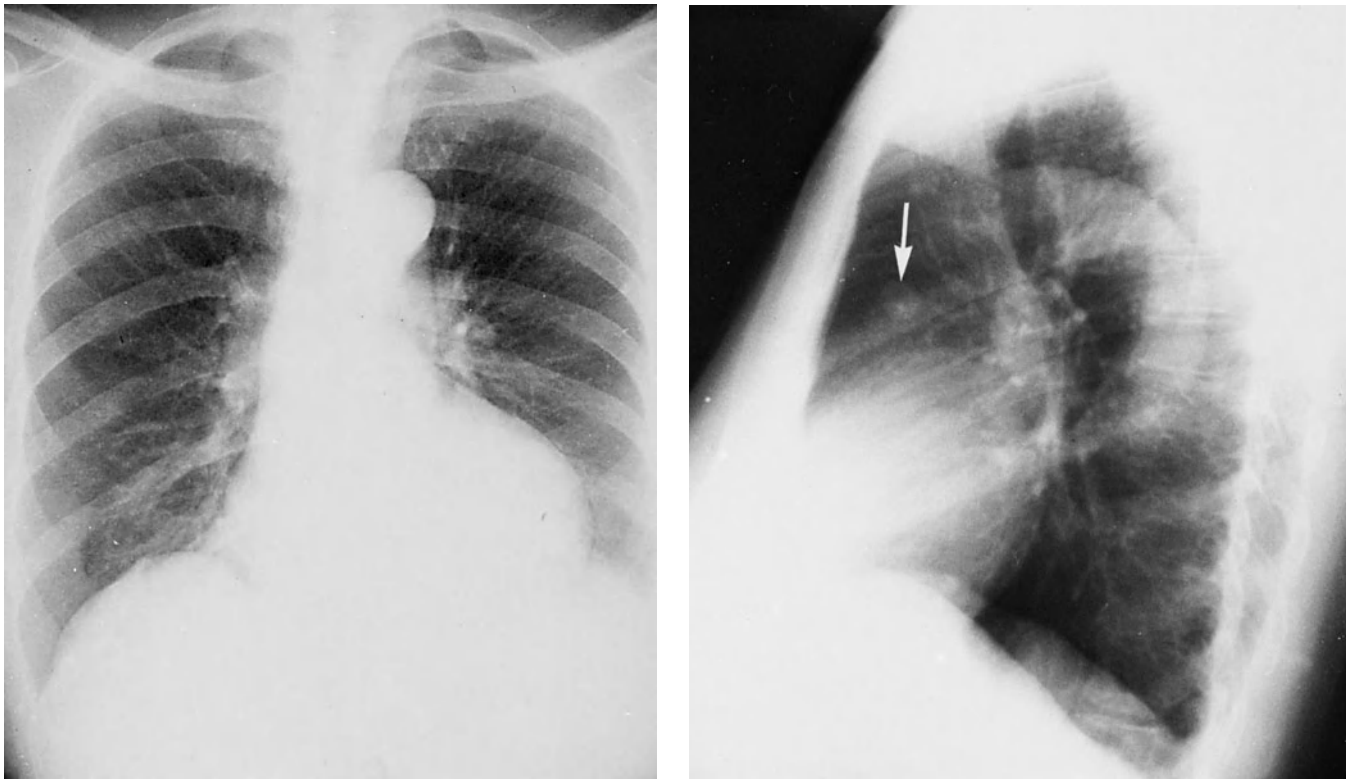
30
CHAPTER

Radiographic Evaluation of the Chest

Wallace T. Miller

Radiographic evaluation of the chest constitutes an important component in assessment of the patient with known or suspected pulmonary disease. In fact, the chest radiograph may provide the earliest or only clue to the presence of clinically significant respiratory disease. This chapter provides a brief overview of chest radiology. First, general aspects are covered; use of more specialized techniques, including computed tomography, nuclear magnetic resonance, and arteriography, is highlighted. Subsequently, radiographic manifestations of diseases that affect the distribution of pulmonary blood flow, the airways, and the lung parenchyma are considered. Finally, disorders are reviewed that are predominantly or exclusively confined to anatomically distinct areas of the thorax, including the mediastinum, diaphragm and chest wall, and pleura. Throughout the presentation, examples of radiographs are provided to highlight the principles and disorders discussed.



A *B*

Figure 30-1 The lateral view in uncovering a solitary nodule. *A*. PA view. No nodule is discernible. *B*. Lateral view. A small nodule (arrow) overlies the left hilus. The nodule proved to be a granuloma.

Although significant emphasis is placed on plain film findings, computed tomography has emerged as the most useful radiographic means of investigating chest disorders. Furthermore, although digital radiography is supplanting traditional film-based radiography in most departments, the descriptions provided about film-based radiography apply equally to digital studies.

GENERAL ASPECTS

In recent years, fresh concepts and new techniques have greatly expanded the diagnostic armamentarium of chest radiology. As a rule, the new approaches have strengthened the underpinnings of conventional methods and our diagnostic abilities. Evaluation invariably begins with routine chest radiographs, supplemented, as indicated, by more specialized techniques. Many of these specialized techniques are largely historical, since computed tomography (CT) and magnetic resonance imaging (MRI) produce a more detailed and sensitive evaluation of chest abnormalities.

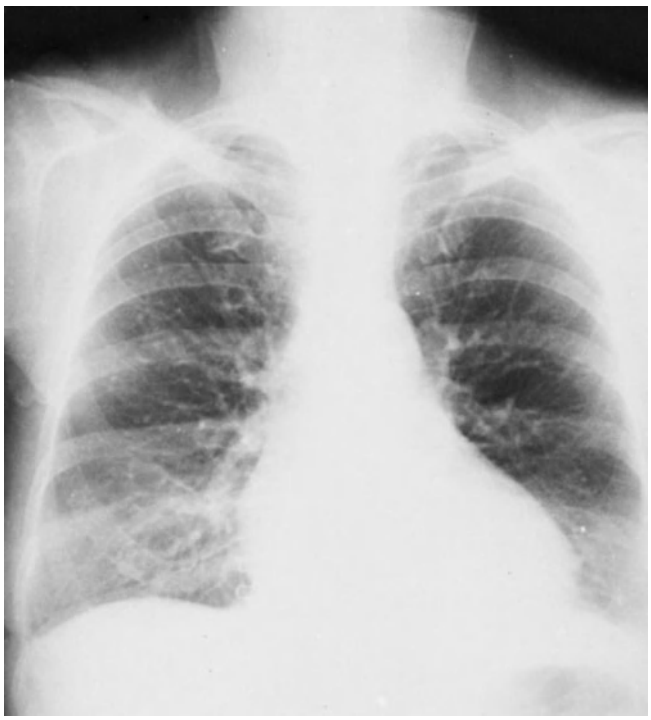
Routine Examination

In asymptomatic patients, a posteroanterior (PA) chest radiograph may be used as the sole screening procedure. This projection is easiest to interpret, since the anatomy is quite familiar, and most pathological respiratory conditions are demonstrable in this view. Ideally, a lateral view should also be part of the routine examination. The lateral view adds valuable information about areas that are not well seen in the PA projection. This is particularly true of the anterior portion of the lung, adjacent to the mediastinum—an area that may be obscured by the overlying heart and aortic shadows (Fig. 30-1). The vertebral column is also seen to better advantage on the lateral view. A small pleural effusion is best seen, and often only seen, as blunting of a costophrenic sulcus posteriorly (Fig. 30-2).

In determining which costophrenic angle is blunted, correct identification of each hemidiaphragm on the lateral view is helpful. If the lateral radiograph is taken in the left lateral position, as is usual, the magnified ribs are on the right side; the unmagnified ribs are on the left side and are associated with the corresponding left hemidiaphragm (Fig. 30-2). In addition, the outline of the left hemidiaphragm is often obscured anteriorly because it merges with the heart shadow. Finally, the left hemidiaphragm may be recognized from its proximity to the stomach bubble, especially if the left hemidiaphragm is higher than the right.

Supplementary Plain Radiographs

In addition to the PA and lateral chest radiographs, other projections serve special purposes, although routine use of CT scanning has markedly diminished the frequency of use of these special films.



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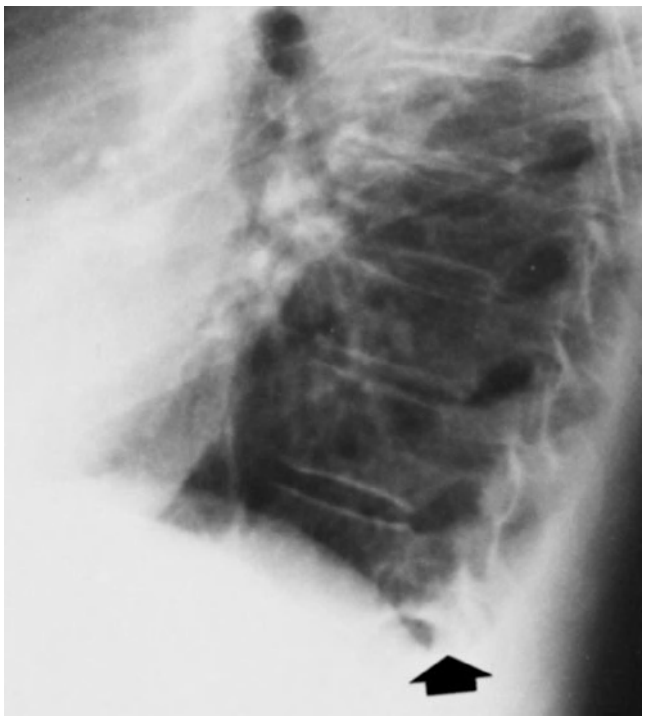

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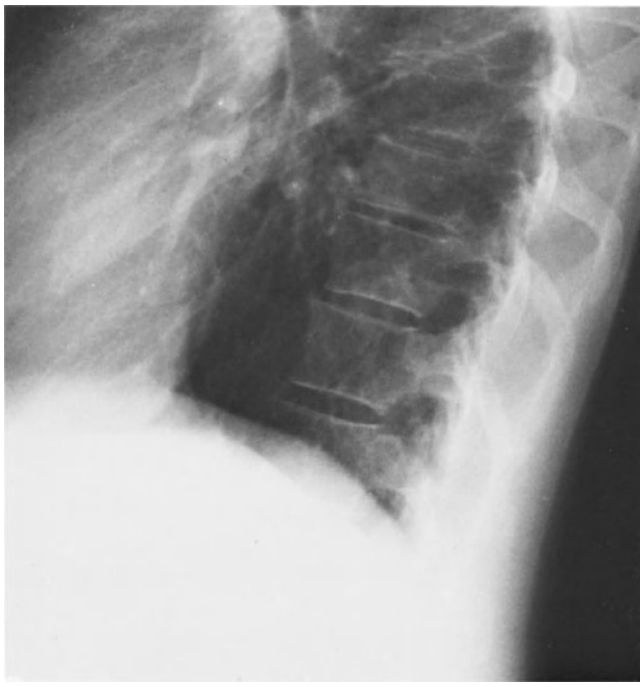


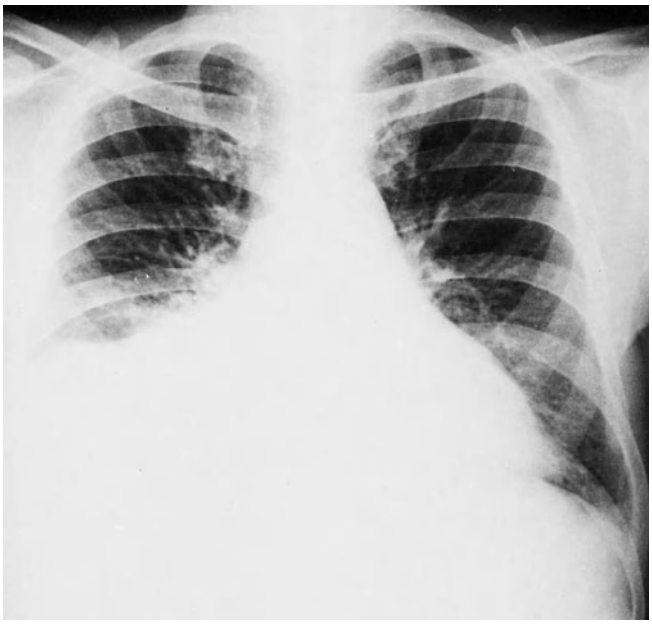
C

Figure 30-2 The lateral view in uncovering a small pleural effusion. *A*. PA view. No evidence of a pleural effusion. *B*. Lateral view. The right costophrenic sulcus is blunted (arrow). *C*. Lateral view. After treatment for heart failure, the effusion is gone. Note the magnification of the posterior (right) ribs.

Oblique views are sometimes invaluable in confirming or delineating a pulmonary mass or infiltrate from structures that overlie it on the PA and lateral views. Barium in the esophagus serves as a useful adjunct in clarifying the location of middle mediastinal lesions on oblique films.

In interpreting oblique films, the clinician will find it useful to keep in mind that a pulmonary lesion that maintains a fairly constant relationship to the heart as the patient is rotated lies in the anterior portion of the chest; a lesion that maintains a constant relationship to the spine is in the posterior portion if the chest.

The *lateral decubitus* projection (Fig. 30-3*C*) is often used to identify the presence of a pleural effusion. As little as 25 to 50 ml of pleural fluid can be visualized, even though 300 ml may be required to blunt the costophrenic sulcus on the PA view. The decubitus view is particularly useful in determining if blunting of the costophrenic sulcus is due to a freely mobile pleural effusion or pleural thickening. Although a pleural effusion may be an important finding,



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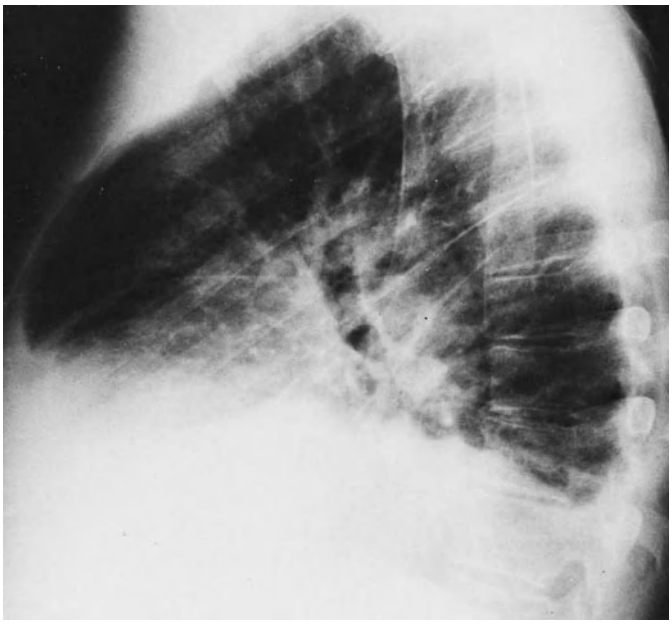

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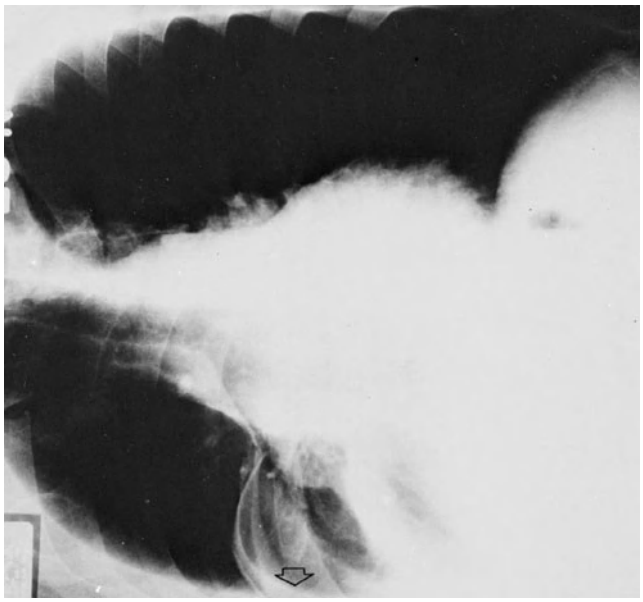


C

Figure 30-3 Infrapulmonary effusion. Neither the PA view (*A*) nor the lateral view (*B*) shows blunting of the costophrenic sulcus. However, elevation of the right hemidiaphragm suggests the presence of an infrapulmonary effusion. A right lateral decubitus film (*C*) shows the presence of a free pleural effusion on the right. The effusion was secondary to congestive heart failure.

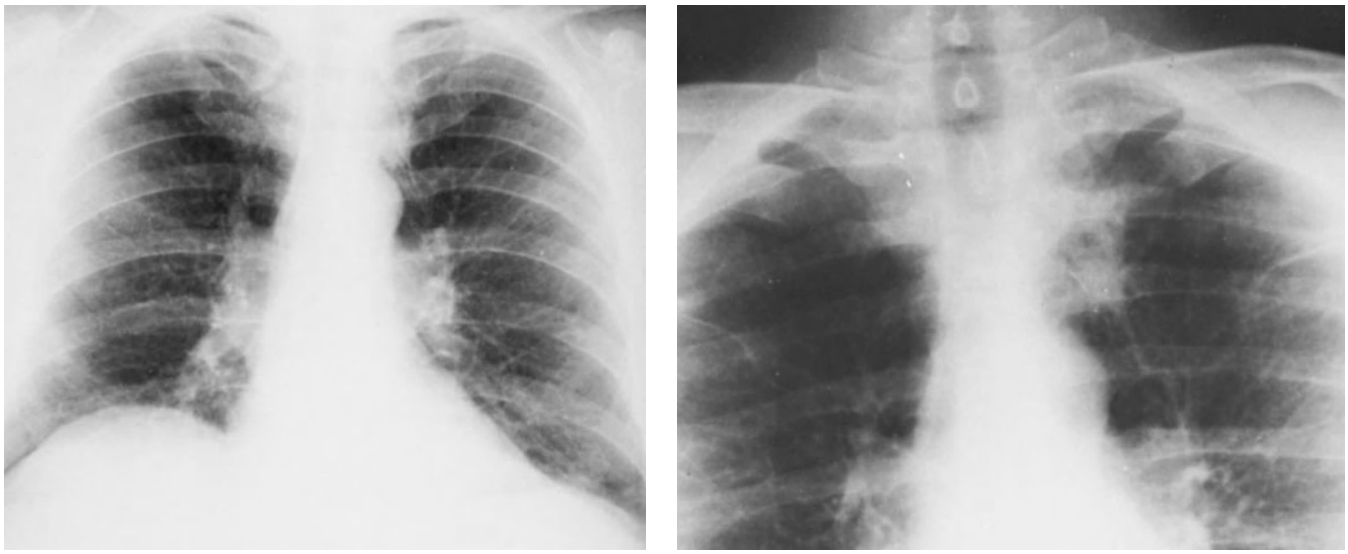
pleural thickening most often is a sequel to a remote exudate or blood in the pleural space; usually it is clinically unimportant. Distinction between pleural thickening and loculated fluid may be difficult.

On the PA film, shadows created by the first rib and clavicle may make interpretation of the lung apices difficult (Fig. 30-4*A*). The *lordotic* projection enables evaluation of the apices by displacing these overlying shadows (Fig. 30-4*B*). The lordotic view may also be useful in demonstrating collapse of the right middle lobe.

The *over-penetrated grid* radiograph (Fig. 30-5*A*) is useful for evaluating densities that lie behind the heart or diaphragm and are poorly seen on routine radiographs. Using digital imaging, the same effect can usually be obtained by appropriate windowing; hence, use of the over-penetrated grid radiograph is now seldom made. *Expiratory* films may disclose air trapping or a pneumothorax that is poorly shown on the inspiratory film.

Laminography

Historically, a technique known as *laminography* (also known as tomography, body section radiography, or planigraphy) utilized movement of the radiography tube and film about a fixed point to generate a radiograph of a tissue plane that is several millimeters thick; the designated plane is in focus, while surrounding anatomic details are blurred. In effect, this technique provided a view of a thin slice of lung and affords a "close look" at a suspected abnormality. It was useful in demonstrating the presence of calcification within a



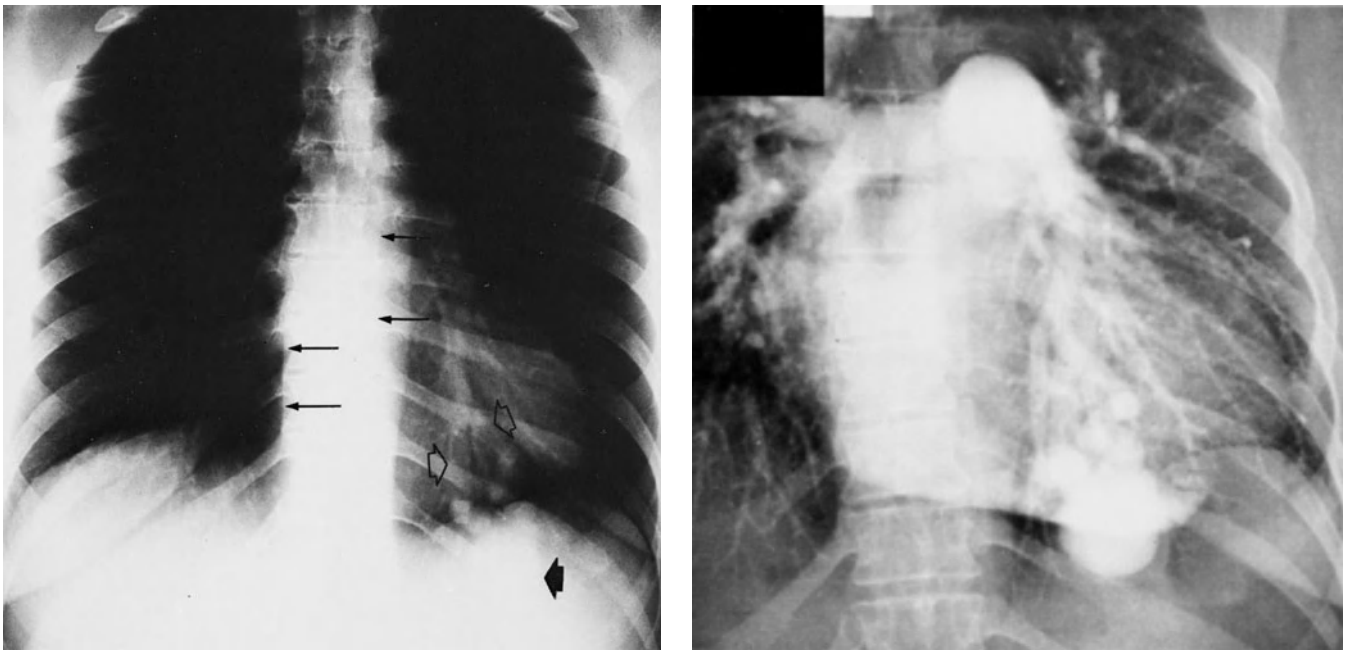
A *B*

Figure 30-4 Carcinoma of the left upper lobe. *A*. PA view. A small nodule is present in the left upper lobe adjacent to the mediastinum, just above the aortic knob. *B*. Lordotic view. The nodule is much more apparent. It proved to be a primary adenocarcinoma of the lung.

pulmonary nodule and, occasionally, in providing insight into its benign or malignant cause (e.g., the presence of scattered, "popcorn" calcifications, implying a benign process). Laminography has been supplanted completely by CT imaging.

Fluoroscopy

Fluoroscopy of the chest may be used for examining the movement of pulmonary and cardiac structures and for localizing a pulmonary lesion that is visible in only one of the two conventional radiographic projections. It is particularly



A *B*

Figure 30-5 Pulmonary arteriovenous malformation. *A*. Overpenetrated grid (Bucky) radiograph shows a nodule behind the diaphragm (closed arrow) with feeding artery in draining veins (open arrows). *B*. Pulmonary angiogram confirmed the diagnosis of arteriovenous malformation. Also visible bilaterally on the overpenetrated Bucky film are the posterior paraspinal lines (small arrows). The left posterior paraspinal line is medial to the aorta. The right paraspinal line is ordinarily not discernible; however, it can be seen in this patient because small osteophytes arising from the vertebral bodies displace the pleura laterally on the right.

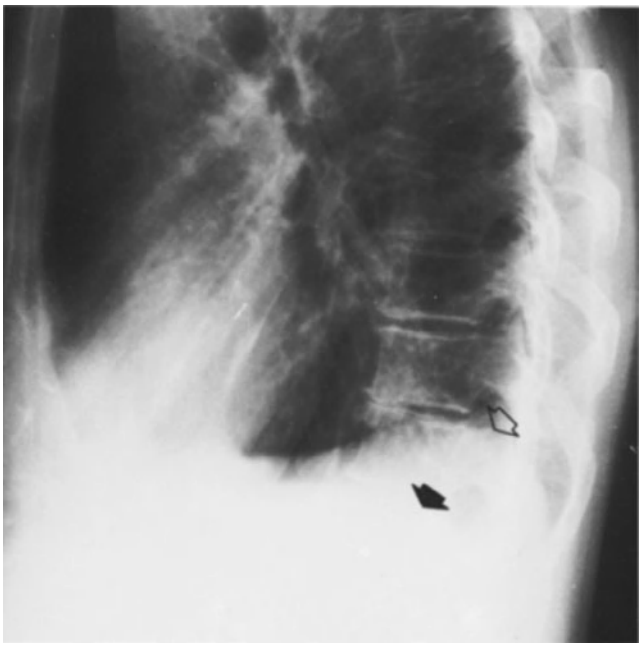


Figure 30-6 Partial eventration of the diaphragm. The lateral view shows elevation of the posterior portion of the right hemidiaphragm (open arrow). The normal contour of the left hemidiaphragm (closed arrow) appears immediately beneath. This partial eventration is due to a localized weakness in the posterior aspect of the right hemidiaphragm.

helpful for examining diaphragmatic motion. When one is searching for diaphragmatic paralysis, the patient is best fluoroscoped in the lateral projection, allowing motion of both hemidiaphragms to be observed simultaneously. A paralyzed hemidiaphragm moves paradoxically. This paradoxical motion may not be present during quiet breathing, but it usually becomes readily apparent during a quick, short "sniff" (*sniff test*). Localized weakness of part of one hemidiaphragm (i.e., *diaphragmatic eventration*) (Fig. 30-6) is often misinterpreted as diaphragmatic paralysis. This error can be avoided by performing fluoroscopy with the patient in the lateral projection; partial eventration is then readily observed as paradoxical motion of one portion of the hemidiaphragm, while the remainder of that hemidiaphragm moves normally. Eventration of an entire hemidiaphragm is impossible to distinguish from paralysis, since in both instances the entire hemidiaphragm moves paradoxically.

Fluoroscopy is sometimes useful in determining whether a nodule is truly in the lung. In an upright subject, nodules that are in the lung move in the caudal direction with inspiration, while nodules in the chest wall or ribs move in the cephalad direction. CT has largely supplanted fluoroscopy for this use; however, it is significantly more expensive, and fluoroscopy remains an option for evaluating certain pulmonary nodules.

Fluoroscopy of the heart may be useful in demonstrating calcifications in cardiac valves and in coronary arteries, but these areas are much better evaluated by CT or MRI. Fluoroscopy may suggest the presence of pericardial effusion much more convincingly than does the chest radiograph. However, fluoroscopy is rarely definitive for detecting a pericardial effusion, and other procedures, particularly ultrasound, CT, and MRI, are generally used to confirm a suspected pericardial effusion.

In the past, fluoroscopy was used as a screening procedure for routine examination of the chest. This is no longer acceptable for several reasons: (1) the patient's x-ray exposure is much greater during a short fluoroscopic examination than during the performance of standard chest radiographs; (2) small lesions in the lung fields are easily overlooked at fluoroscopy; and (3) no permanent record of the fluoroscopic examination is created.

Computed Tomography

Computed tomography (CT) is a radiologic technique for scanning cross-sections of the entire body. The underlying principle is the production of radiographic absorption profiles that are made at different angles in the same cross-sectional plane. A pencil-thin beam or beams of x-rays passes through the body as the radiographic tube rotates around the patient, and the transmitted radiation is detected by a sodium iodide crystal. By means of electronic transformation, the signals are fed into a computer, which synthesizes them into a radiographic image that displays the relative absorption coefficients of each small area in the plane of the scan. The technique is highly accurate, and its sensitivity to differences in density is considerably greater than that of the standard radiograph. Multidetector CT scanners now use multiple beams, so that 4 to 64 images are created simultaneously and at a much faster rate than when a single detector is used.

While the plain chest radiograph remains the primary radiologic technique in evaluating the chest, CT has added tremendous insight into disorders of the lungs, mediastinum, and chest wall. Cross-sectional images depicted by CT provide a huge added dimension in the investigation of chest pathology, and the increased resolution permits identification of many findings that are not visible on the plain radiograph (Fig. 30-7). This increased sensitivity is particularly true for small nodules, although the heightened sensitivity

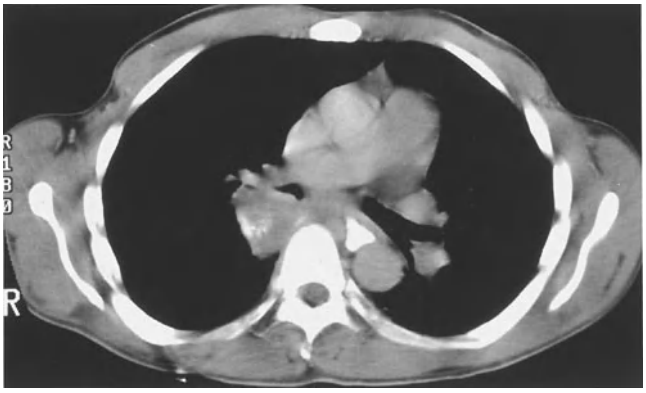
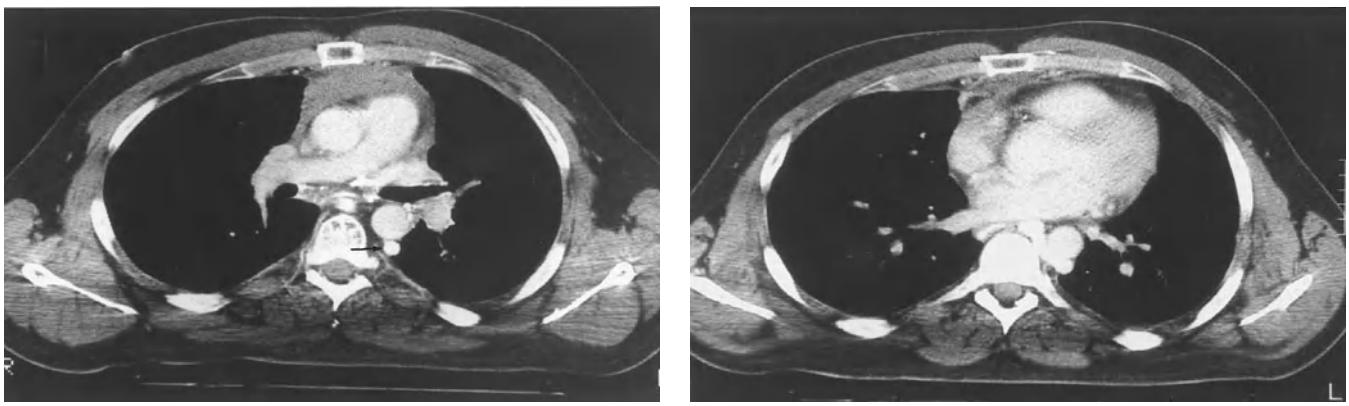


Figure 30-7 CT showing lung carcinoma not seen on routine chest radiograph. A large mass narrowing the right main stem bronchus can be seen in the right lower lobe. The mass contains some calcification.



A *B*

Figure 30-8 CT demonstrating Hodgkin's disease obstructing the superior vena cava. *A*. A mass is seen in the anterior mediastinum, just beneath the sternum. The mass completely obstructs the superior vena cava, which cannot be seen. However, the accessory azygos vein (arrow) is unusually bright, since it is carrying blood that would ordinarily pass through the superior vena cava. *B*. A lower section shows contrast material crossing into the azygos vein, where it then enters the superior vena cava, adjacent to the right atrium.

for unimportant small nodules is the bane of chest CT. In addition, the mediastinum, which is somewhat of an "occult" area on the plain radiograph, is seen in wonderful anatomic detail. Lymphadenopathy may be readily seen, and mediastinal lesions of uncertain nature may be elucidated (Fig. 30-8). The use of intravenous contrast material as part of the examination permits separation of vascular from nonvascular mediastinal lesions and identification of vascular invasion by neoplasm (Fig. 30-9). The technique is also extremely useful in investigating chest wall lesions or the extension of pulmonary or pleural tumors into the chest wall (Fig. 30-10)—an important consideration, since the chest wall is not readily studied with the plain radiograph unless bone destruction is present.

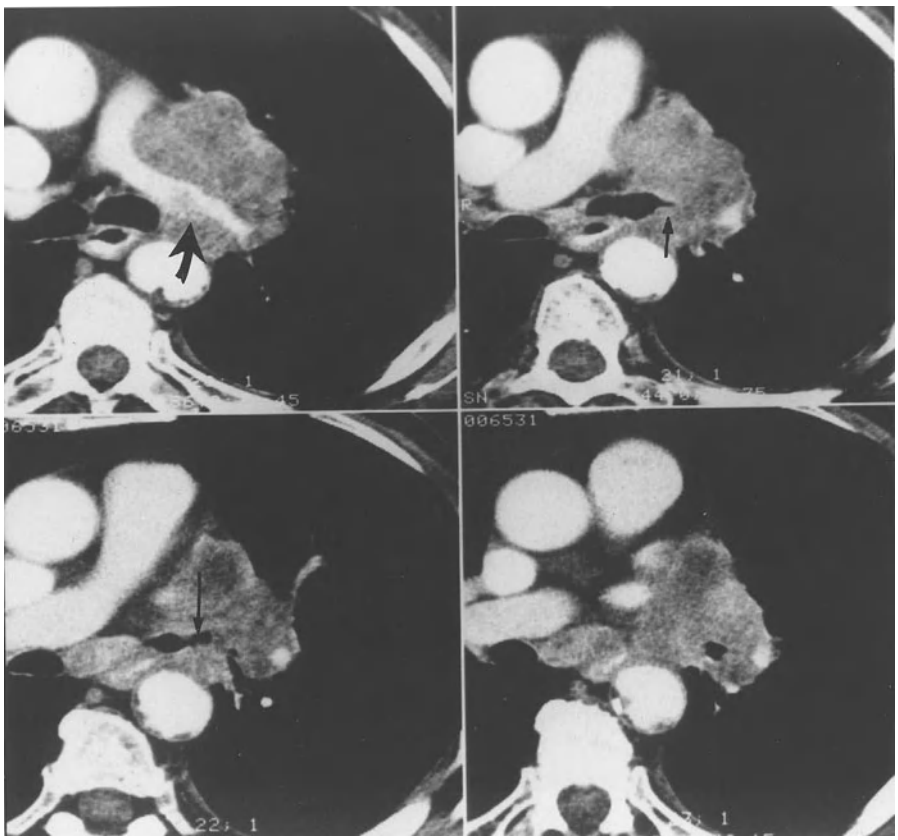


Figure 30-9 CT demonstration of extent of left upper lobe carcinoma. A mass is seen invading the pulmonary artery (large arrow) and left main stem bronchus (small arrows).

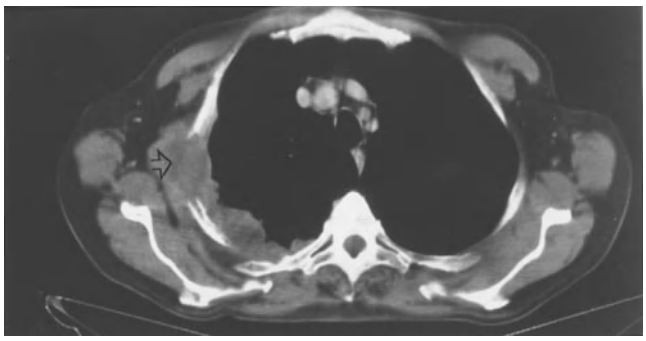
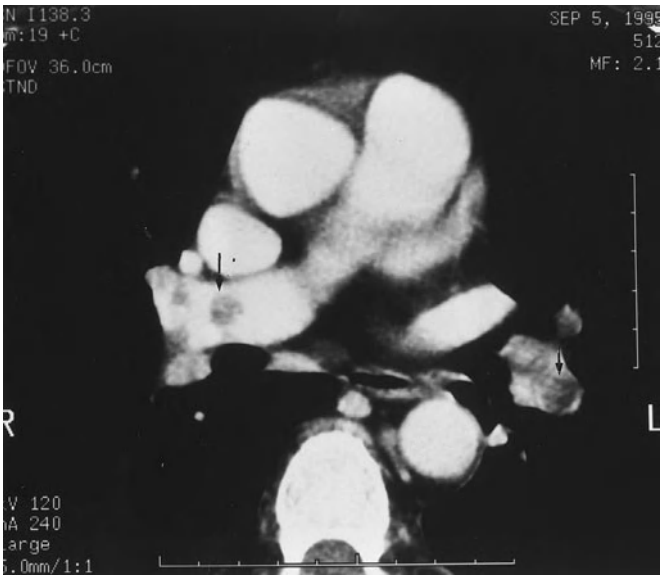


Figure 30-10 Mesothelioma extending into the chest wall. A pleural mesothelioma is seen on the right side; it directly invades the chest wall (arrow). The nodular character of the pleural involvement is characteristic of mesothelioma.

CT Angiography

CT angiography is an exciting application of helical (spiral) CT technology which has been made especially useful since the emergence of multidetector imaging. Axial, multiplanar, reformatted, and three-dimensional images of the vascular system are possible using this technique.

CT angiography has emerged as an excellent tool for identifying pulmonary embolism and has largely supplanted pulmonary angiography and scintigraphic ventilation-perfusion lung scanning. Direct visualization of pulmonary emboli by CT angiography carries a specificity similar to pulmonary angiography and a sensitivity similar to ventilation-perfusion scanning (Fig. 30-11). The technique is also useful in identifying chronic thromboembolic disease. Various aortic lesions, such as aortic dissection (Fig. 30-66), traumatic



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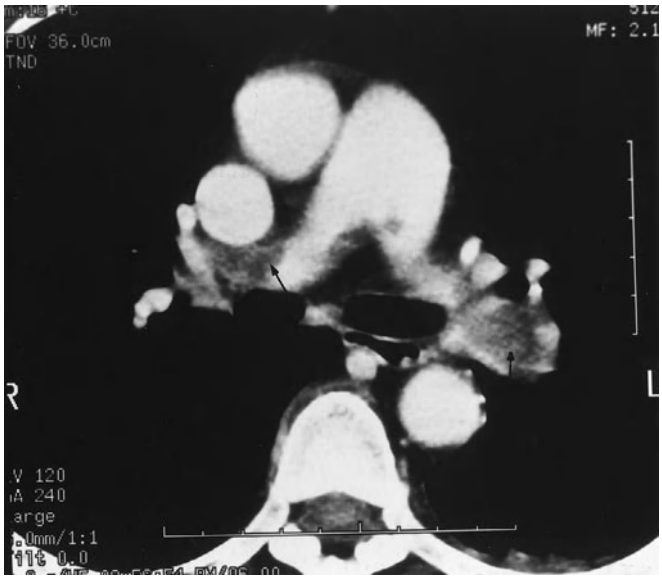

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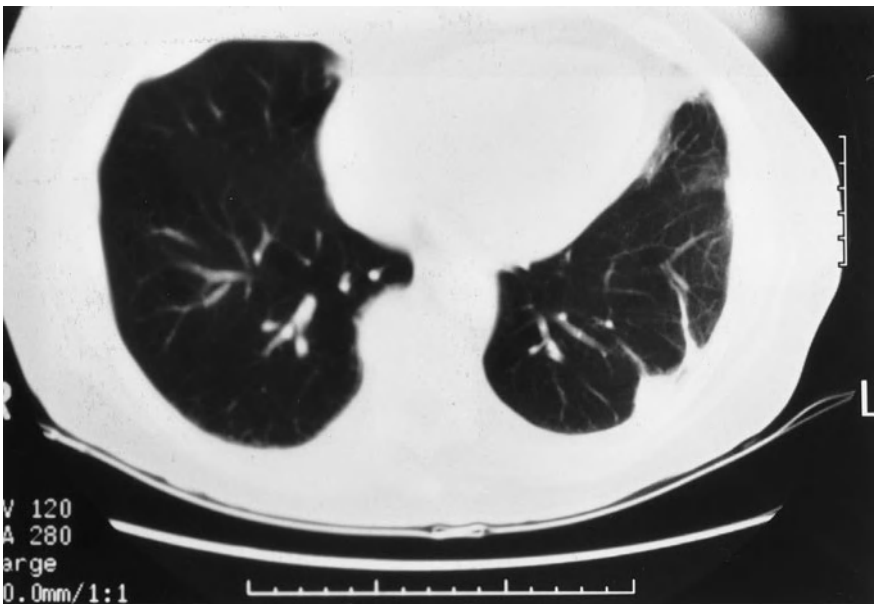


C

Figure 30-11 Spiral CT showing pulmonary embolus. *A* and *B*. Axial tomographic cuts at two levels show multiple central pulmonary emboli (arrows). *C*. Lung windows demonstrate a pulmonary infarct in the left lower lobe.

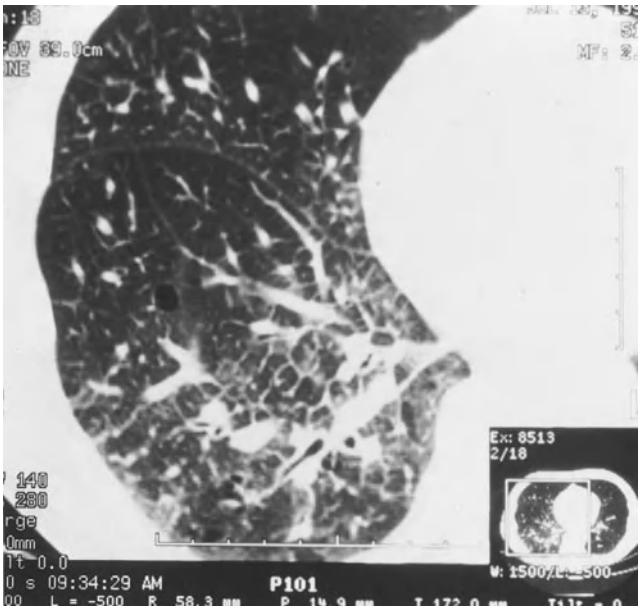


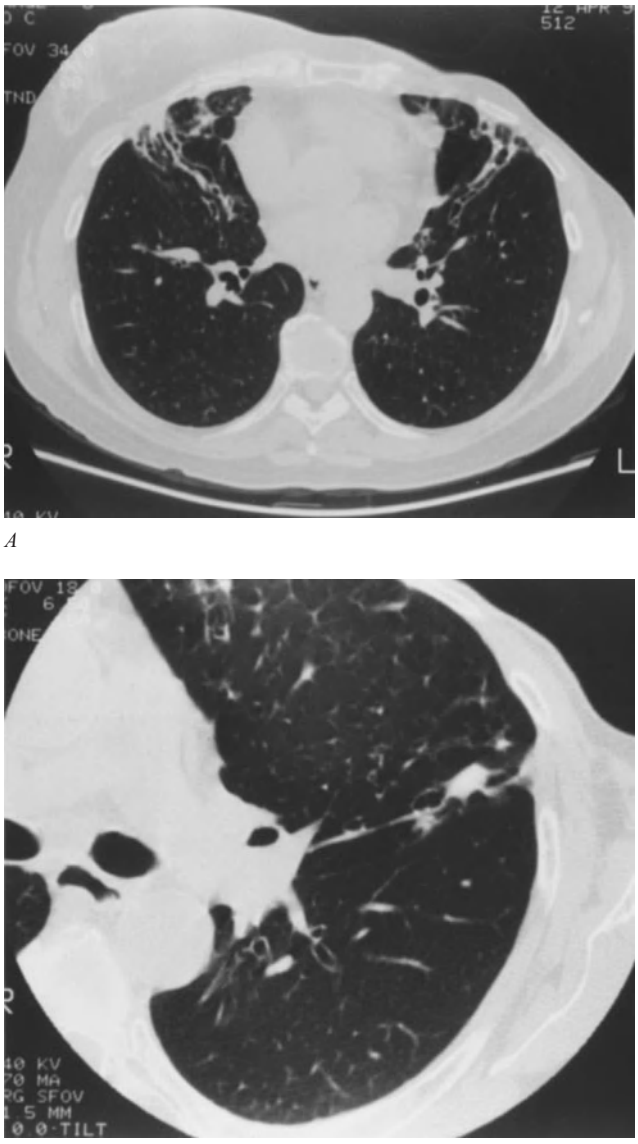
Figure 30-12 High-resolution CT of interstitial lung disease due to pancreatic carcinoma. Pulmonary lobules are nicely outlined by an interstitial process that affects the interlobular septae. This pattern is characteristic of lymphangitic spread of carcinoma, which, in this patient, was due to pancreatic carcinoma.

pseudoaneurysm, penetrating aortic ulcers, aortic aneurysms (Fig 30-24), and vascular anomalies of the aorta are well visualized using CT angiography. In addition, pulmonary venous malformations are readily recognized noninvasively. CT also has great usefulness in recognition and evaluation of cardiac disease.

High-Resolution CT

High-resolution CT is a special method for evaluating pulmonary pathology. The technique is based on generation of images of very thin anatomic slices (1 mm vs. 7 to 10 mm for the usual CT slice) and a special "bone algorithm" for reconstruction of the information obtained in each slice. The result is a very high-contrast image that provides excellent insight into certain pulmonary disorders.

High-resolution CT is primarily useful in identifying interstitial lung disease and bronchiectasis (Figs. 30-12 and 30-52). This technique has supplanted bronchography in evaluation of bronchiectasis (Fig. 30-13), as it is of comparable diagnostic accuracy and is noninvasive. In addition, high-resolution CT is helpful in identifying low-grade interstitial lung disease which may not be visible on the plain radiograph. While useful in stratifying differential diagnostic considerations in interstitial lung disease, high-resolution CT does not, at this time, completely supplant tissue biopsy. However, some clinicians will establish a diagnosis of usual interstitial pneumonitis (UIP) on the basis of clinical presentation and a characteristic CT appearance. In general, the technique serves mainly as an adjunct diagnostic method. While not ideal for studying mediastinal and chest wall lesions, high-resolution CT images are adequate to investigate these areas if the main



A

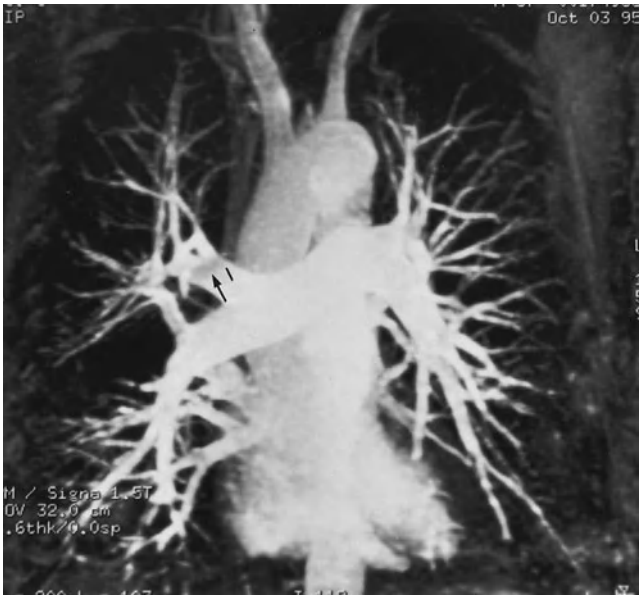
B

Figure 30-13 Bronchiectasis. *A*. Focal areas of tubular bronchiectasis are demonstrated in the middle lobe and lingula. This is a common manifestation of nontuberculous mycobacterial infection, in this case Mycobacterium avium intracellulare (MAI). *B*. High-resolution scan from another patient demonstrates more subtle bronchiectasis, with many small areas of invasion in the lingula. This was also secondary to MAI infection.

objective is delineation of the extent of the pulmonary process. In most instances, a routine, unenhanced CT study is performed prior to the high-resolution study to better evaluate the mediastinum, bones, and small pulmonary nodules that can be overlooked on the high-resolution images (since only *samples* of the lung are imaged, rather than consecutive contiguous slices).

Nuclear Magnetic Resonance

Magnetic resonance imaging (MRI) or nuclear magnetic resonance (NMR) is a technique that uses radiowaves modified by



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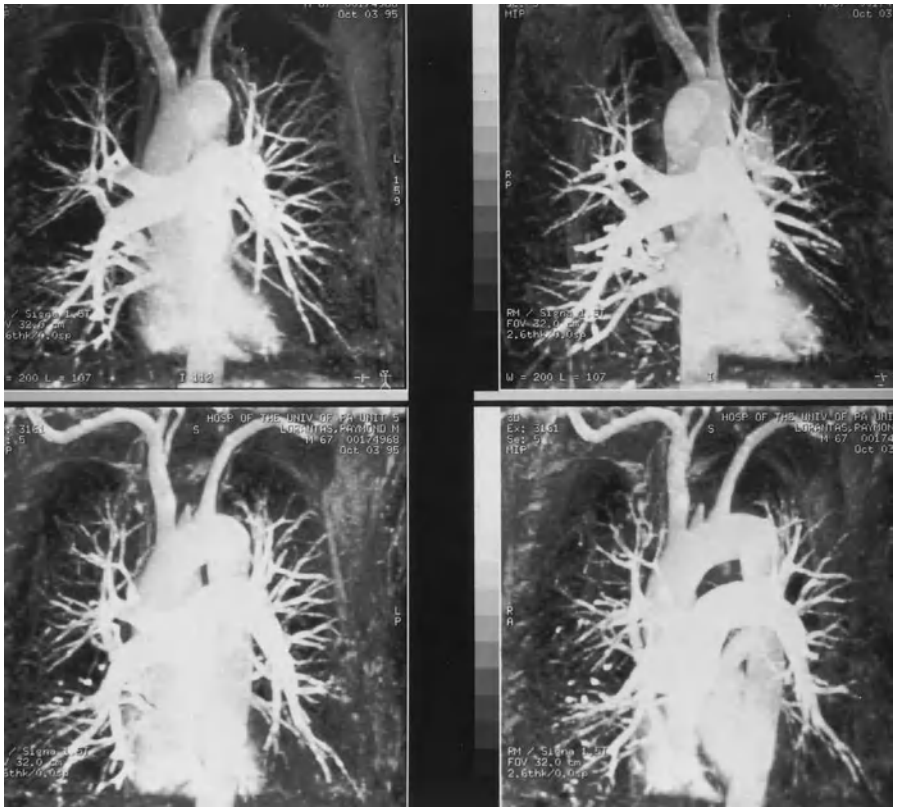


B

Figure 30-14 Pulmonary embolus demonstrated by "time of flight" MRI. This technique shows the blood vessels in detail, rivaling images obtained with pulmonary arteriography. *A*. Pulmonary embolus can be seen in the right upper lobe (arrow). *B*. Reproductions in various degrees of obliquity show that the defect of the pulmonary embolus remains constant.

a strong magnetic field to produce a diagnostic image. The images generated are somewhat similar to CT images. However, using MRI, vascular structures are usually well seen without the use of contrast material, although intravenous gadolinium can be administered for better vascular evaluation. In addition, with MRI, different images and different information can be obtained by manipulation of the radiowave frequency and timing of the impulses delivered.

Although MRI has not had quite as great an impact as CT in the investigation of pulmonary lesions, it has great usefulness in the study of vascular lesions of the pulmonary vessels and mediastinum. In some institutions, MRI has

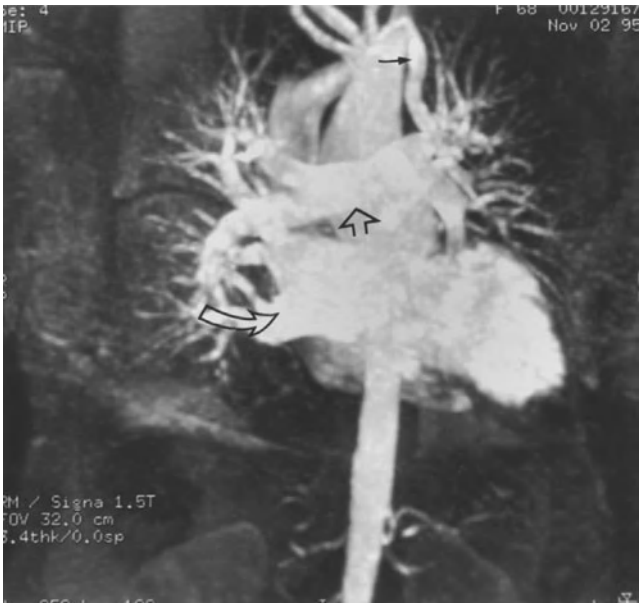


Figure 30-15 MRI demonstration of partial anomalous pulmonary venous return. Time of flight image shows the pulmonary arteries (straight arrow), pulmonary veins (curved arrow), and an anomalous pulmonary vein entering the superior vena cava (small arrow).

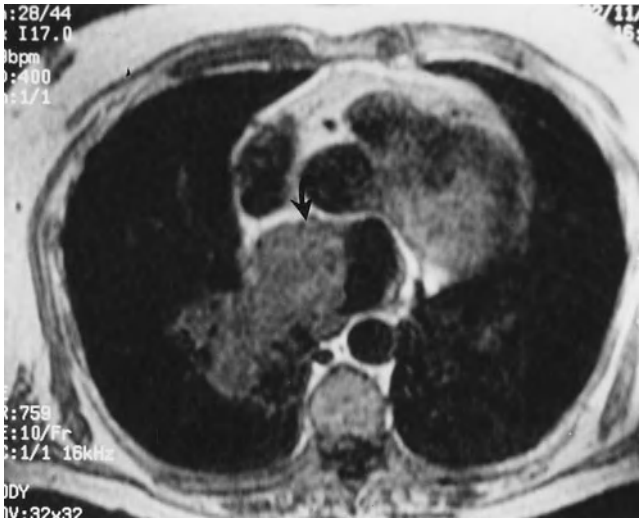
become the primary technique used in the study of aortic dissection (Fig. 30-62), although CT is equally good, somewhat faster, and much more readily available. MRI may also have a major role in the investigation of pulmonary embolism, either acute or chronic (Fig. 30-14). Finally, MRI has become a major means of investigation of congenital heart disease and shows great promise in the evaluation of myocardial ischemia.

In addition to use of intravenous administration of gadolinium as a "contrast agent" to allow better visualization of vascular structures, a variety of MRI scanning techniques (e.g., "time of flight" imaging, etc.) further enhance the technique's utility (Figs. 30-15 and 30-16). Scanning can now be done extremely quickly, almost rivaling CT in rapidity of image acquisition.

MRI provides a unique feature in investigating the thorax and other body parts: the images obtained can be reconstructed in any one of several anatomic planes. While the standard MR image is usually an axial view, similar to that obtained with CT, sagittal and coronal images can be easily created from the information obtained at the time of the study (Fig. 30-14) and are usually routinely obtained. With the newer multidetectors, reformatted coronal and sagittal images with CT rival those of MRI.

Contrast Examinations

Air in the bronchi and alveoli is a superb contrast medium, outlining the pulmonary vasculature, heart, aorta and other mediastinal structures, diaphragm, and chest wall. In addition, pathological processes in the lung often produce characteristic changes in the pattern of the pulmonary vessels or air-filled alveoli. Hence, the plain chest film is a very useful



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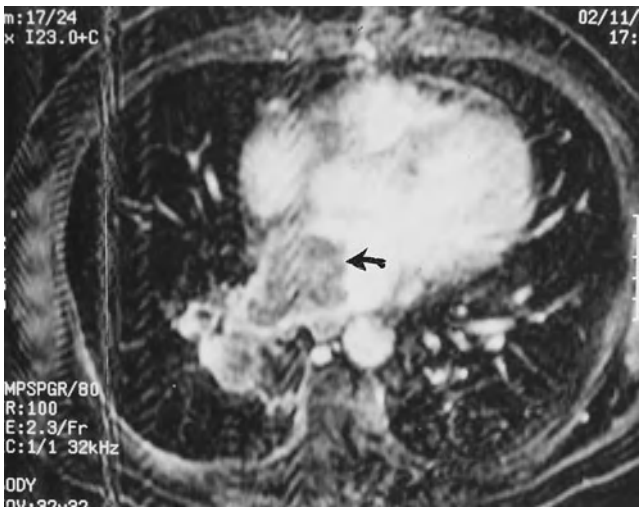


B

Figure 30-16 MRI of metastatic renal cell carcinoma (arrows) to the right lower lobe pulmonary veins and left atrium. *A*. Tumor in the left atrium (T1 image). *B*. Tumor in the pulmonary veins and left atrium (T2 image).

tool in the diagnosis of pulmonary disease, and more sophisticated radiographic techniques are often not necessary. Supplementary information can be gained by placement of contrast material into different components of the chest. Positive contrast material, such as barium sulfate suspension, is commonly introduced into the esophagus; other suitable media are used to visualize cardiac chambers, the trachea and bronchi, pulmonary vessels, vena cava and mediastinal veins, and mediastinal lymphatics. These techniques are very efficient in increasing the information that can be gained on a CT scan. Historically, carbon dioxide and nitrous oxide have been used to outline the right-sided cardiac chambers.

With CT, intravenous contrast material is especially useful in investigating mediastinal lesions and vascular structures. Oral contrast agents (e.g., Gastrografin) may be used to outline the esophagus and the gastrointestinal tract in the

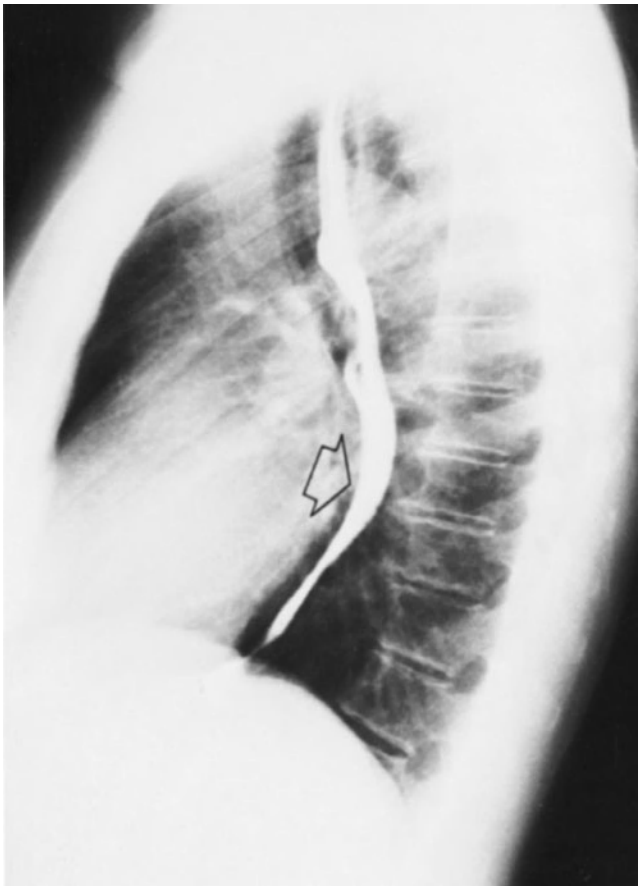


Figure 30-17 Enlarged left atrium. The esophagus is displaced posteriorly by an enlarged left atrium (arrow).

upper abdomen. Similarly, using MRI, administration of intravenous gadolinium is frequently used to better depict vascular structures or highly vascular organs, such as the liver.

Of all the contrast examinations available, the barium swallow, generally carried out under fluoroscopic guidance, is the simplest to perform. A thick mixture of swallowed barium sulfate, with or without gas, outlines the esophageal contour, making it easy to detect displacement of the esophagus by adjacent mediastinal structures, such as tumor-containing lymph nodes or a large left atrium (Fig. 30-17). Abnormalities of the esophagus itself, such as achalasia or tumor, are also easily seen. While CT demonstrates most lesions of the esophagus, especially when oral contrast is administered, the barium swallow is much more sensitive for mucosal diseases, as it sometimes demonstrates esophageal carcinoma which is not well seen on CT.

Although the trachea and major bronchi are readily visualized in the mediastinum and hila on the plain film, bronchography or CT is necessary to better demonstrate the trachea, main stem bronchi, and peripheral bronchi. Historically, bronchography was performed with special contrast material to perform this function, but this has been replaced by CT and is no longer used. Figures 30-18 and 30-19 are bronchograms obtained using oily Dionosil as a contrast agent instilled in the airways.

Pulmonary Angiography

Pulmonary angiography and related interventional radiographic techniques are also discussed in Chapter 32. When used as a diagnostic tool, pulmonary angiography entails rapid injection of a radiopaque dye into the pulmonary circulation through a catheter introduced into the pulmonary arterial tree or into a large systemic vein leading into the right atrium. In the past, angiography, was the gold-standard in investigation of pulmonary thromboembolic disease (Figs. 30-20 and 30-21) (see Chapter 34); however, CT yields comparable information and is much less invasive. Ventilation-perfusion lung scans using radioactive isotopes are also useful in detecting pulmonary embolism (see Chapter 82), but they, too, are currently used less frequently than CT.

Congenital abnormalities of the pulmonary vascular tree, such as hypoplasia or agenesis of the pulmonary artery, arteriovenous malformation, pulmonary varix, or anomalous pulmonary venous return, are also identified using pulmonary angiography (Fig. 30-5*B*). These abnormalities are often suspected on the basis of routine radiographs, but angiography may be used for confirmation. As with pulmonary embolism, both CT and MRI have largely supplanted pulmonary angiography in investigating these lesions (Figs. 30-11 and 30-15).

Pulmonary angiographic procedures may also be used therapeutically (see Chapter 34). Arteriovenous malformations can be treated with pulmonary artery embolization using a variety of embolic materials, as can bleeding from the pulmonary or bronchial arteries. A strategically placed pulmonary artery catheter may be used to infuse streptokinase or other lytic agents to dissolve an acute pulmonary embolus. Similarly, techniques are available to fragment and extract pulmonary emboli through pulmonary artery catheters.

Aortography and Systemic Arteriography

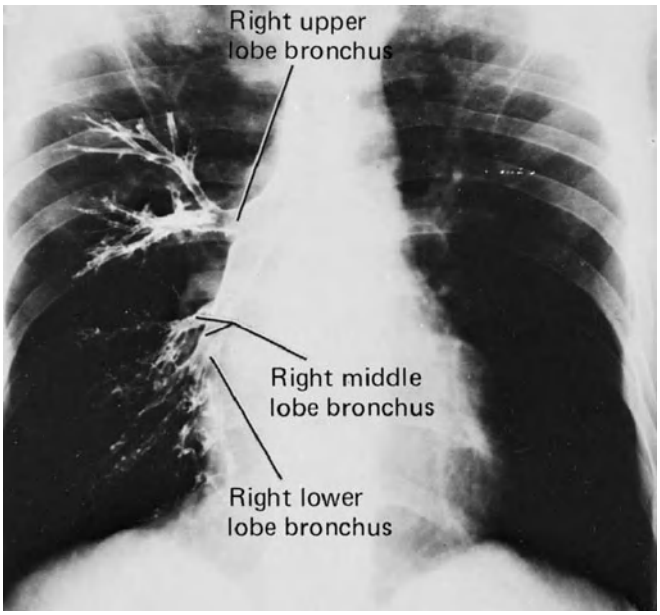
Puzzling shadows in the vicinity of the middle (visceral) compartment of the mediastinum can be explored with aortography, a technique that takes advantage of the fact that the aorta is within the middle mediastinal compartment.

Opacification of the aorta using contrast material usually requires retrograde catheterization of the aorta for direct injection. Middle mediastinal masses frequently prove to be vascular (e.g., dissecting aneurysms of the aorta), saccular or fusiform aneurysms of the aorta (Fig. 30-22), or anomalies or unusual tortuosity of the aorta or great vessels. In current practice, CT or MRI usually makes arteriography unnecessary (Figs. 30-23 and 30-24).

Owing to the dual blood supply of the lung, pulmonary arteriography may not be rewarding in the evaluation of some pulmonary lesions; in these cases, bronchial arteriography may be more useful. In patients with massive hemoptysis due to tumor or infection (e.g., tuberculosis, bronchiectasis, or aspergillosis), the major pulmonary blood supply is usually the bronchial circulation. Embolization of feeding bronchial arteries may yield temporary, or even permanent, control of the bleeding.

Bronchial arteries supply most lung tumors. Infusion of various chemotherapeutic agents into these tumors via the bronchial circulation has been attempted for palliative control of nonresectable malignancies. So far, this has not been a very fruitful approach.

Venography can also be helpful in the diagnostic evaluation of pulmonary abnormalities. After injection of radiopaque material into a large vein of one or both upper extremities, displacement or obstruction of the superior vena cava by mediastinal masses or scarring due to inflammatory



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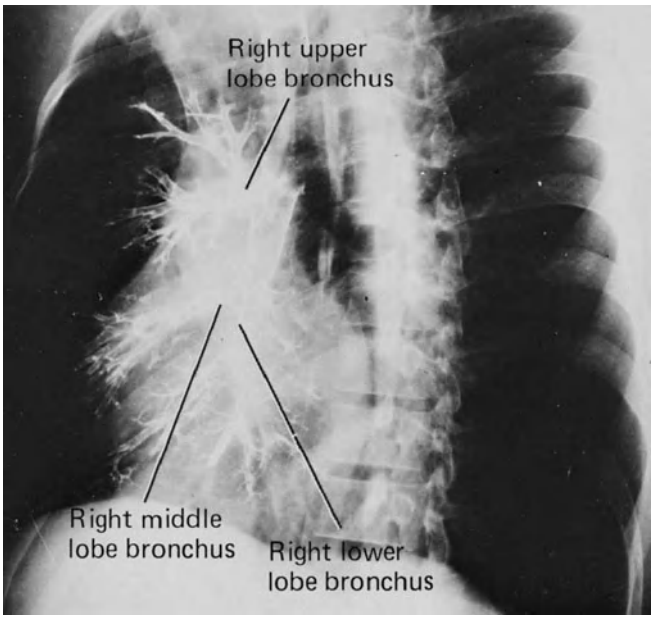

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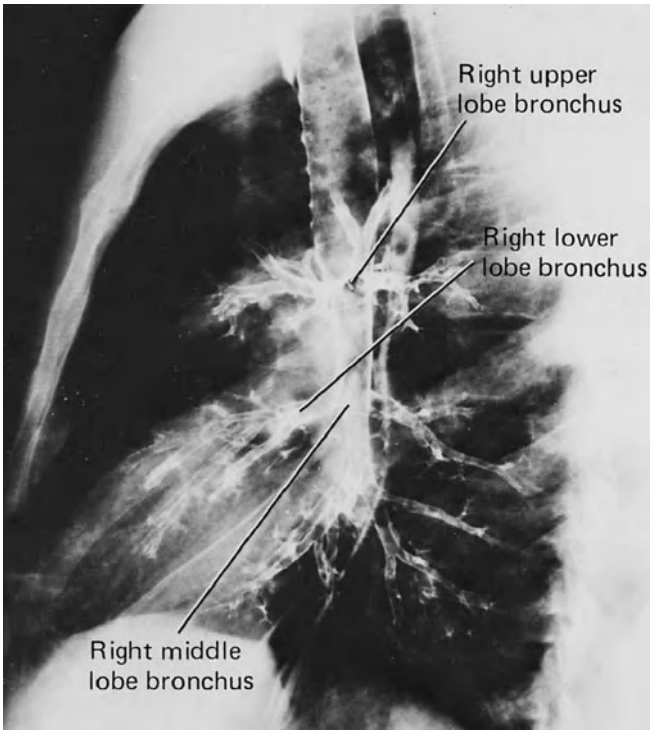

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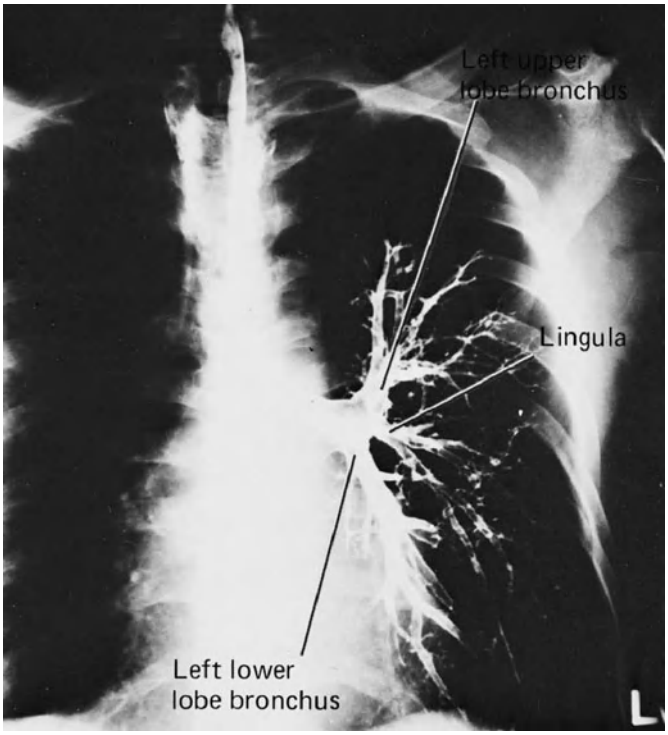
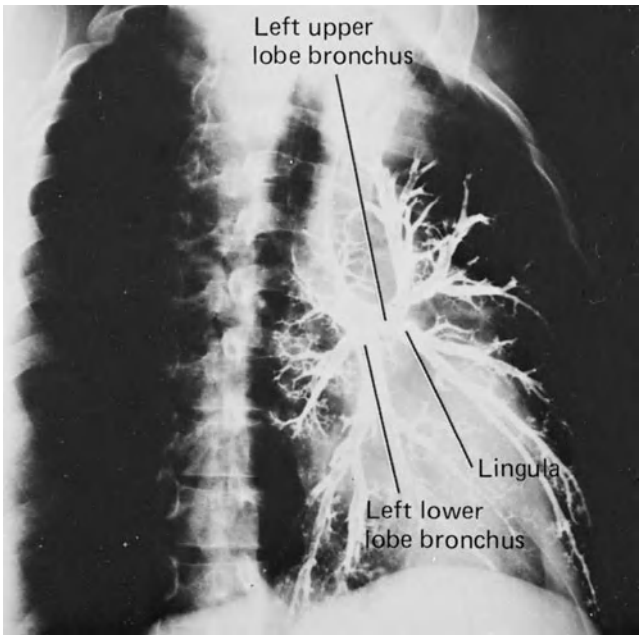


D

Figure 30-18 Normal bronchogram. The normal bronchial anatomy of the right lung is shown in the PA (*A*), oblique (*B*), and lateral (*C*) projections. The corresponding anatomy of the left lung is demonstrated in the PA (*D*) and oblique (*E*) projections. The lateral projection for the left lung appears in Figure 30-19, which also illustrates bronchiectasis. A schematic representation of the bronchial tree in the PA projection appears in Figure 30–38.



E

Figure 30-18 (*Continued*)

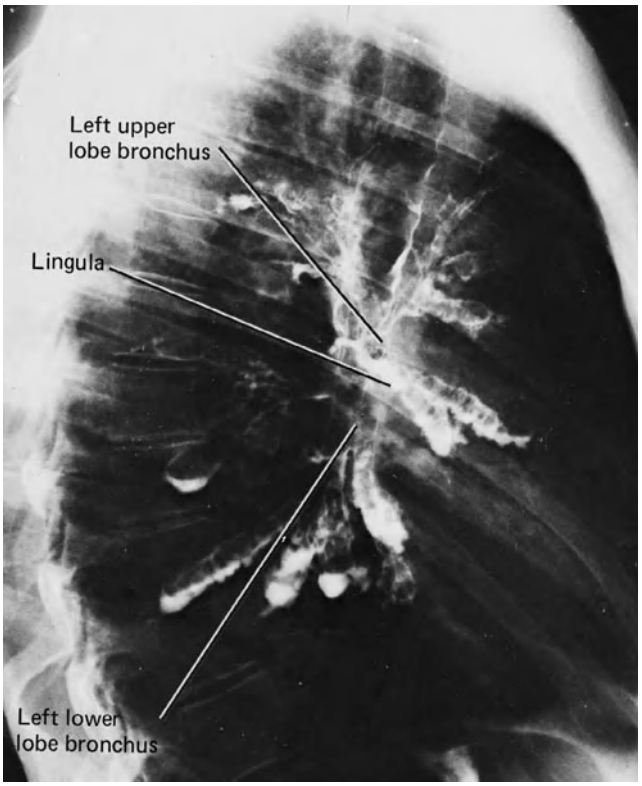


Figure 30-19 Bronchiectasis. The lateral view shows extensive bronchiectasis of the left lung. All the bronchi that contain contrast medium show saccular dilatation of their segments. This was secondary to nonspecific infection.

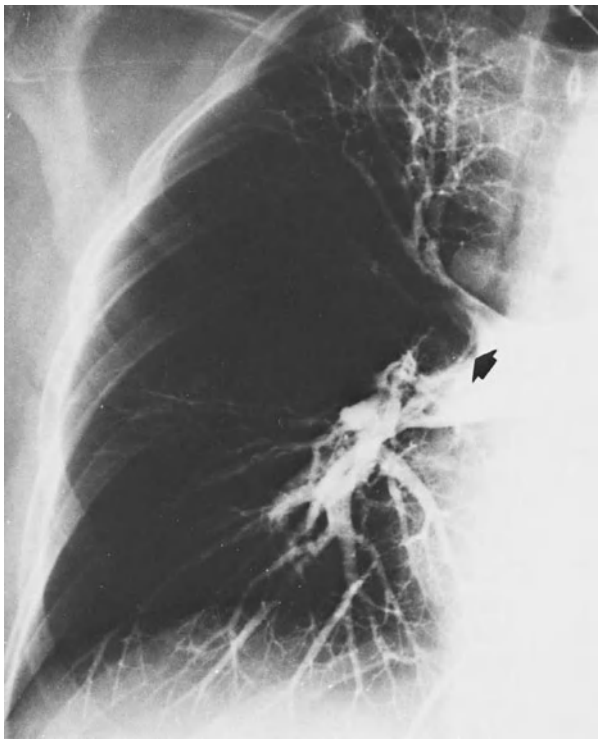


Figure 30-20 Large pulmonary embolus. A large pulmonary embolus is lodged in the right main pulmonary artery (arrow) and has compromised blood flow primarily to the arteries of the right upper lobe. The peripheral vessels in the right mid lung zone are not filled (Westermark's sign).

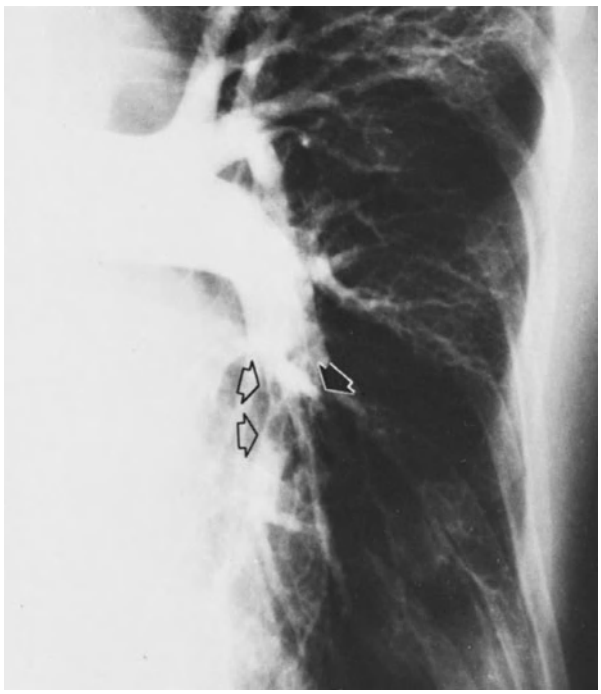
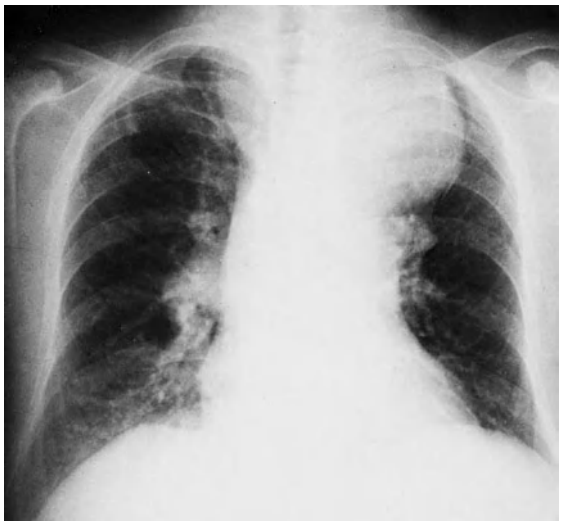


Figure 30-21 Small pulmonary emboli. Angiography shows small filling defects in the posterior basal artery (open arrows). Several of the other basal divisions are cut off (closed arrow). Blood flow to the left upper lobe is well preserved. Angiography was helpful diagnostically in this patient because the lung scan was equivocal.



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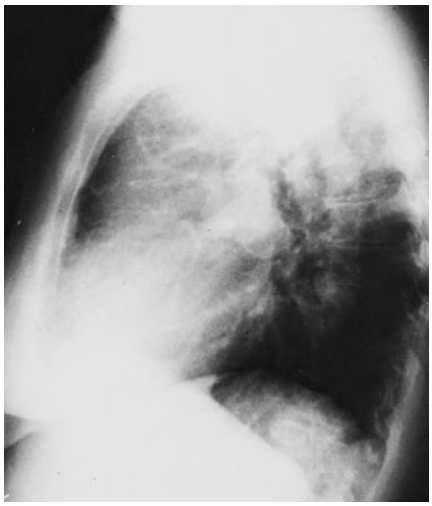

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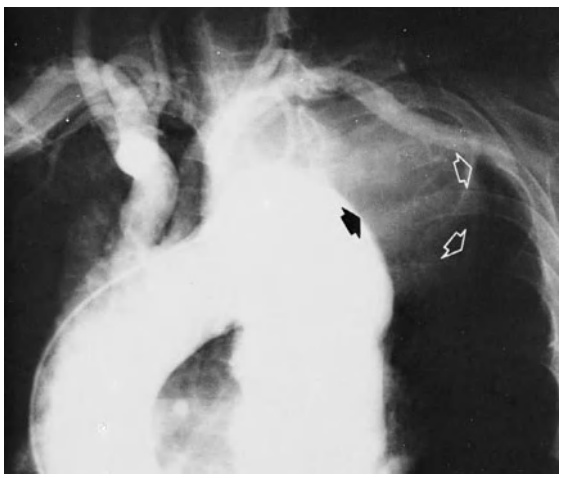


C

Figure 30-22 Aortic aneurysm. *A*. PA view. A large mass is in the left upper mediastinum. *B*. Lateral view. This mass appears to be within the middle mediastinal (visceral) compartment. *C*. Aortogram. The dye column is irregular at the site of the aortic aneurysm (closed arrow), most of which is filled with clot (open arrows).

processes can be identified (Fig. 30-25). The azygos vein can also be opacified, and visualization of this structure is occasionally helpful in evaluating mediastinal lesions or suspected bronchogenic carcinoma. Once again, these techniques have been largely supplanted by CT (Fig. 30-9) and MRI.

Air Contrast Studies

Historically, air has been introduced into various compartments of the chest for diagnostic purposes. For example, deliberate introduction of air into the pleural space (diagnostic pneumothorax) has been used to demonstrate pleural lesions. Diagnostic pneumothorax has fallen out of vogue because other methods, such as thoracoscopy, yield much more definitive and reliable information. Diagnostic pneumothorax and diagnostic pneumoperitoneum have been used to investigate masses in the vicinity of the diaphragm. Air in the peritoneal may also demonstrate a subphrenic abscess. CT or MRI is much less invasive and more definitive.

PULMONARY ARTERIES AND VEINS

The pulmonary arteries are recognized as structures that accompany the bronchi and branch in a similar fashion (Fig. 30-26 *A*). In contrast, the pulmonary veins take a somewhat different course (Fig. 30-26 *B*). In the lower lobes, the pulmonary veins are considerably more caudal than the corresponding arteries; the veins are situated at the level of the eighth to tenth ribs posteriorly, whereas the arteries are at the level of the seventh and eighth ribs. In the upper lobes, the pulmonary veins are lateral to the pulmonary arteries (Fig. 30-15).

On the plain film, the direction taken by a pulmonary vessel is the most useful basis for establishing its identity. Near the hili, particularly in the lower lobes, the pulmonary veins are more horizontal than the pulmonary arteries. At the hili, the pulmonary veins lie below and lateral to the arteries (Figs. 30-15 and 30-26). Although it is often possible to distinguish arteries from veins by plain film, this distinction is seldom useful, and the generic terms *pulmonary vessels* and *pulmonary vasculature* are used. CT and MRI more readily depict the pulmonary arteries and veins. The pulmonary arteries arise from the main pulmonary artery trunk, while the pulmonary veins enter the left atrium (Figs. 30-15 and 30-26).

Distribution of Pulmonary Blood Flow

Blood flow is not uniform in the normal, upright human lung. Moreover, the blood flow pattern shifts with changes in posture, during exercise, and in a variety of heart and lung diseases. In the normal pulmonary circulation, gravity is the predominant determinant of the pattern of blood flow. Under the influence of gravity, hydrostatic pressure in pulmonary arteries, capillaries, and veins decreases by approximately 1 cm H_2O per centimeter of distance from the bottom to the top of the lung. Accordingly, in the upright position, blood flow

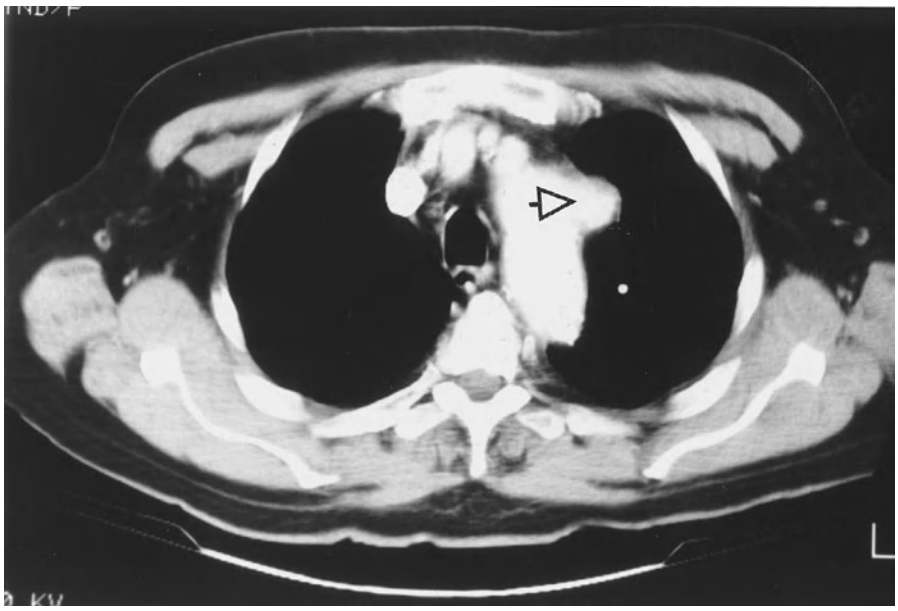


Figure 30-23 Aortic aneurysm shown by CT. A saccular aneurysm of the aortic arch (arrow) is readily demonstrated.

is minimal at the apex and maximal at the base. In the supine position, blood flow becomes much more uniform. If the lung is inverted, the normal pattern is reversed, so that flow to the apex, now dependent, increases considerably and exceeds blood flow to the base (Fig. 30-27). During walking or with any mild exercise in the upright position, total pulmonary flow increases, but flow to the lung apex increases proportionately more than flow to the base, resulting in a more uniform distribution.

If pulmonary arterial pressure at the top of the lung fails to exceed alveolar pressure, capillaries in the apices collapse. In the normal lung, pulsatile pulmonary blood flow suffices to perfuse the apices; but when pulmonary arterial pressure falls, as in hemorrhagic hypotension, the normal marginal perfusion of the apices may give way to cessation of blood flow. Gravity plays less of a role once an increase in pulmonary vascular resistance has raised pulmonary arterial pressure to hypertensive levels.

Lung disease often modifies the pattern of pulmonary blood flow by mechanical means and by development of pulmonary vasoconstriction (Fig. 30-28). Heart disease may also affect the pattern of flow. For example, in left-to-right intracardiac shunts, pulmonary blood flow not only increases but also becomes more uniform than normal. The pattern

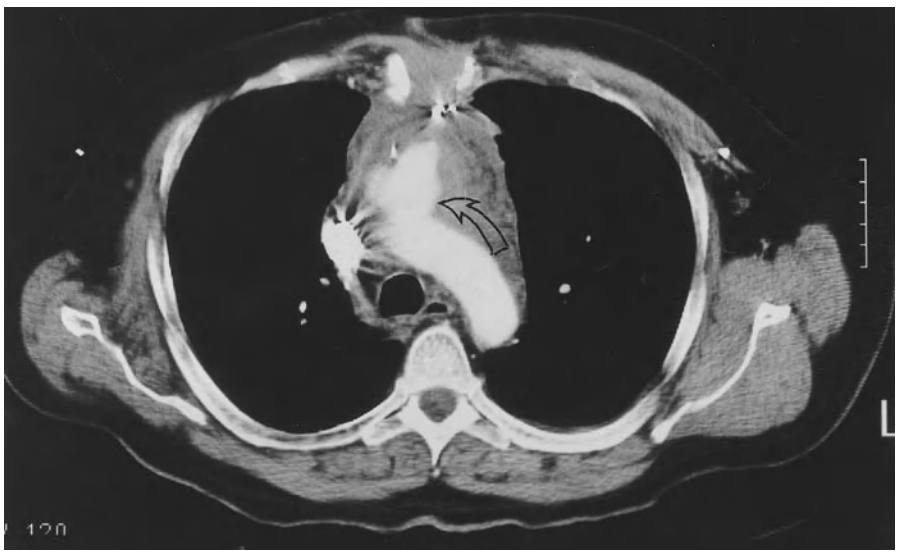


Figure 30-24 Aortic pseudoaneurysm demonstrated by CT. Anterior mediastinal infection led to development of a pseudoaneurysm at an aortotomy site. The CT not only demonstrates the pseudoaneurysm (arrow) but also shows masses caused by infection in the anterior mediastinum and chest wall.

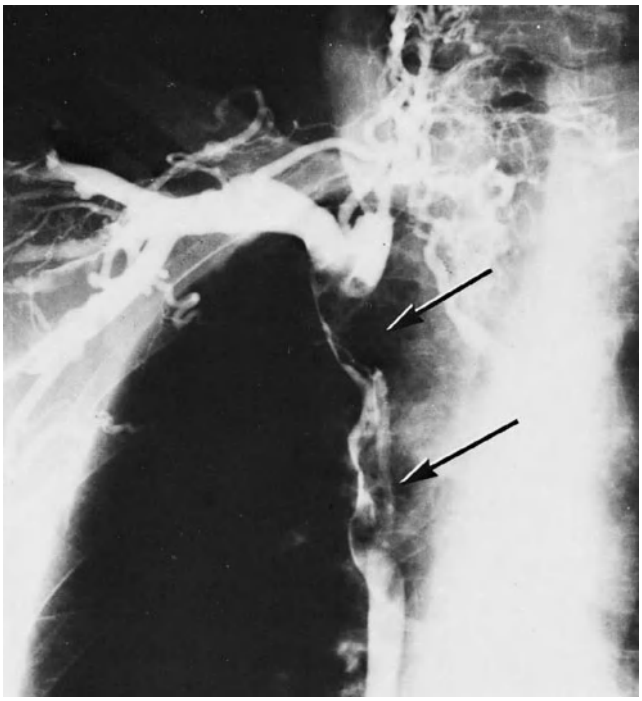
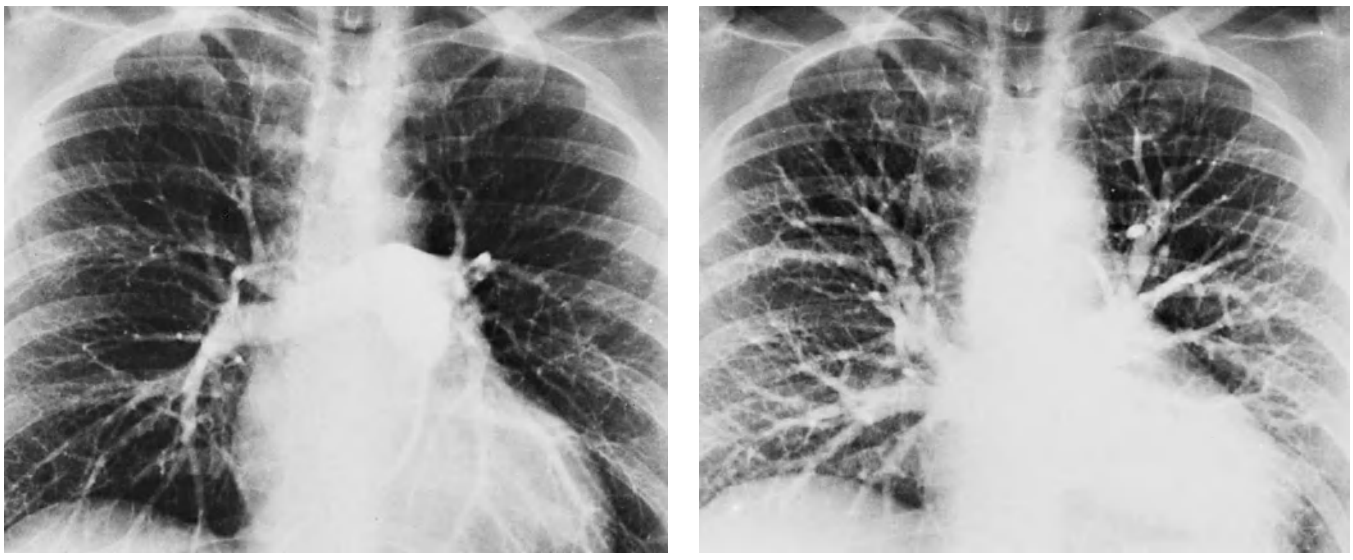


Figure 30-25 Superior vena caval invasion by metastatic tumor. A superior venacavogram shows invasion of the superior vena cava in several places (arrows) by metastatic tumor involving the mediastinal lymph nodes. Today, this would be identified by CT.

is quite similar to that in exercise. In heart disease associated with high pulmonary venous pressure (e.g., chronic left ventricular failure or mitral stenosis), the distribution of blood flow tends to become more uniform early in the disease. In time, the apices become relatively hyperperfused as a result of interstitial edema, pulmonary fibrosis, and hypoxic vasoconstriction of the lung bases. As a consequence, pulmonary vascular resistance at the lung bases is increased in the setting of pulmonary venous hypertension, and blood flow is directed toward the apices (Fig. 30-29). In prolonged, severe pulmonary venous hypertension, further constriction of the pulmonary vasculature occurs diffusely through the lungs, resulting in the "pruned tree" appearance of pulmonary arterial hypertension. Chronic lung disease or idiopathic pulmonary hypertension (Fig. 30-30*A*) may also result in the radiographic findings of pulmonary arterial hypertension. In general, the diagnostic accuracy of the plain film is much greater for pulmonary venous hypertension than for pulmonary arterial hypertension.

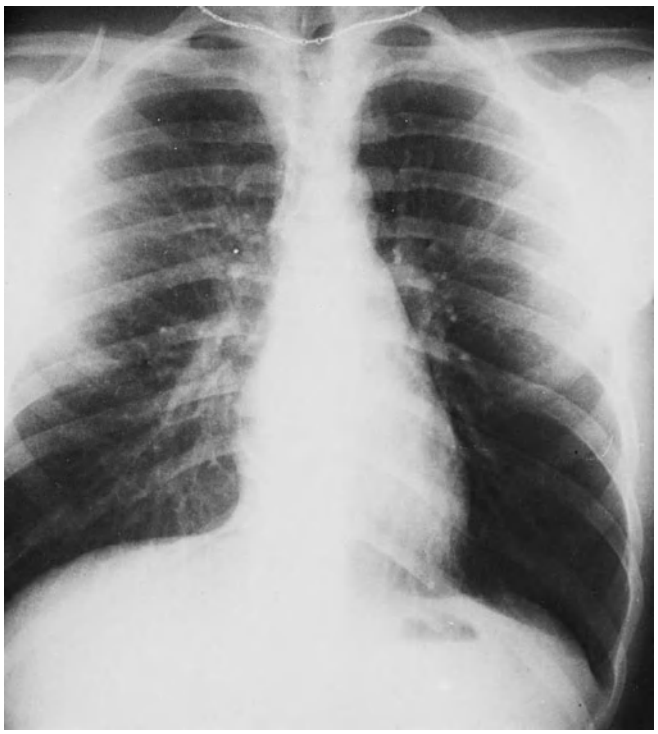
CT and MRI may suggest the presence of pulmonary arterial hypertension. Ordinarily, the aortic diameter is greater than the pulmonary artery, but in pulmonary hypertension, the situation is reversed (Fig. 30-30*B*).

The influence of gravity on the distribution of blood flow bears on the interpretation of the chest radiograph. The mainstay of the concept, illustrated in Fig. 30-31, is that in the normal upright lung, although gravity causes pulmonary arterial and venous pressures to increase from top to bottom of the lung, alveolar pressure remains virtually constant (see Chapter 11). Alterations in the normal relationships among pulmonary arterial, pulmonary venous, and alveolar pressures from top to bottom of the upright lung cause derangements in the pattern of blood flow. For example, a regional increase in alveolar pressure may arise because of "ball-valve" physiology as a result of bronchoconstriction or bronchial obstruction by a foreign body or mucus plug. In chronic obstructive airway disease, this mechanism contributes to



A *B*

Figure 30-26 Pulmonary arteries and veins. *A*. The early phase of the pulmonary angiogram depicts the normal course of the pulmonary arteries. *B*. The late phase shows the normal course of the pulmonary veins. The veins have a more horizontal course than the arteries and enter the hilus below the arteries.



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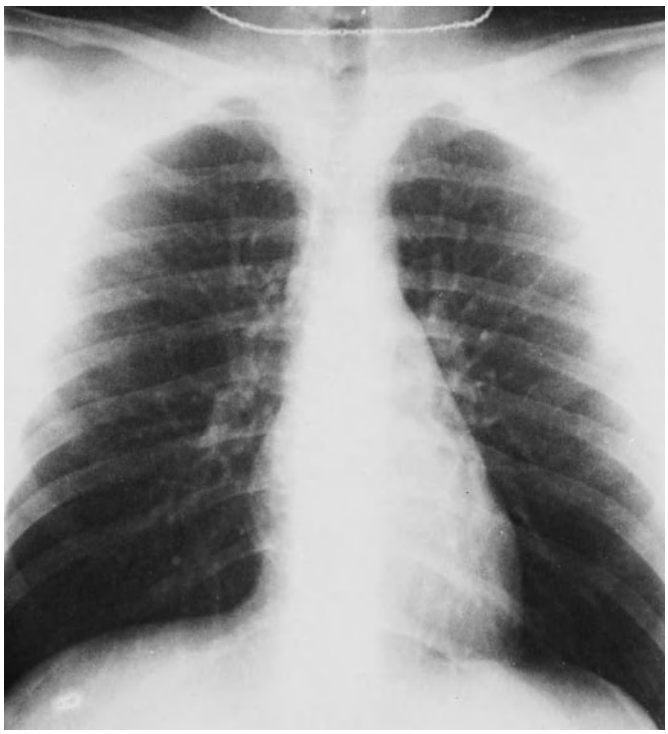

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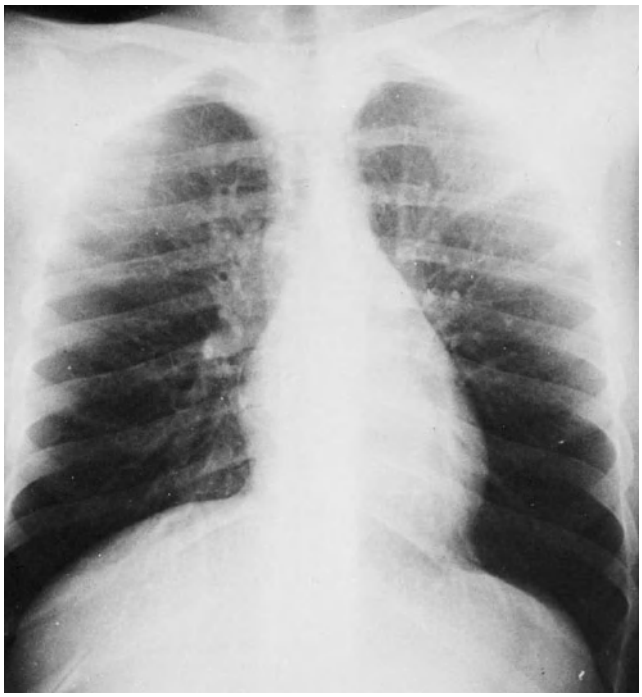
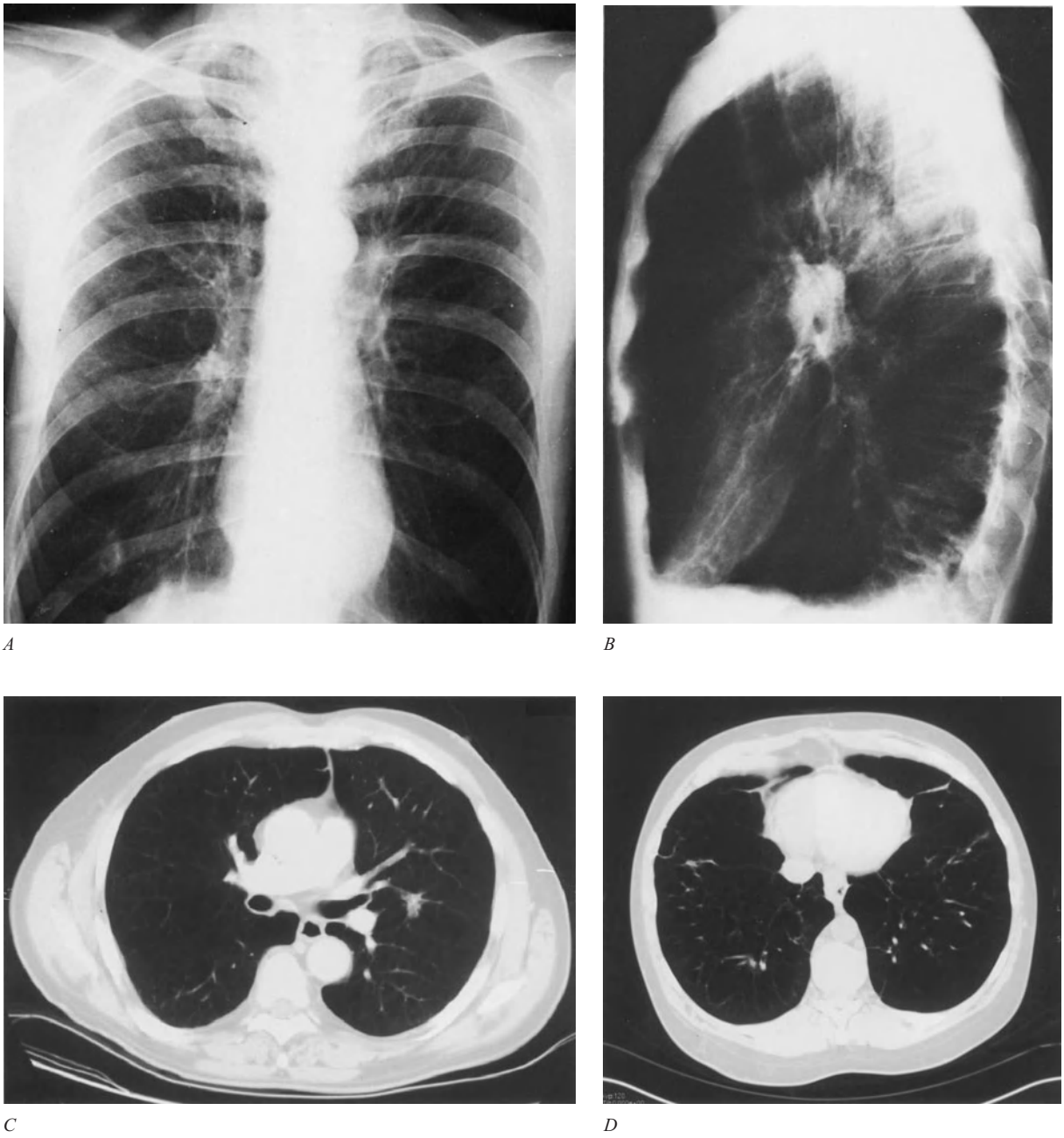


C

Figure 30-27 Effect of gravity on the pulmonary vasculature. Vascular patterns are compared in a normal subject in the erect, supine, and upside-down positions. *A*. Erect posture. The vascular pattern is more prominent at the bases. *B*. Supine position. The vascular pattern is more uniform. *C*. Upside-down position. The vascular pattern is more marked at the apices.

rearrangement of blood flow, adding a functional component to the anatomic effect of obliteration of parts of the pulmonary vascular bed by disease.

Other disease processes also cause a characteristic redistribution of pulmonary blood flow. For example, although uncommonly seen, the oligemic pattern distal to a large pulmonary embolus (Westermark's sign) is of great diagnostic value (Fig. 30-32). In primary pulmonary hypertension, the peripheral vessels are small and the central vessels are quite large, resulting in the pruned-tree appearance of the pulmonary vasculature described earlier (Fig. 30-30*A*). In emphysema, local destruction of pulmonary vasculature results in bizarre and unpredictable patterns of pulmonary blood flow (Fig. 30-28*A*).



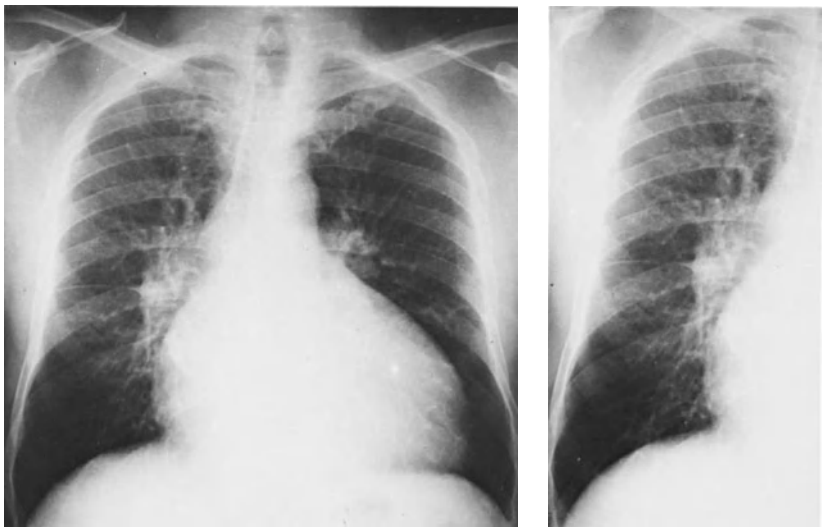
A *B*

C *D*

Figure 30-28 Severe pulmonary emphysema. *A*. PA view. Both lungs appear to be hyper-radiolucent. Blood flow to the left lower lobe is particularly reduced. *B*. Lateral view. The marked hyper-radiolucency is associated with a flat diaphragm, a wide anteroposterior diameter of the chest, and an increase in the retrosternal space. These changes represent advanced emphysema. In mild emphysema, the chest radiograph is usually normal. *C*. CT showing moderate centrilobular emphysema with incidental left upper lobe carcinoma. Multifocal, asymmetric hyperinflation is present. A small nodular infiltrate in the left upper lobe proved to be a primary lung carcinoma. *D*. CT showing panlobular emphysema in α_1-antitrypsin deficiency. Diffuse emphysematous changes are present, primarily at the lung bases.

DISTRIBUTION OF AIR WITHIN THE LUNGS

Just as is the case for pulmonary blood flow, the distribution of ventilation is affected by gravity. Normally, ventilation to the base is greater than to the apex because of the greater alveolar distention caused by gravity and a higher transpulmonary pressure at the apex (see Chapter 11). Changes in ventilation from top to bottom of the upright lung are much more modest than are changes in blood flow. When the lung is supine, ventilation, as well as blood flow, is much more uniform. If the lung is turned upside down, the normal pattern is reversed, so the apex is better ventilated than the base.



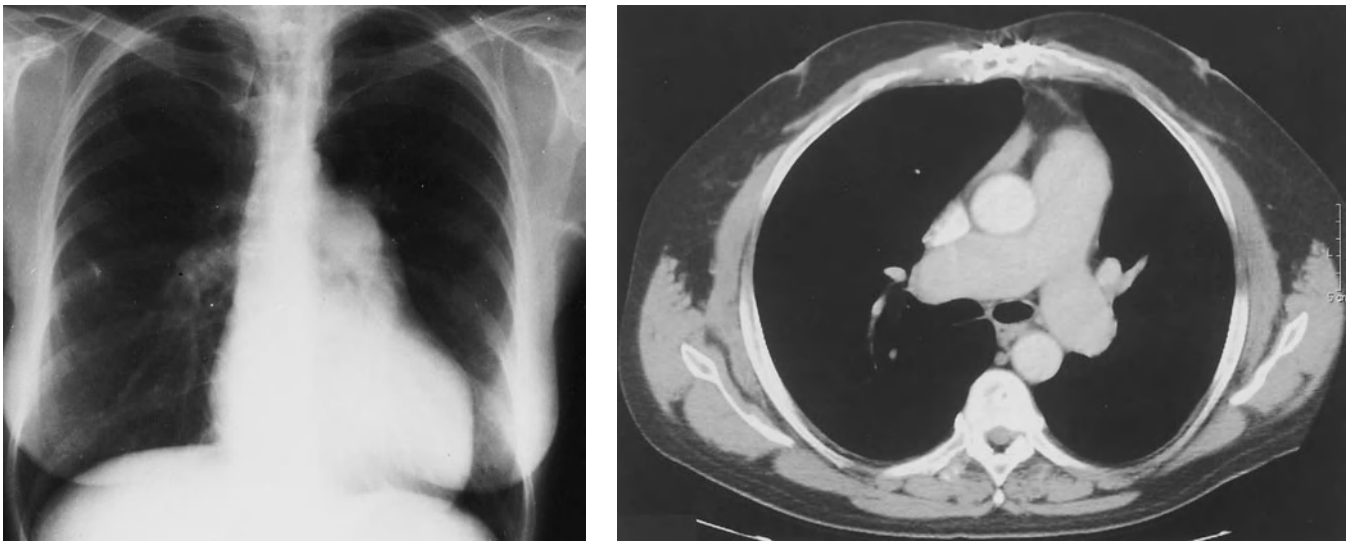
A *B*

Figure 30-29 Pulmonary vasculature (venous hypertension) in mitral stenosis. *A*. PA view. The enlarged left atrium is seen as a double density within the cardiac shadow. Cephalization of the pulmonary blood vessels is also present as a result of an increase in blood flow to the apices, in conjunction with a decrease in flow to the lung bases. *B*. Close-up view. The increase in vascular markings at the apices is more striking.

Radiographic techniques can be of considerable value in providing information about the distribution of air within the lungs. For example, fluoroscopy of the chest and comparison of chest radiographs taken during inspiration and expiration are useful in detecting and localizing air trapping; blebs and bullae appear as avascular, excessively radiolucent areas. Expiratory CT is much more sensitive in demonstrating air trapping, especially in small airways disease and is also much more sensitive in showing disproportionate blood flow to the two lungs. Extensive pleural encasement of one lung often is associated with a disproportionately small hemithorax and diminished ventilation and perfusion of the affected side. Marked reduction in pulmonary vascular markings also occurs in unilateral hypoventilation or hypoplasia of the pulmonary artery (Swyer-James or Macleod's syndrome); the hemithorax on the affected side is also usually small. Syndromes associated with unilateral hypoplasia often show air trapping on the affected side.

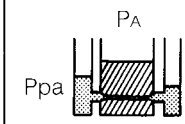
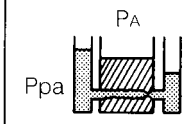
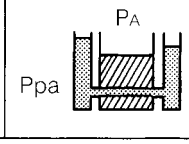
Obstructive Airway Disease

The plain film generally has little to offer in the early diagnosis of obstructive disease of the airways, but CT, especially high-resolution expiratory CT, can be quite useful. Chest radiographs are nearly always normal in patients in whom the airway obstruction is reversible. For example, in asthma, the chest radiograph is usually normal except during an acute episode, when the lungs often appear hyperinflated.



A *B*

Figure 30-30 *A*. Primary pulmonary arterial hypertension. The pulmonary trunk and its right and left main bronchi are markedly enlarged. In contrast, the peripheral vasculature is sparse. *B*. Pulmonary hypertension by CT. Note that the pulmonary artery is much larger than the aorta. This is the reverse of the normal situation and is characteristic of pulmonary hypertension.

Zone		Behavior of capillary	Flow depends on
I $P_A > Ppa > Ppv$		Collapsed	No flow*
II $Ppa > P_A > Ppv$		Starling resistor	$Ppa - P_A$
III $Ppa > Ppv > P_A$		Open or distended	Ppa – Ppv

*Except for flow through corner vessels.

Figure 30-31 Schematic representation of the behavior of small vessels in different parts of the lung. The lung is pictured as consisting of three vertical zones. In zone I, alveolar pressure is greater than arterial pressure, so collapsible vessels in the pulmonary microcirculation close; there is no blood flow. In zone II, arterial pressure exceeds alveolar pressure, which exceeds venous pressure. The pulmonary arterial-alveolar pressure difference determines the blood flow. Microvessels in this zone behave like Starling's resistors. The arterial-alveolar pressure difference increases linearly from top to bottom of the lung and produces corresponding changes in blood flow. In zone III, blood flow is determined by the difference between pulmonary arterial and venous pressures, since venous pressure exceeds alveolar. The collapsible vessels are open, and the pressure difference is constant throughout the zone (*From West JB: Regional Differences in the Lung. New York, Academic, 1977.)*

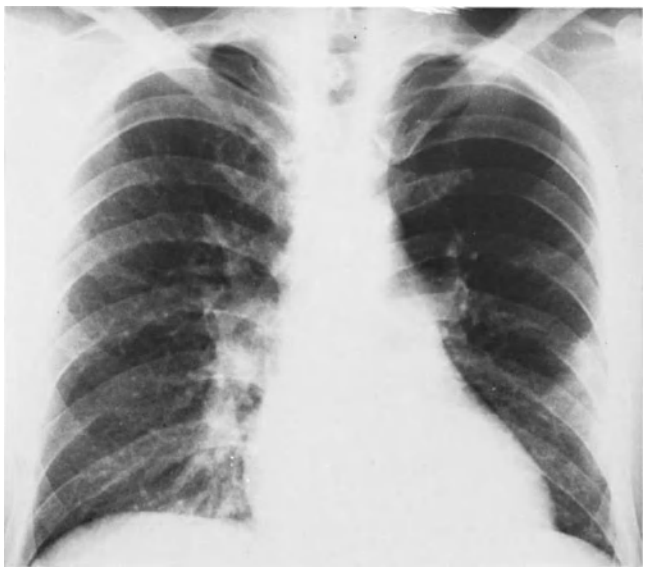


Figure 30-32 Massive pulmonary embolus. The PA view demonstrates marked diminution of the pulmonary vasculature to the left lung, secondary to a chronic massive pulmonary embolus in the left main pulmonary artery (Westermark's sign).

Expiratory CT may show localized air trapping or a "mosaic" perfusion pattern.

Similarly, the diagnosis of chronic bronchitis is a clinical one, based upon a history of chronic sputum production (see Chapter 40) and supplemented by characteristic abnormalities in pulmonary function tests (see Chapter 34). The radiograph rarely provides substantive help. Vascular markings throughout the lung fields are sometimes prominent, but this finding is nonspecific. Once again, expiratory CT may show air trapping which is indicative of small airways disease.

The classic radiographic appearance of more advanced emphysema is hyperinflation and diminution of vascular markings (Fig. 30-28). Hyperinflation is manifested by increased radiolucency of the lungs; low, flat diaphragms; exaggerated verticality of the heart; increased anteroposterior diameter of the chest; and widening of the retrosternal space. Of all these criteria, diaphragmatic flattening is probably the most reliable in supporting a diagnosis of chronic obstructive airway disease, but is seen only in patients with severe emphysema.

Hyperinflation can be simulated radiographically when a normal, robust person exerts a maximal inspiratory effort. The lungs also appear hyperinflated in very slender persons. Therefore, it is unwise to make the diagnosis of emphysema solely on the basis of the radiographic finding of hyperinflation.

CT shows characteristic changes in centrilobular, panlobular, and paraseptal emphysema. In centrilobular emphysema, focal areas of hyperlucency are scattered throughout the lungs, often with an apical dominance. As emphysema

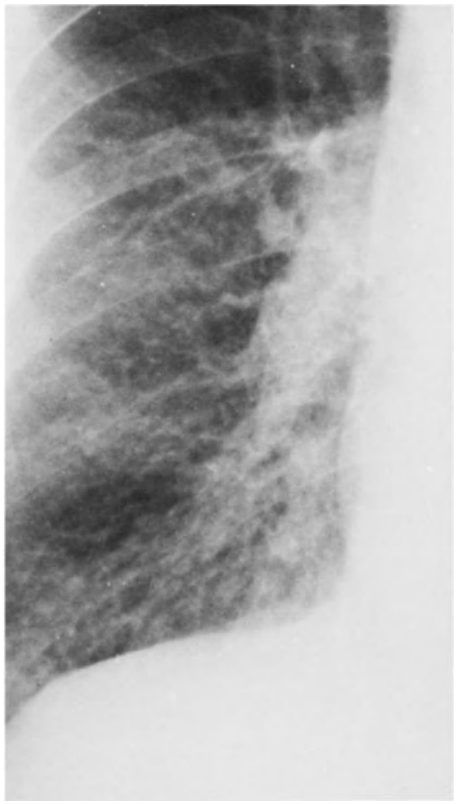


Figure 30-33 Increased markings pattern. The vascular markings are prominent throughout the lung fields. The patient has chronic bronchitis and emphysema. Hyperaeration is minimal.

becomes worse, more lung is involved and bullae may be evident.

In panlobular emphysema, there is diffuse hyperaeration of the lungs, often with a basilar predominance. This pattern is characteristic of α_1-antitrypsin deficiency.

In paraseptal emphysema, there are focal areas of hyperlucency in the periphery of the lungs. Paraseptal emphysema usually coexists with centrilobular emphysema. CT is especially useful in demonstrating the presence and location of bullae when bullectomy or lung reduction techniques are planned (see Chapter 53).

Supplemental plain film evidence for the diagnosis of emphysema can be afforded by examination of the pulmonary vessels. Two distinctly different vascular patterns have been identified in patients with chronic bronchitis and emphysema: arterial deficiency and increased lung markings. Patients who show the arterial deficiency pattern (Fig. 30-28) often have panlobular emphysema and manifest the clinical syndrome of the "pink puffer." Those who have the pattern of increased lung markings (Fig. 30-33) often have centrilobular emphysema and manifest the "blue bloater" syndrome (see Chapter 40). Notably, these radiographic findings occur relatively late in the clinical course of emphysema.

Patients with chronic bronchitis and emphysema who develop pulmonary hypertension usually show the characteristic features of hyperinflation and an abnormal vascular pattern. In addition, they may show distinctive enlargement of the main pulmonary artery and of the hilar pulmonary arteries and oligemia of the peripheral lung fields. These findings constitute important evidence of the existence of pulmonary hypertension. Using CT, pulmonary hypertension is readily recognized when the diameter of the pulmonary artery is greater than the aorta, a reversal of the normal situation.

Attempts have been made to use radiographic techniques to determine lung volumes in patients with chronic bronchitis and emphysema. Numerous measurements made on PA and lateral chest radiographs and on CT have served as the basis for the calculations; results have compared favorably with those obtained directly using body plethysmography. Recently, the radiographic approach has been reinforced by the availability of sophisticated computer techniques, especially with CT. These methods have not been widely adopted, however, because of the availability and accuracy of body plethysmography (see Chapter 34).

Heart Failure Complicating Chronic Bronchitis and Emphysema

Both right and left ventricular failure may occur in the patient with chronic obstructive airway disease, but the underlying mechanisms and radiographic appearances are different. Right ventricular failure in chronic obstructive airway disease is generally a consequence of pulmonary hypertension—which, in turn, is secondary to severe hypoxia and respiratory acidosis. As a consequence of right ventricular failure, lung water increases, but rarely to the point of overt pulmonary edema. In contrast, left ventricular failure is generally caused by unrelated disease of the coronary circulation or left ventricular myocardium; as a result, pulmonary venous pressure is abnormally high, resulting in the formation of hemodynamic pulmonary edema.

Recognition of left ventricular failure in patients with chronic obstructive airway disease is difficult. The low diaphragm and rarefied lungs obscure enlargement of the heart. Changes in pulmonary vasculature that are associated with left ventricular failure are difficult to recognize in the patient with a pattern of increased lung markings. Moreover, pulmonary edema often assumes unusual appearances in patients with underlying structural lung disease. Most helpful is comparison of recent and old chest radiographs, with particular attention focused on changes in cardiac size and vascular pattern. Frequently the presence of left ventricular failure is recognized retrospectively, as heart size decreases and vascular markings become attenuated following diuretic therapy. Comparison with prior CTs is also useful in recognizing heart failure on CT.

DISEASES AFFECTING THE PULMONARY PARENCHYMA

In sorting out the many diseases that can affect the lung parenchyma, knowledge of whether the process involves

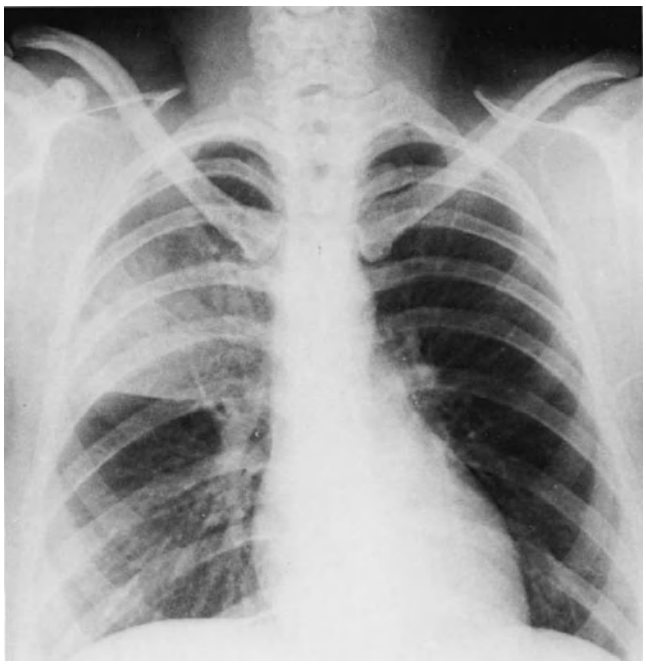


Figure 30-34 Right upper lobe pneumonia. The PA radiograph shows diffuse consolidation of the right upper lobe. The alveolar pattern is characteristic. The radiolucent streaks that run through the consolidation represent air in the bronchi (air bronchogram).

primarily the alveoli or the interstitium is useful. Frequently, but not invariably, this distinction can be made on the chest radiograph.

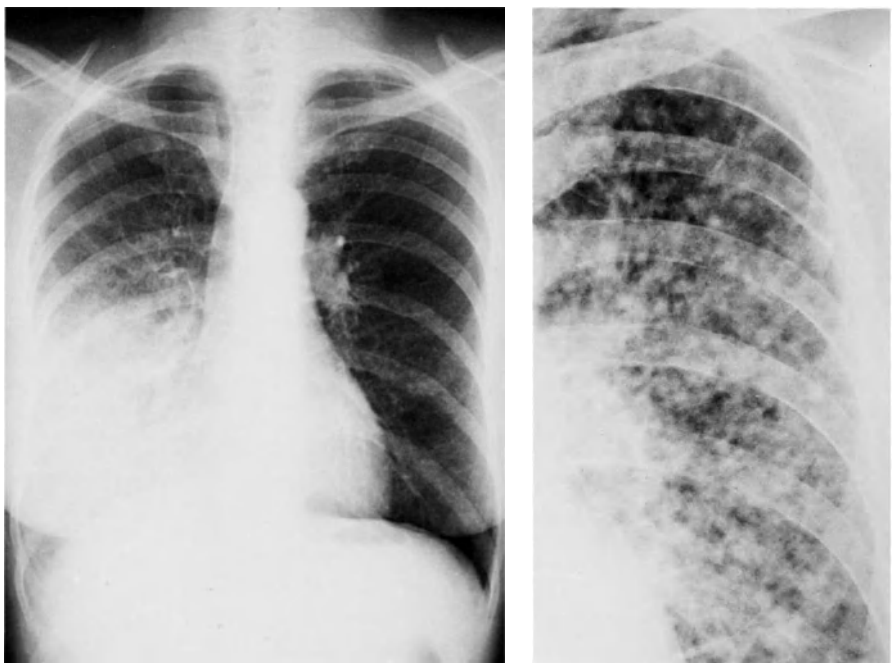
An alveolar radiographic pattern is created when alveolar airspaces are filled with material (e.g., blood, pus, or fluid). Characteristic radiographic features of alveolar filling diseases are exemplified in Figs. 30-34 through 30-36. These features include coalescence of densities and creation of large homogeneous shadows; presence of air bronchograms (i.e., visualization of peripheral bronchi due to consolidation of surrounding alveoli); fluffy, irregular margins of localized areas of consolidation; and usually rapid change in the areas of consolidation.

Localized Alveolar Disease

Localized alveolar disease assumes two primary patterns on the chest radiograph: patchy consolidation of airspaces without a decrease in the volume of the affected area, and consolidation of airspaces associated with a decrease in the volume of the affected area (atelectasis). The differential diagnosis depends largely on the extent to which lung volume is decreased. However, assessment of the magnitude of volume loss is not always useful. For example, while pneumonia usually is associated with minimal or no volume loss, occasionally, volume loss is considerable. On the other hand, atelectasis usually has moderate or severe loss of volume, but in some instances, there may be little or no loss of volume.

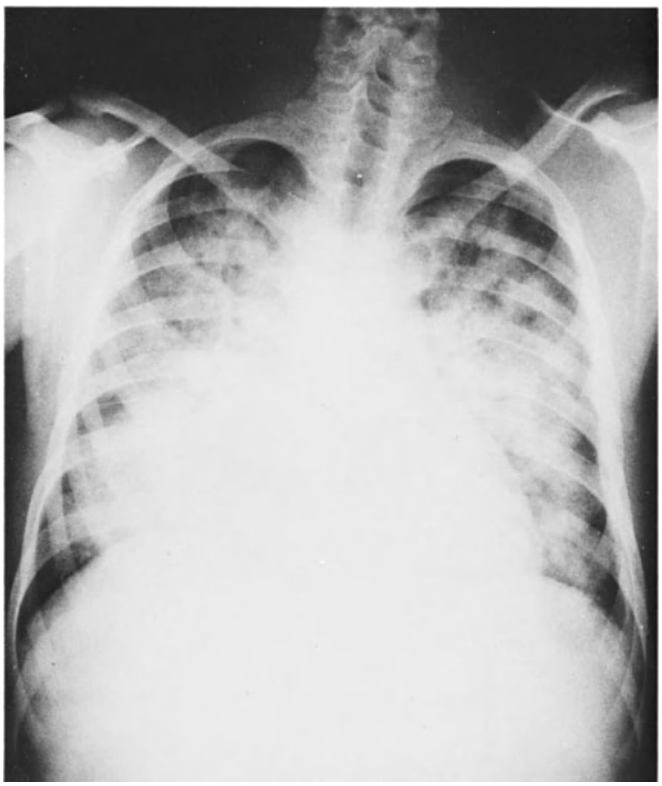
Localized consolidation of alveolar airspaces without loss of lung volume, or with minimal loss, is usually a sign of pneumonia (Fig. 30-34). Consolidation may be localized to a lobe (Fig. 30-35) or a pulmonary subsegment, or it may be more diffuse (Fig. 30-36). Consolidation of a pulmonary subsegment causes a characteristic radiographic pattern (Figs. 30-37 and 30-38). Other causes of consolidation without loss of volume include pulmonary edema (which occasionally occurs as local consolidation, even though more often it is diffuse) and pulmonary infarction (Fig. 30-11*C*).

In most instances, localized pulmonary consolidation without loss of lung volume indicates an acute inflammatory process. If consolidation persists without change for several



A *B*

Figure 30-35 Patterns of alveolar cell carcinoma. *A*. A large area of consolidation in the right lower lobe. The alveolar pattern suggests pneumonia, but was due to lobar alveolar cell carcinoma. *B*. The more distinctive pattern for alveolar cell carcinoma consists of multiple alveolar nodules. The nodules have irregular or fuzzy margins that are characteristic of alveolar, rather than interstitial, nodulation.



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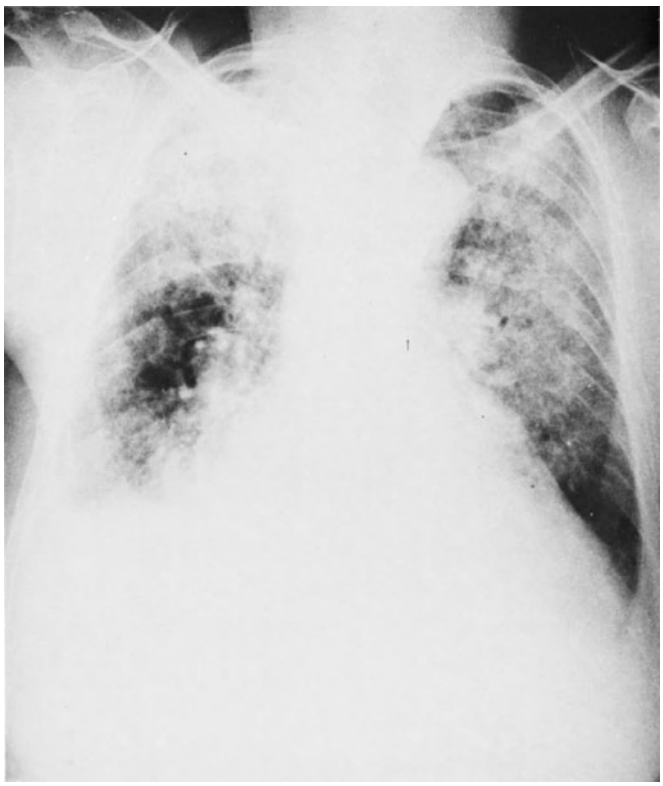

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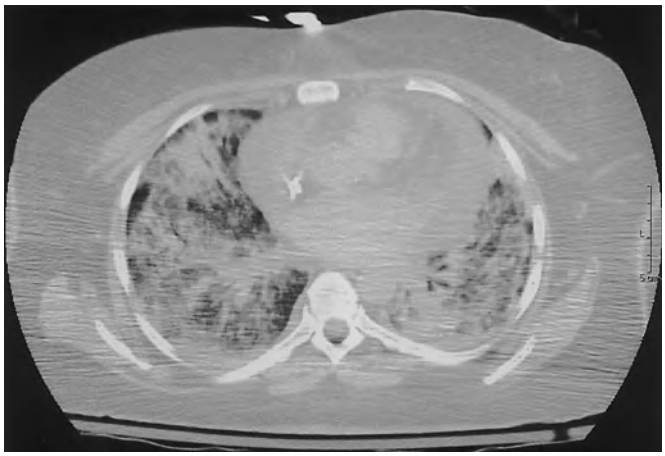


C

Figure 30-36 Pulmonary edema. Pulmonary edema may be either localized or diffuse. *A*. Most distinctive, but not most common, is a "bat wing" pattern of central alveolar consolidation. *B*. Occasionally, pulmonary edema affects one or more areas of the lung and appears as patchy alveolar consolidation. *C*. CT of diffuse pulmonary edema secondary to acute respiratory distress syndrome (ARDS). In this instance, the pattern is indistinguishable from that of other causes of severe pulmonary edema. In some cases of ARDS, the pulmonary edema is very patchy.

weeks, however, a less common pathological process should be suspected, including alveolar cell carcinoma (Figs. 30-35 *A* and 30-39); lymphoma; metastatic carcinoma, particularly from a breast primary; bronchiolitis obliterans organizing pneumonia; fungal infection; eosinophilic lung disease; or granulomatous vasculitis, such as Wegener's disease.

CT is frequently useful in distinguishing between the various causes of localized alveolar disease, although it may not be able to distinguish between atelectasis and pneumonia. The technique is especially useful in depicting the extent of the process (Fig. 30-39). CT is extremely useful in identifying cavitation (Figs. 30-40 and 30-41) and in demonstrating mediastinal adenopathy, which may not have been suspected on plain films.

Loss of volume is also associated with localized consolidation of the lung. In most instances, atelectasis detected radiographically is lobar in distribution, since collapse of anatomic pulmonary units smaller than a lobe (e.g., segments) is prevented by collateral air drift. Lobar patterns of atelectasis are illustrated in Figs. 30-42 through 30-46.

The various patterns of lobar atelectasis are extremely important to recognize, since this radiographic finding is a very common manifestation of carcinoma of the lung or, occasionally, some other endobronchial neoplasm. Atelectasis is also common in the postoperative patient, presumably because of hypoventilation of dependent parts of the lungs and inadequate clearing of respiratory secretions. In this instance,

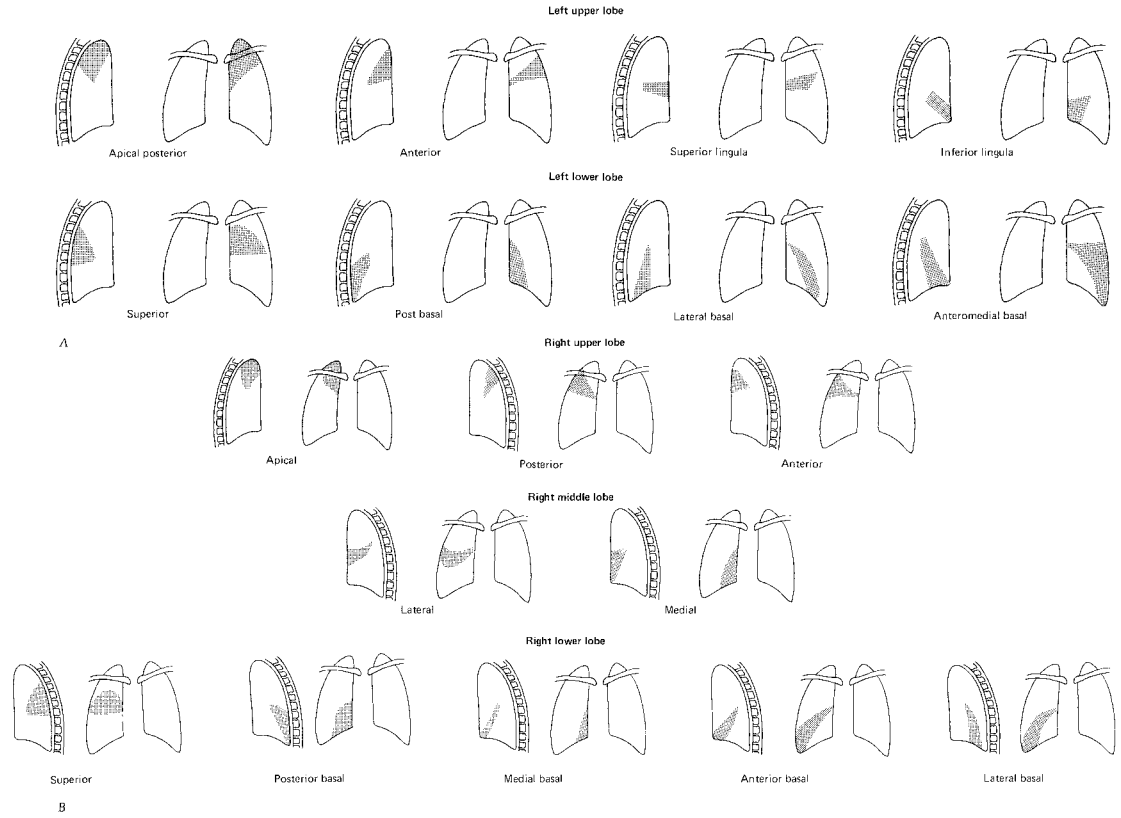


Figure 30-37 Radiographic anatomy of the pulmonary subsegments. Schematic representations of characteristic patterns of consolidation for each of the pulmonary subsegments are shown. *A*. Left lung. *B*. Right lung.

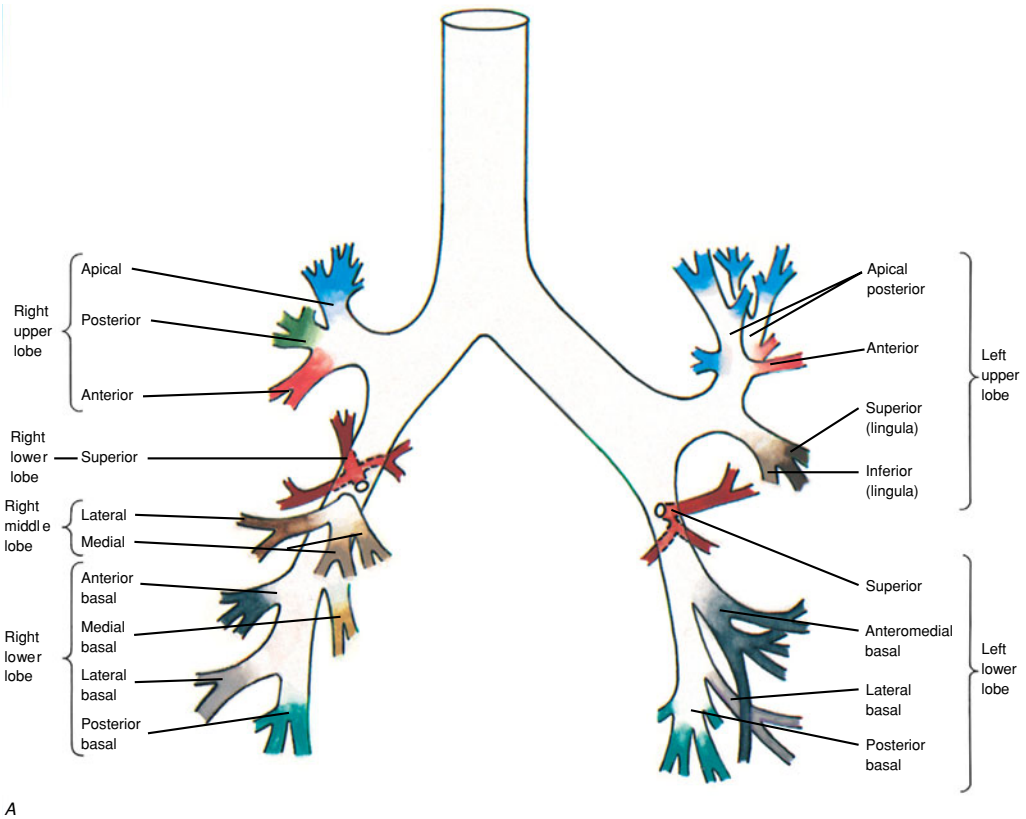


Figure 30-38 Topographic anatomy of the tracheobronchial tree and pulmonary subsegments. *A*. Tracheobronchial tree. *B*. Left anterior. *C*. Left lateral. *D*. Left cutaway. *E*. Left posterior. *F*. Right anterior. *G*. Right lateral. *H*. Right cutaway. *I*. Right posterior.

loss of volume may be minimal or absent. Atelectasis may also occur as a consequence of inflammatory disease of the airways or aspiration of a foreign body.

CT is extremely useful in the evaluation of atelectasis, since the technique may clearly demonstrate the cause—for example, a primary carcinoma of the lung. Conversely, CT may demonstrate an open bronchus, strongly suggesting that the atelectasis is not due to an endobronchial tumor. In this regard, it is important to note that some tumors (e.g., alveolar cell carcinoma and lymphoma) may cause consolidation with an open bronchus.

Atelectasis also invariably accompanies pleural effusions and pneumothorax. With pleural effusions, atelectasis is greatest in the vicinity of the pleural effusion.

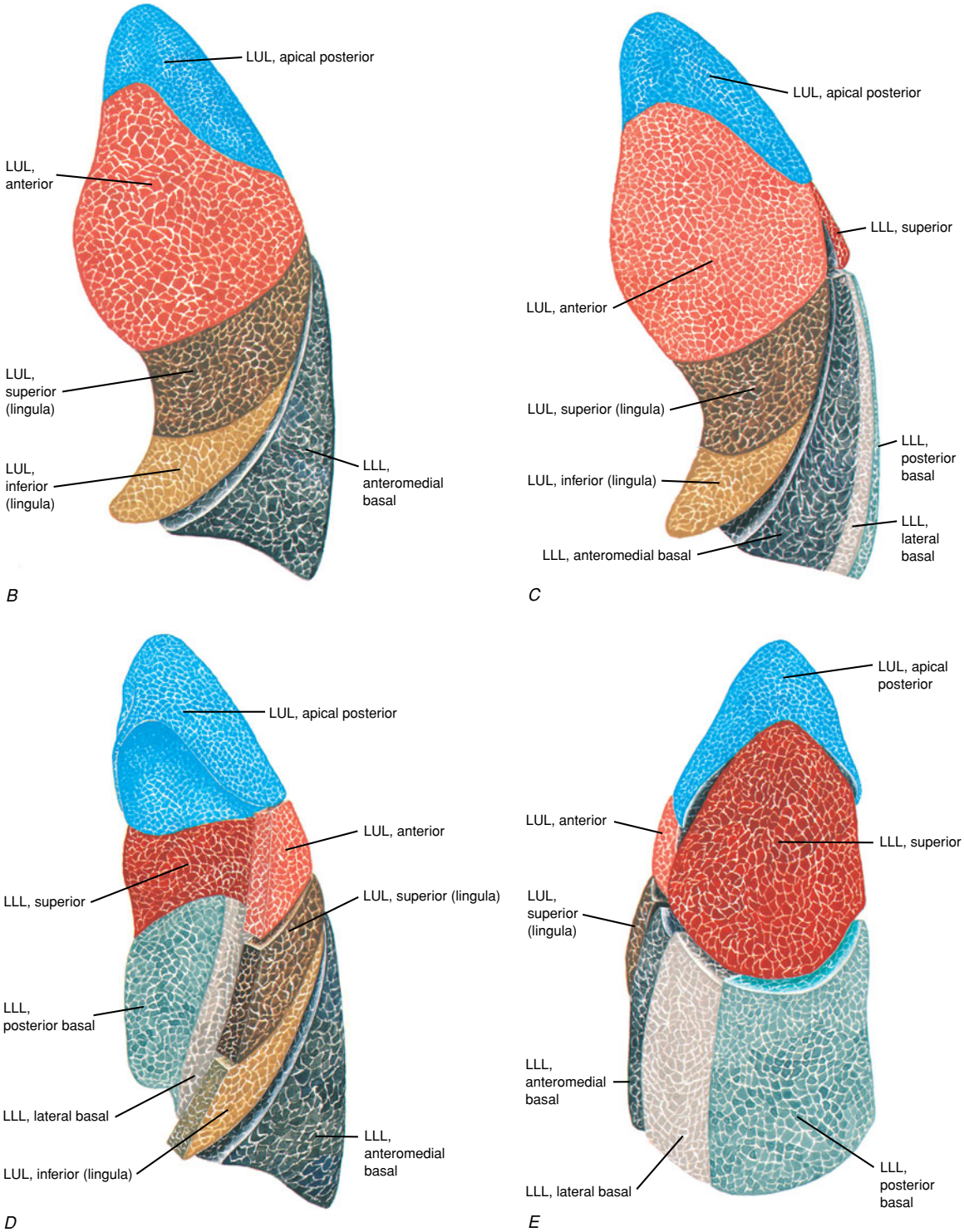
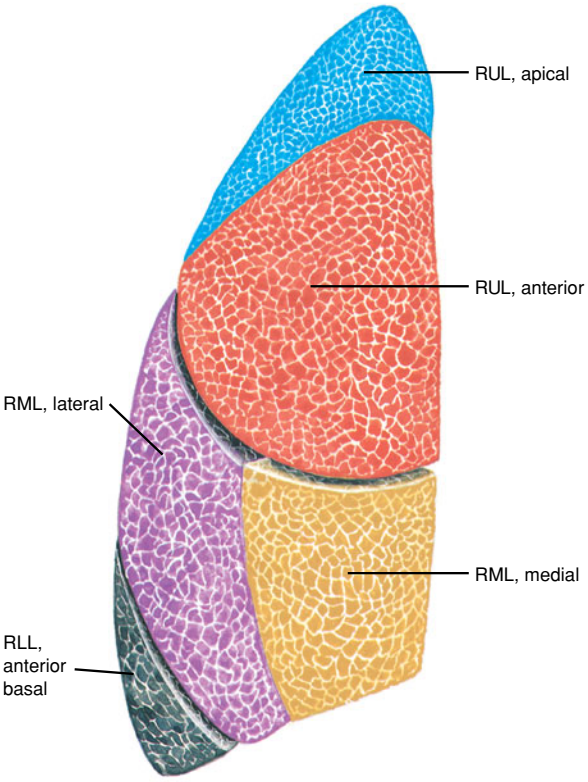


Figure 30-38 (*Continued*)



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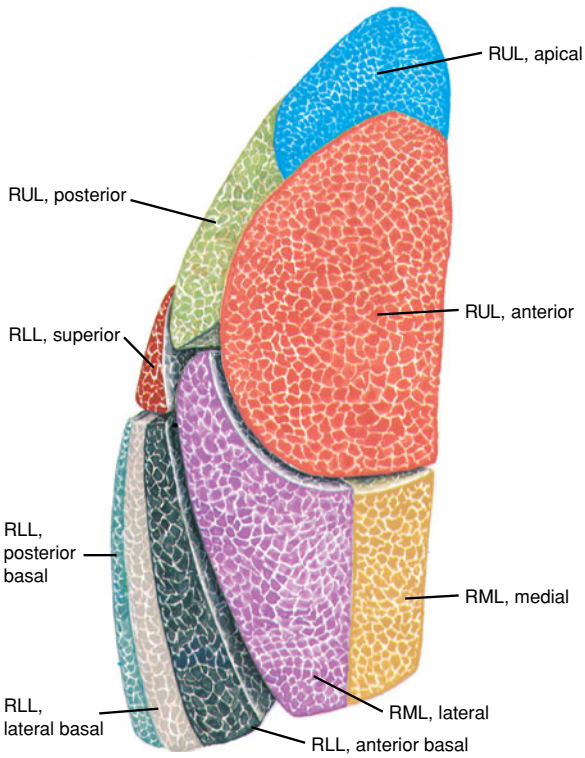

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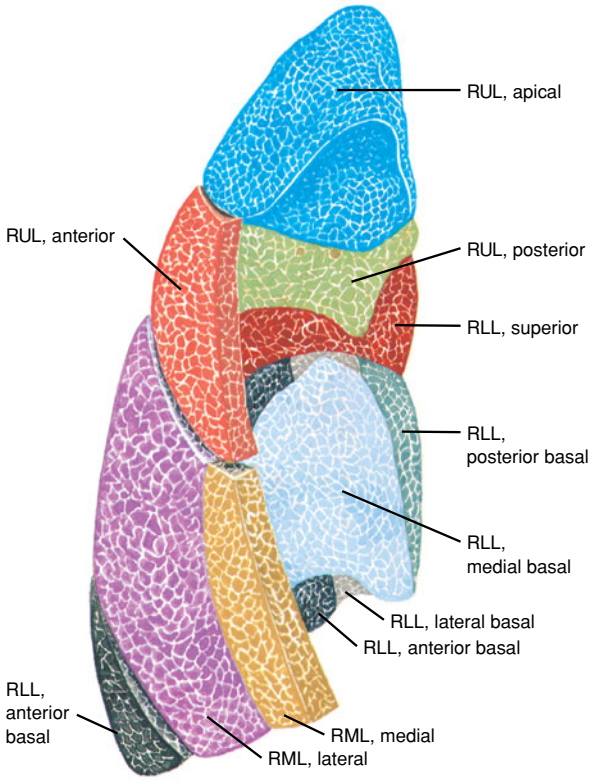

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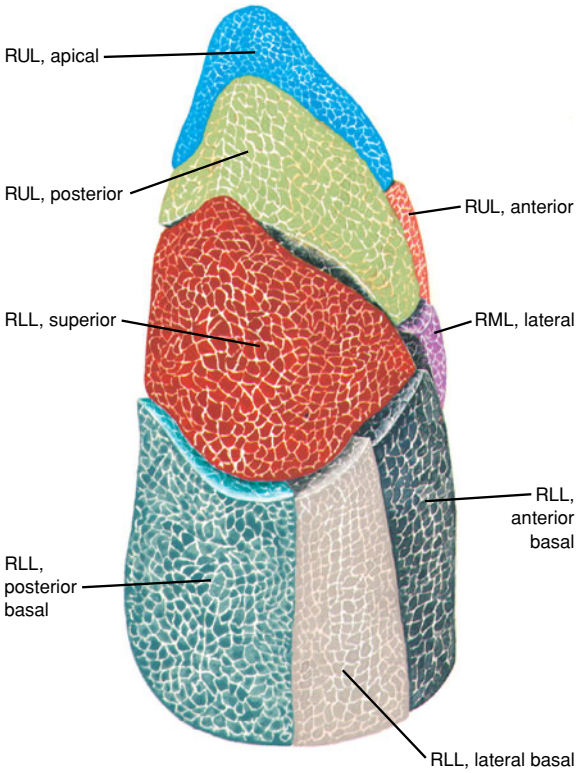


I

Figure 30-38 (*Continued*)

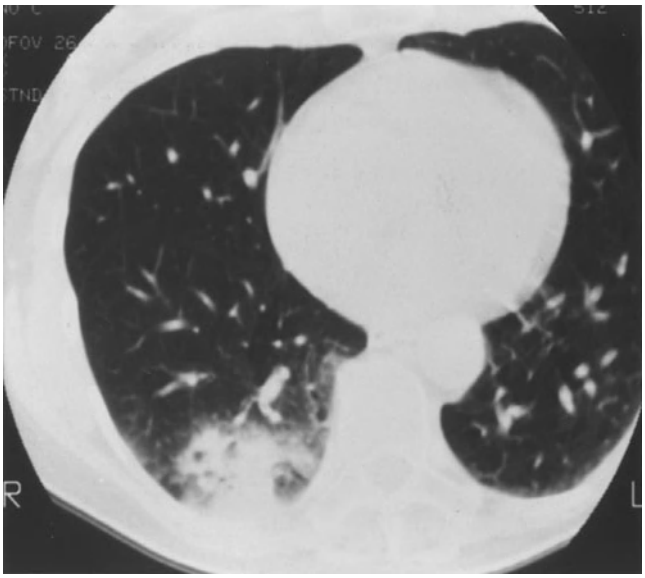


Figure 30-39 CT image of localized alveolar cell carcinoma. A patchy right lower lobe infiltrate is present. The characteristic alveolar infiltrate is most suggestive of pneumonia, but it is consistent with lobar-type alveolar cell carcinoma. The findings are not specific, and in this instance, CT adds little to the diagnosis.

CT may also suggest the diagnosis of rounded atelectasis (Fig. 30-47) and is particularly useful in demonstrating mediastinal adenopathy or the extent of a tumor that invades the mediastinum or great vessels. These findings reveal the anatomic basis for the atelectasis.

Diffuse Alveolar Disease

The prototype of a pathological process affecting the alveoli diffusely is pulmonary edema (Fig. 30-36). Most often, pulmonary edema is secondary to left ventricular failure. However, noncardiac pulmonary edema is common and may have a number of underlying causes, including hypersensitivity reactions to drugs or inhaled toxins, uremia, drug overdose, oxygen toxicity, near-drowning, and, especially adult respiratory distress syndrome (ARDS) (Chapter 145). Cardiogenic pulmonary edema characteristically clears rapidly after appropriate therapy, whereas noncardiogenic pulmonary edema often requires days or weeks to clear.

Other causes of diffuse alveolar disease may mimic pulmonary edema. Diffuse pneumonia and diffuse pulmonary hemorrhage may be indistinguishable and must be differentiated clinically.

If diffuse alveolar consolidation persists for weeks or months, chronic disorders, such as pulmonary alveolar proteinosis (Fig. 30-48*C*), alveolar cell carcinoma (Figs. 30-35 and 30-39), sarcoidosis, hypersensitivity pneumonitis, or desquamative interstitial pneumonitis should be considered.

As with localized disease, CT is often useful in distinguishing one type of diffuse alveolar disease from another. The distribution of the alveolar infiltrates may sometimes be helpful. Multifocal, patchy disease is typical of aspiration pneumonia. ARDS also appears patchy, but is typically less focal. Diffuse pneumonia, pulmonary hemorrhage, and pulmonary edema may be indistinguishable.

Diffuse alveolar disease or focal alveolar disease may be manifest on CT by "ground glass" changes. The term, ground glass opacification, refers to faint alveolar consolidation which is less dense than more extensive consolidation and has an appearance resembling ground glass. This finding is often not explained. If focal, it may be caused by pneumonia or aspiration, and if chronic, may be a manifestation of lung carcinoma or lymphoma. If more diffuse, pulmonary

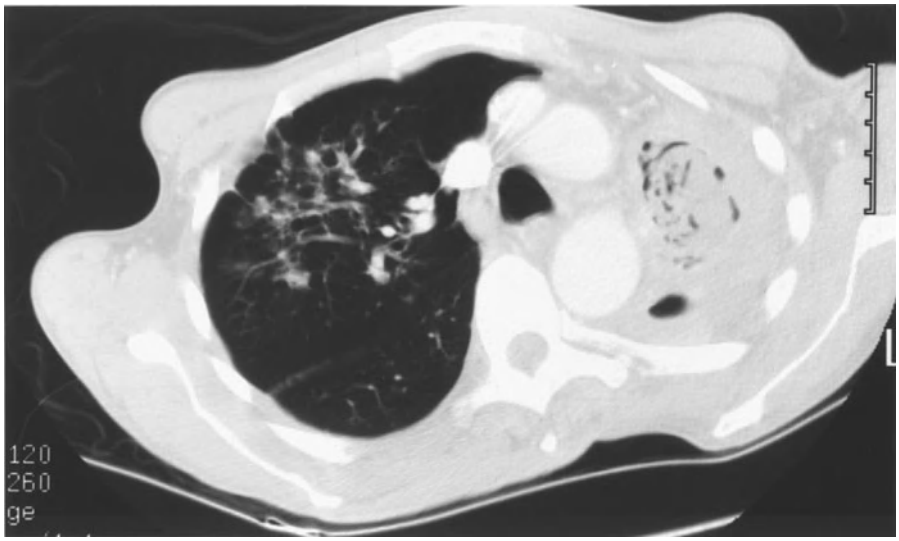


Figure 30-40 CT demonstrating characteristic crescent sign of aspergillosis. A right upper lobe infiltrate is seen that, in this case, was due to tuberculosis. In the left upper lobe, a crescent of air is seen around the matted mycelia of a fungus ball. The finding is characteristic of "noninvasive" aspergillosis.

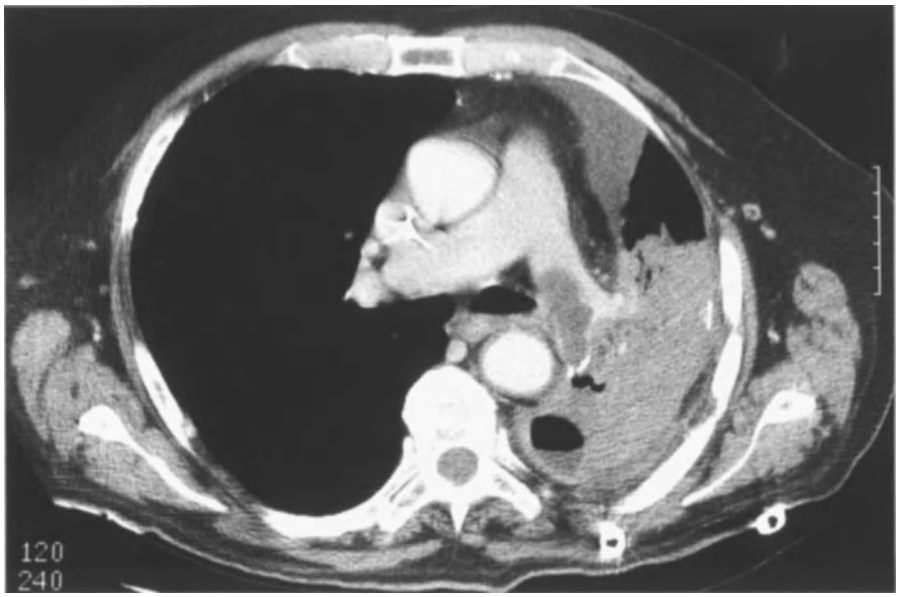


Figure 30-41 CT showing gangrene of the lung due to a pulmonary artery thrombus in the left main and lower lobe pulmonary artery. The patient had a prior left upper lobectomy; in the postoperative period, consolidation of the remaining left lung developed. The scan shows a lung cavity that was not previously suspected, as well as a thrombus in the left pulmonary artery. The cavity represents a rapidly developing lung abscess due to lung infarction (gangrene).

edema or patchy pneumonia may be the cause. Ground glass changes may also be seen in desquamative interstitial pneumonitis, lymphoid interstitial pneumonitis, or nonspecific interstitial pneumonitis.

Interstitial Lung Disease

The plain film features of interstitial lung disease differ from those of the alveolar disorders (Fig. 30-49). In interstitial disease, the pattern is discrete and sharp, rather than fluffy and irregular, and the lesions tend to be diffuse, rather than localized. In addition, coalescence is not a feature, and the small densities are characteristically nodular, reticular, or linear.

Pathological interstitial processes may be acute or chronic, although the chronic causes are more common. Within the acute category, a pattern changing over hours to days usually represents interstitial pulmonary edema. Occasionally, a rapidly changing interstitial pattern represents pneumonia due to *Pneumocystis carinii* or cytomegalovirus. The acute interstitial disorders typically cause a linear or reticular pattern, which is characterized by prominent Kerley's lines throughout the lung fields (Fig. 30-49 *A*).

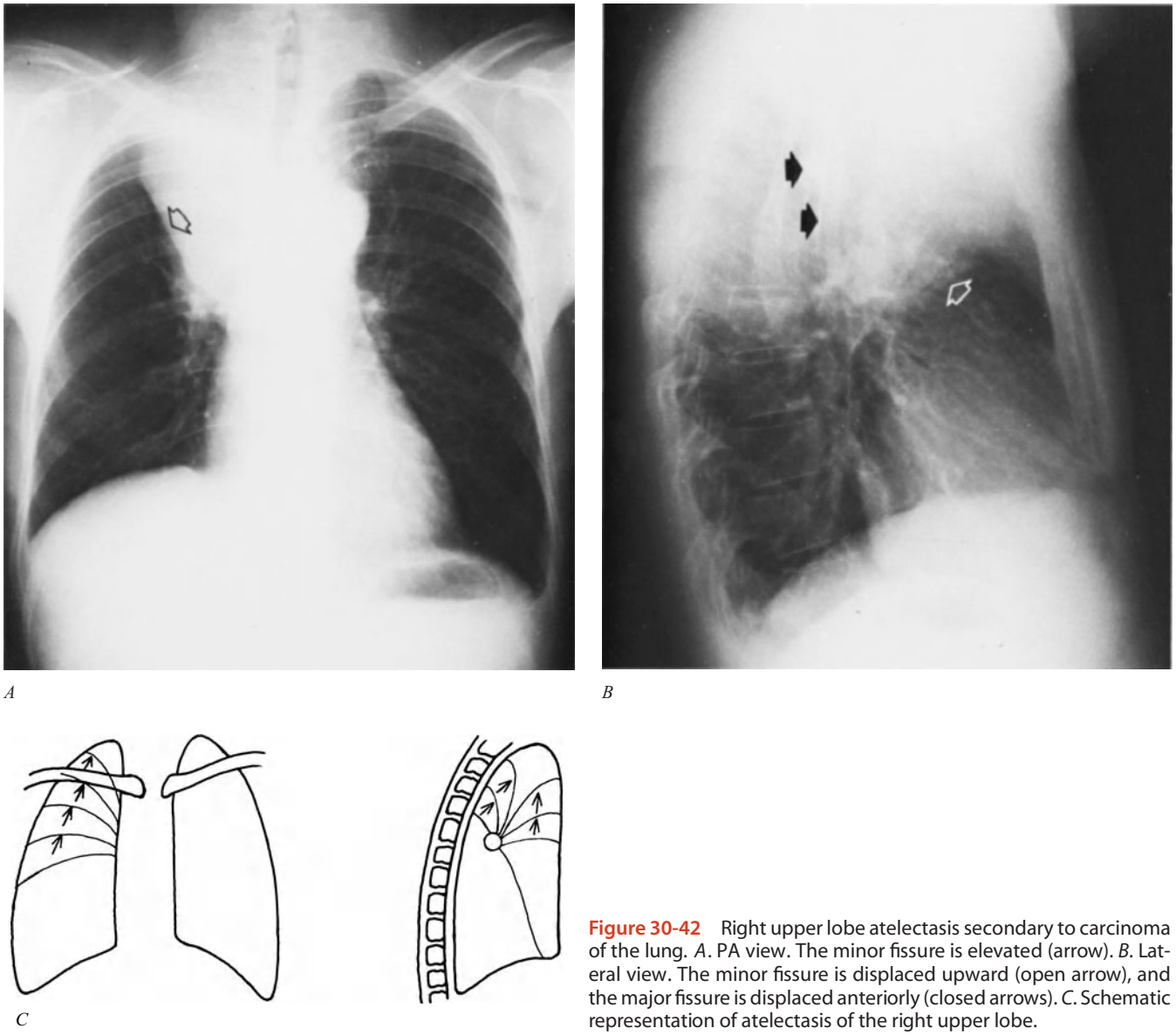
In his original description in 1951, Kerley associated thin, radiographic parenchymal opacities with left ventricular failure. At first, Kerley's lines were thought to represent swollen pulmonary lymphatics. It is now recognized that Kerley's lines usually represent edematous septa within the pulmonary interstitium. Three patterns exist. Kerley type B lines are the most familiar and are particularly prominent at the lung bases, where they appear as straight, thin lines approximately 1 cm long; they are oriented parallel to the diaphragm. Kerley type A lines represent septa deep within the substance of the lungs; they radiate from the hili. Kerley type C lines probably represent coalescence of A and B lines.

Chronic interstitial lung diseases may be caused by a wide variety of diseases (Figs. 30-49 and 30-50), including pneumoconioses; sarcoidosis; lymphangitic spread of tumors; infections, such as miliary tuberculosis, interstitial pneumonia, and fungal diseases; allergic lung disease; collagen vascular diseases; eosinophilic granuloma; and idiopathic interstitial fibrosis. Characterization of the pattern of interstitial disease as nodular, reticular, or linear on the plain film may help in differential diagnosis, since many of the interstitial lung diseases assume, almost exclusively, one of these three patterns.

Interstitial nodules range in size from minute to massive. Large nodules generally represent metastatic tumor (Fig. 30-51). Smaller nodules are found in pneumoconiosis or silicosis, miliary tuberculosis, sarcoidosis (Fig. 30-49 *B*), and allergic lung disease.

Linear densities, as noted previously, are more characteristic of acute lung disease (e.g., interstitial pulmonary edema [Fig. 30-49 *A*] or interstitial pneumonia). A similar, but chronic, pattern occurs in lymphangitic spread of metastatic tumor (Figs. 30-12 and 30-49 *C*).

A reticular pattern suggests collagen vascular disease when the reticular or cystic changes are tiny and are confined primarily to the lung bases (Fig. 30-49 *D*). Asbestosis and UIP also cause a basilar reticular pattern (Fig. 30-52 *A*). Eosinophilic granuloma of the lung sometimes causes



A *B* *C*

Figure 30-42 Right upper lobe atelectasis secondary to carcinoma of the lung. *A*. PA view. The minor fissure is elevated (arrow). *B*. Lateral view. The minor fissure is displaced upward (open arrow), and the major fissure is displaced anteriorly (closed arrows). *C*. Schematic representation of atelectasis of the right upper lobe.

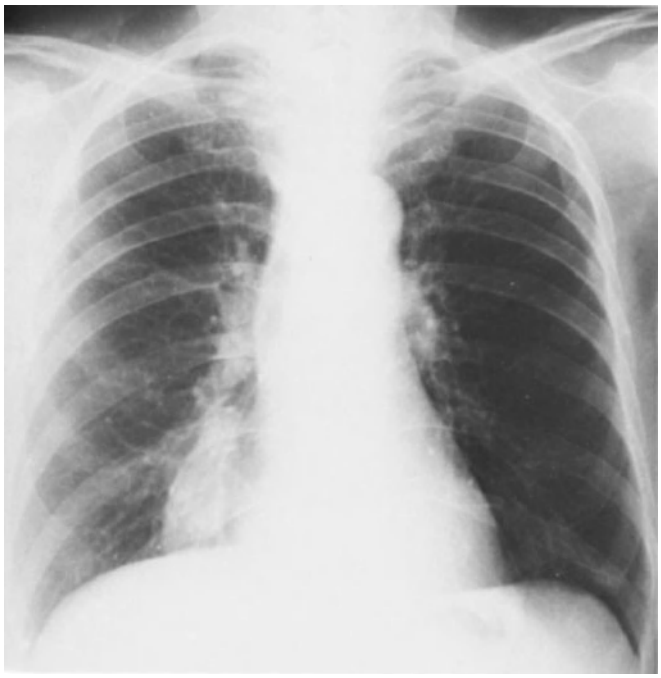
a similar pattern at the lung apices. A larger reticular pattern suggests idiopathic pulmonary fibrosis (IPF) or the end-stage lung pattern that often represents the final common denominator of a variety of chronic interstitial lung diseases.

Most interstitial diseases cause loss of lung volume on the radiograph, since these disorders are restrictive in their pathophysiological effect. However, two interstitial diseases that produce diffuse, small bullous changes are characteristically associated with preserved lung volume: eosinophilic granuloma and lymphangioleiomyomatosis. These are relatively uncommon causes of interstitial lung disease. Notably, patients with interstitial lung disease may have concurrent chronic obstructive pulmonary disease, in which case lung volume may be preserved.

High-resolution CT has emerged as a powerful technique for evaluating interstitial lung diseases. CT can often identify interstitial disease that is not seen on the plain radiograph, and it may also identify the underlying cause. Major indications for high-resolution CT are identification of suspected alveolar or interstitial disease, which is not seen on the chest radiograph, and characterization of the disease (Fig. 30-52).

CT patterns of interstitial lung disease follow, to some degree, the patterns seen on the plain radiograph. Collagen vascular disease and IPF typically have reticular or cystic changes in the periphery of the lung and at the lung bases (Fig. 30-52 *A*). These changes are so characteristic that many authors believe that further diagnostic efforts, such as lung biopsy, are unnecessary. The changes of IPF are virtually impossible to distinguish from those of collagen vascular disease. In most, but not all instances, the presence of collagen vascular disease is recognized prior to discovery of the lung disease.

Asbestosis may also cause reticular and peripheral interstitial lung disease. However, invariably associated pleural plaques are noted, suggesting the diagnosis in a patient



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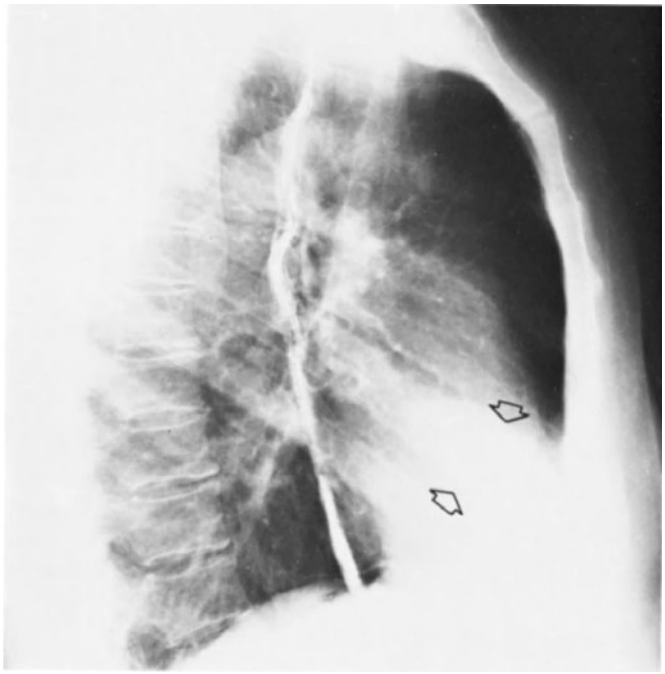

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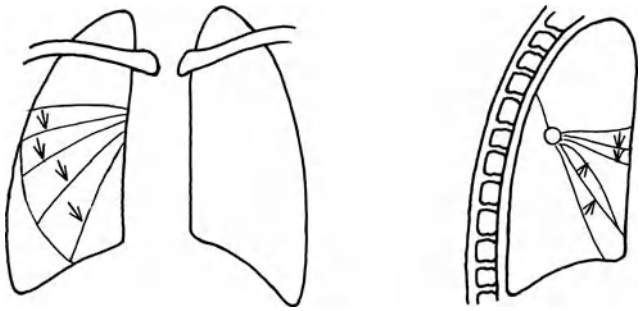


C

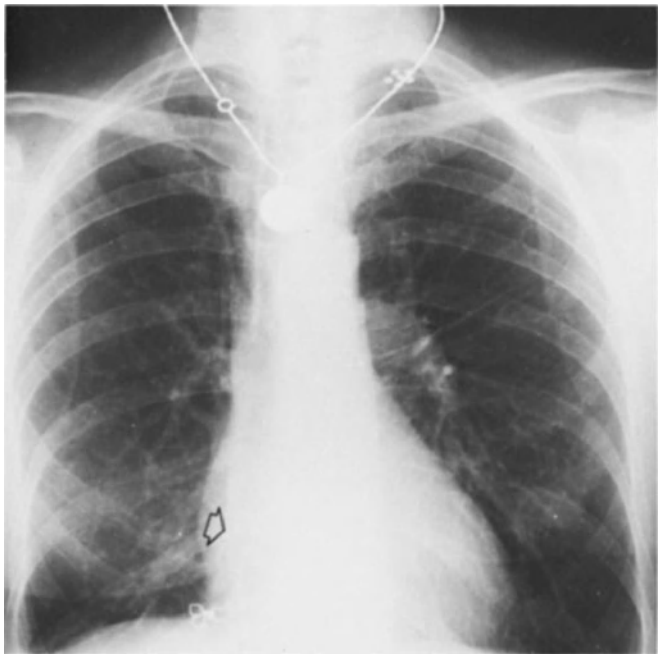
Figure 30-43 Right middle lobe atelectasis secondary to right middle lobe syndrome. *A*. PA view. The middle lobe is collapsed against the right side of the heart. *B*. Lateral view. The major and minor fissures are drawn together (arrows), creating a density that overlies the cardiac shadow. *C*. Schematic representation of right middle lobe atelectasis.

with a long history of asbestos exposure. Occasionally, pleural plaques and IPF can coexist. Asbestosis progresses very slowly; if progression is more rapid, IPF should be suspected.

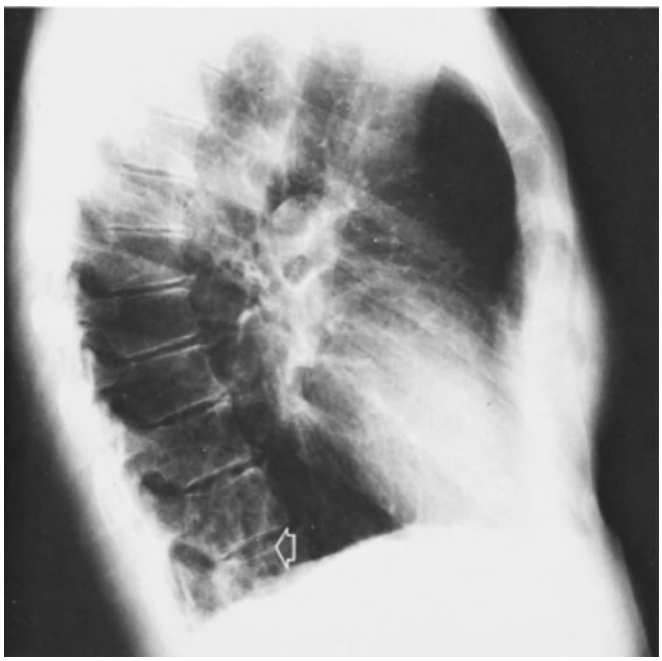
Sarcoidosis, interstitial pulmonary edema (Fig. 30-52*B*), and lymphangitic spread of tumor (Fig. 30-12) demonstrate a bronchovascular (septal) distribution, with linear densities outlining the pulmonary lobule. This septal distribution is extremely characteristic of these three entities. Interstitial pulmonary edema is seen almost exclusively with heart failure or fluid overload and rapidly disappears with appropriate therapy.

Lymphangitic spread of tumor improves only occasionally with chemotherapy and is usually progressive. While usually diffuse, the disorder is often unilateral when due to carcinoma of the lung, and it may occasionally be focal in lung cancer or when due to other tumors. The tumors that most frequently cause lymphangitic spread include carcinoma of the breast (the most common), lung, stomach, and pancreas, and, on occasion, other tumors.

Hypersensitivity pneumonitis frequently is associated with an alveolar or ground glass pattern, and commonly has a mosaic distribution (Fig. 30-52*C*). In addition, hypersensitivity pneumonitis may cause multiple tiny nodules. Several other diseases usually exhibit a nodular pattern. Large nodules are seen almost exclusively in metastatic tumor, but occasionally they are also seen in silicosis. On the other hand, carcinoma of the thyroid may be seen as multiple tiny nodules, although tiny nodules are usually indicative of another process. Miliary tuberculosis and miliary fungus diseases are among those that present with a fine nodular pattern. Sarcoidosis, which usually has a bronchovascular distribution and linear septal pattern, may also be seen as fine nodules. Silicosis also has a fine nodular pattern and invariably is more prominent in the upper lobes than elsewhere. Occasionally, the nodules of silicosis are somewhat larger and may be confused with metastatic tumor. Massive progressive fibrosis, also seen in silicosis, may also be confused with primary or metastatic tumor. Finally, metastatic tumor (Fig. 30-51) and miliary tuberculosis usually are characterized by fine nodules.



A



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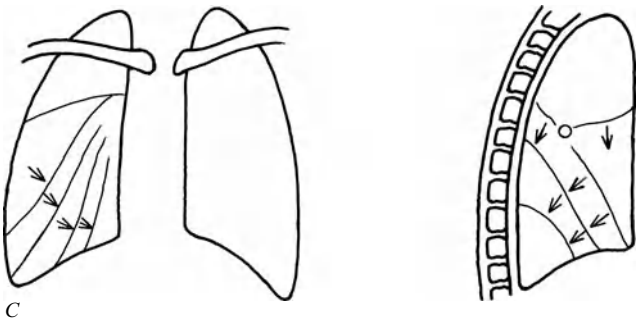


C

Figure 30-44 Atelectasis (severe) of the right lower lobe due to chronic inflammatory disease. *A*. PA view. Secondary signs of atelectasis are present in the right lung: small hemithorax, stretching of the pulmonary vessels, hyperlucent lung, and small hilus. In this instance, these secondary signs are important in suspecting atelectasis. In addition, there is downward displacement of the right hilus, and the collapsed lower lobe can be seen (poorly) through the right heart border (arrow). *B*. Lateral view. The entire right lower lobe appears only as a diffuse density overlying the spine (arrow). The posterior portion of the right hemidiaphragm cannot be identified (silhouette sign). *C*. Schematic representation of collapse of right lower lobe.

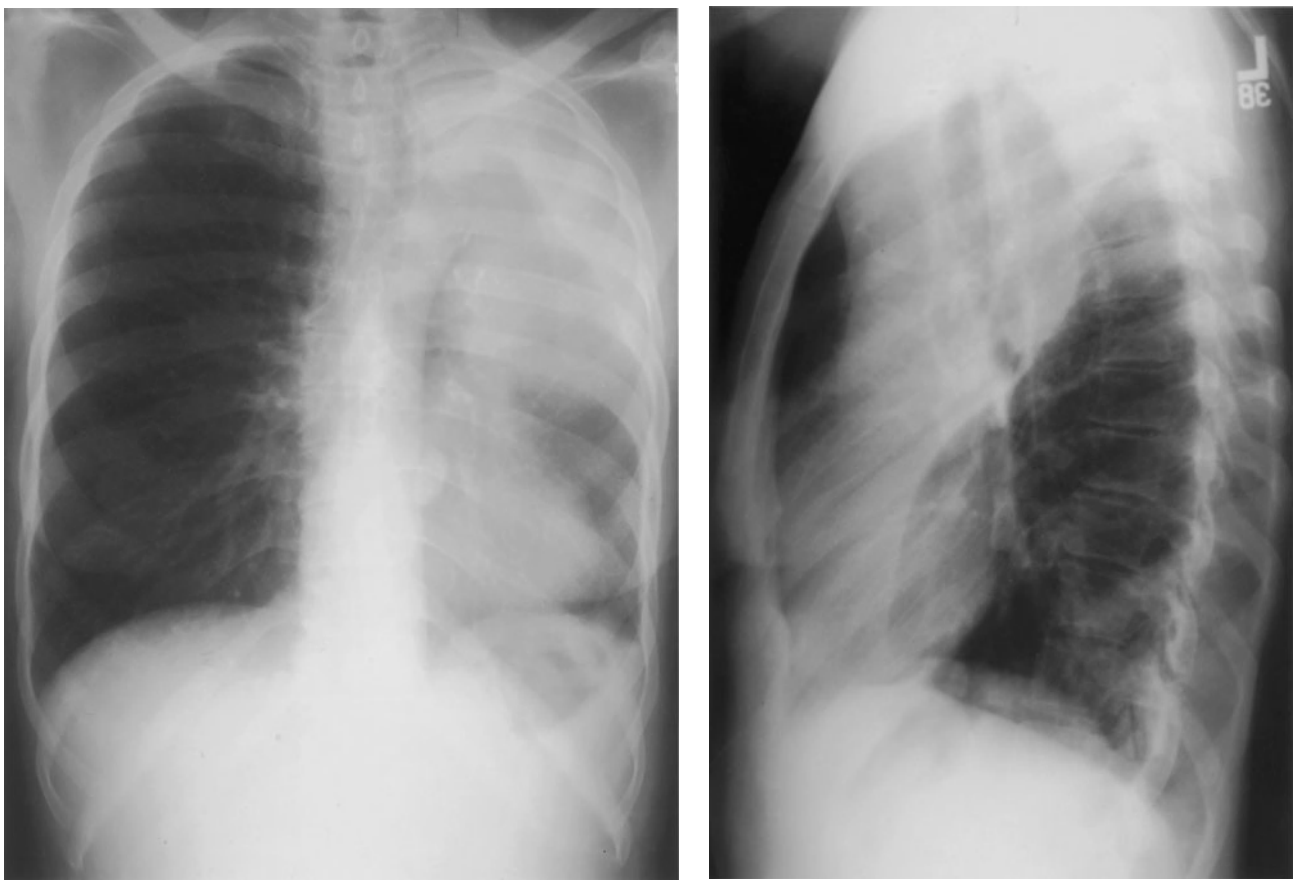
The Solitary Nodule

A wide variety of pathological processes appear on the chest radiograph as a solitary nodule (see Chapter 103). Among the most common are primary carcinoma of the lung, granulomas due to tuberculosis or fungal infection, metastatic carcinoma, and organizing pneumonia. Less common are hamartoma, bronchogenic cyst, bronchial adenoma, arteriovenous malformation, pulmonary sequestration, necrobiotic nodule due to rheumatoid arthritis, Wegener's granulomatosis, lymphoma, inflammatory pseudotumor, and lipoid granuloma. Although the radiograph is invaluable for detection of a pulmonary nodule, it is usually of little help in elucidating the underlying cause. Although certain radiographic aspects of a nodule may suggest its benign or malignant nature, in most instances, histological or cytological proof is required.

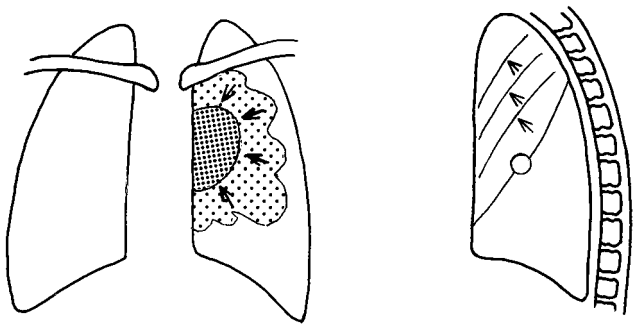
One radiologic clue to the origin of a pulmonary nodule is the character of its border. Ill-defined margins suggest an inflammatory lesion (e.g., tuberculosis or pneumonia) or primary lung carcinoma. A very sharply circumscribed pulmonary nodule with a regular contour is more likely to be a granuloma or hamartoma. However, metastatic tumor often presents with a sharply circumscribed edge, and primary lung neoplasms may present either as sharply circumscribed nodules or nodules with ill-defined margins.

The age of the patient is useful in stratification of the differential diagnosis of a solitary nodule. Primary carcinoma of the lung is extremely rare in patients under 30 years old, whereas in patients older than 50, more than half of solitary nodules on the plain film are primary carcinomas of the lung.

Occasionally, the radiograph may be sufficiently convincing of the benignity of a pulmonary nodule to preclude the need for diagnostic evaluation, including possible thoracoscopy or thoracotomy. Extensive calcification within the nodule suggests that the process is benign; CT may be helpful in demonstrating such calcification. Benignity is suggested by calcification that is central, concentric, diffuse, or punctate ("popcorn" calcification). On the other hand, eccentric calcification is of no diagnostic help, since it occurs in both benign and malignant disease, presumably as a consequence of envelopment of a preexisting benign calcified focus within an expanding neoplastic process.



A *B*



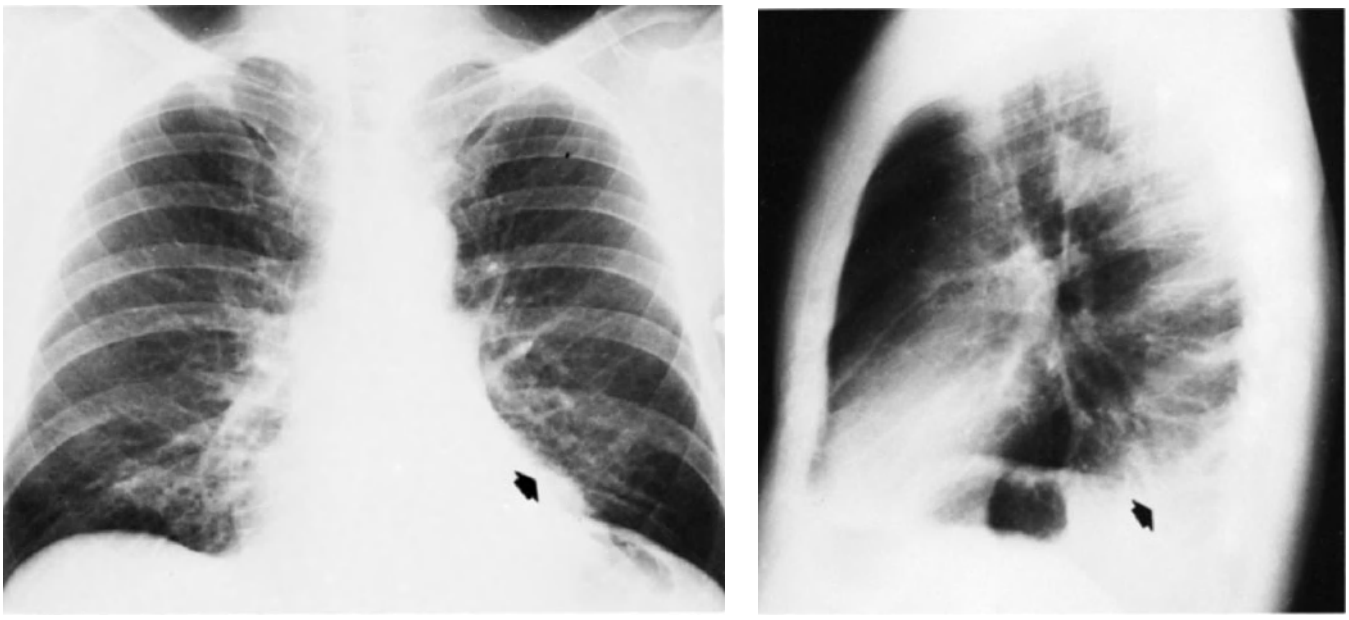
C

Figure 30-45 Left upper lobe atelectasis secondary to carcinoma of the lung. *A*. PA view. The left superior mediastinum and left side of the heart are indistinct, due to collapse of the left upper lobe medially. *B*. Lateral view. The collapsed lung is seen as a density anterior to the major fissure, which is displaced anteriorly. *C*. Schematic representation of collapse of left upper lobe.

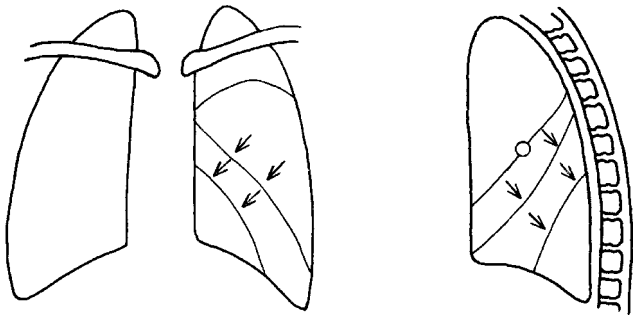
Prominent vascular shadows extending from a nodule suggest that the nodule is an arteriovenous malformation; the shadows actually represent veins. Arteriography is useful in confirming the vascular nature of the lesion (Fig. 30-5*B*). CT and MRI are also helpful in diagnosing arteriovenous malformations and now constitute definitive imaging techniques. A basal lung nodule that is suggestive of a pulmonary sequestration can be definitively identified by CT, MRI, or arteriography if the study demonstrates that the mass is supplied by an anomalous artery arising from the abdominal aorta.

The lung is uniquely suited for serial chest radiographs or serial CT to estimate the size of a solitary pulmonary nodule. This feature has led to the practical concept of *doubling time*—the time required for a tumor to double in volume (not diameter). A previous radiograph in which the nodule was present, even if unrecognized, serves as a useful baseline for estimating the rate of nodule growth. If a nodule does not change in size for 2 years, it is likely that the process is benign. Conversely, any growth of the nodule within 1 year should raise suspicion of malignancy. Usually, malignant tumors grow quickly, with a doubling in volume between 1 and 15 months (Fig. 30-53*C* and *D*). Occasionally, a slowly growing nodule proves to be a primary carcinoma of the lung (Fig. 30-53*A* and *B*)—usually adenocarcinoma or localized alveolar cell carcinoma—or sometimes a carcinoid tumor.

The presence of cavitation within a pulmonary nodule is usually not helpful in determining whether the nodule is



A *B*



C

Figure 30-46 Left lower lobe atelectasis (postoperative). *A*. PA view. The collapsed left lower lobe is seen as a straight line (arrow) behind the left heart border. No vasculature can be seen through the heart shadow, and the medial border of the left hemidiaphragm is obscured by the collapsed left lower lobe (arrow). *B*. Lateral view. Density over spine and absence of left posterior diaphragm. This is difficult to differentiate from a pleural effusion. *C*. Schematic representation of collapsed left lower lobe.

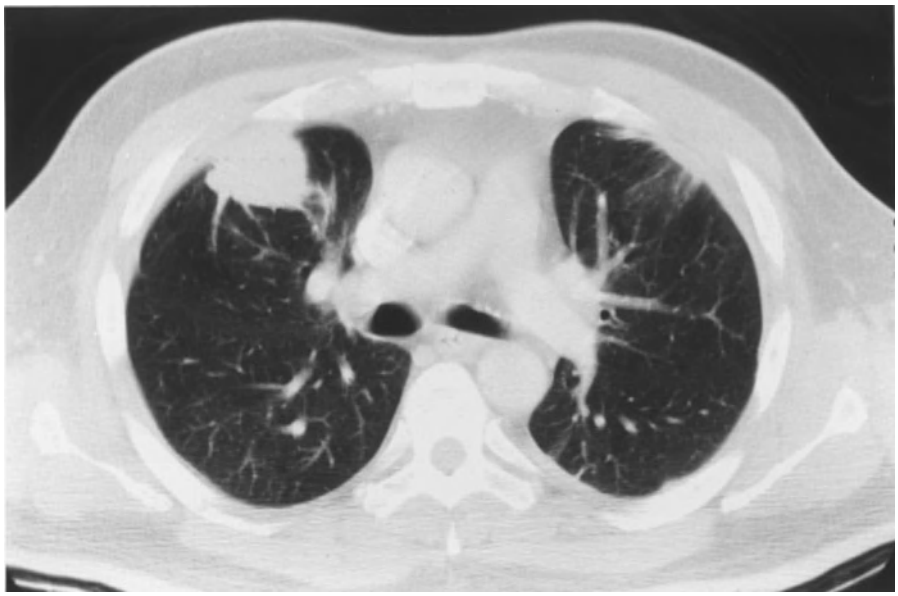
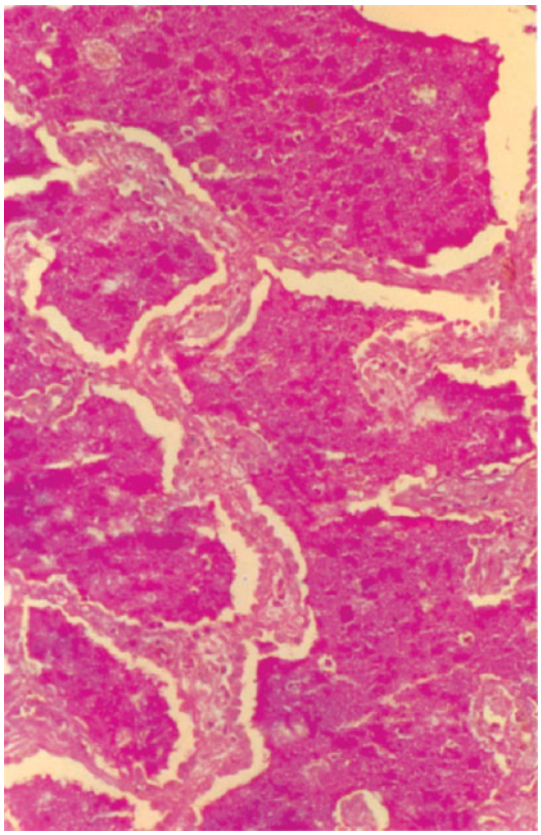


Figure 30-47 CT showing rounded atelectasis. A mass with a "tail" can be seen in the anterior segment of the right upper lobe. Pleural thickening is seen on the left side, with transpulmonary bands extending into the left upper lobe. The mass on the right represents rounded atelectasis, a finding usually associated with asbestos exposure. The changes on the right probably represent an early stage in the development of rounded atelectasis.

A



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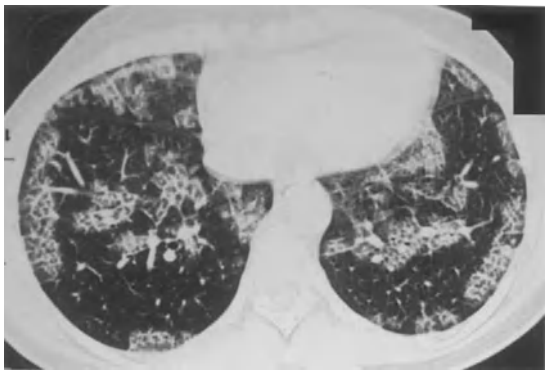
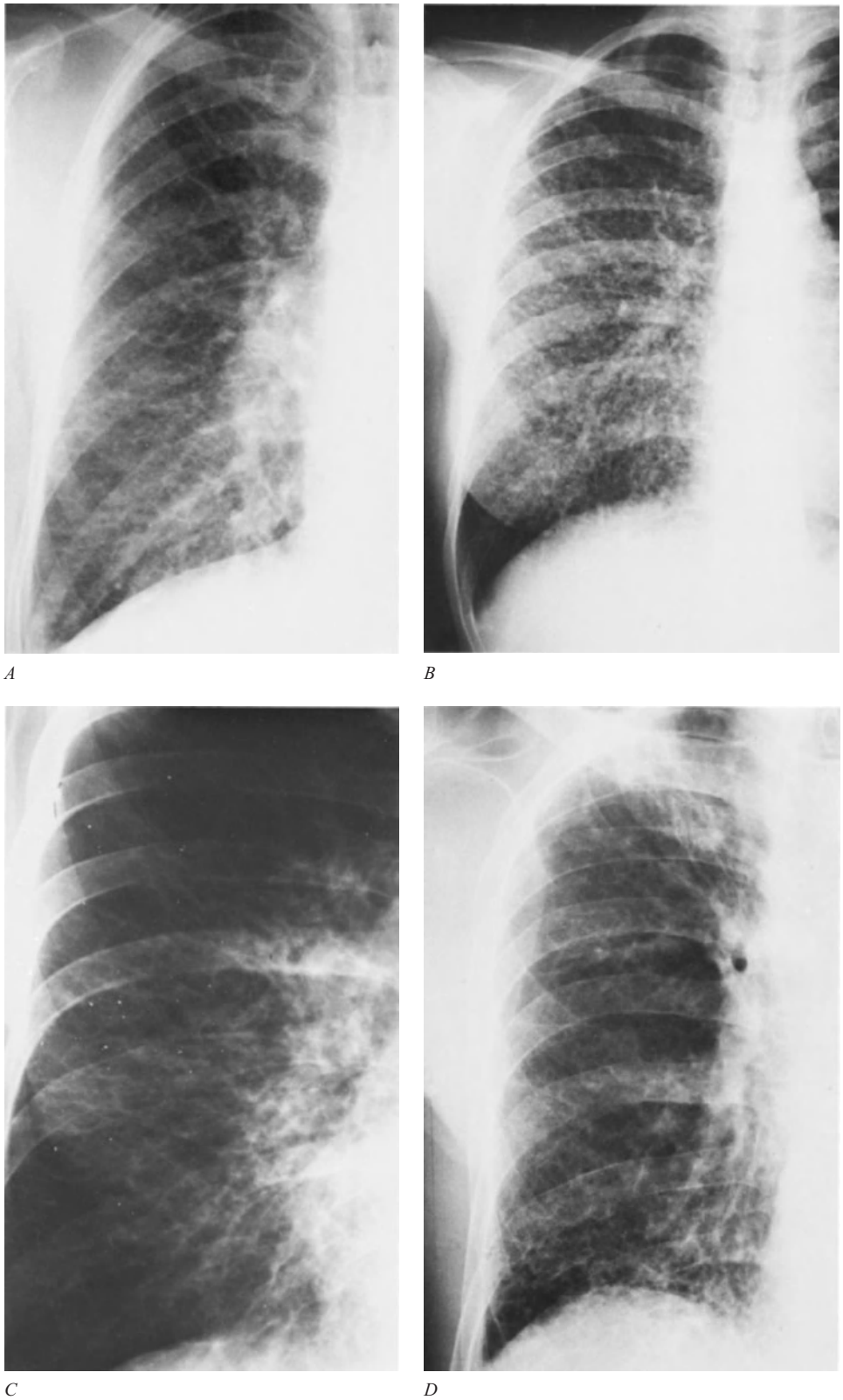


C

Figure 30-48 Anatomic changes in the pulmonary alveolar proteinosis. *A*. Sagittal section of the lung showing homogeneous filling of alveoli as though the lung had been embedded in the proteinaceous material. *(Courtesy of Dr. S. Molten.) B*. Alveolar spaces are filled with granular period acid-Schiff (PAS)–positive material. The alveolar septae are minimally thickened and are lined by hyperplastic type II pneumocytes. PAS stain, ×540. *(Courtesy of Dr. G. G. Pietra.) C*. CT of limited pulmonary alveolar proteinosis, showing the characteristic "crazy paving" pattern.

benign or malignant. Other radiographic features, including the presence of stranding, satellite lesions, or associated pleural disease, are seen in both benign and malignant processes and do not constitute bases for distinction.

A major use of CT is in determining whether a solitary nodule is, indeed, solitary. Many nodules that appear to be solitary on the plain radiograph are shown by CT to be multiple; many of these additional nodules are much smaller



A

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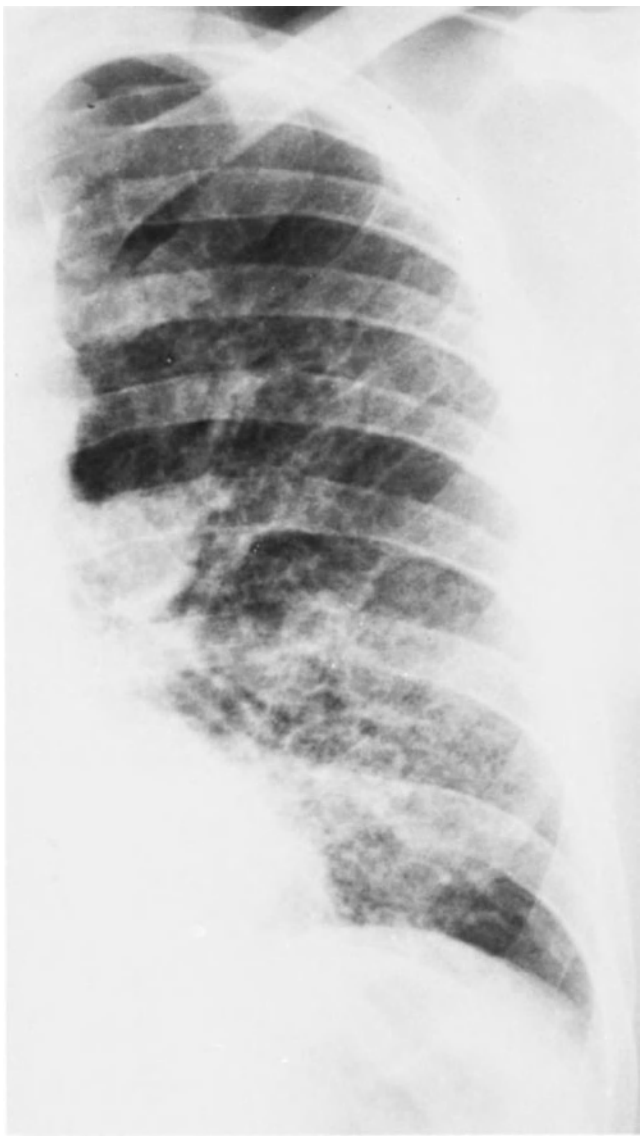
D

Figure 30-49 Diffuse interstitial disease. *A*. Linear interstitial pattern produced by interstitial pulmonary edema. The pattern is caused by fluid in the interstitial spaces of the lungs, particularly in interlobar septae. *B*. Nodular interstitial pattern due to sarcoidosis. Multiple small, discrete nodules involve both lung fields diffusely. Adenopathy is absent. *C*. Lymphangitic spread of tumor. The linear interstitial pattern was caused by metastatic carcinoma of the pancreas. *D*. Reticular or cystic interstitial lung pattern. The pattern is most marked at the bases and is characteristic of idopathic pulmonary fibrosis or collagen vascular disease, particularly scleroderma (as in this patient).



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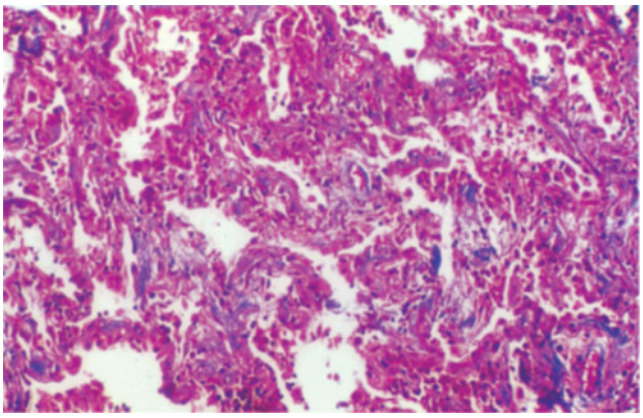

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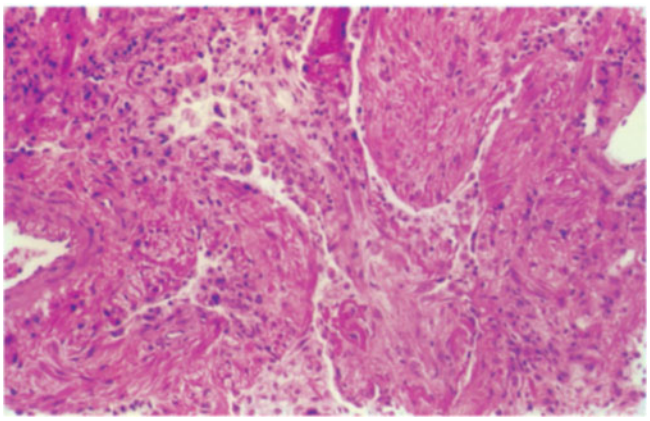

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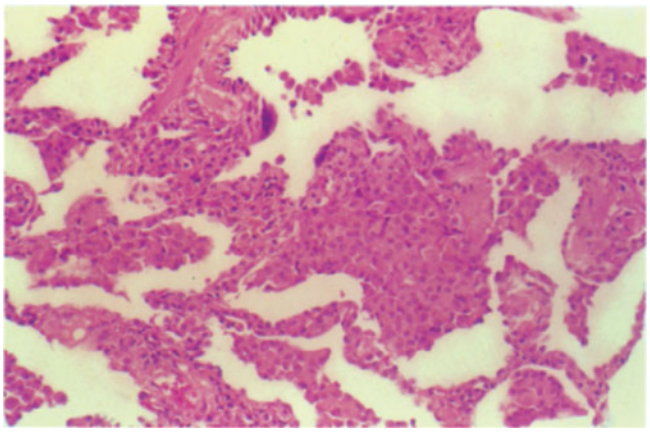

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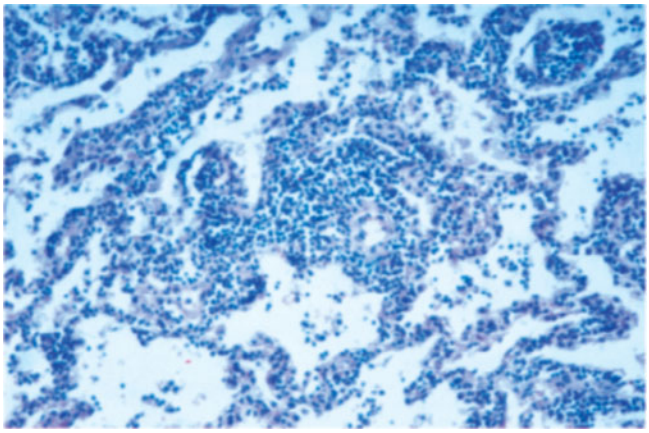


E

Figure 30-50 Different types of interstitial pneumonia. *A*. Chest radiograph of fibrosing alveolitis (usual interstitial pneumonia). *B*. Usual interstitial pneumonia (UIP). The alveolar septa are irregularly thickened by collagen (blue) and mononuclear cells. The airspaces contain desquamated epithelial cells, macrophages, and newly formed fibrous tissue. Masson trichrome, ×540. *C*. Bronchiolitis obliterans (BO). The lumen of a small bronchus is obliterated by fibrin (bright red), collagenous tissue, and macrophages. H&E, ×540. *D*. Desquamative interstitial pneumonia (DIP). The airspaces are filled with desquamated epithelial cells and occasional eosinophils. The alveolar walls are lined by hyperplastic type II cells. Giant cells are also present. H&E, ×400. *E* . Lymphocytic interstitial pneumonia (LIP). The alveolar septa are infiltrated by mononuclear cells, primarily mature lymphocytes, and plasma cells. H&E, ×405. (B *through* E, *courtesy of Dr. G. G. Pietra.*)

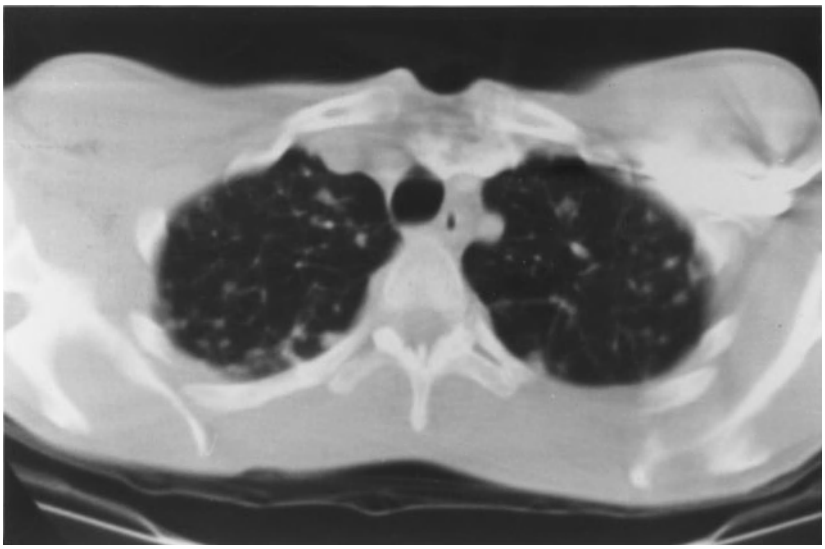
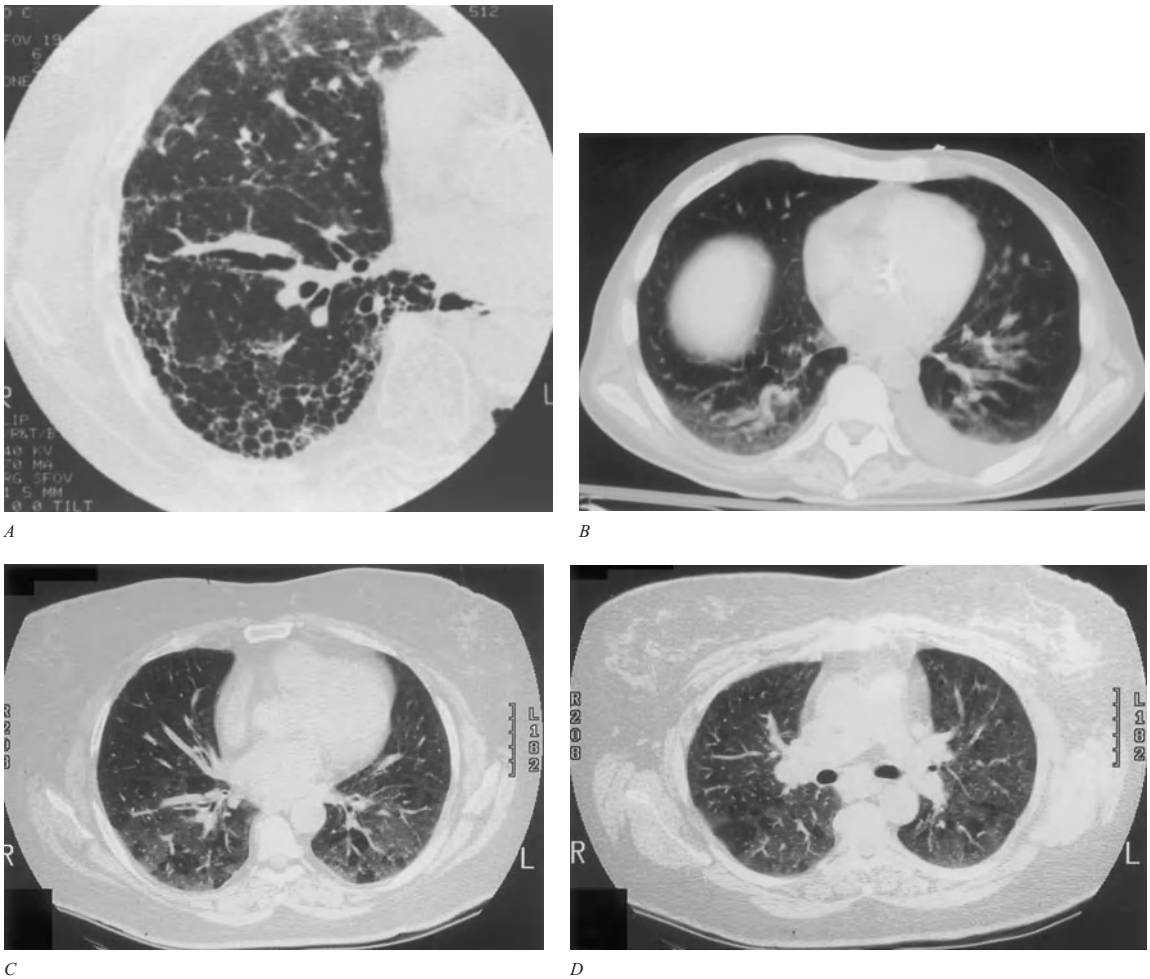


Figure 30-51 Metastatic tumor causing a nodular interstitial pattern. Multiple fine nodules can be seen throughout the lungs. The moderate-size nodules are characteristic of metastatic tumor. Finer nodules suggest miliary tuberculosis or other types of nodular interstitial disease.



A *B*

C *D*

Figure 30-52 High-resolution CT in various interstitial lung diseases. *A*. CT of reticular interstitial lung disease. The characteristic peripheral reticular pattern is from a patient with idiopathic pulmonary fibrosis. Collagen vascular disease causes an indistinguishable pattern. *B*. CT of interstitial pulmonary edema in congestive failure. Pleural effusions and prominent vessels are due to congestive heart failure. Linear densities are seen surrounding the lobules in the right lower lobe, adjacent to the right hemidiaphragm. These findings are characteristic of interstitial edema, but they might also be seen in lymphangitic spread of carcinoma. *C*. Chronic beryllium disease. CT shows ground glass changes in a mosaic distribution. *D*. Mosaic pattern due to small airways disease. This is frequently indistinguishable from hypersensitivity pneumonitis.

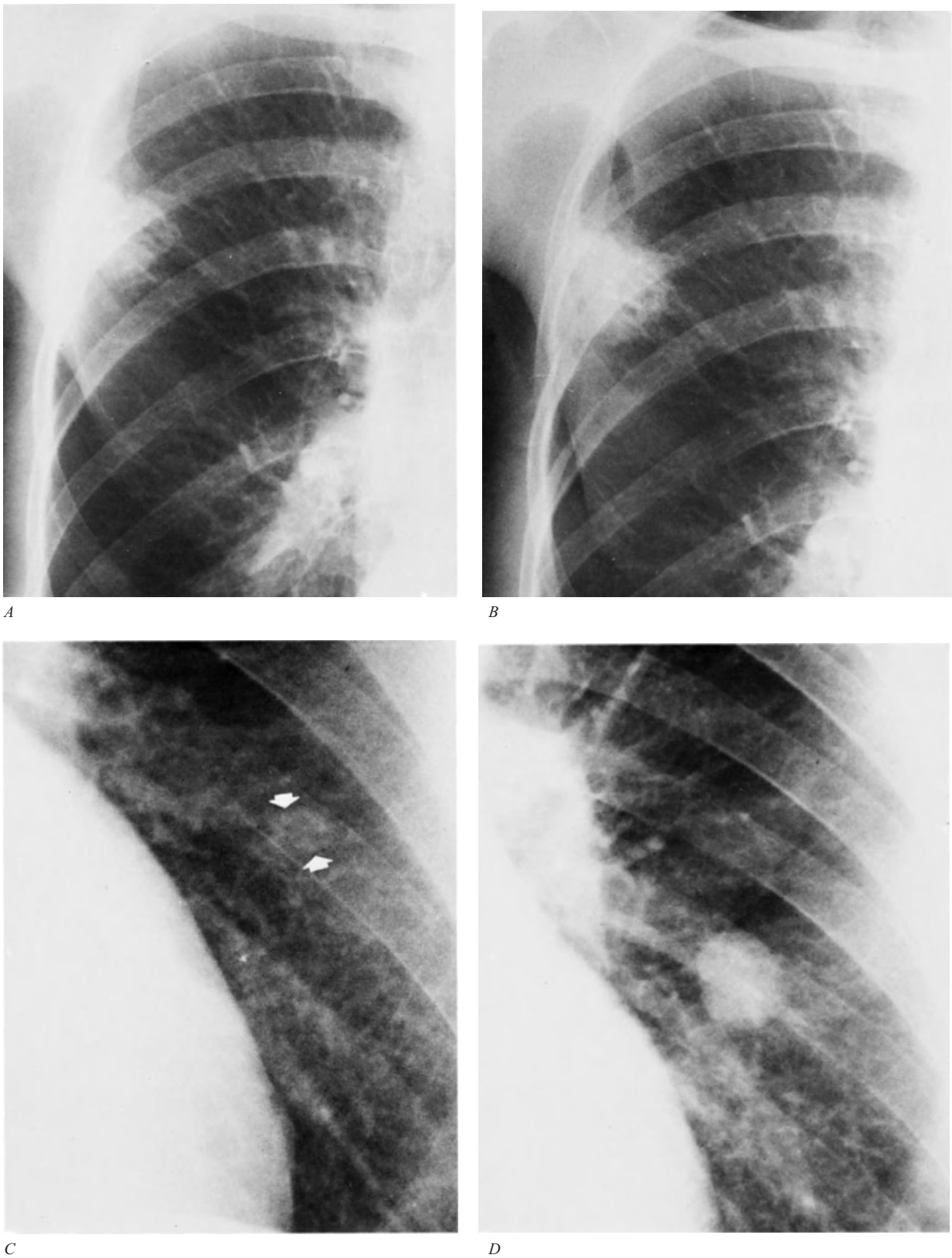


Figure 30-53 *Top:* Carcinoma of the lung with a long doubling time. An interval of 18 months elapsed between *A* and *B*. The right upper lobe lesion, which enlarged minimally during that time, proved to be squamous cell carcinoma of the lung. *Bottom:* Carcinoma of the lung with a short doubling time. An interval of 4 months elapsed between *C* and *D*. The nodule was not detected on the first radiograph (*C*). It proved to be a small cell carcinoma of the lung.

than the original nodule identified. The presence of multiple nodules suggests the diagnosis of metastatic tumor.

A major problem of chest CT is identification of one or several small nodules as an incidental finding. These nodules usually measure 5 mm or less in size and are almost always benign. Current thinking is that, in the absence of a known primary tumor, follow-up in 1 year is adequate to demonstrate stability of multiple nodules, and earlier follow-up is not necessary. However, with a solitary nodule, earlier follow-up (e.g., at 3 months) is prudent.

Like the plain film, CT is only marginally helpful in characterizing a pulmonary nodule. A "stellate" or "crablike" nodule is highly likely to be a primary lung carcinoma, although not invariably so. CT is excellent in demonstrating calcification in a nodule, usually indicative of a benign process (see above). CT may also demonstrate fat in a nodule, characteristic of a hamartoma. It may also demonstrate the draining vein of an arteriovenous malformation or the feeding artery of a sequestration.

Definitive diagnosis of the solitary pulmonary nodule is only rarely possible with radiographic techniques alone. Sputum cytology; bronchoscopy with bronchial washings, brushings, and biopsy; transthoracic lung aspiration or biopsy; thoracoscopic biopsy; or open lung biopsy may be necessary (see Chapters 36 and 37).

Multiple Pulmonary Nodules

Although a solitary pulmonary nodule that is seen on the plain film may be benign or malignant, the presence of multiple nodules strongly suggests metastatic tumor. Occasional exceptions to this rule include rheumatoid nodules (Fig. 30-54), fungal infections, alveolar sarcoidosis, and Wegener's granulomatosis. CT is often not very helpful when multiple pulmonary nodules have already been identified on the plain chest radiograph.

As previously noted, CT detects a large number of small pulmonary nodules which are not visible on the chest radiograph. If these are 5 mm or less and multiple, they are usually benign if the patient has no known primary tumor; radiographic follow-up is appropriate.

Left Ventricular Failure

Failure of the left ventricle is generally easy to recognize on the chest radiograph. The heart is enlarged, and the pulmonary vasculature is prominent. Changes in the size of the heart and central vessels are most evident on consecutive radiographs.

In chronic left ventricular failure, chronic dependent edema and interstitial fibrosis at the lung bases result in redirection of pulmonary blood flow from the bases to the apices; the vessels of the upper lobes become more prominent than those of the lower lobes, a finding referred to as *cephalization*. Interstitial edema often accompanies pulmonary venous congestion and is manifested by a diffuse increase in interstitial markings, usually in a linear distribution (Fig. 30-49*A*); Kerley's lines are characteristic features of interstitial edema.

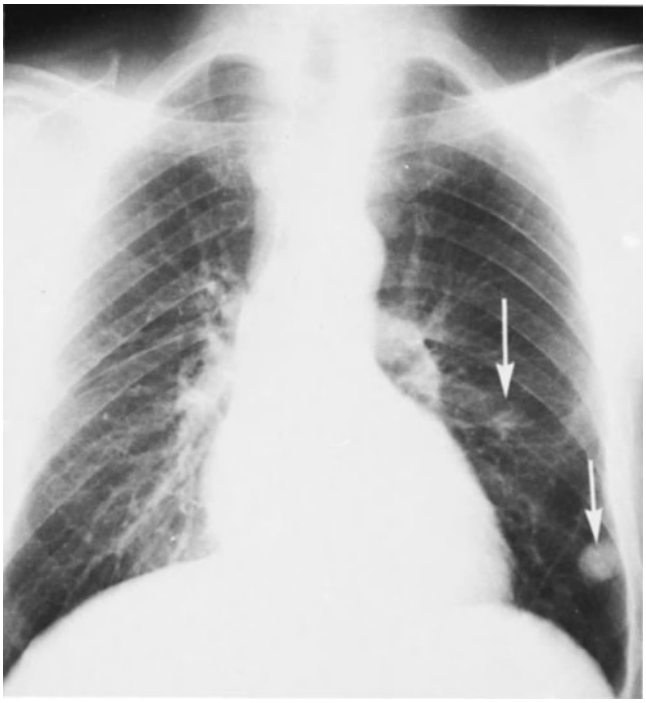


Figure 30-54 Rheumatoid nodules. The nodules in the left lung of this patient with rheumatoid arthritis regressed 4 months later.

Alveolar edema may follow the development of interstitial edema and is characterized by diffuse bilateral consolidation (Fig. 30-36).

As on the plain film, heart failure on CT is first manifest as increased vascular markings. This is more easily recognized if a prior CT is available for comparison. As the heart failure progresses, interstitial pulmonary edema occurs, easily identified as increased interstitial markings with a septal pattern. Further progression leads to ground glass changes or frank alveolar edema.

Pleural effusions often accompany biventricular heart failure. At first, the pleural effusions are associated with prominence of the pulmonary vascular markings, cephalization, or both. However, while the pulmonary congestion clears in response to therapy, the pleural effusions often remain after the pulmonary vessels have returned to normal size. Pleural effusions in congestive heart failure may be unilateral or bilateral. If unilateral, the effusion most commonly occurs on the right side. As noted previously, recognition of left ventricular failure is difficult in the patient with obstructive lung disease because hyperinflated lungs and an elongated heart make it difficult to recognize cardiomegaly and pulmonary vascular engorgement. Comparison with previous films is paramount in recognizing subtle changes in cardiac size and in pulmonary vascular engorgement.

THE MEDIASTINUM

The anatomic delineations of "compartments" of the mediastinum are not defined consistently throughout the medical

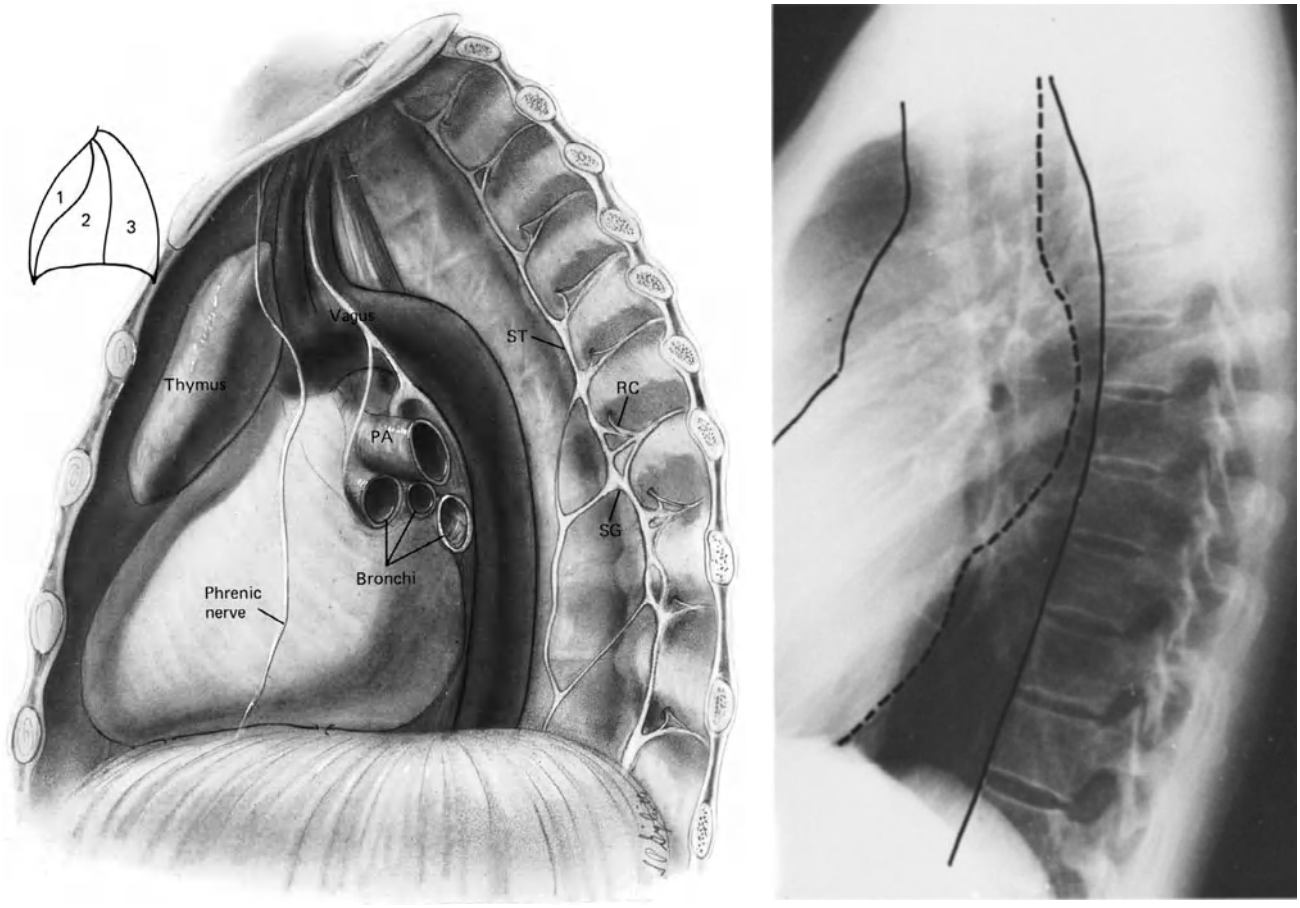


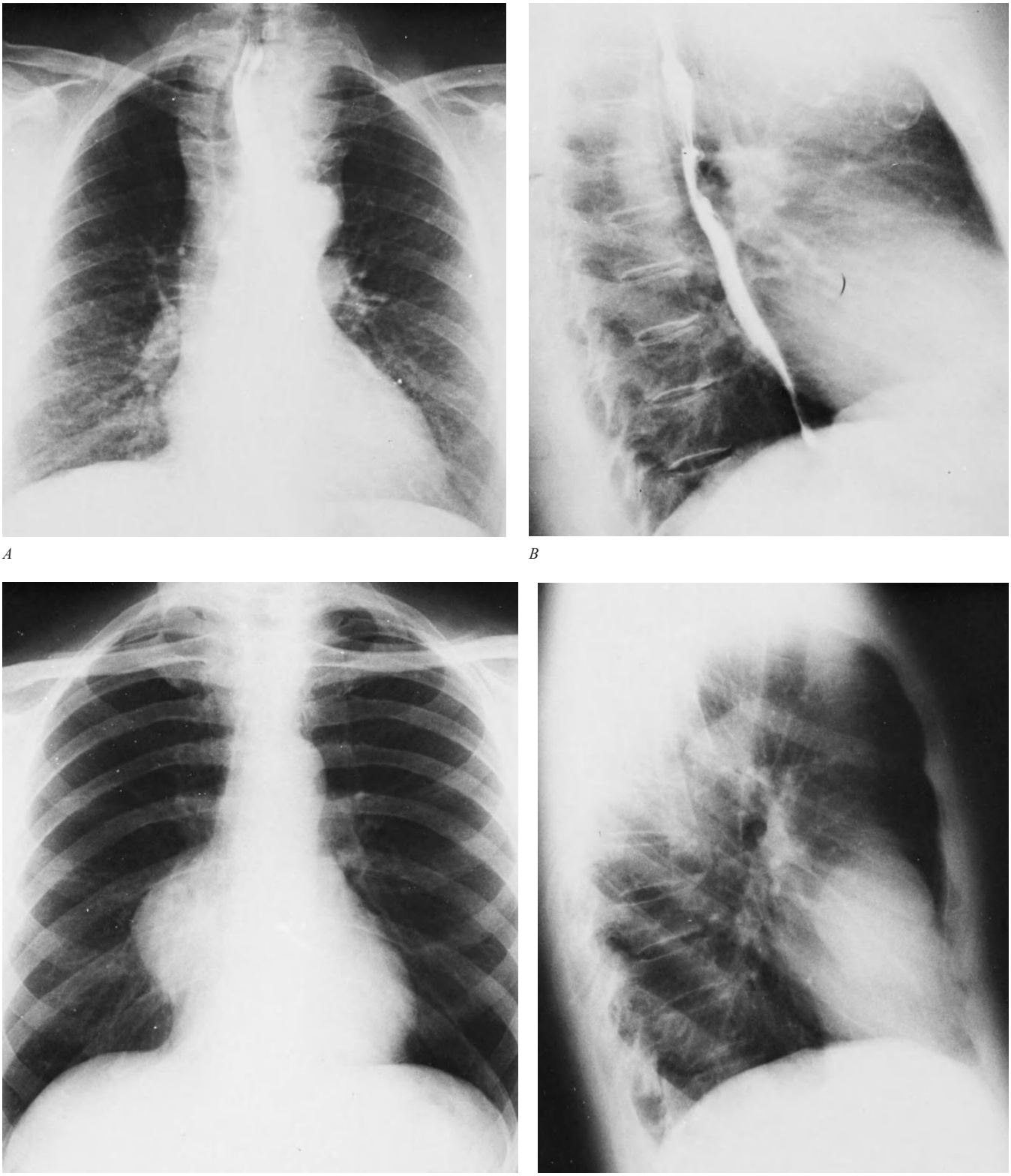
Figure 30-55 Compartments of the mediastinum. *A*. Anatomic view of the compartments of the mediastinum. The subdivisions in the small schematic (top left) correspond to those designated by the solid black lines in *B*. PA = pulmonary artery; ST = sympathetic trunk; SG = sympathetic ganglion; RC = ramus communicans. (*From Jones KW, Pietra GG, Sabiston DC: Primary Neoplasms and Cysts of the Mediastinum, in Fishman AP (ed), Pulmonary Diseases and Disorders, New York, McGraw-Hill, 1980, pp 1490–1521.) B*. Radiographic division of the mediastinum. The closed lines delineate the anterior, middle, and posterior compartments. The dashed line represents the division of the middle and posterior mediastinum that is conventionally used by anatomists.

literature. For radiographic diagnosis, a simple classification has been employed (Fig. 30-55): (1) The *anterior* compartment, which extends from the sternum anteriorly to the heart, aorta, and brachiocephalic vessels posteriorly, comprises only the thymus and a few lymph nodes. (2) The *middle*, or *visceral*, compartment contains the heart, great vessels, trachea and its branches, esophagus, and descending aorta. It extends from the posterior border of the anterior compartment to the anterior border of the vertebral column. These boundaries differ from the anatomist's classification (Fig. 30-55 *A*), which relegates portions of the esophagus and the descending aorta to the posterior mediastinum. (3) The *posterior* compartment contains the vertebrae and the paravertebral sulci. Applying this classification to the lateral chest radiograph, or to the CT, one may categorize mediastinal masses readily according to their position with the mediastinum.

Abnormalities in the anterior compartment include enlarged lymph nodes, substernal goiter, thymus and thymic tumors, and teratomas. Distinction among these can be made on the basis of their position within the anterior mediastinum and their appearance. Thyroid masses invariably lie high in the anterior mediastinum and displace the trachea and esophagus (Fig. 30-56 *A* and *B*). On CT, the thyroid has characteristic enhancement. Small thyroid nodules, usually a goiter, are frequently detected by CT as an incidental finding.

Benign, or minimally invasive, thymomas and teratomas generally lie below the aortic arch and present as single, well-demarcated masses (Fig. 30-56 *C* and *D*). If the outline of the mass is irregular by plain film or CT, the capsule likely has been breached and the thymoma or teratoma is invasive. However, invasive tumor may be present and not be recognized by radiographic means. In addition, invasive thymoma or teratoma may be indistinguishable from a lymphoma which is confined to the anterior mediastinum.

Lymph node enlargement is generally diffuse, often nodular or lumpy in character on the plain film (Figs. 30-57 and 30-58), and evident as a characteristic appearance on



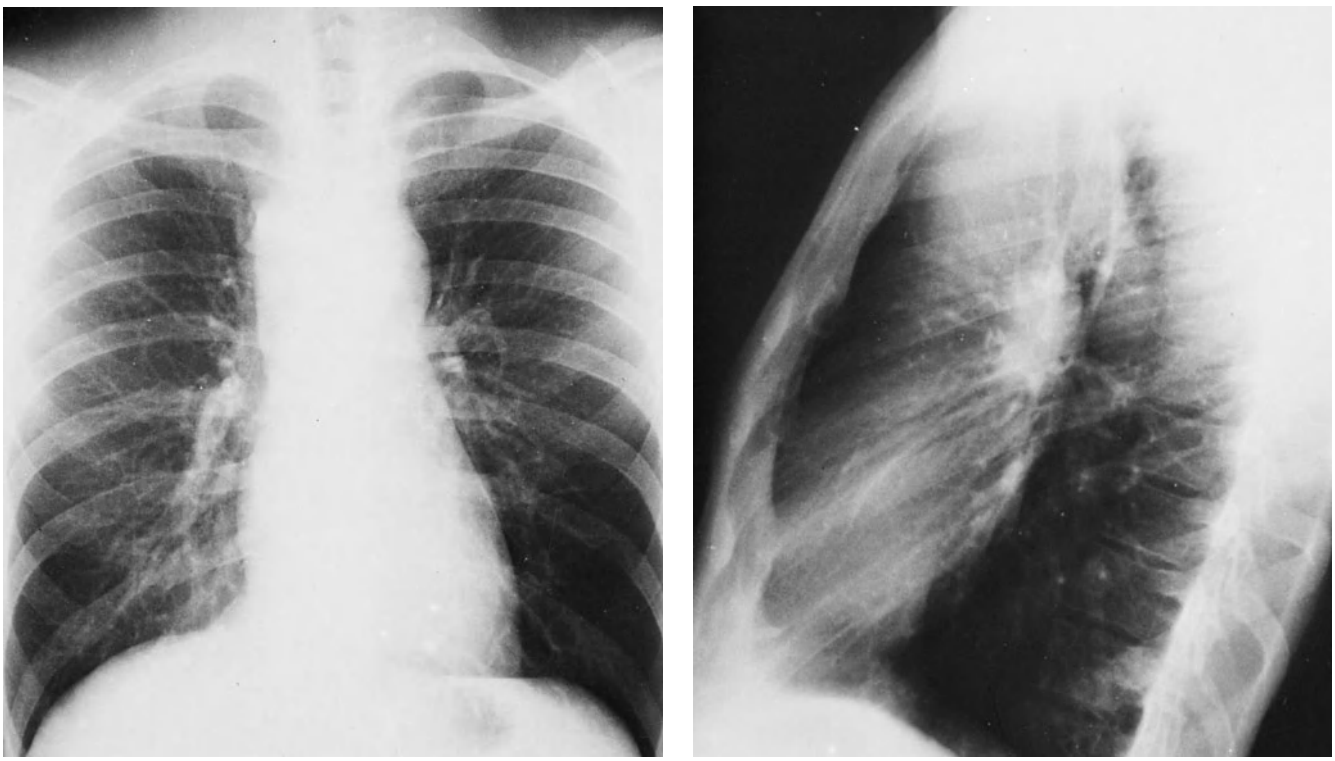
A

B

C

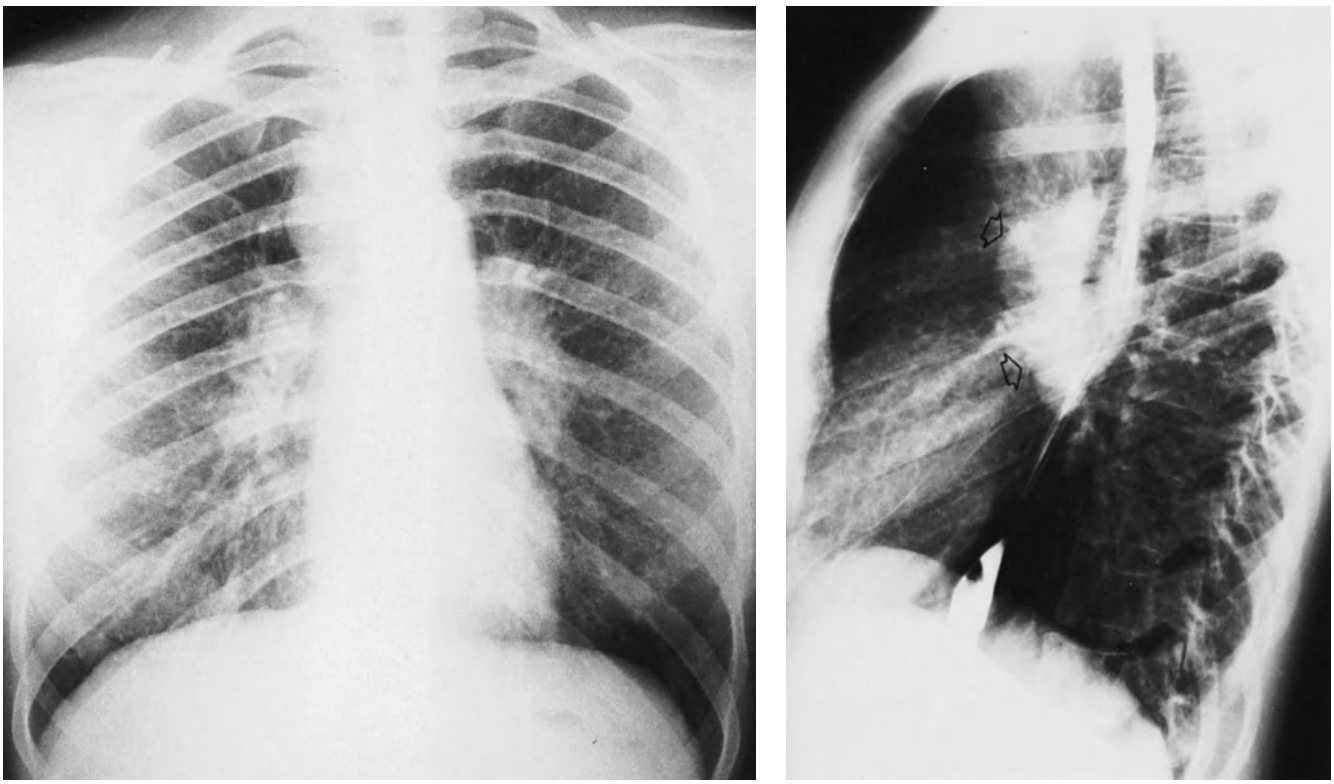
D

Figure 30-56 Substernal thyroid. *A*. PA view. A large mass in the neck extends below the clavicle. The trachea and esophagus are displaced to the right. *B*. Lateral view. The trachea and esophagus are also displaced posteriorly. Several calcifications are present within the mass. Thymoma. *C*. PA view. A discrete mass (thymoma) lies along the right heart border. *D*. Lateral view. The mass also overlies the anterior portion of the cardiac shadow. Despite being radiographically well circumscribed, the mass may be either invasive or noninvasive thymoma.



A *B*

Figure 30-57 Hodgkin's disease. *A*. PA view. A lobulated mass widens the mediastinum on both sides of the trachea. *B*. Lateral view. The mass lies anterior to the trachea.



A *B*

Figure 30-58 Sarcoidosis. *A*. PA view. A mass is present in the right paratracheal area, and both hili are enlarged. *B*. Lateral view. The hilar enlargement (arrows) is striking. Enlargement in these three node-bearing areas is characteristic of sarcoidosis.

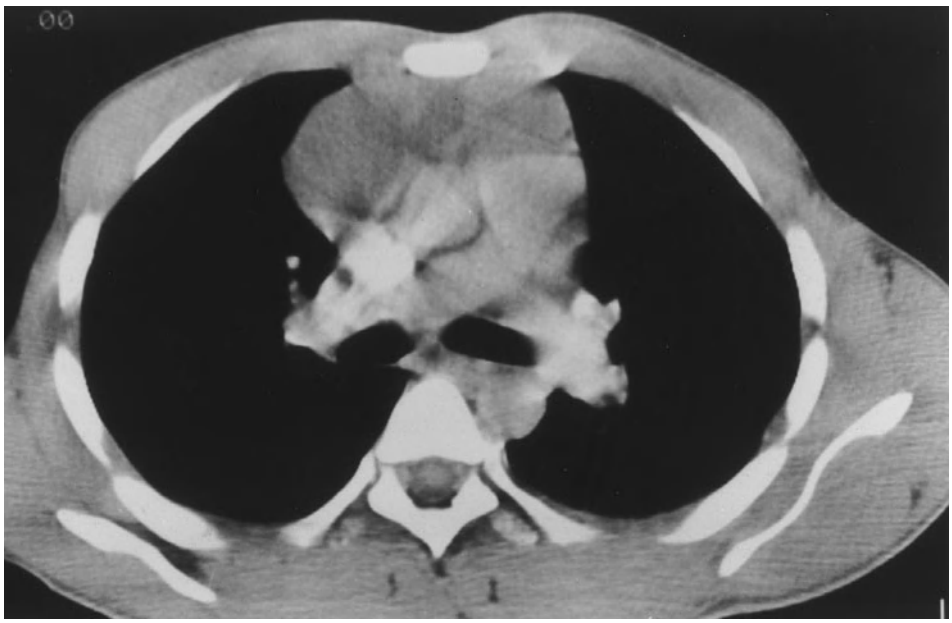


Figure 30-59 Malignant teratoma. A poorly circumscribed, diffuse mass can be seen anterior to the great vessels. Although the mass could represent lymphadenopathy from a number of causes, it is also consistent with malignant thymoma or teratoma. In this patient with AIDS, the mass was shown to be a teratoma.

CT. Enlarged anterior mediastinal lymph nodes are usually accompanied by enlarged lymph nodes in the middle mediastinum, making it easy to separate lymphoma from invasive thymoma or teratoma. Occasionally, differentiation may be impossible (Fig. 30-59).

Lymph node enlargement may be produced by metastatic tumor, particularly from a primary neoplasm of the lung, or by sarcoidosis, lymphoma, or primary tuberculosis. Less common causes of mediastinal lymphadenopathy include other inflammatory processes, such as fungal infection or infectious mononucleosis.

The middle compartment of the mediastinum contains all of the mediastinal viscera, as well as lymph nodes. Lymphadenopathy in the middle compartment is quite common and is generally seen as a diffuse mass, often associated with enlargement of one or both hili (Fig. 30-58). CT often demonstrates mediastinal adenopathy which is not visible on the plain film (Fig 30-60).

A localized middle mediastinal mass may be caused by an aneurysm or other anomaly of the aorta or great vessels (Fig. 30-61). Its vascular nature is suggested by proximity to the aortic shadow and is readily confirmed by CT, MRI, or aortography (Figs. 30-62 and 30-66). Duplication cysts of the esophagus and the tracheobronchial tree are also common in the middle compartment. These localized masses are smooth and well circumscribed; generally, they do not contain air. Bronchogenic cysts commonly occur at the tracheal carina, whereas esophageal duplication cysts are characteristically located near the distal end of the esophagus (Fig. 30-63 *A* and *B*). However, esophageal and bronchogenic cysts may occur anywhere within the middle compartment. On CT, a duplication cyst often has a fluid density (as measured in Hounsfield units); however, not infrequently, fluid in the cyst is proteinaceous and of high density, erroneously suggesting that the cyst is a solid mass.

A dilated esophagus is sometimes seen on the chest radiograph as a long tubular mass in the middle compartment (Fig. 30-63 *C* and *D*) and is readily identified by CT. Tumors of the esophagus or trachea may also present as more localized mediastinal masses by chest radiograph; usually, CT is required for recognition. An esophageal tumor may involve primarily the mucosa and may not be well seen on the CT when it is clearly demonstrated on a swallowing study.

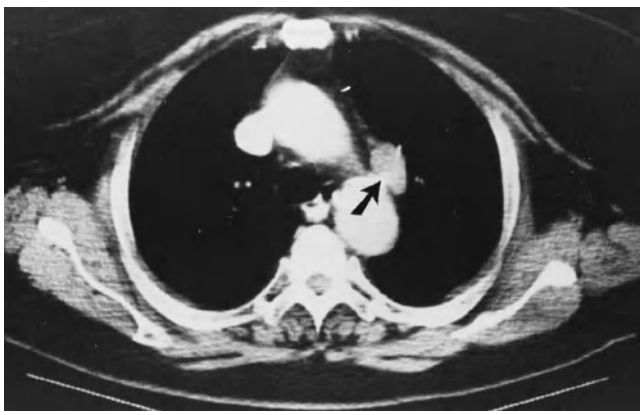
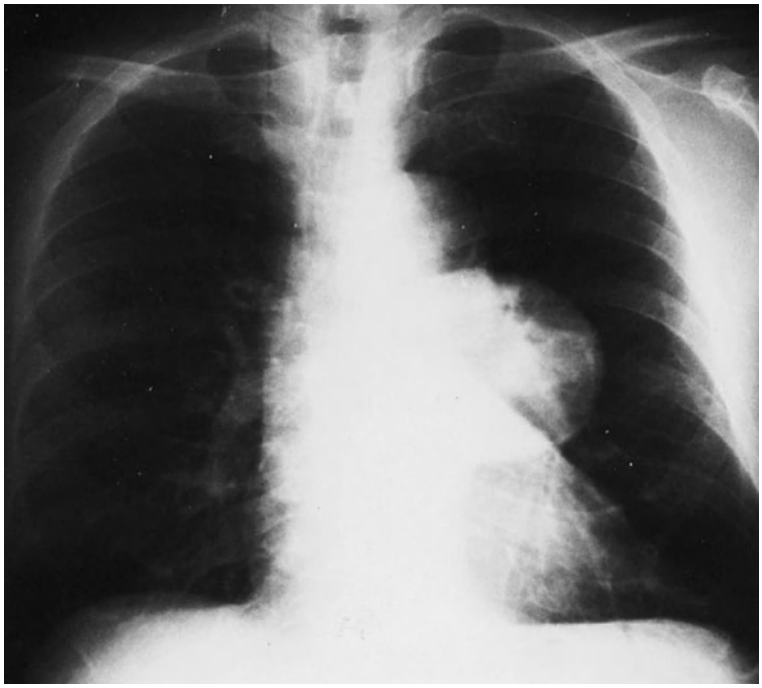


Figure 30-60 Mediastinal mass not seen on the routine chest radiograph. A large lymph node (arrow) is well seen on the CT scan lying just anterior to the descending aorta. This could not be seen on the routine chest radiograph. This node contained adenocarcinoma, and its presence on the scan was an important finding in staging a primary carcinoma of the left lower lobe.



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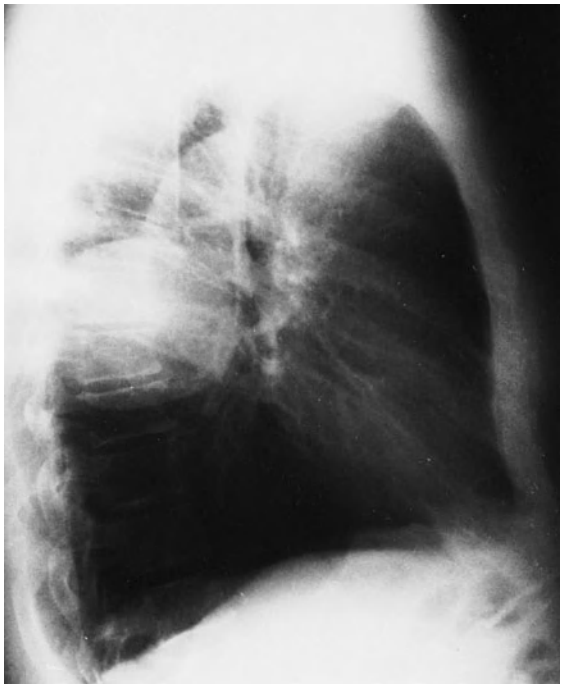

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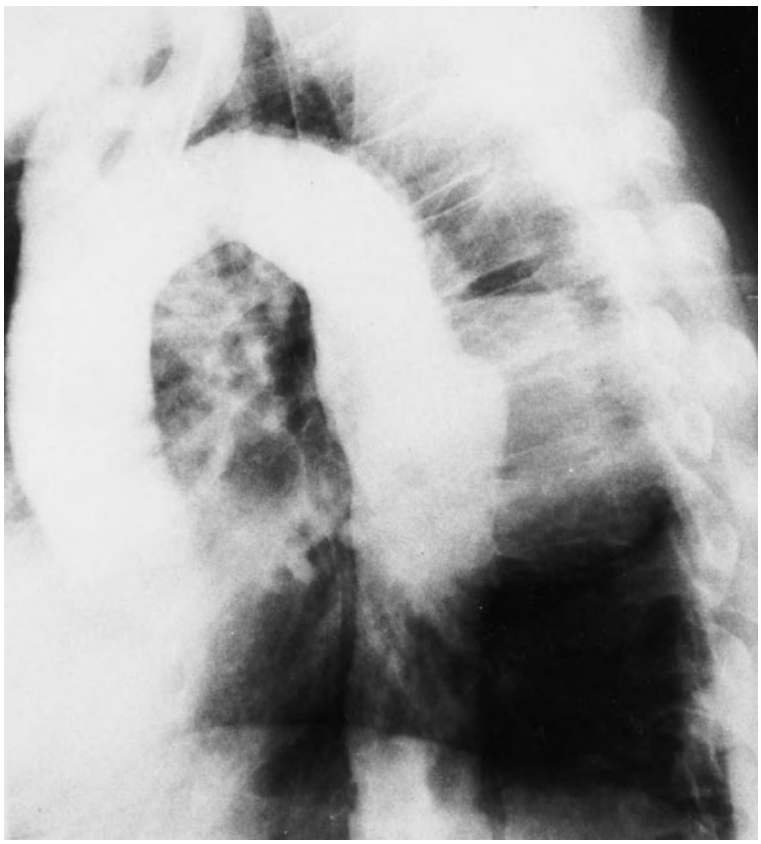
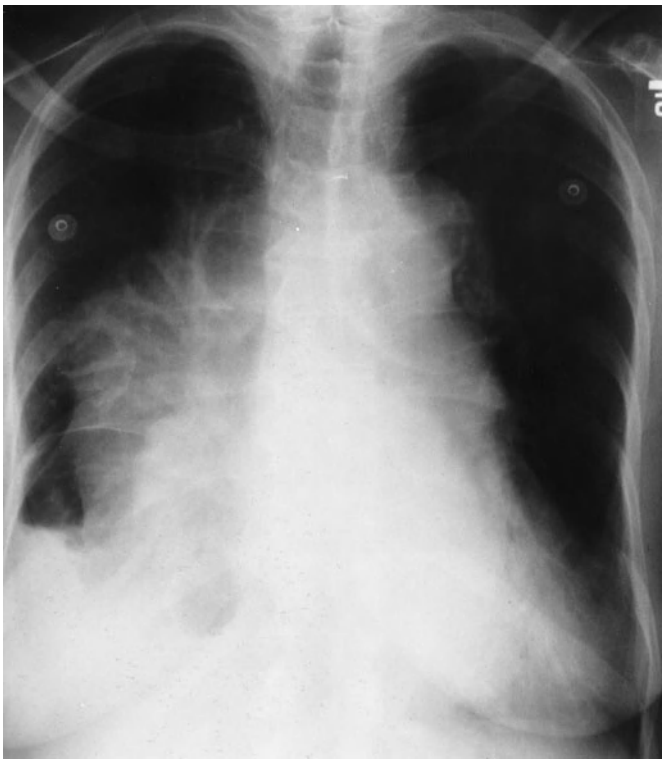


C

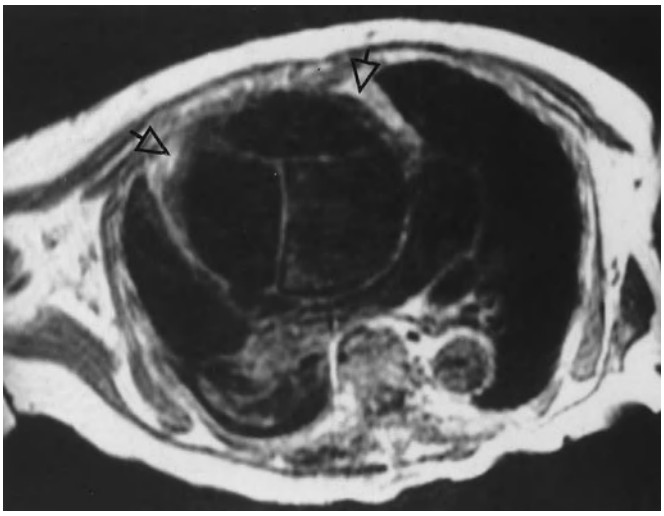
Figure 30-61 Mediastinal mass. *A*. Aortic aneurysm, PA view. A mass is seen to the left of the aorta. *B*. Aortic aneurysm, lateral view. The mass is also posterior to, and intimately associated with, the aorta. *C*. Aortic aneurysm, aortogram. An irregularity in the wall of the opacified aorta indicates the aneurysm. Most of the aneurysm is filled with clot. This type of mass may be mistaken for a neurogenic tumor in the posterior mediastinal compartment.

Radiographs taken with barium in the esophagus are particularly helpful in characterizing middle compartment masses on plain film and, occasionally, on CT.

In the posterior (paraspinal) compartment, the most common radiographic abnormalities are neurogenic tumors (Fig. 30-64). However, tumors or infections of the vertebral column may also present as masses in the posterior compartment (Fig. 30-65). CT or MRI usually distinguishes between a neurogenic tumor, which is unilateral and paraspinal in location, and lesions which erode or destroy the vertebrae and



A



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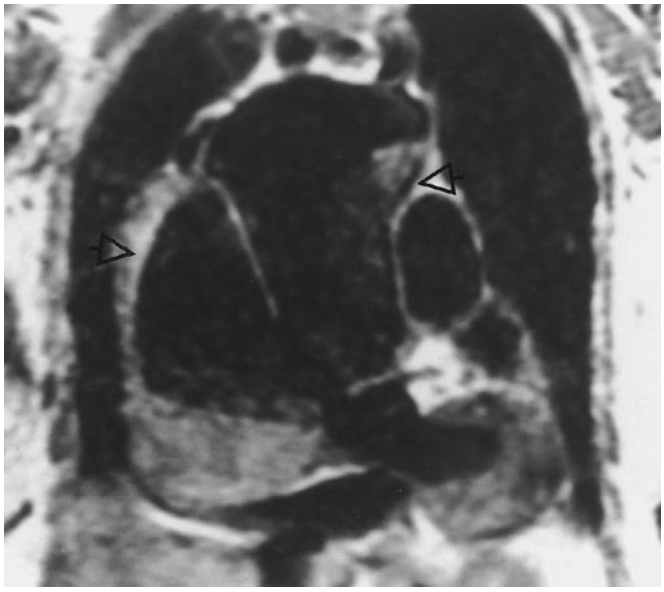


C

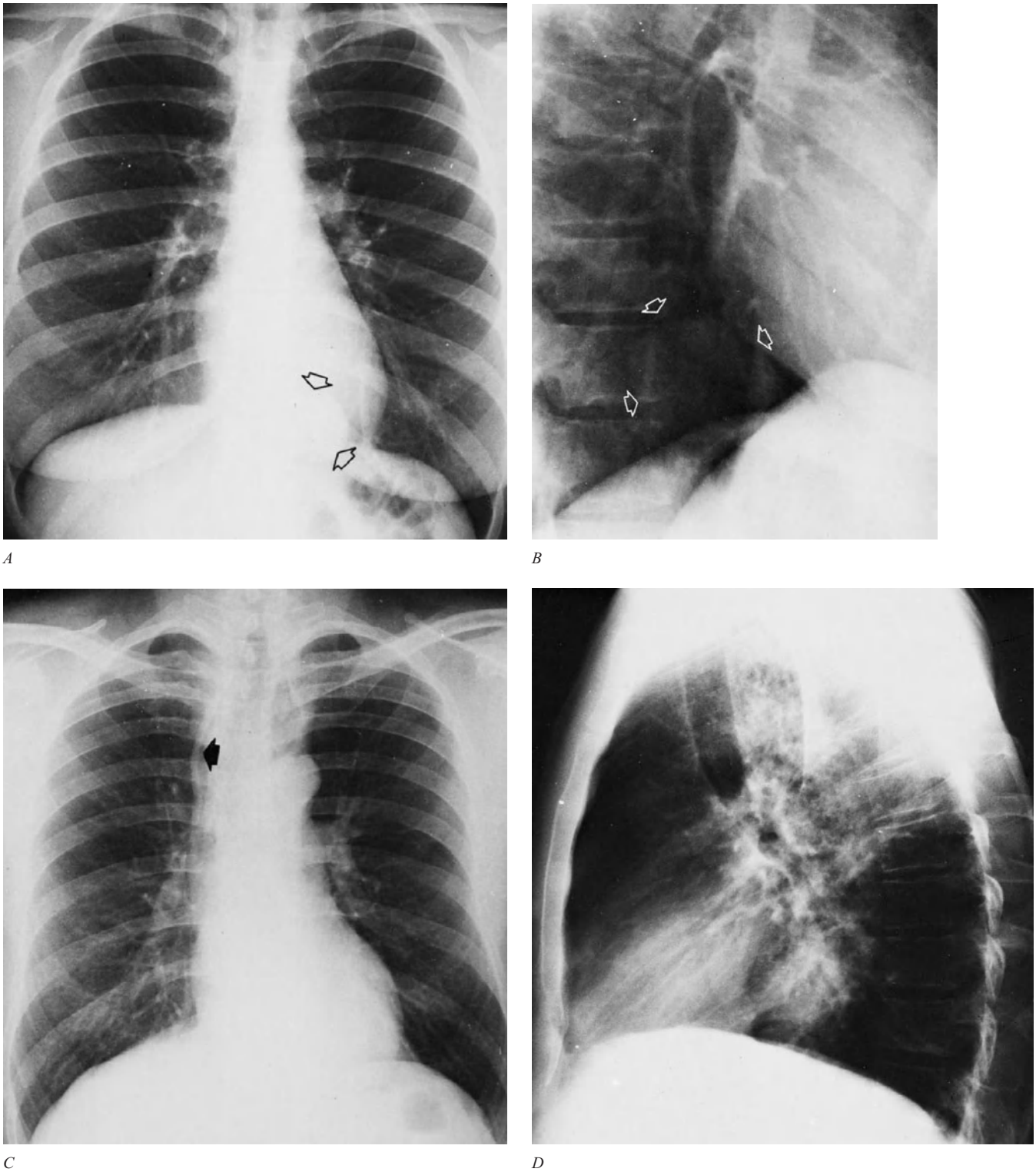
Figure 30-62 Dissecting aortic aneurysm demonstrated by MRI. *A*. A large anterior mediastinal mass was suspected in the plain chest film. *B*. An axial MRI shows a huge dissecting aneurysm of the ascending aorta (arrows) containing multiple septations (arrows). *C*. A sagittal image is more graphic in its depiction of the huge ascending aortic aneurysm (arrows).

are generally present on both sides of the vertebral column. MRI findings are characteristic for neurogenic tumors.

A variety of radiographic lines or stripes seen in and around the mediastinum on the PA radiograph can be very useful diagnostically. Most useful among these is the *posterior paraspinal line,* which is a pleural reflection to the left of the thoracic spine (Figs. 30-5 and 30-65). The posterior paraspinal line is related to the descending aorta; it is seen on the right side if the descending aorta is on the right. Tumors or inflammatory diseases in the vertebral bodies displace the posterior paraspinal line to the left, creating a posterior paraspinal line on the right, where one is not ordinarily present. Large spurs arising from the vertebral body on the right also push out the pleura, creating a paraspinal line (Fig. 30-5*A*).

DIAPHRAGM AND CHEST WALL

The left hemidiaphragm is generally lower than the right; in only about 9 percent of subjects is the left hemidiaphragm



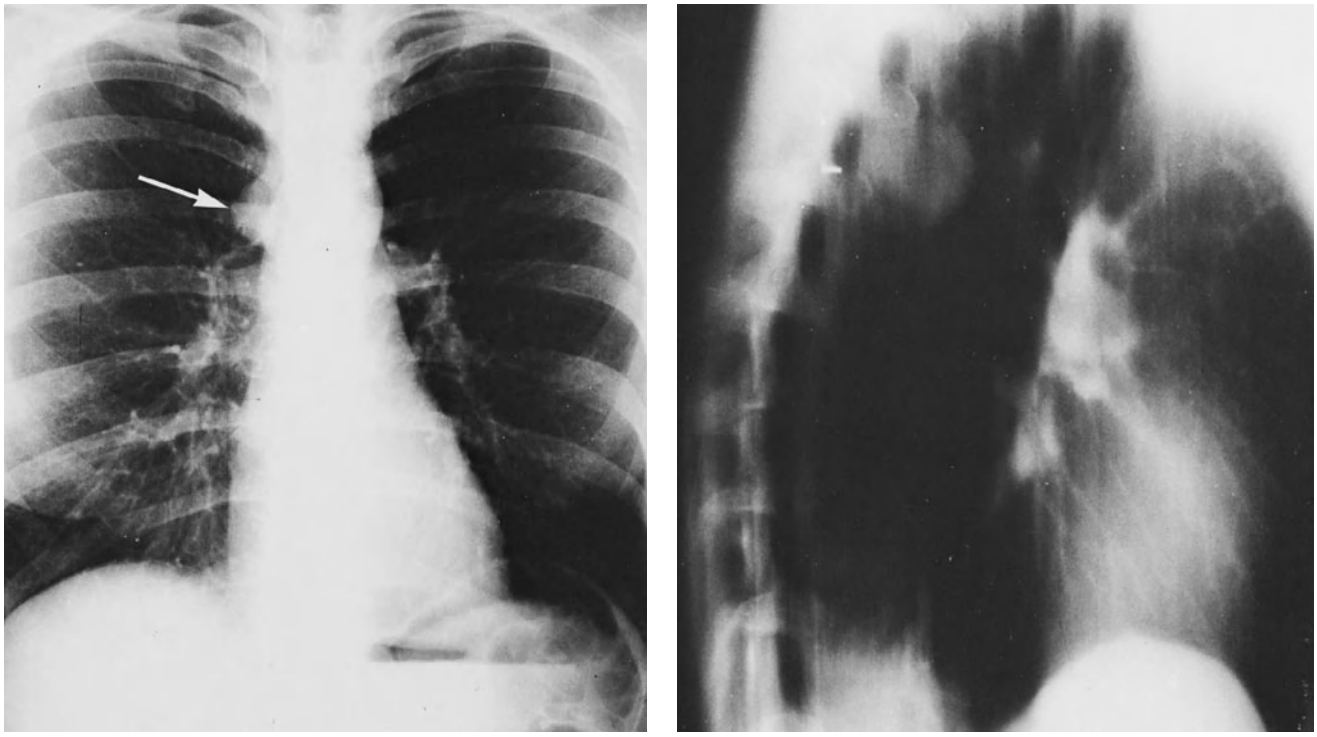
A

B

C

D

Figure 30-63 Esophageal duplication cyst. *A*, *B*. The small round mass behind the heart (arrows) has the characteristic location and appearance for an esophageal duplication cyst. Achalasia. *C*. PA view. The dilated esophagus is visible as a mass along the right mediastinum. Air outlines the wall of the upper esophagus above the aortic arch (arrow). *D*. Lateral view. The mass consists of an amorphous cluster of material lying posterior to the trachea and the heart (debris in the esophagus), displacing the trachea anteriorly.



A *B*

Figure 30-64 Neurogenic tumor (pheochromocytoma). *A*. PA view. A small mass (arrow) lies to the right side of the spine. *B*. Lateral view. The mass overlies the spine. The location is typical for a neurogenic tumor, usually a schwannoma or ganglioneuroma. This mass proved to be a thoracic pheochromocytoma.

higher. Variations in diaphragmatic contour are common. Most common is a localized eventration of the diaphragm (Fig. 30-6), in which a segment of diaphragmatic muscle is replaced by a thin fibrous membrane. The use of fluoroscopy in identifying local eventration of the diaphragm was described previously.

Foramina traverse the normal diaphragm to connect the thorax and abdomen. Sometimes the foramina enlarge sufficiently to allow herniation of abdominal viscera into the chest. The paired foramina of Morgagni lie anteriorly and medially; hernias through one of these foramina occur frequently on the right (Fig. 30-67 *A* and *B*), but rarely on the left. Generally, diaphragmatic hernias contain only omentum or fat, but they may sometimes contain colon. Hernias through the centrally placed esophageal hiatus (Fig. 30-67 *C–E*) are much more common than those through the foramina of Morgagni. The stomach is the usual herniating viscus; less often, the hernia contains colon or small bowel. Traversing the diaphragm posteriorly and slightly laterally are the paired foramina of Bochdalek. The massive congenital hernias occasionally seen in newborns generally occur through a large foramen of Bochdalek, usually on the left side. Hernias through these foramina are unusual in adults; when present, they may contain a kidney.

Traumatic diaphragmatic hernias occur secondary to traumatic rupture of the diaphragm, usually in the setting of a motor vehicle accident. Any viscus may protrude through the rupture; stomach and colon are common (Fig. 30-67 *F*). The actual herniation may occur days, weeks, or many months after the diaphragmatic injury. Delayed hernias often create a confusing radiographic picture. These hernias may be difficult to recognize on axial CT. Coronal reconstructions or MRI may be useful.

On the plain film, masses of the chest wall may cause bone destruction or erosion; if they do not, they may not be readily visualized. The masses also may be seen if they protrude into the lung as densities. Most lesions of the chest wall are metastatic tumors of the ribs, but primary tumors of the ribs and soft-tissue sarcomas also occur. Their encroachment into lung tissue causes a characteristic shadow that has smooth margins and tapering edges and is generally seen well in only one of the two standard views of the chest (Fig. 30-68 *A*). This characteristic configuration has been designated the *extrapleural sign.* Since many pleural lesions mimic the extrapleural sign, bone destruction is the key finding in accurate identification of an extrapleural mass. CT is extremely useful in the evaluation of chest wall lesions (Fig. 30-10), which often are not well seen or are poorly characterized on routine radiographs. CT readily shows bone destruction and the soft-tissue mass in the chest wall. Clinically palpable chest wall masses may not be visible on the plain film if they do not involve the ribs or protrude into the thoracic cage. In this instance, CT imaging is important. MRI also is an excellent technique for demonstrating chest wall masses.

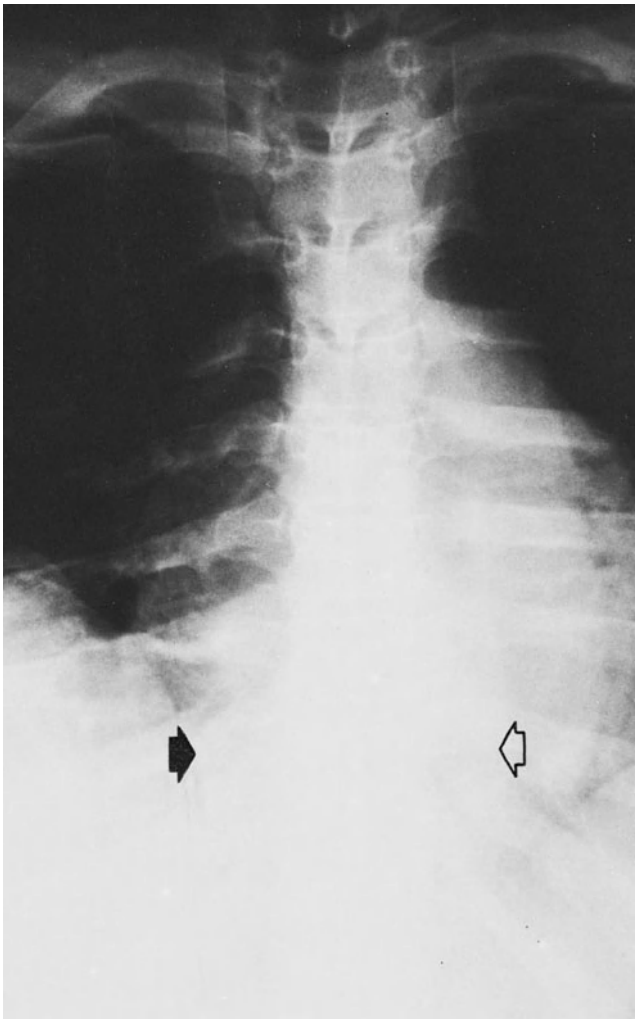
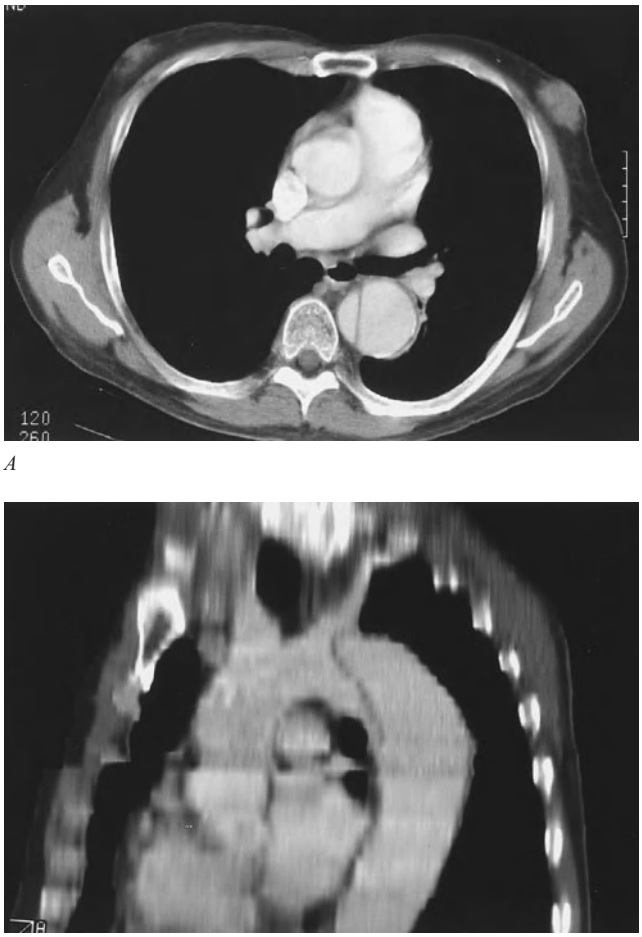


Figure 30-65 Tuberculosis. The normal left paraspinal line is displaced laterally (open arrow) by a paraspinal mass; the right paraspinal line, which is usually not seen, is present and displaced laterally (closed arrow). These findings are characteristic of infection involving the spine, in this case tuberculosis.

In addition to hernias through the diaphragm, tumors of the diaphragm occasionally present as masses seen on the chest radiograph. MRI is ideally suited to demonstration of diaphragmatic lesions, since coronal sections are much better than transaxial ones for this anatomic region. This is also true for pleural lesions, such as a pleural fibroma. With axial images, clear demonstration that a pleural lesion is in the chest (above the diaphragm), rather than in the abdomen, may be difficult. Coronal images will usually clearly demonstrate the location of the lesion.

PLEURA

The pleura and its disorders are considered in Chapters 85 through 88. Radiographic involvement of the pleura is generally manifested by pleural fluid, localized or diffuse pleural thickening, or pleural nodules.



A

B

Figure 30-66 Dissecting aortic aneurysm shown by CT. *A*. A sagittal image shows a dissecting aneurysm in the descending aorta; a prominent flap is seen medially, crossing the aortic lumen. *B*. An oblique sagittal reconstruction of the image shows the flap in the proximal descending aorta.

Pleural Effusions

Fluid in the pleural cavity appears radiographically as a homogeneous opacity that generally occupies a dependent position. A small pleural effusion that is barely perceptible or is overlooked on the PA view is often readily apparent on the lateral radiograph as blunting of the posterior costophrenic sulcus (Fig. 30-2). The best non-CT radiographic study for demonstrating small quantities of pleural fluid is the lateral decubitus film (Fig. 30-3*C*). Using this technique, as little as 25 ml of fluid can be detected. Larger pleural effusions usually blunt the lateral costophrenic sulcus on the PA radiograph as well (Fig. 30-68*B*).

Occasionally, pleural fluid remains between the diaphragm and the lung (i.e., is infrapulmonary or subpulmonic), displacing the lung upward, so that the lateral costophrenic angle remains sharp (Fig. 30-3). The presence of an infrapulmonary accumulation of fluid should be suspected if the diaphragm appears elevated, if the costophrenic sulcus is blunted posteriorly, or if the stomach bubble is separated from

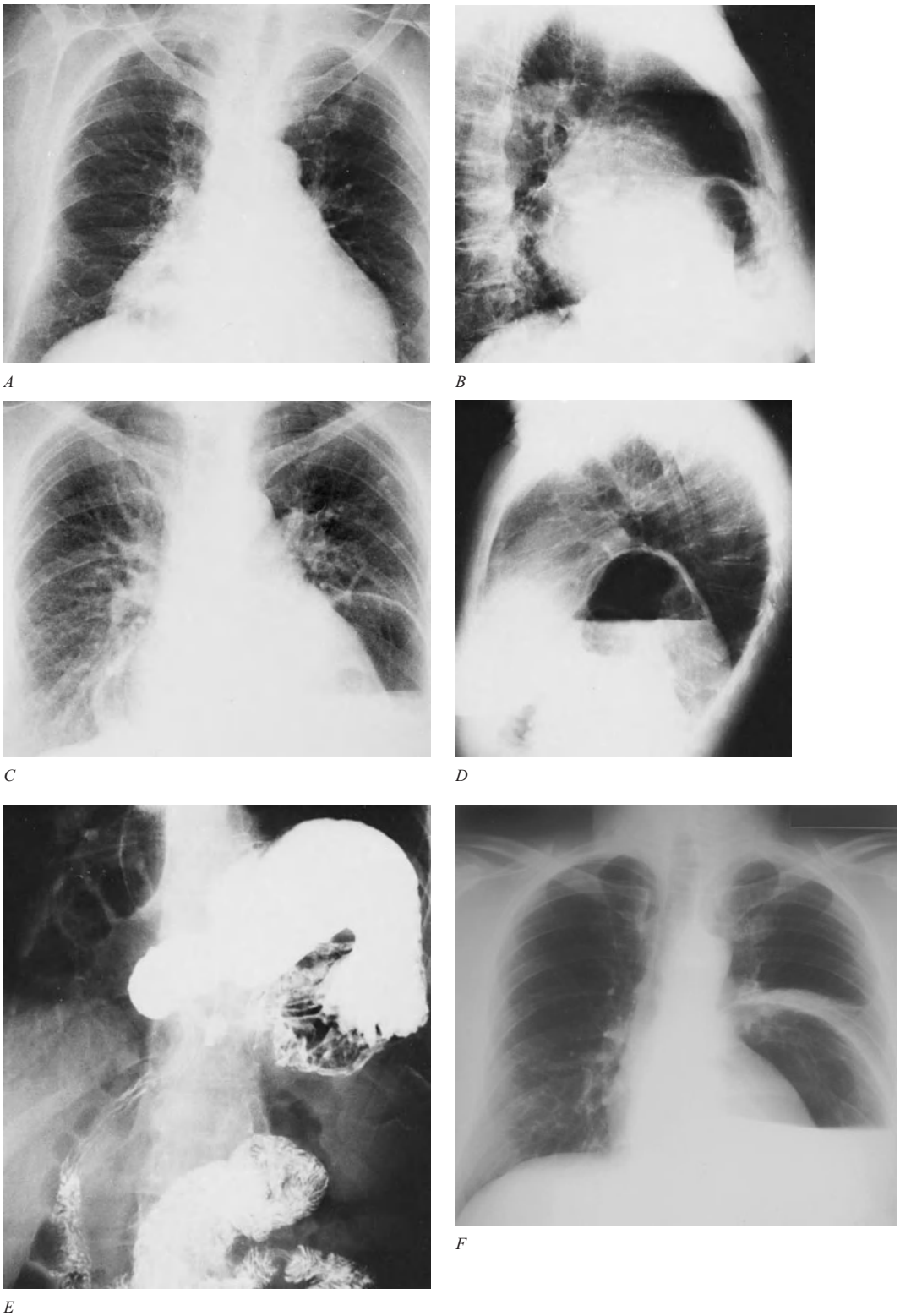


Figure 30-67 Foramen of Morgagni hernia. *A*. PA view. *A* mass containing a loop of bowel lies just to the right of the cardiac silhouette. *B*. Lateral view. The mass is also anterior to the cardiac silhouette. The location of the mass is characteristic for a foramen of Morgagni hernia. The hernia usually contains only omentum, but in this instance, it also contained a loop of colon. **Hiatus hernia**. *C*. PA view. An air-fluid level is present in the left chest and must be differentiated from an elevated diaphragm with underlying stomach. *D*. Lateral view. The mass is also posterior to the heart. *E*. An upper gastrointestinal series demonstrates the air-fluid level to be within the stomach, which has herniated into the chest and lies in an upside-down position. **Traumatic hernia**. *F*. PA film of the chest shows an air-fluid level in the left chest, quite similar to the above hiatal hernia. However, this was a traumatic hernia of the diaphragm with stomach herniated through the diaphragm and gangrenous at surgery.

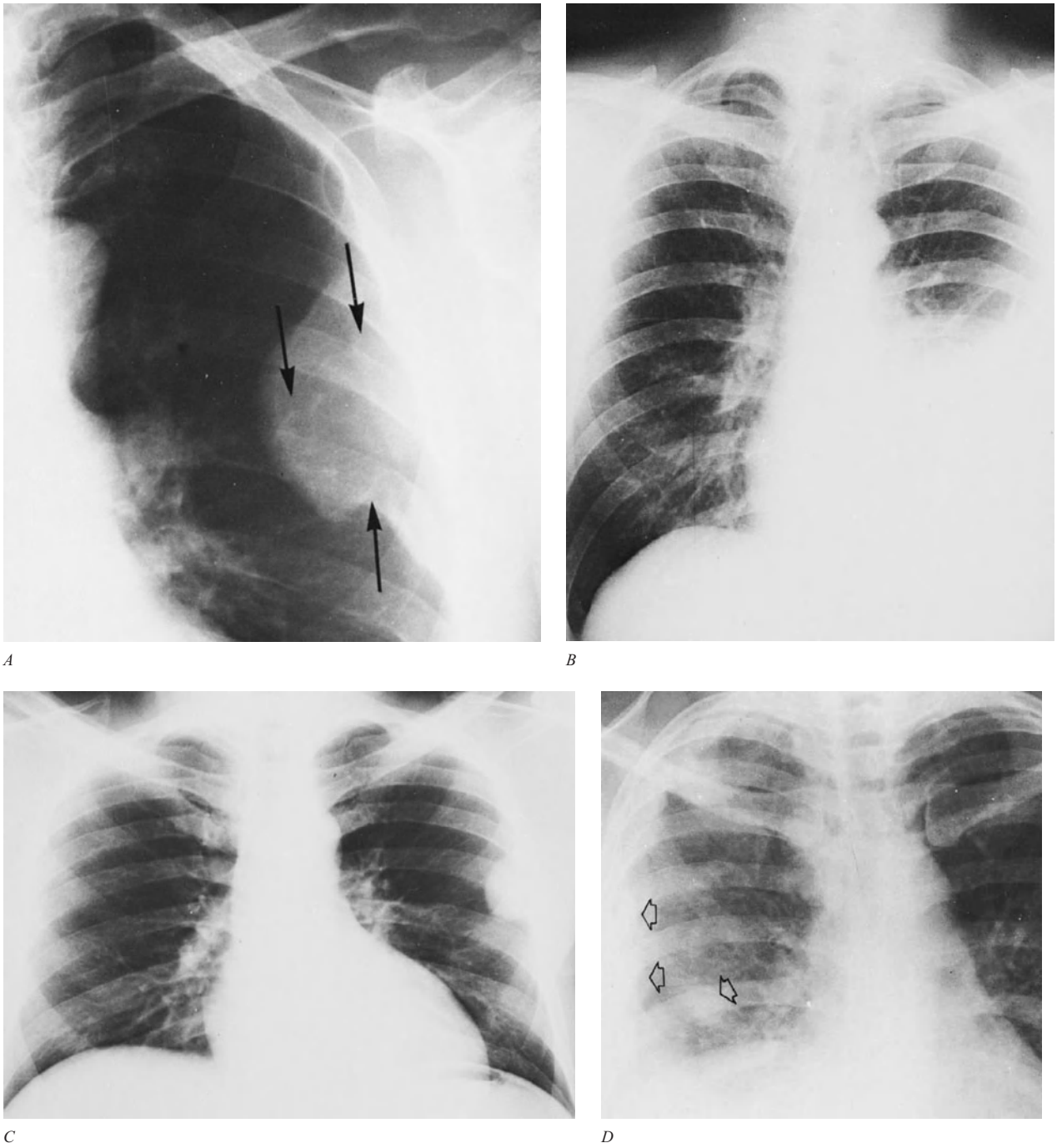


Figure 30-68 *A*. Rib metastasis (extrapleural sign). A smooth mass protrudes into the lung. This mass has tapering edges, characteristic of an extrapleural lesion. The destroyed anterior rib (arrows) is secondary to a metastatic tumor that is invading the rib. *B*. Rheumatoid effusion. The characteristic meniscus of a free pleural effusion is seen in the left hemithorax. This patient had rheumatoid arthritis. *C*. Pleural lipoma. A smooth mass along the left lateral chest wall proved to be a lipoma. *D*. Pleural metastases. A right pleural effusion, showing a meniscus, blunts the right costophrenic sulcus. The lobulation along the right lateral chest wall is characteristic of tumor nodulation (arrows).

the dome of the apparent hemidiaphragm by more than a few millimeters. CT is especially sensitive in identifying pleural effusions (Fig. 30-69). These effusions may be small and not visible on the plain film. In the intensive care unit, where most plain films are obtained in supine patients, CT imaging is helpful in the diagnosis of pleural effusions.

Pleural fluid sometimes is loculated and difficult to distinguish from localized pleural thickening. Loculated pleural fluid in an interlobar fissure assumes a cigar-shaped configuration on the lateral radiograph, and it sometimes simulates a mass. This mass, known as a "phantom tumor," disappears as the fluid is eliminated. CT readily recognizes these loculated

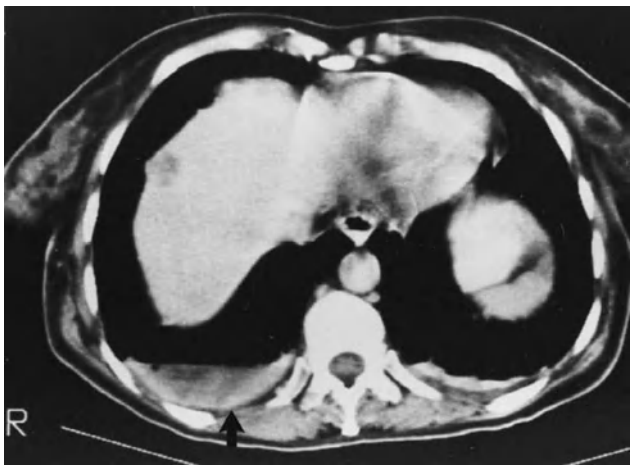
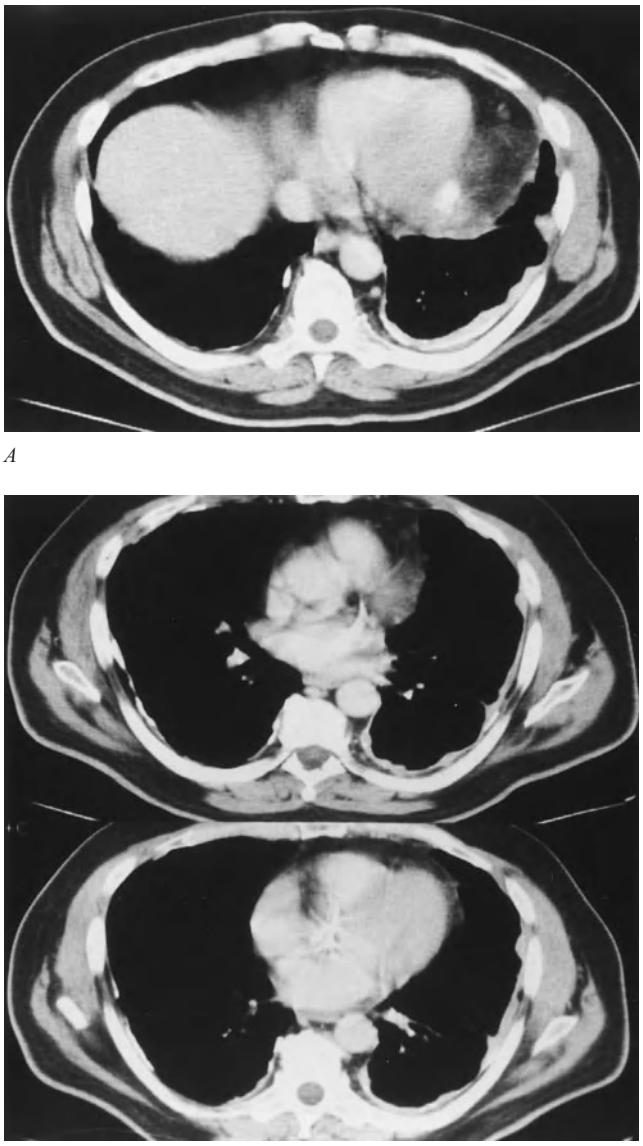


Figure 30-69 A small right pleural effusion (arrow) is identified by CT. This was not seen on the routine chest radiograph. Pleural thickening is seen in a similar location of the left side.

effusions. The loculation is usually indicative of a high concentration of protein in the fluid, frequently due to infection or tumor.

Bilateral pleural effusions are usually caused by heart failure or ascites. Occasionally, they are due to collagen vascular disease or metastatic tumor.

Common causes of unilateral pleural effusions include tuberculosis, pneumonia, pulmonary infarction, metastatic tumor, primary pleural tumor, lymphoma, collagen vascular disease, chest trauma, ascites, and intra-abdominal inflammatory processes, such as subphrenic abscess or pancreatitis. Thoracentesis and pleural biopsy may be necessary to establish the nature of a pleural effusion that has been recognized radiographically. CT and MRI are usually not useful in determining the exact cause of a pleural effusion. The lumpy, masslike character of a mesothelioma or metastatic tumor can be nicely demonstrated by CT (Figs. 30-68*D* and 30-70); such findings are often apparent on the plain chest radiograph. Many mesotheliomas demonstrate only a pleural effusion, without any specific findings to indicate the malignant nature of the process. CT or MRI may show associated mediastinal adenopathy that was not suspected on the plain radiograph.



A

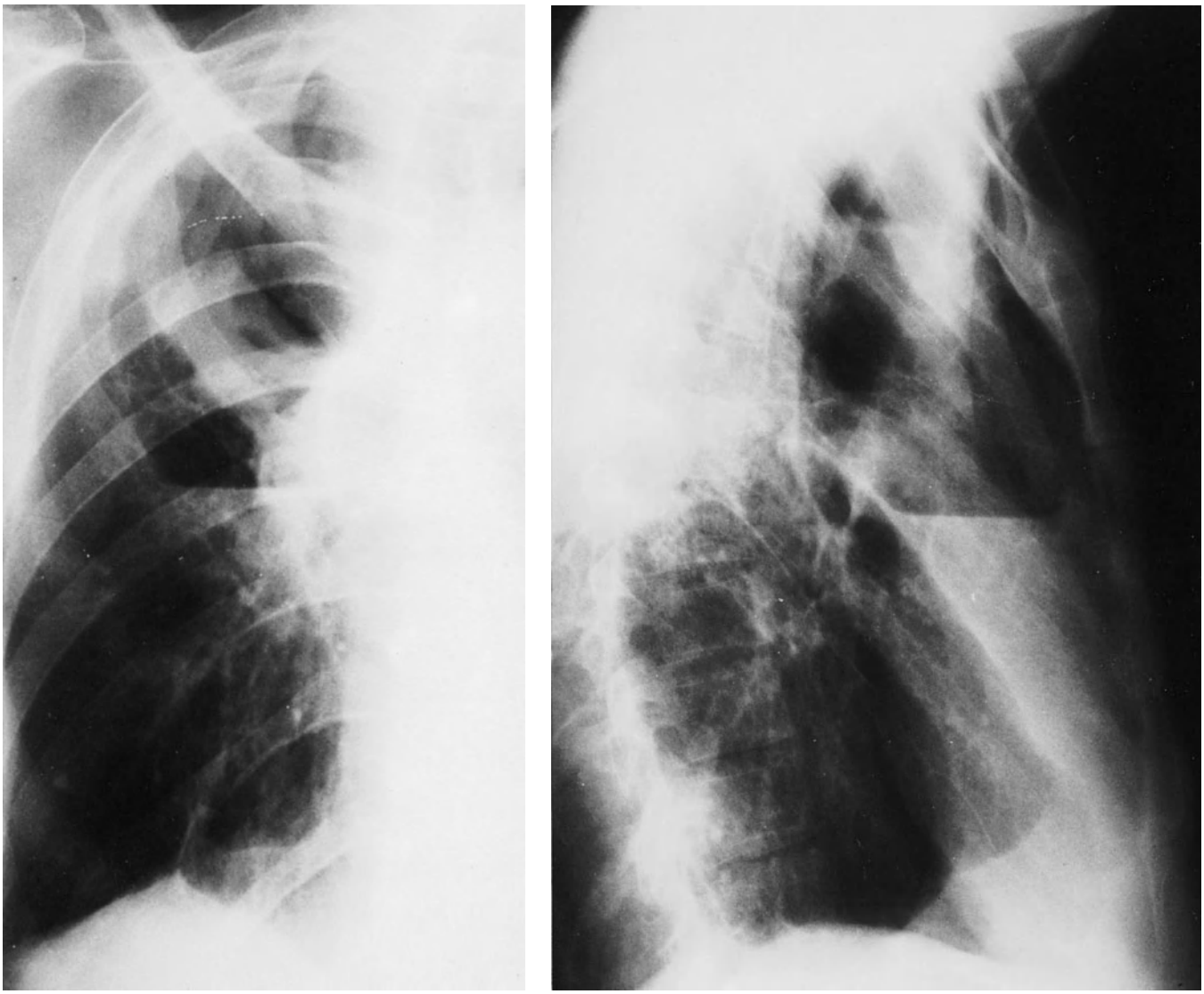
B

Figure 30-70 Pleural mesothelioma. Asbestos-related pleural plaques are seen in the right chest; pleural thickening and pleural calcification are present. On the left side, the pleura is thickened and quite lumpy. This is characteristic of mesothelioma, but the finding is not specific for this disorder and could be due to metastatic tumor. Mesothelioma might also present as a nonspecific pleural effusion.

Pleural Thickening

Fibrosis of the pleura may be localized or generalized. Localized pleural thickening is common at the lung apices and is suggestive of tuberculosis. Most often, however, apical scarring, commonly seen on CT, remains unexplained and is attributed to aging. Blunting of the costophrenic sulcus is occasionally the result of a previous pleural effusion. A costophrenic sulcus that appears to be blunted laterally on the PA radiograph, but not posteriorly on the lateral radiograph, usually represents pleural thickening, rather than pleural fluid.

Generalized pleural thickening confined to one hemithorax is usually secondary to previous tuberculosis, empyema, or hemothorax. Bilateral pleural thickening, either localized or generalized, is strongly suggestive of asbestos exposure. Although such thickening is sometimes accompanied by pleural calcification or interstitial lung disease, pleural thickening may be the sole radiographic manifestation of asbestos exposure. Pleural plaques are more commonly seen using CT imaging, and the associated calcification is more readily appreciated than on the plain film.



A *B*

Figure 30-71 Hydropneumothorax. *A*. Posteroanterior view. A distinct air-fluid level is seen overlying the left hilus. *B*. Lateral view. The fluid and air are anterior to the hilus. This is difficult to differentiate from a lung cavity, but the very thin edge suggests that this is in the pleural space. This was a hydropneumothorax and was secondary to a postoperative bronchopleural fistula.

Pleural Nodules

A localized pleural nodule suggests a benign pleural tumor, such as a fibrous tumor of the pleura or lipoma (Fig. 30-68*C*). The nodule may be difficult to distinguish from a localized area of pleural thickening, but generally it is larger and more symmetric in contour. On CT, these nodules generally have a characteristic appearance: the greatest diameter of the mass is in its center, and its edges are flat and tapering; the appearance is similar to the extrapleural sign, described previously.

Unilateral, diffuse pleural nodulation (Fig. 30-68*D*) usually indicates diffuse mesothelioma or metastatic malignancy, although empyema can sometimes be quite nodular in appearance. Mesotheliomas and pleural metastatic tumor are impossible to distinguish radiographically; they also may be difficult to distinguish histologically. Both are commonly associated with pleural effusion. As in the case of pleural effusions, CT is extremely useful in identifying localized or diffuse pleural abnormalities, but is somewhat limited in determining their cause.

Pneumothorax

In the conventional upright radiograph, air within the pleural cavity is best seen at the apices, where the thin line of visceral pleura surrounding the partially collapsed lung is easily identified. If doubt exists, a radiograph taken during expiration may make a pneumothorax more obvious. In supine patients, or in patients with pleural adhesions, pneumothorax may be

seen only at the bases, medially or laterally. CT is useful in demonstrating small pneumothoraces, which may not be appreciated on conventional radiographs.

Trauma, including that of iatrogenic origin, is the most common cause of pneumothorax. Spontaneous pneumothorax occurs in a variety of conditions. Most often the cause is unknown. On occasion, pneumothorax may be clearly attributed to a ruptured apical bleb. Diffuse lung disease, such as eosinophilic granuloma, is sometimes the cause of spontaneous pneumothorax.

Chronic pneumothoraces are almost invariably associated with pleural effusions. The interface of air and fluid in the pleural space causes the fluid to assume a flat line (Fig. 30-71), rather than the usual curved line configuration (meniscus) seen when air is absent. A pneumothorax is ordinarily rapidly reabsorbed or replaced by fluid in the pleural space. A chronic pneumothorax strongly suggests a bronchopleural fistula.

PORTABLE CHEST EXAMINATION

Use of portable radiographic studies in evaluation of seriously ill patients is routine. Interpretation of the portable radiograph is often difficult, since the film may be technically limited. Despite its problems, the portable radiograph usually provides useful information in postoperative patients, who may be difficult to examine clinically, and in mechanically ventilated, critically ill patients.

Localized pulmonary consolidation seen in the postoperative radiograph generally indicates one of three possibilities: pulmonary contusion, pneumonia, or atelectasis (segmental or lobar). Pulmonary contusion, common after thoracic surgery, is generally noted immediately after the surgery; it resolves gradually. In contrast, pneumonia usually occurs after the second or third postoperative day. Radiographic findings may be diffuse or localized: when localized they are difficult to distinguish from atelectasis; when diffuse, pneumonia may mimic pulmonary edema. Patchy multifocal pneumonia is common and frequently due to aspiration.

Atelectasis is a prevalent postoperative complication. It usually occurs in the lower lobes and is more common on the left. An increased density behind the cardiac shadow or obliteration of the diaphragmatic shadow behind the cardiac silhouette constitutes presumptive evidence of left lower lobe atelectasis. Frequently, distinction between atelectasis and pleural fluid based on a portable radiograph is difficult.

Basilar atelectasis, also known as platelike atelectasis, Fleischner's lines, or discoid atelectasis, frequently occurs in very ill patients, particularly after abdominal surgery. Manifestations include linear densities at the bases that generally are oriented parallel to the diaphragmatic surface; the densities do not follow the usual patterns of lobar collapse. Basilar atelectasis is considered an indication of poor diaphragmatic motion and often occurs with abdominal pain. Basilar atelectasis may be seen in patients who are obese or who have impaired diaphragm motion or diaphragm eventration (Fig. 30-72).

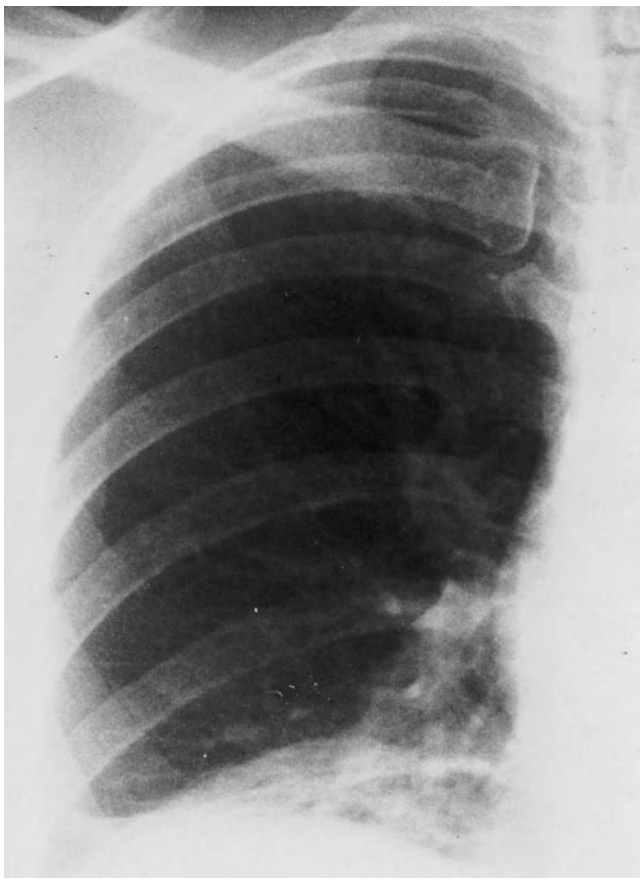


Figure 30-72 Platelike atelectasis. A linear density above the right hemidiaphragm in the postoperative patient represents platelike atelectasis. The configuration of this density does not correspond to that of a pulmonary subsegment, and it crosses segmental boundaries.

Pleural effusions are often difficult to identify in a portable examination, since the patient is rarely upright in bed or optimally positioned; a lateral radiograph is generally not available. On occasion, a large pleural effusion mimics lower lobe atelectasis. Although difficult to perform, portable decubitus radiographs can be useful in distinguishing a pleural effusion from atelectasis. Using CT imaging, pleural effusions, both large and small, are frequently seen, even when not suspected on the portable film.

In patients who have recently undergone thoracic surgery, fluid may accumulate in the extrapleural space in the area of the incision, simulating a loculated pleural effusion. With mediastinal incisions, mediastinal fluid accumulation is detected as diffuse widening of the mediastinal shadow. Comparison with earlier films is particularly useful in evaluating the process.

Left ventricular failure or fluid overload is another common clinical problem that is often difficult to recognize on the portable radiograph. Distortions in heart size produced

by inconsistent distances of the radiographic tube from the patient's chest complicate study interpretation. Enlargement of the pulmonary vessels is the most reliable sign of left-sided heart failure or fluid overload. The finding must be interpreted with care, however, since portable radiographs are often made while the patient is supine, resulting in redistribution of blood flow toward the apices. Pulmonary interstitial edema and alveolar edema are additional signs of left-sided heart failure that are generally recognizable in the portable radiograph. The presence of diffuse alveolar consolidation generally signifies pulmonary edema. In the critically ill patient, however, pulmonary edema is often noncardiac in origin (see Chapters 144 and 145). Massive aspiration or diffuse community-acquired or nosocomial pneumonia may also produce the radiographic picture of diffuse alveolar consolidation.

CT has become an indispensable tool in evaluating critically ill patients. Although significant challenges exist in transporting mechanically ventilated or hemodynamically unstable patients to the radiology department, the information gleaned may be critical to proper management. For example, CT imaging may elucidate an unexplained finding, or disclose a process not evident on the portable film. An unsuspected pneumonia or pleural effusion (perhaps, even a large effusion) may be demonstrated, or details, such as cavitation, may be appreciated. CT may be useful in helping elucidate the cause of diffuse alveolar consolidation by suggesting the presence of cardiogenic pulmonary edema, ARDS, or pneumonia, including that due to aspiration.

Finally, many institutions have incorporated into their routine critical care practices a daily multidisciplinary conference in which radiologists review current studies with clinicians managing the patients. The resultant clinical-radiographic correlation provides invaluable insight into the cause of the radiographic findings.

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31

Pulmonary Cytopathology

Prabodh K. Gupta • Zubair W. Baloch

In his *Atlas of Exfoliative Cytology,* George N. Papanicolaou described the success and utility of cytopathology in detection and diagnosis of malignant lesions of the respiratory tract. Over the past 40 years, development of flexible fiberoptic bronchoscopy, transthoracic and transbronchial needle aspiration, and ultrasound-guided transesophageal and transbronchial fine-needle aspiration have broadened the methods by which cytological materials are obtained. These advances, coupled with refinements in specimen collection, cytopreparation, and ancillary laboratory diagnostic techniques, have established pulmonary cytopathology as an accurate, economical, safe, and rapid diagnostic procedure.

THE CYTOPATHOLOGY REPORT

A number of neoplastic and nonneoplastic pulmonary lesions can be accurately diagnosed with cytological techniques. For a valid and reliable diagnosis, the specimen must be satisfactory—that is, representative of the lesion(s) under investigation, adequate in cellular quantity and preservation,

and prepared and examined by experienced and qualified laboratory professionals. A cytopathology report should carry the same clinical and diagnostic significance as does a report from a representative histological study. The value of collaborative interaction between the clinician and laboratory personnel cannot be overemphasized. Relevant clinical information must be furnished to, and reviewed by, the cytopathologist. While cytological findings, at times, may be nonspecific, consultation between clinician and cytopathologist can help with patient management.

PULMONARY SAMPLES

A wide variety of pulmonary specimens may be examined cytologically; the most commonly employed are described below.

Spontaneously Produced Sputum

Spontaneously expectorated sputum has been a mainstay in the diagnosis of pulmonary lesions. While some patients readily produce a representative sputum sample, the collection procedure can be time consuming, uneconomical, and inefficient. Typically, three to five deep-cough specimens are obtained on consecutive days after the patient is instructed in the proper technique for providing a satisfactory specimen: after mouth rinsing and throat cleaning, the patient takes a deep breath, holds it for up to 20 seconds, and then coughs. With this method, material is forcefully expectorated from the airways. The procedure should be repeated for up to 30 min to produce a sufficient quantity of a representative specimen.

In addition to mucus and mature and immature squamous cells exfoliated from the oral cavity, the specimen may contain lymphoid cells from the tonsils and adenoids. A satisfactory specimen is one that is representative of the bronchial mucosa and pulmonary parenchyma and contains macrophages (generally, carbon-bearing) derived from the alveolar spaces. Inspissated mucus from the terminal airways (Curschmann's spirals) and columnar cells from the bronchial tree and nasopharynx can also be seen (Fig. 31-1). The presence of only squamous cells indicates an unsatisfactory sample. However, exfoliated cells from upper airway epithelial lesions may be seen in such samples.

Induced Sputum

Many patients, particularly those who are asymptomatic, generally are unable to spontaneously produce a satisfactory sputum specimen by deep coughing. These patients may be "induced" to produce a diagnostic sample representing the respiratory mucosal surface and associated lesions. Induction techniques vary, but generally they involve inhalation of a preheated (37°C) hypertonic saline solution or mucolytic agent (Mucomyst) for 10 to 15 min. The patient is asked to cough for up to an additional 20 min; a pooled sputum sample is then collected and submitted for examination. Following initial sample procurement, the patient is instructed to collect more specimens for 2 to 3 days. The additional specimens, which are valuable diagnostically, should be pooled and preserved in a polyethylene glycol-alcohol mixture according to Saccamanno's technique (see below) or in commercially available preservatives following the vendor's recommendations.

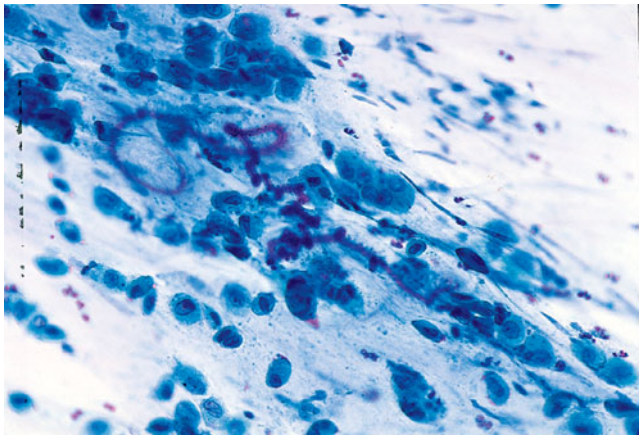


Figure 31-1 A satisfactory pulmonary cytology specimen (bronchial washing). Note the presence of macrophages, a Curschmann's spiral, and a few macrophages, indicative of a deep cough and pulmonary contents. Squamous cells most often indicate oral material. (Papanicolaou stain, ×105.)

Bronchial Washings

Cytological examination of bronchial washings has been in use for many years. While normal saline may be used to obtain bronchial washings, use of a physiological solution, such as Normosol or Plasmalyte, is preferable. Fresh specimens should be submitted to the laboratory. Fresh smears may be made on-site and fixed immediately in 95 percent ethyl alcohol for at least 20 min; alternatively, spray fixation (Surgipath cytology fixative) may be employed. Such preparations are diagnostically inferior to fresh specimens processed using cellulosic (Millipore) filters or other concentration techniques.

Segmental sampling of the bronchial tree (while taking adequate precautions against contamination of the specimen) may be useful in lesion localization. When delays are expected in specimen submission and processing, the material may be fixed by mixing the specimen with an equal volume of 50 percent ethyl alcohol or liquid-based cytology preservative, as specified by the vendor (ThinPrep or SurePath).

Bronchoalveolar Lavage

Bronchoalveolar lavage (BAL) consists of instillation of a physiological solution (normal saline, Normosol, or Plasmalyte) into a specified area of the pulmonary parenchyma, followed by aspiration (Chapter 36). The material obtained represents sampling of 1 to 3 million alveoli (about 1 percent of all alveoli).

BAL samples are most useful in investigating diffuse alveolar processes, such as *Pneumocystis carinii* pneumonia, viral infections, chemotherapy- or radiation-related changes, or lesions with transalveolar spread, such as alveolar proteinosis and bronchoalveolar cell carcinoma. Additionally, BAL has been used in the study of various immunologic, inflammatory, and infectious processes occurring within the alveolar spaces, including lymphomas, post-transplant lymphoproliferative disorders (PTLD), interstitial lung diseases, and inhalation-related disorders. Notably, only rarely are interstitial lung diseases diagnosed using BAL. However, the specimens obtained may be useful for differential cell counts and special ancillary investigations, including flow cytometry or immunohistochemical studies. BAL specimens must be differentiated from bronchial washings, as the cellular contents and diagnostic yields of the two specimens are different; while the bronchial wash represents the mucosal surface, BAL contains material from alveolar spaces.

Bronchial Brushings

Bronchial brushings represent material obtained though catheter-based brushing of airway mucosa or lesions under direct visualization or fluoroscopic guidance. The specimens are particularly useful because morphologic details are usually well preserved and representative of mucosal lesions. Fresh specimens should be submitted to the laboratory. Alternatively, the saline-immersed brush can be mixed with an equal volume of 50 percent ethanol or proprietary collection fluid for concentration methods when a delay in specimen delivery is expected.

Direct smears are prepared by rolling the brush on a clean glass slide, followed by immediate fixation using 95 percent ethanol. Caution must be exercised in their evaluation, since poorly preserved cells may appear hyperchromatic, have altered nucleocytoplasmic (N:C) ratios, and mimic undifferentiated tumors. Bronchial reserve cells, often seen in such specimens, may be mistaken for small-cell neoplasms.

In hypersensitivity and inflammatory processes, proliferative goblet cells and columnar cells are commonly seen and may be associated with eosinophils and Curschmann's spirals. Ciliocytophthoria (CCP), another manifestation of hypersensitivity reactions or viral infections, also may be observed in bronchial specimens. Proliferative mucosal cells may appear as cohesive aggregates; the cilia, which can be located centrally, may be inconspicuous. These so-called "creola bodies" may be mistaken for well-differentiated adenocarcinoma.

Postbronchoscopy Sputum

Cytological analysis of postbronchoscopy sputum specimens may be of diagnostic value. The patient is directed to collect morning sputum specimens for 2 to 3 days following bronchoscopy. These samples are more cellular and may be representative of the underlying pathology. Caution in interpretation is necessary, however, since extremely reactive and bizarre bronchial cells may be seen. An adequate clinical history and communication between bronchoscopist and cytopathologist are necessary for proper interpretation of post-bronchoscopy specimens. The technique may be of particular value in patients who are unwilling or unable to undergo additional diagnostic procedures. Specimens can be pool-collected in 50 percent ethanol or a proprietary preservative.

Transbronchial Aspiration

Transbronchial aspiration of pulmonary masses and intrathoracic and mediastinal lymph nodes is generally used to evaluate peritracheal, peribronchial, and, occasionally, anterior mediastinal lesions. An aspirating needle is introduced through the bronchoscope and directed to the area of interest. Considerable experience is needed for specimen collection and interpretation. On-site evaluation of specimens improves diagnostic accuracy and reduces the number of passes necessary. In situations where on-site evaluation is not available, specimens can be submitted to the laboratory in 50 percent ethanol or a proprietary preservative.

Percutaneous Transthoracic Fine-Needle Aspiration

Localized pulmonary parenchymal abnormalities are frequently evaluated using transthoracic fine-needle aspiration (FNA) under imaging guidance. The technique is extremely accurate, rapid, and cost-effective; results are comparable to those from tissue biopsies. Diagnostic sensitivity ranges from 75 to 95 percent and specificity from 95 to 100 percent. Complications include bleeding and pneumothorax. The incidence of tumor cells seeding along the needle track is extremely low. While on-site cytological evaluation is valuable and preferred, specimens may be submitted to the laboratory in appropriate transport media. Use of a large-bore needle during aspiration may result in excessive bleeding, rendering on-site specimen preparation and evaluation difficult.

Endobronchial and Endoscopic Ultrasound-Guided Fine-Needle Aspiration

Ultrasound-guided transbronchial and transesophageal fine-needle aspiration (FNA) are useful procedures in the evaluation of peripheral lung and mediastinal lesions, respectively. Radiation exposure is diminished, and a high degree of diagnostic accuracy is provided.

SPECIMEN PROCESSING

A variety of techniques are employed in the cytopreparations of pulmonary specimens.

Direct Smears

Direct smears, prepared by trained laboratory personnel using the "pick and choose" technique, are best made from fresh, unfixed specimens. A biologic hood and necessary infectious precautions are employed. Any thick, pink, or dark suspicious areas are transferred to clear, prelabeled slides for preparation of smears. At least four smears should be made from each sample and fixed immediately in 95 percent ethanol or spray-fixed for Papanicolaou stain. The remaining material may be processed as described below.

Saccamanno's Fixative

Saccamanno's fixative is used in a popular technique in which a mixture of 50 percent ethyl alcohol and polyethylene glycol (Carbowax 1540) is added to the specimen. The specimen is either smeared directly on glass slides or used to prepare a slurry after mixing in a blender and subsequent centrifugation. However, alcohol causes coagulation of proteinaceous material, making direct smearing of the specimen difficult. Furthermore, blending may result in fraying of the delicate cell cytoplasm and cilia. This technique is useful in detection of squamous carcinoma, other large-cell tumors, and certain infections; it is less valuable for the diagnosis of tumors with neuroendocrine differentiation.

Cytospin Preparations

Cytospin preparations can be prepared from either fixed or fresh specimens. At least four slides should be examined from each specimen when the technique is used exclusively for specimen evaluation.

Liquid-based preparations (ThinPrep or SurePath) are popular cell concentration techniques and are superior to cytospin slides. Pulmonary specimens are collected and preserved in a vendor-provided solution and are submitted to the laboratory. The preparation background is clean, and cytological examination is easier. In addition, slide preparations can be used for other special investigations, such as morphometry or immunocytochemistry. However, cells may clump together and appear hyperchromatic. In addition, delicate morphologic and background features, such as necrosis and inflammation, are often lost, limiting evaluation and diagnosis.

Cellulosic (Millipore) Filters

Cellulosic (Millipore) filters are used in processing fresh pulmonary specimens. An 8-nm pore filter is employed in the collection of cells; fixation artifacts are minimal. Adequate sampling, maintenance of intercellular relationships, and background features are facilitated using this technique. In addition, morphologic details and cellular preservation are excellent. However, the procedure is expensive and time-consuming, and it requires a special setup and experienced technicians.

Cell Block

Slides prepared using the cell block technique may permit accurate diagnosis when specimens contain abundant abnormalities. However, when cells of interest are limited, cell block preparations are suboptimal for diagnosis. In symptomatic patients, cell blocks have been found to improve cancer diagnosis by at least 50 percent compared with direct-smear slides prepared from induced sputum. In addition, cell blocks can be used for a variety of histochemical and immunocytological studies.

Ancillary Laboratory Diagnostic Techniques

Specialized investigations, such as immunocytochemistry, electron microscopy, flow cytology, or microbial cultures may be undertaken in evaluating selected cytology specimens. Based upon the on-site evaluation of fine-needle aspirates and cytological findings, specimens for these special studies can be appropriately collected and processed. The techniques are especially useful in differentiation of adenocarcinoma from mesothelioma, diagnosis of bronchoalveolar carcinoma, elucidation of specific microbial infections, and further characterization of poorly differentiated tumors and lymphomas. In addition, molecular diagnostic procedures may be applied in the diagnosis of pulmonary infections.

NORMAL BRONCHOPULMONARY CYTOLOGY

A variety of cells representing tracheobronchial tree and pulmonary parenchyma are seen in a pulmonary specimen that has been obtained using the previously described techniques. Notably, heavy oropharyngeal contamination can occur in sputum specimens obtained spontaneously or following induction, and in bronchial washings.

Squamous Cells

Squamous cells are seen commonly in expectorated specimens as uniform, flat cells with pyknotic nuclei; sometimes the nuclei are vesicular and enlarged. Most cells are large and keratinized and vary minimally in size. Atypical pleomorphic, small, hyperkeratinized cells with altered N:C ratios and hyperchromasia (dysplastic squamous cells) may be observed with oropharyngeal and laryngeal squamous lesions. The presence of abnormally shaped keratinized cells, with little inflammation and background necrosis, should prompt examination of the upper airway (Fig. 31-2).

Mechanical irritation in the oral cavity, generally by ill-fitting dentures or other prosthetic devices, can cause exfoliation of bizarrely shaped keratinized cells noted in small tissue fragments. Small, dense, keratinized metaplastic cells may be seen in patients who are endotracheally intubated or who have undergone tracheostomy. Chronic pulmonary diseases can often lead to squamous metaplasia and atypical cell

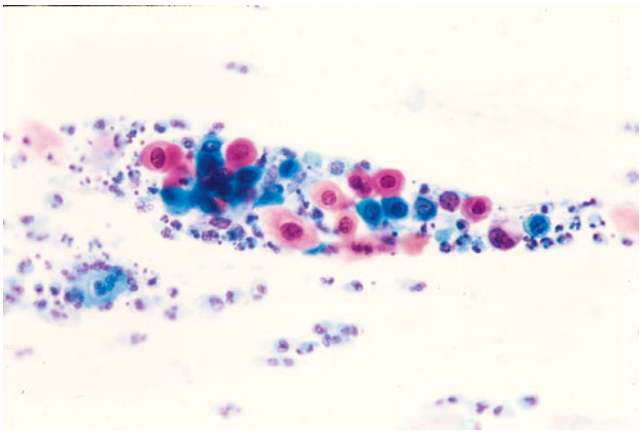


Figure 31-2 Upper airway brush specimen showing squamous cell carcinoma of the larynx. Note the group of small abnormal, keratinized cells occurring in a necrotic background. The patient had a normal chest radiograph. (Papanicolaou stain, ×166.)

morphology, causing concern about underlying malignancy. Finally, oropharyngeal contamination is extremely common in bronchial washings. The presence of fungal organisms (e.g., *Candida*) does not necessarily represent pulmonary infection. These observations must be interpreted in light of clinical features (Fig. 31-3).

Ciliated Bronchial Columnar Cells

Ciliated bronchial columnar cells may occur singly and in small tissue fragments. These columnar cells contain basally located, vesicular nuclei and pale cytoplasm. The cells have cilia of uniform length; they exhibit periodicity and attach at right angles to the terminal plates. The cilia must be accurately identified because, almost always, true cilia, which are visible by light microscopy, do not occur on malignant cells. Cellular degeneration and trapped mucus can be a source of error in

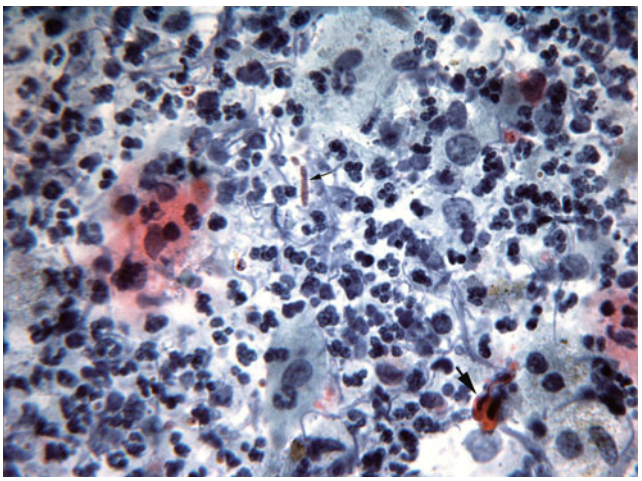


Figure 31-3 Bronchial wash specimen. Note intense, acute inflammatory exudate and filament of *Candida* organisms (arrow). The findings are common and represent oral contamination. (Papanicolaou stain, ×166.)

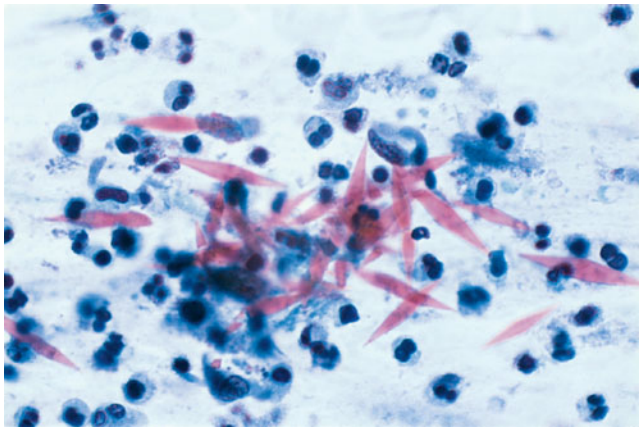


Figure 31-4 Bronchial washing showing Charcot-Leyden crystal in a patient with bronchial asthma. Note the numerous needle-shaped crystals occurring in an acute inflammatory background. The crystals are organophilic with the Papanicolaou method. (Papanicolaou stain, × 166.)

the proper identification of cilia. Fragmented ciliated cells (CCP) may occur in hypersensitivity and reactive conditions, as well as viral infection of the respiratory tract (as discussed below).

Goblet Cells

Goblet cells are recognized less commonly in normal pulmonary specimens. When present, they appear as swollen, pale cells. In general, goblet cells possess a single large vacuole or multiple small vacuoles that may contain mucus. Hyperplastic columnar and goblet cells may be seen in chronic pulmonary diseases, such as bronchitis or bronchial asthma, and in allergic conditions. In bronchial asthma, Curschmann's spirals may also be observed in cytological specimens. These are composed of a mucus shroud with numerous neutrophils and some eosinophils. Occasionally, needle-shaped Charcot-Leyden crystals, which appear orangophilic with Papanicolaou staining, may be seen (Fig. 31-4).

Hyperplastic bronchial columnar cells may appear quite bizarrely. They occur in tight tissue fragments with overlapping, hyperchromatic and enlarged, reactive nuclei that contain prominent nucleoli. On careful examination, such structures, known as creola bodies, reveal cilia on the edge or cell surface (Fig. 31-5). Creola bodies are a common cause of a false-positive diagnosis of adenocarcinoma. Similar hyperplastic structures can be seen in postbronchoscopy sputum specimens. The occurrence of large numbers of mucus-producing columnar cells without discernable cilia in tissue fragments obtained by FNA may be indicative of well-differentiated, mucin-producing adenocarcinoma.

Alveolar Macrophages

The presence of alveolar macrophages and type II pneumocytes in a pulmonary specimen are excellent criteria for specimen adequacy. These cells occur singly and are round or

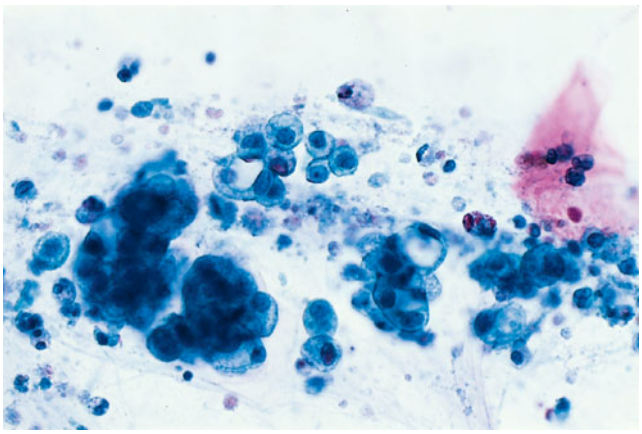


Figure 31-5 Bronchial washing showing creola bodies. Note the numerous glandular structures. Cells have prominent nucleoli, hyperchromasia, and evidence of mucus production. Some cells reveal terminal plates and cilia. Cilia may be few, poorly stained, and difficult to recognize. (Papanicolaou stain, ×208.)

cuboidal; typically, they have a kidney-shaped, vesicular nucleus which may contain a single, prominent nucleolus. Cell cytoplasm is pale and demonstrates fine vacuolation. Occasionally, ingested foreign material (carbon) or blood products (e.g., hemosiderin) may be observed in the cytoplasm. Multinucleated forms may occur in bronchoalveolar specimens obtained from patients who have pulmonary alveolar proteinosis or granulomatous diseases, or who have been exposed to pollutants (Fig. 31-6).

Alveolar macrophages must be examined in the context of the specimen background. Whereas evidence of old hemorrhage and necrosis may suggest a neoplasm, acute inflammation may signify an inflammatory process. Pulmonary infarcts, organizing pneumonia, prior chemotherapy, and other factors produce atypical cellular changes in macrophages and epithelial cells. The cytopathologist must be provided with proper clinical information in evaluating these specimens.

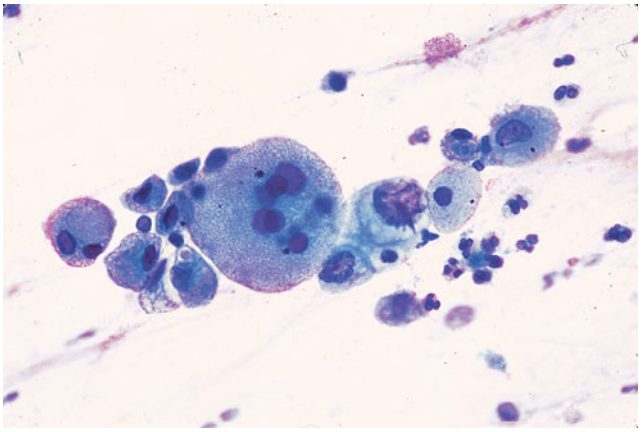


Figure 31-6 Bronchial washing showing multinucleated giant cell in pulmonary specimen from a cigarette smoker. Note the acute inflammatory background, mucus, and foreign body–type giant cell. (Papanicolaou stain, ×208.)

Pulmonary macrophages can be stained with CD68 immunochemical antibodies. Such immunocytochemical studies can be diagnostically useful in establishing the precise nature of atypical or other questionable cells.

TOXIC ENVIRONMENTAL INHALATION EFFECTS

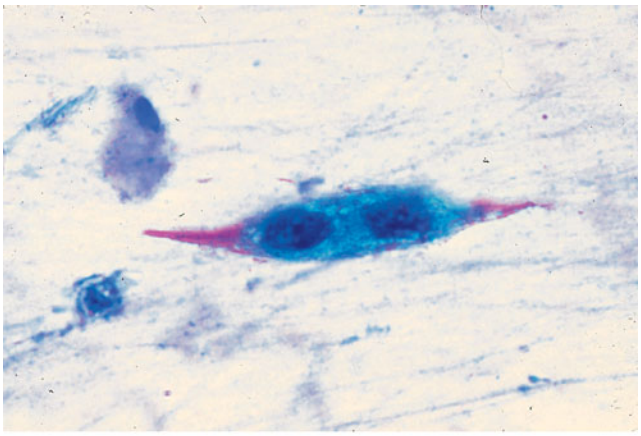
Respiratory squamous and columnar cells and alveolar macrophages react to various environmental pollutants. As examples, the cytological responses of these cells to cigarette smoke, asbestos, beryllium, and "crack" cocaine are described briefly below.

Cigarette Smoke

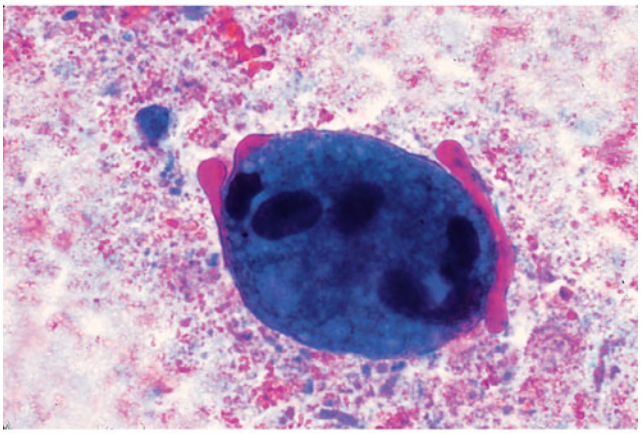
Exposure of the respiratory system to cigarette smoke leads to accumulation of a golden-brown, refractile pigment within pulmonary macrophages. The pigment may be indistinguishable from carbon and hemosiderin particles. Alveolar macrophages may be ringed by material composed of α_1-antitrypsin, which stains orange-red with Papanicolaou stain. This material has been further investigated using appropriate immunocytochemical procedures. Intracellular α_1-antitrypsin may be tapered at one or both ends of the macrophage, creating a "tailed" appearance. Affected cells have been termed "pink-tailed" macrophages (Fig. 31-7).

Asbestosis

Asbestosis generally arises from exposure to dust containing mainly chrysolite and other forms of asbestos fibers. Elongated asbestos bodies, also referred to as ferruginous bodies, may be observed in pulmonary specimens from subjects exposed to asbestos. Ferruginous bodies vary in size from 4 to 5 nm to over 200 nm. They are commonly dumbbell-shaped; a central translucent fiber core is surrounded by layers of a material containing minerals (iron, calcium) and mucopolysaccharide. The color of ferruginous bodies is variable, from a pale golden yellow to dark brown or black. The outer coat tends to be segmented and oriented at right angle to the long axis of the fiber. Ferruginous bodies are generally accompanied by a tissue reaction comprised of macrophages and giant cells (Fig. 31-8). On rare occasions, needle-shaped asbestos fibers without any surrounding deposits are observed within the macrophages. Besides asbestos exposure, ferruginous bodies are also observed following inhalation of other minerals and fibers. No definitive correlation between the presence of ferruginous/asbestos bodies and occupational exposure to asbestos fibers has been observed. Although large numbers of ferruginous bodies may be seen after massive exposure to asbestos, occasional ferruginous bodies are observed as a nonspecific finding. Prussian blue staining for iron compounds helps further identify ferruginous bodies.

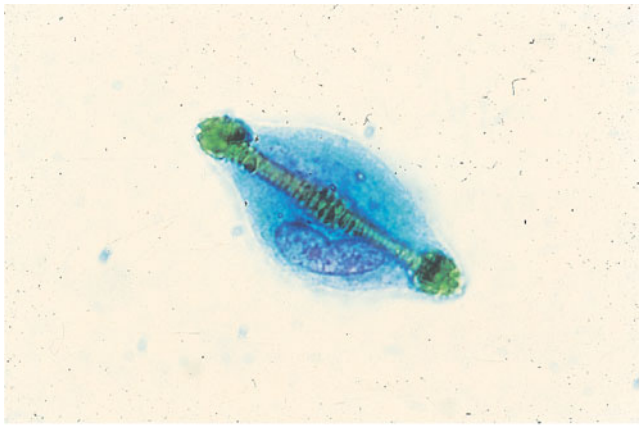


A

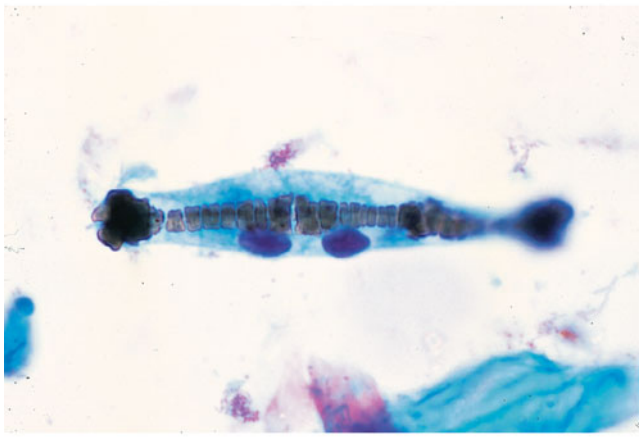


B

Figure 31-7 *A.* Bronchial washing showing "pink-tailed" macrophages in pulmonary specimen from a patient with a 15 pack-years cigarette-smoking history. *B.* Even distribution of α_1-antitrypsin around macrophages. While α_1-antitrypsin is distributed in the "points" in *A,* it is seen in close apposition to the cell in *B.* (Papanicolaou stain, ×330.)



A



B

Figure 31-8 Induced sputum showing ferruginous bodies in pulmonary specimens from a shipyard worker. *A.* Details of the central fiber core are visible. *B.* The surrounding core with segmented appearance is evident. (Papanicolaou stain, ×330.)

Berylliosis

Chronic exposure to beryllium and certain other heavy metals may result in profound pneumocyte proliferation and giant-cell formation. Multinucleated giant cells tend to be syncytial and often occur as large tissue fragments (Fig. 31-9). Variable numbers of lymphocytes may be present in the background. Clinical correlation is necessary before the cytopathologist can establish such a diagnosis.

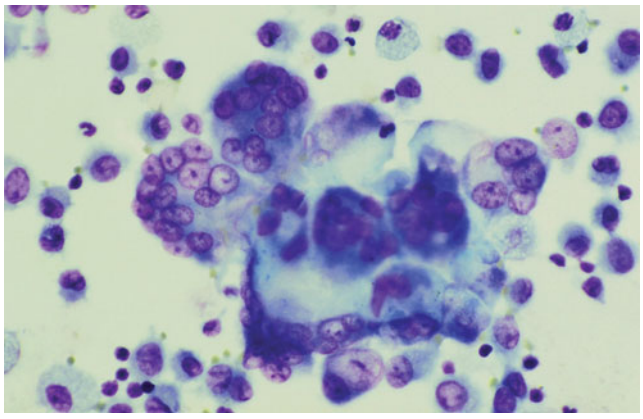


Figure 31-9 Bronchoalveolar lavage specimen showing multinucleated giant cell in beryllium exposure. Note the extremely large foreign body–type giant cell and alveolar macrophages (Diff-Quik stain, ×208.)

Crack Cocaine Inhalation

Repeated inhalation of recreational drugs may result in accumulation of large quantities of "black soot" within the alveoli and pulmonary macrophages (Fig. 31-10). The occurrence of large amounts of carbonaceous material within macrophages obtained by BAL appears to be unique to this patient population. The finding of similar pigmented macrophages within pleural fluid cells has been reported.

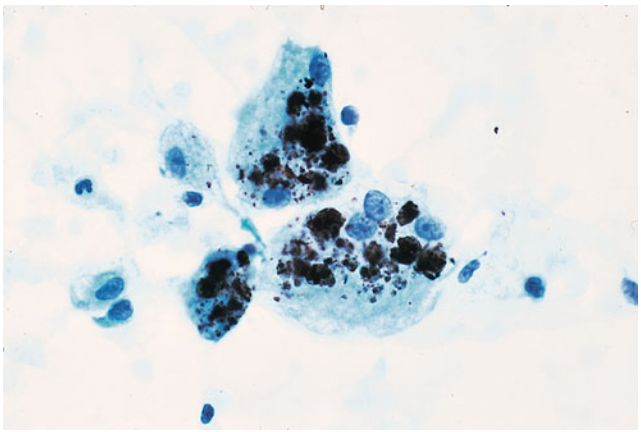


Figure 31-10 Bronchoalveolar lavage specimen showing pulmonary macrophages in a crack cocaine user. Note the abundant pigmented material in the cytoplasm of the cells, some of which appear reactive. Occurrence of pigment, per se, is a nonspecific finding. (Papanicolaou stain, ×208.)

INFECTIONS

A variety of infections of the respiratory tract result in cytopathological changes seen in specimens obtained by the aforementioned methods. The following sections outline changes that may be observed in pulmonary specimens obtained from patients with common bacterial, fungal, viral, or parasitic respiratory infections.

Bacterial Infections

Although bacterial infections of the respiratory tract are extremely common, cytopathology does not offer much help in their diagnosis or management. In selected cases, cytopathology may be useful.

Actinomycosis

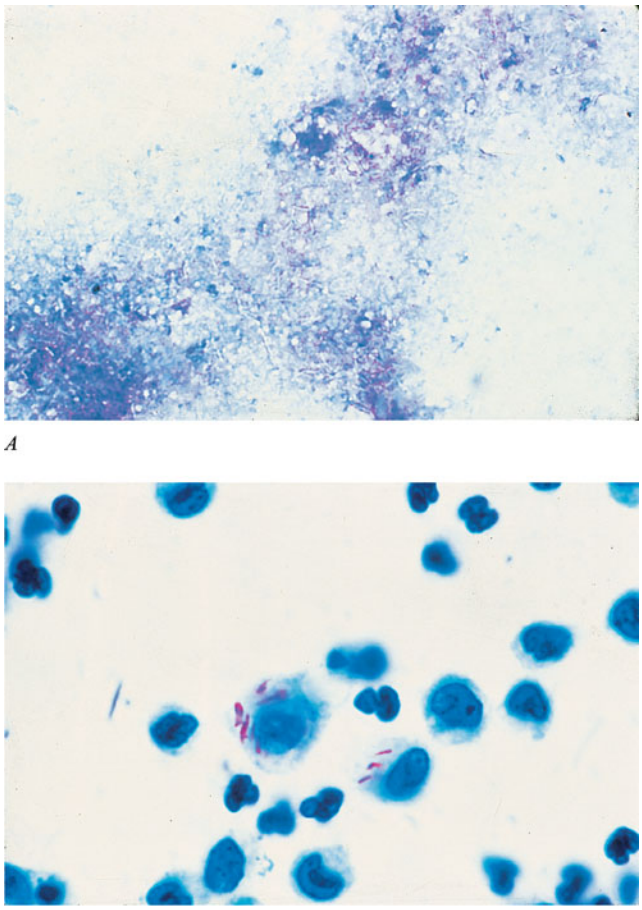
In patients with infection caused by species of *Actinomycetes*, pulmonary specimens generally contain large aggregates of filamentous, branching, thin organisms seen as tight, "woolly" clumps in an acute inflammatory background. The organisms are easily recognized in routine preparations and are correctly identified using appropriate immunohistochemical techniques. Diagnostic interpretation is made in view of the clinical and radiographic features. The constellation of these findings is important, since occurrence of actinomycetes in the oral cavity is extremely common, and morphologic detection may not indicate pulmonary infection.

Nocardiosis

Nocardia may be associated with pneumonia and cavitary pulmonary lesions. The organisms are visualized as delicate, nonseptate, filamentous, branching structures. The diagnosis can be made on specimens obtained from FNA or bronchoscopy. Generally, a histochemical (modified acid-fast) stain is used for further identification.

Mycobacteriosis

Acid-fast organisms may be detected in a variety of pulmonary specimens from patients with mycobacterial infections. Both tuberculous and nontuberculous mycobacterial infections are seen in immunocompetent and immunosuppressed patients. In immunosuppressed patients (e.g., those with human immunodeficiency virus [HIV] infection), the sample background is variable and may not be diagnostically helpful; only foamy macrophages, neutrophils, and a few lymphocytes may be seen (Fig. 31-11). While infection with *Mycobacterium tuberculosis* may yield only a few organisms in respiratory samples, specimens obtained from patients with atypical mycobacterial infections may yield numerous organisms that are identified easily by histochemical stains. Appropriate cultures should be performed in all such cases for a specific microbiologic diagnosis.



A

B

Figure 31-11 Fine-needle aspirate of the lung, atypical mycobacterial infection. *A.* Note the necrotic background, lack of inflammatory cells, and "ghost" forms of bacillary organisms. These can be seen in air-dried smears using Romanovsky's stain (Diff-Quik stain, ×330). *B.* Induced sputum specimen showing acid-fast, intracellular, atypical mycobacterium organisms. (Ziehl-Neelsen stain, ×330.)

Fungal Infections

A number of fungal organisms can be easily recognized in pulmonary specimens using the Papanicolaou stain. These include both true pathogens and a number of contaminants. Appropriate mycobial cultures should be performed if clinicopathological correlation is lacking and a specific diagnosis of the fungal type is important.

Candidiasis

Candida albicans may be seen as budding yeast forms in many specimens that are not freshly prepared and that have been stored at room temperature before fixation. This finding is of little clinical significance and is generally not reported by the cytology laboratory. In contrast, the occurrence of filamentous *Candida* forms, especially in specimens obtained by FNA, may be clinically important and should be reported. Such findings are seen in patients who are immunocompromised or suffer from diabetes or other disabling conditions. A laboratory report of *Candida* organisms in pulmonary specimens such as spontaneous or induced sputum or bronchial washings should be correlated with clinical and radiographic observations.

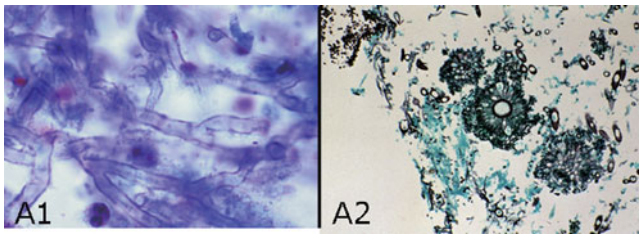
Aspergillosis

Aspergillus-related pulmonary disorders are quite varied in their clinical presentation. While establishing the presence of true tissue invasion may be difficult, the presence of the organism in pneumonic or cavitary lesions can be diagnosed cytologically. Most parenchymal infections are caused by *A. fumigatus,* although infections with *A. niger* and *A. flavus* also occur. Sputum specimens, bronchial washings, bronchial brushings, and FNAs can be diagnostic.

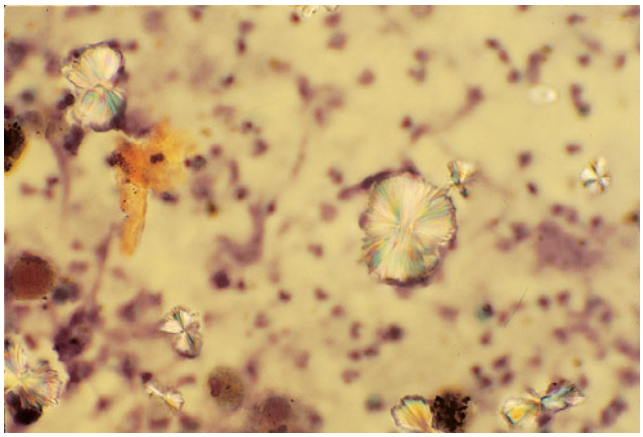
Since *Aspergillus* is an opportunistic airborne organism that sometimes contaminates pulmonary specimens, care should be exercised in reporting infection with *Aspergillus* if it is seen only on one slide or one set of slides. The presence of an acute inflammatory background and clinical and radiologic correlation are necessary for accurate diagnosis. The organisms are seen as broad, filamentous structures that branch at acute angles. In immunosuppressed patients with overwhelming infections, "fruiting bodies" (conidiospores) can be seen. Birefringent calcium oxalate crystals may occur in specimens containing *Aspergillus;* they are more commonly observed with *A. niger* (Fig. 31-12). Epithelial cells may show metaplastic and atypical morphologic features.

Cryptococcosis

Patients with cryptococcosis may be asymptomatic. Organisms can be visualized in sputum, bronchial washings, bronchial brushings, or FNA specimens. Most commonly, narrow-necked, budding yeast forms are observed; they demonstrate marked variation in size (5 to 40 nm) (Fig. 31-13). The organism has a surrounding mucopolysaccharide-rich capsule that can be stained with mucicarmine or other histochemical agents (Fig. 31-14). In fresh, unfixed specimens, an India-ink preparation outlines the organisms quite well.



A



B

Figure 31-12 *A1.* Bronchoalveolar lavage (BAL) specimen showing broad filamentous forms and acute angle branching of *Aspergillus. A2.* BAL specimen showing fruiting bodies (conidiospores). *B.* Bronchial washing specimen. Calcium oxalate crystals in association with *Aspergillus* infection seen with partially polarized light. (*A1.*, Papanicolaou stain, ×260; *A2.*, Papanicolaou stain ×160; *B.*, Papanicolaou stain, ×208.)

Occasionally, broad filamentous forms are observed (Fig. 31-15). Infection may present as noncaseating granulomas with multinucleated giant cells and macrophages.

Histoplasmosis

Pulmonary infection with *Histoplasma capsulatum* may be asymptomatic or associated with signs and symptoms that

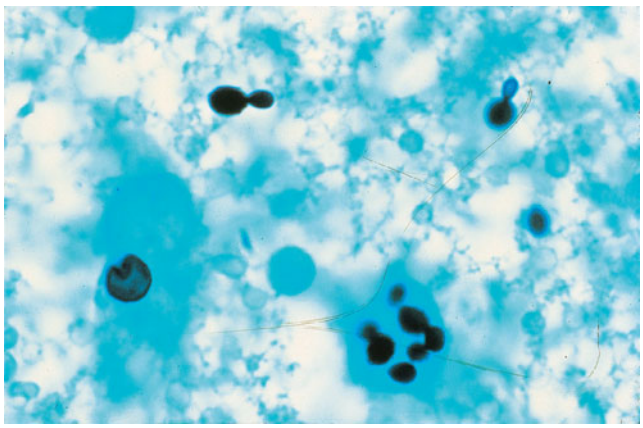


Figure 31-13 Bronchial washing showing *Cryptococcus.* Note the numerous budding organisms. Budding is narrow, and organisms show variation in size. (Silver methenamine stain, ×260.)

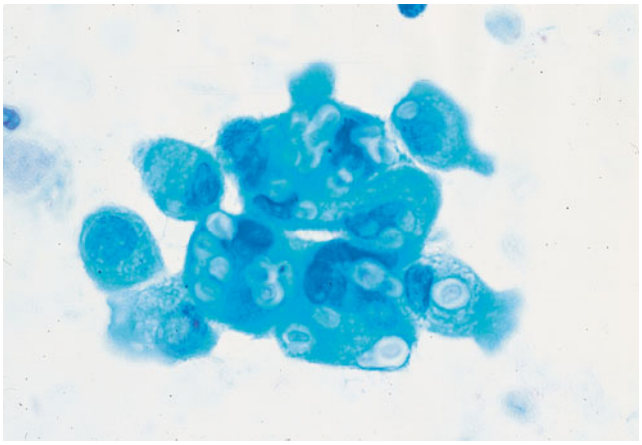


Figure 31-14 Bronchial washing showing *Cryptococcus*. Intracytoplasmic organisms show variation in size and a pale thick capsule. (Papanicolaou stain, ×330.)

mimic tuberculosis. The organisms are small, budding yeast forms, (2 to 4 nm) and are generally intracellular, occurring within the pulmonary macrophages, the bronchial epithelial cells, or neutrophils. Organisms are best identified using a silver-methenamine technique (Fig. 31-16).

Blastomycosis

Patients with respiratory infection caused by *Blastomyces dermatididis* may be asymptomatic or have signs and symptoms of chronic suppurative pulmonary disease. A clinical history demonstrating exposure in an endemic area (e.g., Ohio, Mississippi River Valley, or southeastern U.S.) is usually helpful. The organism is seen as a budding yeast, generally with single, broad-based refractile walls. The budding form has a short neck, and the daughter bud is found in close apposition to the mother bud.

Coccidioidomycosis

Patients with coccidioidomycosis generally present with features of a respiratory tract infection, including productive

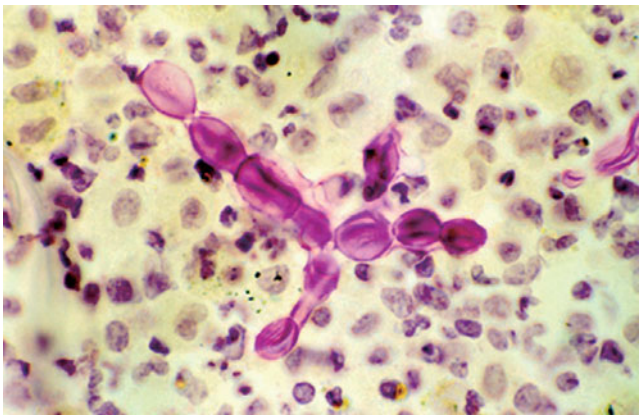


Figure 31-15 Bronchoalveolar lavage showing *Cryptococcus*. Note the broad, filamentous forms. Budding organisms are seen at the tips of the filaments. (Mucicarmine stain, ×330.)

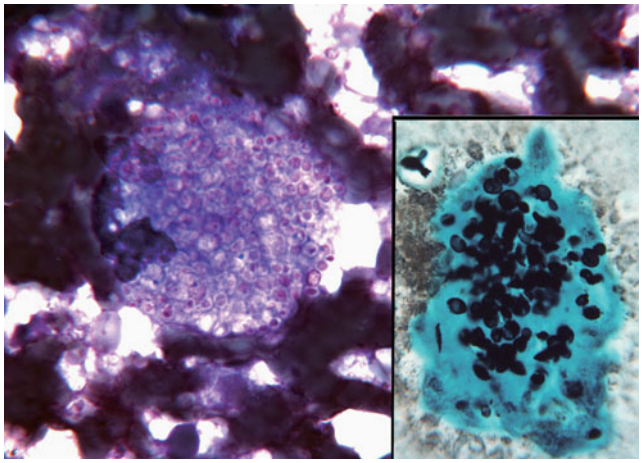


Figure 31-16 Fine-needle aspiration lung. *Histoplasma capsulatum* within the macrophages. Insert shows details and budding fungal forms. (Diff-Quik stain, ×260; *insert*, silver methenamine stain, ×330.)

cough; alternatively, the principal clinical finding may be a solitary pulmonary mass. *Coccidioides immitis* is found in dry, sandy areas of the southwestern U.S. (e.g., California, Arizona, New Mexico, and Texas). The organism is large (20 to 60 nm) and occurs as a nonbudding spherical structure. Spherules have a distinct thick wall and contain a variable number of endospores. The endospores are small (1 to 3 nm), round, and nonbudding. With most specimens, the background examination reveals a heavy acute inflammatory exudate that obscures the faintly stained organisms. Pulmonary fine-needle aspirates can be helpful in the diagnostic evaluation of solitary pulmonary nodules caused by coccidioidomycosis (Fig. 31-17).

Pneumocystis Pneumonia (PCP)

Pneumocystis carinii infection was originally described by Carlos Chagas in 1909 and confirmed a year later by Antonio

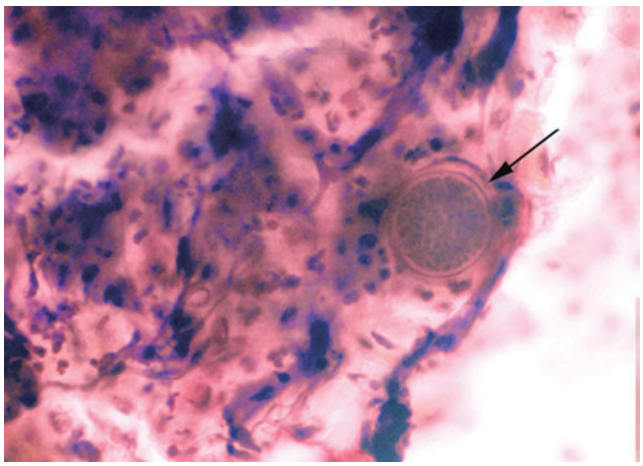


Figure 31-17 Fine-needle aspiration of lung. Coccidiodomycosis infection. Fungal spherule containing endospores (arrow). (Papanicolaou stain, ×330; case courtesy of Dr. Tunda Farkas.)

Carinii. Recently, *Pneumocystis jiroveci* was proposed as the organism's new name.

Infection with *P. carinii* has been most commonly reported among patients with underlying neoplastic or immunodeficiency diseases, particularly the acquired immunodeficiency syndrome (AIDS). Systemic chemotherapy for neoplastic diseases and transplantation also may result in immunosupression and subsequent infection.

Initially regarded as a parasite, *P. carinii* is now considered a fungus, based on ribosomal RNA studies. Attempts to culture the organism have been unsuccessful. *P. carinii* occurs in zygote or sporocyte forms, which are 1 to 5 nm in diameter and have a distinct nucleus. Up to eight spores may occur within the cyst, which measures 6 to 8 nm in diameter—roughly the size of a red blood cell. Organisms infect adjacent tissue after being liberated from the ruptured cysts. *P. carinii* infects alveolar macrophages; in rare instances, the organism may be seen in macrophages in pleural fluid, lymph nodes, or other reticuloendothelial cells.

Although, historically, PCP was often diagnosed from examination of tissue obtained by surgical lung biopsy, carefully collected cytology specimens obtained by fiberoptic bronchoscopy give comparable or better results with minimal patient risk. The technique is sensitive, rapid, and economical. While early reports on the diagnostic yield from examination of induced sputum specimens were encouraging, the findings have not been uniformly confirmed. The best results are obtained using BAL. *P. carinii* infection may be suspected upon inspection of routine Papanicolaou stains, as well as hematoxylin-and-eosin–stained pulmonary specimens. For a definitive diagnosis, a variety of histochemical, immunologic techniques are routinely used. Recently, molecular procedures have been used in identification of PCP. Zygote forms can be visualized using selected stains (e.g., Romanovsky's); basic dye (crystal violet, toluidine blue); and periodic acid-Schiff (PAS), Papanicolaou, and Gram-Weigert's stains. The most commonly used histochemical procedure, the silver-methenamine (Grocott) stain, outlines the cyst wall. Immunocytochemical and monoclonal antibody techniques can be used to identify the organisms, as well as the cyst walls.

Cytomorphology

In air-dried specimens prepared using the Romanovsky's, Papanicolaou, or hematoxylin-eosin methods, *P. carinii* appears within the alveolar material or foamy "coagulum" (Fig. 31-18). The fungal organisms occur in cyst forms that may contain sporocytes (see above). In silver-methenamine (Grocott) and Gram-Weigert's stained preparations, the cysts frequently collapse, giving a crescent or "poached egg" appearance (Fig. 31-19).

The sensitivity of the staining techniques varies according to the quality of preparation, content of pulmonary material, and duration of therapy before the diagnostic procedure is performed. Silver-methenamine and some of the immunologic techniques may give negative results in specimens collected from patients who have received prior therapy. After treatment, the cysts undergo lyses, with fragmentation of the walls, necrosis, and ingestion of the organisms by pulmonary macrophages (Fig. 31-20). Among commonly used histochemical stains, Gram-Weigert's appears slightly more sensitive and specific than silver-methenamine; Giemsa's stain is the least sensitive technique.

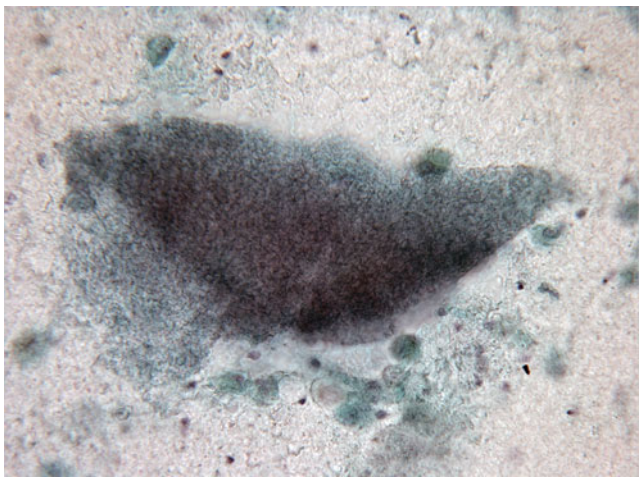


Figure 31-18 Bronchial washing specimen. *Pneumocystis carinii* occurring as intra-alveolar cast "coagulum". (Papanicolaou stain, ×260, Millipore preparation.)

Great care must be exercised in interpretation of silver and special stains for *P. carinii.* Yeast forms of *Candida* arising from oral contamination of sputum and other specimens may resemble *P. carinii* cysts. However, these yeast forms lack the soft, wrinkled, "poached egg" appearance. In addition, they occur in oral mucoid material, not in the proteinaceous, granular alveolar contents or coagulum. In situ hybridization and molecular techniques provide results similar to other diagnostic procedures; however, quantitative differences exist.

Other fungi, including *Paracoccidioides, Mucor,* and *Sporothrix,* are seen occasionally in pulmonary specimens.

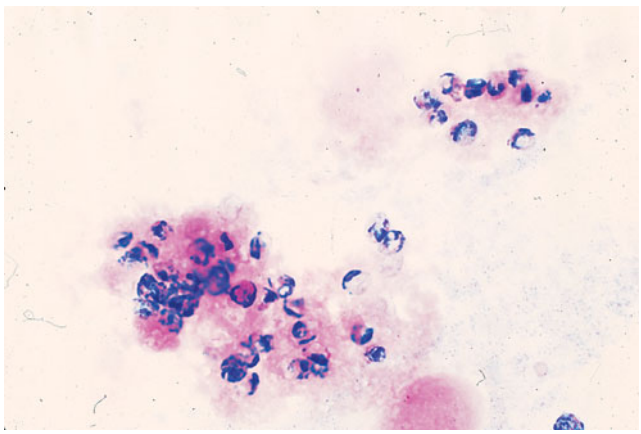


Figure 31-19 Bronchoalveolar lavage showing *Pneumocystis carinii.* Note the cluster of organisms with collapsed cyst walls and central clearing. These forms should be distinguished from the yeast form of *Candida*, which is commonly seen in pulmonary specimens. (Gram-Weigert's stain, ×260.)

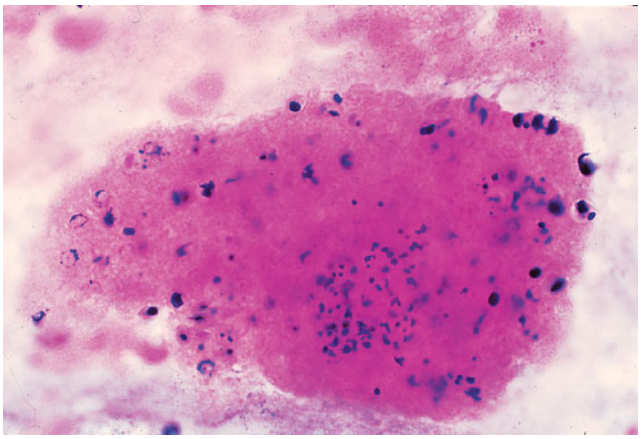


Figure 31-20 Bronchoalveolar lavage showing *Pneumocystis carinii* infection after therapy. Note the degenerated and ghost forms of the organisms in the alveolar cast material. (Gram-Weigert's stain, ×330.)

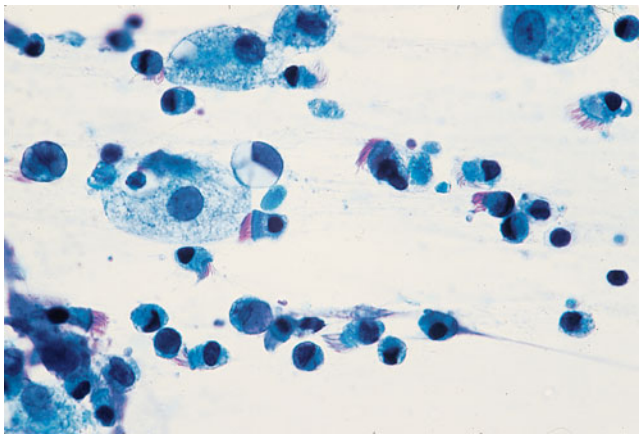
Viral Infections

Pulmonary specimens may reveal specific or nonspecific viral effects on cell components. When infected, bronchial epithelial cells may demonstrate CCP, noted previously. In CCP the cells degenerate when the cytoplasmic tip and attached cilia are exfoliated. The basal portion of the cell shows a pyknotic, degenerated nucleus (Fig. 31-21). Specimens generally have an acute inflammatory background and may contain numerous reactive bronchial cells that can be mistaken for neoplasm. CCP also may be observed in some pulmonary hypersensitivity states.

Herpes Simplex Virus

Herpes simplex virus (HSV) may infect the oral mucosa, tracheobronchial tree, or pulmonary parenchyma. The finding of HSV in a pulmonary cytological specimen is useful in localizing infection to the lower respiratory tract only when the specimen is "uncontaminated," (i.e., is obtained by FNA, tracheal aspiration, bronchial washing, or BAL). Clinical-radiologic correlation is necessary in most cases. When pulmonary parenchymal infection is present, the specimen background is extremely inflammatory, showing numerous neutrophils, abundant mucus, and cellular degeneration. Unless adequate pulmonary material is carefully examined, pulmonary HSV infection can be easily overlooked.

The infected cells may be small (10 to 15 nm) and round and contain intranuclear evidence of the virus as a "ground glass" appearance. This pattern is commonly seen with tracheobronchial infection or in specimens obtained from aspiration of material through a tracheotomy tube. In cases of severe pulmonary infection, multinucleated giant cells demonstrating internuclear molding, intranuclear acidophilic inclusions, or a gelatin chromatin pattern may be seen (Fig. 31-22). Care should be exercised in distinguishing HSV inclusions and prominent nucleoli within bronchial cells.



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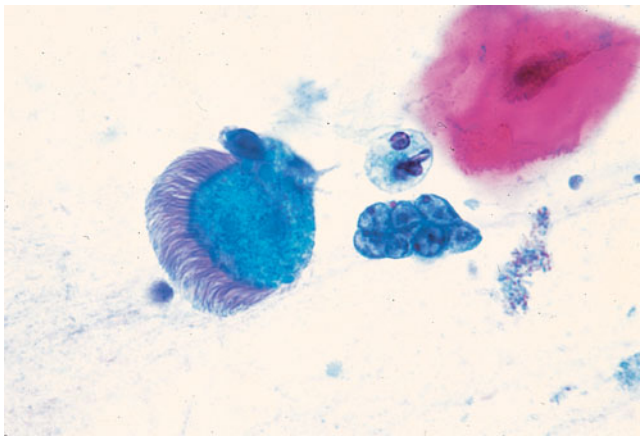


B

Figure 31-21 *A.* Bronchial washing specimen showing ciliocytophthoria (CCP) in a case with pulmonary viral infection. Note numerous fragmented, ciliated columnar cells and macrophages. *B.* Details of CCP. Note the cilia in a degenerated cell. (Papanicolaou stain: *A.,* ×208; *B.,* ×330.)

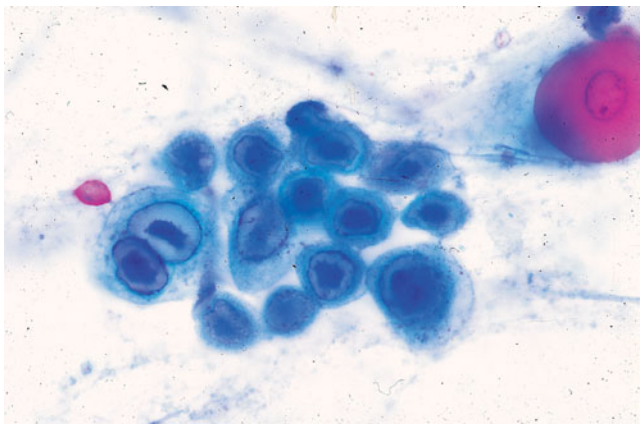


Figure 31-22 Bronchial washing showing herpes simplex virus (HSV). Note the large single cells with prominent intranuclear inclusions and gelatinous nuclear chromatin. (Papanicolaou stain, ×260.)

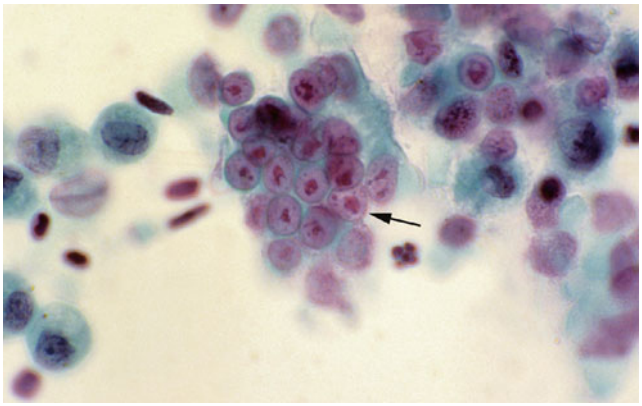


Figure 31-23 Bronchial brush from a patient with lung transplant showing cytomegalovirus (CMV). Note the large, intranuclear acidophilic inclusions with radiating chromatin threads. (Papanicolaou stain, ×330; Millipore preparation.)

Cytomegalovirus

A member of the herpes virus family, cytomegalovirus (CMV) may infect the bronchial epithelium and alveolar lining cells. Infection is common among immunocompromised patients. Infected cells show cytomegaly and large, generally distinct acidophilic intranuclear inclusions. Thin strands of nuclear chromatin bridge the space between the inclusion and the nuclear envelope (Fig. 31-23). Occasionally, the inclusions are basophilic and intracytoplasmic. In rare instances, CMV-infected cells may show multinucleation. Pulmonary HSV infection may occur concurrently with CMV. Viral infection may occur in a polymicrobial environment. CMV can occur with pneumocystis, HSV, and other pulmonary infections.

Respiratory Syncytial Virus

Respiratory syncytial virus (RSV) is often not recognized in routine cytological specimens. The virus produces two types of inclusions within bronchial and alveolar lining cells: (1) dense acidophilic inclusions with clear halos around them, and (2) "smudge" cells, which contain a basophilic nucleus with obliteration of chromatic details.

Para-influenza Virus

Para-influenza infection in the upper respiratory tract produces a variable number of infected columnar cells, which demonstrate eosinophilic degeneration and cytoplasmic inclusions. The inclusions are considered degenerative, rather than viral, particles (Fig. 31-24).

Adenovirus

Although more common in children and infants, adenovirus infection can also occur in adults. Depending upon the duration of the disease, intranuclear inclusions can be seen in bronchial columnar cells (Fig. 31-25).

Other Viruses

Multinucleation and eosinophilic cellular inclusions may be observed in measles infection. Human papillomavirus (HPV)

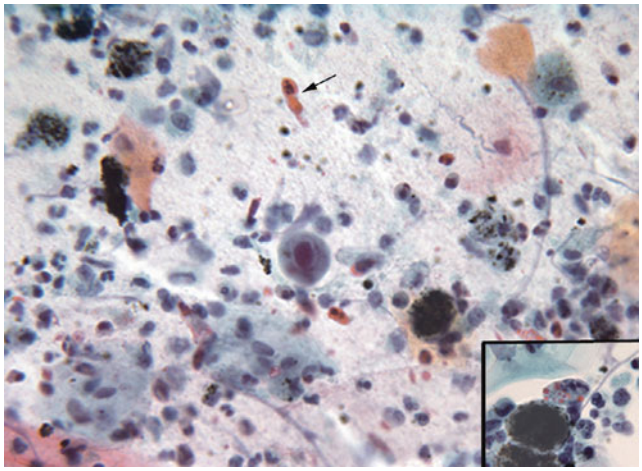


Figure 31-24 Bronchial washing in para-influenza viral infection. Note organophilic cytoplasmic changes affecting columnar cells (arrow). Insert shows multiple cytoplasmic inclusions. (Papanicolaou stain, ×260; *insert,* ×330.)

may cause tracheal papillomatosis and produce fragments of squamous epithelium containing typical koilocytes, which are squamous cells with eccentric, vesicular nuclei and a distinct cytoplasmic halo or cavity. The cells contain intranuclear HPV antigens, which can be demonstrated by use of various tissue and molecular techniques. Most airway HPV infections are caused by viral types 6 and 11.

Parasitic Infections

A number of parasitic infections may occur in the lung. They are seen almost exclusively in either endemic areas or among immunosuppressed patients.

Strongyloidosis

Pulmonary infection with *Strongyloides stercoralis* may be seen in patients with AIDS or those who are iatrogenically immunosuppressed (e.g., by prolonged corticosteroid

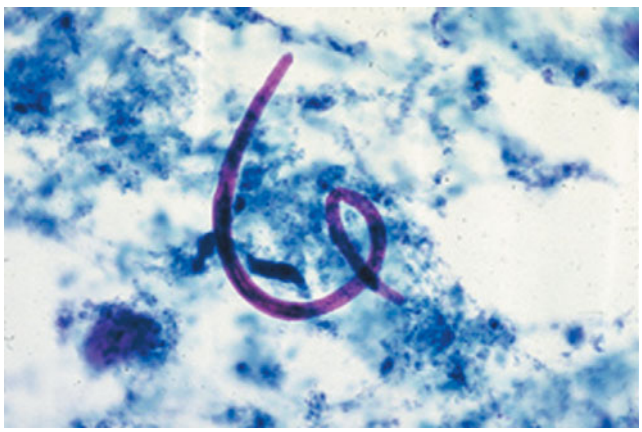


Figure 31-25 Bronchial brush specimen in adenovirus infection. Numerous intranuclear eosinophilic inclusions (arrow) are seen infecting the bronchial cells. (Papanicolaou stain, ×330.)

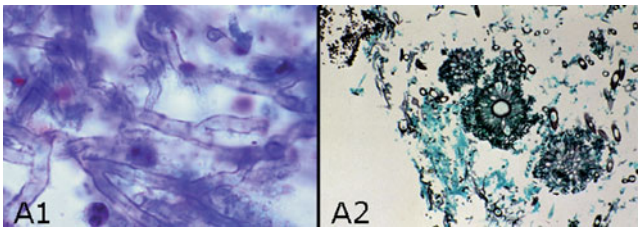


Figure 31-26 Spontaneously produced sputum specimen from a patient with AIDS. Strongyloides filariform larva present in a necrotic background. (Papanicolaou stain, ×110.)

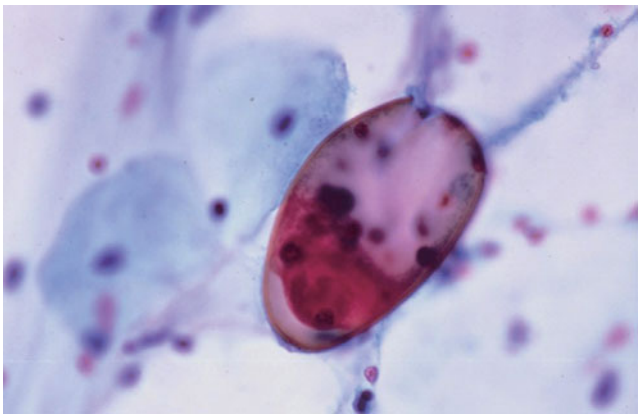


Figure 31-27 Induced sputum specimen showing *Paragonimus* egg. (Papanicolaou stain, ×110.)

administration). Filariform larvae, which are easily identifiable, may be seen in bloody sputum specimens. The larvae measure up to 500 nm in length and contain a gullet and notched tail. Ova may be observed in some sputum specimens (Fig. 31-26).

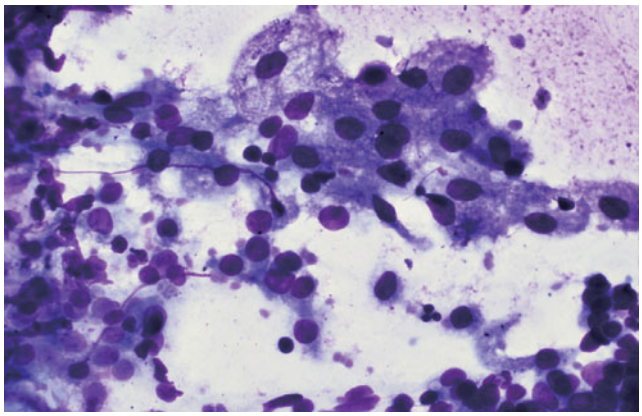
Uncommonly, other parasites, including *Echinococcus, Entamoeba,* microfilaria, *Toxoplasma* and *Paragonimus* (Fig. 31-27), may infect pulmonary tissues and be diagnosed cytologically. *Trichomonas* infection also has been identified in pulmonary specimens obtained from immunosuppressed patients.

OTHER NON-NEOPLASTIC CONDITIONS

Cytopathological findings may be observed in a number of other non-neoplastic conditions. Some of the common ones that can be detected in pulmonary specimens are described below.

Aspiration Pneumonia

Generally, both severe acute inflammation and foreign-body giant-cell reactions may be observed in pulmonary specimens obtained from patients with aspiration pneumonia. The latter reaction is related to the duration of the disease. Often the aspirated material can be recognized in pulmonary specimens.



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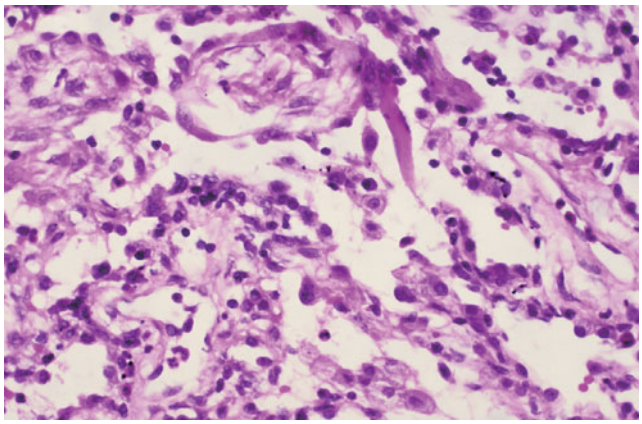


B

Figure 31-28 Fine-needle aspiration of lung showing organizing pneumonia. *A.* Note the hyperchromatic, atypical alveolar cells (Diff-Quik, ×260). *B.* Pulmonary core biopsy showing similar cells lining the alveolar spaces (H&E, ×166).

Organizing pneumonia can produce both radiographic and cytological changes affecting the alveolar lining cells that may mimic a neoplastic process (Fig. 31-28).

Lipid Pneumonia

Lipids may enter the respiratory system through exogenous sources (e.g., by ingestion, aspiration, or use of nasal sprays containing emollient particles) or through endogenous routes (e.g., from the bone marrow after injury—fat embolism). Cytologically, large foamy cells with small vesicular nuclei may be seen, either singly or in small tissue fragments (Fig. 31-29). The presence of endogenous or exogenous fats can be confirmed by appropriate histochemical stains. Differentiation and diagnosis can be valuable for infants and children with pneumonia.

Pulmonary Infarction and Intra-alveolar Hemorrhage

A radiographic lesion due to pulmonary infarction may be aspirated on clinical and/or radiographic suspicion

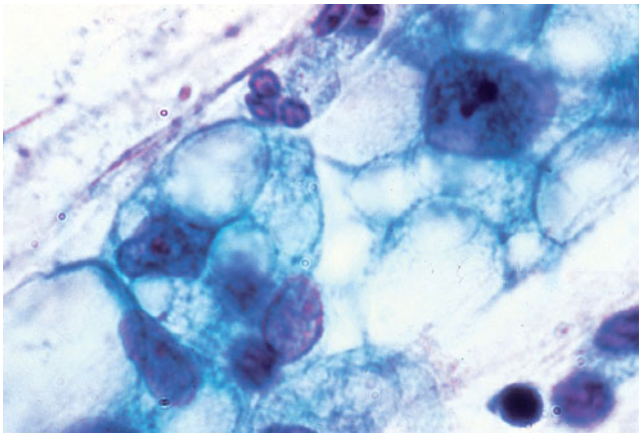


Figure 31-29 Bronchial washing showing lipid pneumonia. Note the large vacuolated cells with hyperchromatic nuclei and prominent nucleoli. Such cells can be mistaken for adenocarcinoma. (Papanicolaou stain, ×260.)

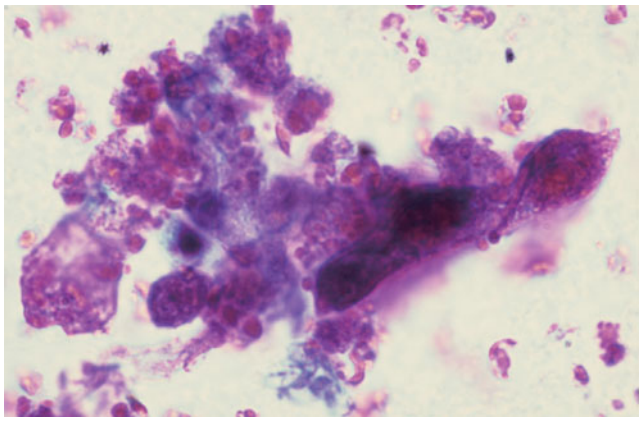
of malignancy. These specimens often contain numerous macrophages containing ingested hemosiderin. The hemoglobin metabolite occurs as dark green or brown intracellular clumps that can be stained histochemically. Extremely bizarre, reactive bronchial cells may accompany such macrophages and pose a diagnostic challenge (Fig. 31-30).

Bronchoalveolar lavage or bronchial washing performed following lung transplantation or in the setting of a number of autoimmune or other disorders may contain numerous alveolar macrophages which contain golden-brown, fine intracytoplasmic pigment (Fig. 31-31). Pigmented macrophages occur in a background of fresh hemorrhage and reactive bronchial epithelial cells in specimens obtained from patients with acute intra-alveolar hemorrhage, such as that which occurs in Goodpasture's syndrome (Fig. 31-32).

Sarcoidosis

Cytological diagnosis of sarcoidosis is considered accurate and cost-effective. Pulmonary specimens (especially BAL) obtained from patients with suspected parenchymal involvement with sarcoidosis, may reveal diagnostic cytological changes. Typical findings include a clean background, a few lymphocytes, Langhans'-type multinucleated giant cells, and syncytial forms of histiocytic cells. Giant cells often have a clear cytoplasm and vesicular or pyknotic nuclei (Fig. 31-33). These giant cells should be distinguished from the multinucleated cells associated with cigarette smoking, bronchial irritation, or pneumonia. The multinucleated giant cells from cigarette smokers often contain golden-brown pigment; numerous reactive columnar cells characterize the irritative processes; the pneumonic processes commonly include an inflammatory background. Concentrically laminated Schumann's bodies or spiderlike asteroid bodies may be observed in pulmonary specimens. Important to note is that these findings are uncommon and not specific for sarcoidosis.

Sarcoidosis is usually diagnosed by the finding of noncaseating granulomas within lung tissue or lymph nodes in



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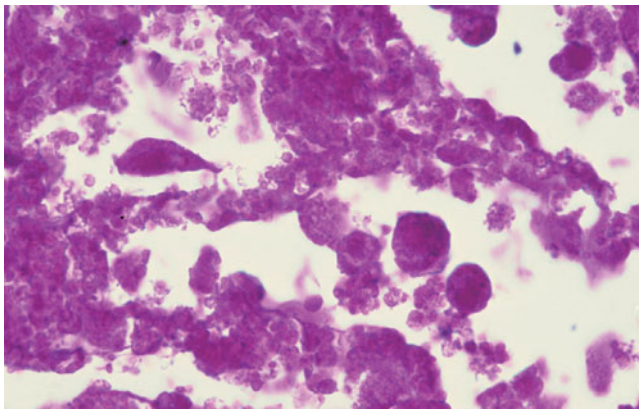
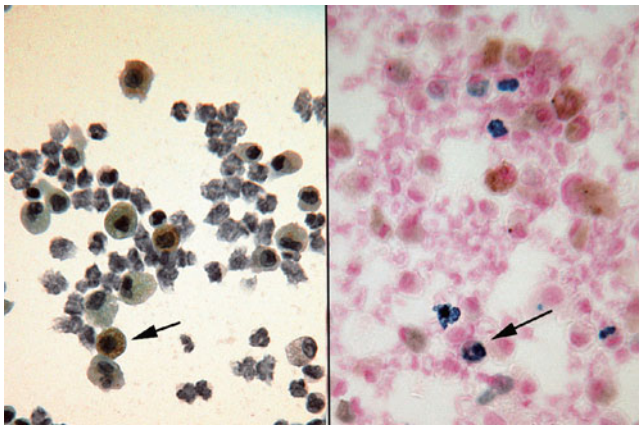


B

Figure 31-30 Fine-needle aspiration. Pulmonary infarct. *A.* Note the numerous degenerated macrophages and alveolar cells which have lost morphologic features and contain ingested red blood cells. *B.* Corresponding lung core biopsy revealing similar changes. (*A.* Papanicolaou stain, ×260; *B.* H&E stain, ×260.)



A *B*

Figure 31-31 Bronchoalveolar lavage specimen from lung transplant patient showing intra-alveolar hemorrhage. *A.* Note golden-brown pigment (arrow) within the macrophages and acute inflammatory background. *B.* Hemosiderin pigment revealed by Prussian blue reaction (arrow). (*A.* Papanicolaou stain, ×260; *B.* Prussian blue reaction, ×260.)

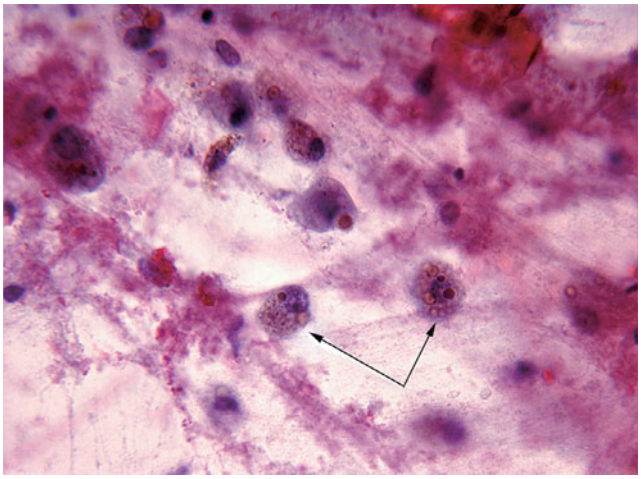
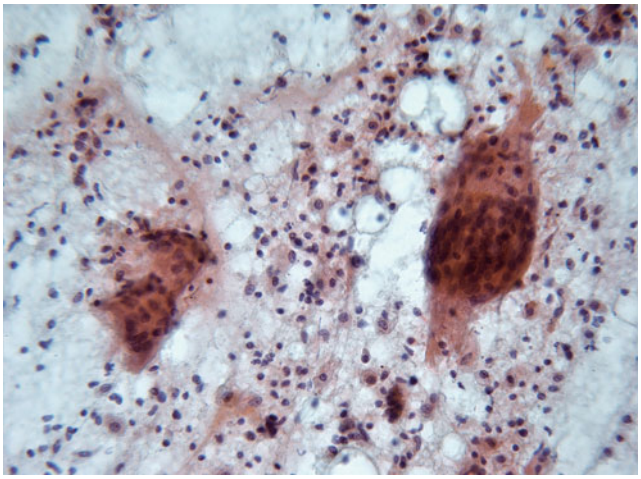


Figure 31-32 Bronchoalveolar lavage specimen showing intra-alveolar hemorrhage in Goodpasture's syndrome. Note extensive fresh blood in the background and numerous blood-filled macrophages (arrow). (Papanicolaou stain, ×260.)



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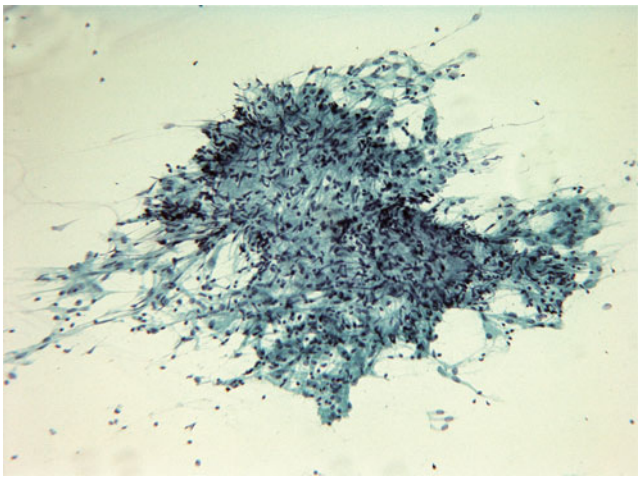


B

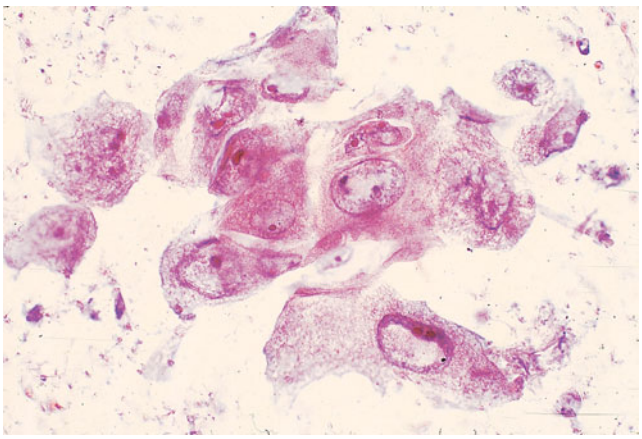
Figure 31-33 Sarcoidosis. *A.* Bronchial brushing. Note numerous multinucleated giant cells and lymphocytes occurring in a non-necrotic background. *B.* Perihilar lymph node aspiration. Note noncaseating granulomas with lymphoid and epithelioid cells. (Papanicolaou stain: *A.*, ×166; *B.*, ×83.)

the absence of an alternative explanation for granulomatous inflammation (Fig. 31-33*B*). Additional studies for acid-fast and fungal organisms should be performed in all cases in which noncaseating granulomas are found.

Radiation and Chemotherapy Effects

Some of the most bizarre and atypical cytological changes can be seen in pulmonary specimens obtained after radiation or chemotherapy. The value of obtaining a proper clinical history in this regard cannot be overemphasized. Radiation may affect squamous, bronchial, and alveolar lining cells. The effect is long-term and dose-dependent. General features include cytomegaly and karyomegaly; N:C ratios are unaltered. Irradiated nuclei are generally pale and have a finely divided, evenly distributed chromatin (Fig. 31-34). Cells reveal minimum pleomorphism and contain prominent acidophilic inclusions. The cytoplasm may be variable, dense, or vacuolated.

Chemotherapeutic agents, including alkylating drugs (e.g., busulfan and cyclophosphamide) and antimetabolites



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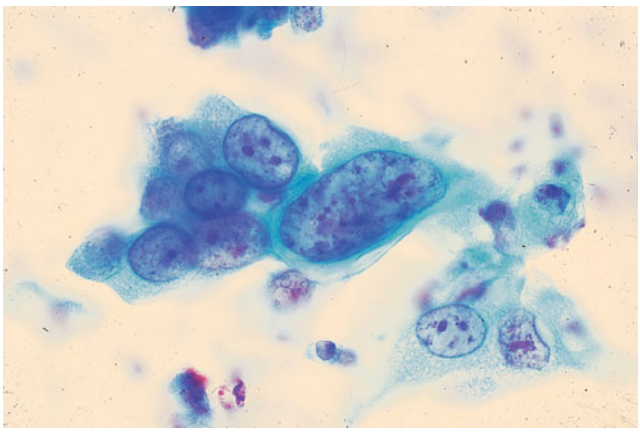
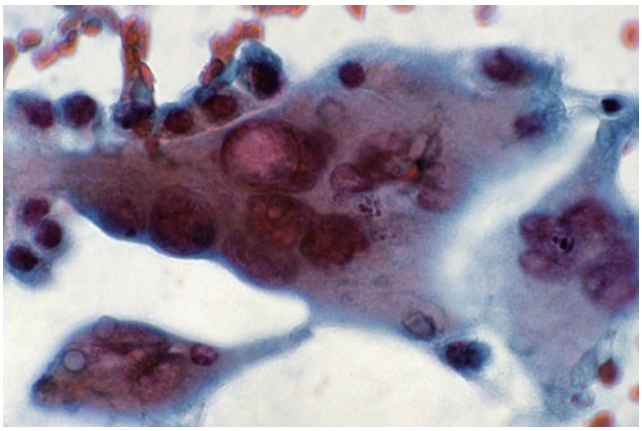


B

Figure 31-34 Bronchial washing. *A.* Radiation changes in bronchial epithelial cells. Note the extremely bizarre cells with marked variation in size. *B.* Prominent nucleoli are evident. Cells have thin and uniform nuclear membranes and pale chromatin. (Papanicolaou stain, ×260.)



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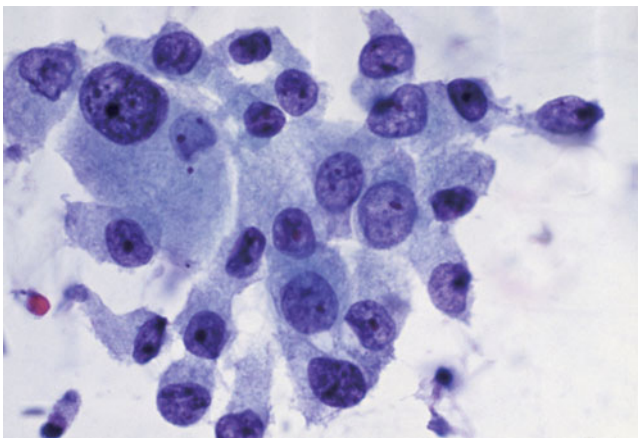


B

Figure 31-35 Bronchial washing showing chemotherapy effect on bronchial epithelial cells. *A.* Note the bizarre cells with cytomegaly, nuclear atypia, hyperchromasia, and lack of nuclear details. (Papanicolaou stain, ×330.) *B.* Bronchoalveolar lavage specimen showing atypical alveolar cells that can be mistaken for malignancy. (Papanicolaou stain, ×260.)

(e.g., methotrexate and azathioprine), generally produce changes that affect bronchial epithelial cells and type II pneumocytes. These cells enlarge and become hyperchromatic, although the chromatin remains uniform and generally does not show abnormal clumping and clearing. Nucleoli are single or multiple and appear prominent. The nuclei may appear smudged, with loss of chromatin granularity and nuclear detail (Fig. 31-35). Great care should be exercised in diagnosing neoplasm in such cases. A proper history, comparison of cells with the original tumor, and familiarity of cytomorphologic changes are useful adjuncts to correct diagnosis. Similar cellular changes may be associated with amiodarone therapy.

PULMONARY NEOPLASMS

In the United States in 2005, lung cancer will have accounted for approximately 163,000 deaths; 172,000 new cases will have been diagnosed. Only 16 percent of lung cancers are detected when the disease is localized, with an associated 5-year survival rate exceeding 60 percent. Regional and distant metastases are present in over 70 percent of cases at time of diagnosis; overall 5-year survival in this group is under 20 percent.

Early Lung Cancer Detection

In some lung cancers (e.g., squamous cell carcinoma), precursor lesions, including squamous dysplasia and in situ changes, precede development of invasive cancer. Early detection of this tumor type may improve survival. However, the multicentric origin of tumors, along with coexisting illnesses, contributes to mortality. Furthermore, moderate, atypical squamous metaplasia of the bronchial epithelium represents a lesion that, in a significant number of cases, may develop into squamous carcinoma. Application of molecular techniques to analysis of sputum specimens can detect moderately and markedly atypical metaplastic cells in patients at risk of subsequent lung cancer, a second primary tumor, or recurrent tumor. Attempts to identify the "at-risk" population using immunocytochemical techniques have been only partly successful. The labor and costs associated with sputum collection, sampling, and cell concentration have contributed to limited use of these techniques. Molecular methods are currently being evaluated for early lung cancer detection.

Based on experience from an early Veterans Administration study, and using the evolution of cervical cancer as a model, a multi-institutional, early lung cancer detection project was launched by the National Cancer Institute in the early 1970s. Guidelines were outlined for early lung cancer detection using chest radiographs, sputum cytology, and, when indicated, fiberoptic bronchoscopy. In addition, treatment methods were delineated for "early" cancer, which was defined as an unsuspected, asymptomatic tumor detected by cytological or imaging techniques.

Nearly 30,000 high-risk participants were screened using sputum cytology or chest radiographs (or both) at three participating centers. Cases were followed for up to 15 years. While sputum cytology and chest radiography detected a number of presymptomatic, early-stage lung cancers (especially squamous cell carcinomas), higher resectability and survival rates among the study group did not result in a lower overall mortality.

Established Lung Cancer

Although pulmonary cytology in its present form has been used for detection and diagnosis of lung cancer for about 50 years, the earliest description of the technique dates back to 1767, when exfoliated respiratory cells were first described. In patients with suspected pulmonary malignancies, examination of a single, expectorated sputum has a low diagnostic yield of nearly 20 percent; when five early-morning, deep-cough specimens are examined, the yield is as high as 90 percent. The type of pulmonary specimen (random, early-morning, induced, pooled, bronchial washing, bronchial brushing, transbronchial aspiration, or transthoracic needle

Table 31-1

Histological Classification of Lung Tumors

1. **Epithelial tumors**
   - ***a. Benign***
     - i. Papillomas
     - ii. Adenomas
       1. Alveolar and papillary adenoma
       2. Adenoma of salivary gland type
       3. Mucinous cystadenoma
   - ***b. Preinvasive lesions*** (dysplasia, carcinoma in situ, atypical adenomatoid hyperplasia, diffuse idiopathic pulmonary neuroendocrine hyperplasia)
   - ***c. Malignant***
     - i. Squamous cell carcinoma
     - ii. Adenocarcinoma
       1. Acinar adenocarcinoma
       2. Papillary adenocarcinoma
       3. Bronchioalveolar carcinoma
       4. Adenocarcinoma with mixed subtype
     - iii. Large cell carcinoma
     - iv. Adenosquamous carcinoma
     - v. Carcinoma with pleomorphic, sarcomatoid, or sarcomatous elements
     - vi. Carcinoid tumor (typical and atypical)
     - vii. Carcinoma with salivary-gland type
2. **Soft-Tissue tumors**
3. **Mesothelial tumors**
4. **Miscellaneous tumors** (hamartomas, sclerosing hemangioma, thymoma, clear cell tumor)
5. **Hematopoietic and lymphoid lesions**
6. **Secondary tumors**
7. **Unclassified tumors**
8. **Tumorlike lesions** (tumorlet, Langerhans' cell histiocytosis, inflammatory pseudotumor)

Source: Modified from Travis WD, Colby TV, Corrin B, et al: Histologic Typing of Lung and Pleural Tumors, 3rd ed. World Health Organization. Berlin, Springer, 1999.

aspiration), technique of collection (fresh or fixed), quantity of specimen examined, and technique of specimen preparation have bearing on the value of pulmonary cytology in cancer detection. Additionally, the location of the lesion, associated pathology, and sampling techniques may contribute to the number of diagnostic tumor cells present in a specimen.

The two most important issues addressed in the diagnosis of pulmonary neoplasm are whether the tumor is primary or metastatic and, if primary, whether the cell type is small cell or non–small cell. The World Health Organization (WHO) classification of lung tumors is summarized in Table 31-1.

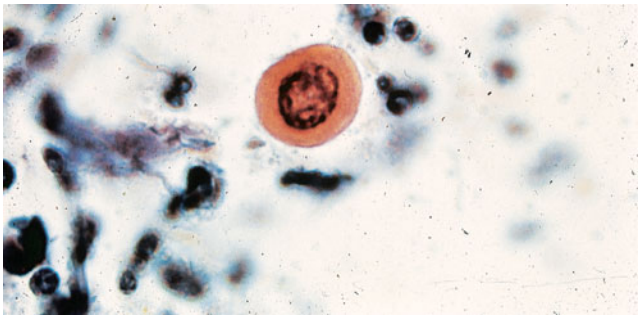
Non–Small-Cell Lung Carcinoma

Squamous Cell Carcinoma

Squamous cell carcinoma accounts for almost one-third of all primary pulmonary malignancies. The cytomorphologic diagnosis of squamous cell cancer is highly accurate and approaches 100 percent. Tumor cells detected in expectorated sputum or bronchial washings generally are more keratinized and poorly preserved than those obtained using bronchial brushing or FNA.

From a cytology perspective, early squamous cell carcinoma is the best-studied lung tumor; definitive precursor (dysplastic) and early (in situ) lesions have been documented. In situ tumor cells are recognizable as single cells with a high N:C ratio, hyperchromatic nuclei with no nucleoli, and an even chromatin pattern with some chromatin clumping and clearing. Cytoplasm is frequently keratinized (Fig. 31-36). The dysplastic cells can occur in small tissue fragments, especially in bronchial brush specimens. The metaplastic bronchial lining cells associated with mechanical irritation (e.g., tracheal intubation), infections (e.g., bronchitis, bronchiectasis, abscess, viral infection), or prior radiation or chemotherapy can mimic dysplastic squamous cells.

Invasive squamous cell carcinoma often leads to a mass or cavitary lesion with tumor necrosis and secondary



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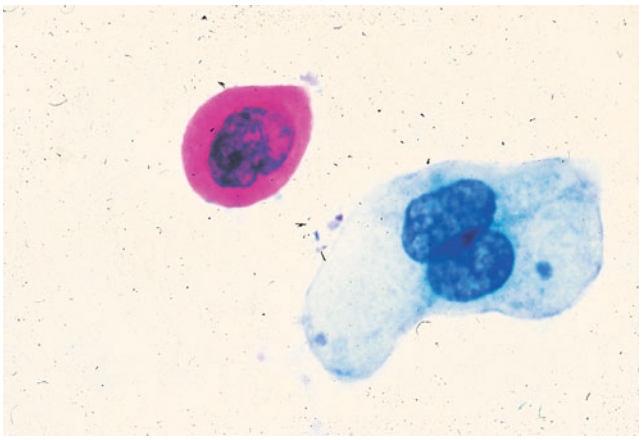


B

Figure 31-36 Bronchial washing showing "early" lung cancer. The cells in *(A)* and *(B)* represent nuclear and cytoplasmic features that are indicative of early squamous cell carcinoma. (Papanicolaou stain: *A.,* ×260; *B.,* ×330.)

infection. The background of such specimens may display acute inflammation, necrotic debris with numerous infarcted, necrotic cells lacking nuclear detail, and malignant features. The well-preserved tumor cells are pleomorphic and may appear as "tadpole" or fiber forms. Bizarre, irregularly shaped cells with obvious malignant features (nuclear membrane irregularities, abnormal chromatin clearing and clumping, and prominent nucleoli) can occur. Squamous differentiation of the cytoplasm is variable (Fig. 31-37). Examination of cells for intercellular bridges or keratohyaline granules is necessary before a definitive diagnosis of squamous cell carcinoma can be established. However, these cytoplasmic features are almost always absent in cases of poorly differentiated squamous cell carcinoma.

Adenocarcinoma

Pulmonary adenocarcinoma can be diagnosed relatively easily in bronchial washings and brushings when the tumor is located within central airways; however, diagnosis is extremely difficult with peripheral tumors or scar-associated malignancies. The latter require direct sampling by FNA under radiologic guidance.

The cells from adenocarcinoma generally occur in tissue fragments, which may appear as acinic and papillary

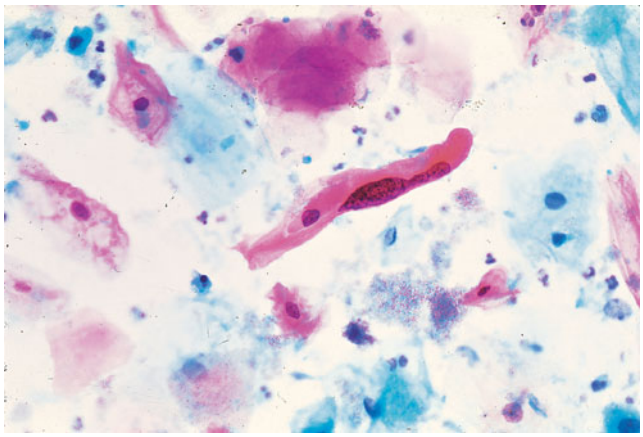


Figure 31-37 Induced sputum showing invasive squamous cell carcinoma. Note an obvious malignant cell with necrotic background and numerous squamous cells. (Papanicolaou stain, ×208.)

structures (Fig. 31-38). Cells have a soft cytoplasm that may contain evidence of mucin secretion. Tumor cells may exhibit bizarre, malignant nuclei with obvious nuclear membrane and chromatin abnormalities and prominent nucleoli. Nucleoli can be variable in number and are usually large and abnormally shaped. Shedded cells obtained from postbronchoscopy specimens, following viral infections, or during pulmonary infarction can be mistaken for tumor cells.

Bronchoalveolar Cell Carcinoma

The cytological diagnosis of bronchoalveolar cell carcinoma can be problematic due to lack of obvious malignant features. The key diagnostic features include presence of a monotonous tumor cell population arranged in papillary and acinic formations. The individual tumor cells show a prominent single

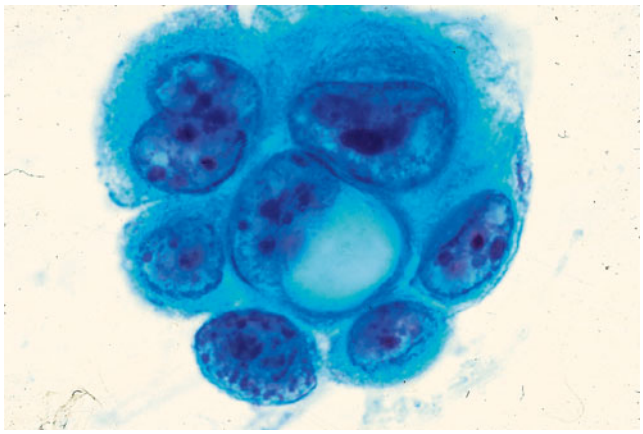
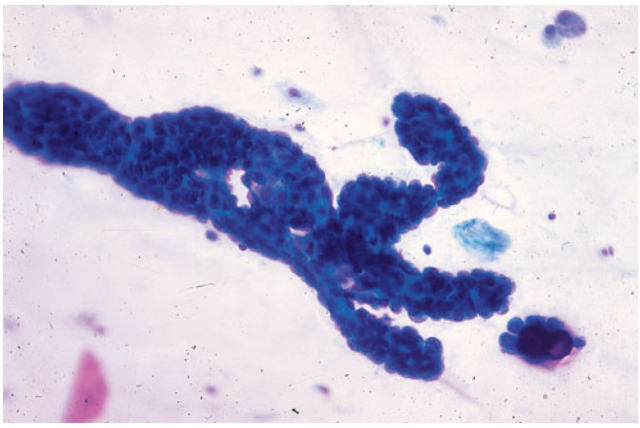


Figure 31-38 Bronchial washing showing adenocarcinoma of the lung. Note glandular features with nuclear chromatin and nucleolar variability. Evidence of mucus secretion is present in the cell in the center of the field. (Papanicolaou stain, ×330.)



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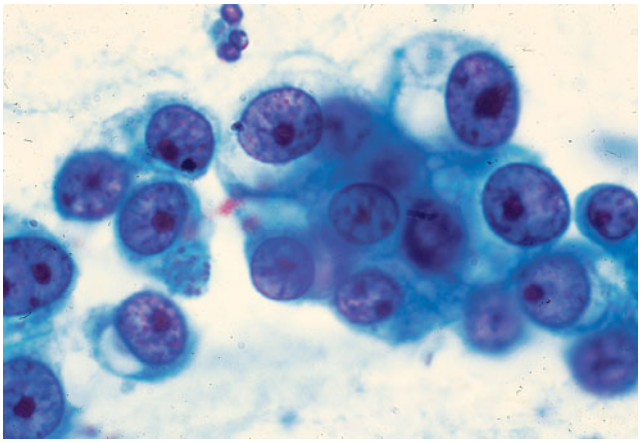

B

Figure 31-39 Bronchial washing showing bronchoalveolar carcinoma. *A.* Papillary formation. *B.* Prominent nucleoli and tenacious intercytoplasmic connection (TIC). (Papanicolaou stain: *A.,* ×105; *B.,* ×330.)

nucleolus and cuboidal or columnar cell forms, with or without intracytoplasmic mucus (Fig. 31-39). Occasionally, calcified psammoma bodies may be seen; tumor cells may display intranuclear grooves or inclusions. Under these circumstances, in patients with a history of papillary thyroid carcinoma, immunohistochemical stains for thyroglobulin are necessary to differentiate between a primary lung tumor and metastatic thyroid cancer. Tenacious intracytoplasmic connections, when present, are helpful diagnostically. Cytological diagnosis can be extremely accurate (60 to 80 percent). Bronchoalveolar tumor cells can often be confused with reactive bronchial cells, which may be seen with inflammation or after instrumentation or treatment.

Large-Cell Undifferentiated Carcinoma

Large-cell undifferentiated carcinoma represents a group of tumors that cannot be easily subclassified. Cells occur in tissue fragments. They show marked pleomorphism and classic malignant features (Fig. 31-40). These tumors can demonstrate features of both squamous cell and adenocarcinoma.

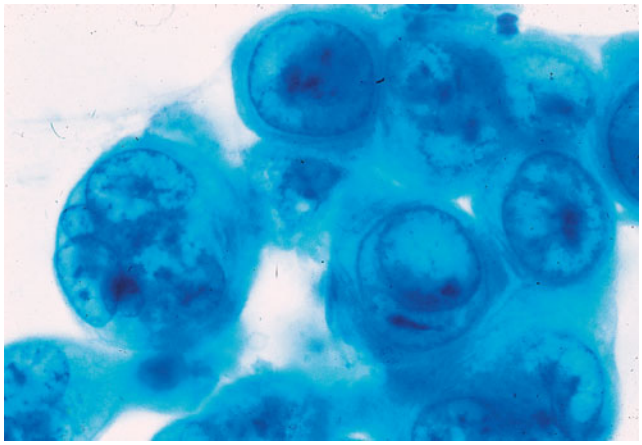

Figure 31-40 Bronchial washing showing large-cell undifferentiated carcinoma. Note that the malignant cells lack any obvious differentiation. (Papanicolaou stain, ×330.)

Small-Cell Undifferentiated Carcinoma

Small-cell undifferentiated carcinoma is relatively easy to diagnose when the specimen is of good technical quality. Well-preserved cells are an absolute requirement for cytological diagnosis of small-cell undifferentiated carcinoma. In fresh smears or monolayer preparations, tumor cells are seen in syncytial groups and as singly scattered cells. The cells have a high N:C ratio and uniformly distributed chromatin. Nuclei are absent or inconspicuous, intercellular molding is prominent, and cytoplasm is delicate and scant (Fig. 31-41). Individual tumor-cell necrosis or apoptosis is common. The background usually shows extensive tumor necrosis and strands of basophilic material representing DNA from fragmented fragile tumor nuclei. However, these cytological findings may not be prominent in the new monolayer cytological preparations. Subclassification of the tumors as oat cell or intermediate varieties may be possible, but this distinction is generally impossible on the basis of cytological preparations.

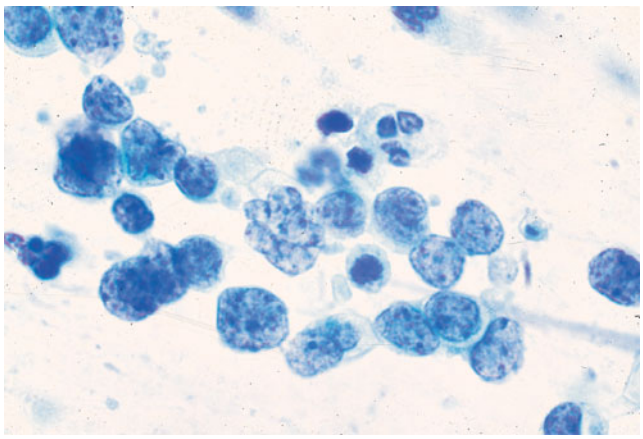

Figure 31-41 Bronchial washing showing small-cell undifferentiated carcinoma. Note the soft cells with uniformly granular chromatin, intercellular molding, and scant cytoplasm. (Papanicolaou stain, ×330.)

Great care needs to be exercised in the proper diagnosis of small-cell undifferentiated tumors. Lymphoid cells from tonsils and adenoids, reserve cells, degenerated bronchial columnar cells, or lymphoma may resemble small-cell carcinoma of the lung. Diagnostic accuracy with this tumor type approaches 100 percent in certain laboratories; most centers report 70 to 80 percent predictability of cytological diagnosis.

Not all small-cell tumors possess typical morphologic features. The tumors may contain a few prominent nucleoli, coarser chromatin, and a variable amount of cytoplasm. Such tumors are best classified as "undifferentiated tumors with neuroendocrine features." Immunocytochemical stains for chromogranin and neuron-specific enolase and ultrastructural studies are helpful in diagnosis.

Other Neuroendocrine Tumors

Carcinoid

A majority of pulmonary carcinoid tumors occur submucosally and do not exfoliate diagnostic cells. Diagnostic cells can, however, be obtained by bronchial brush and FNA techniques. When present, the cells are small and round or oval; they possess scant, delicate cytoplasm and contain one or two nucleoli. The cells exist in microacinic formations or in trabecular and papillary structures. Intercellular molding, pleomorphism, or necrosis are usually not observed.

Atypical Carcinoid

Atypical carcinoid tumors are classified morphologically as midway along the pathological spectrum between carcinoids and small-cell undifferentiated carcinomas. These tumors show neuroendocrine differentiation on the basis of morphology and immunohistochemistry. Although cells may not have the nuclear features typical of a small-cell carcinoma or the microacinic and trabecular pattern of a carcinoid, they can reveal occasional mitoses and focal necrosis.

Lymphoma

A diagnosis of lymphoma may be made from pulmonary specimens. A proper clinical history and use of marker studies are necessary for accurate diagnosis. Hodgkin's disease can be diagnosed by recognition of typical Reed-Sternberg cells in a variety of pulmonary specimens.

Metastatic Tumors

Malignant melanoma and breast, prostate, kidney, and gastrointestinal tumors commonly metastasize to the lungs. Knowledge of the patient's history, coupled with typical morphologic changes and immunohistochemical studies, is often helpful. Patients with an extrapulmonary primary tumor may develop a primary pulmonary malignancy; concurrent or sequential development of malignancies is common in cigarette smokers, particularly laryngeal and pulmonary squamous cell tumors.

Immunocytochemistry of Lung Tumors

Immunocytochemistry can often be used as an adjunct in the morphologic diagnosis of lung tumors. The technique is often needed to differentiate between primary and metastatic tumors and between and small-cell and non–small-cell carcinoma.

Primary pulmonary tumors, including small-cell cancers and adenocarcinomas, express thyroid transcription factor (TTF-1) and cytokeratin-7; rarely, they are positive for cytokeratin-20. TTF-1 can also be seen in primary thyroid tumors, although primary lung tumors do not express thyroglobulin. Carcinoembryonic antigen (CEA) is seen in lung adenocarcinoma; however, it can also be seen in adenocarcinoma of pancreas, colon, breast, or other organs.

Pulmonary neuroendocrine tumors, both benign and malignant, express neuroendocrine markers, chromgranin-A, synaptophysin, neuron-specific enolase, and CD56. These tumors also express cytokeratin-7 and TTF-1. Interestingly, small-cell carcinomas may also express calcitonin.

CONCLUSIONS

Cytology is an accurate, economical, rapid technique that can be useful in diagnosing a large number of nonneoplastic and neoplastic pulmonary lesions. Proper sampling, procurement of high-quality specimens, adequate specimen preparation, careful examination of material, and correlation with clinical and radiographic features are essential for accurate diagnosis.

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32

Interventional Radiology in the Thorax: Nonvascular and Vascular Applications

Aalpen A. Patel • Scott O. Trerotola

Over the last few decades, medicine has seen the birth and growth of the field of interventional radiology (IR). IR complements various diagnostic and therapeutic surgeries or replaces them entirely. IR techniques are image-guided, minimally invasive methods that usually carry less morbidity compared to their surgical counterparts.

From a historical perspective, the first percutaneous needle biopsy of the lung was performed (without image guidance) in 1882. Thereafter, lung biopsy was used mainly for determining the microbial agent(s) causing lobar pneumonia. Due to high complication rates with early techniques, percutaneous biopsies fell out of favor until fine needles were developed. When computed tomography became available, image-guided transthoracic lung, pleural, and mediastinal diagnostic interventions became more widely adopted, especially for percutaneous drainage of pleural, lung, and mediastinal collections.

Additional radiography-based interventions were developed through application of vascular approaches in the 1960s, including bronchial arteriography. Subsequently, embolotherapy of the bronchial arteries for hemoptysis was described in the 1970s. Thereafter, refinements in catheter technology and techniques established bronchial artery embolization as an accepted component of the management of patients with hemoptysis. Embolotherapy has also been used in the pulmonary arterial circulation to treat pulmonary arteriovenous fistulae.

Endovascular techniques have also proved useful in foreign body retrieval from the heart and pulmonary arteries. With the advent of intravascular stents, surgical conditions, such as superior vena cava syndrome, can be treated using endovascular techniques. Modification of prior designs and introduction of new vena cava filters that have small introduction sheaths have also made percutaneous caval interruption routine for interventional radiologists.

As IR develops into an evidence-based practice, its techniques will become more widely accepted and adopted by other specialties as their own. IR has now become a full-fledged clinical specialty, providing outpatient and inpatient consultation and follow-up.

This chapter focuses on the most common and pertinent techniques and presents them as either nonvascular or vascular interventions. Adjunctive imaging modalities employed include ultrasound (percutaneous or intraluminal), fluoroscopy, computed tomography (CT), and magnetic resonance imaging (MRI). Each modality has its advantages and disadvantages; the first three modalities are most commonly used; MRI holds much promise.

Although some interventional radiologists are actively involved in procedures such as thoracic aortic endograft placement for aneurysmal disease, these procedures will not be discussed in this chapter. Likewise, treatment of peripheral vascular disease of the thoracic vessels using balloon angioplasty or stents is commonplace in IR, but is beyond the scope of this chapter. Bronchial and esophageal stent placement is often performed by interventional radiologists, but these topics are covered in Chapter 36.

IMAGE-GUIDED NEEDLE PROCEDURES IN THE THORAX

Appropriate use of image-guided, needle-based procedures in diagnosing chest lesions entails consideration of indications for the procedure, expected results, recognized complications, and post-procedure management.

Application of Diagnostic Methods

As with any procedure or test, image-guided sampling of thoracic structures is performed when a clinical or therapeutic decision rests upon it (e.g., when the histology of a lung nodule needs to be established prior to treatment), or when pleural fluid requires sampling for determining whether infection, malignancy, or other processes are present. CT and ultrasound are the most commonly used adjunctive imaging modalities employed for this procedure, especially when collections are too small to be reliably accessed using bedside techniques. Ultrasound is useful when a pleural fluid collection requires aspiration or when a tissue mass is in contact with the parietal pleura and intervening air is absent.

Needle aspiration or biopsy may be used to evaluate any lesion in the lung, pleura, or mediastinum, especially if it is not visible bronchoscopically and if it is safely accessible using a needle. Clinical circumstances in which needle aspiration or biopsy is commonly used include: (1) a new or enlarging lung nodule seen on chest radiograph or CT scan; (2) multiple nodules noted in a patient with known prior or current malignancy; (3) persistent pulmonary infiltrates or consolidation of unknown cause; (4) a hilar mass with nondiagnostic results on bronchoscopy; and (5) a suspected, but unconfirmed empyema or malignant pleural effusion.

Several relative contraindications to lung biopsy or aspiration are recognized. As with any procedure, risks must be weighed in relation to benefits. The risk of complications is obviously increased in the presence of baseline lung function abnormalities or coagulation defects. Furthermore, patients who plan air travel within 6 weeks of the procedure (possibly increased risk of delayed pneumothorax), prior pneumonectomy, presence of pulmonary arterial or venous hypertension (possibly increased bleeding risk), and lack of patient cooperation (despite administration of conscious sedation) increase the risk. Finally, one absolute contraindication to needle biopsy is a vascular lesion, such as aneurysm or arteriovenous malformation—entities that are usually recognized by careful review of preprocedural imaging studies.

Tools and Techniques

Patient evaluation prior to the biopsy is essential. Published recommendations include that the INR be less than 1.4, platelets greater than 100,000, and recent FEV_1 greater than 35 percent predicted. At our institution, less stringent guidelines for coagulation parameters are used: INR less than 1.5 and platelets greater than 50,000.

The biopsy may be performed using a fine needle (cytopathological evaluation) and/or a cutting needle, the choice of which is based upon operator expertise, availability and expertise of a cytopathologist, and suspicion as to whether the mass is malignant or benign (requiring a confirmatory diagnosis). Coaxial techniques traverse the pleura fewer times than non-coaxial techniques; they may be faster and may carry less risk of pneumothorax.

Results

Fine-needle biopsy has a diagnostic accuracy of 64 to 97 percent. Accuracy is a function of the size of the lesion and on-site availability of a cytopathologist. Sensitivity of a cutting needle biopsy ranges from 74 to 95 percent, and accuracy of a benign diagnosis is improved with use of a cutting, rather than fine, needle. For suspected, but unproved, infections in immunocompromised patients, the diagnostic yield ranges from 73 to 79 percent.

Complications

The most common complications of needle biopsy of thoracic lesions are pneumothorax and hemoptysis. The pneumothorax rate is a function of chest wall thickness, lesion size, and depth of the lesion below the chest wall surface, among other factors. Whether obstructive lung disease affects the risk of pneumothorax is controversial. In one study, patients whose lesions were $\leq$2 cm in diameter had a rate of pneumothorax that was eleven times greater than those whose lesions were >4 cm. Patients with subpleural lesions had four times the rate of pneumothorax as those whose lesions were deeper than 2 cm.

The incidence of pneumothorax ranges from 0 to 60 percent for a fine-needle biopsy (average, 20 percent), with 1.6 to 18 percent (average, 5 percent) requiring a chest tube; the

incidence of pneumothorax is 26 to 54 percent for a cutting needle biopsy, with 3.3 to 15 percent requiring chest tube insertion. Hemorrhage, with or without hemoptysis, occurs in fewer than 10 percent of patients. The risk of bleeding may be ten times higher for lesions deeper than 2 cm from the pleura compared to more superficial abnormalities. Most biopsy-related complications do not have secondary adverse consequences. The death rate from needle biopsy is very low (estimated at 0.02 percent).

Postprocedural Care

The patient should be placed such that the biopsy entry site is in a dependent position for 2 hours, thereby decreasing air leakage as the weight of the lung helps to appose the two pleural layers. A chest radiograph with the patient in an erect position is obtained immediately and 2 hours after the procedure. If no pneumothorax is present, the patient is discharged. If after 2 hours a pneumothorax is present, the chest radiograph is repeated at 4 hours; if the pneumothorax is resolved, or is small and stable, the patient is discharged and asked to return the next day for repeat chest radiography. If the patient is symptomatic, or the pneumothorax is moderate or large or enlarging, a small catheter with a one-way (Heimlich) valve is inserted. The patient may be discharged to return the next day for a chest radiograph and clinical evaluation in which the catheter is clamped for 2 hours. If the pneumothorax has resolved and does not recur after the clamping, the chest tube may be removed.

DRAINAGE OF THORACIC COLLECTIONS

Since the advent of CT, image-guided drainage or aspiration of air or fluid collections in the thorax (lung parenchyma or pleural space) has become increasingly popular. The documented safety and effectiveness of this intervention have made it an alternative to surgical options in many patients. Image-guided aspiration or drainage may be performed for virtually any collection in the thorax.

Empyema and Other Pleural Collections

Annually, approximately 65,000 patients in the United States and United Kingdom (combined) develop empyemas or complicated parapneumonic effusions. Twenty percent of these patients die; the associated health care costs are estimated to approach $500 million.

The early stage of an evolving empyema (stage I), the so-called exudative phase, can usually be treated using medical therapy. The intermediate stage (stage II), or fibrinopurulent phase, requires catheter drainage. The late stage (stage III), or organizing phase, responds less favorably to catheter drainage alone and usually requires lung decortication. In fact, some thoracic surgeons recommend early decortication as initial therapy for stage III empyema.

A comprehensive description of drainage technique is beyond the scope of this chapter, but an initial aggressive approach is recommended. Some investigators recommend early aggressive management of complex empyema with multiple catheter placements (if needed for multiple loculations) and use of fibrinolytic agents (to allow complete drainage of locules and partial debridement of the pleural surface).

Technical success is virtually 100 percent. Clinical success is 70 to 89 percent in previously unviolated empyemas, and 80 percent in those who have had a prior surgically placed chest tube. Most failures occur in stage III empyema (range of success, 11 to 30 percent). Formation of an extensive pleural peel may prevent catheter insertion or cavity collapse. Instillation of fibrinolytics into the pleural cavity may help prevent fibrin deposits and loculations. Clinical success rate ranges from 62 to 100 percent. In one recent, randomized, placebo-controlled trial, the clinical success rate was 82 percent for streptokinase-treated patients (250,000 IU daily) vs. 48 percent for those receiving placebo ($p = 0.01$). In addition, fewer referrals for surgery (9 percent vs. 45 percent; $p = 0.02$) were noted in the treatment group.

Although allergic reactions (nonanaphylactic) to streptokinase have been reported, and concern exists over a potential systemic thrombolytic effect, up to 1.5 million units of streptokinase have been used safely. In addition, urokinase is also effective when compared to saline alone for intrapleural treatment of loculated parapneumonic effusions. Compared with placebo, intrapleural instillation of urokinase is effective in improving chest-tube drainage and the radiographic appearance of the chest; early use of urokinase may be more effective than late use when catheter drainage alone has failed. Comparison of urokinase with streptokinase shows no difference in effectiveness.

Since urokinase is no longer available in the United States, alternative agents have been sought. Tissue plasminogen activator (t-PA) has been shown to be effective in reducing the duration of required chest tube placement in children with complicated parapneumonic effusions (using 4 mg of t-PA in 30 to 50 ml of saline instilled through the chest tube, which is clamped for 1 hour before applying suction to the tube). No adverse events have been noted. One retrospective study suggests that t-PA may be even more effective than urokinase in improving the early radiographic appearance of the chest. In our practice, 10 mg of t-PA in 50 ml of saline is instilled through the chest catheter, followed by 20 ml of a saline "flush." If possible, the patient's position is rotated every 10 min for 1 h before the catheter is connected to suction.

Some theoretical and observed complications of intrapleural fibrinolysis include hemorrhage, allergic reactions, transient chest pain, and promotion of bronchopleural fistula formation. Although, in theory, intrapleural instillation of thrombolytic agents may alter systemic coagulation parameters, many studies have shown that this effect does not

occur. Furthermore, although hemorrhage is also possible, it is rarely observed.

Lung Abscess

Most lung abscesses are successfully treated using medical therapy. However, the mortality rate associated with lung abscess remains high, and ranges from 15 to 20 percent. In 10 to 20 percent of pyogenic lung abscesses, a conservative approach fails, and surgical management (e.g., lobectomy) may be considered. Less invasive approaches, including endoscopic or percutaneous drainage, have been used successfully.

Percutaneous management of lung abscess remains somewhat controversial. In one comprehensive review, the success rate was about 85 percent. The causes for failure included multi-loculation and presence of a thick abscess wall. The procedure complication rate was just under 10 percent. Overall mortality rate related to the abscess was about 5 percent.

Additional studies are needed to establish percutaneous catheter drainage as the standard of care in patients who fail medical therapy. However, the technique is appealing because it results in immediate external drainage of pus without the need for thoracotomy, and it reduces the risk of aspiration of purulent material into the airways. For patients who fail medical therapy (e.g., after 10 to 14 days of treatment) or who have abscesses greater than 4 cm in diameter, and who are not fit for surgical intervention, percutaneous catheter drainage should be considered. Complications of the procedure include empyema, bronchopleural fistula, pneumothorax, hemothorax, intrabronchial hemorrhage, and catheter occlusion.

Lung Cancer

Since the introduction in 1990 of ultrasound-guided thermal ablation of malignant hepatic lesions using radiofrequency electrode needles, open radiofrequency ablation (RFA) and percutaneous RFA under imaging guidance have been increasingly employed. Use of RFA in treatment of renal cell carcinoma and bone and lung tumors has been described more recently, and results are promising. Other thermal ablation methods, including cryoablation and microwave ablation, may also have a future role in management of lung tumors. Adjunctive use of radiotherapy or chemotherapy with RFA is also being explored.

As pulmonary RFA is still considered investigational, delineation of indications for its use is difficult. An "ideal" candidate for RFA is a patient without underlying lung disease whose pulmonary lesion is small (2 to 3 cm), peripheral, and distant from vital intrathoracic structures. However, until evidence supports use of RFA as a primary treatment modality, its value currently lies in treatment of patients who are inoperable because of severe underlying lung disease.

As with many IR-based procedures, application of RFA in treating lung tumors is performed with the patient under moderate sedation. When the patient's cardiopulmonary status is questionable, an anesthesiologist may be consulted to provide a greater level of anesthesia oversight.

Many RFA probes of differing size and design are available (e.g., water-cooled, monopolar, bipolar, or expandable [umbrella-like]) (Fig. 32-1). Each delivers an alternating current, which agitates tissue ions and generates frictional heat, leading to cell death. Any cross-sectional imaging modality may be used in conjunction with RFA; however, due to limitations of ultrasound in imaging air-filled structures, CT is the preferred modality in treatment of lung tumors; MRI may have a niche role.

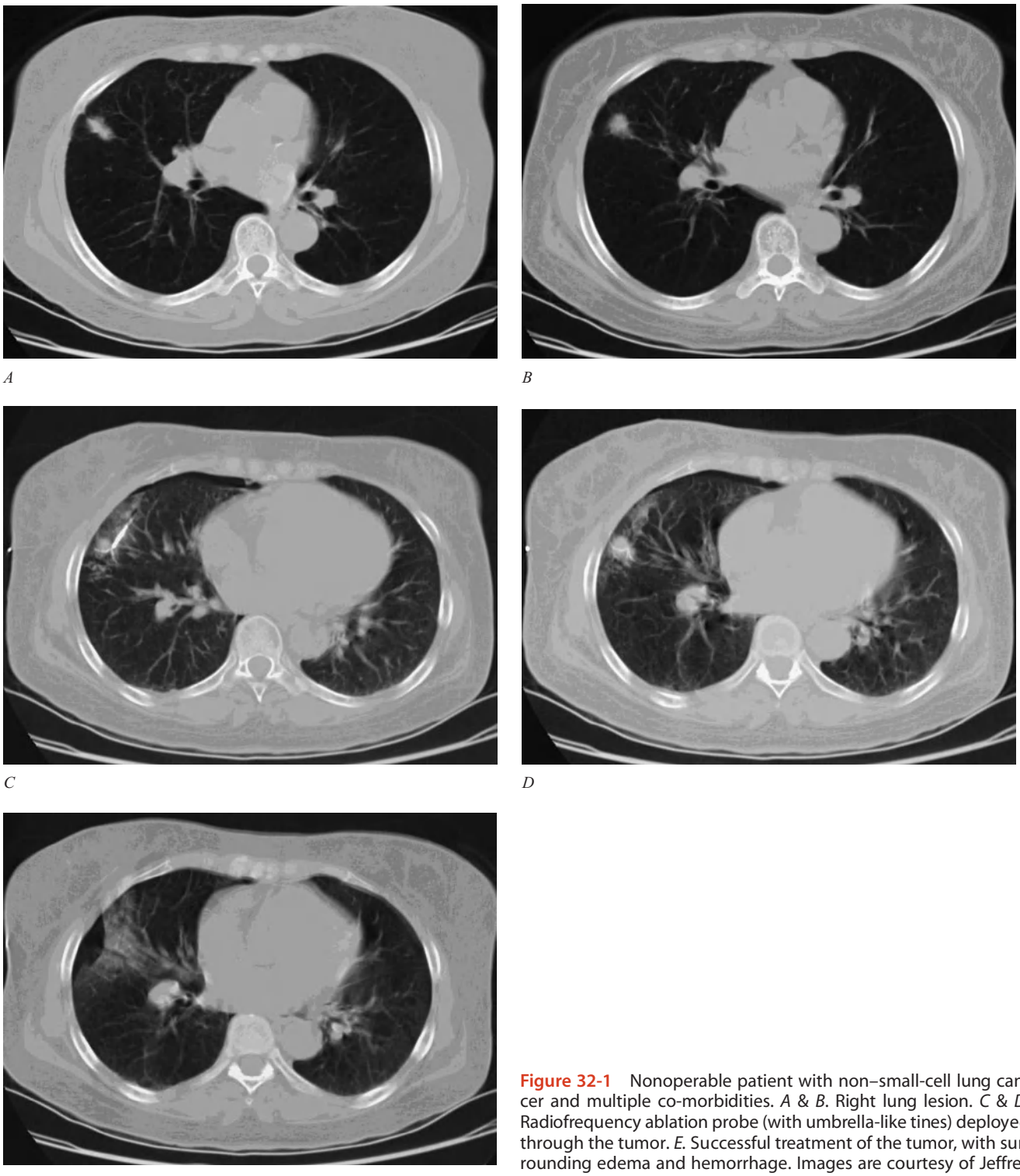
Depending on the tumor size and its proximity to vascular structures, more than one probe or more than one treatment (after probe repositioning) may be needed to achieve complete tumor ablation. The end point for a treatment session may be impedance-based or temperature-based. Although few data about ablation size in human lung cancer are available, some guidance may be derived from extrapolation of findings from a study in which a mean tumor size of 2.2 $\pm$ 0.6 cm was associated with a mean RFA time of 12 min, 9 sec.

According to a recent review of prior studies using RFA in treating primary and secondary lung tumors ranging in size from 0.7 to 12 cm (mean range, 2.7 to 5.2 cm), complete ablation was achieved in 38 to 91 percent. The highest rates of complete ablation were achieved in treatment of small tumors (mean size, 2.0 cm). In a study of 30 patients, most of whom had primary bronchogenic carcinoma, complete ablation was achieved using RFA in all tumors that were less than 3 cm in diameter; mean survival in this group was 19.7 months, more than twice that for tumors greater than 3 cm in diameter, in whom mean survival was 8.7 months.

The complication rate for RFA is similar to that for percutaneous lung biopsy. The rate of pneumothorax is 20 to 40 percent; 10 to 15 percent of patients sustaining a pneumothorax require a chest tube. Other complications include pleurisy, pleural effusion, pulmonary hemorrhage, and productive cough; death has been reported. In patients with large tumors, tumor cavitation and formation of a bronchopulmonary fistula have been reported.

Aspergilloma

Although surgical resection of a symptomatic aspergilloma is definitive, not all affected patients are surgical candidates. Indeed, aspergilloma formation is frequently associated with underlying lung disease, such as chronic obstructive pulmonary disease (COPD), sarcoidosis, lung abscess, tuberculosis, or pulmonary complications related to chronic immunosuppression. In this context, embolization of bronchial arteries has been used as a temporizing measure to control massive hemoptysis (see below). Unfortunately, in the absence of definitive treatment of the aspergilloma, recurrent bleeding is likely. Furthermore, systemic antifungal agents have a limited role in the primary treatment, as they are unable to penetrate the fungal mass. Consequently, intracavitary instillation of antifungal agents has been performed.



A *B*

C *D*

E

Figure 32-1 Nonoperable patient with non–small-cell lung cancer and multiple co-morbidities. *A* & *B*. Right lung lesion. *C* & *D*. Radiofrequency ablation probe (with umbrella-like tines) deployed through the tumor. *E*. Successful treatment of the tumor, with surrounding edema and hemorrhage. Images are courtesy of Jeffrey Solomon, M.D.

Typically, the cavity is accessed under imaging guidance (usually CT imaging), and the antifungal agent (e.g., amphotericin B) is instilled. Liquid-, gelatin-, and paste-based formulations of the agent have been employed. A relative contraindication to performing the technique is endotracheal intubation and limited ability to reposition the patient—circumstances that put the patient at risk for spillage of the therapeutic agent into the airways and related complications.

In one study of 40 patients with aspergillomas who were treated using amphotericin paste to completely fill the cavities, hemoptysis stopped in all; however, adjunctive bronchial artery embolization was required in six. The aspergillomas

resolved and serum tests for *Aspergillus* became negative in 65 percent, although complete disappearance of both the aspergillomas and cavities was observed in only 7.5 percent. In a smaller series, which used a liquid mixture of amphotericin and gelatin that solidified rapidly at body temperature when injected into the cavities, resolution of the aspergillomas was observed in 3 out of 4 patients. In the fourth patient, the aspergilloma decreased in size, but pneumonectomy was required for recurrent hemoptysis.

BRONCHIAL ARTERY EMBOLIZATION

Massive hemoptysis (300 to 600 ml or greater per 24 h) may be due to a wide variety of causes (among the more common are tuberculosis, aspergilloma, bronchiectasis, lung cancer, and a variety of chronic infectious or inflammatory processes) and carries a significant mortality rate (50 to 85 percent) when treated conservatively. Even when pulmonary resectional surgery is undertaken emergently, the mortality rate is 35 to 40 percent. Although definitive therapy is surgical resection of the bleeding source, not all patients are surgical candidates, due to severe underlying lung disease. In these patients, therapeutic arterial embolization plays an important role in mitigating the hemoptysis.

The two major indications for bronchial artery embolization include: (1) palliative therapy for patients who have acute, massive hemoptysis and who are not surgical candidates; and (2) preoperative intervention to stop active bleeding, thereby allowing definitive surgical therapy to be performed electively. A less common, and more controversial, indication is recurrent, moderate hemoptysis for which conservative management in the nonsurgical candidate has clearly failed.

A preoperative chest CT and bronchoscopic evaluation help with lateralization and further localization of the source, which has obvious therapeutic implications. An initial descending thoracic aortogram may also provide useful information. Knowledge of whether nonbronchial arteries supply the region is helpful, particularly in the setting of hemoptysis due to inflammatory processes. In this regard, CT arteriography has recently been shown to be helpful in planning bronchial artery embolization. Failure to embolize these additional vessels may be responsible for early treatment failure. The embolic agent of choice is polyvinyl alcohol particles (usually, 350 to 500 microns in diameter). Use of other microembolic agents has also been described. Although true contrast extravasation at the bleeding site is frequently not observed, detection of abnormal vascularity in an area localized by direct visualization or by imaging should prompt embolization of the branch (Fig. 32-2).

Since the anterior and posterior spinal arteries receive branches from bronchial arteries and some nonbronchial arteries (e.g., intercostals and cervical and thyrocervical trunks), care must be taken to avoid embolization of these branches. An absolute contraindication to performance of the procedure is inability to avoid embolization of these branches, as this may lead to transverse myelitis (see below).

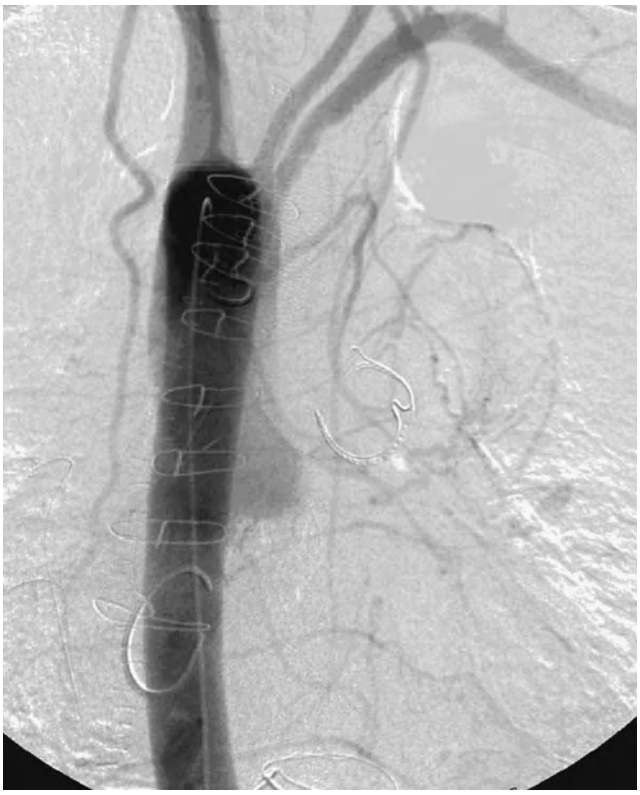
Bronchial artery embolization is initially effective (i.e., during the first month following the procedure) in controlling massive hemoptysis in over 75 percent of patients. However, the long-term success rate is less favorable: 10 to 50 percent of patients experience a recurrence months to years later. If the underlying disease process is not addressed, recurrence of bleeding is not unexpected. Recruitment of additional vessels, recanalization of occluded vessels, incomplete therapeutic embolization, and new bleeding from pulmonary arterial sources (5 percent) contribute to the recurrences.

The most feared complication of bronchial artery embolization is transverse myelitis due to nontarget occlusion of radiculomedullary branches. Transverse myelitis occurs in 1.4 to 6.5 percent of patients undergoing the procedure. Other complications include chest pain (24 to 91 percent), transient dysphagia (0.7 to 18.2 percent), and, rarely, bronchial necrosis, nontarget embolization of abdominal viscera leading to ischemia, pulmonary infarction, and transient cortical blindness due to occipital cortex embolization.

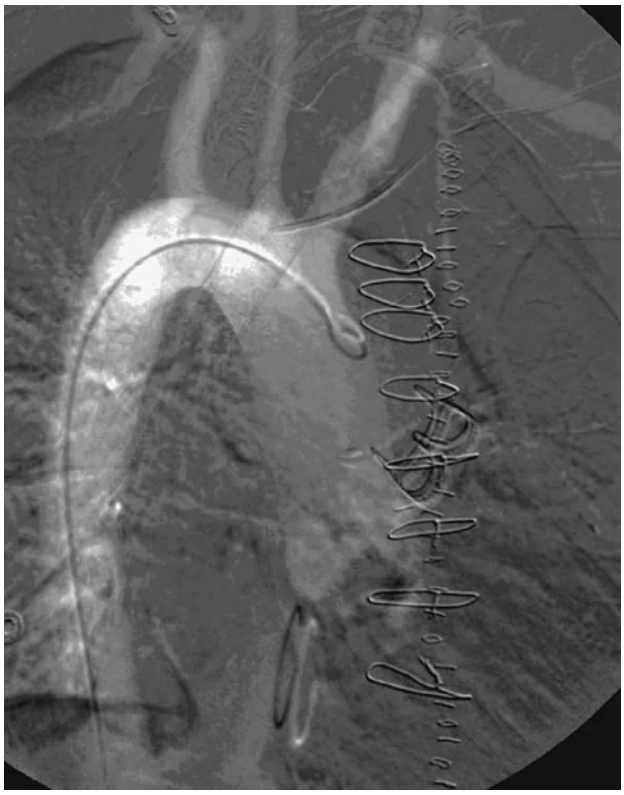
EMBOLIZATION OF PULMONARY ARTERIOVENOUS MALFORMATIONS

Pulmonary arteriovenous malformations (PAVM) are dilated vascular shunts that connect directly the pulmonary artery and pulmonary vein. PAVM occur most often in patients with hereditary hemorrhagic telangiectasia (HHT), a genetic disorder with an autosomal-dominant pattern of inheritance. While the effects of the resultant right-to-left shunt may be transparent and well compensated, paradoxical embolization and vascular rupture are possible. Hence, accurate diagnosis and appropriate treatment are warranted.

Patients who have PAVM identified serendipitously (e.g., during whole-body CT screening or imaging performed for other reasons) should proceed directly to embolization. In addition, they should also be evaluated for HHT, ideally in a center with expertise in the disorder. Patients with HHT and their first-order family members should be screened using contrast (bubble) echocardiography. Those with a positive study should proceed to CT scanning. We prefer high-resolution pulmonary CT angiography with intravenous contrast; however, care must be taken with any intravenous injection in these patients, because of the potential risk of paradoxical embolization of an air bubble through these right-to-left shunts. All patients with identified PAVM should proceed to treatment to prevent the risk of paradoxical emboli, which can result in brain abscess and cerebrovascular events, as well as less common complications, such as hemoptysis. Ideally, PAVM embolization should be performed in centers that regularly perform large numbers of the procedure. Centers devoted to the diagnosis and management of HHT are located



A



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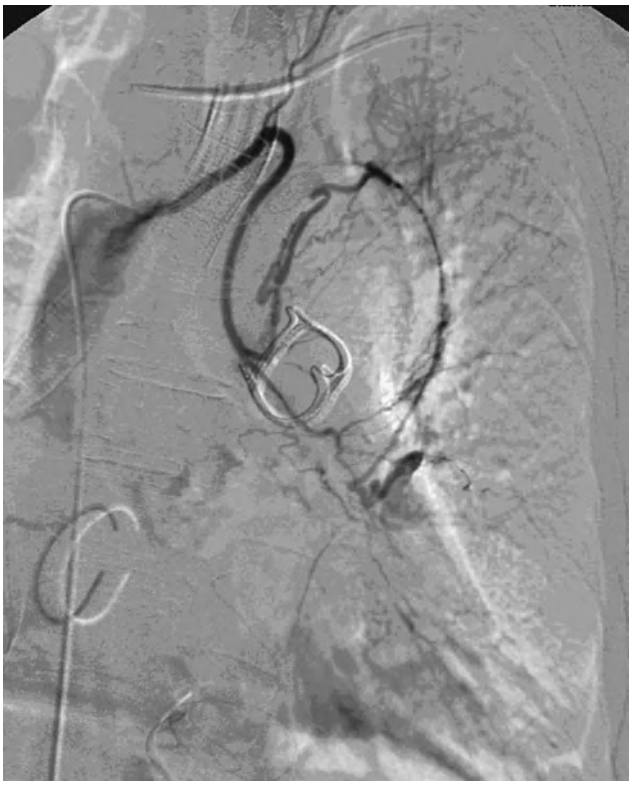

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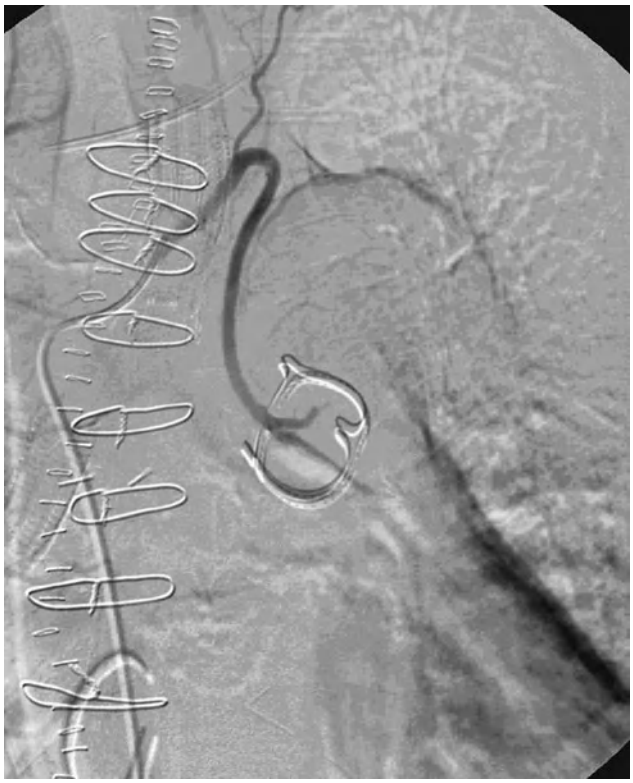


D

Figure 32-2 Patient with tetralogy of Fallot and previous surgical repair who presented with bronchoscopically documented bleeding from the left upper lobe. *A* & *B*. Bronchial arteries supplying left upper lobe are hypertrophied and originate from the concave surface of the aortic arch (rare anatomic variant). *C*. Selective catheterization of bronchial artery. *D*. Disappearance of flow to abnormal area.

throughout the world; 10 such centers are located in North America.

A long-standing recommendation has been to treat only those PAVM with feeding arteries 3 mm and larger in diameter. However, improvements in catheter and imaging technology, coupled with emerging evidence that paradoxical emboli can occur in patients with feeding arteries much smaller than 3 mm, have prompted us to undertake treatment of any readily accessible vessel, including those as small as 1.5 mm in diameter (Fig. 32-3).

Although some interventional radiologists perform the procedure on an inpatient basis, we treat patients on an outpatient basis. Bilateral pulmonary arteriography using digital subtraction technique is performed to create a "roadmap" and to identify PAVM undetected by CT. However, in the era of multislice CT scanning, use of digital subtraction is becoming far less important. After identifying the vessel(s) supplying the PAVM, each lesion is treated by embolization of the feeding artery, usually using stainless steel or platinum coils, although many other devices have been described, including detachable balloons and nitinol plugs (Fig. 32-4).

The technical success rate for the procedure is 88 to 100 percent. Although shunt fraction remains abnormal in 60 to 100 percent of patients, improvement in dyspnea (in previously symptomatic patients) or hypoxia is frequently noted. Small lesions have a potential for growth and should be evaluated by CT scanning every 5 years. Despite embolization of visible PAVM in patients with HHT, other subclinical lesions account for persistent right-to-left shunting; the contrast echocardiogram remains positive in most patients following PAVM embolization. Thus, patients should receive prophylaxis for endocarditis for life. In patients without HHT who have a solitary PAVM, follow-up CT scanning and endocarditis prophylaxis may not be necessary.

Although bronchial artery embolization is safe, complications can arise, including pleurisy (with fever and occasional pulmonary infarction), nontarget embolization, and stroke. Pleurisy is noted in 3 to 16 percent of patients within the first few days following the procedure. Delayed pleurisy is noted in up to 5 percent of patients; it responds well to nonsteroidal anti-inflammatory agents. If a superimposed infection is suspected, a course of antibiotics may be needed. The most feared complications of PAVM embolization are nontarget embolization and stroke; fortunately, these are rare (less than 1 percent) when the procedure is performed by experienced interventional radiologists.

VENOUS PERCUTANEOUS TRANSLUMINAL ANGIOPLASTY AND STENTING

Obstruction of the superior vena cava (SVC), brachiocephalic vein, or subclavian vein may be caused by benign or malignant conditions. Inflammatory lesions, radiation, and trauma sometimes result in scarring, causing venous obstruction. Chronic central venous access devices also may lead to thrombosis or occlusion. Tumors may cause obstruction via direct invasion or external compression. Since the surgery required for symptomatic central venous obstruction is very invasive and, at times, not possible, endovascular management using stent placement or percutaneous transluminal angioplasty (PTA) has become a standard mode of treatment. (The treatment of benign venous stenosis or occlusion is not discussed here.)

In the case of malignant obstruction of the SVC and its tributaries, treatment using endovascular techniques, in particular stent placement coupled with balloon angioplasty, is commonly employed. In SVC or brachiocephalic vein occlusion due to primary or metastatic malignant tumors (e.g., primary lung cancer, lymphoma, or malignant adenopathy), the vessel should be stented primarily and angioplasty performed. Increasing evidence supports the use of early stenting in symptomatic malignant occlusion of the SVC as safe and effective in achieving rapid improvement in symptoms.

Relative contraindications to performing the procedure are extensive peripheral thrombosis and low cardiopulmonary reserve. Patients must be able to lie flat, and in patients with SVC syndrome, this occasionally precludes percutaneous management or creates the need for general anesthesia. Preoperative imaging using magnetic resonance venography (MRV) or CT venography of the central veins may be used to plan the approach and technique. Ultrasound imaging is not adequate for evaluation of the central veins.

The clinical success rate after recanalization of central veins is 68 to 100 percent. Most symptoms, including face, neck, and upper limb edema, resolve in 1 to 4 days—far faster than with radiation therapy. A small retrospective study in patients with non–small-cell lung cancer showed that stent placement achieved more rapid symptomatic relief and more frequent complete resolution of SVC obstruction than did radiation therapy.

Compared to alternatives such as no treatment, radiation, or chemotherapy, complications of stent placement and PTA are relatively uncommon and minor. Major complications, such as stent misplacement or migration, transient cardiac arrhythmias, pulmonary embolization, venous rupture, hemomediastinum, and pulmonary edema, are uncommon.

INTRAVASCULAR FOREIGN BODY RETRIEVAL

For decades, interventional radiologists have employed techniques for intravascular foreign body retrieval. A variety of instruments, including catheters, tip-deflecting wires, snares, baskets, and forceps, used alone or in combination, has been

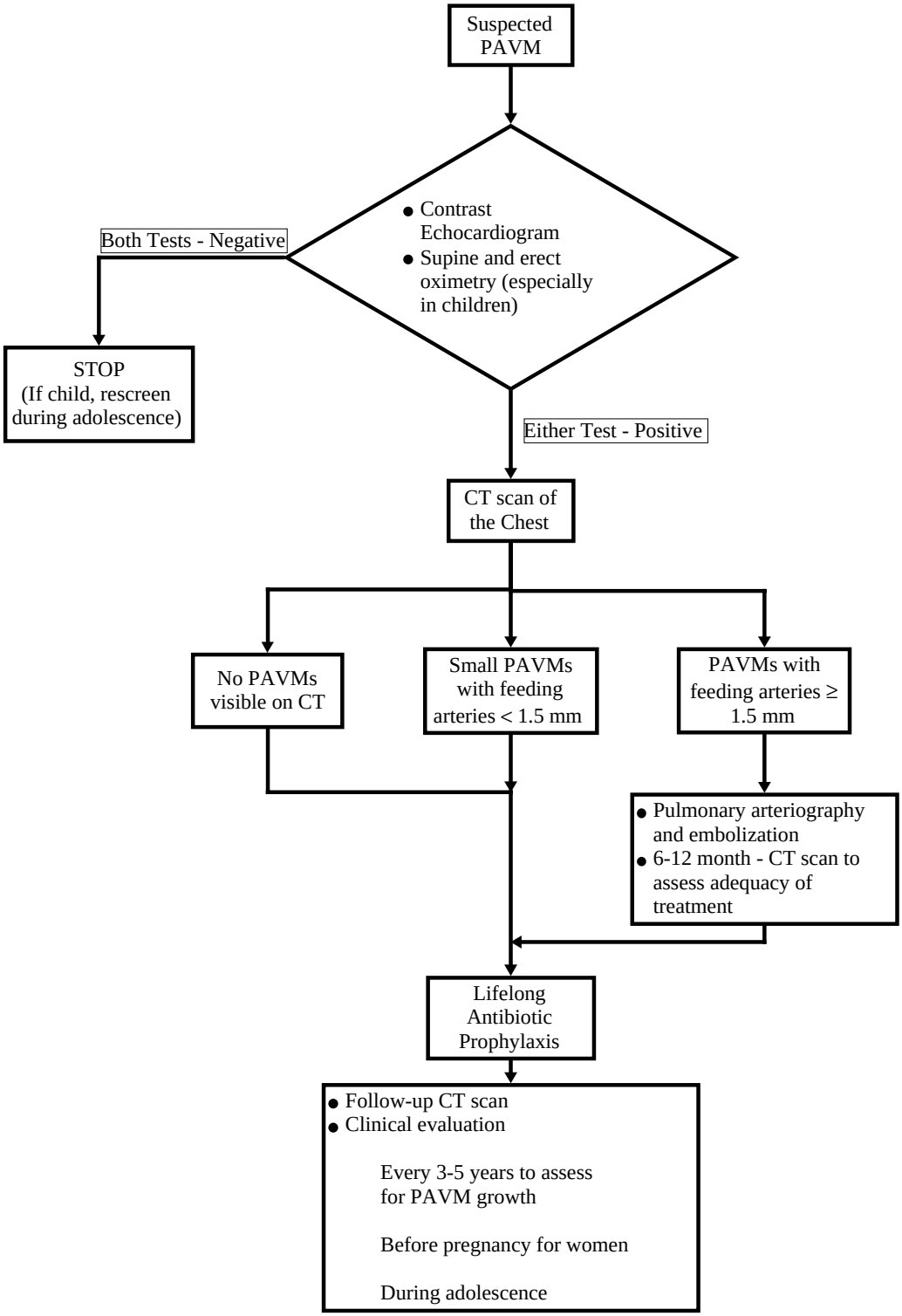
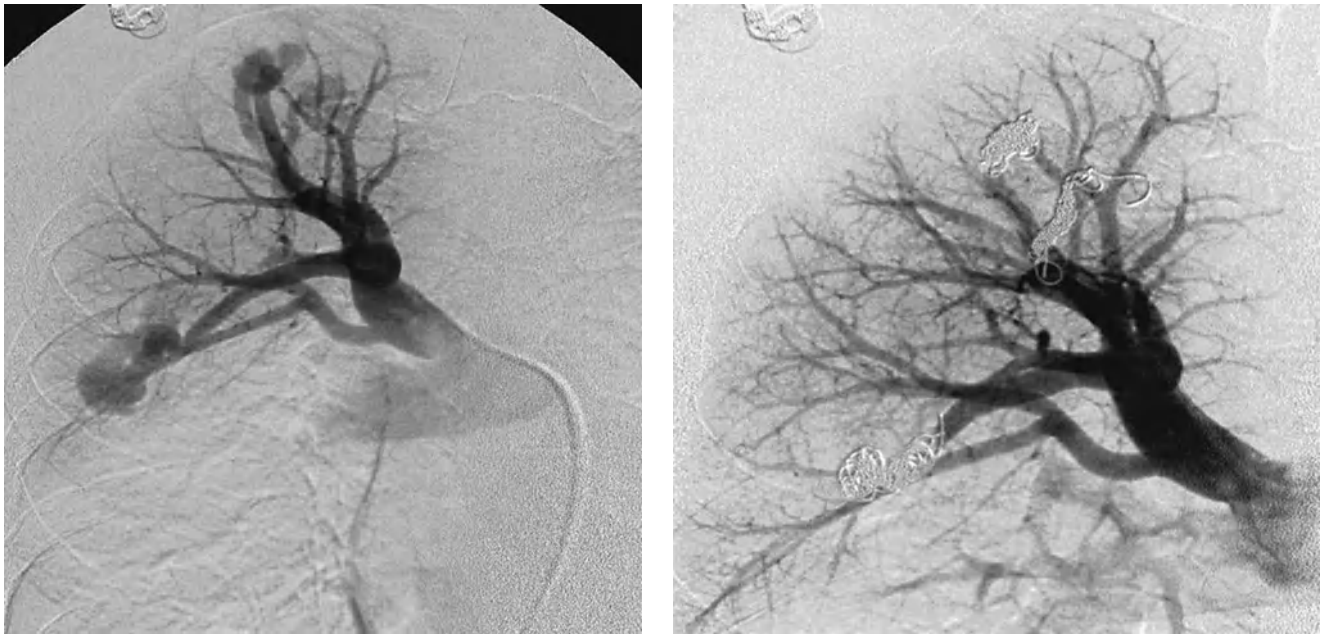


Figure 32-3 Management algorithm for patients with suspected pulmonary arteriovenous malformations (PAVM). (*Modified version of the algorithm from Pollack JS, White RI, Jr: Pulmonary arteriovenous malformation, in Baum S, Pentecost MJ (eds): Abrams Angiography, Interventional Radiology, 2nd ed. Philadelphia, Lippincott Williams & Wilkins, 2006, p 935.*)



A *B*

Figure 32-4 *A.* Pulmonary arteriovenous malformations (PAVM) in the right lung. At least three PAVM are visible. *B.* Embolization using soft platinum coils. Note that shunting through the PAVM is eliminated, but very little of the surrounding lung parenchyma has been sacrificed.

applied to percutaneous foreign body retrieval from the venous system and hollow organs. These procedures constitute the standard of care for most intravascular foreign body retrievals (Fig. 32-5).

THORACIC DUCT EMBOLIZATION

Iatrogenic chylothorax (incidence, 0.1 to 0.4 percent), in which the daily output of chyle may exceed 1000 ml, is a serious complication of thoracic surgery. The problem can be controlled by direct ligation of the thoracic duct (TD). However, since surgical intervention carries a significant mortality rate (11.8 to 16 percent), application of percutaneous methods has been sought.

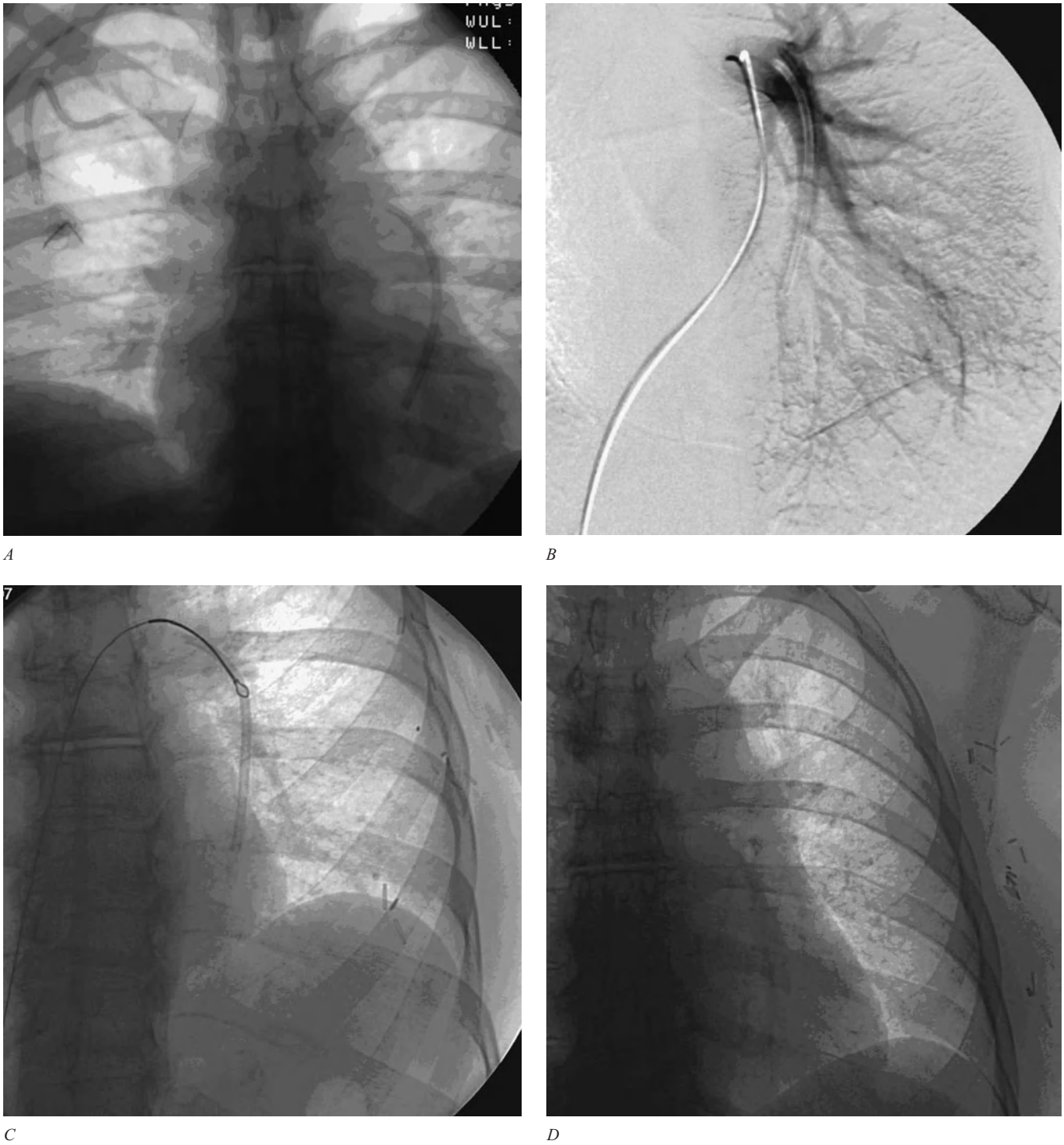
TD ligation is commonly used to treat high-output chylothorax or chylous pleural effusions if there is no improvement after 1 to 2 weeks of conservative management, including implementation of a low-fat diet or total parenteral nutrition, administration of somatostatin, and chest tube drainage. As patients lose chyle over this time, the combined loss of fluid, proteins, lipids, electrolytes, and T lymphocytes leads to malnutrition, increased susceptibility to infection, and increased operative risk. Under these circumstances, TD embolization should be considered as an initial alternative to surgical TD ligation.

Percutaneous transabdominal catheter-directed embolization or needle disruption of retroperitoneal lymphatics is effective and minimally invasive. In one series of 42 patients with chylothorax due to a variety of etiologies, treatment with percutaneous TD embolization using microcoils, particles, glue, or lymphatic collateral disruption resulted in a partial or complete response rate in 3 to 6 weeks of 74 percent. The procedure carries a minimal risk of serious complication or death; however, as the frequency with which the procedure is performed increases, the complication rate will likely grow (Fig. 32-6). The technique is not suitable for treating chylothorax resulting from malignancy.

PULMONARY ARTERY THROMBECTOMY

Traditional therapies for pulmonary embolism include anticoagulation, systemic thrombolysis, and surgical thrombectomy. More recently, endovascular techniques, such as catheter-directed thrombolysis, mechanical thrombolysis (clot fragmentation), and embolectomy have been described. These may be used in conjunction with pulmonary artery stent placement. However, the precise role of these more aggressive approaches is very controversial.

Use of a Greenfield thrombectomy device in major pulmonary embolism has been shown to improve cardiac output and carries a success rate of 91 percent. Although small, nonrandomized trials and case reports have described the utility of catheter-directed mechanical clot fragmentation or extraction, no randomized trials of systemic thrombolysis vs. surgical or catheter-based techniques for treatment of pulmonary embolism have been published.

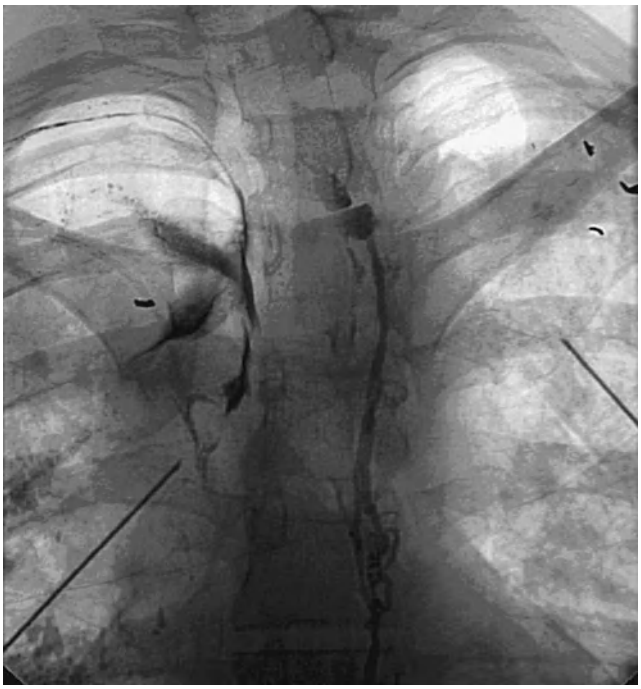


A *B*

C *D*

Figure 32-5 *A.* Surgically placed subclavian port on the left. Note the broken catheter fragment overlying the left pulmonary artery. *B.* Following selective catheterization using femoral approach, the pulmonary arteriogram shows patency of the artery. *C.* "Gooseneck" snare used to engage and capture the catheter. *D.* The catheter fragment has been removed through a common femoral vein sheath.

In a small, multicenter trial of 34 patients with pulmonary embolism who were given either intravenous or intrapulmonary t-PA infusions, neither approach demonstrated a clear advantage over the other. Frequently, comorbid conditions make open surgical thrombectomy or thrombolytic therapy in these usually critically ill patients untenable. Under the circumstances, percutaneous thrombectomy and thrombolysis remain options. Treatment of pulmonary embolism is discussed in detail in Chapter 82.



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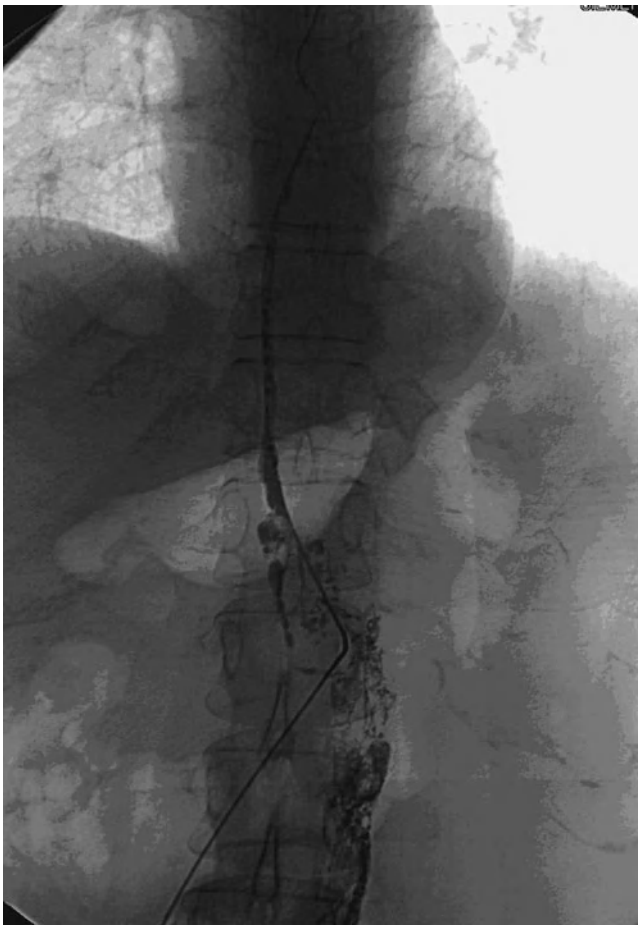

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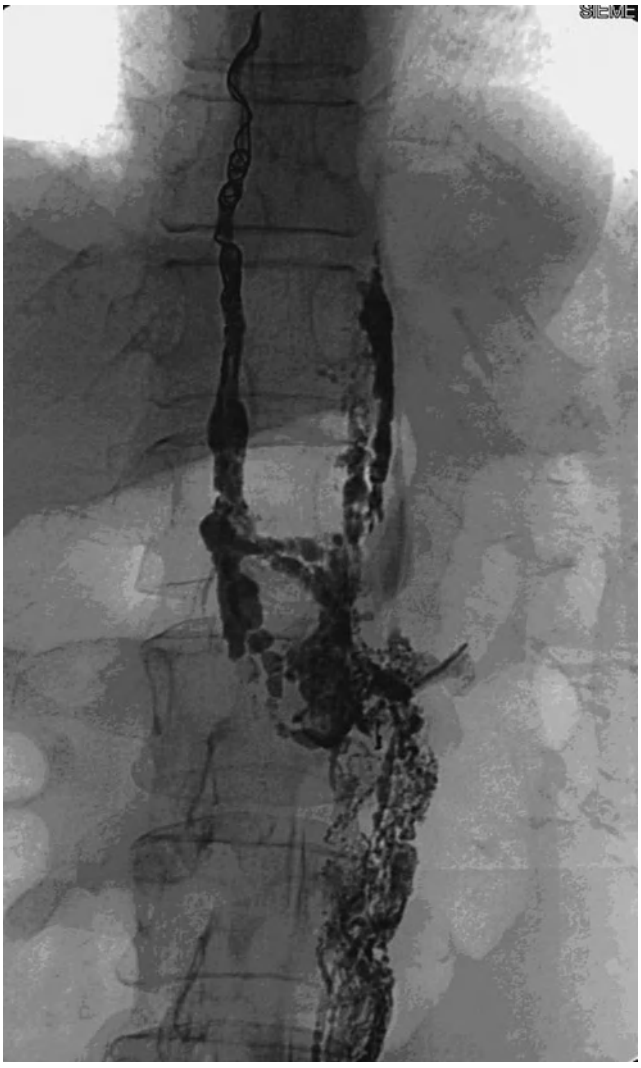

C

Figure 32-6 Gunshot wound to thorax resulting in thoracic duct injury and massive chylothorax. *A.* Lymphangiogram shows contrast leakage just above the left sternoclavicular joint. *B.* Cisterna chyli at L1 level shown in a patient different from the one shown in *A*. Lymphatic access achieved via one of the cisterna chyli's tributaries. *C.* Successful embolization of thoracic duct using platinum microcoils and cyanoacrylate glue. Images are courtesy of Maxim Itkin, M.D. and Andrew Kwak, M.D.

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33

Scintigraphic Evaluation of Pulmonary Disease

Abass Alavi • Daniel Worsley • Ghassan El-Haddad

Use of radiopharmaceuticals has made it possible to assess regional pulmonary function in a variety of pulmonary disorders. In 1955, ^{133}Xe was introduced for the study of regional ventilation. Shortly thereafter, it became possible to evaluate regional pulmonary blood flow using $^{15}CO_2$ by inspiration or ^{135}Xe by injection. In 1964, intravenous injection of ^{133}I-macroaggregated albumin made it feasible to obtain perfusion scans of the lungs. Although these techniques rapidly gained wide acceptance as tests of regional abnormalities in ventilation and pulmonary blood flow, the main practical application has been in the diagnostic evaluation of patients with suspected pulmonary embolism. Increasingly, the role of nuclear medicine in respiratory medicine has been expanded to include disorders such as preoperative assessment of lung function, inflammatory lung disease, and lung cancer. The more widespread availability of positron emission tomography (PET) and integrated PET/CT (computed tomography) has provided powerful tools to aid in the

diagnosis, staging, and management of patients with lung cancer.

RADIOPHARMACEUTICALS AND TECHNIQUES IN VENTILATION-PERFUSION LUNG SCANNING

Clinical application of perfusion lung scanning was first described in 1964, when iodine 131–labeled macroaggregates of albumin was utilized in the evaluation of pulmonary perfusion. Currently, the agents of choice for pulmonary perfusion imaging are technetium 99m–labeled human albumin microspheres (^{99m}Tc HAM) and macroaggregated albumin (^{99m}Tc MAA). ^{99m}Tc MAA particles range in size from 10 to 150 μm; however, more than 90 percent of injected particles measure between 10 and 90 μm. ^{99m}Tc HAM particles are relatively uniform in size and range between 35 and 60 μm. However, ^{99m}Tc MAA is considered the agent of choice for routine perfusion lung scanning because of its availability, short residence time in the lungs, and relatively low cost.

Radiolabeled particles are injected intravenously while the patient is in the supine position, thereby limiting the effect of gravity on regional pulmonary arterial blood flow. Following the administration of ^{99m}Tc MAA, particles are mixed uniformly with the blood that is flowing to the heart; the particles then lodge in precapillary arterioles in the lungs. The usual administered dose of radioactivity is between 74 and 148 MBq (2 to 4 mCi).

The distribution of particles in the lungs is proportional to regional pulmonary blood flow at the time of injection. Approximately 200,000 to 500,000 particles are injected during a routine clinical perfusion lung scan. The normal adult human lung contains approximately 300 million precapillary arterioles and 300 billion capillaries. Therefore, only about 0.1 percent of precapillary arterioles are blocked following the procedure. In addition, the blockage of pulmonary precapillary arterioles by ^{99m}Tc MAA is transient; the biologic half-life in the lung ranges between 2 and 6 h. In pediatric patients and patients with suspected or known right-to-left shunts, pulmonary hypertension, prior pneumonectomy, or a single lung transplant, the number of particles injected should be reduced. A minimum of 60,000 particles is required to obtain an even distribution of activity within the pulmonary arterial circulation and avoid potential false-positive interpretations. We routinely inject 100,000 and 200,000 particles of Tc-99m MAA when performing perfusion scintigraphy in patients with known pulmonary hypertension or in patients who have undergone single lung transplantation. Animal studies have demonstrated that perfusion imaging will detect greater than 95 percent of emboli that completely occlude pulmonary arterial vessels greater than 2 mm in diameter. A routine perfusion scan should include at least six views of the lungs; anterior, posterior, right and left lateral, and right and left posterior oblique views (Fig. 33-1). Right and left anterior oblique views may be helpful in selected cases. In spite of imaging in multiple projections, the perfusion scan may underestimate perfusion abnormalities. A solitary segmental perfusion defect within the medial basal segment of the

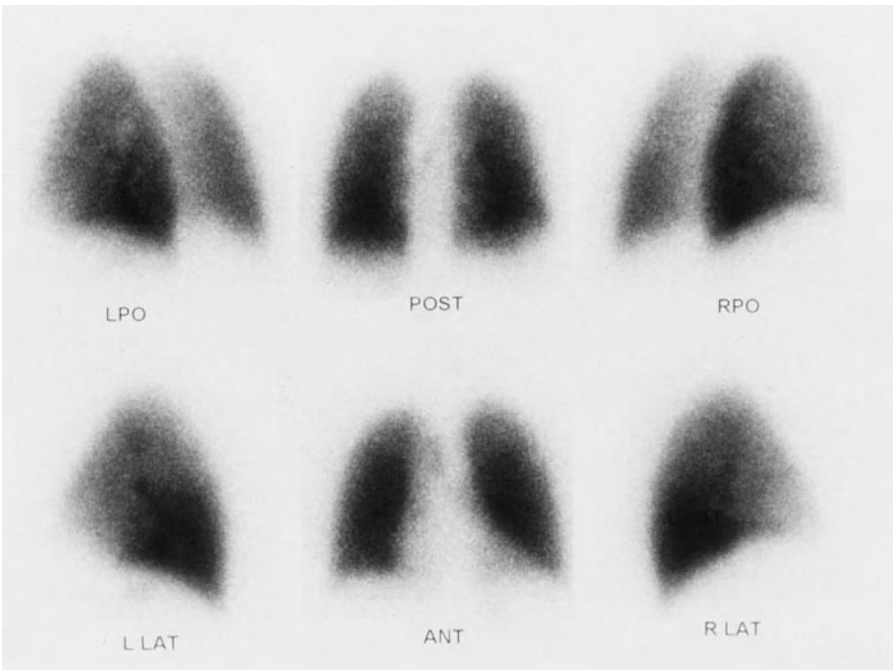


Figure 33-1 Normal perfusion scan using ^{99m}Tc MAA. The distribution of particles is uniform, with a minimum gradient of activity from lung apex to base. The six views (left posterior oblique, posterior, right posterior oblique, right anterior oblique, anterior, left anterior oblique) shown correspond to those shown in subsequent figures.

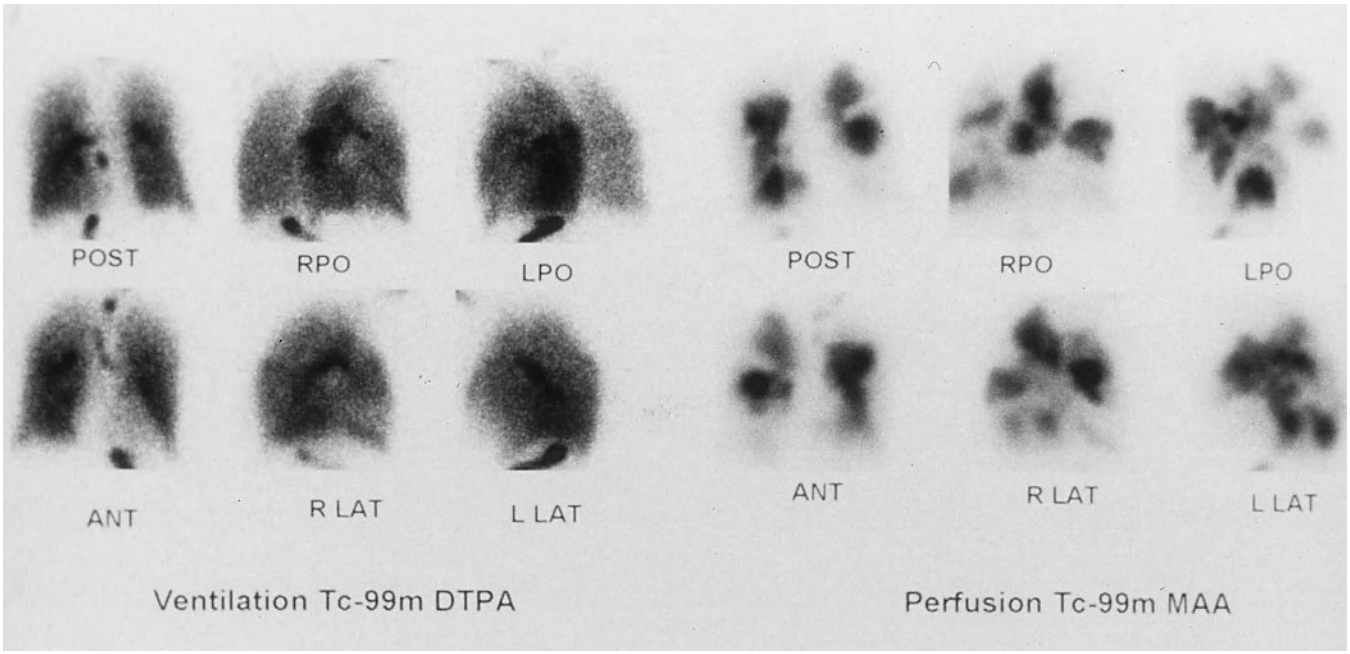


Figure 33-2 High-probability scan for pulmonary embolism. Ventilation scan utilizing ^{99m}Tc DTPA aerosol is within normal limits. Perfusion scan shows large segmental defects in both lungs. This combination of findings is most consistent with pulmonary embolism.

right lower lobe is completely surrounded by normal lung. Consequently, a perfusion defect in this segment will not be detected on planar perfusion imaging.

Perfusion lung scans are routinely utilized to examine patients with suspected pulmonary embolism. Unfortunately, perfusion imaging is sensitive, but not specific, for diagnosing pulmonary embolism. Virtually all lung diseases (including tumors, infections, asthma, and chronic obstructive pulmonary disease) may cause decreased pulmonary arterial blood flow in the affected lung zones. Therefore, combined use of perfusion and ventilation studies can improve the diagnostic specificity of lung scanning for pulmonary embolism. Pulmonary embolism almost always causes abnormal perfusion, while ventilation is preserved *(mismatched defects)* (Fig. 33-2). In contrast, in parenchymal pulmonary disorders, decreased ventilation and perfusion are noted in the same lung region *(matched defects)*. Conditions in which the ventilation abnormality may appear larger than the perfusion abnormality *(reverse mismatch)* include airway obstruction, mucus plug, atelectasis, and pneumonia (Fig. 33-3). Patients with metabolic alkalosis or patients treated with inhaled albuterol fail to respond to hypoxic insults by vasoconstriction and may demonstrate reverse mismatch (perfusion of poorly ventilated sites) on ventilation-perfusion scans.

^{133}Xe has been widely used to determine regional ventilation in the lungs. However, other tracers, such as xenon 127, krypton 81m, and, recently, the technetium 99m–labeled aerosols—Technegas and Pertechnegas—are utilized for this purpose. Studies that compare various ventilation agents are limited; however, based on the data available, there appear to be no major differences with regard to diagnostic yield among various radiopharmaceuticals.

Utilizing a closed breathing system and ^{133}Xe, the first inspiration image demonstrates regional ventilation in major airway systems (Fig. 33-4). Equilibrium images are obtained while the patient rebreathes the gas for several minutes. Regions of the lung that appear to ventilate poorly in the initial

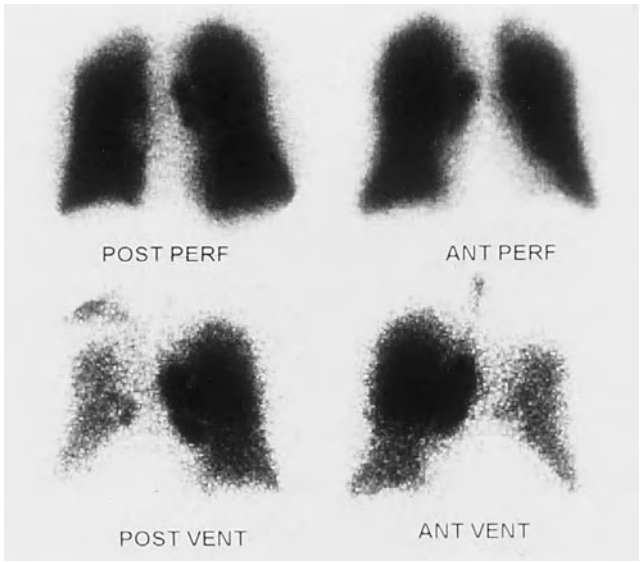


Figure 33-3 Reverse ventilation-perfusion mismatch. Posterior and anterior perfusion scans appear within normal limits (upper row). Posterior and anterior aerosol ventilation scans show significantly reduced perfusion in the left lung.

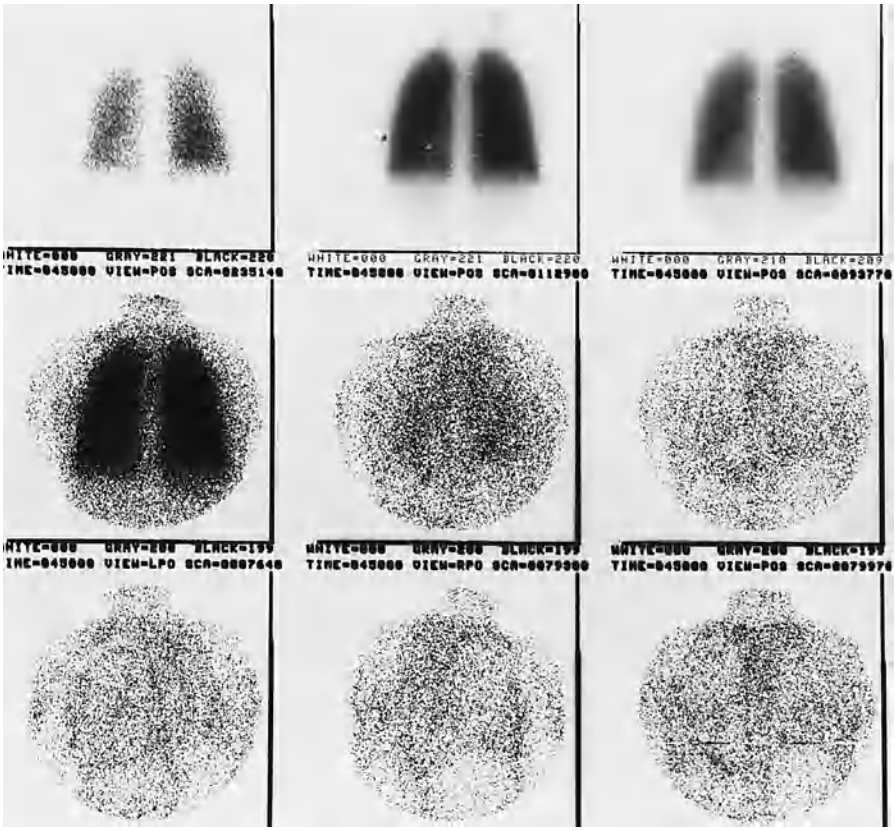


Figure 33-4 Normal ventilation scan using ^{133}Xe. The distribution of gas is uniform during the wash-in and equilibrium-phase images (left to right in upper row). During the washout phase, the radioisotope is rapidly cleared from both lungs (lower-row images). Ventilation images were obtained in the posterior projection.

image may fill in the equilibrium phase of the study because of collateral air drift. During the washout phase, while the patient inspires room air, areas of poor ventilation are detected as focal spots of gas retention on the image. Diagnostic yield from the ventilation-perfusion scan is significantly higher if studies are performed in the erect, rather than supine, position. Generally, for technical reasons (lower energy of gamma radiation of ^{133}Xe compared to ^{99m}Tc), ventilation images with ^{133}Xe are obtained before perfusion imaging.

The imaging technique for ^{127}Xe is similar to that for ^{133}Xe. However, because ^{127}Xe has a higher energy than ^{99m}Tc, ventilation scanning with ^{127}Xe can be performed following perfusion imaging. The advantages of acquiring ventilation imaging following perfusion studies are that the patient can be positioned so ventilation to the areas of the lungs that reveal the greatest perfusion abnormality can be imaged with optimal detail and ventilation imaging may be avoided altogether in selected cases when the perfusion lung scan appears normal.

However, ^{127}Xe scanning has several disadvantages. It is more costly than ^{133}Xe and requires medium energy collimation, which degrades image resolution. With either ^{133}Xe or ^{127}Xe, images can be obtained only in a limited number of views—in contrast to perfusion images, which are obtained in multiple projections.

Krypton 81m is a noble gas that can be used to evaluate regional ventilation. This radioactive gas has a very short physical half-life (13 s), and images acquired with this agent reveal ventilation to major airway systems only. However, the short physical half-life of ^{81m}Kr allows generation of images of the lungs in multiple projections. ^{81m}Kr is produced from a rubidium 81 generator. The parent radionuclide has a physical half-life of 4.7 h, which limits the useful lifetime of the generator to only 1 day. As with ^{127}Xe ventilation studies, imaging with ^{81m}Kr is generally performed following the perfusion scan.

Technetium-labeled aerosol studies can be performed following the inhalation of several preparations, including ^{99m}Tc DTPA (diethylene triamine penta-acetic acid), ^{99m}Tc sulfur colloid, ^{99m}Tc pyrophosphate, ^{99m}Tc MDP (methylene diphosphate), and ^{99m}Tc glucoheptanate. The most popular is ^{99m}Tc DTPA. However, this agent has a relatively short residence time within the lung, especially in smokers. In such patients, use of ^{99m}Tc-labeled sulfur colloid or pyrophosphate may be more appropriate. ^{99m}Tc-labeled radioaerosols have particles between 0.5 and 3 μm in size and are produced by utilizing commercially available nebulizers. The patient generally breathes from the nebulizer for 3 to 5 min or until 37 MBq (1 mCi) of radioactivity is deposited in the lungs. The regional distribution of radioactivity in the lungs is

proportional to local ventilation. ^{99m}Tc-labeled radioaerosol studies are generally performed before perfusion imaging. The lungs are imaged in multiple projections, which correspond to those obtained during the subsequent perfusion study. Ventilation studies using ^{99m}Tc-labeled radioaerosols require minimal patient cooperation and can be performed at the bedside and on patients who are on ventilators. Disadvantages of ^{99m}Tc-labeled radioaerosols include the central deposition of radioactivity in patients with chronic obstructive pulmonary disease (COPD) or airway obstruction and the need to dispose of the substantial unused amount of radioactivity that is deposited in the nebulizer.

Central deposition of ^{99m}Tc-labeled radioaerosol in patients with COPD is a major drawback to the use of aerosol agents, and newer agents have been developed to overcome this deficiency, including ^{99m}Tc Technegas and ^{99m}Tc Pertechnegas. These agents are generated by burning ^{99m}Tc pertechnetate in a carbon crucible at very high temperatures, which produces an ultrafine radiolabeled aerosol (particle size, 0.02 to 0.2 μm). Pertechnegas is purged with 5 percent oxygen and 95 percent argon; Technegas is purged with 100 percent argon. This relatively minor change in production of the final preparation causes profound differences in the biologic behavior of particles generated. When inhaled, both agents distribute homogeneously in the lung in proportion to regional ventilation and with very minimal central deposition, even in patients with COPD. Pertechnegas readily penetrates the alveolar epithelial membrane; therefore, its biologic half-life in the lungs is quite short (approximately 6 to 10 min). On the other hand, very little transalveolar or mucociliary clearance is seen with Technegas; thus, residence time in the lung is approximately equal to the physical half-life of ^{99m}Tc (6 h). Both agents require minimal patient cooperation, and only two or three breaths are required to obtain sufficient deposition in the lungs for optimal ventilation imaging. In general, ventilation imaging with both Technegas and Pertechnegas is performed before perfusion imaging. As with ^{99m}Tc-radiolabeled aerosols, multiple views of the lungs corresponding to those acquired during perfusion imaging can be generated with these preparations.

More recently, considerable interest has arisen in imaging based upon antibody fragments and radiolabeled peptides directed against GP IIb/IIIa receptors on the surface of activated platelets. Tc-99m Acutetec, a labeled synthetic peptide which binds to the GP IIb/IIIa receptors, has been used for evaluation of patients with suspected deep venous thrombosis (DVT). The main advantage of the agent is its ability to distinguish between acute and chronic DVT.

Several ^{99m}Tc labeled peptides directed against activated platelets are currently under investigation in evaluation of patients with suspected pulmonary embolism. Radiolabeled peptide imaging has the potential to serve as a single, comprehensive modality in the evaluation of patients with venous thromboembolism. However, at the current time, further studies and development of newer radiopharmaceuticals are required to fully realize this potential.

LUNG SCANNING IN THE DIAGNOSIS OF ACUTE PULMONARY EMBOLISM

Pulmonary embolism (PE) is a common and potentially fatal disorder for which treatment is highly effective in decreasing mortality and morbidity if initiated soon after the event. The accurate and expeditious diagnosis of acute PE can be difficult because of the nonspecificity of clinical, laboratory, and radiographic findings. Approximately 10 percent of patients with PE die within 1 h of the event. For patients who survive beyond the first hour, anticoagulation with heparin or thrombolysis with thrombolytic agents is effective therapy. The mortality in patients with PE who are not treated is as high as 30 percent. In contrast, correct diagnosis and appropriate therapy significantly lower mortality to between 1 and 10 percent.

Although anticoagulant therapy is effective in treating PE and reducing mortality, it is not without risks. The prevalence of major hemorrhagic complications among patients receiving anticoagulant therapy has been reported to be as high as 10 to 15 percent. Therefore, accurate diagnosis of PE is essential, not only to prevent death from recurrent embolism, but also to avoid complications related to unnecessary anticoagulant therapy.

Ventilation-perfusion lung imaging has been shown to be a safe, noninvasive technique in evaluating regional pulmonary function undertaken for a variety of purposes. The technique has been widely used in the assessment of patients with suspected PE. In spite of its proven value in the management of patients with PE and availability of studies suggesting the underdiagnosis of PE, critics have suggested that this powerful method has been overutilized and that it has had a minimal impact on patient outcome.

The first major study that utilized perfusion lung scanning as a screening test for the diagnosis of PE was the Urokinase Pulmonary Embolism Trial (UPET). In more than 90 percent of patients enrolled in the trial, perfusion lung scanning was performed following intravenous administration of ^{131}I-labeled MAA. Since lung imaging was carried out using rectilinear scanners, ventilation studies were not performed during the study. Despite utilizing a suboptimal radiopharmaceutical and imaging equipment, the UPET study established perfusion lung scanning as an effective technique in both screening for PE and assessing restoration of pulmonary blood flow following an embolic event.

Most patients with acute PE either completely lyse the thrombi or partly recanalize the pulmonary artery clots. In UPET, approximately 75 to 80 percent of perfusion defects resolved by 3 months, and those that did not remained largely persistent when followed for 1 year. The degree of clot resolution observed in UPET may represent an underestimate, since ventilation scanning was not performed, and many of the unresolved perfusion defects might have been due to preexisting chronic obstructive pulmonary disease. The defect size at 7 to 10 days following the initiation of therapy was a good predictor of defect size at 6 months. In an American College

of Chest Physicians consensus statement, the recommendation is performance of a follow-up ventilation-perfusion lung scan at 3 months following the initial diagnosis to evaluate clot resolution and serve as a baseline for future comparisons. If patients are unable to return in 3 months, a scan at discharge or 7 days following initiation of anticoagulant therapy may also be useful.

Data from multiple prospective and large, outcome-based studies have reported on the efficacy of ventilation-perfusion scanning in patients suspected of having acute PE and have been recently reviewed.

One prospective study, designed to determine if anticoagulation could be safely withheld in patients with adequate cardiorespiratory reserve who did not have high probability ventilation-perfusion scans or proximal venous thrombosis (as determined by serial impedance plethysmography [IPG]), underscored the pathophysiological concept that venous thromboembolism is a systemic disease, and that pulmonary embolism is merely the respiratory manifestation of the disorder. A total of 874 patients suspected of having PE were enrolled. Ventilation-perfusion lung scan interpretations were classified as normal (36 percent), non–high probability (56 percent), or high probability (8 percent) studies. Forty-seven percent had non–high probability scans and adequate cardiorespiratory reserve, while nine percent had non–high probability scans and inadequate cardiorespiratory reserve (pulmonary edema, right ventricular failure, systolic blood pressure less than 90 mmHg, syncope, acute tachyarrhythmia, or severely abnormal spirometry or arterial blood gases). During a 3-month follow-up period in which patients with non-high probability lung scans, adequate cardiorespiratory reserve, and negative serial IPG studies had anticoagulants withheld, only 2.7 percent had evidence of venous thromboembolism. The conclusion was that selected patients could be managed safely without anticoagulation, confirming findings from previous studies suggesting that the incidence of recurrent PE is very low in the absence of proximal lower extremity venous thrombus. Unfortunately, the criteria used to categorize the probability of PE (normal, nondiagnostic, or high) were different than those used in the Prospective Investigation of Pulmonary Embolism Diagnosis (PIOPED) study, and direct comparison of the two studies is not possible.

In another prospective study of over 1500 consecutive patients with suspected pulmonary embolism who underwent ventilation-perfusion scanning and IPG of the lower extremities, 40 percent had nondiagnostic scans and negative serial IPG studies. All had adequate cardiorespiratory reserve and were managed without anticoagulation. Only 1.9 percent had evidence of DVT or PE on follow-up. The findings suggest that a combination of ventilation-perfusion scanning and IPG can be useful in supporting a decision to withhold anticoagulation in patients who have not had clinically significant PE and who do not have evidence for proximal, lower extremity DVT.

Similarly, in another prospective study of over 1200 patients categorized as having a pretest probability of PE as low, moderate, or high, ventilation-perfusion lung scanning and bilateral lower extremity ultrasound revealed that only 0.5 percent (3 of 665) with low or moderate pretest probability and a non-high probability scan had PE or DVT during the 90-day follow-up period. The authors concluded that patients with clinically suspected pulmonary embolism could be managed safely based on pretest probability and results of a ventilation-perfusion scan. The findings are similar to those from another study of over 1000 patients with suspected PE, 22 percent of whom had a low clinical probability of PE, nondiagnostic lung scan, and negative venous study of the legs. These patients were not treated with anticoagulants, and in follow-up, the prevalence of DVT or PE was only 1.7 percent.

Finally, in the Prospective Investigative Study of Acute Pulmonary Embolism Diagnosis (PISAPED), which utilized perfusion scanning alone in conjunction with the chest radiograph, the sensitivity and specificity of scintigraphy were 92 percent and 87 percent, respectively. The prevalence of PE was high (39 percent). When considered in conjunction with clinical assessment of the likelihood of PE (very likely, possible, or unlikely), the positive predictive value (PPV) of a perfusion scan was 99 percent; the combination of a near-normal or abnormal perfusion scan without segmental defects and low clinical likelihood of PE had a negative predictive value (NPV) of 97 percent. Using standardized clinical assessment and perfusion lung scanning, the authors were able to accurately diagnose or exclude PE (PPV, 96 percent; NPV, 98 percent). CT angiography was required in only a minority of cases having discordant clinical and scintigraphic findings (see below).

Prospective Investigation of Pulmonary Embolism Diagnosis Study

To date, the most comprehensive prospective investigation addressing the role of ventilation-perfusion scanning in the diagnosis of PE has been the PIOPED study. This multiinstitutional study was designed to evaluate the efficacy of various conventional methods for diagnosing acute PE. In particular, PIOPED focused on the sensitivity and specificity of lung scans in the diagnosis of acute PE.

Although the clinical diagnosis of PE is not definitive, results from PIOPED emphasize the importance of incorporating clinical assessment in evaluating patients suspected of having acute PE. As expected, combining clinical assessment with lung scan interpretation improves diagnostic accuracy of the imaging technique. Similarly, although chest radiographic findings alone are not sensitive or specific for PE, they are essential for diagnosing conditions that can mimic PE clinically. Furthermore, chest radiographic findings heavily influence the criteria utilized for estimating the probability of PE based on lung scan patterns.

The sensitivity, specificity, and positive predictive value of ventilation-perfusion lung scans in detecting acute PE are presented in Table 33-1.

One of the limitations of ventilation-perfusion scanning is interobserver variability in scan interpretation. While

Table 33-1

Sensitivity, Specificity, and Positive Predictive Value of Lung Scans in Detecting Pulmonary Embolism in Patients Enrolled in PIOPED

Lung Scan Interpretation (Probability)	Sensitivity	Specificity	Positive Predictive Value
High	40%	98%	87%
High, intermediate	82%	64%	49%
High, intermediate, low	98%	12%	32%

there is generally excellent agreement in categorizing scans as normal or consistent with very low or high probability of PE, interobserver agreement on low-probability and intermediate-probability lung scans is not as good. Use of anatomic lung segment reference charts has been shown to reduce interobserver disagreement when interpreting scans.

Other interpretative pitfalls include false-negative and -positive readings. False-negative interpretations (i.e., low probability read with PE present) do occur, and patients who have a recent history of immobilization (bed rest for 3 days), recent surgery, trauma to the lower extremities, or central venous instrumentation are particularly at risk. In patients with low or very low probability scans who have none of the aforementioned risk factors, the prevalence of PE is only 4.5 percent. Conversely, in patients with low or very low probability scans and one or more of the risk factors, the prevalence of PE is 12 percent and 21 percent, respectively (Table 33-2).

Patients with false-negative lung scans tend to have nonocclusive subsegmental thrombi and a low pulmonary clot burden. In recent years, concern has arisen that a low probability scan may be misleading, resulting in unnecessary mortality in patients who have PE and are not anticoagulated. The prognostic value of a low probability scan is excellent, particularly in patients with a low clinical pretest likelihood of disease or negative lower leg ultrasound. In a series of 536 consecutive patients with these findings, evidence that PE caused or contributed to death within 6 months of imaging was absent.

The most common cause of ventilation-perfusion mismatch in patients who do not have acute PE is chronic or unresolved PE. Other causes include compression of the pulmonary vasculature (e.g., from mass lesions, lymphadenopathy, or mediastinal fibrosis), vessel wall abnormalities (e.g., pulmonary artery tumors or vasculitis), nonthrombembolic intraluminal obstruction (e.g., tumor emboli or foreign body emboli), and congenital vascular abnormalities (e.g., pulmonary artery agenesis or hypoplasia). In patients who have unilateral ventilation-perfusion mismatch (hypoperfusion or absent perfusion) within an entire lung or in multiple contiguous segments and normal perfusion in the contralateral lung, extrinsic compression of the pulmonary vasculature, congenital abnormalities, or proximal PE should be considered. Patients with a suspected false-positive scan or unilateral ventilation-perfusion mismatch often require further imaging using CT angiography.

Table 33-2

Risk Factors and Prevalence of Pulmonary Embolism in Patients with Low Probability and Very Low Probability Lung Scans Enrolled in PIOPED

	Patients with 0 Risk Factors (%)*	Patients with 1 Risk Factor (%)*	Patients with ≥2 Risk Factors (%)*	Total
PE positive	14 (2.2%)	19 (2.9%)	37 (5.7%)	70
PE negative	301 (46.4%)	136 (21.0%)	142 (21.9%)	579
Prevalence of PE	4.5%	12.2%	20.7%	10.8%

** Risk factors include immobilization, trauma to lower extremities, surgery, and central venous instrumentation within 3 months of enrollment.*

Table 33-3

Revised PIOPED Criteria for Interpretation of Lung Scans*

High probability
≥2 Large segmental perfusion defects (>75% of a segment) without corresponding ventilation or radiographic abnormalities
1 Large segmental perfusion defect and ≥2 moderate segmental perfusion defects (25%–75% of a segment) without corresponding ventilation or radiographic abnormalities
≥4 Moderate segmental perfusion defects without corresponding ventilation or radiographic abnormalities
Intermediate probability
1 Moderate to <2 large segmental perfusion defects without corresponding ventilation or radiographic abnormalities
Corresponding ventilation-perfusion defects and radiographic parenchymal opacity in lower lung zone
Single, moderate, matched ventilation-perfusion defects with normal radiographic findings
Corresponding ventilation-perfusion defects and small pleural effusion
Difficult to categorize as normal, low, or high probability
Low probability
Multiple matched ventilation-perfusion defects, regardless of size, with normal radiographic findings
Corresponding ventilation-perfusion defects and radiographic parenchymal opacity in upper or middle lung zone
Corresponding ventilation-perfusion defects and large pleural effusion
Any perfusion defects with substantially larger radiographic abnormality
Defects surrounded by normally perfused lung (stripe sign)
>3 Small segmental perfusion defects (<25% of a segment) with a normal radiograph
Nonsegmental perfusion defects (cardiomegaly, aortic impression, enlarged hila)
Very low probability
≤3 Small segmental perfusion defects (<25% of a segment) with a normal radiograph
Normal probability
No perfusion defects; perfusion outlines the shape of the lung seen on the radiograph

** Criteria generated after completion of prospective study.*

Interpretation Criteria and Amendments to Original PIOPED Criteria

Several diagnostic schemes have been suggested for interpretation of ventilation-perfusion scans. The original PIOPED criteria were developed to interpret the scans generated from the study based upon experience gathered over the preceding decade. However, several revisions of the original PIOPED criteria have been made since its original introduction (Table 33-3). It is now possible to decrease the number of intermediate scan readings and correctly interpret the scans as low probability. Use of revised PIOPED criteria has already been shown to provide a more accurate assessment of angiographically proven PE than the original criteria.

Another now-recognized interpretation nuance is based upon the so-called *stripe sign*, defined as a rim of perfused lung tissue between the perfusion defect and the adjacent pleural surface (Fig. 33-5). In the PIOPED study, the presence of the sign excluded the diagnosis of PE within the affected zone in 93 percent of cases. Therefore, perfusion defects that demonstrate a stripe sign are unlikely to be due to PE, and in the absence of perfusion defects elsewhere, such findings should be interpreted as representing a low probability of PE. The nuclear medicine physician's subjective estimate of the likelihood of PE (without using specific interpretation criteria) correlated well with the fraction of patients with angiographic evidence of PE in the PIOPED study. When interpreting lung scans, experienced nuclear medicine physicians often rely on a complex interaction between information derived from clinical presentation, chest radiographic findings, published criteria, and ancillary findings. Thus, experienced readers (such as the PIOPED investigators) can provide an accurate estimate of the probability of PE based on clinical, radiographic, and scintigraphic findings.

CT Angiography in the Diagnosis of Pulmonary Embolism

More recently, clinicians have employed spiral or helical CT angiography and electron beam computed tomography as an alternative to scintigraphy in the diagnosis of PE.

With CT angiography, acute PE appears as an intraluminal filling defect, which partially or completely occludes

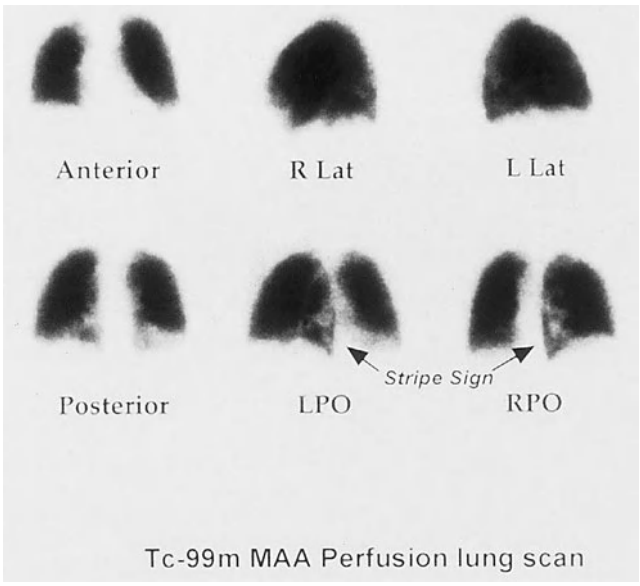


Figure 33-5 Stripe sign. Both left posterior and right posterior oblique views (lower row) demonstrate a defect surrounded by perfused lung. This pattern is very rarely seen in pulmonary embolism.

the pulmonary artery, or as an abrupt vessel cut-off. Commonly, mild vascular distension at the site of the thrombus is present within the affected vessel. Other indirect signs that suggest PE include a dilated central pulmonary artery, dilated right ventricle, or wedge-shaped parenchymal consolidation. In animal models, CT angiography has been shown to detect thrombi in vessels as distal as the fourth division (segmental) pulmonary arteries.

The performance of CT angiography for detection of PE is technically demanding. The sensitivity and specificity of CT angiography for detecting PE range from 53 percent to 100 percent and 75 percent to 100 percent, respectively. The diagnostic performance of CT angiography for detecting subsegmental thrombi is lower than for central PE.

In one prospective study comparing spiral CT angiography and ventilation-perfusion lung scanning, CT angiography had a higher sensitivity than a high-probability ventilation-perfusion scan. The specificity, PPV, and NPV were similar between the two modalities. A more recent study reported a higher sensitivity and specificity for CT angiography than ventilation-perfusion scanning. Spiral CT angiography also provides for higher interobserver agreement and the ability to elucidate an alternative diagnosis for patients with suspected PE.

Limitations of CT angiography include technical failures and incomplete examinations. Patient-related factors which can result in incomplete or suboptimal examinations include orthopnea, poor intravenous access, and inability to breath-hold because of dyspnea. In patients who are unable to breath-hold, respiratory misregistration may occur, degrading image quality. A poor signal-to-noise ratio or vascular enhancement may occur in patients with right heart failure, large right-to-left shunts, or extravasated intravenous lines. Intravenous contrast must be used cautiously, particularly in patients with renal insufficiency. The prevalence of suboptimal CT angiography examinations depends on the technique used and the population examined. In selected patients, technically inadequate studies occur in about 2 to 4 percent . In spite of its technical demands, CT angiography can provide a prompt and accurate diagnosis of PE in most patients.

Studies evaluating the safety of withholding anticoagulation in patients with a negative CT angiogram suggest that in selected patient populations, CT angiography has a high NPV and that anticoagulant therapy may be safely withheld. A meta-analysis of 3500 patients reported that CT angiography is equivalent to convential angiography in ruling-out clinically significant PE. In the authors' opinion, use of spiral CT in the diagnosis of PE has not yet been adequately evaluated, and further prospective studies are required to determine the sensitivity, specificity, and safety of the technique.

PIOPED II, a multicentered, prospective, outcome-based study supported by the National Heart, Lung, and Blood Institute, is designed to assess the accuracy of CT angiography in the evaluation of acute PE. Preliminary data indicate that the sensitivity, specificity, PPV, and NPV of the technique are 83, 96, 86, and 95 percent, respectively.

Recommendations Regarding Use of Ventilation-Perfusion Lung Scans and CT Angiography in Evaluating Suspected Pulmonary Embolism

Proponents of CT angiography suggest that it should be used as the first-line study in patients with suspected PE. Others suggest that ventilation-perfusion lung scanning should remain the first-line test, with CT angiography used in those patients in whom the diagnosis remains uncertain. In patients with a normal chest radiograph, the ventilation-perfusion lung scan is an effective, noninvasive initial study. However, in patients with significant chest radiographic abnormalities, CT angiography is more likely to provide a definitive diagnosis of PE or an alternative diagnosis. Furthermore, the combination of CT angiography and CT venography has the potential to provide a single, comprehensive evaluation of patients with suspected venous thromboembolism.

In summary, based upon results from prospective and outcome-based studies conducted over the last few years, the following conclusions can be drawn regarding use of radionuclide and CT imaging in evaluating patients with suspected PE: (a) A normal ventilation-perfusion scan excludes the diagnosis of clinically significant PE (Fig. 33-6). (b) Patients with very low or low probability scans and a low clinical likelihood of PE have a low (<5 percent) prevalence of PE and generally do not require pulmonary angiography or anticoagulation. (c) Patients with very low or low probability scan, intermediate or high clinical likelihood of PE, and negative serial noninvasive venous studies of the lower extremities generally do not require anticoagulation. In selected cases, CT angiography is helpful in excluding PE and providing an alternative diagnosis. (d) Clinically stable patients with an intermediate

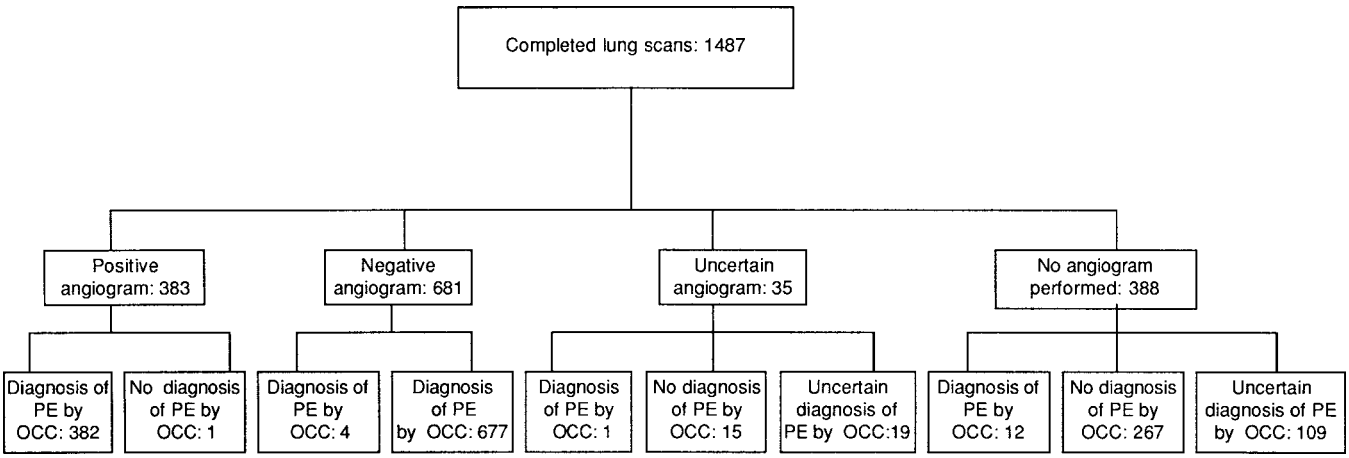


Figure 33-6 Outcome classification of patients enrolled in PIOPED. Data are from patients who completed ventilation-perfusion scans. See text for details. PE = pulmonary embolism; OCC = Outcome Classification Committee.

probability scan require noninvasive venous studies of the legs; if negative, CT angiography is required for definite diagnosis of PE. (e) A clinically stable patient with a high probability scan and high clinical likelihood of PE, or a patient suspected of having a false-positive scan requires treatment; no further diagnostic tests are required to confirm the diagnosis. (f) Clinically stable patients with a high probability scan and a low clinical likelihood of PE require noninvasive venous studies of the legs; if negative, CT angiography may be required for definitive diagnosis.

EVALUATION OF PULMONARY HYPERTENSION

Pulmonary hypertension (PH) as a consequence of chronic pulmonary thromboembolism is a serious and potentially surgically treatable disease. Estimates are that between 0.5 and 4 percent of patients with acute pulmonary emboli eventually develop chronic thromboembolic PH. Unfortunately, the clinical features, laboratory studies, and other noninvasive assessments employed are often unreliable in distinguishing chronic thromboembolic PH from primary and nonthromboembolic secondary PH. Pulmonary angiography is usually required to confirm the diagnosis and determine whether surgical intervention is indicated. Although there have been reports that pulmonary angiography may be performed safely in patients with severe PH, others have documented a high frequency of complications, including death.

Ventilation-perfusion lung scanning is a safe, noninvasive technique that facilitates selection of patients with PH for pulmonary angiography to confirm the diagnosis of chronic PE. In order to prevent potential adverse hemodynamic effects when performing ventilation-perfusion lung scans in patients with PH, the number of ^{99m}Tc MAA particles administered should be reduced. Both ventilation-perfusion lung scanning and pulmonary angiography may produce underestimations of the magnitude of vascular occlusion by chronic emboli, as determined at thromboendarterectomy.

In one study of 25 patients with chronic thromboembolic PH, 96 percent of ventilation-perfusion lung scans were interpreted as high probability for PE; in one patient, the scan was interpreted as intermediate probability. The findings suggest that in chronic PH, CT angiography or pulmonary angiography should be performed in those patients with intermediate or high-probability ventilation-perfusion scans in order to confirm the diagnosis of chronic PE.

Most patients with primary PH or secondary, nonthromboembolic PH have low-probability scans. The distribution of ^{99m}Tc MAA particles within the lungs is diffuse and nonhomogeneous. Patients with PH rarely, if ever, have normal or very-low-probability scans. Thus, a low-probability ventilation-perfusion scan effectively excludes chronic thromboembolism as the cause of PH.

QUANTITATIVE VENTILATION-PERFUSION LUNG SCANNING

In patients undergoing pulmonary resection or lung transplantation, quantitative ventilation-perfusion lung scanning is a useful method for determining regional lung function. The major use of the technique is prediction of postoperative pulmonary function following lung volume reduction for chronic obstructive pulmonary disease or pneumonectomy for other reasons.

Peripheral lung carcinomas are associated with ventilation and perfusion defects that correspond to abnormalities noted on the chest radiograph. In patients with central bronchogenic carcinomas, mismatches between ventilation and perfusion patterns may be noted. In these cases, either the primary lung tumor or adenopathy may compress the main pulmonary artery or vein, which, in turn, may result in decreased perfusion to affected areas. When the airway is

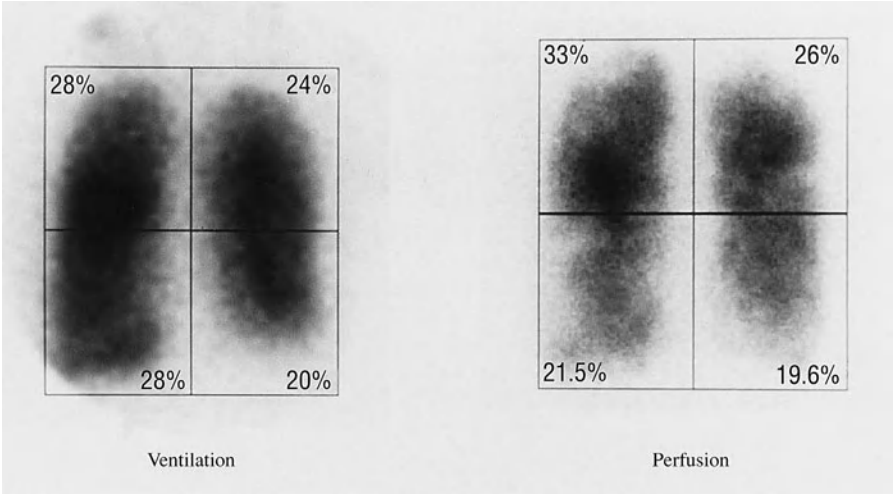


Figure 33-7 Quantitative ventilation-perfusion lung scan. Regional ventilation and perfusion can be quantified by outlining regular or irregular regions of interest and generating ratios that correspond to percent of total pulmonary function. Images shown were analyzed by dividing each lung into two equal rectangles.

partly or totally occluded by cancer, a matching ventilation-perfusion pattern is seen in affected lung zones.

In patients with central tumors, regional perfusion values correlate well with regional lung physiology and can be utilized to predict postoperative pulmonary function. The postoperative FEV_1 is calculated by multiplying the preoperative value by the ratio of the counts in the remaining lung to total lung activity (Fig. 33-7).

ASSESSMENT OF INFLAMMATORY AND GRANULOMATOUS LUNG DISEASE

Gallium-67 citrate and labeled white blood cells are the radiopharmaceuticals of choice for imaging pulmonary infection and inflammation. Gallium-67, which has a physical half-life of 78 h, is an iron analog. Following intravenous administration, approximately 90 percent of the dose injected is bound to transferrin. The kidneys excrete only 25 percent of the administered preparation during the first 24 h after injection. Another 10 percent of the injected activity is excreted in stool over the next several days. The remaining 65 percent is distributed within the body. Typically, gallium is taken up in the liver, skeleton, bone marrow, spleen, nasopharynx, lacrimal and salivary glands, and external genitalia. The precise mechanism of gallium localization at sites of inflammation or infection is not completely understood. Increased vascular permeability, direct bacterial uptake (binding to siderophores), binding to lactoferrin (which is secreted by activated leukocytes), and direct binding to circulating leukocytes have been postulated.

The optimal time for imaging the thorax is at least 48 to 72 h following the administration of gallium. Increased gallium activity in the lungs is a sensitive, but relatively nonspecific, indicator of pulmonary infection or inflammation. A variety of conditions, including acute respiratory distress syndrome, pneumonia, drug reactions (e.g., those due to busulfan, cyclophosphamide, amiodarone, or contrast agent following lymphangiography), pneumoconiosis, idiopathic pulmonary fibrosis, and sarcoidosis may cause increased radiogallium accumulation in the lungs. The intensity and distribution of the pulmonary accumulation can be quantified to determine the degree of parenchymal inflammation. Malignant processes, such as lymphoma, leukemia, mesothelioma, and lung metastases may also result in increased radiogallium uptake when there is focal disease activity.

Gallium-67 Citrate Imaging of the Thorax in the Immunocompromised Host

Diffuse gallium uptake in the lungs of HIV-infected patients who have normal chest radiographs is highly suggestive of *Pneumocystis carinii* pneumonia (PCP) (Fig. 33-8). The sensitivity of gallium scanning for detecting PCP is approximately 95 percent, and when gallium uptake in the lungs is intense (greater than the liver), the specificity also approaches 95 percent.

Other conditions associated with diffuse lung uptake in immunocompromised patients are cytomegalovirus pneumonitis, cryptococcal infections, and lymphoma. Although localized lung uptake may be associated with PCP, particularly in patients treated with prophylactic aerosolized pentamidine, focal accumulation is often secondary to bacterial pneumonia or immunoblastic lymphoma. Focal activity in the lung and corresponding regional lymph nodes is typical for infection with *M. avium-intracellulare* or *M. tuberculosis.* Kaposi's sarcoma does not accumulate radiogallium, but the lesions are clearly visualized following the administration of thallium-201 chloride. Combined imaging with gallium-67 citrate and thallium-201 chloride has been suggested as a way to distinguish Kaposi's sarcoma from PCP and lymphoma in HIV-infected patients.

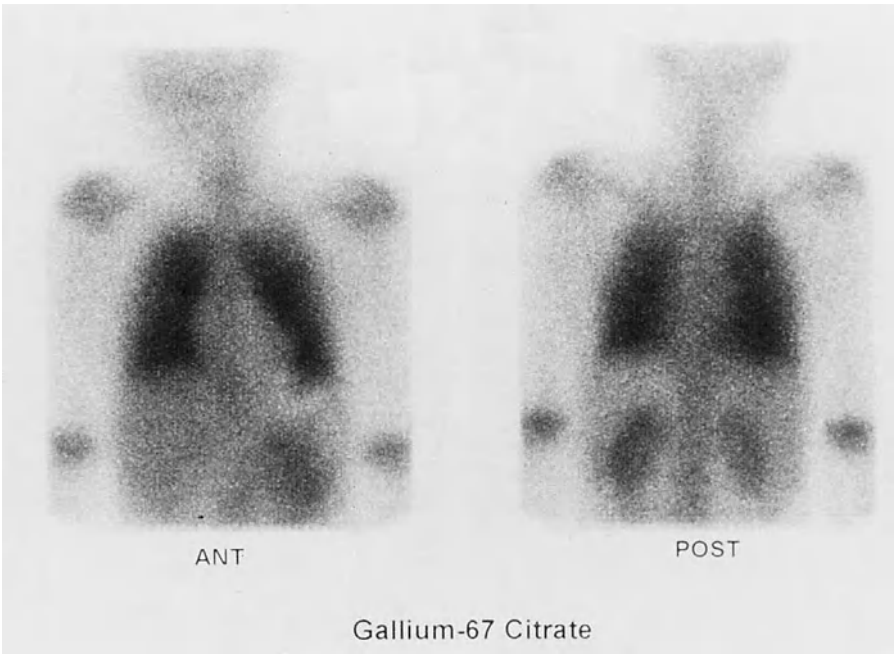


Figure 33-8 *Pneumocystis carinii* pneumonia with diffuse parenchymal lung uptake. Anterior and posterior gallium scans of the chest and abdomen reveal intense uptake of radiogallium, indicating a diffuse inflammatory process in both lungs.

Noninfectious Inflammatory Lung Disease

Gallium-67 citrate lung imaging has been used to quantify the degree of alveolitis in various interstitial lung diseases, particularly sarcoidosis and idiopathic pulmonary fibrosis. In patients with idiopathic pulmonary fibrosis, the intensity of radiogallium uptake has been shown to correlate with the degree of alveolitis assessed by open lung biopsy and the percentage of neutrophils present in bronchoalveolar lavage fluid. However, pulmonary uptake of gallium-67 citrate may be normal in patients with low-grade alveolitis. Unfortunately, pulmonary accumulation of radiogallium in idopathic pulmonary fibrosis is not reliable in predicting the response to treatment with corticosteroids or prognosis. Patients who have normal thoracic gallium scans may eventually develop pulmonary fibrosis, while patients showing a marked increased uptake may remain stable or improve. Therefore, the routine use of gallium-67 scintigraphy in patients with idiopathic pulmonary fibrosis is not recommended.

Scintigraphy with gallium-67 citrate has been advocated for assessment of disease activity in pulmonary sarcoidosis. In patients with sarcoidosis, radiogallium activity in the lung correlates well with the presence of alveolitis detected by lung biopsy and the percentage of T lymphocytes detected by bronchoalveolar lavage. Although it is not specific for sarcoidosis, this disorder is characterized by bilateral, perihilar, or peritracheal uptake of gallium-67 citrate (Fig. 33-9). This appearance, combined with increased uptake in the parotid glands, is virtually pathognomonic for sarcoidosis. Parenchymal activity can also be seen, with or without hilar activity. Parenchymal uptake is usually in the midlung, with relative sparing of the upper and lower lung zones. Gallium-67 citrate imaging in sarcoidosis is useful in selecting the site for lung biopsy and distinguishing fibrotic changes from active inflammatory disease. Several studies have also shown a correlation between the degree of uptake of radiogallium and response to therapy with corticosteroids. Gallium-67 citrate scintigraphy is also useful in assessing extrapulmonary manifestations of sarcoidosis.

SCINTIGRAPHIC ASSESSMENT OF ALVEOLAR-CAPILLARY MEMBRANE PERMEABILITY

Assessment of alveolar-capillary membrane permeability requires the inhalation of ^{99m}Tc-labeled radioaerosols. The rate of aerosol clearance from the lung is measured using a counting probe or gamma camera. Several factors influence the rate at which inhaled aerosols "wash out" from the lungs. The most important determinant is the site of aerosol deposition. Aerosols of relatively small aerodynamic diameter (e.g., ^{99m}Tc DTPA) are deposited largely within the small airways and alveoli, whereas larger particles (e.g., ^{99m}Tc MAA or ^{99m}Tc sulfur colloid) are deposited within the proximal airways. The normal half-time of ^{99m}Tc DTPA washout from the lungs is 86 $\pm$ 26 min. In the presence of epithelial alveolar damage, the clearance of ^{99m}Tc DTPA is accelerated.

A variety of acute or chronic pulmonary conditions may cause increased clearance of ^{99m}Tc DTPA from the lungs,

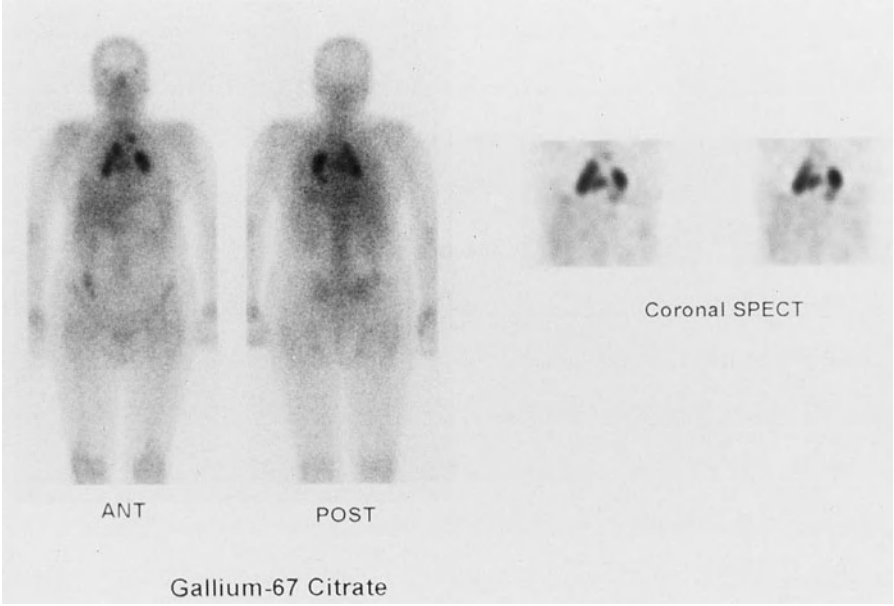


Figure 33-9 Bilateral hilar lymphadenopathy in sarcoidosis. Anterior and posterior whole-body images demonstrate intense uptake of radiogallium in both hilar regions. These areas are clearly defined on tomographic (SPECT) images in coronal planes. Similar patterns are seen in patients with lymphoma.

including pneumoconiosis, idiopathic pulmonary fibrosis, collagen vascular diseases, sarcoidosis, acute respiratory distress syndrome, and pneumocystis pneumonia. Cigarette smoking or physiological factors, such as posture and exercise, also influence epithelial lung clearance. Since increased alveolar-capillary membrane permeability is relatively nonspecific, ^{99m}Tc DTPA clearance studies have been utilized only to assess the effects of therapy in patients with known pulmonary diseases. Comparison of serial studies is of value only if a consistent pattern of distribution of radiopharmaceutical activity is demonstrated on repeated studies. Otherwise, results from such studies are of little help in determining the course of the disease.

EVALUATION OF MUCOCILIARY CLEARANCE

Determination of mucociliary clearance may be obtained after the inhalation of relatively large aerosolized particles, followed by measurement of the rate of clearance with a gamma camera. The rate of mucociliary clearance depends on several factors, including ciliary activity and mucus production. Inhaled particles, such as ^{99m}Tc MAA or ^{99m}Tc sulfur colloid, tend to be deposited within the proximal airways. The normal mucociliary clearance half-time is approximately 24 h. Delayed mucociliary clearance is seen in patients with airway inflammation (e.g., due to COPD, asthma, or viral respiratory tract infections), following bronchial surgery, or after irradiation. Physiological factors, such as aging and sleep, can also delay mucociliary clearance.

POSITRON EMISSION TOMOGRAPHY AND ASSESSMENT OF SOLITARY PULMONARY NODULES AND LUNG CANCER

PET is a nuclear medicine technique that provides images of metabolic or physiologic processes. Application of PET in respiratory medicine has primarily focused on the evaluation of solitary pulmonary nodules and lung cancer. The most commonly used radiopharmaceutical in clinical PET is F-18-fluorodeoxy-D-glucose (FDG). Metabolic differences between benign and malignant tissue can be accurately characterized using FDG-PET.

The mechanism of cellular uptake and initial phosphorylation of FDG is similar to that of glucose. However, once FDG is phosphorylated (to FDG-6-phosphate), it is trapped within the cell and can be imaged using PET (Fig. 33-10). The amount of intracellular FDG is proportional to glucose uptake and, therefore, to the metabolic activity of the tissue. Cells that have undergone malignant transformation have increased glucose transport and metabolism due to accelerated cell proliferation and increased hexokinase activity.

Current indications for PET-FDG imaging in patients with proven or suspected lung cancer include distinction of benign from malignant pulmonary nodules, mediastinal staging of non–small-cell lung cancer, detection of distant metastasis, and diagnosis of recurrent disease.

A solitary pulmonary nodule (SPN), defined as an opacity in the lung parenchyma that measures up to 3 cm and that has no associated mediastinal adenopathy or atelectasis, is commonly indentified on chest radiographs and CT scans and often poses a diagnostic challenge. Thirty to 50 percent of SPN's are malignant and may represent a potentially

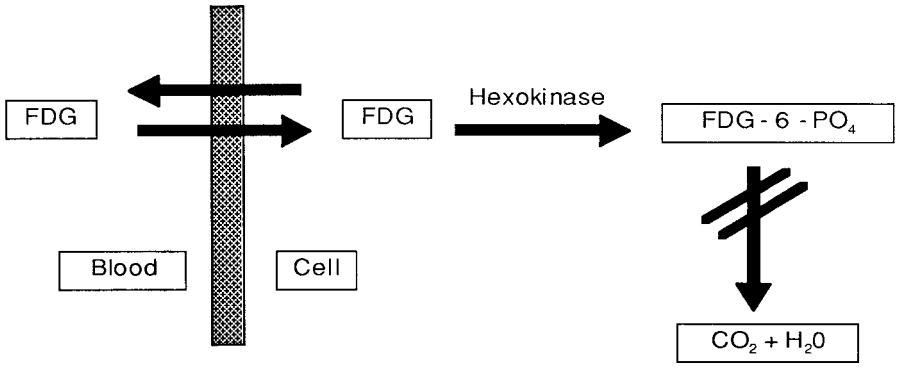


Figure 33-10 Schematic representation of FDG metabolism in metabolically active cell. FDG is preferentially transported through the cell membrane. Following phosphorylation to FDG-6-phosphate by the hexokinase system, FDG remains trapped in the cell for a while, facilitating imaging of the abnormal tissue with PET.

curable stage of bronchogenic carcinoma; however, many represent benign processes. While a number of benign etiologies for SPN's have a characteristic appearance on CT, many can not be characterized accurately using CT and often require further invasive assessment. Increased patient age, a history of smoking, large nodule size, and absence of nodule calcification are features associated with an increased probability of malignancy. FDG-PET provides an accurate, noninvasive diagnostic assessment of SPNs, without the morbidity and costs associated with invasive tissue sampling (Fig. 33-11).

Sensitivity and specificity of FDG-PET in detecting benign and malignant pulmonary nodules range from 92 to 98 percent and 79 to 100 percent, respectively (Table 33-4).

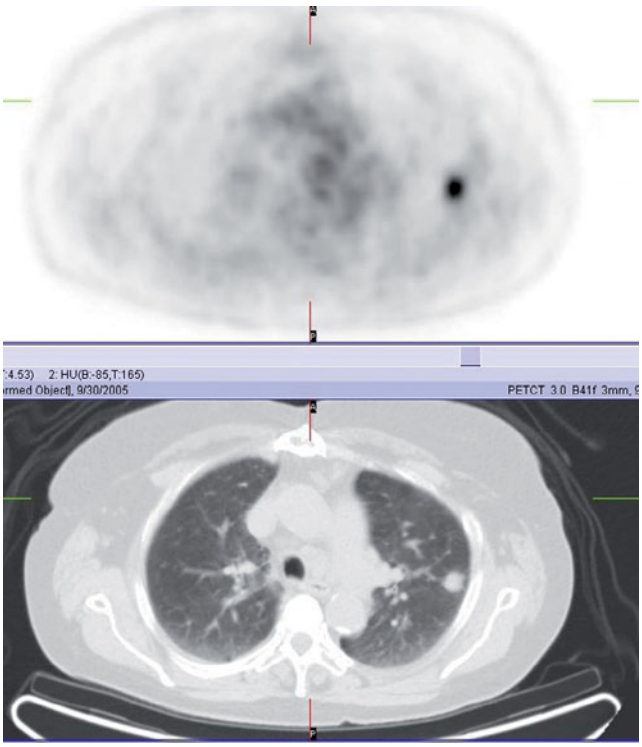


Figure 33-11 Transaxial FDG-PET and CT. Non–small-cell lung cancer in left upper lobe demonstrating increased activity (hypermetabolic) on coregistered FDG-PET/CT images.

In one meta-analysis of 40 studies that included over 1400 focal pulmonary lesions studied with FDG-PET, the technique had an average sensitivity of 97 percent and specificity of 78 percent. No differences were noted between results using a semiquantiative analysis of FDG uptake and those based on qualitative visual assessment. False-positive studies are seen with active inflammation due to aspergillosis, tuberculosis, or sarcoidosis. False-negative results are seen with malignancies which have a low metabolic activity (e.g., bronchoaveolar carcinoma or carcinoid tumors) or are less than 8 mm in diameter.

Nodules having a "ground-glass" or "mixed" appearance on CT scanning are associated with a higher incidence of malignancy than are solid-appearing nodules. Further investigation is necessary to evaluate the role of FDG-PET in evaluating ground-glass lesions. The low accuracy of PET in assessing these abnormalities is likely related to their small size and the cell types that predominate, including pure bronchioalveolar cell cancer or adenocarcinomas with bronchioalveolar features.

As noted, the sensitivity of FDG-PET is a function of lesion size. In one study addressing this issue, the technique's sensitivity in detecting malignancy was 69 percent for nodules ranging from 5 to 10 mm in diameter and 95 percent for nodules greater than 10 mm in diameter. The lower limit of spatial resolution of PET, which is about 5 to 6 mm, is lower than that of CT or MRI. One method aimed at compensating for this limitation is based on using lesion size measured on CT imaging to correct the so-called "standardized uptake value" (SUV), a semiquantitative expression of the intensity of lesion FDG accumulation determined on the PET scan. The SUV of an area in the image is calculated as the amount of tracer in the tissue (microcuries per gram) divided by the amount of radiotracer injected (millicuries) divided by the patient's weight (kilograms).

Lung cancers have a wide range of FDG uptake. Furthermore, while most infectious or inflammatory pulmonary disorders generally have a lower FDG uptake than malignancies, overlap exists. An SUV threshold of 2.5, measured at a single point in time, has been proposed to separate malignant (higher SUV) from benign (lower SUV) disorders.

Table 33-4

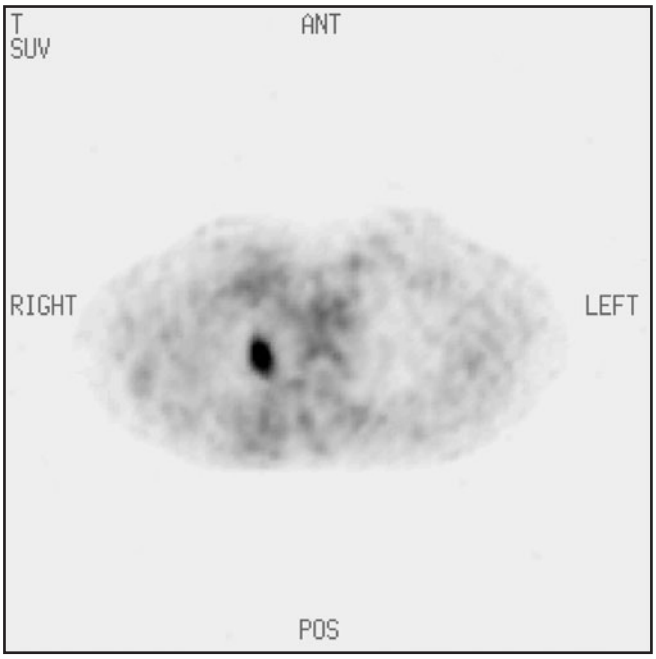
FDG-PET in Evaluation of Solitary Pulmonary Nodules

		Sensitivity		Specificity		
Nodule Size (cm)	**Type of Analysis**	**%**	**95% Confidence Interval**	**%**	**95% Confidence Interval**	**Accuracy (%)**
≤1.5	SUV	80	60–100	95	85–100	88
	Visual	100	100–100	74	55–93	
>1.5	SUV	96	90–100	80	55–100	93
	Visual	98	94–100	60	45–74	91
≤3	SUV	90	82–98	92	85–99	91
	Visual	98	94–100	69	56–82	88
All sizes	SUV	92	82–100	90	79–100	91
	Visual	98	82–100	69	57–81	89

Based on the observation in animal and human studies that FDG uptake by malignant tumors increases over time, while that of inflammatory tissue decreases (Fig. 33-12), dual-time point FDG-PET scanning has emerged as a potentially useful way of enhancing discrimination between benign and malignant diseases. Using this approach, images are obtained 1 and 2 h after administration of FDG. In one study in which an SUV cut-off value of 2.5 and a 10 percent increase in SUV was used to indicate malignancy, the sensitivity and specificity of FDG-PET were 80 and 94 percent, respectively, for the single-time point method, and 100 and 89 percent, respectively, for the dual-time point technique.

Use of Positron Emission Tomography in Lung Cancer Staging

An additional advantage of FDG-PET in evaluating solitary pulmonary nodules is that the technique can be used in staging mediastinal lymph nodes in patients with non–small-cell



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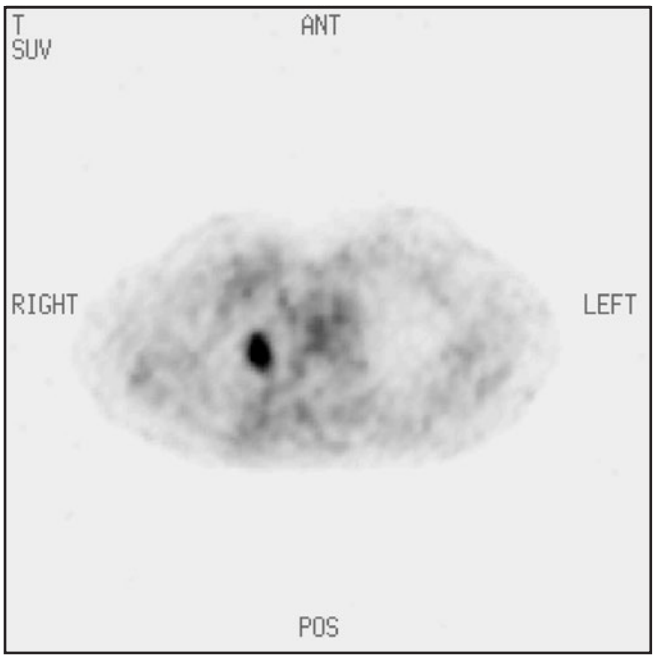

B

Figure 33-12 Transaxial FDG-PET images showing a focus of increased activity in the right upper lobe, corresponding to the patient's non–small-cell lung cancer. Maximum SUV was 8.1 on the first time image (*A*) and increased to 9.7 on the second time image (*B*). Findings are consistent with malignancy.

Table 33-5

Accuracy of FDG-PET in Mediastinal Staging in Lung Cancer

Study	Number of Patients	Sensitivity	Specificity	PPV	NPV
Dunagan et al., 2001	81	0.52	0.88	0.61	0.84
Farrell et al., 2000	84	1	0.93	0.40	1
Liewold et al., 2000	78	0.93	0.78	0.69	0.95
Pieterman et al., 2000	102	0.91	0.86	0.74	0.95
Roberts et al., 2000	100	0.88	0.91	0.75	0.96
Magnani et al., 1999	28	0.67	0.84	0.67	0.84
Marom et al., 1999	79	0.73	0.94	0.85	0.88
Saunders et al., 1999	84	0.71	0.97	0.86	0.93
Vansteenkiste et al., 1998	68	0.93	0.95	0.93	0.95
Vansteenkiste et al., 1998	56	0.86	0.43	0.60	0.75
Bury et al., 1997	64	0.86	1	1	0.96
Guhlmann et al., 1997	32	0.87	1	1	0.89
Steinert et al., 1997	47	0.92	0.97	0.92	0.97
Bury et al., 1996	30	0.88	0.86	0.88	0.86
Sazon et al., 1996	32	1	1	1.00	1
Scott et al., 1996	27	1	1	1.00	1
Chin et al., 1995	30	0.78	0.81	0.64	0.89
Wahl et al., 1994	23	0.82	0.75	0.75	0.82
Summary	**1045**	**0.84**	**0.89**	**0.79**	**0.93**

Notes: Abbreviations: PPV = positive predictive value; NPV = negative predictive value.

lung cancer. The role of FDG-PET in staging of small-cell lung carcinoma remains controversial.

Patients with stage I or II non–small-cell lung cancer are typically referred for surgery, while those with stage IIIb (contralateral mediastinal disease) or stage IV (distant metastases) disease generally are not surgical candidates. Mediastinal staging using CT scanning is based primarily on assessment of lymph node size; nodes less than 1 cm in their short axis are considered benign, while those greater than 1 cm are considered potentially malignant. Using this anatomic approach, mediastinal staging based on CT scanning has a sensitivity of 57 percent and specificity of 82 percent.

In comparison with CT scanning, FDG-PET has a higher sensitivity and specificity for determining node status in patients with non–small-cell lung cancer. The average sensitivity and specificity for FDG-PET are 84 and 89 percent, respectively (Table 33-5). However, a comparison of PET and mediastinoscopy in a study of over 200 patients revealed a PPV for PET of only 45 percent. Therefore, mediastinoscopy is still necessary in the staging of PET-positive mediastinal lymph nodes. PET can also be useful in identifying the optimal site

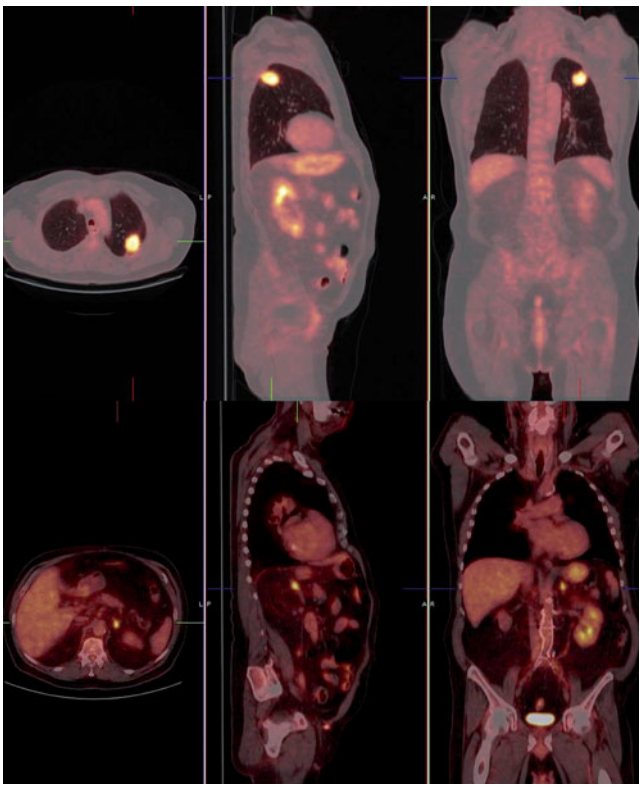

Figure 33-13 Transaxial, sagittal, and coronal composite FDG-PET/CT images (top row) of a patient being considered for pulmonary resection. A hypermetabolic nodule is seen within the left upper lobe, corresponding to the patient's known lung cancer. Composite FDG-PET/CT images (bottom row) demonstrate a small, previously unknown, hypermetabolic focus in the left adrenal gland, which was confirmed as an adrenal metastasis.

for mediastinal lymph node biopsy and aiding selection of additional invasive methods for sampling lymph nodes inaccessible by mediastinoscopy.

In addition to mediastinal evaluation, whole-body FDG-PET imaging may aid in detecting unsuspected distant metastases (Fig. 33-13). In one mutlicenter trial, adddition of PET to the conventional workup prevented unnecessary surgery in one out of five patients with suspected non–small-cell lung cancer. Two common examples of extrapulmonary sites (stage IV disease) of lung metastases are worth considering in this regard: the adrenal glands and bone marrow.

Although benign adrenal adenomas may be abnormal on PET, FDG-PET has a sensitivity of 100 percent and specificity of 80 to 94 percent in detecting adrenal metastases. In detecting bone metastases, compared with bone scintigraphy, FDG-PET has a similar sensitivity but a higher specificity. FDG-PET can detect bone marrow metastases before reactive bone formation takes place or prior to development of gross anatomic abnormalities (Fig. 33-14).

In patients with residual parenchymal abnormalities following radiotherapy for lung cancer, PET-FDG scanning can be used to distinguish between persistent or recurrent cancer and radiation fibrosis. In a study of 35 patients who had recurrent or persistent parenchymal abnormalities following radiotherapy, the sensitivity and specificity of FDG-PET in detecting recurrent tumor were 97 and 100 percent, respectively. Only one patient, who had a very thin pleural tumor rind, had a false-negative study.

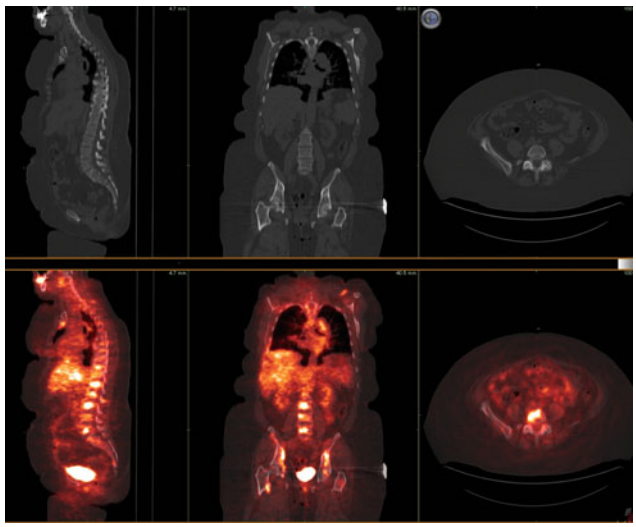

Figure 33-14 PET/CT images (lower row) demonstrate abnormal FDG uptake in the body of multiple lower thoracic and lumbar vertebral bodies, consistent with bone marrow metastases. No clear abnormalities in the CT bone windows (upper row) are evident to suggest bone destruction. Osseous abnormalities are secondary to bone marrow involvement and can be visualized in the later stages of the disease.

In patients treated for lung cancer, FDG-PET offers prognostic value that correlates strongly with survival rate. Patients with positive FDG-PET results have a significantly worse prognosis than those with negative results.

Mesothelioma

Benign fibrous mesothelioma is a rare, nonmalignant, localized tumor of the pleura that is unrelated to asbestos exposure. The tumor can be cured by excisional surgery. In contradistinction, the median survival for patients with malignant mesothelioma is 12 to 18 months. Thus, it is important to differentiate between benign lesions and malignant mesothelioma. Distinction based on histopathological criteria is difficult even for pathologists who specialize in this area.

The radiologic appearances of benign and malignant pleural diseases are very similar. More than 50 percent of patients have a pleural effusion at the time of diagnosis; however, pleural fluid cytology is positive in only approximately 25 percent. Currently, definitive diagnosis is based on thoracoscopic biopsy, which, for malignant mesothelioma, carries the risk of tumor seeding along the operative tract. CT scanning and MRI can not always differentiate between benign and malignant pleural processes.

Findings from CT and MRI studies can be used in tandem with those from FDG-PET in managing these difficult patients. Several studies have shown that FDG-PET can

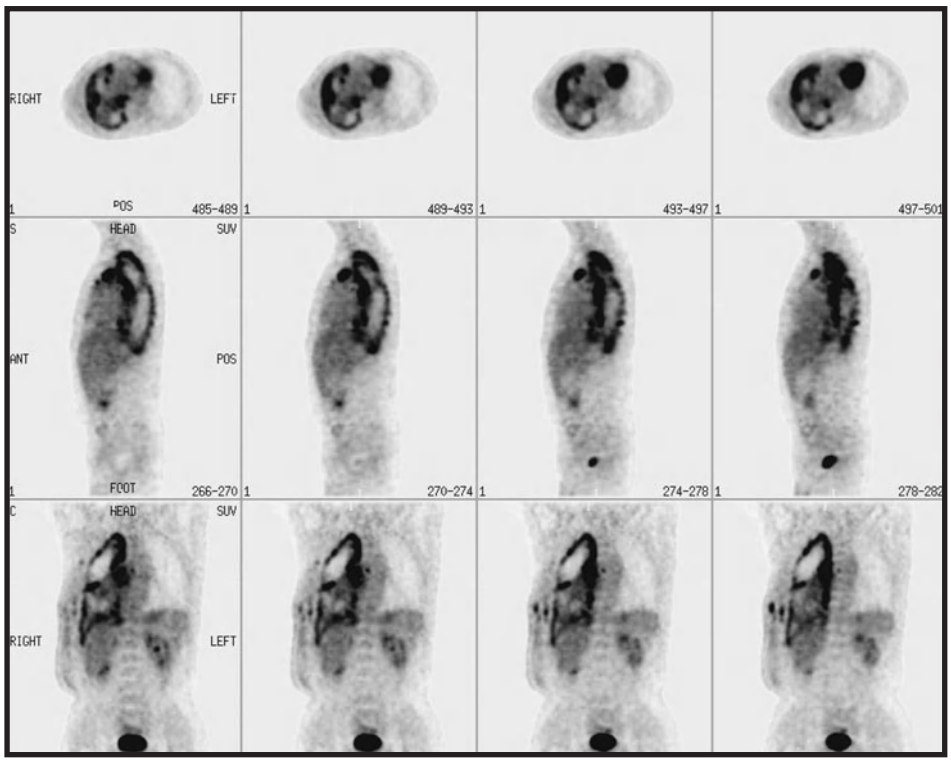

Figure 33-15 Transaxial, sagittal, and coronal views of FDG-PET scan demonstrating diffusely increased FDG activity throughout the diaphragmatic, mediastinal, and lateral right pleura, consistent with malignant mesothelioma.

accurately assess malignant transformation of reactive pleural disease, and in this regard, FDG-PET is clearly superior to CT scanning. Using an SUV cutoff of 2 to differentiate between benign and malignant mesothelioma, FDG-PET has a sensitivity of 91 percent and specificity of 100 percent and provides excellent correlation with thoracoscopic findings.

FDG-PET is also useful in identifying the extent of disease locally and in the mediastinum, evaluating abnormal findings in the contralateral lung, and detecting occult extrathoracic metastases (Fig. 33-15). High levels of FDG uptake correlate with a poor prognosis and shorter survival. FDG-PET also provides a semiquantitative index of disease activity that may be used to monitor the response to conventional or experimental therapies.

Integrated Positron Emission Tomography and Computed Tomography

In recent years, dual-modality integrated PET/CT scanners have been introduced. They hold the promise of improving the overall yield of diagnostic imaging by combining morphological and functional modalities.

In a prospective study of 50 patients with non–small-cell lung cancer, integrated PET/CT provided additional diagnostic information in 41 percent and was significantly more accurate in disease staging than either PET or CT alone. Integrated PET/CT provides important clinical information by virtue of accurate localization of known disease and identification of lesions that do not consistently accumulate FDG, such as carcinoid tumors and bronchioloalveolar carcinoma.

One of the advantages of the combined modality over PET alone in tumor staging is that PET is limited for T (tumor) staging, since the technique does not anatomically define tumor limits. In addition, PET/CT is particularly helpful in planning radiation therapy for patients with lung cancer associated with atelectasis. Currently, radiation therapy planning is based on CT imaging because of the close proximity of important structures to the radiation portals. A number of studies have demonstrated the added benefit of PET in defining and refining radiation treatment volumes, thereby reducing the radiation portal and allowing an increase in dose delivery to target tissues.

PET/CT without CT enhancement is unable to distinguish confined, centrally located tumors from those producing direct invasion of mediastinal structures. Therefore, clinicians still must rely on contrast-enhanced CT scans to help define mediastinal vascular invasion. Furthermore, in patients with extensive mediastinal disease or multiple areas of nodal involvement, N (nodal) staging can be readily accomplished. Exact localization of a solitary metastatic lymph node in the hilum (and, hence, classification as N1 or N2 disease) is somewhat difficult with PET alone; anatomic information provided by CT scanning as part of combined imaging is important for this purpose.

CT information is also essential for precise localization of lymph node metastases in patients with mediastinal shift due to atelectasis or anatomic variants. PET/CT offers the

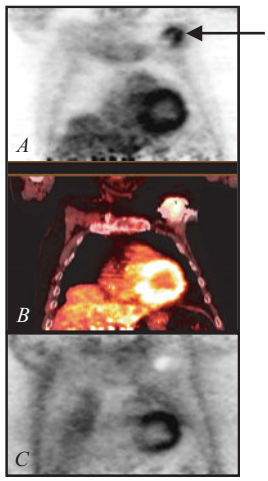

Figure 33-16 An attenuation artifact is seen in the left upper thorax as an area of increased activity on the coronal attenuation-corrected PET images (*A:* arrow). This is caused by an implantable cardioverter defibrillator (*B:* arrow), and corresponds in reality to a photopenic defect on the nonattenuation-corrected images (*C:* arrow).

advantage of determining the exact location of a focal abnormality noted on PET. PET/CT also enables exact localization of FDG in sites altered by radiation.

Assessment of multiple pulmonary nodules using FDG-PET is limited because of false-positive findings in instances of active granulomatous disease, such as tuberculosis, fungal disease, or sarcoidosis, or rheumatoid lesions. In this setting, pattern recognition on CT, in combination with FDG-PET, may improve characterization of the lesions. PET/CT increases the accuracy of malignant pleural mesothelioma staging and is important in determining appropriate therapy in patients being considered for extrapleural pneumonectomy.

Finally, PET/CT also has some limitations related to attenuation artifacts arising from use of high-density contrast agents or indwelling metallic structures, leading to false-positive results on corrected images (Fig. 33-16). Motion and misregistration between PET and CT images can also result in major artifacts in regions adjacent to the heart and diaphragm.

OTHER APPLICATIONS

Radionuclide-based techniques have been applied to investigation of other pulmonary entities, albeit on a much less frequent basis than those described previously.

Pneumonconioses

Pneumoconioses may be progressive, even after dust exposure has ceased. The inhaled particles activate pulmonary macrophages that secrete cytokines that mediate an inflammatory reaction, inducing fibroblast proliferation and collagen deposition. The intensity of pulmonary FDG uptake in pneumoconioses depends on whether active inflammation (increased uptake) or end-stage fibrosis (reduced uptake) predominates at the time of the scan. FDG is taken up by both fibroblasts and alveolar inflammatory cells. In addition, progressive massive fibrosis has been shown to be associated with increased FDG accumulation. The findings from FDG-PET have direct clinical implications; therefore, they are ineffective as therapeutic interventions in end-stage fibrosis. PET imaging using 18F-fluoroproline, which accumulates in lung scar tissue, holds promise for providing early assessment of this category of lung diseases.

Sarcoidosis

Hilar and mediastinal lymph nodes harboring active granulomas due to sarcoidosis accumulate FDG. Although FDG-PET

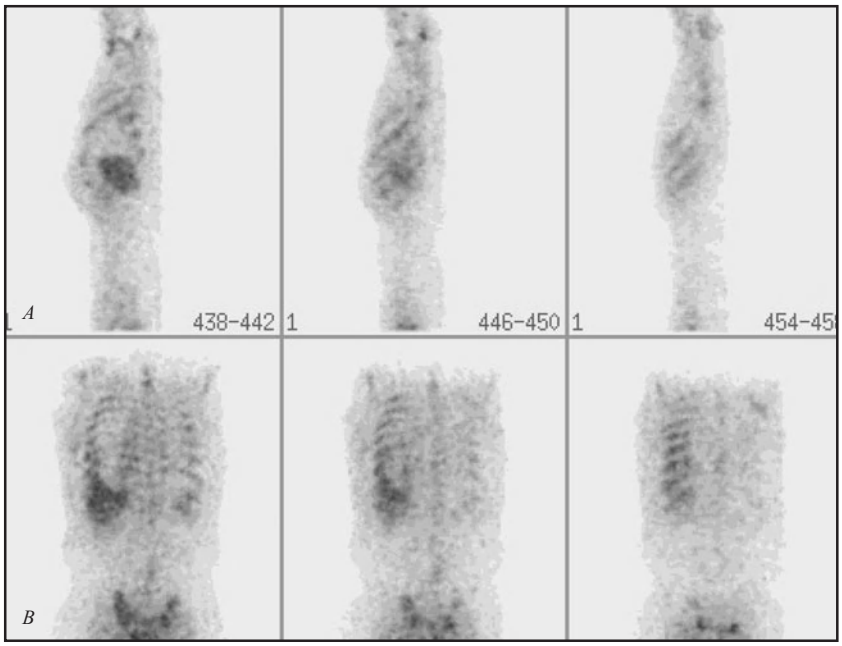

Figure 33-17 Sagittal *(A)* and coronal *(B)* FDG-PET images showing increased FDG uptake by intercostal muscles in a patient with severe COPD.

can not distinguish sarcoidosis from other diseases, such as Hodgkin's or non-Hodgkin's lymphomas, the technique is quite effective in assessing the extent of disease after an initial diagnosis is made. FDG-PET can also provide a means of assessing response to treatment.

Chronic Obstructive Pulmonary Disease and Accessory Muscles of Respiration

Physiologic FDG uptake is noted in strenuously contracting respiratory muscles in patients with COPD. In particular, uptake in intercostal, cervical, and abdominal muscles can be readily identified (Fig. 33-17). Muscular uptake may also be evident in the trapezi, scalenes, sternocleidomastoids, and paraspinal muscles.

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34

Pulmonary Function Testing

Michael A. Grippi • Gregory Tino

The assessment of human pulmonary function dates back to the seventeenth century, when the earliest measurements of tidal volume were noted. In 1700, Humphrey Davy employed a hydrogen dilution technique to measure his own residual volume. Subsequently, John Hutchinson, in his treatise, *On the Capacity of the Lungs and on Respiratory Functions*, defined the functional subdivisions of lung volume and reported the results of vital-capacity measurements performed in more than 1800 subjects. He related these measurements to the subjects' height, age, and weight, thereby establishing a basis for determining normal values.

Progress in development of techniques for pulmonary function testing progressed slowly over the next century. However, in the 1950s, pulmonary physiologists made use of the tools provided by the evolving fields of electronics and computer science. Currently, many techniques exist for assessing both the integrated performance of the cardiovascular and respiratory systems and their individual components. This chapter focuses on commonly used tests of pulmonary function. Detailed assessment of integrated pulmonary and cardiovascular function is described in Chapter 35.

LUNG VOLUMES AND SUBDIVISIONS

Important quantitative aspects of respiratory function are the changes in lung volume with inspiration and expiration and the absolute volume of air that the lungs hold at various times during the respiratory cycle. These volumes and changes in volume are described below.

Definitions and Assessment

For purposes of quantification and comparison, the total volume of gas in the lungs is conventionally subdivided into compartments (volumes) and combinations of two or more volumes (capacities). For many of these subdivisions, the end-expiratory volume—the volume of gas remaining in the lungs at the end of normal expiration—is the point of reference. Lung volumes and capacities are defined in Table 34-1 and are depicted schematically in the tracing shown in Fig. 34-1, which was obtained using a device called a spirometer. The relationships between the volumes recorded directly by the spirometer and the other lung volumes and capacities—including total lung capacity (TLC), functional residual

Table 34-1

Glossary for Static Lung Volumes and Capacities

Term	Symbol	Definition
Volumes		
Residual volume	RV	Volume of air remaining in the lungs after maximal expiration
Expiratory reserve volume	ERV	Maximal volume of air expired from the resting end-expiratory level
Tidal volume	TV*	Volume of air inspired or expired with each breath during quiet breathing
Inspiratory reserve volume	IRV	Maximal volume of air inspired from the resting end-inspiratory level
Capacities		
Inspiratory capacity	IC	Maximal volume of air inspired from the end-expiratory level (the sum of IRV and TV)
Vital capacity	VC	Maximal volume of air expired form the maximal inspiratory level
Inspiratory vital capacity	IVC	Maximal volume of air inspired form the maximal expiratory level
Functional residual capacity	FRC	Volume of air remaining in the lungs at the end-expiratory level (the sum of RV and ERV)
Total lung capacity	TLC	Volume of air in the lungs after maximal inspiration (the sum of all volume compartments)

** The symbol TV is traditionally used for tidal volume to indicate a subdivision of static lung volumes. However, the symbol V_T is used for tidal volume in formulas for gas exchange.*

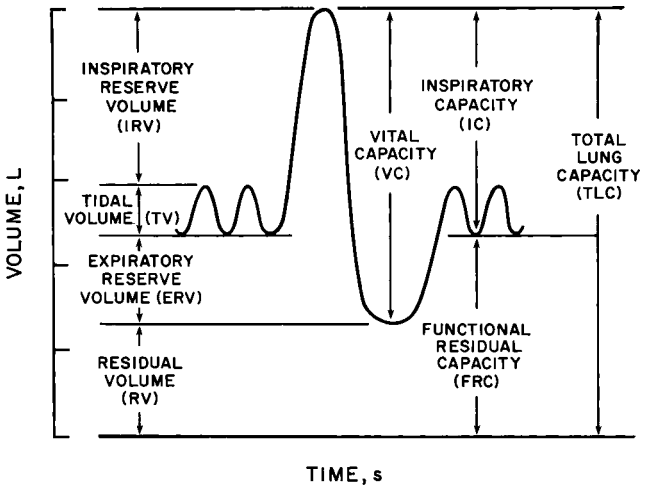


Figure 34-1 The subdivisions of lung volume as recorded by a spirometer. The record is generated on paper calibrated for volume in the vertical direction and time in the horizontal. The term *capacity* is applied to a subdivision composed of two or more *volumes*. The definitions of these subdivisions are found in Table 34-1.

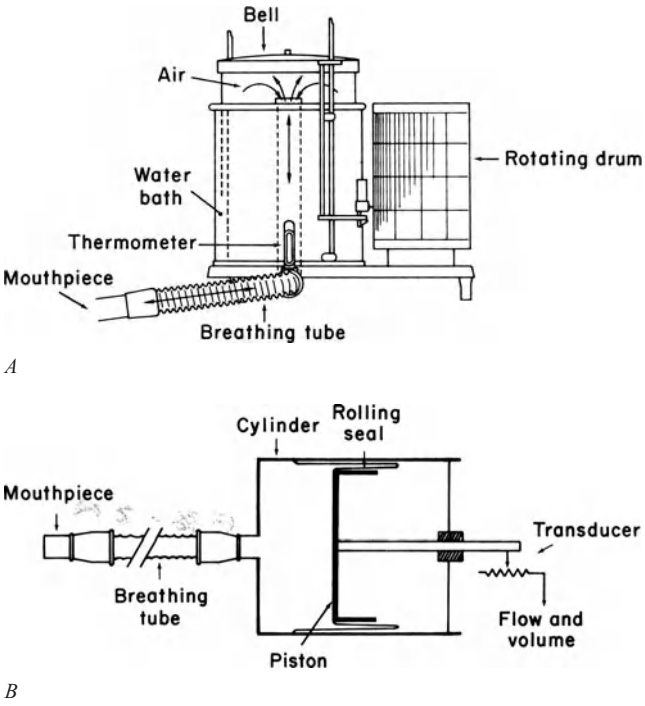


Figure 34-2 Two types of spirometers: water-sealed (*A*) and dry rolling-seal (*B*). Movement of air through the breathing tube results in movement of the bell (*A*) or piston (*B*). The output signal is either mechanical (pen on rotating drum) or electrical (flow and volume as voltage changes). The primary design criteria for these instruments are that inertia and resistance to airflow must be held to negligible levels, and the calibration must be accurate and stable.

capacity (FRC), residual volume (RV), and inspiratory capacity (IC)—are highlighted in the figure.

Spirometers that measure volume or change in volume vs. time have been used extensively in pulmonary function laboratories. Through manual calculations or use of computers, the relationship among volume, flow, and time could be generated to provide a measure of the respiratory system's ability to move air. Two examples of these volume-type spirometers are shown in Fig. 34-2.

In the water-sealed spirometer (Fig. 34-2*A*), a mouthpiece is attached to the tube through which air passes into a lightweight bell that is inverted over a water bath. Air movement through the mouthpiece into the bell during expiration causes the bell to rise; conversely, as air is withdrawn from the system during inspiration, the bell falls. The change in volume with time can be recorded on a calibrated rotating drum or digitally noted by a computer and displayed on a screen in both graphic and numeric formats.

In the dry, rolling-seal spirometer (Fig. 34-2*B*), a cylinder with a rolling plastic seal is substituted for the spirometer bell and its water seal. Movement of air through the mouthpiece effects a change in the position of the piston, which is attached to a variable resistor. The resistor, in turn, generates voltage signals proportional to volume changes reflected in displacement of the piston. These signals are processed by a computer to generate graphic and numeric outputs similar to those of the water-sealed spirometer.

Currently, most pulmonary function laboratories utilize flow-type spirometers using pneumotachographs or rotating turbines to determine airflow. Two types of pneumotachographs are in general use: hot-wire and flow-resistive. In the hot-wire type, air flowing past a heated wire cools the wire, thereby altering its resistance in proportion to changes in airflow. Flow-resistive pneumotachographs contain a resistive element composed of parallel tubes (Fig. 34-3), a wire mesh, or a fibrous, paperlike element. Airflow through the resistive element results in a pressure gradient across the

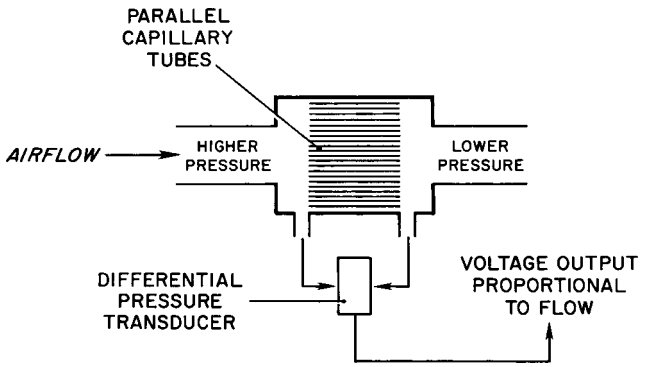


Figure 34-3 Principle of pneumotachography. During unidirectional airflow, a pressure drop is created across a resistive element made up of an array of parallel capillary tubes. The magnitude of the pressure drop is related to airflow, as described by Poiseuille's law for a laminar flow system. The pressure drop is transduced to a proportional voltage output, which can be recorded. A heating element (not shown) maintains the temperature of the expired gas near body temperature.

device, which can be measured by a very sensitive differential pressure gauge. In the model depicted in Fig. 34-3, the array of parallel small-bore tubes maintains a laminar gas flow pattern through the pneumotachograph. As a result, the pressure-flow characteristics of the system can be described by Poiseuille's law:

$$\Delta P = \dot{V}\frac{8\eta l}{\pi r^4}$$

where

ΔP = pressure drop across the resistive element, dyn/cm^2
$\dot{V}$ = gas flow, cm^3/s
η = viscosity of gas, dyn · s/cm^2
l = length of resistive element, cm
r = radius of resistive element, cm

Hence, under laminar flow conditions, the flow of gas in each tube is proportional to the pressure drop across the tube. The calculation for the overall pressure drop across the entire resistive element is based on the parallel arrangement of the array of tubes. The pressure drop across the resistive element is sensed by a pressure transducer and converted to a voltage output that is proportional to flow. The flow signal can be integrated electronically to yield volume. The output signals for flow and volume are displayed on a monitor and recorded.

Minimal standards have been established by the American Thoracic Society and the European Respiratory Society (Table 34-2) for spirometers used either for diagnostic purposes or patient monitoring.

In a diagnostic setting, spirometers are used to: (1) evaluate symptoms, signs, or abnormal laboratory tests; (2) measure the effect of disease on pulmonary function;

Table 34-2

Minimal Recommendations for Diagnostic Spirometry

Test	Range/Accuracy (BTPS)	Flow Range (L/s)	Time(s)	Resistance and Back Pressure	Test Signal
VC	0.5–8 L ± 3% of reading or ± 0.050 L, whichever is greater	0–14	30		3-L cal syringe
FVC	0.5–8 L ± 3% of reading or ± 0.050 L, whichever is greater	0–14	15	<1.5 cm H_2O/L/s	24 standard waveforms 3-L cal syringe
FEV_1	0.5–8 L ± 3% of reading or ± 0.050 L, whichever is greater	0–14	1	<1.5 cm H_2O/L/s	24 standard waveforms
Time zero	The time point from which all FEV_t measurements are taken			Back extrapolation	
PEF	Accuracy: ± 10% of reading or ± 0.30 L/s, whichever is greater Precision: ± 5% of reading or ± 0.15 L/s, whichever is greater	0–14		Mean resistance at 200, 400, 600 L/s must be <2.5 cm H_2O/L/s	26 flow standard waveforms
$FEF_{25-75\%}$	7.0 L/s ± 5% of reading or ± 0.200 L/s, whichever is even greater	±14	15	Same as FEV_1	24 standard waveforms
Instantaneous flows	±5% of reading or 0.200 L/s, whichever is greater	0–14		<1.5 cm H_2O/L/s	Proof from manufacturer
MVV	250 L/min at TV of 2 L within ± 10% of reading or ± 15 L/min, whichever is greater	±14 ± 3%	12–15	<1.5 cm H_2O/L/s	Sine wave pump

Note: BTPS = bady temperature and pressure, saturated with water vapor; VC = vital capacity; FVC = forced expiratory vital capacity; FEV_1 = forced expiratory volume in 1 s; PEF = peak expiratory flow; $FEF_{25-75\%}$ = forced expiratory flow, 25–75%; MVV = maximal voluntary ventilation; TV = tidal volume.
Source: ATS/ERS Task Force: Standardization of lung function testing. Eur Resp J *26:319–338, 2005.*

(3) screen persons at risk of having pulmonary disease; (4) assess preoperative risk; (5) assess prognosis; and (6) assess health status before enrollment in strenuous physical activity programs.

On the other hand, spirometers used for patient monitoring are used to: (1) assess therapeutic interventions, including bronchodilator therapy, management of congestive heart failure, etc.; (2) characterize the course of diseases affecting lung function (e.g., obstructive or interstitial lung diseases, congestive heart failure, or neuromuscular diseases); (3) track pulmonary function in persons working in occupations or receiving medications known to affect the lung; (4) evaluate large numbers of people in disability assessments; and (5) provide data as part of epidemiologic surveys.

In general, the diagnostic spirometer is used to assess a patient's lung function for purposes of comparison with values expected in a normal population. The monitoring spirometer, which is less expensive and more portable, is used to study a patient's performance over time and to study large numbers of people for epidemiologic or other purposes.

The Vital Capacity and Its Subdivisions

Two methods of performing a vital-capacity maneuver can be used: closed-circuit and open-circuit methods. In the closed-circuit method, the seated patient, with nose clip in place, breathes quietly into the apparatus. After several breaths to establish the resting end-expiratory level, which serves as a point of reference for all subsequent measurements, the patient is urged to inspire fully and then, after reaching a plateau at maximal inspiration, to expire maximally. This expiration must be performed slowly and evenly; attempts by the patient with obstructive pulmonary disease to maximize flow often reduce expiratory volumes because of dynamic compression of the airways caused by high positive pleural pressures (see Chapter 9). Figure 34-1 illustrates schematically this relaxed, or as previously known, slow vital capacity maneuver. From this record, tidal volume, inspiratory reserve volume, expiratory reserve volume, vital capacity, and inspiratory capacity are calculated. A similar maneuver in which the subject breathes out as rapidly and forcefully as possible after a maximal inspiration provides a measure of the forced vital capacity. Other timed measurements of expiratory airflow (e.g., the forced expiratory volume in 1 second, or FEV_1) are also determined from this type of record (see "Dynamic Mechanical Properties of the Respiratory System," below).

In the open-circuit method of determining vital capacity, the patient inspires maximally, inserts the mouthpiece, and then exhales with a slow, constant effort to the point of maximal expiration. With this technique, the resting end-expiratory position is not recorded. Thus, only the vital capacity, not its component volumes, can be measured. The open-circuit technique offers some advantages. Since the patient inspires from room air before expiring into the apparatus, concern over acquisition of infection from contaminated inspired air is minimized. In addition, the open-circuit method is generally completed in a shorter time, providing a major advantage when epidemiologic studies are being performed on large numbers of subjects.

Functional Residual Capacity and Residual Volume

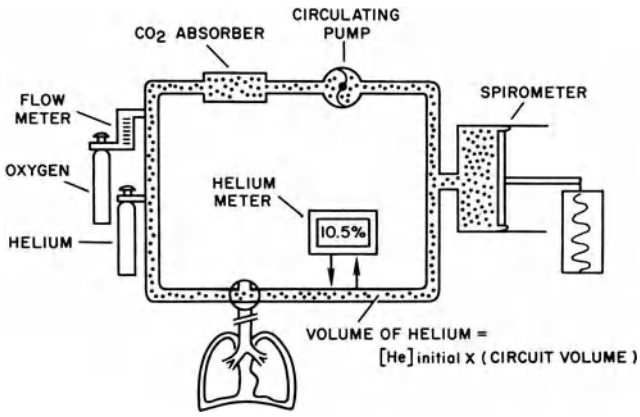
One compartment of the TLC that cannot be measured by spirometry is residual volume (RV), the volume of air remaining in the lungs at the end of a maximal expiration. RV is determined indirectly in three steps: (1) Functional residual capacity (FRC) is typically measured using one of three techniques: closed-circuit helium, open-circuit nitrogen, or total-body plethysmograph. (2) Expiratory reserve volume (ERV) is determined spirometrically. (3) RV is calculated as the difference between FRC and ERV. In principle, it is possible to determine the RV using a dilution technique or body plethysmography after maximal expiration. In practice, however, the resting end-expiratory level is a more reproducible starting point for determining FRC than is the maximal end-expiratory level for determining RV.

Closed-Circuit Helium Method

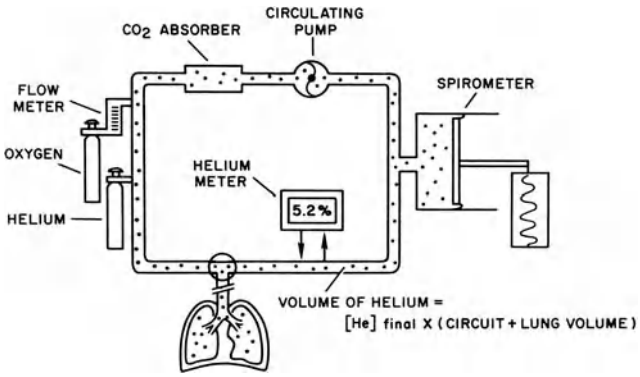
The closed-circuit helium dilution method for determining FRC is a variation of the hydrogen dilution method first used in the early nineteenth century. Both methods take advantage of the virtual insolubility of the test gas in body tissues and the law of conservation of mass. The development and simplification of this test were accomplished over a 20-year span in the mid-twentieth century. Schematic depictions of the principle upon which the technique is based and the apparatus used are shown in Fig. 34-4.

When a fully manual device is used for measuring FRC, the system is prepared by the addition of about 2 L of air and sufficient helium to achieve an initial helium concentration of approximately 10 percent in the apparatus. The patient, with nose clip in place, then breathes room air through the mouthpiece (Fig. 34-4*A*). After a preliminary period of quiet breathing to familiarize the patient with the mouthpiece, apparatus, and environment, and after the baseline resting end-expiratory level is established, the test begins.

At the end of a normal expiration, the valve at the mouthpiece is turned to connect the patient to the spirometer system (Fig. 34-4*B*). As the patient rebreathes from the closed circuit, the blower circulates the gas mixture. The CO_2 is absorbed by soda lime (CO_2 absorber), while O_2 is added through a valve and flowmeter at a rate corresponding to the subject's O_2 consumption. As the helium, which was at first contained entirely within the apparatus, mixes with air contained in the lungs, its concentration, as monitored by the helium analyzer, falls. Stabilization of the helium concentration, indicated by a rate of change in concentration of less than 0.02 percent over a 30-s interval, signals the point at which the helium concentration has equilibrated throughout the lung-breathing circuit system; equilibration, the end point of the test, occurs within 7 min in normal persons. However, in patients in whom the distribution of ventilation is abnormal (e.g., those with chronic obstructive pulmonary



A



B

Figure 34-4 Closed-circuit helium dilution method for measurement of functional residual capacity (FRC). *A.* Spirometer and tubing system with helium before subject begins breathing through the circuit. At the end of an expiration the mouthpiece valve is turned and the patient rebreathes through the circuit. Expired CO_2 is "scrubbed" out of the system, and O_2 is added to compensate for continued O_2 uptake in the lungs. *B.* During equilibration, the measured helium concentration falls, reflecting a dilutional effect of the additional volume (FRC) on the spirometer circuit.

disease) equilibration may take much longer. Upon equilibration, the following equation, based on the law of conservation of mass, is applied:

$$F_{0_{He}} \times V_0 = F_{F_{He}} \times V_F$$

where

$F_{0_{He}}$ = initial concentration of helium
V_0 = initial volume of system, L
$F_{F_{He}}$ = final concentration of helium
V_F = final volume of system, L

The initial volume of the system is the volume of the spirometer and circuit tubing, whereas the final volume consists of the initial volume plus FRC. The latter value is the only unknown in the preceding equation. Corrections are usually made for the small amount of helium dissolved in body tissues during the test and for slight volume changes caused by a respiratory exchange ratio that is not equal to 1.0. Although the method described here is based on a manually operated device, the same principles hold when all the mechanical and computational steps are accomplished with a computer-controlled system.

Nitrogen Washout Method

Conceptually, the nitrogen washout method is similar to the helium dilution method described previously; however, it relies on an open circuit rather than the closed circuit used in the helium dilution method. The open-circuit nitrogen washout method for determining FRC requires that the subject breathe 100 percent O_2 for 7 min; during this period, the concentration of N_2 in expired gas is monitored. When the expired N_2 concentration falls to zero, all the N_2 present in the lungs at the start of O_2 breathing has been "washed out." The total volume of gas expired and the concentration of N_2 in the expired gas are measured.

The calculation of FRC is based on the reasonable assumption that the volume of N_2 in the lungs at the start of the test (i.e., the product of lung volume and the concentration of N_2 in the lungs) is the same as the total volume of N_2 expired and collected during the period of the test (i.e., the product of the total volume of gas expired and the concentration of N_2 in the expired gas):

$$F_{0_{N_2}} \times V_0 = F_{E_{N_2}} \times V_E$$

where

F_{0N_2} = concentration of N_2 in the lungs
V_0 = volume of gas in the lungs, L
$F_{E_{N_2}}$ = concentration of N_2 in the expired gas
V_E = volume of expired gas, L

Since the test is started at the end of a quiet expiration, the volume of gas in the lungs is FRC. This volume is calculated by substituting into the above equation the initial concentration of N_2 in the lungs, estimated at 0.81 in fasting and 0.79 to 0.80 in nonfasting subjects, and the measured values for volume and N_2 concentration of expired gas.

Body Plethysmography

The word *plethysmography* is derived form the Greek *plethysmos*, meaning "enlargement." Although the concept of measuring FRC by recording changes in the volume of the body during "enlargement" of the chest was described in the late nineteenth century, it was not until 1956 that DuBois and coworkers introduced a practical plethysmographic technique, based on Boyle's law, for determining thoracic gas volume.

Any of three types of body plethysmographs can be used: (1) the *pressure plethysmograph*, in which pressure during breathing varies while volume remains constant; (2) the *volume plethysmograph*, in which volume varies during breathing while pressure remains constant; and (3) the *pressure-corrected flow plethysmograph*, which couples the pressure plethysmograph's fidelity of response to high-speed

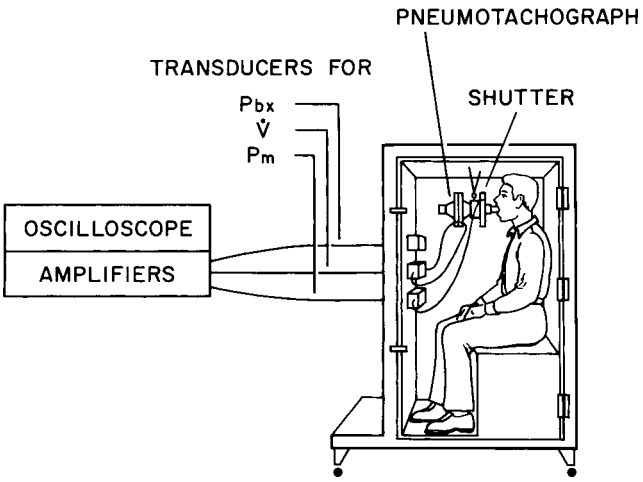


Figure 34-5 Constant-volume, variable-pressure plethysmograph used for measuring functional residual capacity and airway resistance. The device has a fixed volume. Thoracic gas volume changes associated with changes in alveolar pressure are reflected as changes in pressure within the plethysmograph.

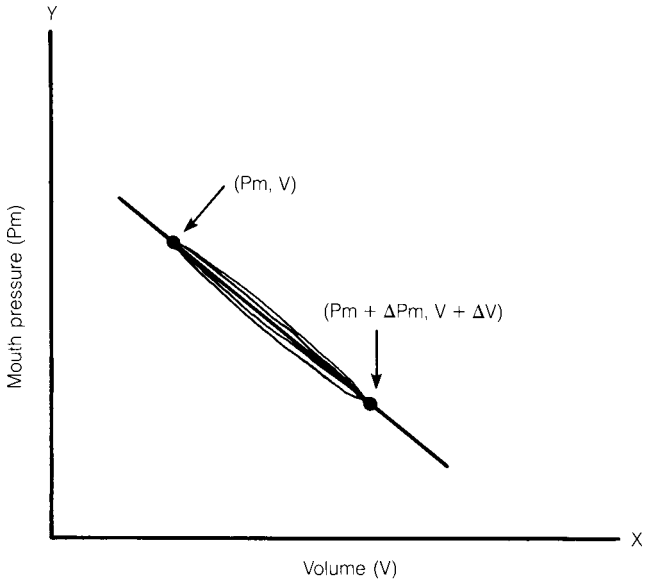


Figure 34-6 Pressure-volume loop obtained from a person seated in a body plethysmograph. Pressure at the mouth represents alveolar pressure; pressure in the box represents thoracic gas volume. After the shutter has closed at end-expiration (Pm, V), the subject attempts to inspire. Pm falls, and the pressure in the box increases. This increase in box pressure is calibrated in terms of an equivalent volume change. The new position of the trace at the end of the inspiratory effort is (Pm + Δ Pm, V + ΔV). The slope of the loop depends on the volume of gas in the lungs when the shutter is closed (FRC).

events with the volume plethysmograph's ability to follow large changes in volume. Since the conceptual basis for all three devices is about the same, only the most popular one—the pressure plethysmograph—will be described.

The pressure plethysmograph (Fig. 34-5) contains a pneumotachograph and transducer for measuring flow and volume and two strain-gauge transducers, one for sensing pressure at the mouth (Pm) and the other for sensing pressure in the box (Pbx). A solenoid-operated shutter mechanism is situated between the mouthpiece and the pneumotachograph. The three transducers are connected to an amplifying and monitoring system so that box pressure (or lung volume) and mouth pressure are displayed simultaneously on the X and Y axes, respectively, of an oscilloscope (Fig. 34-6).

In order to determine FRC, the patient, seated comfortably within the box with nose clip in place, is asked to breathe quietly through the mouthpiece. At the end of a quiet expiration, the shutter is closed and the patient is instructed to pant gently against it. The panting movements cause both mouth pressure and box pressure to change. With each inspiratory effort, as mouth pressure falls and gas in the lungs is rarefied, lung volume increases. Because the plethysmograph is a closed box, the increase in lung volume produces a corresponding increase in box pressure. With each expiratory effort, as lung volume decreases, box pressure falls. Because the shutter is closed while the measurements are made, mouth pressure equals alveolar pressure (P_A). These oscillations in mouth pressure and box pressure or lung volume appear on the oscilloscope as a closed loop (Fig. 34-6). Measurement of the slope of this loop is used to determine the volume of gas in the lungs at the time of shutter closure—i.e., thoracic gas volume (TGV or V_{TG}). When the occlusion occurs at resting end-expiratory lung volume, the measurement yields FRC (see below).

Applying Boyle's law to the plethysmographic determination of lung volume,

$$PV = (P + \Delta P)(V + \Delta V)$$

where

P = pressure in the lungs at end expiration (atmospheric pressure), cm H_2O
ΔP = change in pulmonary pressure produced by respiratory efforts, cm H_2O
V = volume of gas in the lungs at end expiration (FRC), L
ΔV = change in gas volume in the lungs produced by compression (during expiration) and rarefaction (during inspiration) secondary to respiratory efforts, L

In the pressure plethysmograph, ΔV is sensed as a change in pressure within the box, and ΔP is determined from the change in mouth pressure during breathing efforts against the closed shutter.

Rearranging the above equation and solving for V yield:

$$V = \frac{\Delta V}{\Delta P}(P + \Delta P)$$

However, since ΔP is small compared to P (atmospheric pressure), it may be disregarded. The equation then becomes:

$$V = P \times \frac{\Delta V}{\Delta P}$$

where

V = functional residual capacity, L
P = atmospheric pressure, cm H_2O
$\Delta V/\Delta P$ = inverse of slope of the loop on the oscilloscope

Therefore, the only unknown in this equation is V, which can be calculated by incorporating values for barometric pressure and the inverse of the slope of the plot of mouth pressure vs. box pressure ($\Delta P/\Delta V$).

Comparison of Methods

Compared to the dilution and washout techniques, body plethysmography is, by far, the fastest method available for determining FRC. Indeed, it enables several determinations to be made per minute. Although the equipment required for body plethysmography is more expensive than that required for the other methods, in a busy laboratory this technique generally proves to be more economical because of the time saved and the additional uses to which the equipment can be put (e.g., measurement of airway resistance; see "Airway Resistance," below). Technically, the test is only slightly more difficult than the inert gas dilution method.

Sources of error inherent in the use of body plethysmography and discrepancies between results obtained by body plethysmography and the inert gas techniques should be noted. In patients with chronic obstructive pulmonary disease (COPD) and asthma, values for FRC obtained by body plethysmography may be artifactually high because of pressure differences between the mouth and alveoli generated during panting across narrowed airways. Consequently, pressures recorded at the mouth during shutter occlusion of the airway underestimate changes in alveolar pressure.

The inert gas dilution and washout methods are similar both in principle and in results. The values for FRC with these techniques match those from the body plethysmograph except in persons in whom considerable areas of the lungs are poorly ventilated, usually due to obstructive airway disease. In these individuals, complete mixing or washout of the indicator gas is very slow, at times requiring 45 min or longer. Because of the slow equilibration of gas concentrations in the poorly ventilated areas, the usual time allotted for the test is inadequate, resulting in a lower value for FRC by the washout methods than by body plethysmography. One strategy commonly used to deal with this problem is to prolong the washout time. The primary advantage of these techniques over body plethysmography is that they can be used in persons for whom the plethysmograph is impractical (e.g., those with marked obesity, skeletal abnormalities, or claustrophobia).

Temperature Correction Factors

By convention, all lung volumes described above and airflows (see below) are expressed in terms of body temperature and pressure, saturated with water vapor (BTPS). This practice enables direct comparison of pulmonary function data from laboratories operating at different ambient temperatures and altitudes. To convert the volume of gas collected in a volume-type spirometer under ambient conditions (i.e., ambient temperature and pressure, saturated with water vapor, or ATPS) to BTPS, a conversion factor is applied (Table 34-3). Previously, it was presupposed that ambient air entering a spirometer was cooled *immediately* to ambient temperature and remained saturated with water vapor (ATPS). Under this assumption, only ambient temperature was considered in determining the appropriate correction factor. However, studies have addressed the assumption that expired gas is immediately cooled, as well as the practical consequences of temperature correction errors. The American Thoracic Society recommends temperature correction of results from volume-type spirometers based on *measured* gas temperature at the time of testing.

Table 34-3

Factors for Converting Volumes from ATPS to BTPS at Barometric Pressure of 760 mmHg*

Ambient Temperature, °C	Multiplier to Convert Volumes to BTPS†
20	1.101
21	1.096
22	1.091
23	1.085
24	1.080
25	1.074
26	1.069
27	1.062

* *Based on Boyle's, Charles's, and Dalton's laws.*
† *Volume at ATPS × multiplier = volume at BTPS.*
Note: ATPS = ambient temperature and pressure, saturated with water vapor; BTPS = body temperature and pressure, saturated with water vapor.

Radiographic Assessment of Lung Volume

Although initial reports describing use of radiographic techniques to measure lung volumes date back over 40 years, these methods have not found widespread use in adult populations. More sophisticated computed tomography (CT) applications have demonstrated good correlation with plethysmographic and gas dilution techniques in normal individuals, but

significant differences can arise in patients with a wide variety of lung diseases.

STATIC MECHANICAL PROPERTIES OF THE RESPIRATORY SYSTEM

Exploration of the elastic properties of the respiratory system and their effect on lung volumes and work of breathing began in earnest during the earlier part of the twentieth century. Although the groundwork had been laid centuries before (by Robert Hooke's *The Theory of Springs* in 1678), between 1923 and 1956 investigators provided a wealth of information about the elastic properties of the respiratory system and its components and the work done in overcoming these elastic forces during breathing.

Static Compliance of the Lungs

The elastic properties of the lungs are determined by relating the change in the volume of air contained in the lungs to the corresponding change in the recoil force of the lungs. Change in lung volume is most easily measured by determining the volume of gas inspired or expired at the mouth. Although expedient, this approach to determining the elastic properties of the lungs can underestimate the change in lung volume when incorporated into techniques (see below) that require the subject to expire gently against a closed shutter, a maneuver that compresses thoracic gas. However, the problem can be circumvented by placing the subject in a volume plethysmograph that uses a spirometer attached to the plethysmograph to record changes in thoracic gas volume due to gas compression.

The recoil force of the lungs, measured as the transpulmonary pressure (Fig. 34-7), is the difference between the alveolar and pleural pressures (P_A and Ppl, respectively). Alveolar pressure is determined as the pressure at the airway opening (Pao)—i.e., the mouth—when airflow is arrested and the glottis is open. The pleural pressure is determined indirectly by measuring the pressure in the esophagus using an esophageal balloon catheter. This technique, first introduced in 1949, has been improved over the years and provides accurate reflections of changes in pleural pressure at all lung volumes except those below FRC.

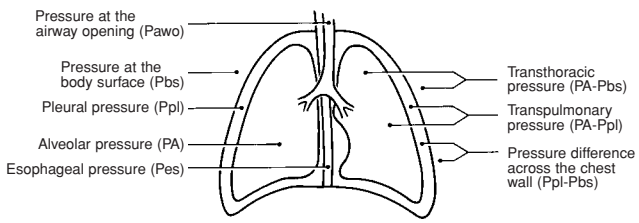


Figure 34-7 Schematic representation of the chest depicting pressure terms and gradients used in analysis of the mechanics of breathing. The expressions for individual pressure measurements on the left are relative to atmospheric pressure. Pleural pressure (Ppl) is not routinely measured directly but is approximated by esophageal pressure (Pes) measured with a balloon catheter.

A thin rubber balloon, about 10-cm long, is placed over a small-diameter polyethylene catheter. Several holes in the terminal portion of the catheter allow pressure to be transmitted from the balloon, through the catheter, to a transducer. The balloon is positioned in the lower third of the esophagus, where esophageal pressure and, therefore, balloon pressure accurately reflect the pressure acting on the lung surface (pleural pressure). Use of an elongated balloon of low volume helps to minimize changes in pressure due to esophageal contractions. By conveying mouth pressure and esophageal pressure to opposite sides of a differential pressure transducer, an output signal is generated that is proportional to the difference between these two pressures—i.e., the transpulmonary pressure P_A – Ppl.

To determine the elastic properties of the lungs, the patient, with esophageal balloon in place, is seated in a closed body plethysmograph. The patient then breathes ambient air through a tube to the outside until the volume trace, inscribed by the plethysmograph spirometer, indicates that the end-expiratory level is stable. At this juncture, the patient is instructed to first inspire slowly to TLC and then to expire slowly to the resting end-expiratory level (FRC). This maneuver is then repeated; during the second expiration, the shutter is activated to occlude the airway intermittently. Since each closure of the shutter interrupts the expiration briefly, the recorded trace of expiratory volume vs. time displays a staircase pattern (Fig. 34-8*A*). The plateau resulting from each closure of the shutter marks a finite period of zero change in lung volume as the lungs empty during expiration. Associated with each plateau is a corresponding plateau in transpulmonary pressure.

The relationship between the change in volume and the change in pressure is a measure of the *recoil force* of the lungs at each of the lung volumes that are registered (Fig. 34-8*B*). The resulting curve provides several useful indices of the elastic behavior of the lungs. The slope of the curve over the range corresponding to the tidal volume is the *static lung compliance.* The transpulmonary pressure attained at TLC is the *maximal static recoil pressure.* The ratio of the maximal static recoil pressure to the corresponding maximal lung volume is the *coefficient of retraction.* However, since these values are derived from only small segments of the curve, inspection of the total static pressure-volume curve remains the most comprehensive means of assessing the elastic properties of the lungs.

Static Compliance of the Chest Wall

Functionally, the chest wall includes the bony thorax, intercostal muscles, overlying soft tissue, pleura, and diaphragm. The chest wall is distensible and has its own distinctive elastic properties. In the normal, end-expiratory, resting position of the respiratory system (FRC), the inward recoil of the lung is balanced by the outward recoil of the chest wall (Fig. 34-9*B*). As the volume of the thoracic cavity enlarges

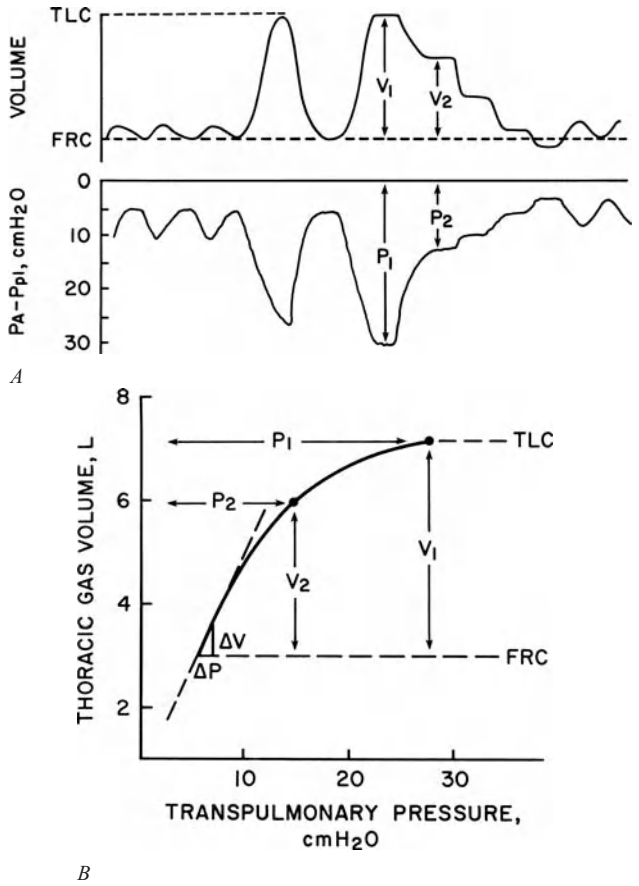


Figure 34-8 Measurement of the elastic properties of the lungs. *A.* Recordings of changes in lung volume and transpulmonary pressure (P_A-Ppl) using the esophageal balloon technique described in the text. Simultaneous measurements of volume and pressure are obtained during periods of arrested airflow at lung volumes ranging from total lung capacity (TLC) to just below functional residual capacity (FRC). *B.* Thoracic gas volume is plotted on the ordinate and transpulmonary pressure on the abscissa. The curve formed by the plot using values from *A* describes the elastic properties of the lungs. The slope of the line, $\Delta V/\Delta P$, over the range of the tidal volume is the static compliance of the lungs.

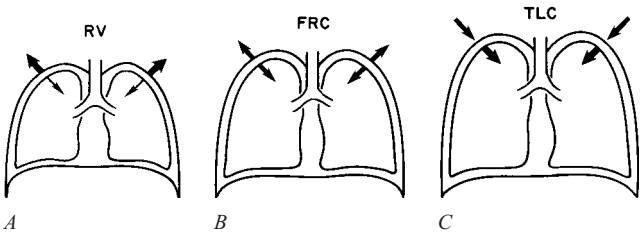


Figure 34-9 Schematic depiction of elastic recoil vectors across the lung and chest wall as determined by the level of inflation. *A.* At residual volume (RV), the outwardly directed recoil pressure of the chest wall is large and the inwardly directed recoil pressure of the lung is small. *B.* At functional residual capacity (FRC), the recoil pressures of the lung and chest wall are equal and in opposite directions. *C.* At total lung capacity (TLC), both recoil pressures are directed inward, and each contributes substantially to the overall recoil pressure of the respiratory system.

progressively during inspiration from FRC to TLC, the outward recoil pressure of the chest wall lessens, becoming zero at approximately 70 percent of TLC; beyond this point, the chest wall begins to recoil inwardly (Fig. 34-9*C*). Conversely, as the chest wall is compressed below FRC by the action of the expiratory muscles, the natural outward recoil tendency is increased (Fig. 34-9*A*).

In practice, assessment of the elastic properties of the chest wall is accomplished by first determining the compliance curve of the respiratory system as a whole and then subtracting the contribution of the lungs. For a given lung volume, the pressure across the chest wall, Ppl – Pbs (Fig. 34-7), is simply the difference between the transthoracic (P_A – Pbs) and transpulmonary (P_A – Ppl) pressures. As indicated above, Ppl is determined using an esophageal balloon catheter.

Elastic Properties of the Respiratory System as a Whole

The elasticity of the respiratory system as a whole is determined by measuring the change in volume resulting from a change in pressure applied to the system—i.e., the transthoracic pressure (P_A – Pbs)—*while the respiratory muscles are completely relaxed.*

The first method used for this evaluation employed the relaxation technique described by Rahn and colleagues. The subject breathes quietly into an apparatus consisting of a spirometer, a shutter, and a pressure transducer connected to the subject's side of the shutter (Fig. 34-10). After a period

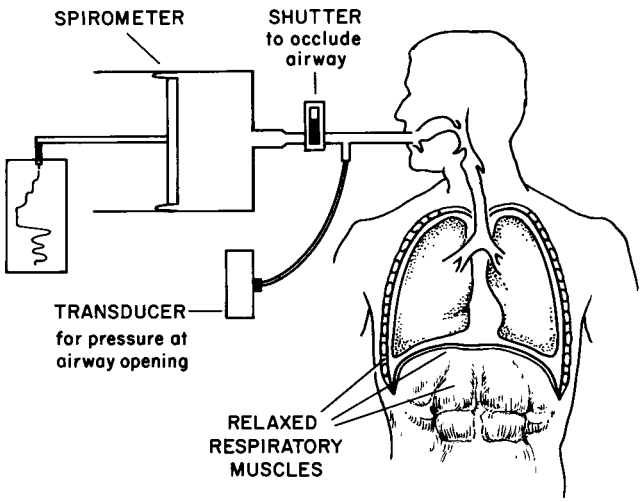


Figure 34-10 Relaxation technique for measurement of elastic recoil pressure of the respiratory system. After a period of normal tidal volume breathing, the subject inspires to total lung capacity (TLC). A shutter in the airway is closed, and the subject relaxes his or her respiratory muscles. The shutter is periodically opened, permitting exhalation of a small volume of air measured by the spirometer. Airway pressures are recorded at times of shutter closure (i.e., during no airflow, when mouth pressure equals alveolar pressure). A pressure-volume curve is then constructed from the simultaneously recorded values for pressure and volume.

of quiet breathing, the subject is instructed to inspire maximally; the shutter is closed at peak inspiration, and the subject is then asked to relax the respiratory muscles completely while keeping the glottis open. Periodically, the shutter is opened, allowing a small volume of air to move from the subject into the spirometer; the shutter is then closed again. This maneuver is repeated until FRC is reached. During the periods of arrested airflow, pressure at the mouth (Pao) is equal to the pressure in the alveoli (P_A). Provided the pressure at the body surface is atmospheric and the respiratory muscles are completely at rest, this value represents transthoracic pressure. In practice, however, full relaxation of the respiratory muscles is difficult, and a contribution by them to the pressure at the airway opening is frequently unavoidable.

A more practical technique entails the application of continuous positive pressure to the airways during spontaneous breathing. The subject breathes quietly into a water-sealed spirometer until a constant end-tidal level is achieved. A weight is then placed on the spirometer bell to increase the pressure in the respiratory system and, thereby, to raise the resting end-expiratory lung volume. This procedure is repeated using several different weights so that a pressure-volume curve of the total respiratory system can be constructed.

The individual pressure-volume curves for the lungs and chest wall and the composite curve for the intact respiratory system are shown in Fig. 34-11. As illustrated, the elastic recoil of the chest wall alone is determined by subtracting the recoil pressure of the lung from that of the total respiratory system. Chest wall elasticity is an important determinant of the subdivisions of lung volume and the overall compliance of the respiratory system; the latter is, in turn, an important determinant of the work of breathing.

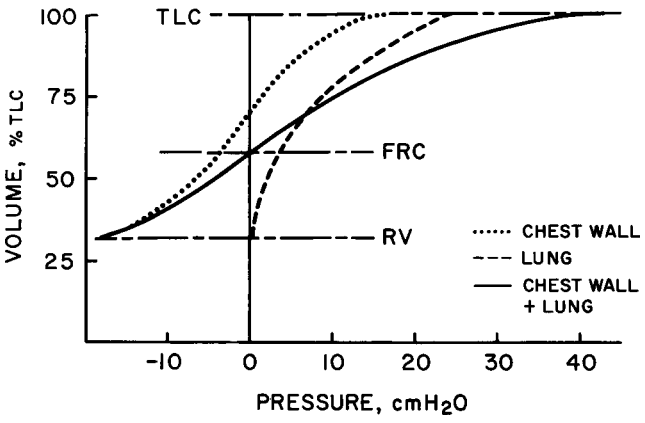


Figure 34-11 The pressure-volume curves of the respiratory system and its components. The elastic recoil pressures of the total respiratory system (solid line) over the vital capacity range are the sum of the recoil pressures of the lung (dashed line) and chest wall (dotted line). At functional residual capacity (FRC), the chest wall recoil pressure is counterbalanced by the lung recoil pressure. The net result is a total system recoil pressure of 0. The total system recoil pressure is obtained by relaxation pressure or continuous positive-pressure breathing techniques. The chest wall recoil pressure is calculated as the difference between the recoil pressure of the entire respiratory system and the recoil pressure of the lungs.

Several features of the pressure-volume relationships shown in Fig. 34-11 are worth emphasizing. As lung volume approaches RV, the elastic recoil pressure of the respiratory system is largely due to the outwardly directed recoil pressure of the chest wall. At RV, the contribution of the lung to the recoil pressure of the respiratory system is minimal. At the other extreme of lung volume, TLC, elastic recoil pressure is high and directed inwardly, due to the combined elastic recoils of the lung and chest wall. At FRC, the outwardly directed recoil of the chest wall balances the inwardly directed recoil of the lung, and the transthoracic pressure is zero (i.e., $P_A - Pbs = 0$). Indeed, the system "comes to rest" at FRC because of the counterbalancing of these forces at that volume. Since alveolar pressure at FRC is zero, no pressure gradient exists for airflow. Therefore, the system remains stationary until acted upon by the muscles of inspiration or expiration.

Elastic Properties of the Respiratory System in Health and Disease

The elastic properties of the respiratory system are altered by a wide variety of diseases that can affect the lung parenchyma or chest wall, either selectively or in concert. Most instances of clinically significant reductions in static compliance are due to abnormalities in the lung. The two standard clinical measures of the elastic properties of the lung are static lung compliance and maximal static recoil pressure.

Static lung compliance (Cst,L) is determined over the linear portion of the pressure-volume curve, between FRC and a lung volume corresponding to FRC plus 0.5 L. Normal values vary among laboratories, ranging from 0.147 to 0.375 L/cm H_2O, with a mean of 0.262 L/cm H_2O. Some variability is related to age and sex; Cst,L decreases with age and is higher in males than in females.

Maximal static recoil pressure is the recoil pressure at TLC. Once again, normal values vary. Data from one series of 51 normal subjects are shown in Table 34-4.

In disease states characterized by an increased elastic recoil pressure, such as diffuse interstitial fibrosis, the pressure-volume curve is shifted to the right and the static lung compliance decreases (Fig. 34-12*A* and *B*). The increased elastic recoil pressure contributes to a decrease in FRC and TLC. By expressing the volume axis of the pressure-volume curve in terms of *percent predicted TLC* (Fig. 34-12*B*), instead of *absolute TLC* (Fig. 34-12*A*), the reduction in maximal lung volume is clearly evident (i.e., maximal recoil pressure is increased, despite the reduced TLC).

In contrast to the effects of fibrosis, emphysema, which destroys alveolar walls and enlarges alveolar spaces, reduces lung elastic recoil pressure (Pel). This change increases both TLC and FRC. The shift of the pressure-volume curve upward and to the left (Fig. 34-12*A* and *B*) indicates that lung compliance increases and that the maximal recoil pressure decreases. If the volume axis is expressed as percent predicted

Table 34-4

Normal Maximal Static Recoil Pressures for Adults (cm H_2O)

	Male Age (Years)			Female Age (Years)		
	25–35	**36–64**	**65–75**	**25–35**	**36–64**	**65–75**
Mean ± SD	35.9 ± 8.5	33.0 ± 8.7	33.0 ± 2.9	36.4 ± 5.8	25.7 ± 4.0	23.7 ± 3.9
Range	24.0–48.0	21.5–48.0	17.0–42.2	21.0–48.0	20.0–30.0	18.0–31.6

Source: Data from Knudson RJ, Clark DF, Kennedy TC, et al: Effect of aging alone on mechanical properties of the normal adult human lung. J Appl Physiol *43:1054–1062, 1977.*

TLC (Fig. 34-12*B*), the increase in lung volume is more clearly demonstrated.

As noted previously, disorders affecting primarily the chest wall can also significantly alter the elastic properties of the respiratory system. Among these are obesity, kyphoscoliosis, and fibrothorax. These disorders limit chest wall excursion and lung expansion and reduce FRC. In addition, they produce decreases in static compliance of the lung and chest wall and maximal recoil pressure.

Respiratory Muscle Strength

Ventilatory performance depends not only on the mechanical properties of the lungs and chest wall, but also on the strength of the respiratory muscles. Evaluation of respiratory muscle strength was undertaken as early as the mid-nineteenth century. Subsequently, using simplified methods of measurement, Black and Hyatt established normal values (Table 34-5).

The maximal pressure generated by an isometric contraction varies directly with the resting length of the muscle. Consequently, values for maximal inspiratory and expiratory pressures depend on the lung volume at which the tests are performed (Fig. 34-13). When TLC is less than 70 percent of the predicted value, the maximal expiratory pressure will be low. Similarly, when RV exceeds 40 percent of the predicted TLC, the maximal inspiratory pressure will be low.

The only equipment required for measurement of maximal inspiratory or expiratory pressure is an aneroid vacuum and pressure gauge. To determine maximal expiratory pressure, the patient is urged to inspire fully to TLC and then to expire as forcefully as possible into the gauge. The highest pressure attained and held for at least 1 s is the *maximal expiratory pressure* ($P_{E_{max}}$). The *maximal inspiratory pressure* ($P_{I_{max}}$) is determined by having the patient inspire maximally from the gauge after having expired completely to RV. The value recorded is the lowest pressure attained and held for at least 1 s.

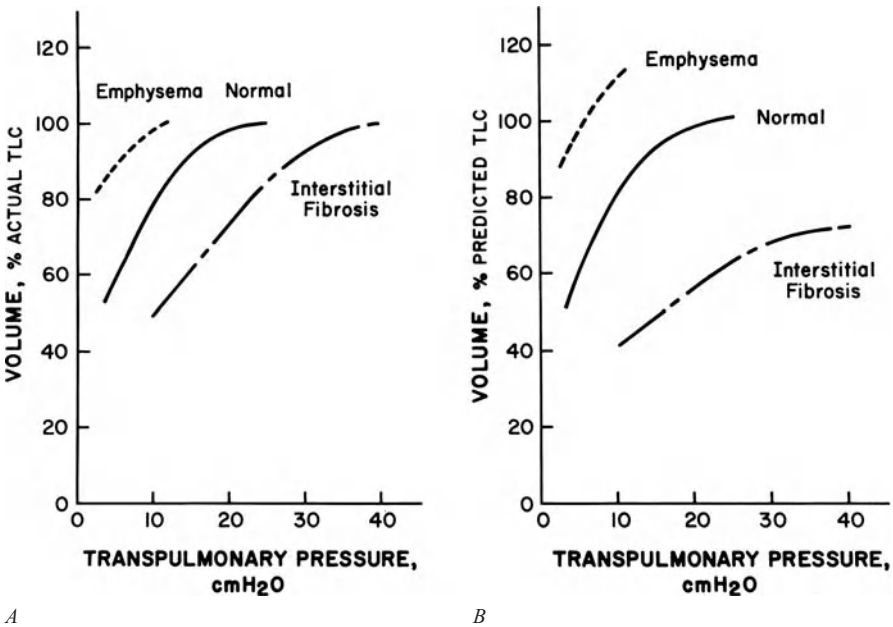


Figure 34-12 Pressure-volume curves of the lungs in health and disease. *A.* Volume expressed as percent of actual total lung capacity (TLC). Differences in transpulmonary pressures in normal and diseases states are evident. Changes in lung volume that occur with disease are demonstrated on the plots. *B.* Volume expressed as percent of predicted TLC. In addition to the differences in transpulmonary pressures, alterations in lung volumes in the disease states are evident.

Table 34-5

Prediction Equations and Lower Limits of Normal for Maximal Inspiratory ($P_{I_{max}}$) and Maximal Expiratory ($P_{E_{max}}$) Pressures (cm H_2O)*

	$P_{I_{max}}$		$P_{E_{max}}$	
	Predicted Mean (cm H_2O)	**Lower Limit of Normal**	**Predicted Mean (cm H_2O)**	**Lower Limit of Normal†**
Male	143 − (0.55 × age)	71	268 − (1.03 × age)	111
Female	104 − (0.51 × age)	39	170 − (0.53 × age)	88

**Age range = 20 to 86 years.*
† Independent of age.
Source: Equations and lower limits of normal from Black LF, Hyatt RE: Maximal respiratory pressures: Normal values and relationship to age and sex. Am Rev Respir Dis *99:696–702, 1969.*

Measurement of maximal static respiratory pressures is particularly important in evaluating respiratory muscle weakness in patients with neuromuscular disease, as described in Chapter 93. In such patients, spirometric tests are often normal, despite respiratory muscle weakness, because maximal pressures are not required to achieve maximal expiratory flow rates.

Another useful function of these measurements is in examining patients whose coordination in performing spirometry or whose degree of motivation is suspect. In such patients, determination of maximal pressures is often helpful in determining whether optimal efforts are being expended during pulmonary function testing (see "Approach to Interpreting Commonly Performed Pulmonary Function Tests," below).

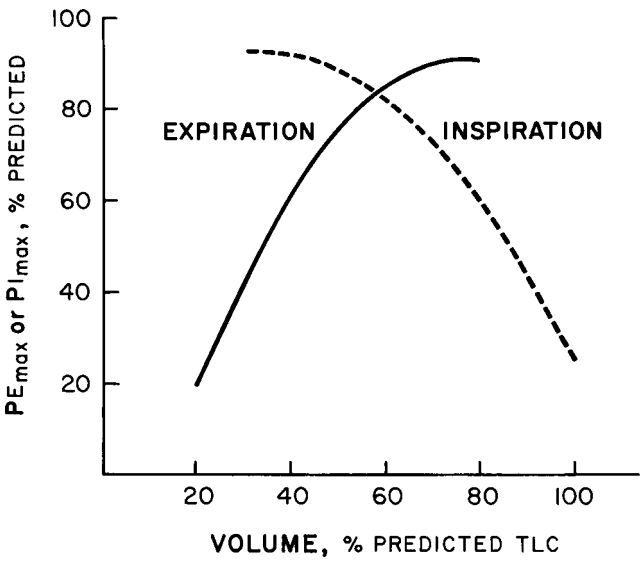


Figure 34-13 Effect of lung volume on maximal inspiratory (dashed line) and maximal expiratory (solid line) pressures. See text for discussion.

DYNAMIC MECHANICAL PROPERTIES OF THE RESPIRATORY SYSTEM

The static tests of pulmonary function described in the previous section are based on measurements of volume and pressure made while airflow is arrested. These static tests are particularly useful in defining the elastic properties of the respiratory system. Considerable additional information can be gained from tests done during airflow (i.e., under "dynamic" conditions).

Although measurements of static lung volumes began about 300 years ago, the assessment of pulmonary function during airflow began in 1933, when the test now known as the *maximal voluntary ventilation* was first proposed. This test did not become popular until a few years later, when Cournand and Richards developed regression equations to determine normal values. Subsequently, investigators proposed that the volume of air expired during specific time intervals be determined. In 1955, determination of the average airflow during the middle half of a forced expiratory vital capacity was described. Determination of these indices of dynamic lung function is now generally part of the battery of tests, both static and dynamic, included under the designation *spirometry.*

The more practical tests of dynamic function can, for convenience, be divided into four categories: forced vital capacity, flow-volume curves, maximal voluntary ventilation, and airway resistance. Other dynamic tests, including assessment of airway reactivity and the function of small airways, will be considered separately.

Forced Vital Capacity

Both expiratory and inspiratory measurements of the forced vital capacity are routinely made in pulmonary function laboratories. Unless otherwise specified, FVC refers to the forced *expiratory* maneuver.

Forced Expiratory Vital Capacity

The forced expiratory vital capacity is measured during expiration. The maneuver entails two steps: a full inspiration to TLC, followed by a rapid, forceful, maximal expiration (to RV) into a spirometer. The forced expiratory vital capacity (FVC) is normally equal to the relaxed or slow vital capacity (VC). However, a discrepancy between FVC and VC appears in obstructive disease of the airways: the FVC is less than the VC. The relationship between expired volume and time during an FVC maneuver is used to determine airflow during expiration and the volume of air expired within designated intervals; these values provide an indirect measure of the flow-resistive properties of the lung. The FVC is displayed in one of two ways: expired volume plotted against time (Fig. 34-14) or airflow plotted against lung volume—i.e., an expiratory "flow-volume curve" (see below).

The normal volume-time display of the FVC consists of a smooth curve with a gradually and progressively decreasing slope. Irregularities in the curve suggest either a failure of coordination or a suboptimal effort. At times, the onset of the forced expiration is unclear (Fig. 34-15) because of hesitation on the part of the patient. When this occurs, the start of expiration ("zero time") is determined with the "back extrapolation" method (Fig. 34-15): a tangent taken through the part of the curve with the steepest slope is extrapolated back to the maximal inspiratory volume; the point of intersection is considered to be the time of onset of expiration. Several values are commonly determined from the volume-time plot of the forced vital capacity (Table 34-6, Fig. 34-14): (1) the *volume expired in the first second*, expressed either as an absolute volume (FEV_1) or as a percentage of the forced vital capacity (FEV_1/FVC%); (2) *the volume expired in the first 3 seconds*, expressed either as an absolute volume (FEV_3) or as a percentage of the forced vital capacity (FEV_3/FVC%); and (3) *the forced mid-expiratory flow rate* ($FEF_{25-75\%}$). The $FEF_{25-75\%}$ is determined by locating the points on the volume-time curve corresponding to 25 and 75 percent of the FVC and then calculating the slope of a straight line passing through those two points. The slope of this line represents the average airflow over the mid-portion of the FVC.

Although the *relaxed* or *slow vital capacity* (VC) may be normal or only modestly reduced in patients with obstructive disease of the airways, the volume-time relationship of the FVC maneuver is usually distinctly abnormal in such

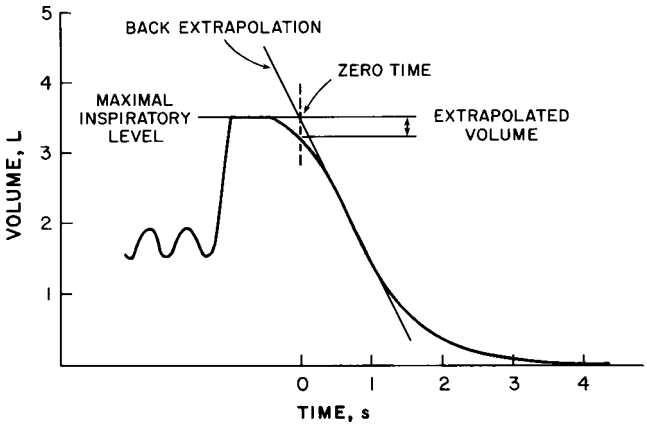


Figure 34-15 Technique of back extrapolation for determining the zero time in calculation of FEV_1. Zero time is determined as the point of intersection of a tangent drawn through the steepest portion of the spirogram and a line drawn horizontally through the maximal inspiratory level.

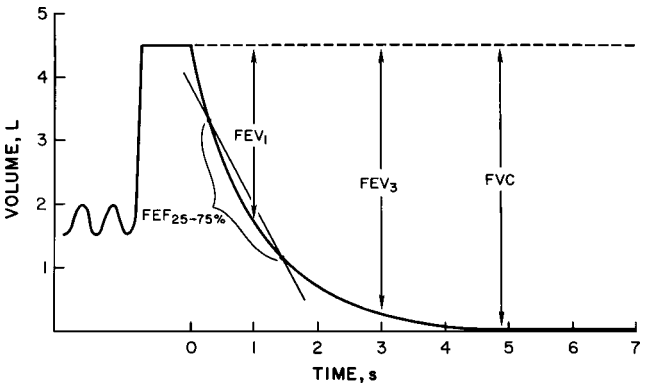


Figure 34-14 Forced expiratory vital capacity maneuver. After an initial period of tidal volume breathing, the patient inspires maximally to total lung capacity (TLC) and then exhales as rapidly and as forcefully as possible into a spirometer. Shown on the left of the tracing are a series of tidal volume breaths and the maximal inspiration to TLC. The forced expiration begins at time 0. Nearly all the volume is exhaled in the first 3 s of the maneuver. The values for FVC, FEV_1, and FEV_3 are measured from the maximal inspiratory level. The $FEF_{25-75\%}$ is the slope of the line connecting the points on the volume-time trace that correspond to 25 percent and 75 percent of the FVC.

Table 34-6

Values Obtained from Forced Expiratory Volume-Time Curves

FVC (BTPS), L	Forced vital capacity; the total volume expired
FEV_1 (BTPS), L	Volume of air expired in the first second
FEV_1/FVC%	Volume of air expired in the first second, expressed as percent of the FVC
FEV_3/FVC%	Volume of air expired in the first 3 s, expressed as percent of the FVC
$FEF_{25-75\%}$ (BTPS), L/s	Forced mid-expiratory airflow

Note: BTPS = body temperature and pressure, saturated with water vapor.

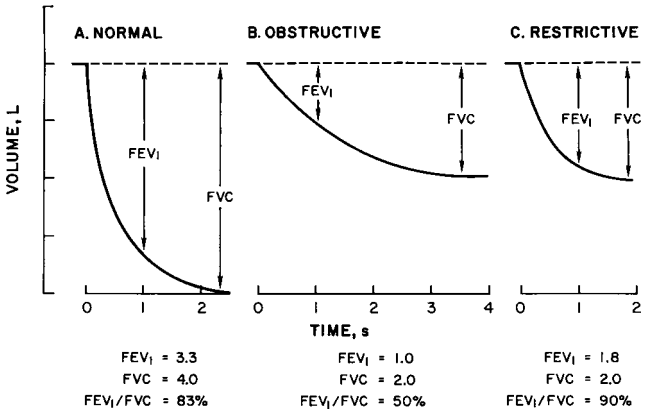


Figure 34-16 Representative spirograms from a normal subject (*A*), a patient with obstructive lung disease (*B*), and a patient with restrictive lung disease (*C*), obtained during a forced expiratory vital capacity maneuver. In the normal subject, expiration is completed within 3 s, and 83 percent of the volume is expired in the first second ($FEV_1/FVC\% = 83$). In the patient with obstructive disease, expiration is prolonged, and only half the volume is expired in the first second ($FEV_1/FVC\% = 50$). In the patient with restrictive disease, although the magnitude of the reduction in exhaled volume is the same as in the obstructed patient, most of the volume is exhaled within the first second ($FEV_1/FVC\% = 90$).

patients (Fig. 34-16*A* and *B*). Most obvious is a flattening of the slope of the curve at any given lung volume, reflecting the reduced airflow. In addition, the duration of the forced expiratory maneuver is prolonged. Normally, expiration is complete within 6 s; in obstructive airway disease, expiratory airflow may continue for 10 to 12 s. These changes in the expiratory airflow reduce the FEV_1 and FEV_3, the $FEV_1/FVC\%$, the $FEV_3/FVC\%$, and the $FEF_{25-75\%}$.

Restrictive lung disorders reduce the slow VC. However, the *configuration* of the volume-time relationship may not be abnormal (Fig. 34-16*C*). Although the FEV_1 and FEV_3 are reduced because of the reduced vital capacity, the $FEV_1/FVC\%$ and $FEV_3/FVC\%$ remain normal or even exceed normal values. Often, because of the reduced VC, the $FEF_{25-75\%}$ is also less than predicted.

Forced Inspiratory Vital Capacity

Measurement of the forced inspiratory vital capacity (FIVC) consists of two steps: (1) full expiration to RV, followed by (2) a rapid maximal inspiratory effort (Fig. 34-17). The rate of airflow over the middle half of the forced inspiratory vital capacity ($FIF_{25-75\%}$) is determined using a procedure similar to that described previously for the $FEF_{25-75\%}$.

In normal subjects, the $FIF_{25-75\%}$ is greater than the $FEF_{25-75\%}$. Since inspiratory flow is more dependent on effort than is expiratory flow, a fall in the $FIF_{25-75\%}$ is usually a more sensitive indicator of respiratory muscle dysfunction or a suboptimal effort than is the $FEF_{25-75\%}$. When airway resistance is high, a disproportionate fall in $FIF_{25-75\%}$ relative to $FEF_{25-75\%}$ suggests an extrathoracic site of airway obstruction (see "Approach to Interpreting Commonly Performed Pulmonary Function Tests," below).

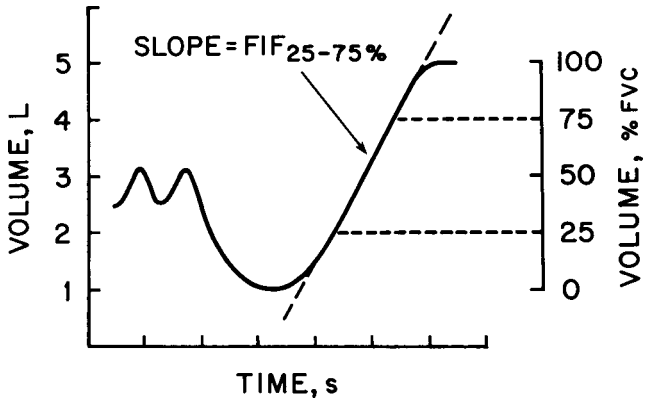


Figure 34-17 Forced inspiratory volume-time curve. The $FIF_{25-75\%}$ is the slope of a line between the points on the trace corresponding to 25 percent and 75 percent of the inspired volume.

Flow-Volume Relationships

In addition to analysis of the relationship between volume and time depicted on a spirogram, examination of the relationship between flow and volume provides useful information about lung function. A flow-volume curve, which shows the relationship between lung volume and maximal airflow as lung volume changes during a forced expiration, is shown in Fig. 34-18. The test comprises four phases of breathing into a

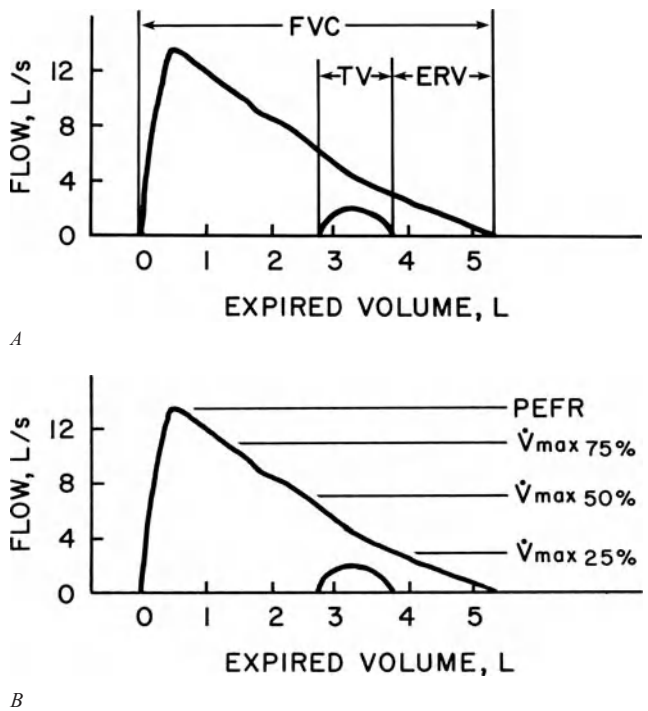


Figure 34-18 Flow-volume plots during forced expiration (outer trace) and quiet expiration (inner trace). *A.* The subdivisions of lung volume. *B.* The common flow measurements. PEFR = peak expiratory flow rate; $\dot{V}_{max\,75\%}$, $\dot{V}_{max\,50\%}$, and $\dot{V}_{max\,25\%}$ = flows at 75, 50, and 25 percent of the vital capacity, respectively.

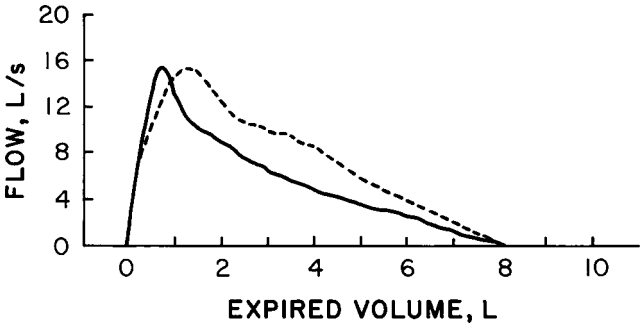


Figure 34-19 Comparison of the flow-expired volume curve (solid line) with a simultaneously recorded flow-thoracic gas volume curve (dashed line). The difference between the two curves results from the compression of gas in the lungs during a forced expiration.

spirometer: (1) tidal breathing for several breaths, (2) a maximal inspiratory effort to TLC, followed by (3) a maximal expiration to RV done as forcefully and quickly as possible, and (4) another maximal inspiratory effort to TLC. Volume is displayed on the horizontal axis and airflow on the vertical axis. Airflow is measured at the mouth using a pneumotachograph; volume is measured either by integrating the pneumotachographic record during expiration or as a change in thoracic gas volume, determined by a pressure-corrected flow plethysmograph. The records obtained by the two techniques for determining volume differ because the body plethysmograph senses compression of intrathoracic gas during a forced expiration, whereas measurements of volume made at the mouth do not (Fig. 34-19). Differences between curves obtained with the two techniques for measuring volume are most marked in patients with airway obstruction in whom considerable gas compression occurs during a forced expiration.

For the sake of comparison, tracings of flow vs. volume and volume vs. time, recorded during the same forced vital capacity maneuver and aligned by using a common volume axis as the abscissa, are shown in Fig. 34-20. Selected measurements are more evident in one tracing or the other (e.g., maximal expiratory flow in the flow-volume curve and FEV_1 in the volume-time curve).

Comparison of serial curves from a single person or curves from different subjects requires that the curves be aligned on the volume (horizontal) axis so that points of maximal inspiration or maximal expiration coincide. As may be seen in Fig. 34-21*A*, which illustrates typical curves from a normal subject and two patients, one with pulmonary fibrosis and the other with obstructive airway disease, the information provided by this form of representation is limited (i.e., the vital capacities and airflows from the patients are abnormally low). The limitation stems from the fact that the change in volume during expiration is shown relative to the *maximal inspiratory level* rather than to an *absolute volume* of gas in the lungs (i.e., RV or TLC). When RV or TLC is known so that absolute volumes can be plotted on the horizontal axis (Fig. 34-21*B*), additional insight is gained into the flow-volume relationship depicted in Fig. 34-21*A*. The patient

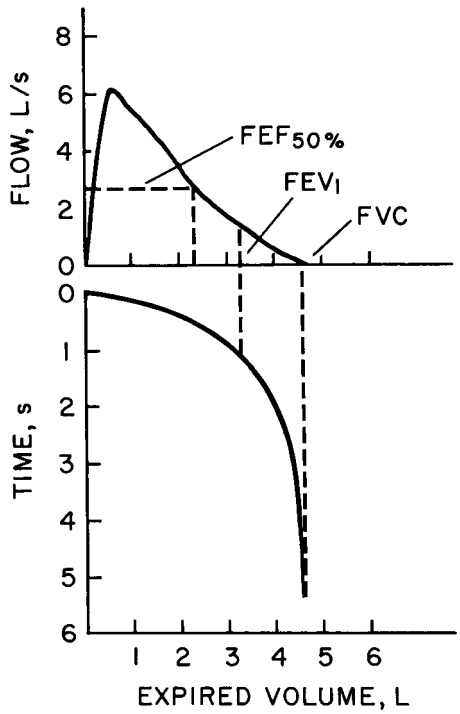


Figure 34-20 Flow-volume and volume-time curves depicting the same forced expiration aligned along a common volume axis (abscissa). Points corresponding to the FEV_1, FVC, and $FEF_{50\%}$ obtained from the volume-time plot are shown on the flow-volume curve.

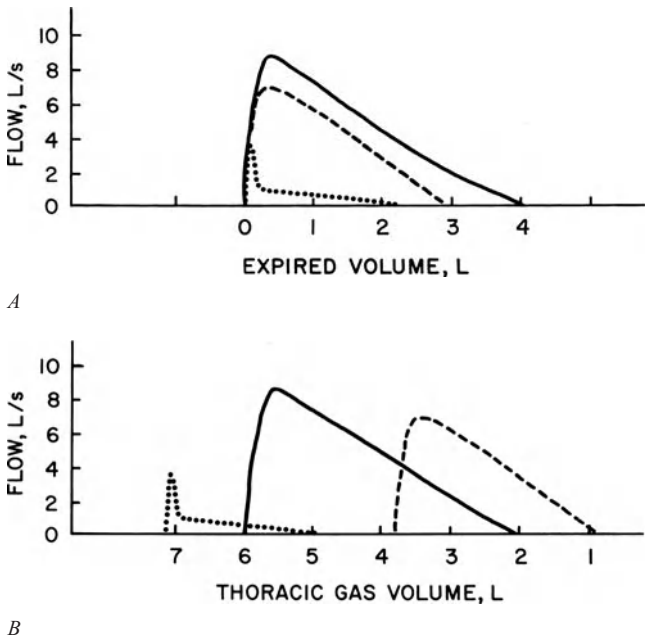


Figure 34-21 Airflow at different lung volumes. *A.* Flow-volume curves aligned at total lung capacity (TLC). *B.* Flow-volume curves displayed relative to thoracic gas volume. Although the curves aligned at TLC (*A*) show striking differences in the pattern of airflow, they provide no insight into the relationship between lung volumes and airflow. See text for discussion.

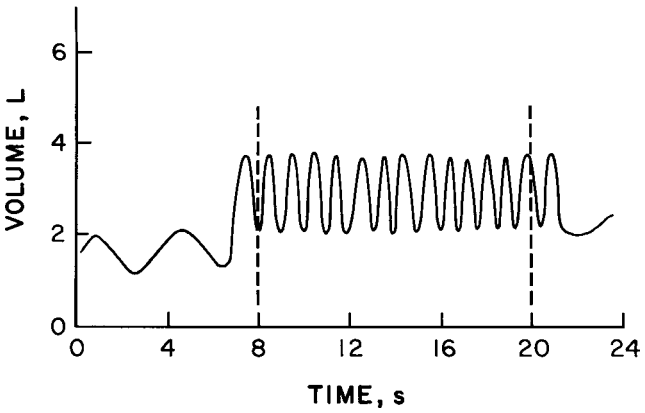


Figure 34-22 Maximal voluntary ventilation (MVV). After a period of relaxed breathing, the subject breathes rapidly and as forcefully as possible. The total volume of air inspired over 12 s and expressed in L/min is the MVV.

with obstructive disease of the airways manifests a reduction in expiratory airflow at elevated lung volumes, which should enhance airflow. In contrast, the reduced rate of airflow in the patient with pulmonary fibrosis is normal, or even supranormal, when the lung volume at which the airflow occurs is taken into account (i.e., the reduced airflow is primarily a function of the reduced lung volume, rather than of airway obstruction).

Maximal Voluntary Ventilation

The previous considerations of dynamic lung function focus on a single timed maximal expiratory or inspiratory maneuver. In contrast, the maximal voluntary ventilation (MVV) depends on the movement of air into and out of the lungs during continued maximal effort throughout a preset interval (Fig. 34-22). The MVV is a simple, informative test that provides an overall assessment of effort, coordination, and the elastic and flow-resistive properties of the respiratory system.

In performing the test, the patient is urged to breathe as hard and as fast as possible. As a rule, the patient automatically adjusts frequency and tidal volume for optimal performance. However, extremes of frequency or tidal volume are to be avoided, since neither panting nor slow deep breathing leads to the highest possible values. The total volume that is expired during a 12-s interval, expressed in liters per minute (BTPS), is the maximal voluntary ventilation. In some patients the test cannot be done because of an inability to continue the necessary effort for 12 s.

A normal value for MVV indicates that the overall integrated performance of the respiratory system is intact, thereby excluding moderate to severe restrictive or obstructive disease. In addition, a normal value suggests that the elastic and flow-resistive properties of the respiratory system, respiratory muscle strength, coordination of respiratory performance, and motivation of the patient are all normal. Although this test is very useful in detecting overall disturbances in integrated performance and diffuse tracheobronchial and pulmonary parenchymal diseases, other tests are required to pinpoint specific disorders.

The difference between the MVV and the resting minute ventilation is the *breathing reserve*. At one time, a low breathing reserve was correlated with the breathlessness in lung diseases. However, this determination is now primarily of historical interest.

Respiratory Resistance

Total respiratory resistance (Rrs) is the resistance to airflow and chest expansion offered by the airways (Raw), chest wall (Rw), and lung tissue (Rti):

$$\text{Rrs} = \text{Raw} + \text{Rw} + \text{Rti}$$

Although the overall resistance of the respiratory system can be determined with a technique employing forced oscillation, this approach has, to date, exhibited limited practical usefulness. In addition, further methodologic refinements permitting determination of *pulmonary resistance*—the sum of airway and tissue resistances (Raw + Rti)—have not proved to be worthwhile clinically, particularly since measurement of transpulmonary pressure with an esophageal balloon is necessary. Other variations of the determination of resistance measurements have also been explored. However, the only clinically useful measurement of resistance is airway resistance, which is now routinely determined in pulmonary function laboratories.

Airway Resistance

Airway resistance (Raw) is defined as the ratio of the driving pressure (P) for flow to the actual rate of airflow ($\dot{V}$) along the airways (i.e., the mouth, nasopharynx, larynx, and central and peripheral airways):

$$\text{Raw} = \frac{\Delta P}{\dot{V}}$$

where ΔP, the drop in pressure over the entire length of the airways, is determined as the difference between alveolar pressure (P_A) and pressure at the mouth (Pm) or airway opening (Pao).

Although airflow and pressure at the airway opening are easily measured, the difficulty in measuring alveolar pressure prevented the routine determination of airway resistance until DuBois and colleagues introduced the plethysmographic technique in 1956.

With this technique, the patient, seated in the body plethysmograph, pants at a rate of about two breaths per second while airflow is measured using a pneumotachograph. During inspiration and expiration, gas in the alveoli is alternately rarefied and compressed, causing changes in pressure within the sealed plethysmograph. The relationship between plethysmograph pressure and airflow during the panting maneuver is displayed on the X and Y axes of an oscilloscope (Fig. 34-23).

While the panting continues, a shutter at the airway opening is closed so that airflow is transiently interrupted.

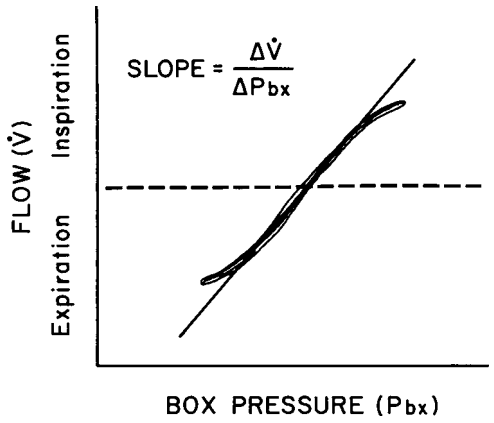


Figure 34-23 Plot of airflow (V̇) vs. body plethysmograph pressure (Pbx). The slope of this curve, in the range of 0 to 0.5 L/s of inspiratory flow, divided into the slope of the loop obtained when the shutter is closed (see Fig. 34-7) provides a measure of airway resistance (Raw).

Using the technique employed in the determination of FRC, changes in pressure in the plethysmograph (equivalent to changes in lung volume) and at the mouth are displayed on the X and Y axes, respectively, of the oscilloscope (Fig. 34-6). However, since airflow is zero while the shutter is closed, the pressure at the mouth equals alveolar pressure (Pao = P_A).

Panting while the shutter is open allows the determination of the relationship between airflow (V̇) and plethysmograph pressure (Pbx)—i.e., V̇/Pbx. Similarly, panting against a closed shutter enables the determination of the relationship between alveolar pressure (P_A) and plethysmograph pressure—i.e., P_A/Pbx. Airway resistance is calculated by dividing the slope of the loop obtained by plotting P_A vs. Pbx while the shutter is closed by the slope obtained by plotting V̇ vs. Pbx while the shutter is open:

$$\text{Raw} = \frac{P_A/\text{Pbx}}{\dot{V}/\text{Pbx}} = \frac{P_A}{\dot{V}}$$

where

Raw = airway resistance, cm H_2O/L/s
P_A = alveolar pressure, cm H_2O
V̇ = airflow, L/s

Raw is measured during a panting maneuver for several reasons: (1) The rapid respiratory frequency in panting circumvents the poor low-frequency response characteristics of many plethysmographs. (2) The small inspired and expired volumes, which minimize temperature fluctuations in the plethysmograph that would otherwise occur as tidal breaths of air at body temperature, are exchanged with breaths of air at room temperature. (3) During panting, the glottis remains open, thereby minimizing its contribution to overall airway resistance. Use of plethysmographs linked to microprocessors that automatically correct for temperature-related volume differences has made possible the determination of airway resistance during quiet breathing instead of during panting.

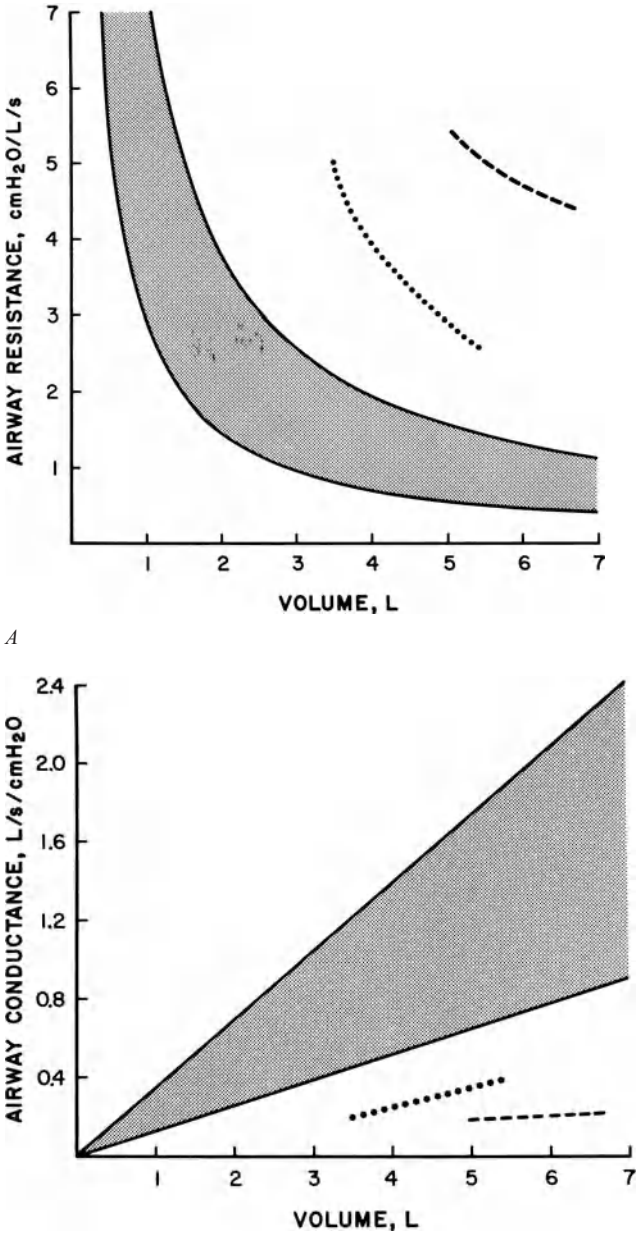


Figure 34-24 The relationship between airway resistance (*A*) and airway conductance (*B*). The shaded area represents the predicted normal range. Values are shown for an asthmatic patient before (dashed line) and after (dotted line) bronchodilator therapy. Airway resistance increases as lung volume decreases. Conversely, airway conductance, the inverse of resistance, decreases as lung volume decreases.

Airway resistance varies inversely with lung volume: it is low at large lung volumes and increases curvilinearly as lung volume and, consequently, airway diameters are reduced (Fig. 34-24*A*). In contrast, the inverse of airway resistance, airway *conductance*, is linearly related to lung volume (Fig. 34-24*B*). Interpretation of a given value for airway resistance or airway conductance requires that the lung volume at which the measurement is made be taken into account. *Specific conductance* (SGaw) is calculated by dividing airway conductance by the lung volume.

Table 34-7

Categorization of Increased Airway Resistance (Raw)

Category	Raw (cm H_2O/L/s)
Mild	2.8–4.5
Moderate	4.54–8.0
Severe	>8.0

Source: Modified from Ries A and Clausen JT, in Wilson AF (ed), Pulmonary Function Testing: Indications and Interpretations, *Orlando, FL, Grune and Stratton, 1985.*

Defining the range of normal for Raw is difficult because of the lack of data obtained from populations sorted into smoking and nonsmoking groups and because of the inter- and intraindividual variations of Raw with lung volume. One classification scheme proposed for defining normal and abnormal Raw in adults in whom FRC exceeds 2 L is given in Table 34-7.

At times, an apparent discrepancy occurs between forced expiratory flow rates and values for airway resistance. For example, although the FEV_1 and $FEF_{25-75\%}$ may be abnormally low (suggesting some degree of airway obstruction), Raw may be within normal limits (arguing against appreciable airway obstruction). This apparent contradiction arises because Raw is determined during *inspiration*, when airways are enlarged because of surrounding negative pleural pressure, whereas FEV_1 and $FEF_{25-75\%}$ are determined during a forceful *expiration*, when airways are compressed by high positive pleural pressures. Therefore, the discrepancy is simply a manifestation of dynamic airway obstruction in which the narrowing is confined to expiration.

Measurement of Exhaled Nitric Oxide

Over the last two decades, the important role of nitric oxide (NO) in a variety of biologic processes has been described. The concept that NO is a marker of airway inflammation, and, hence, has a potential role as a measure of airway function in the setting of inflammatory airway diseases, has been investigated. Studies have demonstrated that, at least in asthma, levels of exhaled NO are elevated during exacerbations (when other measures of airway inflammation show activity), even in the absence of symptoms or changes in spirometry. Levels of NO decrease with inhaled corticosteroid use and rise with corticosteroid tapering. Some advocate measurement of exhaled NO as part of routine chronic asthma management.

Standards have been developed for measuring exhaled NO levels. While exhaled NO measurement has not yet assumed the status of a "standard" pulmonary function test, pulmonary function laboratories will likely soon add the test to their repertoires.

AIRWAY REACTIVITY

The dynamic tests of airway function described previously are designed to determine intrinsic properties of the airways in a subject breathing room air at rest. In many clinical situations, such as evaluation of chronic cough, assessment of airway hyperresponsiveness is desirable. This section reviews *bronchoprovocation testing* (BPT), which assesses reactivity of the airways to selected pharmacologic or environmental agents.

Background

One test of bronchial reactivity that has been incorporated into routine pulmonary function testing is determination of the effect on airflow of administration of a nebulized bronchodilator agent. However, BPTs are designed to quantify the degree of bronchoconstriction following the application of a particular stimulus. A number of tests of bronchial reactivity are currently in clinical use (Table 34-8). Among the agents

Table 34-8

Tests of Bronchial Reactivity

Test	Reference
Inhalational challenges	
Pharmacologic agents	
Methacholine	Chai et al: *J Allergy Clin Immunol* 56:323–327, 1975
Histamine	Chai et al: *J Allergy Clin Immunol* 56:323–327, 1975
Carbocholine	Orehek et al: *Br Med J* 1:123–125, 1975
Specific antigens	
Toluene diisocyanate	Salvaggio: *J Allergy Clin Immunol* 64:646–649, 1979
Bacillus subtilis	Salvaggio: *J Allergy Clin Immunol* 64:646–649, 1979
Pollen	Spector: *J Allergy Clin Immunol* 64:580–586, 1979
Molds	Spector: *J Allergy Clin Immunol* 64:580–586, 1979
House dust	Spector: *J Allergy Clin Immunol* 64:580–586, 1979
Exercise-induced asthma	
Cold-air challenge	Strauss et al: *N Engl J Med* 297:743–747, 1977
Dry-air challenge	Hahn et al: *Am Rev Respir Dis* 130:575–579, 1984
Isocapnic hyperventilation	Eschenbacher et al: *Am Rev Respir Dis* 131:894–901, 1985

used for inhalation challenges are methacholine, histamine, carbocholine, and specific antigens chosen in accord with the patient's history. In addition to the inhalation challenge tests in which pharmacologic agents are used, tests of bronchial reactivity may be based on inhalation of cold or dry air, isocapnic hyperventilation, or exercise.

Indications for Bronchoprovocation Testing

The principal indication for BPT is a history suggestive of bronchospasm induced by an environmental or occupational agent, generally in the setting of normal pulmonary function tests (including determination of airflow before and after administration of an inhaled bronchodilator). For example, comparison of FEV_1 before and after administration of a pharmacologic agent such as methacholine or histamine can be useful in establishing the diagnosis of asthma. Also, inhalation of a suspected specific antigen may be useful in uncovering asthma when skin tests are equivocal, or in proving that asthma is occupation-related. In some instances, exercise testing may disclose airway hyperreactivity in persons who are free of bronchoconstriction while at rest. Airway hyperresponsiveness to methacholine may presage an accelerated decline in pulmonary function. However, the impact of therapy with agents like inhaled bronchodilators or corticosteroids in preventing progression is unclear.

Table 34-9

Concentrations and Cumulative Doses of Methacholine Employed in the Methacholine Challenge Test

Methacholine Concentration (mg/ml)	Cumulative Dose (Inhalation Units)*
0.1	0.5
0.5	3
1.0	8
2.0	18
5.0	43
10.0	93
25.0	218

** After five inhalations of a nebulized solution containing methacholine in a concentration of 1 mg/ml.*

Methods of Bronchoprovocation Testing

Several methods of BPT are in general clinical use. These include methacholine challenge, exercise challenge, and antigen challenge, each of which is described briefly below.

Inhalation Challenge: Methacholine

Inhalation challenge using methacholine has become popular because of standardization of the technique, ease and safety of performing the test, and high sensitivity of the test in detecting asthma. Methacholine is a synthetic cholinergic agent that evokes airway smooth-muscle constriction. Because baseline pulmonary function and breathing pattern influence the site of deposition of the inhaled methacholine particles and, thereby, the response, a standard method for aerosolizing the agent is used to ensure reproducible results.

One method in common use is that of intermittent aerosol generation. Standardization entails the delivery of a 0.6-s pulse of airflow at 20 lb/in^2 to a nebulizer, which, in turn, discharges particles that range from 0.3 to 4 μm in diameter into the airways. Methacholine for delivery by aerosol is prepared in concentrations ranging from 0.1 to 25 mg/ml using bicarbonate-buffered isotonic saline (containing 0.4 percent phenol) as the diluent. The cumulative dose delivered is expressed in inhalation units. One inhalation unit is equivalent to the single inhalation of a solution containing 1 mg of methacholine per milliliter (Table 34-9).

At the outset, the patient is challenged with five inhalations containing only aerosolized diluent. The necessity of the diluent step has been recently questioned. In addition to adding time and expense, it may force a greater absolute drop in FEV_1 needed to prove bronchial hyperreactivity. A fall in FEV_1 below 90 percent of the baseline value (i.e., the prechallenge control FEV_1) establishes that the airways are hyperreactive, and therefore, the test is terminated. However, if the FEV_1 does not fall below 90 percent of the control value, increasing concentrations of methacholine are given in stepwise increments of five-breath inhalations. The breaths are taken slowly from FRC to TLC. Then, 1 to 1.5 min after each dose, an FVC maneuver is performed. The interval between each increase in concentration is kept to a minimum because the response is judged in terms of the *cumulative* dose. However, the deep inspiration that immediately precedes the expiratory portion of the FVC maneuver may decrease bronchomotor tone in airways narrowed by methacholine. This effect lasts up to 6 min, thus limiting the shortest acceptable interval between dosage steps. If the postchallenge FEV_1 falls below 80 percent of the control FEV_1, or if the patient experiences cough or chest tightness at any step, the test is stopped. The magnitude of the bronchoconstrictor response to inhalational challenge is related to the control FEV_1. A lower baseline FEV_1 (even in the normal range) correlates with increased bronchial reactivity. Additional measurements of dynamic airway function (e.g., specific conductance) may provide supplemental data but also prolong the study. Another dosing option in use is the 2-min tidal breathing protocol. This protocol typically yields results similar to the one previously described.

The results are plotted on four-cycle semilog graph paper: the number of cumulative inhalation units, expressed logarithmically, against the FEV_1, as percent of control

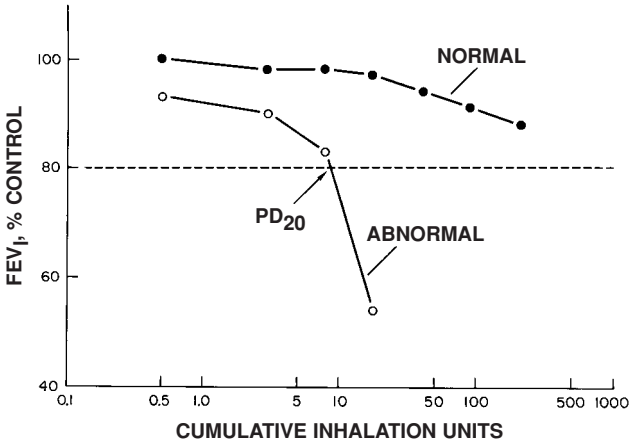


Figure 34-25 Plot of FEV_1, percent control vs. cumulative dose of methacholine administered by inhalation (logarithmic scale), to a normal subject and a subject with hyperreactive airways. The PD_{20} is the cumulative dose, which results in a 20 percent drop in the FEV_1 from the baseline measurement (after inhalation of diluent alone). In the subject with normal airway reactivity, the maximal cumulative dose of methacholine administered fails to elicit a 20 percent drop in FEV_1.

(Fig. 34-25). A curve is constructed through the points; the dose corresponding to the point at which the FEV_1 is 80 percent of the control FEV_1 is designated as the *provocation dose*, or PD_{20} FEV_1.

Exercise Challenge

Persons without a history of asthma who develop cough, wheezing, or dyspnea after exercise may have exercise-induced bronchospasm (EIB). In these individuals, an exercise test may prove useful in establishing the diagnosis. Such exercise testing in asthmatics can be useful to assess the degree of impairment during exercise, or the impact of therapies.

Several factors that may influence the outcome of the test should be kept in mind. The temperature and humidity of the laboratory should be tightly controlled. Some centers use dry air inhalation during exercise. In addition, the duration of the test needs to be monitored. The goal of testing for EIB is to produce at least 4 min of exercise at the target heart rate and ventilation. Exercise should not continue for more than 6 to 8 min, in order to avoid "run-through" of the bronchospasm (i.e., reversal at the end of the test).

The type of exercise also influences the outcome. As a rule, the more intense the exercise, the more likely is bronchoconstriction to occur. Free-range running provides the most potent stimulus for bronchoconstriction, followed by treadmill running, bicycle ergometry, swimming, and walking. An asthmatic may swim comfortably at a level of exercise that is incapacitating on the treadmill. The motor-driven treadmill or electromagnetically braked cycle ergometer are the preferred modes of exercise for formal testing.

The FEV_1 is the most useful measurement made during testing for EIB. Measurements are made just before and immediately after the exercise and at 5-min intervals for the following 30 min. A decrease in FEV_1 of 10 percent or more below the pre-exercise value constitutes a positive test. Some have suggested that a decrement of 15 percent is of greater diagnostic value. False- positive responses can occur in patients with vocal cord dysfunction or abnormal posterior arytenoid motion.

Inhalation Challenge: Antigen

Compared with the relatively safe methacholine challenge test, BPT using a specific antigen is unpredictable and potentially hazardous. Since establishing the minimum dose required to induce bronchoconstriction is difficult, too much of the antigen may be given. A late response, far more severe than the initial one, often develops about 6 h after the challenge. Despite these reservations about antigen challenge, testing is warranted under certain circumstances: (1) to uncover a particular agent in the environment that causes bronchoconstriction; (2) to establish the diagnosis of occupational asthma; (3) to prove that bronchoconstriction is caused by a particular antigen after routine skin tests have failed to support the clinical suspicion; and (4) to convince a skeptical patient about the cause of his or her asthma. Recommendations for preparing concentrations of antigens and the technique of antigen challenge testing are specific to the antigen in question and may be found in the literature. These tests should only be performed in laboratories that have considerable experience with BPT.

Precautions and Contraindications in Bronchoprovocation Testing

Although the overall risk of serious complications is low, BPT may be unnecessary, invalid, or even dangerous in some circumstances (Table 34-10). For example, the patient who manifests appreciable airway obstruction by conventional testing may develop life-threatening airway narrowing during BPT. In such a patient, a simple bronchodilator study would be more appropriate and informative. If bronchodilators fail to reverse the increase in airway resistance, and if it is important

Table 34-10

Bronchoprovocation Testing: Precautions and Contraindications

- Baseline FEV_1/FVC% <70
- Recent upper respiratory tract infection
- Recent influenza vaccination
- Recent administration of bronchodilator
- Ingestion of caffeine within 6 h before testing
- Cold-air breathing, hyperventilation, exercise within 6 h before testing
- Recent acute myocardial infarction or cerebrovascular accident, uncontrolled hypertension, or known aortic aneurysm

to prove that bronchial hyperreactivity does exist, BPT is sometimes done, with extreme caution, on another day, as antigen dosages are titrated carefully and details of the procedure monitored closely.

Absolute contraindications include severe airways obstruction (FEV_1 less than 50 percent predicted), myocardial infarction or stroke in the preceding 3 months, uncontrolled hypertension, or known aortic aneurysm. Moderate airflow limitation, pregnancy, lactation, and concurrent use of cholinesterase inhibitor medication represent relative contraindications.

A recent viral upper respiratory tract infection can cause airway hyperreactivity for up to 6 weeks in normal subjects. Similarly, influenza vaccination increases responsiveness to inhalation challenges in asthmatics for a few days to a week. In these conditions, BPT should not be undertaken until the sensitization effects of the infection or vaccination have worn off. Also, bronchodilators, including caffeine, should be withheld for at least 6 h before BPT, if possible, in order to prevent blunting of the bronchoconstrictor response. Finally, cold air, hyperventilation, and exercise should be avoided for at least 6 h before testing in order to prevent the induction of a refractory period or late response that would overlap the test results.

SMALL-AIRWAY FUNCTION

Up to this point, discussion of tests of dynamic lung function has addressed the tracheobronchial tree as a unit. Sometimes, however, particularly in cigarette smokers, obstructive disease is confined to the peripheral airways (i.e., those 2 mm or smaller in diameter). Because of their small contribution to airway resistance, estimated to be about 10 to 38 percent (at a lung volume equivalent to 50 percent of vital capacity), the small airways can undergo considerable damage before the usual tests of either static or dynamic lung function become abnormal. Consequently, efforts have been made to develop tests aimed at early detection of small-airway disease in the hope of early intervention to limit progression of the disease. The nature of small-airways obstruction and its impact on progression of COPD are currently being investigated.

In obstructive disease of the peripheral airways, the small airways' contribution to overall resistance increases, and abnormalities in their function may be detected from the expiratory vital capacity maneuver. In particular, abnormal values for $FEF_{25-75\%}$, in conjunction with normal values for FVC and FEV_1, are often useful in identifying small-airway disease. The basis for this approach is that $FEF_{25-75\%}$ measures airflow during the effort-independent part of the FVC, when the small airways contribute substantially to the limitation of airflow.

In addition to limiting airflow during expiration, obstruction of small airways results in abnormal distribution of ventilation to peripheral lung units. This abnormality forms the basis for two tests that, although not commonly performed, merit additional comment because of the relevant underlying physiology: frequency dependence of dynamic compliance and closing volume.

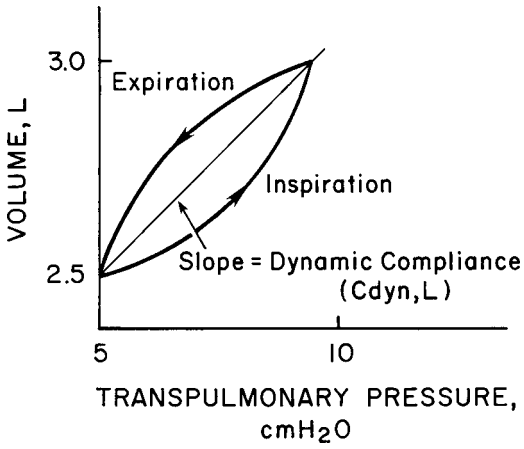


Figure 34-26 Measurement of dynamic lung compliance (Cdyn,L). During the inspiratory and expiratory phases of the respiratory cycle, a loop relating volume to transpulmonary pressure is generated. The slope of a line drawn through the points of zero airflow (at end-inspiration and end-expiration) is the dynamic compliance. Determination of Cdyn, L can be done at a variety of respiratory frequencies to assess the frequency dependence of compliance (Fig. 34-27).

Dynamic Compliance

Dynamic compliance, defined as the change in lung volume during airflow produced by a given change in transpulmonary pressure, is normally independent of breathing frequency. However, under conditions of nonuniformity of ventilation throughout the lung, increases in breathing frequency are associated with a fall in dynamic compliance. This frequency dependence of compliance was first noted in a patient with emphysema.

During the test, the patient, with an esophageal balloon in place, first inspires maximally to TLC and then expires to the resting end-expiratory position (FRC); the patient then breathes at a normal tidal volume and respiratory rate (15 breaths/min). In order to enable the patient to monitor these parameters, tidal volume and the resting end-expiratory level are displayed on an oscilloscope within sight of the patient. At the same time, changes in tidal volume and transpulmonary pressure are displayed on another oscilloscope (Fig. 34-26). The slope of the line connecting the end-inspiratory and end-expiratory points on the pressure-volume loop (i.e., the points of zero airflow) is the dynamic compliance. This procedure is repeated with breathing frequencies of 30 and 60 breaths per minute. Values for dynamic compliance (Cdyn,L) at the various frequencies are expressed as a ratio of the dynamic compliance to the static inspiratory compliance (Cst,L) or as a percentage of Cst,L (Fig. 34-27) for the same range of tidal volumes.

In normal subjects, Cdyn,L/Cst,L remains above 0.8, even at frequencies greater than 60 breaths/min. However,

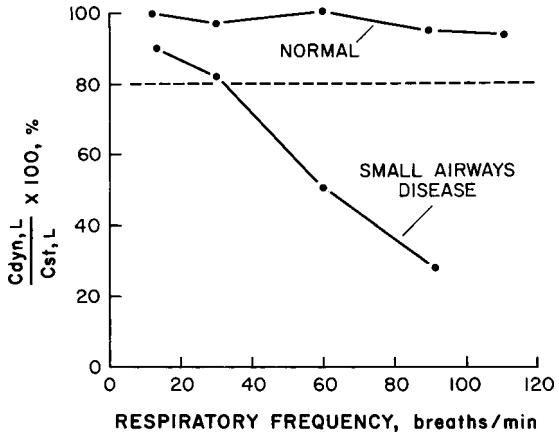


Figure 34-27 Determination of frequency dependence of dynamic compliance. Dynamic compliance is determined as shown in Fig. 34-26 and is expressed as a percentage of static lung compliance (Cdyn, L/Cst, L × 100, %) at a variety of respiratory frequencies. Normally, Cdyn, L is ≥80 percent of Cst, L and is independent of respiratory frequency. In patients with obstructive airway disease, including those with disease limited to the small airways, Cdyn, L falls relative to Cst, L as respiratory frequency increases.

in the presence of obstructive disease of the small airways, Cdyn,L/Cst,L falls progressively to values below 0.8 as breathing frequency increases. It is worth emphasizing that interpretation of frequency dependence of compliance with regard to small-airway disease is valid only if the static compliance and overall airway resistance are normal. Abnormalities in these other measurements indicate disease that is not likely to be confined to the small airways and for which frequency dependence of dynamic compliance is another manifestation. The physiological basis for the fall in Cdyn,L/Cst,L as respiratory frequency increases is the presence of unequal time constants throughout the lung (see Chapter 9).

Closing Volume

In 1949, Fowler described the single-breath nitrogen washout test for assessing the uniformity of ventilation throughout the lungs. In performing this test, the patient first expires maximally to RV before filling his or her lungs by taking a maximal breath of 100 percent O_2. During the subsequent expiration, the concentration of nitrogen at the mouth is continuously recorded and plotted against the volume of expired gas. Originally, interest focused on the initial part of the tracing that depicts the changing concentration in expired nitrogen as the first 750 to 1200 ml of gas is exhaled. Over this range, the change in nitrogen concentration in persons with normal lungs is less than 2.5 percent. In contrast, when abnormal lungs or disease of the tracheobronchial tree result in abnormal intrapulmonary distribution of inspired gas, the change in nitrogen concentration exceeds 2.5 percent.

Almost 20 years later, Fowler's test was modified to include a bolus of xenon at the beginning of inspiration and to record the concentration of xenon during the following expiration. Abrupt changes in the concentration of expired xenon as RV was approached suggested that important information about the small airways could be obtained from the terminal portion of the curve.

These observations with xenon rekindled interest in Fowler's original technique and also directed attention to the terminal portion of expiration. The procedure is depicted in Fig. 34-28. To perform the maneuver for this measurement, the seated patient takes two deep breaths of air and then expires to RV. At the end of this maximal expiration, a valve is opened so that the patient can take a full breath of 100 percent

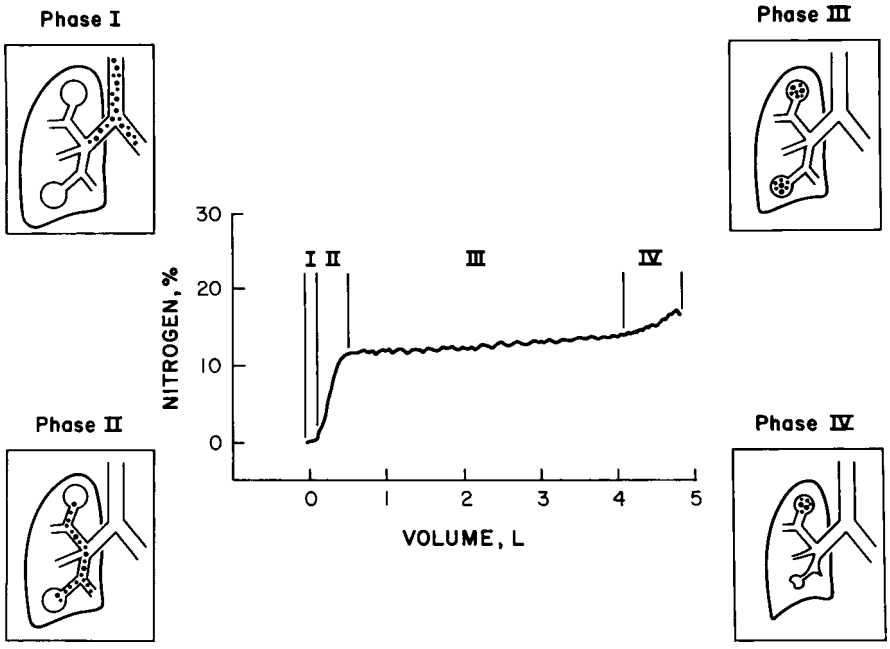


Figure 34-28 Contributions of different lung regions to the nitrogen concentration-volume curve obtained during the single-breath nitrogen washout test. See text for discussion.

O_2 to TLC. The patient then expires slowly to RV while N_2 concentration and expired volume are continuously recorded.

Four distinct phases can be identified in the continuous record relating N_2 concentration to expired volume. Phase 1, the initial expirate, contains virtually no N_2, since it derives from the O_2-containing dead space. Phase 2 represents a mixture of gases from the dead space and the alveoli. Phase 3 is due to a mixture of gases from alveoli located at the apices, midlung fields, and bases. Phase 4, characterized by an upward shift in N_2 concentration, is caused by closure of alveoli in the dependent parts of the lungs at low lung volumes. This final expirate derives from alveoli in the middle and upper regions of the lungs, where N_2 concentrations are higher than at the bases.

The explanation for these phases resides in the intrapulmonary distribution of gases during the respiratory maneuvers used in performing the test. In the normal upright person, a gradient of pleural pressures exists from apex to base, so that pleural pressure is more negative at the apices than at the bases. Because the alveoli at the bases operate on a lower portion of their pressure-volume curve (Fig. 34-11), they expand more than do apical alveoli per unit change in pleural pressure. However, the less negative pleural pressures and decrease in elastic recoil pressure at the bases also cause small airways to close during expiration as lung volume approaches RV. Thus, the pleural pressure gradient from top to bottom of the chest causes nonuniform distribution of gas within the normal upright lungs.

In the single-breath nitrogen washout test, a breath of 100 percent O_2 is taken, starting from RV. At RV, small basal airways are closed. Therefore, at the start of the O_2 breath, the N_2-containing air remaining in the dead space is preferentially drawn into the middle and apical lung zones as 100 percent O_2 gradually replaces air in the dead space. As the inspiration continues, the small airways at the bases open. Since their compliances are greater than those in the middle or at the top of the upright lungs, the inspired O_2 is then preferentially distributed to the bases.

During the expiration from TLC, the four phases then represent, as indicated above, the sequential emptying of dead-space gas and a mixture of dead-space and alveolar gas, followed by mixtures of alveolar gases from different parts of the lungs, as determined by the preceding intrapulmonary distribution of inspired O_2.

The volume from the onset of phase 4 to the completion of the full expiratory maneuver is termed the *closing volume* (CV). In healthy young adults, the normal closing volume averages about 10 percent of the vital capacity. Narrowing or obstruction of small peripheral airways causes closing volume to enlarge. The closing volume also increases progressively as people grow older, so that by the age of 50, the closing volume sometimes reaches 25 percent of the vital capacity. Cigarette smokers consistently experience an increase in closing volume. In both aging normal persons and cigarette smokers at any age, a decrease in pulmonary elasticity seems to be responsible for the increase in closing volume.

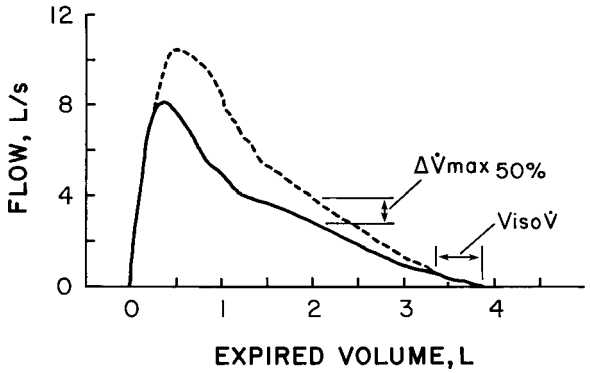


Figure 34-29 Maximal expiratory flow-volume curves generated in breathing room air (solid line) and breathing a helium-oxygen mixture (dashed line). The airflows achieved with the less dense helium mixture are higher than those with air at all but the lowest lung volumes. The point of first intersection of these two curves demarcates the volume of isoflow (Viso $\dot{v}$). The difference between the flows achieved when 50 percent of the vital capacity has been expired is the $\Delta V_{max,\%}$. The use of these measurements as indicators of small-airway disease is described in the text.

Helium-Oxygen Flow-Volume Curves

In 1963, the effects of changes in gas density and viscosity on maximal expiratory flow throughout the vital capacity range were described. Almost 10 years later, gas density and viscosity related concepts were applied to determine the site of airway obstruction in asthma. These principles were then applied for the specific purpose of detecting obstruction of small airways when other tests of pulmonary function were within normal limits.

The use of a helium-oxygen mixture to detect small-airway disease requires comparison of two maximal expiratory flow-volume curves, one that is generated while the patient breathes air and the other while the patient breathes helium and oxygen (Fig. 34-29). At least three maximal expiratory flow curves are obtained with room air and three with helium-oxygen.

In normal subjects, at lung volumes greater than 10 percent of the vital capacity (VC), the primary site of resistance to airflow is in the larger airways, where flow is turbulent and, therefore, density-dependent. At these lung volumes, the flow attained with the helium-oxygen mixture will be higher than that attained with air. At lung volumes less than 10 percent of the VC, the primary site of resistance is in the smaller airways, where flow is laminar and, therefore, not density-dependent. In this circumstance, the less-dense helium mixture has no effect on flow (Fig. 34-29). In disease of the small airways, the primary site of resistance shifts at large volumes from the larger to the smaller airways. As a result, the flow-enhancing effect of the less-dense gas disappears at volumes well above 10 percent of the VC.

In practice, two sets of maximal expiratory flow-volume curves are obtained, one while the subject is breathing air and the other after three VC breaths of the helium-oxygen mixture to replace at least 95 percent of the alveolar N_2. Comparisons

are then made of the superimposed curves (Fig. 34-29). One comparison is made at 50 percent of the VC in order to compare maximal expiratory flows (i.e., the $\Delta\dot{V}_{max,50\%}$); the other is at the volume at which the flows become identical—i.e., the *volume of isoflow* (V_{iso} $\dot{V}$). The curves are superimposed at RV or TLC, as long as the vital capacities of each curve are within 2.5 to 5.0 percent of the largest VC recorded.

The percentage change in expiratory flow while breathing helium-oxygen compared to air at 50 percent of the VC, $\Delta\dot{V}E_{max,50\%}$, is calculated as:

$$\Delta\dot{V}E_{max,50\%} = \frac{\dot{V}E_{max,50\%}(\text{helium-oxygen}) - \dot{V}E_{max,50\%}(\text{air})}{\dot{V}E_{max,50\%}(\text{air})} \times 100$$

where $\dot{V}E_{max,50\%}$ (helium-oxygen) and $\dot{V}E_{max,50\%}$ (air) are the expiratory flows at 50 percent of the VC during helium-oxygen and air breathing, respectively. As noted previously, the volume of isoflow is normally less than 10 percent of the VC; when it is increased, it indicates small-airway obstruction. The $\Delta\dot{V}E_{max,50\%}$ is also specific for small-airway disease, and unlike the closing volume, it is considered to be unaffected by changes in the elastic properties of the lung. Questions remain, however, about the validity and sensitivity of tests of density dependence of flow in assessing small-airway disease. Although they are conceptually attractive, the practical value of helium-oxygen flow-volume curves in detecting small-airway disease is debatable.

GAS EXCHANGE FUNCTIONS

Traditional measurements of the gas exchange functions of the lung include oxygen uptake ($\dot{V}O_2$), carbon dioxide elimination ($\dot{V}CO_2$), respiratory dead space (V_D), alveolar gas composition (P_{AO_2} and P_{ACO_2}), diffusing capacity for carbon monoxide ($D_{L_{CO}}$), and arterial blood gas tensions (Pa_{O_2} and Pa_{CO_2}). These determinations require a steady state of the ventilation and circulation and constant body stores of O_2 and CO_2. A steady state with respect to O_2 implies that O_2 uptake measured at the mouth equals the rate of O_2 transport across the alveolar membrane, and that, in turn, both rates are equal to O_2 consumption by the tissues. The same type of definition applies to CO_2 exchange in the tissues, in the alveolar capillaries, and at the mouth.

Ventilation, Oxygen Uptake, and Carbon Dioxide Elimination

The total volume of air breathed per minute ($\dot{V}E$) is the *minute ventilation*. It is equal to the product of the tidal volume (V_T) and the breathing frequency (f). As a rule, minute ventilation is determined by measuring the volume of expired gas relative to time. When the measurement is performed manually, the necessary equipment includes gas-collecting bags, low-resistance directional valves, a stopwatch, and a device for measuring gas volume. In practice, the patient, with nose clip in place, breathes through a mouthpiece for at least 3 to 5 min while expired gas is vented to the atmosphere. This preliminary period is intended to put the patient at ease and to achieve a steady state of respiration and circulation. When steady heart rate and breathing pattern are achieved, a valve is turned without the patient's knowledge, and expired gas is collected for 3 min.

The minute ventilation is determined by dividing the total volume of expired gas collected in the spirometer by the time of collection (3 min). The average tidal volume is obtained by dividing $\dot{V}E$ by the number of breaths per minute. Values for minute ventilation and tidal volume are expressed in terms of body conditions (BTPS). In the resting adult, the minute ventilation is typically 6 to 8 L/min; the corresponding tidal volume is 0.4 to 0.6 L.

The quantity of CO_2 in inspired air is negligible. Consequently, the amount of CO_2 produced per minute ($\dot{V}CO_2$) can be calculated as the product of the expired volume of ventilation ($\dot{V}E$) and the concentration of CO_2 in the expired air (F_{ECO_2}):

$$\dot{V}CO_2 = V_E \times F_{ECO_2}$$

Oxygen uptake ($\dot{V}O_2$) is calculated as the difference between the amounts of O_2 in inspired and expired air:

$$\dot{V}O_2 = (\dot{V}I \times F_{IO_2}) - (\dot{V}E \times F_{EO_2})$$

where

$\dot{V}I$ = inspired volume of ventilation, L/min
F_{IO_2} = concentration of O_2 in the inspired air
F_{EO_2} = concentration of O_2 in the expired air

In the steady state, O_2 uptake by alveolar capillary blood exceeds CO_2 output from alveolar capillary blood. As a result, the expired volume of gas is less than the corresponding inspired volume. Since N_2 does not undergo exchange in the lungs, the difference between CO_2 output and O_2 uptake results in a higher concentration of N_2 in expired air than in inspired air. Based on the change in nitrogen concentration, the inspired volume of ventilation can be calculated from the expired volume of ventilation:

$$\dot{V}_I = \dot{V}_E \frac{F_{E_{N_2}}}{F_{I_{N_2}}}$$

where

$F_{E_{N_2}}$ = concentration of N_2 in expired air
$F_{I_{N_2}}$ = concentration of N_2 in inspired air

In the normal, resting subject who is tested after several hours of fasting, the ratio of CO_2 output to O_2 uptake, the *respiratory exchange ratio* (R), is about 0.8. The respiratory exchange ratio at any instant is calculated by simultaneously determining the P_{O_2} and P_{CO_2} in an alveolar gas sample. As indicated above, in the steady state, the R determined by sampling alveolar gas equals the R of alveolar capillary blood, which, in turn, equals the R of the tissues. The steady-state R, when

alveolar gas, blood, and tissue are all in dynamic equilibrium, is the *respiratory quotient* (RQ). Hence, in the steady state, when the O_2 and CO_2 stores of the body are not changing, the RQ, reflecting cellular metabolism, can be determined by analyzing alveolar gas for O_2 and CO_2.

Unlike tidal volume and ventilation, which are expressed in terms of BTPS, $\dot{V}O_2$ and $\dot{V}CO_2$ are given in terms of standard temperature and pressure, dry (STPD).

Dead Space

Not all of the air breathed participates in gas exchange. Part of each breath remains in the mouth, nose, pharynx, larynx, trachea, bronchi, and bronchioles. This volume, the *anatomic dead space*, is about equal, in milliliters, to the subject's ideal body weight, in pounds (e.g., about 150 ml in a typical adult male). Inspired air reaching alveoli that are not exposed to pulmonary capillary blood also does not participate in gas exchange. This volume plus the anatomic dead space equals the *physiological dead space*. In a normal person, the anatomic and physiological dead spaces are virtually identical and constitute about one-third of the tidal volume.

Determination of the physiological dead space has proved to be of practical importance in a variety of clinical conditions. It is calculated by considering each breath (V_T) to consist of dead space (V_D) and an alveolar volume that participates in gas exchange (V_A):

$$V_T = V_D + V_A$$

Physiological dead space can be calculated using a modification of the *Bohr equation*, which recognizes that all of the test gas expired derives from two sources: the physiological dead space and the alveolar gas-exchanging volume. If we use CO_2 as the marker gas, the total amount of CO_2 eliminated per minute equals the sum of the CO_2 coming from the dead space per minute and from the alveolar compartment per minute:

$$\dot{V}_E \times F_{ECO_2} = (\dot{V}_D \times F_{ICO_2}) + (\dot{V}_A \times F_{ACO_2})$$

where

$\dot{V}_E$ = minute ventilation, L/min
F_{ECO_2} = fractional concentration of CO_2 in expired gas
$\dot{V}_D$ = minute dead space ventilation, L/min
F_{ICO_2} = fractional concentration of CO_2 in inspired gas
$\dot{V}_A$ = alveolar ventilation, L/min
F_{ACO_2} = fractional concentration of CO_2 in alveolar gas

Since, in a subject breathing room air, F_{ICO_2} is practically zero, the last equation is generally simplified as follows.

$$V_E \times F_{ECO_2} = V_A \times F_{ACO_2}$$

where V_E and V_A represent volumes of ventilation, rather than rates.

Recalling that $V_A = V_T - V_D$ and substituting partial pressures for the fractional concentration terms, the relationship becomes:

$$V_E \times P_{ECO_2} = (V_T - V_D)P_{ACO_2}$$

where P_{ECO_2} and P_{ACO_2} are the partial pressures of CO_2 in mixed expired gas and alveolar gas, respectively.

Assuming that arterial blood and alveolar gas are in equilibrium with respect to CO_2, when Pa_{CO_2} is substituted for P_{ACO_2} and the equation rearranged, it becomes:

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

Thus, if arterial blood is sampled during collection of expired gas, and if the partial pressures of CO_2 in expired gas and arterial blood are determined, the physiological dead space can be calculated. In order for the physiological dead space to be separated from the total dead space determined by the above equation, the dead space of the apparatus is subtracted from the value for total dead space.

Alveolar Gas Composition

In normal subjects, values for P_{O_2} and P_{CO_2} in an end-tidal sample approximate mean alveolar values. However, when imbalances exist in alveolar ventilation and blood flow because of lung disease, inhomogeneity in alveolar gas composition often invalidates the use of end-tidal gas tensions as a measure of mean alveolar gas composition.

In practice, mean alveolar P_{O_2} ($\bar{P}_{AO_2}$) and mean alveolar P_{CO_2} ($\bar{P}_{ACO_2}$) are often determined indirectly. Arterial P_{CO_2} is assumed to equal mean alveolar P_{CO_2} on the grounds of the narrow arteriovenous difference for P_{CO_2} across the lungs, the high solubility of CO_2, and the presumed role of pulmonary capillary blood as a tonometer. Mean alveolar P_{O_2} is calculated using the alveolar gas equation:

$$\bar{P}_{ACO_2} = P_{IO_2} - \bar{P}_{ACO_2}\left(F_{IO_2} + \frac{1 + F_{IO_2}}{R}\right)$$

The alveolar gas equation takes advantage of the fact that the total pressure of gases in the alveoli is equal to the sum of the partial pressures of the individual gases. This equation simply states that the mean alveolar P_{O_2} is the difference between inspired P_{O_2} and mean alveolar P_{CO_2}, allowing for a correction factor when the respiratory exchange ratio differs from 1.0.

Diffusing Capacity

The diffusing capacity of the lung for carbon monoxide (D_{LCO}) can be determined by steady-state, rebreathing, and single-breath methods. The most frequently used method is a modification of the single-breath method first described in 1915 and subsequently modified in 1957. Although the single-breath test has been shown to exhibit a large interlaboratory variation, it has proved to be a valuable measure of lung function in a wide variety of disease states. In fact, with continuing refinement of the standards, the variability, which

may be as much as 12 percent or greater, is likely to decrease; however, the variability will probably not be reduced to the range for vital capacity measurements (about 4 percent).

The diffusing capacity is intended to provide an estimate of the rate at which test molecules—usually carbon monoxide (CO)—move by diffusion from alveolar gas to pulmonary capillary blood. Factors that influence the measurement are the physicochemical properties of the test gas, the extent and thickness of the alveolar-capillary barrier, the resistance to diffusion offered by the red blood cell membrane, and the reaction rates of the test gas and hemoglobin, and pulmonary capillary blood volume. As a rule, the diffusing capacity is interpreted as an index of the surface area engaged in alveolar-capillary diffusion. Clinical entities that can reduce the diffusing capacity include parenchymal lung diseases, particularly interstitial lung disease, emphysema, pulmonary hypertension, and anemia. Polycythemia and alveolar hemorrhage syndromes, on the other hand, may increase the diffusing capacity.

Carbon monoxide has emerged as the most practical test gas because of its affinity for hemoglobin. The diffusing capacity for CO is defined as the amount of CO transferred per minute per mmHg of driving pressure:

$$D_{L_{CO}} = \frac{\dot{V}_{CO}}{\bar{P}_{A_{CO}} - \bar{P}_{c_{CO}}}$$

where

$D_{L_{CO}}$ = the diffusing capacity of the lung for CO, ml/min/mmHg (STPD)
$\dot{V}_{CO}$ = the amount of CO transferred, ml/min
$\bar{P}_{A_{CO}}$ = the mean alveolar PCO, mmHg
$\bar{P}_{c_{CO}}$ = the mean capillary PCO, mmHg

Since the blood P_{CO} in nonsmokers is essentially zero, the term $\bar{P}_{c_{CO}}$ is customarily neglected. In practice, $D_{L_{CO}}$ is determined by calculating $\dot{V}_{CO}$ as the difference between inspired and expired samples and estimating the mean alveolar Pco. Generally, one of two techniques is used to determine $D_{L_{CO}}$: the single-breath or the steady-state technique.

The Single-Breath Method

The breathing maneuvers required for the single-breath method consist of tidal breathing for a few breaths, unforced expiration to RV, and then a single full, rapid inspiration of a gas mixture containing approximately 0.3 percent CO and an inert gas—traditionally, 10 percent helium. (Some newer systems use methane.) The breath is held for 10 + 2 s and then rapidly expired. An inspiratory time of less than 4 seconds, and a sample collection of no more than 3 s are required. Longer expiratory times and sample collection time greater than 3 s should be noted in the test report. The initial portion of the expirate containing dead-space gas is discarded; the remainder is collected, and the concentrations of CO and helium are measured. A variety of automated systems are commercially available for performing the single-breath diffusing capacity. However, the essential components in all systems are a source of the special inspired gas mixture, a device for measuring the volume of gas inspired and expired, rapid response analyzers to measure the concentration of gases (see below), a timer, and appropriate valving and collection devices to trap the desired portion of the expirate.

The diffusing capacity of the lung for CO is calculated according to the following equation.

$$D_{L_{CO}} = \frac{V_A \times 60}{(\text{barometric pressure} - 47)} \times \text{time} \times \ln \frac{F_{A_{CO}}, \text{initial}}{F_{A_{CO}}, \text{final}}$$

where

V_A = alveolar volume
$F_{A_{CO}}$, initial = alveolar concentration of CO at start of breath hold
$F_{A_{CO}}$, final = alveolar concentration of CO at end of breath hold

The concentration of CO in the alveoli at the start of the period of breath holding ($F_{A_{CO}}$, initial) is calculated from the inspired concentration of CO and, for helium-based systems, the inspired concentration of helium and the expired concentration of helium, according to the equation

$$F_{A_{CO}},\ \text{initial} = \frac{F_{E_{He}}}{F_{I_{He}}} \times F_{I_{CO}}$$

where

$F_{E_{He}}$ = expired concentration of helium
$F_{I_{He}}$ = inspired concentration of helium
$F_{I_{CO}}$ = inspired concentration of CO

The concentration of CO in the alveoli at the end of the breath-holding period ($F_{A_{CO}}$, final) is equal to the concentration of CO in the expired gas. The alveolar volume (V_A) is determined in one of two ways. Originally, V_A was calculated as the sum of the RV, determined by the closed-circuit helium or body plethysmograph techniques described previously, and the volume of inspired gas, as recorded on the spirometer. Later, V_A came to be calculated from the single-breath dilution of helium that occurs during the determination of $D_{L_{CO}}$. Finally, the time of breath holding is measured (in seconds) from the spirometer recording of the maneuver.

Although the single-breath method is relatively simple and has the advantage of requiring no blood samples, breath holding is clearly artificial, and the maneuver is difficult for dyspneic patients. Therefore, a steady-state method is sometimes used.

The Steady-State Method

In the steady-state method, a gas mixture containing 0.1 percent CO is breathed until the rate of CO uptake from the lung is constant. CO uptake ($\dot{V}_{CO}$) is determined from the difference between the amount of CO in the inspired and expired gas using an equation similar to that presented previously for calculation of O_2 consumption.

Comparison of Single-Breath and Steady-State Methods

Certain differences between the single-breath and steady-state techniques merit special mention. The single-breath method is more popular because it is relatively easy to perform; it is well standardized, and it is less affected by nonuniformity of ventilation in comparison to the steady-state method. However, one drawback is that the patient is required to perform an inspiratory vital capacity maneuver of at least 88 percent of the VC and to hold his or her breath for 10 s. Another is that the test is extremely difficult to perform during exercise. The steady-state method is more attractive intrinsically than the single-breath method, since it requires no respiratory maneuvers and can be done during exercise. However, it does require an arterial blood sample (for determination of P_{CO_2}), and it is technically more difficult to perform.

The steady-state method for determining diffusing capacity tends to give lower values for the resting subject than does the single-breath method. The discrepancy is generally attributed to the fact that the surface area for diffusion is smaller during the quiet tidal breathing employed in the steady-state method than during the full inspiration to TLC, as required in the single-breath method. Also, during quiet breathing, some areas of the lung receive considerably less ventilation than during a breath hold at TLC.

Factors Other than Diffusion That Influence Test Results

A low D_{LCO} need not indicate a diffusion defect. A number of additional respiratory and nonrespiratory factors may reduce or increase the D_{LCO}. A reduction in the lung volume alone can reduce the D_{LCO}. Therefore, some laboratories "normalize" the diffusing capacity for lung volume by dividing D_{LCO} by alveolar volume—a manipulation that assumes a linear relationship between D_{LCO} and V_A, which is not the case.

Anemia artificially decreases the D_{LCO} as determined by either method, but the effect of low hemoglobin concentration can be adjusted by application of a correction factor. Conversely, polycythemia and intrapulmonary hemorrhage tend to increase the value for D_{LCO}. In fact, an unexpectedly high value for D_{LCO} may be a helpful clinical clue in detecting radiographically occult pulmonary hemorrhage.

Although the equation for D_{LCO} assumes that the CO back pressure in blood is negligible, the blood of a heavy smoker sometimes contains as much as 10 percent CO Hb. Such levels of CO Hb will be accompanied by appreciable concentrations of dissolved CO in the plasma. The resulting back pressure of CO will reduce the D_{LCO}. A correction equation may be applied to adjust the D_{LCO} for this effect.

Altitude also affects the D_{LCO}. P_{AO_2} falls with increasing altitude above sea level. The reduction in P_{AO_2} allows CO to diffuse more rapidly into the blood. A specific adjustment should be made for inspired oxygen partial pressure.

Measurement of diffusing capacity is quite useful in the evaluation of patients with a number of pulmonary conditions. Decrement in D_{LCO} has been shown to predict exertional hypoxemia. In addition, D_{LCO} levels have been correlated with disease severity and prognosis in primary pulmonary hypertension, idiopathic pulmonary fibrosis, and alveolitis associated with systemic sclerosis.

Arterial Blood Gas Composition

The determination of arterial P_{O_2} and P_{CO_2} provides useful information about the overall efficiency of external gas exchange. Heavy reliance is placed upon them for this purpose in managing acute respiratory failure, particularly in intensive care units. Less dramatic, but important, is their use in a variety of other settings (e.g., exercise testing) and for assorted calculations (e.g., the alveolar-arterial O_2 gradient and respiratory dead space).

Technique for Sampling Arterial Blood

Arterial blood is sampled either through an indwelling arterial catheter or by percutaneous arterial puncture. Sampling through an indwelling catheter avoids the acute changes in ventilation that can result from apprehension and pain associated with percutaneous puncture.

Three anatomic sites are generally used for obtaining arterial blood samples: the radial, brachial, and femoral arteries. For several reasons, the radial artery is the preferred sampling site. Because of its superficial location at the wrist, the radial artery is easy to palpate and easy to compress by direct pressure, facilitating hemostasis when sampling is complete. In addition, no large veins lie in its immediate vicinity. Furthermore, the ulnar artery usually provides an adequate collateral circulation to the hand in the rare instance of postsampling thrombosis of the radial artery.

Arterial blood samples are drawn anaerobically into plastic or glass syringes coated with heparin. Because room air at sea level has a P_{O_2} of approximately 150 mmHg and a P_{CO_2} of approximately zero mmHg, air bubbles in the syringe will artificially increase the arterial P_{O_2} and reduce the arterial P_{CO_2}. The sample either is immediately analyzed or is placed on ice in order to minimize the metabolism of blood cells, particularly the white cells. If the icing precaution is neglected and the analysis is delayed, the P_{aCO_2} of the sample will increase and the P_{aO_2} and pH will decrease; the rate of change depends on the temperature of the sample and the elapsed time before analysis (Table 34-11).

Interpretations

Analysis of arterial blood gases as part of pulmonary function testing is based primarily on determination of P_{aO_2}, P_{aCO_2}, and pH. As a rule, these parameters are measured directly. Other values, including O_2 saturation, bicarbonate concentration, and base excess (or deficit), are usually calculated. This section deals with the interpretation of P_{aO_2}, P_{aCO_2}, and pH. Additional consideration of arterial blood gases, with particular reference to acid-base balance, is found in Chapter 14.

Arterial P_{O_2} (P_{aO_2})

The physiological determinants of normal P_{aO_2} have been described elsewhere. For example, normal values for arterial P_{O_2}

Table 34-11

In vitro Changes in Arterial Blood Gas Values at 37°C

Measurement	Change over 10 Min
pH (units)	−0.01
P_{CO_2} (mmHg)	+1.000
O_2 content (vol %)	−0.001

Source: Data from Kelman GR, Nunn JF: Nomograms for correction of blood P_{O_2}, P_{CO_2}, pH, and base excess for time and temperature. J Appl Physiol *21:1484–1490, 1966.*

depend on altitude (Table 34-12). Therefore, normal values for arterial P_{O_2} in Denver (altitude of approximately 1500 m) are less than those at sea level by about 20 mmHg.

Arterial P_{O_2} also decreases with age. A regression equation can be used to predict the decrease:

$$Pa_{O_2} = 109 - 0.43 \text{ (age in years)}$$

Table 34-12

Effect of Altitude on Mean Alveolar and Arterial O_2 Pressures

Altitude (Feet)	Barometric Pressure (mmHg)	Ambient P_{O_2} (mmHg)	Alveolar P_{O_2} (mmHg)
0	760	159	103
1000	733	154	98
2000	707	148	94
3000	681	143	90
4000	656	138	85
5000	632	133	81
6000	609	128	77
8000	565	118	69
10,000	523	110	61
12,000	484	101	54

Source: Modified from Wasserman K: Clin Notes Respir Dis *12:3–10, 1973.*

The standard deviation of this relationship is ±4.10 mmHg. A third physiological influence is body position. Assumption of the supine position causes abdominal contents to displace the diaphragm cephalad, thereby closing small airways at the lung bases and creating ventilation-perfusion inhomogeneities that decrease Pa_{O_2}.

Many more pathological conditions than physiological states can lower Pa_{O_2}. In each instance, however, arterial hypoxemia may be attributed to one or more of the following generic mechanisms: alveolar hypoventilation, ventilation-perfusion mismatch, diffusion impairment, and venous admixture ("shunt"). Considerations of the individual disorders within these categories and the mechanisms leading to hypoxemia are found throughout this book.

Arterial Pco_2 ($Paco_2$) and pH

In a steady state, the level of Pa_{CO_2} reflects the level of alveolar ventilation. In the absence of a disorder in metabolic acid-base balance, an increase or decrease in Pa_{CO_2} beyond normal limits indicates a primary disorder in alveolar ventilation. A summary of these disorders and useful criteria for distinguishing among them, based on arterial blood gas composition, are given in Table 34-13.

Acute *respiratory alkalosis*, produced by alveolar hyperventilation, is characterized by hypocapnia (Pa_{CO_2} less than

Table 34-13

Classification of Primary Respiratory Disorders of Acid-Base Balance

Disorder	Definition
Acute respiratory alkalosis (acute alveolar hyperventilation)	Pa_{CO_2} below lower limit of normal (<36 mmHg), with accompanying alkalemia (pH > 7.44)
Chronic respiratory alkalosis (chronic alveolar hyperventilation)	Pa_{CO_2} below lower limit of normal, with pH normal (or near normal) due to renal compensation and lowered serum bicarbonate concentration (<19 mEq/L)
Acute respiratory acidosis (acute alveolar hypoventilation	Pa_{CO_2} above upper limit of normal (>44 mmHg), with accompanying acidemia (pH < 7.36)
Chronic respiratory acidosis (chronic alveolar hypoventilation)	Pa_{CO_2} above upper limit of normal, with pH normal (or near normal) due to renal compensation and elevated serum bicarbonate concentration (>30 mEq/L)

36 mmHg) and an appropriately elevated pH (greater than 7.44). In time (e.g., 24 h or more), renal compensation occurs, and the concentration of bicarbonate in serum decreases. If alveolar hyperventilation continues, a chronic respiratory alkalosis, partly or completely "compensated," ensues.

A low $Paco_2$ is not necessarily indicative of a primary disturbance in alveolar ventilation. Instead, it may be a consequence of respiratory compensation (partial or complete) for metabolic acidosis; this possibility is signaled by the coexistence of hypocapnia and a low pH (under 7.36). Since the kidney and respiratory system do not overcompensate for acid-base derangements, the coexistence of hypocapnia and acidemia suggest the presence of two primary disturbances.

Acute respiratory acidosis, caused by alveolar hypoventilation, is characterized by an abnormally high $Paco_2$ (over 44 mmHg) and a subnormal pH (under 7.36). Again, in time (24 h or more), renal compensation for the primary respiratory disorder restores the serum bicarbonate concentration and blood pH toward normal. A high value for $Paco_2$ may also reflect respiratory compensation for a primary metabolic alkalosis ($[HCO_3^-]$ greater than 30 mEq/L). In this circumstance, however, blood pH will be abnormally high (pH over 7.44), rather than low. In general, the elevation in $Paco_2$ in compensation for metabolic alkalosis does not exceed about 55 mmHg. A $Paco_2$ exceeding this value in the setting of a metabolic alkalosis suggests the likely coexistence of a primary respiratory acidosis.

This discussion has been limited primarily to alterations in arterial blood gas values in primary respiratory acidosis or alkalosis. Metabolic derangements often complicate the picture. These disorders are considered elsewhere (see Chapter 14).

Testing for Air Travel-Related Hypoxemia

Travel in commercial jet airliners typically results in exposure of passengers and crew to conditions equivalent to about 6000 to 8000 feet above sea level. For individuals with normal pulmonary gas exchange, the resulting Pao_2 falls within a clinically acceptable range. However, for many patients with lung disease, the resulting Pao_2 may well be problematic, even in those patients who do not require supplemental oxygen at sea level. Consequently, assessment of patients with chronic lung diseases, particularly COPD and interstitial lung diseases, has become part of the repertoire of tests offered by many pulmonary function laboratories.

One approach to estimating the resultant Pao_2 during air travel is based upon use of regression equations (Fig. 34-30). Using the patient's resting Pao_2 at sea level and his or her FEV_1 percent of predicted, the expected in-flight Pao_2 can be estimated. Some experts advocate use of the nomogram for determining which patients ought to undergo hypoxia inhalation testing (HIT), while others advocate performance of HIT for all traveling patients at risk for in-flight hypoxemia.

HIT is based on the observation that exposure to hypoxic gas mixtures can reproducibly mimic the Pao_2 arising

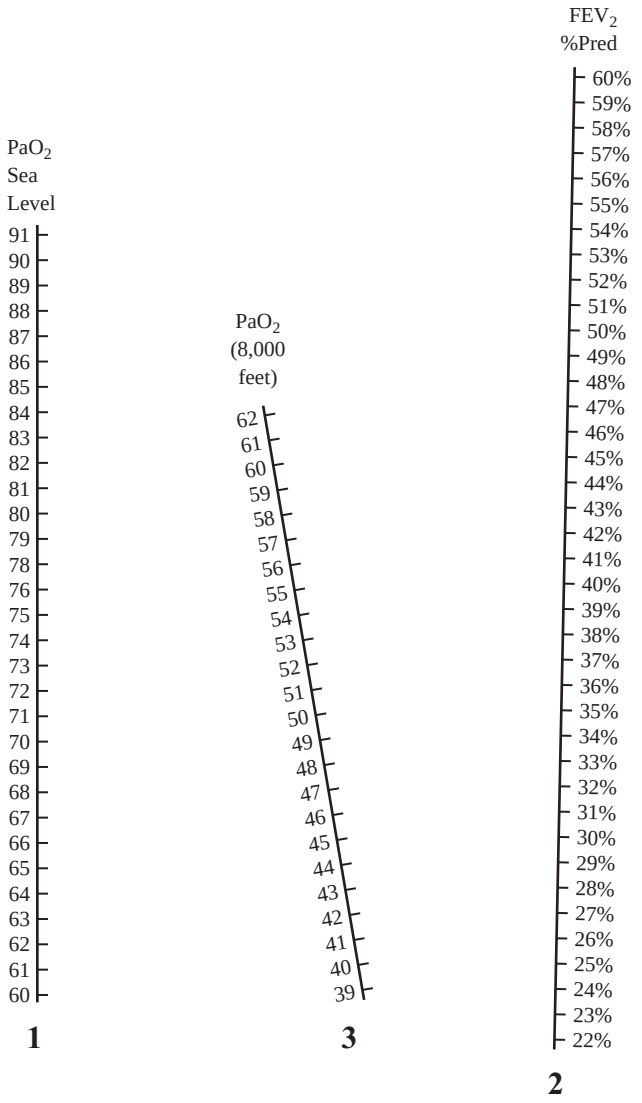


Figure 34-30 Nomogram for predicting in-flight oxygen tension. Using a straight edge, the patient's resting Pao_2 at sea level (Column 1) is aligned with his or her FEV_1% of predicted (Column 2). The expected in-flight Pao_2 (Column 3) is estimated as the value where the line crosses the center scale. *(From Dillard TA, Ewald FW: The use of pulmonary function testing in piloting, air travel, mountain climbing, and diving. Clin Chest Med 22:803, 2001.)*

under true hypobaric conditions. Exposure to 15.1 percent oxygen for 20 min reliably duplicates the resultant Pao_2 at 8000 feet. During performance of the test, the patient, with nose clips in place, breathes from a reservoir though a mouthpiece. The electrocardiogram is monitored, and arterial blood gases are obtained at the conclusion of the test. Supplemental oxygen can then be titrated and prescribed according to the findings.

CONTROL OF BREATHING

The rate, depth, and pattern of breathing reflect a complex interplay of neurohumoral and chemical regulatory

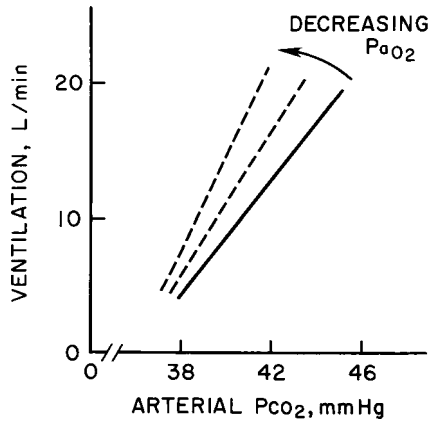


Figure 34-31 Linear relationship between minute ventilation ($\dot{V}_E$) and arterial P_{CO_2}. The dashed lines show the increased slope of the relationship of $\dot{V}_E$ vs. P_{CO_2} as P_{aO_2} decreases.

mechanisms that drive the respiratory apparatus. Tests used to evaluate the control of breathing, based on assessment of the ventilatory response to controlled hypercapnia or hypoxia, are uncommonly performed in the clinical setting. However, since these tests highlight important physiological mechanisms that affect the level and pattern of ventilation, they are summarized below.

Ventilatory Response to CO_2

The ventilatory response to changes in P_{aCO_2} is linear over a broad range (Fig. 34-31). Determination of the ventilatory response to controlled hypercapnia generally is based on one of two methods: the steady-state method or the rebreathing method.

Steady-State Method

After a control period in which CO_2-free air is breathed to establish a baseline, the patient is subjected to two or more periods of breathing CO_2-enriched air. Care is taken to achieve a steady state of ventilation and circulation during each exposure. Especially at the higher concentrations of inspired CO_2, at least 10 to 20 min is required for a steady state to be reached in alveoli, arterial blood, cerebrospinal fluid, and the chemosensitive areas of the brain. The ventilatory response to CO_2 is then determined from a plot of $\dot{V}_E$ vs. P_{aCO_2}. In patients without underlying lung disease, end-tidal CO_2 concentration is often substituted for P_{aCO_2}. In addition, in order to eliminate the influence of variations in arterial PO_2 on the ventilatory response to CO_2, the inspired gas is enriched with O_2 during the control and test periods.

Rebreathing Method

This method entails rebreathing a CO_2-enriched gas mixture from a bag for approximately 4 min. The validity of the approach requires rapid equilibration of CO_2 among alveolar gas, arterial and mixed venous blood, and the chemosensitive areas of the brain. The bag is filled at the outset with a mixture of 7 percent CO_2 in O_2; O_2 is substituted for air in this mixture to avoid the ambiguity of a hypoxic stimulus to ventilatory drive.

The result of the CO_2 rebreathing test is described by use of two terms: (1) the *slope* of the line relating change in ventilation response to change in end-tidal P_{CO_2} ($\Delta\dot{V}_E/P_{CO_2}$), determined by using the method of least squares linear regression analysis, and (2) the *x-intercept* of the relationship between $\dot{V}_E$ and end-tidal P_{CO_2}.

Normal Response to CO_2 and Modifying Influences

As indicated above, the normal increase in ventilatory response to increasing concentrations of inspired CO_2 is linear. Normal responses are categorized as low (under 1.5 L/min/mmHg), intermediate (1.5 to 5.0 L/min/mmHg), or high (more than 5.0 L/min/mmHg). Most normal persons (about 80 percent) have an intermediate ventilatory response. A variety of factors, both genetic and environmental, seem to influence the ventilatory response to CO_2 (Table 34-14).

Ventilatory Response to Hypoxia

The response to acute hypoxia in normal persons is largely determined by the peripheral arterial chemoreceptors, as long as the level of hypoxia is mild to moderate. Even at sea level, the level of arterial P_{O_2} in normal persons provides an appreciable chemoreceptor drive, accounting for about 10 percent of the minute ventilation. Unlike the linear response of $\dot{V}_E$ to progressive hypercapnia, the response to hypoxemia is curvilinear (Fig. 34-32). The magnitude of the ventilatory response to a decrease in arterial P_{O_2} depends on the P_{aCO_2}, increasing as the concentration of CO_2 in arterial blood is increased.

As may be seen from the hyperbolic curves in Fig. 34-32, the rate of change in ventilation is greater over the lower range of oxygenation (when P_{aO_2} falls below 60 mmHg). Not shown in Fig. 34-32 is the depression of ventilation brought about by severe hypoxemia, presumably because of the central depressing effect of severe hypoxia on respiratory neurons.

Although tests for assessing the ventilatory response to hypoxia are less well standardized than those for measuring the hypercapnic response, they, too, may be conveniently categorized into steady-state and non–steady-state methods. In one steady-state method, successive ventilatory responses are determined to a series of increasingly severe hypoxic gas mixtures, each administered for at least 10 min; P_{aCO_2} is kept constant by the addition of CO_2 to the inspired gas mixture as hypoxia-induced hyperventilation develops. In another, the effect of hypoxia on the slope of the plot of $\dot{V}_E$ vs. P_{CO_2}, as P_{O_2} is lowered from hyperoxic (at least 200 mmHg) to hypoxic (40 mmHg) levels, is determined. The normal response to diminished inspired oxygen concentrations is characterized by an increase in sensitivity (slope) without a change in the CO_2 threshold.

Three non–steady-state techniques are currently in use. In the hypoxic rebreathing test, the subject rebreathes a hypoxic gas mixture containing 7 percent CO_2. As arterial hypoxemia intensifies, causing an increase in ventilation and

Table 34-14

Factors Associated with an Altered Ventilatory Response to CO_2

Factor	Reference
Depressed Response	
Endurance training	Byrne-Quinn et al: *J Appl Physiol* 30:91–98, 1971
Aging	Peterson et al: *Am Rev Respir Dis* 124:387–391, 1981
Genetic/racial predilection	Beral et al: *Lancet* 2:1290–1294, 1971
Metabolic alkalosis	Koboyashi et al: *Am Rev Respir Dis* 147:1192–1198, 1993 Heinemann, Goldring: *Am J Med* 57:361–370, 1974
Narcotics, barbiturates, and other CNS depressants	Lambertsen: *Handbook of Physiology*, section 3, *Respiration*, vol I. Washington DC, American Physiological Society, 1964, pp 545–555.
Neurological disorders (encephalitis, brain stem disease)	Plum, Brown: *Ann NY Acad Sci* 109:915–931, 1963
Myxedema	Zwillich et al: *N Engl J Med* 292:662–665, 1975 Duranti et al: *Am J Med* 95:29–37, 1993
Obesity-hypoventilation syndrome	Zwillich et al: *Am J Med* 59:343–348, 1975
Chronic obstructive pulmonary disease (COPD)	Flenley, Millar: *Clin Sci* 33:319–334, 1967
Accentuated Response	
Metabolic acidosis	Heinemann, Goldring: *Am J Med* 57:361–370, 1974
Drugs (e.g., aminophylline, salicylates, thyroxine, progesterone)	Lambertsen: *Handbook of Physiology*, section 3: *Respiration*, vol I. Washington, DC, American Physiological Society, 1964, pp 545–555

in CO_2 elimination into the closed circuit, the P_{CO_2} in the system is held constant at a predetermined level by the diversion of a fraction of the expired gas through a CO_2 absorber. The ventilatory response is determined at two or more levels of P_{CO_2}, since the hypoxic response is influenced by P_{CO_2}. An alternative rebreathing test induces progressive hypoxemia by adding N_2 to the inspired gas mixture over a 20-min period. Finally, in a relatively simple test, the patient induces a transient drop in arterial P_{O_2} by inhaling pure N_2 for a few breaths. The relationship between $\dot{V}_E$ and P_{aO_2} is plotted; the slope of the relationship is the sensitivity to hypoxia. Because the duration of the hypoxia is brief, presumably only the peripheral chemoreceptors are stimulated. No adjustment is made for the drop in P_{CO_2} that occurs during the hypoxia-stimulated increase in ventilation.

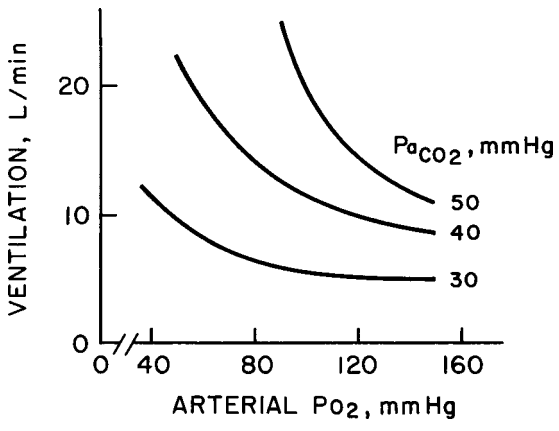


Figure 34-32 The curvilinear relationship between ventilation and arterial P_{O_2} at various levels of arterial P_{CO_2}. The rate of change of ventilation as P_{O_2} falls (slope) increases precipitously at a P_{O_2} of approximately 60 mmHg when P_{CO_2} is 40 mmHg. The abrupt increase in ventilation occurs at a higher P_{O_2} when the level of P_{CO_2} is elevated, and at a lower P_{O_2} when the prevailing P_{CO_2} is lower.

Normal Responses to Hypoxia and Modifying Influences

The normal ventilatory response to acute hypoxia varies among individuals. Several factors may influence the relationship (Table 34-15). A high ventilatory response to CO_2 may be associated with a high sensitivity to hypoxia; in addition, higher levels of arterial P_{CO_2} are associated with a higher ventilatory response to hypoxia. Interestingly, in long durations of hypoxia before the test period, as is the case in native residents at high altitude or persons with cyanotic congenital heart disease, a blunted response to acute hypoxia is observed. Finally, a variety of other clinical disorders, including myxedema and hypothyroidism, autonomic nervous system dysfunction, chronic narcotic addiction, and the chronic use of methadone, are characterized by a reduced hypoxic response.

Table 34-15

Factors Associated with an Altered Ventilatory Response to Hypoxia

Factor	Reference
Depressed Response	
Long-standing hypoxia	
High-altitude dwelling	Severinghaus et al: *Respir Physiol* 1: 308–334, 1966
Congenital cyanotic heart disease	Blesa et al: *N Engl J Med* 296: 237–241, 1977
Aging	Kronenberg et al: *J Clin Invest* 52: 1812–1819, 1973
Hypothyroidism	Zwillich et al: *N Engl J Med* 292:662–665, 1975
Riley-Day syndrome	Edelman et al: *J Clin Invest* 49:1153–1165, 1970
Chronic use of methadone	Marks: *Am Rev Respir Dis* 108:1088–1093, 1970
Following carotid endarterectomy	Wade et al: *N Engl J Med* 282: 823–829, 1970
Accentuated Response	
Heightened CO_2 response	Rebuk et al: *J Appl Physiol* 35: 173–177, 1973
Hypercapnia	Rebuck, Woodley: *J Appl Physiol* 38: 16–19, 1975

Nonventilatory Measures of Ventilatory Drive

Measurement of ventilation in response to acute hypoxia or hypercapnia provides a useful index of respiratory output when the ventilatory apparatus (thorax, diaphragm, abdominal muscles, lung, and airways) is normal. This situation obviously does not apply in certain neuromuscular disorders in which the thorax and diaphragm behave abnormally. In addition, it does not apply in some instances of pulmonary disease, notably obstructive airway disease, in which the respiratory apparatus may not be capable of responding normally, even though it is intact and chemosensitivity is normal. In this instance, a decrease in ventilatory response may be attributable to the excessive mechanical load placed on the muscles of respiration.

When ventilation fails to provide a reliable measure of the ventilatory drive (efferent discharge from the respiratory neurons), the diaphragmatic electromyograph (EMG) or the pressure generated by the inspiratory muscles during the first 0.1 s of an occluded inspiration (the $P_{0.1}$) has been used for the clinical assessment of the control of breathing.

The electrical activity of the diaphragm is directly related to neural activity of the phrenic nerve. Therefore, it provides a measure of efferent neural traffic to the diaphragm. The diaphragmatic EMG may be recorded in patients by placing the tip of an esophageal catheter, containing bipolar electrodes, at the level of the diaphragm.

The second approach to obtaining a nonventilatory measure of ventilatory drive is the determination of $P_{0.1}$, which is the negative pressure generated by the inspiratory muscles during the first 100 ms of an inspiratory effort made against an occluded airway. During this brief period, contraction of the respiratory muscles is virtually isometric, and the force generated correlates with activity recorded by the diaphragmatic EMG.

In performing the test, airflow in the inspiratory line of the breathing circuit is randomly interrupted during the preceding expiration. The 100-ms period has proved to be so brief as to be imperceptible, thereby obviating any corrective action by the subject during the breath against the occlusion. However, the $P_{0.1}$ is far from foolproof. A major concern is that $P_{0.1}$ is affected by resting lung volume: $P_{0.1}$ is reduced when FRC is abnormally high, a common occurrence in obstructive disease of the airways.

ASSESSMENT OF INTEGRATED FUNCTIONS: 6-MINUTE WALK TEST

A complete evaluation of a patient with respiratory symptoms often requires assessment of exercise capacity, in addition to traditional pulmonary function tests and radiographic studies. A number of exercise studies can be employed, including cardiopulmonary exercise tests (Chapter 135), cardiac stress tests, and EIB protocols. One of the most widely used, practical modalities is the 6-minute walk test (6MWT). Despite its simplicity, the 6MWT has become a powerful tool in the evaluation of functional status and prognosis of patients with a variety of functional impairments.

Technical Aspects

The 6MWT is performed indoors. There is an initial period of rest in a chair for at least 10 min, during which baseline vital signs are taken. The patient then stands and is asked to rate baseline dyspnea and overall fatigue using the Borg scale (from 1 to 10). The patient, walking at a comfortable pace, completes 60-m laps on a walking course that is 30 m in length. Cones are used to mark the turnaround points. For patients using supplemental oxygen, the oxygen is delivered at standard rate, or as prescribed by a physician, or as determined by protocol. The patient should not carry or push the oxygen source during testing. The number of laps and a post-walk Borg scale assessment are recorded, as is the total distance walked over 6 min (6MWD).

Although pulse oximetry during the 6MWT is considered optional, it has become standard at many institutions. In some cases, pulse oximetry can be used to titrate levels of oxygen supplementation. Obtaining a high-quality oximeter signal is imperative.

A number of sources of variability are inherent in the 6MWT. A modest training effect has been reported when two studies are performed within one week. Concomitant medication use can also impact the 6MWT. Improved test performance, for example, occurs after bronchodilator use in patients with COPD. Shorter height, female sex, and higher body weight are associated with reduced performance. Despite these factors, the 6MWT has been found to have excellent reproducibility, especially when performed in evaluation of specific clinical entities, such as idiopathic pulmonary fibrosis.

Several modifications of the 6MWT are in clinical use. During a *shuttle-walking test*, the patient walks on a 10-m course while the walking speed is increased every minute until the patient cannot reach the turnaround point within the set time. The *timed walk test (TWT)*, which has been designed for patients with idiopathic pulmonary fibrosis, has three stopping criteria based on changes in oxyhemoglobin saturation.

Absolute contraindications to performing the 6MWT include unstable angina or myocardial infarction within 1 month of the study. Resting tachycardia of greater than 120 beats per minute, systolic blood pressure greater than 180 mmHg, or diastolic blood pressure greater than 100 mmHg are relative contraindications. The study should be terminated if the patient develops chest pain, severe dyspnea, leg cramps, diaphoresis, or profound oxyhemoglobin desaturation.

Interpretation

Although the 6MWT is limited in its inability to provide objective measures of functional capacity, such as oxygen uptake, the test provides very useful clinical information. In addition, it realistically represents the patient's functional capacity during physical effort that more closely reflects his or her daily activity. Reliable reference equations establishing standard performance during a 6MWT in healthy patients are not currently available.

The 6MWT has several indications, most notably, measurement of the response to a number of medical and surgical interventions. Pulmonary rehabilitation clearly improves 6MWT performance in patients with COPD, while pharmacologic interventions for pulmonary arterial hypertension and heart failure, among other disorders, have also been shown to favorably affect test results. Lung transplantation (unilateral and bilateral) and lung volume reduction surgery for emphysema have been shown to significantly improve results of the 6MWT.

The 6MWT also has been used to assess functional status in patients with COPD, cystic fibrosis, heart failure, and peripheral vascular disease, and in determining eligibility for, and timing of, lung transplantation. In the absence of well-established reference standards, the clinical value of performing a single test in these patient groups is limited. Serial studies are likely to be more useful than a single 6MWT.

Recently, a number of publications have established the value of the 6MWT in predicting morbidity and mortality from heart and lung disease. Results from the test have been shown to have an inverse relationship with mortality in severe COPD. Walk distance and velocity, as well as magnitude of oxyhemoglobin desaturation, are correlated with survival in idiopathic pulmonary fibrosis. Similar correlations have been made in heart failure and primary pulmonary hypertension.

Finally, at some institutions, results of the 6MWT are used to not only establish the presence of exertional hypoxemia, but also to titrate supplemental oxygen with activity.

QUALITY CONTROL IN THE PULMONARY FUNCTION LABORATORY

Meaningful interpretation of pulmonary function tests requires confidence in the accuracy and reproducibility of results provided by the pulmonary function laboratory. Previously, it was tacitly assumed that all data from all laboratories, especially when reported as "percent predicted," were equally reliable. In recent years, the fallacy of this assumption has been explicitly recognized, and steps have been taken to standardize equipment and procedures and to ensure accuracy, reproducibility, and uniformity in testing and reporting. To accomplish this goal, both analytical and nonanalytical factors must be taken into account.

Nonanalytical Factors in Quality Control

A familiar example of a confounding influence that may distort test results is the anxious patient who pauses outside the laboratory door to "calm the nerves" by smoking one or more cigarettes before undergoing pulmonary function testing. Cigarette smoking before the diffusing capacity of the lungs is determined can generate enough carboxyhemoglobin to reduce a normal value to subnormal levels.

Another example of a nonanalytical factor is the failure to achieve patient understanding and comfort for tests that usually require patient cooperation. Unfortunately, a preliminary explanation before the patient arrives at the laboratory or prior exposure of the patient to the laboratory and its personnel is usually impractical. Use of explanatory sheets or descriptive brochures may prove helpful. If such materials are not available, laboratory personnel are obligated to make the patient comfortable and even perform "practice runs" before undertaking final testing.

When the patient arrives at the pulmonary function laboratory, an assessment should be made of his or her prior experiences. Did the patient undergo other tests or procedures that could alter the outcome of the pulmonary function tests in question? Is the patient fatigued or in pain? Should a period of rest precede the tests in order to ensure optimal performance? If delay is impractical, the test report should include the fact that the patient was fatigued or in pain.

Medication use before pulmonary function testing can seriously affect the results. For example, self-administration of bronchodilators before testing can artificially enhance tests of airflow. If medications have been taken before the patient arrives at the laboratory, the time of administration should be part of the record. Also, a request for pulmonary function test results for patients who regularly take bronchodilators should indicate whether the tests are to be done without interruption of the regular schedule of medications, whether bronchodilators are to be discontinued before the test is done, or whether regular bronchodilators are to be discontinued so that the effects of bronchodilation can be tested. Appropriate comments about bronchodilators are part of the report.

A major nonanalytical cause of misinterpreting results is the inappropriate application of predicted normal values to the patient population by the laboratory (see "Approach to Interpreting Commonly Performed Pulmonary Function Tests," below). For example, normal values based on data obtained using physically fit hospital personnel do not necessarily apply to those who have a sedentary existence. Noncomparable race, as well as lifestyle, may complicate comparisons. Anthropological differences among control and test populations are not easily reconciled. Extraordinary height, weight, or age cannot be easily extrapolated if corresponding subjects are not represented in the control group. Using patient-reported height, rather than making measurement of patient height, may introduce an error in the selection of appropriate normal values. Comparison of control and test results at different altitudes can be invalid if due regard is not paid to the influence of hypoxia on certain measurements (e.g., diffusing capacity).

Analytical Factors in Quality Control

Performance of pulmonary function tests is replete with opportunities for error. The equipment, techniques, use of control values, and calculations are potential sources of error. In an attempt to minimize errors, standardization of techniques has been advocated. For example, with respect to performing the forced vital capacity maneuver, guidelines have been established for the number of attempts required, acceptable variability between efforts, and methods for selecting test data in order to arrive at acceptable results. To avoid misuse of spirometers, criteria have been set for minimal performance with respect to capacity, accuracy, and frequency response of various spirometers; in addition, standards have been developed for determining the single-breath diffusing capacity. Potential sources of discrepancies—such as breath-holding time, concentration of hemoglobin, dead space of the equipment and the patient, F_{IO_2}, volume of the alveolar sample, number of tests, and acceptable variability in results—are taken into account.

Quality Control of Test Results

Guidelines for standardization play a major role in reducing discrepancies between laboratories. However, measures are also required to ensure accuracy and reproducibility within any given laboratory. Among the elements of control that merit consideration are calibration, validation of calibration, and performance of a control measurement. *Calibration* is the adjustment of an instrument's output so that it validly reflects a known input. *Verification of calibration* entails introduction of the same known input and demonstration that the correct output is reproduced. *Performance of a control measurement* refers to the testing of a substrate that has known properties, similar to those usually tested, to prove the accuracy of the instrumentation. One example of the application of these principles is blood gas analysis. Use of control measurements derived from tonometered blood or commercially prepared buffer solutions is now widespread.

Unfortunately, similar controls do not exist for pulmonary function tests. Therefore, laboratory technologists have the responsibility for continuing to be alert, not only with respect to faithful observance of guidelines for standardization but also to detect in-house sources of error (e.g., a leak in the system, malfunction of gas analyzers, faulty analog-to-digital converters, and faulty electronics that reduce frequency response).

Responsibility and Cost in Quality Control

All who work in the laboratory must be concerned with quality control, despite the frequent temptation to cut corners. Indeed, one common rationalization for not doing so is the misguided impression that quality control, as described above, is too expensive. Time has to be set aside for the technologist to care for and calibrate equipment, to establish proper control values for the laboratory, to search for inconsistencies in the data and interpretation, and to keep up with changing standards. Also, equipment and supplies, including calibrating syringes and calibrating gases, are expensive. However, when put into the balance, the cost and waste of producing erroneous results exceed, by far, the expense of practicing quality control.

Infection Control

Given the relatively close contact between patients and technical staff during performance of pulmonary function tests, the issue of infection control is one that must be carefully considered. To date, the role of pulmonary function equipment in transmission of disease appears to be minimal. Although the presence of potential pathogens on laboratory mouthpieces, valves, and tubing has been well documented, implication of these organisms in the transmission of disease has not been established. Nevertheless, the potential hazards should be recognized and appropriate care exercised.

Infection control begins with practice of the basic principles of hygiene. Staff should always wash their hands between patients and use protective gloves when handling potentially contaminated equipment. Care must be taken in working with mouthpieces, nose clips, and any other implements that come in contact with mucosal surfaces. These

devices, if reused, should be disinfected or sterilized after each use. Other equipment—manifolds, tubing, etc.—should be sterilized on a regular basis. In fact, guidelines from the American Thoracic Society call for the disinfection or sterilization before reuse of any equipment surface with visible condensation from expired air.

Because of recent growing concern over cross-contamination among patients and laboratory personnel, manufacturers now produce a variety of in-line filters and disposable pneumotachographs. Care should be taken, however, to assure that response characteristics of the test equipment are not driven to unacceptable levels by use of these devices. Current literature on this topic should be consulted regularly.

APPROACH TO INTERPRETING COMMONLY PERFORMED PULMONARY FUNCTION TESTS

A standard battery of pulmonary function tests is commonly used to identify and quantify abnormalities in the performance of the respiratory system. An organized approach to interpreting these studies is critical. Once a patient's baseline values are established, the tests are valuable in tracking the course of the disorder and its response to treatment.

Results of pulmonary function tests are interpreted by comparing individual patient data with reference or predicted values for normal subjects. Ideally, predicted values should be generated from large groups of well-defined, normal or healthy subjects with proper distribution of anthropometric characteristics such as sex, age and height, and ethnic background. Despite dedicated attempts to improve prediction formulas, however, many still fail to take into account important sources of discrepancy, such as the racial and ethnic backgrounds of the patients and the control population, the effects of altitude and exposure to air pollution, and effects of inordinate body size or old age. As a result, not all sets of predicted normals are applicable in pulmonary function laboratories outside the immediate vicinity of the patient populations from whom the data were collected. Extrapolation beyond the characteristics of the reference population should be avoided.

Recently published guidelines from a joint Task Force of the American Thoracic Society (ATS) and European Respiratory Society (ERS) recommended that in the United States, ethnically appropriate reference equations from the National Health and Nutrition Examination Survey (NHANES) III be used for individuals between the ages of 8 and 80 years. The ATS/ERS Task Force did not recommend any specific set of reference equations for laboratories in Europe, but it suggested the need for an investigation conducted throughout Europe to derive contemporary equations for prediction of normal lung function.

The same ATS/ERS Task Force recommended that each pulmonary function test result falling below the fifth percentile of the frequency distribution of values measured in the reference population be considered abnormal. If normal test results fall in a normal distribution, values below the fifth percentile can be estimated using Gaussian statistics. If the distribution of normal values is non-Gaussian, the lower limit of normal is estimated using a nonparametric technique (e.g., the 95th percentile method). Traditionally, but without a sound statistical basis, most laboratories have used an arbitrary cutoff of 80 percent predicted to define normal. While this method may be reasonable in children, errors may arise if it is applied to adult test results.

Interpretation Scheme and Classification of Abnormal Patterns

A variety of schemes have been proposed for sorting out abnormalities in pulmonary function test results. Many are based on initial categorization of findings reflective of one of four basic patterns described below.

An *obstructive* pattern stems from narrowing of any portion of the airways—from upper airway to bronchioles less than 2 mm in diameter—that results in a reduction of maximal airflow in relation to maximal volume.

A r*estrictive* pattern is elicited by diseases of the lung, chest wall, pleural space, or neuromuscular respiratory apparatus that reduce lung volumes, particularly TLC, and vital capacity.

A *combined obstructive-restrictive* pattern results from pathological processes that reduce lung volumes, vital capacity, and airflow, and that also include an element of airway narrowing.

Finally, *abnormal gas transfer* may be noted as part of one of the aforementioned patterns or in isolation and reflects an abnormality in the alveolar-capillary membrane, impairing oxygen uptake from alveolar gas to pulmonary capillary blood.

Overlap among categories is not uncommon. For example, widespread interstitial disease, as in idiopathic pulmonary fibrosis, often shows a pattern that indicates important components of both restrictive disease and abnormal gas transfer.

One useful sequence recommended by the ATS/ERS Task Force for analyzing a conventional battery of pulmonary function test results is illustrated in Fig. 34-33.

Analysis begins with evaluation of the ratio of FEV_1 to VC. While, historically, the ratio of FEV_1 to FVC (FEV_1/FVC%) served as the basis for distinguishing obstructive disorders from normality or restrictive disease, the ATS/ERS Task Force currently recommends using as the denominator the FVC, *or* the VC ("slow" VC or SVC), *or* the FIVC, whichever is greatest. If the ratio is less than the lower limit of normal (i.e., below the fifth percentile) and the VC (defining VC as any of the three previously noted vital capacity measurements) is at or above the lower limit of normal, the pattern is obstructive. If TLC is not at or above the lower limit of normal, a mixed obstructive-restrictive pattern is

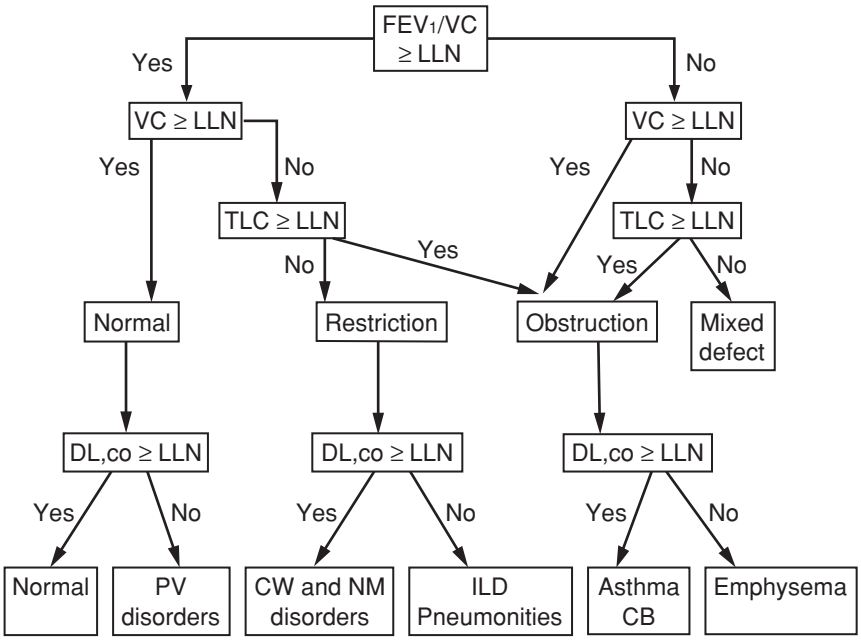


Figure 34-33 Proposed sequence of test review in the interpretation of pulmonary function tests (see text for discussion). LLN, lower limit of normal; PV, pulmonary vascular; CW, chest wall; NM, neuromuscular; ILD, interstitial lung disease; CB, chronic bronchitis. *(From Pellegrino R, Viegi G, Brusasco V, et al: Interpretive strategies for lung function tests. Eur Respir J 26:948, 2005.)*

suggested. Distinction between asthma and chronic bronchitis on the one hand, and emphysema on the other, is based upon whether the D_{LCO} is normal (asthma or chronic bronchitis) or reduced (emphysema). The previous practice of using a value for FEV_1/FVC% of less than 70 percent to define obstruction results in misdiagnosis of airway obstruction in men over 40 years and women over 50 years, as well as overdiagnosis of COPD in elderly, asymptomatic nonsmokers.

If FEV_1/VC and VC are each equal to or greater than the respective lower limits of normal, spirometry is considered normal; measurement of the D_{LCO} can then help distinguish between normal pulmonary function and pulmonary vascular disorders. If VC is below the lower limit of normal, a reduced TLC supports a diagnosis of restriction, while a normal TLC indicates an obstructive pattern. Once again, in the setting of a restrictive pattern, measurement of D_{LCO} can be used to distinguish between pulmonary parenchymal disorders and disorders of the chest wall or respiratory muscles. Note that according to these guidelines, an obstructive pattern may be diagnosed in the setting of a *normal* FEV_1/VC, if VC is reduced and TLC is normal or elevated.

Once the predominant abnormality is defined with initial pulmonary function testing, the whole battery may not be necessary in following the course of the disease or in assessing its response to treatment. For example, particular determinations, such as spirometry, may suffice in patients with airway diseases. Notably, according to the ATS/ERS guidelines, the severity of the abnormality in each of the obstructive, restrictive, or mixed patterns is expressed on the basis of the FEV_1 (Table 34-16). Standards have been established for defining significant changes in results over time: a 15 percent or greater change in FVC or in FEV_1, or a greater than 10 percent change in D_{LCO} is considered significant.

Assessing Respiratory Muscle Strength and Effort

One additional measurement that is frequently useful in assessing results of routine spirometry is assessment of respiratory muscle strength. Respiratory muscle strength is expressed in terms of peak inspiratory ($P_{I_{max}}$) and peak expiratory ($P_{E_{max}}$) pressures, determined under static conditions. The technique was outlined in a previous section. Any of a number of factors may be responsible for low peak inspiratory or expiratory pressures (Table 34-17): suboptimal effort, fatigue, weakness of the respiratory muscles, deformity of the chest wall, or intrinsic diseases of the lungs or chest wall. Although

Table 34-16

Grading of Severity of Abnormal Spirometry Based on FEV_1

Severity	FEV_1 Percent Predicted
Mild	>70
Moderate	60–69
Moderately severe	50–59
Severe	35–49
Very severe	<35

Source: Modified from Pellegrino R, Viegi G, Brusasco V, et al: Interpretive strategies for lung function tests. Eur Respir J *26:948–968, 2005.*

Table 34-17

Conditions Associated with Reduced Peak Inspiratory ($P_{I_{max}}$) and Expiratory ($P_{E_{max}}$) Pressures

Condition	$P_{I_{max}}$	$P_{E_{max}}$
Poor effort	↓	↓
Fatigue	↓	↓
Neuromuscular disease	↓	↓
Increased lung volume	↓	N
Decreased lung volume	N	↓

Note: ↓ = decreased; N = normal.

the first three factors characteristically reduce both peak inspiratory and expiratory pressures, disease of the lungs or chest wall often reduces, selectively, one or the other peak pressure. Thus, diseases that reduce lung volumes (e.g., widespread interstitial fibrosis) and shorten the length of the expiratory muscles at the end-inspiratory position generally reduce maximal expiratory pressure. Conversely, diseases that increase lung volume, such as obstructive airway disease, by decreasing the inspiratory muscle length at end-expiration generally reduce maximal inspiratory pressure.

If airflow during spirometry is reduced, determination of the peak inspiratory and expiratory pressures may be helpful in suggesting the mechanism. Many pulmonary function tests depend on the cooperation of the patient. Poorly reproducible peak flows that are consistently subnormal raise the question of poor effort. Conversely, consistently low values that occur despite maximal effort may signal neuromuscular disease.

Additional Details of Pulmonary Function Test Results in an Obstructive Pattern

Included in the obstructive pulmonary disorders (Table 34-18) are chronic obstructive diseases of the airways (chronic bronchitis and emphysema), bronchiectasis, asthma, small-airway disease, and upper-airway obstruction.

Except for diseases confined to the small airways, as noted previously, the hallmark of the obstructive pattern is a reduction in the FEV_1/VC%. Notably, some healthy subjects have a reduced FEV_1/FVC% and an FEV_1 in the normal range. The clinical significance of these findings is unclear. Results of additional tests (e.g., lung volumes, $D_{L_{CO}}$, assessment of bronchodilator responsiveness) may help distinguish those with airway obstruction from true normals. Measurement of airway resistance (Raw) or specific airway conductance (SGaw) may be useful in assessing airway obstruction in subjects unable to perform a maximal forced expiratory maneuver.

Changes in lung volume commonly accompany the abnormal findings on spirometry but, as indicated in Fig. 34-33, lung volume measurement is not mandatory in establishing

Table 34-18

Causes of an Obstructive Pattern

Disease Process	Anatomic Location of Lesion	Cause of Reduced Airflow
Chronic obstructive pulmonary disease (COPD)		
Chronic bronchitis	Large and small (<2-mm diameter) airways	Narrowing of airways by fibrosis, secretions, edema
Emphysema	Lung parenchyma	Loss of lung elastic recoil
Cystic fibrosis	Large and small airways	Narrowing of airway by fibrosis, retained secretions, edema Loss of elastic recoil
Asthma	Large and small airways	Narrowing of airways by smooth-muscle contraction, edema, retained secretions
Small-airway disease	Small airways	Narrowing, stenosis of small airways
Upper-airway obstruction	Major, central airways (trachea, main bronchi)	Anatomic or functional narrowing of upper airway

the presence of obstruction. Frequently, but not invariably, lung volumes are abnormally high. Typically, all three lung volumes—RV, FRC, and TLC—are increased.

In addition to uncovering the pattern of chronic obstructive airway disease described previously, certain additional tests provide insight into the sites and mechanisms of obstructive airway disease.

Reversible vs. Irreversible Obstructive Airway Disease

The response to inhaled bronchodilators traditionally has been used to help distinguish between chronic obstructive airway disease (chronic bronchitis and emphysema), in which airway resistance is virtually fixed, and asthma, in which bronchoconstriction is a prominent feature. This is an oversimplification, since a sizable minority of patients with COPD manifest a bronchodilator response. Furthermore, the absence of a bronchodilator response in a laboratory setting does not necessarily predict lack of a clinical response.

A universally agreed upon definition of reversibility is lacking. Expressing change in FEV_1 or FVC as a percent of predicted values may be more advantageous than expression of changes in the values relative to baseline. In general, an increase in FEV_1 or FVC of at least 12 percent above baseline *and* an absolute increment of at least 200 ml is considered evidence of significant bronchodilation. If the increase in spirometric values is not significant, a decrease in lung volumes toward normal may be an indication of bronchodilator responsiveness.

Chronic Bronchitis vs. Emphysema

Although chronic bronchitis and emphysema usually coexist, occasionally one or the other exists in virtually pure form. Two pulmonary function tests have proved valuable in distinguishing between the two—diffusing capacity (D_{LCO}), which is routinely measured, and static lung compliance (Cst,L), which is uncommonly measured clinically. Emphysema, characterized by a loss of alveolar units and a decrease in alveolar surface area, is associated with a low D_{LCO}, whereas the D_{LCO} in chronic bronchitis is usually normal or near normal.

The loss of alveolar units in emphysema also causes a decrease in the elastic recoil pressure of the lungs. As a result, Cst,L is increased in emphysema, whereas it is usually not appreciably altered in chronic bronchitis.

Small-Airway Disease

In obstructive disease of the small airways (i.e., those less than 2 mm in diameter), expiratory flow is usually normal, except at low lung volumes (i.e., the FEV_3 and $FEF_{25-75\%}$ are abnormally low). Other, uncommonly performed tests for isolated, small-airway disease, including the helium-oxygen flow-volume loop, nitrogen washout test, and frequency dependence of dynamic compliance, would also be anticipated to be abnormal. Lung volumes and D_{LCO} are normal. Bronchodilators are virtually without effect.

The practical value of tests of small-airway function is problematic. At one time, high hopes were held that early detection of small-airway disease might reinforce measures, such as cessation of smoking, that would prevent or arrest progression to irreversible obstructive disease of the airways. However, enthusiasm for testing for small-airway disease has waned, since it is still unclear if small-airway disease is a reversible phase in the evolution of clinically significant obstructive airway disease that affects larger bronchi.

Upper-Airway Obstruction

The designation *upper-airway obstruction* is an umbrella for anatomic or functional narrowing of the large upper airways—the larynx, extra- and intrathoracic trachea, and lobar bronchi. Although upper-airway obstruction of any cause may reduce expiratory or inspiratory airflow, an alteration in the contour of the flow-volume loop has proved to be the most reliable abnormality in conventional pulmonary function testing. The observation from routine spirometry that the ratio of FEV_1 to PEFR (peak expiratory flow rate) exceeds 8 ml/L/min should prompt careful performance and review of the flow-volume loop, as described below.

Upper-airway obstruction can be divided into three major types: (1) fixed obstruction, (2) variable extrathoracic obstruction, and (3) variable intrathoracic obstruction.

A *fixed obstruction*, such as tracheal narrowing by scar tissue at the site of a previous tracheotomy, is one in which the geometry and cross-sectional area of the lesion do not change during the respiratory cycle. Characteristically, both inspiratory and expiratory flows are affected about equally (Fig. 34-34*A*).

A *variable obstruction* is one in which the configuration of the obstructive lesion changes with the phases of respiration. Depending on its location in the tracheobronchial tree (extra- or intrathoracic), this type of lesion usually affects predominantly either inspiration or expiration.

The inspiratory arm of the flow-volume loop is primarily affected by a *variable extrathoracic* obstruction, leaving the expiratory limb relatively unaffected (Fig. 34-34*B*). The abnormal configuration of the flow-volume loop is attributable to the following sequence: during forced expiration, tracheal pressure exceeds atmospheric, so that the degree of obstruction decreases; conversely, during forced inspiration, intratracheal pressure becomes less than atmospheric and the trachea tends to collapse.

The expiratory arm of the flow-volume loop is primarily affected by a *variable intrathoracic* obstruction (Fig. 34-34*C*). The following sequence is responsible for producing this abnormality in the flow-volume loop: during forced expiration, as pleural pressure reaches and then exceeds intratracheal pressure downstream from the lesion (i.e., toward the mouth), the obstruction tends to increase; conversely, during a forced inspiration, as intratracheal pressure exceeds pleural pressure, the intrathoracic obstruction decreases.

Variable intrathoracic lesions often coexist with obstructive airway disease. In considering a variable intrathoracic lesion, the respective roles played by obstructive disease of the airways (i.e., chronic bronchitis, emphysema, and

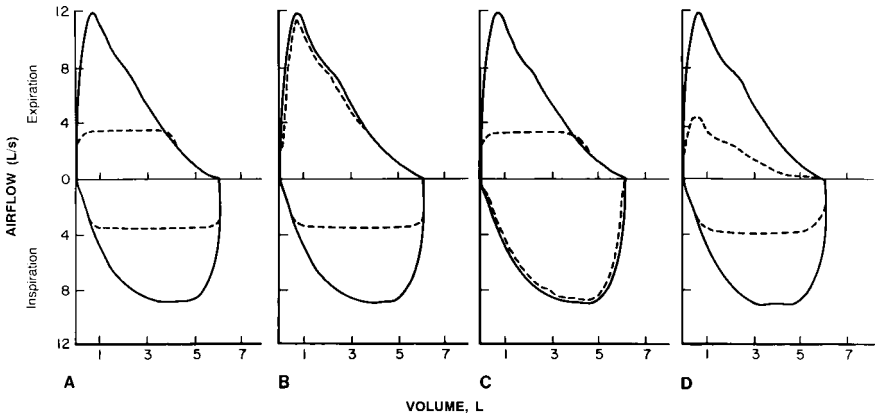


Figure 34-34 Schematic flow-volume loops in four pathological conditions. *A.* In a fixed upper-airway obstruction, both inspiratory and expiratory limbs are truncated. *B.* In a variable extrathoracic obstruction, the inspiratory limb is flattened while the expiratory limb is not altered. *C.* In a variable intrathoracic obstruction, the expiratory limb is flattened while the inspiratory portion is unchanged. *D.* In chronic obstructive airway disease, although expiratory airflow is reduced, the tapering in airflow during expiration is generally maintained so that the configuration of the loop is different from that in variable intrathoracic obstruction.

asthma) and an obstructive upper-airway lesion (anatomic or functional) in deforming the flow-volume loop must be determined. Fortunately, this distinction is often possible. Although both upper-airway obstruction and obstructive airway disease (reversible and irreversible) do decrease maximal expiratory flow, the shapes of the flow-volume curves are frequently quite distinctive (Fig. 34-34*C* and *D*). Thus, in obstructive airway disease, despite a decrease in airflow, the expiratory limb of the loop generally retains its normal configuration (Fig. 34-34*D*)—i.e., an early peak in flow, followed by gradual tapering. In contrast, in upper-airway obstruction (fixed and variable intrathoracic), the expiratory limb is flat and flow is decreased throughout most of expiration (Fig. 34-34*C*).

In addition to changes in the shape of the flow-volume loop, clues from routine pulmonary function tests often alert the clinician to the possibility of upper-airway obstruction. As noted previously, when FEV_1/PEFR is greater than 8, the possibility of upper-airway obstruction should be considered. Finally, the presence of any of the following may also provide clues: $FEF_{50\%}/FIF_{50\%}$ of at least 1, where $FEF_{50\%}$ and $FIF_{50\%}$ are the forced expiratory flow at 50 percent of FVC and the forced inspiratory flow at 50 percent of FIVC, respectively; $FIF_{50\%}$ less than 100 L/min; and $FEV_1/FEV_{0.5}$ at least 1.5.

Distinguishing test features of disorders producing an obstructive pattern are summarized in Table 34-19.

Additional Details of Pulmonary Function Test Results in a Restrictive Pattern

The restrictive pattern (Table 34-20) characteristically occurs in several groups of disorders including: (1) a primary disorder of the lung parenchyma in which functional tissue is lost through disease (e.g., an alveolar filling process, such as pneumonia, tumor, atelectasis, or fibrosis); (2) surgical removal of lung tissue (e.g., lobectomy); (3) constrictive disease of the

Table 34-19

Distinguishing Features of Disorders Producing an Obstructive Pattern

Disorder	FEV_1	FVC	$FEV_1/VC\%$	Response of FEV_1 to Administration of Bronchodilator	Tests of Small-Airway Function	Lung Volumes	D_{LCO}	Flow-Volume Loop
COPD								
Chronic bronchitis	↓	↓	↓	NC	ABN	↑	NL	ABN
Emphysema	↓	↓	↓	NC	ABN	↑	↓	ABN
Asthma	↓	↓	↓	↑	ABN	↑	NL	ABN
Small-airway disease	NL	NL	NL	NC	ABN	NL	NL	NL
Upper-airway obstruction	↓	↓	↓	NC	NL or ABN	NL or ↑	NL	ABN*

** Configuration frequently characteristic for upper-airway obstruction.*

Note: ↓ = decrease; ↑ = increase, NC = no significant change; NL = normal; ABN = abnormal.

Table 34-20

Causes of a Restrictive Pattern

Disease Process	Anatomic Location of Lesion	Cause of Pulmonary Function Test Abnormality
Primary parenchymal disease	Lung parenchyma	Loss of lung tissue → reduced volumes and flows
Surgical removal of lung tissue	Lung parenchyma	Loss of lung tissue → reduced volumes and flows
Diseases of pleura and chest wall	Pleura, chest wall	Limited expansion of thoracic cavity → reduced volumes and flows
Reduced generation of expiratory force	Central nervous system, peripheral nerves, neuromuscular junction, muscles of respiration	Reduced muscle tension → reduced expiratory flow, atelectasis

pleura and chest wall (e.g., extensive pleural fibrosis, large pleural effusion or pleural mass, kyphoscoliosis, obesity); and (4) neuromuscular diseases, notably those in which the generation of respiratory force is reduced (e.g., disorders of the spinal cord, peripheral nerves, neuromuscular junction, and muscle).

The diagnosis of restriction is based upon the finding of a normal FEV_1/VC and reduced VC in the setting of a decreased TLC. While TLC generally is reduced in most disorders producing a restrictive pattern, FRC is usually preserved in disorders characterized by decreased respiratory force (e.g., the neuromuscular disorders) and is reduced in the others. In neuromuscular disorders, ERV is decreased because of loss of expiratory force, so that RV is often increased. In the other types of restrictive disorders, RV is usually reduced.

Whether or not the $D_{L_{CO}}$ is reduced in the restrictive disorders depends on the underlying disease process. Primary parenchymal disorders and removal of lung tissue decrease the diffusing surface area and reduce $D_{L_{CO}}$. Diseases of the pleura and chest wall that limit thoracic excursion during the inspiratory VC maneuver, which is part of the technique for determining $D_{L_{CO}}$, also reduce this measurement.

Additional Details of Pulmonary Function Test Results in a Mixed Obstructive-Restrictive Pattern

Occasionally, a battery of pulmonary function tests demonstrates features of both obstructive and restrictive patterns. Most often, the mixed pattern is characterized by a low $FEV_1/VC\%$ (indicating obstructive airway disease) and VC and reduced TLC (indicating coexisting restrictive disease).

A number of disorders can produce the mixed obstructive/restrictive pattern. Sarcoidosis and interstitial fibrosis, when severe, generally result in this pattern because the parenchymal disease causes restriction and narrowing of the airways by adjacent fibrosis, evoking signs of airway obstruction. The mixed pattern also occurs in complicated situations when there is more than one cause (e.g., a lobar pneumonia or large pleural effusion occurring in a patient with underlying chronic bronchitis or emphysema).

Isolated Decrease in the Efficiency of Gas Transfer

An isolated reduction in the D_{LCO} suggests one of two possible abnormalities: (1) interstitial lung disease that is so mild as not to affect measurements of airflow or lung volume, or (2) widespread occlusive disease of the pulmonary microcirculation (e.g., due to an inflammatory process or multiple small emboli). In occlusive vascular disorders, tests of airflow and lung volume are usually normal. Although other disorders can also decrease D_{LCO}, almost invariably they also reduce airflow, lung volumes, or both. Quantification of the degree to which the D_{LCO} is reduced by any of these processes is indicated in Table 34-21. Notably, interlaboratory differences are substantial for measurements of D_{LCO}.

Table 34-21

Categorization of Reduction in Efficiency of Gas Transfer: Measurement of D_{LCO}

Severity	D_{LCO}, Percent Predicted
Mild	>60, but less than lower limit of normal
Moderate	40–60
Severe	<40

Source: Modified from Pellegrino R, Viegi G, Brusasco V, et al: Interpretive strategies for lung function tests. Eur Respir J *26:948–968, 2005.*

Table 34-22

Characteristic Alterations in Pulmonary Function Tests According to the Major Patterns of Abnormality

Pattern	Airflow ($FEV_1/VC\%$)	Airflow Response to Bronchodilators	Volumes	Lung D_{LCO}
Obstructive				
Irreversible	↓	↔	↑	↔ or ↓
Reversible	↓	↑	↑	↔
Small-airway disease	↓	↔	↔	↔
Upper-airway obstruction	↓	↔	↔ or ↑	↔
Restrictive				
Parenchymal disease	↔ or ↑	↔	↓	↓
Surgical resection	↔	↔	↓	↓
Pleural, chest wall disease	↔	↔	↓	↔
Reduced expiratory force generation	↔	↔	↓	↔
Mixed obstructive-restrictive	↓	↔ or ↑	↓	↓
Isolated reduction in efficiency of gas transfer	↔	↔	↔	↓

Note: ↓ = decreased; ↑ = increased; ↔= no change or normal.

Summary of Approach to Interpretation

Pulmonary function tests are designed to detect common disorders. Test interpretation relies heavily on recognition of major patterns of abnormality (Table 34-22). These patterns often suggest pathogenetic mechanisms and are helpful to the clinician in arriving at a diagnosis. The degree of abnormality provides a quantitative measure of the extent of involvement at a particular time. Moreover, repeated testing makes it possible to pace and quantify the course of the illness and to assess the effects of therapeutic interventions.

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35

Principles and Applications of Cardiopulmonary Exercise Testing

Karl T. Weber • Ahmad Munir

Cardiopulmonary exercise testing draws on the recognition that the thorax is a structure for the transport of the respiratory gases involved in metabolism and that the function of its components—diaphragm, heart, lungs, rib cage, and corresponding skeletal muscles—is to transport O_2 to and CO_2 from metabolizing tissues. The transport of O_2 and CO_2 must adjust to physiological and pathophysiological stresses that augment the body's consumption of oxygen ($\dot{V}_{O_2}$) and carbon dioxide production ($\dot{V}_{CO_2}$). During strenuous levels of muscular work, for example, $\dot{V}_{O_2}$ may rise eightfold, accompanied by increased $\dot{V}_{CO_2}$. Cardiovascular or ventilatory disease can disrupt the unit's functional integrity. Severe disease may elicit abnormality in respiratory gas transport that may be evident at rest, when the O_2 requirements of the body are modest. Lesser disease may allow resting pulmonary function to be preserved but abnormal respiratory gas transport becomes apparent when the unit is stressed by an increase in the oxygen requirement.

Cardiopulmonary exercise testing includes the monitoring of respiratory gas exchange ($\dot{V}_{O_2}$ and $\dot{V}_{CO_2}$), minute ventilation ($\dot{V}_E$) and its components, tidal volume and respiratory rate, together with blood pressure, heart rate, and the electrocardiogram. Cardiopulmonary exercise testing represents a useful approach in the clinical evaluation of a wide variety of disorders and circumstances. This chapter addresses physiological principles and the clinical application of cardiopulmonary exercise testing in the evaluation of major disorders that impair cardiac or pulmonary function.

Table 35-1

Oxygen Utilization, Content, Transport, and Extraction

$\frac{O_2 \text{ utilization}}{250 \text{ ml/min}}$	$\begin{cases} = \text{Cardiac output} \cdot (\text{arterial } O_2 \text{ content} - \text{venous } O_2 \text{ content}) \\ = 5000 \text{ ml/min} \cdot (19 \text{ ml/dl} - 14 \text{ ml/dl}) \end{cases}$
$\frac{\text{Arterial } O_2 \text{ content}}{19 \text{ ml/dl}}$	$\begin{cases} = \text{Hemoglobin} \cdot \%\text{ saturation} \cdot O_2 \text{ combining capacity} \\ = 14 \text{ gm/dl} \cdot 0.96 \cdot 1.34 \text{ ml/gm} \end{cases}$
$\frac{\text{Venous } O_2 \text{ content}}{14 \text{ ml/dl}}$	$= 14 \text{ gm/dl} \cdot 0.96 \cdot 1.34 \text{ ml/gm}$
$\frac{\text{Arteriovenous } O_2 \text{ difference}}{5 \text{ ml/dl}}$	$\begin{cases} = \text{Arterial } O_2 \text{ content} - \text{venous } O_2 \text{ content} \\ = 19 \text{ ml/dl} - 14 \text{ ml/dl} \end{cases}$
$\frac{O_2 \text{ transport}}{950 \text{ ml/min}}$	$\begin{cases} = \text{Cardiac output} \cdot \text{arterial } O_2 \text{ content} \\ = 5000 \text{ ml/min} \cdot 19 \text{ ml/dl} \end{cases}$
$\frac{O_2 \text{ extraction}}{25\%}$	$\begin{cases} = \frac{\text{Arteriovenous } O_2 \text{ difference}}{\text{Arterial } O_2 \text{ content}} \cdot 100\% \\ = \frac{19 - 14}{19} \cdot 100\% \end{cases}$

Source: Reproduced from Weber KT: Gas transport and the cardiopulmonary unit, in Weber KT, Janicki JS (eds), Cardiopulmonary Exercise Testing: Physiologic Principles and Clinical Applications. Philadelphia. Saunders. 1986. pp 15–33.

PRINCIPLES, DEFINITIONS, AND CLINICAL APPLICATION OF CARDIOPULMONARY EXERCISE TESTING

The metabolic gas transport unit, also referred to as the "cardiopulmonary unit," links metabolizing tissues to the atmospheric supply of O_2. O_2 transport to the tissues must be precise and based upon prevailing need. CO_2 produced by tissues must be eliminated into the atmosphere in an equally efficient manner.

Resting Oxygen Uptake and Transport

Concepts and calculations pertaining to $\dot{V}_{O_2}$ and O_2 content, transport, and extraction are reviewed in Table 35-1. The heart and lungs accommodate to the metabolic requirements of tissues on a moment-to-moment basis, according to physiological priorities. Tissue requirements for O_2 dictate a certain$\dot{V}_E$ and cardiac output. In an average-sized person, the resting $\dot{V}_{O_2}$ averages 250 ml/min or 3.5 ml/min/kg body weight (one metabolic equivalent) and is associated with a $\dot{V}_E$ of 8 to 10 L/min and cardiac output of 4 to 6 L/min. O_2 transport, also termed O_2 delivery, ranges between 730 and 1040 ml/min and is more than adequate to satisfy the resting $\dot{V}_{O_2}$. On average, 25 percent of the arterial O_2 content is extracted by tissues. O_2 delivery and extraction increase during physiological stress in proportion to the increase in O_2 demand. Factors that normally determine O_2 availability at rest and during exercise include cardiac output, hemoglobin concentration and the percent of its O_2 saturation, and O_2 extraction.

Exercise Oxygen Uptake and Transport

$\dot{V}_E$ and O_2 delivery increase during exercise. Strenuous work can increase $\dot{V}_E$ eight to ten times its resting level. Ventilation normally poses no limitation on the ability of tissues to conduct aerobic work. In contrast, the extent to which cardiac output rises during progressive work is less dramatic. In untrained subjects, cardiac output increases four to five times its resting value. Cardiac output rises 600 ml/min for every 100 ml/min increment in $\dot{V}_{O_2}$. This is considered to be the normal "gain" setting between the heart and its cardiac output and $\dot{V}_{O_2}$. O_2 availability during physical activity is further ensured by enhanced O_2 extraction and circulatory autoregulation. Reflex and humoral influences produce vasoconstriction in tissues that are less metabolically active, permitting a greater apportionment of blood flow to exercising muscle.

Physiological limits to the increase in cardiac output and O_2 extraction (approximately 75 to 80 percent of arterial O_2 content) determine the aerobic capacity of untrained subjects to incremental exercise. Beyond these physiological limits, any additional increment in work is not accompanied by an increase in O_2 uptake; a plateau in $\dot{V}_{O_2}$ is reached. This plateau is termed the *maximal oxygen uptake* ($\dot{V}_{O_2max}$). The results of cardiopulmonary exercise testing, including the $\dot{V}_{O_2max}$, are shown in Fig. 35-1 for a 40-year-old man

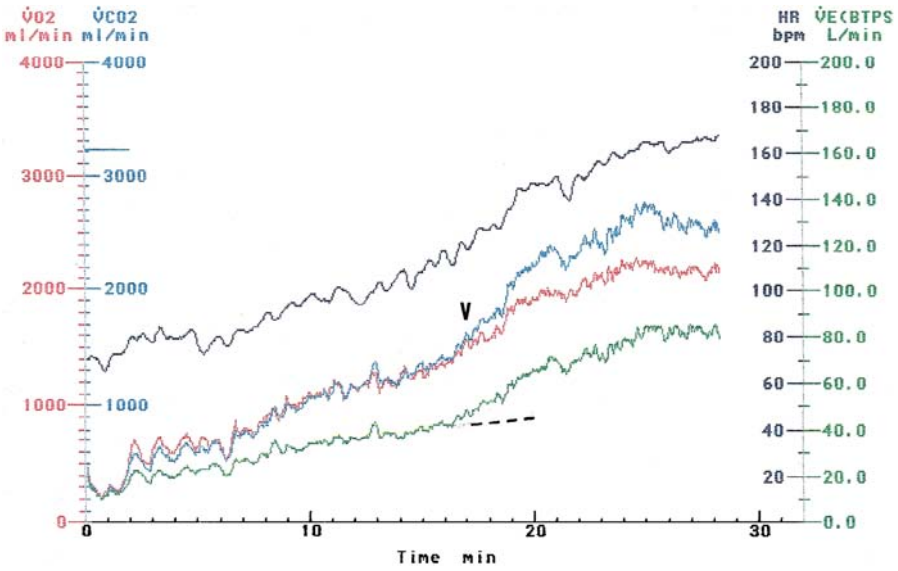


Figure 35-1 Cardiopulmonary exercise response in a 40-year-old man without heart or lung disease. Shown are 2 min of standing rest, followed by incremental treadmill exercise. Individual responses (color coded) include oxygen uptake ($\dot{V}_{O_2}$), carbon dioxide production ($\dot{V}_{CO_2}$), minute ventilation ($\dot{V}_E$), and heart rate (HR). Maximal O_2 uptake, a plateau in $\dot{V}_{O_2}$ was attained after the crossover of $\dot{V}_{CO_2}$ and $\dot{V}_{O_2}$ (arrowhead), representing the anaerobic threshold (AT) and accompanied by a disproportionate (broken line) rise in $\dot{V}_E$.

without heart or lung disease. The individual responses in $\dot{V}_{O_2}$, $\dot{V}_{CO_2}$, $\dot{V}_E$, and heart rate are illuminated during progressive increments in treadmill work. A $\dot{V}_{O_2max}$ of 2198 ml/min (27.2 ml/min/kg) was attained. This is a true plateau in $\dot{V}_{O_2}$, with $\dot{V}_{O_2}$ remaining invariant for 2.5 stages (5 min) of exercise.

$\dot{V}_{O_2max}$ should not be equated to, or used as synonym for, peak $\dot{V}_{O_2}$ achieved during symptom-limited exercise. $\dot{V}_{O_2max}$ reflects the individual's aerobic capacity—a physiological capacity of the cardiovascular system. In an average-sized, untrained individual whose maximum cardiac output and arteriovenous oxygen difference are 20 L/min and 12 ml/dl, respectively, a $\dot{V}_{O_2max}$ of 2400 ml/min is expected. In athletes, a greater cardiac reserve and enhanced capacity for oxidative metabolism by trained skeletal muscle provide a greater aerobic capacity. In patients with heart disease, in whom the ability to increase cardiac output during exercise is impaired, $\dot{V}_{O_2max}$ is proportionally reduced.

Carbon Dioxide Production

The right heart "accepts" metabolically produced CO_2, and the alveolar exchange surface expels the CO_2 into the atmosphere. CO_2 is a major respiratory stimulant that maintains eucapnia. Between 75 and 80 percent of O_2 is converted to CO_2. Accordingly, resting $\dot{V}_{CO_2}$ averages 190 ml/min and represents a *metabolic source* of CO_2. The resting $\dot{V}_{CO_2}/\dot{V}_{O_2}$ ratio, or respiratory gas exchange ratio (R), typically ranges between 0.75 and 0.85. The absolute value of R depends on the proportion of carbohydrates and fats provided by the diet. $\dot{V}_{O_2}$ and $\dot{V}_{CO_2}$ increase proportionally during physical activity as long as an adequate amount of O_2 is available to sustain oxidative metabolism.

During strenuous muscular work, $\dot{V}_{O_2}$ increases to a level at which the heart is unable to provide O_2 at the required rate. Consequently, tissue O_2 availability becomes inadequate. Working skeletal muscle calls upon less efficient anaerobic metabolism to derive energy. This leads to lactate production from working muscle which exceeds that normally produced. This *nonmetabolic source* of CO_2 is derived from rapid buffering of the lactate by bicarbonate; the CO_2 that is generated serves as a respiratory stimulant. The accompanying increase in $\dot{V}_E$ maintains eucapnia and increases the respiratory gas exchange ratio which is greater than that associated with aerobic metabolism. Anaerobic metabolism during a progressive exercise test is heralded by the disproportionate rise in $\dot{V}_E$ and $\dot{V}_{CO_2}$ relative to $\dot{V}_{O_2}$. The corresponding level of $\dot{V}_{O_2}$ at which anaerobic metabolism occurs is termed the *anaerobic threshold* (AT). The point during exercise at which $\dot{V}_{O_2}$ exceeds $\dot{V}_{O_2}$ and $\dot{V}_E$ rises disproportionately is shown in Fig. 35-1. Anaerobiosis normally occurs when 60 percent or more of a person's aerobic capacity has been reached. For the 40-year-old man whose exercise response is shown in Fig. 35-1, the AT occurred at a $\dot{V}_{O_2}$ of 18.8 ml/min/kg, or 69 percent of his $\dot{V}_{O_2}$max.

Clinical Application of Cardiopulmonary Exercise Testing

In patients with mild to moderate cardiovascular or respiratory disease, symptoms of fatigue or breathlessness frequently limit physical activity. Because their quality of life is compromised, they seek, or are referred for, medical evaluation.

Re-creating muscular work in a monitored setting permits an evaluation of the nature and severity of such symptoms and the relative importance of abnormal heart or lung function. This strategy provides information that surpasses that available from measures of heart and lung function determined at rest, such as ejection fraction, lung volumes, or airflows. The continuous monitoring of $\dot{V}_{O_2}$, $\dot{V}_{CO_2}$, $\dot{V}_E$, respiratory rate, and tidal volume during incremental exercise can be performed simply and on a breath-by-breath basis. Data shown in Fig. 35-1 are displayed throughout the test. The choice of a particular cardiopulmonary exercise test depends on the nature and expression of the clinical disorder and the particular problem to be addressed. For most clinical evaluations, isotonic forms of exercise afford an acceptable and reproducible form of exercise for patients with heart or lung disease. However, even though noninvasive cardiopulmonary exercise testing in patients with lung disease may help to identify the impairment in aerobic capacity, the abnormalities in ventilation and the severity of the abnormalities, these parameters are not necessarily diagnostic. For example, $\dot{V}_{O_2max}$, AT, or exercise $\dot{V}_E$ does not identify the underlying structural defect responsible for a patient's abnormal response. This diagnosis may require invasive monitoring during cardiopulmonary exercise testing to identify specific hemodynamic abnormalities. Echocardiography and specialized pulmonary function studies may be required.

Noninvasive Treadmill Exercise

Walking represents a common daily exercise rather than a specialized skill. A patient who walks into the physician's office or down a hospital corridor can walk on a treadmill at 1.0 or 1.5 mph, zero grade. Treadmills are programmable. The Bruce protocol, which employs specific increments in treadmill speed and slope over short periods to evaluate myocardial ischemia, may not be useful for patients with limited exercise tolerance. A modified Naughton protocol of gradually progressive exercise (Table 35-2) is useful for patients with heart or lung disease who have a wide range of exercise tolerance. In this protocol, the first two stages of exercise constitute very low workloads and serve as a warmup for patients with heart or lung disease of minor severity; in contrast, these stages represent near-maximal exercise for patients with more advanced disease.

$\dot{V}_{O_2max}$ is defined as $\dot{V}_{O_2}$ that remains invariant (less than 1 ml/min/kg for 30 s or more) despite increment in workload. An invariant $\dot{V}_{O_2}$ for at least two stages of exercise is preferred (Fig. 35-1). $\dot{V}_{O_2max}$ follows the AT, and this definition of $\dot{V}o_2max$ presumes that the AT has already been achieved. The AT generally occurs at 60 percent of a patient's aerobic capacity. $\dot{V}_{O_2max}$ associated with incremental treadmill exercise provides a greater aerobic capacity than does cycle ergometry because it works a larger group of muscles. A patient's aerobic capacity to incremental treadmill exercise is used to grade the functional impairment (Table 35-3). $\dot{V}_{O_2max}$ is an objective measure of functional status—in contradistinction to the New York Heart Association classification, which is

Table 35-2

Modified Naughton Treadmill Exercise Protocol

Stage	Speed	Grade	Physical Activities
1	1.0	0	Driving a car Sitting and writing or eating
2	1.5	0	Dressing; knitting Walking to bathroom Light auto repair
3	2.0	3.5	Shave self in bathroom Wash entire body Food shopping
4	2.0	7.0	Sexual activity Raking leaves Plastering
5	2.0	10.5	Stacking firewood Mowing lawn (powered) Walking down stairs
6	3.0	7.5	Scrubbing floors Gardening Walking up stairs
7	3.0	10.0	Lifting and carrying 65–80 lb Carpentry Climbing hills (no load)
8	3.0	12.5	Digging Snow shoveling Climbing stairs (20-lb load)
9	3.0	15.0	Beyond this level, work loads are equal to very vigorous exercise (e.g., skiing, basketball)
10	3.4	14.0	
11	3.4	16.0	
12	3.4	18.0	
13	3.4	20.0	
14	3.4	22.0	

Source: Reproduced from Weber KT, Janicki JS, McElroy PA: Cardiopulmonary exercise (CPX) testing, in Weber KT, Janicki JS (eds), Cardiopulmonary Exercise Testing: Physiologic Principles and Clinical Applications. Philadelphia, Saunders, 1986, pp 151–167.

Table 35-3

Classification of Cardiac and Circulatory Failure

Class	Severity	$\dot{V}_{O_2max}$ (ml/kg/min)	Anerobic Threshold (ml/kg/min)	Predicted Cardiac Index (L/m²/min)
A	Mild to none	>20	>14	>8
B	Mild to moderate	16 to 20	11 to 14	6 to 8
C	Moderate to severe	10 to 16	8 to 11	4 to 6
D	Severe	6 to 10	5 to 8	<4

Source: Adapted from Weber KT, Janicki JS, McElroy PA: Cardiopulmonary exercise (CPX) testing, in Weber KT, Janicki JS (eds), Cardiopulmonary Exercise Testing: Physiologic Principles and Clinical Applications. Philadelphia, Saunders, 1986, pp 151–167.

based on perceptions and biases of the patient and physician. The determination of O_{2max} by treadmill is reproducible in patients with a wide variety of cardiovascular disorders. A $\dot{V}_{O_2max}$ of under 20 ml/min/kg has been designated as the cutoff for grading impairment of aerobic capacity; adult men and women, including the elderly (over 65 years of age), have an expected $\dot{V}_{O_2max}$ greater than 20 ml/min/kg.

The duration of symptom-free treadmill exercise should not be equated with the $\dot{V}_{O_2max}$. Treadmill time suffers from not having an objective, quantitative end point. Differences in gait and body weight create different levels of work for equivalent stages of treadmill exercise. Symptom-limited exercise time is subject to patient motivation and physician bias. Peak heart rate attained during exercise is also a less precise measure of $\dot{V}_{O_2max}$. This is particularly true in patients with atrial fibrillation.

Determination of the AT can be defined according to one or more criteria. These include: (1) a disproportionate rise in $\dot{V}_{CO_2}$, $\dot{V}_E$, or R relative to $\dot{V}_{O_2}$ and (2) a disproportionate rise in end-tidal O_2 relative to end-tidal CO_2. These criteria can best be applied to data on breath-by-breath respiratory gas exchange. In our laboratory, a simple strategy is used. The AT is identified as the level of $\dot{V}_{O_2}$ attained during treadmill work after the plots of $\dot{V}_{O_2}$ and CO_2 cross, when R exceeds 1.0. Figure 35-1 depicts the crossover in $\dot{V}_{CO_2}$ and $\dot{V}_{O_2}$ from breath-by-breath gas exchange data monitored throughout incremental treadmill exercise. It also demonstrates the point at which $\dot{V}_E$ rises disproportionately. Measured days or weeks apart, this noninvasive determination of the AT is reproducible in a wide range of patients with cardiac or circulatory failure and correlates with the lactate threshold.

The normal ventilatory response to incremental treadmill exercise consists of an increase in $\dot{V}_E$ created by an increase in respiratory rate and tidal volume. Ventilatory reserves, represented by maximal voluntary ventilation (MVV) and vital capacity determined during routine pulmonary function testing, are only partly utilized during light, moderate, and maximal exercise by normal persons. The ratio of maximal exercise $\dot{V}_E$ to MVV reflects use of this ventilatory reserve. Exercise $\dot{V}_E$ in normal subjects and patients with predominant cardiovascular disease rarely exceeds 50 percent of MVV. The same is true of the ratio between maximal exercise tidal volume and vital capacity. These limitations in ventilatory responses are consistent with a ventilatory effort that can be voluntarily sustained at rest without the appearance of fatigue or breathlessness.

An oximeter, worn on either an earlobe or a finger, affords noninvasive monitoring of arterial O_2 saturation during exercise. This is a useful screening procedure in patients in whom O_2 desaturation might be anticipated (e.g., those with congenital heart disease with right-to-left shunt, restrictive or obstructive lung disease, or pulmonary vascular disease). Normal subjects and patients with chronic cardiac or circulatory failure do not develop arterial hypoxemia (arterial O_2 saturation under 90 percent) during exercise. In patients in whom oximetry indicates O_2 desaturation, confirmatory evidence from direct measurement of arterial blood gases during repeat exercise may be advisable.

Thus, incremental treadmill exercise can be used to determine the following: the AT with a submaximal test, the AT and $\dot{V}_{O_2max}$ with a maximal test, the ventilatory response to submaximal or maximal exercise, and arterial O_2 desaturation during submaximal or maximal exercise.

Invasive Treadmill Exercise

Invasive hemodynamic monitoring may be necessary for better definition of the nature and severity of an underlying cardiopulmonary disorder. A triple-lumen flotation catheter can be safely used for hemodynamic monitoring during upright exercise. The hemodynamic response to incremental treadmill exercise in normal subjects is characterized by a progressive increase in cardiac output, accompanied by minimal increments in left and right ventricular filling pressures. The increase in cardiac output occurs because of an increment in stroke volume, which is most apparent at low and moderate

workloads, and because of an increase in heart rate, which accompanies the exercise response. Systemic O_2 extraction increases progressively during incremental exercise to exceed 70 percent at maximal workloads. An increase in the concentration of lactate in mixed venous blood, demonstrated by sampling pulmonary arterial blood, occurs when O_2 extraction exceeds 60 percent and when the subject is working at greater than 60 percent of $\dot{V}_{O_2max}$.

Systolic and mean arterial pressures increase during upright exercise. Because of skeletal muscle vasodilation, arterial diastolic pressure remains essentially unchanged during exercise. Systemic vascular resistance falls by 50 percent to approximately 600 dynes · s · cm^{-5} during incremental, isotonic treadmill exercise. In normal persons, pulmonary artery systolic, mean, and diastolic pressures increase only minimally during exercise and only at higher workloads. Pulmonary vascular resistance, like systemic vascular resistance, falls 50 percent to about 60 dynes · s · cm^{-5} during incremental isotonic exercise.

CHRONIC CARDIAC FAILURE

In physiological terms, *cardiac failure* is defined as an impairment in cardiac output secondary to a disease process affecting the myocardium. Ischemic heart disease and dilated cardiomyopathies are examples of disease entities that can result in chronic cardiac failure. $\dot{V}_{O_2max}$ and the AT each predict cardiac reserve and, thereby, the severity of cardiac failure. These parameters further serve to demonstrate objectively a patient's functional capacity, which is not predictable by the cardiac ejection fraction. Patients with an ejection fraction of under 20 percent may still be able to swim.

Systolic Dysfunction

In patients with chronic cardiac failure, $\dot{V}_{O_2max}$ attained during incremental treadmill exercise is primarily a function of maximal cardiac output. This conclusion has been confirmed by numerous studies. An impairment in aerobic capacity is gauged according to the exercise AT and $\dot{V}_{O_2max}$ and assigned a functional class, as reviewed in Table 35-3. These parameters are, in turn, used to predict maximal exercise cardiac index (or cardiac reserve). Examples of $\dot{V}_{O_2max}$ and the AT attained by two patients with chronic cardiac failure (one class B, the other class C) are given in Fig. 35-2. To measure $\dot{V}_{O_2max}$ in such patients, they must be exercised to exhaustion. The AT is achieved at submaximal workloads short of exhaustion; it, too, stratifies the degree of cardiac dysfunction.

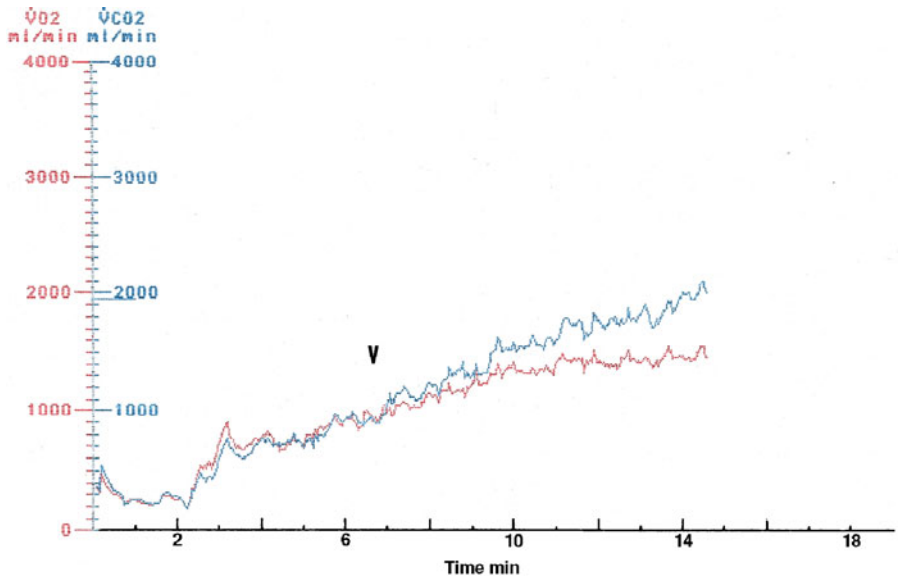
Validation of these concepts was obtained during treadmill exercise using invasive measures of cardiac output and mixed venous lactate concentration. Patients had chronic cardiac failure of varying severity (classes A to D) due to either ischemic or myopathic heart disease. In each exercise class, the arteriovenous O_2 difference rose to 12 ml/dl or more at maximum exercise, corresponding to a systemic O_2 extraction in excess of 70 percent, suggesting that O_2 extraction had reached maximal physiological levels. The reduction in aerobic capacity of a patient with chronic cardiac failure is, therefore, due primarily to impaired cardiac reserve. The cardiac output–O_2 relation to progressive treadmill exercise for these patients is given in Fig. 35-3. For each exercise class, cardiac output is presented as a percentage of $\dot{V}_{O_2max}$ (set equal to 100 percent) that existed at rest and throughout each stage of exercise. Cardiac output increased by 600 ml/min/m^2 for each dl/min/m^2 increase in $\dot{V}_{O_2}$ in each class. This indicates that the heart responds to tissue O_2 requirements irrespective of the severity of heart failure, but it is limited by the maximal cardiac output that it can attain. Differences in cardiac output achieved at peak exercise are seen between classes. Progressive reductions in cardiac reserve are responsible for different aerobic capacities observed in these patients. $\dot{V}_{O_2max}$, therefore, serves as a noninvasive measure of peak exercise cardiac output and is given for each functional class in Table 35-3.

The cardiac output response to exercise is a function of the increases in stroke volume and heart rate. Responses in stroke volume for patients in chronic cardiac failure are shown in Fig. 35-4 for each exercise class. In class A and B patients, stroke volume rises 50 percent during lighter workloads that represent less than 60 percent of $\dot{V}_{O_2max}$; at larger workloads, further increments in stroke volume are less apparent. A 25 percent rise in stroke volume occurs at submaximal exercise in class C patients, whereas in class D patients, exercise stroke volume is no different from its resting value. Exercise stroke volume is a result of several factors, including systolic wall stress, mitral or tricuspid regurgitation that may appear during exercise, and depressed myocardial contractility.

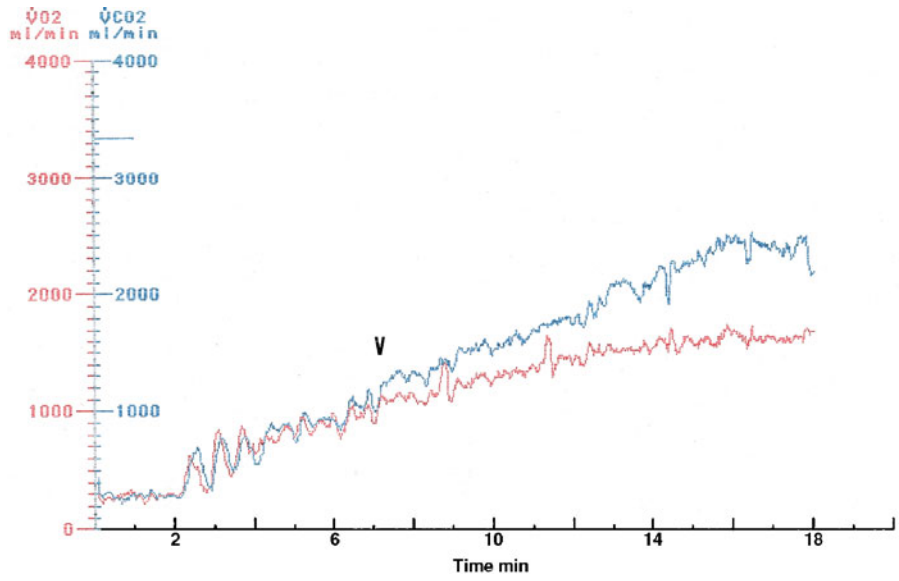
For each functional class of chronic cardiac failure, the heart rate–$\dot{V}O_2$ response to upright incremental exercise is represented by a common slope. The average slope is 3.6 beats per minute for every 1-ml/min/kg increment in $\dot{V}_{O_2}$. Peak heart rate achieved is a function of maximal workload performed. Maximal exercise heart rate is, therefore, different for each class. In class D patients, the increase in heart rate is the sole mechanism by which cardiac output increases during exercise.

Some patients with chronic cardiac failure deviate from this heart rate–$\dot{V}_{O_2}$ relation by having an inappropriate sinus tachycardia, either at rest and throughout exercise, or simply during exercise. In the presence of a reduced ejection fraction and ventricular dilation, this inappropriately rapid heart rate further compromises exercise cardiac output and reduces aerobic capacity. Under these circumstances, β-adrenergic receptor blockade is useful in attenuating the resting or exercise heart rate. Such chronotropic dysfunction (see below) to exercise may also apply to patients with chronic atrial fibrillation. An example of an inappropriate rapid heart rate during incremental treadmill exercise (Naughton protocol) is given in Fig. 35-5 for a patient with atrial fibrillation and dilated cardiomyopathy of uncertain origin.

As in normal persons, lactate production appears in patients with chronic cardiac failure when systemic O_2 extraction exceeds 60 percent. Mixed venous lactate concentration



A



B

Figure 35-2 Cardiopulmonary exercise test results for a 45-year-old woman (*A*) and a 40-year-old man (*B*), each with ischemic heart disease and chronic cardiac failure. Only $\dot{V}_{O_2}$ and $\dot{V}_{CO_2}$ are shown, to better demonstrate the anaerobic threshold (AT) and $\dot{V}_{O_2max}$ attained by each patient. In panel *A*, the AT was seen with a $\dot{V}_{O_2}$ of 11.6 ml/min/kg and a $\dot{V}_{O_2max}$ of 16.5 ml/min/kg. This represents a functional class B response. The AT and $\dot{V}_{O_2max}$ are 8.5 and 13.7 ml/min/kg, respectively (panel *B*). This corresponds to functional class C.

during exercise increases above resting values when 60 percent or more of $\dot{V}_{O_2max}$ is attained. Given differences in aerobic capacity between exercise classes, different workloads are associated with this lactate threshold (Fig. 35-6). In class D patients, in whom the cardiac output response is limited, the lactate threshold occurs at very light workloads ($\dot{V}_{O_2}$ of 5 to 8 ml/min/kg). Corresponding values for class C, B, and A patients are 8 to 11 ml/min/kg, 11 to 14 ml/min/kg, and more than 14 ml/min/kg, respectively. Thus, the lactate threshold and the $\dot{V}_{O_2max}$ reflect the severity of chronic cardiac failure, as given in Table 35-3. A noninvasively determined AT based on measurements of respiratory gas exchange, as discussed previously, corresponds to the invasively measured lactate threshold.

In chronic cardiac failure, the left ventricular filling pressure during exercise, as gauged from recordings of the occlusive wedge pressure, increases to a different degree in each exercise class (Fig. 35-7). In class A patients, the rise in wedge pressure during isotonic exercise rarely exceeds 18 mmHg. This resembles a normal response. In class B patients, more dramatic elevations in exercise wedge pressure—to 25 mmHg or higher—frequently occur. Resting filling pressure

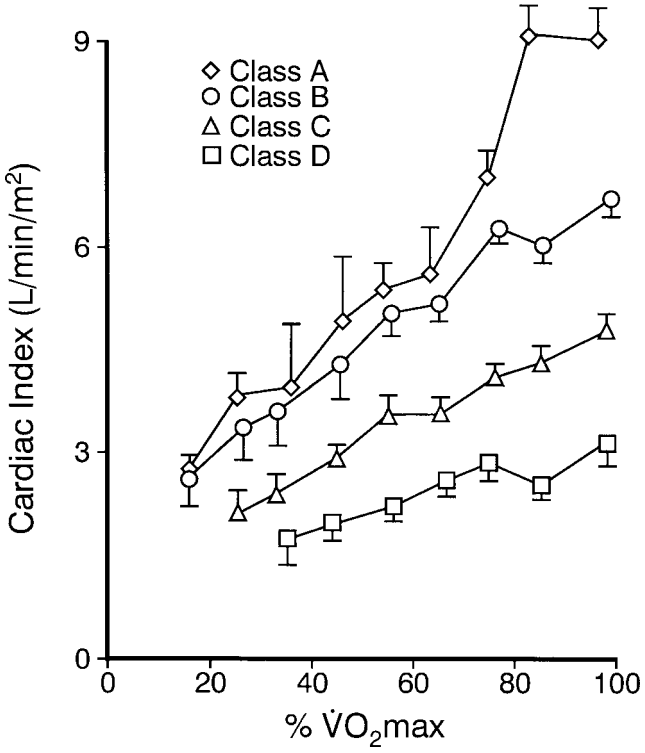


Figure 35-3 Relationship between treadmill exercise cardiac index and normalized aerobic capacity for patients with chronic cardiac failure of diverse origin and severity, subdivided according to each functional class. *(From Weber KT, Janicki JS: Cardiopulmonary exercise testing for evaluation of chronic cardiac failure. Am J Cardiol 55:22A–31A, 1985.)*

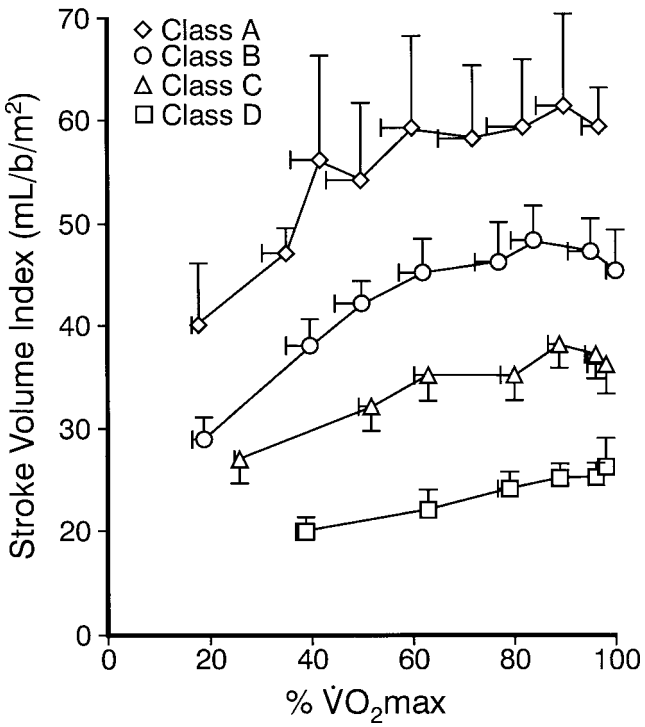


Figure 35-4 Relationship between treadmill exercise stroke volume index and normalized aerobic capacity for patients with chronic cardiac failure of varying severity, as expressed by each functional class. *(From Weber KT, Janicki JS: Cardiopulmonary exercise testing for evaluation of chronic cardiac failure. Am J Cardiol 55:22A–31A, 1985.)*

is increased in class C and D patients; a further increase may occur during upright exercise, often to levels in excess of 30 mmHg. Despite these marked levels of pulmonary venous pressure, patients do not develop evidence of pulmonary congestion after exercise. Moreover, elevations in wedge pressure neither predict exercise cardiac reserve and aerobic capacity nor are responsible for exertional dyspnea in these patients. Dyspnea corresponds with the lactate threshold and a disproportionate rise in $\dot{V}_E$ relative to $\dot{V}_{O_2}$. Despite dyspnea, patients can be encouraged to exercise to exhaustion, attaining $\dot{V}_{O_2max}$. In patients with acute cardiac failure, pulmonary congestion

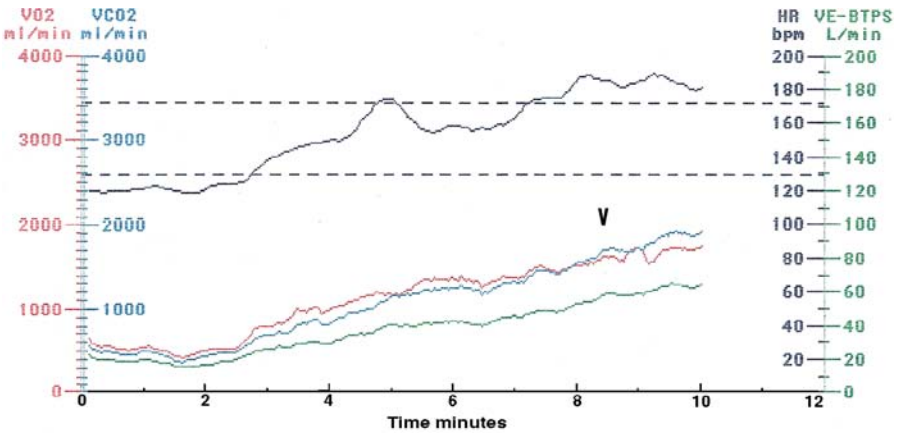


Figure 35-5 Cardiopulmonary exercise test results in a 48-year-old man with atrial fibrillation and dilated (idiopathic) cardiomyopathy. Note the rapid heart rate at rest and throughout incremental treadmill exercise. Predicted maximum heart rate range in this patient is shown by the broken lines. He achieved this rate during the first stage of exercise and exceeded it during the last stage of exercise. This is an inappropriate heart rate response. The anaerobic threshold (AT) is 13 ml/min/kg (arrow), in keeping with functional class B. He did not achieve $\dot{V}_{O_2max}$ and, therefore, had a peak $\dot{V}_{O_2}$ of 15 ml/min/kg.

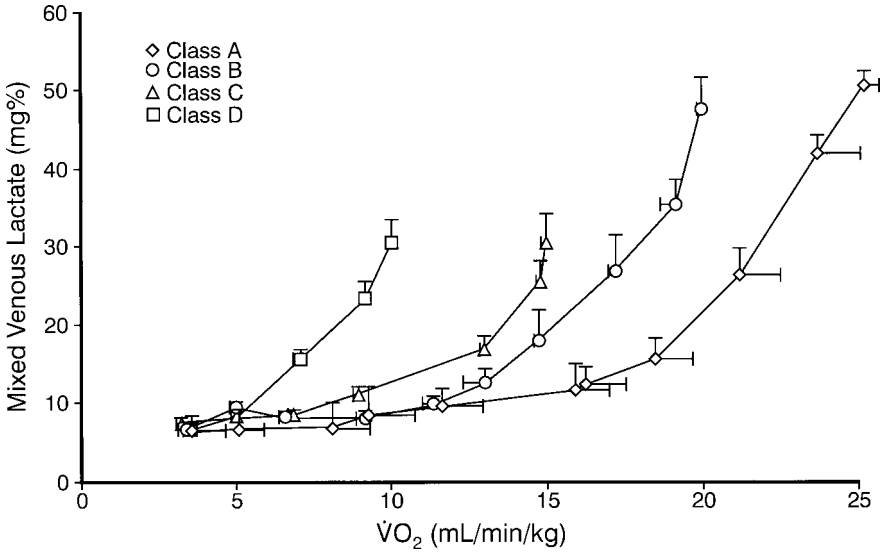


Figure 35-6 Relationship between mixed venous lactate concentration and $\dot{V}_{O_2}$ to incremental treadmill exercise for patients with chronic cardiac failure of varying severity, as expressed by each functional class. *(From Weber KT, Janicki JS: Cardiopulmonary exercise testing for evaluation of chronic cardiac failure. Am J Cardiol 55:22A–31A, 1985.)*

and dyspnea correlate with the increase in wedge pressure; pulmonary edema occurs when hydrostatic pressure exceeds the colloidal osmotic pressure of 25 mmHg.

$\dot{V}_E$ rises appropriately during incremental exercise in patients with chronic cardiac failure. The response in $\dot{V}_E$ corresponds most closely to $\dot{V}_{CO_2}$ throughout exercise (aerobic and anaerobic work) and is sufficient to sustain alveolar ventilation, thereby preventing hypoxemia and hypercapnia.

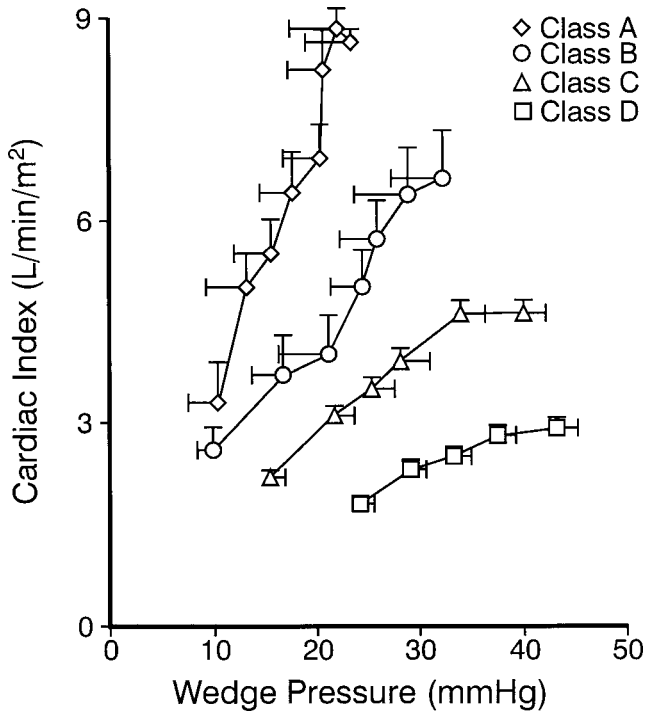


Figure 35-7 Relationship between treadmill exercise cardiac index and occlusion wedge pressure in patients with chronic cardiac failure, subdivided according to functional class. *(From Weber KT, Janicki JS: Cardiopulmonary exercise testing for evaluation of chronic cardiac failure. Am J Cardiol 55:22A–31A, 1985.)*

Maximum $\dot{V}_E$ attained during exercise is less than 50 percent of MVV. Thus, these patients do not exhaust their ventilatory reserve in responding to exercise, even when their pulmonary compliance may be adversely affected by the chronic pulmonary congestion and increments in pulmonary venous pressure that appear during exercise. In order to minimize the work of breathing during exercise, class C and D patients use a pattern of rapid, shallow breathing to increase $\dot{V}_E$. Thus, the rise in tidal volume during exercise above its resting value is modest and compatible with a substantial portion of each breath being wasted in ventilation of the anatomic dead space. The response of class A and B patients more closely approximates that of healthy persons, in whom respiratory rate rises progressively during incremental exercise and the increase in tidal volume occurs early during the transition from rest to low-level exercise.

Diastolic Dysfunction

In 30 percent or more of patients with symptomatic heart failure, primary diastolic dysfunction is responsible. The ejection fraction is normal or only minimally impaired in these patients. Diastolic dysfunction relates to an inability of the left ventricle to accommodate left atrial and pulmonary venous blood flow during diastole without a marked increase in filling pressure. Abnormal diastolic relaxation and filling typically appear in patients with chronic ischemic heart disease (with previous myocardial infarction), in those with hypertensive heart disease, and in the elderly. Responsible mechanisms are thought to include abnormal tissue structure, as occurs with the accumulation of fibrous tissue or infiltration with amyloid and abnormal handling of calcium by the sarcoplasmic reticulum. Factors extrinsic to the myocardium may also contribute. Examples include the interaction between the pressure- or volume-overloaded right ventricle with the left ventricle and the interplay between the heart and pericardium.

Invasive cardiopulmonary exercise testing, together with incremental bicycle exercise, has been used to address the hemodynamic response of patients with primary diastolic dysfunction. Most patients studied had systemic hypertension, and many were elderly; all had a clinical history of pulmonary congestion. Peak exercise $\dot{V}_{O_2}$ was reduced, owing to a reduction in the responses of the cardiac output and stroke volume; arteriovenous O_2 difference increased above 10 ml/dl. The level of $\dot{V}_{O_2}$ achieved with exercise correlated with the peak response of the cardiac output. In comparison to age-matched controls, expected exercise-associated increments in left ventricular end-diastolic volume were not seen and were accompanied by increased left ventricular filling pressure. Thus, abnormalities in diastolic filling abrogated the Frank-Starling mechanism, thereby restricting the rise in cardiac output during exercise; this finding may explain symptoms of fatigue and breathlessness that these patients experience on exertion.

Primary diastolic dysfunction has been observed in patients following cardiac transplantation in which there is an abnormal blunting of the stroke volume and heart rate responses to exercise. Despite the slower exercise heart rate in the transplanted, denervated heart, in which diastolic filling periods would accordingly be longer, diastolic dysfunction is present, limiting the response of the cardiac output to exercise. Abnormal diastolic function has also been observed in the elderly and contributes to impaired exercise cardiac output response.

Chronotropic Dysfunction

Cardiac reserve during exercise depends not only on systolic and diastolic function but also on heart rate and rhythm, including a coordinated contraction of the atria and ventricles. Cardiopulmonary exercise testing has been used to address the contribution of abnormal heart rate and rhythm on the AT and $\dot{V}_{O_2 max}$, broadly categorized here as chronotropic dysfunction. This includes abnormal sinus tachycardia, bradyarrhythmias, atrioventricular dissociation, and atrial fibrillation. Cardiopulmonary exercise testing has proved useful in the evaluation of pacemaker function and technique. Improvements in the AT at submaximal levels of work have been demonstrated for single-chamber, activity-triggered pacing compared with fixed-rate atrial or ventricular pacing. It, too, can help determine the optimum upper rate limit in heart failure patients with pacemakers. This can be determined by the highest pacing rate that still produces an increase in oxygen consumption. With recent advancements in pacemaker technology, cardiac resynchronization therapy (CRT) is being increasingly offered to patients with heart failure. In a study involving patients with CRT undergoing cardiopulmonary exercise testing, significant increments in peak $\dot{V}_{O_2}$, $\dot{V}_{O_2}$ at AT and in all ventilation and metabolic parameters occurred. Patients with baseline $\dot{V}_{O_2}$ of less than 14 ml/min/kg had the most benefit. Similarly, patients with severe heart failure and atrial fibrillation had better hemodynamic performance with chronic biventricular pacing than with left ventricular pacing alone.

Survival and Prognosis

Various gas exchange parameters have been used to assess prognosis in patients with heart failure, including AT, peak $\dot{V}_{O_2}$, and $\dot{V}_E/\dot{V}_{CO_2}$ slope (a marker of ventilatory efficiency). $\dot{V}_{O_2}$ at AT and $\dot{V}_{CO_2}$ slope are less subject to patient motivation or premature cessation of exercise and, hence, are more useful parameters. Class D patients with little or no exercise cardiac reserve (Table 35-3) with AT less than 8 ml/min/kg have a marked reduction in 1- and 2-year survival as contrasted to class A and B patients with respective exercise cardiac index responses of greater than 8 and 6 to 8 L/min/m^2. $\dot{V}_{O_2}$ at AT, combined with $\dot{V}_E/\dot{V}_{CO_2}$, is a better prognostic indicator than peak $\dot{V}_{O_2}$ alone. A low peak $Paco_2$ with exercise is responsible for the prognostic power of $\dot{V}_E/\dot{V}_{CO_2}$ slope and by itself is also an independent prognosticator. Resting end-tidal CO_2 has been shown to be a predictor of cardiac-related events. Another $\dot{V}_{O_2}$ kinetics parameter that is a strong predictor of survival and is less dependent on motivation is the mean response time ($\dot{V}_{O_2}$ deficit/$\Delta\dot{V}_{O_2}$). In the recovery period, slow normalization of $\dot{V}_{O_2}$ is associated with a poor prognosis.

The fluctuations in breathing patterns and its association with prognosis have also been studied in patients with heart failure. Cyclic fluctuations in minute ventilation at rest that persist during effort (external oscillatory ventilation) are associated with poor prognosis whereas oscillations at rest alone are not.

Efficacy of Medications

The response to various heart failure medications on gas exchange and hemodynamics has been evaluated. Patients with heart failure who are taking spironolactone have a significant increase in peak oxygen consumption, D_{LCO}, and membrane diffusing capacity. In addition, in one study, use of an angiotensin-receptor blocker (losartan), along with an angiotensin-converting enzyme (ACE) inhibitor, resulted in a significant increase in peak $\dot{V}_{O_2}$ and exercise capacity. However, in another study, addition of candesartan to an ACE inhibitor had no such effect. Finally, in patients with chronic heart failure who were taking carvedilol, determination of peak $\dot{V}_{O_2}$, which has been used as a prognostic marker in this group of patients, was not found to be useful.

Exercise Training

Exercise training improves exercise tolerance and peak $\dot{V}_{O_2}$ in patients with heart failure and left ventricular dysfunction. Exercise training in moderate stable heart failure results in favorable qualitative, rather than quantitative, changes in skeletal muscle. Correction of maximum oxygen uptake for skeletal muscle mass is a more sensitive measure of changes associated with exercise training than is total body mass. Only a

progressive, increasing workload seems to markedly improve oxygen uptake.

Ischemic Heart Disease

Ischemia can be diagnosed during cardiopulmonary exercise testing with the help of ST segment changes during incremental exercise on a treadmill or an ergometer. The sensitivity and specificity of ST changes for ischemia is not high. Parameters of gas exchange on cardiopulmonary exercise testing can be used to improve the diagnostic ability of the exercise-induced ST changes. In one study, which examined the duration of "O_2 pulse flattening" and changes in $\dot{V}_{O_2}$ relative to the work rate slope along with electrocardiographic ST changes, sensitivity increased from 46 to 87 percent and specificity from 66 to 74 percent. In another study, exercise cardiac output, estimated from $\dot{V}_{O_2}$ at AT, correlated with multivessel coronary artery disease, adverse cardiac events, and clinically driven revascularization. In patients who experienced myocardial infarction and who subsequently underwent 3 weeks of exercise training, a significant improvement in peak $\dot{V}_{O_2}$ was found.

CHRONIC CIRCULATORY FAILURE

Circulatory failure, in physiological terms, refers to an inability of the heart to increase its cardiac output in a manner commensurate with prevailing $\dot{V}_{O_2}$. Responsible factors may be extrinsic to the myocardium and include such entities as valvular heart disease, intrinsic pulmonary vascular disease, pericardial disease, and anemia.

Valvular Heart Disease

Mitral or aortic valve disease may alter the functional integrity of the cardiopulmonary unit by impairing the heart's ability to increase cardiac output in accord with increments in $\dot{V}_{O_2}$. Pathophysiological alterations that result from chronic valvular disease and that determine the clinical course and outcome following valve replacement include right heart overload and structural remodeling of the pulmonary vasculature and lung interstitium. The more marked the preoperative impairment in cardiac reserve, the poorer the long-term prognosis. Similarly, the greater the elevation in pulmonary vascular resistance, the more delayed is its return to normal levels and the slower the postoperative abatement of symptoms. The decision for surgical intervention requires an assessment of cardiopulmonary status—one that can be assessed noninvasively and monitored over time to detect a decline in cardiac reserve. Noninvasive cardiopulmonary exercise testing serves this purpose. Because of the heightened risk of syncope and the myocardial ischemia and arrhythmias that can occur during exercise in patients with aortic valvular stenosis, these patients should exercise with extreme caution, if at all.

Incompetence of the mitral and aortic valves is an example of a disorder that can result in chronic circulatory failure.

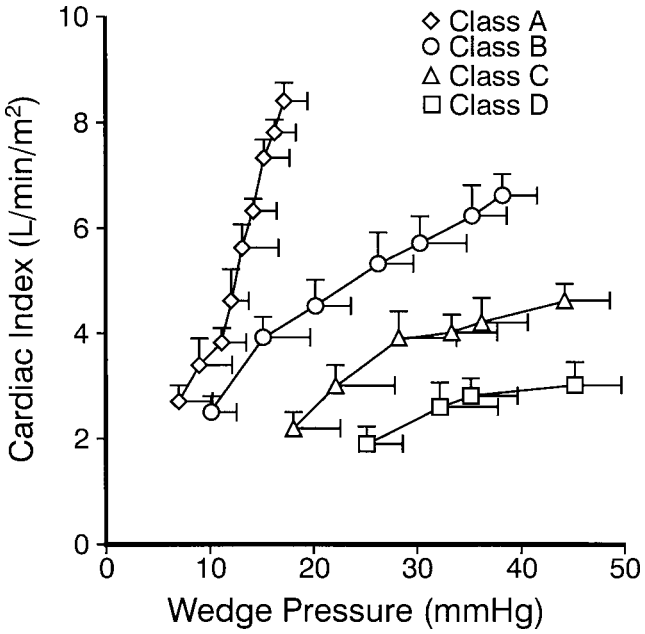


Figure 35-8 Relationship between treadmill exercise cardiac index and wedge pressure in patients with chronic mitral or aortic regurgitation, divided according to functional class. *(From Weber KT, Janicki JS (eds): Cardiopulmonary Exercise Testing: Physiologic Principles and Clinical Applications. Philadelphia, WB Saunders, 1986.)*

Each creates a volume overload on the left ventricle. The onset of ventricular dysfunction is generally unpredictable and may initially appear only during vigorous levels of physical activity. As dysfunction progresses, symptoms appear at lower levels of activity and, finally, at rest.

Resting cardiac output is often not distinguishable among class A, B, C, or D patients with mitral or aortic regurgitation. Cardiac reserve is reduced, however, and, accordingly, so is aerobic capacity. No impairment in systemic O_2 extraction has been reported. Thus, as in chronic cardiac failure, any observed decrease in aerobic capacity must be due to a decline in maximal cardiac output. To the extent that cardiac output can increase, the exercise cardiac output–$\dot{V}_{O_2}$ relation is preserved among these classes, averaging 600 ml/min/m^2 for every dl/min/m^2 rise in $\dot{V}_{O_2}$. Responses in cardiac output and wedge pressure for each exercise class are given in Fig. 35-8. As in chronic cardiac failure, marked increases in wedge pressure are seen in class C and D patients; this is also true for class B patients with mitral or aortic regurgitation. However, these patients do not develop clinical evidence of pulmonary congestion following exercise, and dyspnea correlates with the lactate threshold. In these patients, exercise wedge pressure does not presage aerobic capacity or functional class.

AT can be used as an alternative measure in patients with valvular incompetence who are unable to attain $\dot{V}_{O_2max}$. The lactate threshold occurs at 60 to 70 percent of the patient's aerobic capacity and corresponds to a level of systemic O_2 extraction of 60 percent or more. Figure 35-9 depicts the response of mixed venous lactate concentration as a function

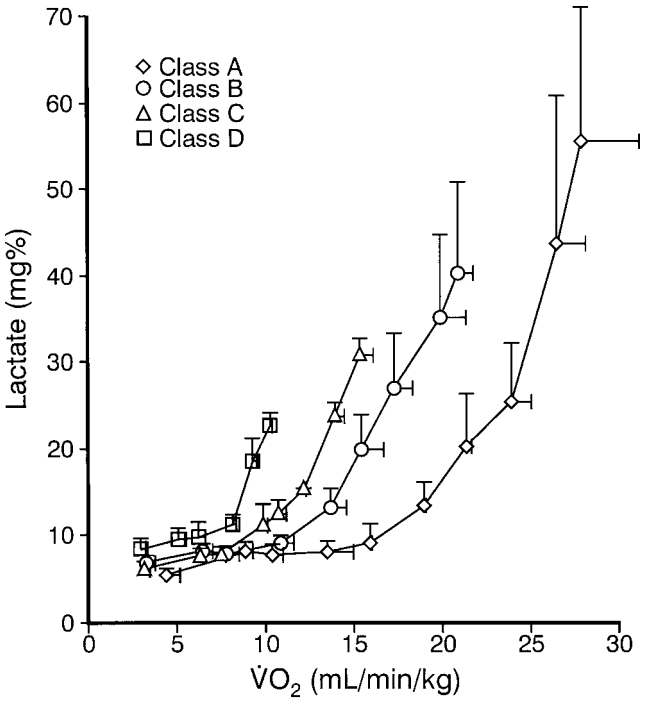


Figure 35-9 Relationship between mixed venous lactate concentration and $\dot{V}_{O_2}$ observed during incremental treadmill exercise in patients with chronic mitral or aortic regurgitation. As in chronic cardiac failure, the lactate threshold (lactate >12 mg/dl) occurs at different levels of $\dot{V}_{O_2}$, depending on functional class. *(From Weber KT, Janicki JS (eds): Cardiopulmonary Exercise Testing: Physiologic Principles and Clinical Applications. Philadelphia, WB Saunders, 1986.)*

of O_2 for each exercise class with mitral or aortic regurgitation. As in patients with chronic cardiac failure, the lactate threshold occurs at progressively lower levels of work as the severity of valvular disease increases. The invasively measured lactate threshold correlates well with the value obtained using noninvasive respiratory gas exchange measurements (see above).

The reduced mitral valve orifice that accompanies rheumatic mitral valvular stenosis leads to left atrial chamber enlargement, pulmonary venous hypertension, and pressure overload of the right heart. Pulmonary vascular resistance in most patients ranges between 200 and 600 dynes · s · cm^{-5}. Mitral stenosis is responsible for reduced left ventricular filling at rest and during exercise. An exercise-associated increase in heart rate reduces the diastolic filling period, thereby further curtailing left ventricular filling.

Cardiac output fails to rise appropriately during exercise in patients with chronic circulatory failure due to mitral stenosis. For most symptomatic patients, cardiac output fails to increase appropriately during symptom-limited exercise because of a limited stroke volume response. Systemic O_2 extraction increases markedly during exercise, as do pulmonary capillary wedge and mean pulmonary artery pressures. Preoperative assessment of mitral stenosis should include not only calculation of mitral valve area but also exercise test-determined cardiac reserve and functional status. A decision regarding surgery should be based on these objective measures and clinical judgment, not simply on a laboratory-based calculation of reduced valve area.

A preoperative assessment of patients undergoing valvular surgery using cardiopulmonary exercise testing can help predict the degree of postoperative recovery. Preoperative peak $\dot{V}_{O_2}$ of 19 ml/min/kg and greater in patients undergoing surgery for mitral and aortic regurgitation correlates with higher percentage of patients attaining New York Heart Association (NYHA) functional class I at 1 year after surgery. $\dot{V}_{O_2max}$, along with AT, has been used to follow the course of postoperative rehabilitation and training in patients who have had valve surgery. Exercise parameters can be helpful in assessing patients with valvular disease when there is a discrepancy between symptoms and echocardiographic data. A $\dot{V}_{O_2max}$ less than 75 percent of predicted in patients with moderate-to-severe mitral stenosis correlates with higher transvalvular gradients and higher pulmonary artery pressures at the end of exercise than in patients who have $\dot{V}_{O_2max}$ greater than 75 percent of max predicted.

Obstructive Sleep Apnea

Cardiopulmonary exercise testing can be performed safely in patients with sleep apnea to evaluate abnormalities in gas exchange and the response to continuous positive airway pressure therapy. Patients with moderate to severe obstructive sleep apnea have impaired exercise capacity, low peak $\dot{V}_{O_2}$, and low AT. The abnormal parameters on cardiopulmonary exercise testing can be improved by continuous positive airway pressure therapy. In one study involving patients with severe sleep apnea, 2 months of treatment using nasal continuous positive airway pressure resulted in higher right ventricular ejection fraction, peak $\dot{V}_{O_2}$, peak $\dot{V}_{O_2}$/kg, AT, and oxygen pulse.

In patients with heart failure who have central sleep apnea (CSA) mortality rate is higher than in patients without CSA. Patients with heart failure often lack the classic symptoms of CSA; hence, its presence may be underestimated. Treating CSA in patients with heart failure benefits cardiac function. Patients with heart failure and CSA have a highly augmented ventilatory response to exercise. This is manifested by a significantly increased slope of $\dot{V}_E/\dot{V}_{CO_2}$, which correlates with the severity of sleep apnea. Thus, patients with heart failure who have an increased $\dot{V}_E/\dot{V}_{CO_2}$ slope should be considered for a full sleep study to confirm the presence of sleep apnea.

Congenital Heart Disease

Patients with cyanotic congenital heart disease have limitations in exercise tolerance. Cardiopulmonary exercise testing can be used to objectively assess these patients' exercise limitation and ventilatory efficiency.

In a study of 25 adults with uncorrected cyanotic congenital heart disease, peak oxygen uptake and Pao_2 were

significantly reduced compared to normal; $Paco_2$ was only slightly reduced. Ventilatory efficiency, expressed as $\dot{V}_E/\dot{V}_{CO_2}$, was markedly impaired at rest and during exercise. $\dot{V}_E/\dot{V}_{CO_2}$ correlated more strongly with patients' symptoms than did hypoxemia and peak oxygen uptake. For corresponding NYHA classes, patients with adult congenital heart disease and those with heart failure demonstrate no significant differences in peak $\dot{V}_{O_2}$.

In adults, cardiopulmonary exercise testing has also been used for assessing the response to transcatheter-based closure of atrial septal defects. Increased peak oxygen uptake, peak oxygen pulse, and vital capacity have been reported, as have improvements in the prolonged $\dot{V}_{O_2}$ and $\dot{V}_{CO_2}$ slopes, reflecting improvement in recovery from maximal exercise.

Pulmonary Hypertension

Pulmonary hypertension is expressed as an abnormal elevation in resting or exercise pulmonary artery pressure. Chronic left heart failure and the accompanying increase in left atrial pressure remain the most common cause of pulmonary *venous* hypertension. Pulmonary *arterial* hypertension (PAH) accompanies intrinsic pulmonary vascular disease or arteriolar vasoconstriction associated with hypoxemia due to intrinsic lung disease. PAH creates right ventricular pressure overload and an impediment to left ventricular filling. Accordingly, exercise cardiac output is compromised and aerobic capacity declines.

Patients with PAH have been studied during elective right heart catheterization using a triple-lumen flotation catheter and subsequent exercise testing. Resting and peak treadmill exercise hemodynamic responses are given in Table 35-4. At rest, right heart and pulmonary arterial pressures exceeded the normal range. Right ventricular systolic pressure at rest was in excess of 50 mmHg, and in one-fourth of patients it approximated or exceeded left ventricular (and systemic arterial) systolic pressure. Resting wedge pressure was normal in these patients. Calculated pulmonary vascular resistance exceeded the upper range of normal (170 dynes $\cdot$ s $\cdot$ cm^{-5}) in all patients; in more than one-third, it was above 1000 dynes $\cdot$ s $\cdot$ cm^{-5}, approximating systemic vascular resistance.

Peak cardiac output attained with maximal exercise for each functional class (Table 35-3) is similar to that observed for chronic cardiac failure and valvular heart disease. The impairment in exercise cardiac output is related to the extent to which pulmonary vascular resistance is increased. Patients with a markedly increased resting pulmonary vascular resistance (above 1000 dynes $\cdot$ s $\cdot$ cm^{-5}) proved to be functional class D. In this group of patients with intrinsic pulmonary vascular disease, arterial O_2 desaturation during exercise was not observed, emphasizing the importance of compromised cardiac reserve—a function of the inability of the right ventricle to generate sufficient pulmonary blood flow to sustain left ventricular filling and, thereby, systemic blood flow. Patients with PAH stopped exercising because of breathlessness or fatigue or both; none experienced retrosternal chest pain, light-headedness, or syncope; none developed arrhythmias. In most, it was possible to determine the $\dot{V}_{O_2max}$; in all, the AT could be attained (see above). Cardiopulmonary exercise test results for a 42-year-old woman with PAH are shown in Fig. 35-10.

Table 35-4

Resting and Peak Exercise Hemodynamics for Patients with Nonhypoxic Pulmonary Vascular Disease and Pulmonary Hypertension

		Resting	Exercise
PA	(mmHg)	29 ± 9	47 ± 20
RVSP	(mmHg)	52 ± 30	86 ± 37
RVDP	(mmHg)	7 ± 4	16 ± 10
PCW	(mmHg)	10 ± 3	22 ± 14
PVR	(dynes $\cdot$ s $\cdot$ cm^{-5})	412 ± 319	302 ± 331
CO	($L/m^2/min$)	2.8 ± 1.6	5.3 ± 2.2
AP	(mmHg)	106 ± 6	130 ± 8
Art O_2 sat	(%)	97 ± 2	96 ± 2

Note: PA = mean pulmonary artery pressure: RVSP and RVDP = right ventricular systolic and diastolic pressures, respectively; PCW = wedge pressure; PVR = pulmonary vascular resistance; CO = cardiac output; AP = mean arterial pressure.

Source: Reproduced from Weber KT, Janicki JS: Pulmonary hypertension, in Weber KT, Janicki JS (eds), Cardiopulmonary Exercise Testing: Physiologic Principles and Clinical Applications. Philadelphia. Saunders. 1986. pp 220–234.

In patients with hypoxic pulmonary vasoconstriction, upright isotonic exercise also results in an increase in mean pulmonary artery and right ventricular systolic and diastolic pressures. In many of these patients, pulmonary vascular resistance increases during exercise because of marked hypoxemia, with arterial O_2 saturation ranging between 70 and 80 percent. This response can be attenuated with use of supplemental O_2.

Patients with PAH have significant ventilation-perfusion mismatch; during exercise, ventilation is increased. This abnormality in ventilatory inefficiency is reflected in the reduction in end-tidal CO_2 concentration ($pETco_2$). The reduction in end-tidal CO_2 concentration is proportional to the decrease in percent predicted $\dot{V}_{O_2}$ and increase in mean pulmonary artery pressure. In normal subjects, $pETco_2$ increases from rest to attainment of AT, whereas in patients with PAH, $pETco_2$ decreases from rest to AT. During cardiopulmonary

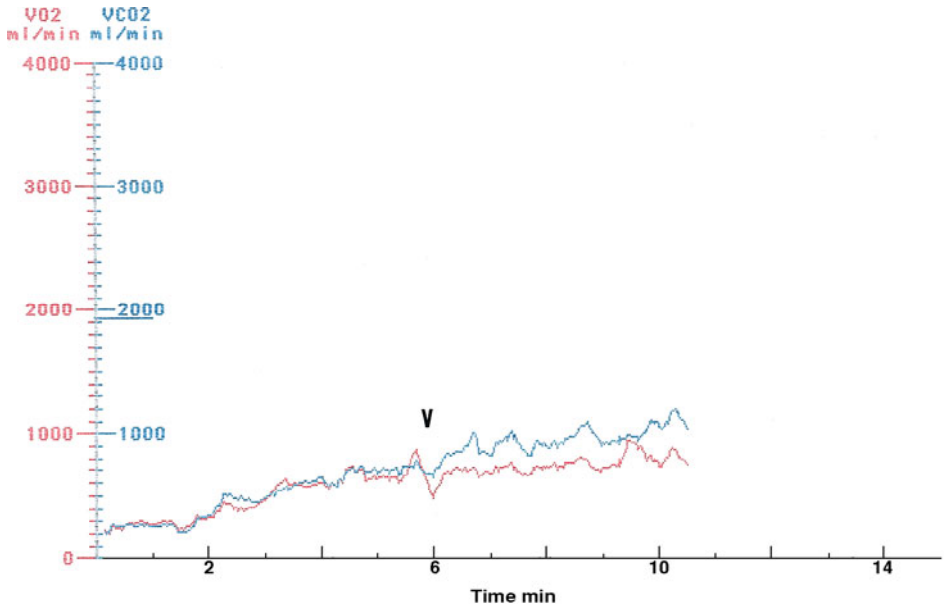


Figure 35-10 Cardiopulmonary exercise test results for a 42-year-old woman with pulmonary arterial hypertension of uncertain origin. The first 2 minutes represent standing rest. The patient attained the anaerobic threshold (AT) (7 ml/min/kg) during stage 2 of exercise (1.5 mph, 0 grade) and a $\dot{V}_{O_2max}$ of 10 ml/min/kg, corresponding to functional class D.

exercise testing, the slope of regression between CO_2 production and minute ventilation can also be used to assess the ventilation-perfusion mismatch. At the same peak $\dot{V}_{O_2}$, the $\dot{V}_E/\dot{V}_{CO_2}$ slope is greater in patients with PAH than those with cardiac dysfunction. Conversely, for the same slope of $\dot{V}_E/\dot{V}_{CO_2}$, patients with left ventricular dysfunction have a lower peak $\dot{V}_{O_2}$.

The measurement of cardiopulmonary exercise testing-based parameters in patients with PAH is reliable and reproducible, even in patients with limited exercise tolerance. The parameters correlate well with decreases in D_{LCO} and NYHA class. Even in children with pulmonary hypertension, peak $\dot{V}_{O_2}$ strongly correlates with pulmonary vascular index. Cardiopulmonary exercise testing can be used for the objective assessment of safety and efficacy of treatment strategies in patients with PAH. Peak $\dot{V}_{O_2}$ is an independent, strong predictor of survival in these patients.

CHRONIC LUNG DISEASES

In a normal subject performing maximal exercise, $\dot{V}_E$ rarely exceeds 50 percent of MVV; similarly, tidal volume uncommonly exceeds 50 percent of vital capacity. Given this large ventilatory reserve, exercise is not normally limited by ventilation. This is not the case in patients with lung disease, in whom ventilatory reserves are reduced. Other factors that may limit exercise in patients with lung disease are altered lung mechanics, impaired gas exchange with arterial hypoxemia and the appearance of pulmonary hypertension, and respiratory muscle fatigue.

Obstructive Lung Disease

Exercise intolerance commonly accompanies chronic obstructive pulmonary disease (COPD), with dyspnea limiting physical activity to modest levels of work. Patients with COPD have a higher $\dot{V}_E$ for any given workload; this is largely due to increased dead space ventilation. Given their reduction in MVV and greater exercise $\dot{V}_E$, these patients often exercise with a ratio of $\dot{V}_E$ to MVV that exceeds 75 percent. Use of such a large portion of this ventilatory reserve cannot be sustained, accounting for breathlessness and termination of exercise. This generally occurs in patients with moderate to severe COPD before they have reached their AT, implying a ventilatory, rather than cardiac, limitation to exercise. The workload at which patients terminate exercise represents a peak $\dot{V}_{O_2}$; it is not their $\dot{V}_{O_2max}$, as can be attained in patients with chronic cardiac or circulatory failure in whom ventilatory responses pose no limitation to exercise.

In severe emphysema, D_{LCO} is reduced in keeping with alveolar capillary destruction. In such patients, a significant fall in arterial O_2 saturation often occurs during exercise. This is in contrast to patients with chronic bronchitis, in whom arterial O_2 saturation may actually increase. The improvement in oxygenation in these patients is a result of improved ventilation in areas with low ventilation-perfusion ratios. D_{LCO} portends exercise-induced arterial O_2 desaturation: patients who have a D_{LCO} less than 55 percent predicted are most likely to experience hypoxemia during exercise. Several factors account for limited exercise tolerance in the setting of arterial hypoxemia: (1) reduced O_2 delivery to exercising muscles, including those associated with respiration; (2) increased chemical drive to respiration and corresponding inappropriate $\dot{V}_E$

for a given level of work; and (3) secondary pulmonary vasoconstriction.

By measuring $\dot{V}_{O_2}$ peak in patients with COPD undergoing cardiopulmonary exercise testing, an objective assessment of exercise capacity can be made. Peak $\dot{V}_{O_2}$ in severe COPD correlates with resting forced expiratory volume in 1 second (FEV_1) (percent predicted), total treadmill time, and total metabolic equivalent values. Cardiopulmonary exercise testing can better define respiratory limitations than pulmonary function testing alone in patients filing for disability due to COPD-related shortness of breath (see Chapter 39).

The increase in breathing capacity during exercise in patients with COPD, as measured by the ratio of $\dot{V}_E$/MVV, correlates with peak $\dot{V}_{O_2}$; it can be predicted by the FEV_1/percent of forced vital capacity (FVC,%) assessed during routine pulmonary function testing. In chronic COPD, peak $\dot{V}_{O_2}$ can be estimated using equations that take into account patient walking distance and pulmonary function tests. However, the correlation between measured and estimated peak $\dot{V}_{O_2}$ is not strong enough to predict exercise capacity. If peak $\dot{V}_{O_2}$ is to be used for clinical decision making, it should be measured, rather than estimated. Furthermore, patients with COPD have skeletal muscle abnormalities that may contribute to reduced exercise capacity. Peak $\dot{V}_{O_2}$ in COPD correlates well with fat-free mass, a bioimpedance index of muscle mass.

In COPD, physiological parameters measured by cardiopulmonary exercise testing also have prognostic implications. Based on multivariate analysis, the slope of the relationship between Pao_2 and $\dot{V}_{O_2}$ is most closely associated with survival. Similarly, Pao_2max, along with measured FEV_1, have been found to be independent predictors of mortality. Overall, in COPD, a linear relationship exists between peak $\dot{V}_{O_2}$ and pulmonary function test parameters.

Restrictive Lung Disease

Patients with known interstitial lung disease, a diverse group of disease entities, experience limiting dyspnea on exertion. This may be secondary to reduced ventilatory reserve or development of arterial O_2 desaturation. Dyspnea may appear on exertion in a patient with an abnormal chest radiograph before pulmonary function studies are abnormal.

Exercise testing may be indicated in patients with interstitial lung disease to detect abnormal ventilatory reserve and its response over time. Patients with interstitial lung disease tend to breathe at a higher respiratory rate and lower tidal volume than do normal subjects for any given $\dot{V}_{O_2}$. Because they have a reduced MVV, their ability to exercise is limited by nearly full utilization of their reduced ventilatory reserve.

As in patients with airway disease, D_{LCO} is a good predictor of arterial O_2 desaturation during exercise in patients with interstitial lung disease. Most patients with a D_{LCO} below 60 percent develop arterial O_2 desaturation. If a patient has a normal D_{LCO}, he or she is unlikely to develop exercise-induced arterial O_2 desaturation. Measurement of D_{LCO} can be used to screen patients for exercise studies. Finally, the degree of arterial O_2 desaturation during exercise correlates with the reduction in D_{LCO}.

Cardiopulmonary exercise testing is a sensitive test for detecting abnormalities in gas exchange. In one study that dealt with biopsy-proven sarcoidosis, cardiopulmonary exercise testing predicted pulmonary dysfunction earlier than did physical examination, chest radiography, or spirometry. In survivors of severe acute respiratory distress syndrome (ARDS), aerobic capacity assessed by cardiopulmonary exercise testing was found to be abnormal in 41 percent of patients in whom mild pulmonary function abnormalities were not enough to explain the low-exercise capacity. Cardiopulmonary exercise testing has also been used prognostically in patients with interstitial lung disease.

EVALUATION OF EXERTIONAL DYSPNEA

Normally, a person is unaware of the act of breathing and the fact that 500 to 750 ml of air enters and leaves the lungs 10 to 15 times each minute. Minute ventilation ($\dot{V}_E$) increases secondary to normal or abnormal chemical stimuli (e.g., hypercapnia, hypoxemia, acidemia) or anxiety. When breathing is perceived to be inappropriate relative to the level of physical activity, it is considered to be an abnormal awareness of breathing that is termed breathlessness, shortness of breath, or dyspnea. Dyspnea on exertion is common in patients with heart disease, pulmonary parenchymal or airway disease, and pulmonary vascular disease. Deformities of the chest wall and diseases associated with weakness of the respiratory muscles are also accompanied by breathlessness on exertion. Dyspnea may seriously hinder a patient's ability to carry out muscular work, thereby compromising quality of life. The evaluation of dyspnea includes historical information that characterizes the symptom onset, severity, and relationship to exercise, and the patient's underlying physical condition and customary daily activity. Other associated symptoms—such as palpitations, anginal chest pain, and light-headedness—must be taken into consideration.

An objective and reliable estimate of dyspnea on exertion and its severity can be gauged from exercise testing. Dyspnea occurs when $\dot{V}_E$ is excessive relative to $\dot{V}_{O_2}$, and when $\dot{V}_E$ is driven by chemical stimuli or altered lung mechanics. Dyspnea during exercise can appear when $\dot{V}_E$ represents an excessive proportion of MVV. An estimation of MVV can be derived by multiplying the patient's FEV_1 by 35. As a corollary, maximal encroachment on the vital capacity by exercise tidal volume cannot be sustained for long. Such ventilatory effort poses a substantial workload on respiratory muscles. An MVV maneuver during pulmonary function testing cannot be sustained for more than a few seconds, while more than 70 percent of the MVV cannot be sustained by normal subjects for more than several minutes. Hence, the ventilatory response to exercise that is associated with dyspnea in

patients with heart or lung disease follows a similar pattern of short-lived, near-maximal ventilation.

The patient with pulmonary vascular disease or advanced interstitial lung disease may be unable to sustain adequate arterial O_2 saturation during exercise. Consequently, hypoxemia may compound the patient's exercise response and may be responsible for a heightened chemical drive to respiration. In the case of COPD, the need to move air through a partly obstructed tracheobronchial tree creates an added workload on respiratory muscles. Airflows in these patients are already compromised at rest and must increase with exercise; they may approach peak expiratory flows observed with maximal effort during pulmonary function testing.

Patients with mild, moderate, or severe cardiac or circulatory failure rarely use more than 50 percent of their ventilatory reserve at maximal exercise, and they do not experience arterial O_2 desaturation during exercise. If one estimates MVV from the FEV_1 (as noted above), for an FEV_1 of 1, 2, or 3 L, MVV is expected to equal 35, 70, or 105 L, respectively. In patients with chronic cardiac or circulatory failure, maximum exercise $\dot{V}_E$ has been found to range between 62 and 29 L per min for class A through D patients. Hence, unless there is a major reduction in MVV (or in FEV_1 to less than 3 L), these patients will not have a ventilatory limitation to exercise.

Finally, patients are able to cross their AT and, if encouraged, may reach their point of exhaustion attaining $\dot{V}_{O_2max}$. By monitoring the breath-by-breath response in $\dot{V}_{O_2}$ and $\dot{V}_{CO_2}$ during exercise, the physician can immediately determine when the patient has achieved the AT and $\dot{V}_{O_2max}$. These end points are not attained in the patients with lung disease or those with coexistent heart and lung disease in whom the respiratory system is the primary limitation to exercise. Table 35-5 summarizes the salient points used to differentiate primary ventilatory from cardiac or circulatory failure as the cause of exertional dyspnea, as detected by exercise testing.

Table 35-5

Ventilatory vs. Cardiac/Circulatory Failure as the Predominant Cause of Exertional Dyspnea

Ventilatory Failure
1. Exercise maximum $\dot{V}_E$ utilizes > 70% of MVV
2. Exercise-associated arterial hypoxemia
3. Failure to cross AT and to achieve $\dot{V}_{O_2max}$
Cardiac/Circulatory Failure
1. Cross AT and can achieve $\dot{V}_{O_2max}$
2. Maximum exercise $\dot{V}_E$ does not exceed 50% of MVV
3. Does not develop arterial hypoxemia with exercise

Note: AT = anaerobic threshold; MVV = maximal voluntary ventilation.

OTHER APPLICATIONS OF CARDIOPULMONARY EXERCISE TESTING

Cardiopulmonary exercise testing, with its ability to foretell cardiac and ventilatory reserves, has proved useful in clinical decision making in a variety of circumstances, including assessment of a patient's candidacy for cardiac transplantation and preoperative assessment of preoperative risk.

Cardiac Transplantation

The severity of chronic cardiac and circulatory failure is gauged according to $\dot{V}_{O_2max}$ and the AT (Table 35-3) and is used to predict exercise cardiac reserve. This approach has been applied to patients with systolic dysfunction secondary to chronic ischemic heart disease or dilated (idiopathic) cardiomyopathy, who are considered to be potential candidates for cardiac transplantation. Neither the ejection fraction nor resting hemodynamic parameters (e.g., resting cardiac index or wedge pressure) help to predict the severity of cardiac failure or functional capacity and are no longer a mainstay in decision making. The same is true for subjective evaluation of functional status using the NYHA criteria. Incremental exercise testing, with identification of AT and peak $\dot{V}_{O_2}$ achieved thereafter, has emerged as a valuable tool to address cardiac reserve and functional capacity objectively and to predict survival. In fact, consensus has been reached on recommending transplantation using clinical criteria in combination with functional stratification based on the results of exercise tests.

Class D patients, having little or no cardiac reserve, have a marked reduction in 1- and 2-year survival and, therefore, are candidates for urgent transplantation. Class C patients, who have a modest increment in cardiac output with exercise, are probable candidates. On the other hand, class A and B patients in whom cardiac reserve remains intact, or class B patients in whom cardiac reserve is only minimally impaired, do not have an adequate indication for transplantation. Decision is deferred, and serial exercise studies are used to assess recovery or deterioration in the setting of optimal medical therapy.

Incremental exercise testing may also provide useful information after cardiac transplantation, including recovery of cardiac and ventilatory reserves. The importance of diastolic dysfunction in limiting exercise tolerance following cardiac transplantation was reviewed earlier. A blunted heart rate response to exercise is expected in these patients due to cardiac denervation. Such chronotropic incompetence is demonstrated in Fig. 35-11, along with the results of exercise testing.

Surgical Risk Assessment

Preoperative incremental exercise testing has proved useful in assessing postoperative morbidity and mortality in the elderly and in patients with underlying heart or lung disease who are scheduled for major intrathoracic or intra-abdominal

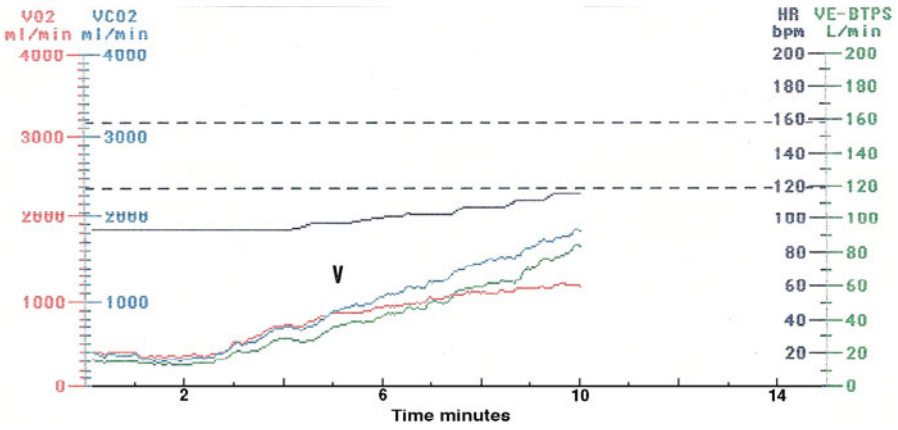


Figure 35-11 Cardiopulmonary exercise test results for a 62-year-old male cardiac transplant recipient. During this incremental treadmill test this patient attained an anaerobic threshold (AT) and $\dot{V}_{O_2max}$ of 8 and 11 ml/min/kg, respectively. Note the blunted heart rate response (predicted peak heart rate range shown as broken lines).

surgery. The premise underlying this approach is based on a recognition that during and after surgery, there may be a need to call on cardiac and ventilatory reserves—namely, the ability to increase cardiac output and maintain O_2 delivery, and to increase $\dot{V}_E$ and prevent hypoxemia. Several studies have demonstrated the utility of measuring the AT and peak $\dot{V}_{O_2}$ using exercise testing to estimate these reserves, and to identify patients prone to postoperative complications. Pulmonary function testing proved insensitive in forecasting postoperative course. Class C and D patients, with little or no cardiac reserve, had a greater number of morbid and mortal events following surgical interventions than did class A or B patients. Class A patients had few, if any, postoperative complications and no mortality. Therefore, the risk of complications could best be gauged by a patient's preoperative aerobic capacity. Direct assessment of the AT or $\dot{V}_{O_2max}$ and prediction of cardiac reserve, and, by inference, ventilatory reserve, supersede the value of an age-determined impairment in aerobic capacity.

AT is a particularly important parameter in assessing preoperative risk. It provides an objective assessment that is independent of patient motivation and does not require inordinate amounts of exercise. In a large study of elderly patients undergoing major intra-abdominal surgery, an AT of less than 11 ml/min/kg, along with preoperative ischemia, was associated with high mortality. Patients evaluated by cardiopulmonary exercise testing who have an unfavorable AT can be admitted electively to intensive care units for optimization of hemodynamics prior to major surgery.

Patients undergoing other major surgeries, such as radical esophagectomy with three-field lymphadenectomy, have also been risk-stratified using cardiopulmonary exercise testing. Extensive fluid shifts are expected in the postoperative period with surgical interventions on the lymphatic system. Cardiopulmonary exercise testing can provide a thorough assessment of the cardiopulmonary reserve in such patients. For example, in one study, a peak $\dot{V}_{O_2}$ of 800 ml/min/m^2 was associated with low risk of complications. Similarly, in another study of patients undergoing repair of an abdominal aortic aneurysm, those with a peak $\dot{V}_{O_2}$ less than 20 ml/min/kg had a higher incidence of adverse complications. Finally, a study of patients undergoing liver transplantation demonstrated that patients dying within 100 days of transplantation were more likely to have had a preoperative peak $\dot{V}_{O_2}$ less than 60 percent of predicted and an AT less than 50 percent of predicted peak $\dot{V}_{O_2}$ than those who survived.

Patients with lung cancer have a high likelihood of concomitant COPD and coronary artery disease due to the common risk factor of smoking. Surgery might offer the only chance of cure in these patients and often implies resection of a variable portion of the lung tissue surrounding the cancer to ensure eradication. Removal of functional lung tissue in an already compromised cardiopulmonary system resection can be risky. It is imperative that a preoperative assessment of cardiopulmonary reserve be made before such a surgery. Cardiopulmonary exercise testing in such patients provides an objective assessment of cardiopulmonary reserve. In addition, peak $\dot{V}_{O_2}$, along with FEV_1 and D_{LCO}, has been used to risk-stratify these patients. Correcting peak $\dot{V}_{O_2}$ for weight and expressing it as a percentage of predicted improves the predictive power of peak $\dot{V}o_2$measurements. Elderly patients, females, and patients with short stature may have a peak $\dot{V}_{O_2}$ below the absolute cutoff value, but they may still be eligible for surgery when peak $\dot{V}_{O_2}$ is expressed as percent of predicted.

The predictive value of peak $\dot{V}_{O_2}$ is greater in patients with an FEV_1 less than 70 percent of predicted. Peak $\dot{V}_{O_2}$ less than 50 percent of predicted is associated with high complication rates. Patients with peak $\dot{V}_{O_2}$ greater than 50 percent of predicted can undergo surgery without excess mortality. A peak $\dot{V}_{O_2}$ less than 10 ml/min/kg is generally considered prohibitive for surgery. Risk-stratification based upon peak $\dot{V}_{O_2}$ is particularly useful in patients undergoing lung resection who have borderline pulmonary function (predicted postoperative FEV_1 or D_{LCO} less than 40 percent). In these patients, a peak $\dot{V}_{O_2}$ less than 15 ml/min/kg is associated with

an increased risk, and peak $\dot{V}_{O_2}$ less than 10 ml/min/kg carries a very high risk of postoperative complications (see Chapter 38 for additional discussion).

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36

Bronchoscopy, Transthoracic Needle Aspiration, and Related Procedures

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Gustav Killian reported his experience with the first bronchoscopy in 1898. Technological advances during the next century facilitated development of bronchoscopy as a pivotal diagnostic and therapeutic tool in pulmonary medicine. Although a number of bronchoesophagologists contributed to refinement of the technique based upon use of a rigid instrument, the advent of flexible fiberoptic bronchoscopy, pioneered by Ikeda in 1967, opened new horizons to clinicians.

More recently, transthoracic needle aspiration and biopsy have been added to the pulmonologist's diagnostic armamentarium. These techniques are particularly useful for evaluating localized or peripheral lung lesions. Transthoracic needle aspiration permits acquisition of material for cytologic and microbiologic analysis, while transthoracic needle biopsy provides tissue for histological study.

This chapter comprises an overview of bronchoscopy, transthoracic needle aspiration and biopsy, and related techniques. Following a general discussion of bronchoscopy and associated general instrumentation, indications for the technique and patient preparation are considered. Specific applications of diagnostic and therapeutic bronchoscopy are discussed. Subsequently, safety factors related to bronchoscopy and complications of the technique are reviewed. Finally, transthoracic needle aspiration and biopsy are described.

TYPES OF BRONCHOSCOPY AND GENERAL INSTRUMENTATION

In the first three-fourths of the twentieth century, pulmonary endoscopy was performed with open-tube steel bronchoscopes. The advent of fiberoptic technology and, subsequently, miniaturized electronics permitted application of flexible endoscopy, as discussed below.

Rigid Bronchoscopy

The initial bronchoscope, developed by Killian in Europe and further perfected by Chevalier Jackson in the United States, was a rigid metal tube that permitted either spontaneous or mechanical ventilation. Over the decades, rigid bronchoscopes of various lengths and sizes, which are adaptable for diverse applications in children and adults, have become available. With development of fiberoptic and advanced electronic technology, the flexible bronchoscope has, to a large extent, replaced the rigid bronchoscope for most diagnostic and some therapeutic indications.

Both rigid and flexible modern systems are equipped with optic capabilities for airway observation alone. With the rigid bronchoscope, various types of telescopic rods, equipped with circumferential illumination, permit direct and magnified visualization. Specially designed telescopes allow viewing not only directly forward but also at oblique and lateral angles. Various diagnostic and therapeutic accessories can be inserted through the rigid bronchoscope while the patient remains ventilated.

In recent years, development of small cameras based on charge coupled device (CCD) technology has facilitated transmission of bronchoscopic images to television monitors, enhancing the education of trainees and permitting improved documentation of bronchoscopic findings.

Flexible Fiberoptic and Videobronchoscopy

Although the optical resolution of early fiberoptic bronchoscopes was inferior to that of rigid devices, their flexibility, ease of manipulation, and simplicity of use, which permit rapid examination under topical anesthesia, have made flexible bronchoscopy the primary endoscopic procedure in pulmonary diseases.

Unlike the larger-bore rigid bronchoscope, the flexible bronchoscope varies from ultra-thin—allowing for neonatal endoscopy—to larger, adult-size therapeutic devices. The diameter of the working channel permits aspiration of secretions or introduction of accessories required for diagnostic or therapeutic purposes (see below). With flexible bronchoscopy, the patient's ventilation is assured by airflow around the bronchoscope, between the external wall of the device and the tracheobronchial tree. Thus, the appropriate selection of bronchoscope size is crucial.

Recent technological advances have permitted the replacement of fiberoptic systems by a miniaturized CCD camera at the tip of the scope that provides electronic transmission of images to a television monitor. Flexible bronchoscopes are more fragile and more prone to damage than are rigid metal instruments. Appropriate care and adherence to safety techniques during procedures, as well as during routine cleaning and maintenance of the instruments, help assure extended instrument life and reduce repair costs.

PATIENT PREPARATION AND MONITORING DURING BRONCHOSCOPY

Most fiberoptic bronchoscopies are performed after patient premedication with sedative agents. Most frequently, a combination of a short-acting benzodiazepine (e.g., midazolam) and a narcotic agent (e.g., fentanyl) is used. The sedatives are generally administered along with an anticholinergic medication (e.g., atropine or glycopyrrolate) in order to reduce the risk of vasovagal reactions and to minimize airway secretions. Local anesthesia of the upper airway, larynx, and tracheobronchial tree is achieved with inhaled or bronchoscopically instilled lidocaine. Although rigid bronchoscopy was performed initially with minimal anesthesia and later under general anesthesia, the recent trend has been to perform the procedure with patients either breathing spontaneously or ventilated with a jet ventilator, often under total intravenous anesthesia (TIVA) with drugs such as propofol or remifentanil. With appropriate monitoring, good oxygenation and adequate ventilation can be assured.

Success of bronchoscopy, whether diagnostic or therapeutic, depends, in large part, on proper preparation of the patient, including relief of anxiety, muscle relaxation, cough suppression, and adequate anesthesia. Time spent in achieving these goals will be well worth it in reducing the risks of complications and in increasing the ease of performance of the procedure. As with any other procedure, analysis of the risk-benefit ratio helps reduce the complication rate. During and shortly after the procedure, appropriate monitoring of hemodynamic parameters (heart rate, rhythm, and blood pressure), oxygenation, and ventilation contributes to the safety of bronchoscopy.

DIAGNOSTIC BRONCHOSCOPY ACCESSORIES

The working channel of the fiberoptic or videobronchoscope, although of relatively small diameter, allows the insertion of

various diagnostic and therapeutic accessories. Specially constructed accessories of larger caliber have been developed for use with the rigid bronchoscope.

Biopsy Forceps

Simple visualization of lesions is usually not sufficient to determine a precise diagnosis and to guide management. Pathological confirmation through biopsy is frequently required. A variety of instruments with improved distal control (i.e., control beyond the tip of the bronchoscope) have been developed that permit tissue cutting and retrieval of biopsy specimens.

The cutting cups of biopsy forceps may be round or elliptic and may have smooth or jagged edges. The use of nonserrated edges, however, seems to reduce tissue trauma and the concomitant risk of bleeding. The biopsy procedure is simple and generally associated with only minimal complications in the case of a visible lesion. Even peripheral lesions, which are not visible through the bronchoscope, may be biopsied. With diffuse parenchymal or interstitial lung disease, specimens may be obtained without fluoroscopic guidance. With smaller or focal lesions, however, the diagnostic yield of biopsies increases when fluoroscopy is used. The recent development of new electromagnetic and remote guidance systems suggests that further improvement in the diagnostic yield of bronchoscopic biopsies can be expected.

Bronchial Brushes

Lesions not accessible to direct biopsy with a forceps can be approached with a bronchial brush. This device consists of a rigid central wire surrounded by brushes of various sizes and shapes. To-and-fro movement of the brush against the adjacent tissue produces minor trauma but enables collection of ample specimens for cytologic or microbiologic analysis.

In some clinical circumstances, there is a need to obtain from the lower respiratory tract an uncontaminated specimen for microbiologic studies. A brush protected by an additional sheath and tip may be passed through the working channel of the bronchoscope (protected brush specimen, as discussed below). In these cases, special attention is needed not to use an excessive amount of local anesthetic or saline lavage, since these solutions contain bacteriostatic material that may inhibit microbial growth. The diagnostic yield depends on use of proper technique, appropriate choice of brush, and careful collection and preservation of the specimen.

Needles for Aspiration and Biopsy

The first performance of a transbronchoscopic needle aspiration (TBNA) through a rigid bronchoscope was reported by Schieppati in 1958. Wang then developed a flexible needle technique, using a fiberoptic bronchoscope in 1978. Initially, several models of needles were designed to obtain cytological material; subsequently, histological specimens from peribronchial mediastinal and hilar lymph nodes were obtained with larger-bore needles. These biopsy needles are also useful in the diagnosis of endobronchial and submucosal lesions, and can serve as a complementary technique to percutaneous needle aspiration of peripheral pulmonary nodules or masses.

The tip of the needle is protected by a metal hub during the insertion and withdrawal to avoid damage to the flexible scope. Perforation of the working channel of the scope may occur if the needle is advanced in an exposed position. The diagnostic yield depends on two factors: optimization of the bend of the tip of the bronchoscope and proper performance of bronchial wall puncture by the needle through the intercartilaginous space. Familiarity with the type of needle used increases the success rate.

TBNA is generally safe, although pneumothorax and hemomediastinum can occur. Clinically significant bleeding is extremely rare, particularly when a 22-gauge needle is used, even if a major vessel is inadvertently punctured or if the patient suffers from superior vena cava syndrome.

Dedicated Catheters and Balloons

Various investigational protocols for study of lung diseases use the technique of bronchoalveolar lavage (see below) and collection of uncontaminated specimens. In performing this procedure, selective aspiration catheters are necessary. These bronchoscopically guided, double-lumen catheters are wedged in the selected bronchus. After inflation of a balloon and isolation of the bronchus, instillation of fluid through the central lumen of the catheter is followed by aspiration of the fluid. In another application, the low-pressure balloon catheters contribute to estimation of airway diameter before the insertion of a stent (see below). Sometimes, inflation of the balloon at the tip of the bronchoscope permits enlargement of the lumen and eventual penetration of the bronchoscope beyond the area of stenosis, allowing exploration of peripheral airways.

Endobronchial Ultrasound

Endobronchial ultrasound (EBUS) enhances traditional white light bronchoscopy (WLB) by providing real-time, 360-degree images that reach beyond the bronchial lumen, providing information unattainable by airway inspection alone. In general, higher acoustic frequencies afford only shallow penetration, but result in high-resolution images; lower frequencies provide deeper tissue penetration, but impaired image resolution. The quality of the ultrasonic image depends primarily upon adequate contact of the probe with the airway wall, depth of penetration of the ultrasound wave, and spatial resolution of different structures. EBUS uses a frequency in the range of 20 MHz, which allows a tissue penetration depth up to 5 cm. However, the abundant presence of air in the lung, which distorts the ultrasound image by reflecting sound waves, is a major obstacle to obtaining adequate images. Currently, probes reduce artifact arising from air-filled bronchi by transmitting sound through a fluid- or gel-filled balloon.

While EBUS has been used in a variety of clinical scenarios, its role in clinical practice remains to be fully defined. Currently, the three main indications for EBUS are: (1) evaluation of endobronchial masses, (2) aspiration of mediastinal lymph nodes (Fig. 36-1), and (3) facilitation of the distinction between neoplastic and benign mediastinal masses.

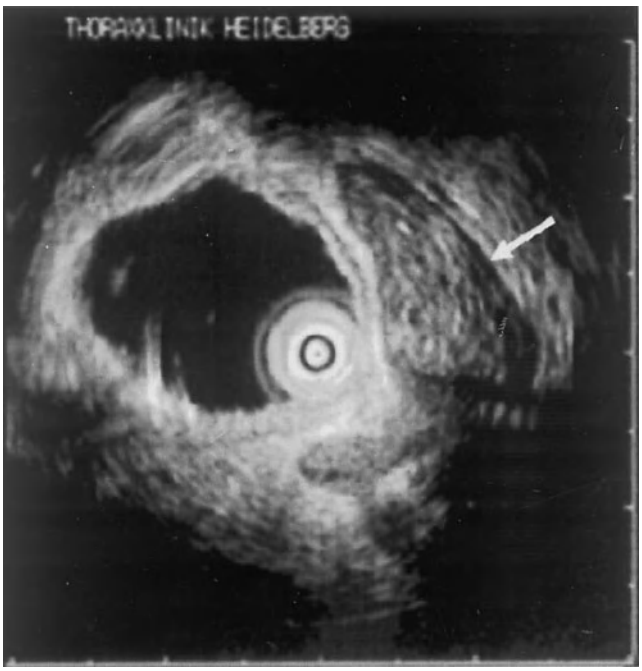


Figure 36-1 Endobronchial ultrasound (EBUS) image of an enlarged lymph node. EBUS image from the left main carina demonstrates an enlarged subcarinal lymph node (white arrow). *(Courtesy of Felix Herth, M.D.)*

Less frequent indications include assessment of mediastinal infiltration by tumor, evaluation of anastomotic recurrences, and identification of submucosal lesions. Identifying submucosal lesions may be useful prior to planned thoracic resections in determining the likely bronchial margin of an infiltrating tumor. In some cases, patients diagnosed with "early" carcinomas are found by EBUS to harbor extensive intraluminal disease as well as regional lymph node metastases. EBUS may also be used as an adjunct to planning of interventional procedures, such as endobronchial stenting, photodynamic therapy (vs. use of brachytherapy), and laser photoablation.

APPLICATIONS OF DIAGNOSTIC BRONCHOSCOPY

Although the initial indications for bronchoscopy described by Killian and Jackson centered primarily on therapeutic applications, both recognized the central role the technique plays in visual examination of the tracheobronchial tree and in diagnosis of various pulmonary diseases. Development of the flexible bronchoscope and various accessory instruments that can be inserted via the working channel has extended bronchoscopic exploration to the lung periphery.

Assessment of Airway Anatomy and Function

Thorough bronchoscopic evaluation begins with examination of the upper airways. Special attention should be paid to the integrity of air passages and the function of the nasopharynx and larynx. The vocal cords should be examined for the presence of polyps and tumors, and for evidence of cord paralysis.

Once the upper-airway inspection is completed, a systematic evaluation of the lower respiratory tract should be performed. Critically important is the distinction among normal anatomy, anatomic variations without clinical significance, and frankly pathological conditions. These considerations have important implications regarding potential diagnostic and therapeutic approaches. For example, finding an abnormal branching of a bronchus may be of no clinical significance. On the other hand, such an abnormality could explain symptoms of frequent infections due to impaired ventilation and drainage of the affected area. Special skills and observational experience are required for bronchoscopic examination after surgery, especially following creative bronchoplastic procedures or lung transplantation.

Assessment of airway integrity, with special attention to dynamic changes in airway caliber during either relaxed breathing or forced expiration and coughing, may be crucial in determining appropriate therapeutic maneuvers. Flexible bronchoscopy is superior to rigid bronchoscopy for this assessment. Relaxation and prolapse of the membranous portion of the trachea and main bronchi secondary to destruction of elastic connective tissue may account for exacerbations of expiratory airflow obstruction. On the other hand, finding localized, posttraumatic chondromalacia has very different therapeutic implications. On the basis of these bronchoscopic determinations, the choice of performing an open surgical approach or bronchoscopic therapeutic correction may be made.

Bronchoscopic examination generally permits evaluation and localization of congenital or postsurgical pathological changes in bronchial integrity, such as tracheoesophageal or bronchopleural fistulas. Bronchoscopic observation and early diagnosis of bronchial rupture after chest trauma also greatly influence further therapy and prognosis. The same is true for evaluation of postsurgical anastomoses following reconstructive surgery or lung transplantation.

Advances in airway management of critically ill patients who require prolonged intubation or tracheotomy have resulted in reduction in the incidence of tracheal injuries. Tracheal injuries documented by bronchoscopy are not rare, however. Important complications of tracheotomy include tracheal stenosis, tracheomalacia, and tracheoinnominate fistula. Complications specific to the use of percutaneous tracheotomy, which is increasingly used in the intensive care unit, include flaps of cartilage protruding into the tracheal lumen and extraluminal placement of the tracheostomy tube. Such complications can have significant bearing on clinical outcome.

Evaluation of Tracheobronchial Mucosa

Careful examination of the mucosal surface is crucial in the formulation of differential diagnosis. Rapid development of

granulation tissue is frequently associated with reaction to a foreign body. Inflammatory mucosal reactions, although not very characteristic, should raise the possibility of mycobacterial infection, nonspecific viral and nonviral infections, and other granulomatous diseases, such as sarcoidosis.

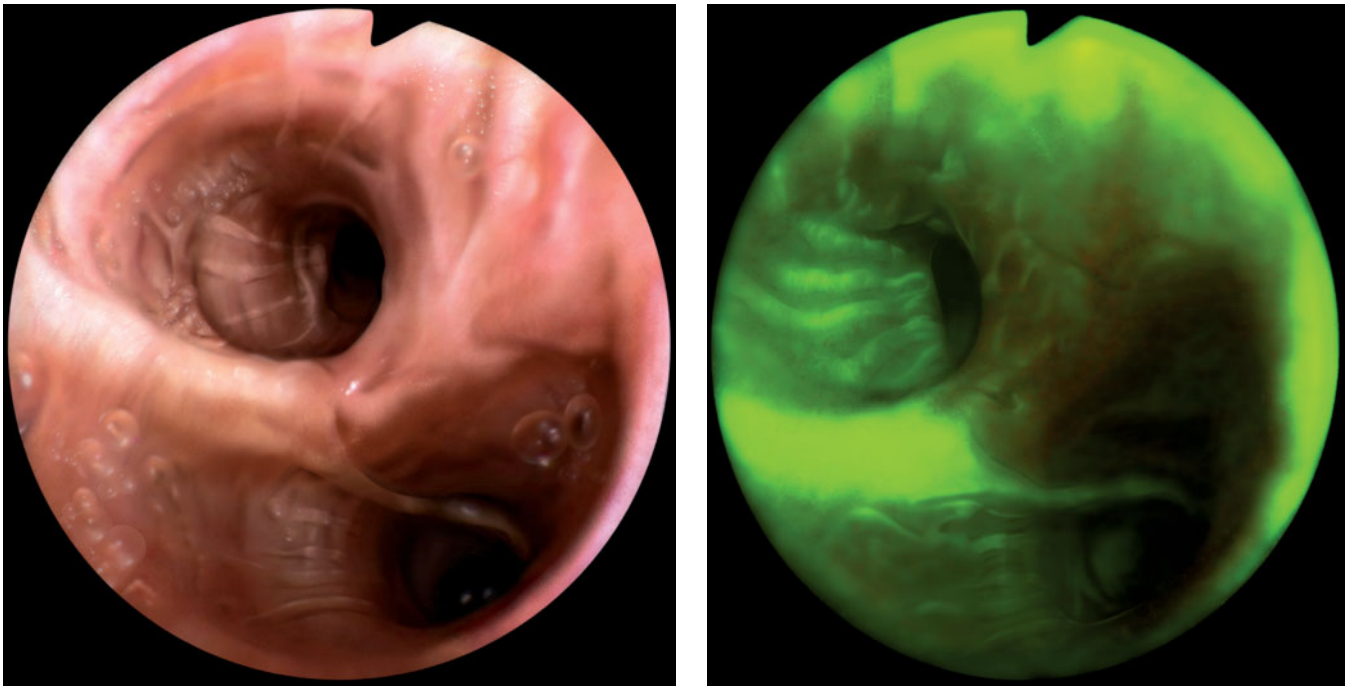
The distinction between normal, pale-pink mucosa and hypervascular areas in the tracheobronchial tree may provide important diagnostic clues. Most frequently, changes in mucosal coloration are associated with an inflammatory reaction due to bronchitis. These findings are, however, very distinctive from small hemangiomas or vascular distentions due to compression by enlarged, neoplastic lymph nodes. Similarly, a network of small mucosal lymphatics may be visible, with lymphatic interruption due to surgery, radiation therapy, fibrosis, or malignancy. This is most frequently associated with local edema, which contributes to airflow obstruction. In addition, distinct and characteristic mucosal discoloration can be observed in Kaposi's sarcoma.

Ulcerations of the mucosa are more characteristic of Wegener's granulomatosis or malignancy. Loss of the usual mucosal luster and presence of a roughened surface may alert the expert bronchoscopist to an early infiltrative or neoplastic process. Previously sustained injuries are characterized by the formation of mucosal and submucosal fibrosis, resulting in airway retraction or distortion.

Recently, various photosensitizers have been applied for the bronchoscopic evaluation of the tracheobronchial mucosa. Photosensitizers, such as hematoporphyrin derivative (HPD) and Δ-aminolevulinic acid (Δ-ALA), are retained more selectively by neoplastic tissues. When stimulated by blue light (wavelength approximately 440 nm), tissues containing these photosensitizers (i.e., tumors, but not normal tissues) emit weak fluorescence in the red spectrum (wavelength approximately 630 nm). The low-intensity fluorescence can be captured by specially designed image intensifiers. The technique may be helpful in cancer detection or in the delineation of tumor limits. Use of photosensitizers, however, is cumbersome and associated with skin photosensitivity and risk of sunburn. For these reasons, photosensitizer-mediated photodynamic techniques are not practical for diagnostic purposes.

Recent technological developments permit observation and analysis of tracheobronchial mucosal surfaces using the discriminant characteristic of tissue autofluorescence. It is well known that when stimulated with light of a specific wavelength, normal tissues emit specific fluorescence. Changes in the structural integrity of the same tissues due to pathological processes modify or suppress the autofluorescence. The fluorescent emissions are too low in intensity to be seen by the human eye. With the use of a monochromatic light source, computer-controlled image analysis, and a sophisticated camera attached to a fiberoptic bronchoscope, the airways can be examined for varying degrees of autofluorescence as an indicator of early-stage malignant changes (Fig. 36-2).

The acquisition of images is obtained in real-time and helps in the detection of minute areas of change in normal



A *B*

Figure 36-2 White light and autofluorescence images of carcinoma in situ. Standard white light bronchoscopy demonstrates normal-appearing mucosa. Fluorescence endoscopy demonstrates abnormal-appearing tissue (reddish brown area), which was confirmed as carcinoma in situ by histological evaluation. *(Courtesy of Xillix Technologies Corp.)*

tracheobronchial mucosal fluorescence. Biopsies from areas of abnormal fluorescence increase the rate of detection of small, premalignant (dysplasia) or early malignant (carcinoma in situ) lesions in the tracheobronchial tree. Confirmation is provided by biopsy of the suspect or abnormal areas under direct bronchoscopic control, followed by pathological review. Attempts are underway to develop bronchoscopic spectrophotometric techniques for study of metabolic functions in vivo and performance of "optical biopsies," which provide information on specific tissue components—e.g., changes in intracellular concentrations of nicotinamide adenine dinucleotide phosphate (NADPH) or other cellular constituents. Another promising technique, opitical coherence tomography (OCT), is analogous to ultrasound imaging except that infrared light waves, rather than acoustic waves, are used. At present, OCT can resolve structures as small as 3 μm, rendering this imaging technique superior to conventional CT or magnetic resonance imaging for detecting microscopic airway abnormalities. The ability to acquire such precise views in real-time may have important clinical implications in the near future.

Evaluation of Hemoptysis

One of the most frequent indications for bronchoscopy is hemoptysis. Bronchoscopic evaluation can be of help in determining the precise location and source of bleeding. The choice of instrument (rigid vs. flexible scope) and timing of the procedure are dictated by clinical circumstances. Studies have shown that active bleeding and its site are visualized more commonly with early bronchoscopy (within 48 hours) than with more delayed examination. In the case of a normal chest radiograph and hemoptysis, traces of bleeding are commonly seen, but not the site of origin. In these circumstances, examination using an ultrathin flexible instrument may be beneficial in identifying the source of bleeding in a peripheral airway, once the more proximal airways have been cleared of blood by the therapeutic scope. In some instances, bronchoscopy becomes useful not only as a diagnostic method, but also as a therapeutic procedure (see below).

Evaluation of Peribronchial Structures

The trachea and bronchi are surrounded by mediastinal and parenchymal structures. Developmental or pathological changes in these organs may be noted during bronchoscopic evaluation. An enlarged goiter or thymus can compress upper airways, resulting in airflow obstruction. Lymphadenopathy may produce structural changes, including widening of the carina due to subcarinal involvement and compression of other bronchi—as, for example, in the right-middle-lobe syndrome. Calcification of peribronchial lymph nodes may result in erosion of the bronchial wall and formation of a broncholith. These lesions are potential sources of obstruction, infection, or dangerous hemoptysis.

Development of the techniques of transbronchoscopic needle aspiration (TBNA) and biopsy (TBNB) has permitted sampling of peribronchial lymph nodes (Fig. 36-3). These transbronchial approaches provide us with diagnostic options that pose much less risk and a lower complication rate than mediastinoscopy; in addition, they are less costly.

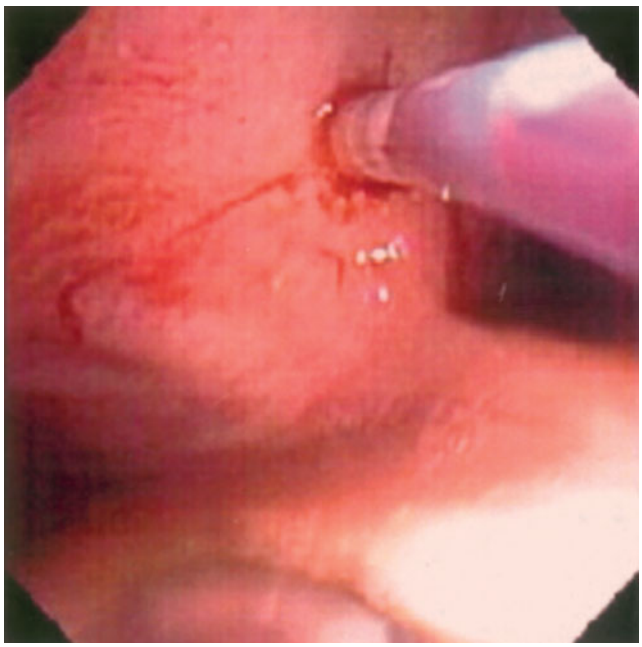


Figure 36-3 TBNA of subcarinal lymph node using a 21-gauge transbronchial needle.

Diagnosis and staging of lung carcinoma are the major indications for use of TBNA. The procedure is particularly useful for patients who are marginal or poor surgical candidates; in these patients, more invasive approaches, such as mediastinoscopy or mediastinotomy, may be obviated. TBNA has proven particularly useful with the employment of rapid on-site evaluation (ROSE), where a cytopathologist present in or near the bronchoscopy suite can evaluate obtained specimens in real-time. However, because of a high false-negative rate (approximately 25 percent), a negative result with TBNA should prompt consideration of more invasive staging methods (e.g., mediastinoscopy). A positive TBNA is more likely in the presence of significant adenopathy noted on CT scanning, the presence of endoscopically visible tumors, subcarinal lymph nodes greater than 2 cm in diameter, or an abnormal-appearing carina.

The use of image guidance with TBNA, such as CT fluoroscopy, electromagnetic guidance, or EBUS, is promising and may provide higher diagnostic yields with TBNA. The use of EBUS in combination with TBNA for the evaluation of mediastinal adenopathy has been most extensively evaluated. Endobronchial ultrasound-directed TBNA (USTBNA) appears to increase diagnostic accuracy and may be particularly useful in centers where ROSE is unavailable.

Until recently, the major limitation with USTBNA has been the need for the EBUS and TBNA components to be performed sequentially. A newly developed bronchoscope with an additional working channel that incorporates EBUS allows

for real-time needle insertion and aspiration under direct lymph node visualization. Early studies suggest an improved diagnostic yield for hilar and mediastinal adenopathy using this modality.

Recently, the use of TBNA has been extended to the diagnosis of benign processes, including infection and granulomatous disease. In HIV-positive patients with mediastinal adenopathy, TBNA can provide a definitive diagnosis in as many as one-third of the patients, sparing them more invasive procedures. The ability to obtain core biopsy specimens using a TBNA histology needle has proven particularly useful for diagnosing sarcoidosis. Traditionally, sarcoidosis is documented by the presence of noncaseating granulomata in lung parenchyma obtained by transbronchial biopsy during fiberoptic bronchoscopy. However, the sensitivity is only about 60 to 70 percent, and many patients require further invasive testing, such as surgical lung biopsy. The addition of TBNA to transbronchial biopsy can provide the diagnosis in over 85 percent of cases of sarcoidosis.

Performance of Bronchial and Parenchymal Biopsies

Improvements in bronchoscopic instrumentation since the days of Chevalier Jackson have permitted performance of endobronchial biopsies, as well as biopsy of peripheral lung lesions. Knowledge of the underlying disease process has a significant influence on the choice of study procedures and risk of complications. In the case of diffuse lung diseases, such as sarcoidosis, use of fluoroscopy has not been demonstrated to improve the diagnostic yield of transbronchial biopsies. Fluoroscopy is useful, however, in providing information regarding the proximity of the forceps to the pleura and in more rapidly establishing the diagnosis of complications (e.g., pneumothorax).

Bronchoscopically visible lesions are generally biopsied with minimal risk; if bleeding occurs, it can usually be controlled easily (Fig. 36-4). The diagnostic yield of bronchoscopy for peripheral lesions depends on a number of factors, including lesion size, its location in the lung, and on the relationship between the lesion and bronchus. The presence of a bronchus sign on chest CT predicts a much higher yield of bronchoscopy for peripheral lung lesions. In these cases, fluoroscopy is mandatory to assure proper positioning of the brush, biopsy forceps, or needle. An exciting new area is the potential application of EBUS in evaluation of peripheral pulmonary nodules. EBUS allows for acquisition of diagnostic tissue via transbronchial biopsy with fewer passes and may permit differentiation between benign and malignant nodules based entirely on nodule architecture. In the future, peripheral EBUS nodule characterization may even obviate the need for pathological diagnosis in certain patients with suspicious nodules.

The diagnosis of various infectious diseases can be established using a variety of transbronchoscopic sampling techniques. The role of bronchoscopic biopsy has been reaffirmed in immunocompromised hosts, in whom documentation of the precise pathogen is crucial for appropriate therapy. For example, while the presence of cytomegalovirus in bronchoalveolar lavage fluid may not be diagnostic, documentation of intracellular inclusion bodies on a biopsy specimen is practically pathognomonic. Simple, cost-effective transbronchoscopic tissue sampling can obviate much more complicated, expensive, and higher-risk transthoracic needle biopsy or thoracic surgical procedures.

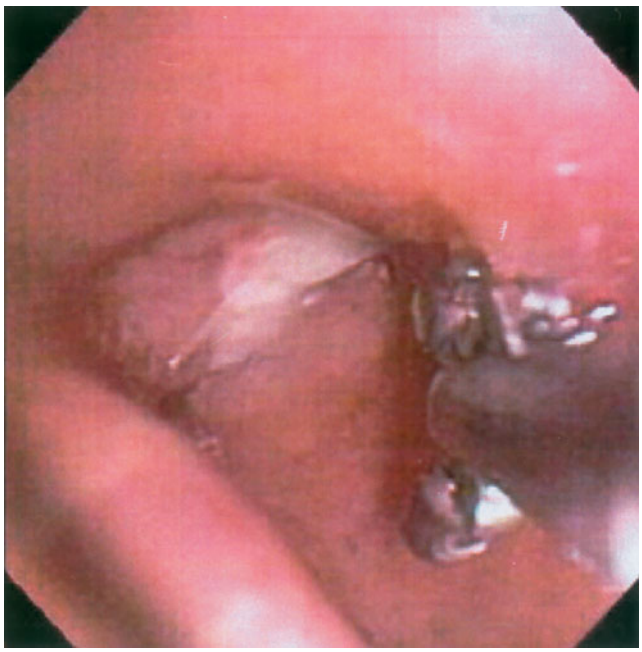


Figure 36-4 "Hot" forceps biopsy of a vascular endobronchial lesion. Use of the electrocautery forceps allows for safe, hemostatic biopsy of friable or vascularized endobronchial lesions (such as bronchial carcinoids), while obtaining pathologically interpretable tissue biopsy specimens.

Sampling of Airway and Alveolar Constituents

Bronchoscopy provides easy and relatively safe access to material in the tracheobronchial tree and distal alveolar spaces. A variety of studies are routinely performed on specimens obtained from the airways and alveolar spaces using several techniques. For example, aspirated secretions can be sent for microscopy and culture to determine the offending organism in cases of infection or suspected infection. Cytologic analysis of bronchoscopically obtained materials can provide proof of malignancy. With the advent of lung transplantation, the success of the procedure depends, in large measure, on the early diagnosis of rejection or infection in these immunocompromised subjects. The most commonly employed bronchoscopic techniques for sampling the airways and alveolar spaces include "bronchial washing," bronchial brushing (see above), and bronchoalveolar lavage.

Bronchoalveolar Lavage

A very useful bronchoscopic technique is bronchoalveolar lavage (BAL). BAL is safe, even in critically ill patients, when

biopsy or brushings are not recommended because of the risk of bleeding. Normal saline solution, devoid of any bacteriostatic material, is instilled into distal airspaces through the "wedged" bronchoscope and then aspirated through the instrument's suction channel. The fluid collected in this manner is analyzed for gross appearance to detect possible alveolar hemorrhage. The fluid may also be subjected to a variety of tests, depending on the clinical circumstances: microbiologic testing, specific cytologic analysis and cell count, immunologic parameters, presence of various biochemical mediators related to pathological processes, tissue markers, polymerase chain reaction, electron microscopy, flow cytometry, and DNA probes.

The value of BAL is well documented in the diagnosis of diffuse parenchymal diseases, such as eosinophilic pneumonia, eosinophilic granuloma, and pulmonary alveolar proteinosis. It remains investigational in the evaluation of many other diseases—e.g., sarcoidosis, hypersensitivity pneumonitis, and idiopathic pulmonary fibrosis. Overall, the diagnostic yield of BAL is very much dependent on specific patient characteristics, underlying pathological process, and many technical factors.

Application of Quantitative Microbiologic Techniques

Two bronchoscopic methods that are useful in the diagnosis of pulmonary infections are quantitative BAL and protected-specimen brush (PSB). They are, perhaps, most useful in the setting of suspected ventilator-associated pneumonia (VAP), wherein a patient who is endotracheally intubated and receiving mechanical ventilation has signs of infection and an abnormal chest radiograph. Intubated patients experience colonization of their upper and lower airways with nosocomial organisms. Because of an abnormal mucociliary clearance mechanism, these patients are at greater risk for developing pulmonary infections. In addition, mechanically ventilated, intubated patients are often treated empirically with broad-spectrum antibiotics and, therefore, are at greater risk for infection with resistant organisms and unusual lower respiratory tract pathogens.

When quantitative cultures are used, growth above a certain threshold is required to diagnose VAP, whereas growth below the threshold is assumed to be due to colonization or contamination. The American Thoracic Society's position statement allows for the use of either a quantitative or semi-quantitative strategy (e.g., tracheal aspirates) in suspected VAP. However, evidence suggests that quantitative cultures are more reliable in documenting the presence of pneumonia.

Protected Specimen Brush

PSB uses a double-catheter system in which an outer cannula and distal, biodegradable plug protect the bronchoscopic brush within the inner cannula from contamination with secretions in the upper airway and suction channel of the bronchoscope. When the bronchoscope is positioned proximal to the segmental orifice of interest, the PSB inner cannula is advanced into a subsegment and the protective distal plug ejected. The brush is then advanced peripherally, rotated gently, and retracted into the inner cannula. The inner cannula is subsequently retracted into the outer cannula and the bronchoscope removed from the airway. The distal portion of the catheter is cleaned with 70 percent alcohol and the brush clipped into saline solution under sterile conditions. The PSB is then submitted for quantitative bacterial culture within 15 minutes of performance of the procedure. The threshold for diagnosis of VAP with PSB is 10^3 colony-forming units (CFU) per milliliter. PSB appears to have higher specificity than sensitivity for the presence of VAP—a positive result greatly increases the likelihood of pneumonia being present.

Quantitative Bronchoalveolar Lavage

Quantitative BAL entails the performance of a standardized BAL, with infusion of at least 120 ml of saline for adequate sampling of a pulmonary subsegment. Quantitative culture of the aspirated material is performed to determine the number of CFU recovered. For quantitative BAL, a threshold of 10^4 or 10^5 CFU per milliliter is used for the diagnosis of pneumonia. The detection of pneumonia by quantitative BAL culture has a sensitivity of 42 to 93 percent and a specificity of 45 to 100 percent.

Quantitative BAL may be superior to PSB in the diagnosis of VAP, since BAL samples a much larger proportion of lung parenchyma; PSB samples only a single bronchial segment. Protected BAL, which requires the use of a balloon-tipped catheter with a distal ejectable plug inserted through the suction channel of the bronchoscope, has a greater specificity than standard BAL. A quantitative BAL strategy which uses detection of intracellular organisms in recovered cells to diagnose pneumonia provides information in a rapid time frame, but it does not identify the etiologic pathogen. BAL techniques incorporating molecular testing in addition to microbiologic cultures are also being evaluated.

TECHNIQUES USED IN THERAPEUTIC BRONCHOSCOPY

Since the introduction of bronchoscopy, the technique has been used not only for observation but also for treatment of local airway disorders. As with any clinical intervention, the guiding rule for treatment always remains, "If I can do no good, I will at least do no harm."

Rigid Bronchoscopic Debulking or Balloon Dilatation

Rigid bronchoscopes have beveled tips, which are ideal for coring through large tumors in the airways and for dilating strictures. In addition, they have large internal diameters, which facilitate debridement of tumors, evacuation of

clots, and ventilation. Despite advances in other adjunctive endoscopic techniques, rigid bronchoscopic recanalization remains the treatment of choice for life-threatening tracheobronchial obstruction.

In less urgent cases of obstruction caused by malignant tumors, balloon dilatation has become an attractive alternative to dissection using a blunt rigid bronchoscope. High-pressure angioplasty catheters with various balloon lengths and diameters were commonly used in the past. Currently available balloons, designed specifically for tracheobronchial use (e.g., CRE balloon, Boston Scientific Corp., Cambridge, MA), are expandable to specific diameters by application of defined atmospheric pressure. The balloons are inserted through the working channel of the bronchoscope under fluoroscopic guidance or direct visualization. The balloon, filled with saline or radiopaque liquid, is inflated at the site of the stenosis until a smooth, uniform lumen of predictable diameter is attained. Major risks of the technique are rupture of the bronchial wall, bleeding, and postprocedure airway edema. This technique is often used in combination with bronchoscopic laser therapy and placement of a tracheobronchial stent for the treatment of airway stenosis.

Balloon bronchoplasty has also been used successfully to treat other disorders, including tuberculosis, fibrosing mediastinitis, and strictures associated with lung transplantation or prolonged intubation. The technique is less successful when used alone to treat stenosis accompanied by extrinsic airway compression, and it is contraindicated in patients with tracheobronchomalacia.

Although in the majority of cases, balloon dilatation is performed while the patient is under general anesthesia, treatment of many airway lesions (e.g., short fibrotic strictures) can be accomplished with use of a flexible bronchoscope while the patient is under conscious sedation. Complications of balloon dilatation of airway lesions include bronchospasm, chest pain, airway perforation, pneumothorax, and pneumomediastinum.

Endobronchial Laser Therapy

Perhaps, the most widely known technique in interventional pulmonology is laser bronchoscopy. Lasers produce a beam of monochromatic, coherent light that can induce tissue vaporization, coagulation, hemostasis, and necrosis. Although useful in the ablation of endoluminal malignant tumors, bronchoscopic laser therapy is also beneficial in the treatment of other tracheobronchial disorders, including inflammatory strictures, obstructive granulation tissue, amyloidosis, and benign tumors such as hamartomas.

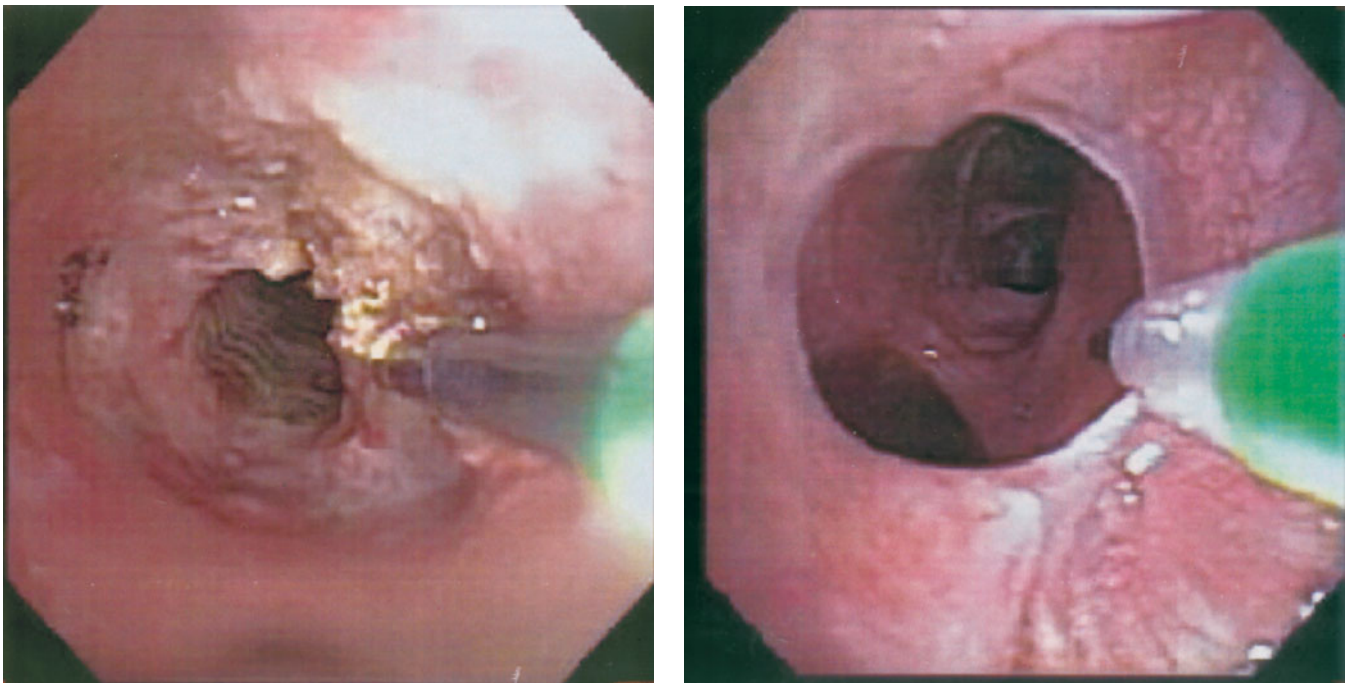
Since the initial report of endobronchial laser ablation of an obstructive neoplasm by Laforet in 1976, several types of lasers have become available for the management of tracheobronchial obstruction. The carbon dioxide (CO_2) laser, used mainly by otolaryngologists, allows shallow penetration of tissue (to a depth of 0.1 to 0.5 mm) and highly precise cutting; however, it has minimal hemostatic properties and, traditionally, was used in conjunction with rigid bronchoscopy. Recently developed technology has facilitated delivery of CO_2 laser energy via unique reflective fiberoptic probes (OmniGuide, Inc., Cambridge, MA), allowing applications with flexible laryngoscopy and flexible bronchoscopy. The CO_2 laser, with its fine control of tissue ablation, is ideal in the management of laryngeal lesions (e.g., webs, vocal cord nodules, etc).

Interventional pulmonologists primarily use the neodymium:yttrium aluminum garnet (Nd:YAG) laser, which provides deeper penetration of tissue (to a depth of 3 to 5 mm), superior photocoagulation, and improved hemostasis, but with less precision in cutting. Photocoagulation using an Nd:YAG laser can be performed through a rigid or flexible bronchoscope, but rigid bronchoscopy remains the preferred method for treatment of patients who have respiratory distress due to severe tracheobronchial obstruction or active intraluminal bleeding.

Use of a laser in the tracheobronchial tree requires careful consideration of the anatomic location and configuration of the lesion. If the lesion is in close proximity to the esophagus or pulmonary artery, endobronchial laser therapy poses a risk of fistula formation. Use of laser therapy in a patient with tracheobronchial narrowing due to extrinsic compression may result in perforation of the airway. In addition, prolonged obstruction of the airway (for more than 6 weeks) may lead to refractory atelectasis or bronchiectasis, minimizing the benefits of endobronchial recanalization. The potential for airway recanalization in the setting of long-standing endoluminal obstruction can be assessed by bronchography or perfusion scanning.

Although endobronchial laser therapy is generally safe and well tolerated, complications may arise and include cardiac arrhythmias, airway perforation, pneumothorax, hemorrhage, hypoxemia, or endobronchial fire (ignition of the bronchoscope or endotracheal tube). In rare cases, pulmonary edema or fatal pulmonary venous gas embolism has been reported. Patients with standard silicone endotracheal tubes or silicone tracheobronchial stents, and those who require high concentrations of supplemental oxygen, are at increased risk for endobronchial fire. Fortunately, the overall risk is less than 0.1 percent. The overall rate of mortality attributable to endoscopic laser therapy is quite low, not exceeding 0.3 to 0.5 percent in several large series.

Success rates and complications directly related to laser therapy are not different when the procedure is performed under general anesthesia through the rigid bronchoscope or under topical anesthesia and conscious sedation through a flexible bronchoscope. Nd:YAG laser photoradiation therapy has demonstrated a single-modality recanalization rate of greater than 90 percent for endobronchial obstruction of large central airways, but it is less successful with peripheral lesions or with associated extrinsic airway compression. Laser therapy may improve the likelihood of successful weaning from mechanical ventilation in patients with advanced lung cancer who present in respiratory failure. In addition, photocoagulation with an Nd:YAG laser is an invaluable treatment for patients with airway obstruction due to benign endoluminal tumors.



A *B*

Figure 36-5 Electrocautery. Use of electrocautery accessory devices for *(A)* treatment of a malignant endobronchial lesion with associated tissue destruction (cautery probe) or for *(B)* management of an endobronchial web related to posttransplant anastomotic stricture (cautery knife).

Endobronchial Cryotherapy and Electrocautery

Cryotherapy and electrocautery are excellent, cost-effective alternatives to laser therapy for the management of tracheobronchial obstruction. The depth of penetration and resulting injury are, however, much more difficult to control. As with the Nd:YAG laser, both electrocautery and cryotherapy can be administered through a rigid or flexible bronchoscope. The effects of electrocautery on tissue are similar to those of the Nd:YAG laser, with tissue destruction induced by intense coagulation and vaporization (Fig. 36-5). Argon plasma coagulation (APC) is similar to electrocautery, except that it uses argon gas to conduct the electrical current rather than a contact probe. APC has a depth of penetration of only a few millimeters and is, therefore, more suitable for treatment of superficial and spreading lesions. Cryotherapy probes induce tissue necrosis through hypothermic cellular crystallization and microthrombosis. Specially designed probes are inserted via the bronchoscope until they contact the target tissue. Through the channel in the probe, liquid nitrous oxide or liquid nitrogen is introduced, resulting in the rapid creation of an "ice ball" (approximate temperature, −20°C) at the end of the tip. This freezing effect is maintained for about 20 s; the area is then rewarmed, resulting in thawing. Treatment of an endobronchial lesion using a cryoprobe requires several freeze-thaw cycles.

Cryotherapy and electrocautery have been used successfully to relieve airway obstruction caused by benign tracheobronchial tumors, polyps, and granulation tissue. These techniques—cryotherapy in particular—may be superior to lasers for distal lesions because of the lower risk of airway perforation. Similarly, carcinoma in situ and mucosal dysplasia may be adequately treated using cryotherapy or electrocautery alone, although multiple treatments may be required for optimal results. Cryotherapy is a safe treatment for infiltrative lesions of the airway, and according to anecdotal reports, the technique has proved beneficial in patients with posttransplantation anastomotic stenosis and in those with foreign-body aspiration. In fact, cryotherapy may be the modality of choice for the removal of endobronchial blood clots and mucus plugs.

Endobronchial cryotherapy is generally not effective for paucicellular lesions that are relatively impervious to freezing, such as fibrotic stenoses, cartilaginous or bony lesions, or lipomas. Furthermore, endobronchial cryotherapy, unlike either laser therapy or electrocautery, cannot be used to achieve rapid relief of symptomatic airway obstruction. The most common serious complication of both electrocautery and cryotherapy is hemorrhage. The estimated incidence of clinically significant bleeding in patients treated with electrocautery is 2.5 percent.

Endobronchial Brachytherapy

Brachytherapy is the treatment of tumors with radiation delivered internally through implanted radioactive seeds or inserted wires. This technique ensures the delivery of a maximal therapeutic dose of radiation to the tumor with

a minimal effect on normal surrounding tissues. Endobronchial brachytherapy involves the bronchoscopic insertion of a thin, hollow catheter through a malignant obstruction under fluoroscopic guidance. A radioactive implant is then inserted into the catheter and left in position for a predetermined period (2 to 40 hours, depending on the dose rate).

In 1922, Yankauer reported the use of rigid bronchoscopic brachytherapy for the palliation of airway obstruction due to malignant tumors. Modern techniques, including the use of flexible bronchoscopes, polyethylene afterloading catheters, and ^{192}iridium implants, were first described in 1983. Since the development of techniques involving high dose-rate delivery in the 1980s, endobronchial brachytherapy has become a particularly attractive option for outpatient treatment.

Relief of airway obstruction is the primary goal of endobronchial brachytherapy, although curative treatment may be attempted in conjunction with external-beam radiation in selected patients. Brachytherapy is safest and most effective for central airway lesions, although in one study, small peripheral tumors proved to be more responsive than bulkier central tumors. Among patients with obstruction due to malignant tumors, rates of recanalization range from 60 to 90 percent, with decreased dyspnea, cessation of hemoptysis, and relief of cough in most cases. Brachytherapy has also been used for the prevention and treatment of airway stenosis related to recurrent growth of granulation tissue in patients with lung transplants.

Endobronchial brachytherapy may require multiple treatments to be effective. It is generally used as an adjunct to either Nd:YAG photocoagulation or conventional external-beam irradiation in an effort to achieve both rapid and sustained recanalization in patients with obstruction due to malignant tumors. Brachytherapy may also be administered in conjunction with placement of an endobronchial stent in patients with extrinsic compression of the airways due to malignant tumors. Brachytherapy works best with submucosal and peribronchial malignant disease.

Serious complications of brachytherapy include massive hemoptysis and fistula formation. Because of the risk of fatal hemorrhage, every effort should be made to rule out involvement of central vessels before treatment is administered. The incidence of serious complications varies widely, with rates as low as 0 to 10 percent in some of the largest studies, and as high as 30 to 40 percent in smaller studies.

Photodynamic Therapy

Photodynamic therapy (PDT) is currently approved by the Food and Drug Administration for the palliation of airway obstruction caused by malignant tumors and as an alternative to surgery in selected patients with minimally invasive central lung cancer. PDT works on the principle that certain compounds, such as hematoporphyrin derivatives, function as photosensitizing agents, rendering malignant cells susceptible to damage from monochromatic light. Tumor necrosis occurs as a result of cellular destruction through the generation of oxygen-free radicals or by ischemic necrosis mediated by vascular occlusion resulting from thromboxane A_2 release. The selective effect of PDT on malignant cells is thought to be due to the differential uptake and retention of photosensitizing agents in neoplastic cells rather than in normal cells. This selectivity effect appears to be most pronounced approximately 24 to 48 hours after infusion of the photosensitizing agent. For this reason, bronchoscopic treatment of target lesions is often performed 1 to 2 days after the agent has been injected. Given the delayed onset of action of PDT, it is not useful in patients with acute respiratory distress from tracheobronchial obstruction. Frequent bronchoscopies are often required to debride necrotic tissue.

Ideal candidates for PDT include patients with airway obstruction due to malignant polypoid endobronchial masses, those with minimal extrinsic airway compression, and patients with minimally invasive tumors of the central airways. Although surgical resection remains the treatment of choice for early lung cancer, some patients refuse surgery or are deemed inoperable because of high surgical risk. PDT may represent an appropriate alternative. Response rates are highest in patients with small tumors and minimal depth of penetration. In patients with bulky tumors, endobronchial PDT may substantially reduce the obstruction, with objective increases in spirometric measurements and subjective improvements in dyspnea and the quality of life. Metastatic tumors have also been treated successfully with PDT. Complications of PDT include increased skin photosensitivity and hemoptysis resulting from extensive tumor necrosis.

Tracheobronchial Stenting

The medical term "stent" was first used to denote a device that supported the healing of gingival grafts, developed by the British dentist, Charles R. Stent. The term has since been used to refer to any device designed to maintain the integrity of hollow tubular structures, such as the coronary arteries and the esophagus. Anecdotal reports of attempts to use stents in the tracheobronchial tree date back to 1915. The Montgomery T tube, designed in the 1960s, was the first reliable, dedicated airway stent. However, stent implantation in the lower trachea and bronchi did not become standard medical practice until Dumon's 1990 report on the safety and ease of placement of a dedicated airway stent made of silicone.

Two main types of endobronchial stents are in use today: tube stents made of silicone or plastic and self-expandable metallic stents (SEMS). Silicone stents, including the Dumon stent, are usually placed via rigid bronchoscopy while the patient is under general anesthesia. These stents are inexpensive and easy to remove from the airway; they provide protection from tumor ingrowth and cause minimal irritation to adjacent normal tissues. Potential complications of silicone stents include migration, formation of granulation tissue, and inspissation of secretions. Bifurcated silicone and composite stents are also available for the palliation of distal tracheal and main carinal lesions. These stents have been

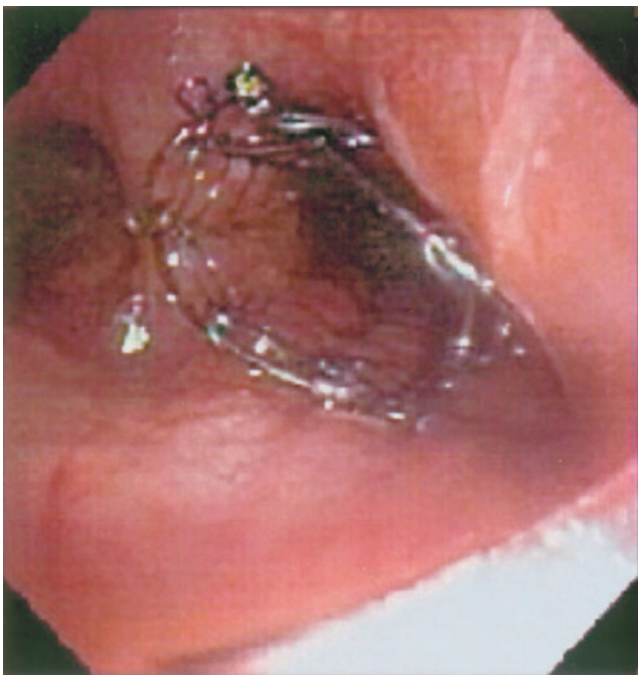


Figure 36-6 Self-expandable metallic stent (SEMS). Uncovered stent placed in right main-stem bronchus for malignant extrinsic compression (Ultraflex, Boston Scientific Corp., Cambridge, MA).

effective in the management of carinal compression associated with malignant tumors, tracheoesophageal fistulas, and tracheobronchomalacia.

Unlike silicone stents, SEMS can be placed with the use of a flexible bronchoscope, and they are less likely to migrate and are more likely to preserve normal mucociliary clearance (Fig. 36-6). Metal stents remain fairly expensive, however, and if they are misplaced in the airway, rigid bronchoscopy is often required for their removal. In addition, mucosal inflammation and the formation of granulation tissue are common at the proximal and distal ends of metal stents, and endoscopic intervention may be required to restore airway patency. Long-standing SEMS often require rigid bronchoscopic techniques for complete removal. For all these reasons, SEMS are not recommended for most patients with nonmalignant airway stenoses.

Endobronchial stents have a critical role in a multimodal endoscopic approach to both benign and malignant stenoses of the airways. Stenosis due to locally advanced bronchogenic carcinoma, for example, can be treated with a combination of endoscopic laser therapy and stent implantation in order to prevent respiratory failure. Stent placement can also be used to maintain airway patency after endobronchial brachytherapy or can be combined with laser therapy and balloon dilatation in the endoscopic management of fibrotic strictures.

Most studies of the efficacy of endobronchial stent placement have had impressive results. Dumon and colleagues reported excellent clinical outcomes and few complications with the use of silicone stents in patients with extrinsic airway compression due to malignant tumors, but a lower success rate among patients with tracheal stenosis caused by other disorders. The most common complications are stent migration, granulation tissue formation, and secretion inspissation. In limited studies, success rates, broadly defined as symptomatic relief, have ranged between 78 percent and 98 percent. In studies of patients who had been intubated because of respiratory failure due to unresectable tracheobronchial and mediastinal disease, stent placement facilitated extubation in nearly all the patients.

The benefits of stent placement appear to persist in patients who survive for a period of several months or years after implantation. Long-term follow-up data, however, are limited to benign disease, since the mean follow-up period in patients with airway compression due to malignant tumors does not usually exceed 3 to 4 months. Some authors have reported poor long-term results with use of metal stents in patients with fibro-inflammatory stenosis due to nonmalignant disorders. In addition, case reports describe massive hemorrhage associated with the use of stents in patients with extrinsic compression attributable to aneurysmal dilatation or congenital malformations of the aorta.

APPLICATIONS OF THERAPEUTIC BRONCHOSCOPY

Therapeutic bronchoscopy may be used in a wide variety of settings, the most common of which are described below.

Control of Hemoptysis

In cases of hemoptysis, bronchoscopy may be of value not only for diagnosis, but also for emergency management of endobronchial bleeding. Because of difficulties with visualization, instruments with large and maximally effective suction channels should be used. In assessment of massive bleeding, when the need to remove large clots is anticipated, rigid bronchoscopy is generally preferred.

When continuous suctioning of blood fails to clear the airways, other means can be used. An iced saline solution can be instilled along with vasoactive drugs, such as epinephrine, to induce spasm of the bleeding vessels. The bronchoscope itself can also be used to stem the bleeding by tamponade of the bleeding site or to occlude the lumen of the bronchus from which the bleeding originates. The same effect, perhaps with better local control, can be achieved using bronchoscopic balloon catheters. Specially designed catheters have been developed for introduction through the working channel of the flexible bronchoscope, some permitting subsequent removal of the scope while the tamponading balloon remains in place. Another effective method for control of visible sources of bleeding, particularly from endobronchial neoplasms, is Nd:YAG laser photocoagulation.

Endoluminal Airway Obstruction

Endoluminal obstruction of the tracheobronchial tree may result from various benign and malignant processes. The most

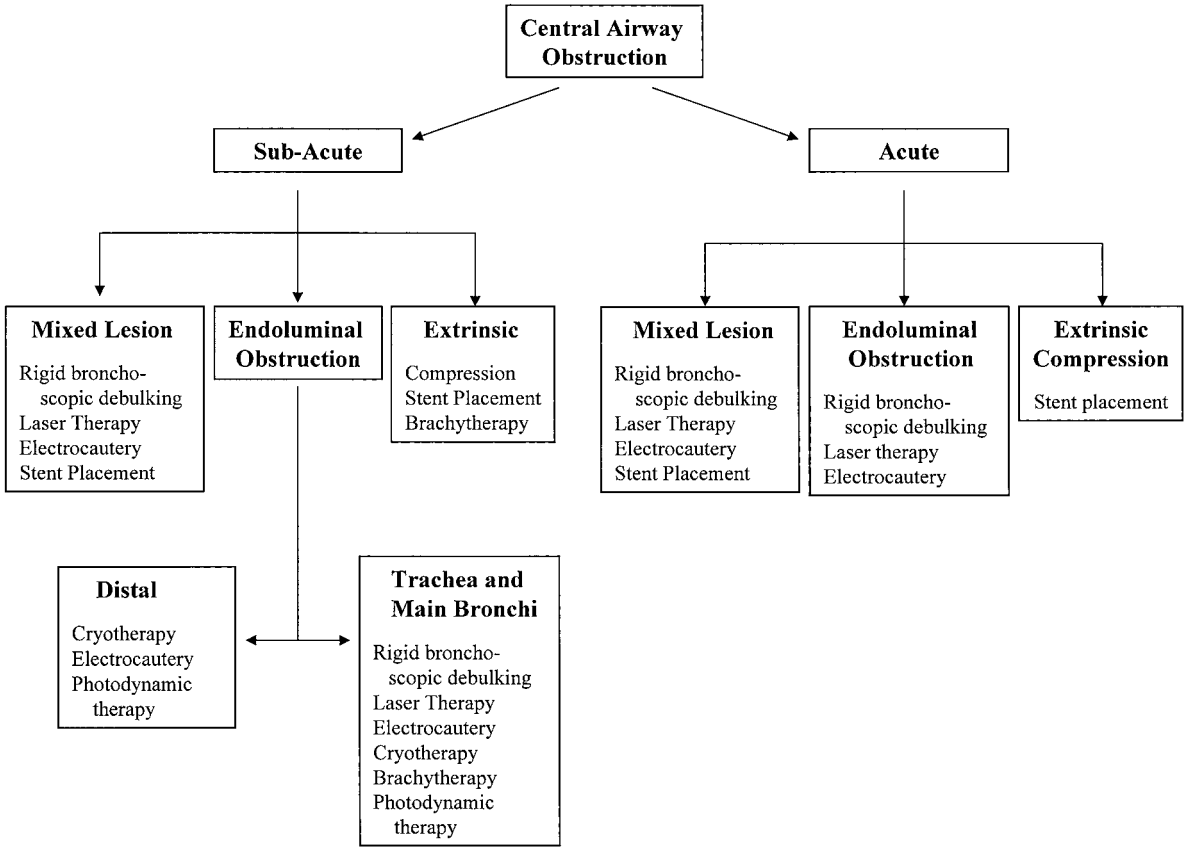


Figure 36-7 Algorithm for the management of central-airway obstruction due to malignant tumor. This treatment algorithm addresses both acute and subacute central-airway obstruction, as well as the location and type of lesion—characteristics that can be determined using CT and diagnostic bronchoscopy.

common cause of endobronchial obstruction is advanced bronchogenic carcinoma. In patients with inoperable tumors of the central airways, restoration of airway patency may provide palliation and may even prolong life, particularly in the case of impending respiratory failure.

Signs and symptoms of central airway obstruction vary, but often include wheezing, cough, stridor, hoarseness, hemoptysis, and chest pain. A careful pretreatment evaluation should be performed to distinguish symptoms attributable to focal tracheobronchial lesions from those related to underlying diffuse airflow obstruction, parenchymal lung disease, or both. Mild-to-moderate tracheal stenosis, for example, may contribute only marginally to the degree of dyspnea experienced by a patient with severe chronic obstructive lung disease. Although pulmonary function testing and thoracic imaging techniques such as computed tomography (CT) and magnetic resonance imaging may be useful in the evaluation of a patient with suspected obstruction of the central airway, bronchoscopy—either rigid or flexible—remains the diagnostic gold standard. Increasingly, however, three-dimensional reconstruction CT imaging—so-called "virtual bronchoscopy"—is being applied as a reliable, noninvasive method of assessing the nature and extent of airway obstruction.

The bronchoscopic approach to the management of endoluminal obstruction depends on the location of the lesion, presence or absence of associated extrinsic compression, and degree of clinical urgency (Fig. 36-7). Rigid-bronchoscopic debulking, with adjunctive laser therapy or electrocautery, is recommended when airway recanalization must be performed on an emergency basis. If endobronchial obstruction is accompanied by marked extrinsic compression, placement of a stent may be beneficial.

The complexity of a lesion is equally important in determining the best approach to resection. Tracheal webs, for example, are often managed by laser resection alone, whereas complex fibrotic strictures may warrant the combination of rigid-bronchoscopic or balloon dilatation, laser resection, and stent placement. For focal tracheal stenoses in low-risk patients, surgical resection and primary reanastomosis should remain the first-line therapy.

Extrinsic Airway Compression

Extrinsic airway compression usually results from malignant involvement of structures adjacent to the central airways, such as mediastinal lymph nodes or the esophagus, but it may be associated with a benign process, such as fibrosing mediastinitis,

tuberculosis, aneurysmal dilatation of the aorta, or sarcoidosis. Clinical signs and symptoms of extrinsic airway compression often mimic those of endobronchial obstruction. The diagnosis is established on the basis of bronchoscopic evidence of marked airway narrowing in the absence of an endoluminal mass. Chest CT, and increasingly, EBUS have important adjunctive roles in identifying anatomic structures external to the narrowed lumen.

Therapeutic options in the management of extrinsic airway compression are limited. Ablative endoscopic approaches, such as laser therapy, cryotherapy, PDT, and electrocautery are contraindicated because of the risk of airway perforation. Although some patients with malignant disease may benefit from endobronchial brachytherapy, tracheobronchial stent placement is the palliative treatment of choice for patients with symptomatic extrinsic airway compression.

Tracheobronchomalacia

Diffuse or focal tracheobronchomalacia is perhaps the most challenging disorder encountered by the interventional pulmonologist. Cartilaginous tracheobronchomalacia, as seen in patients with postintubation injury or relapsing polychondritis, reflects a loss of the structural integrity of the trachea or main-stem bronchi due to destruction of the airway's cartilaginous rings. Membranous, or crescentic, tracheobronchomalacia is manifested by airway collapse during exhalation as a result of laxity of the membranous portion of the trachea and main bronchi and is usually seen in patients with long-standing chronic obstructive pulmonary disease. Focal tracheobronchomalacia may be a complication of long-standing intubation or an anastomotic complication after lung transplantation. Tracheobronchomalacia is best diagnosed on the basis of flexible bronchoscopy, with the patient breathing spontaneously, although dynamic CT scanning, with images obtained on inspiration and expiration, is often helpful.

The endoscopic treatment of choice for patients with diffuse tracheobronchomalacia is the insertion of a standard or bifurcated silicone tracheobronchial stent. This intervention is more likely to be successful in patients with the cartilaginous type of tracheobronchomalacia than in those with the membranous type. For those patients with membranous tracheobronchomalacia, a trial of stenting with a silicone endoprosthesis should be performed. For those who benefit in terms of decreased respiratory symptoms and improved pulmonary function, surgical placation or buttressing of the posterior membrane can be performed with good results. For many patients with focal tracheobronchomalacia, surgery is the best therapeutic option. An alternative treatment for selected patients with diffuse tracheobronchomalacia is the pneumatic stent afforded by noninvasive ventilatory techniques, such as nasal continuous positive airway pressure.

Removal of Foreign Bodies

Foreign body aspiration is more likely to occur in children than in adults, with most occurring in children younger than 3 years. In children the obstruction most often involves a main-stem bronchus, whereas in adults the majority of foreign bodies are wedged distally, most commonly in the right lower lobe. Prior to the development of bronchoscopy, most foreign body aspirations resulted in high morbidity and mortality, commonly from postobstructive pneumonia. Until the introduction of the flexible bronchoscope, all foreign body removals were accomplished with the rigid bronchoscope. Even at present, it is well accepted that the rigid bronchoscope is the tool of choice for the removal of foreign bodies, especially in children. The advantage of the rigid instrument resides in its larger access channel, permitting use of more adaptable retrieval tools, and its ability to provide and control the patient's ventilation. In adults, a flexible bronchoscopy is the most common initial diagnostic tool and allows for successful removal of the foreign body in the majority of cases.

Various types of instruments have been developed for use with bronchoscopy for the removal of foreign bodies, including grasping forceps, balloon catheters, retrieval baskets, snares, and magnetic extractors. The choice of instrument depends on the specifics of the type of foreign body and its location in the tracheobronchial tree. Grasping forceps may be helpful in the retrieval of hard objects with an irregular surface. Smooth objects or organic material (e.g., nuts or food particles) may require use of expandable baskets or a combination of balloon catheters, suction devices, and grasping forceps. A frequently used technique employs a Fogarty balloon catheter to dislodge the foreign body and to bring it proximally into the trachea prior to attempting removal using other instruments (Fig. 36-8).

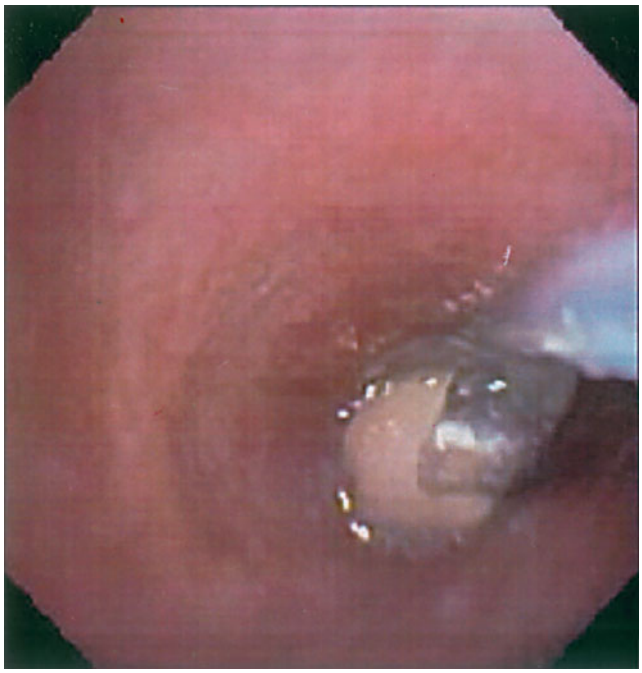


Figure 36-8 Flexible bronchoscopic-mediated foreign body removal from the distal right bronchus intermedius using balloon catheter.The Fogarty embolectomy balloon catheter is inflated beyond the foreign body and used to dislodge it to a more proximal location where it can be easily grasped and removed with a basket or snare.

Special attention should be paid to the period after removal of the foreign body—a time when complications can occur. Patients should be observed for any signs of hemoptysis or subglottic edema. Trauma inflicted during the extraction or forceful manipulation of instruments greatly accentuates the risk of postoperative complications, particularly if oversized instruments are used or if the bronchoscopy is prolonged.

Aspiration of Secretions

According to a survey of bronchoscopists conducted in the United States, removal of retained secretions is cited as a leading indication for therapeutic bronchoscopy. Bronchoscopic aspiration of secretions may be indicated in patients presenting with weakness of respiratory muscles (e.g., due to underlying neuromuscular disease or the postoperative state) or disorders leading to recurrent aspiration of food or excessive upper-airway secretions. In critically ill or mechanically ventilated patients, removal of secretions and mucous plugs usually can be rapidly achieved with the flexible bronchoscope. A flexible scope with a large-diameter suction channel should be chosen for this procedure. The nature of the retained material—its consistency and viscosity—may dictate frequent bronchoscopies to relieve segmental or lobar atelectasis due to inspissated mucous plugs. Underlying pulmonary diseases, such as bronchiectasis, may aggravate the retention of airway secretions. Bronchoscopic aspiration of secretions should not be considered "routine" in the postoperative period or in other conditions where good chest physiotherapy and maintenance of adequate pulmonary toilet can be more effective.

Two specific disorders are worth highlighting in the context of therapeutic bronchoscopy: pulmonary alveolar proteinosis (PAP) and allergic bronchopulmonary aspergillosis (ABPA). In PAP, BAL for clearance of alveolar material is a time-honored therapeutic procedure that may be facilitated by use of a bronchoscopic approach. In ABPA, lavage with saline solution may be insufficient to remove tenacious impactions (described as "plastic bronchitis"). In these circumstances, use of bronchoscopic forceps or snare may prove helpful.

Closure of Bronchial Fistulae

Flexible bronchoscopy can be a useful intervention in confirming the diagnosis of suspected bronchopleural fistula and specifying its precise location. Depending on the location and the size of the fistula, it can be approached bronchoscopically and an attempt made to seal it. Simple tamponade using the body of the flexible bronchoscope or a balloon catheter provides only temporary relief. Many different techniques have been employed, including introduction of irritating substances—e.g., silver nitrate, with the object of stimulating reactive granulation tissue formation. Several potentially useful agents have been described, including Gelfoam, autologous blood patch, cryoprecipitate, and thrombin injection to create fibrin clot. Small bronchial openings in an otherwise normal bronchus following thoracic surgery respond much better, with a higher rate of success of bronchoscopic sealing. It is much more difficult to achieve good obliteration of the fistula when the fistula is infected or is due to an underlying malignancy.

SAFETY FACTORS IN BRONCHOSCOPY

Bronchoscopy is a specialized procedure that requires extensive training. Familiarity with both the physiology and anatomy of the airways and other intrathoracic structures is essential. Any diagnostic or therapeutic manipulation should be considered in relation to the underlying condition of the patient, localization of the area of investigation, and other surrounding structures in the thorax. It is essential to develop good communication between the bronchoscopist and other members of the team. While the bronchoscopist concentrates on the field of work—which, as seen through the bronchoscope, is two-dimensional—other team members are responsible for monitoring the patient (oxygen saturation, blood pressure, heart rhythm, etc.) and checking and maintaining the adequacy of ancillary equipment (suction, oxygenation, and accessories such as forceps, balloons, catheters, and laser light guides). Risks are decreased if, for example, special attention is paid to the control of accessories during their manipulation beyond the tip of the bronchoscope. Premature deployment of the needle biopsy device or inappropriate bending of the bronchoscope while an instrument is inside the flexible portion can result in perforation of the bronchoscope. Activation of the laser with a broken light guide inside the bronchoscope or inadequate protrusion of the tip of the fiber beyond the bronchoscope may result in airway fires or severe burns to the patient. Attention to details and proper maintenance of the equipment, including accessories, enhance safety for the patient and staff. Diagnostic yield and therapeutic results are also improved. Last, but not least, proper knowledge and application of safety standards and maintenance procedures decrease the cost of bronchoscopy.

COMPLICATIONS OF BRONCHOSCOPY

Bronchoscopy is a potentially hazardous procedure. Complications are generally due to inappropriate preparation of patients before bronchoscopy, effects of local or general anesthesia, and manipulation of various instruments. Appropriate training and experience of the bronchoscopist and supporting team are crucial in reducing the rate of complications.

Anesthesia and Related Blood Gas Abnormalities

Approximately half of the life-threatening complications of diagnostic bronchoscopy are associated with premedication and use of topical anesthesia. Risk is significantly increased

in the elderly, and in those with serious concomitant illnesses. Predisposing factors include cardiovascular disease, chronic pulmonary disease, renal and hepatic dysfunction, seizures, and altered mental status. Mild sedation, anxiolysis, muscular relaxation, and anterograde amnesia increase patient cooperation and permit quicker and less traumatic procedures. Doses of benzodiazepines, opiates, anticholinergics, and topical anesthetics must be adjusted if there is underlying organ dysfunction. Conscious sedation using short-acting benzodiazepines (e.g., midazolam) offers significant anterograde amnesia; its use has reduced the incidence of potentially dangerous hypotension and respiratory depression.

Inadequate topical anesthesia potentiates coughing, gagging, and patient discomfort and increases the risk of injury during bronchoscopy. However, topical anesthetics such as lidocaine, the most frequently used agent, are absorbed systemically through the respiratory mucosa, increasing the risk of cardiac or central nervous system toxicity. These complications are more likely to occur in patients with underlying low cardiac output, hepatic dysfunction, and oropharyngeal candidiasis. Another, less frequent complication of excessive lidocaine use is methemoglobinemia and resultant tissue hypoxia.

Skillful manipulation of rigid and flexible bronchoscopes reduces the risk of injury to the upper airways, which can result in life-threatening laryngospasm during or after completion of the procedure. Particular caution must be exercised in patients with underlying bronchospastic disorders, superior vena cava syndrome, or history of angioedema.

Introduction of the bronchoscope under general anesthesia or under conscious sedation with topical anesthesia frequently results in a decrease in oxygenation and in hypoventilation, with demonstrable increases in Pa_{CO_2}. In patients with underlying chronic lung disease, severe hypoxemia may occur, triggering life-threatening cardiac arrhythmias.

All patients undergoing bronchoscopic procedures should be monitored continuously (electrocardiogram, blood pressure, O_2 saturation, and, if indicated, expiratory CO_2 concentration). Use of supplemental oxygen during the procedure should be routine. Bronchoscopy probably should not be performed in patients who are unable to maintain a Pa_{O_2} of 65 mmHg while an FI_{O_2} of 1.0 and full ventilatory support are administered.

Significant oxygen desaturation may occur during BAL. The degree of desaturation is directly related to the duration of the procedure and the volume of lavage fluid used. Return to the prebronchoscopy level of O_2 saturation may be prolonged after removal of the bronchoscope, and supplemental O_2 should be continued throughout the procedure and during the postbronchoscopy observation period.

Fever and Infection

In patients with underlying valvular cardiac disease and those predisposed to endocarditis, the American Heart Association recommends use of prophylactic antibiotics before rigid bronchoscopy, but not before flexible bronchoscopy. Antibiotic prophylaxis is mandatory, however, in patients with prosthetic valves, surgical vascular shunts, or a history of endocarditis.

Appearance of transient fever after bronchoscopy is not unusual and generally does not require any therapy. However, persistent fever in the setting of progressive radiographic infiltrates necessitates antibiotic therapy. The incidence of fever is increased in the elderly, in those with underlying chronic pulmonary disease or documented endobronchial obstruction, and in those with bronchoscopic interventions for malignancy. The incidence of fever and extension of pulmonary infiltrates increase with the volume of BAL fluid and the total number of pulmonary segments lavaged. In most cases, these complications resolve spontaneously within 24 h. The incidence of postbronchoscopic infections is higher in immunocompromised hosts and those with chronic suppurative lung disease (e.g., cystic fibrosis).

Airway Obstruction and Perforation

The advent of interventional bronchoscopy has resulted in complications not ordinarily seen with diagnostic bronchoscopy. Inappropriate use of lasers has resulted in endobronchial burns and bronchial perforations associated with catastrophic bleeding, pneumomediastinum, or pneumothorax. Endobronchial edema may also occur as a result of laser thermal effects.

As noted previously, airway stent insertion is associated with several complications. Stents may not be properly adapted to the diameter of the airway, resulting in either incomplete stent deployment or stent migration, possibly engendering life-threatening airway obstruction. The presence of this palliative endoprosthesis in the airway may predispose to difficulties with secretion clearance and accumulation of inspissated mucus. Placement of SEMS may result in severe local airway reactions, particularly at the edges of the device, producing granulation tissue, hemorrhage, or bronchial perforation.

Pneumothorax

Most of the serious complications directly due to bronchoscopic intervention have been reported in association with performance of transbronchial biopsies. Pneumothorax following transbronchial biopsy occurs in about 4 percent of cases, even when the procedure is done under fluoroscopic guidance. The impact of fluoroscopy on the incidence of pneumothorax remains controversial. Uncontrolled studies have not found a difference in the incidence of pneumothorax following transbronchial biopsy when performed with and without fluoroscopy.

The risk of pneumothorax is not related to the size of the bronchoscopic biopsy forceps. The incidence of pneumothorax is increased, however, in immunocompromised hosts. This is likely due to the increased risk of pneumothorax associated with *Pneumocystis* pneumonia (PCP). The

risk is also elevated in mechanically ventilated patients, with peripheral lung biopsies, and in the presence of bullous lung disease. For these reasons, a postbronchoscopic expiratory chest radiograph is routinely performed. In case of a significant pneumothorax, a chest tube should be inserted immediately to avoid oxygen desaturation and/or tension physiology.

Hemorrhage

One of the most frequently reported complications related to bronchoscopy is hemorrhage—a complication that can be largely avoided by proper evaluation of the patient before the procedure. An incidence of postbronchoscopy hemorrhage of 45 percent has been reported in uremic patients. For these reasons, a blood urea nitrogen (BUN) level above 30 mg/dl or a creatinine level above 3 mg/dl should be considered relative contraindications to bronchoscopy. Similarly, patients with known underlying bleeding disorders, especially those caused by platelet dysfunction or thrombocytopenia, have an increased risk of bleeding (epistaxis or hemoptysis) during bronchoscopy. Bronchoscopy should not be performed if the platelet count is below 50,000/mm^3; transbronchial biopsy or aggressive interventional procedures (laser therapy, bronchoplasty, or stent placement) are probably safe only with platelet counts above 75,000/mm^3.

Manipulation of the bronchoscope, mechanical trauma, vigorous suctioning, endobronchial brushing, and biopsy may result in bleeding in 1 to 4 percent of patients without underlying risks for hemorrhage. Hemorrhage can also occur with inadvertent perforation of pulmonary vessels during transbronchial needle aspiration or biopsy.

Overall, when bronchoscopy is performed by an experienced endoscopist, backed up by a well-trained team and appropriate facilities, mortality and morbidity are very low.

TRANSTHORACIC NEEDLE ASPIRATION AND BIOPSY

Indications and Contraindications

Transthoracic needle aspiration (TTNA) was first used for the diagnosis of pulmonary disease in 1883, when Leyden performed the procedure on three patients with pneumonia. In 1886, Ménétrier reported the use of TTNA in the diagnosis of lung carcinoma. Since that time, many published series have described the use of TTNA for the diagnosis of a variety of benign and malignant thoracic lesions, using fluoroscopic, CT, or ultrasound guidance. The related technique of transthoracic needle biopsy (TTNB) provides core biopsy material from pulmonary nodules for histological examination. The ability to analyze histology is critical in establishing a definitive diagnosis for certain disease states (e.g., histoplasmosis, sarcoidosis) in which cytologic aspiration is inadequate in documenting the characteristic noncaseating granulomas. TTNB also provides improved diagnostic accuracy in lymphoma, both Hodgkin's and non-Hodgkin's varieties, in which anatomic structure is important in delineating the type of lymphoma and in distinguishing between clonal, neoplastic processes and inflammatory conglomerations of lymphocytes. Histological specimens may improve the yield in the diagnosis of pulmonary hamartomas, characterized by the presence of cartilage and/or adipose tissue.

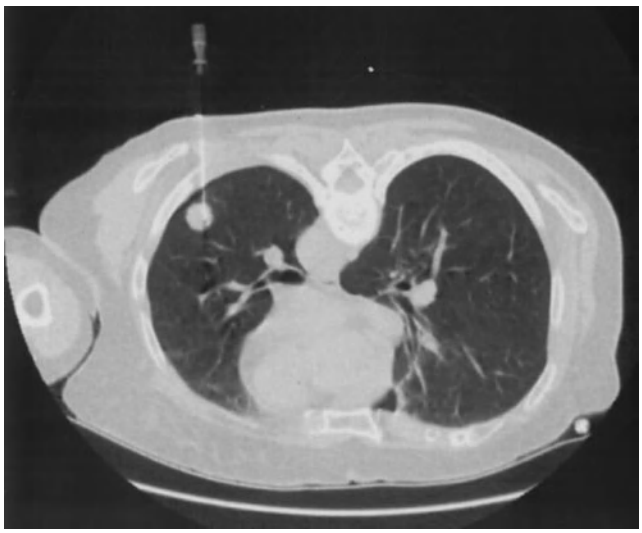


Figure 36-9 Transthoracic needle aspiration of pulmonary nodule. CT scan image of TTNA performed for a 2-cm right-lower-lobe nodule using a 22-gauge Westcott needle (Becton Dickinson & Co, Franklin Lakes, NJ). The needle can be seen entering the nodule. *(Courtesy of Ana Kolansky, M.D.)*

The major indications for TTNA or TTNB include evaluation of solitary lung nodules and masses (Fig. 36-9), mediastinal and hilar lesions, metastatic disease to the lung from a known extrathoracic malignancy, chest wall invasion by lung carcinoma, and pulmonary consolidation or infiltrates that are likely to be of infectious origin.

With the "reemergence" of thoracoscopy and recent development of video-assisted thoracic surgical techniques, patients can more easily undergo complete excision of pulmonary nodules. In the past, many pulmonologists performed TTNA as the initial diagnostic procedure for intrapulmonary lesions, especially those in the lung periphery. Physicians are now faced with the dilemma of whether to send patients directly to thoracoscopic biopsy for a definitive answer. Two commonly used strategies—the use of positron emission tomography (PET) or serial CT scanning—can be used to obtain additional evidence regarding the likelihood of malignancy. In appropriately selected patients, the presence of a PET-positive lesion or a lesion increasing in size on serial CT scans may obviate the need for TTNA.

Few absolute contraindications to TTNA exist. These include an uncooperative patient or one with an intractable cough, as patients must be able to suspend respirations for 5

to 10 s while the needle crosses the pleura. In addition, TTNA is absolutely contraindicated in patients with a suspected pulmonary hydatid cyst because of the risk of capsule rupture and systemic dissemination. Relative contraindications include bullous emphysema, pulmonary arterial hypertension, and coagulation or platelet disorders. Patients with bullous emphysema are at increased risk of developing symptomatic or tension pneumothoraces after TTNA, although most induced pneumothoraces are small and can be treated conservatively. Those with pulmonary hypertension who undergo TTNA have a higher chance of developing pulmonary hemorrhage and significant hemoptysis.

Technique

Proper technique in performing TTNA is critical in obtaining adequate material for reliable interpretation. In addition to the mechanics of needle insertion and aspiration, the choice of needle type and careful specimen processing are important aspects of the procedure.

Choice of Needle

Many needle types are available for TTNA. They vary in both length and width. In the early 1960s, TTNA was performed using large-bore cutting needles; significant hemorrhagic complications were reported. More recently, thin-needle aspiration has become standard with devices ranging in size from 18- to 22-gauge. Coaxial needle systems have been introduced for the purpose of obtaining multiple samples from a single pleural penetration. These systems are also useful for procuring specimens for histological evaluation.

Radiographic Guidance

Most transthoracic needle procedures are performed with fluoroscopic guidance, which allows for real-time imaging of pulmonary lesions during needle insertion and specimen retrieval. CT has been used to guide TTNA of pulmonary lesions, typically those that are too small to be seen fluoroscopically or are centrally located and adjacent to major vascular structures. Because CT-guided TTNA is not typically done using real-time visualization, the procedure takes longer to perform and requires several transthoracic passes to obtain diagnostic material. Not surprisingly, CT-guided TTNA is associated with an increased incidence of pneumothorax (up to 60 percent in some series). Ultrasound guidance of TTNA offers the advantage of real-time lesion imaging, easy portability, and absence of exposure to ionizing radiation for both the clinician and the patient. Ultrasound is used most commonly for peripheral lung lesions that extend to the pleural edge, or for the diagnosis of mediastinal masses. The sensitivity of ultrasound-guided TTNB of pulmonary and mediastinal lesions larger than 3 cm may be as high as 96.8 percent; the rate of pneumothorax is less than 2 percent.

Needle Insertion

The lesion is localized by fluoroscopic guidance, and the overlying skin is marked and anesthetized with 1 percent lidocaine. With the patient lying as still as possible, the aspiration needle is inserted perpendicularly through the anesthetized region into the lesion, as seen under fluoroscopy. The needle may be seen to displace the lesion, or if properly positioned, the needle will move in concert with the lesion during quiet breathing. If the needle is seen to move independently of the lesion during respiration, it is positioned unsatisfactorily.

Ideal aspiration technique necessitates having the tip of the needle as close to the center of the lesion as possible. A 20-ml lockable syringe containing approximately 3 ml of sterile saline is attached to the needle hub, and the tip is maintained in proper position using fluoroscopic guidance. Suction is then applied by pulling the syringe plunger back and locking it into position with clockwise rotation. While suction is sustained with the locked syringe, the needle tip is advanced and withdrawn about 0.5 to 1 cm within the lesion under real-time fluoroscopic guidance. The needle is then removed from the chest, suction is released, and the aspirated material is flushed into a specimen container. Several samples should be obtained to increase the diagnostic yield. With a necrotic mass, aspiration should also be performed in peripheral locations of the lesion in order to obtain viable cells and to decrease the risk of false-negative results.

Results

TTNA and TTNB have excellent success rates in the diagnosis of primary or metastatic pulmonary malignancies; for TTNA, the sensitivity is 85 to 95 percent. Major causes of false-negative results in malignant disease are inadequate sampling of the lesion and aspiration in an area of necrosis or postobstructive pneumonia. In addition, small, central malignant lesions may be difficult to diagnose accurately with TTNA. Aspiration of vascular tumors, such as angiosarcoma, carcinoid, or metastatic renal cell carcinoma, may yield a bloody aspirate with few, if any, malignant cells. TTNA rarely leads to misclassification of primary pulmonary neoplasms, with a reported rate of misdiagnosis of small-cell carcinoma of 0 to 1.1 percent. False-positive results are extremely rare (under 0.5 percent) and are typically reported in the setting of inflammatory processes, such as tuberculosis, radiation fibrosis, organizing pneumonia, and pulmonary infarction.

Specific diagnosis of a benign lesion with TTNA is more problematic, with published sensitivities ranging widely, from 11.7 to 68 percent. A TTNA that is negative for malignancy does not rule out the presence of neoplastic disease, especially if the aspirate was unsatisfactory. The degree of suspicion of malignancy in a particular clinical situation becomes extremely important in dictating the next step following a negative TTNA. For a smoker with a high risk of bronchogenic

carcinoma, the proper course may lead to videothoracoscopic biopsy of the lesion, whereas in a young, otherwise healthy nonsmoker, close observation with serial CT scans may be the preferred option.

Complications

As mentioned previously, the most common complication of both TTNA and TTNB is pneumothorax; incidence rates reported in the literature vary from 8 to 61 percent. A small percentage of the pneumothoraces are clinically significant; only about 8 percent require thoracostomy tube drainage. Preexisting lung disease—in particular, bullous emphysema—is the most significant predisposing factor to development of pneumothorax after TTNA or TTNB. Other risk factors are deep lesions, increased number of transthoracic passes, crossing more than one pleural surface with the needle, and increased patient age. The vast majority of patients who develop clinically significant pneumothoraces after the procedure have an underlying diagnosis of chronic obstructive pulmonary disease.

Uncommon complications of TTNA and TTNB include hemorrhage and hemoptysis, although these are typically minor. Cases of fatal hemorrhage from tracheobronchial obstruction from clot and subsequent asphyxia after use of large-bore (18-gauge) cutting needles have been reported.

Air embolism is a rare complication caused by creation of a communication between atmospheric air and a pulmonary vein. To minimize this risk, the needle should never be left open to air while in the chest, and the patient should be discouraged from deep breathing, straining, or coughing during the procedure. The procedure should be halted and the needle withdrawn if the patient is actively coughing. If an air embolism is suspected, 100 percent oxygen should be administered through a non-rebreather face mask and the patient placed in the left lateral decubitus position, with the head down: this position optimizes capture of air in the right heart. The patient should be transferred immediately to a hyperbaric chamber.

SUMMARY

Technological advances in diagnostic and therapeutic bronchoscopy continue to improve our ability to perform minimally invasive, accurate evaluations of the tracheobronchial tree and to perform an ever-increasing array of therapeutic and palliative interventions. The continued development of imaging technologies will certainly provide improvements in many of the modalities described above. Future improvements will include refinements in video and ultrasound imaging technology and the development of newer modalities, such as molecular imaging. With the continued refinement of interventional modalities, therapeutic bronchoscopy may soon provide alternative therapies for conditions that are traditionally treated with surgery. These opportunities will need to be accompanied by well-designed studies to delineate the appropriate use of these techniques in clinical practice.

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37

Thoracoscopy

Larry R. Kaiser

Thoracoscopy is a type of surgery in which a motivated medical specialist can develop a level of expertise that puts certain procedures well within his or her reach. These procedures are complementary to bronchoscopy in many instances and aid greatly in the diagnostic evaluation and potentially in therapy for a number of patients, especially those with pleural disease. Within the past several years, videothoracoscopy has, in many ways, changed the way pulmonary medicine and thoracic surgery are practiced, allowing us to alter the approach to a number of clinical problems.

HISTORICAL PERSPECTIVE

In the early 1920s, Jacobaeus, a Swedish physician, used a cystoscope in the pleural space to lyse pleural adhesions as an adjunct to collapse therapy in the treatment of pulmonary tuberculosis. He subsequently used this technique of thoracoscopy to localize and diagnose benign and malignant lesions of the pleura and pulmonary parenchyma. Despite the work of Jacobaeus, the procedure was performed only on a limited basis in the United States and was never truly endorsed. In one of the early textbooks of thoracic surgery, Lilienthal mentioned thoracoscopy but warned against its routine use in patients with tuberculosis because of the risk of significant bleeding and the perceived possibility of spreading infection within the pleural space.

Thoracoscopy evolved mainly as "pleuroscopy," which was used as an adjunct to other procedures in the *diagnosis* of pleural pathology—specifically in cases of an effusion of unknown cause, in which the thoracentesis was negative and a closed pleural biopsy was nondiagnostic. In many of these cases, the presence of malignancy was proved at the time of pleuroscopic examination. A number of instruments were used for thoracoscopic examination, including rigid bronchoscopes, mediastinoscopes, and flexible bronchoscopes, as well as rigid fiberoptic thoracoscopes. A mediastinoscope offered a large working channel and excellent visualization of the pleural space; an effusion could be drained, biopsies taken, and pleurodesis effected with talc. The procedure was mainly of diagnostic utility and, other than pleurodesis, offered little in the way of therapeutic applications. It was possible to biopsy the lung, but only small pieces could be removed, and the area that was amenable to biopsy was limited.

The availability of the charged coupling device, a silicon chip that is light sensitive, led to the sufficient miniaturization of a video camera so that, when coupled to a fiberoptic telescope, it was practical for use in the operating room by providing a magnified image projected on a video monitor that allowed the operating surgeon to work with an assistant (Fig. 37-1). Previously, it was possible only for a single operator to work with the thoracoscope, but the videothoracoscope frees up the surgeon's hands and allows more complex procedures to be performed. The power of this technique has

This chapter has been slightly modified from the version that appeared in the third edition of *Fishman's Pulmonary Diseases and Disorders.*

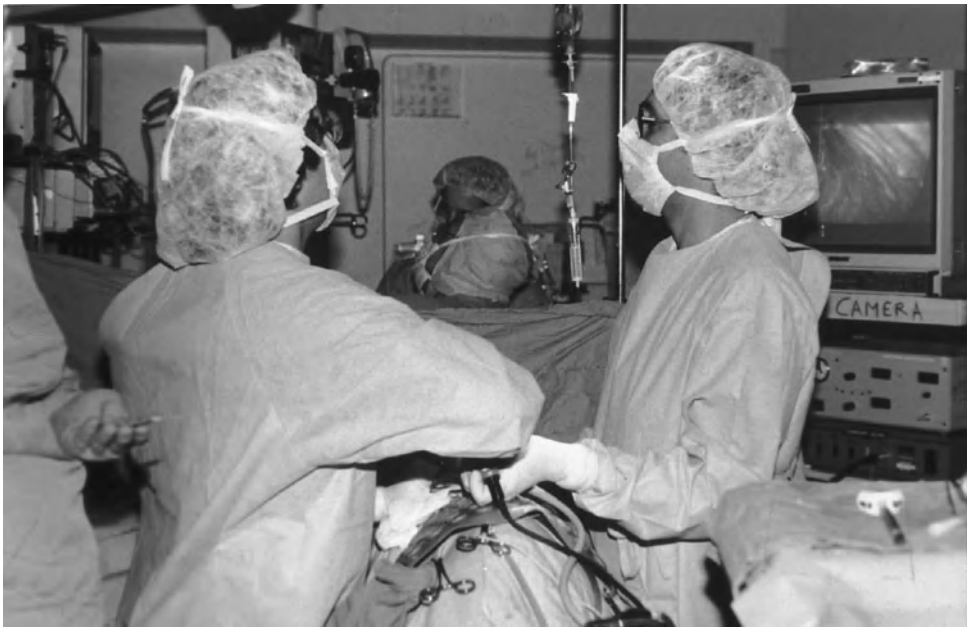


Figure 37-1 Surgeons carrying out a videothoracoscopic procedure. Note the video monitors, which allow the surgeon and assistants to view the surgical field. The work area is kept between the surgeon and the monitor.

been amply demonstrated by the rapid rise of laparoscopic cholecystectomy, a procedure that changed the specialty of general surgery in a remarkably short time. It was not long before a number of thoracic surgeons began to adapt this new technique for work in the chest, even though thoracoscopy had never been a mainstay in the practice of most such surgeons.

CURRENT TECHNIQUES

The term video-assisted thoracic surgery (VATS) encompasses all procedures performed with the thoracoscope, including those that are purely "thoracoscopic."

The bony thorax provides its own space once the lung is collapsed, so that insufflation of gas, used in the abdomen to create a working space, is unnecessary and even slightly dangerous. The space in the chest is created simply by placing an endobronchial tube and collapsing the ipsilateral lung. This requires a general anesthetic, but certain procedures—namely, those involving the parietal pleura—may be performed with only regional anesthesia and intravenous sedation, since the lung collapses in the spontaneously breathing patient once the negative, intrathoracic pressure is lost.

The patient is placed on the operating table in the lateral decubitus position, and the chest is prepared and draped as for a thoracotomy. Incision placement depends somewhat on the procedure to be performed, but the location of the incision for insertion of the videothoracoscope remains constant in the seventh or eighth intercostal space aligned with the anterior superior iliac spine. A 1-cm incision is made, deepened to the intercostal muscles, as if one were inserting a chest tube. Indeed, it is through this incision that the chest tube is placed at the conclusion of the surgical procedure. Entry into the chest is made with the index finger, to assure safety. Occasionally, the lung is adherent to the chest wall, and these adhesions must be broken up with the index finger to allow for placement of the trocar sheath. Additional incisions are made as needed—usually arrayed in a triangular fashion, which facilitates instrument placement and allows one to work in coordination with an assistant (Fig. 37-2). It

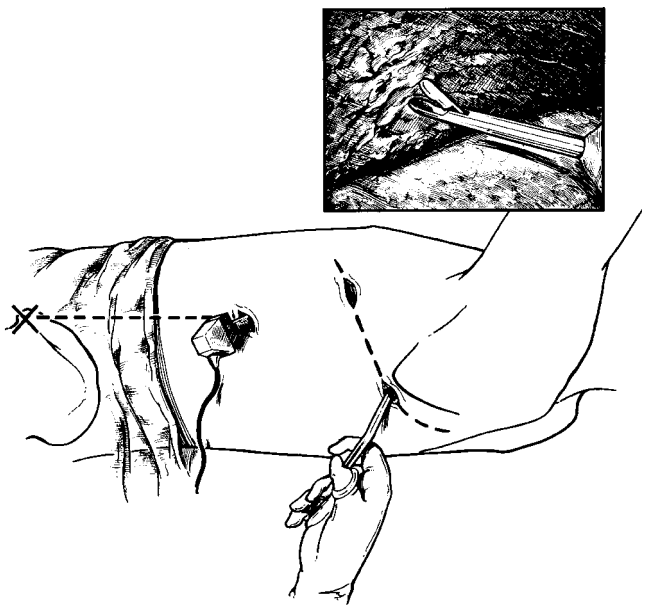


Figure 37-2 For most cases three incisions are used, as shown. The thoracoscope most commonly is placed through the inferior incision, allowing other instruments to be placed through the two opposed incisions. *Inset:* A view within the chest, as would be seen on the monitor, of a biopsy forceps in place to take a specimen of parietal pleura.

is best to work with two video monitors, which are placed at the head of the table on each side, so that both the operator and the assistant may have an unobstructed view of the surgical field. As long as one maintains the surgical field between oneself and the video monitor, the image is as it seems—that is, forward is forward, backward is backward, etc. It takes some adjustment to become accustomed to working in three dimensions while being able to see in only two.

The instrumentation available for thoracoscopy has been slowly improving. Instruments designed specifically for laparoscopy proved to be poor for this new application. Grasping the lung without teating the parenchyma proved to be especially difficult with these instruments. The most significant development in instrumentation, one that markedly expanded the utility of thoracoscopy, was the introduction of the endoscopic linear stapler. This instrument, more than any other, propelled thoracoscopy out of an almost purely diagnostic realm into the mainstream of therapeutic applications.

SPECIFIC PROCEDURES

Pleural Disease

For many physicians, closed pleural biopsy has become a dying art—and perhaps it should be—with the emergence of videothoracoscopic techniques that allow one to biopsy specific areas of the parietal pleura under direct vision. The major, but certainly not the only, indication for thoracoscopy in the management of pleural disease remains the undiagnosed pleural effusion. In the past, the patient with an empyema often was forced to undergo thoracotomy for débridement and decortication to rid the space of infection and allow the lung to reexpand. With thoracoscopic techniques, many of these patients may now avoid thoracotomy, especially if they are seen early in the course of the empyema. Thoracoscopic débridement and decortication are indicated in the febrile patient with a pleural effusion in whom tube thoracostomy provides incomplete drainage. The fibrinous nature of the exudate precludes complete drainage with a tube alone, and mechanical débridement is required. Likewise, videothoracoscopic techniques have proved useful in the management of the organized posttraumatic hemothorax, in which a chest tube is unable to effectively drain the organized clot and debris.

Benign pleural tumors, specifically solitary fibrous tumors, do occur; most commonly they arise from the visceral pleural surface and are ideal lesions for thoracoscopic resection (Fig. 37-3).

Videothoracoscopy has also increased our ability to deal successfully with malignant pleural effusions, especially those in which loculations are present. When tube thoracostomy results in incomplete drainage or one attempt at chest tube pleurodesis has failed, thoracoscopy—whereby the chest is evacuated under direct vision and talc is insufflated—is the procedure of choice. Hartman and colleagues compared the thoracoscopic insufflation of talc in patients who underwent tube thoracostomy and sclerosis with either tetracycline or bleomycin. Talc pleurodesis was performed under local anesthesia supplemented with intravenous sedation. For patients

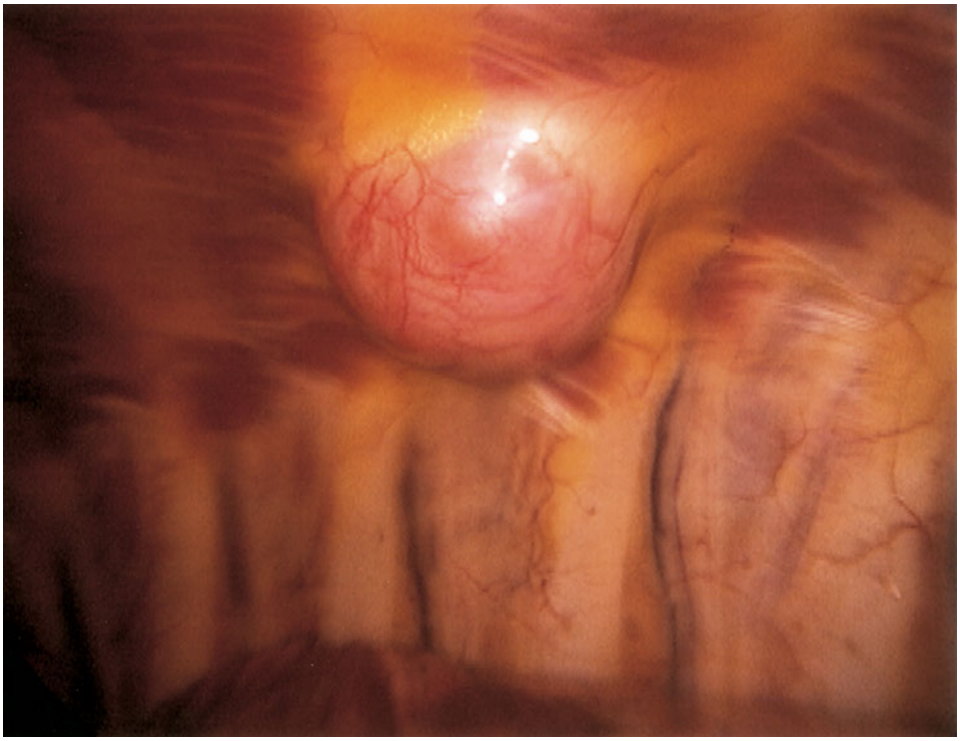


Figure 37-3 A benign schwannoma arising from the parietal pleural surface--a lesion that is easily amenable to thoracoscopic excision.

in the talc group, there was a 97 percent rate of successful pleurodesis at 30 days and 95 percent at 90 days. This is significantly better than results seen in patients treated with the tube thoracotomy, only 33 percent of whom had achieved a successful pleurodesis at 30 days. The results were slightly better when bleomycin was used in the tube thoracostomy group. Patients sclerosed with talc seemed to have less pain following the procedure. The ability to perform thoracoscopic talc pleurodesis under local anesthesia may make the technique attractive for most patients with malignant effusions. In a randomized, prospective trial, Dresler and colleagues examined the outcomes of treating malignant pleural effusions with talc poudrage administered by thoracoscopy versus an instillation of talc slurry through a chest tube.Overall, there was no significant difference in the primary outcome of malignant effusion recurrence at day 30. However, subgroups of patients, including those with breast cancer and lung cancer, were significantly more likely to be effusion free at 30 days when treated by thoracoscopy. Morbidity and mortality were similar in both groups, although there were more respiratory complications in the thoracoscopy group.

Parenchymal Disease

Transbronchial lung biopsy is often successful in providing diagnostic material in patients with diffuse pulmonary infiltrates. In situations in which a transbronchial biopsy fails to provide diagnostic material, a VATS procedure is indicated. Before the advent of videothoracoscopy, many of these patients were treated empirically, usually with steroids. Lung biopsy, which required a thoracotomy, albeit a "mini" one, was reserved for patients who either failed empiric therapy or were desperately ill and in intensive care. The empiric approach probably is warranted and may, in fact, be preferred in the non-neutropenic cancer patient with acute pneumonitis, for whom broad-spectrum antibiotic therapy usually is the treatment of choice. In the nonimmunocompromised patient, usually with a chronic interstitial process, serious consideration must be given to obtaining a piece of lung tissue. The pulmonologist must make a judgment as to whether a transbronchial lung biopsy is indicated—a decision that must take into account the most likely diagnostic possibility and whether a transbronchial specimen will be adequate to establish that diagnosis and the small but very real risks of bleeding and pneumothorax. VATS lung biopsy consistantly provides diagnostic material. Burt and colleagues found a 94 percent diagnostic yield from open lung biopsy versus 59 percent for transbronchial biopsy in a series of 20 patients subjected to both procedures.

Before the introduction of videothoracoscopy, a thoracotomy was required solely for the purpose of obtaining a piece of lung tissue. The thoracotomy usually consisted of a small inframammary incision into the chest through the fourth or fifth intercostal space, a procedure that can be done expeditiously and allows one to obtain enough lung parenchyma to make a diagnosis. There should be minimal morbidity with this approach, and it still represents the best approach to lung biopsy in the critically ill, hemodynamically fragile patient who is ventilator dependent (requiring high peak airway pressures and high inspired oxygen concentration), for whom transport to the operating room represents a substantial risk. The "mini" anterior thoracotomy does not require single-lung ventilation and thus avoids the potential morbidity and mortality associated with exchange of the endotracheal tube for an endobronchial tube in these high-risk patients. However, the surgical exposure achieved by this approach can significantly limit the area of lung that may be accessible for biopsy. It is also difficult to obtain tissue from more than one site of the lung with this approach.

In most patients, however, VATS wedge lung biopsy, which we and others have referred to as "closed lung biopsy," represents the best alternative to the "mini" thoracotomy. It offers the advantage of excellent visualization of the entire lung so that suspect areas can be biopsied under direct vision and all areas of the lung can be reached with relative ease. The technique avoids spreading of the ribs, which seems to be one of the factors responsible for the pain that results following thoracotomy, including anterior thoracotomy. It may be that thoracoscopic biopsy causes less postoperative pain, which may be important in weaning patients from a ventilator in the immediate postoperative period, and results in a shorter hospital stay. In a nonrandomized, retrospective study using historical controls, Ferson and colleagues from two other centers compared a group of 47 patients undergoing thoracoscopic lung biopsy with a group of 28 patients who had had open wedge resection via limited thoracotomy. Adequate tissue for diagnosis was obtained for all patients in both groups. Mean surgical time was significantly longer in the thoracoscopic group (69 vs. 93 minutes), but, as would be expected, the time decreased as additional experience was gained. The authors excluded from the study patients requiring mechanical ventilation and still found that hospital stay was significantly shorter in the group undergoing thoracoscopic biopsy (4.9 vs. 12.2 days). There were significantly more complications in the open group (50 percent incidence) than in the VATS group (19 percent), a finding that no doubt explains the variation in duration of hospital stay. All surgeons engaged in the study believed that thoracoscopic biopsy provided better visualization of the entire lung than a "mini" thoracotomy.

Our own experience with 80 thoracoscopic lung biopsies in non–ventilator-dependent patients confirms the above-mentioned findings. Diagnostic tissue was obtained in all cases, and in several our ability to provide tissue from different areas of the lung greatly aided in establishing a diagnosis. The mean hospital stay in our series was 1.9 days, significantly shorter than that of Ferson and colleagues. There was no mortality and no significant morbidity, including no prolonged air leaks. When lung biopsy is indicated, thoracoscopic biopsy is our procedure of choice for nonventilated patients. For patients requiring mechanical ventilation, in most cases we prefer a limited anterior thoracotomy with minimal rib spreading—a simple procedure that can be

performed expeditiously and avoids the need for single-lung ventilation.

Thoracoscopic lung biopsies were reported before the advent of VATS techniques and before the linear stapler was available. With a cup biopsy forceps, pieces of lung parenchyma were obtained, and an insulated electrocautery provided the only means of hemostasis. Daniel and colleagues compared results obtained in the era before the advent of video technology with those obtained by current methods. In 30 patients undergoing thoracoscopic cup biopsy, there were 10 deaths and one prolonged air leak that required a thoracotomy for repair. Mean hospital stay was 16.6 days. In contrast, 11 patients underwent videothoracoscopic biopsy with one death and a mean hospital stay of 8.2 days. The significantly better hemostatic as well as aerostatic qualities of the linear stapler than those of a cup biopsy forceps and the larger amount of tissue obtained using a stapler clearly are advantageous. These authors also noted no advantage to either endoscopic approach over limited thoracotomy in patients requiring mechanical ventilation.

The availability of VATS lung biopsy should prompt earlier referral for lung biopsy of patients with interstitial disease who either would be treated empirically and not referred for biopsy or would be referred in desperation at the time of marked decompensation, usually after being intubated and ventilated. Utilizing these techniques to obtain an earlier tissue diagnosis in patients with interstitial lung disease should improve management and, it is hoped, improve the long-term outlook.

VATS techniques have also had a major impact on the management of spontaneous pneumothorax in the two major groups of patients who present with this problem: young patients with apical blebs and older patients with bullous emphysema. Primary spontaneous pneumothorax in a young person typically can be managed nonsurgically, with the likelihood of recurrence being approximately 30 percent. Surgical treatment for a first-time pneumothorax classically has been reserved for patients with persistent air leaks (longer than 1 week), those whose occupations require them to experience extremes in atmospheric pressure, and those who live in isolated areas without access to medical care. Otherwise, surgery is indicated after a first recurrence or for the patient who has experienced bilateral pneumothoraxes. Surgery for a spontaneous pneumothorax has required either a thoracotomy with stapling of apical blebs and, at times, a pleurectomy or, more recently, a transaxillary thoracotomy with excision of blebs and pleural ablation or pleurectomy to create pleural symphysis. These are both substantial procedures for what is really a trivial problem in terms of what needs to be done intraoperatively. An alternative approach to management, mentioned here only to be dismissed, involves installation of talc or other sclerosant via tube thoracostomy.

VATS management of spontaneous pneumothorax provides a simple surgical alternative that is associated with minimal morbidity. With recognition that in young patients the pneumothorax usually results from rupture of a bleb located at the lung apex or occasionally in the apical portion of the superior segment of the lower lobe, the surgical procedures include resection of the apical blebs and mechanical pleural abrasion to effect a pleural symphysis (Fig. 37-4). The blebs are easily visualized with the thoracoscope and excised with several applications of the linear stapler. The parietal pleural surface is mechanically abraded with a gauze sponge, which creates enough inflammation to cause pleurodesis. Talc or other sclerosing agents are not recommended for these young patients. Obliteration of the apical blebs alone probably would be sufficient, and the contribution of the pleurodesis is probably minimal. A very low recurrence rate is expected (less than 5 percent) following this procedure, similar to that achieved after a transaxillary procedure or formal thoracotomy; the handling of the blebs is identical no matter which approach is used.

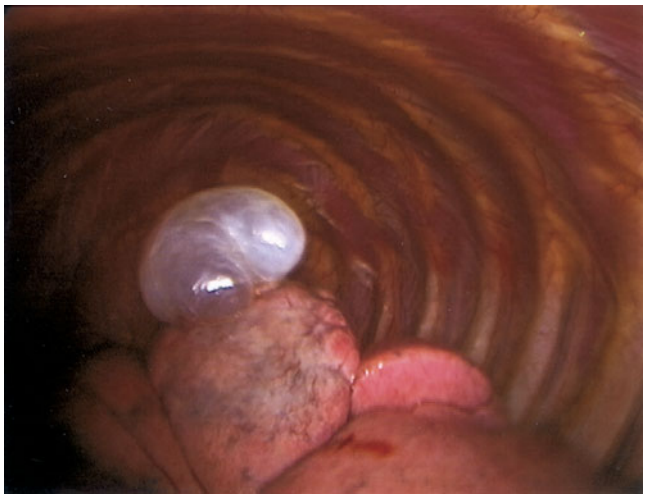


Figure 37-4 Thoracoscopic appearance of a typical apical bleb responsible for a spontaneous pneumothorax, usually in a young person. These are most commonly found at the lung apex, but they can also occur at the apex of the superior segment of the lower lobe.

Cannon and associates performed thoracoscopic excision of apical blebs in nine patients with primary spontaneous pneumothorax and noted one recurrent small apical pneumothorax that resolved without treatment. We performed 70 thoracoscopic procedures for primary spontaneous pneumothorax over a 4-year period. We noted three recurrences, two in patients with catamenial pneumothorax, at the time of their first menstrual period following the procedure, and one in a patient with routine apical blebs. The lesion responsible for catamenial pneumothorax is unknown, and we were unable to detect any pathology at the time of the procedure. These patients experienced recurrence despite the performance of what was believed to be adequate pleurodesis, but the recurrences were early, probably before the development of pleural adhesions. Allen's team reported on 46 patients who underwent wedge excision and pleurodesis for spontaneous pneumothorax. Only one patient required conversion to an open procedure. Seven patients had persistent air leaks (more than 10 days), and two of these required thoracotomy for correction. No recurrences have been seen with

a median follow-up time of 25 months. Median hospital stay was 5 days. Our own experience, along with that of other groups, suggests that hospital stay after VATS operation for spontaneous pneumothorax is closer to 2 days; prolonged air leaks following the procedure, causing longer hospital stays, are rare.

Indications for surgery for spontaneous pneumothorax have not changed significantly despite the availability of the VATS technique, which allows most patients to leave the hospital on the first or second postoperative day. Patients with primary pneumothorax are managed with either aspiration of the pneumothorax or chest tube placement. We used to wait 7 days for an air leak to seal before proceeding with surgery. We now wait only 48 to 72 hours before recommending the thoracoscopic procedure, which allows the patient to leave the hospital sooner than if treated in the conventional fashion. The decision for earlier surgery is justified by the decreased morbidity associated with the VATS procedure when compared with an open procedure, even the transaxillary approach. In a patient treated conservatively for a first-time pneumothorax, recurrence on the same side or a pneumothorax on the opposite side is an indication for surgery. If the pneumothorax occurs on the same side as the first one, we operate only on that side. With a contralateral pneumothorax, both sides should be operated on, since the consequences of spontaneous bilateral pneumothoraxes may be devastating. Bilateral VATS procedures conducted with a single anesthetic may be performed without significant additional morbidity, especially in young patients. If necessary, thoracic epidural analgesia may be used in the early postoperative period. VATS excision of apical blebs and mechanical pleural abrasion constitute the procedure of choice when surgery is indicated in a patient with spontaneous pneumothorax.

Pneumothorax occurring secondarily to a process other than the apical blebs seen in young people can also be managed with a VATS approach. In these situations, the pathology may be somewhat more complex, and one needs to search for the air leak and repair it, usually by stapling; but fibrin glue, the neodynium-YAG laser, and the argon beam coagulator have also been used with success. Over a recent 2-year period, we performed 13 procedures for so-called secondary pneumothorax—seven in patients with emphysema who presented in respiratory distress after developing a pneumothorax, two for persistent air leaks following thoracotomy and lobectomy, one in a patient with AIDS and bilateral pneumothoraxes secondary to *Pneumocystis carinii* infection causing necrotic parenchymal cavitary lesions, and three in patients with metastatic sarcomas. We were successful in managing the air leak in 12 patients; one patient was converted to open thoracotomy. Cannon and colleagues operated on six patients with secondary pneumothorax, two of whom subsequently required a thoracotomy to deal with persistent air leaks following the thoracoscopic procedure. Although recognizing that some patients may still require thoracotomy, we prefer to attempt a VATS approach for an air leak because these patients often have significantly compromised pulmonary function and avoidance of a thoracotomy is advantageous. If a surgeon develops an interest and gains experience with VATS techniques, the frequency of conversion to an open procedure should remain low. It requires a commitment on the part of the surgeon, however, especially early in one's experience, to take the extra time that may be required to complete some of the more complex procedures rather than quickly converting to an open operation.

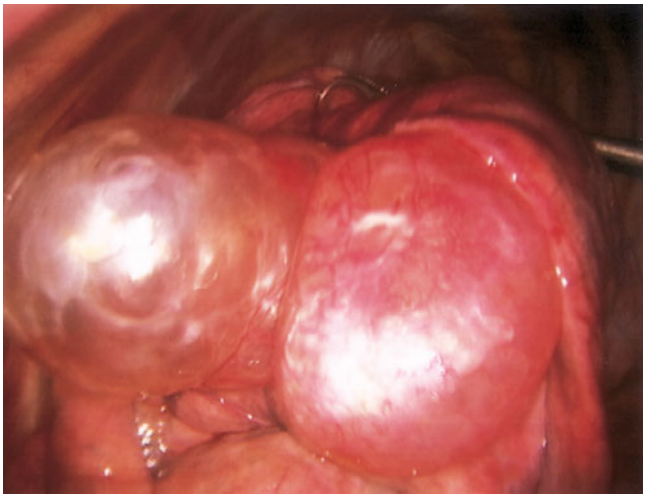


Figure 37-5 A giant bulla occurring as an isolated finding, resulting in compression of adjacent lung parenchyma. Excision usually offers significant relief of symptoms.

The management of bullous lung disease has also changed with the introduction of VATS techniques. The standard indication for surgery in patients with bullous emphysema is the presence of a giant bulla causing significant compression of adjacent, relatively normal lung parenchyma (Fig. 37-5). These giant bullae are readily recognizable on a plain chest radiograph, and a computed tomography (CT) scan helps to define the presence and extent of compressed lung tissue. The major factor that enters into a decision on whether bullectomy is likely to result in improvement in a patient's condition relates to the compressed lung parenchyma and whether there is significant compressed parenchyma to expand and fill the pleural space after bullectomy. A residual space after bullectomy promotes the development of a persistent air leak and, in a small percentage of cases, an empyema, with resultant devastating consequences and usually a prolonged hospital stay. Reviewing a series of chest radiographs performed over the preceding several years to determine the progression in the size of the bullae allows for an assessment of the amount of compressed adjacent lung tissue. Pulmonary function studies should document a decrease in function, and the patient should note a decrease in exercise tolerance. Patients who fulfill these criteria are ideal candidates for VATS bullectomy.

The procedure itself requires obliteration of the bulla with the avoidance of air leaks, if possible. We prefer to use the argon beam coagulator, which, when applied at a low power

setting, causes the wall of the bulla to shrivel although the bulla is not entered. Once the bulla has shrunk, the base may be delineated and then stapled in an attempt to minimize air leak. The walls of the bulla may be used as a buttress for the staple line. Alternatively, a piece of prosthetic material, specifically bovine pericardium (PeriGuard, Biovascular Medical, St. Paul, MN), may be used to reinforce the staple line to prevent air leaks. Performing a VATS procedure rather than open thoracotomy in these markedly compromised patients, most of whom are oxygen dependent and have FEV_1 well under 1 L, seems to be preferable. Still, in the early postoperative period these patients are most at risk of secretion retention and pneumonia—which, for many, would be a terminal event. Thus, postoperative pain management and aggressive chest physiotherapy are of major importance. We use thoracic epidural analgesia provided by a continuous infusion of narcotic for pain management in the early postoperative period so that patients may cough more effectively. Patients are extubated as soon as possible, ideally at the completion of the surgical procedure.

Unfortunately, giant bullae do occur in some patients with bullous emphysema. Wakabayashi identified 17 cases of giant bullous disease among more than 500 cases of bullous emphysema seen over a 3-year period. Of more than 2000 thoracoscopic cases reported to the Video Assisted Thoracic Surgical Study Group (VATSSG) Registry, only 33 (1.8 percent) were for excision of giant bullae.

Diffuse emphysema, with or without a bullous component, is a significantly greater clinical problem in terms of numbers of patients affected. Until recently, the therapeutic options of these patients were extremely limited, with oxygen therapy and bronchodilators being the mainstay for those with a reversible airway component. The reintroduction of a surgical procedure, volume reduction, which has been shown to be efficacious in some cases, may offer many of these desperate patients some relief from their symptoms. Although the initial procedure of volume reduction for diffuse emphysema, as described by Cooper and colleagues, entailed a median sternotomy and bilateral excision of lung parenchyma, other authors have reported on either unilateral or bilateral VATS procedures to accomplish essentially the same outcome. Kotloff and associates compared a series of patients from the University of Pennsylvania who underwent volume reduction via sternotomy with a group undergoing the procedure via a VATS approach. Patients who underwent a bilateral VATS procedure fared as well as those undergoing sternotomy in terms of functional improvement. There were fewer postoperative deaths in the VATS group, but the difference was not statistically significant. The National Emphysema Treatment Trial (NETT), a multi-center NIH-sponsored trial designed to evaluate the efficacy of lung volume reduction surgery as a treatment for chronic obstructive pulmonary disease, compared outcomes in patients undergoing lung volume reduction by a video-assisted approach versus a sternotomy approach. Median hospital stay was recduced by use of the thoracoscopy approach, whereas complication rates were not signicantly different.

PULMONARY NODULES

The solitary indeterminate pulmonary nodule is a problem confronted routinely by pulmonologists. In light of the emergence of VATS as a minimally invasive procedure that can be performed with low morbidity even in compromised patients, we must examine closely the current management of a patient who presents with an indeterminate nodule. Whereas in the past definitive management required open thoracotomy, with its attendant morbidity, this no longer is the case. Thoracoscopy offers the opportunity both to definitively make the diagnosis and to treat many of these lesions and, therefore, causes a refocus in our thinking.

The salient question posed by the presence of a pulmonary nodule is a very simple one: Is it malignant? If a previous radiograph demonstrates a lesion that has not changed in size over several years, one can be reasonably certain of the benign nature of that lesion. Depending on the series, approximately 40 percent of resected nodules are malignant, and primary carcinoma of the lung accounts for the majority of malignant nodules. A number of factors point to a benign diagnosis, although none are absolute. We may be far less suspicious of a nodule occurring in a nonsmoker, especially if the person is 35 years of age or younger. Lesions larger than 3 cm in diameter are likely to be malignant. Specific patterns of calcification may also be associated with benign lesions, and CT comparison with a phantom of known density may further support a benign diagnosis. Even when all these factors have been taken into consideration, a histologic diagnosis is required in most cases. If benignity cannot be proved, malignancy must be assumed.

The diagnostic procedures available to the pulmonary physician are very good at establishing a diagnosis of malignancy but fall short in obtaining a "positive" diagnosis of benign disease. The diagnostic yield from fiberoptic bronchoscopy varies from 20 to 80 percent, but a specific benign diagnosis is made only 10 percent of the time. With these figures, it is hard to justify the performance of a bronchoscopy if one is looking to make a diagnosis of benign disease. Unfortunately, percutaneous needle aspiration biopsy does not fare much better. Although its sensitivity in making the diagnosis of malignancy is high (64 to 97 percent), a specific benign diagnosis can be made only about as often as the rate achieved bronchoscopically. A "negative" needle biopsy is of no help and necessitates a further diagnostic procedure, whereas a diagnosis of malignancy essentially tells us what we already know: The lesion has to be excised.

Mack and colleagues, in a multicenter study, have looked closely at the role of thoracoscopy in the diagnosis of the indeterminate solitary pulmonary nodule. Over an 18-month period, 242 patients with solitary nodules were treated. A wedge excision of the lesion that included some surrounding normal lung parenchyma was accomplished with an endoscopic stapler alone in most cases. A definite diagnosis was obtained in all cases; there was no mortality or major morbidity, and minor complications (atelectasis, pneumonia, prolonged

air leak) occurred in only nine patients (3.6 percent). In two patients, the nodule could not be located and a thoracotomy was required; otherwise, a benign diagnosis was obtained in 127 patients (52 percent), while malignancy was found in 115 (48 percent). When a primary lung cancer was identified, formal open thoracotomy and anatomic resection were carried out in patients with adequate pulmonary reserve. The average hospital stay for patients undergoing thoracoscopy alone was 2.4 days.

In a series of 771 VATS procedures at the Mayo Clinic, wedge excision of a pulmonary nodule was performed in 234 patients. There were no deaths in this group of patients, and the most common complication was a prolonged air leak, which occurred in 3.0 percent of patients. The median hospital stay was 3 days. The lesion was found to be malignant in 107 patients, and all patients found to have bronchogenic carcinoma underwent an open thoracotomy for anatomic pulmonary resection and lymph node sampling.

It is hard to argue against a technique that has a sensitivity and specificity of 100 percent and can be done with no mortality and minimal morbidity. But is it necessary to excise so many benign lesions? If we could be certain of the benignity of a lesion, there would be no reason to excise it. It is the uncertainty of the benign diagnosis in most cases that presents the most compelling argument for thoracoscopic excision of most solitary pulmonary nodules. All questions are answered and the uncertainty disappears with one procedure.

Certain lesions are not considered for VATS excision. For lesions greater than 3 cm in diameter, the likelihood of malignancy is so high (greater than 90 percent) that in the absence of metastatic disease, thoracotomy and anatomic resection—i.e., lobectomy—should be the first procedure undertaken. The CT scan aids greatly in localizing the nodule, and we have found it to be the only localizing study that is required. Even deep-seated lesions may be palpated and located, a technique that becomes easier with experience. In our experience with 400 thoracoscopic excisions of pulmonary nodules, we have failed to locate the nodule in only four cases, all early in our experience. Our technique relies heavily on instruments, specifically designed for thoracoscopy, that greatly facilitate the procedure, especially in grasping or moving the lung to the palpating finger (Fig. 37-6). Centrally located lesions, which lie in close proximity to hilar structures, are not suitable for VATS wedge excision and require open thoracotomy.

There is some controversy regarding the optimal management of the solitary nodule that proves to be a carcinoma. Is a VATS wedge excision sufficient treatment for a T1 (less than 3 cm) primary lung carcinoma? Based on current knowledge, we believe that wedge excision is not optimal treatment for primary lung cancer, even a small T1 lesion. A wedge excision is a compromise procedure that is acceptable only for the patient who otherwise cannot tolerate a thoracotomy and anatomic resection. Among other factors, a wedge excision removes no regional lymph nodes and thus staging is inadequate. Local recurrence is significantly higher after wedge excision than after lobectomy. Several authors have performed large series of nonanatomic resections for patients with marginal pulmonary function, and VATS excision, with its low morbidity, may offer another alternative. The Lung Cancer Study group addressed the question of limited resection versus lobectomy for T1 N0 lesions in a prospective, randomized trial. In this study of carefully staged patients proven conclusively to have N0 disease, there was a significantly higher incidence of local recurrence in those who underwent limited resection, but at 3 years there was no survival difference between the two groups. However, a reexamination of the data at 5 years showed a statistically significant survival advantage for the lobectomy group. Wedge excision for bronchogenic carcinoma as a definitive procedure, whether carried out via a VATS approach or open thoracotomy, must be considered a compromise and should be reserved for patients whose pulmonary function is so marginal as to preclude lobectomy.

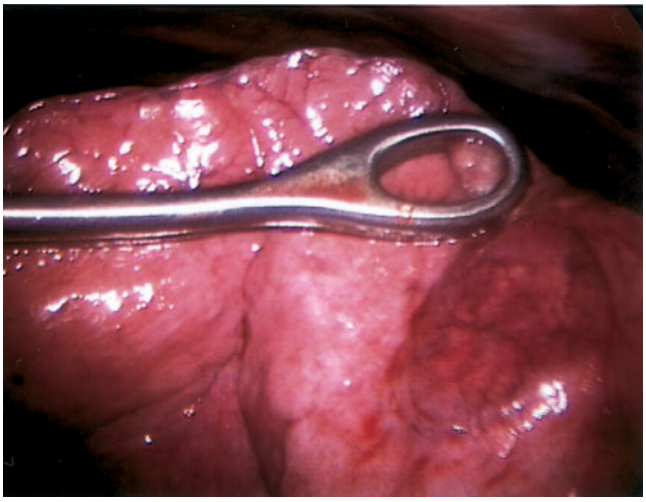


Figure 37-6 A modified ring forceps grasping the lung and moving the lung into position either for wedge excision of a nodule or for palpation of the area to identify the nodule. The forceps is able to grasp the lung without tearing the pulmonary parenchyma, a situation that commonly occurs if the lung is grasped with an instrument with a small surface area.

Anatomic resections (mainly lobectomy) have been performed using a VATS technique that requires a small (6 cm) "utility" incision, but usually without the need for rib spreading—which, theoretically, should minimize postoperative pain (Fig. 37-7). A randomized trial comparing VATS lobectomy with standard muscle-sparing thoracotomy and lobectomy failed to show significant enough differences to justify the routine use of the VATS approach—which probably subjects the patient to a slightly greater risk of intraoperative catastrophe, although no intraoperative deaths have been reported. Roviaro and colleagues performed 52 VATS lobectomies and four pneumonectomies in patients with T1 N0 or T2 N0 lesions. In seven patients it was necessary to convert to an open procedure, three for bleeding during the dissection. There were no deaths related to the procedure. Others have reported the feasibility of performing VATS lobectomy or segmentectomy. A large randomized trial demonstrating

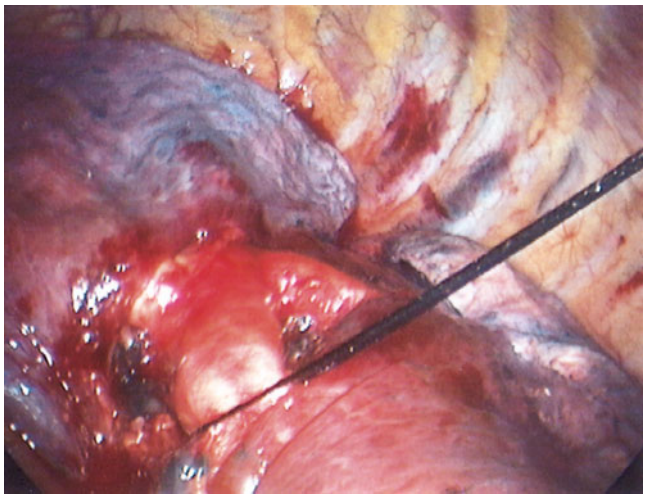


Figure 37-7 View of a video-assisted lobectomy showing the pulmonary artery in the fissure of the left lung. Note the basilar segmental trunk and the branch to the superior segment of the lower lobe. The procedure is performed with visualization provided by the video camera and access via a small utility incision through which regular instruments are inserted but without spreading the ribs.

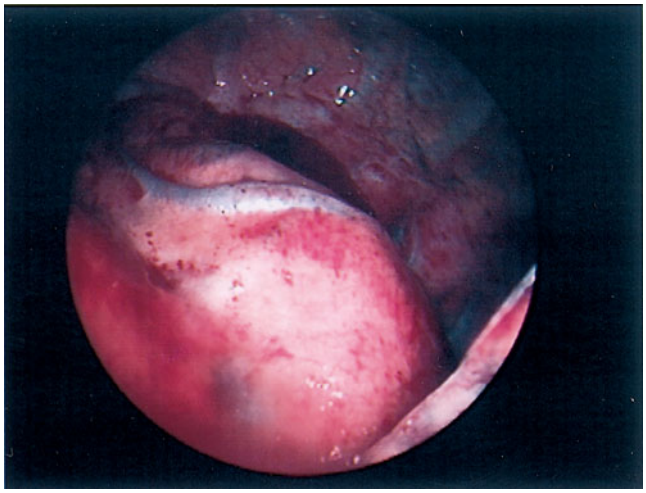


Figure 37-8 The aortopulmonary window, a common site for lymph node involvement when the primary tumor is in the left upper lobe (level 5, subaortic, and level 6, para-aortic). These lymph node locations cannot be reached by standard cervical mediastinoscopy, and videothoracoscopy provides an ideal way both to visualize this area and, when appropriate, to take biopsies.

the superiority of a VATS approach over an open procedure is lacking. VATS lobectomy has not found widespread acceptance, nor is the public demanding it. A few centers continue to perform the procedure regularly.

MEDIASTINAL PROCEDURES

VATS has proved useful as an adjunct to more conventional procedures used in the invasive staging of lung cancer. Mediastinoscopy remains the gold standard for invasive staging of the mediastinum, but lymph nodes in the posterior subcarinal space (level 7) and in the aortopulmonary window (level 5) are not accessible. VATS offers an unmatched ability to visualize the aortopulmonary window and sample lymph nodes in this region (Fig. 37-8). The same is true for the subcarinal space when it is approached from the right side. A VATS staging procedure is not a substitute for mediastinoscopy, but in certain situations directed by findings on the chest CT scan, it may add valuable staging information. This is particularly important because of the interest in preoperative therapy (neoadjuvant) for patients proved to have N2 (mediastinal) lymph node disease.

The utility of VATS is limited for assessing resectability, especially if one is trying to document direct invasion of mediastinal structures (either T3 or T4), but it is of use occasionally. Dissection often proves difficult and potentially hazardous, and there is no substitute for putting one's hand on a lesion of questionable resectability. VATS proves extremely useful, however, in documenting the absence of diffuse pleural metastatic disease if this possibility has been raised (usually by the presence of a pleural effusion).

Many primary lesions of the mediastinum prove to be ideal for VATS management. Lesions in all compartments of the mediastinum are easily accessible, and whether biopsy only or complete excision is the intent, VATS techniques save many patients from having to undergo thoracotomy.

To approach a lesion in the anterior mediastinum, the patient is positioned with the side to be operated on tilted up at approximately 30 degrees instead of in the full lateral position. Often a small inframammary incision is employed. We have utilized a VATS approach to accomplish 15 thymectomies, nine of them for encapsulated thymomas (Fig. 37-9).

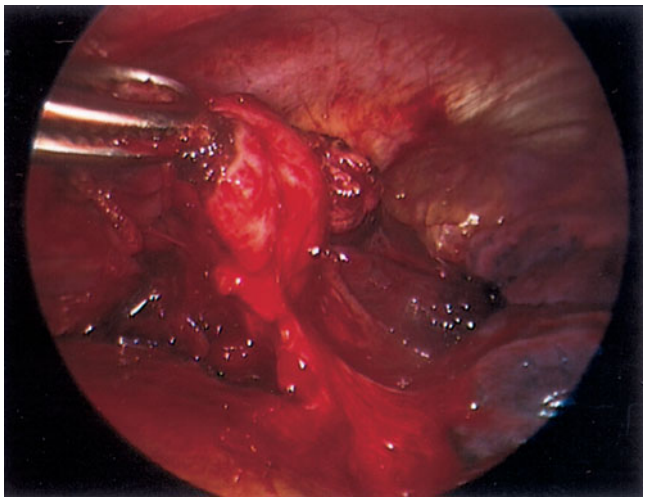
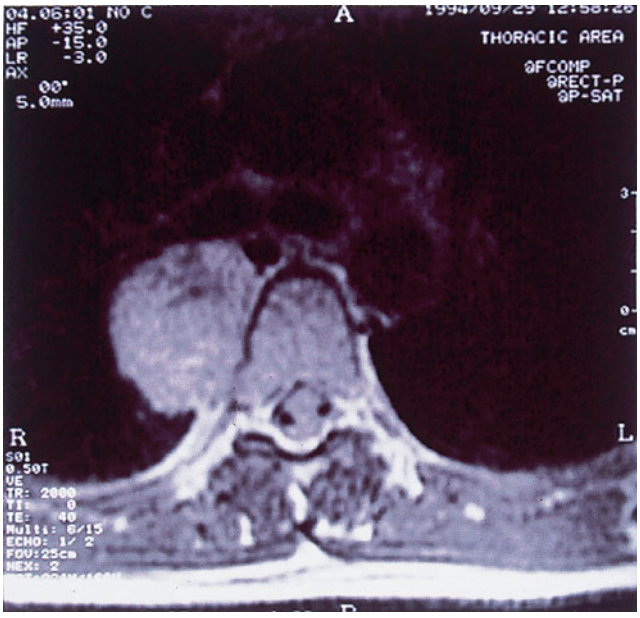


Figure 37-9 A well-encapsulated thymoma being dissected off the pericardium. The cervical portions of the thymus gland have been mobilized by a transcervical approach so that a total thymectomy--the goal of the operation in patients with myasthenia gravis--could be carried out.



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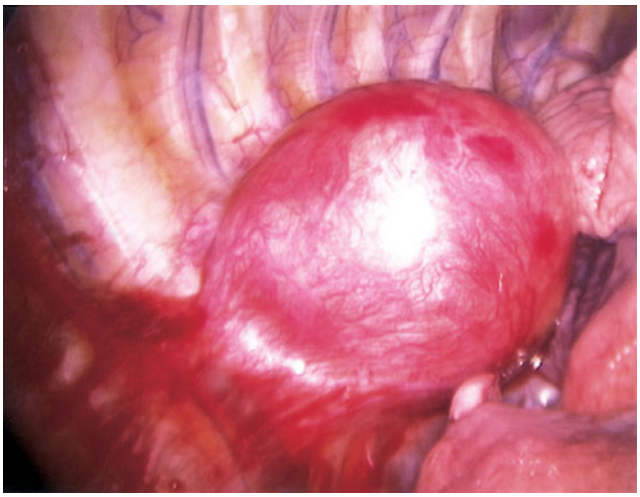

B

Figure 37-10 *A*. MRI scan showing a posterior mediastinal mass sitting in a paravertebral location. Lesions in this location usually are neurogenic, and this lesion proved to be a ganglioneuroma. *B*. View at the time of the videothoracoscopy showing the lesion seen in *(A)*. This lesion was able to be completely excised with a videothoracoscopic approach.

A VATS procedure is contraindicated for presumed invasive thymomas. In patients with myasthenia gravis and a thymoma, a total thymectomy is mandatory and may be facilitated by combining a transcervical approach with the VATS exposure. The thymus gland is initially mobilized in the neck, and branches to the innominate vein are divided. The mobilized gland is then tucked down into the mediastinum, the neck closed, and the patient positioned for VATS. The thymoma is mobilized and the dissection completed with the removal of the gland and tumor through one of the chest incisions. Attempting to excise the tumor and perform a total thymectomy with a VATS approach alone is possible but more difficult, because of the need to extend the dissection well up into the neck.

The patient with a large, diffuse mediastinal mass from which tissue is required for diagnosis may also, at times, benefit from a VATS approach. Many of these lesions are more readily accessed for biopsy through an extrapleural, parasternal approach by excision of the costal cartilage (usually the second). Lesions that are not close to the anterior chest wall may be approached and readily sampled with a VATS approach.

The posterior mediastinum is also the site of either solid or cystic lesions that are amenable to VATS resection. We have resected eight posterior mediastinal lesions, including schwannomas (four) and bronchogenic cysts (four) (Fig. 37-10). Incisions used to approach these posterior or mediastinal lesions differ slightly from those used for access to the anterior mediastinum. Overall, we have performed a total of 85 VATS procedures for mediastinal pathology without mortality and with minimal morbidity.

OTHER PROCEDURES

Pericardial Drainage

A pericardial drainage procedure, so-called pericardial window, may be accomplished through either the right or left chest with a VATS procedure. It is, in fact, often easier to perform this procedure from the right side, where a larger area of pericardium is visible and there is more space in which to work. That being said, a subxiphoid approach to pericardial window usually is simpler, less invasive, and more expeditious, and accomplishes the same goals without the need to insert a double-lumen endobronchial tube and place the patient in the lateral decubitus position. If a large window is believed necessary, there may be an advantage to the VATS approach.

Sympathectomy

The sympathetic chain is easily visualized, as it lies along the vertebral bodies (Fig. 37-11). The magnification provided by VATS facilitates the performance of a sympathectomy. Either dorsal or lumbar sympathectomy may be performed, and bilateral procedures may be accomplished under the same anesthetic, with minimal morbidity. Dorsal sympathectomy may be indicated for palmar hyperhidrosis, reflex sympathetic dystrophy, or other upper-extremity pain syndromes. The superior cervical (stellate) ganglion is readily visualized and preserved, in order to avoid producing a Horner's syndrome. Lumbar sympathectomy may be useful for the management of pancreatic pain, particularly when caused by malignant disease. This requires a bilateral procedure to achieve maximal symptom relief.

In the treatment of chylothorax, VATS may be employed to ligate the thoracic duct. The thoracic duct is most readily identified in the right chest just as it courses through the aortic

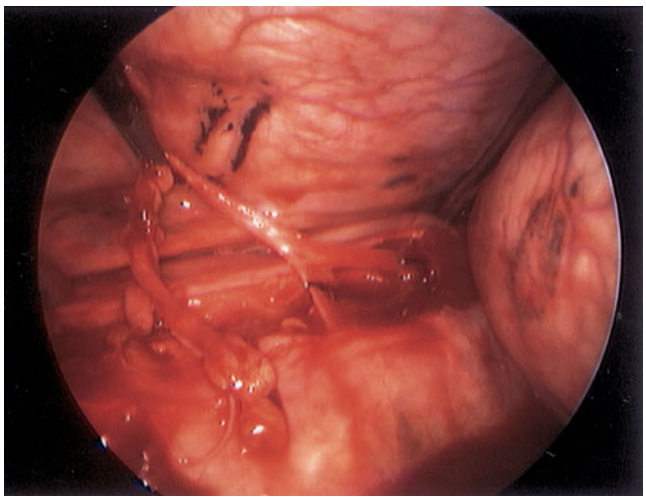

Figure 37-11 The sympathetic chain being mobilized off the vertebral bodies. Ganglia are easily seen as are the various branches of the nerve.

hiatus. In most patients, at this level it is still a single trunk running along the vertebral bodies between the aorta and the esophagus. We have performed 10 thoracic duct ligations for chyle leaks; in two patients, it was necessary to convert to an open procedure to successfully ligate the duct.

VATS provides excellent exposure to the thoracic spine, and procedures such as drainage of abscesses, biopsy of vertebral bodies, discectomy, and anterior releases for kyphoscoliosis have all been carried out successfully, thereby avoiding thoracotomy. Because of the early success and significantly less morbidity in these patients, this technique is becoming the approach of choice in many centers.

COMPLICATIONS

We reviewed the complications that resulted from our initial 266 VATS procedures. There were no deaths, and complications were not life threatening. Ten patients had air leaks lasting longer than 7 days. Eleven patients were electively converted to an open procedure when the intended VATS procedure could not be completed successfully. Bleeding requiring blood transfusion occurred in five patients, and five patients developed superficial wound infections. Data collected on 1358 patients from the VATSG Registry show a similar spectrum of complications, along with 2 percent mortality. As in our series, prolonged air leakage was the most frequent complication; significant bleeding requiring transfusion occurred in only 15 cases (1 percent). To date, no consistent pattern of major complications resulting from VATS has been reported. DeCamp and coauthors list 127 complications occurring in 121 of 595 patients undergoing videothoracoscopy at Brigham and Women's Hospital. Most of the complications were either prolonged air leakage or supraventricular dysrhythmias. We are aware of at least 10 instances of tumor seeding of VATS incisions, and there is at least one report of a death as a result. There appears to be a slightly higher incidence, although still around 3 percent, of recurrent pneumothorax following VATS procedures for spontaneous pneumothorax. Whether this is simply a function of the "learning curve" remains to be determined. The fact that VATS procedures in general have been performed with minimal major morbidity is commendable, since the technology and skills are relatively new to most surgeons.

CONCLUSIONS

Video-assisted thoracic surgical procedures have proved to be extremely useful in the diagnosis and treatment of various thoracic problems. Improvements in video technology have made it feasible for a surgeon and an assistant to work together, and developments in instrumentation, especially staplers, have made many procedures commonplace that previously seemed impossible. Cost issues still need to be carefully examined. Are the more sophisticated techniques and more expensive equipment saving money or expending more resources? If we are expending more resources, is there enough significant benefit to the patient to justify the added expense in this time of cost consciousness? In at least one study, the cost of a thoracoscopic wedge excision ($n = 45$) was less than that of a wedge excision done via thoracotomy ($n = 31$), but the difference was not statistically significant. Disposable instrument costs were significantly higher in the thoracoscopy group. There was no significant difference in the length of hospital stay for the two groups, but in the thoracoscopy group the length of stay was longer than expected. Cost savings potentially should come from a shorter length of stay, and, ultimately, if patients return to work sooner, the overall cost to society should be less, although admittedly this is difficult to measure.

With the tremendous strides made in the development of equipment for videothoracoscopy, there was a great rush on the part of thoracic surgeons to perform as many types of procedures as possible with this new technique. Now that the initial rush is over, we are beginning to appreciate just where these techniques have the greatest application. Some procedures for which there was tremendous early enthusiasm are being performed with less frequency; others have withstood the early shakedown period and have proved their worth over the conventional open procedure, resulting in a benefit to patients.

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38

Perioperative Respiratory Considerations

Horace M. Delisser • Michael A. Grippi

Postoperative pulmonary complications constitute a significant cause of morbidity and mortality following surgery. Managing patients at risk for postoperative pulmonary problems requires an understanding of the predictable changes in pulmonary physiology that occur with surgery and anesthesia, as well as knowledge of factors associated with development of postsurgical respiratory compromise. Despite the availability of several screening tests, a careful history and physical examination continue to be the cornerstone of preoperative pulmonary evaluation. Although a number of measures can be employed before and after surgery to minimize the risk of respiratory complications, close patient monitoring and early detection are essential.

This chapter focuses initially on changes in pulmonary function with surgery. Pulmonary risk factors before, during, and after surgery are reviewed prior to discussion of preoperative evaluation of the patient for surgery, including lung resectional surgery. Finally, recommendations are made regarding preoperative preparation and postoperative prophylactic measures.

CHANGES IN PULMONARY FUNCTION WITH SURGERY

Many postoperative respiratory complications relate to exaggerations of the expected postoperative changes in pulmonary function that occur as a result of the surgery itself, anesthesia, or various pharmacologic interventions. Hence, an appreciation of normal postoperative pulmonary physiology is useful in understanding a number of pulmonary problems

Table 38-1

Changes in Pulmonary Function with Surgery

Reduction in lung volumes
Diaphragm dysfunction
Impaired gas exchange
Respiratory depression due to residual effects of anesthesia or postoperative narcotics
Impaired cough and mucociliary clearance

Source: From Goldmann DR, Brown FH, Guarnieri DM (eds), Perioperative Medicine. *New York, McGraw-Hill, 1994, with permission.*

seen following surgery. Five principal categories of change in pulmonary function with surgery may be considered: (1) lung volumes, (2) diaphragm function, (3) gas exchange, (4) control of breathing, and (5) lung defense mechanisms (Table 38-1).

Lung Volumes

The pattern of pulmonary function abnormalities following thoracic and abdominal surgery is restrictive, characterized by moderate to severe reductions in vital capacity (VC) and smaller, but more important, reductions in functional residual capacity (FRC). The degree of impairment is similar after upper abdominal and thoracic surgery. Smaller changes in VC and FRC are noted with lower abdominal surgery; superficial or extremity surgery is usually unassociated with any significant or persistent changes in lung volumes. During the first 24 h following upper abdominal surgery, VC and FRC may be reduced by more than 70 percent and 50 percent, respectively, and they may remain depressed for more than a week. Consequently, it is not surprising that pulmonary complications are seen more often with thoracic and upper abdominal procedures than with surgery involving the lower abdomen or extremities (see "Intraoperative Risk Factors" below).

Reductions in other lung volumes, including total lung capacity (TLC), inspiratory capacity (IC), expiratory reserve volume (ERV), and residual volume (RV) have been noted. While the forced expiratory volume in 1 second (FEV_1) is decreased, the ratio of FEV_1 to the forced vital capacity (FEV_1/FVC%) remains unchanged, indicating that major airway obstruction does not occur.

Since patients undergoing superficial or extremity surgery do not experience major changes in lung volumes, residual or carryover effects from general anesthesia do not appear to play a primary role in this regard. In fact, studies show that in many patients, FRC in the early postoperative period is unchanged from baseline. An alternative proposal for the reduction is that postsurgical pain and associated muscle splinting may impair lung mechanics. However, since effective pain control using epidural anesthesia or intercostal nerve block fails to fully restore VC or FRC to preoperative levels, other causes must be operative. A growing consensus is that diaphragm dysfunction is an important contributing factor (see below).

The reduced FRC is of major physiological significance postoperatively. Its importance can be understood when the phenomenon of airway closure and the concept of closing capacity (CC) are considered. FRC is the lung volume at the end of a normal tidal expiration. CC is the lung volume at which small airways in the lung bases begin to close during expiration because of a reduction in airway radial traction. The relationship between the two is a key factor in the development of postoperative changes in lung function (Fig. 38-1).

In a normal lung, FRC is always greater than CC, and the airways remain open throughout a tidal breath. However, when CC is greater than FRC, lung volume fails to increase sufficiently during tidal breathing to open all the airways and, consequently, some alveolar units remain closed during a breath. Such regions constitute areas of atelectasis. An intermediate state exists when CC exceeds lung volume for part of the time during each tidal breath. Under these circumstances, the airways open for only a portion of the respiratory cycle, creating areas of low ventilation relative to perfusion. In summary, any circumstance that reduces FRC below CC or that increases CC above FRC produces regions of reduced ventilation and atelectasis (Table 38-2).

Diaphragm Function

Diaphragm dysfunction has been recognized as an important factor contributing to the postoperative reduction in lung volumes. In patients undergoing cholecystectomy, the diaphragm's contribution to quiet tidal breathing after surgery is reduced. This impairment is not due to postoperative pain. Measurements of transdiaphragmatic pressure during maximal phrenic nerve stimulation following upper abdominal surgery indicate that decreased central nervous system output to the phrenic nerves, possibly as a result of inhibitory reflexes arising from sympathetic, vagal, or splanchnic receptors, may be the important etiological factor.

Gas Exchange

Postoperative hypoxemia occurs commonly. There are two phases in its development. The initial phase occurs in the first several hours following anesthesia and surgery. The underlying mechanisms are related largely to the residual effects of the anesthesia and include ventilation-perfusion mismatch, anesthetic-induced inhibition of hypoxic pulmonary vasoconstriction, right-to-left shunting, alveolar hypoventilation, depressed cardiac output, and increased oxygen consumption

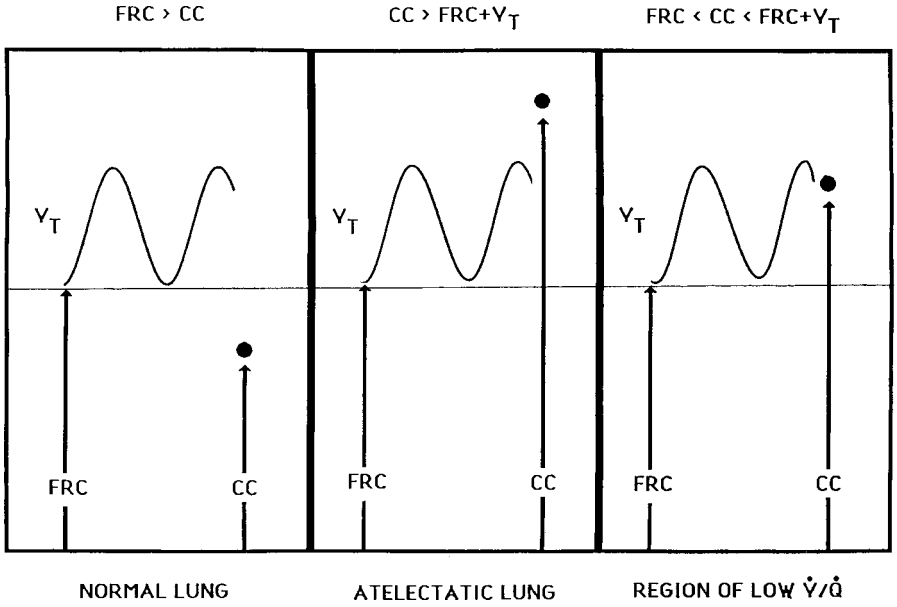


Figure 38-1 The relationship between functional residual capacity (FRC) and closing capacity (CC). See text. *(From Goldmann DR, Brown FH, Guarnieri DM (eds): Perioperative Medicine. New York, McGraw-Hill, 1994, with permission.)*

by peripheral muscle. This phase resolves within 24 h following superficial surgery.

A second phase of hypoxemia that may persist for several days or weeks is seen after thoracic and upper abdominal surgery. This phase correlates with reductions in FRC and changes in the FRC-CC relationship. Although alterations in the FRC-CC relationship predominate, other processes may contribute to late postoperative hypoxemia: (1) alveolar hypoventilation (see "Control of Breathing" below); (2) increased dead space ventilation due to rapid, shallow breathing; and (3) decreased mixed venous oxygen tension due to increased oxygen consumption, impaired cardiac output, and reduced oxygen carrying capacity.

Table 38-2

Conditions That Alter the Relationship between Functional Residual Capacity (FRC) and Closing Capacity (CC)

Decrease FRC	Increase CC
Supine position	Advanced age
Obesity	Smoking
Pregnancy	Chronic obstructive pulmonary disease (COPD)
General anesthesia	Pulmonary edema
Abdominal pain	

Source: From Goldmann DR, Brown FH, Guarnieri DM (eds), Perioperative Medicine. *New York, McGraw-Hill, 1994, with permission.*

Control of Breathing

Respiratory depression is a common feature of the postoperative period. Two factors are responsible. First, residual effects of preanesthetic or anesthetic agents inhibit respiratory drive and reduce the ventilatory response to hypercapnia, hypoxia, and acidemia. Second, narcotics given for postoperative analgesia depress both hypercapnic and hypoxic ventilatory drives, resulting in decreased tidal volume, reduced minute ventilation, and increased Pa_{CO_2}. Narcotics also alter the pattern of breathing, reducing the frequency of sighs or eliminating them entirely; in susceptible patients, narcotics may precipitate sleep apnea.

Lung Defense Mechanisms

Several mechanisms protect the lung from environmental and infectious insults. Two of the most important—cough and mucociliary transport—are compromised after surgery, contributing to an increased risk of pulmonary infection. Postoperative pain or the excessive use of narcotics may inhibit coughing; in addition, altered lung mechanics decrease the expulsive force generated with each cough. Mucociliary clearance is impaired for up to a week following upper abdominal surgery. Although an ineffective cough reflex contributes significantly to reduced mucociliary clearance, several additional mechanisms are involved. These include: (1) cilia damage from endotracheal intubation and inhalation of dry, hyperoxic gas mixtures; (2) reduced tracheal mucus velocity due to the presence of an endotracheal tube; (3) anesthetic-induced inhibition of mucociliary transport; and (4) atelectasis.

Table 38-3

Pulmonary Complications Associated with Thoracic Surgery

Procedure	Complication	Incidence
Coronary artery bypass grafting	Phrenic nerve damage	10%
	Late pleural effusions (arising after discharge)	Not reported in literature
Thoracotomy with lung resection	Bronchopleural fistula or empyema*	5–20%
Median sternotomy	Sternal wound infection (mediastinitis or osteomyelitis)	1–2%
Esophagectomy, gastrectomy	Anastamotic leak	3–6%

** Higher for patients with sarcoidosis and aspergilloma.*
Source: From Goldmann DR, Brown FH, Guarnieri DM (eds), Perioperative Medicine. *New York, McGraw-Hill, 1994, with permission.*

PULMONARY COMPLICATIONS

The criteria used for defining postoperative pulmonary morbidity have varied considerably in published reports, although it is clear that, from a broad perspective, five major categories of complications may be considered: (1) atelectasis; (2) infection, including acute tracheobronchitis and pneumonia; (3) exacerbation of underlying chronic lung disease; (4) prolonged mechanical ventilation and respiratory failure; and (5) thromboembolic disease. With thoracic surgery, several additional unique problems have been noted (Table 38-3).

The variability in defining postoperative pulmonary complications has resulted in reported incidences in the literature ranging from 5 to 90 percent. In general, a healthy, young nonsmoker of normal weight has a very low risk of postoperative pulmonary complications (1 percent or less). However, a number of factors have been identified that are associated with the development of postoperative pulmonary complications (Table 38-4). They include preoperative factors (chronic lung disease, smoking, general state of health, age, obesity, nutritional status, and antecedent respiratory tract infection), intraoperative factors (type and duration of anesthesia, surgical site of operation, and type of surgical incision), and postoperative factors (immobilization and inadequate pain control).

PREOPERATIVE RISK FACTORS

A number of patient-related factors have been implicated in the development of postoperative respiratory complications.

Table 38-4

Factors Associated with Development of Postoperative Pulmonary Complications

Preoperative	Intraoperative	Postoperative
Chronic lung disease	Type of anesthesia	Immobilization
Smoking	Duration of anesthesia	Inadequate pain control
General state of health	Surgical site	
Age	Type of surgical incision	
Obesity		
Nutritional status		
Antecedent respiratory tract infection		

Chronic lung disease (particularly obstructive airway disease), cigarette smoking, and the patient's overall state of health are the most important preoperative risk factors. In addition, age and obesity are relatively minor factors. The precise risks associated with malnutrition and recent viral infections are unknown.

Chronic Lung Disease

The following discussion focuses on the operative risks in patients with three common categories of chronic lung disease: (1) chronic obstructive pulmonary disease, (2) restrictive lung diseases, and (3) pulmonary vascular diseases.

Chronic Obstructive Pulmonary Disease

Since chronic obstructive pulmonary disease (COPD) is the most common chronic pulmonary disorder, most studies addressing the impact of preexisting lung disease on surgical risk have focused on this entity. The reported incidence of postoperative pulmonary complications in patients with COPD varies from 25 to 100 percent and is influenced by type of surgery, magnitude of preexisting respiratory impairment, and criteria used to define complications. Although not precisely quantified in the literature, the risk for postoperative respiratory complications appears to increase significantly (greater than 50 percent) when the FEV_1 is below 65 percent of predicted. The risk is also increased in patients who are hypercapnic.

In patients with severe disease, an important issue is whether a critical level of lung function exists below which the risk of developing a major, potentially life-threatening pulmonary complication is so high as to make anesthesia and surgery too dangerous. In the 1950s, such a prohibitive threshold or level was proposed. Subsequent studies, however, have failed to support this hypothesis. Patients with an FEV_1 as low as 450 ml have been found to tolerate surgery safely. Hence, patients should not be denied necessary operative procedures solely on the basis of marginal lung function. As with all medical interventions, the potential benefits of the operative procedure must be weighed against the operative risk.

The increased incidence of postoperative pulmonary complications in patients with COPD is due, in part, to an increase in the CC, favoring the development of areas of low ventilation-to-perfusion ratios and atelectasis. In addition, in patients who continue to smoke, impaired ciliary function and chronic tracheobronchitis may be contributing factors.

Restrictive Lung Diseases

The risk of pulmonary complications in patients with restrictive lung diseases who undergo surgery is unknown. Although some experience has been reported with patients undergoing thoracic and corrective orthopedic surgery (see below), very little data exist with regard to abdominal and extremity surgery. One might expect a higher incidence of postoperative respiratory complications in these patients for two reasons: (1) FRC is reduced, favoring the formation of areas of poor ventilation and atelectasis; and (2) coughing, and thus the ability to clear respiratory secretions, is impaired.

Experience with postoperative pulmonary complications has been reported in three relatively common situations for patients with restrictive disorders: (1) sarcoidosis complicated by aspergilloma and hemoptysis; (2) corrective surgery for kyphoscoliosis; and (3) myasthenia gravis with associated thymoma.

Sarcoidosis may progress to diffuse interstitial fibrosis and cavitary changes, primarily involving the upper lobes (see Chapter 67). These cavities are prone to infection with *Aspergillus* species and aspergilloma formation, with subsequent development of recurrent and, at times, life-threatening hemoptysis. These patients generally have very poor lung function and, hence, are managed conservatively. However, if supportive medical therapy fails, patients may require thoracotomy and lung resection. Unfortunately, the postoperative course is rarely problem-free and is often complicated by the development of a bronchopleural fistula or empyema.

Corrective surgery in patients with kyphoscoliosis may involve anterior or posterior spinal fusion procedures or a combination of the two. In addition to correction of the primary orthopedic abnormality, an important indication for performing these procedures is progressive deterioration of pulmonary function. Postoperative respiratory complications have been reported in up to 20 percent of these patients, with pleural space-related processes (e.g., pneumothorax, pleural effusion, bronchopleural fistula, and empyema) among the most common. Important risk factors include: (1) nonidiopathic scoliosis, (2) open anterior spinal fusion procedures, (3) age greater than 20 years, (4) mental retardation, (5) preoperative hypoxemia, and (6) obstructive pulmonary function tests. Video-assisted thoracopic (VAT) approaches have emerged as alternatives to open thoracotomy, and initial studies indicate that outcomes of anterior fusion by a VAT procedure and thoracotomy are similar.

Most patients with myasthenia gravis will, during the course of their disease, undergo thymectomy. Risk factors for postoperative pulmonary complications include chronic myasthenia gravis (greater than 6 years), severe bulbar weakness, preexisting respiratory illness, need for large doses of pyridostigmine, and reduced maximal static expiratory pressure (less than 50 cm H_2O or 66 percent of predicted). The preoperative VC has not been found consistently to be a significant predictor of respiratory morbidity following thymectomy. Historically, up to 30 percent of these patients required mechanical ventilation for more than 3 days following the surgery. However, more recent routine use of plasma exchange in patients with bulbar or generalized myasthenia gravis has significantly reduced the duration of postoperative ventilatory support and time in the intensive care unit. Virtually all patients with the disorder are treated with anticholinesterases, which are usually discontinued prior to surgery in order to minimize tracheobronchial secretions. However, controversy exists regarding whether these agents should be restarted immediately after surgery or withheld for 24 to 48 h following thymectomy.

Pulmonary Vascular Diseases

The risk of postoperative pulmonary complications in patients with underlying pulmonary vascular disease and intact respiratory mechanics is not known. However, one might anticipate an exaggeration of, or prolongation in, the hypoxemia seen postoperatively (see "Gas Exchange" above). In addition, pulmonary reserve in these patients is usually reduced; hence, additional pulmonary insults are less likely to be tolerated.

Smoking History

Smoking increases the risk of postoperative respiratory complications, independent of the association of smoking with COPD. Given the well-documented adverse changes in respiratory epithelium and pulmonary function that correlate with the degree of tobacco consumption, such an association is not surprising. In individuals undergoing coronary artery bypass graft surgery, the risk of smoking becomes significant when tobacco use exceeds 20 pack-years. A statistically significant reduction in complications occurs only when patients discontinue smoking for at least 8 weeks prior to surgery. This finding is consistent with studies showing that abnormalities in pulmonary function may persist up to several months after smoking cessation.

Although smoking cessation of more than 2 months is associated with a decreased risk of postoperative respiratory complications, some initial retrospective studies actually showed a paradoxical increase in pulmonary complications in patients who stopped smoking only a few weeks or days prior to surgery. However, a more recent prospective analysis found no evidence for increased pulmonary complications in patients who quit smoking within 2 months prior to a thoracotomy.

General State of Health

Overall clinical status, as categorized by the American Society of Anesthesiologists' (ASA) classification (Table 38-5), correlates with development of postoperative pulmonary complications. For patients undergoing abdominal surgery, an ASA classification of II or higher is a powerful predictor of increased risk of respiratory problems after surgery.

Age

Based primarily on retrospective data from the 1950s and 1960s, advanced age has long been considered a major risk factor for postoperative pulmonary complications. However, recent work suggests that age may not be as significant as originally believed, once other confounding variables are controlled. For example, in a study of 520 patients undergoing elective thoracic or abdominal surgery, no association between age and postoperative pneumonia was found. These findings appear to hold true even when lung tissue is resected. In addition, in a study of patients undergoing thoracotomy for lung cancer, despite a somewhat higher 30-day postoperative mortality in patients over age 70 years, the incidences of postoperative pulmonary complications and hospital stay were not increased, and actual survival was not decreased in the older group.

Table 38-5

American Society of Anesthesiologists' (ASA) Clinical Classification

ASA I:	Otherwise healthy patient undergoing elective surgery
ASA II:	Patient with single system or well-controlled disease which does not affect daily life
ASA III:	Patient with multisystem or well-controlled major system disease which limits daily activity
ASA IV:	Patient with severe, incapacitating disease which is poorly controlled or end-stage
ASA V:	Patient who is in imminent danger of death and is not expected to survive 24 h

Obesity

A number of changes in respiratory mechanics and pulmonary function occur with obesity. The accumulation of fat in the chest wall, diaphragm, and abdomen may reduce total respiratory compliance by more than 60 percent—a change that is amplified when the patient assumes the supine position. The reduced compliance, in turn, increases the work of breathing. Consequently, minute ventilation, oxygen consumption, and carbon dioxide production are further increased beyond baseline values, which are already elevated as a result of increased metabolic demands imposed by the obese state.

Normally, spirometry in obese patients does not indicate airway obstruction. However, a reduction in ERV is found consistently. The magnitude of the reduction correlates with the degree of obesity. Areas of low ventilation relative to perfusion and atelectasis are seen (see "Lung Volumes" above). In addition to these mechanical changes, obese patients appear to have a larger gastric volume and lower pH than do non-obese patients and may be predisposed to aspiration.

Despite what might be predicted based on the changes in lung function described above, retrospective reviews of obese patients undergoing abdominal surgery do not show an increased incidence of pneumonia or atelectasis compared to non-obese patients undergoing similar procedures. The few prospective studies on the risk in obesity of postoperative pulmonary complications have yielded conflicting results. However, in these studies, small numbers of patients have been

studied, liberal definitions of obesity have been employed, patient height has not been routinely considered, and the degree of obesity has not been noted precisely. In studies showing a correlation between obesity and postoperative respiratory morbidity, the principal complication has been atelectasis. Thus, although obesity may increase the risk of some postoperative pulmonary complications, the precise magnitude and significance of the risk are unknown. However, since respiratory complications (e.g., bacterial pneumonia, acute respiratory failure, or prolonged mechanical ventilation) occur in only 4 to 7 percent of morbidly obese patients undergoing gastric bypass surgery, in the absence of other cardiopulmonary disease, the risk of postoperative pulmonary complications associated with obesity appears not to be excessive.

Obesity is, however, clearly a risk factor for obstructive sleep apnea syndrome, which may be unmasked or exacerbated because of use of postoperative analgesics or narcotics. Since sleep apnea occurs in individuals of normal weight, all patients should be questioned about symptoms of the disorder (see Chapter 97).

Nutritional Status

The effects of malnutrition and severe starvation on the respiratory system include a reduced ventilatory response to hypoxia, decreased diaphragmatic muscle function, impaired cell-mediated and humoral immunity, and alterations in the elastic properties of the lung (see Chapter 154). Some evidence of malnutrition can be found in many hospitalized patients, but it is unclear whether the degree of malnutrition usually noted produces clinically significant changes in pulmonary function. In addition, although patients whose nutritional status is compromised may be at higher risk for developing postoperative pulmonary complications, aggressive preoperative nutritional support has not been shown to decrease postsurgical pulmonary morbidity.

Antecedent Respiratory Tract Infection

Enhanced airway reactivity and increased airway resistance may persist for several weeks beyond resolution of the acute symptoms of a viral respiratory tract infection. In addition, diaphragmatic dysfunction has been shown to be impaired during viral infections. Although no published studies have addressed the effect of concurrent viral infections on postoperative pulmonary morbidity, a delay in elective surgery is generally advised, given the changes in airway reactivity and diaphragm function in this setting.

INTRAOPERATIVE RISK FACTORS

Several intraoperative factors have been associated with the development of pulmonary complications after surgery. These include the type of anesthesia, the length of the procedure (as determined by the duration of anesthesia), the surgical site, and the type of surgical incision.

Type of Anesthesia

The pulmonary effects of general anesthesia are addressed in detail elsewhere (see Chapter 147). They include impairment of oxygenation and carbon dioxide elimination. These effects result from anesthetic-induced changes in the shape and motion of the chest wall and diaphragm, which, in turn, lead to increases in alveolar dead space, shunt fraction, and ventilation-perfusion mismatching. The alterations in lung function may contribute to pulmonary morbidity.

Because of the effects of general anesthesia on gas exchange, regional anesthesia has been used as an alternative in patients with underlying pulmonary disease. Indeed, epidural anesthesia to a T4 sensory level does not appear to alter FRC, VC, FEV_1, the alveolar-arterial oxygen gradient, shunt fraction, or cardiac output. Many clinicians have the impression that these strategies lower the incidence of postoperative respiratory complications. However, with the exception of several reports showing a reduced risk of postoperative thromboembolism, studies to date have not been well designed and have not consistently demonstrated that regional anesthesia results in a lower incidence of other postoperative pulmonary complications.

Duration of Anesthesia

The incidence of pulmonary complications increases significantly for procedures lasting longer than 3 to 4 h. Patients whose procedure lasts 4 h or more are five times more likely to suffer postoperative pneumonia than those whose procedures last less than 2 h.

Surgical Site

The development of postoperative pulmonary complications correlates strongly with the anatomic site of operation. The complication rate (excluding thromboembolic disease) is less than 1 percent for non-thoracoabdominal procedures, less than 5 percent for lower abdominal surgery, and greater than 5 percent for upper abdominal surgery (with reported complication rates ranging from 7 to 76 percent). For thoracotomy with lung resection, the complication rate also depends on a number of other factors, including: (1) the presence of underlying lung disease, (2) the amount of functional lung removed, and (3) the extent to which the "bellows" function of the lung is impaired (see "Evaluation for Lung Resection" below).

Type of Surgical Incision

For abdominal procedures, vertical laparotomy incisions carry a higher incidence of postoperative complications than do horizontal incisions. Abdominal laparoscopic procedures and thoracoscopic lung resection have gained widespread acceptance because of reduced patient discomfort, shortened length of hospitalization, and faster patient return to full activity. Since the magnitude of incisional pain is usually less, and since patients typically ambulate sooner, the incidence

of postoperative respiratory problems associated with these less invasive procedures is likely to be reduced. Thus, not surprisingly, laparoscopic cholecystectomy, compared with open cholecystectomy, demonstrates better preservation and faster recovery of lung volumes, less postoperative pain and analgesia use, and higher arterial oxygen saturations.

POSTOPERATIVE RISK FACTORS

Inadequate pain control, prolonged bed rest, and inactivity contribute to the development of respiratory complications following surgery.

Inadequate Postoperative Analgesia

Effective pain control is vital in the early postoperative period, since pain inhibits coughing and deep breathing and discourages early mobilization—factors that contribute to an increased risk of pulmonary complications. Obstacles to good postoperative analgesia include hesitancy of the patient to report pain for fear of being labeled a "bad" patient and anxiety of caregivers in administering narcotics because of side effects.

Immobilization

Prolonged bed rest and inactivity following surgery impact the risk of postoperative respiratory complications in several ways. FRC decreases by 500 to 1000 ml in moving from the upright to the supine position, favoring the development of atelectasis. Increased ambulation is associated with better patient mobilization and clearance of secretions. As discussed elsewhere (see Chapter 82), lack of patient movement in the postsurgical period is a major risk factor for deep venous thrombosis and pulmonary embolism.

PREOPERATIVE EVALUATION

The principal elements in preoperative evaluation of the surgical patient are: (1) the history and physical examination, (2) the chest radiograph, (3) arterial blood-gas analysis, and (4) pulmonary function tests (Fig. 38-2).

History and Physical Examination

A careful history is an essential component of the preoperative evaluation. The following issues should be reviewed: (1) smoking history; (2) history of respiratory symptoms (e.g., cough, chest pain, dyspnea), including symptoms of sleep apnea; (3) extent of preexisting lung disease; and (4) history of recent respiratory tract infection. The physical examination is rarely helpful in identifying pulmonary risk factors. When the history is negative, the physical examination is typically unremarkable. However, the initial physical examination supplements the history and provides a baseline for future comparisons.

Chest Radiograph

The preoperative chest radiograph is usually unrevealing if risk factors and abnormal physical findings are absent. Although the admission or screening chest radiograph is more likely to show an abnormality in individuals with known cardiopulmonary disease, the study usually simply confirms the presence of previously known abnormalities; only occasionally does it result in an alteration in management. Thus, a preoperative chest radiograph is indicated when there are new or unexplained symptoms or signs, when there is a history of underlying lung disease and no recent chest radiograph, or when thoracic surgery is planned.

Arterial Blood-Gas Analysis

Since an elevated Pa_{CO_2} is associated with an increased incidence of postoperative respiratory morbidity in patients with significant chronic lung disease, an arterial blood-gas analysis should be done preoperatively in these patients. It is also recommended that an arterial blood-gas specimen be obtained in patients who, by either history or physical examination, have a new significant pulmonary process or who are undergoing lung resection. Data do not support use of arterial blood-gas analysis as a routine preoperative screening test.

Pulmonary Function Tests

An increased risk of respiratory complications has been demonstrated only in the obstructive category of pulmonary disorders. Although there are theoretical reasons to expect a higher incidence of postoperative respiratory problems in patients with restrictive lung diseases (see "Preoperative Risk Factors" above), currently, no data correlate the degree of restriction (as assessed by lung volumes) with subsequent pulmonary morbidity. Hence, although a complete battery of pulmonary function tests is useful in evaluating suspected restrictive lung disease, spirometry to evaluate for airway obstruction is all that is required to screen patients at risk.

Indications for preoperative pulmonary function testing include the presence of cough or unexplained dyspnea, a history of chronic lung disease, a history of cigarette smoking (greater than 20 pack-years), and planned lung resection (discussed below). Current data do not support the routine use of these studies to evaluate the pulmonary risks of advanced age, obesity, malnutrition, or abdominal surgery. Finally, normal pulmonary function tests do not guarantee a complication-free postoperative course and do not lessen the need for diligent and attentive respiratory care following surgery.

EVALUATION FOR LUNG RESECTION

In evaluating patients for lung resection, the clinician must consider two issues: (1) What are the surgical morbidity and mortality for the patient with significant underlying chronic lung disease? (2) Will postoperative lung function be adequate? A number of approaches have been used over the years

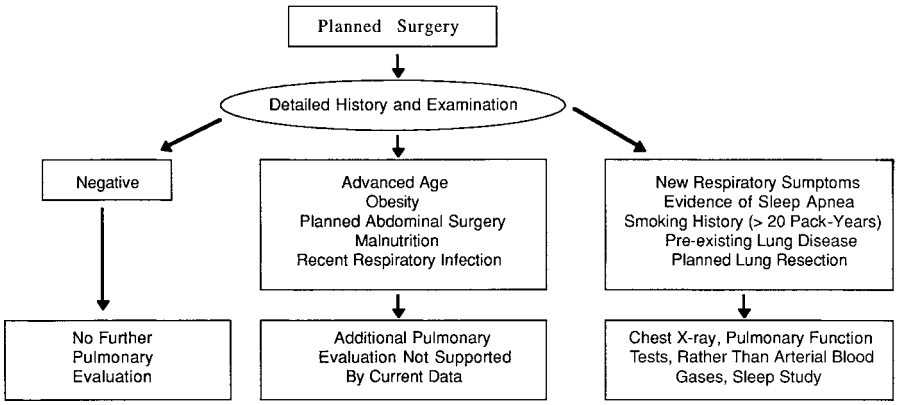


Figure 38-2 Algorithm for preoperative pulmonary evaluation. See text for discussion.

to address these questions. Several, including pulmonary function tests, lung scans, and arterial blood-gas analyses are used routinely; others are used less commonly.

Pulmonary Function Tests, Lung Scans, and Arterial Blood-Gas Analyses

Studies have shown that the risk of postoperative respiratory complications following lung resection (especially pneumonectomy) increases significantly when the FEV_1 is less than 2 L or when the FVC or maximal voluntary ventilation (MVV) is less than 50 percent predicted. For these "high risk" patients, a number of additional tests have been used to estimate postoperative pulmonary function. The most helpful have been quantitative perfusion and ventilation scintigraphy.

Ventilation and perfusion lung scans are equally accurate in calculating the postoperative FEV_1, although perfusion scanning is more commonly used because it is technically easier to perform. These scans measure the relative blood flow or ventilation to one lung or lung region and can be used to predict postoperative FEV_1.

For pneumonectomy, the predicted postoperative FEV_1 is calculated as:

$$\text{Predicted postoperative } FEV_1 = \text{preoperative } FEV_1 \times \text{percent perfusion to remaining lung} \quad (1)$$

For lobectomy, regional quantitative perfusion scans may be used. Alternatively, the postoperative FEV_1 may be predicted using the following equation:

$$\text{Predicted postoperative } FEV_1 = \text{Preoperative } FEV_1 \times (\text{number of lung segments remaining after resection divided by total number of segments in both lungs}) \quad (2)$$

Equation (2) appears to provide information as accurate as that obtained from perfusion studies. When these calculations are inaccurate, they tend to *underestimate* the predicted postoperative FEV_1.

A predicted postoperative FEV_1 of 800 ml has been used as a cutoff for withholding resectional lung surgery, based on the clinical impression that below 800 ml many patients are disabled and develop carbon dioxide retention. Indeed, studies employing this threshold report "acceptable" surgical and postoperative morbidity and mortality. However, no prospective studies have confirmed the significance of this value. Furthermore, the physiological implications of an FEV_1 of 800 ml depend upon a number of factors, including the patient's body size. Therefore, calculation of percent predicted FEV_1 might be of greater value in determining operability. A predicted postoperative FEV_1 of greater than 40 percent predicted has been proposed as a safe criterion in patients undergoing pulmonary resection. Finally, recognizing that most patients who undergo resectional lung surgery have lung cancer and that this malignancy has virtually a 100 percent mortality without surgery (for non–small-cell tumors), caution must be exercised in applying exclusionary criteria.

Finally, as noted previously, hypercapnia in the setting of chronic lung disease is associated with a higher incidence of postoperative respiratory morbidity. Hypoxemia is, however, not as good a predictor of subsequent pulmonary morbidity. In fact, resection of areas of the lung having significant ventilation-perfusion mismatch may *improve* the level of oxygenation postoperatively. A preoperative arterial blood-gas analysis should be obtained in all patients with preexisting lung disease undergoing pulmonary resection. Although supportive data are lacking, it is common practice to obtain an arterial blood-gas sample in all patients undergoing resectional surgery, even those without significant underlying lung disease. This determination serves as a basis for comparison with subsequent intra- and postoperative measurements.

Additional Tests for Evaluating Patients for Lung Resection

Several additional tests, including measurement of diffusing capacity, assessment of exercise capacity, bronchospirometry, the lateral position test, and unilateral pulmonary artery occlusion have been advocated in preoperative evaluation of the candidate for lung resection.

Studies on the predictive value of the preoperative diffusing capacity in assessing operative risk have yielded conflicting results. However, determination of predicted

postoperative D_{LCO} using a formula similar in concept to Eq. (1) may be useful. A predicted postoperative D_{LCO} less than 40 percent of the predicted normal value appears to be associated with a high risk of operative morbidity and mortality.

A number of investigators have found measurement of maximal oxygen consumption during cardiopulmonary exercise testing ($\dot{V}O_2max$) to be useful in predicting postoperative morbidity and mortality. A $\dot{V}O_2max$ less than 15 to 20 ml/kg/min is associated with an increased incidence of postoperative complications. In addition, exercise-induced arterial oxygen desaturation (greater than 2 percent decline) appears to predict postoperative complications, including death and respiratory failure.

The 6-minute walk test and stair climbing are technologically simpler approaches than cardiopulmonary exercise testing and have been used clinically to evaluate the exercise capacity of patients undergoing lung resection.

Studies in patients evaluated for lung volume reduction surgery indicate that those unable to complete a 6-minute walk of more than 500 feet are unacceptable candidates for lung resection. However, for those who maintain an oxygen saturation greater than 90 percent on 2 L of supplemental oxygen while exceeding 700 to 900 feet during a 6-minute walk, morbidity and mortality with lung resectional surgery are less than 10 percent and 1 percent, respectively.

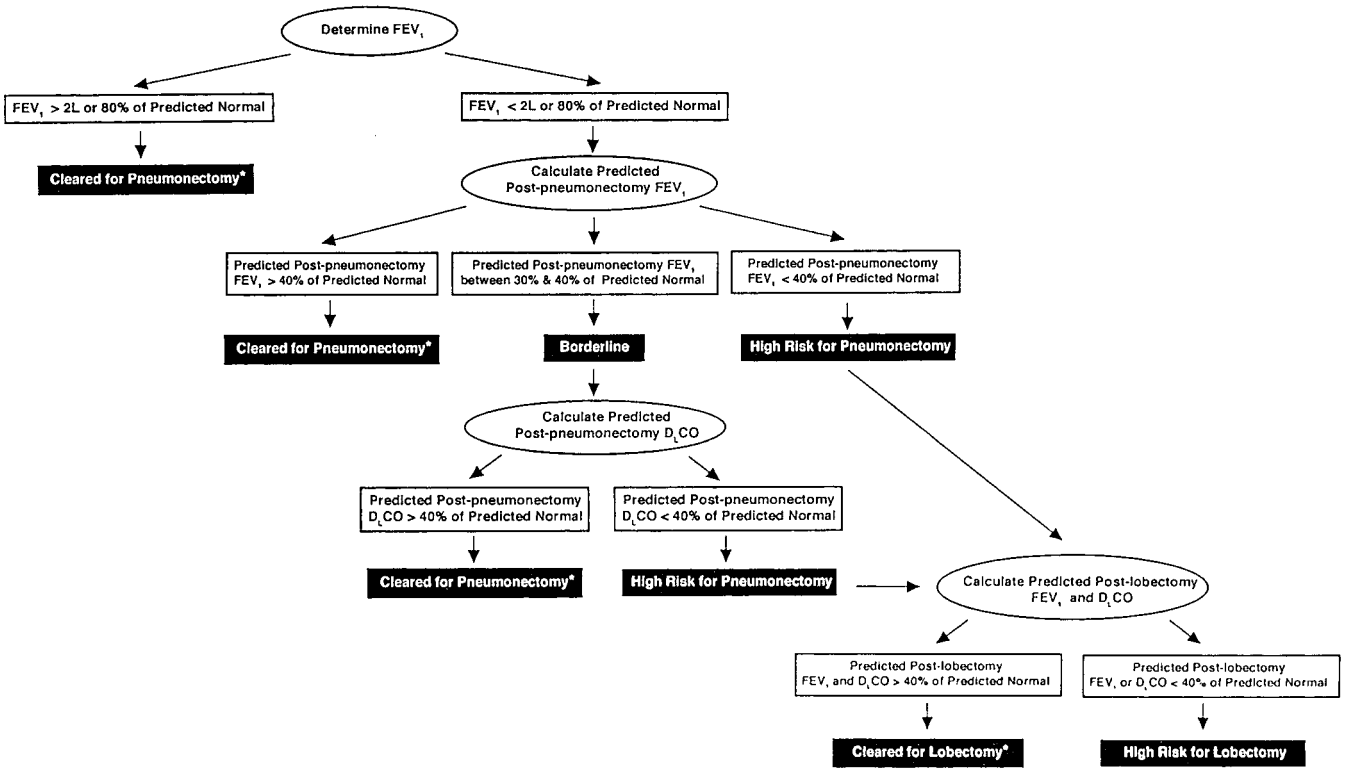
Retrospective studies have demonstrated a significant risk of postoperative pulmonary complications in patients who are unable to climb two flights (where one flight is the equivalent of 12 steps).

Bronchospirometry (the measurement of oxygen uptake in each lung, individually), the so-called lateral position test, and measurement of pulmonary artery pressure during temporary, unilateral pulmonary artery occlusion are techniques used in the past to assess the risk of thoracotomy in borderline patients. These tests are now of historical interest because of technical problems and concerns over reproducibility of results.

Recommended Approach

In evaluating patients for lung resection, the following approach should be considered (Fig. 38-3).

Operability for pneumonectomy is determined in the event that this procedure should become necessary, either to remove the tumor completely or because of an intraoperative complication. If the preoperative FEV_1 is 2 L or greater, or at least 80 percent of the predicted normal value, the patient is "cleared" for pneumonectomy; no further testing is required. If the preoperative FEV_1 is less than these values, the predicted post-pneumonectomy FEV_1 should be determined. The patient is cleared for pneumonectomy if the predicted



*If confirmatory evidence of operability is required, an exercise test can be performed.

Figure 38-3 Algorithm for preoperative evaluation for lung resection. See text for discussion.

postoperative FEV_1 is at least 40 percent of the predicted value. The patient is considered borderline if this number is between 30 and 40 percent of the predicted value; the patient is considered to be at high risk for pneumonectomy if the value is below 30 percent.

For the borderline patient, or for the patient with radiographic evidence of interstitial lung disease or significant dyspnea despite an "operable" FEV_1 or predicted postoperative FEV_1, the predicted post-pneumonectomy D_{LCO} should be determined. The patient is cleared for pneumonectomy if this value is at least 40 percent of the predicted value.

If confirmatory evidence of operability is required, particularly for the borderline patient, an exercise test should be performed. The patient is cleared for pneumonectomy if the $\dot{V}O_2$max is at least 15 to 20 ml/kg/min and arterial oxygen saturation declines less than 2 percent.

If the patient cannot tolerate a pneumonectomy but, from a technical standpoint, appears to be a good candidate for lobectomy, the appropriate steps in Fig. 38-3 should be followed for calculation of the predicted post-lobectomy FEV_1 and D_{LCO}.

Importantly, for selected borderline patients with emphysema and potentially resectable lung cancer, consideration should be given to combined cancer resection and lung volume reduction. This is particularly worth considering if the emphysema is heterogeneous and primarily involves the lobe to be resected.

When respiratory insufficiency occurs as a result of pulmonary resection, it is manifest early (i.e., within the first several weeks following operation). After 3 months, respiratory insufficiency directly attributable to the surgery is rare.

PREOPERATIVE PREPARATION

Surprisingly, few studies have specifically addressed the question of whether aggressive, preoperative pulmonary preparation decreases postoperative pulmonary morbidity and mortality. Although data on preoperative preparation are limited, for patients with significant obstructive airway disease, intensive preoperative respiratory therapy (bronchodilators, corticosteroids, antibiotics, and chest physiotherapy) does appear to reduce the incidence of postoperative respiratory complications by more than 50 percent.

Several preoperative prophylactic measures should be considered in patients undergoing elective surgery (Table 38-6).

Pulmonary function in patients with obstructive airway disease should be optimized. Therapy may include any or all of the following: bronchodilators, corticosteroids, antibiotics (when there is evidence of infection), and chest physiotherapy (if excessive secretions are present). When possible, these interventions should be implemented 48 to 72 h prior to surgery.

Ideally, for at least 8 weeks prior to surgery, smoking should be discontinued. As noted previously, recent data indicate that complication rates are not increased by shorter periods of abstinence; therefore, even when 8 weeks of abstinence is not possible, patients should still be advised to quit smoking prior to surgery.

In severely obese patients, if patient compliance can be achieved, weight reduction should be attempted.

Finally, patient education on the importance of coughing and pain control, proper use of an incentive spirometer, and deep breathing exercises should take place preoperatively.

Table 38-6

Preoperative Pulmonary Preparation

Optimization of airway function in patients with obstructive lung disease (bronchodilators; corticosteroids, antibiotics, and chest physiotherapy, when indicated)
Smoking cessation (ideally, a minimum of 8 weeks prior to surgery)
Weight reduction for severely obese individuals
Patient education (deep breathing exercises, importance of coughing and pain control, use of incentive spirometry)

Source: From Goldmann DR, Brown FH, Guarnieri DM (eds), Perioperative Medicine. *New York, McGraw-Hill, 1994, with permission.*

POSTOPERATIVE PROPHYLACTIC MEASURES

Several postoperative measures may be employed in an attempt to prevent respiratory complications (Table 38-7).

Table 38-7

Postoperative Measures for the Prevention of Respiratory Complications

Early patient mobilization and ambulation
Prophylatic lung expansion maneuvers (incentive spirometry, deep-breathing exercises, continuous positive airway pressure [CPAP]
Provision of adequate analgesia (including patient-controlled analgesia, intercostal nerve blocks, and epidural anesthesia)
Prophylaxis against thromboembolism

Early patient mobilization and ambulation should be encouraged. As noted previously, these measures are important postoperatively in reducing the incidence of atelectasis, in promoting the clearance of secretions, and in decreasing the risk of thromboembolic disease.

Prophylactic lung expansion maneuvers should be initiated. Two equally effective measures are deep breathing exercises and incentive spirometry. Intermittent positive pressure breathing (IPPB) is generally ineffective and costly and is associated with several adverse effects. Reports of intermittent continuous positive airway pressure (CPAP) applied by face mask indicate that it is at least equivalent to deep breathing exercises and incentive spirometry in preventing and treating atelectasis. However, while CPAP may be useful in the patient who cannot cooperate with inspiratory maneuvers, its role in the management of patients capable of taking deep breaths is unclear.

Adequate analgesia should be provided. Traditionally, parenteral narcotics have been used for postoperative analgesia, despite the risk of respiratory depression. Unfortunately, concerns over adverse respiratory effects may lead to inadequate dosing and inadequate pain relief. To overcome this problem, alternative approaches, including use of patient-controlled analgesia, epidural analgesia, and intercostal nerve blocks, have been employed. These alternative techniques provide analgesia equivalent or superior to parenteral narcotics, but published data conflict as to how effective they are in reducing postoperative pulmonary complications.

Prophylaxis for thromboembolism is an important consideration, as discussed in Chapter 82.

Finally, careful monitoring for postoperative complications constitutes a key element in all surgical patients.

Several postoperative interventions have been shown to be ineffective, including the use of "blow bottles," carbon-dioxide–induced hyperventilation, chest physiotherapy in the absence of excessive secretions or sputum production, and routine application of positive end-expiratory pressure in mechanically ventilated patients.

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Evaluation of Impairment and Disability Due to Lung Disease

Paul E. Epstein

Evaluation of disability due to pulmonary impairment is performed for a variety of reasons, including assessment of eligibility for government entitlement programs, litigation following a workplace injury, and evaluation of fitness for placement in a specific job. For purposes of the discussion that follows, the term *impairment* is used to denote a measurable decrease in normal organ function. The term *disability* is used to indicate the total effect that decreased function has on that person's ability to carry out activities of daily living, including the ability to work.

Most evaluations of pulmonary impairment are initiated when a worker complains that he or she can no longer perform the duties of a particular job that were previously accomplished without difficulty. Self-assessment of inability to work is almost always too subjective to be useful to organizations or government agencies that award disability benefits, and the subjective impression of the worker must be verified by a knowledgeable examiner. The worker's treating physician often provides important information about physical impairment, but it is common practice to seek additional evaluation from a specialist or subspecialist who performs an independent medical examination.

The information required for determining the degree of impairment and disability status depends on the purpose of the evaluation. For those seeking benefits under government-sponsored disability programs, the question is

simply whether or not the individual is able to take part in gainful employment. For litigation purposes, the critical questions are whether an employee has been injured on the job (and, if so, what is the severity and permanence of the injury), whether the injury has been totally disabling or whether another type of work is possible, and whether or not workplace restrictions are needed if work is resumed. For workers attempting to be placed in a particular job, the question is whether or not respiratory function is sufficient to perform the job successfully. Each of these questions should be answered as carefully as possible on the basis of objective data.

The need for independent medical assessment arises from a concern that many factors are in play when a claim for disability is filed. Some of these concerns arise because there is a need for standardization of disability criteria in fairness to others who are seeking disability benefits. To deal effectively with this concern, various professional organizations have published standards that are commonly used to estimate an applicant's degree of impairment and to assess the risks involved in performing a particular job.

Another reason for requiring independent assessment is that both the worker and the employer may bear significant financial impact from a determination of disability, and it is the physician's responsibility to provide an unbiased opinion of the severity of impairment.

Finally, claims of disability frequently arise from a workplace injury and evoke anger and other emotions that have little to do with the physical effects of the injury. Legal proceedings that often follow such an injury require that the evaluator identify the portion of the impairment that is attributable to loss of function and separate it from other extraneous issues. The physician must approach the evaluation process as an impartial observer whose primary role is to provide a scientific basis on which disability determination can be made. The physician must avoid taking the role of advocate for one party or another.

Pulmonary physicians play an important, but limited, role in disability evaluation that is confined to determining the worker's degree of pulmonary impairment. Clearly, there are gradations of impairment, and not all impairment leads to disability. In fact, disability determination requires knowledge not only of the impaired person's physical abilities, but also his or her education, skills, job experience, and the availability of appropriate work. Finally, determination of disability depends on the laws and regulations governing the award of benefits. Physicians are not usually expert in the entirety of this knowledge base.

This chapter reviews an approach to the evaluation of pulmonary impairment, the types of information that should be collected in an attempt to answer the pertinent questions, the standards used by various professional organizations to quantify the degree of impairment, and the major programs that use this information in coming to a determination of disability.

METHODS OF EVALUATING IMPAIRMENT

While the claimant or worker initiates the process of disability evaluation, the physician sets the framework for assessment of the degree of impairment. The primary goal in evaluating physical impairment is to provide an objective, valid, reliable, repeatable, and reproducible appraisal of the individual's respiratory condition. In this context, validity means that measurements made in the process of evaluation actually test meaningful aspects of physical capability. Reliability means that changes in the individual's condition will be accurately reflected in the results of appraisal. Repeatability means that there will be close agreement of results when successive measurements are performed using the same instrument, at the same sitting. Reproducibility means that if the tests are repeated by other observers at other times, the results will be similar (or at least within acceptable limits of variability).

The concept that a physician can evaluate an individual in a medical office and perform laboratory tests that provide meaningful information about his or her ability to perform specific tasks in the workplace makes many assumptions that are not strongly evidence-based. Ideally, the physician might achieve the best understanding of the claimant's physical capability by observing him or her perform the tasks necessary to carry out a particular job. Unfortunately, that type of observation is not practical and can not be standardized. For these reasons and others, it is important to understand that many compromises must be made in the evaluation procedure. While some government entitlement programs prescribe arbitrary criteria for eligibility for benefits, in general, the process of impairment evaluation is at least partially based on judgment that requires concordance of several lines of investigation. In the case of pulmonary evaluation, these include history and symptom review, physical examination, radiographic examination, and pulmonary function testing.

Medical History

In addition to documentation of prior medical conditions, an important part of the medical history, in the context of impairment/disability evaluation, is an applicant's occupational and exposure history. The examiner must carefully collect a chronological history of jobs held, specific job duties, time spent in each position, specific chemical or dust exposures encountered at each job site, and an accounting of accidental exposures or physical injury on the job. Many work-related abnormalities resemble other diseases and cannot be diagnosed correctly without a validated exposure history. Industrial facilities are required by the Occupational Safety and Health Administration (OSHA) to maintain material safety data sheets (MSDSs) on all chemicals used in the manufacturing process and to make them available to the employee upon request. These MSDSs can provide valuable help to the physician in evaluating the cause of pulmonary dysfunction.

Table 39-1

Medical Research Council Breathlessness Scale

Grade 1	Are you ever troubled by breathlessness except on strenuous exercise?
Grade 2	*If yes:* Are you short of breath when hurrying on the level or walking up a slight hill?
Grade 3	*If yes:* Do you have to walk slower than most people on the level? Do you have to stop after a mile or so (or after 30 min) on the level at your own pace?
Grade 4	*If yes to either:* Do you have to stop for a breath after walking about 100 yards (or after a few minutes) on the level?
Grade 5	*If yes:* Are you too breathless to leave the house or breathless after undressing?

Table 39-2

American Thoracic Society/Division of Lung Diseases Respiratory Symptoms Questionnaire

Mild	Do you have to walk more slowly on the level than people of your age because of breathlessness?
Moderate	Do you have to stop for a breath when walking at your own pace on the level?
Severe	Do you ever have to stop for a breath after walking about 100 yards or for a few minutes on the level?
Very Severe	Are you too breathless to leave the house or breathless on dressing or undressing?

The most common symptoms that lead to pulmonary impairment/disability evaluation are dyspnea, cough, and wheezing. Dyspnea is entirely subjective and is, therefore, difficult to quantitate. Nonetheless, it is of such importance that a number of dyspnea severity scales have been devised for its evaluation. Measurement of dyspnea is an attempt to discriminate between feelings of breathlessness that are experienced by normal people in performing physical tasks and the heightened feelings of air hunger experienced by people with disordered physiology performing the same tasks. One of the earliest and most useful dyspnea scales is the Medical Research Council Breathlessness Scale, which designates five progressively more severe grades of dyspnea based on the answers to questions about common activities of daily life (Table 39-1).

Another instrument that is widely used for evaluating the severity of dyspnea is based on the American Thoracic Society/Division of Lung Diseases Respiratory Symptoms questionnaire, shown in Table 39-2.

The usefulness of scales such as these is limited because of their frankly subjective nature, but the intensity of dyspnea should be consistent with other, more objective measures of respiratory impairment.

In the context of disability evaluation, cough and sputum production must be viewed as acute, subacute, or chronic, depending on the duration of the symptoms. By definition, acute cough lasts up to 4 weeks; subacute cough lasts between 4 and 12 weeks; and chronic cough lasts more than 12 weeks. Only the chronic forms of cough and sputum production are relevant with regard to disability evaluation.

Recognizing the fact that these symptoms can be important concomitants of disabling disease, two features must be recognized. First, it is difficult to quantitate the severity of cough and sputum production and, therefore, it is not easy to integrate them into a system of progressive gradation of disability. Second, they often accompany objectively quantifiable diseases such as asthma, chronic obstructive pulmonary disease (COPD), interstitial fibrosis, or diseases that are characterized by abnormalities on imaging studies, such as bronchiectasis, suppurative lung disease, or neoplasm. As a result, cough and sputum production should not be used as independent indicators of disability, but rather as signposts that help the physician identify what kind of objective evaluation will most likely lead to appropriate classification.

A history of wheezing, on the other hand, can provide important context for the evaluation of impairment. The temporal characteristics of the onset of wheezing, as well as its association with the workplace (or with particular exposures), often helps identify a specific cause of impairment. Wheezing that occurs primarily on workdays and improves during weekends or during vacations is highly suggestive of work-related asthma. The examiner should also be aware that some workplace exposures produce not only wheezing during work but may also cause repetitive nocturnal wheezing after the day's work has been completed. A history of wheezing that begins immediately after starting a new job implies a different kind of respiratory tract abnormality than a history that is characterized by a latency period between the date of employment and onset of wheezing. Each of these patterns can help the physician identify a particular cause of wheezing and can indicate methods appropriate for protecting the worker from ongoing respiratory tract injury.

Physical Examination

Even though the results of physical examination are less precise and less quantifiable than other techniques used in impairment/disability evaluation, for a variety of reasons this method of assessment retains value even in "high-tech" settings. First, the physician has a unique opportunity to assess the applicant's ability (and willingness) to function in normal circumstances and is better able to verify the reasonableness of laboratory findings. Since financial considerations are usually at stake in determinations of disability, physical examination provides an opportunity for the physician to identify malingering as a possible cause of abnormal test results. Second, physical examination often provides clues to alternative explanations for abnormal laboratory results that might be missed if only laboratory test results and imaging studies were considered. For example, a finding of conjunctival pallor on physical examination may lead to reevaluation of the significance of a diminished diffusing capacity on pulmonary function testing. Since pallor suggests anemia (a common, reversible cause of diminished diffusing capacity), as opposed to intrinsic pulmonary disease (commonly due to irreversible causes of decreased diffusing capacity, such as pulmonary fibrosis or emphysema), physical examination may add value to pulmonary function testing. Third, physical examination can help direct attention to additional causes of physical impairment that were previously unrecognized. Careful cardiac assessment often uncovers evidence of extrapulmonary disease that helps explain complaints of dyspnea. On the other hand, pursed-lip breathing, a barrel-shaped chest, inspiratory crackles, expiratory wheezing, and digital clubbing remain valuable diagnostic observations that help verify the pulmonary origin of respiratory complaints and abnormal pulmonary function test results.

Imaging Studies

A routine chest radiograph remains the most widely used and universally accepted imaging study in the diagnosis of pulmonary impairment resulting from pneumoconiosis, despite the fact that radiographic findings correlate poorly with physiological abnormalities or functional ability. The International Labor Organization (ILO), a specialized agency of the United Nations, first published the ILO International Classification of Radiograph of Pneumoconioses in 1950 as an epidemiologic tool to standardize radiographic interpretation of dust-related lung diseases. This classification system was subsequently revised in 1980 and in 2000. It has been adopted as a standard for the presence and severity of pneumoconiosis by many government disability programs, both in the United States and in other countries. The National Institute of Occupational Safety and Health (NIOSH) offers a certification examination to practitioners wishing to qualify as experts in the ILO system (B Reader certification).

Computed tomography of the chest is generally accepted as more sensitive in detecting both pleural and pulmonary parenchymal abnormalities than plain films of the chest. However, it is much more expensive and administers a higher radiation dose than plain film radiography. High-resolution computed tomography (HRCT) of the chest has proven to be extremely helpful in the differential diagnosis of interstitial lung disease. Like the plain film, correlation between HRCT findings and functional measures are not strongly evidence-based. Despite its clear-cut diagnostic value, HRCT has not been adopted as a standard for disability evaluation.

Pulmonary Function Testing

Most of the standard evaluation schemes for impairment/disability evaluation depend on relatively simple pulmonary function testing. Spirometry and diffusing capacity measurements are generally accepted as appropriate criteria upon which functional judgments are made, since the severity of airways obstruction and abnormalities of gas transfer have been most reliably associated with decreased ability to function in activities of daily living and in the ability to work. Furthermore, these simple tests fulfill requirements that equipment used for testing be widely accessible and that adequate standards for repeatability and reproducibility be met. The American Thoracic Society (ATS) periodically publishes requirements for standardization of equipment and test interpretation. The most recent ATS statements were published in association with the European Respiratory Society (ERS) and have gained worldwide acceptance.

In addition to standardization of both the equipment and techniques of test administration, an important issue in pulmonary function interpretation is the choice of an appropriate normal reference population against which the test taker is compared. Many large populations of normal subjects have undergone pulmonary function testing and have been used to develop reference values for this purpose. Current recommendations of the ATS/ ERS task force suggest that prediction values be chosen on the basis that the reference population is of a similar age range and has the same anthropometric, racial, ethnic, socioeconomic, and environmental characteristics as the individuals being tested. The individual being tested should be asked to self-identify his or her own racial or ethnic group. Although it is most desirable to match the person being tested to an ethnically similar reference group, if none is available an adjustment factor, based on published data, may be used for volume measurements. Various adjustment factors have been recommended for use in these circumstances, since African Americans and Asians have been noted in a number of large surveys to have somewhat smaller lung volumes than Caucasians (about 12 percent and 6 percent smaller, respectively). Hence, individuals may be incorrectly classified as having abnormal pulmonary function as a result of the wrong reference values having been chosen. No race adjustment should be made for the ratio of forced expiratory volume in 1 second to the forced vital capacity percent (FEV_1/FVC%) prediction.

Arterial Blood Gas Analysis

Arterial blood gas testing is rarely used by itself as a criterion of impairment since the test is more invasive than other, more common methods of evaluation. Furthermore, abnormalities of pulmonary function are usually present in association with blood gas abnormalities. Resting hypoxia is sometimes used as a modifying factor in adjusting the assessment of severity of impairment. If arterial blood gas analysis is used as a criterion of disability (as in the Black Lung program), the altitude at which the measurements are made must be specified and abnormal studies must be repeated at an interval of at least 3 to 4 weeks.

Cardiopulmonary Exercise Testing

Cardiopulmonary exercise testing (CPET) is sometimes helpful in evaluating impairment, particularly in individuals whose pulmonary function is moderately abnormal, but whose symptoms are more severe than would be expected from the results of routine testing. Both the ATS and the American Medical Association (AMA) support use of CPET in selected circumstances and provide criteria for impairment based on the results. CPET is seldom helpful when routine pulmonary function tests are either normal or severely abnormal, since the results do not affect determination of disability.

The other circumstance in which CPET is helpful is in assessing the ability of the subject to perform a specific job. Maximum oxygen uptake ($\dot{V}_{O_2max}$) measured during CPET is used to determine the maximum peak exercise level that the individual can achieve. Many experts assume that a worker can perform sustained exertion to a level of approximately 35 to 40 percent of their $\dot{V}_{O_2max}$, although this assumption is not firmly evidence-based. A number of investigators have published estimates of the energy requirements for various jobs, and these can be used to judge the likelihood that an individual is able to perform a specific occupational function. A full description of performance techniques and methods of interpretation of CPET is provided in Chapter 35. The ATS and the American College of Chest Physicians have published a joint consensus statement on the subject.

Bronchoprovocation Testing

Bronchoprovocation testing is a method of evaluating bronchial hyperreactivity in individuals who are suspected of having asthma. The method is important in impairment/disability evaluation because occupational asthma, the presence of which may have significance in judging ability to continue certain types of employment, may not be apparent on routine pulmonary function testing performed between attacks. Evaluation schemes of both the AMA and the ATS take bronchial hyperreactivity into account in assessing impairment. The ATS has published guidelines for performing methacholine bronchial challenge studies and interpretation of the results (see Chapter 34).

AMA GUIDES TO THE EVALUATION OF PERMANENT IMPAIRMENT

The American Medical Association (AMA) has developed guidelines for assessing physical impairment that are widely accepted by governments and legal systems as the standard of evaluation for loss of physical function. These guidelines are continually updated by expert panels that are convened by the AMA and published periodically in book form under the title, "Guides to the Evaluation of Permanent Impairment." Most state workers' compensation programs in the United States, as well as the federal governments of many other countries, use the AMA standards in assessing an individual's ability to work.

According to the AMA Guides, impairment is defined as "a loss, loss of use, or derangement of any body part, organ system, or organ function." It should be obvious from such a broad definition of impairment that not all impairments lead to inability to perform activities of daily living or inability to take part in occupational activities. However, identification of a specific impairment allows the evaluator to initiate an impairment rating that estimates the percentage of loss of function of a particular organ.

Varying percentages of lost function are grouped into four severity classes. Class 1 constitutes 0 percent functional loss (for instance, an observable abnormality caused by an anatomic variation); class 2 indicates that there is objective evidence for a 10 to 25 percent impairment of the whole person as result of organ dysfunction; class 3 indicates a 26 to 50 percent impairment of the whole person; and class 4 is 51 to 100 percent impairment of the whole person. In other words, according to the AMA Guides, impairment rating requires that the evaluator first recognize that an abnormality is present, then identify the cause of the abnormality and objectively evaluate the severity of deviation from normal function, and finally, translate the severity of dysfunction into a numerically based classification that estimates how much of an effect the organ dysfunction has on the individual's ability to carry on the activities of daily living.

Evaluation of the severity of impairment is largely based on results of easily obtainable pulmonary function tests that include spirometry and diffusing capacity. Studies must be performed after the individual has achieved maximal medical improvement and is judged to be in stable condition. If possible, respiratory medications are discontinued 24 hours prior to testing. Spirometry is performed initially; if the $FEV_1/FVC\%$ is below 70, the test is repeated following administration of an inhaled bronchodilator. The equipment, its calibration, test performance, and methods of interpretation must conform to recommendations of the ATS Statement on Standardization of Spirometry. Diffusing capacity measurement is also performed according to ATS recommendations. Physicians evaluating physical impairment using the AMA Guides may also use cardiopulmonary exercise studies. Levels of oxygen consumption required to perform various intensities of work have been published and are used in

Table 39-3

Impairment Classification for Respiratory Disorders

Pulmonary Function Test	Class 1 0% Impairment of the Whole Person	Class 2 10%–25% Impairment of the Whole Person	Class 3 26%–50% Impairment of the Whole Person	Class 4 51%–100% Impairment of the Whole Person
FVC	≥ lower limit of normal	≥60% of predicted and < lower limit of normal	≥51% and ≤59% of predicted	≤50% of predicted
FEV_1	≥ lower limit of normal	≥60% of predicted and < lower limit of normal	≥41% and ≤59% of predicted	≤40% of predicted
FEV_1/FVC%	≥ lower limit of normal	N/A	N/A	N/A
$D_{L_{CO}}$	≥ lower limit of normal	≥60% of predicted and < lower limit of normal	≥41% and ≤59% of predicted	≤40% of predicted
$\dot{V}_{O_2max}$	≥ 25 ml/kg/min or >7.1 METS	≥20 and < 25 ml/kg/min or 5.7–7.1 METS	≥15 and < 20 ml/kg/min or 4.3–5.7 METS	<15 ml/kg/min or <1.05 L/min or <4.3 METS

FVC, forced vital capacity, FEV_1, forced expiratory volume in 1s; D_{LCO}; diffusing capacity of the lung for carbon monoxide; $\dot{V}_{O_2max}$, maximum oxygen uptake.

the AMA Guides to classify levels of impairment. Table 39-3 shows the rating impairment method based on AMA Guides. Several specific pulmonary disorders merit special consideration with regard to the Guides.

Asthma

Standard criteria for classification of respiratory impairment are most easily developed for diseases that cause a fixed level of lung damage, producing decrements in pulmonary function that can be measured reproducibly by serial pulmonary function testing. However, asthma is a disorder that is defined by variability over time, with airflow obstruction that may revert toward normal, either spontaneously or as a result of medication administration. As a result, individuals with even moderately severe asthma may appear normal by pulmonary function testing during periods between exacerbations. This unique variability in lung function in asthma creates difficulty for the physician attempting to evaluate a particular level of impairment caused by the disease, especially if the evaluation is performed during a period of quiescence.

Asthma occupies a unique niche among the disorders which prompt an assessment of respiratory impairment and disability evaluation. Asthma affects about 5 percent of the entire population of the United States and is responsible for substantial amounts of time lost from work and school. The attendant economic impact is huge. No matter what the underlying cause of asthma, frequent attacks degrade quality of life and are a common cause of inability to work.

Workplace exposures frequently exacerbate an underlying asthmatic condition (work-related asthma) or cause sensitization of the respiratory tract to materials found uniquely in the workplace (occupational asthma). Previous attempts to classify the level of impairment caused by asthma have depended on historical assessment of the number of exacerbations per year, as indicated by hospitalizations or unscheduled visits to the physician's office. Unfortunately, this type of assessment introduces extraneous variability into the objective process of standardization of disease severity that results from differences in the patient's ability to self-manage exacerbations, the primary care physician's knowledge, and the emergency room's guidelines for managing acute asthmatic attacks.

In the interest of standardizing evaluation of asthma severity, the AMA Guides incorporate the objective evaluation criteria previously published by the ATS. The AMA Guides assign percentage impairment ratings according to the criteria. In addition to providing more objective standards for judgment, the new AMA classification system for asthma offers the additional advantage that evaluation can be performed during periods of stability, even if spirometry is normal at the time of testing.

Table 39-4

Impairment Classification for Asthma Severity

Score	Postbronchodilator FEV_1	% FEV_1 changes after bronchodilator	PC_{20} (mg/ml)	Minimum Medication Needed
0	≥ lower limit of normal	<10%	>8 mg/ml	No medication
1	≥70% of predicted	10%–19%	8 mg/ml to >0.6 mg/ml	Occasional, but not daily, bronchodilator and/or occasional, but not daily, cromolyn
2	60%–69% of predicted	20%–29%	0.6 mg/ml to ≥0.125 mg/ml	Daily bronchodilator, and/or daily cromolyn, and/or daily low dose inhaled corticosteroid (≤ 800 μg of beclomethasone or equivalent)
3	50%–59% of predicted	≥30%	<0.125 mg/ml	Bronchodilator on demand and daily high-dose inhaled corticosteroid (> 800 μg of beclomethasone or equivalent), or occasional course (1–3 courses per year) of systemic corticosteroid
4	< 50% of predicted	N/A	N/A	Bronchodilator on-demand and daily high-dose inhaled corticosteroid (> 1000 μg of beclomethasone or equivalent), and daily or every-other-day systemic corticosteroid

FEV_1, forced expiratory volume in 1 s; PC_{20}, concentration of methacholine required to decrease FEV_1 by at least 20%.

Using the AMA Guides, four types of information are evaluated in assessing impairment from asthma: (1) postbronchodilator FEV_1, (2) percentage change in FEV_1 following bronchodilator administration, (3) results of bronchoprovocation testing, and (4) assessment of the minimal amounts of medication required to keep the patient's asthma under control.

Postbronchodilator FEV_1 values denoting levels of increasing severity of asthma are shown in Table 39-4 and range from the lower limit of normal to less than 50 percent of predicted. If the FEV_1 is less than 70 percent of predicted, additional evaluation is based on the percentage of reversibility of FEV_1 following bronchodilator administration.

When the FEV_1 is greater than the lower limit of normal, bronchoprovocation testing is performed. Both the ATS and AMA methods of evaluating asthma severity take advantage of the fact that even when there is no active bronchospasm, asthmatic airways show nonspecific hyperresponsiveness to irritant materials, including dust, smoke, and certain chemicals (e.g., methacholine and histamine).

If the results of spirometry are initially normal, methacholine bronchoprovocation testing is performed and the degree of bronchial hyperresponsiveness classified according to the concentration of methacholine required to decrease the FEV_1 by at least 20 percent—a measurement known as the PC_{20}.

A final criterion for asthma severity depends on the minimum amount of medication required to keep the disease under control. Disease requiring higher amounts of medication and systemic corticosteroids is considered more severe.

The evaluating physician calculates an asthma impairment score by adding the numerical values assigned to the results of measurements of postbronchodilator % change in FEV_1 (or PC_{20}), and minimum medication requirement. The total score is used to assign an impairment class, as shown in Table 39-5.

Classification of Impairment Resulting from Other Pulmonary Diseases

Special criteria are applied by the AMA Guides to certain pulmonary diseases that are influenced by factors other than decrements in pulmonary function.

Table 39-5

Impairment Rating for Asthma

Total Asthma Score	Impairment Class	% Impairment of the Whole Person
0	I	0
1–5	II	10–25
6–9	III	26–50
10–11, or asthma not controlled despite maximal treatment (i.e, $FEV_1 < 50\%$ despite use of prednisone at >20 mg/day)	IV	51–100

Lung Cancer

Patients with lung cancer are presumed to be severely impaired (class 4) for at least 1 year following diagnosis, even if surgical resection appears to have been successful in curing the disease. If, 1 year after diagnosis, the patient continues to show no evidence of persistence or recurrence of the disease, reevaluation according to the criteria provided in Table 39-5 may lead to reclassification at a lower level of impairment. Any evidence of recurrence of lung cancer mandates retention of a classification of severe impairment.

Hypersensitivity Pneumonitis

Hypersensitivity pneumonitis may produce no permanent pulmonary impairment if the disease is recognized early in its course and the affected person is removed from exposure to the causative material (usually a high-molecular-weight organic dust, but occasionally, a low-molecular-weight chemical). Even when there has been timely resolution of the pulmonary function abnormality, individuals with a history of hypersensitivity pneumonitis should be permanently removed from exposure. Subacute and chronic forms of the disease caused by repeated exposures often produce pulmonary fibrosis that results in restrictive lung disease. An obstructive component in the subacute and chronic forms of the disease may also be observed. Abnormalities may become permanent features of impairment and should be assessed according to the criteria provided in Table 39-3.

Pneumoconiosis

Pneumoconiosis resulting from exposure to a variety of inorganic dusts that produce pulmonary fibrosis (e.g., asbestos, silica, or coal dust), or those producing granulomatous disease and fibrosis (e.g., beryllium), usually alter pulmonary function in a manner that can be assessed by pulmonary function testing and are classified according to criteria provided in Table 39-3.

Although not all cases of pneumoconiosis are associated with physiological impairment, the AMA Guides suggest that recognition of a pneumoconiosis should prompt the physician to recommend limitation of further exposure to the causative material. In the cases of silicosis and coal workers' pneumoconiosis, development of disease depends on the dust burden in the lung and pathological progression that occurs long after exposure has ceased. In fact, the latency period between exposure and disease manifestation is measured in decades, rather than years, so that failure to remove a worker from further exposure to the responsible dusts may progressively increase the risk of worsening disease. Therefore, in order to avoid further accumulation of dust in lung tissue, recognition of radiologic manifestations of these diseases should prompt removal from mining employment, particularly in relatively young individuals.

Berylliosis

Chronic beryllium disease causing pulmonary fibrosis is mediated by an immune process and is not necessarily dependent on total dust burden in the lung. Regardless of whether a beryllium worker has abnormalities of pulmonary function that fulfill AMA criteria for impairment, once a diagnosis of chronic beryllium disease is made, the evaluating physician should recommend complete cessation of beryllium exposure, since even small amounts may cause further pulmonary fibrosis.

Obstructive Sleep Apnea

Although individuals with obstructive sleep apnea characteristically have daytime somnolence and may have cognitive defects that make adequate work performance difficult, well-documented criteria that provide guidance in determining fitness for employment are lacking. The AMA Guides recommend that impairment determination be left to the judgment of a sleep specialist.

AMERICAN THORACIC SOCIETY CRITERIA FOR EVALUATION OF IMPAIRMENT OR DISABILITY

The American Thoracic Society (ATS) has published a series of guidelines and official statements regarding performance and interpretation of pulmonary function testing. The last ATS statement that was specifically devoted to the general subject of impairment/disability criteria was published in 1986. Since that time, several updates of portions of the statement dealing with the evaluation of pulmonary function test interpretation and asthma, partially in the context of the evaluation

of disability, have been published. In general, the AMA has adopted standards of impairment that have been published by the ATS.

The ATS assigns severity ratings to specific results of spirometry and diffusing capacity, but it does not assign percentage impairment ratings. According to ATS criteria, pulmonary impairment is considered mild if the FEV_1 is greater than 70 percent predicted (but less than the lower limit of normal, based on 95 percent confidence intervals); moderate if it is 60 to 69 percent predicted; moderately severe if it is 50 to 59 percent predicted; severe if it is 35 to 49 percent predicted; and very severe if it is less than 35 percent predicted. On the other hand, FEV_1% predicted does not correlate well with the severity of upper-airway obstruction and may underestimate the severity of obstruction in very severe COPD. Furthermore, FEV_1% predicted correlates poorly with symptoms.

The degree of severity of a decrease in diffusing capacity is judged to be mild if the value obtained is less than the lower limit of normal, but greater than 60 percent predicted; moderate if it is between 40 and 60 percent predicted; and severe if it is less than 40 percent predicted. The ATS acknowledges the fact that, in general, the level of pulmonary function is related to the ability to work and function in daily life. The level of pulmonary function is also recognized as having an association with morbidity and prognosis.

Standards of impairment evaluation for asthma published by the ATS in 1993 form the basis for impairment ratings adopted in the AMA Guides in 2000. Since that time, the ATS has updated its own guidelines for assessing and managing asthma.

DISABILITY EVALUATION UNDER SOCIAL SECURITY

The United States Social Security Administration has two programs that provide financial and rehabilitative benefits to disabled individuals. Both programs require objective demonstration of disability using medical standards set forth in the Social Security Act. Importantly, the standards for disability required by the Social Security Administration are not necessarily the same as those required by other federal programs. Furthermore, while Social Security criteria for disability are uniform across all states, they differ markedly from the criteria developed by each individual state in regard to workers' compensation programs. In addition, they are quite different from those endorsed by insurance companies from which many people purchase policies.

The Social Security Act provides two pathways by which individuals can access disability benefits. The first is through Title II of the act (known as Social Security disability insurance); this is a program that is available to individuals who are insured as a result of their contributions to the Social Security trust fund (through taxes on employment earnings during their work careers). The second is through Title XVI of the act (known as supplemental security income, or SSI); this program is available to disabled individuals who have limited income or resources but, who, for one reason or another, are not covered by contributions to the Social Security trust fund.

For adults, the definition of disability is the same whether application for benefits is made under Title II or Title XVI of the Social Security Act. The Social Security Administration defines disability as "the inability to engage in any substantial gainful activity by reason of any medically determinable physical or mental impairment(s) which can be expected to result in death or which has lasted or can be expected to last for a continuous period of not less than 12 months."

The methods used for disability evaluation under Social Security are important for the physician to understand for two reasons: first, because it is a common and important source of financial support for many patients who are under the care of pulmonary physicians, and second, because the pulmonary physician often takes an active role in helping determine eligibility. Unlike workers' compensation programs, the cause of disability is not relevant in awarding benefits. The sole criterion for granting benefits is whether or not the claimant is able to participate in gainful employment.

Evaluation of disability under Social Security is a staged process, beginning with application to a local Social Security field office or the Office of Disability Determination Services (DDS). The DDS gathers objective medical information primarily from the treating physician (who is the preferred source of medical evaluation). If the available information is insufficient to make a determination of disability, the DDS may purchase additional testing and examination from a consultative examiner (CE), such as a pulmonary physician.

The Social Security Administration has decided that certain specific impairments of each major body system are severe enough to prevent a person from engaging in any gainful employment and, therefore, serve as prima facie evidence that disability exists. These impairments have been codified and are known as the Listings of Impairments. Listings include specific severities of abnormalities for various diseases, including COPD; chronic restrictive ventilatory disease; chronic impairment of gas exchange; asthma; cystic fibrosis; pneumoconiosis; bronchiectasis; mycobacterial, mycotic, and other chronic persistent infections of the lung; and cor pulmonale due to chronic pulmonary vascular hypertension.

If a claimant cannot meet the severity criteria of the Listings, he or she may still receive award of benefits by presenting the medical information pertinent to his or her case to the DDS. An initial judgment may then be made by the DDS, but the claimant has the right to challenge an unfavorable decision and to have it reviewed by other members of the DDS staff. If the decision is still unfavorable, the claimant may appeal to the Office of Hearings and Appeals for review by an administrative law judge, who may request expert physician testimony before making a decision. Once again, the claimant can request that an unfavorable decision be reviewed by an appeals council.

Table 39-6

Social Security Listings for Severity of COPD According to FEV_1

Height without Shoes (cm)	Height without Shoes (in)	FEV_1^* ≤
≤154	≤60	1.05
155–160	61–63	1.15
161–165	64–65	1.25
166–170	66–67	1.35
171–175	68–69	1.45
176–180	70–71	1.55
≥181	≥72	1.65

**L, BTPS (liters, body temperature and pressure standardization).*

Table 39-7

Social Security Listings for Severity of Restrictive Lung Disease According to FVC

Height without Shoes (cm)	Height without Shoes (in)	FVC_1^* ≤
≤154	≥60	1.25
155–160	61–63	1.35
161–165	64–65	1.45
166–170	66–67	1.55
171–175	68–69	1.65
176–180	70–71	1.75
≥181	≥72	1.85

**L, BTPS (liters, body temperature and pressure standardization).*

SOCIAL SECURITY LISTINGS

An examination of the criteria that determine eligibility for Social Security benefits according to the Listings is helpful in understanding the process.

Chronic Obstructive Pulmonary Disease

In order for COPD to fulfill criteria for the Social Security Listings, the measured FEV_1 must fall at or below the values shown in Table 39-6.

Asthma

Claimants with asthma can meet the Listings criteria either on the basis that they fulfill the pulmonary function abnormalities noted previously for COPD, or because the severity of their disease is such that it requires physician intervention at least six times a year, despite following a prescribed therapeutic regimen. Inpatient hospital treatment lasting more than 24 hours is viewed as equal to two attacks requiring physician attention.

Restrictive Lung Disease

For chronic restrictive ventilatory disease, the FVC must be equal to or less than the values shown in Table 39-7.

Abnormalities of Gas Exchange

In order to reach the severity required for inclusion under the listings for chronic abnormalities of gas exchange, the single breath D_{LCO} must be less than 10.5 ml/min/mmHg or less than 40 percent of the predicted normal value.

Arterial blood gas abnormalities are also considered valid indicators for Social Security Listings, as long as they are performed in the prescribed manner and indicate the required severity of pulmonary disease. Simultaneously, measurements of Pa_{O_2} and Pa_{CO_2} using arterial blood gas analysis must be performed with the claimant at rest and in stable condition. He or she must be awake and in a sitting or standing position. Furthermore, arterial blood gas analysis must be performed on two occasions which are at least 3 weeks apart but within 6 months of one other. The arterial blood gas results must also be interpreted with recognition of the altitude at which they were obtained. With these requirements in mind, a claimant will meet the Listings if arterial blood gas findings are equal to or less than those shown in Table 39-8. Of note is the fact that according to the Listings, measurement of pulse oximetry is not accepted as prima facie evidence of severe pulmonary disease.

Pneumoconiosis

In order for a person to meet the Listings criteria for pneumoconiosis, a radiographic diagnosis must first be made according to appropriate imaging techniques. The severity of the disease is then judged on the basis of the functional deficits shown in Tables 39-6, 39-7, and 39-8, for obstructive disease, restrictive disease, or abnormal gas exchange.

Cystic Fibrosis

Patients with cystic fibrosis qualify for benefits under the Listings if they have an FEV_1 that is less than or equal to the

Table 39-8

Social Security Listings for Severity of Gas Exchange Abnormalities According to Arterial Blood Gas Results*

Pa_{CO_2} and Pa_{O_2} (mmHg) from Column 2 or 3	At altitude ≤3000 ft, Pa_{O_2} (mmHg) ≤	At altitude 3000–6000 ft, Pa_{O_2} (mmHg) ≤
≤30	65	60
31	64	59
32	63	58
34	61	56
35	60	55
36	59	54
37	58	53
38	57	52
39	56	51
≥40	55	50

* *Fulfillment of blood gas criteria shown denotes severe impairment and qualifies applicant for disability status.*

levels listed in Table 39-9; or if they have episodes of bronchitis, pneumonia, hemoptysis, or respiratory failure that require physician intervention at least six times annually (one hospitalization for more than 24 hours counts as two outpatient visits); or if there is persistent pulmonary infection with symptomatic episodes requiring intravenous or nebulized antibiotic therapy at least every 6 months.

Cor Pulmonale Due to Chronic Pulmonary Vascular Hypertension

Qualification for benefits under the listings for patients with cor pulmonale requires clinical evidence of the disease and either a measured mean pulmonary artery pressure greater than 40 mmHg or arterial hypoxemia to the levels shown in Table 39-8.

Mycobacterial, Mycotic, and Other Chronic Persistent Infections of the Lung

These diseases meet standards for inclusion under the listings only when the degree of functional abnormality reaches the levels outlined previously for obstructive disease, restrictive disease, or abnormalities in gas exchange (Tables 39-6, 39-7, and 39-8).

Table 39-9

Social Security Listings for Severity of Cystic Fibrosis According to FEV_1

Height without Shoes (cm)	Height without Shoes (in)	FEV_1^* ≤
≤154	≤60	1.45
155–159	61–62	1.55
160–164	63–64	1.65
165–169	65–66	1.75
170–174	67–68	1.85
175–179	69–70	1.95
≥180	≥71	2.05

* *L, BTPS (liters, body temperature and pressure standardization).*

STATE WORKERS' COMPENSATION PROGRAMS

Until the early part of the twentieth century, US federal and state-based programs to compensate workers for injuries sustained on the job did not exist. The only legal recourse available to a worker injured on the job was to sue his or her employer through the usual tort system of the courts. Such legal proceedings were often heavily weighted in favor of the employer. Worse still, the legal concept of occupation-related disease (as opposed to occupational injury) was not widely recognized by the courts at that time.

As the Industrial Revolution became progressively more established in Europe and the United States during mid- and late nineteenth century, however, the problem of workplace injuries and occupation-related diseases became ever more important as large numbers of workers left the farm for urban employment in factories and other industrial environments where they were frequently adversely affected by working conditions. By the late nineteenth century, Great Britain had passed legislation that afforded some protection to injured workers, and a few decades later the United States followed suit by passing legislation modeled on the British system. However, because the US Supreme Court at that time interpreted the US Constitution as forbidding federal legislation from covering private-sector employers, the federal government kept workers' compensation legislation at arms' length, leaving each state to work out its own solution to the

problem. As a result, significant variations occurred from state to state in the details of coverage and management systems for workers' compensation, with legislation that was enacted at varying times in a pattern that formed what was essentially a patchwork quilt that eventually covered all 50 states.

Despite the history of independent development of legislation in each state, certain unifying concepts emerged in the way state programs were crafted. In each state, concepts of coverage were hotly contested on the one hand by powerful industrial concerns and on the other hand by labor unions which had recently found their voice in the formation of a strong labor movement. One of the concepts, finally accepted by all stakeholders, marked a dramatic change in the way claims were handled.

In what amounted to an epiphany of understanding between the parties, the interaction between the employer and the injured employee changed from a frankly adversarial relationship to a no-fault system that focused on providing help to the injured employee without consideration of which party was at fault in causing the injury. Both the employer and the employee had to give up certain rights in order to develop a system that would fairly serve all parties. The employee gave up almost all rights to sue the employer for workplace injuries, but, in return, received automatic acceptance of the right to receive free medical care for the immediate injury, cash benefit payments during the period of disability, and rehabilitation services to facilitate a return to work. These services are commonly provided through insurance carriers that sell workers' compensation policies to employers.

Most states require the employer to purchase insurance coverage for their workers, although some states maintain a workers' compensation pool (which the employer can purchase from the state), and some states allow large companies to self-insure. The employer usually has the right to maintain a panel of physicians who evaluate injured employees. In most states, the employee has the right to choose his or her treating physician, but the rates of payment to the physician may be set by law. If the employee has lost time from work as a result of injury, cash benefits are paid for temporary disability according to a formula that varies from state to state with regard to payment size and period of time allowed for each type of disability. Benefits may be awarded for temporary total disability, permanent partial disability, or permanent total disability. Some cash payments are known as "scheduled" losses if they involve injuries, such as loss of arms, hands, fingers, legs, feet, toes, eyes, and ears, while others are "nonscheduled," such as injuries to lungs, heart, back, and so forth. Most states use the classification system of the AMA Guides to the Evaluation of Permanent Impairment (described in detail above) to determine the severity of nonscheduled losses.

FEDERAL WORKERS' COMPENSATION

The first legislation to providing workers' compensation for civilian federal employees to pass the test of constitutionality by the US Supreme Court was signed into law by President Theodore Roosevelt in 1908. However, this program was extremely limited in both scope and benefits and was restricted to very hazardous jobs. Not until 1916 was more comprehensive legislation covering civilian government employees passed in the form of the Federal Employees' Compensation Act. The legislation is administered by the Office of Workers' Compensation Programs. Subsequently, a few additional federal programs were passed by Congress, including the Merchant Marine Act, Longshore and Harbor Workers' Compensation Act, Black Lung Benefits Act, and Energy Employees' Occupational Illness Compensation Program Act. The last two programs are of particular interest to pulmonary physicians because the programs deal specifically with occupational lung diseases, and because the criteria for awarding benefits are radically different from one another.

BLACK LUNG BENEFITS

The federal Black Lung program grew out of the federal Coal Mine Health and Safety Act of 1969. This act was modified by the Black Lung Benefits Act in 1972, which set eligibility criteria for the award of benefits; the act since has been amended several times. While providing funding for benefits is primarily the responsibility of the mining company responsible for the injury, it is not unusual in the coal mining industry to find that either the company had gone out of business or that no specific mine can be identified as responsible. The Black Lung Benefits Revenue Act, therefore, set up a trust fund, funded by an excise tax on coal that was mined and sold in the United States. Eventually, management of the Black Lung program became the responsibility of the US Department of Labor, administered through the Office of Workers' Compensation Programs, Division of Coal Mine Workers' Compensation.

A coal miner applying for Black Lung benefits must supply to the Division of Coal Mine Workers' Compensation medical evidence of pneumoconiosis, including the following: a chest radiograph, along with a report of the findings using the International Labor Organization (ILO) classification system; a report of physical examination detailing the occupational and medical history as well as all manifestations of chronic respiratory disease; pulmonary function test results; and arterial blood gas results. The submitted chest radiograph should fulfill the ILO criteria for radiographic quality and must be interpreted as showing at least category 1/0 pulmonary parenchymal interstitial abnormalities, indicating pneumoconiosis (according to the ILO International Classification of Pneumoconioses). Preferably, the chest radiograph should be interpreted by a NIOSH-certified B Reader or a board-certified or board-eligible radiologist. Pulmonary function tests, recorded as flow-volume loops, must provide measurements of FVC and FEV_1 and calculation of the FEV_1/FVC ratio. Measurements of maximal voluntary ventilation (MVV) may also be used to support a claim for disability. Arterial blood gas analysis is initially performed at

rest, but if the results do not fulfill criteria for disability, the study may be repeated during exercise.

The Department of Labor has published detailed tables of spirometric and arterial blood gas values delineating criteria for total disability. For example, according to the tables, a 55-year-old male who is 5' 10" tall is considered totally disabled if the FVC is less than or equal to 2.71 L, or the FEV_1 is less than or equal to 2.14 L. At any age or height, the applicant is considered totally disabled if the FEV_1/FVC% is less than or equal to 55 percent, or the $PaO_2$is 60 mmHg or less (at sea level, with the $PaCO_2$ between 40 and 49 mmHg).

Importantly, for the purposes of the Black Lung Benefit Act, pneumoconiosis is defined as "a chronic dust disease of the lung and its sequelae, including respiratory and pulmonary impairments arising out of coal mine employment." Included in this definition are not only the diseases that chest physicians usually consider as pneumoconioses (e.g., coal workers' pneumoconiosis, anthracosis, anthracosilicosis, massive pulmonary fibrosis, silicosis, or silicotuberculosis), but also what the act notes as "legal pneumoconiosis" (i.e., any chronic restrictive or obstructive pulmonary disease arising out of coal mine employment).

ENERGY EMPLOYEES' OCCUPATIONAL ILLNESS COMPENSATION PROGRAM ACT

The Energy Employees' Occupational Illness Compensation Program Act (EEOICPA) was signed into law in 2000 and provides benefits to workers who have acquired disease in the course of their work in the nuclear defense industry. This includes employees and former employees of the Department of Energy at nuclear weapons factories, as well as private contractors and subcontractors who supplied the facilities. The two major toxic exposures encountered by these workers include beryllium (used in the manufacture of ballistic missile nose cones) and radiation. Chronic beryllium disease, as a result of exposure to beryllium dust, produces a granulomatous disease of the lungs that commonly causes progressive pulmonary fibrosis. Radiation exposure is a major cause of cancer, including lung cancer. In contradistinction to Black Lung evaluation, the EEOICPA has adopted the standards of the AMA Guides to the Evaluation of Permanent Impairment as the method of rating impairment and disability.

AMERICANS WITH DISABILITIES ACT

Although many physicians think of impairment assessments as inquiries that follow an injury or are conducted at the end of employment, in reality, some of the most important assessments of physical abilities are made at the start of a job. Until relatively recently, people with any type of physical impairment were excluded from employment because of unreasonable fear that an impaired employee would be a detriment in the workplace. The Americans with Disabilities Act (ADA), which was enacted in 1992, produced a fundamental change in the way physical impairments are viewed within the business and legal communities.

Many of the regulations established by the ADA deal with the removal of physical barriers that prohibit impaired workers from entering and functioning within the workplace. Others are specifically directed at removing bias and prejudice from the opportunity to enter the workforce itself. While the ADA has not altered the methods of impairment evaluation used by physicians, it does have a substantial impact on the timing of evaluations and the way these evaluations are reported and used. For instance, while pre-employment physical examinations were commonly requested by industrial and commercial firms prior to enactment of the ADA, they are no longer allowed, due to the perceived risk that a qualified individual might be excluded from employment because of an impairment that has little or nothing to do with the requirements of the job. Prior to making a job offer, employers are no longer allowed to ask if a prospective employee has a physical impairment, although they may ask if he or she can perform the duties of the job. Once a job offer is made and accepted, physical examination is permissible to confirm that the job can be performed in a safe and acceptable manner. In fact, the employer is legally permitted to make a job offer conditional on the applicant passing a physical examination, as long as the same physical requirements are required for every employee in the same job category. These examinations, known as pre-placement physicals, must deal only with job-related issues and must be consistent with business necessity.

The other major change in the determination of work-related physical fitness is that businesses are required to make reasonable accommodation for physical impairments as long as the impairments do not interfere with the essential requirements of the job.

The two concepts of forbidding non–job-related impairment to preclude employment and of making reasonable accommodation for the presence of a non-essential disability can be illustrated in the following scenarios.

Consider a prospective employee who has severe COPD, with an FEV_1 of 50 percent predicted and D_{LCO} of 59 percent predicted; the individual has no history of recurrent infections or excessive absences from work. On the basis of his physical condition, this individual cannot be excluded from a job as an accountant, but he might legally be denied a physically demanding job, such as a firefighter, who must regularly carry heavy equipment into smoke-filled buildings and climb many flights of stairs. The essential work of an accountant does not involve physical exertion, and the applicant's physical condition would not adversely affect his performance in the workplace. On the other hand, the work of a firefighter would be dangerous to a person with severe pulmonary disease.

As a second example, consider a prospective employee who has the same pulmonary function tests as noted in the first scenario. The individual applies for a position in a factory

where the main job responsibility is watching the flow of products on a conveyor belt and pressing a stop button if a malfunction arises. Once a day, the employee is required to lift to shoulder height a 75-pound bag. While it would be difficult for the employee to perform the lifting activity, a reasonable accommodation would be either to provide help from another employee, or to install a hydraulic lifting device. Employers are not, however, required to make unreasonably extensive changes to a work area or to undertake "action requiring significant difficulty or expense" in order to accommodate an otherwise qualified applicant.

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PART

IV

Obstructive Lung Diseases

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40
CHAPTER

Pathologic Features of Chronic Obstructive Pulmonary Disease: Diagnostic Criteria and Differential Diagnosis

Joanne L. Wright • Andrew Churg

Chronic obstructive pulmonary disease (COPD) is a general name for the chronic airflow obstruction that develops most often as a result of chronic tobacco smoking. The pathology of COPD encompasses a variety of pathologic lesions in the airways, lung parenchyma, and pulmonary vasculature, and these lesions can be correlated, to a greater or lesser degree, with changes in pulmonary function tests and clinical appearances. In general, although the mechanisms involved are complex, airflow obstruction can be attributed largely to a marked increase in airways resistance secondary to a variable mix of structural abnormalities involving all or many of the compartments of the airway. However, in individual cases, it

may be difficult to prove associations between physiological abnormalities and pathologic changes. The recently developed Global Initiative on Obstructive Lung Disease (GOLD), classifies patients with COPD purely upon indices of airflow and thus far there is only limited integration with pathologic findings.

This chapter presents the pathologic features of COPD and how these findings can be differentiated from other lesions associated with airflow obstruction.

HISTORY OF PATHOLOGIC DESCRIPTIONS OF COPD

The word emphysema is derived from Greek and means "to blow into," hence "air-containing" or "inflated." Although "voluminous lungs" and lungs "turgid particularly from air" were described respectively by Bonet in 1679, and Morgagni in 1769, the first description of enlarged airspaces in emphysema in the human, together with illustrations, was furnished by Ruysh in 1721, followed by Matthew Baillie in 1807, who not only clearly recognized and illustrated emphysema, but also pointed out its essentially destructive character.

Laennec, writing in the early 1800s, made a number of seminal contributions to the basic descriptions of pathologic changes in COPD. He was the first to make a clear-cut distinction between interstitial emphysema and emphysema proper, and related the enlarged airspaces to the clinical syndrome of emphysema. He also recognized that air trapping and increased collateral ventilation were features of emphysematous lungs, and that the peripheral airways were the primary site of obstruction in emphysema. Furthermore, he noted that airspaces enlarged with increasing age, and he distinguished these changes from emphysema. He was the first to describe an association of emphysema with chronic bronchitis and to clearly describe the pathology of bronchiectasis.

Little of major importance was added to the gross descriptive morphology of emphysema for almost the next 150 years. The foundation of modern knowledge of the pathologic anatomy of pulmonary emphysema was laid by J. Gough in 1952 when he described centrilobular emphysema and distinguished it from panlobular emphysema. The paper section technique developed by Gough and Wentworth was largely responsible for this advance, as it made examinations of sections of entire inflated lungs possible and simple (Fig. 40-1). A comprehensive microscopic description of emphysema was then provided by McLean, who demonstrated the relationship of destruction to inflammatory alterations of the bronchioles, and also discussed alterations of the vasculature.

Figure 40-1 Gough sagittal section. Paper mount. Normal lung. *(This section and subsequent sagittal sections courtesy of Dr. S. Moolton.)*

LESIONS OF THE LUNG PARENCHYMA IN COPD: EMPHYSEMA

A major problem in describing the pathologic features of emphysema has been the lack of a generally accepted and easy to apply definition. In 1959, a Ciba Guest Symposium defined emphysema in anatomic terms as "a condition of the lung characterized by increase beyond the normal of airspaces, distal to the terminal bronchiole, either from dilatation or from destruction of their walls." Subsequent definitions differed in that destruction of respiratory tissue became a requirement: "Emphysema is a condition of the lung characterized by

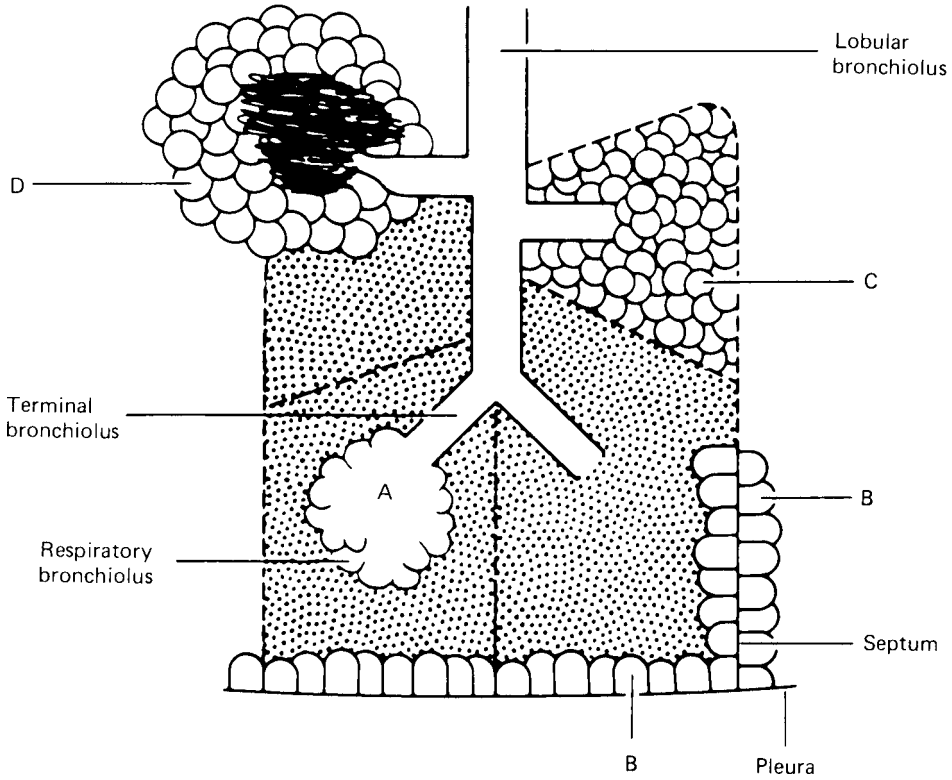


Figure 40-2 Anatomic varieties of emphysema. *A*. Centriacinar (centrilobular). *B*. Paraseptal (distal acinar). *C*. Panacinar (panlobular). *D*. Irregular (scar). The dashed lines mark the edge of the acinus. Only centriacinar and panacinar emphysema are commonly observed in COPD.

abnormal, permanent enlargement of the airspaces distal to the terminal bronchiole, accompanied by destruction of their walls." This requirement separates emphysema from enlargement of airspaces unaccompanied by destruction, the latter now being termed overinflation.

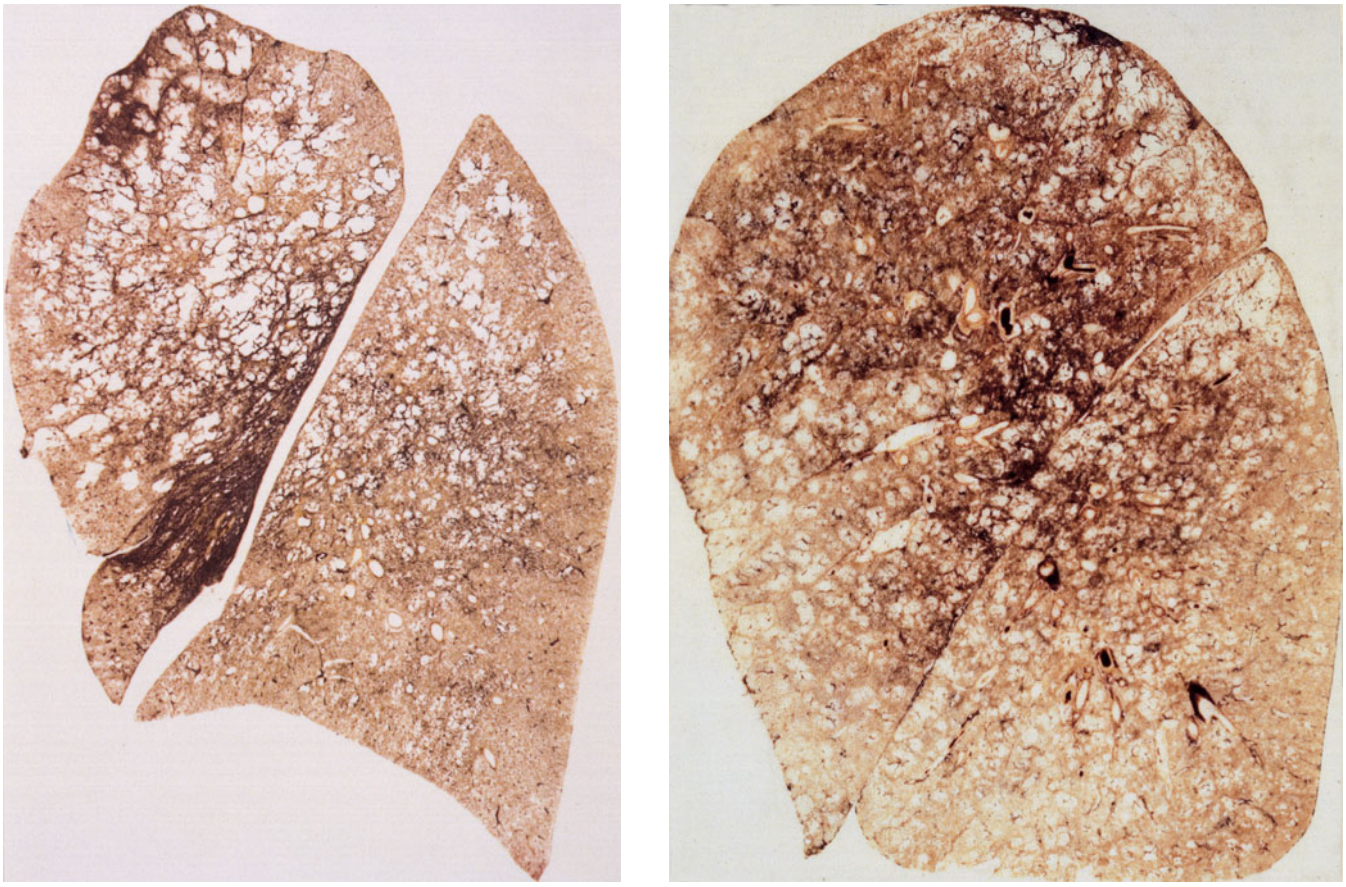
Destruction has been similarly difficult to define in an unambiguous way. A committee of the National Institutes of Health proposed that destruction was present when "there was nonuniformity in the pattern of respiratory airspace enlargement so that the orderly appearance of the acinus and its components is disturbed and may be lost." They recognized that emphysema was a subset of airspace enlargement defined as "an increase in airspace size as compared with the airspace of normal lungs. The term applies to all varieties of airspace enlargement distal to the terminal bronchioles, whether occurring with or without fibrosis or destruction." While these definitions, when strictly applied, would eliminate airspace enlargement due to overinflation or failure of septation, they would not eliminate airspace enlargement due to reorganization of the airspaces, such as is found in honeycomb lung.

Classification of Emphysema

Not only is emphysema defined in terms of lung structure, it is also classified in similar terms; therefore, several anatomic definitions are important. The part of the lung involved in emphysema is the acinus, which is defined as the unit of lung structure distal to the terminal bronchiole (final generation membranous bronchiole) and that consists of three orders of respiratory bronchioles: a single order of alveolar ducts, followed by the alveolar sacs, and finally the alveoli. Alveolar ducts are entirely alveolated and characteristically contain smooth muscle around the mouths of their alveoli. While the walls of alveolar sacs are also formed entirely by alveoli, muscle is absent. Alveolar pores of Kohn (also known as vents, stomata, or fenestrae) are normal components of adult alveoli, responsible for collateral ventilation. However, they may also be an initial site of destruction in the development of emphysema, particularly centriacinar emphysema.

The acinus is a three-dimensional anatomic structure, but it cannot be easily identified by gross examination. What can be seen instead on the surface of lung slices is the secondary lobule of Miller, defined as the tissue bounded on four sides by interlobular septa or pleura. Lobules vary tremendously in size, but are generally 2 to 4 cm on a side, and contain between three to five acini. The terminal bronchiole and subtending respiratory bronchioles tend to be situated in the center of the lobule. For this reason "centrilobular" emphysema and "panlobular" emphysema are reasonable and widely used approximations for the more accurate "centriacinar" and "panacinar" emphysema (see below) (Fig. 40-2).

The ways in which the acini are involved determine the classification of emphysema. There are four recognized patterns (Fig. 40-2). The acinus (and lobule) may be more or less uniformly involved; this is panacinar (panlobular) emphysema. The proximal portion of the acinus (center of the lobule) may be dominantly involved; the best term for this lesion is proximal acinar emphysema, although the usual term



A *B*

Figure 40-3 Pathologic subtypes of emphysema. *A*. Predominantly centriacinar emphysema. Emphysema is more severe in upper lobes. *B* . Predominant panacinar emphysema. Emphysema is more severe in the lower lobes.

is centrilobular or centriacinar emphysema. Alternately, the proximal portion of the acinus may be normal, and the distal part (alveolar sacs and ducts) may be dominantly involved. This is distal acinar emphysema, more commonly referred to as paraseptal emphysema since the lesion is accentuated along lobular septa where the peripheral parts of the acini lie. Finally, the acinus may be irregularly involved, producing irregular emphysema or paracicatricial emphysema, so called because it is usually associated with obvious scarring.

Morphology of Emphysema

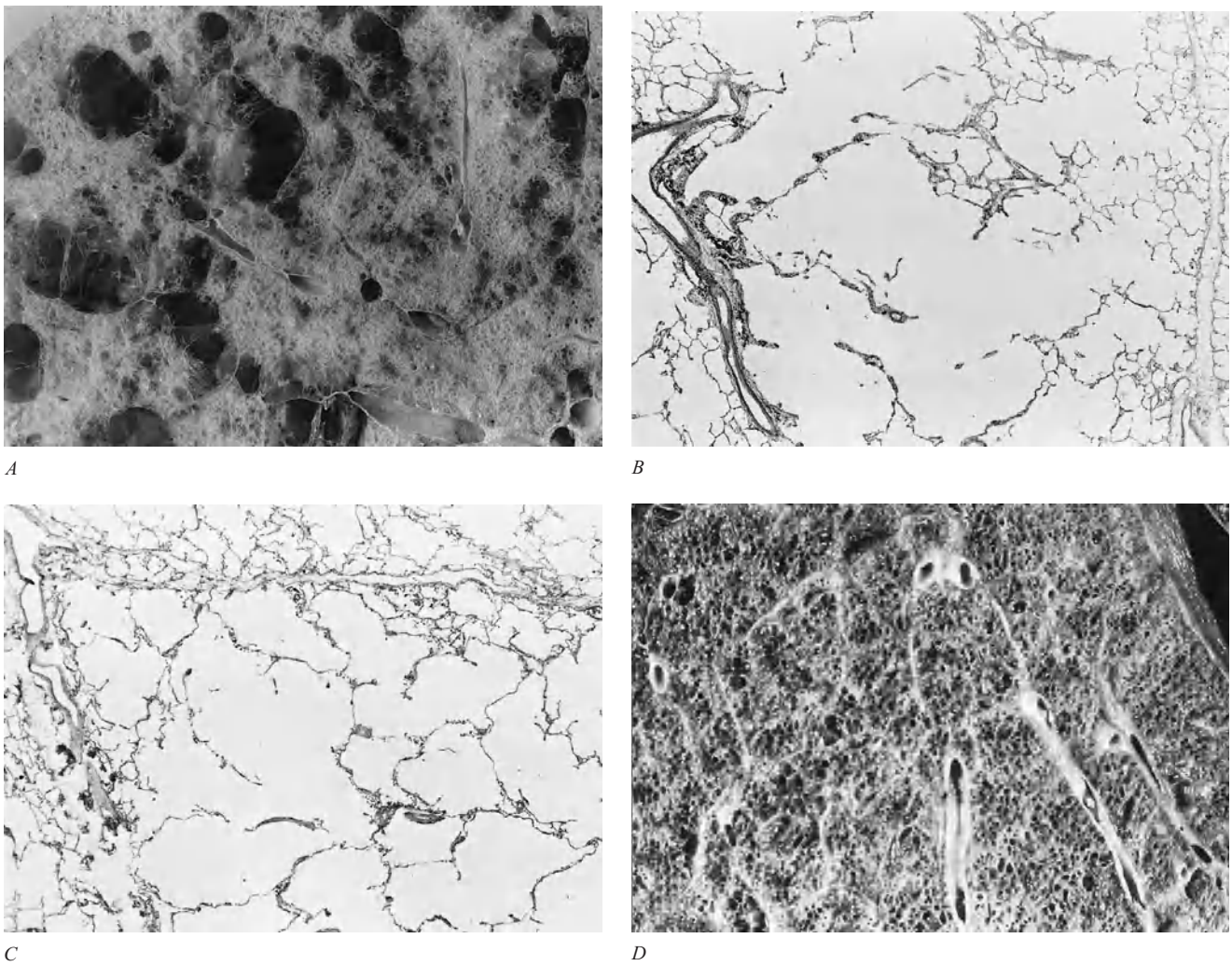
Centrilobular Emphysema

This destructive lesion of the respiratory bronchioles has a number of characteristic features on gross examination of the lung. In the *classical* lesion, the enlarged, destroyed respiratory bronchioles coalesce in series and in parallel to produce sharply demarcated emphysematous spaces, separated from the acinar periphery (the lobular septa), by intact alveolar ducts and sacs of normal size. The walls of the emphysematous spaces and adjacent tissue characteristically contain variable amounts of black pigment.

The lesions vary qualitatively as well as quantitatively even within the same lung. There is striking irregularity of involvement of lobules, and even within the same lobule. The lesions are usually more common and become more severe in the upper than in the lower zones of the lung (Fig. 40-3 *A*, Fig. 40-4*A*,*B*). Most affected are the upper lobe, particularly the posterior and apical segments, and the superior segment of the lower lobe. In cases of severe CLE, the destruction proceeds toward the periphery of the lobule, and the distinction between CLE and PLE becomes blurred.

In CLE, alveolar pores are abnormal in size and shape, and occasionally contain epithelial debris and macrophages. Although there are numerous pores of variable size in the emphysematous areas, there are also increased numbers of pores in the grossly normal areas, and accentuation of these changes in the center of the lobule. Thus, it appears that in CLE the pores of Kohn are possibly the initial site of destruction.

There is increased cellularity in the alveolar walls of cigarette smokers, and when this has been quantified, the parenchyma in severe emphysema has increased numbers of neutrophils, macrophages, eosinophils, and both CD4 and CD8 T lymphocytes. There is also a significant inflammatory cell infiltrate in the airspaces in severe emphysema, with the same cells types increased. Although not readily apparent grossly or on standard histological stains, use of histochemical stains or biochemical analysis demonstrates that collagen is increased in both centrilobular and panlobular emphysema.



A

B

C

D

Figure 40-4 *A,B*. Gross and histologic sections illustrating centriacinar; and (*C,D*) panacinar emphysema. *A*. Cut surface from a lung with centriacinar emphysema showing holes in the center of lobules surrounded by relatively normal parenchyma. The severity varies among lobules. *B*. Microscopic section showing that the airspace enlargement in centriacinar emphysema is most marked adjacent to the abnormal respiratory bronchiole, corresponding to the center of the lobule. Also, some of the alveolar walls of the abnormal airspaces are thickened and fibrotic (H&E × 16). *C*. Cut surface of a lung slice showing how the entire lobule is uniformly affected in panacinar emphysema. *D*. Microscopic section demonstrating that in panacinar emphysema, the airspaces adjacent to the lobular septa are enlarged to the same degree as those in the center of the lobule (H&E × 16).

Panlobular Emphysema

The recognition of mild panlobular emphysema is very difficult. The normal lung has a very characteristic appearance when seen through a dissecting microscope: The multifaceted alveoli form a contrast to the larger, cylindrical conducting structures that are alveolar ducts and respiratory bronchioles. In panlobular emphysema the distinction between alveolar ducts and alveoli becomes lost as alveoli lose their sharp angles, enlarge, and then lose their contrast in size and shape with the ducts, resulting in simplification of the lung architecture, with formation of small box-like structures. As the process becomes worse, the architectural derangement becomes more obvious, with progressive effacement and loss of the orderly arrangement of the lung until little remains other than the supporting framework of vessels, septa, and bronchi. The best way to see panlobular emphysema grossly is to examine lung slices immersed in a water or fixative bath and then immediately after removal from the bath. The immersed specimen shows enlarged airspaces and, when the slices are lifted from the bath, panlobular emphysema can be suspected because the lung parenchyma "falls away" from the supporting structures and protrudes slightly above them. In contrast to centrilobular emphysema, panlobular emphysema is usually worse in the lower lobes (Fig. 40-3*B*).

Histological examination is a sensitive method of recognizing panlobular emphysema. The pattern is again one of simplification with diminishing contrast between alveoli and alveolar ducts (Fig. 40-4*C,D*). Despite the greater extent of tissue destruction, in panlobular emphysema the pores of Kohn are more uniform and inconspicuous than those found in centrilobular emphysema.

Panlobular emphysema is the characteristic lung lesion seen in α-1-antitrypsin deficiency. Panlobular emphysema may also occur as a consequence of permanent obliteration of airways (obliterative bronchiolitis, constrictive bronchiolitis). Most often, obliteration of airways results in collapse of the distal lung parenchyma and dilatation of the bronchi proximal to the obliterated airways. This is the sequence of events in postinfective bronchiectasis. In some instances, however, the lung parenchyma does not collapse, but remains fully expanded or becomes emphysematous. The parenchymal sequel to bronchial and bronchiolar obliteration depends on the extent of the obliteration and the amount of collateral ventilation between adjacent airspaces distal to unobstructed airways. If collateral ventilation is present, then the units distal to the obliterated airways will remain expanded by virtue of the air reaching them by collateral ventilation, producing overexpansion and destruction of lung parenchyma beyond the obliterated airways. The terms Swyer-James or MacLeod's syndrome are applied when this process affects most of one lung but spares the other.

Distal Acinar Emphysema: Paraseptal Emphysema

The original description of distal acinar emphysema is generally credited to Loeschcke, who described collections of subpleural bullae. It was Heard, however, who first noted that the lesions could extend into the substance of the lung, where they lay along the septa, and coined the term "paraseptal" emphysema. Since the distal part of the acinus (alveolar sacs and ducts) is dominantly involved, emphysema is most striking adjacent to the pleura (superficial emphysema or mantel emphysema), along lobular septa (paraseptal emphysema), at the margins of lobules and acini (periacinar emphysema), and along vessels and airways, which, when cut longitudinally, display a linear pattern. The characteristic morphology is that of multiple contiguous, enlarged airspaces, varying from <0.5 mm to >2 cm in diameter.

Paraseptal emphysema is usually limited in extent, and is found most commonly along the anterior and posterior parts of the upper lobe and along the posterior surface of the lower lobe. When extensive, it is usually more severe in the upper half of the lung. Gough has stressed that it is associated with fibrosis of the tissue between the enlarged airspaces, and this is certainly a common finding.

Irregular Emphysema

Irregular emphysema is logically named, because the acinus is indeed irregularly involved in it. Irregular emphysema is almost invariably adjacent to a scar, giving name to the synonyms scar or paracicatricial emphysema. Most scars within the lung are usually small and the emphysema is limited in extent. The severity of irregular emphysema depends on the extent of damage to lung tissue, and multiple scars through the lung may lead to multiple foci of irregular emphysema.

Differential Diagnosis of Emphysema (Table 40-1)

Gas Trapping

The lungs of an asthmatic who has succumbed during an attack are usually characterized by gas trapping, and thus

Table 40-1

Differential Diagnosis of Airspace Enlargement

	Distribution	Enlarged Structure
Centrilobular emphysema	Upper lobes, center of lobule	Alveolar ducts, alveoli
Panlobular emphysema	Lower lobe, uniform in lobule	Alveoli
Paraseptal emphysema	Apical, adjacent to septum	Alveoli
Irregular emphysema	No typical site, adjacent to scars	Alveoli
Aging	Uniform in lung	Alveolar ducts
Compensatory alterations	Uniform in lung	Alveoli
Obstructive alterations	Affected area	Alveoli
Genetic alterations	Uniform in lung	Lack of septuation
Asthma	During acute attack	Alveoli
Honeycomb lung	Variable—often subpleural	Total remodeling

remain inflated, with focal areas of atelectasis. In a patient with longstanding asthma who has died from other causes, or has had a lung resection, there may still be areas of atelectasis. Focal bronchiectasis can be found also, particularly in the anterior segment of the upper lobe. However, parenchymal destruction is not a feature of asthma, and thus gross, microscopic, and morphometric analyses will all be normal in the chronic asthmatic.

Nonemphysematous Airspace Enlargement

Although not part of the differential diagnosis of COPD, nonemphysematous airspace enlargement also occurs in infancy. In congenital lobar hyperinflation (emphysema), the lobes are overinflated rather than emphysematous, but in some instances they may be polyalveolar. Some other genetic abnormalities will also give enlarged airspaces, but this is due to failure of septation with a simplified rather than a destroyed alveolar framework.

At the other side of the age spectrum, the term senile emphysema was once used to describe the enlarged airspaces found in the aged. On gross examination, lungs round out with increasing age. An analysis of Gough sections showed increases in anteroposterior distance, height, perimeter, and area of the lung up to the age of 59 years. After this age, only the anteroposterior diameter continued to increase significantly, thus "rounding" the lung dimensions. This change is due to an increase in the volume proportion of alveolar duct air, with shallower and flatter alveoli, a process termed ductectasia. There is no evidence of lung destruction; thus, the condition does not fulfil the criteria for emphysema.

If a part of the lung collapses or is removed, the remaining lung can expand to fill the increased amount of space available, a process known as compensatory overinflation. The exact way that this happens and the limits of the process are unknown. However, no tissue destruction has occurred and, by definition, this is not emphysema. It is not clear how much larger the overinflated lung can become, or how it expands to reach the new and larger volume. It is generally thought that the possible extent of overinflation is modest and that all the parts of the acinus are equally expanded.

Obstructive overinflation can occur in adults, and two mechanisms may be involved. In one, the obstruction in the bronchus may act as a ball valve, so that air enters on inspiration but does not leave on expiration. Alternatively, the bronchus may be completely obstructed and air may be trapped behind channels of collateral ventilation. Whatever the mechanism, the affected part of the lung can expand considerably. Obstructive overinflation differs in a number of ways from compensatory overinflation, although, in both, the lung contains too much air per unit of lung and lung tissue.

Honeycomb Lung

The airspace enlargement that occurs in cryptogenic fibrosing alveolitis (usual interstitial pneumonia) and other fibrotic lungs diseases could possibly be confused with emphysema. While honeycomb spaces are enlarged airspaces, they are the result of parenchymal remodeling with formation of new airspaces, rather than destruction of normal airspaces, and thus have thickened and irregular walls with none of the structure of an acinus. They are lined by bronchiolar epithelium, and often contain mucus; the walls have abundant and well collagenized connective tissue, which may also contain impressive amounts of muscle and sometimes fat. There is usually interstitial inflammation in the form of varying degrees of lymphocytic and plasma cell infiltration.

LESIONS OF THE LARGE AIRWAYS IN COPD

The majority of studies in this area have focused upon the lesions present when the clinical signs and symptoms of chronic bronchitis are also present.

Gross Findings

Gross lesions in the large airways are few and subtle. Bronchial pits are the dilated openings of one or more mucous glands into the epithelium. They are most often found along the margins of the cartilaginous rings and at the bifurcations of the airways. In nonbronchitis the pits can be seen using a hand lens or a dissecting microscope, but in chronic bronchitis, the ducts may be distended with mucus and the mucus may protrude into the lumen of the bronchus and be visible grossly. It is not correct to refer to these as diverticula. First, these are protrusions of normal ducts; and second, they do not extend through all of the muscle coats of the bronchial wall.

While enlarged bronchial pits are the most obvious gross lesions in COPD, careful examination of lung specimens will show that the bronchi do not taper progressively as they approach the pleura, and they also display prominent circular ridges, probably due to bands of hypertrophic smooth muscle. Mucus may be present in the airway lumen, particularly in subjects with chronic bronchitis.

Microscopic Findings

The intraluminal mucus found in the airways of subjects with COPD contains a mixed population of epithelial cells and acute and chronic inflammatory cells; large numbers of neutrophils can be found during an exacerbation.

Detailed microscopic analysis of the large airways in COPD reveals alterations in the entire airway wall (Fig. 40-5). Epithelial changes are mild in degree and are not necessarily consistent from patient to patient. Epithelial sloughing can occur, but in most instances the epithelium is generally intact and shows only mild goblet cell or squamous cell metaplasia, both of which appear to be more marked if the subject has symptoms of chronic bronchitis. The reticular basement membrane thickness is within the normal range.

The thickness or area of mucous glands in subjects with COPD in general, or chronic bronchitis in particular, is increased over a population mean, but has a distribution that extensively overlaps that of normals and asthmatics.

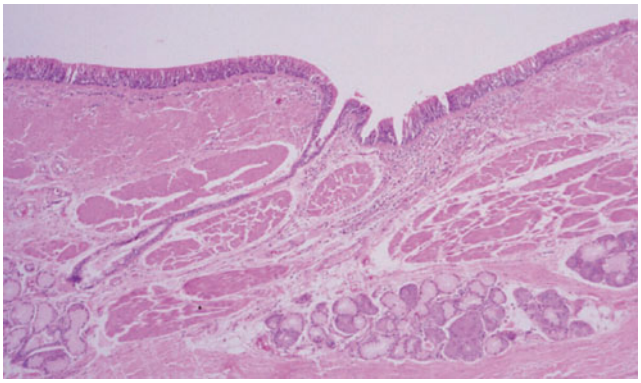


Figure 40-5 Large airway from a subject with chronic bronchitis. The overall wall is thickened with inflammation and fibrosis, and there is prominence of the smooth muscle in addition to the bronchial mucous glands.

Interestingly, there appears to be a decreased percentage of serous acini in these glands, a feature that apparently does not occur in asthma.

Thickening of the inner wall (area internal to the muscular layer) appears to be the most consistent component of airway wall thickening in the large airways of subjects with COPD, and appears to be generalized. This increase in thickness can be partially attributed to edema and hyperemia of the bronchi, but is also due to an increase in fibrous tissue or other matrix proteins.

In the large airways of subjects with COPD, increases in the thickness of the muscular layer have not been consistently identified. Although some studies have found that the average proportion of muscle in main, lobar, and segmental bronchi was approximately doubled in patients with chronic bronchitis and airflow obstruction, others have found that a substantial number of patients fell within the normal range.

Alteration in the amount of cartilage in COPD does not appear to be a consistent finding. While some studies described cartilage atrophy in chronic bronchitis and/or emphysema, or circumferentially arranged cartilage that extended farther distally in nonbronchitis than bronchitis, this was not supported by other reports. However, histological signs of cartilage damage, as judged by loss of cellular or pericellular metachromasia and vacuolated or empty lacunae can be consistently identified.

The large airways in COPD show a mild, usually mixed, inflammatory infiltrate. Bronchus-associated lymphoid tissues (BALT) is not consistently found, but its frequency appears to be considerably higher (82 percent) in smokers than nonsmokers (14 percent). Bronchial biopsy analysis consistently shows an increase in CD8 T cells, with eosinophils and neutrophils found during exacerbations. Chronic inflammation can also be found around the bronchial glands, particularly in subjects with chronic bronchitis.

Differential Diagnosis (Table 40-2)

Asthma

In asthma the large airways are not dilated, but mucus plugs are classically identified in the large airways of subjects with fatal or near-fatal asthma, and the mucus may be continuous with that present in the ducts of the mucus glands. Visible bronchial pits are not a standard feature of asthma, and although the airway wall may be thickened, this is usually not apparent grossly.

In the large airways of subjects with asthma, desquamation of the epithelium is a common feature, and this may be worse in people who have persistent rather than intermittent activity. Sloughing of cohesive epithelial clusters produces the Creola bodies found in cytology specimens. Goblet cell metaplasia can be marked in both asthma and bronchiectasis, but there is a considerable degree of variability, so that this feature cannot be used in isolation to distinguish among the airways of subjects with COPD, asthma, and bronchiectasis. These epithelial cell changes result in an overall thickening of the epithelium in asthma, but not in COPD. In asthma, the reticular basement membrane (lamina reticularis) is characteristically thickened. This alteration occurs early in the course of disease, and remains even when the asthma is mild or well controlled.

The airways of asthmatics demonstrate a greater severity of inner wall thickening, with values double those found in patients with COPD. The increase in thickness is due to variable increases in fibrous tissue, inflammatory cells, edema fluid, and vascular prominence. Analysis of the muscular wall in subjects with severe or fatal asthma compared with normals or those with COPD shows a marked increase in amount of muscle, with a lesser increase in asthmatics who died *with* rather than *from* their asthma There has also been a suggestion that the increase in muscle mass may occur relatively early during childhood.

Neutrophils are the predominant cell present in the mucus of patients with bronchiectasis, while eosinophils and accompanying Charcot Leyden crystals are the hallmark of asthmatic mucus. As noted, the cartilaginous destruction present in polychondritis is severe and associated with chronic inflammation, thus easily distinguishing the two processes. Depending upon the severity of the inflammation in bronchiectasis, there may be significant cartilaginous destruction.

Airways from fatal and near-fatal asthma also contain isolated aggregates of lymphoid cells, roughly in the same proportion as that present in COPD. However, in asthma, by contrast to COPD, there is an inflammatory infiltrate consisting of activated eosinophils, and activated CD4 T cells in the submucosa, and both mast cells and neutrophils within the glands. There is little in the literature regarding the inflammatory cell infiltrates present in the airway walls in bronchiectasis. Compared with asthma, there appear to be fewer eosinophils, but a similar population of CD 45 (as opposed to any specific subtype) lymphocytes, with both cell types having a greater density in the inner, as opposed to the outer aspect of the airway.

Bronchiectasis

In bronchiectasis, there is by definition an abnormal and permanent dilatation of the bronchi, and this is usually present to a much greater degree than is found in COPD, and is often

Table 40-2

Pathologic Differential Diagnosis of Large Airway Lesions in COPD

	Dilatation	Structural Distortion	Pits	Glands	Submucosal Fibrosis	Basement Membrane	Epithelium	Lumenal Mucus	Cartilage	Muscles
Chronic bronchitis	√	Fibrosis and inflammation	√	√	√	X	Goblet cell metaplasia	√	√	√/X
Asthma	Focal	Focal	X	√	√	√	Goblet cell metaplasia	√	X	√
Bronchiectasis	√	Fibrosis and inflammation	√	√/X	√	X	Focal goblet cell metaplasia	√	√	X
Tracheobronchiopathia osteoplastica	√	Bony nodules	X	X	X	X	X	X	√	X
Tracheomegaly	√	X	Diverticula	X	X	X	X	X	X	X
Relapsing polychondritis	√	√	X	X	X	X	X	X	√	X

Check mark indicates that the feature is present; X indicates that the feature is absent.

accompanied by airway distortion. There is exaggeration of the muscular ridges and the presence of multiple bronchial gland–based pits. The large airway walls can be thickened and/or irregularly thinned as a result of inflammation and fibrosis, and there is often inspissated mucus or actual purulent material.

Miscellaneous Conditions

Tracheobronchomegaly (Mounier-Kuhn syndrome) is characterized by a marked dilatation of the trachea and major bronchi, with diameters 5 to 10 cm above normal values. In this condition there are multiple true diverticula, with outpouchings formed of membranous tracheal tissue between the cartilaginous rings, with atrophy or absence of elastic fibers.

Patients with tracheobronchopathia osteoplastica have an obstructive pulmonary function pattern; however, unlike the trachea and large airways in COPD, cartilaginous and bony nodules are present in the subepithelial space (submucosa). Relapsing polychondritis shows variable dynamic expiratory and/or inspiratory obstruction depending on the size and location of the airways involved. In this disease, however, the obstruction is due to impaired airway clearance of inflammatory debris, and an ineffective cough because of dynamic upper airway collapse. The airways are dilated and the walls are thickened because of the extensive fibrosis and chronic inflammation due to the immunological nature of this condition. In particular, the cartilaginous plates show extensive destruction.

LESION OF THE SMALL AIRWAYS IN COPD

In the context of COPD, small airways refer to airways with an internal diameter of 2 mm or less. In COPD, intraluminal mucus can be found in the small airways, and there appears to be an overall relationship between the degree to which the airways are occluded by mucus and the FEV_1. Goblet cells are rare in normal small airways, but goblet cell metaplasia is a frequent finding in the airways of patients with COPD.

Similar to the large airways, there is alteration of the all of the small airway wall compartments in patients with COPD (Fig. 40-6). These changes result in an overall decrease in the internal bronchiolar diameter and, as assessed by a conformity index, produce significant deformity. Similar results are obtained from three-dimensional reconstructions. Detailed measurements of the airway walls show that the increased wall thickness is due to increases in the epithelium, subepithelial fibrous tissue compartment (submucosa, lamina propria), smooth muscle, and adventitia. Although the adventitia is thickened, there is a loss of alveolar attachments to the airway wall, an important process because it allows early airway collapse on expiration.

One of the earliest histological abnormalities that can be detected in cigarette smokers is the presence of macrophages in the lumen of the respiratory bronchioles. However, an inflammatory infiltrate can also be identified within the walls

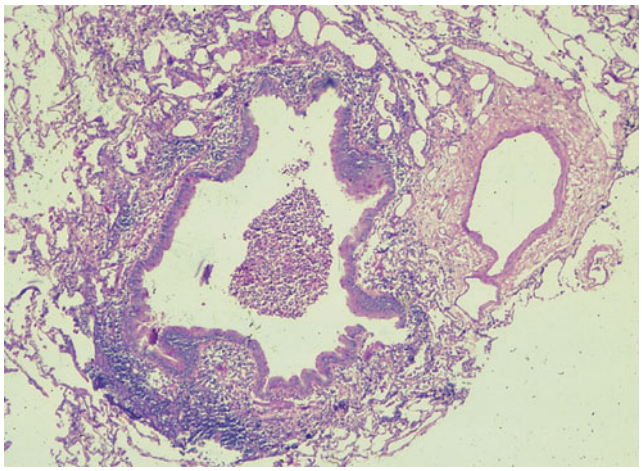


Figure 40-6 A small airway from a subject with COPD. The lumen contains mucus and inflammatory debris. There is goblet cell metaplasia of the epithelium. The subepithelial (submucosal) layer is increased in thickness due to an increase in fibrous tissue and inflammatory cells.

of both membranous and respiratory bronchioles in subjects with COPD. When examined in conjunction with the GOLD (Global Strategy for the Diagnosis, Management, and Prevention of Chronic Obstructive Pulmonary Disease) stage, the proportion of airways which had measurable neutrophils appear to be increased in GOLD stages 2 to 4, and airways with measurable macrophages show a progressive increase from GOLD stage 0 to 4, while there does not seem to be any alteration in the percentage of airways that contain eosinophils among the GOLD stages. The percentage of airways with CD4, CD8, and B cells also increase with GOLD stage, but when these data are expressed as total accumulated volume, only the B cells and CD8 cells show progressive increases. The presence of lymphoid follicles is markedly increased in GOLD stages 3 and 4.

Differential Diagnosis

Asthma

Mucous plugs and goblet cell hyperplasia are markedly increased in the small airways of asthmatics and this increase is generally much greater than is seen in COPD. In addition, the basement membrane thickness is approximately 20 percent greater than that found in either normals or patients with COPD. The peripheral airways of asthmatics have an inflammatory infiltrate that features lymphocytes and eosinophils, with many of the inflammatory cells in the adventitial, as opposed to the submucosal compartment. The data regarding the vessels in the submucosa are controversial, with some studies suggesting that they are congested, but not increased in number, in asthmatics compared with COPD, and others demonstrating an increased number of vessels, but a lesser total area in asthma compared with COPD. Although smooth muscle is increased in asthmatics, the increase is not as great as that present in the large airways. Moreover, the distribution of smooth muscle increase in the bronchial tree may be quite different, with some patients displaying a generalized

increase, while in others the increase is restricted to the larger airways. Overall, the small airways in asthmatic subjects who have died because of their disease have a greater area of subepithelial fibrous tissue, smooth muscle, and adventitial fibrous tissue than do subjects who died with their disease, which in turn have a greater area than do the airways of subjects with COPD. Thus, although the same qualitative changes are present in both asthmatics and COPD, they are more severe in asthmatics and most severe in cases of fatal asthma. Interestingly, there appears to be a loss of alveolar attachments in cases of fatal asthma, although this is less than that present in the airways of patients with COPD.

Follicular Bronchiolitis

Follicular bronchiolitis is characterized by narrowing of the bronchioles due to adventitial and subepithelial lymphoid follicles, and accompanied by a lymphoplasmacytic inflammatory infiltrate. The condition is classically found in patients with rheumatoid arthritis or those with IgA deficiency. This process can mimic severe COPD small airways disease, but the inflammatory infiltrate is generally magnified compared to COPD, while there is little goblet cell metaplasia in the airway epithelium.

Panbronchiolitis

The presence of foamy macrophages in the airway wall and lumen and extending down into the alveolar ducts and alveoli is a feature of the condition known as panbronchiolitis, originally described in Japan but now known to occur worldwide. Follicular hyperplasia of the peribronchiolar lymphoid tissue is frequent, and bronchiolectasis is found in the more advanced lesions.

Constrictive Bronchiolitis

The term constrictive bronchiolitis appears to have been coined by Gosink et al. In constrictive bronchiolitis, the airway lumen is occluded by a progressive thickening of the subepithelial (submucosal) space. Both the membranous and respiratory bronchioles are involved, and show transmural inflammatory cell infiltrates, occasionally with epithelial necrosis. Mucous plugs can also be identified. As the process evolves, the inflammatory infiltrate wanes, and greater amounts of fibrous tissue can be demonstrated both in the peribronchial and subepithelial portions of the airway, acting to narrow or obliterate the airway lumen. Lesions of constrictive bronchiolitis, particularly in the organized phase, may be difficult to demonstrate, and may require elastic stains to outline the obliterated airway. Thus, the lesions in COPD differ from constrictive bronchiolitis only in degree.

Mineral dust–induced airways disease is a distinctive type of constrictive bronchiolitis, characterized by a stereotypic response of the small airways to high doses of particulate, regardless of the specific mineral dust involved. The lesions consist of fibrosis and thickening of the walls of both the membranous and respiratory bronchioles, sometimes extending down the alveolar ducts, the latter finding providing diagnostic discrimination from tobacco smoke–induced airways disease, which tends not to involve the alveolar ducts. Pigment deposition is highly variable, and is not a diagnostic feature.

Proliferative Bronchiolitis

The lesions of proliferative bronchiolitis have been elegantly described and illustrated. Within the lumens of the membranous and respiratory bronchioles are plugs of organizing fibroblastic (granulation) tissue. Occasionally, ulceration of the epithelium can be seen, and early lesions may have fibrin. The granulation tissue is formed of a pale matrix with proliferating spindle cells, accompanied by chronic inflammatory cells. As the lesions age, the granulation tissue usually shrinks and contracts. However, in a certain proportion of cases, the bronchiolar cells proliferate over the granulation tissue, and incorporate it into the subepithelial space, leaving an irregular airway lumen.

Although acute bronchiolitis, be it bacterial or viral in nature, is usually easily distinguished from the lesions of COPD by the presence of extensive epithelial damage, healed lesions may show nonspecific airway fibrosis and chronic inflammation, or the residua of proliferative bronchiolitis. Interestingly, latent adenoviral infection has been suggested as a contributor to airflow obstruction in adults by amplifying the inflammatory response in the bronchioles of cigarette smokers. Airway disease complicating other diseases may also need to be distinguished from that of COPD. For example, post-transplant bronchiolitis or airways disease in patients with inflammatory bowel disease (both Crohn's disease and ulcerative colitis) include both proliferative and constrictive bronchiolitis. Inflammatory bowel disease may also have large airway involvement.

LESIONS OF THE VESSELS IN COPD

There are no consistent alterations in the large elastic pulmonary arteries of subjects with COPD. Atheromata can be found, but unless there is pulmonary hypertension, the incidence is probably not greater than that found in a carefully matched population.

Cigarette smokers, with or without pulmonary hypertension, have an increase in arterial muscle media thickness as well as intimal fibrosis in the muscular arteries, and progressive muscularization of the small arterioles. Increases in intimal thickness with longitudinal muscle formation are a common feature in lungs of patients with COPD (Fig. 40-7). There appears to be a progressive increase in the numbers of smaller muscularized arteries, percent medial thickness, and percent intimal thickness of muscularized arteries from nonsmokers, to smokers without obstruction, to smokers with airflow obstruction.

The lesions of primary pulmonary hypertension and hypertension secondary to vascular shunting also include intimal fibrosis and increased muscular media thickness. Intimal fibrosis is often cellular in its early phases, but progresses to concentric laminar fibrosis, which can almost totally obliterate the vessel lumen. These changes are of much greater

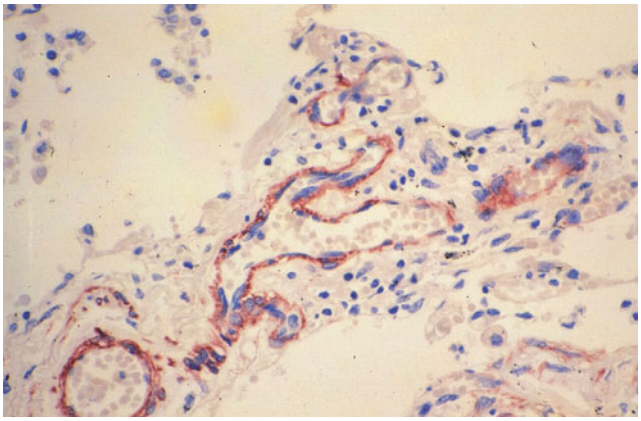


Figure 40-7 A small pulmonary artery from a subject with COPD. These vessels, situated adjacent to the alveolar ducts, are normally poorly muscularized, but in this case, the vessel has a distinct circumferential muscular layer.

severity than those identified secondary to COPD. Vasculitis, fibrinoid necrosis, and plexiform lesions are never found in COPD. Lesions of chronic thromboembolic disease include eccentric intimal thickening, and the occasional formation of webs due to recanalization of the thrombi.

SUMMARY

There are a number of pathological alterations of the lung in COPD. These involve almost all of the lung compartments, including the parenchyma, vasculature, and large and small airways. These changes can overlap the pathologic findings present in other diseases associated with airflow obstruction, or other diseases that are manifested in the lung. It is important to be able to make the distinction among these diseases. Although the pathologic alterations roughly correlate to alterations in pulmonary function, it is important to remember that their individual contributions are not well worked out. Thus, it may be difficult on an individual patient basis to proceed from a clinical classification such as the GOLD classification to a mechanistic/pathologic explanation of the airflow obstruction.

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Chronic Obstructive Pulmonary Disease: Epidemiology, Pathophysiology, and Pathogenesis

Robert M. Senior • Jeffrey J. Atkinson

For many years, chronic obstructive pulmonary disease (COPD) was defined as "a disease state characterized by the presence of airflow obstruction due to chronic bronchitis or emphysema; the airflow obstruction is generally progressive, may be accompanied by airway hyperreactivity, and may be viewed as partially reversible." In the past few years a new definition has been presented by the Global Initiative on Obstructive Lung Disease (GOLD) and by a Task Force of the American Thoracic Society (ATS) and the European Respiratory Society (ERS). Both GOLD and ATS/ERS state that "COPD is a disease state characterized by airflow limitation that is not fully reversible. The airflow obstruction is usually both progressive and associated with an abnormal inflammatory response of the lungs to noxious particles and gas." The ATS/ERS definition also states that COPD is both preventable and treatable and that COPD is a systemic disease. A secondary feature of both the GOLD and the ATS/ERS definitions is a scoring system for staging the severity of COPD based upon the post-bronchodilator forced expiratory volume in the first second (FEV_1) (see Chapter 42).

EPIDEMIOLOGY

COPD occurs worldwide, but it is a major health problem principally in societies where cigarette smoking is common and the average life span extends into the sixth decade or

beyond. Although COPD occurs predominately in smokers, nonsmokers also develop COPD. In a survey of COPD deaths in the United States in 1993, 16.7 percent of individuals who died with COPD were never-smokers (smoked fewer than 100 cigarettes during their lifetime) of whom approximately one-third, an estimated 12,900, had COPD listed as the primary cause of death. A history of asthma was significantly associated with death from COPD in nonsmokers. In undeveloped countries, burning biomass for heating and cooking results in COPD among nonsmokers.

COPD has a prevalence of 4 to 10 percent in adults in populations in whom lung function has been measured. The National Health Interview Survey, an annual survey of approximately 40,000 United States households, has yielded an estimate of 10 million adults in the United States with a physician-based diagnosis of COPD. Other estimates, such as that from the Third National Health and Nutrition Examination Survey (NHANES III), that included spirometry along with questionnaires and a physical examination, done between 1988 and 1994, have yielded even more impressive prevalence figures. According to NHANES III, COPD affects 23.6 million adults in the United States, of whom 2.4 million have severe disease. Thus, approximately 10 percent of the United States adult population might be classified as having COPD, and of this group about 10 percent have advanced disease. Impressive as these figures are, they are reasonable considering the estimates for COPD-related physician visits, emergency department visits, hospitalizations, and deaths. Indeed, these prevalence figures may be underestimates since COPD is likely unrecognized in some groups such as elderly persons with low incomes. Irrespective of the precision of the prevalence estimates, it is clear that COPD is a major health burden.

The death rate from COPD in the United States has been rising in recent decades in contrast to falling death rates from heart and cerebrovascular diseases over the same interval. COPD is now the fourth most common cause of death in the United States, accounting for approximately 4.5 percent of all deaths. Moreover, COPD is a contributory factor in another 4.3 percent of deaths. Currently, men still have a higher mortality rate from COPD than women (83 vs. 57 per 100,000), but the mortality rate is rising in women and is stable in men. Among women, the death rate from COPD has more than doubled in the past 20 years, and in the year 2000 more women than men died from COPD.

The percentage of smokers in the adult population in the United States has dropped over the past several decades from more than 50 percent to about 25 percent. The drop has been most striking among men. Accordingly, morbidity and mortality from COPD may decline in the years ahead, reflecting these favorable trends in smoking practices in recent decades. However, COPD is certain to remain a major health problem in the United States into the foreseeable future since there are an estimated 48 million smokers in the United States and smoking is common in young people. Among high school students 23 percent are current smokers, with a slightly higher incidence for boys (25 percent) than girls (21 percent), while among middle-school children 10 percent are smokers, equally so among boys and girls. The problem of COPD worldwide is destined to be profound in the future. The World Health Organization reports that 15 billion cigarettes are smoked daily worldwide and predicts that COPD will rank fifth in life-years lost to premature death and disability in 2020.

RISK FACTORS

Risk factors for the development of COPD may be broadly divided into those related to environmental exposures and those that are host-based (Table 41-1). Smoking and alpha 1-antitrypsin (α_1-AT) deficiency are risk factors for which the data are most compelling, but even for these risk factors much remains to be determined about the specific mechanisms involved. Some factors listed may be a composite of other individual risk factors. A low socioeconomic status, for example, is notable in this regard as it might be linked to COPD through deficient medical care for respiratory infections, occupational exposure to inhaled particulates, and exposure to household allergens. The following sections consider smoking, occupational exposures, childhood lower respiratory infections, airway hyperresponsiveness, and genetic factors other than α_1-AT deficiency which is discussed separately later in the chapter.

Environmental

Smoking

Smoking tobacco accounts for 80 to 90 percent of the risk of developing COPD in the United States. Accelerated deterioration of ventilatory function is common among smokers. However, its magnitude is relatively small in most smokers. In males, the loss of FEV_1 in excess of the normal decline

Table 41-1

Risk Factors for COPD

Environmental	Host-based
Smoking	Genetic factors
Occupational exposures	Asthma/airway hyperreactivity
Air pollution	
Childhood respiratory infections	
Low socioeconomic status	

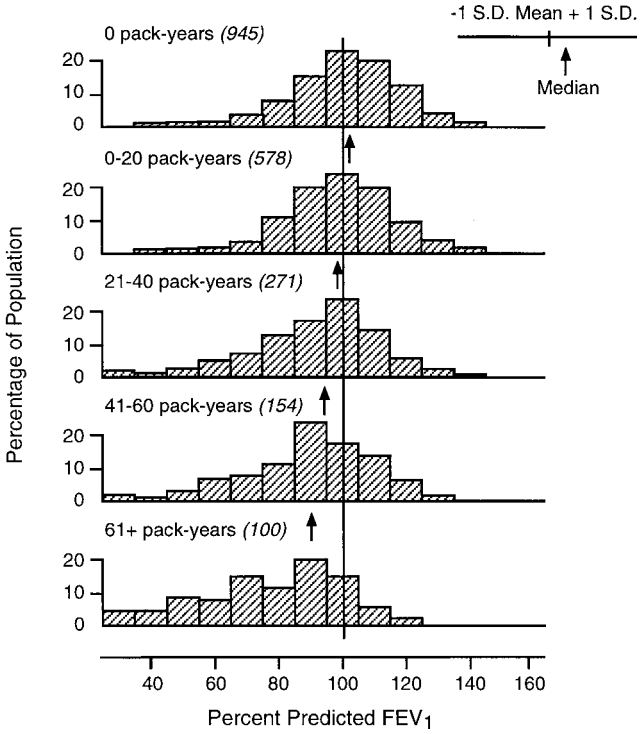


Figure 41-1 Distribution of percent predicted FEV_1 in adults with varying pack-years of smoking. Subjects with "respiratory trouble" before age 16 are excluded. The proportion of smokers with normal expiratory airflow decreases with increasing pack-years. Nevertheless, many smokers have a normal FEV_1 despite large cigarette-smoking histories. Means, medians, and ± standard deviation of the data for each group are shown in the abscissas. The numbers in parentheses are the numbers of subjects. *(From Burrows B, Knudson RJ, Cline M, et al: Quantitative relationships between cigarette smoking and ventilatory function. Am Rev Respir Dis 115:195–205, 1977, with permission.)*

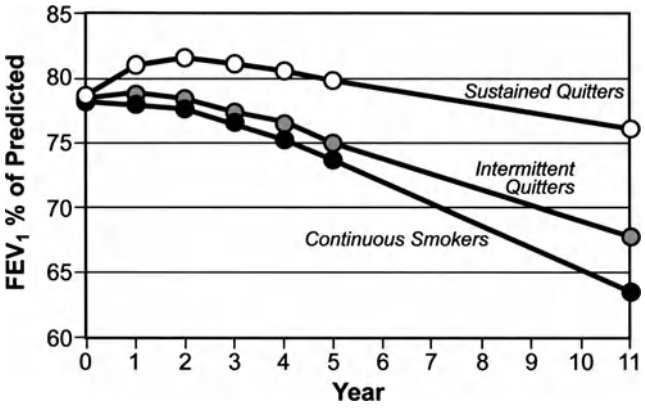


Figure 41-2 Mean post-bronchodilator FEV_1 for participants in the Lung Health Study during 11 years of follow-up in relation to smoking history. Sustained quitters (open circles) and continuous smokers (closed circles). Smokers show progressive deterioration. *(From Anthonisen NR, Connett JE, Murray RP: Smoking and lung function of Lung Health Study participants after 11 years. Am J Respir Crit Care Med 166:675–679, 2002, with permission.)*

with aging is 9 ml per year for each pack-year of smoking; in females, the excess rate of decline is 6 ml. Based on these rates of decline, a man who has smoked one pack daily for 30 years will have an FEV_1 that is 270 ml less than it would have been had he not smoked. However, the relationship between amount of smoking and risk of COPD is unpredictable on an individual basis. Many people with a high number of pack-years still have a normal or near-normal FEV_1, while some people have a reduced FEV_1 with a modest smoking history (Fig. 41-1).

Among smokers who have already sustained reductions in FEV_1, the consequences of continued smoking on ventilatory function are much more impressive than when all smokers are lumped together. The Lung Health Study revealed that among middle-aged smokers with an FEV_1 between 55 and 90 percent of predicted, differences of about 200 ml in FEV_1 developed within 5 years between those who quit and those who did not quit and this difference between smokers and quitters doubled over the next 6 years (Fig. 41-2). Thus, not surprisingly, in smokers who have demonstrated an increased susceptibility to the effects of smoking on ventilatory function, the rate of decline of FEV_1 is much larger than that seen in the average middle-aged smoker who has normal or near-normal ventilatory function. Further evidence of the harmful effects of smoking in susceptible smokers is apparent from the trends in ventilatory function among those who stop smoking. Their rate of decline of FEV_1 reverts to that of nonsmokers.

Occupation

The fact that occupation-related chronic inhalation of particulates and gases carries a risk for COPD has been slow in gaining acceptance. The delay is understandable, since ascertaining the risk of COPD in relation to occupation may be difficult for several reasons. The high prevalence of smoking among workers in certain occupations has been a major confounding factor. Also, workers beginning jobs with a high risk of causing lung disease typically have better lung function than normal (the "healthy worker" phenomenon), obscuring work-related effects among relatively young workers. In addition, among cohorts of workers, those with COPD may drop out, causing an underestimate of risk in follow-up studies confined to those still working.

Despite these difficulties, studies from different groups around the world, urban and rural, workforce-based and community-based, clearly implicate occupations producing exposures to dusts, gases, and fumes as risk factors for COPD. The American Thoracic Society states that 15 percent is a reasonable estimate of the occupational contribution to the population burden of COPD.

Dusts appear to be most significant. Similar to the experience with tobacco smoke, the presence or absence of chronic cough and sputum does not necessarily imply the presence or absence of airflow obstruction. The risk generally relates to the intensity of exposure, but there is considerable individual variability, pointing to the importance of host factors in determining susceptibility. Apart from the recognized

risk in occupations involving exposure to organic and inorganic dusts, many less obviously "risky" occupations may carry an increased risk of COPD. A recent analysis of data from NHANES III, in which smoking and other confounders were taken into account, uncovered slightly increased incidences of COPD in many occupations, including construction, plastics manufacturing, and utility work. The impact of an adverse occupation is likely to be particularly important in individuals who have other factors that raise their risk for COPD. An example of this occurrence was found among agricultural workers with α_1-AT deficiency who had never been regular smokers. These individuals showed significantly reduced FEV_1 values compared to nonsmoking α_1-AT-deficient individuals not involved in agricultural work.

Childhood Lower Respiratory Tract Infections

Childhood lower respiratory tract infections (lower respiratory tract infections) are commonly regarded as a risk factor for COPD. Since lung growth and alveolar development continue into early childhood it is plausible that lower respiratory tract infections during childhood might produce permanent damage or impair lung growth and development. However, although correlations have been found between early (up to around age 2) childhood lower respiratory tract infections and reduced lung function later in life, there is not a correlation with airflow obstruction as judged by the FEV_1/forced vital capacity (FVC) ratio. Furthermore, even in the setting of COPD, LRTIs seem to have only a minor lasting effect on the obstruction. In the Lung Health Study COPD exacerbations in smokers were associated with an additional loss of FEV_1 of 7 ml per year for those having one exacerbation per year. Among nonsmokers exacerbations had no apparent effect on the FEV_1.

HOST FACTORS

Genetic Background

Aggregation of COPD in families and concordance of pulmonary function in twin studies have established a role for genetic predisposition to COPD. The occurrence of reduced maximal expiratory airflow among nonsmoking first-degree relatives of individuals with early onset COPD provides further support. Perhaps most compelling is the marked variability in development of COPD among smokers. However, dissecting specific genetic factors that increase the risk of COPD has proven difficult. α_1-AT deficiency illustrates this difficulty. Even among individuals with this clearly identified genetic risk factor, there is wide, unexplained, variability in the occurrence of COPD.

Polymorphisms of genes involved in protease-antiprotease balance, antioxidant function, inflammation, and immune responses have been implicated in COPD. However, none of these polymorphisms could be confirmed in a recent genetic association analysis of families identified through patients who developed severe COPD at an early age (without α_1-AT deficiency). Failure of confirmation may indicate flaws in previous studies, but differences in COPD phenotypes, ethnic background, or other factors might explain the discrepancies between previous studies and the recent data. A polymorphism in elastin that results in an amino acid substitution and altered elastic fibers has been uncovered in approximately 1 percent of individuals with severe COPD and emphysema. Thus, future studies of the genetic aspects of COPD should extend to extracellular matrix.

Two basic approaches are used to identify the genetic determinants of apparently complex genetic disorders such as COPD: candidate gene analysis and positional cloning. Both rely on polymorphisms in the populations studied and careful characterization of the disease phenotype being targeted. Unfortunately, characterization of the COPD phenotype has been variable, involving parameters of airflow obstruction and/or radiographic evidence of emphysema.

The advantages of a candidate gene approach are that the selection of genes can be guided by information from mouse models or expression profiling experiments. Since only a limited number of genetic variants are typically tested, associations can be uncovered with relatively small populations. However, the disadvantages are that the small sample size can miss associations due to inadequate power and associations discovered may represent linkage to a polymorphism in a neighboring gene, not the gene of interest. These candidate gene association studies are likely more powerful if performed on a relatively genetically isolated and uniform population, but use of isolated populations decreases the ability to generalize findings to other populations. Some polymorphisms change amino acid sequence of a protein, but polymorphisms in the promoter region are often evaluated, so that confirmation of alteration in protein production or activity is necessary. Since many of these studies attempt to examine multiple polymorphisms in the same sample population, adjustment for multiple statistical testing should be applied. As noted above, candidate genes for COPD have been from categories proposed to be involved in the pathogenesis of COPD, such as proteases-antiproteases, antioxidants, and mediators of inflammation, so this approach will not uncover novel mechanisms.

Unlike the candidate gene approach, the positional cloning approach has traditionally been performed in families of affected individuals, using linkage analysis to determine if affected relatives share a region of the genome significantly more often than expected based on random chance. Broad mapping with a genome-wide set of genetic markers is performed on all individuals to evaluate linkage of the phenotype to pieces of chromosomal DNA. The disadvantage of positional cloning is the intensive labor required for the collection, phenotyping, and mapping of a large population of families. The result of linkage analysis is usually identification of a large area on a chromosome rather than a distinct gene. However, unlike the candidate gene approach, linkage analysis can discover unknown or formerly unrecognized genes involved in COPD pathogenesis. Some linkage analysis studies demonstrate that even in the absence of smoking, lung function parameters show heritability, suggesting that some

of the risk for COPD development may be attributable to genetic control of lung development.

In one study a combination of both candidate gene and positional cloning approaches was used. A domain in chromosome 19q that was linked to pre-bronchodilator FEV_1 in smokers in the Boston Early-Onset COPD study was evaluated for single nucleotide polymorphisms (SNPs) in and around the transforming growth factor-β1 (TGF-β1) gene. This study then confirmed the candidate gene findings in a second cohort of patients in the National Emphysema Treatment Trial (NETT), which includes not only the initial phenotype of low pre-bronchodilator FEV_1, but also the presence of radiographically confirmed emphysema. These NETT cases were compared to population-based control subjects. It seems likely that combining both approaches of genetic analysis together with better phenotypic characterization of COPD traits will expand knowledge of the genetic factors affecting the risk of developing COPD. Progress in SNP identification and genotyping technology has made genome-wide association studies possible, which may allow the advantages of both the candidate gene and positional cloning approaches to be applied comprehensively to complex diseases like COPD.

Airway Hyperresponsiveness

Airway hyperresponsiveness (AHR) refers to an acute decline in maximal airflow in response to inhaling potential bronchoconstricting agents such as methacholine or histamine. In COPD, AHR is associated with accelerated decline of FEV_1 and therefore is a negative prognostic marker. Intriguingly, however, AHR does not predict whether there will be some bronchodilator reversibility nor does bronchodilator responsiveness have favorable prognostic significance. The pathological features and mechanistic basis for AHR in COPD are not known, but smoking cessation is associated with reduced AHR.

AHR leads to consideration of the "Dutch hypothesis," which ascribes a role of allergy in the risk of developing COPD. What makes this area problematic is whether AHR, which is common in COPD, precedes or follows the development of COPD. An observation that argues against a causal relationship is that smokers typically do not show AHR until their baseline FEV_1 is already reduced. Confounding an analysis of the relationship is that smoking is common among asthmatics so that asthmatics are likely to be included in groups regarded as COPD.

PATHOPHYSIOLOGY

Many pulmonary function abnormalities occur in COPD, but persistent reduction in maximal forced expiratory flow is the defining physiological feature. Increased airway resistance, increased residual volume, increased residual volume/total lung capacity ratio (RV/TLC), decreased inspiratory capacity, maldistribution of ventilation, and ventilation-perfusion mismatching are also typical features.

Airflow Obstruction

Persistent reductions in FEV_1 and FEV_1/FVC are the characteristic physiological abnormalities of COPD. Measurement of the FVC at 6 seconds (FEV_6) may be an adequate and safer equivalent of measuring the FVC in individuals with severe obstruction. The reduced FEV_1 is not reversible with inhaled bronchodilators, although improvements up to 15 percent are common. In this respect, COPD differs from asthma in which large improvements in airflow with inhaled bronchodilators are characteristic. Maximal inspiratory flow may be relatively well preserved in the presence of a markedly reduced FEV_1. Such discrepancies between inspiratory and expiratory flow suggest that the reduction in forced expiratory flow in COPD is not due to fixed narrowing or obliteration of airways, but instead that there is airway instability with narrowing during forced exhalation.

Airflow during forced exhalation is the result of the balance between the elastic recoil of the lungs promoting flow and the resistance of the airways that limits flow. In normal lungs, as well as in lungs affected by COPD, maximal expiratory flow diminishes as the lungs empty because the lung parenchyma provides progressively less elastic recoil and the cross-sectional area of the airways falls so that resistance to airflow increases. The decrease in flow, coincident with the decrease in lung volume, is readily apparent on the expiratory limb of a flow-volume curve (Fig. 41-3). In the early stages of COPD, the abnormality in airflow is evident only at lung volumes at or below functional residual capacity, appearing as a "scooped out" lower part of the descending limb of the flow-volume curve. In more advanced disease, the entire curve demonstrates decreased expiratory flow.

The relative contributions of diminished elastic recoil and increased airway resistance in reducing maximal expiratory airflow can be quantified from flow-pressure curves (Fig. 41-4). With decreased elastic recoil the curve has a normal slope, but it terminates prematurely. In contrast, with increased airway resistance the slope becomes less steep, reflecting the necessity for increased driving pressure for any level of airflow. In theory, therefore, it is possible to distinguish between emphysema ("decreased elastic recoil") and small airway pathology ("increased airway resistance") as the cause for the reduced FEV_1. The situation is more complex, however, because most people with COPD have both emphysema and small airway pathology. Moreover, elastic recoil and airway resistance are not necessarily separable. Elastic recoil affects the stiffness of small airways. When elastic recoil is reduced, the curve may be shifted to the right because of increased airway collapsibility. Because flow-pressure data are difficult to collect and interpret and are of little help in patient management, sorting among decreased elastic recoil, airway collapsibility, and increased airway resistance as the mechanism of airflow obstruction in COPD is rarely done in clinical practice. Moreover, other data, such as the diffusing capacity

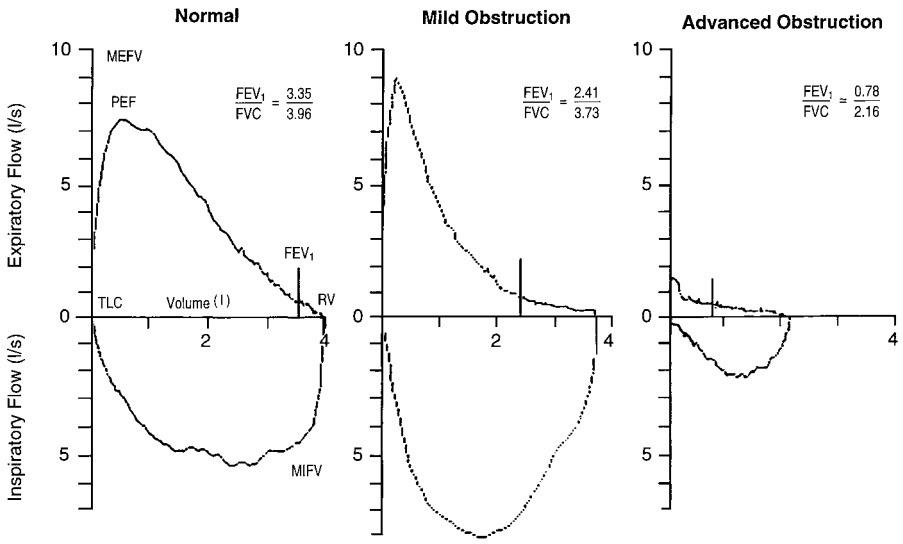


Figure 41-3 Maximum expiratory and inspiratory flow-volume (MEFV, MIFV) curves in a normal subject (left), a subject with mild airway obstruction (middle) due to COPD, and a subject with advanced obstruction (right) due to COPD. The FEV_1 is indicated on the volume axis by a vertical bar. TLC = total lung capacity; RV = residual volume; FVC = forced vital capacity. Note the development of convexity of flow to the volume axis in mild obstruction, despite preservation of a large peak expiratory flow, a normal FVC, and only a small reduction in FEV_1/FVC ratio. Inspiratory flow is normal. In advanced COPD there is marked decrease of FEV_1, FVC, and maximal expiratory airflow generally. Inspiratory flow is also markedly reduced, but spared relative to expiratory flow. *(From Pride NB, Milic-Emili J: Lung mechanics, in Calverley PMA, Pride NB [eds], Chronic Obstructive Pulmonary Disease. London, Chapman & Hall, 1995, pp 135–160, with permission.)*

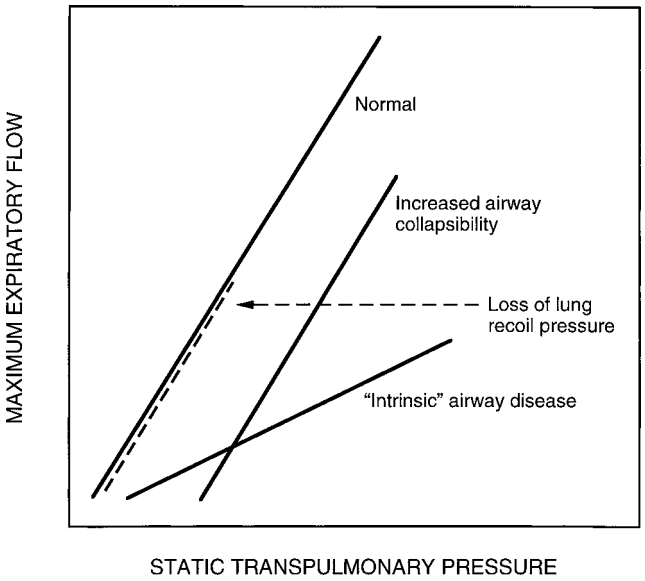


Figure 41-4 Analysis of reduced maximum expiratory flow in COPD from maximum expiratory flow vs. lung recoil pressure curves. With loss of lung recoil pressure–-i.e., "emphysema" (heavy interrupted line)–-the slope of the flow-pressure curve remains normal, but the curve terminates at lower pressure than normal. With intrinsic airway obstruction–-i.e., "bronchitis"–-the slope is reduced. Increased airway collapsibility, which may be a result of decreased elastic recoil, causes the curve to be displaced to the right. Commonly in COPD, the flow-pressure curve has premature termination and a decreased slope and is shifted rightward, indicating that decreased elastic recoil, increased airway resistance, and increased airway collapsibility are all involved in causing the reduced maximum expiratory flow. *(From Pride NB, Milic-Emili J: Lung mechanics, in Calverley PMA, Pride NB [eds], Chronic Obstructive Pulmonary Disease. London, Chapman & Hall, 1995, pp 135–160, with permission.)*

and chest computed tomography may provide estimates of the severity of emphysema. As discussed below, the correlation between FEV_1 is better with small airway pathology than with emphysema.

Although there is considerable variability in the relationships between the FEV_1 and other physiological abnormalities in COPD, certain generalizations may be made. The arterial oxygen tension (Pa_{O_2}) usually remains near normal until the FEV_1 is decreased to about half of the predicted level; even a much lower FEV_1 may be associated with a normal Pa_{O_2}, at least at rest. An elevation of arterial P_{CO_2} (Pa_{CO_2}) is not expected in COPD until the FEV_1 is less than about one-fourth of predicted; even then an elevation in arterial carbon dioxide tension (Pa_{CO_2}) may not occur. Pulmonary hypertension due to COPD that is severe enough to cause cor pulmonale and right ventricular failure occurs only in persons who have a marked decrease in FEV_1 (one-fourth of predicted or less) and chronic hypoxemia (Pa_{O_2} under 55 mmHg), although some elevation of pulmonary artery pressure, particularly with exercise, is common with less advanced COPD.

Maldistribution of Ventilation and Ventilation-Perfusion Mismatching

Maldistribution of ventilation and ventilation-perfusion mismatching are characteristic of COPD and reflect the heterogeneous nature of the disease process as it affects the airways and lung parenchyma. Nitrogen washout during breathing of 100 percent oxygen is delayed because of regions that are poorly ventilated, and the profile of the nitrogen washout curve is consistent with many parenchymal compartments

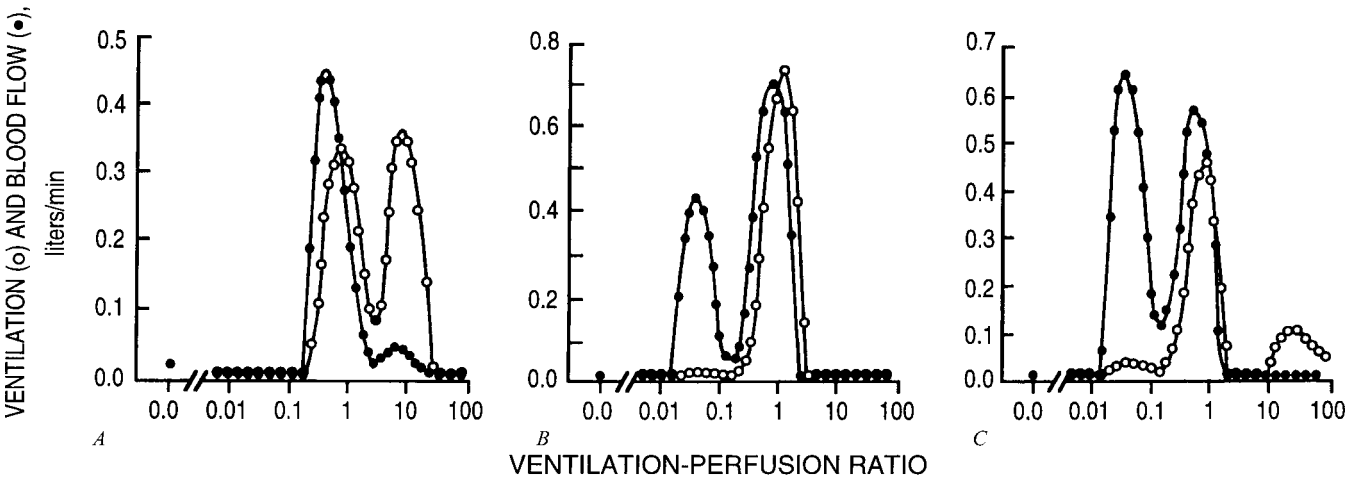


Figure 41-5 Ventilation-perfusion distributions in three persons with COPD determined by the multiple inert gas elimination technique (MIGET). *A*. Regions of high ventilation-perfusion characteristic of "emphysematous," type A COPD. *B*. Regions of low ventilation-perfusion characteristic of "chronic bronchitis," type B COPD. *C*. Regions of both high and low ventilation-perfusion characteristic of many people with COPD. In the normal person, not shown, ventilation-perfusion virtually overlaps and peaks at about a ventilation-perfusion ratio of 1. *(From Wagner PD, Dantzker DR, Dueck R, et al: Ventfl ation-perfusion inequality in chronic obstructive pulmonary disease. J Clin Invest 59:203–216, 1977, with permission.)*

having different washout rates because of regional differences in compliance and airway resistance. Radioisotopic ventilation scanning with ^{133}xenon reveals regional heterogeneity of ventilation in COPD.

The multiple inert gas elimination technique (MIGET), which enables quantification of the ventilation-perfusion profile, has demonstrated different ventilation-perfusion patterns among patients with advanced COPD (Fig. 41-5). In one pattern, so-called type A ("pink puffer") COPD, there is a substantial amount of ventilation distributed to high ventilation-perfusion regions. In a second pattern, called type B ("blue bloater") COPD, there is a substantial amount of pulmonary blood flow perfusing low ventilation-perfusion regions. There are important limitations to this simple classification. First, persons with the clinical features of type A or type B (that is, emphysema or chronic bronchitis) do not necessarily have the expected ventilation-perfusion pattern. Of perhaps greater importance, most people with COPD are not easily classified as either type A or type B. They have both high and low ventilation-perfusion regions. MIGET has also revealed that an increased dispersion of ventilation-perfusion values is already present in the early stage of COPD.

Ventilation-perfusion mismatching accounts for essentially all of the reduction in Pa_{O_2} that occurs in COPD; shunting is minimal. Thus, modest elevations of inspired oxygen are effective in treating hypoxemia due to COPD. If hypoxemia is difficult to correct other problems such as pulmonary emboli or right to left intracardiac or intrapulmonary shunting need to be considered.

Hyperinflation

Hyperinflation, defined in various ways (increased functional residual capacity, increased residual volume to total lung capacity, increased total lung capacity, or decreased inspiratory capacity to total lung capacity) is common in COPD of moderate severity or worse. Hyperinflation might be beneficial as it favors preservation of maximum expiratory airflow because as lung volume increases, elastic recoil pressure increases, airway lumens enlarge, and airway resistance decreases. However, hyperinflation has adverse effects on the mechanics of the thorax, increasing the work of breathing and eliciting dyspnea.

Hyperinflation displaces the diaphragm into a flattened position and, thereby, creates a number of adverse effects (Fig. 41-6). First, because the zone of apposition between the diaphragm and the abdominal wall is lost, positive abdominal pressure during inspiration is not transmitted as effectively to the chest wall, hindering rib cage movement and impairing inspiration. Second, because the muscle fibers of the flattened diaphragm are shorter than those of a more normally curved diaphragm, they are less capable than normal of generating inspiratory pressures. Third, the flattened diaphragm must generate greater tension to develop the transpulmonary pressure required to produce tidal breathing. This follows from Laplace's law, $P = 2T/r$. As the radius of diaphragm curvature (r) increases with diaphragm flattening, the tension (T) required to develop a transpulmonary pressure (P) to generate tidal breathing must increase. Also, with hyperinflation, the thoracic cage, in general, must operate at a mechanical disadvantage. Because the thoracic cage is distended beyond its normal resting volume, during tidal breathing, the inspiratory muscles must do work to overcome the resistance of the thoracic cage to further inflation instead of gaining the normal assistance from the chest wall recoiling outward toward its resting volume. Typically hyperinflation increases further on exercise because airflow obstruction limits lung emptying during rapid breathing. This additional hyperinflation,

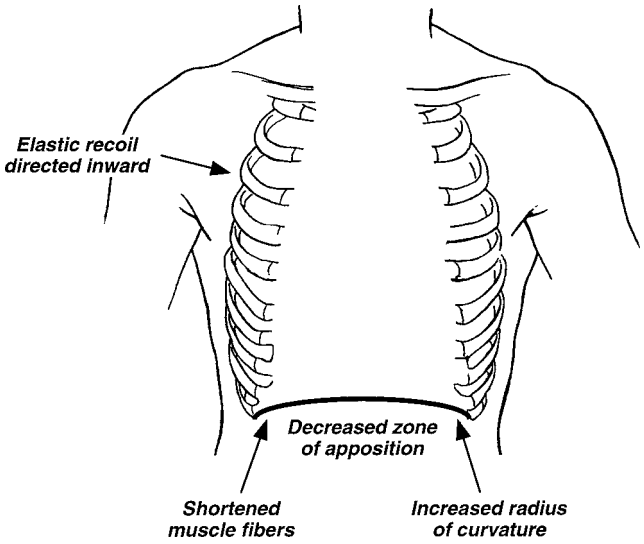


Figure 41-6 Detrimental effects of hyperinflation on diaphragmatic function. Hyperinflation causes flattening of the diaphragm, which (1) decreases the zone of apposition between the diaphragm and the abdominal wall, hindering rib cage movement; (2) shortens diaphragmatic muscle fiber length, decreasing the force that can be generated by the diaphragm; (3) increases the radius of curvature of the diaphragm, thereby decreasing transpulmonary pressure (at constant tension); and (4) directs diaphragmatic muscle fibers medially, impairing inflation with diaphragmatic contraction. In addition, hyperinflation prevents the thorax from assisting inspiration during tidal breathing because the resting volume of the thorax is above the volume at which the rib cage recoils outward during inspiration. *(From Yusen RD, Lefrak SS, and the Washington University Emphysema Surgery Group: Evaluation of patients with emphysema for lung volume reduction surgery. Semin Thorac Cardiovasc Surg 8:1–12, 1996, with permission.)*

designated dynamic hyperinflation, adds to the load on the inspiratory muscles while further reducing their mechanical advantage. The net effect is increased work of breathing, diminished capacity for exercise, and increased dyspnea.

Coincident with hyperinflation, the inspiratory capacity (IC) is commonly reduced in COPD. Reduction of the IC has prognostic significance that is independent of FEV_1. In a study of subjects with moderate to very severe COPD, survival was markedly shorter in 286 individuals whose IC/TLC was less than 25 percent compared to 403 individuals whose IC/TLC was greater than 25 percent, even though the two groups had comparable severity of COPD based on percent predicted FEV_1.

Dyspnea

People with COPD typically seek medical care because of dyspnea. Dyspnea compromises their activities and quality of life. Dyspnea is seldom a complaint until the FEV_1 has fallen below about 60 percent of predicted; however, the correlation between FEV_1 and exercise limitation is not strong. Some individuals with COPD are relatively free of dyspnea despite impressively low levels of FEV_1.

The mechanisms of dyspnea in COPD are not fully understood. Neural signals relating to abnormalities of chest wall and airway mechanics appear to be important. Specifically, an increased sense of effort relating to the pressures needed from the respiratory muscles relative to their maximum pressure-generating capacity is thought to be one factor in producing dyspnea. Signals of "length-tension inappropriateness" from the respiratory muscles due to hyperinflation constitute another. Also, impulses from airways undergoing abnormal dynamic compression during exhalation have been described. Hypercapnia and hypoxemia play only a small role, except in acute situations. Oxygen administration may decrease breathlessness by reducing ventilation during exertion and through poorly understood direct effects not associated with changes in ventilation.

Physiological-Pathological Correlations

Approximately 40 years ago Hogg and colleagues discovered that airways 2 mm or less in internal diameter normally contribute only a minor part of the total airway resistance, but that these airways become the principal sites of increased airway resistance in COPD. Although it is well accepted that the functional obstruction to airflow in COPD is in the small airways, the relative importance of emphysema vs. intrinsic abnormalities of the small airways as the physical basis for the obstruction is still under investigation. Emphysema and small-airway pathology are both present in most persons with COPD so that their relative contributions to obstruction might vary from one patient to another. However, correlations between emphysema severity and airflow obstruction are poor (Fig. 41-7), while a recent analysis found good correlations exist between airway pathology and GOLD classes. Thus, it appears that airflow obstruction in COPD is especially associated with structural abnormalities in the small airways.

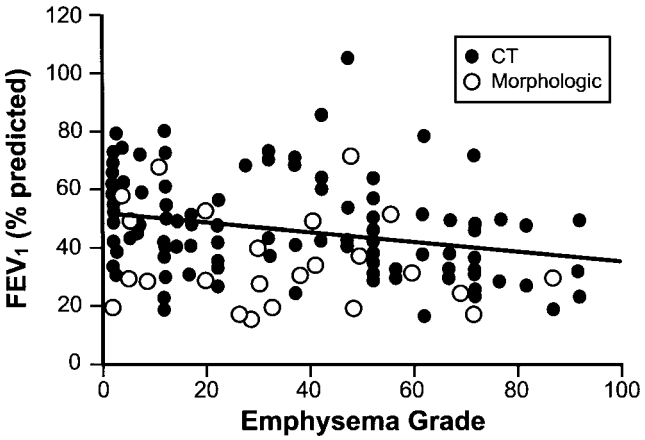


Figure 41-7 Emphysema score vs. FEV_1 (% predicted). Emphysema graded either by direct examination of lung tissue or by chest computed tomography. There is no correlation between emphysema severity and FEV_1. *(From Gelb AF, Hogg JC, Schein M: Contribution of emphysema and small airways in COPD. Chest 109:353–359, 1996, with permission.)*

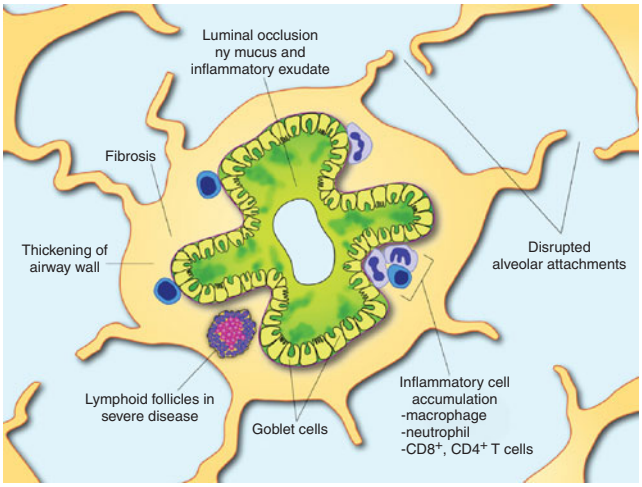


Figure 41-8 Small airway pathology in COPD. Multiple pathological lesions can be found. In some studies, but not all, quantification of these abnormalities correlates with the reduction in FEV_1. *(Reproduced with permission from Senior RM, Silverman EK: XXII Chronic Obstructive Pulmonary Disease. 14 Respiratory Medicine. ACP Medicine. Dale DC, Federman DD, eds. WebMD Inc., New York, 2007 [www.acpmedicine.com].)*

Small airways in the lungs of individuals with COPD typically show multiple abnormalities that include goblet cell metaplasia, replacement of surfactant-secreting Clara cells with mucus-secreting cells, and infiltration of the walls by inflammatory cells that, in severe disease, may include lymphoid follicles (Fig. 41-8) (see Chapter 40).These changes are accompanied by increased connective tissue and mesenchymal cells in the subepithelial and adventitial compartments of the airway walls. Alveolar tissue surrounding small airways normally provides radial traction on bronchioles at points where alveolar septa attach. Loss of these bronchiolar attachments as a result of proteolytic destruction may contribute to airway distortion, narrowing, and instability.

PATHOGENETIC PROCESSES

COPD represents the clinical expression of complex alterations in structure and function of alveolar tissue and small airways. Many processes at the tissue and cellular levels can be implicated, including inflammation, cell proliferation, apoptosis, altered phenotype of lung cells, and remodeling of the extracellular matrix. Numerous mediators, most notably proteinases, oxidants and cytokines, are involved in these processes. Studies in genetically altered mice have proven invaluable in helping to elucidate the pathogenesis of COPD, especially emphysema.

Inflammation

As reflected in the definition of COPD, inflammation occupies a central role in current thinking about the pathogenesis of COPD. The inflammation paradigm is that smoking and other types of inhaled irritants lead to recruitment of inflammatory cells to the lungs and airways and that products of these recruited cells injure lung tissue and disrupt normal mechanisms of lung repair. Indeed, inflammation is prominent in airways and lung parenchyma in biopsies, surgical specimens, and postmortem material from individuals with COPD. Other indicators of inflammation are increased inflammatory cells in bronchoalveolar lavage fluid (BALF) and sputum and increased volatile products of inflammatory cells in exhaled breath. Inflammatory cells associated with COPD include neutrophils, eosinophils, macrophages, and lymphocytes. Once the inflammatory process is initiated by smoking the process may persist long after smoking has stopped.

Unlike nonsmokers, macrophage accumulations are found in respiratory bronchioles in smokers, and BALF from smokers contains many fold increases in macrophages compared to the numbers in BALF from nonsmokers. Besides releasing proteinases that might degrade the extracellular matrix of the lung, alveolar macrophages in COPD make chemotactic factors that recruit other inflammatory cells to the lungs. Likewise, structural cells of the lungs in COPD produce proteinases and chemotactic factors for inflammatory cells. Expression of interleukin-8 (IL-8), macrophage inflammatory protein-1α (MIP-1α), and monocyte chemoattractant protein-1 (MCP-1), for example, are up-regulated in bronchiolar epithelium in COPD. T cells from COPD lungs produce cytokines that stimulate production of matrix metalloproteinases by macrophages. Peptides of elastin are chemotactic for inflammatory cells and, in some experimental models of emphysema the elastin peptides present in the lung are crucial to the inflammatory process, suggesting that destruction of the lung's extracellular matrix may be a self-perpetuating process. In mice, genetically induced overexpression of cytokines such as IL-13 or γ-interferon by lung cells leads to emphysema that is mediated by proteinases from inflammatory cells.

Cellular and humoral immunity may be involved in emphysema pathogenesis. CD4+ and CD8+ T cells and B cells accumulate in alveolar and airway tissue in COPD and form bronchus-associated lymphoid tissue (BALT) in the walls of small airways, and an increasing BALT in small airways correlates with increasing GOLD stage. In mice, exposure of antibodies to endothelial cells elicits alveolar septal cell destruction. Speculation about antigens for immunologically driven emphysema in patients include microbial pathogens, material contained in tobacco smoke, and peptides released from lung extracellular matrix.

Proteinase-Antiproteinase Imbalance

Proteinases of several biochemical classes, and requiring different inhibitors, are implicated in the pathogenesis of emphysema. Serine proteinases, especially neutrophil elastase, and several matrix metalloproteinases (MMPs), especially MMP-1 (collagenase), MMP-9 (gelatinase B), MMP-12 (macrophage elastase), and MMP-14 (MT1-MMP, membrane-type 1 MMP), have been the classes and specific proteinases for which there are the most data.

For many years neutrophils and macrophages were considered to be the exclusive sources of proteinases involved in COPD. Now it is appreciated that other types of inflammatory cells and even structural cells of the lungs may produce proteinases that promote emphysema. Besides degrading matrix proteins, proteinases may exert other effects that relate to the pathogenesis of COPD, such as releasing cell-bound and matrix-bound chemokines, activating growth factors, and inducing expression of mucin genes. However, α_1-AT deficiency is still the only situation of proteinase-antiproteinase imbalance in COPD in which both the proteinase (neutrophil elastase) and its inhibitor (α_1-AT) have been definitively established. It must be emphasized that little is known about proteinases in the pathogenesis of the small-airway pathology of COPD. Virtually all of the information about proteinases in COPD pertains to emphysema. Accordingly, we discuss proteinases below in the context of the pathogenesis of emphysema.

Oxidant-Antioxidant Imbalance

Reactive oxygen species in cigarette smoke or released by inflammatory cells and structural cells of the lungs in response to smoke may lead to lung injury (see Chapter 25). Up to 20 mg of tar may be deposited in a smoker's lung per cigarette smoked. This tar contains more than 10^{17} stable, long-lived radicals per gram. The gas phase of tobacco smoke contains 10^{15} organic radicals per puff of smoke, although in general these small oxygen- and carbon-centered species are more short-lived and reactive than the radicals in the particulate phase. Tobacco smoke appears to "prime" neutrophils and alveolar macrophages to generate elevated amounts of reactive oxygen species, such as hydrogen peroxide, hydroxyl radicals, and superoxide radicals. The lung tissue of smokers also contains significantly more iron than that of nonsmokers, providing a catalyst for the production of hydroxyl radicals from H_2O_2. Additionally, smokers demonstrate increased production of neutrophil myeloperoxidase, which is capable of yielding oxidized halogens such as hypochlorous acid (HOCl). Oxidants can modify and inactivate proteins, protease inhibitors (such as α_1-AT and secretory leukoprotease inhibitor [SLPI]), and histone deacetylase 2 (HDAC2), which is involved in glucocorticoid mediated anti-inflammatory responses. Oxidants can also affect lipids and DNA, and some specific end products, such as 4-hydroxy-2-nonenal (4-HNE) and 8-hydroxy-2′-deoxyguanosine (8-OHdG), may be markers of COPD.

Directly relevant to the inflammatory hypothesis of COPD, oxidants can promote inflammation and proteinase expression via intracellular signaling pathways that involve mitogen-activated protein kinases (MAPK), nuclear factor (NF)-κB, and other pro-inflammatory signaling molecules (Fig. 41-9). Oxidants can induce apoptosis. Oxidants may also facilitate proteinase-mediated extracellular matrix degradation by enhancing matrix molecule susceptibility to proteolytic cleavage, and may participate in nonenzymatic degradation as in the case of the effects of hydroxyl radicals on type I collagen. In experimental animals the combination of cigarette smoke and elastase leads to greater emphysema than either insult alone, suggesting that these insults do not elicit identical responses.

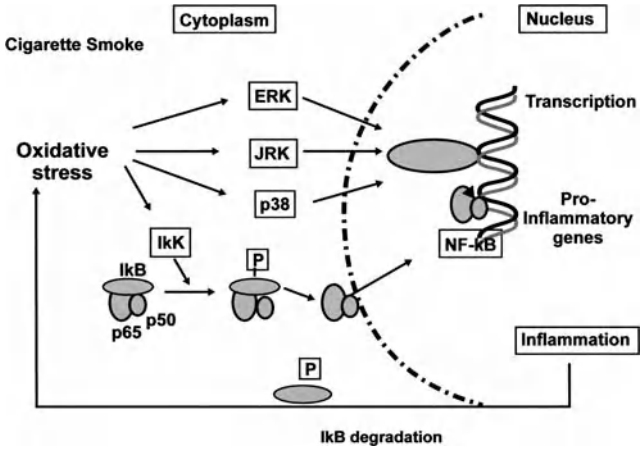


Figure 41-9 Activation of signal pathways by oxidative stress. Ap-1 = activating protein 1; erk = extracellular signal-related kinase; ikk = inhibitor kb kinase; jnk = c-jun n-terminal kinase; nf-b = nuclear factor b; p = phosphate. *(From MacNee W: Pulmonary and systemic oxidant/antioxidant imbalance in chronic obstructive pulmonary disease. Proc Am Thorac Soc 2:50–60, 2005, with permission.)*

A number of antioxidant enzymes protect against oxidative injury. Intracellular oxidant concentrations are controlled by copper- and zinc-dependent superoxide dismutases in the cytoplasm and a manganese-dependent form in mitochondria. H_2O_2 is eliminated by catalase and glutathione peroxidase. Additional antioxidants include α-tocopherol and ascorbate, which are enriched in epithelial lining fluid. Gene profiling of airway epithelium in long-time smokers suggests that the glutathione pathways are induced, but the catalase and superoxide dismutases are not. Experimental evidence for the importance of the antioxidant system in protection against cigarette smoke– induced damage is apparent in mice lacking the master antioxidant regulator, nuclear factor E2-related factor (Nγf-2). When these mice are exposed to cigarette smoke they develop emphysema whereas identical mice that have normal Nγf-2 are resistant to the development of emphysema. Interestingly, the underlying mechanisms for emphysema vary between mouse strains. The capacity to mount antioxidant responses appears to influence the capacity to generate antiproteases as Nγf-2– deficient mice develop more severe emphysema in response to intratracheally administered elastase than controls. Thus, it appears that Nγf-2 protects against the development of emphysema not only by regulation of oxidant/antioxidant balance, but also by influencing inflammation and protease/antiprotease balance.

Although the antioxidant defense system may be compromised by the oxidative stress imposed by smoking, this has not been proven. In fact, some evidence suggests that

protective mechanisms are enhanced. The antioxidant capability of alveolar macrophages from smokers is increased and glutathione levels in alveolar lining fluid are elevated. Ascorbate and α-tocopherol levels in smokers are difficult to interpret, with increased levels in macrophages and decreased levels noted in serum and alveolar lining fluid.

Apoptosis

An early theory of emphysema development was that alveolar vascular destruction preceded loss of alveolar tissue. Recent data suggest that this speculation may have merit since blockade of vascular endothelial growth factor (VEGF) signaling in alveolar endothelial cells or genetic down-regulation of VEGF production in alveolar epithelium produces apoptosis and noninflammatory emphysema in rodents. The same result can be achieved by instilling the pro-apoptotic protein caspase-3 into the lungs. These experimental studies may actually have relevance to human emphysema as apoptotic cells can be found in emphysematous lungs and smokers' lungs but not in nonsmokers' lungs. In vitro, cigarette smoke induces apoptosis of several lung cell types. The mechanisms by which apoptosis leads to emphysema are still not well understood, but in the caspase-3 study mentioned above apoptotic alveolar type II cells degraded elastin. An important feature of experimental models of emphysema due to apoptosis is that there is minimal inflammation. In contrast to the expanding body of information linking emphysema to apoptosis, there is only scant information about apoptosis of the cells of small airways in COPD. Much remains to be learned about apoptosis in the context of COPD.

Mucus Hypersecretion

Airway mucus is a normal protective barrier that is constantly replenished and cleared in health (see Chapter 8). Mucin glycoproteins, the main components of mucus, have a core protein rich in serine and threonine, to which carbohydrates and cysteine residues are attached. It is secreted from submucosal glands and airway goblet cells. In COPD there is hyperplasia of goblet cells and hypertrophy of glands with an increase in the ratio of glandular mucus cells to serous cells. The changes in COPD are associated with an alteration of the mucus proteins (MUCs) to favor a predominance of MUC5B over the typical MUC5AC form, and an increase in the MUC2 form, which is uncommon in normal lung mucus. Other alterations in the mucus layer in COPD include greater acidity, less mucin glycosylation, and decreased antimicrobial peptides. Mediators responsible for mucus hypersecretion include proteinases (neutrophil elastase and MMP-9), cytokines (tumor necrosis factor α, TNFα), oxidants, dual oxidase, TNFα-converting enzyme (TACE), and epidermal growth factor receptor (EGFR) ligands.

Determining the relationship between chronic cough and sputum in patients with COPD and the natural history of COPD has been elusive. Reports vary from finding weak to strong correlations between cough and sputum production and COPD progression, COPD exacerbations, and mortality. A relationship between chronic mucus hypersecretion in small airways and adverse outcomes is plausible as histological analysis of small-airway pathology in COPD demonstrated that the extent of small-airway luminal obstruction by mucus correlated with the GOLD stage. However, the correlation with the GOLD stage was stronger for inflammatory cell infiltration into the walls of the small airways than the luminal mucus obstruction.

PATHOGENESIS OF EMPHYSEMA

General Concepts

The standard definition of emphysema is "a condition of the lung characterized by abnormal, permanent enlargement of airspaces distal to the terminal bronchiole, accompanied by destruction of their walls, and without obvious fibrosis." Although overt fibrosis may not be a finding, studies since this definition was enunciated indicate increased collagen per unit volume of airspace wall in emphysematous lungs associated with active synthesis of extracellular matrix. Also, emphysematous tissue has been found to exhibit both apoptosis and proliferation of alveolar cells. Accordingly, emphysematous lung tissue should be viewed as undergoing remodeling rather than simply a destructive process.

The pathogenesis of emphysema was obscure until 1963 when Laurell and Eriksson reported an association between deficiency of serum α_1-AT and chronic airflow obstruction with emphysema. At approximately the same time Gross and associates described the first reproducible model of emphysema by injecting the plant proteinase papain, a potent elastase, into the lungs of rats via the trachea. Together, these observations led to the proteinase-antiproteinase hypothesis of emphysema which has been the prevailing concept of the pathogenesis of emphysema ever since.

According to the proteinase-antiproteinase hypothesis, there is normally a steady or episodic release of proteolytic enzymes into the lung parenchyma, principally from inflammatory cells. Under normal conditions plasma proteinase inhibitors, especially α_1-AT, permeate lung tissue and prevent proteolytic enzymes from digesting structural proteins of the lungs. Proteinase inhibitors synthesized locally in the lungs also contribute to the antiproteinase "shield". Emphysema results when there is an imbalance between proteinases and antiproteinases in favor of proteinases due to an augmentation of proteinase release in the lungs, a reduction in the antiproteinase defense within the lungs, or a combination of both increased proteinase burden and decreased proteinase inhibitory capacity. It is important to appreciate that proteolytic injury to the extracellular matrix of the lung does not necessarily operate throughout the lungs as a whole. In fact, proteolytic events are tightly controlled and occur at or near the surface of cells. Thus, "imbalance" between proteinases

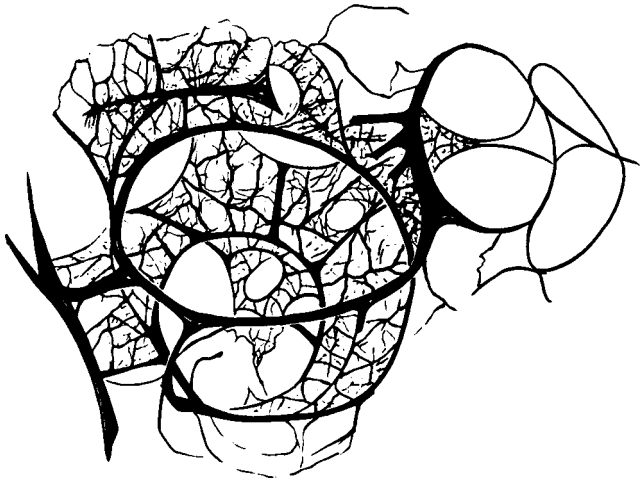


Figure 41-10 Alveolar elastic fiber network. Artist's sketch of the elastic fibers in the parenchyma of human lung showing how elastic fibers form a helix encircling the alveolar ducts and penetrate into alveolar septae. *(From Pierce JA, Ebert RV: Fibrous network of the lung and its change with age. Thorax 20:469–476, 1965.)*

and their inhibitors probably should be viewed as operating in microenvironments immediately surrounding cells.

Lung Elastic Fibers

The original observations linking proteinases and emphysema led to the concept that destruction of alveolar elastic fibers is a key to emphysema development. Indeed the proteinase-antiproteinase hypothesis of emphysema pathogenesis became, in fact, the "elastase-antielastase hypothesis".

Structurally, the extracellular matrix of the lung is organized into three interdependent cable systems: (1) an axial system that extends from the central airways through the peripheral airways to the alveolar ducts; (2) a parenchymal system that comprises the matrix of the alveolar septae; and (3) a peripheral system that arises from the visceral pleura and extends into the interlobular septae, forming a fibrous sac around the lung. Distal to the respiratory bronchioles, the axial system forms a helix encircling the alveolar ducts, extending into the interstitium of alveolar walls. Elastic fibers, of which elastin is the main component, loop around alveolar ducts, form rings at the mouths of the alveoli, and penetrate as wisps into the alveolar septae, where they are concentrated at bends and junctions (Fig. 41-10). Elastic fibers, which possess rubberlike reversible extensibility, come under tension and provide elastic recoil throughout the respiratory cycle. Unlike elastic fibers, the interstitial collagen fibers in alveolar septa are nondistensible and have high tensile strength. They can be thought of as relaxed ropes that straighten during inspiration and become taut at total lung capacity.

Elastin is resistant to many proteinases, most notably the collagenases that cleave interstitial collagens. However, there are a number of enzymes that may come in contact with the lung that can degrade elastin (Table 41-2). Elastic fibers in the lung normally last a full human life span. There is virtually no elastin synthesis in the normal adult lung, but animal studies indicate that elastin synthesis can be reinitiated in the adult lung.

Table 41-2

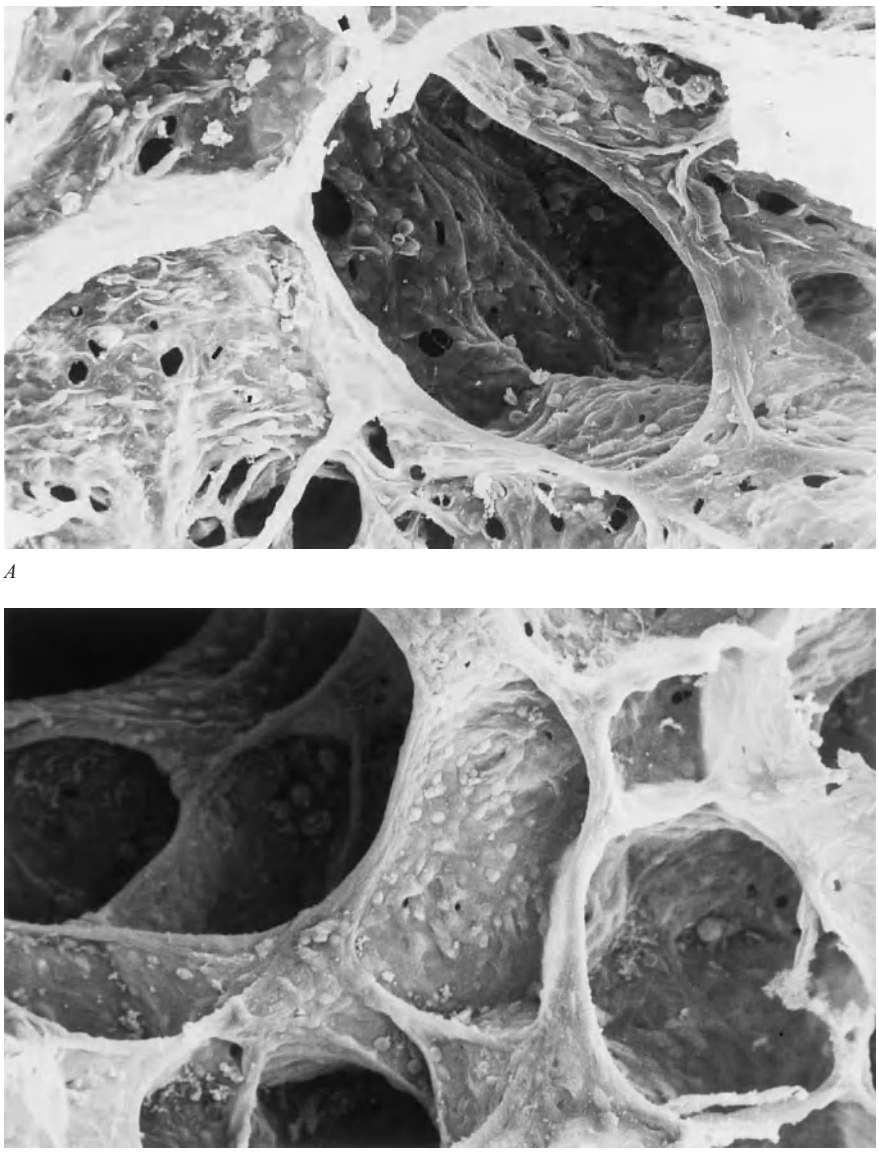
Elastolytic Proteinases that May Affect the Lung Parenchyma

Proteinase	Cell of Origin
Neutrophil elastase	Neutrophil (Monocyte)
Proteinase 3	Neutrophil (Monocyte)
Cathepsin G	Neutrophil (Monocyte, mast cell)
MMP-9 (Gelatinase B)	Macrophage, neutrophil, eosinophil, fibroblast, epithelial cell
MMP-12 (Macrophage elastase)	Macrophage
Cathepsin L	Macrophage
Cathepsin S	Macrophage

Note: Parentheses denote minor cellular sources.

Histological studies of emphysematous lung tissue support the hypothesis that elastic fibers are perturbed in emphysema. There are fragmented elastic fibers in α_1-AT deficiency and poorly formed elastic fibers and clumps of elastin in smokers with centriacinar emphysema. The latter changes appear to be from aberrant synthesis of new elastin and resemble the findings in the lungs in emphysema induced experimentally with elastase.

What little is known about lung repair in response to elastolytic proteinases derives from animal research. After an intratracheal injection of human neutrophil elastase into an experimental animal, acute depletion of elastin occurs, followed by a burst of synthesis of extracellular matrix including elastin. Over a few weeks, the elastin content of the lungs returns to normal, although the lungs display emphysema. The elastic fibers, like the elastic fibers in human emphysema, appear disorganized. Thus, even if elastin expression can be reinitiated in the adult human lung, the production of normal elastic fibers is not achieved. This is not surprising as production of elastic fibers entails temporally and physically coordinated expression of the many components of the elastic fiber. One way in which smoking may impair lung elastic



A

B

Figure 41-11 Holes in alveolar walls in early emphysema. Scanning electron micrographs of alveolar walls from surgically resected specimens: lung with mild emphysema (*A*) and non-emphysematous lung (*B*). Holes are more numerous in alveolar walls in the emphysematous lung than in the normal lung. Original magnification ×250. *(From Nagai A, Inano H, Matsuba K, et al: Scanning electron microscopic morphometry of emphysema in humans. Am J Respir Crit Care Med 150:1411–1415, 1994, with permission.)*

fiber synthesis is by inhibiting lysyl oxidase, the enzyme that catalyzes the first step in the conversion of tropoelastin monomers to the elastin polymer.

Lung Collagen Turnover

Although elastases and elastic fiber destruction dominate thinking about the pathogenesis of emphysema, degradation of alveolar wall collagen and aberrant collagen deposition in alveolar tissue may also be involved. Indeed, collagen destruction may be the critical event in some forms of experimental emphysema. Mice genetically engineered to harbor a transgene that leads to expression of human MMP-1 (collagenase) in lung tissue develop enlarged alveoli, bullous lesions, and reduced collagen fibers in alveolar walls and pleura. Depending on the level of transgene activity the lung lesions can start early after birth or later, indicating that the emphysema is post-developmental. Besides showing that collagenase activity can lead to emphysema, results with these mice also indicate that proteinases causing emphysema can be from structural cells of the lungs, as there is minimal inflammation in the lungs, and that emphysema can occur without obvious disruption and faulty resynthesis of elastic fibers as the elastic fibers in these lungs look normal.

In emphysematous lungs the pores of Kohn are larger and more numerous than in normal lungs (Fig. 41-11). Because interstitial collagens and basement membrane collagens are prominent in alveolar walls, it seems plausible that collagenous structures undergo degradation in the process of increasing the number and size of these interalveolar pores.

Proteinases

The high risk of emphysema among smokers with severe α_1-AT deficiency is the most compelling evidence linking a

proteinase, in this case neutrophil elastase, to emphysema. Thus far, gene profiling of emphysematous lung tissue has shown only limited changes in proteinases and proteinase inhibitors compared to control lung tissue. Success in protecting mice from smoke-induced emphysema through knockouts of proteinase genes or by treatment with proteinase inhibitors has reinforced the proteinase-antiproteinase hypothesis. Neutrophil elastase and several MMPs, some released by neutrophils, and others produced by alveolar macrophages and structural cells of the lungs have been the predominant proteinases implicated in emphysema.

Neutrophil Elastase

Ever since the discoveries of α_1-AT deficiency and neutrophil elastase, this proteinase has been prominent in the consideration of emphysema pathogenesis. Neutrophil elastase is a serine proteinase. Like other serine proteinases it has conserved histidine, asparagine, and serine residues that form a charge relay system that functions by transfer of electrons from the carboxyl group of asparagine to the oxygen of serine. The serine then becomes a powerful nucleophile that is able to attack the carbonyl carbon atom of the peptide bond of the substrate. It is synthesized as a pre-proenzyme in the endoplasmic reticulum, processed by cleavage of the signal peptide (pre-) and removal of a dipeptide (pro-) by cathepsin C. Its synthesis occurs in the bone marrow during a very specific stage in myeloid development and it is stored in azurophil granules as an active packaged protein. It has activity against elastin and other extracellular matrix proteins, as well as many non-matrix substrates. Because neutrophils can concentrate it on their plasma surface, it may function in the extracellular environment despite large excesses of α_1-AT and other inhibitors.

Following the early connection of α_1-AT and neutrophil elastase, later evidence implicating neutrophil elastase in the pathogenesis of emphysema has included: (1) increased presence of neutrophil elastase, both free and in complex with α_1-AT, in BALF of people with emphysema; (2) the presence of neutrophil elastase in emphysematous lung tissue; and (3) finding that mice lacking neutrophil elastase ("knockouts") show significant protection from the development of emphysema in response to chronic inhalation of cigarette smoke. Although neutrophil elastase may be the predominant elastase associated with emphysema, other enzymes in the lung have elastase activity (Table 41-2).

Matrix Metalloproteinases (MMPs)

For many years neutrophil elastase dominated thinking about proteinases and emphysema. In recent years, however, MMPs have become a focus. MMPs are a family of neutral proteinases that degrade extracellular matrix and modify many other substrates. This enzyme family can be subdivided based on secretion vs. membrane association. Membrane-type MMPs are linked to the cell surface and are more resistant to inhibition by secreted antiproteinases than MMPs in pericellular spaces. MMPs are secreted as inactive proenzymes, which are activated at the cell membrane surface or within the extracellular space by proteolytic cleavage of the N-terminal domain. Catalytic activity is dependent on coordination of a zinc ion at the active site and is specifically inhibited by members of another gene family, tissue inhibitors of MMPs known as the tissue inhibitor of metalloproteinases (TIMPs) (see below). Although the name implies that MMPs are directed at extracellular matrix, MMPs may exert proteolytic activity against other substrates such as α_1-AT and various cytokines. Accordingly, MMPs may promote the development of emphysema in diverse ways.

Individual members of the MMP family can be loosely divided into groups based on their matrix-degrading capacity. As a whole, they are able to cleave all extracellular matrix components at neutral pH. The collagenolytic MMPs have the unique capacity to cleave native triple helical interstitial collagens, but have a restricted substrate specificity and are unable to degrade elastin or basement membrane molecules. In lung tissue exhibiting emphysema, various cell types express MMP-1 (collagenase 1), MMP-2 (gelatinase A), and membrane-type 1 MMP (MT1-MMP; MMP-14). In other types of analyses, MMPs associated with COPD include MMP-8 (collagenase 2) and MMP-9 (gelatinase B) in BALFs and MMP-12 (macrophage elastase) in alveolar macrophages.

MMP-8 (neutrophil collagenase) and MMP-9 (gelatinase B) are stored within specific granules in neutrophils from which they are readily released by a variety of stimuli. Alveolar macrophages produce multiple MMPs, including 2, 9, 12, and 14. However, MMPs are scarcely expressed in normal lung tissue. Their production and activity are carefully controlled during normal repair and remodeling processes. With chronic inflammation, regulation of MMPs may go awry, and MMPs may be overexpressed and produced at inappropriate sites. MMP-12 is up-regulated in alveolar macrophages of cigarette smokers. Elimination of MMP-12 by gene targeting protects mice from emphysema induced by cigarette smoke. As already noted, overexpression of MMP-1 in the lungs of transgenic mice leads to enlarged airspaces characteristic of emphysema. In advanced emphysema, alveolar type II cells produce MMP-1 and smoke exposure induces MMP-1 expression by human airway epithelial cells and lung fibroblasts in cell culture. Accordingly, there is considerable evidence implicating both elastolytic and collagenolytic MMPs in the pathogenesis of emphysema.

Cysteine Proteinases

Human alveolar macrophages can produce multiple cysteine proteinases, including cathepsins L and S which have large active pockets with relatively indiscriminate substrate specificities that include elastin and other matrix components. These enzymes have their maximum activity at acidic pH, but cathepsin S retains about 25 percent of its elastolytic capacity at neutral pH, making it approximately equal to neutrophil

Table 41-3

Proteinase Inhibitors in the Lung Parenchyma

Inhibitor	Cell of Origin	Class of Proteinases Inhibited
α_1-antitrypsin	Hepatocyte (Mononuclear phagocyte)	Serine*
α_2-macroglobulin	Hepatocyte Lung fibroblast (Macrophage)	Serine, MMP† Cysteine
TIMPs (1,2,3,4)‡	Resident lung cell	MMP
SLPI§	Resident lung cell (Macrophage)	Serine#
Elafin	Large-airway epithelial cell	Serine
Cystatin C	Bronchial epithelial cell (Macrophage)	Cysteine

NOTE: *Parentheses denote minor cellular sources.*
* *α_1-antitrypsin has its greatest affinity for neutrophil elastase*
† *Matrix metalloproteinase*
‡ *Tissue inhibitors of metalloproteinases*
§ *Secretory leukocyte protease inhibitor*
# *SLPI does not inhibit PR3*

elastase. Thus, these enzymes have the capacity to cause lung destruction if they are targeted to the cell surface or extracellular space, especially if macrophages can acidify their microenvironment.

Proteinase Inhibitors

Considerations of proteinase inhibition in COPD have tended to focus on α_1-AT. However, other inhibitors may serve important antiproteinase functions in lung tissue (Table 41-3).

Inhibitors of Serine Proteinases

Low-molecular-weight serine proteinase inhibitors are abundant in airway fluid and, hence, are thought to represent the primary defense against proteinase-mediated airway damage. Secretory leukoprotease inhibitor (SLPI) is a 12-kDa protein produced by mucus-secreting and epithelial cells in the airway, as well as type II pneumocytes. SLPI inhibits neutrophil elastase and cathepsin G and many other serine proteinases, but not proteinase 3. Elafin, also produced by airway secretory and epithelial cells, is released as a 12-kDa precursor that is processed to a 6-kDa form that specifically inhibits neutrophil elastase and proteinase 3. These inhibitors are able to inhibit neutrophil elastase bound to substrate, giving them an added dimension that α_1-AT lacks.

Airway mucus contains several other substances that partly inhibit neutrophil elastase, including polyanionic molecules, such as mucins, other glycosaminoglycans, and fatty acids. DNA, released from inflammatory leukocytes, binds to SLPI, greatly enhancing its rate of association with neutrophil elastase. The relative contribution of each of these molecules to proteinase inhibition is unknown.

Tissue Inhibitors of Matrix Metalloproteinases (TIMPs)

TIMPs are a family of four proteins that form tight noncovalent bonds with all MMPs. All TIMPs inhibit all MMPs, except TIMP-1 which does not inhibit membrane type (MT)-MMPs. Structurally TIMPs have a wedge-shaped N-terminal domain that competes with substrate for the catalytic site; however, the C-terminal domain can bind to specific pro-MMPs without inhibiting pro-MMP activation. TIMP-2 is secreted complexed to pro-MMP-2 in fibroblasts and interacts with MT1-MMP in the activation of pro-MMP-2.

TIMPs are secreted from many cell sources and are abundant in tissues. Cell-specific production and microenvironment localization appear to play an important role in the balance between MMPs and TIMPs. TIMP-3 is more highly glycosylated and interacts with matrix and cell-surface proteoglycans while the other TIMPs are secreted and

freely diffusible. TIMP-1 is the most highly inducible whereas TIMP-2 expression is more constitutive.

Alveolar macrophages secrete TIMP-1 and TIMP-2. Cytokines, such as interferon-γ, inhibit MMP-1 and MMP-12 expression in macrophages, with little effect on TIMPs; while TGF-β induces TIMP-1 expression and inhibits MMP production. Thus, MMPs and TIMPs may be coordinately regulated, perhaps limiting tissue injury during normal remodeling associated with inflammation. Alternatively, regulation may become discoordinate, leading to proteolysis of extracellular matrix or fibrosis.

In COPD, TIMP-1 is elevated in sputum and tissue homogenates, but may not be in excess of MMPs. Other TIMPs have been less well studied, but TIMP-3 knockout mice have enhanced pulmonary inflammation and impaired lung development that resembles emphysema. A TIMP-2 polymorphism associated with COPD has been uncovered in a Japanese population, but it is unclear if this polymorphism has any effect on TIMP-2 protein expression.

Cystatins

Cystatins represent families of cysteine proteinase inhibitors, some of which are strictly intracellular, while others such as cystatin C possess a signal peptide and are secreted by a variety of cells. Cystatin C, composed of a single, non-glycosylated, chain (13 kDa), forms reversible 1:1 complexes with enzymes. It is the most ubiquitous cystatin. It has been found in all human tissues and body fluids, providing protection against tissue destruction by intracellular cathepsin enzymes leaking from cells. It is produced by alveolar macrophages.

Overall View of the Pathogenesis of Emphysema

Degradation of lung elastin by elastase activity from inflammatory cells is probably the predominant mechanism for emphysema in most smokers. However, the biology of emphysema is clearly complex and still incompletely understood. It includes inflammatory cell recruitment, proteinase-antiproteinase imbalance, oxidant-antioxidant imbalance, and responses of lung cells to proteinases and oxidants from inflammatory cells and to constituents of tobacco smoke (Fig. 41-12). It may also involve humoral and cellular immunity. Degradation of extracellular matrix components besides elastin, particularly collagens, may be an important feature. In some situations apoptosis of lung cells may precede degradation of extracellular matrix. Senescence of lung cells, a recently identified phenomenon in emphysema, has unclear implications, but suggests that lung repair mechanisms are depressed.

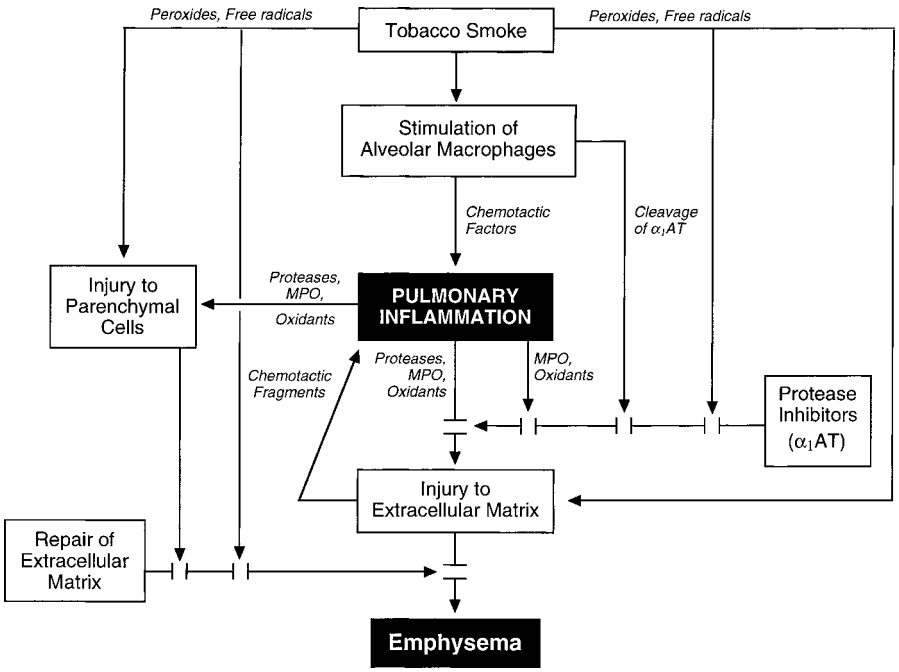


Figure 41-12 Schematic of concepts of the pathogenesis of emphysema due to smoking. Smoke leads to induction and release of chemotactic factors by alveolar macrophages and resident structural cells causing an accumulation of several types of inflammatory cells in the lungs. Smoke-stimulated resident cells and the recruited cells release proteinases and oxidants that damage or degrade extracellular matrix in the walls of alveoli, alveolar ducts, and respiratory bronchioles. Smoke also induces senescence and apoptosis of structural cells (injury to parenchymal cells) which leads to release of products that injure tissue and reduces the capacity of the tissue to repair. Smoke further affects lung homeostasis by inactivating proteinase inhibitors, such as α_1-AT. Peptides released from damaged extracellular matrix, notably from elastin, are chemotactic for inflammatory cells so that degradation of the extracellular matrix leads to a feedback loop that perpetuates inflammation. Not shown is the possibility that cellular and humoral immune processes are also involved.

ALPHA 1-ANTITRYPSIN DEFICIENCY

Background

Human plasma contains at least six proteins that function as proteinase inhibitors. Together, they make up about 10 percent of the total plasma protein. At a concentration of 150 to 350 mg/dl, alpha 1-antitrypsin is present in the highest concentration of all of the plasma proteinase inhibitors. α_1-AT is a member of a family of serine proteinase inhibitors called serpins.

α_1-AT is a glycoprotein of 52 kDa synthesized primarily by the liver. Mononuclear phagocytes are a secondary source. It consists of a single polypeptide chain of 394 amino acids. Carbohydrate side chains account for 12 percent of the molecular mass. The 12.2-kb gene that encodes α_1-AT is on the proteinase inhibitor (PI) locus on chromosome 14. This site is near the gene for α1-antichymotrypsin, the inhibitor for cathepsin G which, like neutrophil elastase, is a proteinase contained in the azurophil granules of neutrophils. The α_1-AT gene has seven exons and six introns. Exons four through seven code for the mature protein. Of note, the first two exons and a segment of the third exon are encoded in the transcript expressed in macrophages, but not in hepatocytes. α_1-AT is an acute-phase reactant. Plasma levels rise with trauma, estrogen therapy, use of birth-control pills, and during pregnancy, however the levels do not rise to normal among individuals with severe deficiency.

Proteolytic inhibition of neutrophil elastase and other serine proteinases by α_1-AT involves cleavage by the proteinase of the reactive site of α_1-AT between methionine[358] and serine[359]. The result is an altered, "relaxed" α_1-AT conformation in complex with the proteinase. Formation of the complex renders the proteinase inactive, and because the complex is quite stable, inactivation is essentially permanent. α_1-AT inhibits many serine proteinases and does so at a 1:1 molar basis. However, α_1-AT associates with neutrophil elastase much faster than with trypsin or other serine proteinases. Indeed, the association with neutrophil elastase is so fast in comparison with other serine proteinases that inhibition of neutrophil elastase is almost certainly the primary function of α_1-AT. The capacity of α_1-AT to inhibit neutrophil elastase and other serine proteinases besides trypsin has led some authors to prefer the designations α_1-PI or α_1-antiproteinase, but the name α_1-AT has become a fixture.

From the genetic standpoint, α_1-AT is transmitted in a co-dominant fashion. Thus, the gene product from each parent is expressed in the offspring. More than 100 different α_1-AT alleles are known, most of which are SNPs that do not alter expression of the protein or its function and, therefore, have no clinical significance.

The nomenclature for α_1-AT polymorphisms uses letters to specify the allelic variants. The original letters were chosen to reflect electrophoretic mobility: F = fast, M = medium, S = slow, and Z = ultraslow. The normal allele, M, exists in more than 95 percent of the US population, with the S and Z alleles being the next most common, having frequencies of 3 percent and 2 percent, respectively. Homozygosity for the Z allele, Pi ZZ, is associated with severe deficiency of α_1-AT (less than 15 percent of normal) and accounts for virtually all of the individuals with severe α_1-AT deficiency. In the United States its incidence is about 1 in 3000 people. It is rare in Asians and infrequent in African Americans.

Heterozygosity of the M allele with either the S or Z allele is very common. There are an estimated 15 million MS and 7 million MZ individuals, respectively, in the United States and comparable numbers in Europe. Despite numerous studies, it is still not yet clear whether the Pi MZ phenotype carries an increased risk of COPD. If there is an increased risk it appears to be small or is limited to an as yet undefined subset of MZ individuals. The MS phenotype does not carry an increased risk, but SZ heterozygosity is associated with increased risk.

The abnormality in the Z protein is a point mutation in a single nucleotide at codon 342 that results in coding for lysine instead of glutamic acid. This amino acid substitution changes the charge attraction between the amino acids normally present in positions 342 and 290 in α_1-AT and prevents the formation of a fold in the molecule. With this change in tertiary structure, the molecule is susceptible to dimerization with another α_1-AT molecule; the dimerization can result in polymerization of α_1-AT in the endoplasmic reticulum that impedes secretion of the protein from the cell (Fig. 41-13). Inability to secrete α_1-AT from the hepatocyte explains the low levels of the protein in plasma and other body fluids. Polymers may also form in the lung. α_1-AT polymers are chemotactic for inflammatory cells which may help to explain the marked accumulation of inflammatory cells in the lungs of individuals with α_1-AT deficiency.

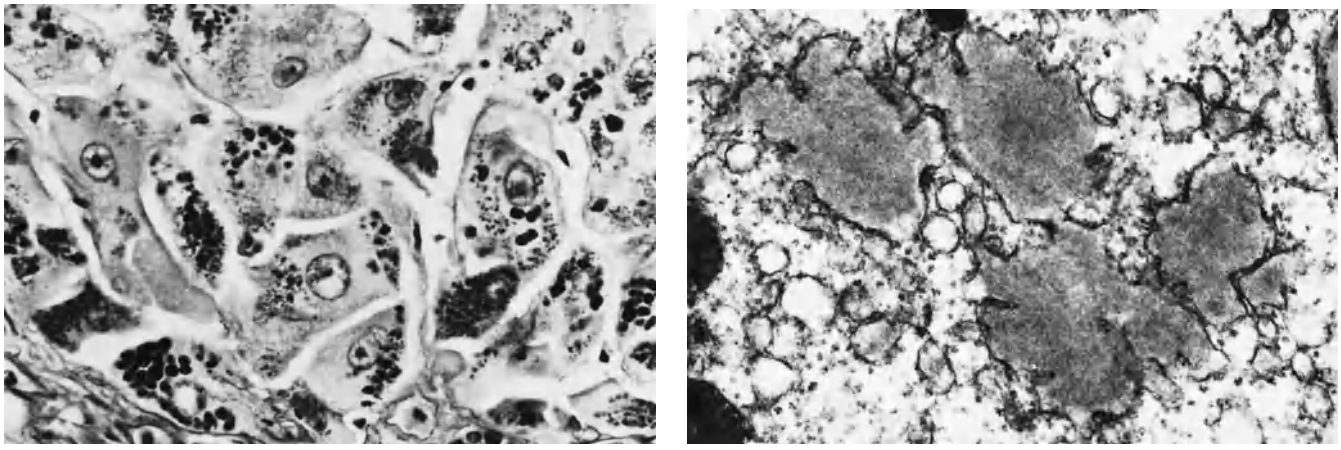
The Z form of α_1-AT has a much slower rate of association with neutrophil elastase than the association rate of normal α_1-AT with neutrophil elastase. Thus, not only do persons with the Pi Z phenotype have a deficiency of α_1-AT protein, but their α_1-AT is less effective than normal α_1-AT as an inhibitor of neutrophil elastase.

In contrast to the Z variant, the S variant of α_1-AT, which involves a single nucleotide substitution of glutamic acid[264] with valine, does not accumulate in the liver. This protein is less stable, presumably owing to loss of a salt bridge between the glutamic acid in position 264 and the lysine in position 387, and it polymerizes more slowly than the Z protein.

Quantification of serum α_1-AT concentration is done routinely by immunoassay. To confirm an immunoassay showing severe deficiency phenotyping is done in specialized laboratories by isoelectric focusing in the pH range of 4.0 to 5.0 (Fig. 41-14). Typing with molecular probes may be performed to definitively identify α_1-AT genotypes, but there is seldom an indication for this procedure to be performed in clinical practice.

Clinical Aspects

Alpha 1-antitrypsin deficiency may be suspected in adults as a result of respiratory symptoms, evidence of liver disease, or



A *B*

Figure 41-13 Globular cytoplasmic inclusions in hepatocytes in Pi Z α_1-AT deficiency. *A*. Periodic acid–Schiff stain after diastase digestion (×1250). *B*. Electron micrograph showing dilated cisterns of endoplasmic reticulum containing α_1-AT in a hepatocyte. These correspond to the globular inclusions in panel A (×25,000).

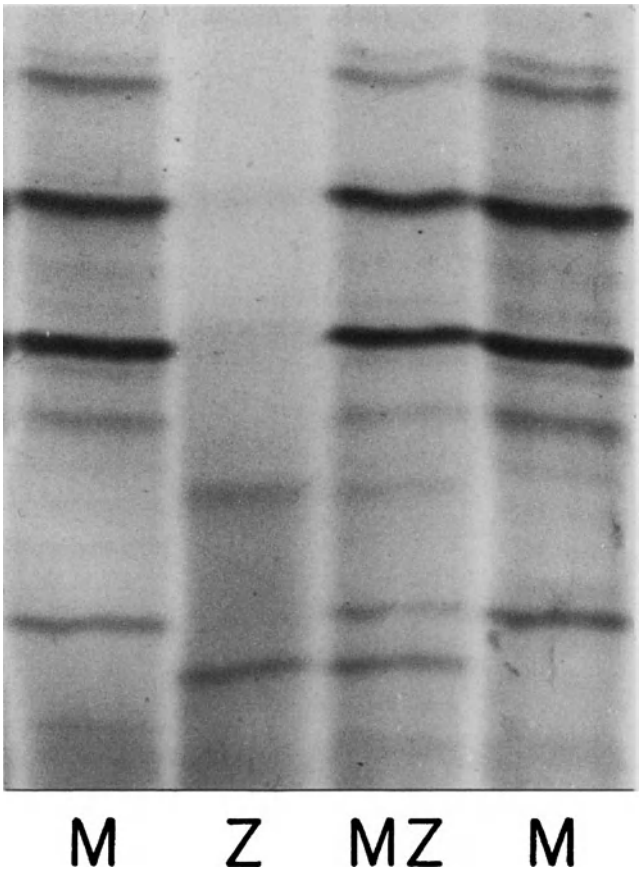


Figure 41-14 Patterns of Pi M, Pi Z, and Pi MZ α_1-AT on isoelectric focus. By this analysis, α_1-AT has microheterogeneity and thus appears as multiple bands. Pi M and Pi Z have distinctly different band patterns, while Pi MZ has a pattern that combines the patterns of both Pi M and Pi Z. (*Courtesy of John A. Pierce, M.D.*)

rare clinical manifestations such as panniculitis. In practice, however, most (about 80 percent) patients are discovered because of chronic respiratory symptoms and most of the rest are detected from screening for α_1-AT deficiency prompted by finding the deficiency in a family member. Liver disease is the mode of presentation in only a small percentage of adults with α_1-AT deficiency. Because of its infrequency in the practice of most physicians, the diagnosis of α_1-AT deficiency may not be suspected for a number of years after the onset of chronic respiratory symptoms, and often the patient has been seen by several physicians before the diagnosis is established.

Lung Disease

In the classic situation, the patient with Z type α_1-AT deficiency presents with the typical symptoms of COPD, especially shortness of breath, but is atypical on the basis of being rather young, often around age 40. The patient has hyperinflation, an increased total lung capacity, a decreased diffusing capacity, and radiographic changes consistent with emphysema that include hyperlucent lower lung fields reflecting the pathology (Fig. 41-15). This classic patient reports a mild smoking history relative to the severity of his/her COPD and may describe other family members with chronic respiratory symptoms.

In fact, however, there are many exceptions to this classic picture of α_1-AT deficiency. Wheezing, cough and sputum mimicking asthma, or chronic bronchitis that is poorly responsive to standard therapy may be the predominate symptoms. Evidence of emphysema may be minimal relative to the severity of the airflow obstruction. Finally, no other family members may have chronic respiratory symptoms, including siblings or other close relatives, even some who also have severe deficiency.

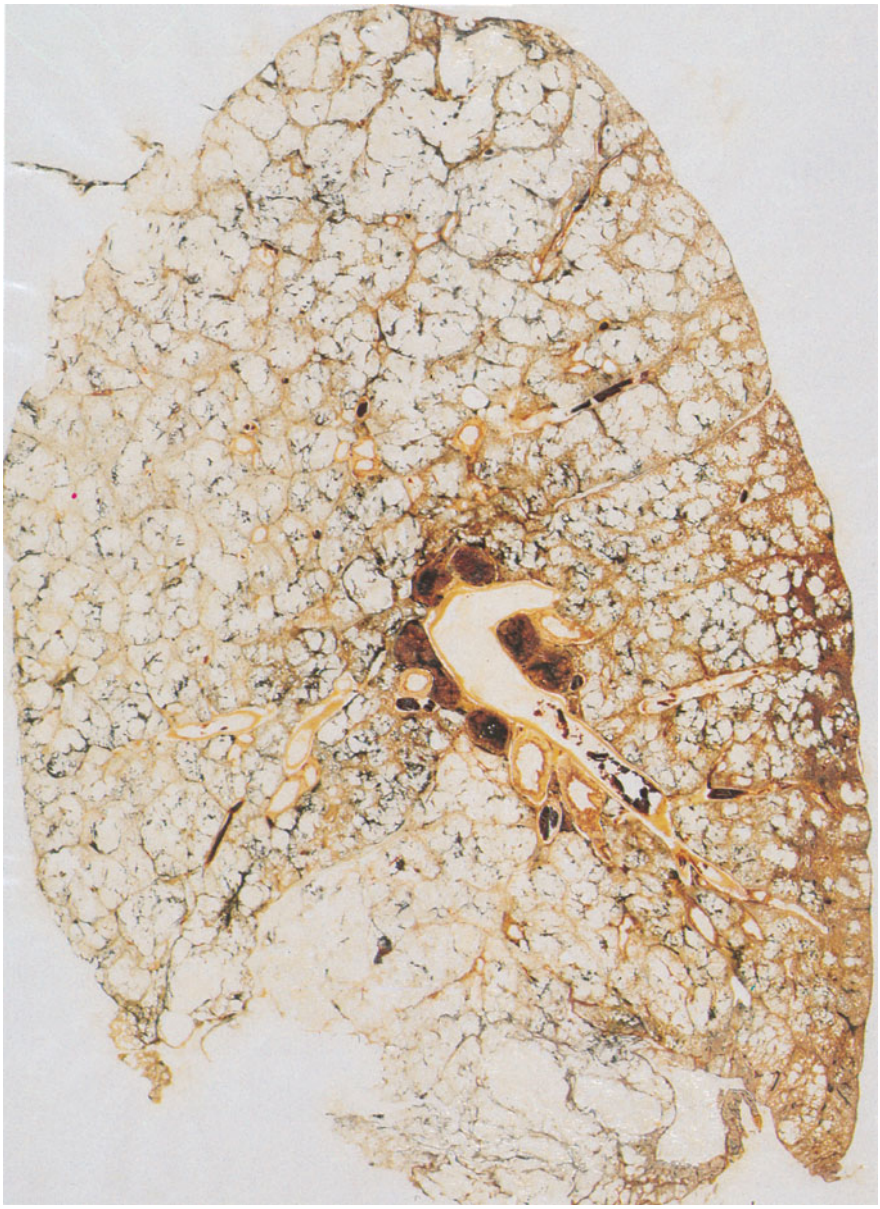


Figure 41-15 Lung pathology of Pi Z-type α_1-AT deficiency. Panacinar emphysema that is worst in the lung base. Paper-mounted whole lung section.

Because the presentation of α_1-AT deficiency can deviate so much from the classic presentation, some experts in this field advise that everyone diagnosed with COPD be screened for α_1-AT deficiency by the routine immunoassay. Other indications for screening include asthma that is not fully reversible despite aggressive therapy, recurrent bronchitis with or without bronchiectasis, a family history of the deficiency, and chronic liver disease without apparent risk factors. It is estimated that there are approximately 100,000 Pi Z individuals in the United States, of whom only around 10,000 are known, in part because they have few or no symptoms that lead to medical attention or, as noted above, clinicians do not think of the diagnosis.

Smoking is highly deleterious and hastens the development of COPD in most people with the deficiency. The typical Pi Z individual who smokes has respiratory symptoms by age 40, about 15 years earlier than equally deficient individuals who have never smoked. However, some Pi Z individuals reach advanced age with minimal respiratory symptoms.

Liver Disease

α_1-AT deficiency can present as liver dysfunction in infancy in various forms ranging from asymptomatic jaundice to frank liver failure. In most instances the clinical manifestations are mild and resolve. However, α_1-AT deficiency represents one of the main indications for liver transplantation in children. In adults, liver abnormalities may be limited to tests of liver function. Clinical manifestations seldom present before middle age. However, among Pi Z individuals who live beyond age 60, liver abnormalities are common and may overshadow respiratory symptoms. Indeed, among those individuals who

have not smoked and for other unexplained reasons avoid significant pulmonary function deterioration, hepatic cirrhosis and associated complications is the predominant terminal illness. In such individuals there is also a high incidence of hepatic cell carcinoma.

Alpha 1-antitrypsin deficiency is a paradoxical situation in which there is a severe systemic deficiency of α_1-AT despite substantial production of α_1-AT by the liver. The distinction between what is happening in the liver and what is happening systemically is clinically important. Infusions of α_1-AT, or other techniques under investigation for boosting systemic α_1-AT levels, can compensate for a severe systemic α_1-AT deficiency and so help protect the lung, but these approaches do not correct or ameliorate problems associated with the accumulation of abnormal α_1-AT in liver cells. At present, liver transplantation is the only treatment for the liver defect.

CONCLUDING COMMENT

Better understanding of COPD is imperative. This potentially disabling and fatal disease is already epidemic in many countries and appears destined to become epidemic worldwide in coming decades given trends of smoking prevalence.

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42

Chronic Obstructive Pulmonary Disease: Clinical Course and Management

Robert A. Wise

In past decades, the treatment of COPD has been approached by many physicians and patients alike with a nihilistic attitude, assuming that the disease was progressive, incurable, and untreatable. More recently, as our understanding of the clinical epidemiology and value of therapy of COPD has improved, this attitude has changed. Physicians have come to approach COPD in the same way as other chronic diseases, such as diabetes, rheumatoid arthritis, and coronary artery disease. With modern comprehensive treatment, the diagnosis of COPD is compatible with prolonged survival, good quality of life, and independent functional status for many who have this illness. The purpose of this chapter is to summarize the current understanding of the course of COPD and best approaches to treatment.

OVERVIEW OF COPD

Chronic obstructive pulmonary disease (COPD) is a disorder that is characterized by slow emptying of the lung during a forced expiration. In practice, this is measured as the FEV_1/FVC ratio, and the arbitrary definition of airflow obstruction is generally taken to be an FEV_1/FVC ratio lower than 0.70. Because the rate of emptying of the lung falls with advancing age, many elderly individuals demonstrate airflow obstruction even in the absence of a clinical diagnosis of COPD. Several disorders cause chronic airflow obstruction: long-standing asthma, cystic fibrosis, bronchiectasis, bronchiolitis obliterans, lymphangioleiomyomatosis,

panbronchiolitis, silicosis, Sjögren's syndrome, and diffuse interstitial processes such as eosinophilic granuloma and sarcoidosis. The diagnosis of COPD is usually limited to individuals who have chronic airflow obstruction associated with tobacco smoke or some other noxious inhalant, and it is usually not difficult to distinguish it from other causes of chronic airflow obstruction. The most commonly associated clinical disorders associated with COPD are emphysema and chronic bronchitis. *Emphysema* is defined anatomically by airspace enlargement due to disappearance of alveolar septae (see Chapter 40). This leads to the characteristic loss of elastic recoil, which, in turn, causes slowing of airflow from the lungs, hyperinflation, and air-trapping (see Chapter 41). *Chronic bronchitis* is characterized by chronic cough and sputum production, which is present in about one out of three people with early COPD. Chronic cough and sputum production in cigarette smokers is often, but not always, associated with chronic airflow obstruction. When chronic mucus hypersecretion is associated with airflow obstruction, it is often called *chronic obstructive bronchitis*. The anatomic correlates of chronic bronchitis are mucus gland hyperplasia and goblet cell metaplasia in large and medium-size airways. Patients with COPD also have *small and medium-size airway involvement* with inflammation, narrowing, tortuosity, and fibrosis that contributes to the airflow limitation. Some patients with a long-standing history of asthma develop airflow obstruction that is not completely reversible, episodes of cough and wheeze, and chronic sputum production. These individuals are often classified as having *chronic asthmatic bronchitis* and tend to have a somewhat better prognosis for survival than those with typical tobacco-related COPD. Physicians have a tendency to classify women as having asthma and men as having COPD despite similar medical histories.

NATURAL HISTORY OF COPD

COPD results from an increase in the rate of decline in lung function over time. Normal nonsmoking adults lose FEV_1 at a rate of 30 ml/y, thought to be the consequence of the aging-related loss of elastic recoil of the lung. Persons who develop COPD may start in early adulthood with lower levels of lung function and also have increased rates of decline. Studies of patients with COPD show an average annual decline in FEV_1 of 45 to 69 ml/y (Fig. 42-1*A*). This leads to the insidious loss of ventilatory reserve capacity that often is asymptomatic and unrecognized by patients and physicians alike. Chronic bronchitis may be dismissed as an innocent "smoker's cough" because patients fail to understand that it is abnormal to produce daily sputum. As ventilatory reserve decreases, people with mild COPD tend to limit strenuous activities, so breathlessness with activities of daily living is not ordinarily an early symptom of the disease. When the ventilatory reserve decreases to the extent that mild exertion such as climbing stairs, bed making, or carrying groceries is limited, patients tend to seek medical advice. In some cases, the first clinical presentation of disease is an acute episode of bronchospasm, dyspnea, or even respiratory failure in association with a respiratory infection or exposure to respiratory irritants. Thus, the onset of COPD may appear precipitous

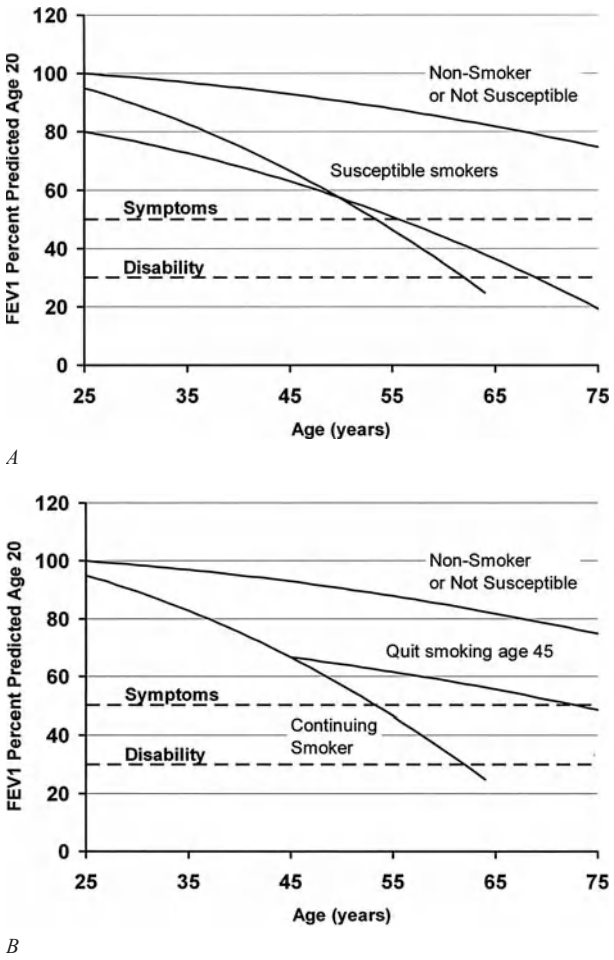

Figure 42-1 *A*. The natural history of COPD is presented for three hypothetical individuals. Pulmonary function is plotted as the percent of predicted lung function for a young adult who has attained maximal lung growth. Those who do not smoke, or are not susceptible to cigarette smoke typically lose about 25 percent of their young adult lung function throughout life. Individuals are susceptible to the adverse effects of smoking because of increased decline of lung function, or low lung function in young adult life. Although the abnormality of lung function is detectable for many years, symptoms do not develop until there is loss of approximately 50 percent of lung function (upper dashed line), which occurs in middle age or later. If the disease progresses, it may lead to substantial disability within a decade of the onset of symptoms (lower dashed line). *B*. The natural history of COPD is displayed for a hypothetical continuing smoker, and an individual who quit smoking at age 45. The axes are identical to those in (*A*). If an individual ceases smoking in the asymptomatic phase of COPD, the rate of decline of lung function reverts toward normal. In this example, the detection of abnormal lung function and cessation of smoking has a substantial effect of delaying the onset of respiratory symptoms. This plot is modified from the work of Fletcher and Peto and is commonly referred to as Fletcher curves. *(From Fletcher C, Peto R. The natural history of chronic airflow obstruction. Br Med J 1:1645–1648, 1977.)*

even though it is the cumulative result of decades of progression.

People who discontinue smoking with mild to moderate degrees of airflow obstruction cease the rapid decline in FEV_1, and have better survival (Fig. 42-1*B*). The improvement in survival depends largely upon the stage of disease. Persons who quit smoking with earlier disease have better outcomes compared with those who continue to smoke or those who quit smoking later in the disease. Once the disease is advanced, the inflammatory response persists and the rate of decline of lung function tends to progress. Because there are many years of asymptomatic decline in lung function, it is possible to diagnose COPD with forced expiratory spirometry before the disease is apparent and implement aggressive smoking intervention programs. There is no consensus whether it is necessary to screen for COPD among all cigarette smokers. Opponents of using spirometry for case-finding argue that the finding of a normal test would not alter physician behavior because all smokers should be encouraged to quit. It has also been argued that a normal spirometry test might provide a false sense of complacency for active smokers. Moreover, current evidence does not support the idea that drug treatment of asymptomatic individuals provides any benefit. Those who support the use of spirometry for COPD case-finding argue that early detection and aggressive smoking intervention have been proved to halt disease progression, and the finding of abnormal spirometry may encourage patients and health care professionals to be more aggressive with smoking cessation.

With the progression of COPD comes progressive exercise limitation. This is due to the increased work of breathing as ventilation increases with exercise. With increased respiratory rate, patients develop dynamic hyperinflation—a condition in which the end-expiratory lung volume does not return to the static end-expiratory volume of functional residual capacity (FRC). The hyperinflation that occurs causes increased work of breathing and exacerbates dyspnea. An indicator of dynamic hyperinflation is the inspiratory capacity (IC), which progressively falls with increasing ventilation. Measures that reduce dynamic hyperinflation, increasing IC, can improve exercise capacity. These include alterations in breathing pattern, oxygen supplementation, helium inhalation, and use of inhaled bronchodilators.

As COPD progresses, ventilation-perfusion inhomogeneity causes an increase in the alveolar-arterial oxygen difference. Eventually, alveolar hypoxemia leads to pulmonary hypertension, which becomes manifest as cor pulmonale. The alveolar hypoxemia may be compounded by alveolar hypoventilation—manifest by arterial hypercapnia. Physical findings indicative of cor pulmonale are venous engorgement, edema, and physical findings of pulmonary hypertension and right ventricular failure. Chest imaging shows central enlargement of the pulmonary arteries. Once cor pulmonale is clinically apparent, survival is markedly reduced in proportion to the elevation of pulmonary artery pressure. Chronic respiratory failure is defined by chronic hypoxemia (sea-level resting $Pa_{O_2} \leq 60$ mmHg or 8 kPa) with or without attendant hypercapnia ($Pa_{CO_2} > 45$ mmHg).

Patients with advanced COPD may restrict their activities to a bed-and-chair lifestyle because of severe exercise incapacitation. This limitation can lead to social isolation, depression, and skeletal muscle deconditioning which, in turn, further restrict activity and impair quality of life. Protein and calorie malnutrition occurs as the consequence of impaired nutritional intake caused by dyspnea. Malnutrition is augmented by increased metabolic demands caused by increased basal oxygen consumption, inefficient skeletal muscle oxygen utilization, and cachexia-producing cytokines such as tumor necrosis factor alpha.

DIAGNOSIS OF COPD

Physical examination and chest imaging are insensitive methods for diagnosis of COPD. Physical findings of hyperinflated lungs such as low-lying diaphragms, decreased breath sounds, and hyperresonant chest percussion are highly specific for COPD, but usually only in advanced disease. One study has suggested that a distance between the thyroid cartilage and the sternal notch less than 4 cm in a smoker older than age 45 is highly indicative of the presence of COPD. Clubbing of the fingers is not common in COPD and, if present, suggests another diagnosis such as bronchiectasis, asbestosis, or lung cancer. High-resolution computed tomography (HRCT) of the lung, analyzed by quantitative measures of lung density, is a promising technique for early detection of emphysema, but the role of HRCT in early detection and monitoring of COPD is not established at present. α_1-Antitrypsin deficiency is an uncommon, but not rare, condition associated with premature emphysema. Testing for α_1-antitrypsin deficiency is indicated in those most likely to have the disorder (see Chapter 41 and Table 42-1). Although controversial, some experts advocate that all patients with COPD should be tested for α_1-antitrypsin deficiency. HIV/AIDS is also associated with premature emphysema, and screening for HIV should be performed for persons with emphysema and HIV risk factors such as intravenous drug use or high-risk sexual activity.

The diagnosis of COPD, classification of its severity, and progression of the disease can be monitored with spirometry, a simple, noninvasive, and inexpensive test. The FEV_1/FVC ratio, reflecting the rate of emptying of the lung, is used to define the presence of an obstructive ventilatory defect, commonly defined as a ratio less than 0.70. Once airflow obstruction is established, the severity of the disease is classified by the reduction of FEV_1 compared with a healthy reference population. Table 42-2 shows the widely used GOLD classification of COPD severity based on the FEV_1. Lung volume measurements, by plethysmography, helium dilution, nitrogen washout, or single-breath methods typically show hyperinflation (elevated TLC) and air trapping (elevated residual

Table 42-1

Conditions suggesting alpha-1 anti-trypsin deficiency

Early-onset emphysema (age under 45 years)
Emphysema in a nonsmoker
Emphysema predominantly in lung bases (pan-acinar)
Necrotizing panniculitis (Weber-Christian disease)
c-ANCA positive vasculitis (e.g., Wegener's granulomatosis)
Family history of early onset emphysema or non-smoking–related emphysema
Bronchiectasis without other etiology

volume [RV]), and thus are useful to exclude restrictive lung diseases. The carbon monoxide diffusing capacity (D_{CO}) is an indicator of emphysema and is roughly inversely correlated with the anatomic extent of emphysema in patients who have an FEV_1 greater than 1.0 L.

PROGNOSIS OF COPD

After COPD becomes clinically apparent, the median survival is about 10 years. The prognosis may vary widely, however, and physicians are poor prognosticators of survival in COPD. In part, this is because the disease is one of widely varying rates of progression, and, in part because death is often due to susceptibility to intercurrent illness and other smoking-related illness such as lung cancer rather than progressive respiratory failure.

Several factors have been identified that predict poor survival in COPD. These include low FEV_1, active smoking status, hypoxemia, poor nutrition, the presence of cor pulmonale, resting tachycardia, low exercise capacity, severe dyspnea, poor health-related quality of life, anemia, frequent exacerbations, co-morbid illnesses, and low carbon monoxide diffusing capacity. Patients with an FEV_1 less than 35 percent predicted have about 10 percent mortality per year. If a patient reports that they are unable to walk 100 meters without stopping because of breathlessness, the 5-year survival is only 30 percent. A multidimensional prognostic index that takes into account several indicators of COPD prognosis is the BODE index (*b*ody mass index [BMI], *o*bstructive ventilatory defect severity, *d*yspnea severity, and *e*xercise capacity). See Table 42-3 for calculation of the BODE prognostic score. The components are derived from measures of the body mass index (weight in kg/height m^2), FEV_1 percent predicted, and the modified Medical Research Council dyspnea score (Table 42-4). A BODE score greater than 7 is associated with a 30 percent 2-year mortality; whereas a score of 5 to 6 is associated with 15 percent 2-year mortality. If the BODE score is less than 5, the 2-year mortality is less than 10 percent.

Table 42-2

Classification of COPD Severity

Stage	Characteristics
I Mild COPD*	FEV_1 80% predicted
II Moderate COPD*	FEV_1 50%–79% predicted
III Severe COPD*	FEV_1 30% to 49% predicted
IV Very Severe COPD*	FEV_1 <30% predicted or <50% predicted with room air Pa_{O_2} <60 mm Hg (8.0 kPa)

* *Postbronchodilator FEV_1/FVC 0.70.*
Adapted from the 2006 GOLD COPD guidelines, www.goldcopd.com; Celli BR, MacNee W: ATS/ERS Task Force. Standards for the diagnosis and treatment of patients with COPD: A summary of the ATS/ERS position paper. Eur Respir J *23:934; 2004.*

TREATMENT OF STABLE COPD

The goals of treatment of COPD are to prevent progression and complications of the disease, relieve symptoms, improve exercise capacity, improve quality of life, treat exacerbations, and improve survival.

Education

The diagnosis of COPD can be a life-changing event for people, so understanding the nature and prognosis of the disease is an important and underemphasized aspect of care. There is a wide divergence of understanding of the implications of having COPD, and many patients do not understand that COPD comprises both the diagnoses of emphysema and chronic bronchitis. Table 42-5 lists topics that should be discussed with COPD patients. It is neither possible nor effective to cover all of these topics in a single session, so several sessions with repetition and expansion of the educational messages is necessary. Supplemental written materials or referral to a health educator is also necessary for many patients. Local and national volunteer health organizations provide useful educational materials and group educational sessions. Special counseling is needed for patients with α_1-antitrypsin

Table 42-3

Calculation of the BODE Index*

	Points on the BODE Index			
Variable	**0**	**1**	**2**	**3**
FEV_1 (% predicted)	≥65	50–64	36–49	≤35
Distance walked in 6 min (meters)	≥350	250–349	150–249	≤149
MMRC dyspnea scale	0–1	2	3	4
Body-mass index (kg/M^2)	> 21	≥21		

** The BODE index is calculated as the sum of points from each row.*
Adapted from: Celli BR, Cote CG, Marin JM, et al: The body-mass index, airflow obstruction, dyspnea, and exercise capacity index in chronic obstructive pulmonary disease. N Engl J Med *350:1005–1012; 2004.*

deficiency and their family members to determine whether genetic testing is necessary or desired. In patients with advanced disease, discussions about end-of-life planning and advance directives regarding life support are often welcomed by patients and initiate discussions between the patient and family. Patients should be encouraged to discuss information that they obtain from newspapers or the Internet, as some may be instructive, but others are incorrect. Physicians should

Table 42-4

Modified Medical Research Council Dyspnea Scale (MMRC Scale)

Grade	Description
0	Not troubled with breathlessness except with strenuous exercise
1	Troubled by shortness of breath when hurrying on the level or walking up a slight hill
2	Walks slower than people of the same age on the level because of breathlessness or has to stop for breath when walking at own pace on the level
3	Stops for breath after walking about 100 yards or after a few minutes on the level
4	Too breathless to leave the house or breathless when dressing or undressing

Adapted from: Mahler DA, Wells CK: Evaluation of clinical methods for rating dyspnea. Chest *93:580–586; 1988.*

Table 42-5

Patient Education Topics for Office Management of COPD

Risk factors for COPD
Smoking cessation advice and instruction
Reduction of noxious environmental exposures
Immunization for influenza and pneumococcus
Nature and prognosis of COPD
Indications, dose, benefits, and adverse effects of medications
Proper inhaler and nebulizer use
Strategies to improve adherence with prescribed treatment
Pacing, arm support, and other strategies to minimize dyspnea
Importance of regular exercise and social interaction
Options for pulmonary rehabilitation programs
Recognition and early treatment of exacerbations
Indications for and proper use of supplemental oxygen
Options for surgical management if indicated
Advanced directives for end-of-life care

be prepared to deal with patients' sense of guilt, as many view COPD as a self-induced disease. Caregivers need to address the reality that COPD is often stigmatized by patients, their families, and other health care providers. The physician should let the patient understand that nicotine dependence is a strong physical addiction and difficulty quitting smoking is not a measure of moral weakness or lack of will. The general message provided should be realistic, but positive. Current treatments for COPD can usually improve quality of life, restore activity levels, maintain social interactions, and reduce the frequency of complications.

Prevention of COPD Progression and Complications

Presently, there are no proven treatments that prevent the progression of COPD in patients who continue to smoke cigarettes. *Smoking cessation,* however, does prevent the excessive decline in lung function and should be a primary goal for physicians caring for COPD patients. Patients with mild or moderate COPD may not know that they have underlying lung disease that can be halted by smoking cessation, or may adopt a fatalistic attitude that it is too late for help. Even severely impaired patients who are dyspneic at rest or use continuous oxygen may continue to smoke cigarettes or relapse after quitting. A smoking history should be obtained at each patient encounter because many patients fail to volunteer the extent of their smoking or report a smoking relapse following cessation. In patients who do smoke, achieving cessation should be a primary and persistent goal of treatment. Approaches to smoking cessation are given in detail in Chapter 43. For patients who do smoke, a direct, unambiguous, and personalized smoking cessation message should be given by the physician. The message should emphasize the harm of continued smoking, the benefits of cessation in terms of activities that are meaningful for the individual, and the understanding that smoking cessation is a realistic and achievable goal. Assistance with pharmacologic adjuncts such as nicotine replacement therapy, varenicline, or bupropion and referral to smoking cessation groups should be offered. Follow-up of smoking status and repeated smoking cessation messages should be performed at each encounter.

Exposure to respiratory irritants should be avoided in the workplace as well as the home. Although heavy occupational dust exposure rarely is the primary cause of COPD, exposure to dusty occupational jobs in smokers can increase the lung function deterioration from smoking and increase symptoms of cough and sputum. Respiratory protective equipment should be worn by COPD patients exposed to heavy dust concentrations. There is no level of FEV_1 that absolutely prohibits the use of respiratory protective equipment, but patients with COPD often experience untoward breathlessness with these masks because of the increased dead space and increased inspiratory resistance. Thus, many COPD patients need to change their work environment if they cannot tolerate protective devices. If COPD is complicated by allergy or overlaps with allergic asthma, environmental control measures should be instituted to the extent that these strategies are helpful. Smoking of marijuana and cocaine may cause airway irritation, and although there is no convincing evidence that they contribute to progression of COPD, their use ought to be discouraged.

Pneumococcal vaccination is recommended, although the evidence of its particular efficacy in COPD is lacking. Annual *influenza immunization* can prevent or attenuate this potentially fatal infection. The killed vaccine is preferred, as cold-attenuated live influenza vaccines have not been approved for use in older patients and those with underlying lung disease. For individuals who are not immunized, prophylaxis with amantadine or rimantadine during an influenza epidemic can often prevent infection with influenza A, although recent reports have shown increasingly resistant strains of influenza and side-effects may limit usefulness. During influenza epidemics, the use of neuraminidase inhibitors such as zanamivir and oseltamivir can minimize severity of infection if taken within 48 hours of onset of illness and are useful against both influenza A and B, and may limit the spread of infection.

Replacement therapy with α_1-antitrypsin should be considered for those individuals with severe deficiency. Observational studies suggest that individuals with moderate degrees of impairment (FEV_1 35 to 65 percent predicted) appear to benefit most in terms of preservation of lung function and improved survival. The human plasma-derived preparation of α_1-antitrypsin is administered intravenously in a dose of 60 mg/kg weekly. Although the replacement treatment is derived from pooled human plasma, the risk of viral transmission is low and immunization for hepatitis B is not required prior to initiating therapy. Monitoring of immunoreactive serum levels of α_1-antitrypsin does not accurately reflect the enzymatic activity in the blood or alveolar lining fluid and is not necessary to adjust treatment dose. Alternative dosage schedules, use of recombinant preparations, specific protease inhibitors, or aerosolized preparations may be available in the future.

Exercise and Rehabilitation

Regular prudent self-directed exercise is recommended for all individuals with COPD to prevent the muscle deconditioning that often accompanies the disorder. Individuals should be encouraged to perform at least 20 to 30 minutes of constant low-intensity aerobic exercise such as walking at least three times per week. Even the most severely impaired patients with COPD can usually attain an exercise regimen of 30 minutes of walking at 1 mph (i.e., one-half mile in 30 minutes). It is important to instruct patients that they should exercise to a level of dyspnea that is tolerable for the entire exercise period. Patients should understand that dyspnea, by itself, is not injurious to the heart or lungs, but patients should pace themselves to avoid severe dyspnea that disrupts activity, can lead to panic reactions, and is distressing to onlookers. Patients who demonstrate desaturation with exertion may be prescribed supplemental oxygen for exercise. Some may

benefit in terms of exercise capacity and training effect even if they do not have demonstrable oxygen desaturation. Many patients, particularly those with marked hyperinflation, find that they can ambulate better with the use of a rolling walker that supports the arms, improving the mechanical advantage of the accessory muscles in the neck.

Formal rehabilitation programs offer a comprehensive approach to exercise training, patient education, nutritional counseling, group support, and psychological support that cannot be efficiently provided in the physician's office. Rehabilitation programs are established as an effective component of COPD management and should be offered to patients who have substantial limitation in daily activities. A detailed discussion of rehabilitation is provided in Chapter 44.

Nutritional Support

In patients with very severe COPD (FEV_1 less than 35 percent predicted) about half show protein-calorie malnutrition. Reasons for this include increased resting metabolic demands, inadequate caloric intake due to dyspnea and anorexia, and possibly elaboration of cachexia-associated inflammatory cytokines such as TNF-α, IL-1, and IL-6. Patients with a BMI of less than 90 percent of normal have increased mortality and decreased exercise capacity. Muscle wasting and loss of bone mass may be present even in patients who have normal BMI. Although clinical trials of nutritional supplementation have been disappointing, it is prudent to monitor body weight in COPD patients and encourage caloric supplementation as needed since those patients who do gain weight show improved survival. High-fat diets have the theoretical advantage of offering higher caloric content with lower CO_2 production than high carbohydrate diets, but there is no convincing evidence that this strategy is clinically superior to a well-balanced diet. For patients with less advanced disease, a balanced diet with avoidance of overweight or underweight is a rational goal. In particular, patients with mild to moderate disease who quit smoking tend to gain excessive weight which might adversely affects lung function.

Sleep Disorders in COPD

Sleep disturbances, including insomnia and daytime hypersomnolence, are common symptoms in patients with COPD, and are often overlooked because of the focus on breathlessness and exercise intolerance. The causes for sleep symptoms are multifactorial and include anxiety/panic disorder, depression, resting hypoxemia, nocturnal bronchospasm, sleep apnea, and nocturnal oxygen desaturation. Patients with COPD often relate insomnia to a fear of suffocation or death during sleep, a situation that may respond to repeated reassurance, cognitive therapy, or small doses of anxiolytics or antidepressants. Patients with resting hypoxemia treated with low-flow nasal oxygen often report improved sleep quality. Nocturnal bronchospasm, more common among those with an asthmatic component to their disease, may respond to longer-acting bronchodilators, or rearrangement of the dosing schedule to provide nocturnal coverage. In some cases, treatment for gastroesophageal reflux by elevation of the head of the bed and prescription of acid suppressant drugs can help. Sleep apnea syndrome, probably not more common in COPD patients than the general community, has particularly severe complications in COPD. Patients with COPD and sleep apnea, the so-called "overlap syndrome" are prone to develop pulmonary hypertension and daytime hypercapnia. Accordingly, symptoms of sleep apnea such as snoring, intermittent nocturnal breathing, and daytime hypersomnolence should be sought in patients with COPD. If present, then formal sleep studies and treatment with continuous positive airway pressure (CPAP) are indicated. Nocturnal oxygen desaturation (NOD) is common during rapid eye movement sleep in patients with COPD. The causes are not entirely understood, but contributing factors include hypoventilation, ventilation-perfusion mismatch, respiratory muscle dysfunction, and increases in upper airway resistance. NOD is thought to be associated with poorer sleep quality and pulmonary hypertension. It is controversial whether NOD is associated with poorer survival. However, small studies have shown inconclusive results about the utility of treating nocturnal oxygen desaturation.

Current guidelines do not recommend that all patients with COPD have nocturnal oxygen monitoring, nor do they recommend treatment with supplemental oxygen or nocturnal ventilation if NOD is found. Many physicians, though, will prescribe these diagnostic studies and treatments for selected symptomatic patients, and most insurance companies will provide reimbursement for such treatment. Patients who have resting room air daytime hypoxemia should be prescribed nocturnal oxygen at the same flow rate as used during the day, and it is usually not necessary to monitor nocturnal oxygen saturation in such patients.

Air Travel

Patients with COPD should not avoid air travel, but must be aware of the medical and regulatory issues that are involved. Modern airplanes are pressurized to an equivalent altitude of approximately 5000 to 8000 feet, but may, on occasion, pressurize to an equivalent altitude of 10,000 feet without providing emergency oxygen. Many patients with COPD who do not use sea-level oxygen can tolerate short flights without supplemental oxygen. As flight distance becomes longer, the flying altitude becomes higher and the cabin pressure becomes lower, so transcontinental or transoceanic flights should prompt medical advice. The general rule of thumb used by the commercial airline industry is that patients who can ambulate 50 meters without stopping are safe for air travel. A more conservative approach is to estimate the Pa_{O_2} during air travel by performing a high altitude simulation test. High altitude simulation can be performed by administering 15 percent oxygen via a face mask or by using 100 percent nitrogen in a 40 percent Venturi mask. If the oxygen saturation falls below 86 percent or 50 mmHg, then supplemental oxygen is recommended. Formulas are available to estimate

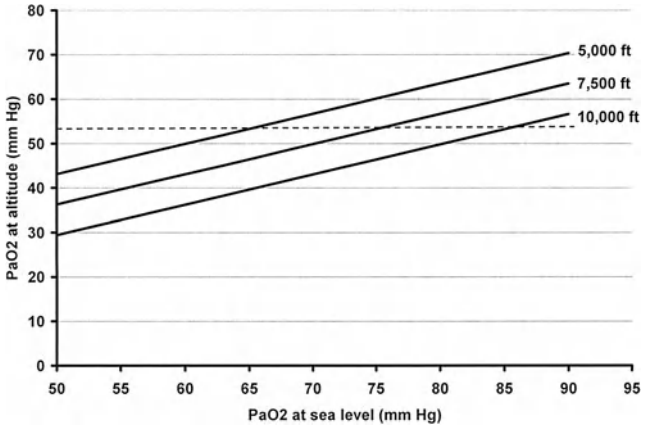

Figure 42-2 Estimated Pa_{O_2} at altitude based on resting sea level arterial oxygen tension. Isopleths are drawn for the range of cabin pressures that occur on commercial aircraft. The dashed line is drawn at 54 mmHg, which indicates a threshold for prescribing supplemental oxygen for air travel. The nomogram is derived from the data of Gong et al. *(Gong H Jr, Tashkin DP, Lee EY, et al: Hypoxia-altitude simulation test. Evaluation of patients with chronic airway obstruction. Am Rev Respir Dis 130:980–986, 1984.)*

altitude hypoxemia from sea-level room air blood gases. Figure 42-2 provides a nomogram for estimating altitude Pa_{O_2} from sea-level room-air arterial oxygen tensions. If estimated altitude Pa_{O_2} is used, it is prudent to prescribe oxygen for estimated altitude Pa_{O_2} of 54 mmHg or lower. Patients who use oxygen supplementation at sea level should increase their resting oxygen prescription by a flow rate of 2 L/min. For patients with COPD who travel by air frequently, low-cost finger pulse-oximeters that are marketed to airplane pilots can be used to adjust their oxygen flow.

Airlines have inconsistent policies with respect to providing supplemental oxygen for travelers, so it is important to check with the airline service desk prior to booking travel. In the past, it was required that airlines provide compressed oxygen tanks for travelers. Recently the United States Federal Aviation Administration has promulgated regulations that permit some approved portable oxygen concentrators to be carried on board by passengers as personal luggage with a physician's statement of need.

Long-Term Oxygen Therapy

In addition to smoking intervention in early COPD, treatment of resting daytime hypoxemia with oxygen is a treatment that prolongs survival. The two strongest indications for prescription of long-term oxygen therapy are: (1) resting room-air $Pa_{O_2} \leq 55$ mmHg or oxygen saturation ≤ 88 percent while a person is in usual state of health; and (2) resting room-air Pa_{O_2} 56 to 60 mmHg or oxygen saturation 88 to 89 percent with supporting evidence of chronic hypoxemia such as polycythemia, pulmonary hypertension, cor pulmonale, or psychological impairment. Oxygen is usually administered by nasal cannula, with the flow rate adjusted to maintain a resting saturation greater than 90 percent. The usual starting flow rate is 2 L/min, although some patients with severe hypercapnia require lower flows. A few patients, particularly those with concomitant interstitial pulmonary disease or cardiac disorders, require higher flow rates.

The most convenient and cost-effective oxygen source at home is usually a concentrator device that uses a molecular sieve to extract oxygen from room air. For ambulation, small compressed air cylinders or liquid oxygen reservoirs that can be carried provide patients with the ability to leave their homes. Conserving devices such as reservoirs or demand valves permit portable ambulatory oxygen tanks to last up to 10 hours at flow rates of 2 L/min. Compressed oxygen cylinders or liquid oxygen reservoirs should be provided to patients who use electrically driven oxygen concentrators for emergency use in the event of a power failure. Ideally, oxygen should be used constantly 24 hours per day. At least 18 hours of oxygen per day, however, has been show to have substantial benefit over 12 hours per day. If continuous oxygen supplementation is prescribed following an exacerbation of COPD, it is recommended to check arterial oxygen levels in 6 months, as many patients will no longer require oxygen.

Nasal drying or congestion is a common symptom for those who use continuous oxygen. This may be alleviated to some extent by alternating the nasal cannula from one nostril to the other or placing it in the mouth for periods. Copious watery nasal secretions often respond well to ipratropium nasal spray, and dry, crusted nasal mucosa is treated with hourly instillations of saline nasal spray. Other nasal disorders that are aggravated by oxygen, such as allergic rhinitis or vasomotor rhinitis, should be considered and treated with appropriate therapy such as intranasal corticosteroids or cromolyn.

Smoking or exposure to any open flame, of course, is prohibited by the danger of fire and airway burns in those who use oxygen. This is a surprisingly common cause of burns in the United States, with estimates that up to 50 percent of patients on oxygen continue to smoke to some extent. Accordingly, it is safer to counsel patients to discontinue oxygen while smoking or cooking over an open flame if they insist on doing these imprudent activities. Patients at particular risk are those who live alone, have cognitive impairment, and do not have functioning smoke detectors.

Transtracheal oxygen administered via a percutaneous catheter is useful for patients who need high oxygen concentrations or in whom use of a nasal cannula is not tolerated because of local nasal adverse effects or cosmetic preference. Transtracheal oxygen has the advantage of decreasing effective dead space ventilation and permitting lower flow rates to provide high oxygen concentrations. However, the catheter and insertion site require meticulous care to prevent complications such as local infection or mucus concretions. On occasion, the catheter insertion site may lead to a pneumothorax or pneumomediastinum. High flow rates with humidified oxygen via transtracheal catheters may augment ventilation and reduce hyperinflation.

Ambulatory oxygen, although not shown to improve survival, may be provided for patients who desaturate with exertion. Some, but not all, patients show improved exercise

capacity and reduced breathlessness. There is a growing body of evidence that suggests that oxygen supplementation may also benefit COPD patients who do not have exercise desaturation by reduction in minute ventilation and diminution of dynamic hyperinflation. Because it permits greater exercise intensity, oxygen supplementation is also a useful adjunct for aerobic conditioning during pulmonary rehabilitation.

Treatment of Anemia

Anemia, usually mild, is present in about 10 percent of patients with severe COPD, similar to other chronic inflammatory diseases, and is a poor prognostic indicator. Although there is no evidence that COPD, per se, causes anemia, patients with COPD have a lower erythropoietic response to hypoxia than healthy people at altitude. For patients who are anemic and breathless, restoration of normal hemoglobin content reduces resting minute ventilation and work of breathing, which presumably improves exercise capacity. Thus, pending definitive clinical trials, it is prudent to test for anemia and treat it appropriately in patients who are markedly symptomatic.

Drug Therapy

Over the past several decades, the evidence base for use of drug therapy in COPD has expanded, and provides an objective and generally optimistic picture that such treatment is effective. Bronchodilators and anti-inflammatory agents are used in COPD to reverse bronchoconstriction and improve airflow limitation. The goals of drug therapy are not only to improve lung function, but also to improve quality of life, exercise capacity, and prevent exacerbations. No drug treatment is known to diminish the decline in pulmonary function with continued smoking, or substantially reduce mortality, but large and long-term clinical trials needed to definitively determine this have not yet been done for newer agents. Recent evidence however suggests that a combination of inhaled steroids and long-acting bronchodilators may improve survival as well as reduce exacerbations. Proposed future drug treatments that might alter progression of COPD are under active investigation, including inhibitors of cytokines, proteases, and oxidative stress. There is a poor correlation between the effect of bronchodilating drugs on lung function and symptom relief, so monitoring of treatment requires attention to patient-centered outcomes as well as lung function. Small amounts of bronchodilation can cause considerable improvement in functional capacity through decrease in dynamic exercise hyperinflation; and reduction in days of exacerbation can make considerable improvement in patients' quality of life.

The usual approach to drug treatment for COPD is to sequentially add agents using the minimum number of agents and the most convenient dosing schedule, starting with the agents having the greatest benefit, best tolerance, and lowest cost. One approach to step-up therapy is provided in Figure 42-3. Inhaled bronchodilators are the foundation

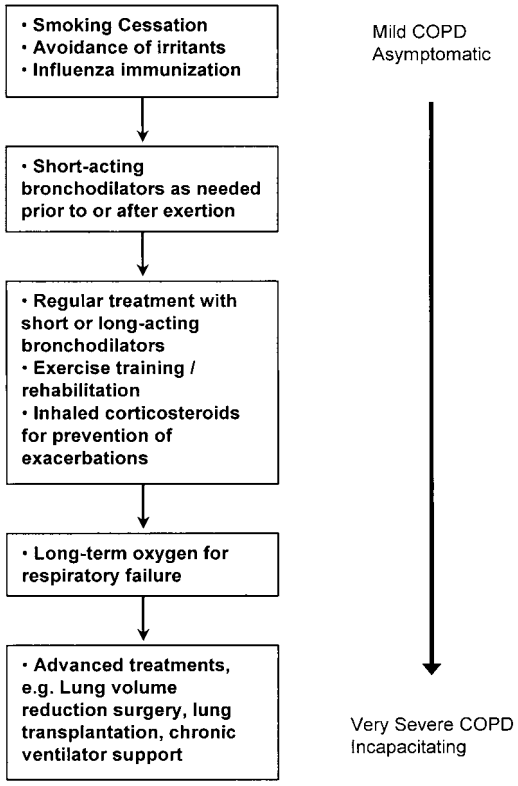

Figure 42-3 Step-care approach to treatment of COPD. Treatments are sequentially added to maximize functional status and minimize symptoms. Patients with greater impairment receive more advanced treatments. At each phase of treatment, assessment of lung function, symptoms, and functional status are used to evaluate need for additional treatments. If patients are stable for 6 to 12 months, consideration should be given to trial reductions of treatment.

of treatment for COPD. They are given on a regular basis to maintain bronchodilation and on an as-needed basis for relief of symptoms. Most breathless patients benefit from regular use of a maintenance bronchodilator. Both beta-agonist and anticholinergic classes are available in short duration (4- to 6-hour) and long-duration (12- to 24-hour) forms (Tables 42-6 and 42-7). The choice of bronchodilator class and duration of effect depends upon the preference of the patient and the cost of the preparation. Combination of different classes of bronchodilators is often more effective than increasing the dose of a single agent, and combination inhalers can simplify treatment regimens. Patients with advanced COPD often use a combination of bronchodilators, including long-acting maintenance anticholinergics and beta agonists as well as symptomatic use of shorter-acting bronchodilators. Individuals with frequent exacerbations often benefit from a combination inhaler of corticosteroids and long-acting bronchodilator. Long-acting oral preparations of theophylline are useful adjuncts in cases in which inhaled medication is too expensive or not acceptable for the patient. Chronic use of systemic corticosteroids should be reserved for individuals with very frequent or life-threatening exacerbations who cannot tolerate their discontinuation. Response to treatment is judged by symptomatic improvement, functional status,

Table 42-6

β-Sympathomimetic Agonists

Drug Name	Onset of Action (min)	Inhalation Peak Effect (min)	Duration of Effect (h)	Dosage Form
Metaproterenol	1–5	30–60	2–5	Metered-dose inhaler, 650 μg/puff
				Nebulized solution, 5%, or premixed 0.4%–0.6% ampules
Terbutaline	1–5	—	2–5	Oral tablets 2.5 or 5.0 mg
				Injection, 1 mg/ml
Pirbuterol	5	30–60	4–5	Metered-dose inhaler, 200 μg/puff
Albuterol	5–15	60–90	3–6	Metered-dose inhaler, 90 μg/puff
				Nebulized solution 0.5% or premixed 0.083% ampules
	30	—	6–12	Oral tablets 4.0 to 8.0 mg, rapid and slow-release forms
Levalbuterol				
Salmeterol	10–20	180	12	Metered-dose inhaler, 25 μg/puff
				Dry powder inhaler, 50 μg/dose
Formoterol	2–10	120	12	Dry powder inhaler, 12 μg/dose

frequency of exacerbations, and spirometry. If patients are doing well for 6 to 12 months on a stable treatment regimen, then it is reasonable to see if a trial withdrawal of one of the drug components can be tolerated.

Inhaled agents are administered by metered dose inhaler (MDI), dry powder inhaler (DPI), or as a nebulized solution. The selection of route of administration is made by cost and convenience of the device because all are similarly effective if used properly. Many patients find that it is difficult to coordinate an MDI, and addition of a spacer device is helpful. There are many forms of DPI, some more intuitive to use than others, so specific instruction and demonstration is required by most patients. Nebulizers are easier for patients to coordinate, but each treatment takes longer to complete, and they require additional effort to maintain cleanliness. Although nebulized medications are more expensive overall, the cost of the medication is often covered by insurance, so many patients prefer nebulizers for financial considerations.

Table 42-7

Anticholinergic Bronchodilators

Generic Name	Onset of Action (min)	Inhalation Peak Effect (min)	Duration of Effect (h)	Dosage Form
Ipratropium	30	60	6–8	HFA or CFC metered-dose inhaler 17–18 μg/puff
				Nebulized solution 0.02% (500 μg in 2.5-ml vial)
Tiotropium	60	120	>24	Dry powder inhaler 18 μg/dose

Adherence with inhaled medication, particularly when it does not provide immediate symptom relief is poor. Typically about half of patients do not take their medication in the dose or quantity prescribed. Reasons for this include a lack of understanding of the role of the medication, failure of the medication to provide meaningful benefit, complexity of the treatment program, and expense of the treatment. Many patients do not want to confide poor adherence to their physician, so it is important for the physician to ascertain this information in a way that does not interfere with the relationship with the patient. For example, a physician could inquire, "It is often difficult for patients to remember to take all of their medications. Has this been a problem for you?" or "Are you able to afford all your medication?" or "Do you think that your medicines are working for you?" If nonadherence is a problem, the treating physician can undertake actions to improve adherence, such as simplification of the medication program, education about the benefits of treatment, linking drug use to established habits such as meals or tooth brushing, or prescribing less costly drugs.

Proper use of MDIs is difficult for many patients to learn and retain. Repeated review and training of patients in MDI use is an important component of treatment of COPD and asthma. The inhaler should be held about 4 cm from the mouth to minimize deposition of larger droplets in the mouth. The patient should exhale to functional residual capacity and take a slow inhalation to TLC over about 5 seconds. The slow inhalation diminishes impaction of particles in the mouth and larynx. At the initiation of inspiration the patient should actuate the MDI one time. After full inspiration, the patient should hold the breath for about 10 seconds to permit deposition of particles in the distal airspaces. If the patient finds that hoarseness or mouth irritation occurs with inhaler use, this can often be corrected by use of a spacer, slowing the rate of inspiration, and rinsing the mouth after each inhaler use. Although waiting a period of time between inhalations or between different MDIs is sometimes recommended for optimal effect, the benefit is small compared with the inconvenience and risk of worsening adherence. Therefore, it is usually appropriate to permit the patient to take additional inhalations as soon as he or she has rested a few seconds.

If the patient has difficulty coordinating the actuation of the MDI with inspiration, a spacer device or holding chamber can be used. This device is placed directly in the mouth and the MDI can be actuated prior to inspiration. In some circumstances, it is necessary for patients to use a breath-actuated MDI or nebulizer to achieve optimal benefit from inhalational medication. Dry powder inhalers usually require less coordination than MDIs, but there are many different devices, some rather complicated to use. Therefore, each device requires individual instruction and review of technique. (For a compendium of patient instructions, see http://www.ginasthma.com/OtherResources.asp.

Ipratropium bromide is an inhaled anticholinergic drug that causes 4 to 8 hours of bronchodilation through inhibition of vagal stimulation of the airways. Although it is more expensive than beta agonists, it is often used as first-line therapy. The dosage is started at two MDI inhalations three times daily, and can be increased to six inhalations four times daily. Adverse effects are minimal, even with relatively high doses, so the maximum dose is limited by cost and convenience. Local side effects include mouth irritation and cough, which can be diminished by good inhaler technique or use of a spacer. Supraventricular tachyarrhythmias may occur more frequently in patients using ipratropium but are rare. Urinary retention or acute narrow-angle glaucoma are potential but exceedingly rare complications of inhaled ipratropium. Although ipratropium provides sustained benefit in patients with moderate disease, it does not inhibit progression of the disease if smoking is continued.

Tiotropium is an anticholinergic bronchodilator that has the benefit of once-daily dosing, and is more effective than usual doses of ipratropium in bronchodilation, quality of life, and reducing exacerbations. Exercise capacity is improved by reduction in dynamic hyperinflation. Tolerance does not develop with prolonged use. First morning spirometry is improved after long-term use of tiotropium, but it is not yet known whether this reflects sustained improvement in lung function, or it is residual bronchodilation due to the very long duration of action. It is inhaled once daily from a capsule inserted into a dry powder inhaler. Tiotropium is most useful in patients with moderately symptomatic disease who find frequent use of bronchodilators inconvenient or those who have nocturnal or early morning symptoms. Because of the slower onset of bronchodilation, some individuals do not recognize the efficacy of this drug, and use additional short-acting agents for symptomatic use. Proper instruction is needed in use of the inhaler, but the dry powder inhaler does not require as much coordination as a metered dose inhaler. Some patients with mild disease prefer to use once-daily tiotropium rather than as-needed short-acting bronchodilators as initial therapy, which is a reasonable treatment approach.

Short-acting β-adrenergic agonists are used at dosages comparable to those used in asthma. Selective beta$_2$ agonists should be administered by the inhaled route and oral forms reserved for the occasional person who cannot or refuses to take inhaled drugs. Oral beta agonists, although longer-acting, tend to have more side effects such as tremor, tachycardia, and hypokalemia. Albuterol is the most widely prescribed selective beta$_2$- adrenergic bronchodilator and is available in MDI formulations with either CFC or HFA propellants. The typical dose is two inhalations every 4 to 6 hours as an as-needed or regular agent. Pirbuterol has similar pharmacologic properties, but is supplied in a breath-actuated MDI that is easier for discoordinated patients to use effectively without a spacer.

Long-acting inhaled beta agonists such as salmeterol or formoterol are useful because of the long duration of action and documented benefit on quality of life and exercise tolerance. Monotherapy with a long-acting beta agonist is discouraged in treating patients with asthma, but has been used effectively in patients with COPD. Both salmeterol and formoterol are available in dry powder inhaler formulations.

Formoterol has a quicker onset of action and is sometimes used for intermittent symptom relief, but does not permit as frequent re-dosing as short-acting agents. Increasing doses beyond the recommended dose adds little to the bronchodilator effect, but does increase the risk of adverse effects such as hypokalemia, tremor, and tachycardia. Therefore, it is usually advised that patients started on long-acting beta agonists also be provided with a short-acting bronchodilator for as-needed treatment of symptoms.

Combination inhaler therapy with a beta agonist and a short-acting anticholinergic provides better bronchodilation than either agent alone and the simplified treatment regimen may improve adherence. Combinations of inhaled corticosteroids and long-acting bronchodilators provide more bronchodilation than either alone in patients with chronic bronchitis and airflow obstruction.

Theophylline is taken as a long-acting oral preparation once or twice daily. Although it is possible to monitor blood levels, because the drug is protein bound there is a poor correlation between efficacy or adverse effects and serum levels. Theophylline is a bronchodilator; it improves arterial oxygenation and exercise tolerance. If typical side effects such as nausea, vomiting, tremor, or tachyarrhythmias occur, the dose should be adjusted irrespective of serum levels. Prescriptions for theophylline for COPD have diminished in recent years because of the availability of long-acting inhaled agents, but it is still an effective second-line drug for patients who show benefit or prefer inexpensive oral medications. Theophylline has other putative pharmacologic actions that might be beneficial for the COPD patient: improvement in diaphragm contractility, prevention of respiratory muscle fatigue, increased ventilatory drive, potentiation of catecholamine function, prevention of microvascular permeability, increased mucociliary clearance, prevention of late-phase antigen responses, inhibition of mast cell histamine release, and suppression of leukocyte activation. Recent evidence has suggested that the anti-inflammatory effect of theophylline is mediated by augmentation of steroid effects through activation of histone deacetylase (HDAC), an effect that is of particular importance in COPD patients who have lower HDAC activity. Newer agents that are more specific inhibitors of phosphodiesterase-4 have been developed but are not yet marketed in the United States, and hold the promise of similar efficacy as theophylline with lower toxicity.

Oral corticosteroids are effective for treatment of COPD exacerbations. About 10 to 20 percent of chronic symptomatic patients show substantial short-term improvement in pulmonary function, but it is not possible to identify these patients based on clinical characteristics alone. Because of the well-defined long-term adverse effects of systemic corticosteroids, and the ill-defined long-term benefits, most patients should not be maintained on long-term oral or systemic corticosteroids. Patients with COPD who are on chronic corticosteroids can most often taper the dose at the equivalent of 5 mg of prednisone per week, and exclusively reserve their use for exacerbations. Long-term low doses of oral corticosteroids are occasionally needed by patients who cannot afford or tolerate inhaled agents, and who suffer frequent exacerbations. Patients on long-term systemic steroids should receive prophylaxis for osteoporosis with calcium and vitamin D or bisphosphonates, and should be instructed about the need for stress-dose steroids for acute illnesses.

Inhaled corticosteroids do not effectively alter the progression of COPD in those who continue to smoke. Inhaled corticosteroids are most useful in patients who have an overlap between asthma and COPD and those with more advanced disease who have frequent exacerbations. Inhaled corticosteroids can reduce the frequency of exacerbations, improve airways reactivity, and slow the decline in quality of life. In patients with chronic bronchitis and obstructive lung disease, inhaled corticosteroids improve pulmonary function, and the results are additive to those achieved with long-acting bronchodilators. The efficacy of inhaled corticosteroids cannot be predicted based on the response to oral corticosteroids, so it is not necessary to conduct an oral steroid trial prior to initiating this treatment. Combined corticosteroid and long-acting bronchodilator inhalers are available in the United States and throughout the rest of the world and can simplify the treatment regimen. Inhaled corticosteroids, although poorly absorbed, probably do contribute to steroid side effects such as cataracts, capillary fragility, and osteoporosis in susceptible individuals. In most cases, the risk is low compared to the benefit of treatment, but it is prudent to prescribe the lowest effective dose. In patients who are at risk for osteoporosis (i.e., older age, cigarette smoking, low exercise) as most patients with COPD are, it is prudent to recommend prophylactic treatment such as calcium supplements and vitamin D. In those with established osteoporosis, bisphosphonates are advised. Monitoring for osteoporosis with DEXA bone scans is guided by the overall clinical situation and is not required for all patients using inhaled corticosteroids.

Mucolytic agents to control mucus hypersecretion with the use of expectorants and physical means such as high-frequency chest wall oscillation is not of proven benefit in improving lung function, although symptoms are sometimes improved. N-acetyl cysteine a mucolytic with antioxidant properties does not prevent exacerbations, nor does it alter the decline in FEV_1.

TREATMENT OF COMPLICATIONS

Patients with advanced COPD are prone to develop secondary complications of the disease. The goal of treatment is to restore functional status as quickly and as much as possible and to alleviate distress and discomfort.

Treatment of COPD Exacerbations

COPD exacerbations are characterized by worsening dyspnea, cough, and increased sputum production. There are several formal definitions of a COPD exacerbation, but a useful working definition is that a COPD exacerbation is a worsening of

dyspnea, cough, or sputum production that exceeds day-to-day variability and persists for more than a day or two. On average, patients with COPD have two to three exacerbations per year, but there is wide variation, and the frequency of exacerbations is only roughly correlated with severity of airflow obstruction. The best predictor of future exacerbations is a past history of frequent exacerbations, and these are more common in patients with chronic cough and sputum production. Only half of COPD exacerbations come to the attention of treating physicians, and many of these eventually resolve without specific treatment. Precipitating events include respiratory and nonrespiratory infections, exposure to respiratory irritants and air pollution, or co-morbid conditions such as heart failure, pulmonary embolism, myocardial ischemia, or pneumothorax. The management of these exacerbations depends upon the severity. Indications for hospital evaluation or hospitalization are listed in Table 42-8. Arterial blood gas studies and chest radiographs are useful for evaluating etiology and severity of acutely ill patients. Spirometry during the acute exacerbation is usually not helpful in predicting the severity or duration of the exacerbation. In selected patients with frequent or life-threatening exacerbations, monitoring of FEV_1 with inexpensive home spirometers may facilitate early recognition of exacerbations and communication with health care providers.

For patients treated at home, increasing the frequency and intensity of inhaled short-acting bronchodilators for several days is effective in mild exacerbations. A handheld inhaler and spacer are usually effective, but a nebulizer may be needed for those who cannot coordinate well or who have severe dyspnea. Increasing dyspnea accompanied by a change in the quantity or color of phlegm is usually an indication of bacterial infection and should prompt initiation of antibiotics. The choice of antibiotic is determined by severity of the underlying disease, resistance patterns of likely pathogens, and likelihood of treatment failure (Table 42-9). A course of corticosteroids, equivalent to 30 to 60 mg of prednisone for 7 to 14 days, will shorten the duration of symptoms for patients with exacerbations managed as outpatients.

For patients admitted to the hospital, intensification of inhaled bronchodilator treatment, systemic corticosteroids, and antibiotics are administered. Controlled oxygen supplementation should be provided at the lowest level needed to reverse hypoxemia and minimize the induction of hypercapnia. The selection of the oral or intravenous route for antibiotics and corticosteroids is determined by the severity of the illness and the ability of the patient to tolerate oral medication. Evaluation for the cause of the exacerbation does not have to be extensive if it responds to initial treatment and conforms to the patient's usual exacerbation pattern. Sputum culture for resistant bacterial strains, a chest radiograph for exclusion of pneumonia and pneumothorax, and an electrocardiogram for exclusion of myocardial ischemia and arrhythmia are useful tests in all hospitalized patients. Echocardiography for assessment of ventricular function, and Doppler venous flow studies, radionuclide, or computed tomographic lung imaging for evaluation of pulmonary thromboembolism need to be performed only in selected cases. Selection of antibiotics for hospitalized patients should be based on local bacterial antibiotic sensitivities, and guided by culture results. Usually a 2-week course of steroids is sufficient for hospitalized patients.

Treatment in an intensive care setting should be undertaken for patients with severe life-threatening exacerbations or those who require more constant attention (Table 42-8). For patients with respiratory failure, noninvasive mask ventilation has proved to be an effective strategy to avert

Table 42-8

COPD Indications for Hospitalization

Indications for Hospital Assessment or Admission for COPD Exacerbation
Sudden onset of new or severe symptoms (e.g., dyspnea)
Inability to sleep or eat because of dyspnea
Severe or very severe underlying COPD
Onset of new physical findings (e.g., edema, cyanosis, change in mental status)
Failure to respond to initial medical treatment
Associated comorbidities (e.g., cardiac, renal, hepatic failure, or diabetes)
Diagnostic uncertainty (e.g., suspected pneumonia or pulmonary embolism)
Unusual presenting symptoms
Older age or frailty
Inadequate home or social support
History of poor adherence with treatment
Indications for ICU Admission for COPD Exacerbation
Severe dyspnea unresponsive to initial treatment
Change in mental status (e.g., confusion, lethargy, coma)
Persistent or worsening hypoxemia, hypercapnia, or respiratory acidosis
Need for sedation or narcotic pain control

Table modified from 2004 GOLD COPD guidelines (www.goldcopd.com) and 2004 ATS/ERS Standards for treatment of COPD.

Table 42-9

Risk Stratification for COPD Exacerbation and Suggested Antibiotic Treatment

Group	Basic Clinical State	Symptoms and Risk Factors	Probable Pathogens	First-Choice Alternatives for Treatment Failure
0	Acute tracheobronchitis	Cough and sputum without other pulmonary disease	Usually viral	If symptoms persist for >10–14 days, then macrolide or tetracycline
I	Chronic bronchitis without risk factors (simple)	Increased cough and sputum, sputum purulence and increased dyspnea	Haemophilus influenzae, Haemophilus spp., Moraxella catarrhalis, Streptococcus pneumoniae	Second-generation macrolide, ketolide, fluoroquinolone, second- or third-generation cephalosporin, β-lactam + β-lactamase inhibitor, doxycycline, trimethoprim/sulfamethoxazole, amoxicillin
II	Chronic bronchitis with risk factors (complicated)	As in group I plus one of the following: FEV_1 <50% predicted, >4 exacerbations/year, cardiac disease, home oxygen use, chronic oral steroid use, or antibiotic use in past 3 months	As in group I plus *Klebsiella* + other gram-negatives. Increased probability of β-lactam resistance	Fluoroquinolone, β-lactam +β-lactamase inhibitor
III	Chronic suppurative bronchitis	As in group II with constant purulent sputum or bronchiectasis. FEV_1 < 35% predicted, or multiple risk factors (e.g., frequent exacerbations and FEV_1 <50%)	As in group II plus *Pseudomonas aeruginosa* and multiresistant *Enterobacteriaceae*	Tailor treatment based on pathogen and sensitivities. For *Pseudomonas* spp., ciprofloxacin is preferred. Hospitalized patients may need intravenous antibiotics.

Adapted from: Balter MS, La Forge J, Low DE, et al: Canadian guidelines for the management of acute exacerbations of chronic bronchitis. Can Respir J *10:3B–32B; 2003.*

endotracheal intubation, shorten duration of illness, and improve outcomes. Institution of mask ventilation requires specialized skills of trained respiratory therapists. Attention needs to be paid to selecting and fitting a comfortable well-sealed mask, and providing a ventilator that minimizes the patient's work of breathing and triggering effort. When noninvasive mask ventilation is not successful in sustaining ventilation, or the patient is too ill to use the mask, endotracheal intubation and mechanical ventilation are needed to treat respiratory failure. The mechanical ventilator should be set to provide minute ventilation that does not overventilate the patient and cause alkalemia, which may ultimately impede liberation from the ventilator. The inspiratory flow rates and inspiratory to expiratory time ratios should be adjusted to provide a prolonged duration of expiration to minimize dynamic hyperinflation (auto-PEEP), which can lead to dyspnea, discoordination, and barotrauma. Weaning and liberation from mechanical ventilation can be hindered by anxiety, oversedation, mucus secretions, intravascular volume overload, myocardial ischemia, or respiratory muscle deconditioning. Survival after an episode of acute respiratory failure for COPD is about 50 percent at 2 years after discharge, with about half of the patients being re-admitted to the hospital within 6 months.

Pneumothorax

COPD is thought to be the most common cause for secondary spontaneous pneumothorax. A pneumothorax can either cause an acute symptomatic exacerbation of COPD

from rupture of a bleb, or may occur during the course of an exacerbation as a consequence of hyperinflation or mechanical ventilation. Because this is a life-threatening but quickly treatable cause for worsening respiratory failure in COPD, it should always be considered in the differential diagnosis for worsening dyspnea in COPD. The physical examination can be misleading because diminished breath sounds are a component of the underlying disease. Imaging studies are usually diagnostic, but at times it can be difficult to distinguish a pneumothorax from an overdistended bulla. If the patient's clinical situation can tolerate it, imaging with inspiratory and expiratory views, or chest computed tomograms can be helpful. In the intensive care unit, upright and supine views sometimes show mobility of the pleural air.

Urgent treatment for the patient *in extremis* is performed by aspirating the pleural space at the second intercostal space anteriorly in the mid-clavicular line. Definitive emergency treatment is placement of a thoracostomy tube, which should be done with care to avoid laceration of a bulla and creation of a broncho-pleural fistula. In patients with advanced COPD, recurrence of a pneumothorax can be life threatening, so definitive pleural sclerosis with surgical or medical thoracoscopy should be strongly considered. Whether one adopts a surgical or medical approach to pleural sclerosis depends upon the clinical situation and preference of the treating physicians.

Cor Pulmonale

Pulmonary hypertension and consequent right ventricular failure, *cor pulmonale,* are usually the consequence of chronic alveolar hypoxia, with secondary contributions from destruction of the alveolar capillary bed, lung hyperinflation, and increased blood viscosity. Diagnosis of pulmonary hypertension and right ventricular failure can be difficult, as physical findings of venous engorgement, and right ventricular hypertrophy and dilatation are late signs. Peripheral edema is poorly correlated with resting right atrial pressure and may reflect fluid retention from activation of the renin-angiotensin-aldosterone system. Functional imaging studies including echocardiography or radionuclide ventriculography are more probative for evaluation of right ventricular function. Doppler echocardiographic measures of pulmonary artery systolic pressure are often inaccurate and may overdiagnose pulmonary hypertension, but a normal value is reassuring that pulmonary hypertension is not present. Once cor pulmonale is present, survival is diminished. If the pulmonary artery pressure exceeds 45 mmHg, the average 2-year survival is less than 2 years.

The primary treatment of cor pulmonale consists of continuous oxygen to overcome hypoxemia and diuretics to control peripheral edema. Digitalis is useful for rate control of atrial fibrillation. Calcium channel blockers and other vasodilators can dilate the pulmonary circulation, but they worsen hypoxemia and their benefit is not established. Phlebotomy increases exercise capacity when the hematocrit exceeds 55 percent, but persistent erythrocytosis suggests inadequate oxygen supplementation or another cause. Anticoagulation, which is considered beneficial in severe pulmonary vascular hypertension of other causes, is of uncertain benefit in patients with pulmonary hypertension caused by COPD.

Supraventricular Arrhythmias

Supraventricular tachyarrhythmias are common in patients with COPD, as a consequence of right atrial enlargement, increased endogenous adrenergic tone, hypoxemia, and drug treatment—specifically theophylline and anticholinergic bronchodilators. Treatment is similar to that in nonpulmonary patients; however, the presence of COPD should not prevent evaluation for treatable causes of arrhythmias such as pulmonary embolism, hyperthyroidism, or valvular heart disease, which may be difficult to diagnose in COPD patients.

Hypercapnia

Chronic hypercapnia secondary to alveolar hypoventilation can be considered an adaptive response to obstructive lung disease by decreasing the work of breathing, preventing respiratory muscle fatigue, and allowing a diminished sensation of dyspnea. The adverse effect of chronic hypercapnia is the development of alveolar hypoxia and consequent pulmonary hypertension. Accordingly, the approach to chronic hypercapnia is the use of supplemental oxygen in controlled concentrations. In patients who are very sensitive to oxygen, it is preferable to provide oxygen in controlled concentrations with Venturi masks rather than nasal cannulae.

Nocturnal ventilation has been effective in reducing daytime hypercapnia in patients with neuromuscular disease and kyphoscoliosis. Short-term trials have shown divergent effects of nocturnal ventilation in patients with COPD. A 2-year controlled long-term trial of nocturnal ventilation in hypercapnic patients with COPD has shown modest improvement in symptoms and quality of life, and a trend toward reduced hospitalization, but only small improvements in daytime hypercapnia. Thus, based on our current state of knowledge, long-term nocturnal ventilation ought to be reserved for selected symptomatic patients with frequent hospitalizations who can tolerate the treatment.

ADVANCED TREATMENTS

For patients who have far-advanced disease evidenced either by severe breathlessness or short life expectancy, more aggressive treatments should be considered. Undertaking these treatments requires thoughtful consideration by patients and their families, and frank discussion of the risks and benefits by the medical caregivers.

Lung Volume Reduction Surgery

Lung volume reduction surgery (LVRS) is a surgical procedure that involves stapled resection of 20 to 30 percent of

the lung bilaterally, usually from the apices. The procedure is equally safe and effective done by median sternotomy or video-assisted thoracoscopy (VATS). The theory behind this procedure is that the remaining lung expands to fill the thorax, thereby increasing its elastic recoil pressure, which improves expiratory airflow. The reduction of lung volume permits the diaphragm to attain a more normal, domed configuration, which improves its mechanical efficiency. Moreover, the preferential removal of unventilated bullae reduces residual volume, permitting an increase in the vital capacity. While some patients show substantial physiological and symptomatic improvement following LVRS, many do not. An algorithm for selection of patients for LVRS, based on distribution of emphysema and functional measures, is presented in Figure 42-4. Generally, LVRS should not be done on patients with an FEV_1 less than 20 percent predicted and either diffusing capacity less than 20 percent predicted or diffuse homogeneous emphysema on HRCT, because these patients have high surgical mortality. The group of patients who fare best with LVRS are those who have emphysema predominantly in the upper lung zones and low exercise capacity despite pulmonary rehabilitation. These patients have improved survival after LVRS and show improved functional status and quality of life. Conversely, patients without upper lobe predominance (i.e., lower lobe emphysema or homogeneous emphysema) and who have adequate exercise capacity after rehabilitation, have worse outcomes after LVRS. In selected cases, resection of a pulmonary nodule may be accompanied by LVRS as an attempt to improve postoperative functional status. Although LVRS was originally proposed as a temporizing measure while patients were awaiting lung transplantation, most LVRS candidates are not suitable candidates for lung transplantation. However, prior LVRS does not alter the outcome of subsequent lung transplantation.

Surgical resection of a single large bulla is rarely indicated for treatment of COPD. Isolated giant bullae are usually the result of an expanding congenital cyst. The generally accepted indication for resection of a single large bulla is that it occupies more than one-third of the hemithorax and causes compression of normal lung. Some believe that a preserved carbon monoxide diffusing capacity is an indicator of those most likely to improve following a bullectomy.

Preliminary studies with nonsurgical approaches to lung volume reduction using bronchoscopically implantable one-way valves to cause lobar atelectasis are currently being evaluated for safety and efficacy. This or other nonsurgical methods may ultimately provide an alternative approach for patients who are not otherwise surgical LVRS candidates.

Lung Transplantation

In younger patients with advanced disease, lung transplantation should be a treatment consideration. Criteria for lung transplantation referral in patients with COPD are an FEV_1 below 25 percent predicted, severe hypercapnia, or severe pulmonary hypertension in patients under the age of 60 years.

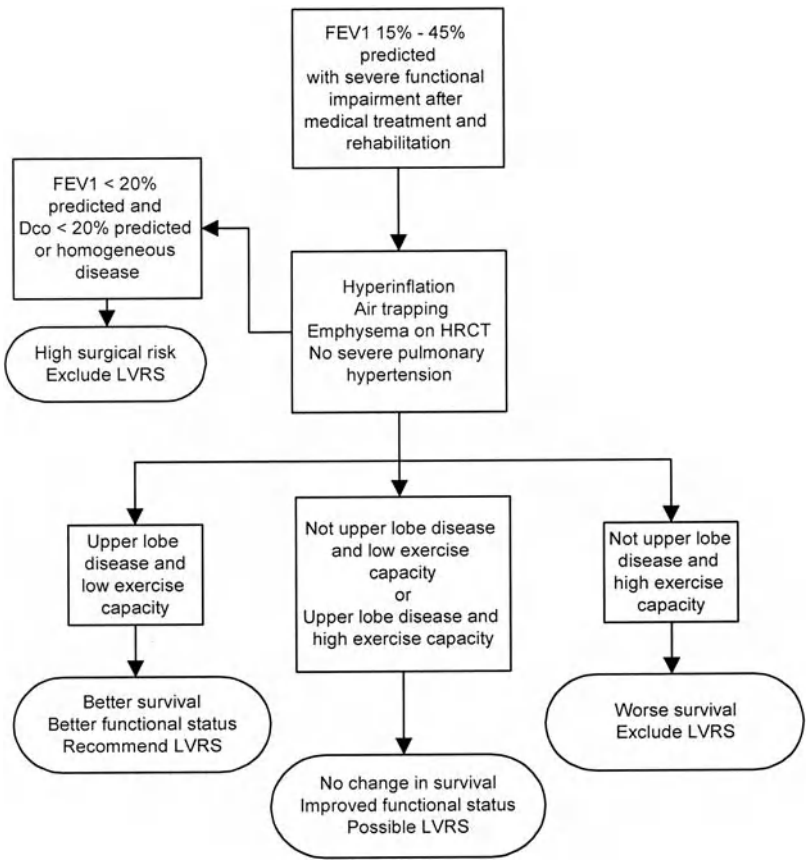

Figure 42-4 Decision tree for selection of candidates for lung volume reduction surgery based on distribution of emphysema on high-resolution computed tomogram and functional impairments.

The traditional recommendation is that patients should be referred for transplantation when their life expectancy is less than 2 years, because this is the average waiting time on a transplant recipient list. In recent years, the waiting time has lengthened to closer to 4 years, so this may influence physicians to make earlier referrals. Other co-morbid conditions such as poor nutritional status, chronic mycobacterial infection, severe osteoporosis, or suboptimal psychosocial support are considered relative contraindications. Current smoking, recent malignant disease, major organ system failure (particularly renal), or chronic hepatitis B or C infections are considered absolute contraindications. Lung transplantation may be either unilateral or bilateral depending upon the availability of donor organs and preference of the transplant surgeon. Generally, younger patients and those with accompanying bronchiectasis are considered better candidates for bilateral lung transplantation.

COPD is the most common indication for lung transplantation, accounting for nearly 40 percent of all lung transplants and about half of single lung transplants. This is accounted for by the high prevalence of COPD as well as the better survival for COPD than other transplant indications while awaiting donor organs. However, newly promulgated criteria for prioritization of transplant recipients, based on diagnosis rather than waiting time alone, are likely to diminish the likelihood that COPD patients will receive donor organs. Early survival for patients with COPD following lung transplant is slightly better than other diagnostic groups in the first few years. Overall, 30-day survival is 93 percent; 3-year survival is 61 percent; and 5-year survival is 45 percent. Evidence suggests that COPD transplant recipients do not have better survival than comparable wait-listed candidates, so the rationale for lung transplantation in COPD, in contrast to other diseases, is the demonstrable improvement in functional capacity and quality of life.

Chronic Ventilator Support

Some patients remain on long-term ventilator support following an episode of acute respiratory failure. Most often these patients are treated in a long-term ventilator unit, but some can be managed at home with adequate support. In some cases, the goal of long-term ventilator support is to provide rehabilitation via respiratory care, nutrition, and exercise to eventually be liberated from the ventilator entirely or for substantial portions of the day. In other cases, the goal of care is to provide comfort and support for terminal care without attempts at rehabilitation. Whatever the goal, a coordinated team of physicians, respiratory therapists, physical therapists, nutritionists, social workers, psychologists, and nurses are needed to undertake the care of these patients. The treatment of long-term ventilator patients differs from the treatment of acute respiratory failure in the intensive care unit. Ventilators are less sophisticated in terms of modes of ventilation and monitoring, but more portable. Ventilation is often performed with an uncuffed tracheostomy with an air leak to avoid complications at the cuff site. Sufficiency of ventilation is judged by noninvasive measures of oxygenation and patient comfort. Narcotics in small doses are administered for relief of dyspnea. Diagnostic studies and invasive testing are performed less frequently than in critical care units. Although the care in long-term ventilator units is complex and expensive, the quality of life experienced by patients in chronic ventilator units is similar to that of patients confined to a bed and chair existence by other chronic maladies. The survival of COPD patients on long-term mechanical ventilation is less than those on such treatment for neuromuscular diseases, in part, because of their older age and co-morbidities.

CONCLUSIONS

COPD develops insidiously. However, the disease can be easily detected with simple spirometric testing before symptoms occur, and cessation of smoking can slow or even halt the disease progression and prolong survival. Once the disease is symptomatic, a coordinated, comprehensive, and individualized approach to treatment, both pharmacologic and nonpharmacologic, can increase functional status, prevent complications, and improve the quality of life. Exacerbations of COPD can range from those that are nuisances to those that are life threatening, but treatment can shorten the duration of illness and improve outcomes. In advanced disease, treatments including surgical approaches are directed toward relief of symptoms and prolongation of survival. Thus, although there is certainly need for improvement in our treatment of symptomatic COPD, current treatments are effective and a nihilistic attitude is not warranted.

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43

Cigarette Smoking and Disease

Stephen I. Rennard • Lisa M. Hepp • David M. Daughton

Native Americans discovered the use of the tobacco plant, *Nicotiana tabacum,* during antiquity. By the time Columbus arrived in America, tobacco use was widespread throughout the western hemisphere and was well integrated into Native American cultures. Production of tobacco and its trade represented a major economic activity in the pre-Columbian Americas. Early European explorers learned of the tobacco plant from Native Americans, and by the mid-seventeenth century tobacco was widely used in Europe.

The most important, but not the only, active psychopharmaceutical drug contained in the leaves of the tobacco plant is nicotine. It is likely that this alkaloid, which represents a major metabolic product of the tobacco plant, evolved as a protection against insect predators, as nicotine is a potent insect neurotoxin. Interestingly, nicotine has been exploited in this regard as a commercial insecticide.

Nicotine is a potent euphoriant. On a molar basis, nicotine is more active than such euphoria-inducing drugs as cocaine, amphetamine, or morphine. Nicotine also has a number of other effects on the central nervous system (CNS). For example, nicotine can improve task performance and attention time by measurable degrees in nonhabituated individuals and may have beneficial effects on cognition. Nicotine can also ameliorate anxiety and depression and induce a sense of well-being while causing a state of arousal. In addition, nicotine can attenuate pain. Unfortunately, nicotine is also highly addictive.

NICOTINE ADDICTION

Nicotine exerts its biologic effects on "nicotinic" receptors, a subset of cholinergic receptors whose endogenous ligand is acetylcholine. Nicotinic receptors are homo- or heteropentamers that bind two ligand molecules and form an ion channel. In humans, 17 genes code for distinct component chains, resulting in a very large number of potential pentamers, although only a relative few are believed to have a biologic role. The $(alpha4)_3(beta2)_2$ receptor is believed to be most important in the addicting effects of nicotine, while the $(alpha7)_5$, for example, is believed to mediate some of the cognitive effects of nicotine. In contrast, the muscarinic receptors, the other major class of cholinergic receptors, are single-chain G-protein–coupled receptors.

Support of the addictive potential of nicotine includes the well-described withdrawal syndrome (Table 43-1), evidence that nicotine withdrawal is associated with

Table 43-1

Nicotine Withdrawal Symptoms (DSM-IV)
Dysphoric or depressed mood
Insomnia
Irritability, frustration or anger
Anxiety
Difficulty concentrating
Restlessness
Decreased heart rate
Increased appetite or weight gain

drug-seeking behavior, and the general dose escalation observed early in the habitual use of nicotine in most individuals. Current concepts suggest that both the psychoactive effects of nicotine and its addiction potential depend on its pharmacokinetics. As with many other addicting drugs, the CNS effects of nicotine depend on both the absolute level of the drug and the rate of drug level increase at the receptors in the brain. Smoking is a particularly effective means of delivering nicotine to induce psychoactive effects. When the drug is inhaled into the lungs its lipid solubility allows it to be rapidly absorbed across the alveolar surface into the pulmonary capillary blood. This results in a very rapid increase in nicotine levels in arterial circulation. Consequently, at the level of receptors in the brain, nicotine concentration rises very rapidly following inhalation of a cigarette. This type of pharmacodynamics maximizes not only the psychoactive potential of nicotine, but is also important in its addictive potential. Alternative forms for delivering nicotine, which do not achieve such rapid rises in blood levels, are associated with less psychoactive effect and less addictive potential. These pharmacodynamic principles are important in the use of nicotine replacement as an aid to smoking cessation, as they underlie the basis for nicotine vaccines and provide part of the rationale for partial nicotine agonist therapy (see below).

Nicotine addiction is primarily a pediatric problem. That is, most individuals who become addicted to nicotine become addicted prior to adulthood. In the United States, the peak incidence for developing a regular nicotine habit is in adolescence. Individuals who do not acquire a nicotine habit prior to age 20 are exceedingly unlikely to do so as adults. The demographics of smoking initiation were well known to the tobacco industry. Marketing campaigns designed to promote the image of specific brands of cigarettes were carefully designed and were exceedingly effective in leading to logo recognition among children as young as kindergartners and contributed to brand selection among American adolescents. The susceptibility of children to these campaigns was a major driver in leading to the current ban on tobacco advertising in media likely to be seen by children.

Most children who begin to smoke do so on an occasional basis. Within a few years, however, a regular habit may develop. Most often this habit is characterized by smoking only a few cigarettes daily. The number of cigarettes smoked, however, generally increases for the first 8 to 10 years. Important variations on this pattern exist, suggesting biologic differences among smokers. Some smokers achieve a "mature addiction" very rapidly. In contrast, as many as 15 percent of smokers, termed "chippers," may continue to smoke episodically and may not be fully addicted. Once a smoker achieves a mature addiction, however, cigarette consumption typically remains very constant. Interestingly, the smoker appears to be adjusting nicotine intake. If supplemental nicotine is administered, smokers often reduce their nicotine consumption. Alternatively, if smoking is restricted (e.g., by decreasing the number of cigarettes available), smokers alter their smoking strategy (e.g., by smoking each cigarette more deeply) in order to maintain a relatively constant nicotine intake.

While the pathogenetic mechanisms underlying withdrawal symptoms are incompletely understood, it is generally believed that some withdrawal symptoms are related to decreases in nicotine blood levels below certain thresholds. Some smokers experience nicotine withdrawal at night when sleep interferes with nicotine intake. The concept that nicotine replacement can help ameliorate withdrawal symptoms by maintaining nicotine blood levels is also an important concept underlying nicotine replacement as an aid to smoking cessation (see below).

Smoking is a perfect example of a gene-environment interaction. Twin studies have established a genetic basis for both smoking initiation and smoking persistence. It is likely that many genes affect smoking behavior, and several candidate genes have been suggested. Among these is CYP2A6, the enzyme that normally metabolizes about 70 percent of nicotine into cotinine. Individuals with a null mutation in CYP2A6 are less likely to become smokers, presumably because they "overdose" when they smoke. If they do smoke, they smoke fewer cigarettes and smoke them less intensely and, as might be expected, are at less risk for smoking-related disease.

Nicotine, through its action on the $(alpha4)_3(beta2)_2$ receptors located on the neurons in the mesolimbic system, is believed to modulate release of the neurotransmitter dopamine. Interestingly, other drugs of addiction, including opiates, alcohol, and amphetamines, also modulate dopamine release. Further supporting a key role of dopamine in mediating the addiction to nicotine is the observation that the dopamine antagonist haloperidol increases smoking behavior while the dopamine agonist bromocriptine decreases smoking. Consistent with this, several candidate genes for smoking behavior have been suggested in the pathways of dopamine signaling and metabolism.

SOCIAL AND CULTURAL ASPECTS OF SMOKING

Social factors also play a vital role in smoking. The experience a child has with the initial attempts at smoking appears to be important, as is an individual's attitude toward smoking (i.e., the "image" of the smoker, peer pressure, parental cigarette use, and availability). Social attitudes can account for very low smoking prevalence in some groups. These observations support attempts to place restrictions on smoking in public places and other efforts to "de-normalize" smoking. Nicotine, moreover, is not the only psychoactive compound in cigarettes. While less well studied, monoamine oxidase inhibitors are present, and these may have either direct effects or interact with other psychoactive drugs. Thus, while it is clear that nicotine is a highly addicting psychoactive substance, smoking is highly complex. This complexity suggests that various smokers may smoke for different reasons; some may be relatively casual smokers, while others may be hard core. Understanding the nature of the addiction is likely to become more important as cessation techniques become more sophisticated.

As in ancient America, the use of tobacco products has become well integrated into modern cultures worldwide. Tobacco is a multi–billion dollar industry. In some regions, tobacco is a crucial cash crop in an agricultural economy. In addition, the manufacture, distribution, marketing, and sale of tobacco products employ many individuals worldwide. Taxation on tobacco products has become an important means for the support of many governments. Thus, any changes in tobacco usage are likely to have economic impacts well beyond any health effects.

The use of tobacco not only has an economic role, but a cultural one as well. In some societies, e.g., certain Native American tribes, tobacco usage has religious significance. In other groups, tobacco usage is associated with a strong cultural image. Often this image may have been created through direct efforts of the tobacco industry to market their product. In this regard, advertising messages promoting the image of the cigarette smoker as rugged, independent, and masculine or as sophisticated, independent, and feminine have been developed. While these images of cigarette smoking have their origins in advertising campaigns, the effectiveness of such marketing programs cannot be underestimated. The portrayal of these images in media such as film may help promote smoking. Whatever the reasons, cigarettes clearly have a cultural significance. The social and economic impact of tobacco usage, therefore, must be considered when attempting to deal with smoking as a public health problem.

MASTER SETTLEMENT AGREEMENT

In an effort to combat the public health ramifications of tobacco usage, the Master Settlement Agreement was signed into effect in 1998. It served as a measure to recuperate what states had lost through Medicaid expenditures due to smoking-related illnesses and as a measure to fine the tobacco industry for deceitful actions. Four major United States tobacco companies awarded 46 states $206 billion dollars to be paid over 25 years and to be utilized as the states saw fit. Four states had previously settled separately. Unfortunately, since its inception, many states have failed to use the funding for tobacco control causes, instead using it to fill budget deficits or support other state programs. Among many other actions, the agreement also prohibited advertisements targeted at youth and permitted access to tobacco industry documents.

SMOKING AS A PUBLIC HEALTH PROBLEM

Cigarette smoking is a major public health problem. In fact, it can be considered *the* major public health problem. The number of deaths attributed to cigarette smoking in the United States has been estimated to be in excess of 400,000 annually. This vastly exceeds deaths attributed to other specific causes. The health burden attributable to smoking parallels smoking prevalence. As a result, smoking-induced disease is becoming more common in the developing world, where smoking prevalence has been increasing. In the United States, where comprehensive tobacco control programs have reduced smoking prevalence, the burden of tobacco-related disease has begun to decrease.

Smoking can cause disease through a myriad of effects. Cigarette smoke contains in excess of 6000 compounds. Detailed toxicity studies have been done on relatively few of these inhaled toxins. Some are present in the tobacco plant; others, including much of the carcinogenic nitrosamines, are generated during the processing of the tobacco leaf, and many more toxins are generated during the pyrolysis of the processed tobacco. While the mechanisms of toxicity are legion, tobacco smoke contains compounds that can disrupt DNA, causing both mutations and altering gene expression, bind to and disrupt proteins, and alter cellular lipids. Obviously, such a diverse group of toxins interacts with many biochemical and cellular pathways. It is not surprising, therefore, that individuals whose biochemistry may differ considerably will be heterogeneous in their response to cigarette smoke. Recognizing that there appears to be a wide range of poorly understood inter-individual susceptibilities, tobacco smoke is associated with an increased mortality from atherosclerotic vascular disease, cancer, chronic obstructive pulmonary disease and is associated with a number of other adverse health effects as well (Table 43-2).

CHRONIC OBSTRUCTIVE PULMONARY DISEASE

Cigarette smoking is the major risk factor associated with the development of chronic obstructive pulmonary disease

Table 43-2

Diseases Associated with Cigarette Smoking

- Cardiovascular
  - Atherosclerotic vascular disease
    - Coronary artery disease
    - Carotid vascular disease
    - Mesenteric, renal, iliac
    - Abdominal aortic aneurysm
  - Peripheral vascular disease
    - Thromboangiitis obliterans (Berger's)
    - Deep venous thrombosis
    - Pulmonary embolus
  - Cardiac disease
    - Angina pectoris
    - Coronary artery spasm
    - Arrythmia
- Malignancy
  - Respiratory tract
    - Lung cancer
      - Squamous cell
      - Adenocarcinoma
      - Large cell
      - Small cell
    - Laryngeal cancer
    - Oral cancer
  - Other tissues
    - Esophagus
    - Pancreas
    - Bladder
    - Uterine cervix
    - Kidney
    - Anus
    - Penis
    - Stomach
    - Liver
    - Leukemia
- Lung disease
  - COPD
    - Emphysema
    - Chronic bronchitis
    - Asthma
  - Other lung diseases
    - Idiopathic pulmonary fibrosis
    - Histiocytosis X
    - Respiratory bronchiolitis
    - Goodpasture's syndrome
    - Sleep apnea
    - Pneumothorax
- Gastrointestinal disease
  - Peptic ulcer disease
    - Gastric
    - Duodenal
  - Gastroesophageal reflux
    - Chronic pancreatitis
    - Chron's disease
    - Colonic adenomas
- Dermatologic disease
  - Skin wrinkling
  - Psoriasis
- Reproductive disease
  - Ovarian failure
  - Pregnancy related
    - Prematurity
    - Premature rupture of membranes
    - Spontaneous abortion
  - Decreased sperm quality
  - Fetal effects
    - Low birth weight
    - Impaired lung growth
    - Sudden infant death syndrome
    - Febrile seizures
    - Reduced intelligence
    - Behavioral disorders
    - Atopic disease/asthma
- Effects on children of parental smoking
  - Asthma
  - Rhinitis
  - Otitis
  - Pneumonia
  - Increased risk to smoke
- Rheumatologic disease
  - Osteoporosis
  - Rheumatoid arthritis
- Psychiatric
  - Depression
  - Schizophrenia
- Oral disease
  - Periodontal disease
  - Loss of taste
- Loss of olfaction
- Infectious disease
  - Tuberculosis
  - Pneumococcal infection
  - Meningococcal infection
- Endocrine disease
  - Altered hormonal secretion
  - Graves' disease
  - Antidiuresis
  - Goiter
- Renal
  - Glomerulonephritis
- Benign prostatic hypertrophy
  - Cataracts

Most of the associations of cigarette smoking and disease are based on epidemiologic studies. While in some cases there is clear evidence of an etiologic role of cigarette smoking, in other cases this relationship is not clear. Cigarette smoking, for example, may be associated with something else that is, in fact, etiologically related to a specific disease. In some cases, for example, depression, cigarette smoking may be therapeutic; thus, the association may not be that the smoking causes the disease, but rather the disease causes the smoking.

(COPD) (see Chapter 41). Approximately 80 percent of patients with clinically significant COPD are or have been smokers. The number of individuals with COPD in the United States is estimated to be as high as 23 million, of whom as many as 10 percent have severe disease. Evidence supporting the relationship between smoking and COPD includes a dose-response effect; that is, heavy smokers are at greater risk of developing COPD. Low doses are also likely hazardous, as symptoms of bronchitis and increased risk for COPD have been associated with passive smoke exposure.

On average, expiratory airflow in cigarette smokers decreases twice as fast in smokers (40 ml/y) than nonsmokers (20 ml/y). Although only a minority of smokers, perhaps 15 percent, who lose lung function faster than the average, are commonly diagnosed with COPD, it is likely that as many as 50 percent of smokers will have at least moderate disease and, upon careful questioning, will have evidence of functional compromise. In addition, COPD is a major risk factor for acute cardiac events with even minor decrements in lung function being associated with increased cardiac risk.

Current understanding of the mechanisms by which cigarette smoke leads to the development of COPD is presented in Chapter 41. A number of interacting mechanisms appear to be involved. Emphysema likely develops from lung damage, which can be a result of direct injury from oxidants in cigarette smoke, and the action of oxidants released by inflammatory cells recruited into the lung as a result of smoke exposure. Smoke-generated oxidants may also disrupt the anti-protease protective mechanisms of the lung, creating a milieu more susceptible to protease-induced damage. When damage induced by smoking is not balanced by appropriate repair mechanisms, emphysema may result. In this context, cigarette smoke may disrupt repair processes. Chronic bronchitis appears to result from similar mechanisms in the airway. Inflammation induced by cigarette smoke appears capable of stimulating both acute production of secretions and inducing long-term anatomic changes in the airway. Changes such as goblet cell metaplasia may predispose to a hypersecretory state. Others, such as peribronchial fibrosis, may result in airflow obstruction. The development of autoimmune processes has been suggested to contribute to disease that persists after smoking cessation. The heterogeneity of clinical COPD likely results from varied host responses to the many pathogenetic pathways initiated by cigarette smoke.

MALIGNANCY

The association of smoking with the development of lung cancer is also well established. The risk for developing lung cancer is increased about 20-fold in smokers compared to nonsmokers. Furthermore, smoking is the major risk factor associated with lung cancer. The attributable risk for the development of lung cancer is estimated to be 79 percent in women and 90 percent in men. In further support of the association of cigarette smoking and lung cancer, as with COPD, epidemiologic evidence supports a dose dependency. Specifically, lung cancer risk increases with amount smoked and, most importantly, with the duration of smoking. The increased risk of lung cancer among passive smokers again is suggestive that even low-dose exposures to cigarette smoke carry significant risk.

A direct etiologic role of cigarette smoke in the development of lung cancer is also supported by considerable evidence. The current model of carcinogenesis is a multistage process in which cigarette smoke plays a role at several stages. Both tumor initiators and tumor promoters are present in cigarette smoke. Although many substances in cigarette smoke likely contribute to carcinogenesis, polycyclic aromatic hydrocarbons and nitrosamines have attracted considerable attention. These toxins can lead to acquired somatic cell mutations and persistently altered cellular function. As a result, smokers frequently have epithelial cell abnormalities, which progress from mild metaplastic changes through severe dysplasia and, it is believed, finally to cancer. These lesions are also often widespread raising the possibility that the development of lung cancer in the smoker may be a multi-focal process. These epithelial cell alterations may also contribute to the pathogenesis of other diseases, such as COPD. Interestingly, the development of cancer may depend on host factors. Some potential carcinogens, for example, must be activated in the lung by mixed function oxidases. These enzymes are themselves under genetic control. It has been suggested that varying capacity to induce such enzymes could contribute to varying cancer risk.

Cigarette smoking is associated with several other nonmalignant lung diseases besides COPD (Table 43-2). Nearly all patients with pulmonary histiocytosis X are smokers, suggesting cigarette smoke may have a pathogenetic role in this illness. Similarly, a large number of individuals with spontaneous pneumothorax are smokers. As a result, it has been thought that cigarette smoke–induced damage may contribute to the development of this condition. Malignancies of both the upper respiratory tract and outside the respiratory tract are also associated with cigarette smoking. Cigarette smoking is a major cause of oral and laryngeal cancer. Cigarette smoking, moreover, has been associated with a number of other malignancies (Table 43-2). The mechanism by which cigarette smoking contributes to the development of these various malignancies is not fully established. Cigarette smoke–derived carcinogens are concentrated in the urine and, as a result, the urinary tract, particularly the bladder, is exposed to high concentrations of these toxins.

CARDIOVASCULAR DISEASE

Cigarette smoking is also a major risk factor for the development of cardiovascular disease. In this regard, the impact

of cigarette smoking is of a similar magnitude to that of the other two major risk factors: hypertension and hypercholesterolemia. As with other smoking-related diseases, the cardiovascular risks correlate with the intensity of smoking. Finally, smoking can contribute to cardiovascular disease by contributing to both the chronic development of atherosclerosis and acute cardiac events.

As with COPD and cancer, the epidemiological associations of cigarette smoking and cardiovascular disease are supported by considerable clinical and experimental evidence. In this regard, cigarette smoking can contribute to the development of atherosclerosis through a variety of mechanisms. For example, endothelial injury is associated with the development of atherosclerosis. Cigarette smoking can cause endothelial injury through direct toxicities. In addition, cigarette smoking is associated with tachycardia. Persistent tachycardia is thought to also cause endothelial injury and thus contribute to the development of atherosclerosis. Cigarette smoke per se is not associated with hypertension, but it is associated with hyperlipidemias. In particular, cigarette smoking appears to contribute to increased levels of oxidized low-density lipoproteins, which are believed to be particularly atherogenic. Smokers also have increased levels of circulating neutrophils, which may contribute to atherogenesis through injury of the vascular wall. Finally, smoking exerts effects on blood coagulability. Specifically, fibrinogen levels are increased, and platelet activation may be present. Activation of coagulation can result in release of cytokines, which is believed to contribute to atherogenesis. Microvascular disease is associated with cigarette smoking. It is the major risk factor associated with thromboangiitis obliterans. Smoking is also associated with an accelerated development of microvascular disease when there is concurrent diabetes mellitus. Abdominal aortic aneurysm is highly associated with a history of smoking.

Cigarette smoke can also contribute to acute cardiac events. While smoking does not increase blood pressure chronically, acute smoking is associated with a transient increase in blood pressure. Combined with tachycardia, therefore, smoking is associated with acutely increased myocardial oxygen requirements. This may be one mechanism by which smoking contributes to acute myocardial ischemia. Cigarette smokers also have increased levels of blood carbon monoxide (CO). This impairs oxygen delivery. Increased CO levels, in addition, may also contribute to the increased red cell mass of smokers, which together with increased fibrinogen levels contributes to increased blood viscosity. These factors in turn contribute to the hypercoagulable state associated with smoking and lead to an increased predisposition for the development of acute thrombosis. Finally, cigarette smoking is associated with acute release of catecholamines and the development of coronary vasospasm. Through such mechanisms, cigarette smoking could contribute not only to acute ischemic events, but also to acute arrhythmias.

OTHER ADVERSE HEALTH EFFECTS OF SMOKING

There are also considerable data associating cigarette smoking with a variety of other diseases (Table 43-2). Adverse effects of smoking during pregnancy, for example, are well recognized. Smoking is associated with a twofold increase in premature deliveries. Smoking also has a dose-dependent association with abruptio placenta, placenta previa and premature rupture of placental membranes. Smoking during pregnancy is associated with increased spontaneous abortion. On average, babies of smokers weigh less than those of nonsmokers. With regard to pulmonary disease, infants whose mothers smoked during pregnancy are more likely to develop both sudden infant death syndrome (SIDS) and asthma than are infants whose mothers did not smoke during pregnancy. Smoking is also related to reduced fertility in women, where it is associated with both secondary amenorrhea and irregular menstrual cycles.

In men, cigarette smoking has been associated with impaired sexual functioning. Some studies of sperm quality have shown slight impairments in smokers, but an association with infertility has not been demonstrated. Sexual activity appears to be relatively normal in smokers. Impotence may be increased in smokers, but is generally associated with the development of significant pelvic atherosclerotic vascular disease.

Considerable epidemiologic and experimental data support an association of smoking with the development of peptic ulcer disease. In this context, smoking has been associated with increased gastric acid output, increased duodenal gastric reflux, and has been suggested to decrease gastric blood flow. Smoking may also decrease the effect of antiulcer medications. Finally, smoking appears to potentiate the development of peptic ulcer disease in individuals taking nonsteroidal anti-inflammatory drugs and individuals colonized with *Helicobacter pylori*.

Cigarette smoking is also associated with a number of other diseases (Table 43-2). While the mechanisms by which cigarette smoke can exert these varying effects are not fully understood, currently available data do make some general suggestions. For example, osteoporosis is increased in smokers, particularly in older women. While the mechanism is not fully understood, mineral content is reduced in older smoking women, an effect that may be dependent on reduced circulating hormones and earlier menopause associated with smoking. Smoking is also associated with a number of inflammatory and destructive diseases such as skin wrinkling, psoriasis, chronic pancreatitis, and glomerulonephritis.

It is interesting to note the mechanistic overlap among smoking-related diseases. Activation of inflammatory processes, for example, appears to play an important role in the development of COPD and atherosclerosis, and may also play a role in the development of ulcers, skin wrinkling, pancreatitis, gingivitis, and so on. The destruction of the connective tissue macromolecular framework, particularly elastin,

is believed to play an important role in the development of pulmonary emphysema. Similar processes may also take part in the development of skin wrinkling and gum disease. Moreover, the release of cytokines driving cell accumulation and proliferation is believed to play an important role in the development of chronic bronchitis and atherosclerosis, but may also play an important role in the development of neoplasia. Finally, cigarette smoking appears to alter the release of regulatory molecules. This could account for a myriad of consequences smoking has on endocrine disease, altered immunity, and the CNS.

In support of this "systemic concept" of cigarette smoking are important epidemiologic associations. Thus, while most smokers have an accelerated decline in lung function, only a small percentage are routinely diagnosed with clinically significant COPD. This observation has been interpreted as suggesting that the effects of smoking are not clinically important with regard to lung function in the majority of smokers. Refuting this concept, however, are epidemiologic data associating an increase in mortality primarily from cardiac disease that may occur with even very modest declines in FEV_1. The important point is that the presence of a smoking-related effect, even if not symptomatically important, clearly defines an increased risk group.

SMOKING CESSATION

Background

Since Dr. Luther Terry released the first Surgeon General's report on smoking and health in 1964, the prevalence of adult smokers in the United States has dropped from 40 percent to close to 20 percent. Antismoking awareness has increased worldwide to the extent that smoking bans have become commonplace in public buildings, workplaces, and public transportation. In 1984, Surgeon General C. Everett Koop proclaimed that the United States' number one health goal was to achieve a "smoke free society by the year 2000." Unfortunately, this goal was not achieved, yet the overall incidence of smokers in the adult population in the United States continues to decrease. A more realistic goal of adult smoking reduction to 12 percent in the United States was put into place through Healthy People 2010. Whether this goal will be obtained remains to be determined; however, it still highlights the importance of a smoke-free society. The greatest reductions in smoking have been in states with the most comprehensive tobacco control programs, supporting the effectiveness of currently available interventions. Comprehensive tobacco control programs, including bans on advertising, restriction of sales to minors, and increased price for cigarettes, also appear to be having an effect in reducing smoking initiation and prevalence among high school students. Nevertheless, smoking remains a highly prevalent disorder. Since more than three-fourths of smokers wish to quit, there is need for effective smoking cessation interventions.

Behavioral Approaches

Behavioral interventions for smoking cessation should be recognized as part of all patient-physician interactions. For example, not inquiring and intervening about smoking is also a message. Current concepts suggest that not addressing smoking, when it would have been relevant, sends three messages: (1) the physician does not care if the patient smokes; (2) the physician does not have an effective intervention to offer; and/or (3) the physician does not think the patient will be able to quit. All of these "non-messages" have negative effects, particularly as smokers gradually make the decision to quit. A sense of empowerment and control over the behavior is vital to making and succeeding in a quit attempt. Inadvertently eroding a patient's sense of mastery is an unanticipated adverse consequence of not asking about smoking. In addition, many patients are unaware of the potential available therapies; appropriate information can increase motivation to engage in quit attempts.

A wide spectrum of behavioral techniques has been used to treat cigarette addiction. These include some that are effective, such as individual and group counseling, and many that are not effective, such as education, aversive conditioning, psychotherapy, transcendental meditation, sensory deprivation, hypnosis, and desensitization. Unfortunately, these latter, some of which have been assessed in detail, have tended to isolate smoking cessation interventions from mainstream medical practice.

Smoking Behavioral Intervention Models

Several models have been proposed to both understand and enhance the quitting process.

Stages of Smoking Cessation

Prochaska and DiClemente described the smoking cessation process as involving five stages: precontemplation, contemplation, preparation, action, and maintenance. These stages are viewed as a continuum, with smokers progressing sequentially through each stage. In the precontemplation stage, smokers are not interested in quitting smoking and will likely be nonresponsive to direct intervention. Smokers in the contemplation stage are considering quitting smoking and may be receptive to a physician's advice about the risks and benefits of quitting. In the preparation stage, smokers are actively preparing to quit. The action stage encompasses both initial abstinence and the 6-month postcessation period. The maintenance period commences after the 6-month abstinence period. It is rare for a smoker to progress successfully through these stages in the initial quit attempt. The cycle will likely be repeated several times before smoking cessation is ultimately achieved.

National Cancer Institute's Model for Smoking Intervention

The National Cancer Institute's (NCI) recommended model for smoking intervention is based, in part, on five NCI-supported trials involving more than 30,000 patients and was

later expanded by the Public Health Service. This approach, popularly referred to as "the five As," emphasizes the role of medical professionals to *ask* patients about their smoking status, *assess* their willingness to make a quit attempt, *advise* smokers to stop, *assist* them in their stop smoking efforts, and *arrange* for follow-up visits to support the patient's efforts. This approach utilizes brief intervention techniques and emphasizes the role of physicians as facilitators in the quitting process. Simple advice has been assessed in a number of studies, and a meta-analysis suggests a small but significant benefit of these limited interventions. Physician advice is effective both in the outpatient and hospital setting and may also be effective when given by letter or telephone.

Group Counseling

Group counseling programs for smoking cessation are offered by several commercial and voluntary health organizations. These programs are similar in content and typically include lectures, group interactions, exercises on self-recognition of one's habit, some form of tapering method leading to a quit day, development of coping skills, and suggestions for relapse prevention. Group counseling programs sponsored by voluntary health organizations, such as the American Lung Association, are generally the best cost value for smokers. However, these programs are generally limited to large metropolitan areas and are offered on a sporadic basis. One-year success rates associated with group counseling programs are typically in the 15 to 35 percent range.

Gradual Reduction vs. Abrupt Abstinence

Gradual reduction or tapering intuitively appears to offer smokers the least abrasive way to stop smoking, and may be effective for some. However, gradually cutting down can be stressful when smokers attempt to reduce their cigarette use below their critical blood nicotine threshold. At this stage, smokers may begin to experience tobacco withdrawal symptoms. Rather than suffer prolonged discomfort, many taperers will gradually return to their customary cigarette levels and will not succeed in quitting. One of the negative consequences of tapering is that this method can strongly reinforce the smoker's belief of the underlying need for cigarettes. Abrupt abstinence is often stressful and can lead to tobacco withdrawal symptoms. However, within a few weeks of total abstinence, complete abstainers experience less frequent cigarette cravings than taperers and are less prone to relapse. Cigarette tapering is often a component of many group programs in which gradual cigarette reduction is used as a preparatory stage leading toward a target quit day. In this circumstance, the tapering approach may prove beneficial to some smokers.

Educational Techniques

For years, cigarette smoking was viewed as largely a social or psychological habit. As such, the ability to quit was viewed as a measure of personal motivation and psychological willpower. Motivation to stop smoking, combined with sufficient psychological resources, was seen as a driving force behind successful cigarette abstinence. Thus, if smokers could be educated about the health risks of cigarette smoking, they could theoretically become sufficiently motivated and psychologically empowered to quit. Unfortunately, anticipated benefits of the smoking cessation value of educational awareness messages were overly optimistic and simplistic. Over 80 percent of current smokers indicate they would like but are unable to quit. Educational programs to aid smoking cessation have produced disappointing results, with high long-term failure rates. Nevertheless, education about smoking is still regarded as a useful activity.

Other Modes

The goal of hypnosis in smoking cessation is to enable the smoker to achieve an altered state of consciousness to enhance the ability to quit. Controlled trials of hypnosis have generally been unable to document long-term smoking cessation efficacy. Aversive conditioning is based on the premise that smoking is a learned response that can be extinguished by creating an association between smoking and a negative sensation. Impressive quit rates are generally not seen unless these techniques are combined with other methods, such as individual or group counseling programs. Acupuncture has been advocated, but controlled trials with "sham" acupuncture have not demonstrated an effect.

Pharmacologic Treatment

Two classes of agents, nicotine replacement and bupropion, are approved to aid smoking cessation. In addition, two other agents, clonidine and nortriptyline, are supported by guidelines for "off-label" use as secondary agents. In addition, several other agents are under active investigation and have shown promise.

Nicotine Replacement Therapies

A wide variety of nicotine replacement formulations have been developed, including tablets, polacrilex (gum), transdermal systems, nasal spray, a variety of inhalers, and nicotine toothpicks. Five formulations are currently approved as aids for smoking cessation in the United States, and three are available over the counter. In clinical trials, all have demonstrated about twofold increases in quit rates above placebo.

Nicotine Polacrilex

Nicotine polacrilex gum was the first nicotine replacement therapy to gain Food and Drug Administration approval. It is now commercially available over the counter in 2- and 4-mg forms. In nicotine polacrilex, nicotine is bound to a resin that contains a buffering agent to improve delivery of nicotine through the buccal mucosa. The rate of chewing can influence the rate of nicotine release, and the pH in the mouth can influence absorption as acid foods or drinks convert nicotine base to salt, which, because of its charge, does not cross the buccal mucosa. Ad libitum use of 2-mg nicotine polacrilex is associated with blood nicotine levels less than 40 percent

of customary smoking. At this level of nicotine replacement, many smokers may still experience discomforting tobacco withdrawal symptoms. A fixed dosage regimen of nicotine gum can produce higher blood nicotine levels than ad libitum use.

Although effective in clinical trials, less successful results have been observed with nicotine gum in general practice and unsupervised settings. This may be due, in part, to the difficulty associated with using this pharmaceutical agent.

Nicotine Polacrilex Lozenge

A nicotine polacrilex lozenge is also approved as an aid for smoking cessation, and is available over the counter. Chewing is not required, but acid food and/or beverages impair absorption.

While the potential to develop addiction to nicotine polacrilex is believed to be low, many smokers who have quit continue to use these formulations chronically. This suggests that the pharmacokinetics of nicotine delivery by nicotine polacrilex, which is substantially slower than that of a cigarette, is insufficient to induce addiction, but may be sufficient to sustain it.

Transdermal Nicotine

The primary advantage of transdermal patch delivery systems are ease of use and controlled drug delivery. Several formulations are available over the counter. In general, they achieve nicotine blood levels roughly 40 to 50 percent of that achieved by customary smoking of about 30 cigarettes daily. Transdermal nicotine systems have been repeatedly found to reduce tobacco withdrawal symptoms and significantly enhance smoking cessation rates. Unlike nicotine polacrilex, transdermal nicotine systems have consistently improved quit rates in primary care settings. This difference is likely due to the ease of patch use in this setting. The recommended use period for patches varies according to product, but a minimum of 4 weeks of therapy is probably required to help achieve long-term abstinence. Patches are most commonly worn at night, which provides a level of nicotine when a smoker awakes. Often this is a time when the individual is at risk to relapse since the low nicotine levels are associated both with withdrawal and increased effect of the smoked cigarette. On the other hand, delivery of nicotine at night may disturb sleep, particularly through vivid dreams. Spontaneous long-term use of the patch has not been observed, suggesting that the very slow kinetics of nicotine delivery with this system is insufficient to sustain addiction effectively. In addition, perhaps due to the partial replacement of nicotine, most smokers on patches still experience some tobacco withdrawal symptoms during the first few days of quitting. While these symptoms will likely be less severe compared to quitting cold turkey, some patients will be tempted to smoke and wear patches. Early concerns about increased cardiac risk among individuals who smoked while wearing the patch have not been substantiated. In fact, reduced smoking may decrease cardiac events. However, individuals who continue to smoke and use patches after the 2-week period are unlikely to achieve abstinence. For this reason, simultaneous nicotine patch wearing and smoking should be discouraged.

Nicotine Inhaler

The nicotine inhaler is a plastic nicotine-containing cartridge that fits on a mouthpiece. Nicotine is released when air is inhaled through the device, which is similar in size to a cigarette. The nicotine is not effectively delivered to the lungs as the particle size is too large. Rather, it is deposited and absorbed through the buccal mucosa, which results in pharmacokinetics that resembles nicotine polacrilex. Blood levels depend on the frequency of inhalations but can be about one-third of conventional smoking. It may cause irritation of the throat and mouth and may precipitate bronchospasm in individuals with reactive airways.

Nicotine Nasal Spray

The nasal spray delivers nicotine to the nasal mucosa through which it is absorbed. It has the most rapid pharmacokinetics of the currently available nicotine replacement formulations. Nasal irritation is very common, particularly when initiating therapy.

Combination Therapy

Although not approved by drug regulatory agencies, various combinations of nicotine replacement may have utility for selected individuals who need higher doses. In addition, combination of a transdermal system with an ad libitum modality (e.g., nasal spray) can increase the control of nicotine levels and may result in increased quit rates.

Bupropion

Bupropion is approved as an antidepressant, and several studies have demonstrated its efficacy as an aid in smoking cessation. It is believed to act by potentiating dopaminergic and noradrenergic signaling. The formulations for depression and smoking cessation have different trade names, which has clinical relevance. First, an appropriate diagnosis is often required for reimbursement. Second, care is needed not to prescribe bupropion under one name to an individual already taking it under its other name, as overdosage can result.

In clinical trials, bupropion approximately doubled quit rates compared with placebo. Subjects with a history of depression, however, appeared to benefit from bupropion but did not with nicotine replacement, suggesting that bupropion may be a superior initial choice in such individuals. Combination of nicotine replacement with bupropion has been assessed and appears more effective than either agent alone.

The currently recommended dose is 150 mg daily for 3 days followed by 150 mg twice daily. The quit date should be after a week of therapy so that blood levels are established. The drug is generally well tolerated, although dry mouth and insomnia may occur. In combination with nicotine replacement, an increase in blood pressure may also occur. A reduction in seizure threshold makes the drug contraindicated

among those predisposed to seizures, or with anorexia nervosa or bulimia. As the 150-mg once-daily dose was nearly as effective as the 150 mg twice daily, many practitioners use the lower dose routinely. The appropriate duration of therapy is not established. Clinical trials that formed the basis for approval treated for 7 weeks. However, with prolonged therapy, there is an increase in secondary quits, and therapy for 1 year resulted in more quits than therapy for 7 weeks.

Off-Label Agents

Clonidine

Clonidine is an α-adrenergic agonist active in the central nervous system that is used to treat hypertension. A number of clinical trials have evaluated its efficacy in smoking cessation and have generally shown a trend toward benefit, although individual trials have generally not been statistically significant. Its use is supported by a meta-analysis, and the DHHS guidelines suggest it can be used by experienced practitioners comfortable with the drug.

Nortriptyline

Nortriptyline is a tricyclic antidepressant that has been evaluated for efficacy in smoking cessation in several studies. Both individual studies and a meta-analysis support its benefit as an aid to smoking cessation, and it is also recommended as a possible second-line agent for practitioners comfortable with its use by the DHHS guidelines.

A number of other agents approved for other uses have also been assessed for smoking cessation. None are currently recommended off-label by established guidelines, although several are under investigation. These include topimirate, an antiseizure medication that has shown promise for combined alcohol and tobacco addiction, and selegiline, an agent used as an adjunct in the treatment of Parkinson's disease that has also shown promise in smoking cessation. Several other agents, including selective serotonin reuptake inhibitors (SSRIs) antidepressants, opiate antagonists, and amphetamines have been demonstrated to be without benefit. Anxiolytics have generally been without benefit, but buspirone remains controversial as studies have been mixed.

Investigational Drugs

Several drugs are under active investigation for smoking cessation. Varenicline is an $(alpha4)_3(beta2)_2$ receptor partial agonist that has looked promising in phase 2 and 3 clinical trials. As a partial agonist, it has the potential to mitigate some of the nicotine withdrawal syndrome. Also, as a partial agonist, it may function as an inhibitor and block some nicotine effects, and thus may prevent full relapse if a smoker "slips." Rimonabant is a CB1 receptor antagonist. It appears to attenuate a wide variety of cravings and has shown promise in clinical trials for smoking and for obesity. The potential to treat smoking and control the weight gain that is often associated would be a great boon.

Nicotine Vaccines

Nicotine vaccines are also under investigation. Antibodies can be made to nicotine, if it is presented bound to an appropriate carrier. The antibodies then bind nicotine reversibly. By slowing the delivery of nicotine to the brain, the vaccine would distort the pharmacokinetics of a cigarette. These investigational agents may have utility for long-term relapse prevention or for prevention of smoking initiation.

Practical Aspects of Intervention

Pragmatic Approaches to Smoking Cessation

There is no single "best" approach for smoking cessation. In the past, 95 percent of all successful quitters stopped smoking on their own without any outside intervention. This should no longer be regarded as the treatment of choice, however. Approximately 25 percent of smokers who spontaneously quit, stop smoking without developing tobacco withdrawal symptoms. Many other self quitters, however, do develop tobacco withdrawal symptoms, but the discomfort is not sufficiently powerful to overwhelm their desire to quit. The two critical factors required for successful abstinence are that smokers must have a *reason for quitting* and the *ability to quit.*

Reason for Quitting

Educational activities related to smoking risks are such that almost any smoker can enumerate a number of reasons for quitting smoking. There are exceptions, however, and the impact of specific reasons can vary greatly from person to person. Appropriate education, therefore, is still vital to smoking cessation. The more important issue is whether the reasons for quitting are sufficient to lead to a quit attempt. Often the motivation to make a quit attempt is driven as much by the sense of control as empowerment to succeed. This leads directly to the second factor.

Ability to Quit

Many smokers take a defeatist approach to smoking cessation that leads to a self-restoring pattern of continued smoking. The availability of effective support and, more importantly, of effective pharmacologic interventions should be known to the smoker, as this will encourage quit attempts.

Evaluation Process

In the evaluation process, patients are assessed regarding their motivation or reason to quit and their ability to stop smoking. For patients who indicate they are not currently interested in quitting, the goal is simple: Provide them with a reason for quitting. For some, this may be information about health risks. For others, it may be information about effective interventions. The second component of the evaluation process assesses the smoker's ability to quit. A simple, easy-to-use measure, the Fagerstrom test for nicotine dependence (Table 43-3), can provide a brief assessment of the patient's nicotine dependence. The most important question is time to first cigarette, and smokers who smoke within 30 minutes of awakening are usually heavily addicted to nicotine. These

Table 43-3

Items and Scoring for Fagerstrom Test for Nicotine Dependence

Questions	Answers	Points
1. How soon after you wake up do you smoke your first cigarette?	Within 5 minutes 6–30 minutes 31–60 minutes After 60 minutes	3 2 1 0
2. Do you find it difficult to refrain from smoking in places where it is forbidden (e.g., in church, at the library, at the mates?)	Yes No	1 0
3. Which cigarette would you hate most to give up?	The first one in the morning All others	1 0
4. How many cigarettes do you smoke per day?	10 or less 11–20 21–30 31 or more	0 1 2 3
5. Do you smoke more frequently during the first hours after waking than during the rest of the day?	Yes No	1 0
6. Do you smoke if you are so ill that you are in bed most of the day	Yes No	1 0

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patients and those with Fagerstrom scores greater than or equal to 7 comprise a group of individuals likely to benefit from nicotine replacement therapy. In contrast, patients with low Fagerstrom scores who are able to cope with smoke-free environments for an extended time period (greater than 4 hours) without developing discomforting withdrawal symptoms, may not require nicotine replacement therapy. For these individuals, bupropion may be a better choice for pharmacologic support.

Current guidelines suggest that all individuals who are making a serious quit attempt should be given the best chance for success. Thus, in general, pharmacotherapy should be recommended for all individuals who have no contraindications. As noted below, this approach is probably both the most effective and the most cost effective.

Preparing Smokers for Quitting

By anticipating the problems smokers will likely encounter, clinicians can help guide patients through the pitfalls that await them.

Tobacco Withdrawal Period

The first 3 days of abstinence are usually the most difficult. Tobacco withdrawal symptoms (Table 43-1) generally peak during the first 72 hours, and then gradually subside over a 3- to 4-week period. These symptoms can include restlessness, anxiety, difficulty concentrating, irritability, frustration, depression, and almost unrelenting craving for cigarettes. Common suggestions to help smokers cope with these early withdrawal symptoms in addition to nicotine replacement therapy can include: (1) Be active. Increased activity may curtail some of the drive to smoke. (2) Use deep breathing exercises. The simplest breathing exercise involves nothing more than extended breath holding followed by slow exhalation through pursed lips. (3) Avoid high-risk situations for smoking during the first 3 weeks of quitting. (4) Use plenty of cinnamon gum or chewable candies. (5) Combat strong urges to smoke: the urge to smoke will go away whether one smokes or not.

Cravings

Of all the symptoms associated with nicotine withdrawal, cravings to smoke are the most persistent. Unlike the other symptoms, cravings can also recur long after abstinence is achieved. During the second and third week of abstinence, the craving waves usually occur less frequently, but can sometimes catch smokers off-guard because of their unexpected intensity. The decrease in frequency is greater than the decrease in intensity, and cravings can be precipitated months and years after abstinence if precipitated by specific cues. In this context, cravings recapitulate, in some ways, the grief response. Relapse is commonly associated with concurrent alcohol consumption. It is likely that alcohol, and the associated situations in which it is consumed, serves both as a cue leading to craving and decreases the inhibitions that may prevent smoking. Ex-smokers should be aware of these moments of hazard.

Depression

At some time during the first three months of abstinence, some smokers may experience depression. For many this depression is mild and transient. For a small minority of smokers, quitting smoking may produce a clinical depression that may require antidepressant therapy, counseling, or return to smoking.

Weight Gain

One of the most disheartening components of quitting smoking is weight gain. Rapid weight gain is common during the first 6 to 8 weeks of cigarette abstinence. This is followed by a more gradual increase in weight to roughly 4 kg at 6 months. Average weight gain at 10 years following cessation is 4.4 kg and 5.0 kg for males and females, respectively. The health risks associated with postcessation weight gain are unknown

but are likely surpassed by the health benefits of stopping smoking.

Additional resources are now available to clinicians to help prepare smokers for quitting. Toll-free tobacco quit lines are currently provided by many countries, including the United States and Canada. Research has found that telephone counseling is an effective smoking intervention. Thus, clinicians should encourage every smoker who wishes to quit to utilize the National Quit Line (1-800-Quit Now). Additional support can be found via the internet using smokefree.gov. Using this approach, a smoker can choose to talk with a telephone specialist with either internet instant messaging or telephone support. Both methods are designed to provide smokers with a personalized quit plan.

Health Benefits of Smoking Cessation

Data on the health benefits of smoking cessation largely come from studies of former smokers. In many cases, these are individuals who may have quit smoking because of the development of disease; therefore, they represent a highly selected group. Other data are derived from interventional studies. Many times, however, such interventional studies include smoking cessation efforts together with many other interventions. Finally, such studies are generally designed to assess the intervention. In general, such interventions will only be partially successful at achieving smoking cessation, and the control group is likely to also have some quitters. As a result, the effect of the intervention cannot be equated with the effect of cessation. Nevertheless, smoking cessation is clearly associated with health benefits.

All-cause mortality is significantly decreased among former smokers. The decrease in mortality rates, moreover, is observed among all age groups and in both men and women. Thus, there is little doubt that all smokers, regardless of age or gender, are likely to benefit from cessation.

Most of the reduction in mortality is due to decreased mortality from cardiovascular events. Smoking cessation is associated with a very rapid reduction in acute myocardial events. It is also associated with a more gradual reduction in complications of atherosclerotic vascular disease. These effects are consistent with the concept that smoking contributes to cardiovascular disease by several mechanisms. The rapid reduction in acute events may be due to removing the acute stresses smoking places on the heart. The longer-term gradual effects may be associated with alteration of the atherosclerotic disease process.

Smoking cessation is also associated with significantly improved risk of both respiratory tract and nonrespiratory malignancies. The risk for the development of lung cancer appears to decrease gradually following cessation, although it will never reach that of a nonsmoker.

Smoking cessation is associated with improvement in lung function in subjects with relatively mild impairment. Improvements can be observed in the first 6 months to 1 year following cessation in FEV_1, an observation initially made in several smaller trials and subsequently confirmed in the Lung Health Study. This large study (nearly 6000 individuals) assigned individuals to three groups, no special intervention, and a smoking cessation intervention with or without the addition of the bronchodilator ipratropium. Among the individuals who successfully quit in the intervention program, there was a significant improvement in FEV_1 in the first year following cessation that was dramatically different than the continued decline observed in the continuing smokers in the same treatment group. Follow-up evaluation of this group has demonstrated continued benefits for at least 11 years, and a reduction in mortality. While not assessed in the Lung Health Study, smaller studies have also demonstrated that smoking cessation is associated with improvement in measures of small airways function including closing volume, closing capacity, and the slope phase III of the nitrogen washout curve. While more limited, several studies also suggest that smoking cessation may be associated with partial improvement in the impaired diffusion capacity of a lung for carbon monoxide (D_{LCO}) associated with smoking. This physiological effect may have a correlate in the cellular changes associated with smoking cessation.

Smokers have markedly increased numbers of alveolar macrophages recoverable by bronchoalveolar lavage. Following cessation in normal smokers, the numbers of recoverable alveolar macrophages decreases significantly towards normal. Among individuals with more severe COPD, however, cessation may not be associated with a reduction in inflammation. Cross sectional studies have demonstrated similar inflammation among current and ex-smokers. Other prospective studies suggest persistent inflammation following cessation. How these studies relate to the improved clinical status of COPD patients following cessation remains to be delineated.

Smoking cessation is associated with an improvement in nonspecific respiratory symptoms. Individuals with cough, sputum production, dyspnea, and wheeze have all reported improvement in symptoms in long-term follow-up studies, with symptoms often improving in the first few months. Smoking is the major risk factor for respiratory bronchiolitis, and smoking cessation is usually associated with a dramatic improvement in this condition. It seems reasonable to suggest that clinically recognizable respiratory bronchiolitis represents one end of a spectrum, and the physiologic and cellular changes noted above in asymptomatic individuals represent a more common result of similar pathogenetic mechanisms. Histiocytosis X occurs almost exclusively in smokers. Smoking cessation is generally regarded as an important therapeutic goal for such individuals. There are cases of complete roentgenographic resolution of the changes of histiocytosis X with cessation. While the pathogenetic mechanisms underlying histiocytosis X are unknown, such case reports suggest that at least part of the anatomic abnormalities associated with this condition are reversible with cessation of smoking.

The effect of smoking cessation on other diseases associated with smoking is, unfortunately, somewhat limited. Former smokers have a reduced incidence of peptic ulcer disease and a more rapid rate of ulcer healing than do current

smokers. Similarly, women who are former smokers seem to have ovarian function that more closely resembles never smokers than smokers. These observations are consistent with a benefit of smoking cessation.

Risks of Smoking Cessation

Smoking cessation may be associated with some hazards in selected cases. Nicotine and other components of cigarette smoke may have a significant antidepressant effect, and many endogenously depressed individuals may have empirically found smoking helped alleviate their symptoms. Depression is a well-recognized manifestation of the nicotine withdrawal syndrome. At times, this depression can be of major clinical importance. Exacerbations of colitis have also been associated with acute smoking cessation. These potential adverse effects should not minimize the importance of smoking cessation, but the clinician should be prepared to address them when necessary. Anecdotal reports have suggested that asthma may worsen following cessation. Anti-inflammatory action of toxins contained in smoke such as NO or CO has been suggested to account for such an effect.

Smoking as a Chronic Relapsing Disease

With current therapeutic interventions, only a minority of smokers will achieve permanent abstinence. This has led to the concept that smoking should be regarded as a chronic relapsing disease. The goal, therefore, is to induce remissions that are as robust as possible. When relapse occurs, re-induction at the earliest possible time is appropriate.

HARM REDUCTION

A more controversial approach for smokers who are unwilling or unable to quit at all is that the health consequences may be partially addressed by reducing the exposure to smoke-derived toxins. This approach, termed "harm reduction," has been the subject of an Institute of Medicine report. Three general categories of harm reduction are theoretically possible: (1) administration of agents to counteract the effects of cigarette smoking; (2) smoking reduction; and (3) development of a less toxic cigarette.

Since cigarette smoking is thought to cause its effects through pathogenetic mechanisms that are at least partially defined, it is appealing to use such mechanisms as targets for therapeutic intervention. In this regard, antioxidants to ameliorate the oxidant-induced injury caused by cigarette smoke and protease inhibitors to bolster the antiprotease defenses are both potential therapies. While conceptually appealing, no data exist to suggest that any such approach is of benefit in continuing smokers.

Pharmacologic support may facilitate reduction in smoking. The observation that most smokers maintain a relatively constant nicotine intake creates the possibility that nicotine replacement can help sustain smoking reduction. Smoking reduction has also been achieved with several formulations of nicotine replacement, and there is some evidence for physiological benefit. Short-term smoking reduction, facilitated with the use of nicotine polacrilex gum, was associated with improvements in lower respiratory tract inflammation assessed by bronchoscopy and bronchoalveolar lavage in a group of heavy smokers. In patients with cardiac disease who reduced smoking, measurable improvements in cardiac function were associated with improved oxygen delivery to the heart due to reduced carbon monoxide. Bupropion has also been associated with reduction in smoking, suggesting that several pharmacologic approaches may be possible to quantitatively reduce smoking.

Reducing the delivery of cigarette smoke toxins while still providing the smoker with a satisfactory cigarette has been an important commercial goal. This was a major motivation in the development of filtered cigarettes and of low-tar, low-nicotine cigarettes. Unfortunately, these approaches do not reduce, and may actually increase, exposure to smoke-derived toxins. As most smokers maintain constant nicotine intake, many smokers compensate for altered smoke composition by simply smoking more or changing the way in which each cigarette is smoked. By causing an altered smoking strategy, filtered and low-yield cigarettes may actually deliver more toxins.

Many of the cigarette-derived toxins are generated as a result of pyrolysis. As a result, tobacco products that do not burn have the promise to yield fewer toxins. There has been much interest in oral tobacco products in this regard. Moist snuff, which has low nitrosamine content due to its processing, has been widely used for several decades in Sweden. It has been associated with a measurable decrease in a number of tobacco-related diseases among Swedish men. Several cigarette-like devices have been developed with similar goals. Some burn small amounts of processed tobacco together with a carbon heat source in order to have a taste that more closely resembles a cigarette. Others electrically heat the tobacco. These products appear to deliver fewer toxins in standardized smoking regimes. Limited data are available on physiological effects but, in one study, a reduction in lower respiratory tract inflammation and in airway metaplasia was observed among heavy smokers who switched to a harm reduction product. Whether such products are associated with health benefits, however, remains to be determined.

Harm reduction strategies may have unforeseen problems. Reduced risk products or smoking reduction strategies may encourage smokers to continue and thus discourage quit attempts. Available data, however, suggest the opposite. Smokers who switch to harm reduction products or who reduce with pharmacologic support appear to have an increased rate of subsequent quits. It may be that the sense of mastery that comes with the reduction effort helps make smokes able to quit. There are other potential hazards. Reduced risk products, for example, might be particularly appealing for individuals beginning smoking both because they may be easier to smoke and they are not perceived as having significant risks. Finally, if use of reduced-risk products erodes the social

climate that discourages smoking, such products could increase use of conventional cigarettes.

SMOKING PREVENTION

As noted above, smoking initiation is generally a pediatric problem. Precisely why some children begin smoking is not fully understood. More than two-thirds of children experiment with cigarettes, but only half will eventually smoke regularly. A number of factors are believed to contribute, including the child's social environment and attitude toward smoking, which appears to be based, in large part, on the smoking behavior of parents, friends, and peer group role models. The reasons for initiating smoking, however, are not entirely environmental, as twin studies suggest a genetic basis for smoking as well. Interventions aimed at altering the social milieu are of some benefit. Participation in sporting activities is associated with lower rates of smoking initiation, as is control of affective disorders. Attitudes toward smoking appear to be important factors leading to smoking initiation, which may depend, at least in part, on advertising and marketing programs; hence the effectiveness of bans on advertising.

A second approach to limiting smoking initiation is to restrict the sale of tobacco products to minors. Many states have legal restrictions on such sales. In many cases, however, these laws are not enforced. Active enforcement, however, can lead to a decrease in both experimental smoking and regular cigarette use among younger smokers. For such measures to be effective, they must be uniformly enforced in the community, and vending machines must be made inaccessible to minors. Another approach to restrict tobacco usage by minors is taxation. It has been suggested that increasing tobacco taxes will decrease use, and that this effect will be particularly prominent among less addicted smokers. Because adolescents may have less disposable income, the effect may be even greater. While such an approach is appealing, the magnitude of price changes required is unclear.

Measures aimed at restricting tobacco sales to minors may lead simply to a deferral of smoking initiation. Thus, if measures are effective at delaying smoking initiation among children, it may be that parallel measures will also be required to affect smoking initiation among older adolescents and young adults. Currently available data suggest that smoking behavior among high school students has begun to decrease. There does not appear to be a corresponding increase in smoking among older individuals. These changes are associated with comprehensive tobacco control programs, which therefore seem to have measurable benefits.

CONCLUSION

Cigarette smoking is a complex social and medical issue. The physician has a particularly important role in curbing smoking. Not only must the physician participate in efforts to reduce smoking as a citizen, but as a protector of public health and a possessor of specific expertise in health care matters, the physician must take an active role in health promotion. Such a role includes discouraging smoking initiation among younger patients, encouraging and assisting smoking patients to quit, and participating in social efforts designed to reduce smoking at various levels. A number of policy statements have been prepared regarding smoking and the role of the physician. By implementing these recommendations, it is hoped that cigarette smoking, the number one preventable cause of death in the developed world, eventually can be eradicated.

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Rehabilitation in Chronic Obstructive Pulmonary Disease and Other Respiratory Disorders

Andrew L. Ries

Rehabilitation for patients with chronic lung diseases is well established as a means of enhancing standard pharmacologic and other therapies in controlling and alleviating symptoms and optimizing functional capacity. The primary goal of any rehabilitation program is to restore the patient to the highest possible level of independent function. This goal is accomplished by helping patients and significant others learn more about the underlying disease, treatment options, and coping strategies. Patients are encouraged to participate actively in providing their own health care, become more independent in daily activities, and be less dependent on health professionals and expensive medical resources. Rather than addressing solely reversal of the disease process, rehabilitation focuses on improving disability from disease.

Historically, pulmonary rehabilitation strategies were developed and have been used primarily for patients with chronic obstructive pulmonary disease (COPD). However, pulmonary rehabilitation has also been applied successfully to patients with other chronic lung conditions, including interstitial diseases, cystic fibrosis, bronchiectasis, and thoracic cage abnormalities. It has been used successfully in the evaluation and preparation of patients for surgery, such as lung transplantation and volume reduction lung surgery, and in maximizing recovery after surgery. Pulmonary rehabilitation has been used to facilitate patient recovery from acute processes such as acute lung injury, or exacerbations of chronic lung disease requiring mechanical ventilation or acute hospital care. Pulmonary rehabilitation is appropriate for any

patient with stable lung disease who is disabled by respiratory symptoms. Even patients with advanced disease may benefit if they are selected appropriately and realistic goals are set.

This chapter defines pulmonary rehabilitation and outlines issues related to patient selection and evaluation. Key components of a pulmonary rehabilitation program are described and results of rehabilitation programs reviewed. Finally, the role of rehabilitation prior to and following lung surgery is reviewed.

DEFINITION

In 1999, the American Thoracic Society adopted the following definition:

> Pulmonary rehabilitation is a multidisciplinary program of care for patients with chronic respiratory impairment that is individually tailored and designed to optimize physical and social performance and autonomy.

This definition focuses on three important features of successful rehabilitation. First, the program is *multidisciplinary.* Pulmonary rehabilitation programs utilize expertise from various health care disciplines that is integrated into a comprehensive, cohesive program tailored to the needs of each patient. Second, the program is tailored to the *individual.* Patients with disabling lung disease require individual assessment of needs, individual attention, and a program designed to meet realistic individual goals. Third, the program addresses both *physical and social function.* To be successful, pulmonary rehabilitation must address the social and emotional problems as well as seek to optimize medical therapy to improve lung function.

The interdisciplinary team of health care professionals in pulmonary rehabilitation may include physicians, nurses, respiratory and physical therapists, psychologists, exercise specialists, and others with appropriate expertise. The specific team make up depends upon the resources and expertise available, but it usually includes at least one full-time staff member. Responsibilities of team members generally cross disciplines.

Within this general framework, successful pulmonary rehabilitation programs have been established in both outpatient and inpatient settings and with different formats. A key to success is a dedicated, enthusiastic staff that is familiar with respiratory problems and can relate well to pulmonary patients and motivate them.

PATIENT SELECTION

Any patient with symptomatic chronic lung disease is a candidate for pulmonary rehabilitation (Table 44-1). Appropriate patients are aware of disability from their disease and are motivated to participate actively in their own care in order to improve their health status. Patients with mild chronic disease may not perceive their symptoms to be severe enough to warrant a comprehensive care program. On the other hand, patients with severe disease who are bed bound may be too limited to benefit greatly.

Table 44-1

Patient Selection Criteria for Pulmonary Rehabilitation

Symptomatic chronic lung disease
Stable on standard therapy
Functional limitation from disease
Relationship with primary care provider
Motivated to be actively involved in and take responsibility for own health care
No other interfering or unstable medical conditions
No arbitrary lung function or age criteria

Criteria based on arbitrary lung function parameters or age alone should not be used in selecting patients. Pulmonary function is not a good predictor of symptoms, function, or improvement after rehabilitation. In general, selection should be based upon a person's disability and functional limitation from respiratory symptoms, potential for improvement, and motivation to participate actively in a comprehensive self-care program. Also, pulmonary rehabilitation is not a primary mode of therapy. Patients should be stabilized on standard medical therapy and should not have other disabling or unstable conditions that might limit their ability to participate fully in the program and to concentrate on the necessary tasks.

The ideal patient for pulmonary rehabilitation, then, is one with functional limitation from moderate to severe lung disease who is stable on standard therapy, not distracted or limited by other serious or unstable medical conditions, willing and able to learn about his or her disease, and motivated to devote the time and effort necessary to benefit from a comprehensive care program.

PATIENT EVALUATION

The initial step is screening patients to ensure appropriate selection and to set realistic individual and program goals. The evaluation process includes the following components: interview, medical evaluation, psychosocial assessment, diagnostic testing, and goal setting (Table 44-2).

Table 44-2

Components of a Comprehensive Pulmonary Rehabilitation Program

- Patient evaluation
  - Interview
  - Medical evaluation
  - Diagnostic testing
    - Pulmonary function
    - Exercise
    - Arterial blood gases/oximetry
  - Psychosocial assessment
  - Goal setting
- Program content
  - Education
  - Respiratory and chest physiotherapy instruction
  - Exercise
  - Psychosocial support

Interview

The screening interview is an important first step. It serves to introduce the patient to the program, review the medical history, and identify psychosocial problems and needs. Family members and significant others should be included. Communication with the primary care physician is important to establish the vital link for the rehabilitation staff to clarify medical questions prior to the program and facilitate subsequent recommendations. Care and attention in this initial evaluation helps in setting goals compatible with everyone's expectations as well as appropriate programmatic objectives.

Medical Evaluation

Reviewing medical history helps to identify the patient's lung disease and assess its severity. Other medical problems that might preclude or delay participation may be identified. Available laboratory data should be reviewed, including pulmonary function and exercise tests, rest and exercise arterial blood gas measurements, chest radiographs, electrocardiogram, and pertinent blood tests. Program staff can then determine the need for any additional information or action before the program begins.

Diagnostic Testing

Planning an appropriate rehabilitation program requires accurate, current information. The complexity of the testing procedures performed depends upon individual patient and program goals as well as the facilities and expertise available.

Pulmonary function testing is used to characterize lung disease and quantify impairment. Spirometry and lung volume measurements are most useful. Other tests (e.g., diffusing capacity, maximal respiratory pressures to assess muscle strength) can be added as needed.

Exercise testing helps to assess the patient's exercise tolerance and to evaluate changes in arterial blood gases (e.g., hypoxemia or hypercapnia) with exercise. This may also uncover coexisting diseases (e.g., heart disease). The exercise test is also used to establish a safe and appropriate prescription for subsequent training.

Maximal exercise of patients with chronic lung disease is limited largely by their breathing reserve. Simple pulmonary function tests such as spirometry can be used to estimate a patient's capacity for sustained breathing (maximal ventilation) during exercise. The forced expiratory volume in 1 s (FEV_1) is most useful in this regard. However, lung function only provides an estimate of an individual patient's maximum work capacity. Exercise tolerance depends also on the patient's perception and tolerance of the subjective symptom of breathlessness. Therefore, it is important to exercise patients to assess their physical function and symptom tolerance.

Exercise evaluation for rehabilitation is most easily performed with the type of activity planned for training (e.g., treadmill for a walking training program). Variables measured or monitored during testing should include workload, heart rate, electrocardiogram, arterial oxygenation, and symptoms (e.g., breathlessness). Other measures, such as ventilation or expired gas analysis to calculate oxygen uptake ($\dot{V}O_2$) and related variables may be obtained depending on the interest and expertise of the program staff and laboratory.

Measurement of arterial blood gases at rest and during exercise is important because of the frequent but unpredictable occurrence of exercise-induced hypoxemia. Arterial blood gas sampling during exercise makes testing more complex. The noninvasive estimate of arterial oxygen saturation by cutaneous (e.g., pulse) oximetry is useful for continuous monitoring, but it has limited accuracy (95 percent confidence limits, $\pm$4 to 5 percent).

Psychosocial Assessment

Successful rehabilitation requires attention not only to the patient's physical problems but also to psychological, emotional, and social issues. Patients with chronic illnesses experience psychosocial difficulties as they struggle to deal with symptoms they may not fully understand.

Neuropsychological impairment is common in patients with chronic lung diseases and cannot be accounted for solely on the basis of age, depression, or organic disease. Commonly, such patients become depressed, frightened, anxious, and more dependent on others to care for their needs. Progressive dyspnea is a frightening symptom and may lead to a vicious "fear-dyspnea" cycle: With progressive disease, less exertion results in more dyspnea, which produces more fear and anxiety, which, in turn, lead to more dyspnea. Ultimately, the patient avoids any physical activity associated with both of these unpleasant symptoms.

In addressing these problems, the initial evaluation should assess the patient's psychological state and pay attention to "psychosocial clues" that may be apparent during the screening interview (e.g., level of family and social support, the patient's living arrangement, activities of daily living, hobbies, and employment potential). Important clues in initial interviews may be evident in nonverbal communication, such as facial expression, physical appearance, handshake, and "body space." Cognitive impairment that may limit the patient's ability to participate fully in the rehabilitation program may be identified. Family members and significant others may provide valuable insight and should be included in the screening process and program whenever possible.

Goals

After a patient's medical, physiologic, and psychosocial state have been evaluated, specific goals should be set that are compatible with his or her disease, needs, and expectations. Goals should be realistic in light of the objectives of the program. Family members and significant others should be included in this process so that everyone understands what can and cannot be achieved.

PROGRAM CONTENT

Comprehensive pulmonary rehabilitation programs typically include several key components: education, instruction in respiratory and chest physiotherapy, psychosocial support, and exercise training (Table 44-2). Often, the various components are provided simultaneously; for example, during an exercise session, a patient may learn and practice breathing techniques for symptom control while being encouraged and supported by staff or other patients.

Education

Successful pulmonary rehabilitation depends upon an understanding of lung disease and active involvement by patients and important others in providing social support. Education is an integral component; even patients with severe disease can gain a better understanding of their disease and learn specific means to deal with problems. Instruction can be provided individually or in small groups, but it should be adapted to different learning abilities. Topics discussed commonly include normal lung function, chronic lung disease, medications, nutrition, travel, stress reduction and relaxation, reasons to call the physician, and planning a daily schedule. Individual instruction and coaching may be provided on the use of respiratory therapy equipment and supplemental oxygen, breathing techniques, bronchial drainage, chest percussion, energy-saving techniques, and self-care tips. The general philosophy is to encourage patients to assume responsibility for their own care and become partners with their physician in providing the care.

Despite the importance of education, it is unlikely that increased patient knowledge alone will lead to improved health status. It is more difficult to change patient attitudes and behaviors. Patients require specific, individualized treatment strategies, instruction, and reinforcement. Thus, education is a necessary but not sufficient component of pulmonary rehabilitation.

Respiratory and Chest Physiotherapy Techniques

Patients with chronic lung disease use, abuse, and are confused about respiratory and chest physiotherapy techniques. In pulmonary rehabilitation, each patient's needs for respiratory care techniques should be assessed and instruction provided in proper use. These techniques may include chest physiotherapy to control secretions; breathing retraining techniques to relieve and control dyspnea and improve ventilatory function; and proper use and care of respiratory equipment, including nebulizers, metered dose inhalers, and supplemental oxygen.

Bronchial Hygiene

Patients with chronic lung diseases frequently have abnormal lung clearance mechanisms that increase problems with retained secretions and infection. Therefore, rehabilitation programs teach a variety of chest physiotherapy techniques for secretion control (e.g., coughing, postural drainage, chest vibration and percussion). These are important for patients who experience excess mucus production during exacerbations as well as for those with chronic sputum production. The use of mucolytic agents to reduce viscosity of secretions is of questionable benefit.

Breathing Retraining Techniques

Pulmonary rehabilitation typically includes instruction in breathing techniques, such as diaphragmatic and pursed lips breathing—techniques aimed at helping patients relieve and control breathlessness, improve their ventilatory pattern (i.e., slower respiratory rate and increased tidal volume), prevent dynamic airway compression, improve respiratory synchrony of the abdominal and thoracic musculature, and improve gas exchange. Review of studies evaluating these techniques indicates that improvement in symptoms (e.g., dyspnea) is a more consistent finding than are measurable changes in physiological parameters. The diaphragmatic breathing technique is a maneuver in which the patient consciously coordinates abdominal wall expansion with inspiration and slows expiration through pursed lips. The primary effect is to slow respiratory rate and increase tidal volume.

Pursed-lips breathing is commonly taught to pulmonary patients, particularly those with COPD. This technique was observed by Laennec as early as 1830 and was advocated as a physical exercise for pulmonary patients in the early part of the twentieth century. As a maneuver assumed

naturally by many patients with respiratory disease, pursed-lips breathing is characterized by tensing the lips and narrowing the mouth opening during expiration. The aim is to slow expiration and maintain positive airway pressure in order to "stent the airways open" and prevent collapse.

Oxygen

When chronic oxygen therapy is required, available delivery methods should be reviewed to help select the best system for the patient's needs. Supplemental oxygen is beneficial for patients with severe resting hypoxemia. Long-term continuous oxygen therapy has been clearly shown to improve survival and reduce mortality and morbidity in hypoxemic patients with COPD. The benefits of supplemental oxygen for nonhypoxemic patients or those with intermittent hypoxemia (e.g., during exercise or sleep) are less clearly defined. Although continuous oxygen therapy is feasible and safe, maintaining patients on supplemental oxygen presents several challenges. Handling equipment is particularly difficult for physically disabled and frail patients. Therefore, it is important to assess each person's oxygen needs and provide appropriate instruction.

Several new developments have improved the efficiency of gas delivery systems and patient compliance with continuous oxygen therapy. Liquid oxygen provides more gas with less weight than tanks of compressed gas, particularly in portable systems. Oxygen conserving devices may increase the efficiency of delivery, reducing flow requirements and prolonging the life span of portable gas sources. Transtracheal oxygen delivery may help to improve compliance and avoid problems with nasal catheters; however, patients must be instructed carefully in caring for the catheter.

Exercise

Exercise is important in pulmonary rehabilitation. Considerable evidence supports favorable responses to exercise training in patients with chronic lung diseases. Benefits are both physiological and psychological. Patients may increase their maximum capacity and endurance for physical activity, even though objective measures of lung function do not usually change. Patients may also benefit from learning to perform physical tasks more efficiently. Exercise training provides an ideal opportunity for patients to learn their capacity for physical work and use and practice methods for controlling dyspnea (e.g., breathing and relaxation techniques). Of all the components in a comprehensive pulmonary rehabilitation program, exercise is probably the most costly and labor-intensive, considering the personnel, equipment, and expertise required. Principles of exercise for patients with lung disease differ from those based on normals or other patient populations because of differences in the limitations to exercise and the problems encountered in training.

Many approaches have been used to train the person with chronic lung disease. To be successful, the program should be tailored to the individual's physical abilities, interests, resources, and environment. For general application, techniques should be simple and inexpensive. As in normals and other patients, benefits are largely specific to the muscles and tasks involved in training. Patients tend to do best with activities and exercises for which they are trained. Walking programs are particularly useful. They have the added benefit of encouraging patients to expand social horizons. In inclement weather, many can walk indoors (e.g., at shopping malls). Other types of exercise (e.g., cycling, swimming) are also effective. Patients should be encouraged to incorporate regular exercise into daily activities they enjoy (e.g., golf, gardening). Since many persons with chronic lung disease have limited exercise tolerance, emphasis during training should be placed on increasing endurance. Changes in endurance with rehabilitation are often greater than changes in maximal exercise tolerance and allow patients to become more functional within their physical limits. Increase in maximum exercise is also possible as patients gain experience and confidence.

Exercise Prescription

Selecting a training target based upon a predetermined percentage of predicted maximal heart rate or ($\dot{V}O_2$) is a well-established practice for normals or patients without underlying pulmonary disease. However, in patients with chronic lung diseases, the best method of choosing an appropriate training prescription is less clearly defined. Exercise tolerance in pulmonary patients is typically limited by maximal achievable ventilation and breathlessness. Such patients frequently do not reach their limits of cardiac or peripheral muscle performance.

Much controversy exists regarding the appropriate training intensity target for patients with chronic lung disease. Use of a target heart rate has been advocated by some, although it is recognized that such a target may not be reliable for patients with more severe disease. Many patients with lung disease can be trained at a high percentage of maximal exercise tolerance, with work levels approaching or even exceeding the maximal level reached on the initial exercise test. In a study of 52 patients with moderate to severe COPD, patients were able to perform endurance exercise testing at an average workload of 95 percent of their baseline maximum. After 8 weeks of training, these patients were training at 86 percent of the baseline maximum. In fact, many patients with severe COPD were exercising at levels exceeding their baseline maximum. In another study that examined 59 patients with moderate to severe COPD who trained at levels near their ventilatory limits, a mean peak exercise ventilation of 100 percent of measured maximal voluntary ventilation was achieved after 12 days of training and at 3 months of follow-up. These findings suggest that even patients with advanced disease can be trained successfully at or near maximal exercise levels.

Based on the findings noted previously, some pulmonary rehabilitation programs define exercise targets and progression during training more by symptom tolerance than heart rate, work level, or other physiological measurements.

Ratings of perceived symptoms (e.g., breathlessness) help teach patients to exercise to "target" levels of breathing discomfort. A typical approach is to begin training at a level that the patient can sustain with reasonable comfort for several minutes and then to increase the time or exercise level according to symptom tolerance. Patients are encouraged to exercise daily and increase exercise duration up to 15 to 30 minutes of continuous activity. This graduated program helps patients to achieve a goal of improved tolerance for tasks of daily living, which often require a period of sustained activity.

Blood-Gas Changes

A major problem in planning a safe exercise program for patients with lung disease is the potential for worsening of hypoxemia with exercise. Patients who are not hypoxemic at rest may develop changes in arterial oxygenation that cannot be predicted reliably from resting measurements of pulmonary function or gas exchange. Normal individuals do not become hypoxemic with exercise. In patients with obstructive lung disease, Pa_{O_2} changes unpredictably during exercise. In patients with mild COPD, Pa_{O_2} typically does not change with exercise; in fact, it may even improve. However, in patients with moderate to severe COPD, Pa_{O_2} may increase, decrease, or remain the same. Patients with interstitial lung disease commonly develop worsening oxygenation with exercise.

Based on these observations, it is important to evaluate a patient's oxygenation status both at rest and during exercise. Such testing is also used to prescribe oxygen therapy at rest and with physical activity. With the availability of convenient, portable systems for ambulatory oxygen delivery, hypoxemia is not a contraindication to safe exercise training.

Other Types of Exercise

Exercise programs for pulmonary patients typically emphasize lower extremity training (e.g., walking or cycling). Since exercise conditioning is largely specific to the muscles and tasks involved in training other forms of exercise may be particularly valuable for persons with chronic lung diseases.

Upper Extremity Training

Many patients with chronic lung disease report disabling dyspnea with daily activities involving the upper extremities (e.g., lifting, grooming) at much lower work levels than with the lower extremities. Upper extremity exercise is accompanied by a higher ventilatory demand for a given level of work than is lower extremity exercise. Given the aforementioned muscle specificity of training, upper extremity exercises may be important in helping pulmonary patients cope better with common daily activities.

Ventilatory Muscle Training

The potential role of ventilatory muscle fatigue as a cause of respiratory failure and ventilatory limitation in patients with chronic lung disease has stimulated attempts to train the ventilatory muscles. Techniques of isocapnic hyperventilation, inspiratory resistive loading, and inspiratory threshold loading have been shown to improve function of the respiratory muscles in both normals and patients. In normals, respiratory muscle function does not limit exercise tolerance; therefore, specific respiratory muscle training is unlikely to be of clinical benefit. In patients with COPD, the patient group most extensively studied, improvement in general exercise performance from ventilatory muscle training alone has not been demonstrated consistently. Thus, the role of respiratory muscle training as a routine component of pulmonary rehabilitation has not been clearly established.

Psychosocial Support

An essential component of pulmonary rehabilitation is psychosocial support, the goal of which is to help patients combat progressive feelings of hopelessness and an inability to cope with chronic, progressive disease. Depression is common in patients with chronic pulmonary disorders, as are anxiety (especially anxiety over dyspnea), denial, anger, and isolation. Patients become sedentary and dependent upon family members, friends, and medical services to provide for their needs. Excessive concern over other physical problems and psychosomatic complaints arise. Sexual dysfunction and fear are common and represent often unspoken consequences of chronic lung disease. Patients may also demonstrate cognitive and neuropsychological dysfunction, possibly related to or exacerbated by the effects of hypoxemia on the brain.

Psychosocial support is provided best by a warm and enthusiastic staff who can communicate effectively with patients and devote the time and effort necessary to understand and motivate them. Family members and significant others should be included in activities so that they can understand the disease and help the patient cope. Support groups are also effective. Patients with severe psychological disorders may benefit from individual counseling and therapy. Psychotropic drugs should generally be reserved for patients with more severe psychological dysfunction.

BENEFITS OF PULMONARY REHABILITATION

A growing body of evidence supports the expected results and benefits of pulmonary rehabilitation in the management of patients with chronic lung disease (Table 44-3). Evidence-based guidelines, published by a joint effort of the American College of Chest Physicians (ACCP) and the American Association of Cardiovascular and Pulmonary Rehabilitation (AACVPR), summarized clinical trials in pulmonary rehabilitation. The rehabilitation components included lower extremity training, upper extremity training, ventilatory muscle training, and psychosocial/behavioral interventions. Outcomes evaluated included dyspnea, quality of life, health care utilization, and survival. Based on this review, the Panel rated the highest level of supportive evidence regarding

Table 44-3

Results of Pulmonary Rehabilitation

Decreases in Medical resource utilization (e.g., hospitalizations, emergency room visits) Respiratory symptoms (e.g., breathlessness) Psychological symptoms (e.g., depression, fear)
Increases in Quality of life Physical activity Exercise tolerance (endurance or maximal level of activities of daily living) Knowledge Independence
Return to work possible
No change in lung function
Possible prolonged survival

documented improvements in lower extremity exercise training and in dyspnea after pulmonary rehabilitation. Other positive recommendations included the inclusion of upper extremity exercise training and the improvements in quality of life and health care utilization after pulmonary rehabilitation.

Two meta-analyses evaluated the effects of respiratory rehabilitation on exercise capacity and health-related quality of life. In a review of 14 randomized controlled trials employing systemic exercise as the primary intervention for at least 4 weeks for COPD patients, Lacasse and coworkers found significant improvements for dyspnea and mastery as two important aspects of health-related quality of life, and for maximal and functional exercise capacity. However, functional exercise capacity demonstrated heterogeneity that could not be explained by the sensitivity analyses performed. Cambach and coworkers reviewed 18 controlled studies evaluating the long-term effects of pulmonary rehabilitation on patients with asthma and COPD. Significant improvements were found for exercise tolerance (6-minute walk) and in dyspnea, fatigue, emotion and mastery measures of health-related quality of life. The authors noted heterogeneous results in improvements in maximal exercise capacity.

Several published randomized trials demonstrate important and significant benefits of pulmonary rehabilitation for patients with COPD, including improvements in exercise performance, symptoms, and quality of life. In a clinical trial of rehabilitation versus an education program in 119 patients with COPD, Ries and coworkers reported a highly significant improvement in exercise endurance after rehabilitation that was maintained up to 18 months later. This was associated with a significant decrease in perceived symptoms of breathlessness and muscle fatigue during exercise as well as improvement in maximum exercise tolerance, breathlessness with daily activities, and self-efficacy for walking. A follow-up trial of maintenance versus routine care after pulmonary rehabilitation was conducted in 164 patients with chronic lung disease. Similar to previous studies, both groups demonstrated decline in benefits over the first year of follow-up, although they remained above pre-rehabilitation levels. In comparison to 81 routine care patients, the 83 patients receiving maintenance care of weekly telephone contacts and monthly reinforcement sessions after pulmonary rehabilitation sustained improvement in maximum exercise tolerance at 1-year follow-up. However, a decline in measures of dyspnea, depression, self-efficacy, quality of life, and health care utilization were also observed in both groups. At 2-year follow-up, with both groups receiving routine care, there was a progressive decline in exercise tolerance and other measures of symptoms and morbidity.

In another randomized trial, Berry and colleagues demonstrated the added benefit of a longer-term exercise (18 months) compared to short-term training (3 months) in 140 patients with COPD. Patients in the long-term training group maintained greater improvements in measures of physical function and self-reported disability.

In a randomized controlled trial of 79 older adults with COPD, Emery and coworkers investigated physiological, psychological, and cognitive outcomes of a 10-week pulmonary rehabilitation program. Significant improvements were observed at program completion among 29 patients receiving exercise training, education, and stress management in measures of cardiopulmonary endurance, anxiety, illness-related physical and emotional impairment, and verbal fluency. These changes were not observed among patients receiving a combined intervention of education and stress management or patients with no intervention at all, suggesting that education without exercise may have limited value for the physical and psychological functioning.

Benefits and cost savings associated with pulmonary rehabilitation have been demonstrated not only in highly specialized centers, but also in community-based settings. A collaborative study of 647 patients in 10 centers in California reported significant improvements in dyspnea and quality of life with substantial reduction in health care utilization over 18 months of follow-up (Fig. 44-1).

PULMONARY REHABILITATION AND LUNG SURGERY

Pulmonary rehabilitation has been applied primarily in the medical management of patients with stable, chronic pulmonary disease. In recent years, surgical options for patients with severe, disabling lung disease have been used more frequently. Lung surgery in these patients represents new challenges and may further compromise already reduced lung

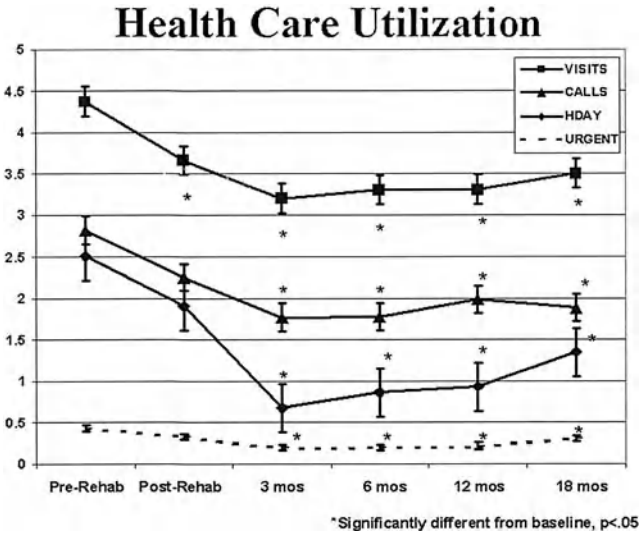

Figure 44-1 Changes in health care utilization over 18 months after pulmonary rehabilitation in a collaborative study of 647 patients in 10 centers in California. Results are presented as mean ± SE. *(From California Pulmonary Rehabfl itation Collaborative Group: Effects of pulmonary rehabfl itation on dyspnea, quality of life and health care costs in California. J Cardiopulmonary Rehabfl 24:52–62, 2004., with permission).*

function. Pulmonary rehabilitation has been found to be a valuable adjunct in preparing the patient for surgery or in postsurgery recovery.

Lung Transplantation

Pulmonary rehabilitation is recommended and used commonly in both the preoperative and postoperative phases of lung transplantation programs. Although the general strategies of rehabilitation may be similar, the individual and program goals and specific program components differ.

Pretransplant Rehabilitation

Patients with advanced lung disease who are candidates for lung transplantation are usually evaluated by the transplant team and then referred for pulmonary rehabilitation after their transplant candidacy is approved. Rehabilitation staff evaluate the patient to assess needs and plan an appropriate program that can be maintained throughout a waiting period, which may last months to years. Since these patients have advanced disease with limited life expectancy, the goals in the preoperative period differ from those that typically apply to rehabilitation in chronic lung disease (Table 44-4).

The overall goals of pretransplant pulmonary rehabilitation are to maintain function, monitor disease progression, prevent complications, provide education about the underlying lung disease and lung transplantation, and offer psychosocial support for patients and families in coping with the stresses of waiting for a potentially life-saving procedure. The exercise training program may be similar to that provided to other chronic lung disease patients, with the exception that

Table 44-4

Goals of Pulmonary Rehabilitation in Lung Transplantation

Pretransplant
- Maintain and increase mobility and exercise tolerance
- Monitor disease progression
- Prevent complications
- Provide education about
  - Underlying disease
  - Transplantation procedures
  - Self-care and self-assessment
- Provide psychosocial support during waiting period for patients and families

Posttransplant
- Improve physical work tolerance
- Monitor clinical status and assess symptoms and oxygenation
- Prevent complications
- Reinforce self-care and self-assessment
- Encourage compliance with medical regimen
- Provide psychosocial support for adaptation to new demands and expectations

patients with primary pulmonary vascular diseases do not typically participate in exercise or other physical activities because of the increased risk of sudden death. Although patients may have some initial improvement in exercise tolerance or endurance as they begin rehabilitation, the primary goal for these patients is to maintain mobility and exercise capacity. Exercise sessions also provide an excellent means to monitor disease progression and to detect, at an earlier stage, problems that commonly occur (e.g., increased breathlessness or reduced arterial oxygenation with exercise).

The goals of education in the pretransplant period are to teach patients about their underlying lung disease, the transplant procedure itself, and expectations following transplantation. Patients can also be taught techniques for self-care and self-assessment that will be useful before and after surgery. The psychosocial stresses of waiting for transplantation are considerable. Many patients feel as though their lives are "on hold." Some may have moved away from family and social support networks to live close to the transplant center. Providing support for patients and families during this time, whether through formal group support sessions or informal contact with supportive staff and other patients, helps patients cope better with these problems.

Posttransplant Rehabilitation

After lung transplantation, patients must learn to cope with a new level of function, new expectations, and a new set of

problems. Rehabilitation for patients in this phase can facilitate physical reconditioning, help implement self-care and assessment techniques, and facilitate coping with the psychosocial adaptations to a new life-style.

Goals of exercise training after rehabilitation are improved physical work tolerance and continued assessment of symptoms and oxygenation as early warning signs of complications, including rejection and infection. Educational goals are focused on self-care and assessment and the importance of compliance with a new medical regimen. Psychosocial support can assist with adaptation to a new set of stresses related to additional demands and expectations from both patients for themselves and significant others. Patients who are used to being sick, disabled, and cared for by others may now be expected to be well, independent, return to work, and provide support for others.

Lung Volume Reduction Surgery

Recently, there has been a resurgence of interest in lung volume reduction surgery (LVRS) in the treatment of patients with severe emphysema. Pulmonary rehabilitation has been recommended as an important modality in the evaluation for and preparation of patients for this procedure as well as in the postoperative recovery phase. Since these patients have severe, disabling chronic lung disease, they are typically good candidates for pulmonary rehabilitation. Enrolling patients in rehabilitation prior to surgery has the advantage of optimizing their functional status, improving physical and psychological symptoms, helping them learn more about their disease and alternative treatment options, and improving their skills for coping and actively co-managing their disease. Patients can then make an informed decision about surgical treatment based upon their optimal level of baseline function. After surgery, similar to the post-transplant period, rehabilitation helps patients to adapt to new levels of function and to reassess symptoms and oxygenation needs.

The National Emphysema Treatment Trial (NETT), a multicenter, randomized clinical trial of medical therapy versus medical therapy plus LVRS, evaluated the benefits and risks of LVRS in patients with severe bilateral emphysema. All patients enrolled in the NETT completed 6 to 10 weeks of pulmonary rehabilitation prior to randomization into medical therapy or medical therapy plus LVRS and participated in a maintenance program of additional rehabilitation after randomization. Results from the prerandomization phase demonstrated significant improvements in exercise tolerance, symptoms and quality of life following pulmonary rehabilitation.

Rehabilitation after Lung Resection

Patients who undergo pulmonary resection frequently experience a significant increase in symptoms and reduced functional status. This is particularly true for patients with underlying chronic lung disease. Most commonly, surgery is used to treat patients with thoracic neoplasms who are deemed to have resectable disease and are operative candidates. Following resection, these patients with already limited lung function have to learn to adapt to a new, lower level of function.

Similar changes may be observed in patients who undergo radiation therapy. Patients in a stable phase of their treatment or in remission may be appropriate candidates for pulmonary rehabilitation. Improvement in health status, physical and psychological symptoms, exercise tolerance, and quality of life—as well as reduced health care burdens—are potential benefits. These patients' survival may be as limited by their underlying lung disease as by their treated malignancy.

SUMMARY AND FUTURE OF PULMONARY REHABILITATION

Pulmonary rehabilitation has been well established as a means of improving functional status and reducing the disability and economic burden of the growing number of patients with chronic lung diseases. In adopting a broad rehabilitation medicine perspective, such programs provide interdisciplinary expertise directed toward the needs of the individual disabled patient.

Much of the experience in pulmonary rehabilitation has been in patients with COPD. However, it is clear that similar benefits can result for patients with other disabling pulmonary conditions. Pulmonary rehabilitation may also play an important role in the preoperative evaluation, preparation, and postoperative recovery of patients undergoing surgical procedures, including lung transplantation, lung volume reduction surgery, and lung resection.

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45
CHAPTER

The Biology of Asthma

Sameer K. Mathur • William W. Busse

Asthma is characterized by intermittent airflow obstruction, airway inflammation, and bronchial hyperresponsiveness. This disorder affects an estimated 5 to 10 percent of the population, and as such is a major health care issue in most Western countries. A precise definition of asthma remains elusive, partly because the cause of this disease has yet to be found. Moreover, it is entirely possible that asthma is not a distinct disease, with a discrete etiology, but rather a "syndrome" with a variety of phenotypes in which various precipitating factors result in similar clinical, physiological, and pathological manifestations. This view of asthma likely explains its varied patterns and presentations, while explaining the common development of intermittent airflow obstruction, airway inflammation, bronchial hyperresponsiveness, and response to treatment.

Twenty years ago, the focus for the study and treatment of asthma had emphasized the mechanisms of acute bronchospasm with the treatment directed toward control of airway smooth muscle tone. With the exception of "severe asthma," the consideration of airway inflammation as an essential component of the disease had been largely neglected. However, with the use of fiberoptic bronchoscopy and biopsy, airway inflammation was found as an underlying feature of asthma and shifted therapeutic emphasis toward

anti-inflammatory medications. This has led to the current belief that bronchoconstriction, airway hyperresponsiveness, and airway inflammation are not mutually exclusive. Rather, acute and chronic inflammation, including airway edema, mucus secretion, and altered bronchial smooth muscle function are important, if not central, to the airflow obstruction and overall reactivity of the airways in asthma. Furthermore, it has been recognized that, although asthma covers a wide spectrum of clinical severity, inflammatory changes may be seen even in the airways of asymptomatic asthmatics. This chapter details our understanding of the mechanisms underlying acute and chronic inflammation in asthma. It focuses on the cellular components of the asthmatic inflammatory response and elucidates how the properties of these cells, and the mediators they produce, contribute to the pathophysiology of asthma.

MODELS OF MECHANISMS OF ASTHMA PATHOGENESIS

The bronchoconstriction and airway inflammation of asthma can be elicited by allergens, respiratory infections, and occupational exposures. Two models have been particularly instructive in the efforts to further understand the pathogenesis of asthma in these settings. They are the late-phase asthmatic response to antigen and the airway changes seen with viral respiratory infections.

Late-Phase Asthmatic Response

Inhalation of antigen can elicit responses to provide insight to allergic airway inflammation. This model for an asthmatic response results in a distinct pattern of airway limitation (Fig. 45-1). In the acute-phase response (APR), inhalation of allergen causes an immediate fall in lung function. This airway response is characterized by wheezing, coughing, and/or shortness of breath. The APR usually resolves within 1 hour and may be followed by a late-phase response (LPR), beginning about 4 to 6 hours after allergen challenge. The LPR often persists for 24 to 48 hours. An isolated LPR is rare and is found primarily in occupational asthma.

Late asthmatic reactions share a number of features with chronic asthma: increased airway responsiveness, decreased responsiveness to bronchodilator therapy, and bronchial inflammation. In asthma patients who exhibit the dual-phase features of an APR followed by the LPR, the LPR is not only more prolonged but also more intense. This is true even though the original apparent stimulus (allergen exposure) for bronchoconstriction has been removed.

The LPR is associated with the recruitment of inflammatory cells into the airway. Many have used bronchoscopy and bronchoalveolar lavage (BAL) to examine the cellular and mediator composition of the airways both before and after allergen challenge. In the past, airway eosinophilia appeared to exhibit the most significant correlation with LPR. However, recent studies with improved detection for basophils indicate that basophil levels correlate more strongly to the LPR in all forms of allergic inflammation, including airway, nasal, and skin (upon skin prick with allergen). Furthermore, in contrast to the BAL fluid from the APR with increased levels of histamine, tryptase, and PGD_2 (prostaglandin D_2) reflecting mast cell activation, the BAL fluid from a LPR contains histamine and tryptase while lacking PGD_2, which is consistent with products from basophil activation. Basophils have also been shown to release Th2 cytokines such as IL-4, IL-5, and IL-13. Thus, although several inflammatory cells including T cells and eosinophils accumulate during the LPR, it is currently thought the basophil is of central importance in mediating the LPR.

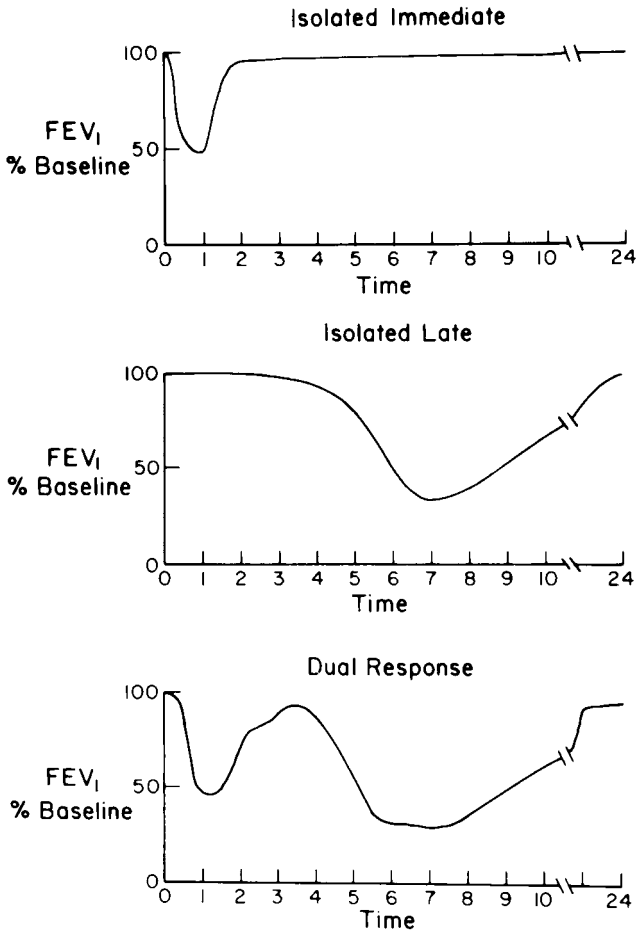

Figure 45-1 Acute and late phases of asthmatic responses (time in hours). (*Based on data from Lemanske RF Jr, Kaliner MA: Late phase allergic reactions, in Middleton E Jr, Reed CE, Ellis EF, et al (eds),* Allergy: Principles and Practice, *vol 1. St. Louis, Mosby–Year Book, 1993, pp 320–361, with permission.*)

Respiratory Viruses and Asthma

Viral respiratory infections increase asthma symptoms in many patients, particularly children. The viruses most typically associated with asthma in epidemiologic studies are respiratory syncytial virus (RSV) and rhinoviruses (RVs). Infection with "cold viruses" normally occurs in the upper airway and entails viral entry into a minority of bronchial epithelial cells. It has been difficult to determine the extent to which

actual viral infection and replication occur in the lower airway or whether viruses adversely affect asthma by indirect means. Experimental infection of subjects with respiratory viruses provides a useful model to establish the mechanisms in the pathogenesis of asthma.

Airway hyperresponsiveness to inhaled histamine may be increased in normal subjects as well as in allergic rhinitis and asthma patients during acute infection with RV, which can persist as long as 4 weeks after virus inoculation. Furthermore, bronchoscopy has shown a prominent acute neutrophilic response to RV infection in normal and allergic subjects. In a subsequent investigation of allergic patients who underwent segmental bronchoscopy and antigen bronchoprovocation 1 month before, during, and 1 month after RV infection, the viral infection also potentiated eosinophilic airway inflammation. Thus, the results of several studies suggest that viral respiratory infections not only increase airway hyperresponsiveness, but also change the pattern of allergic airway response, including the factors responsible for, or contributing to, the neutrophilic and eosinophilic inflammatory responses.

RVs stimulate the production of several mediators from respiratory epithelial cells and mononuclear cells, including IL-8, GM-CSF (granulocyte-monocyte colony stimulating factor), INF-γ (interferon-γ), and RANTES (regulated upon activation, normal T cell expressed). These cytokines and chemokines are important for the recruitment and activation of neutrophils and eosinophils. Thus, viral respiratory infection may modulate the airway environment or the interaction of components of airway inflammation, including cells and mediators, to promote allergic inflammation.

CELLS IN ASTHMA

The inflammatory response in the asthmatic airway is the manifestation of complex interactions between multiple cell types, both resident and recruited, and their molecular mediators. It is characterized by varying degrees of mononuclear cell and eosinophil infiltration, epithelial desquamation, mucus hypersecretion (and airway plugging), smooth muscle hyperplasia, and airway remodeling with subepithelial fibrosis. The presence or recruitment of inflammatory cells into the airway provides the basis for these changes. Each cell type exerts effector and regulatory functions in the pathogenesis of asthma as detailed in this section.

Mast Cells and Basophils

Mast cells are granulocytes generated from a nonmyeloid lineage derived from $CD34^+$ hematopoietic stem cells. Mast cells enter the peripheral circulation in an immature form and differentiate upon localization to a tissue compartment typically adjacent to an epithelial surface such as the skin, lung, and gastrointestinal tract. The differentiation requires IL-3 and the ligand for the c-kit receptor on mast cells, SCF (stem cell factor).

Two types of mast cells are found in humans. The cell subtypes are distinguished primarily by their tissue location and biochemical characteristics: mucosal mast cells (atypical) and connective-tissue mast cells (typical). MCT refers to mast cells containing the neutral protease tryptase alone, while MCTC denotes mast cells containing chymase in addition to tryptase and the other neutral proteases, carboxypeptidase and cathepsin G–like proteins. In the normal human lung, alveoli-associated mast cells are almost exclusively of the MCT type, which also predominate in the subepithelium of the bronchi and bronchioles. In vitro studies indicate that one role for tryptase in asthma pathogenesis includes the increase of airway smooth muscle responsiveness to histamine.

Mast cells are notable for expression of the high-affinity IgE receptor, FcεRI. IgE molecules are constitutively bound to these receptors on the surface of mast cells. Upon encountering an allergen, the antigen-specific IgE molecules are bound with allergen and the subsequent cross-linking of FcεRI receptors activates mast cells. There is the immediate release of preformed mediators including histamine and tryptase. In some mast cells, TNF-α (tumor necrosis factor-α and VEGF (vascular endothelial growth factor) may also be among the preformed mediators. This is followed by the synthesis of leukotrienes (primarily LTC_4), prostaglandins (primarily PGD_2), and cytokines, which all contribute to the inflammatory milieu as discussed below.

Basophils are also derived from $CD34^+$ hematopoietic stem cells via the myeloid lineage; however, in contrast to mast cells, these cells are typically found in the peripheral circulation. Basophils share some common features with mast cells in the expression of FcεRI and tryptase; however, both are expressed at much lower levels than the mast cells. In addition, basophils are also capable of an immediate release of histamine upon activation. It is currently thought that mast cell activation is involved in immediate allergic inflammation, whereas basophils are involved in the late-phase response.

Eosinophils

Eosinophils are granulocytes derived from $CD34^+$ hematopoietic stem cells. The cytokines IL-3, IL-5, and GM-CSF are involved in the stimulation of eosinophil production, growth, and maturation. IL-5 is particularly important in the development and terminal differentiation of eosinophils. Upon exposure to allergen, eosinophils are actively recruited into the airway predominantly by chemokines such as eotaxins. The migration of eosinophils to the airway is dependent on extravasation of peripheral blood eosinophils. This process is highly regulated and occurs via interaction between adhesion molecules on the endothelium (e.g., VCAM-1) and eosinophils (e.g., VLA-4). The activation of these integrins and subsequent recruitment of eosinophils to the airway is the result of cytokine and chemokine signaling, including IL-5, GM-CSF, eotaxin, and RANTES.

Eosinophils have a variety of cell surface receptors, including low-affinity IgE receptors (in contrast to the high-affinity mast cell IgE receptors), cytokine receptors such as the IL-5 receptor (IL-5R), which is thought to be specific for

eosinophils, and receptors for immunoglobulins and complement. Some of these molecules function in the primordial role of eosinophils in host defense against parasitic infectious agents. They are also likely, however, to be important in allergic diseases and asthma.

Upon entry into the airway, eosinophils are able to release numerous mediators including granule proteins, leukotrienes (primarily LTC_4), prostaglandins, and cytokines. Eosinophils contain primary and secondary granules. The primary granules contain Charcot-Leyden crystal protein. The secondary granules contain four principal cationic proteins: MBP (major basic protein) in the dense core, along with the matrix proteins ECP (eosinophil cationic protein), EDN (eosinophil-derived neurotoxin), and EPO (eosinophil peroxidase).

Peripheral blood eosinophilia is a prominent feature of asthma. Autopsy samples from the airways of asthma patients, even those who died of non-asthma causes, and biopsies from asthmatics, even with mild disease, also contain eosinophilic inflammatory cell infiltrates. Similarly, eosinophil numbers are increased in the BAL and tissue after segmental antigen challenge. Immunohistochemical studies have also demonstrated eosinophils and their granule products in the asthmatic airway, and elevated levels of ECP have been found in the BAL and sputum of asthmatics. These observations and several lines of evidence speak to the importance of the eosinophil in the asthmatic process. Among the most compelling are the positive correlation between the levels of blood and airway eosinophilia and the severity of asthma and the subsequent drop in eosinophilia upon effective treatment with corticosteroids.

The specificity of IL-5 for promotion of eosinophil activity led to studies in mice to antagonize IL-5 for the depletion of eosinophils, which resulted in differential effects on airway hyperresponsiveness depending on the mouse strain. The subsequent use of a humanized anti–IL-5 monoclonal antibody in clinical trials succeeded in significantly reducing peripheral blood eosinophil counts with only modest effects (approximately 50 percent reduction) on airway tissue eosinophil counts; however, there was no evidence for improved control of asthma. The lack of efficacy in asthma control has been attributed to deficiencies in experimental design. However, further study of the anti–IL-5 treatment has revealed significant reduction in measures of airway remodeling. Therefore, the role of eosinophils may be in the development of the chronic changes associated with asthma. Recently, two different models of eosinophil deficient mice were created and found to have conflicting results regarding the development of airway hyperresponsiveness upon allergen sensitization and challenge. Thus, the role of eosinophils in acute exacerbations of asthma remains unclear.

Neutrophils

Neutrophils are derived for the $CD34^+$ hematopoietic stem cells. Neutrophils are characterized by a multilobed nucleus and are normally found in the bloodstream and tissues. Neutrophils are terminally differentiated cells that are notable morphologically for their granules, whose synthesis and assembly occur only during early stages of neutrophil development. Primary (azurophilic) and secondary (specific) granules contain various antimicrobial enzymes, neutral proteases, and acid hydrolases. Neutrophils, in contrast to eosinophils, are natural residents of the lung, particularly the lung parenchyma. Airway neutrophilia can be observed in response to viral infections, during nocturnal exacerbations of asthma, and in the BAL fluid of allergic asthmatics 4 hours, but not 24 hours, after inhaled allergen challenge. Neutrophils contain or synthesize a number of molecules with the potential to damage airway tissue and, perhaps more importantly, to act as chemotactic factors or mediators for other inflammatory cells.

T Cells

T cells are thought to be a prominent source of cytokines in the asthmatic inflammatory response. In asthma, an increase in activated T cells is observed in the airway. Furthermore, increased numbers of activated BAL T cells have been correlated with increased bronchial responsiveness and numbers of eosinophils. These observations suggest that T cells may play a critical role is the pathogenesis of asthma by regulating or orchestrating the inflammatory response.

The study of T cells and their relationship to inflammation led to the discovery of "helper" $CD4^+$ T cell subsets called T helper-1 (Th1) and T helper-2 (Th2) cells. These subsets are distinguishable on the basis of their patterns of cytokine production. In addition, a Th0 has been defined which are naïve T cells that have not encountered antigen. Th1 cells are noted for the secretion of IL-12 and IFN-γ, whereas Th2 cells secrete IL-4, IL-5, and IL-13.

It follows that Th2 cells, by virtue of their associated cytokines, can specifically enhance allergic inflammation with promotion of IgE synthesis and eosinophil activation and accumulation. It has been proposed that allergic inflammation represents the predominant activation of Th2 cells and release of their proinflammatory cytokines. In accord with this notion, cells in the BAL fluid from patients with asthma have shown increased mRNA expression for both IL-4 and IL-5. This and other observations suggest that Th2 cells and their associated cytokines play a major role in orchestrating the inflammatory response in the asthmatic airway, in particular its IgE production (IL-4, IL-13), eosinophilia (IL-5), mucus secretion (IL-13), and airway hyperresponsiveness (IL-13).

Although in vitro experiments indicate that Th1 and Th2 cells inhibit the activity of the other, the analyses of animal models of airway inflammation and BAL fluid from human asthma subjects suggests that both Th1 and Th2 cells and their respective cytokines are present, although Th2 does appear to predominate. Given the role of IFN-γ in increasing the expression of adhesion molecules and antigen presentation molecules, it is likely that a coordinated Th1 and Th2 response coexists in asthmatic airway inflammation.

Recently, another subset of $CD4^+$ T cells has been identified: the T regulatory cell. T regulatory cells are characterized by high levels of CD25 cell surface expression, expression of

the FOXP3 transcription factor, and secretion of IL-10 and TGF-β. These cells are noted to have an immunosuppressive function for both Th1 and Th2 cells and are thought to be important in generating and maintaining tolerance to antigen. Furthermore, glucocorticoids or cytokines such as IL-6 are thought to increase or decrease, respectively, the activity of T regulatory cells. Thus, T regulatory cells may represent another critical component in the regulation of airway inflammation.

Macrophage and Dendritic Cells

Macrophage and dendritic cells are phagocytic cells capable of presenting antigen to T cells. Alveolar macrophages are present in abundance within the airway of normal and asthmatic patients and are known to play a critical role in the clearing of microbes from the airway. There are also suggestions that alveolar macrophages can suppress allergic inflammation in the airway by the secretion of Th1 cytokines, including IL-12, IL-18, and IFN-γ. In a rat model, the airway hyperresponsiveness of one strain could be suppressed with the adoptive transfer alveolar macrophage from another non-hyperresponsive strain. This supports a role for alveolar macrophage to modulate airway responses in asthma.

In contrast to the alveolar macrophage, dendritic cells can play either a proinflammatory or tolerogenic role in allergic inflammation. These functions correspond with two distinct subsets of dendritic cells, myeloid and plasmacytoid, respectively. The dendritic cells are present in the lung in an immature form, either adjacent to epithelial cells or in the interstitium. These immature dendritic cells encounter antigen and migrate to a local lymph node, where they mature, characterized by increased expression of MHC class II molecules and B7 costimulatory molecules. The plasmacytoid dendritic cells can then induce tolerance, possibly by inducing T regulatory cells or by providing inhibitory costimulatory signaling via PDL-1 (programmed death ligand-1). In contrast, myeloid dendritic cells are thought to be important both for the initial sensitization with allergen as well as for enhancing the inflammation upon repeat exposure to allergen. Interestingly, repeated exposure to antigen may bypass the requirement for dendritic cells to migrate to a lymph node. In mice, it has been observed that following repeat antigen challenge, the myeloid dendritic cell population increases in numbers significantly within the airway in a mature form. This suggests that these cells may be maturing and interacting with the influx of T cells (predominantly Th2) within the airway itself rather than migrating to a lymph node.

Airway Smooth Muscle Cells

Bronchospasm remains an important component of asthma, particularly acute asthma. Despite this long-standing recognition, the details of airway smooth muscle function, both in normal and asthmatic persons, are still under investigation. It is recognized that the airway smooth muscle contraction is a component of airway hyperresponsiveness. Relaxation of this smooth muscle contraction has been the predominant target of beta-agonist therapy for asthma. However, additional findings of airway smooth muscle cell proliferation and hypertrophy along with subepithelial fibrosis are observed. These changes are thought to be a consequence, in part, of smooth muscle effector functions triggered by inflammatory mediator signaling. Some of the airway smooth muscle immunoregulatory and effector functions are mediated by the secretion of cytokines, chemokines, and extracellular matrix components, including GM-CSF, TGF-β, RANTES, eotaxin, IL-8, MCP-1 (monocyte chemotactic protein-1), fibronectin, collagen, and laminin.

Epithelial Cells and Goblet Cells

Airway epithelium functions as much more than a simple anatomic barrier. These cells actively regulate fluid and ion transport in the airway as well as mucus production. One of the most important activities of the airway epithelium is mucociliary clearance of secretions in conjunction with foreign particles. In addition, epithelial cells also participate in inflammation with the release of several molecular mediators, including cytokines, chemokines, and lipid mediators. Furthermore, epithelial cells are capable of producing endothelins, which are a family of three related peptides with potent bronchoconstrictor activity. Some of the stimuli for endothelin secretion include IL-1, IL-6, IL-8, TNF-α, TGF-β and LPS (lipopolysaccharide). Endothelin secretion is inhibited by IFN-γ and glucocorticoid treatment.

Goblet cells are a component of the bronchial epithelium and comprise up to 25 percent of the epithelial surface. The primary function of goblet cells is to secrete mucin into the airway, which along with other proteins and lipids, produces a thin layer of lubrication in the airway (mucus). The epithelial cells and submucosal glands assist in the production of mucus components. The mucus traps particulate matter and debris within the airway and, in conjunction with the mucociliary clearance apparatus, is able to clear these products from the airway. In asthma, goblet cell hyperplasia and increased mucus production are typically observed. The increased numbers of goblet cells are derived from the proliferation and differentiation of epithelial cells. In asthma, several cytokine signaling pathways, including IL-9 and IL-13, induce goblet cell hyperplasia and increased secretion of mucin into the airway. The clinical sequelae are mucus plugging and obstruction.

MOLECULAR MEDIATORS

The above-mentioned cells are able to coordinate and regulate the inflammatory process with the synthesis and secretion of several different classes of molecular mediators. These mediators have a variety of functions as discussed below.

Cytokines

Cytokines are small-molecular-weight glycosylated signaling molecules secreted by a number of different cell types with

autocrine, paracrine, or endocrine signaling activities. The over 30 cytokines identified thus far are categorized as interleukins, interferons, and growth factors. Cytokine secretion is usually a brief, self-limited event. It may, however, require new mRNA and protein synthesis, which takes place over a matter of hours rather than seconds or minutes. A variety of cytokines have been implicated in the regulation of airway inflammation and thus in the pathogenesis of asthma (Table 45-1). Support for cytokine involvement in inflammation was obtained by the detection of these mediators in the airways of patients with asthma, particularly in bronchoalveolar lavage fluid after allergen challenge and in situ hybridization of retrieved cells or biopsy materials.

The overall effect of the complex cytokine network in the airway depends on a number of factors, including the relative abundance of the various cytokines, their ability to recruit and perpetuate the actions of inflammatory cells such as eosinophils and lymphocytes, and their ability to amplify inflammation by interacting with structural cells such as fibroblasts, endothelial cells, and epithelial cells. There is no question, however, that cytokines are key mediators in the pathogenesis of the chronic inflammation characteristic of asthma.

The recognition that cytokines may have key immunoregulatory activities in the pathogenesis of asthma has led to the development of specific therapeutics to inhibit their function. Currently, humanized monoclonal antibodies, anti-IL-5 and anti-TNF-α, have been used for the treatment of asthma. Neither has yet emerged as the "magic bullet" for the treatment of asthma, although each, in preliminary studies, has been shown to have some clinical efficacy, anti-IL-5 for the prevention of airway modeling and anti–TNF-α or improvement in lung function.

Chemokines

The chemokines are small-molecular-weight proteins, 8-12 kD, that are classified in four categories based on the organization of specific cysteine residues in their protein sequence: C, CC, CXC, CX3C. The predominant function of chemokines is the recruitment or chemotaxis of inflammatory cells. Some chemokines also have additional signaling function. There are corresponding families of chemokine receptors for each class of chemokines. Notably, there is considerable overlap and redundancy in the chemokines and their target receptors.

Since the localization of inflammatory cells into the airway is dependent to a large extent on chemotaxis via chemokine signaling, the chemokine receptors have become an attractive target for asthma therapy. There are currently chemokine receptor inhibitors for CCR5 as well as others in development as potential therapy for asthma.

IgE

Allergic inflammation plays a prominent role in the pathogenesis of asthma. The initial association of IgE with asthma was based on several epidemiological studies. With the increased understanding of the role of mast cell mediators in the pathogenesis of asthma, the importance of IgE in triggering mast cell activation and the resulting airway inflammation was underscored. This relationship between IgE levels and asthma led to the development of a humanized monoclonal antibody directed to IgE for asthma therapy. This antibody (omalizumab, Xolair) has been shown to be effective in the treatment of severe asthma, specifically allowing a significant reduction in dosage of corticosteroids.

Leukotrienes

The leukotrienes are a family of lipid compounds generated from the metabolism of arachidonic acid via the lipoxygenase pathway (Fig. 45-2). These compounds are typically not preformed; rather, they are rapidly synthesized within minutes following activation of the source cell. LTC_4, LTD_4, and LTE_4 are potent bronchoconstrictors that are produced by several cell types, including eosinophils and mast cells. The leukotrienes are also able to increase mucus secretion in the airway and facilitate a plasma leak generating edema in the airway. The use of leukotriene receptor antagonists (e.g., montelukast, Singulair) is currently recommended as a second-line agent in the treatment of asthma (behind inhaled corticosteroids).

Prostanoids

The prostanoids are a family of lipid compounds generated from the metabolism of arachidonic acid via the cyclooxygenase pathway (Fig. 45-2). Most of the prostanoids, i.e., PGD_2, PGF_2, and TxA_2, are potent bronchoconstrictors and can be produced by several cell types including eosinophils and mast cells. However, another prostanoid, PGE_2, has bronchodilatory and anti-inflammatory activity. The use of nonsteroidal anti-inflammatory medications to inhibit cyclooxygenase activity has not been shown to have an appreciable effect on airway inflammation. It has been observed that PGD_2 is the predominant prostanoid involved in asthma. Therefore, specific PGD_2 receptor antagonists are currently being developed to ameliorate some of the bronchoconstriction in asthma.

Nitric Oxide

The role of nitric oxide (NO) in the pathogenesis of asthma is unclear. NO is continually synthesized at low levels in the airways of normal subjects. Cell sources of NO in the respiratory tract include airway epithelial cells, smooth muscle cells, sensory nerves, endothelial cells, and macrophages. At low levels, NO is a bronchodilator and vasodilator that antagonizes endothelin and has protective effects in the airway. Higher levels of NO are found in asthma, secondary to increased inducible NO synthase expression. Higher levels of NO production may be detrimental to airway epithelium. This may be mediated by the ability of NO to react with superoxide anion in inflamed tissue to produce biologic oxidants that could contribute to ongoing tissue damage and chronic asthmatic inflammation. The production of NO is thought to reflect the level or severity

Table 45-1

Cytokines

Cytokine	Primary Source(s)	Primary Target(s)	Effects or Function
bFGF (basic fibroblast growth factor)	Endothelial cells	Fibroblasts	Proliferation of fibroblasts and extracellular matrix formation
G-CSF (granulocyte colony stimulating factor	Monocytes, fibroblasts, epithelial cells	Neutrophils	Proliferation and differentiation
GM-CSF (granulocyte-monocyte colony stimulating factor)	Macrophage, T cells	Eosinophils, neutrophils, macrophage	Proliferation, differentiation, activation, prolonged cell survival, and enhanced cytokine production Degranulation (eosinophils)
IFN-α (interferon)	Monocytes, macrophage	Virus-infected cells	Inhibition of viral replication
IFN-β	Monocytes, macrophage	Virus-infected cells	Inhibition of viral replication
IFN-γ	Th1 cells, CD8+ T cells, natural killer cells	Macrophage CD4+ T cells CD8+ T cells	Differentiation, activation, and expression of Fcγ receptor, MHC molecules, and cytokines Shift in cytokine profile to Th1 phenotype and expression of IL-2 receptor Increased cytotoxicity
IL-1	Monocytes, macrophage	Th2 cells CD8+ T cells B cells	Production of cytokines Production of cytokines and increased cell cytotoxicity Proliferation, differentiation, and Ig production
IL-2	CD4+ T cells	T cells	Proliferation, differentiation, production of cytokines
IL-3	T-cells	Hematopoietic stem cells	Proliferation and differentiation
IL-4	Th2 cells	B cells Th1 cells Th2 cells CD8+ T-cells Natural killer cells	Proliferation, activation, and production of MHC class II, IL-6, TNF, and CD23; class switching to IgE; enhanced production of IgE, IgG1, and IgG4; diminished production of IgM, IgG2, and IgG3 Inhibition of differentiation and IFN-γ production Differentiation Differentiation Inhibition of proliferation
IL-5	T cells	Eosinophils	Proliferation, chemoattraction, adhesion, activation, and degranulation

(*Continued*)

Table 45-1

(*Continued*)

Cytokine	Primary Source(s)	Primary Target(s)	Effects or Function
IL-6	Monocytes, macrophage	B cells	Maturation to plasma cells, class switching to IgA
		Monocytes, macrophage	Production of IL-1 and TNF-α
IL-7	Bone marrow stromal cells	Pre-B cells	Proliferation
		T cells	Proliferation
IL-8	Macrophage	Neutrophils	Chemoattraction and inhibition of adhesion
IL-9	Th2 cells	B cells	Enhanced response to IL-4
IL-10	T cells	Monocytes	Differentiation to macrophage
		Macrophage	Inhibition of MHC class II and adhesion molecule expression; inhibition of IFN-γ, TNF-α, and IL-4
IL-11	Bone marrow stromal cells	B cells	Similar to IL-6
IL-12	Monocytes, macrophage	Natural killer cells	Activation
		Th0 cells	Proliferation and production of IL-2
		Th1 cells	Production of IFN-γ and TNF-α
		Th2 cells	Inhibition of IL-4, IL-5 and IL-10 expression
IL-13	Th2 cells	B cells	Similar to IL-4
		Monocytes	Enhanced expression of MHC class II molecules and integrins; inhibition of IL-1 and TNF expression
IL-14	Activated T cells	Activated B cells	Proliferation of B cells and suppression of Ig secretion
IL-15	Monocytes, macrophage	T cells, natural killer cells	Proliferation and increased cytotoxicity; expression of ICAM-3
IL-16	CD8+ T cells	CD4+ T cells	Proliferation, chemoattraction
IL-17	CD4+ T cells	CD4+ T cells	Proliferation and expression of autocrine factors
IL-18	Macrophage	Activated B cells	Similar to IL-12
IL-19	T cells, B cells, Monocytes		Increased expression of IL-4 and IL-13
IL-20	T-cells	Keratinocytes	Proliferation

Table 45-1

(*Continued*)

Cytokine	Primary Source(s)	Primary Target(s)	Effects or Function
IL-21	CD4+ T cells	?	?
IL-22	Th1 cells, NK cells	Hepatocytes	Increased expression of acute phase reactants
IL-23	Macrophage, dendritic cells	T cells, NK cells	?
IL-24	Monocytes, T cells	?	?
IL-25	CD4+ T cells	T cells, epithelial cells	Increased expression of Th2 cytokines
IL-26	Th1 cells, NK cells	?	?
IL-27	Antigen presenting cell	Naïve CD4 + T cells	Proliferation
IL-28	Mononuclear cells	?	Antiviral activity
IL-29	Mononuclear cells	?	Antiviral activity
M-CSF (macrophage colony stimulating factor)	Monocytes, fibroblasts, epithelial cells	Hematopoietic stem cells	Differentiation of monocytes
PDGF (platelet derived growth factor)	Platelets, monocytes, macrophage	Fibroblasts, smooth muscle	Proliferation and chemoattractant for fibroblasts; active in wound healing, atherogenesis, and airway remodeling
SCF (stem cell factor)	Bone marrow stromal cells, fibroblasts	Mast cells	Chemoattraction, induction of histamine release, differentiation and proliferation
TGF-β (transforming growth factor)	Platelets, mononuclear cells	T cells B cells NK cells Fibroblasts Macrophage	Inhibits proliferation Ig class switch for IgA Inhibits cytotoxicity Proliferation and fibrosis Chemotaxis
TNF-α (tumor necrosis factor)	Monocytes, macrophage, granulocytes	T cells Neutrophils, endothelial cells, epithelial cells	Proliferation, increased cytokine expression Increased phagocytosis, increased MHC class I and II expression, increased adhesion molecule expression

SOURCE: *Busse WW, Lemanske RF. Advances in immunology: Asthma.* N Engl J Med *344:350–362, 2001.*

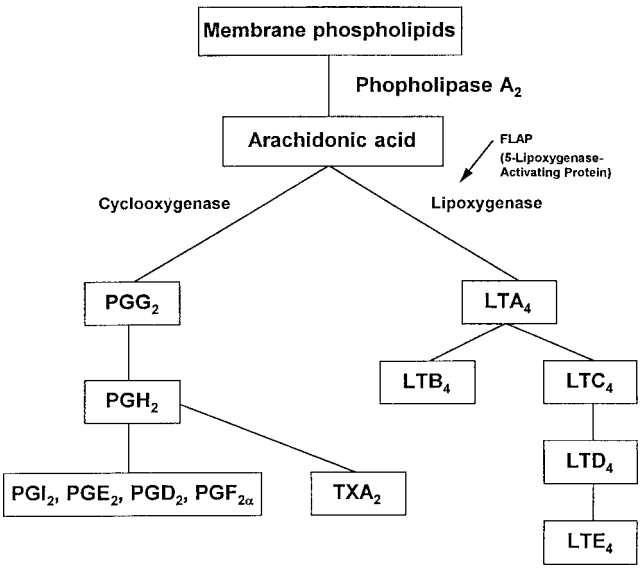

Figure 45-2 Pathways in the formation of prostaglandins, thromboxanes, and leukotrienes.

of airway inflammation. Thus, exhaled NO measurement has been utilized successfully as a tool to reflect the extent of airway inflammation as a measure of asthma control.

Granule Proteins

The granulocytes (mast cells, basophils, eosinophils, and neutrophils) are capable of releasing granule proteins, each of which has been proposed to play a role in the pathogenesis of asthma.

Insights into the kinetics and importance of mast cell mediators have been obtained from measurements of the levels of BAL histamine and tryptase. These studies have demonstrated that mast cell activation is an early event, with elevated BAL histamine and tryptase levels being seen 12 minutes after endobronchial antigen challenge and the levels of tryptase returning to normal by 48 hours. The levels of histamine remain elevated after 48 hours, raising the possibility that non–mast cells (e.g., basophils) are activated and produce the histamine at these later points. Furthermore, the BAL of allergic asthmatic subjects had only moderately elevated levels of tryptase at baseline but higher concentrations of tryptase following antigen challenge. Histamine is capable of inducing bronchoconstriction, increasing vascular permeability to cause edema, and increasing mucus secretion. The role of tryptase is not well established, although there are data to suggest that tryptase can activate inflammatory cells such as eosinophils, mast cells, and epithelial cells by cleaving a family of protease activated receptors (PAR) on their cell surfaces.

Major basic protein (MBP) is the principal protein constituent of eosinophil granules. It is toxic for epithelial tissues, induces airway hyperresponsiveness, and causes histamine release from basophils. Eosinophil cationic protein (ECP) is more cytotoxic to the epithelium than MBP and damages target cells by membrane pore formation. Eosinophil derived neurotoxin (EDN), as the name implies, damages myelinated neurons. Eosinophil peroxidase (EPO) differs from neutrophil and monocyte myeloperoxidases (MPOs); it decreases LTC_4 and LTD_4 degradation and causes histamine release from mast cells.

Neutrophil release of MPO and neutrophil elastase enhances their host defense function and is potentially injurious to normal tissues, including airway epithelium. The primary granules contain MPO and lysozyme as well as hydrolases and proteinases, which are important in tissue penetration by neutrophils. Secondary granules contain lysozyme and collagenases, which can also potentially damage airway tissue. Thus, the neutrophil granule proteins are considered toxic to the airway epithelium and tissue.

ROLE OF ADHESION MOLECULES IN INFLAMMATION

The recruitment of cells from the circulation and their activation in the airways, in part, involves cell-cell and cell-extracellular matrix communication, a process that is facilitated and regulated by adhesion molecules and cytokines. Adhesion molecules are cell surface proteins that have been grouped according to structural and functional similarities. Several categories have been identified, including the selectins, integrins, and members of the immunoglobulin (Ig) gene superfamily. These molecules interact with complementary binding sites (ligands) on respective cells, allowing them to adhere to epithelial or endothelial surfaces and, in some cases, enter the pulmonary interstitium.

Selectins

Three members of the selectin group have been identified: endothelial (E)-selectin, platelet (P)-selectin, and leukocyte (L)-selectin. Both E- and P-selectin are found on endothelial cells, while L-selectin is located only on leukocytes, including lymphocytes, eosinophils, monocytes, basophils, and neutrophils. L-selectin can also be shed from leukocytes and, like P-selectin, may be found in a circulating soluble form, in which it is potentially available to participate in inflammatory reactions.

Integrins

Integrins are found on the surfaces of leukocytes but not endothelial cells. They are classified according to the composition of their various subunits, including several different alpha and beta chains. One line of evidence for the importance of integrins in human disease is the finding that partial or total absence of a β_2-integrin subunit leads to a crucial defect of neutrophil recruitment to sites of inflammation and recurrent, potentially life-threatening bacterial infections in patients with leukocyte adhesion deficiency syndromes. Some integrin interactions that are

important in leukocyte–endothelial cell adhesion and signaling include very late antigen-4 (VLA-4) with lymphocyte function–associated antigen–1 (LFA-1), also known as CD11a/CD18, which also serves as a ligand for intercellular adhesion molecule–1 (ICAM-1) and ICAM-2. Not surprisingly, integrins have also been implicated in tissue repair, platelet aggregation, and tumor invasion, in addition to their other, more general roles in leukocyte binding and recruitment. Integrins are the primary mediators of cell-extracellular matrix adhesion. In asthma, integrins are also important for transendothelial migration of inflammatory cells into the airways.

Ig Gene Superfamily Members

Endothelial proteins of the immunoglobulin gene superfamily share functional as well as structural similarities with immunoglobulin domains. ICAM-1, ICAM-2, vascular cell adhesion molecule–1 (VCAM-1), platelet–endothelial cell adhesion molecule–1 (PECAM-1), and mucosal addressin cell adhesion molecule–1 (MadCAM-1) are all active in later steps of leukocyte–endothelial cell adhesion. These interactions are not final random events, but represent a coordinated effort of cells, cell surface molecules, and cytokines.

Mechanisms of Cellular Migration

There are three major interrelated steps in leukocyte recruitment from the circulation into tissues. They are categorized as adhesion, diapedesis, and chemotaxis (Fig. 45-3). Although the specific molecules and cytokines associated with these processes may vary, depending on the particular cells involved, the following general steps for leukocyte–endothelial cell and extracellular matrix interaction are thought to occur. As leukocytes move through capillary vessels, they initially contact the endothelial cell walls in a random fashion. In vascular beds in the region of inflammation, endothelial cells are "activated," with increased expression of adhesion molecules, such as E-selectin, on their cell surfaces. During flow through vessels with activated endothelial cells, leukocytes begin to "roll" along the endothelial cell luminal surfaces as a consequence of the interactions of adhesion molecules on leukocyte and endothelial cell surfaces. As leukocytes travel near sites of inflammation, locally produced cytokines up-regulate expression of cell surface proteins, including those active in cell adhesion and migration. These activated leukocytes then participate in "firm adhesion," much of which is mediated through interactions of leukocyte integrins (VLA-4, CD11a/CD18) and endothelial cell surface Ig gene superfamily members (ICAM-1, VCAM-1).

The next step is transmigration of leukocytes across endothelial cells and between endothelial cells into the surrounding tissues, i.e., diapedesis. Since there are cell-type specific differences in the expression of adhesion molecules, the pattern of adhesion molecule expression on the endothelium can confer selectivity in recruitment of specific leukocytes. For example, endothelial cell VCAM-1 binds mononuclear leukocytes and eosinophils, but not neutrophils. In contrast, both neutrophil and eosinophil migration across endothelial cells is enhanced by binding to ICAM-1. Various inflammatory mediators, including cytokines and chemokines, induce an increased expression of adhesion molecules and ligands that aid in the preferential recruitment of particular cell types into the tissues. The consequence of these interactions is the recruitment of inflammatory cells into target tissues such as the airway and, frequently, a complete or partial activation of these cells during their transit.

AIRWAY INFLAMMATION IN ASTHMA

Thus far, a description of cells, the mediators they release, and the mechanism for their recruitment into tissue have been presented, but how do they cooperate to generate asthma? It is likely that each of these components plays a role in the pathophysiology of an asthma exacerbation. However, given the heterogeneity in clinical and physiological features of asthma from patient to patient and from trigger to trigger, it is likely that the relative contributions of each cell type and/or mediator can vary. Furthermore, it is clear that multiple cells types are able to express similar sets of molecular mediators; thus, it

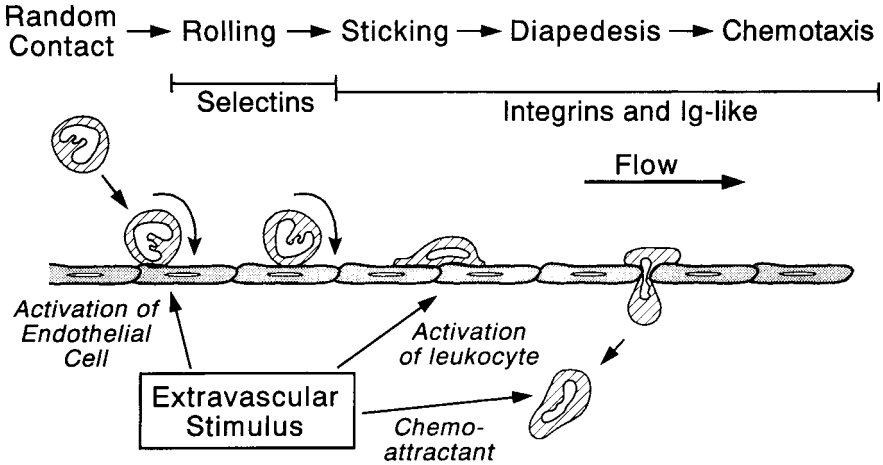

Figure 45-3 Mechanism of leukocyte vascular adhesion and migration into tissues and airways. Leukocytes ''roll" along endothelial cell layer and then selectively adhere firmly to endothelium near inflammatory sites. The adhering leukocytes then migrate into subendothelial tissue. Cell surface molecules (selectins, integrins, Ig superfamily members) facilitate the process. *(Based on data of Carlos TM, Harlan JM: Leukocyte-endothelial adhesion molecules. Blood 84:2068–2101, 1994, with permission.)*

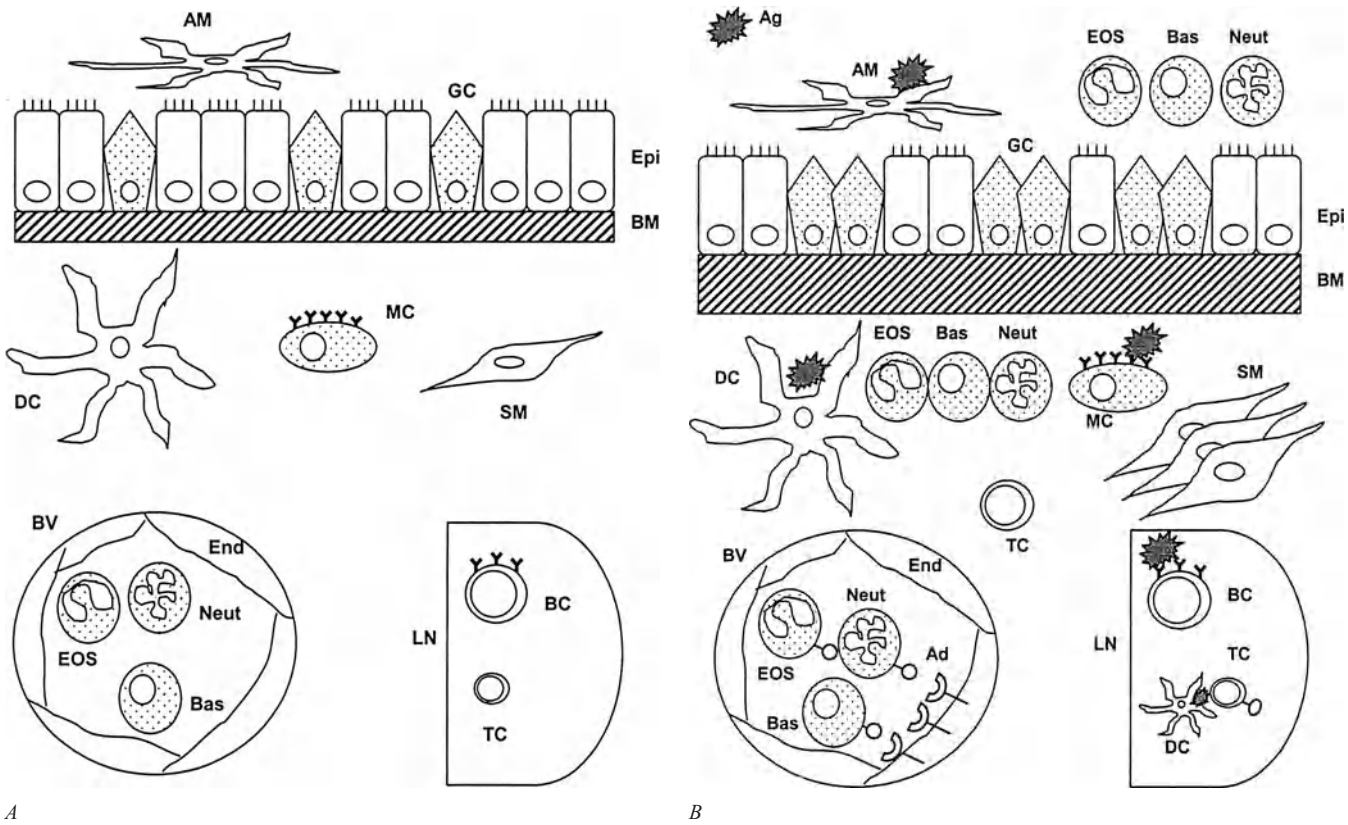

Figure 45-4 *A*. Distribution of cells in airway, lung parenchyma, and pulmonary lymph nodes. *B*. Introduction of antigen induces changes in the airway including: antigen interaction with alveolar macrophage, dendritic cells, mast cells, and B cells; goblet cell hyperplasia; basement membrane thickening; smooth muscle hyperplasia; recruitment of eosinophils, basophils, and neutrophils from the circulation into the lung parenchyma and airway facilitated by adhesion molecule interactions; antigen presentation to T cells in pulmonary lymph nodes; and, recruitment of activated T cells from lymph nodes into the lung parenchyma. AM, alveolar macrophage; GC, goblet cell; Epi, epithelial cell; BM, basement membrane; DC, dendritic cell; MC, mast cell; SM, smooth muscle cell; BV, blood vessel; End, endothelial cell; EOS, eosinophil; Neut, neutrophil; Bas, basophil; Ad, adhesion molecule; LN, lymph node; BC, B cell; TC, T cell; Ag, antigen.

is possible that different patterns of cell activation can result in the same effector responses.

In a quiescent state, the cells involved in the pathogenesis of asthma are resident in the airway tissue, peripheral circulation, or local lymph nodes (Fig. 45-4*A*). Following exposure to an asthma trigger, the inflammatory cascade is initiated resulting in cell activation, cell recruitment, cell hyperplasia, and release of mediators (Fig. 45-4*B*), which collectively yield the hallmark findings of asthma: airway obstruction, mucus secretion, and hyperresponsiveness.

CONCLUSION

Recent cellular and molecular advances have yielded a wealth of information regarding the biology of asthma. There is an extensive cadre of cell and molecular "players" involved in asthma. It is clear that allergic inflammation is the result of a complex interaction of numerous signaling and effector events. The orchestration of this inflammatory response comprises the participation of airway cells, mast cells, and lymphocytes; the generation of proinflammatory cytokines; the recruitment and activation of eosinophils and neutrophils; and the development of factors in the lung that sustain these events to cause persistent airway obstruction and injury. Many questions remain to be answered, including the genetic factors at work in the initiation and regulation of this process and an individual's susceptibility to this process. What is clear is the importance of airway inflammation to altered airway physiology in asthma and the relevance of this component of asthma as a principal therapeutic target. As further research begins to unravel more details regarding the inflammatory response, specific targets will be identified for the development of novel therapies to safely abrogate the inflammatory process and possibly cure asthma.

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46

Asthma: Epidemiology

Andrea J. Apter • Scott T. Weiss

Asthma is a clinical syndrome that affects 20 million Americans and accounts for 12.7 million medical visits yearly. One-third of those afflicted with asthma are children under the age of 18 years. It is estimated that roughly half of these children received their diagnosis prior to the age of 6 years. As a result, the origins of asthma are believed to have a clear genetic component that is often manifest in early childhood. The clinical course of this illness is influenced greatly by exposures, including respiratory viruses, indoor allergens, maternal tobacco smoke, and other physical and social aspects of the environment. Thus, this clinical disease has important consequences in childhood and may have important consequences for adult obstructive lung disease.

Asthma is an extremely common clinical problem and the most common cause of hospitalization for children in the United States. The estimated annual direct and indirect cost of asthma care is rising dramatically and totaled approximately $16 billion in 2001 in the United States according to the National Heart Lung and Blood Institute (NHLBI). In 2002 14.7 million school days were missed due to childhood asthma, while adults missed 11.8 million work days in the same year. The paradox of this illness is that despite important strides in understanding etiologic environmental factors and mechanisms of airway inflammation characteristic of the syndrome, its prevalence and morbidity remain unacceptably high. Although asthma morbidity and mortality rates have been steady over the last few years, the rates are dramatically higher than past 25 years ago and continue to be very significant, particularly for urban minority groups, low-income populations, and children.

The purpose of this chapter is to describe trends in asthma epidemiology, specifically prevalence, hospitalization, and mortality. In so doing, we examine potential reasons for these trends, and the recent research on the interactions of genes and environment. We also examine the relationship of the intermediate phenotypes of airway hyperresponsiveness and allergy to the asthma syndrome and consider a variety of risk factors for asthma occurrence. We conclude with a review of asthma natural history and the implications of the current trends.

DEFINITIONS AND PREVALENCE

The NHLBI defined asthma in 2002 as:

a chronic inflammatory disorder of the airways in which many cells and cellular elements play a role. The chronic inflammation causes recurrent episodes of wheezing, breathlessness, chest tightness, and coughing, particularly at night and in the early morning. These episodes are usually associated with widespread but variable airflow obstruction that is often reversible either spontaneously or with treatment.

Because asthma is a clinical syndrome, there is no gold standard for its diagnosis. As such, physicians employ nonstandardized algorithms for making the diagnosis, such as a history of wheezing or a parental history of asthma in conjunction with a favorable response to a bronchodilator to identify the asthmatic patient. Frequently, age, gender, and other patient characteristics such as smoking status or response to allergen may influence a physician's diagnosis. Rarely are tests of airway responsiveness systematically used to investigate symptomatic patients in the clinical setting.

In general, epidemiologic surveys have tended to rely on historical or questionnaire sources to identify patients with asthma. Asthma cases have been identified, either by physicians or surveys of population groups in whom the definition of who is asthmatic has been left to the patients themselves, surrogates, or the report of the diagnosis having been made by the patient's physician. Clearly, each of these methods of identifying asthma patients has inherent weaknesses. One must, therefore, assume that some bias in the reporting of cases is present and that the biases in each method of gathering data are different.

The National Health Interview Survey (NHIS) is an annual random population household interview survey that provides information on asthma prevalence in the United States. Its data demonstrate an almost doubling of asthma prevalence over the last quarter century, from 3.2 per 100 population in 1981 to 5.5 percent per 100 in 1996 (Fig. 46-1). In 1997 the NHIS questions and methodology were modified, limiting comparisons of prevalence before and after 1997. Instead of asking whether the respondent or a family member had had asthma over the past 12 months the newer version asks, "Has a doctor or other health professional ever told you that you had asthma?" (lifetime prevalence). Information about adults can no longer be obtained from a family member or proxy. If the response is affirmative, an "attack" question is asked, "During the past 12 months have you had an episode of asthma or asthma attack?" Beginning in 2001, if the lifetime prevalence response was positive, a point prevalence or "Current" measure was added asking, "Do you still have asthma?" The data from the "Current" question, is most comparable with previous data, but not exactly the same. It indicates no rise in asthma prevalence over 2001 through 2003. The prevalence in children under 18 years is higher than adults, for example, in 2003, 8.5 per 100 compared with 6.4 (Fig. 46-1).

There is a difference in prevalence by racial/ethnic groups. Until 1997 racial groups were classified as black or white with black population having slightly higher 12-month prevalence. In 2003, with an expanded racial and ethnic classification, the current prevalence was 9.2 for black non-Hispanics, 5.5 for Hispanics, and 6.9 per 100 for white non-Hispanics. It is noteworthy that the rate for Puerto Ricans was 14 per 100.

The current data show a significant modification of prevalence by gender, in that males tend to predominate in this younger age group, whereas gender ratios equalize in the pubertal years, and females predominate throughout the rest of the adult life. For example, the current prevalence for males between 5 and 14 years in 2003 was 10.8 per 100 compared with 8.1 for females, but in adults 18 years and older female prevalence is about twice that for males. Thus, age and gender play an important role in modifying disease prevalence. There does not appear to be substantial regional variation in prevalence rates.

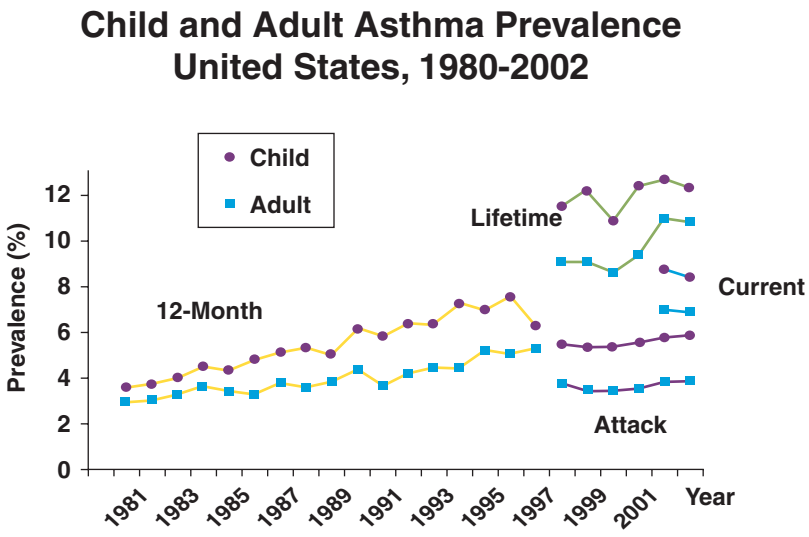

Figure 46-1 National asthma prevalence figures from the National Health Interview Survey (NHIS). This survey was redesigned in 1997. The previous measure of asthma prevalence was a 12-month period prevalence estimate; proxy responses were accepted and no doctor diagnosis was required. This measure was replaced by two others in 1997, both of which required a medical diagnosis of asthma, and proxy reporting was eliminated. One new measure was lifetime prevalence; the second measured the occurrence of an asthma episode or attack in the past 12 months (a period prevalence). In 2001, a point prevalence measure was added to assess current asthma prevalence. If the respondent answered ''yes" to the lifetime question, a second question asked, ''Do you still have asthma?" As can be seen in this graph, children have higher asthma prevalence than adults on all four measures.

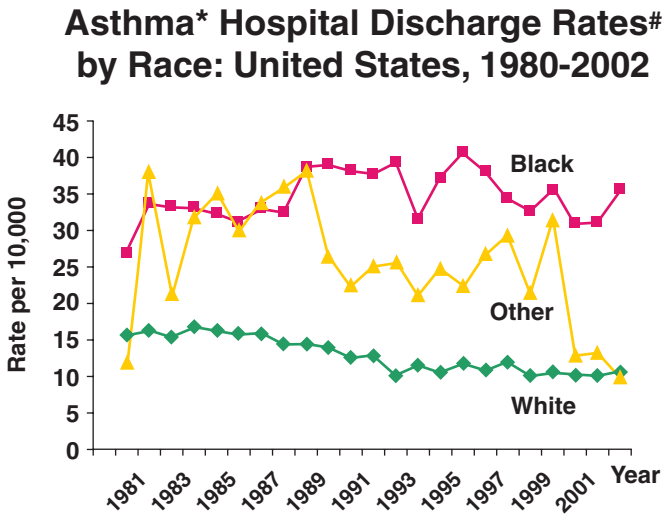

Figure 46-2 Asthma hospital discharge rates per 10,000 population from 1980 to 2002 for three racial groups; black, white, and ''other." During this period, asthma hospital discharge rates have been consistently higher for blacks than whites. Since the late 1980s, asthma *prevalence* has also been higher for blacks than whites, but not sufficiently higher to explain the higher hospitalization rates. The rates for the ''other" group (other than black or white) are more variable because of the relatively smaller size of the population. Source: National Hospital Discharge Survey, National Center for Health Statistics, Centers for Disease Control. *, first-listed diagnosis; #, age adjusted to 2000 US population.

HOSPITALIZATIONS AND EMERGENCY DEPARTMENT VISITS

Data from the National Hospitalization Discharge Survey suggest that hospitalization and emergency department (ED) visit rates for asthma have been reasonably stable from 1980 to 2002 even during a period of rising prevalence (Fig. 46-2). With respect to age, ED visits and hospitalizations are highest among children and particularly among children 0 to 4 years of age, in whom there were 59 hospitalizations and 162 per 10,000 ED visits in 2002. Females are hospitalized and make ED visits more frequently than males. What is particularly striking are racial/ethnic disparities in ED visits and hospitalizations. In 2002, the hospitalization rate for blacks was more than three times that for whites and the ED visit rate was almost five times higher than for whites. These differences are proportionally larger than the milder increase in prevalence in blacks over whites (Fig. 46-3). It is important to note that race data are frequently missing in reviewed records. Since 2000, race data have been absent from about 25 percent of hospital records.

TRENDS IN ASTHMA MORTALITY

Asthma mortality rates in the United States are quite low. Figure 46-4 describes the trends in asthma mortality in the United States between 1979 and 2001. There is an overall decline in deaths since 1998, although 11 percent of that decline can be attributed to the new coding. However, the downward trend in countrywide asthma mortality belies pockets of very high prevalence, morbidity, and mortality in inner-city minority populations.

These mortality rates do not represent a public health concern in an absolute sense, as the number of deaths is still very low. However, the rates do represent a clear public health concern because almost all asthma deaths are preventable, and certain urban and minority areas have extremely high mortality rates, suggesting inadequate care practices.

INTERMEDIATE PHENOTYPES

There are two intermediate phenotypes that contribute to the asthmatic syndrome: airway responsiveness and allergy. Both have a genetic component, and both are influenced by environmental factors. We will discuss these phenotypes and their interrelationship to each other and to asthma.

Airway Responsiveness

Airway responsiveness is measured by quantitating the decline in lung function caused by using increasing doses of a bronchoconstrictive stimulus, such as histamine or methacholine. When the patient's FEV_1 decreases by 20 percent from its initial value, or after a maximum stimulus dose has been administered, the test is terminated. The dose at which this drop occurs is called the *provocative dose* (PD_{20}). Individuals that manifest a PD_{20} at a low dose of stimulus are said to have increased airway responsiveness and are hyperresponsive to the inhaled agent.

Cross-sectional population-based surveys of children and adults conducted in many different countries and using a variety of techniques for measuring airway responsiveness have shown that the prevalence of airway hyperresponsiveness is roughly 20 percent in the general population. The prevalence of increased airway responsiveness exceeds the prevalence of asthma by from two- to fivefold.

These studies have also demonstrated that airway responsiveness is log normally distributed in the general population. An example of this is given in Fig. 46-5. In this population-based study of the distribution of histamine airway responsiveness, symptomatic or asthmatic subjects

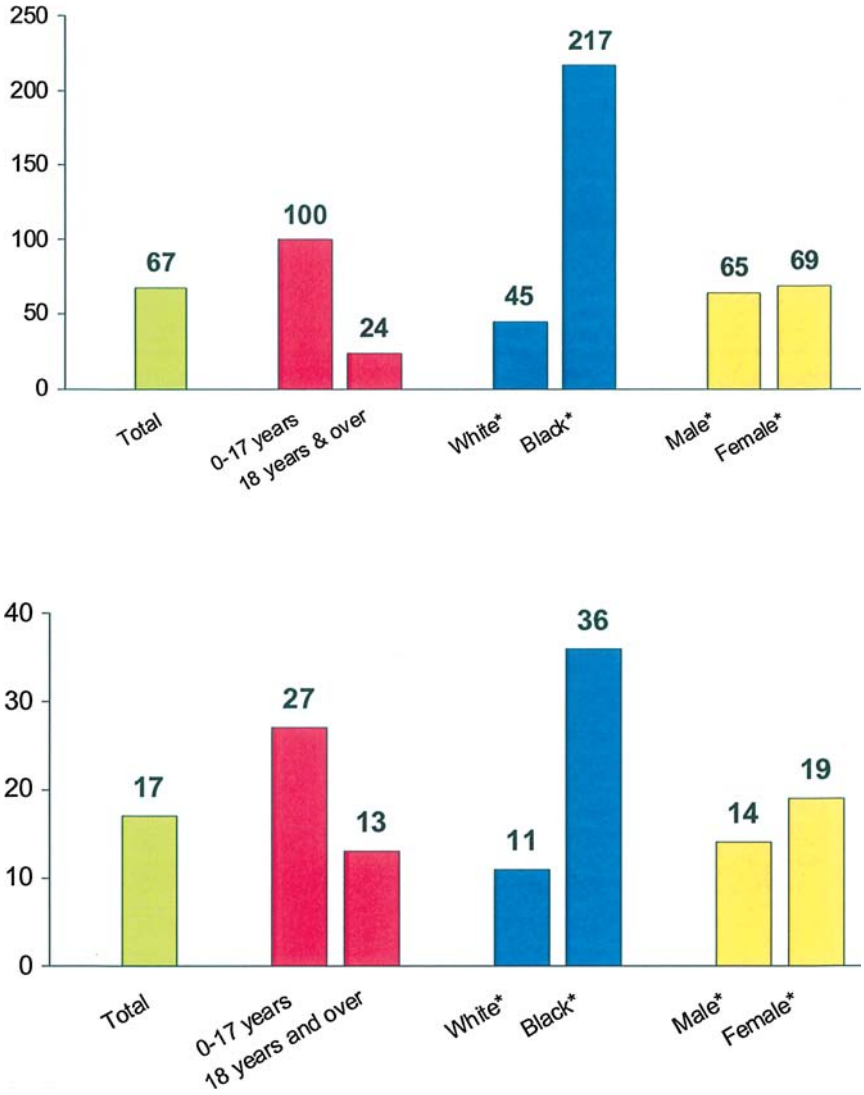

Figure 46-3 Asthma emergency department visits *(top)* and hospitalizations *(bottom)* per 10,000 populations, 2002. Hospitalizations are three times more frequent and emergency department visits almost five times more frequent among blacks. Hospitalizations are more frequent in children than adults. Source: National Hospital Ambulatory Medical Care Survey, National Center for Health Statistics, Centers for Disease Control. *, age adjusted to 2000 population.

appear at the more responsive end of the distribution, but there is considerable overlap with asymptomatic subjects. Other population-based studies have confirmed that a large number of asymptomatic subjects manifest increased airway hyperresponsiveness to this agent.

It has now been well demonstrated in studies of both children and adults that airway hyperresponsiveness antedates and predicts the development of asthma. Increased airway responsiveness carries at least twice the risk for the development of asthma in children and young adults. But increased airway responsiveness is a necessary, but not a sufficient condition for the development of asthma. In all likelihood, subjects who are genetically predisposed have increased airway responsiveness. They then encounter environmental stimuli that generate airway inflammation. The inflammation then moves them in the direction of greater responsiveness and the development of respiratory symptoms. This theoretical paradigm is graphically depicted in Fig. 46-6.

A variety of mechanical factors influence airway responsiveness. First, and most important, is the level of lung function. Individuals with lower levels of lung function are more likely to have increased airway responsiveness. In part, this is simply a mathematical phenomenon. Since airway responsiveness is expressed as a percent change from baseline, baseline value will obviously be important in determining the level at which an individual would be considered responsive (i.e., have a PD_{20}). This can be best understood with a simple mathematical example. A man with a 5-L FEV_1 would be required to drop his pre-challenge level of lung function by 1 L to achieve a PD_{20} for FEV_1. In contrast, a man with a 500-ml FEV_1 will only need to drop his FEV_1 by 100 ml to achieve a comparable PD_{20} for FEV_1. Other factors, such as the central deposition and distribution of the inhaled aerosol, the fact that airflow is inversely proportional to the fourth power of the airway radius, and baseline bronchomotor tone all contribute to the relationship of lung function to airway responsiveness. For this reason, airway responsiveness is likely to be increased at the extremes of age (i.e., in children and older adults) and reduced in young adults between the ages of 15 and 45 years.

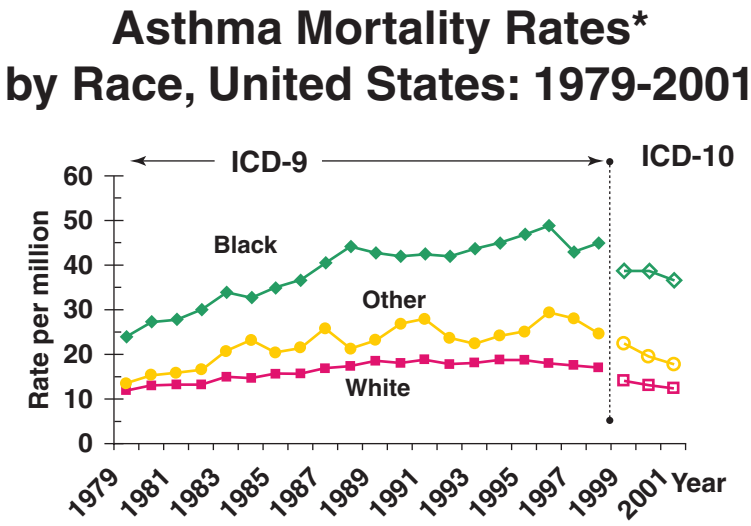

Figure 46-4 Asthma mortality trends. Since1998, both the overall number of deaths and the rate have clearly declined. However, a new mortality coding scheme was implemented in 1999. About 11 percent of the decline in asthma deaths can be attributed to the new coding scheme. This graph shows the difference in mortality rates by race. The green line is the mortality rate for blacks, the red line is for whites, and the yellow line represents all other races combined. Clearly, asthma mortality rates rose for each of these three racial groups during the period before 1995. Source: Underlying Cause of death: National Center for Health Statistics. *, age-adjusted to 2000 population.

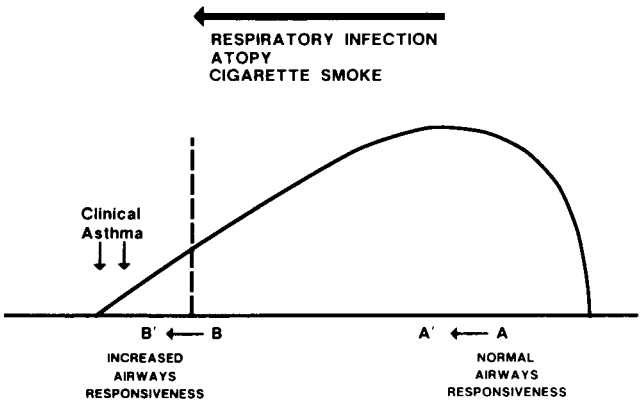

Figure 46-5 The log-transformed distribution of histamine airway responsiveness from a random population of subjects in the Netherlands. Note that symptomatic subjects are more common in the responsive end of the distribution. *(From Rijcken B, Schouten JP, Weiss ST, et al: The distribution of bronchial responsiveness to histamine in symptomatic and in asymptomatic subjects. Am Rev Respir Dis 140:615–623, 1989, with permission.)*

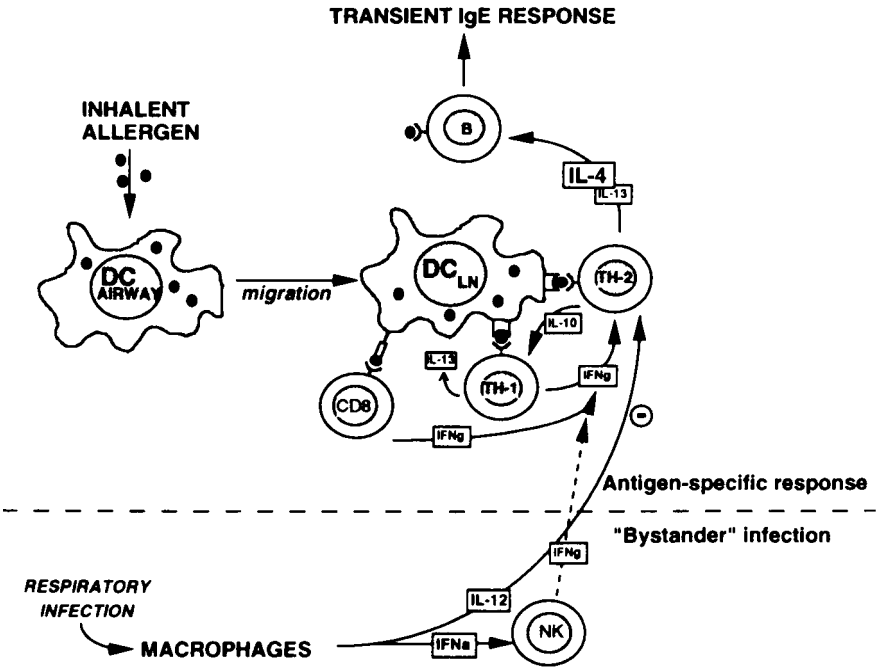

Figure 46-6 The effect of environmental exposures on the population distribution of airway responsiveness acting to move people in a more responsive direction. *(Reprinted from Brown RW, Weiss ST (eds): Seminars in Respiratory Infections, vol. 6, The Influence of Lower Respiratory Illness on Childhood Asthma: Defining Risk and Susceptibility. Seminar Respir Infect 6:225–234, with permission.)*

Allergy

Allergy refers to immediate (Type 1) hypersensitivity to environmental antigens. It is characterized by wheal and flare reactions to skin testing with common environmental antigens, usually with appropriate clinical history. Atopy is the demonstration of allergy and familial aggregation of this trait.

The pathophysiology of the allergic response has been explained by a conceptualization sometimes called the TH1-TH2 paradigm of CD4+ T helper cells. This model, summarized in Fig. 46-7, is also the basis for much recent clinical research seeking to understand the development of asthma. Antigen presenting cells (APCs) display peptide antigens, either allergen or infectious, on their cell surfaces for recognition by naïve T cells (TH0). TH0 differentiate into TH1 or TH2 cells, depending on the nature of the antigen, the characteristics of the APC, local concentration of cytokines, and other factors not fully understood. TH1 cells secrete IFN-γ, while TH2 cells secrete IL-4 and IL-5. For example, activation of APC by microbial products results in production of IL-12 and TH0 cells differentiate into TH1 cells. The presence of IL-4 results in differentiation of TH0 cells into TH2 cells. TH2 cells promote allergic inflammation through the production of cytokines including IL-4, IL-5, and IL-13. IL-4 and IL-13 induce B lymphocytes to differentiate into IgE-producing plasma cells. IL-5 secreted by TH2 cells results in eosinophilopoiesis and resistance to apoptosis. In addition to IFN-γ, TH1 cells produce tumor necrosis factor-β (TNF-β) and IL-2. A TH1 response results in activation of macrophages and natural killer cells and production of IgG1, which plays a role in complement binding and opsonization.TH1 and TH2 cells cross-regulate each other. That is, IFN-γ inhibits TH2 proliferation and IL-4 inhibits IFN-γ–induced macrophage activation. T-regulatory cells are recently characterized cells that inhibit TH1 and TH2 cells.

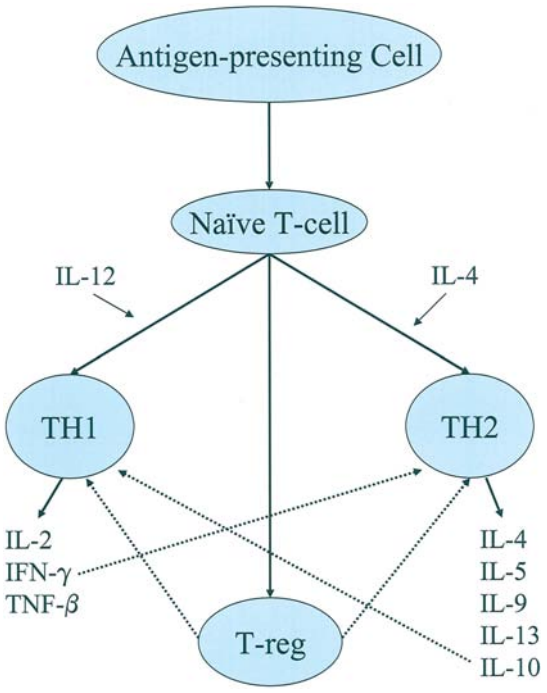

Figure 46-7 The TH1-TH2 paradigm. The figure depicts the developing immune system and the cytokines elaborated by mature CD4+ T lymphocytes in both Th1 and Th 2 cells. It also shows the central role of T-regulatory cells in controlling Th 1 and Th 2 clinical expression.

TH1 and TH2 cells also interact with cells of the innate immune system. The relationship of acute inflammation to chronic irreversible processes in targeted cells like smooth muscle, in airway remodeling, is another area of expanding interest to researchers.

Recent research suggests the TH1-TH2 paradigm is more complex than as described above. In mouse models of asthma, TH1 and TH2 cells have been observed to synergistically promote inflammation and airway hyperresponsiveness. In a birth cohort of 172 children, Heaton et al found allergic diseases and asthma associated with IL-4, IL-5, IgE production, and eosinophilia; but they also found IFN-γ production associated with airway hyperreactivity and skin-test reactivity. Additionally, the investigators found that cytokine patterns among the children were heterogeneous.

Clinical Markers of Allergy

A variety of clinical allergy markers have been utilized in epidemiologic studies of asthma based on the TH1-TH2 paradigm. Specific and total IgE, measured by skin or serologic testing, assess sensitization as well as exposure to environmental antigens and frequently are used to determine the prevalence of allergic responsiveness. Skin test reactivity depends on at least three separate factors: (1) an intact immune system; (2) the presence of IgE-sensitized mast cells that release mediators when exposed to antigen; (3) and skin that can respond to histamine with the development of an inflammatory response, including erythema and induration. Although these manifestations of an allergic response depend on prior exposure to environmental antigen, they do not measure or take into account the level of exposure in the environment.

Total serum IgE, although used in epidemiologic studies, has relatively limited value in the diagnoses of atopic diseases, with the exception allergic bronchopulmonary aspergillosis (see Chapter 49). Although total and specific IgE levels correlate with each other and with skin test results, no level of total IgE avoids misclassifying a significant proportion of those with and without allergic diseases. The limitations in clinical information imposed by these tests limit their utility when they are used epidemiologic studies.

Total and specific IgE measurements appear to be comparable in males and females. Both increase with age and peak at approximately age 15 years. After this time, there is a progressive decline, although the decline in skin test reactivity exceeds the reduction in total serum IgE, perhaps related to local factors in the skin.

Clinical Implications of the TH1-TH2 Paradigm

As indicated, processes that lead to the development of a hypothesized TH2-dominant phenotype in early life are

complex and the subject of ongoing research. It is believed that IgE responses to inhalant allergens are commonly set in early childhood. It is also believed that sensitization, i.e., production of IgE directed at environmental antigens, is not only a function of genetic susceptibility, dose, timing, and duration of allergen exposure, but also may reflect exposure to other environmental antigens, particularly microbial or viral organisms. One hypothesis of the development of atopic disease, the "hygiene hypothesis," states that the development of TH1 responses are dependent upon early exposure to infection. Since newborns are thought to have TH2-dominant immune responses, the development of TH1 responsiveness depends upon exposure to infection. That is, respiratory or gastrointestinal infections may stimulate macrophages to produce interferon-α and IL-12 that stimulate NK cells to produce IFN-γ, which would inhibit the development of a TH2-type response. The Tucson Epidemiologic Study, a birth cohort of 1246 subjects, noted that children who had a nonwheezing lower respiratory tract illness before 9 months of age had lower total IgE levels at 9 months and 6 years of age when compared with children who had no lower respiratory illnesses before 9 months of age. These children were also less likely to be atopic than those who had no lower respiratory tract illnesses. These investigators also found that children exposed to more siblings at home or to day care in the first 6 months of life, presumably exposed to more infections, were protected from the development of asthma between ages 6 and 13 years. Interestingly, investigators from Norway using a birth cohort of 2540 children followed until age 10 did not find a protective effect of early respiratory infections and the subsequent development of asthma or day care attendance. This research confirms the complexity of environmental influences on the immune system. The TH1-TH2 paradigm will need further exploration of its explanatory ability in asthma.

Relationship of Airway Responsiveness and Allergy to Asthma

Atopy and increased airway responsiveness are separate but related factors, both of which contribute to the development of the asthma phenotype. Over 80 percent of childhood asthmatics are atopic and there are many studies of exposure to allergen in sensitive individuals associated with bronchospasm. Thus, exposure and sensitization are linked to airway responsiveness.

But individuals may have airway hyperresponsiveness without atopic manifestations. The introduction of omalizumab, a recombinant, humanized anti-IgE antibody, is helping to elucidate the relationship of airway responsiveness and allergy. Omalizumab lowers total serum IgE and reduces eosinophils in sputum. In some studies it has allowed reduction of corticosteroid therapy, but in others it has failed to show reduce airway hyperresponsiveness, supporting the notion that airway hyperreactivity and allergy have other separate influences.

Current research explores the relationship between exposure to allergen and the subsequent development of asthma. A birth cohort design has been used to examine this relationship. Preventing loss of participants to follow-up makes these studies difficult to conduct. It is also difficult to measure exposure to allergen, that is, to quantify inhalation by subjects, while accounting for intermittent and varying exposure over time and place. Furthermore, there is an imperfect correlation among skin test reactivity, total serum IgE level, and peripheral blood eosinophil count, such that no single phenotypic marker completely defines the atopic state. Nevertheless, in studies of children with atopic parents, exposure is associated with the development of asthma. Sensitization, a reflection of exposure and genetics, has also been associated with the development of asthma. It is likely that where no relationship is found between exposure and the development of asthma, genetic influences are not present, i.e., the majority of the studied families are not atopic.

The Tucson Respiratory Study showed that patterns of wheezing and lung function tend to be established by age 6. Increased sensitization and higher levels of indoor allergens (exposure) may be important risk factors that have changed in the past 30 years, potentially accounting for some of the increased prevalence of asthma. Buildings with synthetic wall-to-wall carpeting, higher humidity, cloth-upholstered furniture, and bed-reduced ventilation have higher levels of house dust mites and other indoor allergens. Evidence from Scandinavian studies suggests that thermally tighter homes have been associated with higher indoor allergen levels. Other risk factors, notably maternal cigarette smoking, childhood respiratory infection, and the effects of poverty, likely contribute to the development of asthma. Such research demonstrates that environmental-gene interactions contribute to the development of asthma.

GENETIC SUSCEPTIBILITY AND GENE-ENVIRONMENT INTERACTIONS

Geneticists describe asthma as a complex disease, a disease in which many genes influence the development and phenotype of asthma, each having only a small influence. Since the human genome project was completed in 2000, remarkable advances have been made in identifying asthma genes.

There are two main types of genetic studies; linkage studies and association studies. In an association study, candidate genes are examined to determine a statistical association between polymorphism in the gene and asthma phenotypes; either cases and controls or trios can be used. These studies focus on known pathophysiology.

Linkage studies start with families with well-characterized phenotypes such as asthma. Genes within families are examined for linkage, the sharing of genes markers that may be located near or at the disease gene. Association studies are then used to follow up and "fine map" the linkage peak. These studies focus on novel genes.

To date five genes: ADAM 33, DPP10, PDH11, GPRA, and HLA-G, have been identified by linkage and fine

mapping. Fifteen other genes: IL1R, IL4, IL4RA, IL13, LTC4S, CTLA4, SCYA11, ADRB2, CD14, SPINK5, NOS1, STAT6, HLA-DRB, FCER1B, TGFB1, have been replicated in four or more genetic association studies. This is more than what has been found for many other complex traits.

ENVIRONMENTAL RISK FACTORS

Below we present some of the most important environmental risk factors for the development or exacerbation of asthma not discussed earlier.

Perinatal Factors

Prematurity carries an increased risk for the development of asthma. Prematurity also is associated with bronchopulmonary dysplasia, a disease characterized by increased airway responsiveness and asthma symptoms. Some investigators have found that low birth weight independent of prematurity has been associated with asthma risk. Note that blacks have higher rates of prematurity than whites; thus, prematurity may contribute to racial differences in asthma prevalence and morbidity. Young maternal age (i.e., less than 20 years) has not been shown to have a consistent independent association with the development of asthma. Despite much research, there is no conclusive evidence that breastfeeding influences atopic sensitization or the development of asthma.

Indoor and Outdoor Allergens

Indoor allergen sources include animals (cats, dogs, rodents); insects (mites, cockroaches); and fungi. Allergens from pets, particularly cats, are well-known precipitants of asthma exacerbations. There has been some recent investigation as to whether exposure to pets would be useful in preventing asthma, but most data indicate an increased risk of the development of asthma in homes of atopic families with pet exposure (i.e., a genetic-environmental interaction). It is noteworthy that animal allergens, particularly cat allergen, can be found in settled dust and in circulating air in homes, school classrooms, and other buildings that never housed a cat.

House dust mites are ubiquitous in all but very dry climates and sensitization to mite body and fecal allergens is associated with asthma. Mites infest fabrics, including mattresses, bedding, floor coverings, and upholstered furniture. The use of wall-to-wall carpets has increased exposure to mites. Covering mattresses and pillows with vapor-permeable fine weave materials, washing bedding in hot (greater than 130°F) water, vacuuming weekly, and removing carpets, especially from the bedroom, reduce mite levels.

Whether reducing exposure results in improvement in asthma outcome has been difficult to ascertain. Horak and coworkers randomly assigned 696 infants to receive mite-impermeable mattress encasings and their parents education about reduction of mite exposure. The control families received educational information in which avoidance of mite exposure was not presented. The investigators were unable to show a protective effect against the development of asthma. In contrast, a recent small study showed efficacy in prevention of asthma exacerbations. Adherence to the demanding protocols for control of mite exposure is difficult and whether control of exposure without other simultaneous interventions like control of environmental tobacco smoke (ETS) or pet exposure is not yet established.

Sensitization to cockroach has been shown to be associated with the development of asthma and asthma morbidity. Although the presence of this allergen is not limited to low-income homes, it has not been studied in more affluent settings. Removal of this allergen is difficult and more research is needed to evaluate the impact on asthma of allergen removal.

Although home and school dampness and the presence of fungi have been associated with reports of respiratory symptoms, it has not been determined whether mold allergens or mold-derived irritants or other factors are involved.

Some recent studies have employed multifaceted environmental interventions making assessment of individual factors impossible. None have been conclusively successful.

Day care establishments may be sources of indoor allergens, including pets, insects, fungi. They also may be sources of gram-negative bacterial endotoxin and lipopolysaccharides, which induce TH1 activity and have been hypothesized to be protective against the development of allergy and asthma. However, longitudinal studies have not consistently supported this notion. A recent study found that day care exposure was associated with increased risk of wheeze in the first 6 years of life in children with a maternal history of asthma. Day care and presumably endotoxin exposure were not protective in this study.

Outdoor allergens include trees, grass, and weed pollen constituents. Susceptible individuals may have increased asthma symptoms at times of pollination. For example, in the Northeast and Midwest grass pollinates in May and June and ragweed in late August and September. Pollens most closely linked to exacerbations of asthma in at-risk individuals are trees such as birch, oak and Western red cedar; grasses; and ragweed.

Smoking and Environmental Tobacco Smoke

Maternal cigarette smoking is a major risk factor for the development of asthma in the first year of life. The risk of developing asthma is roughly twofold in infants born to nonatopic mothers who smoke but increases to almost fourfold in infants of allergic parents with mothers who smoke. The predominant effect of maternal cigarette smoking is due to in utero exposure with decreased lung function at birth. A large population-based birth cohort study from Finland by Jaakkola and Gissler shows that infants of mothers who smoke carry increased risk of developing asthma through the first 7 years of life and only a small fraction of the effect during the first 7 years is mediated by fetal growth. It

is also clear that maternal cigarette smoke exposure is associated with a greater occurrence of lower respiratory tract infections.

ETS exacerbates asthma in children of all ages. Wilson and coworkers evaluated a cotinine-feedback behavioral intervention administered to caregivers which successfully reduced ETS exposure and health care utilization by children with asthma at one year follow-up. In adults, cigarette smoking is associated with the development of airway hyperreactivity. Whether this hyperreactivity represents asthma or COPD can be difficult to determine. Cigarette smoking in asthma produce a synergistic and accelerated decline in lung function. Additionally, the response to corticosteroid therapy used for asthma is reduced in active smokers.

Other Pollutants

Outdoor pollutants implicated in the development or exacerbations of asthma include ozone, sulfur dioxide, particulate matte, and components of motor vehicle exhaust. Measuring exposure to potential pollutants is difficult and correlating exposure with symptoms and exacerbations of disease is very expensive. Most monitoring of pollutants is from fixed external stations. Sometimes proxy measures of pollutant exposure, such as traffic counts, are used. Although potentially more accurate, monitoring of personal exposures is particularly difficult and expensive. Assessing which of the many possible simultaneous outdoor inhalants affects asthma morbidity is also a formidable task. Conclusions drawn from such data may be indirect. An example is the observation that asthma morbidity is highest among low-income individuals who tend to live in less desirable areas, which are frequently those with high traffic volumes and pollution.

There has been much interest in indoor environmental pollutants, such as nitrogen dioxide, sulfur dioxide, volatile organic compounds, and particulate matter, and their possible association with asthma, particularly in inner city homes. As with studies of outdoor pollution difficulties in measurement over time, controlling for other exposures such as allergens, infectious agents, and social determinants of health, while linking exposures to symptoms and physical findings makes research challenging.

Race/Ethnicity and Socioeconomic Status

Asthma prevalence and especially morbidity and mortality are higher in blacks than whites. Whether these racial differences in asthma prevalence, hospitalization, and mortality are solely due to inadequate treatment and access to medical care remains unclear, but there is indisputable evidence of unequal treatment of minority and low income groups by health professionals. Additionally, environmental factors that are the products of poverty, such as urban crowding, exposure to tobacco smoke or other pollutants or allergens contribute to these findings. In one recent paper, maternal exposure to community violence was related to asthma morbidity of children, even controlling for socioeconomic status, housing deterioration, and negative life events such as the death of a family member.

There is much current debate about the relative importance of social and genetic effects and/or gene-environment interactions that might account for the health disparity seen in asthma and other diseases. In most studies race and ethnicity are not well-defined and socioeconomic factors tend to be inseparably linked to ethnicity and race. Perceptions of a persons' race influence social experiences including those with the health system. In a recent survey, black and Hispanic women were more likely to report a doctor's diagnosis of asthma and less likely to report a diagnosis of hayfever or eczema. However, these women had higher mean total IgE levels and were more likely to be sensitized to aeroallergens. The investigators concluded that these findings could represent either under-diagnosis by medical personnel (e.g., fewer referrals to an allergist or other specialist) or under-reporting of symptoms by patients. They also concluded that it was unlikely that genetics alone could explain the differences in sensitization and that these differences more likely were related to differences in housing and community environmental exposures.

There are many ethnic groups within the United States for whom there is no information on asthma morbidity and access to care. It was noted earlier that minority status is missing from 25 percent of surveys of the National Hospital Discharge Survey. This survey finds Puerto Rican ethnic groups have very high morbidity from asthma, while recent studies have not shown the same effect in Mexican groups. Social effects might account for this difference among Hispanic groups. Non-Puerto Rican Hispanics are more likely to be illegal residents, making it less likely that these persons will seek medical care and, less likely that they will be counted in health statistics.

As our cultural and ethnic diversity increases, communication between patient and health care provider becomes more complicated and miscommunication more likely. Miscommunication may result in mistrust of the medical advice, or refusal of treatment and poor adherence and thus contribute to health disparities. Supporting this argument we found patients beliefs in the risks over the benefits of inhaled steroids to be associated with lower adherence. In focus groups, blacks with moderate or severe asthma reported their adherence was influenced by reliance on their own assessment of asthma control over that of the health provider. They expressed concern about adverse effects of inhaled steroid therapy and several had misperceptions of their risks. Such misperceptions can be addressed in the patient-provider encounter. Adherence was also adversely affected by the cost of the medication or its copay and insurers' approval policies and restricted formularies.

Obesity

Obesity has reached epidemic proportions in the United States and has been related to asthma in cross-sectional and longitudinal studies. A number of mechanisms for this

relationship have been proposed. A mechanical effect is postulated to be the result of decreased tidal volume and decreased functional residual capacity leading to reduced ability of the smooth muscles to stretch and thus respond to changes in respiration with exercise. Obesity enhances gastroesophageal reflux, a condition associated with asthma. Immune effects also have been postulated. For example, certain inflammatory cytokines such as tumor necrosis factor-α (TNF-α) and IL-6 are expressed by adipocytes. TNF expression is increased in asthma exacerbations and may have a role in amplifying the inflammatory response of asthma. IL-6 stimulates a Th1 response which may contribute to the inflammation of severe asthma. Leptin, a product of adipocytes, is a member of the IL-6 cytokine family. Whether or not leptin plays a role in asthma is unknown. Because asthma in adults is more common in women and because estrogen is increased in obesity, estrogen has been hypothesized to play a role in a link between asthma and obesity but no such role has been demonstrated.

Since asthma and obesity are both complex diseases, it is possible that some genetic susceptibilities are shared (pleiotropy). There is some evidence for this in that there are regions of the human genome important for both asthma and obesity, such as chromosome 6p, which contains the gene for TNF. Alternatively, it is possible that obesity is related to asthma as an epiphenomenon; that is, that there are shared lifestyle or social exposures, for example, physical exercise or diet, that influence both obesity and asthma. Obesity is more prevalent in the same socioeconomic groups in which asthma is more prevalent. No randomized interventional studies have been completed showing that weight reduction ameliorates asthma.. Clearly, more research is needed.

Respiratory Illness

There is a prominent association between lower respiratory tract viral infections and wheezing illnesses in infancy and increased risk of chronic childhood asthma. Respiratory syncytial virus (RSV) has drawn particular attention, since it is the major cause of bronchiolitis in children and RSV infection is associated with IgE production, airway inflammation, and increased airway responsiveness. Severe RSV bronchiolitis in infancy is associated with the development of chronic wheezing in later life. Respiratory tract infections by rhinoviruses, parainfluenza viruses, influenza virus, and human metapneumovirus during infancy are all associated with childhood wheezing.

It is hypothesized that susceptibility to asthma associated with viral infection in early life results from the interaction of developmental, genetic, and environmental factors. Developmentally, infancy is a time of pulmonary alveolarization and a time when the immune system has not reached full maturity. It has also been observed that most children who wheezed before 2 years of age had few if any respiratory symptoms when studied 3 to 5 years later.

Atopic status and bronchial hyperreactivity may be important genetically determined characteristics that influence whether RSV or other respiratory viral infections increase the risk of developing asthma. Most children who wheezed only during the first 2 years of life had lower levels of lung function when evaluated at age 2 and 6 years. In contrast, children who wheezed early in life and who were still wheezing at age 6 years had normal lung function, but statistically elevated serum total IgE levels when studied during the first year of life. When restudied at age 6 years, they had elevated IgE, but lung function had deteriorated and was below that of individuals who had never wheezed. This has led to the hypothesis that there are two wheezing syndromes associated with lower respiratory tract infection in young children. One occurs in children with small airway caliber who lack bronchial hyperresponsiveness, and have excellent prognosis. The other syndrome, which represents early-onset asthma, is associated with increased prevalence of allergic markers, bronchial hyperreactivity, and a significant decrease in lung function over the first 6 years of life. RSV bronchiolitis is most prominently associated with the development of asthma in patients with a concomitant family history of atopy and/or asthma.

Viral respiratory illnesses trigger asthmatic exacerbations. A number of studies have demonstrated a close temporal relationship, at the individual and population level, between virus infection and asthma exacerbations. These studies have also demonstrated that: (1) in contrast to viral, bacterial infections are not associated with asthmatic exacerbations; (2) viruses precipitate a high percentage of severe (versus mild) asthmatic exacerbations; and (3) viral infections can induce nonspecific increases in airway responsiveness and airway obstruction in children.

PROGNOSIS

The prognosis of asthma in early childhood has been clarified substantially by data from the Tucson Epidemiologic Study. These investigators followed a cohort of children through the first 6 years of life. They characterized four groups of children: "persistent wheezers," who wheezed both before and after the age of 3 years; "transient early wheezers," who wheezed before the age of 3 years and then stopped; "transient late wheezers," who wheezed after age 3 years but not before; and "never wheezers." Fully 40 percent of all children in the Tucson Epidemiologic cohort wheezed in the first year of life.

Significant predictors of persistent wheezing, and hence children at greatest risk for developing chronic asthma, were young maternal age, IgE level at 9 months, parents with asthma, maternal cigarette smoke exposure in utero, abnormal lung function at birth, and male gender. It is likely that early-life wheezing is predominantly a mechanical factor and less due to severe and chronic airway inflammation. It also seems unlikely that allergen exposure predominates as a factor in early childhood.

The characteristics of older children who wheeze are atopy, female gender, and active and passive cigarette smoking. By preadolescence, atopy and environmental allergen exposure are important risk factors for wheezing in children.

In roughly half of all childhood asthmatics, symptoms decrease or disappear by late adolescence and early adulthood. Characteristics that suggest a good prognosis include male gender, precipitation of attacks by viral respiratory illness, and children with airway parenchymal desynapsis (i.e., large lungs but small airways). These children are predominantly male, and, although often atopic, still are likely to outgrow their asthma. In a longitudinal study of children initially 5 to 9 years of age followed over a 13-year period, the effect of asthma on lung growth was different for boys than girls. Boys with asthma had larger growth in vital capacity than boys without asthma and tended to have mild disease. This was associated with fewer hospitalizations for asthma, despite somewhat greater prevalence than in girls. Asthmatic girls, however, had persistent reductions in FEV_1 and were more likely to be hospitalized for asthma, despite an initially reduced prevalence relative to the boys. These data are consistent with asthma being milder in boys in that the boys are more likely to "outgrow" their asthma. Existing data suggest that atopy per se is not a risk factor for asthma persistence. In older adults, airway responsiveness predicts the development of asthma and antedates and predicts accelerated decline in lung function. Active cigarette smoking further increases the risk of asthma in older adults. Several studies suggest that asthma in adults with or without active cigarette smoking is associated with the development of fixed airflow obstruction. The severity of adult asthma is clearly predicted by the severity of childhood asthma, and the persistence of symptoms in childhood and early adulthood is associated with reduced lung function and more severe disease in later adult life.

IMPLICATIONS OF CURRENT TRENDS IN PREVALENCE, MORBIDITY, HOSPITALIZATIONS, AND MORTALITY

Although prevalence, morbidity, and hospitalizations have remained stable recently, these absolute levels remain unacceptably high, particularly for certain minority groups and low-income populations. Risk factors such as obesity, prematurity, young maternal age, and cigarette smoking are all associated with these same patient groups, speaking to social and health care disparities. There are many vulnerable groups for which no data on asthma prevalence and morbidity yet exist. Certainly, genetic differences exist from patient to patient. These differences must be better characterized. Understanding the influence of gene-gene and gene-environment interactions is crucial. Gene-environmental interactions must be carefully studied for all exposures, and particularly for the exposure of socioeconomic status and cultural groups.

ACKNOWLEDGMENTS

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Aspirin- and Exercise-Induced Asthma

Gregory P. Geba

Asthma is well known to be triggered by specific immune factors such as aeroallergen exposures. There are, however, several important nonallergic triggers for the development of asthmatic bronchial obstruction. Two of the most important are aspirin and related nonsteroidal anti-inflammatory drugs (NSAIDs), and exercise. Both of these can provoke airway responses in individuals with established symptomatic aeroallergen-induced asthma or, in some instances, seem to occur in isolation. These two nonspecific triggers may also share pathophysiological mechanisms, including mast cell and leukotriene mediation and appear to be, in part, related to vascular responses that may mediate the airway narrowing.

ASPIRIN-INDUCED ASTHMA

The first report of aspirin-induced asthma (AIA) was made by Hirschberg in 1902. Six decades later, the association between aspirin sensitivity, asthma, and nasal polyps was documented in a classic paper by Samter and Beer. In 1928, the clinical importance of sensitivity to aspirin was highlighted by van Leewen, who challenged 100 asthmatics with aspirin, provoking bronchoconstriction in 16. Several others have made similar observations, documenting a prevalence of aspirin sensitivity in asthmatics that ranges from 5 percent to as high as 30 percent, depending on the characteristics of the asthmatics studied (severity increases risk) and the criteria applied to make the diagnosis.

Aspirin was the first drug recognized to be capable of precipitating asthma. With the development of other analgesic and NSAIDs after 1950, these related agents were also implicated in exacerbations of asthma. In a study of 781 asthmatics observed over a period of 2 years, drugs were found to provoke asthmatic airway responses in 10.5 percent of the patients. Reactions to NSAIDs were thought to be responsible for 77 percent of the exacerbations, with aspirin accounting for two-thirds of the reactions to NSAIDs, or nearly 50 percent of all instances of drug-induced asthma. Thus, although aspirin is the most common drug to induce asthma and the most common NSAID to cause asthma, other NSAIDs are responsible for an important number of attacks of asthma.

Clinical Presentation

Reactions to aspirin can take two distinct forms: *cutaneous*, leading to urticaria and angioedema, and *respiratory*, resulting in rhinoconjunctivitis and bronchospasm. In the former, a subpopulation of patients with established urticaria experienced cutaneous flares of hives with or without angioedema after ingesting NSAIDs. Almost all of these patients were able to ingest the same NSAIDs before the development of urticaria, suggesting that the NSAIDs interact with an underlying urticarial process but do not directly and independently cause the hives. Therefore, avoiding the ingestion of NSAIDs does not eliminate the urticarial syndromes experienced by these patients. In contrast, a small subgroup of patients experienced hives exclusively *after* exposure to these

drugs, without an antecedent history of underlying chronic urticaria. It is postulated, although, not proven, that such patients manifest immunoglobulin E (IgE)-mediated immune responses to some NSAID-related antigen. NSAID avoidance therefore is an effective treatment for urticaria in these patients.

In general, the upper (nasal) and lower (asthma) respiratory manifestations of aspirin sensitivity are generally temporally linked, although sometimes upper respiratory symptoms, typically rhinitis, precede the development of lower respiratory asthmatic reactions to these agents. AIA can occur upon a background of established asthma or can appear de novo without previous symptoms of asthma. This observation has led to the use of more accurate descriptors for this condition such as: aspirin-*intolerant* asthma or aspirin-*exacerbated* respiratory disease (AERD); the latter is used to account for the full spectrum of respiratory symptoms that can be provoked by aspirin.

Clinically, patients often first present with what appears to be an upper respiratory tract illness of viral origin leading to persistent inflammation of the nasal mucosa and paranasal sinuses, which becomes chronic. Chronic nasal inflammation is characterized by impressive mucosal eosinophilic infiltration which frequently leads to the development of nasal polyps. These patients usually cannot be distinguished from asthmatics with sinusitis and nasal polyps until the relationship is established between the ingestion of aspirin or related compounds and exacerbation of asthma. Although nasal polyps were originally described by Samter as part of the classic triad, it is becoming increasingly evident that polyps are often absent. In contrast, almost all cases present with sinusitis. Opacification of one or more sinuses on plain radiographs can be seen in some 90 percent of these patients; an even higher prevalence of sinus disease may be detected by computed tomography (CT) sinus scans that typically show mucosal thickening and, sometimes, air-fluid levels.

Many patients with AIA are not atopic; aeroallergen skin testing is positive in 30 to 60 percent of these patients, but skin tests are negative. For many, IgE levels are in the normal range. The search for NSAID-specific IgEs is often unsuccessful. Furthermore, after acute challenge with aspirin, patients with AIA do not develop blood eosinophilia and fail to produce detectable increases in blood histamine or in complement activity; such increments occur following acute aeroallergen challenge of atopic asthmatics, suggesting that atopic mechanisms are not primarily responsible for the development of this syndrome.

The typical reaction after aspirin ingestion by patients with AIA is the slow development (within 30 min to 4 h, mean 50 min) of nasal congestion with profuse rhinorrhea, cutaneous flushing of the head and neck, mild conjunctivitis, and bronchial obstruction, usually manifested as wheezing. A typical reaction provoked by an oral challenge under laboratory conditions is illustrated in Fig. 47-1. In severe

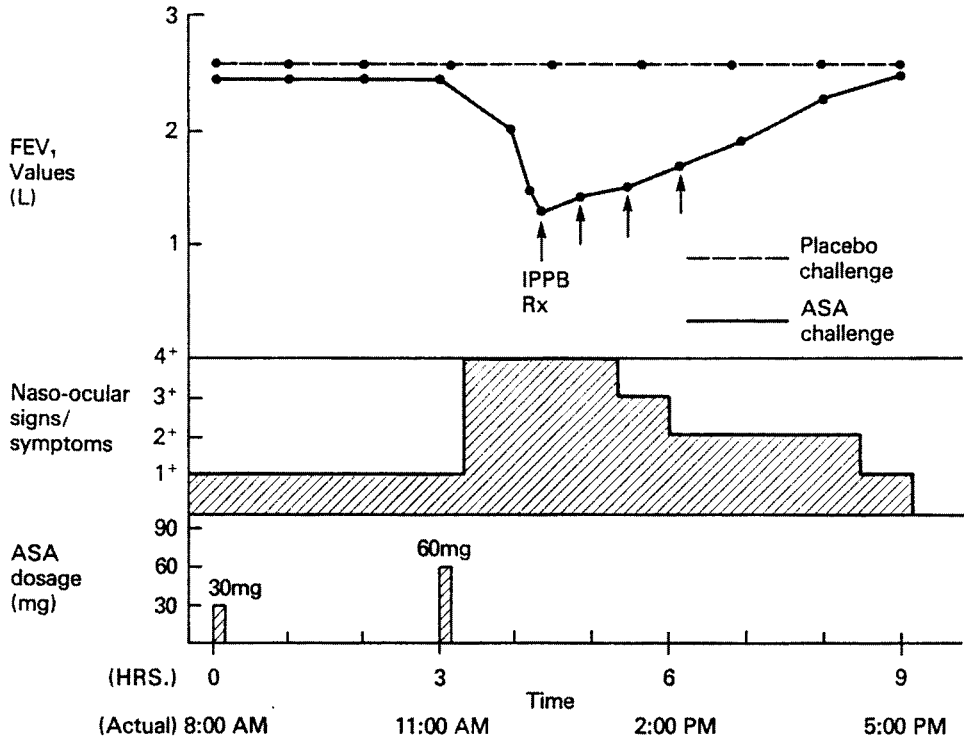

Figure 47-1 Typical reaction to aspirin in AIA. The timeline illustrates the kinetics of respiratory compromise and naso-ocular symptoms after graded aspirin or placebo challenge. IPPB = intermittent positive-pressure ventilation with β-adrenergic agonist bronchodilator. *(Based on data of Stevenson DD, Simon RA: Aspirin sensitivity: Respiratory and cutaneous manifestations, in Middleton E Jr, et al (eds),* Allergy: Principles and Practice. *St. Louis, CV Mosby, 1993, pp 1747–1767.)*

reactions, headache, nausea, and vomiting and acute hypercarbic respiratory failure can occur, culminating in death. Life-threatening responses with faster kinetics have also been reported after systemically administered NSAIDs, such as ketorolac. Combined cutaneous and respiratory reactions (i.e., true urticarial eruptions in association with asthma) occur in less than 3 percent of cases.

Genetics

In contrast to classic atopic asthma, which patients usually develop before the age of 20, AIA typically occurs in individuals in the fourth decade of life. Thus, AIA appears to be an acquired disease. In general, these patients do not have a prior history of exposure and potential sensitization to NSAIDs. Familial predisposition is also rare; in one study a positive family history was noted in only 2 of 500 patients. Men and women are affected equally. Despite the lack of familial association, one study did show an increase in the expression of HLA-DQw2 in one group of such patients. A later study in European patients showed increased expression of HLA-DPB1*0301 (odds ratios [OR]: 4.4 and 5.3) and decreased expression of DPB1*0401 (OR: 0.42 and 0.49) in AIA versus normals and nonaspirin-sensitive asthmatics, respectively. Korean investigators confirmed a higher risk of AIA in patients carrying HLA-DPB1*0301, whereas individuals who carried HLA-DRB1*1302 and/or DQB1*0609 exhibited a higher risk of aspirin-induced urticaria.

Other studies have implicated up-regulation of the expression of leukotriene C_4 (LTC_4) synthase which was found to be increased in blood eosinophils of patients with AIA. In Europeans, single nucleotide polymorphism (SNP) resulting from an A-444C transversion seemed to be associated with increased expression of the LTC_4 synthase and a higher relative risk of AIA (2.62; 95 percent CI: 1.38, 4.98). More recently, the same group showed a functional and gender association of the G-765C polymorphism in the cyclooxygenase-2 (COX-2) promoter region in AIA patients with severe disease. Another group in Japan found a functional promoter polymorphism for the TBX21 gene, the human analog for the T-bet gene in mice; absence of this gene had previously been shown to result in airway eosinophilia and hyperresponsiveness. The polymorphism –1993T-C SNP was in linkage disequilibrium with a synonymous coding 390A-G SNP in exon 1, and was significantly associated with AIA. Others have observed increased transcription or polymorphisms in the 5-lipoxygenase activating protein (ALOX5AP) gene in AIA. New insight may result from the recent observation of selective expression in AIA patients of cysteinyl leukotriene type 2 receptor, but not type 1 receptor, expressed by infiltrating inflammatory cells of the upper airway; this expression was not observed in aspirin-sensitive patients with chronic allergic rhinitis or in normals. Taken together, although much more remains to be discovered, AIA may be a disease with multiple genetic associations, a disease that depends on gene-environment interaction for its expression. A genetic predisposition in individuals who are also exposed to certain environmental factors appears to be required to produce the full manifestations of the disease.

Cross-Reactivity

Cross-reactivity of aspirin with other NSAIDs was first recognized in 1967 by Vanselow and Smith. This report was followed by others of reactions to structurally unrelated NSAIDs, which suggested that these reactions were not atopic. It was subsequently shown that the ability of these drugs to provoke asthma in susceptible patients was related to their ability to inhibit cyclooxygenase and that the degree of cross-reactivity with aspirin was related to the degree to which these agents inhibited cyclooxygenase in vitro. Subsequently the discovery of isoforms of cyclooxygenase have revealed that the dominant form that is inhibited by low doses of aspirin, and capable of eliciting airways responses in AIA, is cyclooxygenase-1 (COX-1). Drugs that are less potent inhibitors of COX-1 but are structurally related to aspirin (e.g., sodium salicylate) at clinical doses do not provoke AIA.

The association of AIA with the COX-1 isoform of the enzyme has been buttressed by studies performed with recently available specific inhibitors of COX-2, which, in clinical doses, nearly completely spare inhibition of COX-1. In two separate studies it has been shown convincingly that selective inhibitors of COX-2 (celecoxib and rofecoxib) do not provoke airway changes typical of AIA in patients known to have the disorder, or in those challenged in the laboratory de novo in the process of diagnosing the disease.

Szczeklik et al challenged 12 known AIA patients with 12.5 and 25 mg of rofecoxib (typical doses given daily for arthritis) who failed to manifest a response physiologically and did not exhibit the increase in urinary leukotriene E_4 (LTE_4) levels expected after aspirin challenge. Stevenson and Simon performed a larger study, which involved 60 patients with documented AERD who received 12.5 and 25 mg of rofecoxib; none reacted. A follow-up study, using highest single doses of rofecoxib reserved for acute pain of limited duration, found that none reacted. Similar data is available for celecoxib at the highest clinical doses. Dahlen et al challenged 27 patients with AERD with doses up to 200 mg of celecoxib without reaction. Even higher doses (400 mg) used by Gyllfors et al were also tolerated by patients with AIA without airway changes (Fig. 47-2) or increases in urinary LTE_4 levels. A list of NSAIDs reported to provoke AIA, and those not associated with AIA, is given in Table 47-1.

A number of other analgesics have long been thought to be well tolerated in patients with AIA. They are also listed in Table 47-1. However, some analgesics formerly considered to be safe for use by patients with AIA were subsequently shown to be capable of provoking bronchospasm if given in large doses. For example, acetaminophen, in doses generally greater than 1000 mg and salicylate, in doses of 2000 mg or more, can provoke significant decreases in forced expiratory volume in 1 second (FEV1) in some aspirin-sensitive asthmatics. Reactions to high doses of these drugs, when they occur, tend to be milder than the reactions seen with aspirin.

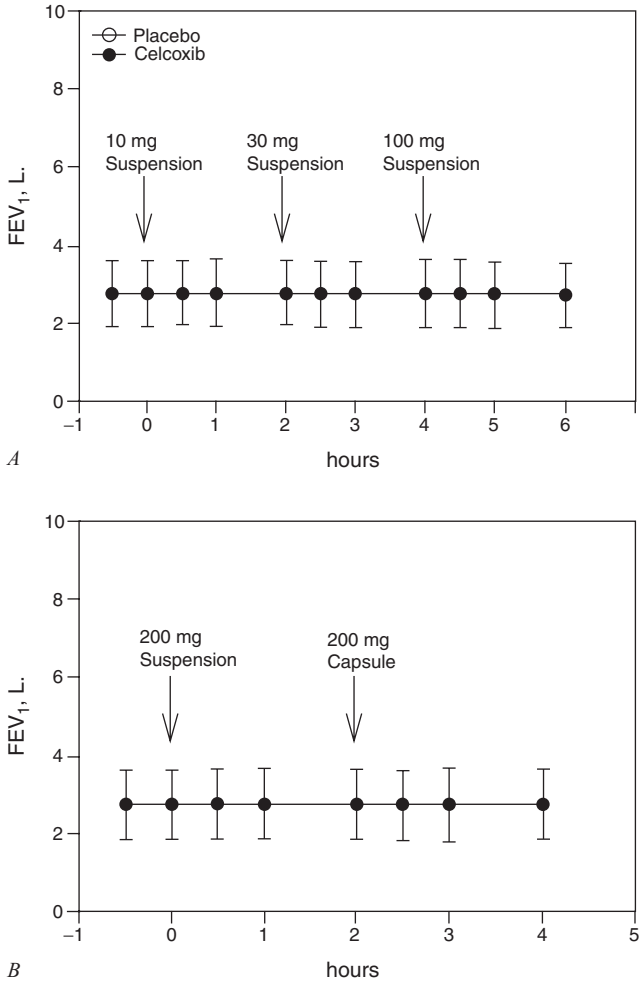

Figure 47-2 Lack of airway bronchoconstriction to increasing doses of a COX-2 inhibitor in aspirin-sensitive asthmatics. FEV_1 measured before and after oral challenge. *Panel A:* Double-blind crossover challenge. *Panel B:* Open label challenge. *(From Gyllfors P, et al: Biochemical and clinical evidence that aspirin-intolerant asthmatic subjects tolerate the cyclo-oxygenase 2-selective drug celecoxib.* J Allergy Clin Immunol *111:1116–1121, 2003.)*

A similar phenomenon has been observed with meloxicam and nimesulide, drugs that inhibit COX-2 somewhat more than COX-1. At typical low clinical doses, they appear to be well tolerated in patients with AIA, however at high doses, cross-reactions may occur.

It is important to note that reactions to NSAIDs (including aspirin, as well as COX-2 selective inhibitors) may be the result of prior sensitization to these drugs and the formation of NSAID-specific IgE antibodies. After a period of sensitization, patients may experience anaphylactic reactions to the specific NSAID; the reactions may manifest as wheezing, urticaria, angioedema, and in some instances, severe, life-threatening hypotension. Although this condition is much less common than non-IgE–mediated reactions to NSAIDs and aspirin which tend to occur after first exposure, it should be considered in the differential diagnosis in an appropriate clinical situation. Avoidance of the causative NSAID prevents relapses.

Table 47-1

NSAIDs in Aspirin-Induced Asthma (AIA)

NSAIDs that Can Provoke Airway Narrowing in AIA

- Carboxylic acids
  - Salicylates
    - Acetylsalicylic acid (aspirin, Easpirin, Zorpin)
  - Acetic acids
    - Indomethacin (Indocin)
    - Sulindac (Clinoril)
    - Tolmetin (Tolectin)
    - Diclofenac (Voltaren)
    - Ketorolac (Toradol)
    - Zomepirac (Zomax)
  - Propionic acids
    - Ibuprofen (Motrin, Advil, Nuprin)
    - Naproxen (Naprosyn)
  - Fenamates
    - Meclofenamate (Meclomen)
    - Mefenamic acid (Ponstel)
  - Enolic acids
    - Piroxicam (Feldene)

NSAIDs and Analgesics that Appear to Be Well Tolerated in AIA

- Sodium salicylate
- Choline salicylate
- Salicylamide
- Dextropropoxyphene
- Acetaminophen in low doses
- Selective COX-2 inhibitors

Although it was initially believed that tartrazine dyes were capable of provoking asthma exacerbations in patients with AIA, this has not been confirmed by further study. Tartrazine doses of 25 to 50 mg, used in a double-blind challenge of patients with proven AIA, did not provoke detectable changes in lung function. This observation supports the view that tartrazine intolerance is extremely rare and that true cross-reactivity with aspirin probably does not exist. Similar conclusions can be drawn regarding the cross-reactivity of other FD&C dyes, sodium benzoate, other benzoic acid derivatives, monosodium glutamate, and sodium and potassium sulfites. None of these agents has been associated with inhibition of COX-1, suggesting that their previous association with the syndrome may have been purely the result of serendipity.

An interesting association has been made of AIA with sensitivity to hydrocortisone. Several case reports were followed by two larger studies demonstrating that a small percentage of patients with AIA may experience acute bronchospasm (15 to 30 min) after the intravenous or intramuscular injection of hydrocortisone. The vehicles and diluents used in the hydrocortisone preparations could not

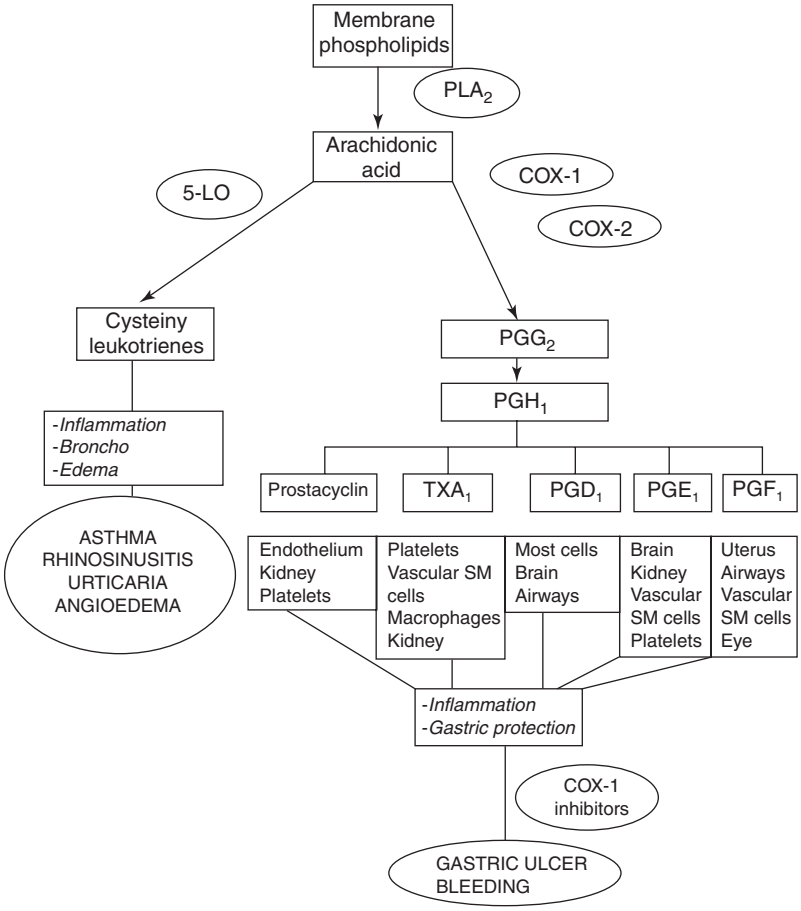

Figure 47-3 Enzymatic pathways of arachidonic acid metabolism. (*From Sanchez-Borges M, et al: Cutaneous reactions to aspirin and nonsteroidal anti-inflammatory drugs.* Clin Rev Allergy Immunol *24:125–135, 2003.)*

be linked to the reactivity. One of these studies showed no bronchoconstrictor response to methylprednisolone, dexamethasone, or betamethasone when given intravenously, demonstrating that these potent anti-inflammatory steroid preparations, related to hydrocortisone but with different chemical structure of their side chains, could be used safely. The mechanism of this reaction is not known, though corticosteroids can reduce phospholipase A_2 (PLA_2) activity (generally decreasing eicosanoid production) and broadly inhibit isoforms of cyclooxygenase, especially COX-2.

Pathogenesis

Although understanding of the genetic predisposition to AIA and identification of provoking agents has increased over the last 5 years, the pathophysiological basis of AIA continues to be a subject of considerable study and is not yet solved, so that initiating and propagating stimuli of this condition are still not known. The dominant theory points to an alteration in the balance between leukotrienes and prostaglandins generated by the lipoxygenase– and cyclooxygenase–dependent pathways of arachidonic acid metabolism. Other attempts to explain the spectrum of symptoms are based on the release of other mediators, most likely from mast cells, basophils, or platelets. These theories include up-regulation of releasability of mast cell-basophil mediators by unknown substances that affect mast cell membranes, greater production than normal of histamine by basophils of patients with AIA, decreased production of prostaglandin E_2 (PGE_2) and enhanced production of leukotriene B_4 (LTB_4) by AIA basophils, and enhanced aspirin-induced release of serotonin and other mediators by AIA platelets. It has been proposed that complement activation may play an important role in these processes. However, the role of complement activation in AIA has been questioned by data that show no significant changes in CH_{50} and C_4 levels in patients who experience an exacerbation of asthma after acute oral aspirin challenge.

Alterations in arachidonic acid metabolism appear to play a central role in AIA. The major pathways of cyclooxygenase and lipoxygenase metabolism of arachidonic acid are illustrated in Fig. 47-3. Arachidonic acid is derived from membrane phospholipid by PLA_2. It is then metabolized via the cyclooxygenase pathway to prostaglandins (COX-2 more than COX-1) and thromboxanes (COX-1 more than COX-2) or via the lipoxygenase pathway to sulfidopeptide (cysteinyl) leukotrienes. The leukotrienes have a variety of effects, including the induction of contraction of bronchial smooth muscle. In contrast, the prostaglandins, in particular PGE_2, act as bronchodilators and may inhibit T- cell–mediated inflammatory responses in the lung. Aspirin and the other NSAIDs that cause AIA inhibit COX-1 activity. A shift occurs after the administration of aspirin or appropriate doses of the other

agents, shunting approximately 90 percent of the arachidonic acid metabolism to the 5-lipoxygenase pathway, decreasing prostaglandin and thromboxane production, and increasing leukotriene generation. In comparison to normal individuals, patients with AIA generate leukotrienes in inordinate quantities after aspirin challenge. Discovery that patients with AIA produce less of the anti-inflammatory mediators lipoxin and 15-epimer lipoxin might enhance effects of this shift. Patients with AIA may also be more sensitive than normal subjects to the bronchoconstrictor properties of leukotrienes (particularly LTE_4) and more susceptible to the loss of the bronchodilating, and potentially anti-inflammatory, effects of PGE_2. The data supporting these conclusions are briefly summarized below.

Several groups have analyzed the nasal lavage fluid from aspirin-sensitive and control patients and found inducible levels of cysteinyl leukotrienes and plasma proteins when patients with AIA were challenged with oral or nasal aspirin. One study found that LTC_4 and LTD_4 levels were not significantly increased in normal subjects, but could be induced to some degree in patients with allergic rhinitis and in those with isolated nasal polyps (increasing by 93 and 69 percent, respectively, above baseline levels). Similarly, although histamine levels increased significantly in the AIA group (greater than threefold increase in total protein) the levels did not increase significantly in the control groups. Analysis of the nasal lavage fluids showed impressive increases in lactoferrin and lysozyme, suggesting that submucosal glands are stimulated by the challenges.

In a follow-up study, the cellular source of these nasal abnormalities was investigated by analysis of nasal lavage fluids induced by aspirin challenge for the presence of mast cell tryptase and eosinophil cationic protein (ECP). Significant increases in nasal tryptase, histamine, and cysteinyl leukotrienes were observed after AIA was provoked in these patients. ECP levels at baseline were variable and did not increase significantly after challenge. These results support the idea that after aspirin challenge, the leukotrienes in the nasal secretions of patients with AIA are probably of mast cell origin. They also suggest that eosinophils are not as important as mast cells in the pathogenesis of the nasal manifestations of AIA. These findings are consistent with earlier work that showed similar increases in *blood* tryptase (4 h) and *urinary* LTE_4 levels (6 h) and decreases in blood eosinophil counts ($p < 0.01$) (6 h) after aspirin challenge.

The metabolism of arachidonic acid in the lung has not been studied as extensively. The available data show both similarities and differences with findings in the nose and circulation. For example, bronchoalveolar lavage fluid (BALF) obtained 30 min after inhalation of threshold doses of lysine-aspirin contained depressed levels of cyclooxygenase-dependent mediators (PGE_2, PGD_2, thromboxane B_2 (TXB_2), and $PGF_{2\alpha}$). However, only small increases occurred in LTE_4 and 5-hydroxyeicosatetraenoic acid (HETE) levels. Lysine-aspirin inhalation also did not elicit a significant increase in tryptase levels in the BALF and led to a significant fall in ECP levels even though baseline eosinophil and ECP levels were higher in the AIA group than in the placebo-treated nonasthmatics. The authors postulated that the altered pulmonary eicosanoid production might be related to the eosinophilic inflammation in the airways of patients with AIA. In order to dissect further the mechanism of bronchospasm in AIA, a number of investigators used inhibitors of leukotriene effector function. The first administered a specific sulfidopeptide leukotriene receptor antagonist via inhalation and noted that it attenuated AIA in five of six subjects by 43 to 74 percent. This was followed by a double-blind, placebo-controlled, crossover study that showed that a specific leukotriene receptor antagonist, given in a single oral dose 1 h before provocative challenge with perithreshold lysine-aspirin inhalant, could almost completely block the development of aspirin-induced bronchospasm. This was achieved without evidence of any direct bronchodilatory effect of the drug before lysine-aspirin challenge, confirming that leukotriene receptor antagonist was effective in preventing analgesic-induced (dipyrone) bronchospasm.

Leukotriene effects in the lung can also be modulated by blocking 5-lipoxygenase activity. The efficacy of this approach was demonstrated in a randomized, double-blind, crossover study in which the 5-lypoxygenase inhibitor zileuton (600 mg orally, 4 times a day, for 6 to 8 days before aspirin challenge) led to a greater than 70 percent reduction in the baseline excretion of urinary LTE_4, a greater than 60 percent reduction in mean maximal urinary concentration of LTE_4 after aspirin challenge, and almost complete suppression of subthreshold and threshold oral aspirin-induced bronchospasm. In addition, naso-ocular, gastrointestinal, and dermal symptoms were reduced to the levels of symptoms produced by placebo challenge. Similar data have been generated with the cysteinyl leukotriene receptor antagonists montelukast and zafirlukast.

In summary, although the mechanism of AIA remains incompletely understood, there appears to be a clear role for lipoxygenase products in the pathogenesis of the disorder. The available data also suggest that mast cells, stimulated by aspirin directly or indirectly, discharge their leukotriene mediators in large amounts into nasal secretions but may not play the same role in the lung. The presence of increased numbers of eosinophils and altered eosinophil phenotype may be more relevant to the pathophysiology in the lung, linked to the airway inflammation that characterizes this disorder. The increased number of these cells probably reflects their recruitment secondary to the release of mast cell–derived mediators, including leukotrienes and cytokines.

Diagnosis

Although some promise exists for the development of in vitro tests to identify patients with AIA based on differential in vitro and platelet responses to aspirin and NSAIDs, these methods have not yet been validated for routine use. AIA is still diagnosed by in vivo testing using placebo-controlled

Table 47-2

Diagnosis of Aspirin-Induced Asthma: Aspirin (ASA) Challenge Protocols

Single-Blind Oral 3-Day Aspirin Challenge

		Test days	
Time	1	2	3
0	Placebo	ASA 30 mg	ASA 100–150 mg
3 h	Placebo	ASA 45–60 mg	ASA 150–325 mg
6 h	Placebo	ASA 60–100 mg	ASA 325–650 mg

Double-Blind Oral Aspirin Challenge

Both tester and patient are blinded to eliminate potential bias.

Bronchial Challenge with Lysine-Aspirin

Time (Min)	Challenge (Lysine-aspirin in mg/ml)
0	Placebo
45	Placebo
90	11.25
135	22.5
180	45
225	90
270	180
315	360
350	360 (10 breaths)

Patients receive four breaths of all doses of lysine-aspirin unless otherwise indicated.

Source: Data from DD Stevenson: Aspirin and NSAID sensitivity. Immunol Allergy Clin N Am *24:491–505, 2004; Stevenson DD, Simon RA: Sensitivity to aspirin and nonsteroidal antiinflammatory drugs, in Middleton E Jr, Reed CE, Ellis EF (eds),* Allergy: Principles and Practice. *St. Louis, CV Mosby, 1993; Phillips GD, Foord R, Holgate ST: Inhaled lysine-apirin as a bronchoprovocation procedure in aspirin-sensitive asthma: Its repeatibility, absence of a late-phase reaction, and the role of histamine.* J Allergy Clin Immunol *84:232–241, 1989.*

oral challenges of persons suspected of having this disorder (Table 47-2). This testing can be performed according to published protocols using single-blind or double-blind approaches. These protocols generally begin with a 3-mg dose of aspirin, although higher initial doses (30 mg) have been recently advocated since, if reactions occur at this dose, they are easily treated. The dosage is then increased to a maximum of 650 mg over a 3-day period. Spirometric pulmonary function is monitored serially during the challenge to assess the degree of bronchial constriction. Airway reactivity to methacholine is not a viable surrogate for spirometry, since aspirin does not consistently alter methacholine sensitivity. Aspirin challenge should probably be reserved for use in research centers experienced with its application and adverse effects. An alternative to oral challenge, used in some centers in Europe for the diagnosis of AIA, and increasingly elsewhere, is the inhalation of stabilized lysine-aspirin, followed by serial lung function measurements, or nasal provocation with aspirin or lysine-aspirin followed by serial rhinomanometry or acoustic rhinometry. Currently, lysine-aspirin is not yet available for clinical use in the United States.

Treatment

Optimal treatment of patients with AIA requires knowledge of the proper approaches to treat acute aspirin-induced bronchial symptoms and associated nasal and sinus pathology. No specific therapy has emerged that can be recommended for the routine treatment of acute bronchospasm provoked by NSAIDs. It has been stated that corticosteroids are not effective after acute aspirin ingestion, and that theophylline and cromolyn sodium play no definite role. Treatment of symptoms after acute ingestion therefore relies mainly on β-adrenergic agonists to reverse bronchospasm, and topical vasoconstrictors for both nasal congestion and eye symptoms. Frequent applications of these agents usually are necessary to maintain nasal and airway potency over the 2- to 6-h duration of the reaction.

On a chronic basis, the treatment of AIA depends on the correct diagnosis and avoidance of aspirin and other cyclooxygenase inhibitors that could cross-react to induce acute bronchospasm. Patients should be instructed that many over-the-counter medications contain aspirin or other

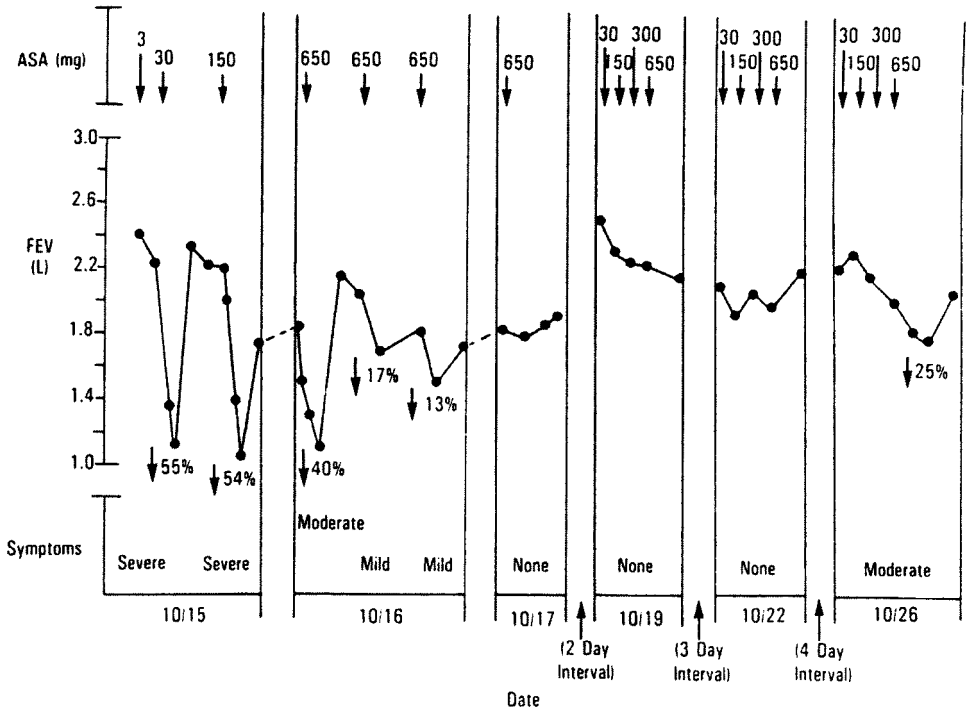

Figure 47-4 Airway desensitization to aspirin challenge in AIA. Timeline of respiratory function and overall symptoms after serial aspirin dosing. The reappearance of respiratory compromise and symptoms after 4 days without aspirin shows the need for continuous aspirin administration to maintain desensitized state. *(Based on data of Pleskow WW, et al: Aspirin desensitization in aspirin-sensitive asthmatic patients: Clinical manifestations and characterization of the refractory period.* J Allergy Clin Immunol *69:11–19, 1982.)*

NSAIDs, and they should carefully read package inserts before using any medication.

Drug treatment of AIA should focus on treating the underlying asthma and the strict avoidance of aspirin and cross-reacting NSAIDs. Currently there also appears to be no role for systemic corticosteroids or theophylline in the prevention of AIA. Some investigators have found that antihistamines, such as clemastine and mast cell stabilizers such as ketotifen, cromolyn and nedocromil, can be effective prophylactically. However, not all subjects who are taking these drugs are protected against bronchoconstriction after aspirin challenge. The 5-lipoxygenase inhibitor zileuton was not found to be effective in preventing FEV_1 decline or naso-ocular reactions to direct aspirin challenge, although it had been shown in a previous study to improve chronic asthma symptoms when added to conventional therapy. In contrast, experience with the cysteinyl leukotriene receptor antagonists has been variable, but mostly positive and may be more effective in those who carry the variant C allele of LTC_{4S} than in noncarriers. Pretreatment with inhaled or systemic steroids or long-acting β-agonist (salmeterol) was shown to at least partially attenuate decrements in aspirin-induced respiratory lung function. The failure of tacrolimus (0.1 mg/kg) (a drug that could potentially affect both T-cell–generated cytokine responses and prevent release of mast cell histamine and leukotrienes) to prevent aspirin-induced respiratory reactions in patients with AERD on aspirin challenge suggests that this agent cannot be relied upon to prevent reactions to aspirin-intolerant asthmatics and cannot be used to facilitate "silent" aspirin desensitization in the patient with AERD.

In individuals in whom aspirin (or cross-reacting NSAIDs) cannot be avoided (i.e., in the setting of cardiovascular prophylaxis) or the efficacy of prophylactic measures cannot be assured, aspirin "desensitization" can be considered. Protocols are available for selected patients (Fig. 47-4). These methods can effectively protect many from experiencing symptoms on exposure to aspirin or NSAIDs and will maintain this level of desensitization as long as aspirin, in doses of 325 to 650 mg a day, is continued. In a study of 25 aspirin-sensitive asthmatics, such therapy decreased nasal symptoms by 67 percent and the severity of asthma by 48 percent. In the largest study of its kind, 172 patients with AERD were desensitized to aspirin from 1995 to 2000; they were subsequently treated then with 1300 mg of aspirin each day and followed for 1 to 5 years. Clinical improvements occurred during the first 6 months: measures of improvement included clinical course, reduction in dose of systemic corticosteroid, and improvement in global assessments; these effects were maintained, but not further enhanced, during the remainder of the study. Approximately 67 percent (115 of 172) improved, 16 failed to improve, 24 discontinued aspirin because of aspirin-related side effects, while another 17 dropped out for other reasons.

It is interesting to note that although there are some reports of the development of increased methacholine reactivity

in patients soon after aspirin challenge, baseline methacholine responsiveness does not seem to be successfully downregulated by aspirin desensitization. Also, there is no firm evidence that aspirin desensitization leads to abatement in skin disease in those with aspirin-urticaria syndrome.

Inhaled PGE_2 was shown to prevent bronchoconstriction in a high proportion of patients challenged with inhaled L-lysine aspirin in two small studies. In two studies using misoprostol, a stable analog of PGE_1, prior to challenge with L-lysine aspirin (400 μg 1 h before) or a predetermined threshold dose of aspirin (400 μg before, followed by 200 μg with the provocative dose of aspirin), evidence was provided of some protection in 7 of 11 patients ($p = 0.024$) and in 6 of 7 patients (statistically only significant at time points 3 h after challenge), respectively. To test whether asthma symptoms might improve on treatment with misoprostol, another group performed a double blind crossover study that showed that misoprostol, given for a period of 6 weeks (at dose of 800 to 1600 μg/d) led to only a small improvement in nasal symptomatology without any effect on asthma control in 17 patients with proven AIA. Thus, evidence for a specific method to control AIA, other than the desensitization methods described above, has not proven to be reliable. Fortunately, for those who require aspirin to prevent disease, such as those on low-dose aspirin, given for cardiovascular prophylaxis, the threshold needed to provoke airway and skin reactions is above that of the dose required for cardiovascular prophylaxis.

The potential contribution of chronic sinusitis to exacerbations of asthma is well established. Aspirin sensitivity, chronic sinusitis, and nasal polyposis are well documented to coexist in AIA. Thus, the presence of these upper-airway disorders must be considered in patients with AIA and effective treatment instituted if they are identified. High-dose topical intranasal corticosteroids can shrink polyp tissue and prevent obstruction of nasal passageways. In the setting of chronic sinusitis, standard approaches—including topical vasoconstrictors, antihistamines, and antibiotics—should also be used. Surgery to drain sinuses and remove polyps has been shown to be effective in the short term; however, polyps can regrow and the sinusitis often recurs. In selected patients in whom aspirin provokes nasal symptoms predominantly, administration of intranasal lysine-aspirin at increasing weekly doses has been used successfully to desensitize such patients and prevent regrowth of polyps in one study. A more recent and larger randomized clinical trial, although underpowered due to dropouts, used a crossover design after withdrawal of intranasal steroids. Lower doses of lysine-aspirin were administered more frequently (16 mg intranasally every 48 h). Results showed encouraging immunohistochemical changes in nasal submucosal inflammatory cells from turbinate tissue, characterized by decreased expression of CysLT1 but no clinical improvement (diary scores of nasal and chest symptoms) or improvement on rhinometry.

Despite aspirin desensitization and careful treatment of the often-associated sinusitis, an appreciable proportion of patients with AIA do not achieve complete control of asthma or nasal symptoms. It is postulated that this failure may reflect permanently remodeled airways or residual allergic triggers that require specific measures for allergy control and anti-inflammatory therapy. Evaluation of the effect of strict avoidance of allergens, specific allergen immunotherapy, more intensive local management of the inflamed nasal mucosa and anti-IgE treatment may help to clarify the role of atopy in the persistence of symptoms after aspirin desensitization.

EXERCISE AND ASTHMA

The first report of exercise-induced asthma (EIA) is attributed to John Floyer in 1698. Nearly 300 years later, interest in this subject grew when it was recognized that exercise or hyperventilation could provoke asthma attacks. EIA can be defined as a condition in which vigorous physical activity triggers acute airway narrowing in persons with heightened airway reactivity. It appears that EIA is always associated with the asthmatic diathesis, although EIA can be seen before other characteristic features of asthma emerge. Various reports indicate that EIA is common, affecting between 50 and 90 percent of all asthmatics and 40 percent of patients with allergic rhinitis without known asthma. Some have suggested that all asthmatics can be shown to manifest airway narrowing in response to thermal provocations of sufficient intensity, whether induced by exercise or hyperventilation. Other individuals susceptible to exercise-induced asthma are first-degree relatives of asthmatics, atopic "nonasthmatics," and patients with cystic fibrosis. Approximately 10 percent of pediatric patients have been found to have EIA, a prevalence higher than that of clinical asthma.

Recent evidence suggests that elite athletes may be predisposed to develop EIA. Surveys conducted of athletes at the Atlanta (summer) and Nagano (winter) Olympic Games showed a prevalence of 16 to 17 percent. The prevalence may actually be higher in those who are regularly exposed to high minute ventilation of the cold, dry air which is typical of winter sports. The prevalence of EIA in figure skating (35 percent) and ice hockey (35 percent) may be responsible for increasing the overall frequency of EIA in winter sports; this high incidence has been documented by Wilber (referenced in Storms, 2005) to be as high as 23 percent.

Clinical Presentation

Patients with EIA generally manifest a series of fairly predictable symptoms and alterations in pulmonary function (Fig. 47-5). Normal individuals and asthmatics generally respond at first to exercise by bronchodilation, probably mediated by the release of catecholamines. This response is short-lived, peaking at midexercise, and is followed by return of normal baseline airway tone at the end of exercise. In patients with EIA, the transient bronchodilation and reversal are followed by bronchoconstriction coincident with symptoms of cough, wheezing, dyspnea, and chest tightness typical of asthmatic attacks. Typically, when provoked by a brief, intense

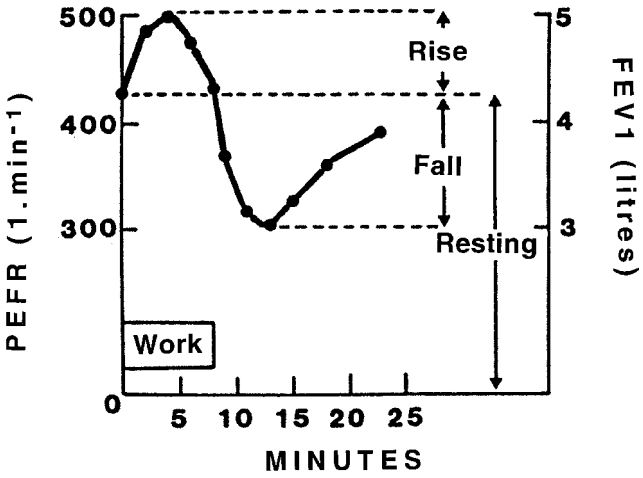

Figure 47-5 Typical pulmonary function changes induced by exercise in EIA. Transient bronchodilation during exercise and bronchospasm after exercise are noted. *(Based on data of Anderson SD: Is there a unifying hypothesis for exercise-induced asthma?* J Allergy Clin Immunol *73:660–665, 1984.)*

exercise period in the laboratory, maximal bronchoconstriction occurs 5 to 10 min after the cessation of exercise and lasts for 30 to 60 min (Fig. 47-5). Rarely, although it can limit the performance of trained athletes, does this form of bronchoconstriction result in ventilatory failure.

In addition to asthma after exercise, many athletes describe dyspnea during exercise. If these athletes are able to continue to exercise despite the initial airway constriction, especially if they can increase their level of activity, relief of bronchoconstriction often occurs. This relief is associated with symptomatic improvement with time that is described as "running through the attack." The development of dyspnea during exercise is related to the development of bronchoconstriction at lower work intensities (simulating a postexercise state), which is avoided by interval training at higher intensities (simulating an exercise state). This has been taken as evidence that airway function during exercise reflects a balance between bronchoconstrictor and protective bronchodilator influences, and that this balance can be influenced by rapid changes in exercise intensity.

The reproducibility of EIA is highly dependent on the specific characteristics of the stimulus and patient-related factors. The net influence of exercise intensity, the temperature and humidity of the inspired air, and the patient's baseline airway reactivity are fundamental in determining whether exercise will lead to bronchoconstriction. The better the asthma is controlled at baseline, EIA may be more difficult to provoke. If climatic conditions vary, even though asthma is not well controlled, EIA may fail to develop. Classic work has shown that for a fixed minute ventilation, cold, dry air inspired during exercise is more likely to provoke EIA than warm, humid air. Thus, EIA is more likely to occur while jogging during the winter than while swimming indoors.

It is interesting that about 50 percent of patients with EIA will not manifest a bronchoconstrictor response after exercise if rechallenged with the same stimulus within 60 min, and thus appear to establish a refractory state. Neither baseline airway obstruction nor the degree of obstruction provoked by exercise can be used to determine who will be refractory to repeated exercise challenges. After 3 h, even patients who are refractory to repeated challenge will again respond to exercise with bronchoconstriction.

Pathophysiology

The mechanisms associated with exercise-induced bronchoconstriction have been studied intensively for more than two decades. Despite this intense scrutiny, and recent application of genetic and molecular techniques, the pathophysiology of this response is still a subject of debate. The theories now appear to have coalesced to two pathogenic schemas that may, or may not, be mutually exclusive. The two theories of pathogenesis focus on the roles of heat exchange, water loss and subsequent airway rewarming, and airway inflammation. The role of inflammation as a reaction to these stimuli or as an enhancer of the effects of these two principles' pathophysiological pathways is probably tied to leukotrienes and related lipoxygenase products.

Heat Exchange and Water Loss

During tidal breathing, heat (via conduction and evaporation) and water (via evaporation) are transferred from the mucosa of the upper airways to the entering air. Since exercise requires marked increases in minute ventilation, exceeding the volume of air that can be inspired through nasal structures, air enters directly through the mouth, bypassing the normal warming and conditioning function of the nose. The lower respiratory mucosa attempts to compensate for the function of the bypassed nose. Heat and water fluxes occur first. The lower airways are cooled and dried and then subject to rewarming by warm blood carried by the bronchial circulation.

In the late 1970s, a number of investigators postulated that EIA was the result of increased heat loss in the airway. This was based on the observation that cold, dry air caused a greater fall in FEV_1 than did hot, dry air and on correlations between heat exchange and the degree of bronchoconstriction. Others, however, showed that the temperature of the inspired air was not crucial for inducing bronchoconstriction and that temperatures of dry inspired air varying as much as 60° could still provoke airway narrowing. This suggested that airway evaporative water loss might be more important than airway cooling. The water loss was predicted to change the osmolarity of the cellular and extracellular components of the airway wall, stimulating increased bronchial blood flow in order to increase the delivery of water. In addition, it was hypothesized that bronchial wall hyperosmolarity increased the release of proinflammatory mediators from resident airway inflammatory cells such as mast cells. This concept was supported by work that demonstrated that changes in the humidity of inspired air, and not temperature, determine the magnitude of EIA. Further support for this construct came

from studies using cold gas mixtures with different water-carrying capacities, which showed a significant correlation between the airway response and the evaporative heat loss, but not the total heat loss or temperature gradient.

In apparent contrast to these data is the considerable body of work that does not support the concept that osmolar changes precipitate EIA. The most important of these showed that increasing minute ventilation at constant humidity increases the severity of EIA.

Airway Rewarming

An important theory that also remains to be proven was offered by McFadden, who proposed that the process of airway rewarming is involved in the pathogenesis of the airway narrowing that occurs in EIA. This theory postulates that loss of heat during exercise leads transiently to a decrease in bronchial blood flow. At the end of exercise, the bronchi undergo reactive hyperemia characterized by vascular engorgement, which leads to compromise of airway caliber and edema of the walls of the airway. The strongest support for this theory is provided by studies that show that the severity of EIA can be controlled by regulation of the thermal gradient during exercise and the rate of rewarming after exercise.

In summary, there is evidence that associates exercise-induced bronchoconstriction with a sequence of events that includes heat loss, water loss, and airway rewarming. However, the degree to which these alterations in temperature and water exchange contribute to the pathogenesis of EIA is still a topic of debate and investigation.

Inflammation and EIA

Theories that postulate a role for inflammatory mediators in the pathogenesis of EIA have recently received new support and are being harmonized with the already considerable evidence that supports a role for inflammation in the pathogenesis of other forms of asthma. New information about exercise suggests that individuals predisposed to EIA, specifically elite athletes, may manifest a degree of airway inflammation that had not been previously recognized. Instead of demonstrating a lower rate of EIA, which would potentially enable a higher level of exercise performance, and which might be expected in those best equipped to excel in sports, elite athletes appear to exhibit a paradoxically higher incidence of EIA and a higher degree of airway inflammation without necessarily manifesting a higher prevalence of underlying clinical asthma.

Older data on the role of inflammation in EIA did not necessarily support this link. One study analyzing the characteristics of BALF from patients with EIA 12 min after exercise failed to find evidence for mast cell mediator release since levels of BAL histamine, tryptase, LTC_4, and PGD_2 were not altered. Similarly, studies performed 1 h and 25 h after exercise did not reveal significant differences in the cellularity of BAL or in the levels of histamine or tryptase.

In contrast, one group studying elite cross-country skiers, found elevated airway T lymphocytes and eosinophils compared to controls. Several others have demonstrated changes in exhaled nitric oxide, which generally decreased with exercise, suggesting a high basal level and ventilatory clearance of this gas associated with airway inflammation. A second group found increases in plasma adenosine after exercise. A third group documented the presence of a late phase airway response after exercise that was demonstrable in 50 percent of competitive athletes studied. Most importantly, the new concept that these changes might be provoked by exercise, rather than be a reflection of underlying inflammation in those who manifest EIA, is supported by studies of Helenius et al, who showed that athletes who stopped high-level training and modulated the amount of exercise they subsequently pursued, experienced reduced asthma symptoms and diminished bronchial responsiveness to histamine.

Leukotrienes in EIA

To determine whether leukotrienes play a role in the pathogenesis of EIA, LTD_4 receptor antagonists and 5-lipoxygenase inhibitors have been used. Studies using an intravenous LTD_4 receptor antagonist administered 20 min before exercise demonstrated significant attenuation of the maximal provoked bronchoconstriction and a decrease in the mean time to recover from bronchoconstriction (8 min for the treatment group versus 33 min for placebo). Similar results were noted by others using oral or inhaled leukotriene antagonists. In general, although the protection was relatively small, it was significant and equivalent in potency to inhaled cromolyn.

The results obtained with peptido-leukotriene antagonists are consistent with those obtained with the effects of a 5-lipoxygenase inhibitor on bronchoconstriction induced by cold, dry air. In the most important study of this kind, a 5-lipoxygenase antagonist was as effective as cromolyn or terbutaline in augmenting respiratory heat exchange. Thus, leukotrienes may mediate the airway inflammation and contribute to the pathogenesis of EIA.

Genetics

Little information is available on the potential genetic underpinnings of EIA. However, this topic has recently received some attention. Using microarray analysis, one group demonstrated enhanced transcription of 5-lipoxygenase (ALOX5) and 5-lipoxygenase activating protein (ALOX5AP) genes. More recently, in studies conducted in a large cohort of Korean children with asthma, others have provided evidence of LTC_4 synthase (A-444C) promoter polymorphisms in association with greater severity of EIA. These observations suggest the potential existence of disease-modifying genes in exercise-induced bronchospasm.

Differential Diagnosis

The diagnosis of EIA is most accurately established by employing validated exercise protocols coupled with pulmonary function testing. However, patients are commonly given a presumptive diagnosis based on their history and physical examination. Important points in the clinical history include the

Table 47-3

Differential Diagnosis of Exercise-Induced Asthma

Cardiac Disease	Functional abnormalities
Coronary ischemia	Vocal cord dysfunction
Mitral valve prolapse	Panic disorders
Atrial myxoma	General
Cardiomyopathy	Deconditioning
Arrythmias	Anemia
Lung disease	
Fixed airway obstruction	
Interstitial lung disease	
Exercise-induced cough	

level and type of exercise that provokes asthma, the timing of symptom onset, the situation that modifies the onset of symptoms, and the precise symptoms experienced. Many of the symptoms of EIA can mimic other conditions that would require an entirely different therapeutic approach (Table 47-3). For example, chest tightness with exercise should be unequivocally distinguished from coronary ischemia. Other cardiac disorders that can mimic EIA are arrhythmias, cardiomyopathies, atrial myxoma, and mitral valve prolapse, all of which can manifest with dyspnea and wheezing. The presence of a murmur, click, or other findings on physical examination should help to identify patients with these conditions. Exercise-induced anaphylaxis can also mimic EIA but will generally exhibit skin manifestations (urticaria), and respiratory symptoms will be less prominent. Two other conditions that have been reported to mimic EIA are fixed glottal and tracheal obstruction, which become noticeable during the increased ventilation of exercise and exercise-induced vocal cord/arytenoids dysfunction but are not present at rest. Some observers have also suggested that panic disorders and the excessive tachypnea associated with deconditioning can be confused with EIA. Symptoms due to these other conditions generally are greatest *during* exercise provocation rather than afterward, when airflow limitation due to EIA usually reaches its peak.

Exercise-induced cough is another phenomenon that can mimic EIA. Both may be induced by changes in the osmolarity of the airways reflecting water loss from the respiratory tract during exercise. The inhalation of humid air also prevents both phenomena. However, EIA and exercise-induced cough respond differently to β-adrenergic agonists, suggesting that they are mediated by different underlying mechanisms. It is postulated that exercise-induced cough is the direct result of changes in osmolarity provoked by airway drying, whereas EIA is due to the release of mediators that results from the process of airway drying. Therefore, although nearly all patients with EIA cough when provoked by exercise, there are patients who have exercise-induced cough without bronchospasm, and thus do not have EIA.

Physiological Documentation

Because a simple history of cough or wheezing may not reliably predict EIA, especially in those in whom a trial of preventive measures has not been successful, formal exercise testing may be required. The clinician needs to document airflow obstruction that reaches a peak during the recovery period, immediately after provocation. Two basic methods of provocation have been used, exercise and the inhalation of dry air (isocapnic hyperventilation, ISH). The latter is an acceptable surrogate for exercise, since the bronchoconstriction it induces is similar to that induced by exercise in terms of magnitude, time course, and refractory period. However, significant differences exist between the two provocation techniques. Exercise provocation, whether performed on an ergometer or a treadmill, leads to significantly greater increases in heart rate, metabolic rate, and oxygen consumption. Exercise, but not ISH, is accompanied by increased numbers of circulating basophils and increased circulating catecholamines and cyclic adenosine monophosphate. The differences in the last two parameters probably explain why the bronchodilatory response that characterizes exercise is not provoked by ISH. ISH does, however, have a number of advantages over exercise. The first relates to the ease with which the ISH protocol can be standardized; the other relates to the finding that oxygen consumption and heart rate are not increased with ISH. As a result, ISH is useful in differentiating EIA from occult cardiac disease and is especially valuable when elderly or cardiac patients are being evaluated.

The most commonly used protocol for the diagnosis of EIA in the United States is that published by O'Byrne et al and modified by Phillips et al (Fig. 47-6). This protocol registers changes in pulmonary function in response to varying rates of ventilation using dry air which contains a fixed CO_2 content of 4.9 percent to maintain isocapnia. Each ventilatory challenge is performed for 3 min; spirometry is performed at intervals thereafter (usually 2, 5, and 10 min after the end of hyperventilation). Serial increase in hyperventilation is continued until maximal voluntary ventilation is reached. If the FEV_1 falls 10 to 20 percent after provocation, the test is considered positive, confirming the diagnosis of EIA. Although some have pointed out that it is not necessary to condition air to subfreezing temperatures in order to perform the test, Scandinavian investigators have shown that assessing bronchoconstrictor responses to whole-body exposure to very cold air resulted in a significant increase in the number of asthmatic patients who experienced bronchoconstriction. Others have pointed out the need to assess athletes in the sport in which they compete, since they may not realize that a significant drop in FEV_1 has occurred due to their conditioning; manifestations of disease during challenge may be needed to document the decrease in lung function.

In order to optimize the validity, repeatability, and practicality of exercise testing for the diagnosis of EIA, a variety of

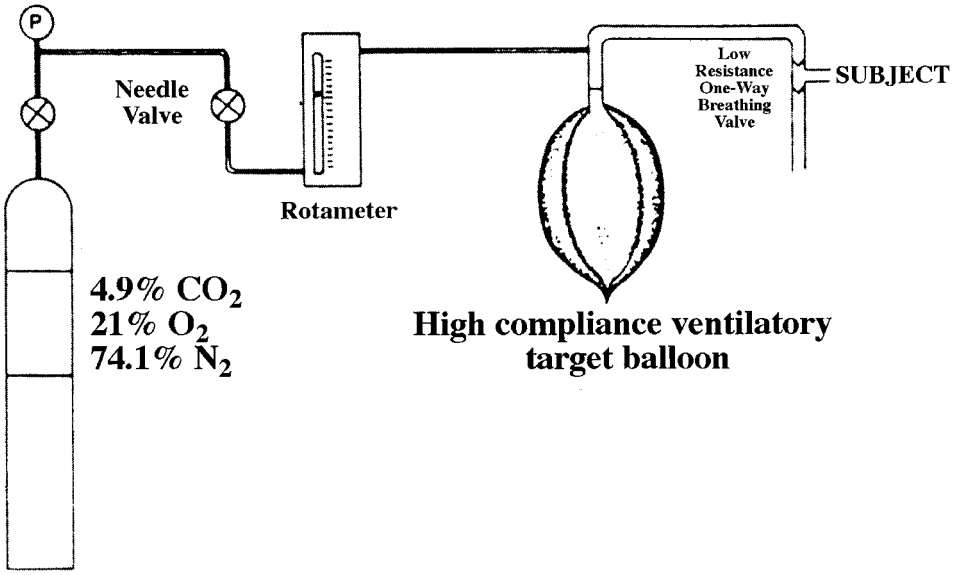

Figure 47-6 Apparatus for isocapnic hyperventilation challenge to diagnose EIA. *(Based on data of Phillips YY, et al: Eucapnic voluntary hyperventilation of compressed gas mixture: A simple method for bronchial challenge by respiratory heat loss.* Am Rev Respir Dis *131:31–35, 1985.)*

testing protocols have been used. Unfortunately, at times the criteria used to define a positive test in these different studies have been arbitrary. Although the optimal diagnostic algorithm for the assessment of EIA is still lacking, recent data reported on athletes from the 2002 Olympic Winter Games, compared eucapnic voluntary hyperventilation (EVH) with exercise testing outdoors in the cold (2°C and 45 percent humidity). The EVH test for 6 min with cold, dry air proved to be best in assessing the presence of EIA.

In addition to the difficulties inherent in the standardization of the challenge protocol, the clinician must be aware of situations that can lead to false-negative evaluations. Specifically, it is important that all drugs that can attenuate bronchoconstrictor responses—such as calcium channel blockers, methylxanthines, cromolyn, and β-adrenergic agonists—be discontinued for a sufficient period before the evaluation.

Treatment

The treatment of EIA depends, in part, on the treatment of the underlying asthma since in general, patients with more severe baseline asthma are most inconvenienced by EIA (Table 47-4). It has been shown that inhaled steroids attenuate the development of EIA during provocation in the laboratory and increase the clinical threshold for developing EIA. Prophylactic measures to prevent EIA include avoiding exercises that expose the patient to cold, dry air and favoring those that expose the patient to humid air during exercise. Patients can reduce the severity of their EIA by breathing through the nose rather than through the mouth during exercise. Face masks (e.g., 3M Cold Weather Mask) can be used by the many people who find it impossible to breathe through the nose during intense exercise. It is still unclear whether physical training and improvement in work capacity can relieve symptoms of EIA. These methods should be useful, at least in theory, since a better-trained athlete may require a lower mandatory minute volume—which may lead to less water loss from the airways and less severe EIA. Two studies—one in Los Angeles and the other in Toronto—showed that exposure of patients with EIA to air high in ozone did not minimize EIA. This suggests that choosing a day to exercise on the basis of ozone will not help prevent EIA. A series of repeated short sprints has been shown to be effective in inducing the refractory state, which might then allow the athlete to exercise maximally without developing EIA. A warm-up period to induce the refractory period has been advocated to improve performance in the competitive athlete. However, this effect may not last for longer than 40 min.

Several classes of drugs have been shown to prevent EIA if administered just before (10 to 15 min) exercise. The

Table 47-4

Treatment of Exercise-Induced Asthma (EIA)

Treatment Immediately Before Exercise (10–20 min before)	Treatment of Underlying Disease (days before)
β-adrenergic agonists	Goal: Improved asthma control
Cromolyn sodium	Inhaled corticosteroids
Nedocromil	Systemic corticosteroids
? Anticholinergics	? Theophylline
? Inhaled furosemide	
? Leukotriene receptor antagonists	

list includes β-adrenergic agonists, cromolyn sodium, anticholinergics, and possibly rapid-release theophylline (see Table 47-4). The β-adrenergic agonists are the most effective drugs for use against EIA. They are 90 percent effective in preventing EIA when used just before exercise. They are especially useful if the patient has some reversible airway obstruction, since they also improve lung function before exercise. Longer-acting β-adrenergic agonists, have also been found to be effective in preventing EIA. The duration of protection they confer may approach 10 h or more. This may be important in preventing EIA in patients who do not have immediate access to an inhaler and anticipate the need for prophylaxis due to exercise scheduled for later in the day (i.e., students). It is interesting that the cough so often associated with EIA, appears to occur independently of the bronchospasm provoked by exercise. Although exercise-induced airway narrowing is prevented by the inhalation of β-adrenergic agonists before exercise, the cough is not.

Cromolyn sodium also has been shown to attenuate bronchoconstriction in most patients with EIA. Since it is not a direct bronchodilator, this medication will not be effective in those who seek reversal of pre-exercise bronchoconstriction. Cromolyn does, however, have two advantages over other agents. First, it does not contribute to tachycardia and is therefore useful in elderly patients or patients with cardiac problems. In addition, cromolyn has been shown to prevent the late bronchoconstrictor response to exercise. Related drugs (including nedocromil, minocromil, and oxatomide, but not ketotifen) have similarly been shown to be effective against EIA.

Anticholinergics, such as ipratropium bromide, prevent airway narrowing after exercise in a high percentage of patients with EIA. They are especially useful in those who experience a rapid bronchodilating response to the drug. However, for most patients, the slow onset of action limits the effectiveness of these agents after bronchodilation has occurred.

Theophylline with its weak bronchodilatory effects, high side-effect profile, and slow onset of action, is not recommended for routine use as pretreatment for EIA. However, it has been shown to confer protection against EIA if 100 to 200 mg is taken 2 h before exercise. Other orally administered drugs that are not commonly used, but have the potential to be helpful in preventing EIA, are terbutaline, albuterol (2 h before exercise), some α-adrenergic agonists, verapamil, and sublingual nifedipine (the last two if taken 30 min before exercise), as well as the inhaled antihistamine clemastine. In addition, terfenadine was shown by one group to prevent EIA. For the elite athlete, only a few of the above drugs are approved for use in competition by the International Olympic Committee. They include inhaled albuterol, terbutaline, cromolyn, and nedocromil and oral theophylline. Long-acting β-agonists and all oral sympathomimetics are not approved.

Other directions in drug therapy for EIA hold promise for the future. Diuretics are known to be of some use in the prevention of EIA in adults. The most recent use of these agents indicates that inhaled furosemide (20 to 30 mg by inhalation 20 min before exercise) also attenuates EIA in children and can be combined with nedocromil to increase the protective effects of the drug. Leukotriene antagonists have been advocated by some, if protection of short-acting β-agonists alone is insufficient. Because of their low side-effect profile, leukotriene antagonists would appear to be well suited as single agents for use against EIA. However, additional head-to-head studies showing efficacy during exercise would be required before these agents can be favored over inhaled β-adrenergic agonists in routine prophylaxis against EIA. Increasingly, the use of performance-enhancing drugs has made it mandatory that competitive athletes with EIA specifically consult such organizations as the World Anti-Doping Agency (WADA; www.wada-ama.org), the U.S. Anti-Doping Agency (www.usantidoping.org), and other agencies such as the National Collegiate Athletic Association to assure that the treatments being used for the prevention of EIA are not prohibited for use in competition.

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Asthma: Clinical Presentation and Management

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Asthma can be defined as an inflammatory disorder characterized by variable airflow obstruction; airway hyperresponsiveness to specific and nonspecific stimuli; and symptoms of wheezing, chest tightness, cough, and, occasionally, dyspnea. Heightened airway responsiveness is a pathognomic feature of asthma. Clinically, increased airway responsiveness manifests as intolerance to air pollution, smoke, strong odors or fumes, and particulate matter such as dust. Exposure to these agents typically results in transient symptoms of cough and chest tightness. Emotional factors such as laughing or crying may exacerbate symptoms in a large number of patients.

Although asthma is frequently referred to as a disease, as if it were a single nosologic entity with a unique pathogenesis, experienced clinicians recognize that this is not the case. Asthma is more likely a syndrome, one that comprises multiple disorders manifesting common symptoms but having distinct and probably different pathogenetic and etiologic mechanisms. Phenotypic heterogeneity is evident not only in terms of the etiologic factors involved but also in terms of the severity and natural history of the disorder among different patients. Asthma has been classified as *extrinsic* or *intrinsic*, depending on the suspected role of allergens as etiologic factors. Atopic subjects are considered to have extrinsic asthma, while nonatopic subjects have intrinsic asthma. However, this nomenclature has been used with diminishing frequency, because it does not aid in establishing an etiologic diagnosis nor does it help in defining treatment strategies. The presence of atopy, often defined by the presence of skin test sensitivity to aeroallergens, does not, by itself, indicate that allergens are important triggers of asthma, since a large percentage of skin-sensitive persons report no allergic symptoms. Moreover, exercise and viral respiratory infections may play a more prominent role than allergens as triggers of symptoms in some atopic subjects. Classifying patients as having intrinsic asthma is problematic also, since it implies that all possible allergens in the environment have been excluded as etiologic factors—a task that is nearly impossible to achieve.

Although allergens are often triggers of acute asthma, there is a growing appreciation of their role as inducers of subclinical inflammation that may lead to enhanced airway responsiveness and greater susceptibility to the provocative effects of exercise and viral infections. In this regard, it is important to understand the distinction between triggers and etiologic factors. Whereas triggers may lead to symptoms, they do so only in susceptible persons who already possess the underlying asthmatic diathesis. In cases of occupational asthma, the disease can often be classified according to its etiology. In these circumstances, not only is the specific agent that triggers symptoms known, but the same agent is usually the underlying cause of asthma. Another category of asthma is that which is exercise induced. The term *exercise-induced asthma* is somewhat misleading, suggesting that exercise is the cause of the asthma. In fact, exercise is not a cause of asthma. Rather, it is one of many nonimmunologic triggers that produce symptoms in patients who already have the disease.

Perhaps the most useful classification of asthma is that based on levels of severity. This approach has facilitated the

development of rational treatment guidelines that have been endorsed by expert physicians throughout the world. This classification, as well as management strategies based on it, is discussed later in this chapter. However, patients move among different severity classes so these schemes have limited usefulness. Future guidelines should place increased emphasis on the burden that asthma places on patients as well as the risks that it poses for them.

CLINICAL PRESENTATION AND DIAGNOSIS

The diagnosis of asthma is made clinically, usually on the basis of a history of typical symptoms and confirmatory, objective evidence of variable airflow obstruction. The diagnosis of asthma is usually made accurately, although the degree of diagnostic accuracy is probably patient-age dependent. For example, asthma diagnosis in young adults is usually not difficult, since there are few other conditions that mimic asthma or confound its clinical presentation. With increasing age, cardiovascular disease and other forms of chronic lung disease are more common, and the differential diagnosis of episodic chest symptoms is more extensive. Finding an irreversible component of airway obstruction in asthmatics adds to the challenge of distinguishing between asthma and tobacco-related chronic obstructive pulmonary disease (COPD), in current and exsmokers. Because the predictive value of clinical and laboratory findings in establishing the diagnosis of asthma appears to decline with advancing age, the probability of misdiagnosis is highest in the elderly, who have the same high asthma prevalence (4 to 7 percent) as younger adults. The following clinical and laboratory manifestations are important in consideration of the diagnosis of asthma.

History

The history of symptoms, their pattern of occurrence, precipitating or aggravating factors, and the profile of a typical exacerbation are important elements of the clinical evaluation. During an acute episode, usual complaints include wheeze and a sensation of chest tightness. Breathlessness may also occur, although this symptom is often interpreted as a sensation of having difficulty inspiring, or "getting air in." This sensation is probably due to dynamic lung hyperinflation that accompanies acute asthma episodes. When there is hyperinflation, further inspiratory efforts are made against a higher respiratory system recoil pressure. Cough may also be present; on occasion, it may be the sole presenting manifestation of an episode of asthma. Symptoms may occur abruptly or evolve slowly over days or weeks. The frequency and severity with which symptoms occur vary considerably within the asthmatic population. Although no single symptom is specific for asthma, wheezing is a useful sign, since most asthmatics complain of more than just rare episodes of wheezing, and nonasthmatics rarely report frequent wheezing. Especially in younger patients, the symptom of chest tightness is also helpful, since it occurs more often in association with asthma than with other pulmonary or cardiac disorders. Chest symptoms that vary by season and are accompanied by symptoms of irritation of other mucous membranes, such as conjunctivitis and rhinitis, are typical of allergic asthma. Whereas pollens and some mold spores are likely to provoke seasonal symptoms, indoor allergens, such as house dust mites, cockroaches, and animal dander proteins are more apt to result in perennial symptoms.

Early-morning symptoms or nocturnal episodes are very common in adult asthmatics. It is important to distinguish whether nocturnal symptoms are due to asthma, gastroesophageal reflux, or angina. Typically, nocturnal asthma symptoms occur between 4:00 and 6:00 A.M.; usually they are relieved with administration of inhaled bronchodilators. This contrasts with gastroesophageal reflux, which causes similar symptoms soon after the patient reclines at night, or cardiovascular symptoms, which can occur at any time.

Viral respiratory infections are a common cause of exacerbations of asthma in adults. The viruses most commonly implicated are rhinovirus, respiratory syncytial virus, influenza virus, and parainfluenza virus. *Mycoplasma* and *Chlamydia* are also associated with exacerbations of asthma; other bacterial infections are not. It should be noted that viral respiratory infections can evoke an increase in airway responsiveness in otherwise healthy persons, causing self-limited episodes of chest tightness, cough, and wheezing that may last for as long as 8 to 12 weeks. Although these episodes are frequently diagnosed as asthma, the disappearance of symptoms after 8 to 12 weeks suggests that the illness was due to a temporary, postviral increase in airway responsiveness.

Exercise-induced Asthma

A history of symptoms after heavy exertion, especially in cold air, is highly suggestive of exercise-induced asthma. Typically, the patient experiences symptoms at the end of exercise, rather than during its performance. Excessive coughing after exercise, sometimes in the absence of wheezing, may also be a sign of asthma. Patients with COPD or heart failure may experience exertional dyspnea, but, as a rule, these patients do not develop symptoms of chest tightness, cough, and wheeze.

Asthma and Aspirin Sensitivity

The association of asthma and sensitivity to aspirin and other nonsteroidal anti-inflammatory drugs (NSAIDs) is well established. Of particular note is the triad of asthma, nasal polyps, and aspirin intolerance. This condition is thought to affect 2 to 3 percent of all asthmatic patients and up to 20 percent of patients with severe asthma. In this syndrome, the first symptom is usually rhinitis. This is followed several years later by the development of aspirin intolerance and asthma symptoms and finally, usually much later, nasal polyps. Nasal polyps are usually bilateral and originate from the turbinates, as well as the paranasal sinuses. Aspirin-induced asthma has been associated with enhanced leukotriene production and

mast cell activation, but mechanisms responsible for these events remain unclear.

Although aspirin-induced asthmatic episodes often resemble allergic reactions, there is no evidence that IgE-related immunologic mechanisms are at work. As a rule, aspirin intolerance is associated with severe asthma that is often resistant to therapy, including glucocorticoid therapy. The diagnosis of aspirin intolerance and asthma is made on the basis of the history and clinical findings of sinusitis and nasal polyps; it can be confirmed by aspirin challenge procedures. β-Adrenergic receptor–blocking drugs, including those contained in topical ophthalmic preparations, can also precipitate severe, acute, and sometimes fatal asthmatic episodes. Accordingly, beta blockers are contraindicated during acute asthma exacerbations and the risk-benefit ratio should be considered before they are used in stable outpatients with asthma.

Occupational Asthma

Asthma related to occupational exposure can often be identified on the basis of a typical history of symptoms during the work week and improvement over the weekend. Symptoms may occur during exposure to the etiologic substance, or they may be delayed until the evening or night after the work day. It is important to distinguish between occupational asthma that is triggered by nonspecific irritants in patients with preexisting or concurrent asthma and asthma that arises de novo as a consequence of exposure to a specific etiologic agent. A number of natural and synthetic chemicals are known to cause asthma by IgE-mediated mechanisms, as well as by nonallergic mechanisms of unknown origin. The diagnosis of occupational asthma is based on a history of typical symptoms, the presence of variable airflow obstruction, and a demonstrable link between asthma and workplace exposure.

Physical Examination

Wheezing, the most characteristic physical finding in asthma, is caused by turbulent airflow through narrowed airways. In asthma, wheezing is usually present during expiration, although it may be present during inspiration as well. The quality of wheezing should not be considered predictive of the degree of obstruction in an individual patient. Patients who are asymptomatic, or who complain only of cough, may demonstrate end-expiratory wheezing, although this is a nonspecific and insensitive sign of asthma. It is important to note that wheezing of any character is not specific for asthma; notably, in cases of very mild or very severe airway obstruction, wheezing may be absent.

Clinical signs of rhinitis, sinusitis, and nasal polyps are seen more commonly in patients with asthma than in those with other chronic lower respiratory tract disorders or congestive heart failure. Chronic sinus disease may be difficult to diagnose on clinical grounds; imaging studies may be required. Marked weight loss or severe wasting is not seen in asthma but is commonly seen in severe emphysema. Signs of hyperinflation and diminished breath and heart sounds are usually observed during an acute exacerbation. Use of accessory muscles of respiration and the presence of pulsus paradoxus are signs of severe airway obstruction and are usually observed during acute episodes. Because ventilatory effort can be diminished with respiratory muscle fatigue, the absence of pulsus paradoxus does not preclude severe airway obstruction. Stridor, a high-pitched inspiratory sound, heard best with auscultation over the upper airways, should prompt a further search for causes of upper-airway obstruction, including vocal cord dysfunction, tracheal or bronchial stenosis, vocal cord paralysis, upper-airway tumors, and airway narrowing due to thyroid enlargement.

Laboratory Studies

The use of laboratory studies in the diagnosis of asthma is largely restricted to spirometry. Skin testing and serologic studies may also be useful in defining allergic triggers of asthma in some patients, although the clinical history often provides more clinically relevant information regarding the relation between symptoms and exposure. Radiographic studies, blood tests, and more extensive lung function studies are used to exclude other conditions that may mimic asthma or complicate its clinical presentation.

Pulmonary Function Tests

Pulmonary function tests are important for confirming the diagnosis of asthma, establishing the severity of the disease, and monitoring the response to therapy. The diagnosis of asthma is usually confirmed by objective demonstration of airflow obstruction by spirometry. In addition, there should be evidence of significant improvement in the 1-s forced expired volume (FEV_1) acutely after bronchodilator administration, or with repeated measurement over time. Unfortunately, there are no standard criteria for judging the degree of reversibility after bronchodilator administration for diagnostic purposes. Although a postbronchodilator increase in FEV_1 of greater than 12 percent is often considered evidence of reversible airway obstruction, this level is arbitrary and lacks sensitivity or specificity for detecting asthma. Clinical experience has shown that there is substantial overlap in the degree of bronchodilator reversibility when one compares patients with asthma to those with COPD. Thus, while a marked spirometric response to inhaled bronchodilator confirms reversibility of airway obstruction and is strongly indicative of asthma, this finding does not rule out COPD, nor does the lack of an acute bronchodilator response rule out asthma.

Since office spirometry is inexpensive and easy to perform, there seems to be little justification for sacrificing diagnostic sensitivity and specificity by using peak expiratory flow (PEF) measurements made in the office for the initial diagnosis of asthma. However, home monitoring of variability in PEF may be of diagnostic use, especially in patients with mild, intermittent symptoms who often demonstrate normal spirometry during physician visits.

Measurement of lung volumes is useful for excluding restrictive lung disease. In asthma, an increase in residual volume is typically seen, reflecting airway closure at a lung

volume that is higher than normal. During acute asthmatic episodes, functional residual capacity and total lung capacity may also be increased.

Measurement of diffusing capacity of the lung (D_{LCO}) deserves mention because of its value in differentiating patients with emphysema from those with asthma. Emphysema, characterized by alveolar septal destruction and loss of pulmonary capillary volume, is associated with a reduced D_{LCO}; by contrast, the D_{LCO} is usually normal or supranormal in asthma.

Bronchial Challenge Testing

Abnormal airway responsiveness, a sine qua non for asthma, is detected in the laboratory by an exaggerated response to inhaled pharmacologic agents, such as histamine, adenosine, or methacholine; or physical stimuli, such as exercise and hyperventilation. The correlation between different airway challenge tests is remarkably good, especially between histamine and methacholine and, to a lesser extent, among other pharmacologic agents, and the physical measures exercise and cold air hyperventilation.

The largest experience with pharmacologic challenge testing is with intermittent and continuous aerosol generation techniques using methacholine or histamine. The two techniques give remarkably similar results when airway responsiveness is expressed as the concentration of drug causing a 20 percent fall in FEV_1 (PC_{20}), as determined from dose-response curves. Some studies have shown that 100 percent of patients with current asthma symptoms demonstrate a PC_{20} at histamine concentrations less than or equal to 8 mg/ml, while others, using methacholine, have reported a sensitivity of approximately 85 percent at the same PC_{20} threshold. False-negative results can be obtained in patients who experience only intermittent symptoms and are tested when they are asymptomatic. Indeed, atopic patients with seasonal asthma symptoms may demonstrate PC_{20} greater than 8 mg/ml when tested "out of season." False-negative challenge responses may also occur in patients with occupational asthma if tests are performed remote in time from exposure to the etiologic agent. Whereas diagnostic tests are more likely to be performed in patients who have had recent symptoms, pharmacologic challenges are generally conceded to have a low false-negative rate. Thus, when a diagnostic threshold PC_{20} of less than or equal to 8 mg/ml is used, pharmacologic challenges are sensitive tests with a high negative predictive value (i.e., a PC_{20} greater than 8 mg/ml excludes a diagnosis of asthma with a high degree of accuracy). Most surveys indicate that the specificity of pharmacologic challenge testing is approximately 90 percent when a PC_{20} of less than or equal to 8 mg/ml is used as the diagnostic threshold. The prevalence of abnormal responsiveness in nonatopic, nonasthmatic subjects who have no history of prior respiratory problems ranges from 5 to 10 percent; in such patients, the term "false-positive" should be used with caution. The significance of abnormal responsiveness in this population is uncertain. For example, it is not known whether the retention of abnormal responsiveness in former asthmatics predisposes to relapse later in life. Likewise, it is not known whether abnormal airway responsiveness predisposes to the subsequent development of asthma or COPD.

Physical measures to assess airway responsiveness include exercise and isocapnic hyperventilation. Both stimuli induce airway obstruction as a consequence of cooling or drying of the airway mucosa. The requirement for strenuous physical work limits the use of such challenges to persons who are physically capable of performing them.

Clinical Application of Bronchial Challenge Tests

The specificity of bronchial challenge tests in the diagnosis of asthma is compromised further by the finding that abnormal airway responsiveness is associated with a number of other disorders, including cystic fibrosis, COPD, and heart failure. Moreover, conditions associated with airway injury or inflammation—such as viral respiratory infections, exposure to pollutants, and exposure to aeroallergens—can induce a temporary state of abnormal responsiveness. Accordingly, pharmacologic challenges are not useful for discriminating between asthma and COPD in patients with abnormal spirometry. Hence, airway challenge testing is used, perhaps most usefully, in evaluating patients who have unexplained chest symptoms and normal spirometry results.

Since the clinical history, by itself, has little value in establishing a diagnosis of asthma in patients with atypical symptoms, bronchial provocation testing may be especially useful for excluding a diagnosis of asthma because of the low false-negative rate and high negative predictive value. Conversely, the finding of abnormal responsiveness in such patients may not be diagnostic of asthma because of the test's poor positive predictive value and the possibility that hyperresponsiveness may also reflect self-limited pathology that occurs with transient airway inflammation secondary to viral infections. In any event, the demonstration of abnormal airway responsiveness may be taken as presumptive evidence of an association between symptoms and abnormal responsiveness, thus providing an objective basis for asthma therapy.

Blood Tests

Arterial blood gases are typically normal in patients with chronic, stable asthma. During an acute, severe episode, hypoxia is often present. Arterial P_{CO_2} is typically reduced owing to hyperventilation. With severe obstruction, arterial P_{CO_2} may rise because of respiratory muscle fatigue and an inability to maintain the required alveolar ventilation.

Peripheral blood eosinophilia (greater than 4 percent or 300 to 400 per mm^3) may be seen in both allergic and nonallergic asthmatics. When present, eosinophilia may be used to support a diagnosis of asthma; however, its absence is of no value in excluding asthma. Unusually high eosinophil counts (greater than 800 per mm^3) suggest the presence of other disorders, such as allergic bronchopulmonary aspergillosis, Churg-Strauss syndrome, tropical eosinophilia, and Loeffler's

syndrome. It should be noted that eosinophilia may not be present if the patient is taking corticosteroids.

Epidemiologic studies have demonstrated an association between asthma and total serum immunoglobulin E (IgE) levels, standardized for age and sex. Whether this association signifies that aeroallergens are prominent etiologic factors, or that immunologic processes in the pathogenesis of asthma are capable of stimulating IgE production as an unrelated phenomenon needs further definition. Studies have also shown a relationship between total serum IgE and asthma in patients with negative skin tests. In addition, other studies have reported that elevations in total IgE are strongly associated with asthma, whereas skin test reactivity is more closely related to allergic rhinitis. Importantly, IgE levels are used to calculate the dose of the anti-IgE antibody omalizumab, when it is used for asthma treatment as discussed below.

Other blood tests may be useful for ruling out vasculitis or allergic bronchopulmonary fungal disease. However, these tests should be employed only when clinical suspicion warrants pursuit of uncommon causes of asthma symptoms.

Sputum Examination

In research studies sputum eosinophil counts have been shown to predict clinical outcomes, particularly exacerbations when corticosteroids are withdrawn, but more research needs to be done before sputum examination can be used as a clinical tool.

Allergy Tests

Tests to determine whether the patient is allergic and to investigate the role of specific allergens as a cause of asthma are of value in some patients, particularly when the clinical history suggests that specific aeroallergens are important triggers in a particular patient, and when asthma symptoms are accompanied by other symptoms typical of allergic disease, such as rhinitis and conjunctivitis. In selected populations, evaluations for perennial or indoor allergens, such as dust mite, cockroach, or animal dander have become increasingly important.

The components of an allergic evaluation include a detailed history of the patient's environment and possible triggers, followed by tests of allergic sensitivity. Sensitivity to a particular allergen (or the presence of specific IgE antibody) can be verified by skin tests or in vitro serum antibody studies. Allergy evaluation is useful for developing avoidance treatment strategies or, in selected cases, for developing immunotherapy regimens.

Radiography

Because the chest radiograph is generally unremarkable in patients with uncomplicated asthma, it is used primarily to exclude other causes of respiratory symptoms. Nonspecific radiographic findings, such as overinflation, prominent hilar vessels, and bronchial wall thickening may be seen. Computed tomography may demonstrate atelectasis, bronchial wall thickening, or mucus impaction.

Exhaled Nitric Oxide

In research studies low eNO values have demonstrated reasonable sensitivity and specificity in discriminating between subjects with asthma and normal subjects, but more research needs to be done before eNO can be used as a diagnostic tool.

Differential Diagnosis

There are a number of conditions to consider in the differential diagnosis of asthma and these are listed in Table 48-1.

Table 48-1

The Differential Diagnosis of Asthma

Condition	Comment
Other airway diseases	
COPD	Significant smoking history Airflow obstruction less reversible Reduced D_{LCO}
Bronchiectasis	Maybe secondary to numerous disorders Patients usually produce purulent sputum Computed tomography usually diagnostic
Reactive airways viral syndrome	Transient, usually resolves after several weeks
Rhinosinusitis	Usually report nasal congestion and post nasal drip Common co-morbid illness accompanying asthma
Gastroesophageal reflux disease	Usually have other complaints but may be silent Common co-morbid illness accompanying asthma
Congestive heart failure	Usually have exertional dyspnea but not at rest Echocardiography helpful
Laryngeal dysfunction	Stridor Diagnosis challenging, laryngoscopy helpful May co-exist with asthma
Upper airway obstruction	May or may not exhibit stridor Flow-volume loop may be helpful Endoscopy diagnostic

MANAGEMENT OF ASTHMA

Successful management of the asthmatic patient requires an appreciation of two basic principles. First, asthma exhibits considerable heterogeneity with respect to etiology, clinical presentation, severity, natural history, and response to therapy. Because of this heterogeneity, it is unlikely that a single management approach will work for all patients. Thus, therapy must be tailored to the individual patient. The second principle recognizes that in each patient, symptom severity may vary considerably over time. For example, some patients may experience a remission of symptoms during adolescence, only to have them recur with even greater severity later in life. Even when the disease remains relatively stable over long intervals, intercurrent flares that arise as a result of seasonal allergies or infection are the rule in asthma. Thus, the patient should be monitored regularly, and treatment should be modified on an ongoing basis to meet the patient's current needs.

Chronic Stable Asthma

A number of comprehensive treatment guidelines drafted by multidisciplinary expert committees have been published. In the following discussion, no attempt is made to recapitulate published guidelines; rather, there is an effort to summarize the recommended general approaches, point out gaps in information, and highlight areas where controversy exists. The management of persistent asthma in adults is highlighted in Table 48-2.

Nonpharmacologic Therapy

Recent studies suggest that patient education and environmental control programs are effective in reducing asthma morbidity, although additional research is needed to better determine which methods are the most effective and which patients benefit the most.

Education

The goal of asthma education is to improve patient understanding of the disease and its management and, consequently, to improve adherence to treatment recommendations. Another aim is to engage the patient in self-management practices, especially in terms of identifying and avoiding asthma triggers and recognizing and treating exacerbations of asthma in their earliest stages.

Controlled trials evaluating structured education and self-management programs for adult asthmatics generally show that such programs result in better asthma control and decreased emergency room visits and hospitalizations. The success of patient education programs is, to a large extent, dependent on their format. For example, individual one-on-one educational sessions and sessions with small groups of patients have been shown to be of comparable efficacy; both are more effective than provision of written materials alone in terms of symptom control, use of proper inhaler technique, application of environmental control practices, and encouragement of physical activity. However, the provision of written materials alone may be sufficient to decrease hospital and emergency room use. Personal contact with a knowledgeable professional is considered superior to provision of either audiovisual or written materials. Like drug therapy, the educational program, as well as the method and frequency of reinforcement, should be tailored to the individual.

The educational program should impart to the patient an understanding of the disease, including the knowledge that symptoms are a product of airflow obstruction and therapy is designed to both prevent and relieve the obstruction. The patient should understand that asthma is a chronic disorder, unlikely ever to go into complete remission, and appreciate that symptoms will fluctuate and occasional exacerbations are to be expected. In addition, reassurance should be provided that, with proper treatment, these events can be minimized; in most cases, a normal lifestyle and life expectancy can be anticipated.

Since educational programs that include self-management strategies are superior, they should also encompass a discussion of the patient's individual treatment plan, including the purpose of different drugs, as well as their side effects. Distinguishing between drugs that control or prevent symptoms and those that relieve symptoms is necessary to reinforcing the importance of "controller" medications that offer no immediate relief of symptoms. Instruction in the proper use of inhaled medications is of obvious importance; so, too, is a description of likely triggers of episodes of asthma and ways to avoid such triggers. Finally, teaching the patient to recognize and intervene in exacerbations during their earliest stages can be helpful in avoiding more serious morbidity and, in some cases, mortality. Educating the patient in self-administration of oral glucocorticoids and providing a telephone number where professional assistance is available around the clock are, in our experience, crucial elements of a management program designed to reduce morbidity and hospitalizations.

Environmental Control

An important, often overlooked part of the management plan for all asthmatics, especially those with severe asthma who remain symptomatic despite intensive drug therapy, consists of measures to control environmental triggers. Avoidance of aeroallergens, viral respiratory pathogens, air pollution, and certain drugs can prevent exacerbations, reduce the need for drug treatment, and decrease utilization of emergency facilities. Of perhaps greater importance is avoidance of factors that may contribute to longer-term, airway inflammation responsible for abnormal airway responsiveness. Allergens from house dust mites, cockroaches, molds, and pets, particularly cats and dogs, have been associated with asthma. While the house dust mite is recognized as a significant cause of asthma throughout the developed world, the relative importance of different indoor allergens may vary among populations. For example, cockroach allergen may play a more prominent role in asthma in inner-city populations. Complete removal from exposure to house dust mites has been shown to reduce

Table 48-2

Management of Persistent Asthma in Adults

Asthma Severity*	**Mild***	**Moderate***	**Severe***
Daytime symptoms	2–6 days/week Usually no reduction in activity	Daily Exacerbations reduce activity	Continual Significant reduction in activity
Nocturnal awakenings	More than two monthly	More than once weekly	Most nights
Relief medication use	Less than daily	Daily	Several times daily
Lung function FEV_1	>80% Predicted	60–80% Predicted	<60% Predicted
PEE variability	<30%	>30%	>30%
Controller medications	Low-dose ICS (highly preferred) OR Leukotriene receptor antagonist OR Theophylline SR	Low–moderate dose ICS + long acting β-agonist OR Low–moderate dose ICS + Leukotriene receptor antagonist OR Low–moderate dose ICS + theophylline SR	Moderate–high dose ICS + long acting β-agonist AND Oral steroids Anti-IgE therapy
Relief medications	Short-acting MDI	Short-acting MDI	Short acting MDI Consider HFN
Diagnose and treat other conditions	Manage environment	Manage environment	Manage environment
	Treat rhinosinusitis	Treat rhinosinusitis Assess for GERD with esophageal pH study	Treat rhinosinusitis Assess for GERD with esophageal pH study
Written action plans	Consider	Recommended, base on PEF/FEV_1	Recommended, base on PEF/FEV_1
Immunotherapy	Consider	Consider	Contraindicated
Monitoring	Annual spirometry	Annual office spirometry Monitor PEF Consider home spirometry	Annual office spirometry Monitor PEF Consider home spirometry
Office visits	Annual	2–3/year	At least every 3 months

ICS = inhaled corticosteroid; PEF = peak expiratory flow; FEV_1 = one second forced expiratory volume; SR = sustained release. Usual or initial outpatient status.

asthma severity and airway hyperresponsiveness. However, incomplete or partial reductions of dust mite counts are of questionable benefit in improving asthma control. Occupational asthma due to low-molecular-weight chemicals is also more likely to abate if patients are completely removed from exposure to the offending agent early in the course of their disease. Most patients with chronic asthma have numerous triggers. Therefore, the impact of avoidance of any single trigger is likely to vary considerably from patient to patient.

Vaccination

Inactivated influenza vaccine may be safely administered to patients with asthma. It seems likely that influenza vaccination would decrease the incidence of exacerbations of asthma; however, this has not conclusively been shown. Patients with

asthma should receive inactivated influenza vaccine if there are no other contraindications and especially if they are elderly or have other co-morbid conditions that increase the risk of death from influenza infection.

Immunotherapy

Allergen immunotherapy also appears to be of benefit in highly selected patients with defined allergic triggers. As a rule, patients who have many allergic triggers tend to benefit less from immunotherapy than those with a single trigger. Patients who have mild- or moderate- persistent asthma not adequately controlled with inhaled medications may be considered for immunotherapy, but those with concomitant nasal symptoms appear to benefit the most. Although serious complications from immunotherapy are rare, they occur more frequently in patients with asthma. Furthermore, because of a high incidence of adverse systemic reactions, persons whose FEV_1 is less than 70 percent of predicted should be considered at high risk of complications from immunotherapy.

Pharmacologic Management

Current guidelines advocate classifying asthma according to clinical severity using symptoms, lung function, and drug use as variables. Disease stratification guides the rational use of controller agents, as discussed below. Drugs currently available to treat asthma (listed in Tables 48-3 and 48-4) are classified as long-term control medications or "controllers" and quick-relief medications or "relievers" on the basis of their principal pharmacodynamic and clinical effect. Thus, short-acting bronchodilators such as inhaled beta agonists or anticholinergics are considered quick-relief medications. Corticosteroids, long-acting beta agonists, leukotriene pathway inhibitors, cromolyn sodium, nedocromil sodium, sustained-release theophylline, and omalizumab are considered long-term control medications, since they are used to achieve and maintain control of symptoms and are usually used daily on a long-term basis. Former nomenclature that classified drugs according to whether or not they had bronchodilator or anti-inflammatory properties is discouraged, since some medications have anti-inflammatory as well as bronchodilator properties.

β-Adrenergic Agonists

Inhaled β_2-adrenergic agonists are the drugs of choice for relief of symptoms due to acute airway obstruction. Short-acting beta agonists have a rapid onset of action and 3- to 6-hour duration of activity. At recommended doses, inhaled beta agonists have few adverse effects. Since regular use of short-acting beta agonists has not been shown to be superior to as needed use of these agents, we recommend that these agents be used as needed.

Long-acting inhaled beta agonists have at least 12 hours duration of action and are not generally recommended for the short-term relief of acute symptoms, although formoterol has an onset of action as rapid as albuterol and can be used as a reliever. *Importantly, whereas long-acting beta agonists are generally the preferred agents to be used with inhaled steroids in combination therapy, they should not be used as monotherapy for the control of asthma of any severity.* The combination of formoterol and budesonide has been demonstrated to be effective when used as both a controller and relief agent and thus provides the advantage of a single device used for both purposes.

Theophylline

Theophylline now is primarily used as an adjunctive therapy, and for its steroid sparing effects, due to its narrow therapeutic index and the availability of safer and more effective alternatives. The steroid sparing effects of theophylline seem to occur at levels below the traditional therapeutic range of 10 to 20 mg/L. Thus, we recommend that the drug be titrated to steady-state serum concentrations of 5 to 10 mg/L or peak concentrations of no higher than 15 mg/L.

Anticholinergic Agents

These agents induce airway smooth-muscle relaxation by blocking muscarinic receptors on airway smooth muscle, inhibiting vagally mediated cholinergic tone. In general, the short-acting anticholinergic agent ipratropium is not as effective as beta agonists as bronchodilators in asthma. It remains to be seen whether the long-acting anticholinergic drug tiotropium will prove to be useful as an asthma treatment.

Glucocorticoids

Glucocorticoid steroids are the most effective agents available for treating persistent asthma. Inhaled steroids improve lung function when compared with placebo and reduce exacerbation rates. Patients with persistent asthma stabilized on inhaled steroids experience increased exacerbations when the steroids are withdrawn. Importantly, retrospective data suggest that the consistent use of inhaled steroids reduces asthma mortality. Finally, although the efficacy of inhaled glucocorticoids is clear, they suffer from important limitations. For example, the dose-response curve of inhaled steroids is relatively flat, meaning that higher doses are only incrementally better than low to medium doses. When there are persistent symptoms, rather than increasing the inhaled steroid dose the addition of long-acting beta agonists, leukotriene receptor antagonists, or theophylline provide superior bronchodilation and improve other outcomes, so that combination therapy is preferred.

Cromolyn Sodium and Nedocromil Sodium

Cromolyn sodium and nedocromil sodium are classified as controller agents, and because they are remarkably safe, these drugs are considered first-line agents in the treatment of children with asthma, although they are inferior to inhaled steroids with respect to most relevant outcomes. In adults, however, the drugs are most often prescribed for patients with mild disease, since responses are unpredictable.

Table 48-3

Asthma Medications

Type	Class	Drugs	Indication/Comment
Quick-relief	Short-acting β-adrenergic agonists	Albuterol: PO, MDI, HFN Levalbuterol: HFN, MDI Pirbuterol: MDI Metaproterenol: PO, MDI, HFN Terbutaline: PO, MDI, SC Isoproterenol: MDI, HFN, IV, SL Bitolterol: MDI, HFN	First-line agents for fast relief of bronchospasm, used for all severity classes MDI β_2-selective adrenergic agonists are preferred
	Adrenergic agonist	Epinephrine: MDI, SC	
	Anti-cholinergic	Ipratropium bromide: MDI, HFN	Also useful for patients intolerant of β-adrenergic agonists
Long-term controllers	Inhaled Corticosteroids	Beclamethasone dipropionate: MDI Budesonide: MDI, HFN Flunisolide: MDI Fluticasone: MDI Mometasone furoate Triamcinolone acetonide: MDI Ciclesonide*	Persistent asthma of any severity, may be used in combination with systemic steroids
	Systemic Corticosteroids	Methylprednisolone: IV, PO Prednisolone: PO Prednisone: PO	Severe persistent asthma not controlled with high dose inhaled steroids or for asthma exacerbations
	Cromones	Cromolyn sodium: MDI, HFN Nedocromil: MDI	Mild persistent asthma
	Long acting β-adrenergic agonists	Salmeterol: MDI Formoterol: MDI Sustained release albuterol: PO	Moderate–severe persistent asthma
	Anticholinergic	Tiotropium	FDA approved for COPD only
	Methylxanthines	Theophylline: PO	Alternate therapy for mild persistent asthma, add on to steroids for moderate–severe persistent asthma
	Leukotriene pathway inhibitors	Montelukast: PO Zafirlukast: PO Zileuton: PO	Alternate therapy for mild persistent asthma, add on to steroids for moderate–severe persistent asthma
	Combinations	Fluticasone/Salmeterol: MDI Budesonide/Formoterol: MDI*	Moderate–severe persistent asthma
	Monoclonal anti-IgE antibody	Omalizumab: SC	Moderate–servere allergic asthma, has steroid sparing properties

PO = oral; MDI = inhaler; HFN = liquid for high flow nebulizer; IV = parenteral; SC = subcutaneous; SL = sublingual.
** Not FDA approved.*

Table 48-4

Detailed Asthma Medications

Type	Class	Mechanism(s)	Indication	Name/route(s)	Dose	Side Effects	Comments
Symptom reliever	Short-acting β_2-adrenergic agonist	β-adrenergic agonist selective for type 2 beta receptor, increases cAMP, activates protein kinase A, and induces bronchodilation by multiple mechanisms	First-line agents for fast relief of bronchospasm	Albuterol: oral, inhaled, and nebulized	Oral: 1 tab every 3–4 h, slow release form available Inhaled: 2 puffs every 4 h, or 30 min prior to exercise for prevention of bronchoconstriction Nebulized: every 3–4 h	Tachycardia, palpitations, nervousness, hypokalemia, tremor	First choice for bronchodilation. Inhaled route is preferred over oral route for faster onset of action and fewer side effects. Increased use or decreased effectiveness may be sign or worsened control. Not recommended for long-term treatment. Chlorofluorocarbon (CFC) propellent in MDI being phased out. HFA formulation has no CFCs. Nebulized solution may be mixed with ipratropium.
				Levalbuterol: Nebulized	Nebulized every 6 to 8 h	Fewer side effects than racemic albuterol	Levo enantomer of albuterol, nebulized combination with ipratropium not studied for compatability. Not been shown to be significantly superior to albuterol.
				Pirbuterol: Inhaled	Inhaled: 1 to 2 puffs every 4 to 6 h		
				Metaproterenol: oral, inhaled, and nebulized	Oral: 1 tab 3–4 times per day Inhaled: 2 puffs every 4 h inhaled Nebulized: every 4 to 6 h		Rare adverse cardiac events have been reported. Not recommended as first-line drug.

	Terbutaline: oral, inhaled, subcutaneous	Oral: 1 tab every 6 h (max 15 mg/d) Inhaled: 2 puffs every 4–6 h Subcutaneous: 0.25 mg, may repeat after 30 min, max 0.5 mg in 4 h		Not recommended as first-line drug as beta agonist side effects more commonly encountered. Intravenous solution available for tocolysis.
	Bitolterol: inhaled, nebulized	Inhaled: 2 puffs every 8 h Nebulized: every 6–8 h		Cannot be mixed with other medications in nebulized solution.
Nonselective beta (β_1,β_2,)-adrenergic agonist	Isoproterenol: inhaled, nebulized, sublingual, intravenous	Inhaled: 1–2 puffs every 4 h Nebulized: 5–15 breaths every 5–10 min, max of 5 times per day Sublingual: 10–20 mg every 3–4 h, max 60 mg per day Intravenous: 2–10 μg per min.	Tachycardia, palpitations, nervousness, hypokalemia, tremor, headache, seizure, paradoxical bronchospasm	Used for anesthesia-induced bronchospasm.
Nonselective (β_1,β_2,α) adrenergic agonist	Epinephrine: Inhaled, subcutaneous	Inhaled: 1–2 puffs every 3 h Subcutaneous: 0.2–0.5 mg every 2 h needed	As for isoproterenol plus convulsions, chills, fever, hallucinations	Not recommended as first-line medication

(*Continued*)

Table 48-4

(*Continued*)

Type	Class	Mechanism(s)	Indication	Name/route(s)	Dose	Side Effects	Comments
	Anticholinergic	Muscarinic receptor antagonist, (subtypes M_3 and M_2), blocks action of acetylcholine on airway smooth muscle resulting in bronchodilation, reduction in mucus secretion	Quick relief of symptoms	Ipratropium bromide: inhaled, nebulized	Inhaled: 2 puffs every 4–6 h Nebulized: every 6 h	Dry mouth, bitter taste, nasal congestion	Alternative for patients intolerant of beta agonists. May be mixed with albuterol in nebulized solution. Slower onset of action than beta agonists.
Long-term controllers	Combination inhalers	Combine the anti-inflammatory properties of glucocorticoids and the bronchodilation of long-acting beta-agonists	First line controller agents for moderate–severe persistent asthma	Fluticasone/ salmeterol Budesonide/ formoterol	Inhaled: 1 puff twice daily Not available in the U.S.	Same as for individual components	
	Inhaled corticosteroids	Anti-inflammatory: effects are broad, bind to glucocorticoid receptors and mediate transcriptional repression of a variety of inflammatory mediators, decreases infiltration of	Mild persistent–severe persistent asthma	Beclomethasone dipropionate Budesonide Flunisolide Fluticasone Mometasone furoate Triamcinolone acetonide	1–3 puffs twice daily One puff twice daily 2–4 puffs per day 1–3 puffs per day 2–3 puffs four times daily or 4–6 puffs twice daily	Skin thinning, easy bruising, adrenal suppression, cataracts, osteoporosis, oral candidiasis, mild growth retardation in children, hoarseness	Mouth washing after use reduces risk of oral candidiasis.

		airways by several inflammatory cell types, reduces cytokine and chemokine secretion by several cell types					
	Systemic corticosteroids	Anti-inflammatory	Severe persistent asthma not controlled with high-dose inhaled corticosteroids or used in taper dosing for asthma exacerbations	Methylprednisolone: intravenous Prednisolone: oral Prednisone: oral	60–500 mg daily in divided doses 5–60 mg daily or every other day	Skin thinning, easy bruising, adrenal suppression, cataracts, osteoporosis, oral candidiasis, psychosis, hyperglycemi a fluid retention	Dose should be titrated to minimum required for desired asthma control
	Cromones	Anti-inflammatory	Mild persistent asthma	Cromolyn sodium: inhaled, nebulized Nedocromil: inhaled	2–4 puffs 4 times per day 2 puffs 4 times per day	Cough Cough, bitter taste	Favorable safety profile, maximum benefit may take 4 to 6 wk.
	Long-acting beta agonists	β adrenergic agonist selective for type 2 beta receptor, increases cAMP, activates protein kinase A, and induces bronchodilation by multiple mechanisms	Moderate–severe persistent asthma	Salmeterol: inhaled Formoterol: inhaled Sustained release albuterol	1 puff every 12 h 1 puff every 12 h 1 tab every 12 h	Tachycardia, anxiety, headache, hypokalemia	Inhaled form has fewer side effects than oral. Salmeterol has both CFC and dry powder forms. Long-acting beta agonists should not be used to treat acute attacks. LABAs should always be used in combination with anti-inflammatory medications for asthma.

(*Continued*)

Table 48-4

(*Continued*)

Type	Class	Mechanism(s)	Indication	Name/route(s)	Dose	Side Effects	Comments
	Methylxanthines	Phosphodiesterae inhibitor, increases cAMP, activates protein kinase A, and induces bronchodilation by multiple mechanisms	Alternate therapy for mild persistent asthma Add-on to steroids for moderate–severe asthma	Theophylline: sustained release: oral	Variable dosing schedules	Nause/vomiting. Toxic level—seizures, tachycardia, arrhythmia	Absorption and dosing dependent on several factors including brand, comorbidities, and medication interactions. Monitoring of drug levels required.
	Leukotriene pathway inhibitors	Cysteinyl-leukotriene receptor type 1 antagonists, blocks action of leukotrienes LTC_4 and LTD_4, reduces inflammation, and causes bronchodilation	Alternate therapy for mild persistent asthma	Montelukast: oral Zafirlukast	1 tab once daily 1 tab twice daily	Rare—neurologic/hepatic complications reported	Association with Churg-Strauss syndrome initially reported but likely due to steroid withdraw and not leukotriene inhibitor.
		5-lipoxygenase inhibitor, reduces production of LTB_4, LTC_4, and LTD_4 by a variety of cell types, reduces inflammation, and is a modest bronchodilator	Add-on to steroids for moderate–severe asthma	Zileuton	1 tab 4 times daily		

	Anti-IgE monoclonal antibody	Binds IgE antibodies	Add-on to steroids for moderate–severe persistent allergic asthma	Omalizumab	150–375 mg subcutaneously every 2 or 4 wks; dosage determined by IgE level before first treatment and body weight	Injection site reaction, rash, headache, anaphylaxis	Not indicated if atopy not present as determined by RAST or skin testing
	Long-acting anti-cholinergic	Muscarinic receptor antagonist, M_3 type selective	Not FDA approved for asthma Consider as add-on controller for severe persistent asthma	Tiotropium	1 puff daily	Dry mouth, urinary retention	Should not be used with ipratropium because of excessive anticholinergic side effects

Lipoxygenase Inhibitors and Leukotriene Receptor Antagonists

Leukotriene pathway inhibitors are a group of compounds that alter the pathophysiologic effects of leukotrienes derived from the 5-lipoxygenation of arachidonic acid. Two classes of agents are available: inhibitors of the 5-lipoxygenase (5-LO) enzyme and cysteinyl-leukotriene receptor type 1 antagonists. Although inhaled corticosteroids are superior asthma controllers, leukotriene pathway inhibitors may be substituted for ICS in selected patients with mild disease and are especially useful when steroids are poorly tolerated, steroid use is not desired by the patient, or there is significant, concomitant rhinosinusitis. Furthermore, leukotriene pathway inhibitors are useful as add-on therapy to inhaled steroids in selected patients with moderate to severe asthma and have steroid sparing effects.

Anti-IgE Monoclonal Antibodies

A monoclonal antibody to IgE (omalizumab) rapidly reduces serum IgE and is an adjunctive agent for atopic asthmatic patients dependent on corticosteroids. Several studies of its use in patients with moderate to severe corticosteroid dependent asthma have shown a significant steroid-sparing effect and a reduction in exacerbation frequency. We recommend that omalizumab be considered for moderate to severe atopic asthmatics, especially when high doses of inhaled steroids or oral steroids are required for disease control. It is most likely to be useful when patients require more than 800 μg of inhaled steroids, take daily oral steroids, have an FEV_1 less than 65 percent predicted, or have required emergency room treatment within the prior year.

Treatment Regimens Based on Severity Classification

The classification of asthma as mild intermittent, mild persistent, moderate persistent, or severe persistent, as presented in published treatment guidelines, allows for a stepwise approach to controller drug therapy (Table 48-2). Current guidelines suffer from significant limitations because patients may frequently move amongst severity groups. Future guidelines will probably more precisely stratify patients based on estimates of asthma burden that account for usual disease severity and the risk posed by individual patient's asthma. This approach recognizes that severity may vary with time and facilitates treatment as a dynamic process, with increments and decrements in drug dosages dictated by changes in severity of illness. Importantly, rigorous adherence to guideline-based therapy will lead to improved asthma control in the majority of patients no matter what the baseline disease severity; this has been demonstrated in a large multinational randomized controlled trial. Although errors in management are most often related to undertreatment with drugs, overtreatment can also be a problem, especially in patients with moderate to severe asthma. In such patients there is a tendency to maintain a static treatment regimen, even after symptoms are controlled and clinical stability is achieved. Treatment goals established in these guidelines include no limitations in activities or missed school or work, no chronic nighttime or daytime symptoms, minimal to no exacerbations, near-normal spirometry, minimal use of quick-relief medications, and minimal to no medication side effects. For all asthma patients, short-acting beta agonists used in recommended doses and delivered by metered dose inhaler are the preferred agents for the relief of acute symptoms though short acting anticholinergic agents are a reasonable alternative. Escalating need for relief medications is an important marker of poorly controlled disease or an exacerbation and should prompt consideration of a step-up in controller therapy or for more severe exacerbations, the initiation of a protocol for acute exacerbations as described later in the chapter.

Mild Intermittent Asthma

Some asthmatic patients experience only mild, intermittent symptoms that are of brief duration. In fact, in a review of drug utilization records from a large health maintenance organization with a pharmacy benefit plan, it was found that approximately 70 percent of patients with asthma use fewer than four canisters of a short- or intermediate-acting beta agonist per year (Fish JE and Peters SP, unpublished observations). The use of inhaled beta agonists on an as-needed basis as sole therapy is usually recommended and is likely to provide satisfactory results with no major side effects for most of these asthmatics.

Patients whose symptoms occur under predictable circumstances (e.g., with exercise or exposure to airborne allergens such as dander and occupational agents) benefit from preventive treatment with an inhaled beta agonist, leukotriene inhibitor, or cromolyn sodium. The treatment of choice is, of course, avoidance of the offending agent, although that is not always possible.

Mild Persistent Asthma

Current treatment guidelines recommend the addition of a long-term control medication on a scheduled, daily basis when mild symptoms are no longer intermittent. Long-term control medications are those that are assumed to alleviate the underlying inflammatory basis of asthma. The low-dose inhaled glucocorticoids are the preferred medications in this group, although alternatives include leukotriene inhibitors, cromolyn, or nedocromil. Although as-needed inhaled steroids have been compared with scheduled inhaled steroids for mild persistent asthma in one randomized trial with promising results, insufficient evidence exists at this time to recommend this approach.

Moderate Persistent Asthma

Current guidelines recommend low-dose inhaled steroids combined with a long acting beta agonist or medium-dose inhaled steroids as preferred therapy. Alternatively, lower-dose inhaled steroids may be combined with a leukotriene receptor antagonist or theophylline based on data from studies demonstrating the steroid-sparing properties of these agents. The anti-IgE antibody omalizumab may be useful, and immunotherapy may be considered in carefully selected

patients. Allergen specific immunotherapy should be utilized only when strict environmental avoidance and medications, including inhaled steroids, have failed to control a patient's asthma and only after careful consideration of the risks. Immunotherapy should only be administered by physicians expert in its use.

Severe Persistent Asthma

For purposes of discussion, severe asthma can be defined as asthma in which symptoms persist despite treatment with high-dose inhaled glucocorticoids and additional therapy in the form of long-acting beta agonists, leukotriene pathway inhibitors, or theophylline. Since severe asthma is frequently caused by poor adherence to drug regimens or exposure to environmental factors or drugs such as aspirin or beta blockers, a thorough investigation of these factors is indicated before the start of additional drug therapy.

For the patient with severe asthma, chemotherapeutic options are quite limited. Although doses of inhaled glucocorticoids can be increased, dosages of theophylline and long-acting beta agonists are limited because of the risk of toxicity. Options include increasing the dose of inhaled glucocorticoids, adding sustained-release theophylline or a leukotriene modifier in patients already taking inhaled glucocorticoids and long-acting beta agonists, and adding a long-acting beta agonist to the regimen for patients already taking inhaled glucocorticoids and theophylline or a leukotriene modifier. As for moderate persistent asthma, the addition of the monoclonal anti IgE antibody omalizumab has been shown to be useful in severe persistent disease. Multiple, well-designed studies have shown benefits in this population including a significant reduction in IgE levels, asthma exacerbations, beta agonist use, and glucocorticoids as well as incremental improvements in lung function.

Leukotriene inhibitors have been studied in patients requiring moderate to high doses of inhaled corticosteroids to maintain control and have been found to have a steroid-sparing effect. In one study, inhaled steroid doses were able to be reduced by nearly 50 percent in those patients taking montelukast. However, further studies are needed to determine the role of leukotriene inhibitors in patients with severe persistent asthma already taking maximal pharmacologic therapy, including high-dose inhaled corticosteroids and long-acting beta agonists. Allergen-specific immunotherapy may be considered in this group; however, the risk of severe events including death is highest in patients with severe asthma.

Patients who fail to achieve symptom control, despite treatment with high-dose inhaled glucocorticoids and one or more long-acting bronchodilators are considered candidates for systemic glucocorticoid therapy. When chronic systemic steroids are needed, oral glucocorticoids are favored over parenteral formulations and, in principle, should be given in the lowest dose possible daily or every other day. For exacerbations or to achieve initial control, oral glucocorticoids may be given in moderate to high doses (0.25 to 1.0 mg/kg/d) for 8 to 21 days, followed by a tapering course to the lowest dose that maintains control. This approach is often sufficient to modify the underlying disease process and to permit better control at lower doses. Although a "threshold dose" of glucocorticoids is required to maintain stability in some patients, this approach may achieve results that are good enough to permit complete discontinuation of oral glucocorticoids.

Whereas potent and higher-dose formulations of inhaled glucocorticoids are now available, it is reasonable to ask whether the administration of increasing doses of inhaled glucocorticoids is more appropriate than prescribing oral steroids. For equivalent therapeutic effects, inhaled glucocorticoids have been shown to produce fewer steroid-related side effects than oral glucocorticoids. Moreover, comparisons of oral prednisolone (40 mg/d) with budesonide (3.2 mg/d) have demonstrated greater systemic toxicity with prednisolone, despite greater efficacy with budesonide. Patients who require high doses of oral glucocorticoids to maintain control of symptoms are referred to as *steroid-dependent* asthmatics. This is in contrast to *steroid-resistant* patients, who fail to demonstrate an improvement in lung function on reasonably high doses of systemic steroids, despite demonstrable improvement with inhaled beta agonists. Steroid resistance may be a primary defect due to an unknown intrinsic abnormality, or it may be a secondary defect related to increased steroid metabolism or the effects of drugs that alter steroid activity. Steroid dependence, on the other hand, is thought to be a reflection of severe disease with intense airway inflammation. In fact, these may simply be semantic differences, since intense airway inflammation itself may alter steroid responsiveness, and steroid dependence may be nothing more than an intermediate form of true resistance. Glucocorticoid resistance in asthma and its potential mechanisms have been reviewed. In patients with severe asthma manifesting steroid dependence or resistance, consideration should be given to the use of alternative anti-inflammatory agents.

Alternative Anti-inflammatory Therapies

Because of the complex array of inflammatory mechanisms putatively at work in asthma, there has been hope that agents such as macrolide antibiotics, gold salts, methotrexate, cyclosporine, colchicine, and others might prove effective in management.

Studies of the steroid-sparing effects of macrolide antibiotics in asthma management have yielded discordant results. Macrolides may alter steroid metabolism, treat chronic, subclinical airway infection from *mycoplasma* and *chlamydia bacteria,* or have other anti-inflammatory effects. In one controlled study, the administration of clarithromycin to subjects with asthma resulted in improvements in lung function, but only in those with demonstrable evidence of *mycoplasma* or *chlamydia* infection.

Because of the lack of long-term efficacy or safety data, the usefulness of gold salts in asthma should be considered unproved.

Several controlled studies of the efficacy of methotrexate in the management of severe asthma have been carried out

with mixed results. In general, the discordant results obtained from these trials suggest that the benefits of methotrexate are not universal and are, perhaps, of questionable significance, particularly in light of the potential for significant adverse reactions to the drug.

In the only controlled trial of cyclosporine (5 mg/kg/d) in steroid-dependent asthmatics, peak flow improved and fewer exacerbations occurred in the treated group during the 12-week trial. However, the treated group experienced frequent side effects, including headache, hypertension, hypertrichosis, paresthesias, and infections with herpes zoster while significant reduction in oral prednisone dose was achieved. More evidence is needed before the use of cyclosporine as a steroid-sparing agent can be recommended.

Colchicine has been shown to relieve symptoms and reduce rescue bronchodilator usage in patients with allergic asthma. Colchicine was compared with placebo as an alternative agent to inhaled steroids in one large study of moderate asthmatics. The main study finding was that colchicine was not superior to placebo as an alternative agent to inhaled steroids. We therefore do not recommend that colchicine be used in lieu of inhaled steroids.

Agents designed to inhibit the effects of cytokine products, such as IL-4 and IL-5, have been studied in clinical trials with disappointing results. Because of the specificity of newer agents, it is likely that some agents will prove more effective in certain patients than others, and the variability in response will reflect differences in the relative importance of different pathogenetic pathways.

Treatment of Associated Conditions

Successful management of asthma often requires treatment of conditions that are thought to aggravate asthmatic symptoms. Asthma may coexist with a number of disorders that affect lung function. Gastroesophageal reflux disease, obesity, and chronic sinusitis are the most common of these disorders associated with poorly controlled asthma.

Gastroesophageal Reflux Disease

Respiratory symptoms including cough, breathlessness, and wheeze have been associated with gastroesophageal reflux disease for more than 40 years. The widely accepted notion that gastroesophageal reflux disease (GERD) can aggravate asthma is based, to a large extent, on empiric observations that antireflux therapy often improves asthma control. In general, most studies, whether they have examined the effect of medical or surgical therapy for GERD on asthma-related outcomes, have employed small numbers of subjects and have suffered from poor study design. A recent meta-analysis in which only data from controlled trials was included, failed to show a consistent effect of anti-reflux therapy on asthma outcomes, including asthma symptoms, medication use, lung function, or nocturnal asthma.

In spite of the lack of data from rigorous clinical trials (or meta-analyses for that matter), many clinicians will assess the possibility that GERD may be aggravating asthma. Ambulatory intraesophageal pH monitoring is a sensitive and specific diagnostic test to verify the diagnosis of GERD. While a negative study is valuable in excluding GERD as a cause of asthma symptoms, a positive study does not indicate that GERD is the cause of asthma symptoms. As a rule, an empiric course of antireflux therapy is necessary to establish a causal relationship.

The diagnosis of GERD should be considered in patients with worsening asthma symptoms after meals or with reclining, patients with intractable nocturnal asthma, patients whose disease is poorly controlled on antiasthma medications, those who require either systemic or high-dose inhaled glucocorticoid therapy, and elderly patients with new-onset asthma. Because of the costs and potential side effects of long-term anti-reflux treatment and the growing appreciation that chronic GERD may have serious consequences, we recommend specialty consultation or ambulatory intraesophageal pH monitoring prior to the initiation of treatment. Empiric treatment should especially be avoided when patients do not have classic reflux complaints. Antireflux therapy should be offered to patients with confirmed GERD who complain of reflux symptoms (heartburn, water brash, regurgitation, dysphagia, hoarseness, and choking) in association with wheezing or other asthma symptoms.

Medical management of GERD consists of weight loss when appropriate, elevation of the head of the bed, avoidance of large meals or recumbency after meals, and medications that raise gastric pH like histamine$_2$-receptor antagonists or proton-pump inhibitors. Usually high doses of medications are needed for adequate acid suppression. Alternatively, studies have demonstrated the efficacy of surgical approaches to GERD, although the effect of anti-reflux surgery on asthma outcomes is not clear.

Chronic Rhinosinusitis

The relationship between asthma and chronic sinusitis is well established, although the underlying mechanisms are not clear. In general, the association between asthma and chronic sinusitis is limited to patients with extensive disease, as determined by patency of the nasal passages and ostiomeatal complex and thickening of the sinus mucosa. Although aggressive treatment of chronic sinusitis is generally believed to result in improved asthma control, there is little published supportive evidence. The treatment of choice for sinusitis includes antibiotics, decongestants, and intranasal topical glucocorticoids. Patients who fail to respond to medical therapy may benefit from endoscopic sphenoethmoidectomy. It should be noted, however, that the results of endoscopic sinus surgery are poorest in patients with asthma, especially those with aspirin sensitivity and polyposis. Specific allergen immunotherapy is particularly useful in asthmatics with concomitant allergic rhinosinusitis and considered after careful consideration of risks and benefits.

Obesity

It has long been felt that obesity contributes to the morbidity of asthma. There is growing epidemiologic evidence that

obesity is associated with asthma. Most prospective studies show an association between body mass index (BMI) and the subsequent development of asthma, however nearly all the studies relied on patient-reported asthma. Indeed in one important study (NHANES III) obese patients reported having more asthma, wheezing, and bronchodilator use but they were less likely to demonstrate airflow obstruction than non-obese patients. Thus, it appears that obese patients are more likely to be misdiagnosed with asthma and to be incorrectly treated. Importantly in one prospective study where the asthma was physician diagnosed, a BMI greater than or equal to 28 was associated with asthma, and this effect appeared to be driven by obese female subjects. The reasons for these associations are not known but are an area of active research. Finally, since intervention studies have shown that weight loss can favorably affect asthma outcomes, it seems prudent to aggressively treat obesity in the asthmatic patient.

Patient Monitoring

In an individual patient, asthma severity may fluctuate with time, owing to changes in environmental exposure or improved disease management, or because of the natural history of the disease. Ongoing treatment should remain consistent with the current disease severity. Hence, just as therapy is "stepped-up" to gain control in symptomatic patients, a gradual reduction in medications, starting with the medication with the greatest toxicity, should be attempted once stability is achieved and sustained for several months. Long-term monitoring of the asthmatic patient is essential for proper adjustment of the management plan. Published guidelines have emphasized the importance of objective measurements over symptoms because of poor patient perception of airway obstruction, especially in patients with long-standing asthma. On the other hand, for some patients, symptoms may be a more sensitive indicator of deterioration than are peak expiratory flow measurements. Clearly, the best strategy for monitoring asthma on a long-term basis is to use both objective and subjective measures. The amount of rescue beta agonist used on a daily basis is also a useful barometer of asthma control.

Peak Expiratory Flow, Spirometry, and Action Plans

Whereas spirometry is recommended to diagnose airway obstruction in the initial assessment of the asthmatic patient, we believe that spirometry and peak flow measurements provide comparable information for monitoring patients on a long-term basis. The historical advantage of peak flow measurements has been their relative ease of performance and lack of expense with self-monitoring on a daily basis. The recent development of hand-held, automated spirometers providing digital output of FEV_1 and data storage capability offers an alternative for home monitoring. Studies have demonstrated that patients can perform home spirometry skillfully after adequate training; however, built-in software that assesses the quality of the forced vital capacity maneuver oftentimes does not perform well. Asthma treatment guidelines have included an enthusiastic recommendation that patients use peak expiratory flow measurements not only to monitor their course but also to dictate self-administered treatment regimens. This recommendation is based on studies showing improvement in subjective, as well as objective, measures of asthma control when patients used peak flow measurements related to their personal best peak flow to adjust medication usage. Moreover, one retrospective study suggested that the usage of action plans was related to reduced mortality. The combination of home monitoring and a comprehensive education and self-management program has been shown to increase pulmonary function, reduce physician visits and emergency room admissions, and reduce use of inhaled beta agonists and prednisone when compared with a program of minimal education and no self-management.

Given the variable nature of asthma and the people it afflicts, it seems unlikely that either peak flow- or symptom-guided self-management would benefit all patients at all times. Clearly, no single treatment algorithm is apt to be the best therapeutic plan for all patients with the same change in peak flow. Likewise, not all patients are capable of executing, or even comprehending, complicated treatment plans. Future studies should focus on whether the benefits of peak flow–guided self-management, if any, outweigh the risks of over treatment that might result from its use. Severely asthmatic patients using home peak flow monitoring tend to use more oral glucocorticoids. Although this may be viewed as a potential benefit of peak flow monitoring, it is unclear whether the increased use is always appropriate or medically warranted. Although the correspondence between peak expiratory flow and its variability and symptoms or other measures of asthma severity is quite good, it is not absolute. It is the authors' opinion that if used, action plans should be written using clear, simple language and should be individualized based on patients' understanding of their asthma, its severity, and their demonstrated ability to comply with instructions. Adherence may be assessed during an initial 2-week assessment period in which patients chart their daily symptoms and lung function measurements. An example of a written action plan is provided in the online supplement.

Markers of Airway Inflammation

The importance of using markers of airway inflammation to monitor disease activity is uncertain. While asthma symptoms, airway responsiveness, and numbers of airway inflammatory cells correlate, the correlations are primarily of statistical interest and are not predictive of one another in an individual patient. For example, there is considerable overlap in airway responsiveness between patients who require only occasional therapy and those who are steroid dependent. That asymptomatic asthmatics with normal lung function have evidence of ongoing airway inflammation is also well established. Defining the marker that best reflects the inflammatory diathesis of asthma is an important scientific challenge.

As discussed above the measurement of bronchial hyperresponsiveness (BHR) is a sensitive tool used for the initial

diagnosis of asthma. Measuring BHR may also have additional utility in the subsequent management of asthma. For example, in one study it was shown that a treatment strategy aimed at specifically reducing BHR was superior to a strategy based on symptoms, medication usage, and PEF measurements (i.e., that suggested by most published guidelines) with regard to reducing exacerbations and improving lung function.

Because of their poor sensitivity and specificity, blood eosinophil counts are not recommended in routine monitoring of asthma severity or as a barometer of airway inflammation. In contrast, sputum eosinophils counts have been shown to predict exacerbations when steroids are withdrawn; however, further study will be needed before measurement of sputum eosinophils can be widely used to monitor patients.

Levels of nitric oxide (NO) in mixed expired gas have been found to be elevated in asthmatics as compared with normal subjects. The level may reflect the degree of underlying airway inflammation. Mixed expired concentrations of NO have been shown to fall during glucocorticoid therapy in patients with severe exacerbations of asthma, suggesting a possible role for NO as an index of disease severity or treatment efficacy. Exhaled NO measurements have been used successfully to titrate inhaled steroids without any loss of asthma control; thus, eNO may be used as a tool in conjunction with other clinical measures to optimize asthma management as recommended by guidelines (i.e., achieving disease control using the lowest doses of medications possible).

Managing Asthma Exacerbations

Asthma especially in its severe forms is characterized by disease exacerbations, and such exacerbations result in substantial morbidity, occasional mortality, and considerable medical and economic costs. The majority of randomized controlled trials of asthma therapies and most studies performed in humans examining asthma pathogenesis have been done in patients with milder asthma. Clinical experience has shown that the majority of exacerbations occur in a minority of asthma patients. Exacerbation-prone patients seem to be at increased risk for attacks of near-fatal asthma. Importantly, when deaths from asthma have been analyzed, most decedents had experienced worsening symptoms of a period of several hours to several days—highlighting the importance of identifying and educating the at-risk patient. It must be recognized that life-threatening episodes can develop in patients whose asthma appears to be mild at baseline. Patients who have baseline severe, poorly controlled disease, those who frequently access the ER, or are frequently hospitalized—essentially those with prior life-threatening episodes—seem to be at the highest risk. These patients should be identified and targeted for intensive disease management including patient education, pharmacologic therapy, and close disease monitoring.

Nonpharmacologic Therapy

Fortunately, the need for mechanical ventilation for acute, severe asthma is an uncommon event because barotrauma occurs frequently in this group. These patients suffer from lung hyperinflation and are difficult to ventilate, but more recently the appreciation that avoidance of barotrauma reduces mortality in acute, severe asthma has resulted in the utilization of lung protective strategies. High transpulmonary pressures can be ameliorated by hypoventilation with resultant permissive hypercapnia, and the use of high inspiratory flow rates that increase expiratory flow time and facilitate lung emptying. Noninvasive positive pressure ventilation may be used safely in carefully selected patients; however, clinical trial data are lacking.

Pharmacologic Management

The cornerstone of therapy for an exacerbation of asthma involves the escalation of both glucocorticoids and quick-relief medications, usually inhaled β_2-adrenergic agonists, with frequent reassessment of the degree of airflow obstruction.

Glucocorticoids

Surprising little is known with regards to the optimal dosing of systemic glucocorticoids in acute asthma, although it is generally felt, for reasons that are poorly understood, that inflammation in acute asthma is relatively resistant to glucocorticoids, hence systemic steroids are often used. For those exacerbations requiring hospitalization typically parenteral steroids in doses ranging from 1 to 10 mg/kg/d of prednisolone or the equivalent in divided doses are used and the steroids tapered at a rate determined by the patient's response. Oftentimes a few days of therapy are required before a noticeable improvement in lung function occurs. Important side effects with parenteral steroids include delirium, hyperglycemia, and fluid retention. Steroids may be tapered once there is a response but it is the authors' opinion that systemic steroids should be tapered over a 2-week period in cases of severe asthma exacerbation. In instances in which there is a prompt response to therapy in the emergency department and the patient is not admitted, lower doses of steroids may be used but systemic therapy is still advised for at least several days and tapering should be done with close outpatient follow-up. In instances in which outpatient oral glucocorticoids are used for less severe exacerbations, we recommend doses in the range of 0.25 to 1 mg/kg/d tapered over a 7- to 14-day period, the initial dose and tapering regimen determined by prior history (i.e., previously successful regimens), severity of the exacerbation, and response. Very mild or subacute exacerbations in asthmatics with mild persistent disease may be managed in some cases by escalating the dose of or initiating inhaled steroids in cases in which patients are taking low-dose steroids or no steroids, respectively.

Bronchodilators

Exacerbations of asthma should never be treated by escalating bronchodilators alone. Fatalities from asthma usually result when patients fail to promptly seek medical attention and commonly patients who died from asthma had self-medicated with escalating doses of quick-relief

medications or long-acting bronchodilators. Although systemic β_2-adrenergic agonists are available it is clear that inhaled β_2-adrenergic agonists are safer and equally efficacious. Inhaled β_2-adrenergic agonists may be used safely in quite high doses with close monitoring. For example, continuous administration of albuterol at doses of 10 mg per hour is a commonly used protocol for acute severe asthma in hospital emergency departments. Intravenous aminophylline, terbutaline, or epinephrine may be used, but the risks of toxicity are much greater than when inhaled β_2-adrenergic agonists are used. Inhaled ipratropium appears to provide further bronchodilation in acute severe asthma.

Other Considerations

Antibiotics are not indicated for acute asthma exacerbations unless there is objective evidence of bacterial pneumonia or co-existing bacterial sinusitis. Oxygen therapy should be used to avoid hypoxia (i.e., oxygen saturation greater than or equal to 92 percent). Oxygen should be titrated to the lowest dose needed since the use of excessive oxygen concentrations can lead to CO_2 retention and a respiratory acidosis in some patients. Prophylaxis for deep venous thrombosis is indicated for the hospitalized asthma patient. Stress ulcer prophylaxis is also indicated given the increased risks imparted by the use of systemic steroids, and this is especially true in the rare patient requiring mechanical ventilation.

Patient Monitoring

Most patients that present to the emergency department with acute severe asthma require intensive bronchodilator therapy and supplemental oxygen. Hypoxia is to be avoided at all costs, so continuous monitoring of oxygen saturation is needed until there is a meaningful response to treatment. High-dose bronchodilator therapy, while generally well tolerated, occasionally causes arrhythmia; therefore, continuous EKG monitoring is also required. Patients who continue to manifest severe airflow obstruction after initial intensive treatment should be admitted to an intensive care unit. When there is clinical improvement but significant obstruction remains, hospitalization is required. In less severe exacerbations patients who promptly respond to treatment in the emergency department may be discharged but close outpatient follow-up is essential.

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49

Allergic Bronchopulmonary Aspergillosis (Mycosis)

Geoffrey Chupp • Carolyn L. Rochester

Allergic bronchopulmonary aspergillosis (ABPA) is an idiopathic inflammatory lung disease characterized by an allergic inflammatory response to the colonization of *Aspergillus* or other fungi in the lung. It was first described in 1952 by Hinson and coworkers and then again in 1967, when Scadding recognized an association of this disease with proximal bronchiectasis in areas previously affected by infiltrates (predominantly in the upper lobes). The first adult case of ABPA in the United States was described in 1968. Although most cases entail hypersensitivity to *Aspergillus* spp. (especially *A. fumigatus)* the finding of a virtually identical clinical syndrome associated with immune sensitivity to *Candida albicans, Helminthosporium* spp., *Curvularia lunata, Drechslera hawaiiensis, Stemphylium languinosum, Saccharomyces cerevisiae,* and *Pseudallescheria boydii* has led to the term *allergic bronchopulmonary mycosis* to describe this syndrome. The precise prevalence of ABPA is unknown, owing in part to variability in diagnostic criteria used in various studies, the lack of distinction between ABPA and mold-sensitive asthma, and to delays in the diagnosis of patients with long-standing disease. Given this consideration it is estimated that ABPA complicates approximately 7 to 14 percent of cases of chronic steroid–dependent asthma and 7 to 15 percent of cases of cystic fibrosis. Most cases of ABPA are recognized in the third to fifth decade of life, but may also present during childhood. In some patients it is likely that ABPA started early in life and continued, unrecognized, until adulthood. Interestingly, familial cases have been reported. The spectrum of disease is broad and can be severe and debilitating, requiring lung transplantation; however, if recognized early and managed aggressively, ABPA is treatable, can remit indefinitely, and progressive lung damage can be avoided. For the purposes of this review, ABPA will be discussed; however, clinicians should be cognizant that diagnostic testing for other fungi needs to be pursued when organisms other than *Aspergillus* spp. are suspected culprits.

PATHOGENESIS

Although the pathogenesis of ABPA is incompletely understood, it is believed to result from a complex immunological reaction to chronic airway colonization by *Aspergillus* (or other relevant fungal) species. *Aspergillus* spp. are ubiquitous, thermotolerant organisms that reside in decaying organic matter. Inhaled spores colonize the airway, proliferate, and result in chronic antigenic stimulation of the airway, tissue injury, and the clinical features of ABPA. While the pathogenesis of ABPA remains poorly understood, it does appear that susceptibility to ABPA, the presence and magnitude of tissue response to *Aspergillus* and the development of clinical disease depend on host factors such as genetic background and T-cell responsiveness to *Aspergillus* antigens.

Investigations into the genetic links to ABPA have produced some interesting results. Best characterized is the

possible link between gene mutations in the cystic fibrosis transmembrane conductance regulator (CFTR) and the pathogenesis of ABPA. CFTR mutations are more common among patients with ABPA compared to the general population and asthmatics without sensitivity to *Aspergillus fumigatus*. Another genetic link to ABPA is that Th2-type T-cell reactivity to selected *Aspergillus* antigens is determined by the presence of MHC Class II DR2 or DR5 alleles, which may predispose patients to the disease, whereas the MHC DQ2 allele may be protective.

At the microscopic level ABPA is characterized by an intense eosinophilic and mononuclear cell inflammatory response that leads to airway injury and bronchiectasis. A role for type I hypersensitivity reactions is strongly suggested by the elevated serum levels of total and *Aspergillus*-specific IgE. Type III hypersensitivity is suggested by the presence of *Aspergillus* precipitins and circulating immune complexes during disease exacerbations. A type IV cell-mediated immune reaction may also be at work, based on the finding of dual (immediate and delayed) cutaneous reactions and in vitro lymphocyte transformation to *Aspergillus* antigen stimulation in some patients.

There has been a substantial amount of work done on the immune response in ABPA. A pathogenetic role for helper T lymphocytes is suggested by a number of findings, including: the presence of increased numbers of airway Th2 cells and levels of soluble interleukin 2 receptors (suggesting T-cell activation) in the circulation of persons with active ABPA; the derivation of *Aspergillus*-specific T-cell clones with T helper–2 (Th2) patterns of cytokine production from the blood of patients with ABPA; the correlations between activated T-cell number, the levels of the T cell–derived cytokines IL-4 and IL-5, and the number of airway eosinophils in the disease; the critical role IL-5 plays in murine models of ABPA; and the increased reactivity of Th2 cells to *Aspergillus* antigens among patients with ABPA as compared with patients with asthma and skin reactivity to *Aspergillus*. In addition to lymphocytes, eosinophils and basophils may contribute to local airway injury and neutrophils likely play a role in airway inflammation and destruction in ABPA as evidenced by the fact that sputum IL-8 levels correlate with sputum neutrophilia, matrix metalloproteinase levels, and FEV_1 among patients with ABPA.

It is also clear that the fungus itself is of substantial pathogenetic importance. *Aspergillus*-derived proteases likely cause epithelial cell injury and protective barrier disruption, which triggers immune hypersensitivity by inducing inflammation or by allowing increased penetration of fungal antigens into the airway wall. *Aspergillus*-derived proteases may also stimulate proinflammatory cytokines such as IL-8, release of growth factors, and may cause tissue damage leading to bronchiectasis. In addition, a variety of other *Aspergillus*-derived antigens (including cytotoxins and heat shock proteins) with demonstrated ability to bind IgE and IgG derived from the blood of patients with ABPA each initiate and drive both the IgE (hypersensitivity) and IgG immune response. *Aspergillus*-derived proteases with antibody-binding capacity can also amplify the inflammatory response. *Aspergillus* antigens such as Aspf1 (a cytotoxic protein), Aspf2 (a fibrinogen binding protein), Aspf5 (a metalloprotease), Aspf6 (manganese superoxide dismutase), Aspf8 (a ribosomal protein), Aspf13 and Aspf18 (serine proteases), as well as Aspf3 and Aspf4 have all been implicated in these processes. Lastly, host response to *Aspergillus fumigatus* antigens includes surfactant proteins (SP) A and D that may play a protective role against ABPA by interfering with binding between *Aspergillus fumigatus* antigens and IgE, although SPD levels do not correlate with acute exacerbations of ABPA in humans.

CLINICAL FEATURES

Although ABPA typically presents in patients with a history of difficult to control asthma, the spectrum of presentation is highly variable and needs to be considered in any patient with moderate to severe asthma and hypersensitivity to *Aspergillus fumigatus*. Typical presenting complaints are nonspecific and include dyspnea, wheezing, poor asthma control, cough (commonly productive of thick, brown mucus plugs), malaise, low-grade fever, and occasionally, hemoptysis. There may be an antecedent history of recurrent asthma exacerbations in conjunction with pneumonias without a culture-identified bacterial source. In addition, a history of atopy with rhinitis, drug allergy, and/or allergic conjunctivitis are common. It is often not until a patient has been repeatedly ill over weeks to months and unresponsive to standard treatments that the diagnosis is considered.

Diagnostic Guidelines

In general, the diagnosis of ABPA is based on appropriate clinical features in combination with supporting radiological and serological findings. While there are no absolutely specific diagnostic criteria (along with the lack of specific clinical findings on presentation and overlap with other common diseases such as asthma, allergy, and bronchiectasis) guidelines have been proposed to aid clinicians in the diagnosis of ABPA (Table 49-1). These guidelines have evolved over time and may be somewhat confusing; however, they can allow for the early detection of ABPA before lung damage occurs and take into account the effect corticosteroids can have on suppressing some clinical features of the disease. ABPA is generally considered to present in two different forms; ABPA-seropositive and ABPA-central bronchiectasis (CB). Patients with ABPA-S may display the following diagnostic criteria proposed by Greenberger and Patterson: (1) history of asthma; (2) total IgE >1000 IU/ml; (3) elevated serum anti-AF IgE and IgG; (4) positive immediate hypersensitivity skin test to *Aspergillus*; and (5) serum precipitins to *Aspergillus fumigatus* or other relevant fungus. (This criterion is considered positive by the presence of an anti-*Aspergillus fumigatus* IgG titer.) These patients may have normal radiographic studies. Patients with ABPA-CB have all of the criteria of ABPA-S and also have

Table 49-1

Criteria for the Diagnosis of ABPA

Seropositive ABPA (ABPA-S)
- History of Asthma (often difficult to control)
- Elevated total serum IgE (usually >1000 IU/ml)
- Immediate skin test reactivity to *Aspergillus fumigatus*
- Elevated specific serum IgE to *Aspergillus fumigatus*
- Presence of serum precipitins or elevared specific serum IgG to *Aspergillus fumigatus*

ABPA central bronchiectasis (ABPA-CB)
- Above criteria are positive
- Central bronchiectasis by high resolution CT scan

Other supportive clinical findings
- Peripheral blood eosinophilia (often absent especially if patient is on oral corticosteroids)
- Patchy, fleeting infiltrates (often absent especially if patient is on oral corticosteroids)
- Expectoration of brown mucuc plugs
- Mucoid-impacted bronchi evident on radiographic studies
- Sputum culture positive for *Aspergillus fumigatus*

central bronchiectasis on high-resolution CT scan or chest x-ray. Patients with ABPA-S tend to have fewer symptoms, lower IgE levels, less severe airflow obstruction, and fewer exacerbations than persons with ABPA-CB. IgE levels fluctuate with disease activity, and a normal IgE level in a symptomatic untreated person virtually excludes the diagnosis. It remains unclear whether ABPA-S is a milder form of the disease (e.g., representing a different host response) or an earlier stage of illness. In addition, patients may have a history of current or previous pulmonary infiltrates, peripheral blood eosinophils (~10,000 cells/m) or expectoration of brown mucus plugs. Identification of *Aspergillus* (or other relevant fungus) in the sputum and dual (immediate and delayed) cutaneous reactions to challenge with *Aspergillus* are also common clinical features of ABPA. Rare cases lacking a history of asthma but meeting the other major diagnostic criteria have been reported.

The differential diagnosis of ABPA includes corticosteroid-dependent asthma without ABPA, tuberculosis, parasitic infections, hypersensitivity pneumonitis, Churg-Strauss syndrome, acute eosinophilic pneumonia (including drug-induced pneumonitis), chronic eosinophilic pneumonia, lymphoma, idiopathic hypereosinophilic syndrome, autoimmune disease, crack/cocaine use, CF, and other causes of bronchiectasis. In addition, the diagnosis of ABPA in patients with mold-sensitive asthma and CF poses particular diagnostic difficulty. This is especially true in asthmatics in the absence of bronchiectasis. Serum precipitins to *Aspergillus* spp. may be present in up to 10 percent and positive immediate skin tests to *Aspergillus* in up to 25 percent of asthmatics. Persons with mold-sensitive asthma or ABPA can have peripheral blood eosinophilia and/or elevated serum total IgE levels. However, most persons with ABPA have 2- to 20-fold higher serum levels of *Aspergillus*-specific IgE and total IgE than do mold-sensitive asthmatics without ABPA. In addition, as mentioned, proximal bronchiectasis is not seen in mold-sensitive asthma but is common in ABPA. A more confusing diagnostic conundrum occurs when considering the diagnosis of ABPA in patients with CF, because patients with CF alone can manifest chronic airflow obstruction, recurrent exacerbations with infections and/or bronchoconstriction, underlying bronchiectasis, pulmonary infiltrates, chronic sputum production, *Aspergillus* colonization of the airways, and positive serum precipitins. Distinguishing ABPA in CF patients is critical because infectious CF exacerbations and the presence of ABPA require different treatments. The steroid treatment required for ABPA may be detrimental in the setting of infection, yet antibiotics alone given for infection may be inadequate to control the inflammation associated with ABPA. Among patients with CF factors associated with the risk of ABPA include: adolescent age, atopy, severe lung disease, and colonization with *Pseudomonas aeruginosa.* ABPA should be suspected in patients with CF who develop clinical deterioration, exhibit a greater than fourfold increase in total serum IgE (especially >1000 IU/ml), have immediate cutaneous reactivity to *Aspergillus* or increase in *Aspergillus*-specific IgE or IgG, and show change in baseline CXR. Annual screening of total serum IgE is recommended—if the level rises >500 IU/ml, immediate cutaneous hypersensitivity testing for reactivity to *Aspergillus fumigatus* or testing for serum anti-*Aspergillus fumigatus* IgE is recommended. One study suggests that the presence of IgE reactive against the purified *Aspergillus* allergens Aspf3 and Aspf4 are useful to distinguish patients with ABPA and CF or *Aspergillus*-sensitive asthma from patients without ABPA.

Clinical Staging of ABPA

Five clinical stages of ABPA have been recognized based on clinical, serological, and radiographic characteristics (Table 49-2). Stage I, the *acute* stage, is characterized by symptoms of moderate to severe asthma, elevated total IgE (typically >1000 IU/ml), an elevated anti-*Aspergillus fumigatus* IgE or hypersensitivity skin test to *Aspergillus fumigatus,* infiltrates on chest radiograph (with or without proximal bronchiectasis), peripheral blood eosinophilia (frequently >2000/mm^3), and positive precipitating or anti-IgG antibodies to *A. fumigatus* (up to fivefold concentration of serum may be required for detection of the precipitating antibodies). Patients with stage II ABPA have disease that is in *remission.* This is characterized by the resolution of symptoms, radiographic clearing, and decreased stabilization of total IgE levels. Remissions are of varying length, can last several months to years or may be permanent, allowing corticosteroid treatment to be tapered or discontinued. Patients with stage III ABPA have *recurrent*

Table 49-2

Client Stages of ABPA

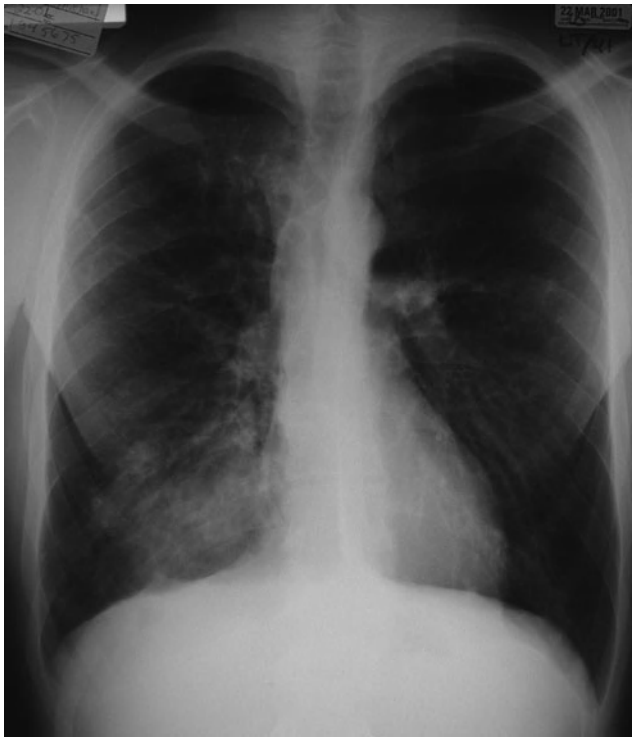
Stage I: Acute
- Acute asthma symptoms
- Elevated serum IgE (>1000 IU/ml)
- Peripheral blood eosinophilia (may be absent in patients treated with oral coricosteroids)
- Fleeting infiltrates on chest x-ray (may be absent in patients treated with oral coricosteroids)
- Positive specific IgE, IgG, skin test reactivity, and precipitins to *A. fumigatus*
- Responds to steroids/antifungal therapy

Stage II: Remission
- Resolution of symptoms
- Resolution of pulmonary infiltrates
- Improvement in eosinophilia and *A. fumigatus* specific blood abnormalities

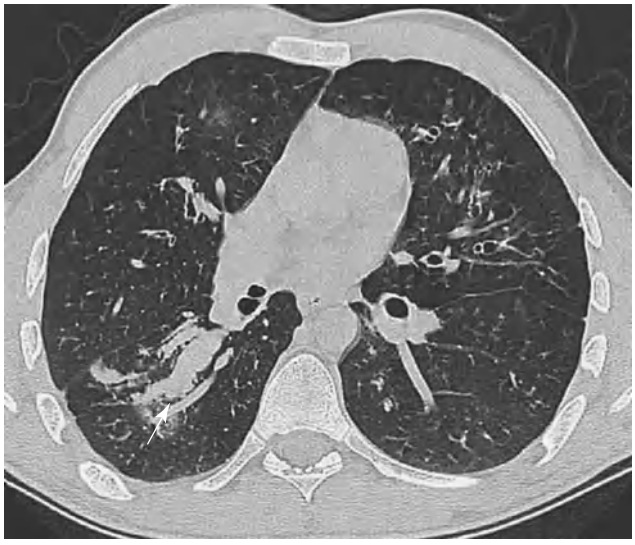
Stage III: Exacerbation/recurrence
- Recurrence/worsenning of clinical symptoms
- Recurrent pulmonary infiltrates
- Rising IgE levels

Stage IV: Steroid-dependent-asthma
- Refractory steriod-dependent asthma
- Persistently elevated serum IgE levels
- Persistently elevated *A. fumigatus*–specific blood abnormalities

Stage V: Fibrotic lung disease
- Refractory steriod-dependent asthma
- Fibrotic lung disease (irreversible obstructive and restrictive defects with impaired diffusing capacity)
- Chronic bronchiectasis symptoms (sputrum production, frequent infections)



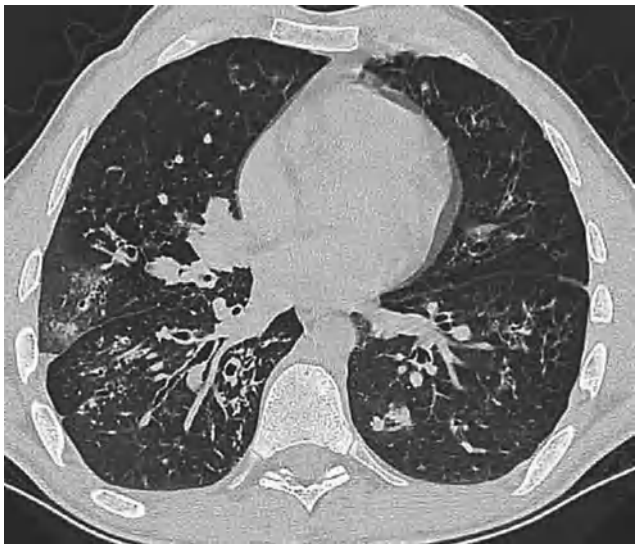
A



B

Figure 49-1 A 27-year-old man with a history of moderate asthma, recurrent bronchitis, and mild hemoptysis. Serological studies were consistent with ABPA (IgE 9,490 IU/ml) and radiographic studies are consistent with bronchiectasis. *A*. PA chest x-ray shows hyperinflated lungs, bronchial dilatation, and right lower lobe opacity consistent with mucoid impaction. *B*. High-resolution CT scan image of impacted bronchus (arrow) and chronic inflammatory changes. *C*. Dilated central bronchus consistent with cylindrical/central bronchiectasis.

disease or disease *exacerbations* (Fig. 49-1). Their disease is characterized by the development of new pulmonary infiltrates or by a >100 percent increase in total IgE. Elevation of IgE may precede clinical or radiological worsening during this stage, and an isolated increase in severity of bronchospasm does not constitute an exacerbation. Although a majority of disease exacerbations are associated with a concomitant increase in symptoms, exacerbations may occur in the absence of any increase in symptoms. Indeed, since up to one-third of patients with radiographic infiltrates may be asymptomatic, evolving progressive lung damage may remain unrecognized. Total serum IgE levels should be monitored every 1 to 2 months for at least a year after diagnosis, and chest radiographs should be performed intermittently. *Aspergillus*-specific IgA levels may also be elevated in the acute or exacerbation stages of disease. Exacerbations are more likely to occur during seasons or environments when mold counts are high. Stage IV ABPA is defined as *steroid-dependent asthma.* In stage IV disease, total IgE, *Aspergillus* precipitins, and *Aspergillus*-specific IgE and IgG typically remain elevated



C

Figure 49-1 (*Continued*)

despite chronic steroid therapy. The frequency of exacerbations may increase. Stage V is defined as *pulmonary fibrosis.* Stage V patients have prominent symptoms of dyspnea; are often steroid dependent because of persistent bronchospasm; frequently have chronic sputum production, recurrent respiratory infections, and irreversible pulmonary function abnormalities (obstruction, restriction, and/or gas exchange abnormalities), and may have cyanosis or clubbing. The serological profile of patients with stage IV disease persists during stage V. Stage V disease is generally thought to be the consequence of longstanding, often unrecognized disease, but may occur occasionally among patients with little prior clinical evidence to suggest the diagnosis (Fig. 49-2).

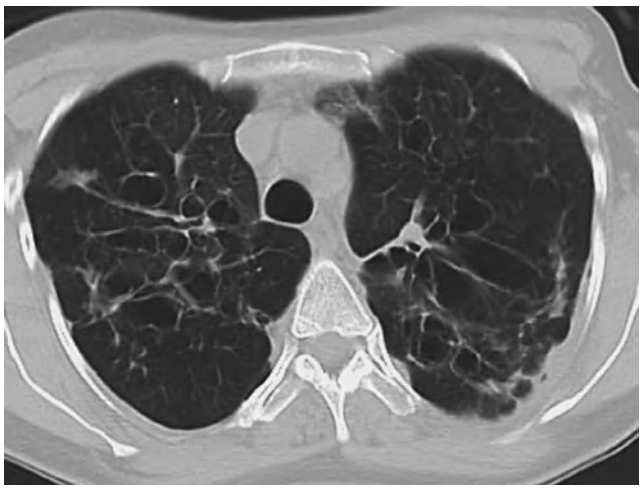


Figure 49-2 Representative CT image of the lungs of a 41-year-old woman who presented with stage V ABPA (IgE 1500 IU/ml). Pulmonary function studies demonstrated severe combined obstructive and restrictive defects. CT shows bilateral upper lobe scarring and emphysematous changes.

DIAGNOSTIC STUDIES

In addition to the blood abnormalities described in the preceding, analysis of BAL fluid from patients with ABPA reveals a moderate eosinophilia and increased levels of *Aspergillus*-specific IgE and IgA but not IgG. On bronchoscopy mucoid impaction may be evident, and bronchial brushings may reveal mucus containing aggregates of eosinophils, fungal hyphae, and eosinophil-derived Charcot-Leyden crystals. Pulmonary function tests typically reveal an obstructive ventilatory defect (due to bronchospasm or mucus impaction of the bronchi) during stages I, III, IV, and often V and may not correlate with the duration of ABPA or asthma. Persons with stage V disease typically also have a restrictive ventilatory defect with a reduced DLCO (Fig. 49-2).

The typical radiographic manifestations of ABPA include parenchymal infiltrates and bronchiectasis (Figs. 49-1 to 49-3). The infiltrates are often irregular and transient (1 to 6 weeks). They have a predilection for upper lobes, although all lobes may be affected. The bronchiectasis is classically cylindric and proximal (central), occurring within the proximal two-thirds of the lung (Fig. 49-1*B*). Mucoid impaction in dilated bronchi leads to a characteristic (but nonspecific) radiographic appearance of ABPA termed the "finger in glove" opacity. "Tramline shadows" (parallel linear shadows extending from the hilum in bronchial distribution and reflecting longitudinal views of inflamed, edematous bronchi), "toothpaste shadows" (representing mucoid impaction of the bronchi), "ring shadows" (dilated bronchi with inflamed bronchial walls seen on end), local consolidation, or lobar collapse are also common features. Involvement of the small airways may lead to centrilobular nodules and branching tree-in bud opacities (Fig. 49-1). Less common radiographic findings include bullous changes, pneumothorax, pleural effusion, cavitating nodular lesions, aspergilloma (Figs. 49-2 and 49-3) and migratory parenchymal opacities, some of which have a ground-glass appearance.

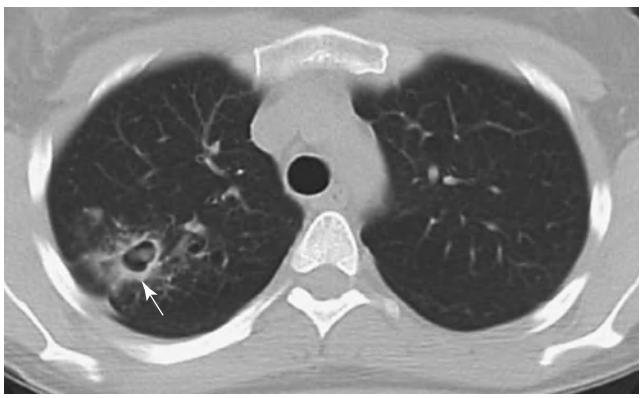


Figure 49-3 A 21-year-old woman with ABPA who responded to treatment with oral corticosteroids and chronic antifungal therapy developed an aspergilloma and hemoptysis (arrow). Amphotericin paste injection failed and the patient ultimately underwent a right upper lobe lobectomy.

High-resolution CT scanning is the most reliable noninvasive means of detecting proximal bronchiectasis.

Open lung biopsy is usually not required to establish the diagnosis of ABPA. Histopathological findings in this disease include intense bronchocentric inflammation with prominent eosinophilia as well as lymphocytes, plasma cells, and monocytes. Bronchi may be filled and/or impacted with copious mucus plugs containing fibrin, Charcot-Leyden crystals, Curschmann spirals, and fungal hyphae. Bronchiectasis of segmental and subsegmental bronchi may be evident. Regions of bronchocentric granulomatosis, eosinophilic pneumonia, eosinophilic microabscess, lymphocytic or desquamative interstitial pneumonitis, proliferative or obliterative bronchiolitis, lipoid pneumonia, or interstitial fibrosis may also be seen.

TREATMENT

Goals in treating ABPA consist of controlling symptoms, preventing exacerbations, and preserving normal lung function. Systemic corticosteroids are the mainstay of therapy for ABPA. Since without treatment ABPA can cause marked chronic lung impairment due to bronchiectasis or pulmonary fibrosis, initiation of appropriate treatment early in the course of disease is essential. Although most data are derived from small uncontrolled trials and there is no definitive proof that corticosteroid therapy prevents the development of central bronchiectasis, retrospective studies have suggested that early therapeutic intervention with corticosteroids may prevent progression to lung fibrosis. Therapy for stage I or III disease should include prednisone, 0.5 to 1 mg/kg a day for 2 weeks, followed by 0.5 mg/kg every other day for 6 to 8 weeks. A subsequent taper (by 5 to 10 mg every 2 weeks) over the ensuing 3 months can then be tried. The duration of treatment must be guided by stage and severity of disease. A low maintenance dose (e.g., 7.5 mg/day) may be required long term to control the disease and prevent recurrence in some patients. Corticosteroid therapy leads to relief of symptoms and decreased airflow obstruction, decreased (>35 percent decrease) serum IgE, reduction in peripheral blood eosinophils, and resolution of pulmonary inflammation and infiltrates. IgE levels should be monitored within 1 to 2 months of an acute episode or exacerbation and should be followed every 2 months thereafter since levels may rise, reflecting disease activity prior to or in the absence of clinical symptoms. Escalation of steroid therapy should be considered if IgE levels rise more than 100 percent. CXR should be monitored every 3 months within the first year of an acute episode or exacerbation, and may be followed yearly thereafter if the disease is quiescent. Pulmonary function testing should be followed up yearly as well. Although treatment of acute exacerbations is believed to be helpful to prevent fibrotic lung disease, it is not clear that early detection and treatment of disease flares that are asymptomatic affect disease progression. Patients with CF and ABPA may derive some symptomatic or functional improvement from steroid treatment. However, patients with CF who are on steroids should be followed closely for development of invasive aspergillosis. It is unclear whether the development of ABPA alters the course of CF disease progression.

Although not advocated as primary treatment, inhaled corticosteroids are useful for control of bronchospasm and can help minimize the dose of systemic steroid necessary to control wheezing. They have been used occasionally as a steroid-sparing agent for the treatment of symptomatic exacerbations and pulmonary infiltrates, and may help maintain stability of lung function. In addition, adjuvant treatment with bronchodilators and antibiotics also helps control bronchospasm and secondary respiratory infection.

In the last decade, the development of oral antifungal agents has brought new hope to patients with ABPA. Even though the current concept is that ABPA is not an "infection," evidence is mounting to support the use of the antifungal agent itraconazole in patients with ABPA. In one randomized controlled study, itraconazole (200 mg bid for 16 weeks) led to significant reductions in corticosteroid dose, decreased IgE levels, greater resolution of pulmonary infiltrates, as well as gains in exercise tolerance or pulmonary function. Among several clinical studies, itraconazole treatment also reduces *Aspergillus* antibody titers, and reduces eosinophilia as compared with placebo. Itraconazole treatment (200 mg/day or every other day) is generally recommended for patients with ABPA who are steroid dependent, have frequent relapses, and in whom the cost and risks are not felt to outweigh the potential benefits. Itraconazole also has demonstrated utility in ABPA associated with CF. If itraconazole is used, steady-state levels should be checked after 1 to 2 weeks, 4 hours after the dose is given, to assess drug absorption, since itraconazole interferes with the hepatic metabolism of several medicines, including cyclosporine, oral hypoglycemics, tacrolimus, terfenadine, cisapride, and midazolam. Particular caution should be exercised in its use among patients taking any of these medications. In addition, physicians must be mindful of adrenal insufficiency associated with itraconazole treatment among patients with ABPA taking inhaled corticosteroids, as itraconazole may cause reduced steroid clearance and/or possible direct suppression of adrenal steroid production. Interval screening for adrenal insufficiency should be considered among such persons. In contrast, the efficacy of itraconazole in ABPA may be less among persons taking agents that raise gastric pH, as this can dramatically reduce drug absorption.

Other antifungal agents, including nystatin, amphotericin B, miconazole, clotrimazole, and natamycin, are generally ineffective in controlling ABPA. Ketoconazole may be effective, but its utility is limited by hepatotoxicity. Efficacy of voriconazole has not yet been studied in ABPA, but anecdotal reports from our center and others suggest similar results to itraconazole. Last, the new biologically engineered antibody omalizumab, directed against IgE, is an intriguing consideration but has not been extensively studied. Given the pharmacokinetics of this agent

omalizumab may be most useful in patients with relatively low IgE levels.

In addition to medical therapy, patients with ABPA should avoid areas and environmental conditions associated with high mold count, such as decomposing organic materials and moldy indoor environments. One should consider the use of HEPA filter devices if such exposures are unavoidable.

PROGNOSIS

With appropriate treatment long-term control of ABPA is feasible, and durable remissions are common. Treatment of stage I disease with corticosteroids typically results in decreased sputum production, improved control of bronchospasm, >35 percent reduction in total IgE within 8 weeks, clearing of precipitating antibodies, and resolution of radiographic infiltrates. IgE levels typically do not completely normalize but rather decrease by approximately one-half of peak levels seen in the acute stage. Progression of stage IV disease to pulmonary fibrosis can be prevented if patients are maintained on low-dose steroids, and most patients with stage V disease have a stable course over several years. Persons with an FEV_1 persistently <0.8 L have a worse prognosis. In addition to severe airflow obstruction and pulmonary fibrosis, long-term complications of ABPA occasionally include the development of an aspergilloma (Fig. 49-3), chronic or recurrent lobar atelectasis, allergic *Aspergillus* sinusitis, or *Aspergillus* tissue invasion and semi-invasive *Aspergillosis.* Transplantation has been undertaken successfully among patients with ABPA, however, post-transplant recurrence of ABPA has been reported.

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50
CHAPTER

Upper Airway Obstruction in Adults

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The upper airway is the segment of the conducting airways that extends between the nose (during nasopharyngeal breathing) or the mouth (during oropharyngeal breathing) and the main carina, located at the distal end of the trachea. Air passes through five conducting compartments on its way to the lung: oral cavity, nose, pharynx, larynx, and trachea. Physiological points of narrowing are the nostrils, the velopharyngeal valve (at the passage between the nasopharynx and oropharynx), and the glottis. Clinically significant obstruction in adults may occur within any compartment (see Chapter 2 for detailed anatomic description). The incidence and prevalence of upper airway obstruction in adults is not known. Malignant etiologies and benign strictures related to airway interventions are becoming more prevalent. Other common etiologies of upper airway obstruction in adults include infection, inflammatory disorders, trauma, and extrinsic compression related to pathology of adjacent structures. Initial management focuses on securing the airway and stabilizing the patient. Some conditions require bypassing the obstruction using translaryngeal intubation or tracheostomy. Definitive management depends on the underlying etiology and may include both medical and surgical interventions. The field of interventional pulmonology offers various new management modalities. This chapter provides a brief overview of upper airway obstruction in adults and focuses on clinical features, assessment, etiology, and management.

HISTORICAL PERSPECTIVE

Obstruction of the upper airway and its management concerned physicians for centuries. In the first century B.C., Asclepiades described tracheostomy to improve upper airway obstruction. In the mid-sixteenth century, the first successful tracheostomy was performed to relieve upper airway obstruction caused by a pharyngeal abscess. In the early nineteenth century, the procedure was used to treat croup, and, subsequently, diphtheria. Reports from the same period indicated that 25 percent of children in Paris who were dying from diphtheria were saved by the procedure. By the turn of the twentieth century, rigid bronchoscopy was used to remove a foreign body from the trachea. Finally, Ikeda introduced the flexible bronchoscope in 1967.

New causes of upper airway obstruction, radiologic techniques to detect upper airway obstruction, and treatment strategies have evolved in recent decades. Malignancy and related obstruction of the upper airway have become more prevalent with increasing tobacco use and exposure to modern environmental toxins. Complications of endotracheal intubation and tracheostomy have become well recognized causes of benign upper airway stenosis. Improvement in pharmacologic agents to treat infectious, inflammatory, and malignant etiologies, as well as developments in radiation oncology, have had significant effects on management of upper airway obstruction. More recently, advances involving anesthetic agents and anesthesia techniques, along with development of sophisticated surgical procedures for reconstruction of the larynx, trachea, and bronchi, have had a considerable impact on the management of this condition. Development of new endoscopic and imaging techniques and introduction of interventional pulmonology also have proved useful in the management of upper airway obstruction.

CLINICAL FEATURES

Upper and Lower Airway Obstruction

The causes of upper airway obstruction are considerably less common than diseases of the lower airways, such as chronic obstructive pulmonary disease (COPD) and asthma. However, symptoms (e.g., dyspnea, noisy breathing,) and clinical signs (e.g., wheezing, diminished breath sounds) may be identical, leading to diagnostic confusion. Since COPD and asthma are much more common, they are often assumed to be the cause of the patient's symptoms.

Significant upper airway obstruction may be obscured for a considerable period of time, resulting in delayed diagnosis and possible catastrophic outcome. When the obstruction develops acutely, asphyxia and death may result within minutes to hours. Therapy for acute asthma or an exacerbation of COPD is ineffective in this setting. When upper airway obstruction develops slowly, a delay in diagnosis may predispose patients to unnecessary complications, including bleeding or respiratory failure, and, in the case of an upper airway malignancy, to advanced and incurable disease.

Symptoms and Signs of Upper Airway Obstruction

The main symptoms of upper airway obstruction are dyspnea and noisy breathing. These symptoms are especially prominent during exercise and also may be aggravated by a change in body position. The patient may complain that breathing is labored in the recumbent position and may have a severely disrupted sleep pattern. Upper airway obstruction in such patients causes sleep apnea syndrome (see Chapter 97), which may resolve completely when the obstruction is relieved. Therefore, daytime somnolence may be a prominent feature of upper airway obstruction. In severely affected patients, cor pulmonale may occur as a result of chronic hypoxemia and hypercarbia.

Typically, significant anatomic obstruction precedes overt symptoms. For example, by the time exertional dyspnea occurs, the airway diameter is likely to be reduced to about 8 mm. Dyspnea at rest develops when the airway diameter reaches 5 mm, coinciding with the onset of stridor. Stridor is a loud, musical sound of constant pitch that usually connotes obstruction of the larynx or upper trachea. Although it should be easy to distinguish stridor from wheezing, which emanates from lower airways, sound recordings from the neck and chest have shown that the sound signals from the asthmatic wheeze and stridor are of similar frequency. This explains why errors in diagnosis can be made and an upper airway obstruction due to a tumor or foreign body may be mistakenly treated as asthma.

Unlike wheezing, which is characteristic of diffuse lower airway narrowing and occurs predominantly during expiration, the musical sounds of stridor usually occur during inspiration and are heard loudest in the neck. Maneuvers that increase air flow, such as voluntary hyperventilation, accentuate stridor. Neck flexion may change the intensity of stridor, suggesting a thoracic outlet obstruction. When the obstructing lesion is below the thoracic inlet, both inspiratory and expiratory stridor may be heard. At times, the character of a patient's voice may be a clue to an upper airway obstruction. Hoarseness may be a sign of a laryngeal abnormality. Muffling of the voice without hoarseness may represent a supraglottic process.

Physiological Assessment

Just as upper airway obstruction must be quite advanced before development of symptoms, physiological abnormalities do not become apparent on lung function testing until severe obstruction occurs. Studies of subjects breathing through tubes of varying diameters suggest that upper airway obstruction must narrow the airway lumen to less than 8 mm in diameter in order to produce abnormalities on a flow-volume loop (see below). This corresponds to an obstruction of more than 80 percent of the tracheal lumen. The forced expiratory volume in 1 s (FEV_1) remains above 90 percent of control until a 6-mm orifice is created. Therefore, spirometry, which is often the first screening test for pulmonary symptoms, may not be an effective way to detect upper airway abnormalities. The peak expiratory flow rate (PEFR) and maximal voluntary

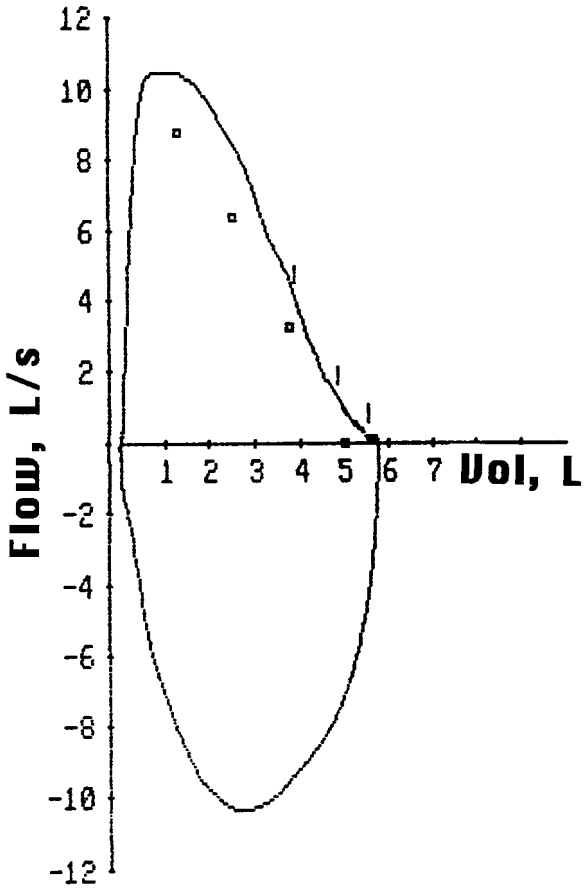


Figure 50-1 Normal flow-volume loop following maximal expiratory *(above)* and inspiratory *(below)* effort. Small vertical lines denote seconds.

ventilation (MVV) are more sensitive than the FEV_1 in detecting upper airway obstruction.

The flow-volume loop, which is a recording of maximal inspiratory and expiratory flow at various lung volumes, is an important tool for the diagnosis of upper airway obstruction. The configuration of the normal flow-volume loop is shown in Fig. 50-1. During a forced expiratory maneuver from total lung capacity (TLC), the maximal flow achieved during the first 25 percent of the forced vital capacity is dependent on effort, i.e., an increase in driving pressure (effort) may result in increased flow. During the remaining 75 percent of the forced vital capacity maneuver, flow is determined by the mechanical properties of the lungs and is not effort dependent. During this portion of forced exhalation, a linear deceleration of flow is caused by dynamic compression of the intrathoracic airways (Fig. 50-2 *A*). An increase in effort and therefore pleural pressure causes further compression of the intrathoracic airways and a further limitation of airflow. At higher lung volumes, flow may be limited by an upper airway obstruction. At low lung volumes, flow may not be affected by an upper airway obstruction, since measurement of flow in this effort-independent portion of the curve represents the function of the peripheral airways. Since the FEV_1 reflects a large portion of flow at these lower lung volumes, it is not a sensitive test for upper airway obstruction.

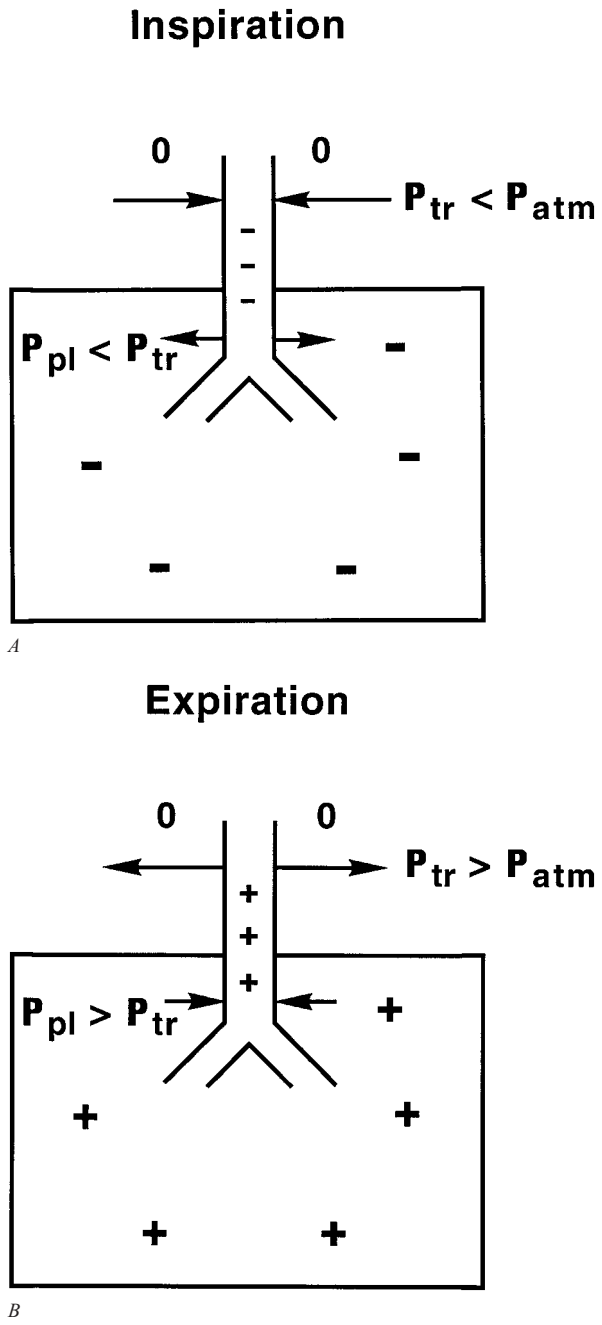
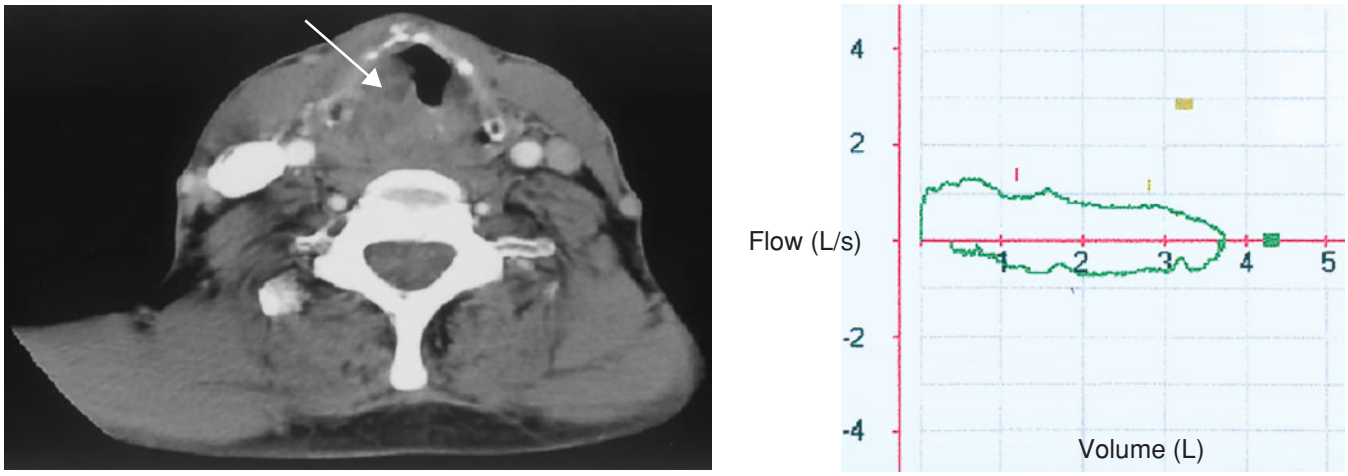


Figure 50-2 Forces acting on intra- and extrathoracic airway walls during inspiration and expiration. 0 = atmospheric pressure; + = positive pressure; − = negative pressure. *A*. During inspiration, extrathoracic tracheal pressure (P_{TR}) falls below atmospheric pressure (P_{ATM}), favoring narrowing of the lumen *(arrows)*. Intrapleural pressure (P_{PL}) becomes negative, favoring airway enlargement *(arrows)*. *B*. During expiration, the extrathoracic tracheal pressure (P_{TR}) becomes positive and, therefore, greater than P_{ATM}, favoring enlargement of the lumen *(arrows)*. Intrapleural pressure (P_{PL}) is positive, causing dynamic compression of the intrathoracic trachea *(arrows)*.

Because the PEFR reflects flow at higher lung volumes, it may be abnormal when the FEV_1 is not.

In generating the flow-volume loop, forced inspiratory flow is limited by effort during the entire inspiratory maneuver. Flow increases from residual volume to near the



A *B*

Figure 50-3 *A*, *B*. Flow-volume loop in fixed upper-airway obstruction due to laryngeal abscess in a 56-year-old man who developed persistent wheezing, hoarseness of voice, and intermittent stridor for 3 months after a brief intubation for asthma exacerbation. Computed tomography scan of the neck shows a laryngeal abscess with significant impingement on the laryngeal inlet. The flow-volume loop demonstrates a plateau of flow during inspiration and expiration; the $FEF_{50\%}/FIF_{50\%}$ ratio is near 1.

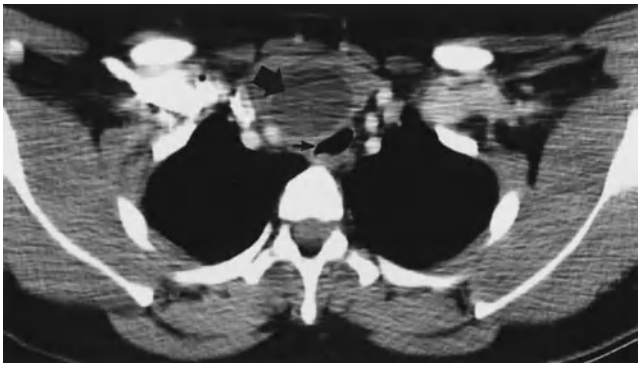
midportion of the curve, where it becomes maximal at the peak inspiratory flow rate. Flow then declines until TLC is reached. The pressure surrounding the extrathoracic portion of the upper airway is atmospheric. The turbulent nonlaminar airflow, which occurs during forced inspiration and causes airway pressure to fall in this portion of the airway, favors slight narrowing of the extrathoracic airway (Fig. 50-2*B*). Peak inspiratory flow, therefore, is less than peak expiratory flow in normal subjects. Because of the dynamic compression of the intrathoracic airways that occurs during exhalation, flow during the middle of inspiration, i.e., the forced inspiratory flow at 50 percent of the forced vital capacity ($FIF_{50\%}$), is usually greater than flow during the middle of forced expiration, i.e., the forced expiratory flow at 50 percent of the forced vital capacity ($FEF_{50\%}$). Typical patterns of the flow-volume loop may be seen, depending on whether the obstruction to flow is "fixed" or "variable," and whether the site of the obstruction is above or below the thoracic outlet or suprasternal notch.

Fixed obstructions of the upper airway are those whose cross-sectional area does not change in response to transmural pressure differences during inspiration or expiration. A fixed obstruction may occur in either the intrathoracic or extrathoracic airways. Irrespective of the site of the obstruction, a fixed lesion results in the flattening of the flow-volume loop. A *variable obstruction* is one that responds to transmural pressure changes, eliciting varying degrees of obstruction during the respiratory cycle. Since the stresses on the intrathoracic and extrathoracic airways are different, changes seen in the flow-volume loop vary according to the site of the obstruction.

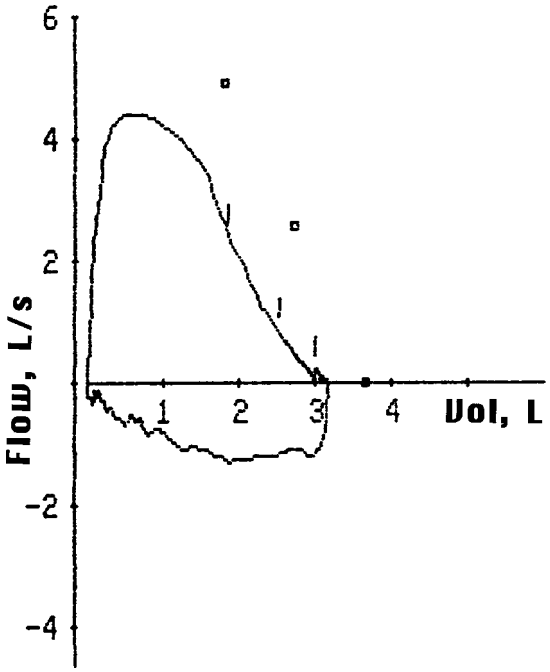
A number of conditions have been associated with nondistensible narrowing of the upper airway and fixed airway obstruction. Benign strictures and malignancy are common examples. Maximal inspiratory and expiratory flow-volume loops with fixed obstruction show constant flow, represented by a plateau during both inspiration and expiration (Fig. 50-3*A*, *B*). On the expiratory curve, the plateau effect is seen in the effort-dependent portion of the curve near TLC; very little change is noted in the effort-dependent portion near residual volume. Since the inspiratory curve is similar in appearance, the ratio of $FEF_{50\%}$ to $FIF_{50\%}$ is normal (close to 1). The forced inspiratory volume in 1 s (FIV_1) and FEV_1 are nearly the same in fixed upper airway obstruction.

Vocal cord paralysis is a common cause of variable extrathoracic obstruction. A variable extrathoracic airway obstruction increases the turbulence of inspiratory flow, and intraluminal pressure falls markedly below atmospheric pressure. This leads to partial collapse of an already narrowed airway and a plateau in the inspiratory flow loop (Fig. 50-4*A*, *B*). Expiratory flow is not significantly affected, since the markedly positive pressure in the airway tends to decrease the obstruction. The ratio of $FEF_{50\%}$ to $FIF_{50\%}$ is high (usually greater than 2). Similarly, the FEV_1 is greater than the FIV_1.

A variable obstruction in the intrathoracic airways reverses the situation. A predominant reduction in maximal expiratory flow is associated with a relative preservation of maximal inspiratory flow. This association occurs because intrapleural pressure becomes markedly positive during forced expiration and causes dynamic compression of the intrathoracic airways. The obstruction caused by an intrathoracic lesion is accentuated and a plateau in expiratory flow occurs on the flow-volume loop (Fig. 50-5*A*, *B*). A plateau of flow suggests that the lesion has caused the airway lumen to reach its minimal size. A flow peak may precede the plateau, suggesting that the obstruction may not affect flow until a certain lung volume is reached. During inspiration, intrapleural

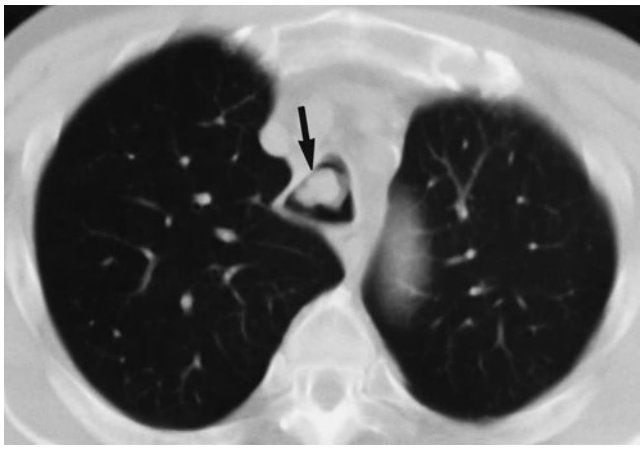


A

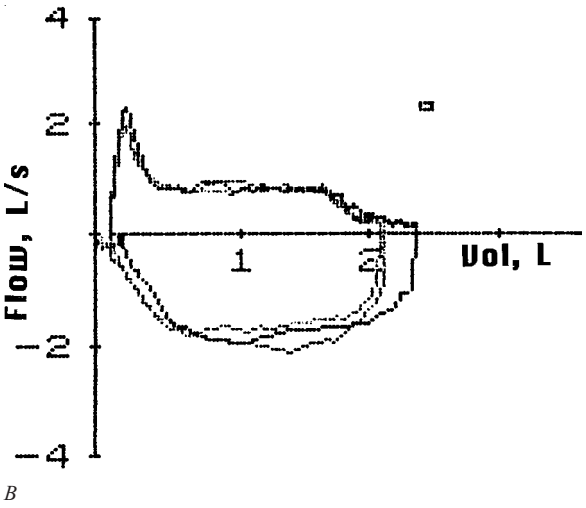


B

Figure 50-4 Variable extrathoracic obstruction due to thyroid cyst in a 32-year-old woman with dyspnea on exertion. *A*. Computed tomography of the neck shows a 10- × 4-cm cystic mass *(large arrow)* in the thyroid gland compressing the trachea *(small arrow)*. *B*. Flow-volume loop shows inspiratory obstruction. $FEF_{50\%}/FIF_{50\%}$ is very high, and the inspiratory curve is flattened.



A



B

Figure 50-5 Variable intrathoracic obstruction due to squamous cell carcinoma of the trachea. *A*. Computed tomography of the chest shows a tracheal lesion *(arrow)*, which was not readily apparent on plain chest radiograph. *B*. Superimposed flow-volume loops show a plateau of expiratory flow preceded by a peak of flow at higher lung volumes. The forced inspiratory flow is preserved in comparison to expiratory flow, but it is also reduced. $FEF_{50\%}/FIF_{50\%}$ is 0.4.

pressure is markedly negative; therefore, the obstruction is decreased. The ratio of $FEF_{50\%}$ to $FIF_{50\%}$ is very low and may approach 0.3. Similarly, the FEV_1 is considerably lower than the FIV_1. Although the flow ratios are similar to those seen in patients with COPD and chronic asthma, these disorders often can be distinguished by the appearance of the flow-volume loop. Thus, the expiratory curve in patients with COPD and asthma is primarily altered in the effort-independent portion of the curve, leading to a characteristic shape unlike the plateau configuration of an upper airway obstruction (Fig. 50-6).

When a hospital laboratory or physician's office is not equipped to perform flow-volume loops, results of other tests, such as routine spirometry, may be helpful. If the forced spirogram shows that the PEFR is reduced disproportionately to the reduction in FEV_1, an upper airway obstruction should be suspected. Other findings that suggest the diagnosis include a ratio of less than 1.0 for the inspiratory flow between 25 percent and 75 percent of the inspired vital capacity ($FIF_{25–75\%}$) and a value of less than 1.0 for the expiratory flow between 25 percent and 75 percent of the expired vital capacity ($FEF_{25–75\%}$). Another indication is an FEV_1 that is decreased to the same degree as the $FEF_{25–75\%}$. The MVV may also be a useful test, since it measures both inspiratory and expiratory flows. A ratio of MVV to FEV_1 of less than 25 percent is often found with upper airway obstruction. Whenever the MVV is reduced in association with a normal FEV_1, a diagnosis of upper airway obstruction should be considered.

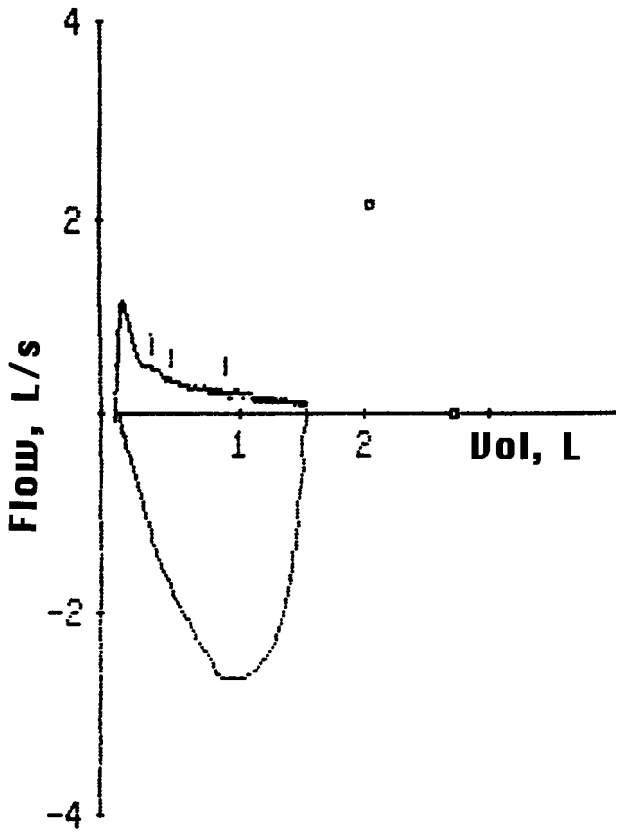


Figure 50-6 Flow-volume loop typical of chronic obstructive lung disease. Very low $FEF_{50\%}/FIF_{50\%}$ and typical curvilinear shape are noted.

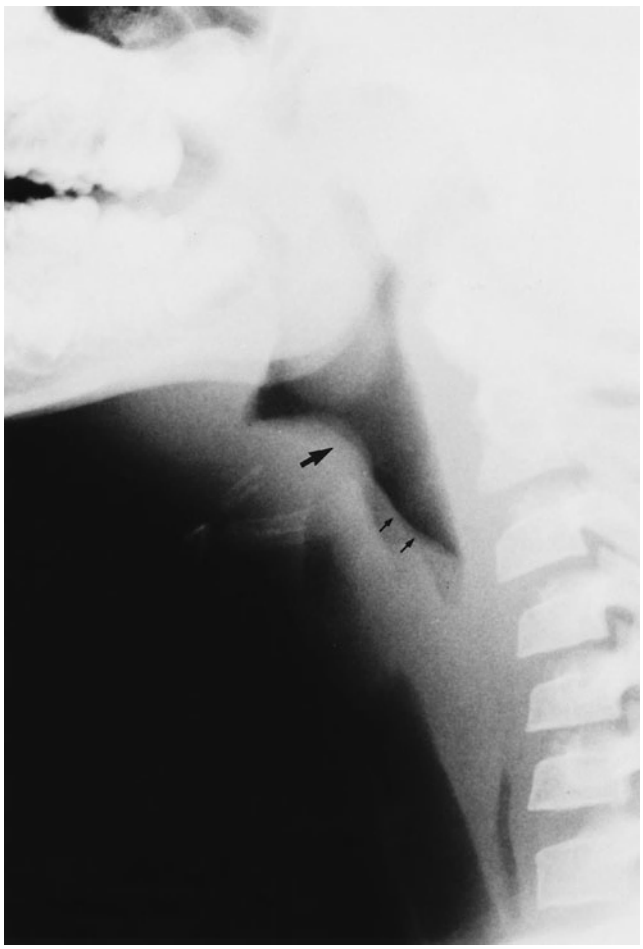


Figure 50-7 Acute epiglottitis. Lateral soft-tissue radiograph of the neck of a patient with stridor shows swelling of the epiglottis *(large arrow)* and loss of normal convexity of the edematous aryepiglottic folds *(small arrow)*.

In contrast to the situation in patients with diffuse obstructive disease of the lower airways (e.g., COPD, asthma), the distribution of ventilation in the lungs is normal, and ventilation-perfusion mismatch does not occur. Hypercarbia is not seen unless the degree of obstruction is very severe, although nocturnal hypercarbia may occur while daytime levels of P_{CO_2} are normal. Hypoxemia is also not present except during exercise and with severe airflow limitation, when it may accompany increases in the level of P_{CO_2}. In contrast to asthma and many instances of COPD, the airflow obstruction caused by an upper airway lesion does not resolve following the inhalation of a bronchodilator.

Radiographic Assessment

When acute airflow obstruction occurs as a result of an abnormality of the extrathoracic airway, roentgenographic studies of the soft tissues of the neck in the emergency setting may be helpful (Fig. 50-7). However, computed tomography (CT) has afforded the most important approach to imaging of the extrathoracic airways (Fig. 50-8). The standard chest roentgenogram is often not helpful in detecting the presence, or the cause, of upper airway obstruction. Occasionally, in patients with chronic airway obstruction, generalized hyperinflation of the lungs may occur; in the absence of asthma or COPD this finding may raise suspicion of occult disease in the central airways. The trachea is usually well visualized on the posteroanterior (PA) and lateral views in chest roentgenograms of good quality. It is located in the midline and is moderately deviated at the level of the aortic arch. However, many standard roentgenograms are underpenetrated so that the trachea may become a "blind spot." In one study, only 13 of 53 tracheal tumors were evident to the radiologist on the standard PA roentgenogram. The use of digital imaging techniques may avoid such pitfalls. However, thoracic CT studies have become the procedure of choice for imaging the upper airway.

The sensitivity of CT scanning for detecting upper airway disease surpasses that of the routine chest roentgenogram (97 percent versus 66 percent, respectively). Helical CT scanning (HCT) minimizes artifacts due to respiratory motion and provides imaging of the whole thoracic volume during a single breath hold. The technique represents an improvement over conventional CT scanning in that it allows detection of intraluminal, submucosal, and extraluminal lesions (Fig. 50-9*A*, *B*) and (Fig. 50-10). Since the early 1990s, HCT has become the preferred noninvasive modality for evaluation of the central airways. The use of HCT using multidetector technology and thin collimation provides high-resolution images of

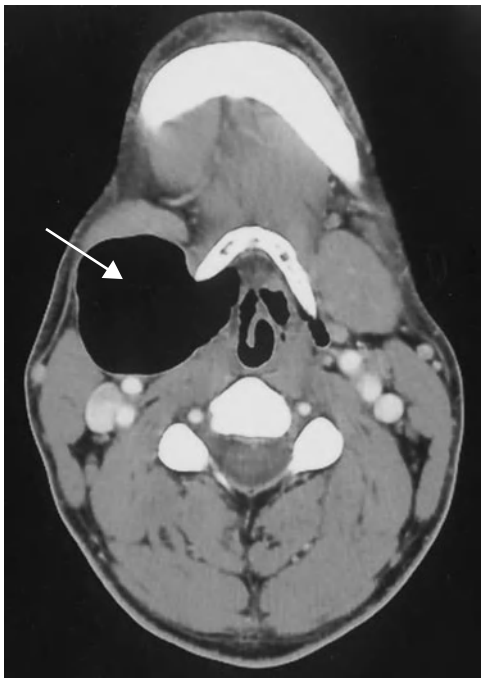
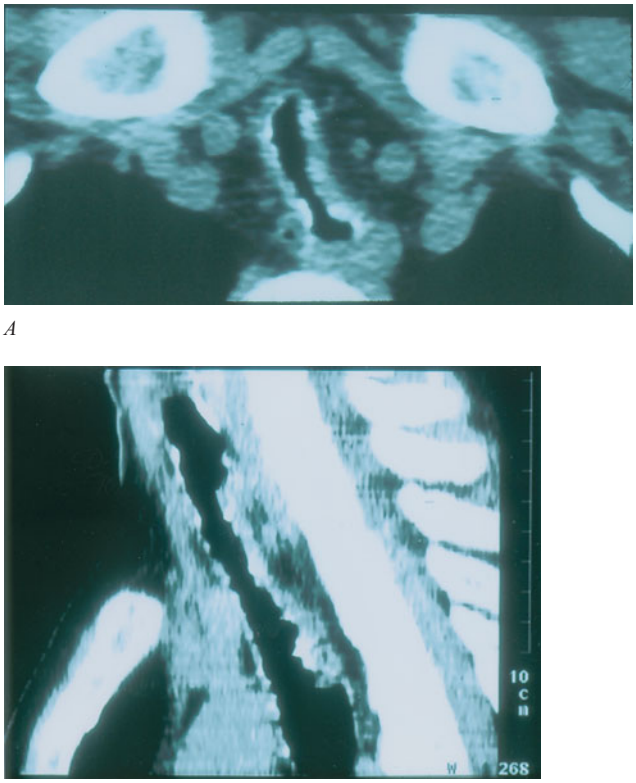


Figure 50-8 Computed tomography scan of the neck demonstrating a large laryngocele compressing the lateral wall of the larynx *(arrow)* causing positional air flow obstruction.

the entire thorax, improved special resolution, greater speed of image acquisition, and excellent contrast enhancement. HCT techniques using multiplanar and three-dimensional reconstruction can provide virtual images of the thorax that enhance the perception of local and diffuse anatomic lesions of the upper airways (Fig. 50-11). The images may demonstrate the degree of tracheal widening or narrowing, show the location and longitudinal extent of abnormalities, assess tracheal wall thickness, and demonstrate associated extratracheal diseases.

The use of paired inspiratory-dynamic and expiratory multislice HCT has proved helpful for the diagnosis of tracheomalacia. Because the maximal degree of collapse in tracheomalacia usually occurs during exhalation rather than at end-expiration, dynamic expiratory imaging is preferable to end-expiratory imaging. If complete collapse is not demonstrated during expiration, then one should confirm the diagnosis by quantitatively measuring the degree of airway luminal narrowing during expiration. Tracheomalacia is generally defined as a reduction in cross-sectional area of greater than 50 percent on expiratory images. The degree of dynamic airway collapse correlates well with findings on bronchoscopy.

Another novel CT-based imaging technique is virtual bronchoscopy. The use of volumetric imaging allows for an intraluminal three-dimensional reconstruction of the airways and surrounding tissues. The technique has been used with a high degree of accuracy in assessing the width, length, and contour of fixed airway lesions, but it has not been effective in defining dynamic airway lesions, such as laryngotracheomalacia.



A

B

Figure 50-9 *A*. Computed tomography scan of the chest demonstrating marked narrowing of the trachea with intraluminal calcified nodular projections in a patient with tracheopathia osteoplastica. *B*. Computed tomography scan of the chest demonstrating multiplanner reformation of the trachea in the sagittal plane of the same patient.

Magnetic resonance imaging (MRI) is another modality that may be used to assess the central airways and surrounding mediastinal structures. MRI provides a multiplane image of the chest without the need for contrast material.

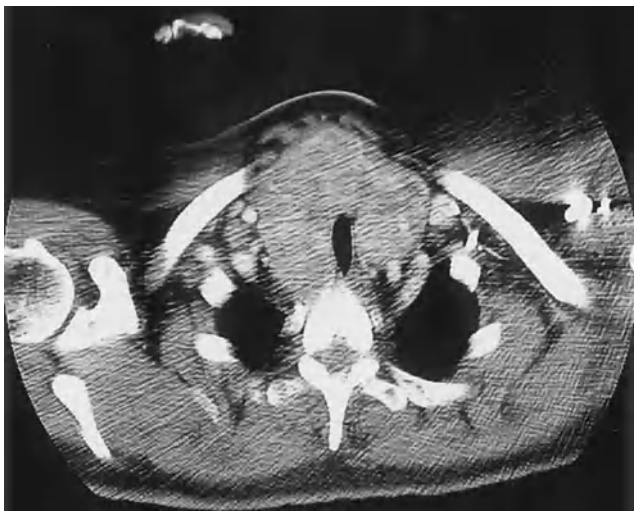
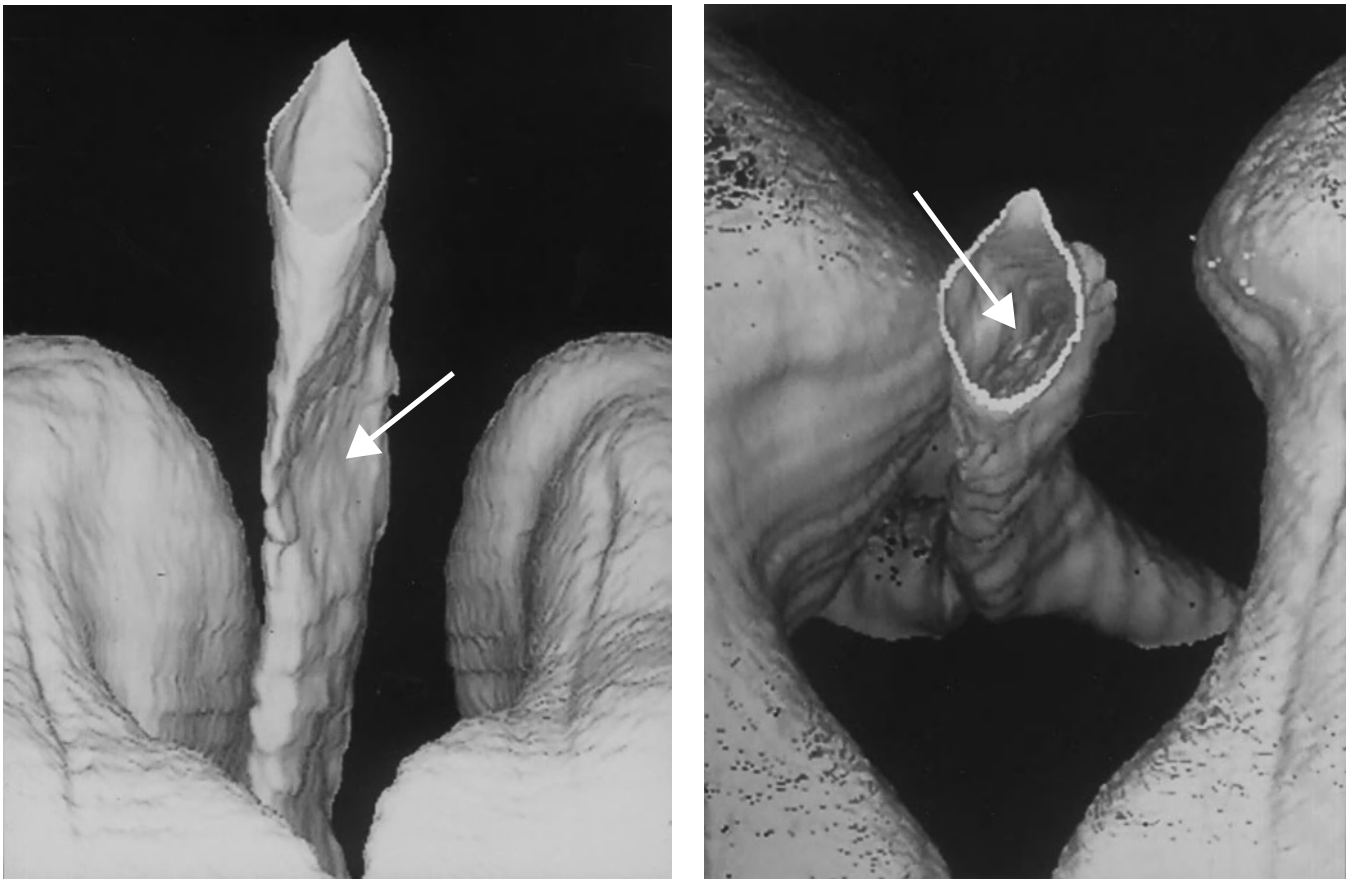


Figure 50-10 Computed tomography scan of the chest demonstrating marked extraluminal compression of the trachea caused by intrathoracic goiter.



A *B*

Figure 50-11 Helical computed tomography scan of the chest with three-dimensional reconstruction of the upper airway showing focal tracheal compression (*A*, *B*).

However, the technique is best used to investigate vascular structures surrounding central airways, such as vascular rings or aneurysms that may compress the trachea, rather than the airways themselves, which are better visualized using CT scanning.

CAUSES OF UPPER AIRWAY OBSTRUCTION

Infection

Deep Cervical Space Infections

Deep cervical space infections occur in potential spaces bounded by the deep cervical fascia. The cervical fascia is divided into a superficial and, a more complex, deep layer. This configuration and complexity divides the neck into functional units. Infection can spread along the planes formed by the cervical fascia. Infections affecting the deep neck tissues may result in life-threatening upper airway obstruction.

Patients with deep cervical space infections may present with sore throat, odynophagia, neck swelling, pain, fever, and dyspnea. Stridor and profound respiratory difficulty are signs of significant upper airway obstruction. Parapharyngeal, peritonsillar, submandibular, and retropharyngeal abscesses appear to be common locations in adults. The bacteriology and initiating event of deep cervical infections appear to have changed over time.

Mixed infections caused by aerobic and anaerobic infections are common and have been reported in up to two-thirds of cases. *Streptococcus viridans* and *Klebsiella pneumonia* are common pathogens. *Staphylococcus aureus, Staphylococcus epidermidis, Streptococcus pneumoniae, Escherichia coli,* and *Haemophilus influenzae* are other agents that are commonly reported. Alpha and beta hemolytic *streptococci* appear to have significantly declined in frequency. Overall, an odontogenic origin is probably most common, with upper respiratory tract infections as an important etiology in children. Intravenous drug abuse, mandibular fractures, iatrogenic and non-iatrogenic traumatic injury to the upper airway, underlying malignancy, and poor underlying immune status are associated conditions. Ludwig's angina—an infection of the submandibular space and the floor of the mouth—is potentially lethal and is commonly associated with significant upper airway obstruction. This entity is usually a cellulitic process and can affect the submandibular spaces bilaterally. In one report, 75 percent of the cases with true Ludwig's angina required tracheostomy.

Treatment of deep cervical infections involves maintenance of oxygenation and ventilation by securing an adequate airway, administration of appropriate antibiotics, and when indicated, use of surgical drainage. Complications of deep cervical infections include upper airway obstruction, Lemierre's syndrome (see below), distant infection, septic embolization, carotid artery rupture, pulmonary embolism, direct extension of infection resulting in mediastinitis and empyema, and rupture of the abscess during intubation or other interventions.

One particularly virulent cervical infection, known as Lemierre's syndrome, arises from a nasopharyngitis or peritonsillar abscess. This lateral pharyngeal space infection results in suppurative thrombophlebitis of the internal jugular vein, septicemia, and metastatic abscess formation, particularly in the lungs and joints. *Fusobacterium necrophorum* is usually the causative agent and has been cultured from blood in over 80 percent of cases. Symptoms begin with a sore throat, fever and painful swelling in the neck, followed by tender lymphadenopathy and tenderness along the sternocleidomastoid muscle (representing thrombophlebitis of the internal jugular vein). Dysphagia, trismus, and upper airway obstruction may occur as a result of swelling of the lateral pharyngeal space. Contrast-enhanced CT scan of the neck is most useful in establishing the diagnosis of thrombosis of the internal jugular vein and may demonstrate soft-tissue abscesses, fasciitis, and myositis, which may require extensive surgical debridement. Without the use of early and appropriate antibiotics, such as high-dose penicillin with metronidazole, or monotherapy with clindamycin, the mortality rate approaches 100 percent.

Epiglottitis

Epiglottitis is an infectious process that causes variable degrees of inflammation and edema of the epiglottis and supraglottic structures. Supraglottitis may be more appropriate term in adults, since the supraglottic structures usually are involved with variable involvement of the epiglottis. This condition can be life threatening. Its prevalence is 0.18 to 9.7 cases per million adults; the mortality rate may be as high as 7.1 percent. Clinical presentation includes odynophagia, with inability to swallow secretions, sore throat, dyspnea, hoarseness, fever, tachycardia, and stridor. In one review, 44 percent of the patients had a normal routine oropharyngeal examination.

Fiberoptic laryngoscopy is necessary to make the diagnosis. The procedure is safe in adults with suspected epiglottitis and should be done without delay. Radiographic studies can be helpful in ruling out other etiologies with similar presentations and in evaluating potential complications. However, the airway must be secured, and radiographic studies should not delay diagnosis or management.

Supraglottitis may involve the base of the tongue, uvula, pharynx, and false vocal cords. The disease may be increasing in prevalence among adults and declining in children, perhaps, reflecting introduction of *haemophilus*-b conjugate vaccines. Young adult males are commonly affected. The disorder appears to be more prevalent in colder, winter months and in smokers. Blood cultures are positive in less than one-third of cases. Although *Haemophilus influenzae* is the most common organism isolated in children, adult supraglottitis may be caused by a variety of organisms, including *Haemophilus influenzae, pneumococci,* group A *streptococci, Staphylococcus aureus, Streptococcus viridans*, a variety of anaerobic organisms, mycobacteria, fungi, and viruses. Throat cultures can be helpful in diagnosis and management; however, treatment should not be delayed while awaiting culture results.

Illicit drug use may be associated with epiglottitis, with inhalation of heated objects (e.g., metal pieces from a crack cocaine pipe or the tip of a marijuana cigarette) causing thermal injury to supraglottic structures. Signs, symptoms, and roentgenographic and laryngoscopic findings are similar to infectious epiglottitis.

Initial antibiotic therapy using a third-generation cephalosporin or extended-spectrum penicillin is reasonable. The prevalence of resistant organisms should be taken into account when choosing empiric antibiotic coverage. Corticosteroids often are used in management of acute epiglottitis despite lack of evidence to support their use. Based on anecdotal case reports, epinephrine is also used.

Patients should be observed closely and experienced staff should be available immediately to secure the airway by intubation or surgical approach, if needed. Securing the airway is extremely important in patients who develop stridor and other signs of significant airway obstruction. Mortality in this group has been reported to be as high as 17.6 percent.

Laryngotracheobronchitis and Bacterial Tracheitis

Laryngotracheobronchitis (croup), an acute viral respiratory illness commonly seen in children, is characterized by narrowing of the subglottic area, causing symptoms of stridor, barking cough, and hoarseness. Adult croup is a rare condition. Rare instances of diphtheric croup have been described in adults; noninfectious membranous tracheitis related to trauma also has been reported.

Acute bacterial tracheitis refers to involvement of the subglottic trachea by bacterial infection and usually follows an episode of viral laryngotracheobronchitis. Thick, purulent exudates and mucosal edema may cause symptoms of upper airway obstruction. *Staphylococcus aureus* appears to be the predominant organism. Prompt antibiotic therapy, close observation with attention to airway compromise, and frequent suctioning are important. Data to suggest effectiveness of steroids or epinephrine in adults are lacking.

Rhinoscleroma is a chronic, progressive granulomatous infection of the upper airway that may cause airflow obstruction. This disorder affects primarily the nose and paranasal sinuses, but also may involve the nasopharynx, larynx, trachea, and bronchi. The causative organism is *Klebsiella rhinoscleromatis.* Rhinoscleroma is endemic in Africa, Asia, and South America and is rare in North America. About 5 percent of patients have diffuse narrowing of the trachea. Prolonged antibiotic therapy with trimethoprim-sulfamethoxazole is effective.

Tuberculosis

The incidence of laryngeal tuberculosis may be on the rise due to the epidemic caused by the human immune deficiency virus. This form of the infection is relatively uncommon, accounting for less than 1 percent of tuberculosis cases. Laryngeal tuberculosis may present as progressive hoarseness and ulceration or a laryngeal mass. In the appropriate clinical context, a positive purified protein derivative (PPD) skin test and acid-fast bacilli in sputum may suggest the diagnosis. However, a biopsy from the laryngeal abnormality usually is required. Biopsy features include granulomatous inflammation, caseating granulomas, and acid-fast bacilli. The true vocal cords and epiglottis are the areas most likely affected. Treatment with antituberculous medications is usually adequate and should be instituted promptly, since the disease is highly contagious. Surgical interventions, including tracheostomy, are reserved for airway obstruction and long-term complications and, in one report, were required in 12 percent of the cases.

Endobronchial tuberculosis may result in significant airflow limitation that is related to the initial lesion or subsequent stricture formation. A barking cough and sputum production are common findings. The diagnosis of tuberculosis can be delayed while the diagnosis of malignancy is being entertained. Early diagnosis and treatment with antituberculous medications should decrease the development of fibrostenosis and resultant airflow limitation. The role of steroids in reducing the incidence of fibrostenotic complications remains unclear and controversial. Management may require endoscopic or surgical approaches.

Upper Airway Malignancy

Head and Neck Cancer

Head and neck cancers, which represent the fifth most common cancer worldwide, develop in the upper aerodigestive tract, including the oral cavity, pharynx, larynx, and related structures. The great majority are squamous cell carcinomas. These cancers share common risk factors, prognosis, treatment, and epidemiology. A 23 percent decline in head and neck cancers has been observed in the United States over the last two decades. The reported annual incidence was 11.2 cases per 100,000 per year from 1992 to 1999, as compared with 14.6 cases per 100,000 per year from 1976 to 1983.

The clinical presentation of head and neck cancer depends on the location and stage. Symptoms include hoarseness, hemoptysis, sore throat, and otalgia; life-threatening upper airway obstruction may be seen. Five percent of newly undiagnosed laryngeal cancers (a subcategory of head and neck cancers) present with severe dyspnea or stridor and may require emergency laryngectomy or tracheostomy.

Tracheal Malignancy

Tumors of the trachea and carina may produce a gradual decrease in airway diameter. Primary malignancies of the trachea are rare in comparison with other upper airway and bronchogenic tumors. In one study, lung cancer was 140 times more common than primary tracheal cancer.

Adenoid cystic carcinoma and squamous cell carcinoma comprise the majority of primary malignant tracheal tumors. Adenoid cystic carcinoma appears to be slightly more common. Dyspnea, cough, hemoptysis, wheeze, and stridor are frequent presenting symptoms. Surgery remains the most effective management. Emergency treatment with procedures to recanalize the airway, including airway stenting, may be necessary pending definitive surgery. Postoperative radiation therapy appears useful for primary tracheal malignancies, particularly when surgical margins are positive. Palliative radiation is used for local control when surgery is contraindicated. Five-year survivals for adenoid cystic and squamous cell carcinomas are reported at 52 percent and 39 percent, respectively. Favorable prognostic factors include negative airway margins at the time of resection and adenoid cystic histology.

Tumor metastases to the tracheal mucosa or direct tracheal extension of lung cancer from parenchymal lesions or lymph nodes are manifestations of locally advanced or metastatic disease, perhaps the most common cause of malignant tracheal obstruction. Metastases to central airways from nonpulmonary malignancy also may occur. Endobronchial metastases from breast, colorectal, renal, ovarian, thyroid, uterine, testicular, nasopharyngeal, and adrenal carcinomas, as well as sarcomas, melanomas, and plasmacytomas, have been described. In an autopsy series of over 1300 patients with solid tumors, metastatic disease to central airways occurred in 2 percent; other series report a higher incidence.

Laryngeal and Tracheal Stenosis

Postintubation and Post-tracheotomy

Concentric scar formation in the larynx or trachea may lead to narrowing and obstruction to airflow. Significant stenosis, defined as obstruction exceeding 50 percent of the lumen, can lead to serious symptoms and functional limitations.

Endotracheal intubation, tracheostomy, and prior laryngotracheal instrumentation account for most cases of laryngotracheal stenosis. The reported frequencies of tracheal stenosis following tracheostomy or laryngotracheal intubation vary widely (0.6 percent to 65 percent). Although injury to the laryngotracheal airway is common following intubation or tracheostomy, the incidence of symptomatic stenosis, demonstrated by radiographs or bronchoscopy, appears to be much lower (less than 2 percent).

Tracheal stenosis in the region of the tube cuff is related to pressure-induced ischemic injury of the mucosa and cartilage and its risk can be minimized by use of large-volume, low-pressure cuffs. The duration of translaryngeal intubation also affects the frequency and severity of laryngotracheal stenosis.

Stenosis following tracheostomy may be above the stoma, at the level of the stoma, at the cuff site, or at the tip of the cannula. Damage to the cartilage above the stoma is a common cause of tracheal stenosis after tracheostomy.

In addition to ischemic mucosal injury and ischemic chondritis, anterior and lateral tracheal wall damage, with "buckling in" fractures of the cartilage, is an important factor. The fractures can be minimized by avoiding excessive pressure on the cartilage during the procedure, selecting the appropriate size and length of the tracheostomy tube, avoiding infection, and using the lowest possible cuff pressure.

Percutaneous tracheostomy is growing in popularity as an alternative to the standard procedure. The ideal anatomic site for percutaneous tracheostomy is between the second and third, or first and second, tracheal rings (not the subglottic space). The incidence of symptomatic tracheal stenosis following percutaneous tracheostomy is comparable to the incidence that occurs after open techniques. When symptomatic tracheal stenosis and tracheomalacia are included as long-term complications, the incidence has been reported to be less than 2.5 percent.

Other Causes of Tracheal Stenosis

Other causes of laryngeal and tracheal stenosis are uncommon. They include airway trauma, including external injury; inhalational burns, irradiation; tracheal infections, including bacterial tracheitis, tuberculosis, and diphtheria; Wegener's granulomatosis; sarcoidosis; amyloidosis; collagen vascular diseases, including relapsing polychondritis, polyarteritis; inflammatory bowel disease; and congenital disorders.

Wegener's granulomatosis may present with significant subglottic stenosis, a complication reported in 16 to 23 percent of patients. Subglottic stenosis may be the only manifestation of Wegener's granulomatosis and have a clinical course distinct from other manifestations of the disease. Endoscopic biopsy of suspected sites of involvement is positive in only 5 percent to 15 percent of cases.

Sarcoidosis may be associated with granulomatous infiltration and obstruction of the upper airways. Laryngeal involvement is more common, but tracheostenosis has been described. Radiographs may show diffuse tracheostenosis, which progresses despite corticosteroid therapy. Bronchoscopy may reveal extensive tracheal narrowing.

Pulmonary amyloidosis includes tracheobronchial manifestations. The chest roentgenogram may show diffuse narrowing and wall thickening involving a long tracheal segment. Involvement is diffuse and circumferential, often with ossification of the amyloid deposits. Bronchoscopy demonstrates multiple plaques on tracheal walls or localized tumor-like masses.

Relapsing polychondritis is a rare systemic disease characterized by recurrent episodes of inflammation of cartilaginous structures. Respiratory manifestations are often severe and may be life threatening. Inflammation occurs in all cartilage types, including the elastic cartilage of the ears and nose, hyaline cartilage of all peripheral joints, and axial fibrocartilage. The most common presenting symptom is pain in the external ear due to auricular chondritis. Respiratory tract involvement may develop years after the first occurrence of auricular chondritis. Symptoms include hoarseness, aphonia, and choking. Tenderness over the thyroid and laryngeal cartilages may be present. When the trachea is involved, endoscopic examination shows inflammation and stenosis. CT demonstrates major airway collapse caused by destruction of cartilaginous rings or airway narrowing due to inflammatory edema and fibrosis. CT findings also include diffuse, smooth thickening of the trachea and proximal bronchi; thickened, densely calcified cartilaginous rings; tracheal wall nodularity; and diffuse narrowing of the tracheobronchial lumen. The posterior tracheal membrane is spared.

Tracheopathia osteoplastica is a rare, benign disease of the trachea and major bronchi in which cartilaginous or osseous nodules project into the airway lumen, often causing considerable airway deformity. The posterior membranous portion of the tracheal wall is spared. The disorder may begin just below the larynx, but most often it affects the lower two-thirds of the trachea. Extension into the proximal portions of the major bronchi may be noted. The condition usually occurs over the age of 50 years and may cause severe airflow obstruction. Its etiology is unknown.

On rare occasion, inflammatory bowel disease produces tracheobronchial stenosis and severe airflow obstruction. The associated airway mucosal inflammation may be steroid responsive early in the course of illness. If fibrosis ensues, medical management has limited success.

Laryngopharyngeal reflux may contribute to subglottic stenosis and, when documented, merits treatment.

Idiopathic progressive subglottic stenosis may be diagnosed in the absence of a clear, underlying etiology. Since most affected patients are female, a hormonal etiology has been proposed. However, estrogen receptors have not been demonstrated in specimens studied.

In addition to medical management, repeated rigid and flexible bronchoscopy-based interventions aimed at reestablishing airway patency may be necessary, particularly in those who are not considered to be surgical candidates or in whom the area of stenosis is complex or extensive. Some experts propose laser-based bronchoscopy as initial management in patients with benign laryngotracheal stenosis, reserving surgery for bronchoscopic failures (see Chapter 36). Others advocate primary surgical intervention, when possible. A multidisciplinary approach incorporating medical and surgical specialists is utilized in many centers.

Tracheomalacia

Tracheomalacia refers to loss of tracheal rigidity and resulting susceptibility to collapse. Tracheomalacia may be diffuse or localized to a tracheal segment. The affected portion may be intrathoracic, in which airway obstruction is accentuated during expiration. Less common is extrathoracic obstruction, in which airway obstruction is most marked during inspiration. Tracheobronchomalacia is the term used to describe the condition when the mainstem bronchi are involved.

Tracheomalacia in adults may be classified as congenital or acquired. The congenital form, described more extensively in children, is related to a variety of congenital

disorders and associated syndromes. The disorder may persist into adult life and is referred to as "idiopathic giant trachea," "tracheomegaly," or the "Mounier-Kuhn syndrome." Bronchiectasis and recurrent respiratory infections are common. Tracheal diverticuli have been reported in more advanced disease. Although atrophy of the longitudinal elastic fibers and muscularis layer has been described, the etiology of these changes is unclear. The diagnosis is made when the diameters of the trachea or right or left mainstem bronchi exceed the upper limits of normal by 3 or more standard deviations.

Acquired or secondary tracheomalacia in adults may be related to a variety of conditions. Tracheostomy and endotracheal intubation are probably the most common etiologies. Usually, limited, focal weakness of the trachea and dynamic airway obstruction are present. Tracheomalacia may be caused by conditions that are associated with chronic pressure on the tracheal wall, inflammation of the cartilaginous support or mucosa, interference with tracheal blood flow, or chronic infection. Traumatic injury to the central airways or surgical interventions also may lead to tracheomalacia.

Symptoms of tracheomalacia include dyspnea, cough, sputum production, and hemoptysis. Wheezing and stridor may be present in patients with significant airway obstruction.

Tracheomalacia is diagnosed by using direct bronchoscopic visualization to confirm significant narrowing of the tracheal lumen during regular, forced expiration. Assessment of the central airways using end-expiratory, dynamic, three-dimensional CT images is useful. Application of continuous positive airway pressure (CPAP) has been reported as beneficial. Surgical intervention may be useful in selected patients. Optimal medical management includes treatment of associated infections.

Extrinsic Compression of the Central Airway

The upper airway is subject to extrinsic compression by a variety abnormalities that involve adjacent structures. The compression may affect the intrathoracic trachea or extrathoracic trachea and upper airway.

Mediastinal Masses and Lymphadenopathy

Rarely, mediastinal masses present with serious limitation to airflow that develop either acutely or indolently. Common symptoms include chest pain, fever, dyspnea, and cough. Based on one large series, approximately 40 percent of mediastinal masses are malignant; 25 percent are cystic. The anterosuperior compartment is the most common site of mediastinal malignancies. Thymic neoplasms and lymphoma are the most common malignancies, followed by neurogenic tumors and teratomas. Both Hodgkin's and non-Hodgkin's lymphomas may be manifested by severe respiratory compromise due to airway compression. A similar syndrome may be due to a metastatic tumor to the mediastinal lymph nodes arising from bronchogenic or other carcinomas.

Patients with large mediastinal masses present a challenge during the perioperative period because of the potential for development of acute upper airway obstruction and other respiratory complications. In adults, complete airway obstruction during induction of anesthesia is rare. Serious pulmonary complications develop intra- and postoperatively in about 4 and 7 percent of patients, respectively. Complications may occur while the patient is placed in the supine position, during induction, or following extubation. Patients with severe symptoms, including stridor, and those with greater than 50 percent airway obstruction appear at high risk for respiratory complications; asymptomatic patients are at significantly less risk. Patients with reduced peak expiratory flow and mixed obstructive-restrictive patterns on pulmonary function testing also appear to be at increased risk for postoperative complications.

Middle mediastinal masses include benign cysts that are bronchogenic, enterogenous (duplication), pericardial, pleural, and thymic in origin. Most bronchogenic cysts are asymptomatic. However, some evoke cough, chest pain, and dyspnea. Severe respiratory distress and compressive symptoms can occur. Usually, cyst contents appear to have the density of water on CT or MRI. However, mucoid contents may give the impression of solid appearance on CT. Surgical resection and transthoracic or transbronchial drainage are options for management. Surgical intervention appears to be the preferred treatment in patients who are symptomatic. The role of interventions, including surgery, in asymptomatic patients is controversial. Enterogenous cysts are usually removed surgically.

Enlarged mediastinal lymph nodes which compress the airway may arise from infectious and noninfectious benign etiologies. One notable example is fibrosing mediastinitis, defined as the presence of excessive mediastinal fibrous tissue that tends to invade and destroy normal structures. The entity is thought to represent a reaction to an infectious granulomatous disease, especially histoplasmosis. The incidence in populations exposed to histoplasmosis remains low. Constriction of the central airways and vessels and the resulting cardiopulmonary limitations may develop several years after the initial infection. Hemoptysis is common, as are cough, dyspnea, and chest pain. CT imaging shows mediastinal fibrosis, calcification, and compression of mediastinal structures. Bronchoscopic findings include concentric airway narrowing and mucosal edema with hyperemia. Unfortunately, hemoptysis tends to be recurrent, and the disease does not respond to corticosteroids or antifungal agents. Surgical intervention is generally ineffective and may be hazardous.

Neck and Thyroid Causes

Retrosternal extension of a diffuse goiter may cause extrathoracic or intrathoracic airway obstruction. Up to 90 percent of patients with substernal goiter report respiratory symptoms. A choking sensation occurs in about one-third of patients with diffuse thyroid enlargement and 14 percent in patients with solitary thyroid nodules. Orthopnea is prevalent when the goiter is intrathoracic and may be enhanced by obesity. Flow-volume loops show evidence of upper airway

obstruction in one-third of patients. Lack of correlation has been reported between symptomatic obstruction and CT findings.

Laryngoceles and saccular cysts, which are abnormal dilatations of the laryngeal saccule (ventricle), are rare. Saccular cysts usually are filled with mucous. Laryngoceles communicate with the laryngeal lumen, resulting in air-filled structures noted on radiographic studies. Laryngoceles may be internal (i.e., confined to the larynx), external (i.e., extending into the thyrohyoid membrane superiorly), or combined. Most are asymptomatic. Hoarseness, dysphagia, pain, or signs of airway obstruction or infection may occur. A neck mass during the Valsalva maneuver may be detectable. Pyocele formation (i.e., infection in the laryngocele) may result in airway obstruction, aspiration pneumonia, or infection of the lateral pharyngeal space. The incidence of laryngeal carcinoma in association with laryngoceles makes close evaluation necessary. Endoscopic and surgical approaches may be employed in management.

Parathyroid cysts may be located in the neck or mediastinum. Fifty percent are accompanied by clinical hyperparathyroidism. Paroxysmal symptoms of airway obstruction can develop. Surgical excision is the treatment of choice; results are generally good.

Cervical osteophytes, common in the elderly, related to either degenerative spinal arthritis or more generalized idiopathic skeletal hyperostosis; the osteophytes may be associated with dysphagia. In addition, airway narrowing and ulcerations due to osteophytes have been reported. The airway compression may make even elective endotracheal intubation difficult, despite adequate preoperative evaluation.

Finally, significant upper airway compression may arise from cervical lymph node involvement with infectious or malignant disorders, hematomas or pseudoaneurysms (related to trauma, surgical interventions, central line placement, or coagulation abnormalities), abscess formation, or other expanding lesions in the soft tissue of the neck.

Esophagus

Involvement of the trachea, glottis, or vocal cords by advanced esophageal cancer is common and associated with a poor prognosis; estimated 1-year survival is less than 10 percent. Airway obstruction requiring stent placement is associated a median survival of 1 to 4 months after the placement. Tracheal obstruction may develop if an esophageal stent is placed in the setting of significant tracheal compromise. Development of tracheoesophageal fistula represents a devastating complication.

Placement of stents simultaneously in the trachea and esophagus is effective palliation for a tracheoesophageal fistula. If such double stenting is anticipated for a fistula or for simultaneous esophageal and tracheal obstructions, the tracheal stent is placed first to ensure patency of the airway, followed by the esophageal stent. Palliative external or local radiation therapy, chemotherapy, or other treatment modalities (e.g., photodynamic therapy) may be effective with or without accompanying airway interventions. The risk of esophageal disruption and rupture should be considered if stenting is performed after these local measures are employed.

Achalasia may cause a variety of pulmonary complications, including cough, aspiration with pneumonia or abscess formation, and rarely upper airway obstruction. Tracheal compression by a dilated megaesophagus is the usual etiology. Ensuring patency of the airway and decompressing the esophagus are necessary in urgent management.

Vascular Causes

Vascular rings, defined as anomalies of the aortic arch or its branches that compress the trachea or esophagus, are rare in adults (incidence less than 0.2 percent). Respiratory symptoms are common.

Right-sided aortic arch occurs in less than 0.1 percent in adults and may be associated with complete vascular rings, while double aortic arch and right-sided aortic arch with aberrant left subclavian artery appear to be the most common etiologies of vascular rings in adults.

The right-sided aortic arch usually crosses over the right mainstem bronchus and descends on either the right or the left side. The vascular ring usually is completed by the ligamentum arteriosum arising from the descending aorta, an aberrant left subclavian artery, or an aortic diverticulum. With a double aortic arch, the left arch crosses over the left mainstem bronchus and joins the descending aorta to complete the ring; the ligamentum arteriosum does not contribute to the vascular ring. Symptoms, resulting from malacia of the compressed airway and resultant dynamic airway obstruction, may be misdiagnosed as exercise-induced asthma. An increase in aortic diameter due to rising blood pressure during exercise, intravenous fluid administration, or anatomic changes with aging may contribute to symptoms. Surgical intervention is indicated in symptomatic patients.

Pulmonary artery sling with anomalous origin of the left pulmonary artery from the right pulmonary artery is very rare in adults. In neonates, the condition is symptomatic and can be fatal without surgical intervention. However, in adults the condition is usually diagnosed incidentally on imaging a patient who has no significant symptoms. This disorder may be associated with a complete tracheal ring, forming the "sling-ring" complex. This condition may present with a right paratracheal mass noted on the chest radiograph.

Compression of the trachea by large aortic or innominate artery aneurysms or pseudoaneurysms may occur and complicate management in the perioperative period. Surgical repair is indicated to relieve symptoms.

Foreign Body Aspiration

Foreign body aspiration, more common in children than adults (in whom the peak incidence is in the sixth decade), is usually recognized from the patient's history. Foreign bodies commonly lodge in the bronchi after migrating through the trachea. In adults, food products are the most commonly aspirated material. The penetration syndrome, defined as the

sudden onset of choking and intractable cough after aspirating a foreign body, with or without vomiting, is often followed by persistent cough, fever, chest pain, dyspnea, and wheezing. Impairment of the normal protective airway mechanisms is common; among the frequent associations are neurologic disorders, trauma with loss of consciousness, sedative or alcohol use, poor dentition, and advanced age. Emergency measures, entailing a food extractor or the Heimlich maneuver, can be life saving. Flexible bronchoscopy is usually successful in removing foreign bodies, although back-up rigid bronchoscopy should be available and is preferred as the primary procedure at some centers. A complicating chemical bronchitis from aspiration of vegetables or nuts may affect visualization and management of the foreign body.

Trauma

Facial Trauma

Emergency access to the airway is necessary in up to 6 percent of cases of facial trauma complicating motor vehicle accidents and other causes of crush injuries. If intubation is difficult or impossible due to the injury or related airway obstruction, emergency cricothyroidotomy or tracheostomy must be considered.

Laryngotracheal Injuries

Blunt and penetrating injuries to the laryngotracheal airway are rare. Without a high index of suspicion, clinicians may miss the diagnosis. The incidence of penetrating injuries appears to be increasing.

Stridor, wheezing, dysphonia, hemoptysis, and general neurological deficits are common. Cervical crepitus and subcutaneous emphysema also may be present. Cervical ecchymoses and hematomas, pneumomediastinum, and pneumothorax should prompt consideration of a laryngotracheal injury.

Management includes prompt securing of the airway, but blind endotracheal intubation should be avoided, since it carries the risk of complete airway obstruction. Some experts recommend tracheostomy as the primary airway management strategy. Awake fiberoptic intubation can be useful. Flexible fiberoptic laryngoscopy, rigid or flexible bronchoscopy, and CT imaging may be helpful in assessing the degree of injury. Unfortunately, the mortality of laryngotracheal injuries remains high (20 to 40 percent). Thoracic injuries and closed head injuries are commonly associated pathologies that can influence management and prognosis.

Inhalation Injuries

Thermal and chemical injuries to the upper respiratory tract may lead to serious consequences, including airway obstruction. Unfortunately, the mortality rate increases significantly when burns are accompanied by inhalational injury. Symptoms can be delayed in becoming manifest, making early recognition and intervention vital in the management of patients with inhalational injuries. The presence of cough, dyspnea, hoarseness, or loss of consciousness; or the findings of singed nasal hairs, carbonaceous sputum, or burns involving the face indicate a high likelihood of inhalation injury.

Early fiberoptic bronchoscopy remains important in evaluation and management of patients with inhalation injuries, enabling the assessment of the extent and severity of the injury, procurement of samples for bacteriologic studies, and fiberoptic intubation, as necessary. Translaryngeal intubation is the standard method of securing the airway in inhalation injury; early tracheostomy is used in some centers. A role for prophylactic corticosteroids or antibiotics is currently not supported by published reports. Significant tracheal stenosis may develop in patients who survive the initial insult, especially when translaryngeal intubation or tracheostomy is necessary.

Endotracheal Tube—Related Trauma

Postextubation stridor, due to glottic edema, laryngospasm, or laryngotracheal stenosis is a serious event. Reintubation rates for upper airway obstruction due to endotracheal tube–related trauma in critically ill patients have been reported to range from 4 percent to 33 percent. An "acceptable" rate is considered to be 5 percent to 15 percent. The cuff leak test does not accurately predict success or failure of extubation. Although the efficacy of corticosteroids or racemic epinephrine in the management of postextubation stridor is not substantiated, both are used extensively in clinical practice.

Translaryngeal intubation may also produce vocal cord paralysis, accounting for 10 to 15 percent of all cases. Paralysis may be unilateral or bilateral. Affected patients present with hoarseness or airway obstruction. Findings may occur immediately after extubation or be delayed. Prolonged intubation, use of a large endotracheal tube (number 8 or larger), placement of the tube cuff close to the vocal cords, or use of excessive cuff pressure are risk factors. The condition usually resolves spontaneously within 10 weeks.

Vocal cord (contact) granuloma may develop 4 to 6 weeks after intubation. Symptoms include prolonged hoarseness, exertional dyspnea, and stridor. Management, using antireflux medications, inhaled and systemic corticosteroids, antibiotics, botulinum toxin injection, speech therapy, smoking cessation, and rest of the voice are usually successful. Surgical intervention is reserved for cases that fail conservative management.

On occasion, dislocation of the arytenoid cartilages occurs during intubation. Rheumatoid arthritis that affects the cricoarytenoid cartilage is a risk factor for this condition. Rigid bronchoscopy or surgical interventions may be needed to reduce the dislocation.

Other disorders that may cause complications during intubation include hyperostosis of the cervical spine due to ankylosing spondylitis and cricoarytenoid joint disease due to systemic lupus erythematosus.

Neuromuscular Disorders

Neuromuscular disorders may affect the bulbar muscles, many of which surround the upper airway. When this occurs, resistance to airflow is increased, and the flow-volume loop

often shows an inspiratory flow plateau typical of variable extrathoracic upper airway obstruction. In addition, a pattern of flow oscillations during inspiration ("sawtooth pattern") may be seen. The abnormal flow pattern, first noted in patients with sleep apnea, is commonly seen in extrapyramidal disorders, myasthenia gravis, and motoneuron disease; it may also be seen in patients who have functional stridor and wheezing (see below). In extrapyramidal disorders, the flow oscillations correspond to vocal cord tremor. In motoneuron diseases, muscle denervation causes irregular muscle fasciculations, resulting in tremor of upper airway muscles.

Upper airway symptoms may be seen in Shy-Drager syndrome with extrapyramidal involvement and in Parkinson's disease. Patients may present with symptoms of chronic dyspnea or with stridor and respiratory failure relieved by endotracheal intubation. Bilateral vocal cord paralysis also results in abnormalities of inspiratory flow and a distinctive flow-volume loop. Bilateral vocal cord paralysis may be a cause of nocturnal stridor, oxygen desaturation, and sleep disruption or, in extreme cases, acute respiratory failure. In adults, causes include familial bulbar spinal muscle atrophy, postpoliomyelitis syndrome, Parkinson's disease, multiple sclerosis, acute poliomyelitis, amyotrophic lateral sclerosis, Guillain-Barré syndrome, brain stem stroke, and large cerebral hemisphere stroke. Non-neurologic causes include laryngeal nerve injury following neck surgery, endotracheal intubation injury, laryngeal trauma, infection, trauma, and thoracic aortic aneurysm. Dystonic extrapyramidal reactions due to neuroleptic medications (e.g., haloperidol) may cause significant upper airway obstruction. The usual reactions to these medications are akathisia, dyskinesia, dysarthria, and dystonic reactions, such as torticollis. Laryngeal-pharyngeal dystonia may cause severe upper airway dysfunction. If not reversed, symptoms can last for days or lead to respiratory arrest.

Vocal Cord Dysfunction

The glottis plays an active role in adjusting airflow, both voluntarily and through reflex control from laryngeal and pulmonary receptors. Normally, the glottic opening widens during inspiration and narrows during expiration. Occasionally, the glottis can become dysfunctional in the absence of organic disease. The disorder, called vocal cord dysfunction, laryngeal wheezing, or laryngeal asthma is characterized by paradoxical closure of the vocal cords intermittently during inspiration. The mechanism is unknown, but psychogenic factors appear to be more likely than a disordered processing of neural input to the larynx.

Signs and symptoms of vocal cord dysfunction resemble those of laryngeal edema, laryngospasm, vocal cord paralysis, or asthma. Wheezing or stridor and shortness of breath are typical and are often so dramatic that they suggest acute asphyxia and respiratory failure. Intubation and other emergency measures are used frequently. Slightly more than half of patients also have asthma. Patients without asthma are predominantly women who have been misdiagnosed as having asthma for an average of 5 years previously. Typically, patients have been treated with large doses of oral corticosteroids; frequent emergency room visits, hospitalizations, and endotracheal intubations characterize the clinical course of many patients.

Psychiatric disorders are common in these patients. Major psychiatric disorders, personality disorders, and sexual and physical abuse are commonly uncovered. Whereas many patients are unaware of their self-induced wheeze or stridor, others appear to derive secondary gain from their symptoms and manifest factitious illness. A high index of suspicion is warranted when the adventitious sounds are loudest over the neck in a patient who presents with wheezing, stridor, or both. Despite their respiratory distress, patients often have little difficulty completing full sentences and can hold their breath; the laryngeal-induced sounds disappear during a panting maneuver.

On pulmonary function testing, patients with vocal cord dysfunction demonstrate a pattern of variable extrathoracic airway obstruction, resulting in an increase in the ratio of $FEF_{50\%}$ to $FIF_{50\%}$. Some patients show a pattern of "sawtoothing," or fluttering of the inspiratory limb of the flow-volume loop, representing fluctuations in the abnormal cord motion (Fig. 50-12). Often, attempts to perform the flow-volume loop maneuver generate variable results from

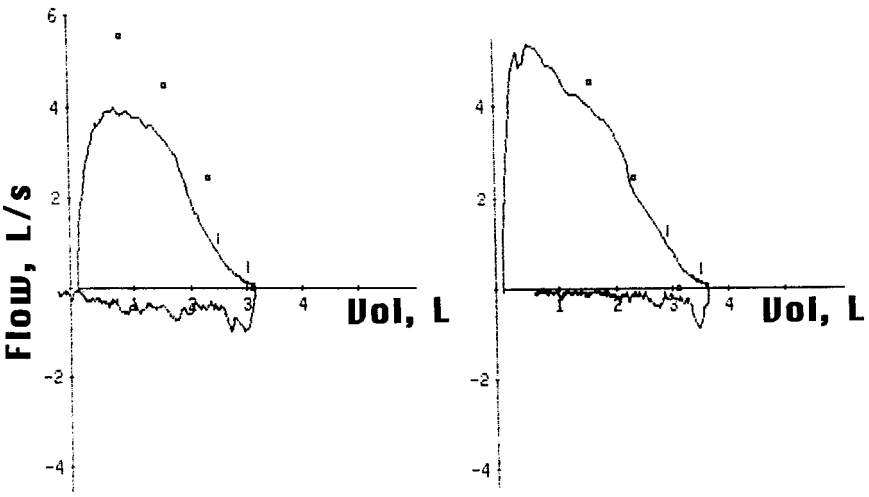


Figure 50-12 Variable extrathoracic obstruction due to vocal cord dysfunction. Two consecutive flow-volume loops from a young woman with inspiratory stridor. Variable effort accounts for the differences in configuration. $FEF_{50\%}/FIF_{50\%}$ in each is very high. The inspiratory loop is flat and demonstrates a sawtooth pattern. This pattern has also been associated with sleep apnea syndrome and various neuromuscular disorders.

test to test. A normal alveolar-arterial oxygen gradient and absence of bronchial hyperresponsiveness are other clues to the diagnosis.

The diagnosis of vocal cord dysfunction is made during direct visualization of the vocal cords during an attack. Inspiratory, anterior vocal cord closure with a posterior glottic chink is seen.

Treatment includes discussion of the diagnosis with the patient, discontinuation of unnecessary medications, and referral to a speech therapist or psychotherapist. The response to bronchodilator therapy is usually poor. Administration of an inhaled helium-oxygen mixture may alleviate symptoms during an acute attack.

Angioedema

Angioedema is characterized by well-demarcated swelling of the face, lips, tongue, and mucous membranes of the nose, mouth, and throat. When the larynx is involved, upper airway obstruction may occur and is fatal in as many as 25 percent of patients. In most instances, the cause of angioedema is unclear; prior exposure to common allergens, such as drugs, chemical additives, and insect bites should be suspected.

Contrary to what might be thought, the most common causes of angioedema are not IgE initiated. They include reactions to histamine-releasing drugs, such as narcotics and radiocontrast materials, to aspirin and other nonsteroidal anti-inflammatory drugs, and to angiotensin-converting enzyme inhibitors. Hereditary angioedema, a rare cause of upper airway obstruction, is an autosomal-dominant trait that occurs in all races. The underlying mechanism is a deficiency in production or function of C1 esterase inhibitor, a serum protease inhibitor that regulates the complement, fibrinolytic, and kinin pathways. Hereditary angioedema is characterized by painless nonpitting edema of the face and upper airway. The disorder usually begins in childhood and becomes more prominent in adolescence. Swelling progresses over many hours and then resolves spontaneously over 1 to 3 days. Despite the slow progression, death may occur from laryngeal obstruction. Physical stimuli (cold, heat, stress) and circulating immune complex diseases (e.g., due to serum sickness or systemic lupus erythematosus) are also known to cause angioedema.

Emergency management includes securing the airway, administration of corticosteroids, and use of antihistamines and epinephrine.

Miscellaneous Etiologies

A variety of uncommon etiologies also may produce upper airway obstruction.

Postpneumonectomy syndrome refers to compression of the left main bronchus between the aortic arch and left pulmonary artery following a right pneumonectomy. The syndrome also may be seen following a left pneumonectomy, sometimes in the setting of a right-sided aortic arch. Mediastinal repositioning prostheses, with or without additional fixation methods, may be useful in selected patients.

Mucus ball formation related to transtracheal oxygen catheters has been well described. Although transtracheal oxygen delivery decreases supplemental oxygen flow requirements by approximately 50 percent during rest and 30 percent during activity, development of symptomatic mucus balls (occurring in up to one-third of patients) remains a major disadvantage of the technique. Death and life-threatening events secondary to airway obstruction have been reported.

Recurrent respiratory papillomatosis in adults, caused by human papilloma virus types 6 or 11 (or, much less commonly, types 16 or 18) may result in upper airway obstruction and death. Although the larynx is most commonly affected, the tracheobronchial tree may be involved, with a predilection toward areas with prior mucosal injury, including tracheostomy sites and tracheal injuries. Lesions tend to progress down through the tracheobronchial tree. Pulmonary parenchymal involvement is rare, but it may be severe, and bronchiectasis, pulmonary nodules, and abscess formation may occur. Malignant transformation is also possible. The course of the disease is difficult to predict. Recurrent endoscopic interventions (debulking), with attendant risk of airway stenosis, are usually required. No controlled trials on the role of antiviral therapy have been conducted. Available data suggest beneficial effects of intralesional cidofovir. Favorable effects also have been reported with the use of interferon-a. Chemotherapy, radiation therapy, and targeted surgical resection are utilized for confirmed malignant transformation.

MANAGEMENT OF UPPER AIRWAY OBSTRUCTION

General Management

The primary goals in management of any patient with upper airway obstruction are assurance of adequate oxygenation and ventilation and management of the underlying condition. If airway obstruction is partial, and the patient's condition is stable, close monitoring and diagnostic studies are appropriate. Depending upon the underlying etiology, temporary measures may include close observation in an intensive care unit, elevation of the head of bed, administration of humidified oxygen, use of a helium-oxygen inhalation mixture (see below), systemic corticosteroids, and inhaled racemic epinephrine, pending definitive medical or surgical management.

A helium–oxygen gas mixture (Heliox) may be useful in management of upper airway obstruction when the obstruction is temporary and reversible. The physiologic rationale for Heliox is based upon a reduction in work of breathing achieved through administration of a low-density gas. In particular, Heliox has a lower density than does oxygen, room air, or a mixture of the two, resulting in conversion of the predominantly turbulent flow at the site of obstruction to a more laminar pattern. Furthermore, since laminar flow requires a

smaller pressure gradient than turbulent flow to achieve the same flow rate, the accompanying work of breathing is less (see Chapter 9). The major limitation of the modality is an inability to deliver gas with an FI_{O_2} of more than 40 percent. Despite physiological evidence and clinical reports of efficacy, prospective, randomized studies demonstrating improved outcome in patients receiving Heliox are lacking, as are data supporting use of corticosteroids or inhaled epinephrine in airway obstruction from a variety of causes.

Securing the Airway

Although under controlled circumstances, a significant portion of so-called difficult airways and intubations may be identified in the course of a thorough preoperative assessment, the patient with impending airway obstruction presents a challenge. Under such circumstances, a critical first concern is deciding whether an artificial airway is needed emergently. Regardless of the airway utilized, emphasis is placed on ensuring adequate oxygenation and ventilation.

Airways judged unsafe for routine management may be addressed according to the "difficult airway algorithm" recommended by the American Society of Anesthesiologists (see also Chapter 163). A difficult airway is defined as a clinical circumstance in which a conventionally trained anesthesiologist experiences difficulty using face mask ventilation, endotracheal intubation, or both.

Airway access in emergency situations may be challenging because the patient frequently is critically ill and can deteriorate quickly. The likelihood of a difficult intubation can be estimated by using the Mallampati score or a modification of the score to assess potential laryngeal exposure and prospects for adequate airway visualization.

A number of parameters, such as mouth opening distance, jaw size, thyromental distance, and cervical range of motion, have been incorporated into airway assessment scoring systems; each parameter has limited sensitivity and specificity. Combining scoring systems provides better accuracy of prediction. The "rule of threes," which is a useful, simple bedside tool, predicts successful direct laryngoscopy if the examiner can place three finger breadths (approximately 6 to 7 cm) between the upper and lower teeth, the mandible and hyoid bone, and the thyroid cartilage and sternal notch. In the emergency setting of upper airway obstruction, the most experienced physician available should secure the airway. Appropriate equipment and monitoring, along with back-up resources for alternative and invasive airway management, should be available.

A variety of invasive and noninvasive techniques are available as alternatives to standard, laryngoscopy-guided orotracheal intubation. Invasive methods include surgical and percutaneous tracheostomy, surgical and percutaneous transtracheal (needle) cricothyrotomy, translaryngeal guided or "retrograde" intubation, fiberoptic endotracheal intubation, and use of a rigid ventilating bronchoscope. Noninvasive techniques include use of specialized laryngoscope blades, guiding and lighted stylets, directional tip control tubes, and esophageal-tracheal (Combitube) or laryngeal mask airways. In selected circumstances, tactile intubation, nasotracheal intubation, or blind orotracheal intubation may be employed.

Cricothyroidotomy

Cricothyroidotomy (either surgical or based on Seldinger technique) has a long history of use in emergency access to the airway when more conservative approaches fail or are contraindicated. Currently, surgical cricothyroidotomy is performed by surgeons, anesthesiologists, and intensive care specialists. In early reports, a high incidence of laryngeal stenosis during intermediate and long-term follow-up was noted, perhaps related to the presence of infectious laryngeal disease or the use of large-bore tubes. In addition, the risk of subglottic stenosis also appears high in patients with prolonged prior intubation. Hence, although the procedure is useful for short-term airway control, tracheostomy should be considered if prolonged airway access is required.

Tracheostomy

Most tracheostomies are performed on intubated patients in the intensive care unit. Percutaneous tracheostomy is rapidly becoming the method of choice in the intensive care unit and is associated with acceptable intraoperative and postoperative complication rates. Advantages of the technique over the traditional procedure include low cost, short procedure time, low complication rate, and elimination of the need to transport critically ill patients to the operating room. Adaptation of percutaneous techniques for emergency situations also has been described.

In a review of over 1100 patients who underwent tracheostomy, 76 percent were performed in patients who required prolonged ventilation, 6 percent for upper airway obstruction, 7 percent for extensive maxillofacial trauma, and 11 percent as an adjunct for head and neck or chest surgeries; only 0.26 percent were performed as emergency procedures. Overall mortality was 0.7 percent.

Bronchoscopy and Interventional Pulmonology

Bronchoscopy, including interventional bronchoscopic techniques, is discussed in Chapter 36. Use of these techniques for managing upper airway obstruction is well established and is briefly summarized below.

Rigid bronchoscopy allows oxygenation, ventilation, and application of various therapeutic interventions, including "coring out" of obstructing lesions, control of bleeding, and removal of foreign bodies. Complications include airway rupture, bleeding, and granulation tissue formation related to mucosal injury.

Electrocautery can be applied through rigid or flexible bronchoscopy. Side effects include bleeding, perforation, and airway fire. Laser therapy, including use of Nd:YAG, argon, and CO_2 lasers, may be useful as well.

Photodynamic therapy, based on creation of a phototoxic cell reaction achieved after activating a drug trapped in target cells by nonthermal laser light, has been employed in treatment of upper airway obstruction. Disadvantages include delay in effect compared with laser therapy and electrocautery and need for follow-up debridement. Bleeding and obstruction from necrotic tumor and edema are potential complications.

Cryotherapy, based on repeated freeze-thaw cycles to achieve cell necrosis and tissue damage is used in benign and malignant disorders of the upper airway. Cryotherapy has excellent hemostatic effects; the incidence of perforation or bleeding is low. Due to the delayed beneficial effect, cryotherapy is not usually used under emergent conditions.

Finally, external beam radiation and brachytherapy are useful modalities for palliative management of airway obstruction and hemoptysis. For external beam radiation, unwanted exposure of adjacent structures is a limiting factor, while hemorrhage, radiation bronchitis, and fistulae with surrounding structures are complications of brachytherapy.

Airway Stents

Airway stents are used in the palliative management of both benign and malignant airway obstruction. Available tracheal stents include expandable metal and silicone prostheses. Major complications include stent migration, granulation tissue formation, and stent interference with mucociliary clearance. In a series of over 1500 patients who had stents placed for upper airway obstruction due to benign or malignant disorders, stent migration was reported in 9.5 percent, granulation tissue formation in 7.9 percent, and obstruction in 3.6 percent.

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51

Cystic Fibrosis

Judith Voynow • Thomas F. Scanlin

Cystic fibrosis (CF) is a common inherited disease that has a high frequency in Caucasians. The disorder affects all exocrine glands, with symptoms involving the lungs and pancreas usually dominating the clinical picture. Two aspects of the disease make CF particularly difficult to both diagnose and manage: tremendous variability in the degree and pattern of involvement of organs in different persons and lack of information about the precise details of the molecular and cellular pathogenesis of the disease, even though the gene responsible for CF and its gene product, an integral membrane glycoprotein, have been identified. This chapter focuses on the pathophysiology and management of CF. Our current understanding of the genetics and underlying molecular biology are highlighted. Complications of the disorder are addressed, and a brief discussion of relevant psychosocial and reproductive issues is provided. Finally, potential future directions in treatment are described, including gene therapy.

GENETICS

CF demonstrates an autosomal-recessive pattern of inheritance. In the United States, the incidence of the disease is approximately 1 in 3000 in Caucasians, 1 in 6000 in Hispanics, and 1 in 10,000 in African Americans. The frequency of unaffected heterozygote carriers of a CF mutation is estimated to be 1 in 26 in persons of Northern European ancestry.

CF is caused by mutations in a single gene named the *cystic fibrosis transmembrane conductance regulator* (CFTR). This gene was identified with an approach known as positional cloning, which permitted mapping of the gene without prior knowledge of the biochemical defect through use of polymorphic DNA markers. The first genetic marker that was found to be linked to CF was paraoxonase. In 1985, the demonstration of the linkage of CF to two DNA markers, D7S15 and D7S8, and to the *met* oncogene established the localization of the CF gene to the long arm of chromosome 7. Following a series of molecular cloning experiments, which included "chromosome walking" and "jumping," a candidate gene was identified. This was proved to be the CF gene in 1989, largely through the discovery of a frequent mutation. Formal proof that this was the CF gene came in 1990 with correction of the chloride secretory defect in CF cells in vitro following transfection of the CFTR gene.

The CF gene spans approximately 230 kb of DNA and contains 27 exons. The mRNA is 6.5 kb and is detected in a variety of tissues, including lungs, pancreas, and sweat glands, which are predominantly affected in pathogenesis of the disease. The deduced polypeptide was predicted to be an integral membrane glycoprotein containing 1480 amino acids (Fig. 51-1; see "Pathogenesis"). Several major and minor splicing variants in the transcripts have been described in individuals with and without CF. In most cases, however, the significance of the alternative splicings is not clear.

The most common CF mutation, and the first to be described, is a three-base deletion in exon 10 that causes a deletion of phenylalanine from position 508 (ΔF508) of the CFTR glycoprotein. This mutation accounts for 66 percent of CF mutations. However, more than 1000 CF mutations have now been reported, and the list continues to grow. In addition, a number of benign sequence variations have been described. A listing of the most common mutations and their relative frequency is included in Table 51-1. The large

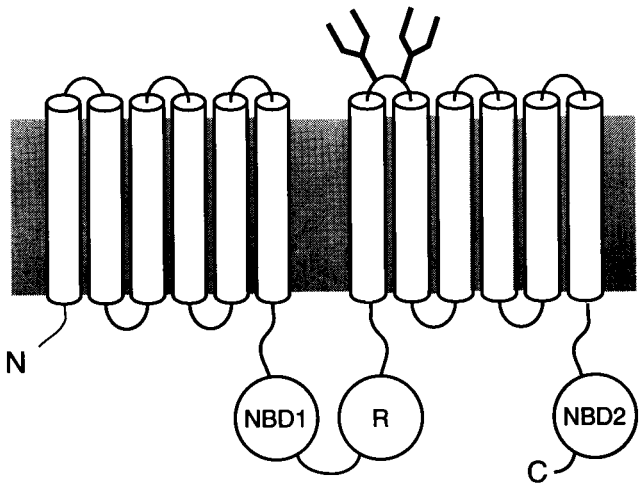


Figure 51-1 Domain model of the cystic fibrosis transmembrane conductance regulator (CFTR). Based on hydrophobicity plots, CFTR has twelve transmembrane spanning domains, two nucleotide (N) binding domains (NBD 1 and NBD 2), and a regulatory (R) domain. The twelve transmembrane domains form the ion channel "pore." In the closed state, the "R" domain is believed to obstruct the channel. Channel opening requires binding of two adenosine triphosphates (ATPs) to the nucleotide binding domains. This model is similar to other ATP-binding cassette transporter proteins that bind ATP and transport ions or micronutrients. *(Modified from Riordan J, Rommens JM, Kerem B, et al: Identification of the cystic fibrosis gene: Cloning and characterization of complementary DNA.* Science *245:1066–1073; erratum 1437, 1989.)*

Table 51-1

Most Common CFTR Mutations in the United States

Name of Mutation	Frequency (%)	Population with High Prevalence
ΔF508	66	
G542X	2.4	Spanish
G551D	2.1	English
3120+1G→A	1.5	African American, Arabian
W1282X	1.4	Jewish-Ashkenazi
N1303K	1.3	Italian
R553X	0.9	Hispanic
621+1G→T	0.9	Multi-ethnic
1717–1G→A	0.7	Italian
3849+10kbC→T	0.7	Hispanic
R117H	0.7	
1898+1G→T	0.4	East Asian
ΔI507	0.3	Hispanic
2789+5G→A	0.3	
G85E	0.3	
R347P	0.2	
R334W	0.2	Multi-ethnic
R1162X	0.2	Multi-ethnic
R560T	0.2	
3659delC	0.2	
A455E	0.2	
2184delA	0.1	
S549N	0.1	Multi-ethnic
711+1G→T	0.1	
R75X	0.2	Hispanic[a]
406–1G→A	0.2	Hispanic[a]
I148T	0.2	Hispanic/French[a]
2307insA	0.2	African American[b]
A559T	0.2	African American[b]
ΔF311	0.2	African American[b]
G480C	0.2	African American[b]
405+3A→C	0.2	African American[b]
S1255X	0.2	African American[b]

Data based on the most frequent mutations found overall in the United States. Mutations that are expressed at higher frequency in Hispanic (a) or African American (b) populations are indicated.

SOURCE: Bobadilla JL, Macek M Jr., Fine JP, et al: Cystic fibrosis: A worldwide analysis of CFTR mutations-correlation with incidence data and application to screening. *Hum Mutat* 19:575–606, 2002.

number of mutations makes accurate detection of a satisfactory percentage of carriers extremely difficult, and carrier screening for the general population has not been recommended or implemented. Testing for 32 of the most common mutations is widely available; such testing will detect approximately 90 percent of the carriers in Caucasians of Northern European descent. In families with an affected individual and known mutations, prenatal diagnosis and carrier testing using direct detection of mutations is accurate and available. In families with a member diagnosed as having CF, but with undetected mutations, sequencing of the complete CFTR coding region and critical intronic regions is now also available to detect rare mutations.

PATHOGENESIS

Discovery of the gene responsible for CF and description of its product, CFTR, have provided the necessary foundation for understanding the pathogenesis of the disorder at the molecular and cellular levels. CFTR is an integral membrane glycoprotein of approximately 170 kD that is expressed in epithelial cells of affected organs. CFTR contains 1480 amino acids, which are arranged in twelve transmembrane domains, two nucleotide binding domains, and a putative regulatory domain (Fig. 51-1). The most common mutation, ΔF508, is a three-base deletion that causes deletion of phenylalanine from position 508, located in the proposed first nucleotide-binding domain. The original structural model, which was based on hydrophobicity plots, has proved to be essentially correct in its main features. CFTR shares many structural features with the "adenosine triphosphate (ATP)-binding cassette" transporter family, which includes P glycoproteins, as well as a number of bacterial transporters. CFTR has been clearly shown to function as an apical chloride channel in airway epithelial cells.

The localization of CFTR to the apical aspect of airway epithelial cells, to the ciliated duct of submucosal gland cells, and to submucosal serous cells, and the role of CFTR as an apical chloride channel fits nicely with the simplest hypothesis to account for the pathogenesis of pulmonary disease in CF: Decreased secretion of chloride and water by airway epithelial cells results in dehydrated mucus (Fig. 51-2). However, CFTR may have other functions, such as regulation of other ion channels, including the epithelial sodium channel. Loss of CFTR causes increased reabsorption of sodium; increased epithelium sodium channel activity alone alters regulation of ions and water, resulting in mucus obstruction of airways. CFTR transports bicarbonate; loss of CFTR function may result in acidification of the small intestinal lumen and, possibly, the airway lining fluid. Alternatively, CFTR may also function in *intracellular* membranes (e.g., endoplasmic reticulum, endosomes, and clathrin-coated vesicles). A consequence of the altered function of CFTR in intracellular membranes may be the mislocalization of glycosyltransferases. Together, these observations may explain abnormalities of

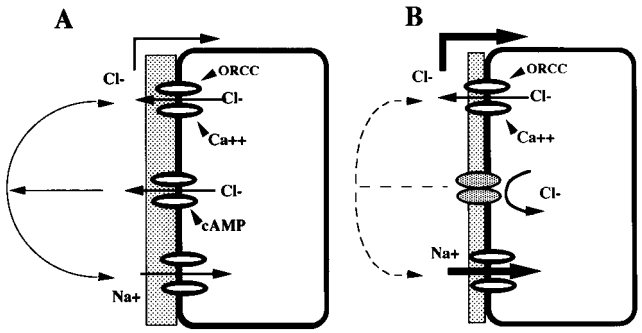


Figure 51-2 Simplified model of ion transport in airway epithelium. *A*. Normal airway cell with multiple apical ion channels. At the top, two different chloride channels are represented, the outwardly rectifying chloride channel (ORCC) and the Ca^{++}-gated chloride channel. In the center, cyclic adenosine monophosphate (cAMP)-gated cystic fibrosis transmembrane conductance regulator (CFTR) is shown. The apical sodium channel is depicted at the bottom. Experimental data suggest that CFTR interacts with the other channels, although the type of interaction is not clear (solid arcs). *B*. CF cell with nonfunctioning cAMP-gated apical chloride transport. The function of the other channels is affected in an unknown manner (dashed arcs). The net result of ion channel activity on the pericellular fluid composition (hatched area) is under investigation. Many questions remain concerning the function of CFTR and ion transport in the airway.

CF glycoproteins: increased sulfation of respiratory mucins, with decreased sialylation and increased fucosylation of both secreted and membrane glycoproteins. Altered glycosylation of airway glycoproteins may significantly impact bacterial-epithelial interactions and innate immune functions in the lung.

In addition to the effect of CFTR on epithelial ion channels and glycoprotein processing, loss of CFTR function negatively impacts innate immunity and accentuates inflammation. Absence of CFTR function is associated with impaired bacterial killing in vitro and defective function of antimicrobials including human beta-defensin 1 and lysozyme. Absence of CFTR is also associated with increased interleukin-8 (IL-8) production and decreased IL-10 in vitro. Furthermore, the presence of excessive, unopposed neutrophil elastase in the airway cleaves complement and immunoglobulins, potentially interfering with bacterial opsonization. CF airways have increased oxidant stress due to neutrophilic inflammation and reduced antioxidants such as glutathione. Finally, tissues in CF have an increased ratio of arachidonic acid metabolites to docosahexaenoic acid metabolites when compared to healthy controls, reflecting an increase in inflammatory lipids in affected tissues, and decreased levels of lipoxin, an anti-inflammatory lipid mediator in airway surface fluid. Together, these factors synergistically increase the inflammatory milieu in the airways in CF.

CFTR mutations have been grouped into four or five classes, depending on the effect of the mutation on the expression, processing, and function of the protein (Fig. 51-3). The most common mutation, ΔF508, is a processing mutation in which very little of the mutant protein reaches the apical

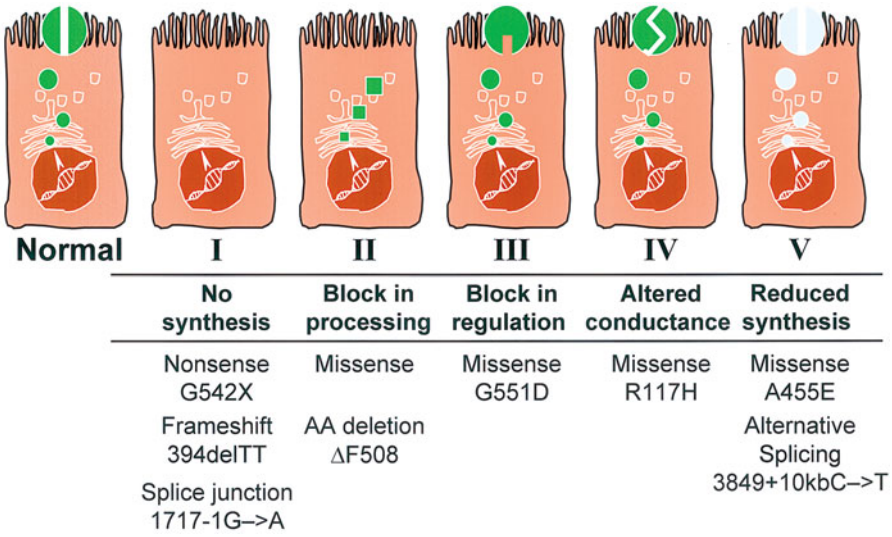


Figure 51-3 Classification of cystic fibrosis transmembrane conductance regulator (CFTR) mutations by molecular and biochemical abnormalities. This schematic depicts the effect of different classes of CFTR mutations on expression and function in the cell. Class I mutations block mRNA transcription. Class II mutations prevent normal CFTR protein processing and localization. Class III mutations permit CFTR localization at the apical membrane but inhibit chloride channel conductance. Class IV mutations result in partial chloride channel conductance. Class V mutations affect transcription, translation, or protein processing resulting in reduced CFTR expression at the apical membrane. Examples of mutations in each class are depicted below the cell models. Epithelial cell models with fingerlike projections depict cilia at the apical surface. Fully processed CFTR protein is depicted by the gray circles embedded among the cilia at the apical surface of the cells. (*From Welsh MJ and Smith AE: Molecular Mechanisms of CFTR Chloride Channel Dysfunction in Cystic Fibrosis.* Cell *73:1251–1254, 1993, with permission.*)

surface. If the mutant protein escapes normal intracellular processing, however, ΔF508 protein functions normally in the apical membrane. Furthermore, only 25 percent of normal CFTR transcripts are properly processed and transported to the cell surface. The remaining 75 percent are degraded before being processed. These data suggest that one therapeutic strategy to overcome the defect in CF is to disrupt normal intracellular processing mechanisms.

PATHOPHYSIOLOGY

In CF, all exocrine glands appear to be affected primarily, albeit to varying degrees. Because exocrine glands perform highly specialized functions in a variety of organs—e.g., in the skin, respiratory tract, gastrointestinal tract, and reproductive system—the number of possible symptoms and complications in CF is large. Table 51-2 highlights the complications and symptoms of CF according to the age groups in which they most often occur. Obstruction of exocrine ducts by viscous secretions appears to play a cardinal role in the pathogenesis of almost all manifestations of the disease. In 10 to 20 percent of patients, the initial manifestation is often *meconium ileus*—i.e., obstruction of the intestine by thick, viscous meconium stool. Chronic pulmonary disease, pancreatic insufficiency, and focal biliary cirrhosis progress gradually throughout the course of the disease, albeit at different rates in different patients. Progressive obstruction of exocrine ducts is a regular feature of the disease except in sweat glands, where obstruction of ducts has not been implicated in pathogenesis.

Respiratory Tract

In the lungs, hypersecretion of viscid mucus and chronic bacterial infection combine to produce a progressive and distinctive type of chronic obstructive airway disease that eventually leads to diffuse, severe bronchiectasis. The earliest pathological lesions are found in the distal bronchioles. Whether the viscid secretions are primary or are secondary to chronic bacterial infections remains unsettled. In favor of a primary disturbance is the demonstration of mucus obstructing submucosal gland ducts in the airways of neonates with CF, who have not yet developed any evidence of bacterial infection or chronic colonization of the airways. With the use of sophisticated culture methods, bacterial pathogens can almost invariably be isolated from the respiratory tract of patients with CF. The most common pathogens isolated from sputum cultures are *Staphylococcus aureus* and *Pseudomonas aeruginosa.* Less commonly found are *Escherichia coli, Klebsiella,* and *Haemophilus influenzae.* In later stages of the disease, *Pseudomonas* usually predominates. By adulthood, more than 80 percent of patients are colonized with *P. aeruginosa.*

Neutrophil-dominated lower-airway inflammation also plays a primary role in the pathogenesis of the characteristic central bronchiectasis of CF. Bronchoalveolar lavage fluid (BALF) demonstrates increased neutrophils and various cytokines, especially IL-8, even in infants whose BALF is sterile.

Table 51-2

Complications and Presenting Symptoms of Cystic Fibrosis by Age Group

Infancy	Childhood	Adolescence/Adulthood
Meconium ileus	Pulmonary infections with *Staphylococcus* and *Pseudomonas*	Chronic bronchitis
Obstructive jaundice	Malnutrition with steatorrhea and pancreatic insufficiency	Pansinusitis
Edema with hypoproteinemia, anemia, and hypoprothrombinemia	Heat prostration with hypoelectrolytemia and metabolic alkalosis	Hemoptysis
Failure to thrive	"Atypical asthma" with clubbing and/or bronchiectasis	Chronic abdominal pain
Intussusception	Esophageal varices	Delayed sexual development
Volvulus	Hypersplenism	Obstructive aspermia
Rectal prolapse	Nasal polyps	
Recurrent pneumonia/bronchiolitis		

Typically, respiratory secretions increase when a patient with CF, already chronically colonized with *Pseudomonas,* develops a viral respiratory tract infection. In turn, the increase in secretions leads to a gradual increase in cough and sputum production and then to an exacerbation of the pulmonary disease, usually manifested by increase in respiratory rate; retraction of the chest during inspiration; and diffuse, coarse inspiratory crackles. Fever and leukocytosis are common. The chest radiograph demonstrates worsening hyperinflation. Both peribronchial thickening and nodular or cystic densities are more marked than usual. Pulmonary function tests show a worsening over baseline. Usually, residual volume (RV) increases; forced vital capacity (FVC) and forced expiratory volume in 1 s (FEV_1) decrease; the forced expiratory flow between 25 and 75 percent of the exhaled vital capacity ($FEF_{25–75\%}$) also decreases. Treatment using antibiotics and chest physiotherapy generally succeeds in restoring most indices of pulmonary function to, or almost to, baseline. However, *Pseudomonas* and *Staphylococcus* persist in sputum cultures.

The most attractive hypothesis to account for the pattern of response to treatment is that therapy reduces the number and, probably, virulence of organisms. Despite the virtual return to baseline after an exacerbation, however, the cumulative effect of repeated episodes is progressive bronchiectasis or atelectasis, or a combination of the two, accompanied by a gradual and irreversible decrease in pulmonary function. The striking degree of airway destruction and relative sparing of the pulmonary parenchyma at autopsy are shown in Fig. 51-4. A simplified scheme illustrating the evolution of the process is shown in Fig. 51-5.

Gastrointestinal Tract

Although pancreatic function may be either normal or abnormal at birth, it gradually becomes increasingly abnormal in most patients with CF as the pancreatic ducts become progressively obstructed by thick, viscous secretions from the exocrine portion of the organ; pancreatic enzymes that are trapped within the ducts lead to autodestruction of the pancreas. A cycle of destruction and obliteration of the ducts is set into motion, leading to cystic dilatation of ducts proximal to sites of obstruction and fibrosis of the body of the pancreas. In advanced stages of the disease, pancreatic fibrosis sometimes causes obliteration of the islets of Langerhans and, consequently, diabetes mellitus.

The liver and biliary tract are also affected in CF. Here too, the primary mechanism appears to be obstruction of ducts by abnormally viscid secretions. The earliest pathological change is focal biliary cirrhosis that may be present in early infancy. In some patients, focal cirrhosis progresses to diffuse cirrhosis and portal hypertension. Some newborn infants with CF develop the *inspissated bile syndrome,* characterized by prolonged obstructive jaundice starting at 2 to 8 weeks of age. The jaundice often clears without therapy. In approximately 20 to 30 percent of patients, the gallbladder is small, presumably because of underdevelopment due to obstruction by viscid secretions. Compared with age-matched controls, the risk of cholelithiasis and cholecystitis is increased in adults with CF.

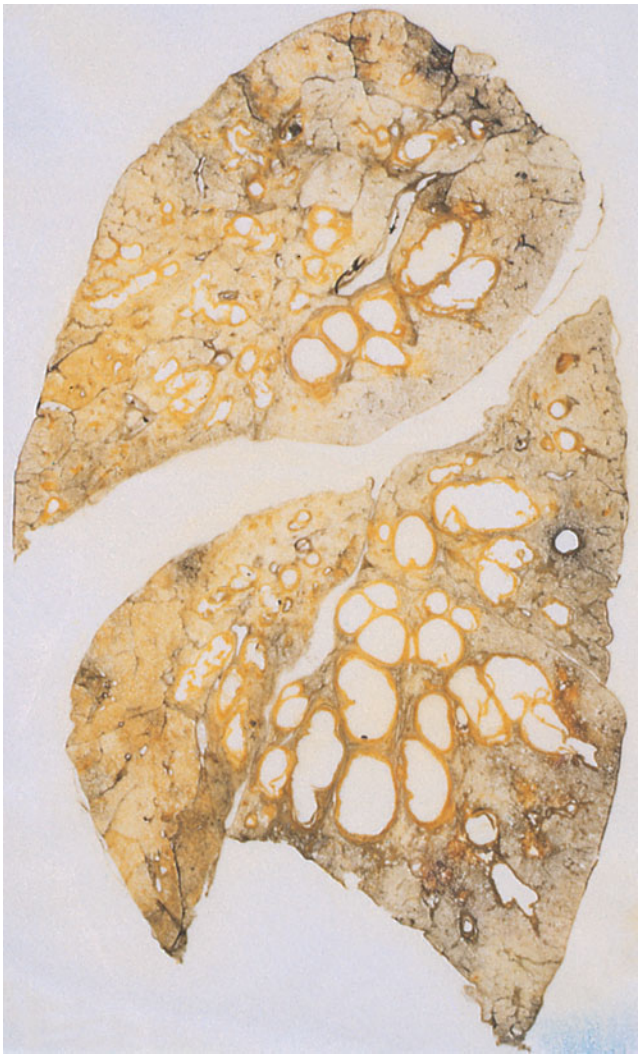


Figure 51-4 Section of lung from autopsy of a patient with CF, demonstrating remarkable dilation of large airways and preservation of intervening pulmonary parenchyma. *(Courtesy of Dr. S. Moolten.)*

The most striking pathological change in the intestines is hyperplasia of the mucous glands and goblet cells. Biochemical abnormalities in intestinal mucins may contribute to malabsorption of specific nutrients and bile acids. Much of the malabsorption in CF can be corrected by administration of pancreatic enzymes. However, the abnormal mucins may lead to slowing of intestinal transit time; the slowing, combined with maldigestion of food substances, sometimes causes fecal impaction in the terminal ileum and ileocecal area, a condition referred to as *meconium ileus equivalent* or distal intestinal obstruction syndrome. The fecal impaction, in turn, occasionally causes volvulus or intussusception of the bowel (Fig. 51-6).

Reproductive Organs

Except for an increase in viscosity and an abnormal midcycle fern pattern in cervical mucus, no consistent pathological changes occur in the female reproductive tract in patients with CF. In the male reproductive tract, however, the vas deferens is either atretic or absent at birth. Although the pathogenesis of this lesion is not certain, viscous secretions may contribute to obstruction in utero, followed by failure of development of the vas deferens. Spermatogenesis and testicular development are otherwise normal. Because of either partial or complete obstruction of the vas deferens, approximately 98 percent of males with CF are aspermic.

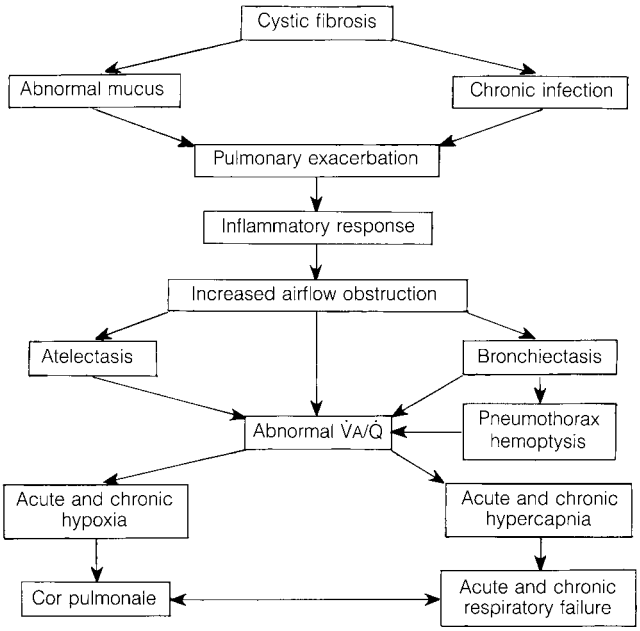


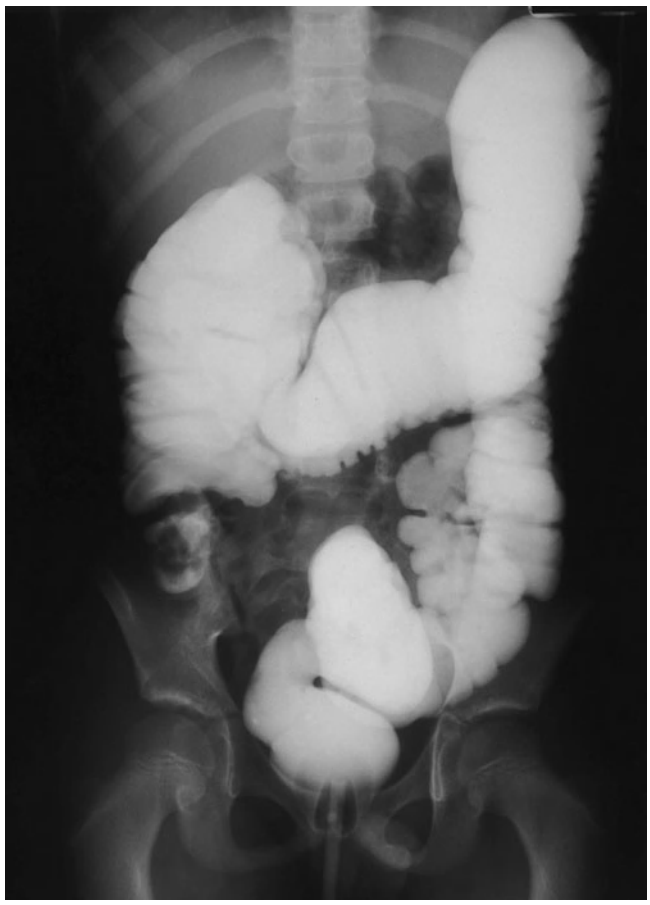
Figure 51-5 Simplified scheme for pathogenesis and progression of pulmonary disease in CF.

Sweat Glands

The sweat glands of patients with CF manifest no distinctive histological changes. Nonetheless, their function is abnormal. Micropuncture experiments have shown that the precursor solution secreted by the sweat glands is isotonic to plasma, both in CF patients and in normal subjects. In normal persons, as the sweat flows along the duct of the gland, sodium and chloride are reabsorbed, so that by the time that the opening at the skin surface is reached, sweat is hypotonic to plasma with respect to both sodium and chloride concentrations. In CF, the relative impermeability to chloride ions is thought to be responsible for the elevated chloride and sodium concentrations which are the basis for the diagnostic test, the quantitative pilocarpine iontophoresis sweat test, and are also responsible for the characteristic increase in potential differences across isolated, perfused sweat glands from CF patients.

DIAGNOSIS

The diagnosis of CF requires the demonstration of abnormally high concentrations of sodium and chloride in the sweat



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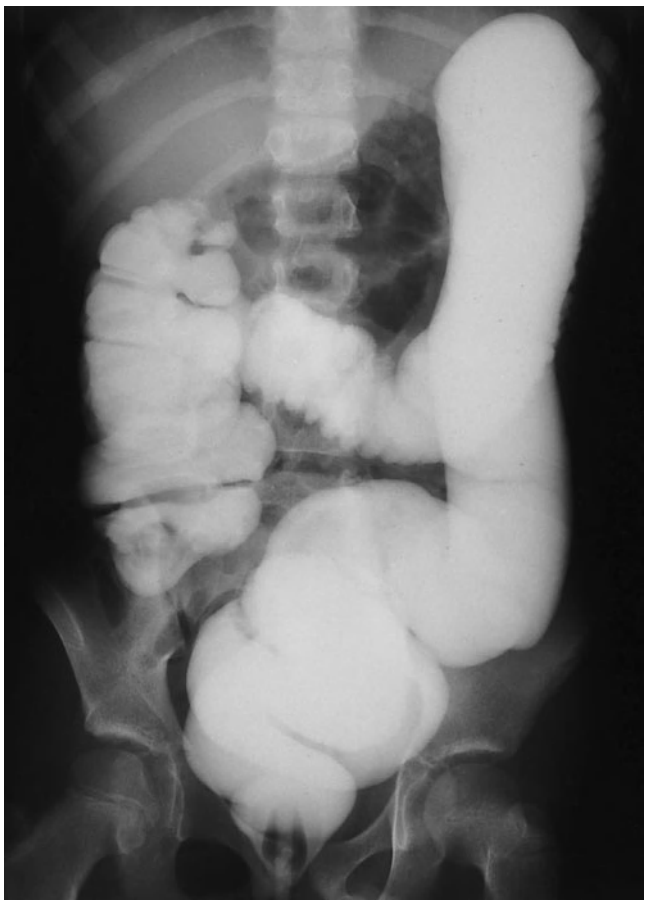

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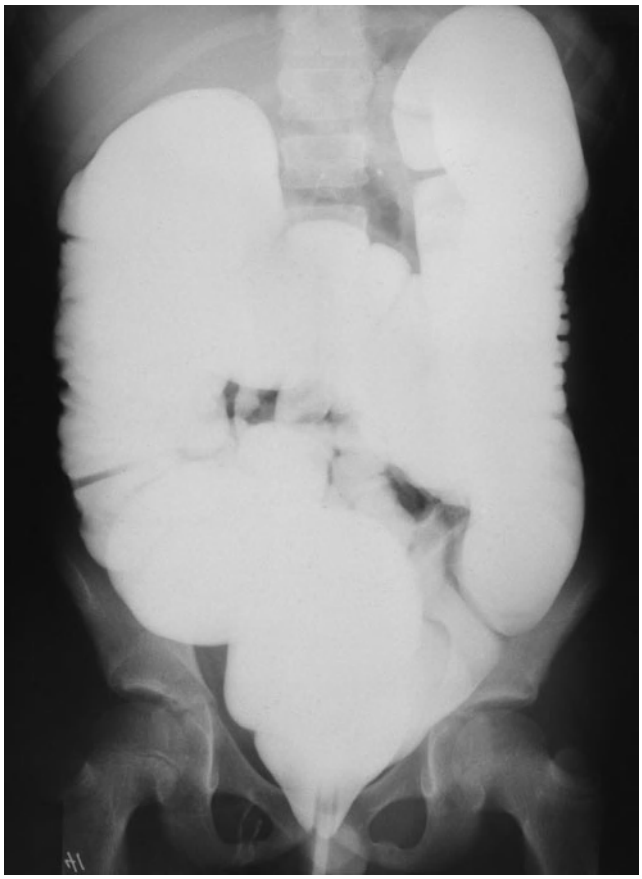

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Figure 51-6 Distal intestinal obstruction syndrome (DIOS). *A*. Presenting Gastrografin enema of a child who had crampy abdominal pain and a right lower-quadrant mass. Fecal impaction with intussception is demonstrated. *B*. Partial resolution of the obstruction following Gastrografin administration. *C*. Complete resolution of the intussception and fecal impaction.

of a person who has the characteristic history and symptoms of CF. The most prominent clinical features are chronic pulmonary disease and pancreatic insufficiency. The most compelling family history for the diagnosis is CF in a sibling. If the clinical picture and/or the family history support the diagnosis, and if two sweat tests using the quantitative pilocarpine iontophoresis method are clearly positive, the diagnosis of CF can be made with assurance. Identification of two pathological mutations, in addition to the characteristic clinical picture, is accepted as a criterion for the diagnosis. However, CF is a complex syndrome (Table 51-2) whose clinical manifestations are sometimes subtle. In addition, the family history is not always straightforward. Therefore, a high index of suspicion, coupled with a battery of clinical tests, is sometimes required to establish the diagnosis, especially in adolescents or young adults.

Since CF occurs with a high frequency in the general population, the diagnosis should be considered routinely in a broad array of differential diagnoses. Although Table 51-2 categorizes symptoms according to the age at which they most often occur, symptoms at any age should prompt consideration of the diagnosis of CF.

The most consistent feature of CF is an abnormally high concentration of sodium and chloride in sweat. Measurement of the chloride concentration is recommended for clinical testing. The only reliable sweat test is based on iontophoresis of pilocarpine, followed by quantitative determination of the concentration of chloride in an adequate, measured volume of sweat. Seventy-five milligrams of sweat is the minimum acceptable amount. When a preweighed, measured pad is used, this amount ensures that an adequate sweat flow rate (1 g/m^2 per min) has been achieved and that the sample is large enough for the determination of chloride by titration. In children, concentrations of chloride of less than 40 mEq/L are usually regarded as normal. However, the average of values for sodium and chloride concentrations are about 20 mEq/L for normal subjects and 95 mEq/L for those with CF. In children, values between 40 and 60 mEq/L are borderline elevated; such values call for further evaluation. As a result of recent experience with CF newborn screening, it has been suggested that sweat chloride values above 40 mEq/L may be diagnostic in the first few months of life.

The concentration of sodium and chloride in sweat increases gradually with age. An age-corrected scale of normal, abnormal, and borderline values of sodium concentration in sweat is available (Fig. 51-7). Conditions other than CF in which the concentrations of sodium and chloride in sweat are abnormally high include malnutrition, adrenal insufficiency, hereditary nephrogenic diabetes insipidus, ectodermal dysplasia, and fucosidosis. Except in some instances of malnutrition, these conditions are readily distinguished from CF. The finding of abnormal concentrations of sodium and chloride in sweat should automatically prompt evaluation of the patient to determine if, and to what extent, other organs are affected.

Genetic analysis can be used to confirm the diagnosis of CF. In patients with minimal symptoms, the diagnosis of CF can be made with certainty if two CF-associated alleles are present. As mentioned previously, screening for 32 of the most common alleles yields an overall sensitivity of 90 percent due to undetected alleles. Therefore, a negative mutation analysis does not rule out a diagnosis of CF, and atypical patients should be followed carefully.

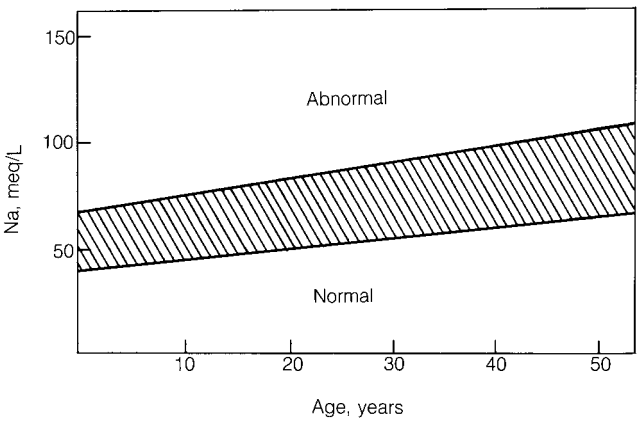


Figure 51-7 Graph of sweat test results vs. age: normal, elevated, and borderline (stippled).

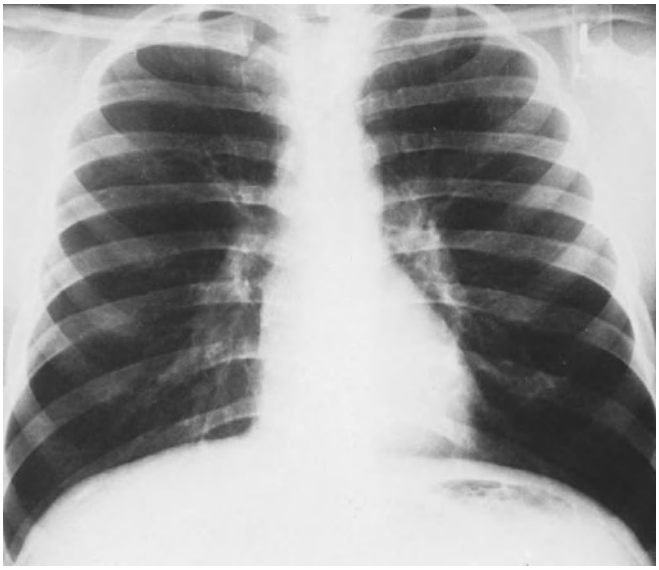
Prenatal screening is standard practice for 11 states. The initial stage of screening uses the neonatal blood spot to determine the concentration of immunoreactive trypsinogen. If this is elevated, secondary screens vary from repeat immunotrypsinogen determination to ΔF508 or 25-32 mutation screen. The screening programs have a sensitivity ranging from 87 to 99 percent. Risks vs. benefits and the relative costs of the screening programs are being evaluated to determine the best approach.

CLINICAL EVALUATION

The evaluation of patients with CF includes chest radiography, tests of pulmonary performance, sputum culture, and assessment of pancreatic, hepatic, and reproductive functions. Each is described below.

Chest Radiography

Rarely is the chest radiograph completely normal in CF. In the person with minor pulmonary symptoms, the manifestations may be questionable (e.g., mild hyperinflation and minimal peribronchial thickening). However, the radiographic findings become more distinctly abnormal as the disease increases in severity. Peribronchial thickening, which is often most prominent in the upper lobes of the lungs early in the course of the disease, usually progresses to affect all lobes. In the advanced stage of pulmonary involvement, ring shadows, cystic lesions, and nodular densities are increasingly apparent, as are areas of bronchiectasis and atelectasis. The central pulmonary artery often enlarges in the middle stages of the disease, but the cardiac silhouette remains within normal



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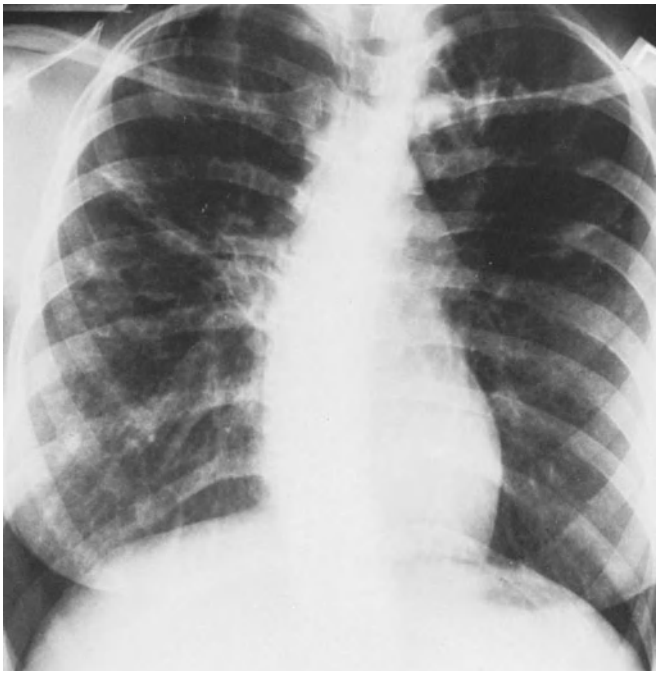

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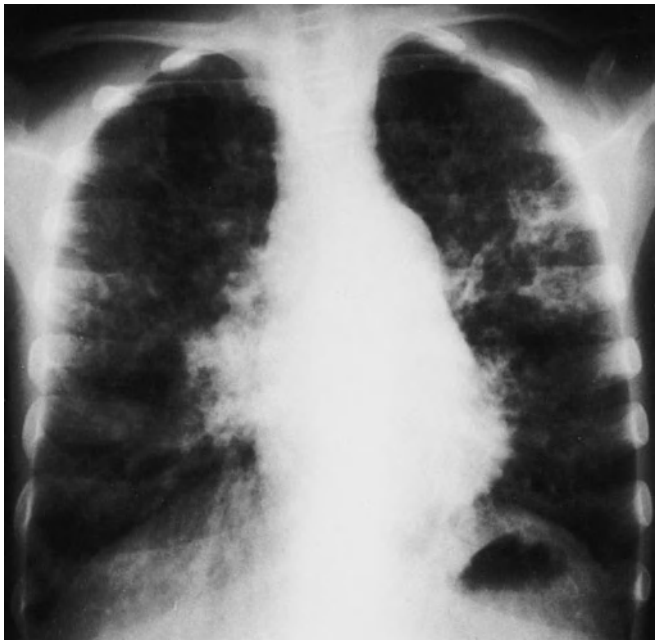

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Figure 51-8 Chest radiographs of three siblings with CF taken when the patients were 17 years of age. *A*. Mild hyperinflation; otherwise normal. Patient is now 32 years old and has been hospitalized once for treatment of electrolyte depletion. *B*. Diffuse peribronchial thickening, mild hyperinflation, and cystic changes in both upper lobes. The patient was hospitalized seven times for pulmonary exacerbations, once for diabetes, and once for hemoptysis. She died at age 34 following complications from lung transplantation. *C*. Severe hyperinflation, diffuse peribronchial thickening, multiple infiltrates, and increased pulmonary vascular markings and heart size. The patient died 1 month later from respiratory failure complicated by congestive heart failure.

limits until the disease is far advanced. The variability in the chest radiograph is illustrated in Fig. 51-8 for three siblings with CF when each was 17 years old.

High-resolution computed tomography (HRCT) scans are more sensitive than plain radiographs. The most common abnormalities described are "ground glass opacities." Early bronchiectasis is easily detected on the CT scan, even when routine chest radiographs are normal, as seen in Fig. 51-9.

Pulmonary Performance

The lungs of patients with CF are usually morphologically and functionally normal at birth. Over time, accumulation of tracheobronchial secretions and recurrent infections progressively impair pulmonary function in almost all patients. In the fully developed clinical syndrome, all the pulmonary function abnormalities seen in chronic bronchitis, emphysema, and asthma may occur. However, one complicating regular feature of CF—bronchiectasis—modifies pulmonary performance. Chronic, local infection and airway damage increase the compliance of bronchiectatic airways, resulting in airway collapse during rapid expirations or cough. The usefulness of pulmonary function testing in CF is twofold: tracing the natural history of the disease and assessing the value of therapeutic interventions.

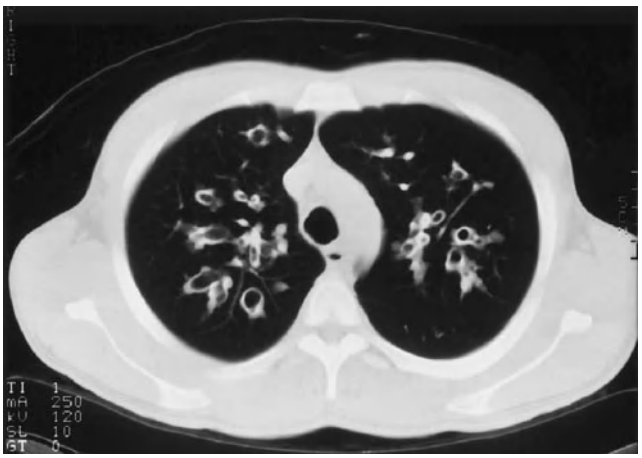


Figure 51-9 High-resolution chest computed tomography scan from a patient with CF. Marked bronchiectasis with peribronchial thickening is shown in the upper lobes.

The earliest stages of the pulmonary disorder are the most difficult to quantify. In infants, tests are limited almost entirely to those that do not depend on the patient's understanding and cooperation. A variety of methods to measure infant pulmonary function have been devised; one method, the raised volume rapid thoracoabdominal compression technique, requires sedation of infants but provides values most similar to standard spirometric values, and has detected reduced pulmonary function in infants with CF. After age 6 years, pulmonary function tests originally designed for adults may be performed quite readily on children. Changes in pulmonary performance throughout the natural history of CF can be described with confidence.

Obstruction in Small Airways

The small airways—i.e., the bronchioles—are vulnerable to obstruction early in the course of CF. At this stage, as in cigarette smokers, results of tests for small-airway disease are apt to be abnormal, while those of tests for obstruction of large airways are still normal. Three factors interact in causing the obstruction: (1) intrinsic disease of the smaller airways, often in association with bronchiectasis in the proximal, larger airways; (2) viscid secretions, impaired ciliary action, and impaired cough; and (3) progressive decrease in lung elastic recoil.

The progressive reduction in lung elastic recoil in CF is predominantly a function of overinflation due to intrinsic airway disease, rather than loss of pulmonary parenchyma. This mechanism differs from that in chronic bronchitis and emphysema, in which the combined effects of parenchymal destruction and overinflation are responsible for the decrease in elastic recoil. Emphysema is not a regular feature of CF. In some patients, emphysema occurs only late in the course of the disease (Fig. 51-4).

Airway smooth-muscle tone increases only slightly in CF. Exercise elicits bronchodilation, followed shortly thereafter by bronchoconstriction. Both the bronchodilation and bronchoconstriction are far less impressive in CF than in asthma. Indeed, exaggerated bronchomotor responses in CF raise the possibility of superimposed asthma. In distinguishing between contributions to airway obstruction by intrinsic airway disease caused by CF and asthma, maximal expiratory flow-volume curves are sometimes helpful.

Because of the bronchiolar locus of the early lesions in CF, abnormalities in breathing frequency–dependent tests (e.g., dynamic lung compliance), in volume-dependent tests (e.g., closing volume), and in maximal expiratory flow ($V_{E_{max}}$) at low lung volumes are demonstrable, even though results of tests of large-airway function (e.g., FEV_1 and airway resistance) are still normal.

Change in Lung Volumes

As with chronic bronchitis, emphysema, and asthma, RV in CF increases. Thereafter, an increase in functional residual capacity and, sometimes, in total lung capacity is seen. Later during the course of the disease, air-trapping occurs, manifest as an elevated ratio of RV to total lung capacity. This change decreases the compliance of the lung and increases the work of breathing.

Abnormalities in Gas Exchange

Early in the evolution of the pulmonary abnormalities in CF—i.e., when tests of small-airway function alone are abnormal—ventilation-perfusion abnormalities usually result in widening of the alveolar-arterial oxygen gradient and an increase in the ratio of dead space to tidal volume (V_D/V_T). These abnormalities portend increasing inhomogeneities in alveolar ventilation and blood flow as the affected child grows to adulthood. The diffusing capacity for carbon monoxide (D_{LCO}) is low at rest and does not increase normally during exercise. This observation is difficult to reconcile with the preservation of the gas-exchanging surface of the lungs (in the absence of emphysema) until late in the course of the disease (Fig. 51-4).

As obstructive disease of the airways progresses and exaggerates the imbalances between alveolar ventilation and blood flow, arterial hypoxemia develops; pulmonary hypertension, cor pulmonale, and right ventricular failure follow, in turn. Late in the course of the disease, hypercapnia and respiratory acidosis contribute to the final picture of respiratory failure. At this juncture, the ventilatory response to inhaled CO_2 is depressed. Bouts of infection punctuate the course of the illness; during each episode, pulmonary function deteriorates, but it usually returns toward baseline, except in the preterminal stages of the disorder.

Sputum Culture

The unique respiratory flora isolated from sputum cultures from patients with CF are helpful in establishing the diagnosis and in guiding the antimicrobial therapy for acute exacerbations. In many patients with CF, *P. aeruginosa* and *S. aureus* are found alone, or in combination with other organisms, in the sputum. Once present, the organisms, especially *Pseudomonas,* are rarely eradicated, despite use of intermittent or

continuous antibiotics administered intravenously, orally, or by nebulization. Although these organisms are sometimes found in sputum cultures from patients with pulmonary diseases other than CF, their association with the disorder is so consistent that a dedicated attempt to obtain a sputum culture is an integral part of the evaluation of all patients, including infants and young children, suspected of having CF. Conversely, isolation of *S. aureus* or *P. aeruginosa* in sputum in a child or young adult should raise the suspicion of CF.

Pancreatic Function

The evaluation of pancreatic function is an important part of establishing the diagnosis of CF, since almost 90 percent of patients have pancreatic insufficiency. In infants with pancreatic insufficiency due to CF, the most striking feature of the history and physical examination is often failure to thrive; the record of bowel movements may disclose only loose or frequent stools. In the older child, whose diet includes more fat and protein, a history of bulky, foul, malodorous stools is often easier to elicit. Documentation of malabsorption is best accomplished by collection of stools for 72 h while the patient is ingesting a known quantity of fat (approximately 100 g per day) and measurement of the stool fat content. A malabsorption coefficient of greater than 7 percent is usually considered abnormal; in patients with CF, the malabsorption coefficient often is around 20 to 30 percent.

In infants and young children, the determination of trypsin or chymotrypsin activity in a properly collected stool specimen is an accurate way to determine the content of pancreatic enzymes. In older patients, however, trypsin or chymotrypsin activity in a stool sample may be artificially low because of a delayed transit time that causes partial inactivation of the enzyme. In some instances, a secretin stimulation test may be helpful in demonstrating pancreatic insufficiency. For this purpose, a triple-lumen tube is introduced into the duodenum. The response to secretin is usually abnormal: the volume of secretion is small, the fluid is viscid, and the bicarbonate ion concentration is low. This test is not often used in children because it is cumbersome to perform. More recently, determination of fecal elastase-1 in a stool sample has been described as an accurate, easily obtained screening test to classify patients with CF as pancreatic insufficient or pancreatic sufficient.

For infants, the serum immunoreactive assay for trypsin is used in some centers as a screening test for pancreatic insufficiency. As a rule, serum levels of trypsin are abnormally high in CF, usually reflecting ongoing destruction of the pancreas. However, the assay does not provide an accurate measure of pancreatic function. Endocrine function of the pancreas is usually preserved in children, but approximately 50 percent of all adult patients are overtly diabetic by age 30 years.

Liver Function

Evaluation of liver function is an important part of the evaluation of CF. In infants and children, the concentrations of bilirubin and transaminases in serum sometimes increase transiently. However, concentrations of these substances are usually normal, even in patients with mild or moderate focal biliary cirrhosis. The prothrombin time is sometimes prolonged, owing to a combination of malabsorption and decreased synthesis of clotting factors by the liver. Occasionally, patients present with bleeding esophageal varices from advanced cirrhosis; endoscopy and upper gastrointestinal contrast studies are often helpful in demonstrating the varices.

Semen Analysis

Occasionally, a man who is found to have aspermia during the course of an evaluation for infertility is found to have CF. In men with CF, a complete semen analysis is part of the evaluation. Azoospermia is found in more than 98 percent of men with the disorder.

Mutation Analysis

Numerous attempts have been made, with limited success, to characterize phenotype on the basis of genotype. In general, homozygotes for ΔF508 have pancreatic insufficiency; patients with CF who have pancreatic insufficiency tend to have a worse prognosis. Several mutations, including R117H, are associated with pancreatic sufficiency and a mild phenotype. However, a direct association of a particular genotype with progression of the pulmonary disease has not been found.

An interesting genotype-phenotype correlation is the increased frequency of genotype R117H in males with congenital bilateral absence of the vas deferens (CBAVD). Males affected with this recessive disorder lack a vas deferens, but they are otherwise completely healthy and have normal sweat test results. Approximately 35 percent of chromosomes of patients with CBAVD carry a CF-associated mutation. To complicate this phenotype-genotype correlation further, 8 percent of patients with CBAVD without clinical CF have two CF-associated mutations. Genetic testing is not required to establish or confirm the diagnosis of CF when a compatible history and physical examination and abnormal sweat test results are found. Genetic testing is useful in identifying patients who have a compatible history and physical examination but whose sweat test results are negative. Certain alleles associated with CF (e.g., 3849 + 10kbC → T) are associated with nasal polyposis and bronchiectasis but normal sweat test results. The diagnosis of CF can be made with confidence in these patients. More problematic are persons with atypical presentations, normal sweat test results, and at least one CF-associated mutation. For example, mutations in at least one CFTR allele are associated with idiopathic chronic pancreatitis. More extensive genotyping should be attempted for all patients with a high clinical suspicion for CF (see "Genetics") because mutation analyses may become clinically relevant if specific therapies depend on the types of mutations present (see "Genetics" and "Future Directions").

Patients with the same genotype may have dramatically different phenotypes, raising the possibility that modifier

genes play an important role in determining the CF phenotype. Several potential candidate modifier genes are being evaluated for their impact on lung disease severity, including α_1-antitrypsin, HLA antigens, nitric oxide synthase, mannose-binding lectin, transforming growth factor β (TGFβ), tumor necrosis factor α (TNFα), and β_2-adrenergic receptor. Polymorphisms of TGFβ, have been associated with severe lung disease in a large, well-characterized cohort. Modifier genes may also affect function of other organs in CF; a modifier locus on chromosome 19 is associated with meconium ileus.

ATYPICAL CLINICAL PRESENTATIONS

Atypical clinical presentations confound the diagnosis of CF in adults; a high index of suspicion is required to establish the diagnosis. Approximately 6 percent of all CF is diagnosed after age 18 years. Late presentations of CF tend to occur in persons with pancreatic sufficiency; indeed, overweight or well-nourished persons may have CF. Recovery of unusual gram-negative organisms, mucoid *Pseudomonas* species, or *S. aureus* from sputum of asthmatics with persistent sputum production, chest radiographic abnormalities, or clubbing should prompt referral for sweat testing. Recurrent sinusitis and nasal polyposis may be the only manifestations of CF in a mildly affected person. Isolation of *P. aeruginosa* from deep nasal cultures should raise the suspicion of CF. Frequently, the sinus findings on CT mimic fungal sinusitis, demonstrating concentric, inhomogeneous material. Occasionally, persistent inflammation produces bony destruction that is mistaken for previous surgical intervention. Sweat testing and referral to a CF center should be considered for men with azoospermia or CBAVD.

TREATMENT

Intensive, comprehensive CF treatment programs designed to deal with particular symptoms, correct deficiencies, and prevent progression and complications of the disease have led to a dramatic increase in the median age of survival (Fig. 51-10). Although the value of comprehensive treatment is beyond question, far less certain are the utility of each component of the treatment plan and the level of each component necessary in a given patient. At present, the best approach still appears to be determination of the type and degree of abnormality in individual patients and design of a treatment program that will improve or maintain function of the organ systems affected.

To ensure that the treatment regimen meets the needs of the individual patient, that necessary treatment is not omitted, or that side effects of prescribed treatments do not go unnoticed, it is often desirable to hospitalize the patient for diagnosis and evaluation. Hospitalization also provides an excellent opportunity for counseling the patient, parents, and

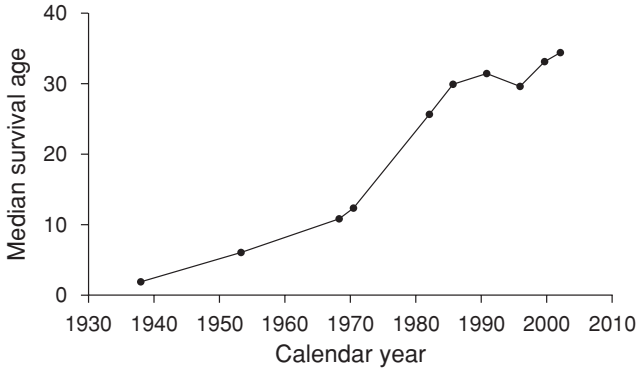


Figure 51-10 Median survival in patients with CF at various times since the first description of CF. Data before 1970 are gleaned from then-current literature. Data since 1985 are from CF Foundation Data Registry and represent projections of median survival age for a child born in that year with CF. *(From Davis PB: Cystic fibrosis since 1938.* Am J Respir Crit Care Med *173:474–482, 2006, with permission.)*

family about the diverse aspects of the diagnosis, treatment, prognosis, and inheritance pattern of CF. Hospitalization provides the opportunity to monitor the response of individual patients to each component of the therapeutic program.

An important aspect of the care of patients with CF is the network of more than 100 CF centers that exist throughout the United States and the larger network throughout the world. Most larger centers use a team approach to the care of patients. A CF care team usually includes physicians, nurses, respiratory therapists, physical therapists, nutritionists, social workers, and genetic counselors.

Management of the Pulmonary Disease

More than 90 percent of the patients with CF die from respiratory failure or pulmonary complications. The goals of treating the pulmonary disorder in CF are to prevent and treat the complications of airway obstruction and infection. Although management of the pulmonary disorder consists of many components applied in combination, the individual components of therapy are discussed separately below.

Chest Physiotherapy

Almost all treatment programs for CF include a strategy intended to clear pulmonary secretions in order to prevent complications arising from airway plugging by viscous secretions. Chest physiotherapy—i.e., "percussion and postural drainage"—performed regularly, is the most widely prescribed method. In infants and young children, chest physiotherapy is generally performed routinely, twice daily. In addition to manual chest percussion and postural drainage, there are several other effective modalities for chest physiotherapy. These alternative measures include the high-frequency chest-wall oscillatory vest; the flutter device, a small pipelike device that produces an oscillating resistance during a forced expiratory maneuver; the acapella device that produces both positive expiratory pressure and an oscillating resistance

during forced expiratory maneuver; positive expiratory pressure mask; intrapulmonary percussive ventilation; autogenic drainage and active cycle of breathing; and exercise. Some form of physiotherapy that is effective in mucus clearance is required daily because without chest physiotherapy, pulmonary function deteriorates. At present, most CF centers recommend that all patients with CF attempt to maintain clearance of pulmonary secretions with a method that is applied regularly (e.g., twice daily). An additional recommendation is that chest physiotherapy be applied more often during an exacerbation of the chronic pulmonary infection. Unfortunately, the recommendation of chest physiotherapy on a regular basis—a time-consuming and often arduous form of treatment—is difficult to implement without considerable support and encouragement from family and health professionals.

Antibiotics

During the past few decades of treatment of CF, antibiotics have proved to be the key element responsible for increased survival. A reasonable approach balances the dangers of overzealous administration of antibiotics against progressive airway damage and bronchiectasis resulting from untreated infection. The approach is based on sputum culture at the time of diagnosis and at regular intervals thereafter. When signs and symptoms herald an exacerbation of pulmonary infection (i.e., increased cough or sputum production, dyspnea, decreased exercise tolerance, decreased appetite) or new abnormalities on the physical examination (i.e., increased respiratory rate, use of accessory muscles, changes on auscultation of the chest including decreased breath sounds, new crackles or wheezes, weight loss), new abnormalities on the chest radiograph, or a decline in pulmonary function tests, chest physiotherapy is increased and appropriate antibiotics are given orally, or for severe exacerbations, intravenously.

Currently useful agents for treating staphylococcal infections include dicloxacillin, cephalexin, the newer cephalosporins, clavulanic acid combinations, and macrolides. Early in the course of the pulmonary disease, a small fraction of *Pseudomonas* strains may be sensitive to tetracycline, trimethoprim-sulfamethoxazole, or chloramphenicol. Occasionally, even *Pseudomonas* strains considered resistant according to laboratory sensitivity tests apparently respond to these antibiotics. A mechanism that has been proposed to account for this phenomenon is that even though the antibiotic is not bactericidal, it may inhibit either growth of the organism or its production of exotoxin and proteases. Ciprofloxacin, a quinolone derivative that can be given orally, is initially effective against many strains of *Pseudomonas* and has gained widespread use in the outpatient management of CF. A major disadvantage in its use is that resistance often develops after a few courses of treatment.

For treatment of a severe pulmonary exacerbation of CF caused by methicillin-resistant *Staphylococcus*, vancomycin or linezolid are indicated. For *Pseudomonas,* a combination of an aminoglycoside given intravenously and a semisynthetic penicillin is generally used. This combination is presumed to act synergistically on *Pseudomonas*, and the *Pseudomonas* is less likely to become resistant to either antibiotic.

The most popular antibiotic combination currently in use is tobramycin and ceftazidime. In order to achieve high levels of antibiotics in the airways and in secretions, the aminoglycoside is generally administered in higher doses. For example, tobramycin, 10 mg/kg per day in three divided doses, is given instead of 7.5 mg/kg per day in three divided doses. The resulting concentrations in serum are monitored. Instead of the usual therapeutic serum levels for tobramycin of 4 to 8 μg/ml, the goal in treating patients with CF is a serum level of 8 to 10 μg/ml; some centers advocate even higher levels. Serum antibiotic concentrations, renal function, and hearing acuity are monitored to avoid toxic reactions. The higher serum levels of 8 to 10 μg/ml do not seem to elicit greater toxicity than the usual levels. No advantage has been demonstrated for further increments in dosage.

Some of the newer antibiotics—e.g., piperacillin, meropenem, and ceftazidime—are also quite effective against *Pseudomonas.* Although they may be effective at first when given alone, resistance often develops quickly. Usually, these agents are used in combination with an aminoglycoside. Because the sensitivity and resistance patterns of the *Pseudomonas* often change, various combinations are tried at different times, with clinicians relying on sensitivities from recent isolates to determine which is most effective for the particular strain of *Pseudomonas.* For other resistant gram-negative organisms, such as *Burkholderia cepacia, Stenotrophomonas maltophilia,* and *Achromobacter xylosoxidans,* other antibiotic combinations are indicated, including ceftazidime, meropenem, ciprofloxacin, minocycline, aztreonam, chloramphenicol, or trimethoprim/sulfamethoxazole

Staphylococcus, Pseudomonas, and other gram-negative organisms, such as *B. cepacia, A. xylosoxidans,* and *S. maltophilia*, once found in the sputum, are rarely eradicated. However, most other manifestations of an exacerbation of pulmonary disease abate during a 2-week course of antibiotics administered intravenously; for example, the densities seen on the chest radiograph decrease, the white blood cell count decreases, fever and respiratory rate decrease, and pulmonary function test results, which often deteriorate at the start of an exacerbation, return to their previous baseline. Although many patients begin to show improvement after 5 to 7 days, most CF centers continue antibiotics intravenously for at least 2 weeks in order to decrease the relapse rate and to avoid a decrease in the interval between exacerbations. Indeed, some centers routinely recommend a 3- to 4-week course of intravenous antibiotics to treat an exacerbation of a pulmonary infection. In the occasional hospitalized patient who experiences a relapse or manifests an increase in symptoms shortly after administration of intravenous antibiotics is stopped, long-term intravenous administration of an aminoglycoside can be continued with use of a heparin lock. This technique may be helpful in allowing the patient to return home while still receiving effective doses of aminoglycosides.

Another approach that has been advocated is administration of antibiotics by inhalation—the rationale of which

is to increase antibiotic concentrations in airways infected by *Pseudomonas*. Although it has been argued that inhalation will not deliver effective concentrations to diseased portions of the lungs because of interference with ventilation by local airway obstruction, inhaled antibiotics appear to be helpful in some instances. Inhaled, preservative-free tobramycin, 300 mg twice daily for 28 days on and 28 days off (cycling therapy), improved pulmonary function (FEV_1 increased by 10 percent) at the end of the third treatment cycle (20 weeks) compared to placebo. One concern about inhaled tobramycin as a chronic therapy is the risk of bacterial resistance. In addition, questions regarding selection of patients and timing and duration of treatment remain unanswered.

Another antibiotic which has been studied as a chronic therapy in CF is azithromycin. Azithromycin, 250 mg or 500 mg thrice weekly, was evaluated in CF patients colonized with *P. aeruginosa*. After 6 months of therapy, patients on azithromycin had a modest improvement in FEV_1 (6.2 percent), increased weight gain, and decreased rates of pulmonary exacerbations. However, the same issues are raised for chronic azithromycin therapy as were raised for chronic inhaled tobramycin: the long-term issues of benefit, risk of antibiotic resistance, and cost.

Mist and Mucolytics

Mist therapy, delivered by having the patient sleep in a mist tent or through intermittent inhalation of an aerosol, was a common form of treatment of CF several decades ago. The goal was to "liquefy" respiratory secretions. However, the treatment could not be demonstrated to be helpful, and the use of mist tents has been discontinued. Intermittent aerosols are still used to deliver bronchodilators and mucolytics.

A number of mucolytic agents have been tried over the years. One that has endured is *N*-acetylcysteine. In the test tube, this agent is quite effective in dissolving mucin components and in decreasing the viscosity of sputum from patients with CF. Although some centers have found this agent to be a useful adjunct to therapy in CF, others have encountered an inordinate frequency of complicating bronchospasm or tracheitis. Some difficulties noted in the past can now be attributed to the use of a 20 percent (undiluted) solution of *N*-acetylcysteine, which can be irritating because of its extremely high osmolarity. The incidence of side effects may be decreased greatly by use of a 5 percent solution; during an exacerbation, when cough and sputum production increase, the 5 percent solution is inhaled two or three times per day, before chest physiotherapy. Should the patient develop bronchospasm, demonstrated by physical examination or by pulmonary function testing, a bronchodilator is used. If successful, the bronchodilator and the *N*-acetylcysteine are administered jointly by inhalation. However, should the bronchospasm persist despite use of the bronchodilator, *N*-acetylcysteine is not administered.

In 1994, Pulmozyme, a DNA-cleaving enzyme, was approved for use in patients with CF following a large phase III multicenter trial. More than 900 patients were enrolled for a 6-month period. Three dosing regimens were employed: placebo, 2.5 mg inhaled once daily, and 2.5 mg inhaled twice daily. The treatment groups showed a 5 percent improvement in FEV_1 over placebo, as well as a slightly lower relative risk of exacerbation of lower respiratory tract infection after 6 months. There was no difference between the once- and twice-daily treatment groups. A second study revealed that Pulmozyme, inhaled once daily over 96 weeks, maintained pulmonary function and decreased the relative risk of respiratory tract exacerbations in young CF patients with normal FEV_1 ($\geq$85 percent). Currently, this drug is in fairly widespread use for CF. However, questions regarding patient selection and timing and duration of use of this expensive drug remain unanswered.

Inhaled therapy with hypertonic saline was recently evaluated in CF. Patients inhaled 7 percent hypertonic saline twice daily following a bronchodilator for 48 weeks; results revealed only a modest improvement in FEV_1, but a significant reduction in the number of pulmonary exacerbations and days lost from school or work. It remains to be established how this therapy will fit into the maintenance therapy program for CF patients.

Bronchodilators and Anti-Inflammatory Agents

Bronchodilators are often used in treating the pulmonary manifestations of CF. Their use should be individualized. For example, in many patients, bronchospasm that is reversible with bronchodilators at one point in the course of the illness may prove refractory a short time later. Some patients undergo deterioration in pulmonary function following use of bronchodilators. In infants who are audibly wheezing, a bronchodilator can be tried. In older patients, pulmonary function testing provides a more objective and quantitative measure of bronchodilator effectiveness.

Corticosteroids have been used with good results in infants with severe obstructive airway disease that does not respond to antibiotics and bronchodilators and in patients with CF in whom the pulmonary disease is complicated by severe asthma or allergic bronchopulmonary aspergillosis. Preliminary observations initially suggested that patients with CF would benefit from long-term administration of alternate-day corticosteroids, based on the presumption that corticosteroids would decrease the airway inflammatory response. However, in a large, placebo-controlled, multicenter trial of alternate-day corticosteroids administered in two dosage regimens (1 mg/kg and 2 mg/kg), the development of many side effects precluded a general recommendation for long-term corticosteroid treatment in CF. Subgroup analysis led to the suggestion that patients with moderately severe obstructive airway disease and those with chronic *Pseudomonas* infection might benefit from treatment for periods of less than 1 year. Beneficial effects were sufficient to prompt further studies of anti-inflammatory agents in CF. A controlled 4-year trial of high doses of ibuprofen in 40 patients with CF showed improvement in the rate of decline of pulmonary function in children. Questions remain whether side effects that might

accrue with continued therapy will justify the gains. In concert, these two studies suggest that future development of a lung-specific anti-inflammatory agent with fewer systemic side effects may offer a promising approach.

Nutritional Support

Patients with CF require careful evaluation to determine if partial or complete pancreatic insufficiency is present and to design a nutritional program to correct any deficiencies. The mainstay in managing the pancreatic insufficiency of CF is use of pancreatic enzyme preparations currently available in the form of enteric-coated capsules containing coated microspheres. These pancreatic enzymes are ingested along with any food that contains protein, fat, or complex carbohydrates. The dosage is adjusted to ensure a relatively normal pattern of bowel movements, adequate weight gain or maintenance of ideal weight for height, and a decrease in bowel symptoms, such as cramping and flatulence.

The development of colonic strictures was first noted following the introduction of pancreatic enzymes with lipase contents of 25,000 units per capsule. Capsules with more than 20,000 units are no longer available. Subsequent recommendations urge caution in prescribing high total doses of lipase with any preparation; recommendations are to limit use to less than 2500 units/kg per meal. Since strictures have apparently developed in several patients using doses as low as 6000 units/kg per meal, it has been recommended that for patients who require higher doses to maintain nutritional status or to control bowel symptoms, the enzyme requirement be documented by measuring the coefficient of fat absorption and other causes pursued to account for symptoms.

As a rule, patients with CF are advised to consume a double dose of a multivitamin preparation and a vitamin E supplement each day. Infants, those in whom the prothrombin time is prolonged, and those who take antibiotics uninterruptedly require supplemental vitamin K. Vitamin A supplementation is required in children with significant fat malabsorption and failure to thrive; however, care must be taken to avoid hypervitaminosis A. Supplemental salt is needed by patients in order to prevent electrolyte depletion, metabolic alkalosis, and heat prostration. For infants, 1 to 2 g of salt per day is added to the feeding formula; children and adults are encouraged to salt their foods liberally and to take salt-containing liquids and snacks during hot weather.

Although it is true that pulmonary function is the predominant factor in determining morbidity and mortality in CF, it is becoming increasingly clear that overall patient status is closely tied to nutritional status. Importantly, achieving and maintaining normal weight for age and height for age are closely associated with maintenance of lung function in young children and adults. Data from the national 2004 CF Registry indicate that 15.7 percent of CF patients are below the fifth percentile of weight for age and that mortality is increased in this group.

Despite use of pancreatic enzyme replacement, the correction of pancreatic insufficiency is incomplete; accordingly, patients require more than 100 percent of recommended caloric intake. In some, an even greater caloric intake is necessary because of increased energy expenditure due to increased work of breathing secondary to chronic pulmonary infection. Aggressive nutritional supplementation, using either oral supplements or nocturnal nasogastric feeding of hydrolyzed formulas, has been helpful in the short term in promoting weight gain at this stage of disease. Hyperalimentation is occasionally required in infants with meconium ileus and in other special circumstances.

NATURAL HISTORY AND PROGNOSIS

A comprehensive treatment program for CF has unequivocally improved overall survival of patients. Thirty years ago, the median survival was only a few years of age; currently, it is about 35 years (Fig. 51-10). However, because CF is a complex disorder that affects different organs to different degrees, it is difficult to describe a "typical course" for a patient with CF. Some patients die in childhood or adolescence, while others survive beyond age 40 years.

An important determinant of the natural history of CF is the severity of the pulmonary disease and the rate at which it progresses. Although most patients' condition improves in response to therapy, skillful management does less to influence the course of the severely affected than that of the mildly affected patient.

A variety of scoring systems have been devised for CF. The clinical scoring system devised by Shwachman and Kulczycki and the chest radiograph scoring system devised by Brasfield and associates are widely used. However, although these and more elaborate scoring systems are useful in categorizing patients according to the severity of illness, none has proved useful in prognosticating the course of an individual patient.

Because CF is a genetic disease, the question of a familial pattern of severity is often raised. Figure 51-8 shows chest radiographs of three siblings with CF; the radiographs demonstrate mild, moderate, and severe disease in individuals in the same family. The capsule histories, which are included in the figure legend, also illustrate the variability in courses experienced.

Patients with CF can be categorized not only with respect to severity of illness, but also with regard to survival. For example, more than half of patients with CF who underwent surgery for meconium ileus before 1965 died in the first 2 months of life. Although this situation had improved markedly by 1976, the survival rate for patients with meconium ileus was still not as good as for all other patients with CF. In addition, the survival rate was much lower for females than for males, especially in adolescents. In recent years, differences between the patients in these groups have declined or disappeared. Because of improvements in the collection of mortality statistics, comparison of current data with those from previous years may be somewhat misleading, but

Table 51-3

Hypoelectrolytemia and Metabolic Alkalosis in Two Cystic Fibrosis Patients

	Serum Electrolytes, mEq/L				
Patient	**Na**	**K**	**Cl**	**CO_2**	**Serum pH**
No. 1	123	2.2	49	48	7.60
No. 2	125	2.4	55	41	7.63

SOURCE: Modified from Scanlin TF: Cystic fibrosis, in Fleisher G, Ludwig S (eds), *Textbook of Emergency Pediatrics.* Baltimore, Williams & Wilkins, 1983, pp 532–556, with permission.

50 percent-survival age has not been increasing as rapidly in recent years as in the 1970s and 1980s (Fig. 51-10). Furthermore, there is a difference in outcomes among individual CF centers.

COMPLICATIONS

The course of CF is often characterized by a gradual decrease in pulmonary function, punctuated by further abrupt declines during exacerbations. Malnutrition, when present despite therapy, usually correlates best with the severity of the pulmonary disease. However, the course of CF may be suddenly altered by certain complications of the disease.

Hypoelectrolytemia and Metabolic Alkalosis

Hypoelectrolytemia and metabolic alkalosis are serious complications that are especially apt to occur during periods of hot weather, when losses of sodium and chloride increase. Electrolyte depletion may be life-threatening, especially in infants and young children (Table 51-3). Prompt fluid replacement with isotonic saline is critical.

Intestinal Obstruction

Acute or chronic crampy abdominal pain attributable to some degree of intestinal obstruction is common in patients with CF. If the obstruction is incomplete and manifested solely by a tender right lower-quadrant mass, medical therapy using oral *N*-acetylcysteine and mineral oil, GoLytely, or MiraLax is recommended. If these measures are unsuccessful, hyperosmolar enemas using an agent such as methylglucamine diatrizoate (Gastrografin) may dislodge the fecal mass. Patients with a history of crampy abdominal pain are occasionally noted to have radiographic evidence of intestinal obstruction, manifested by dilated bowel loops and air-fluid levels. After the neonatal period, intestinal obstruction is referred to as meconium ileus equivalent. An impacted fecal mass may serve as the leading edge for a volvulus or intussusception (Fig. 51-6). If either of these is present and not resolved with hyperosmolar enema, surgery is required. Careful pre- and postoperative management is essential to avoid the deterioration in pulmonary function that may follow the use of anesthesia.

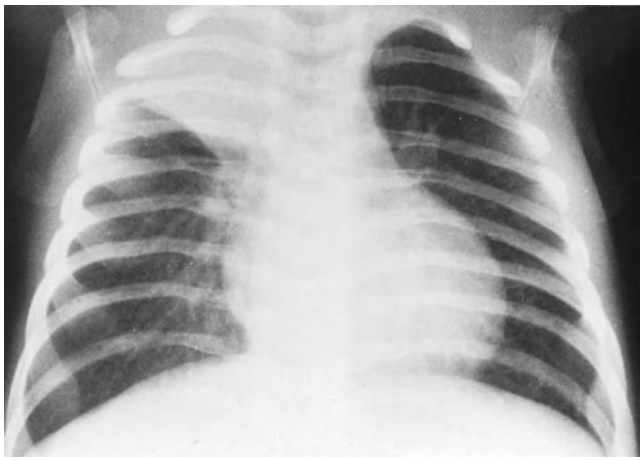
Liver Disease

Cholestasis is often asymptomatic and detected by elevated serum alkaline phosphatase and transaminases on routine yearly studies. To prevent the progression to fibrosis and cirrhosis, treatment with the hydrophilic bile acid, ursodeoxycholic acid, should be initiated. Persistent hepatomegaly or splenomegaly, persistently elevated transaminases, or complications of portal hypertension establish significant liver involvement. Although cirrhosis occurs in fewer than 5 percent of people with CF, esophageal varices and portal hypertension may cause upper gastrointestinal bleeding in these patients. Once bleeding has been identified as due to varices and hemoptysis has been excluded, therapeutic endoscopy with a sclerosing agent or band ligation is undertaken. For patients with severe involvement, transjugular intrahepatic portosystemic shunting or surgical portosystemic shunts can effectively decompress esophageal varices by decreasing portal pressure.

Liver transplantation is another option for many patients with CF who have end-stage liver disease. Bleeding esophageal varices or vitamin K–resistant prolongation of the prothrombin time should prompt evaluation for liver transplantation. Criteria for priority transplantation include bleeding varices not responsive to sclerosis, severe ascites, and encephalopathy. Ideal candidates are those with an FEV_1 of at least 50 percent of predicted. Colonization with a multidrug-resistant or panresistant strain of *Pseudomonas* is a relative contraindication to transplantation. In patients in whom poor pulmonary function or drug-resistant pulmonary infection is an issue, double organ (liver and lung) transplantation may be considered. However, this surgery has been successfully accomplished only several times to date. Despite concerns about worsening airway infection during transplant-associated immunosuppression, liver transplantation in patients with CF does not worsen their pulmonary status.

Atelectasis

Atelectasis of a lung segment or lobe sometimes occurs in CF. Acute atelectasis is generally associated with few symptoms (Fig. 51-11*A*). If it is untreated, however, the end result of atelectasis is a severely bronchiectatic segment or lobe (Fig. 51-11*B*). Vigorous chest physiotherapy, in conjunction with antibiotics, is often successful in reexpanding the affected lung region. Bronchoscopy is occasionally helpful. As a rule, however, bronchoscopy is no more effective than chest physiotherapy and pulmonary pharmacotherapy. Resection of a persistently atelectatic or bronchiectatic lobe is undertaken only when the remaining areas of the lung are in relatively good condition, overall pulmonary function is good, and the evidence convincing that the affected segment is responsible for intolerable symptoms (fever, cough, or sputum production).



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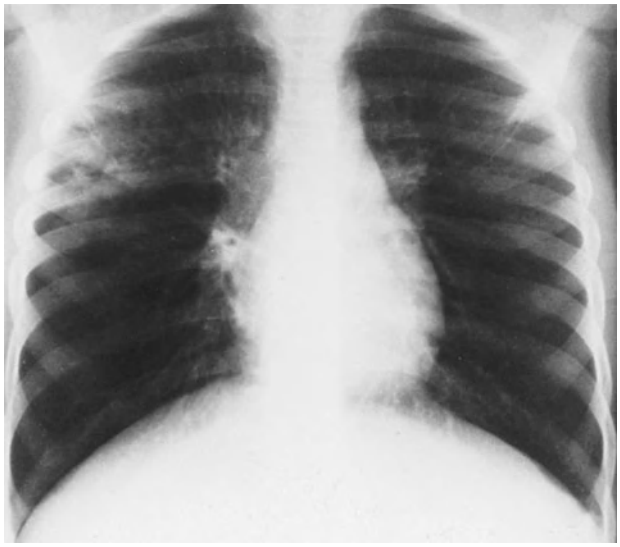

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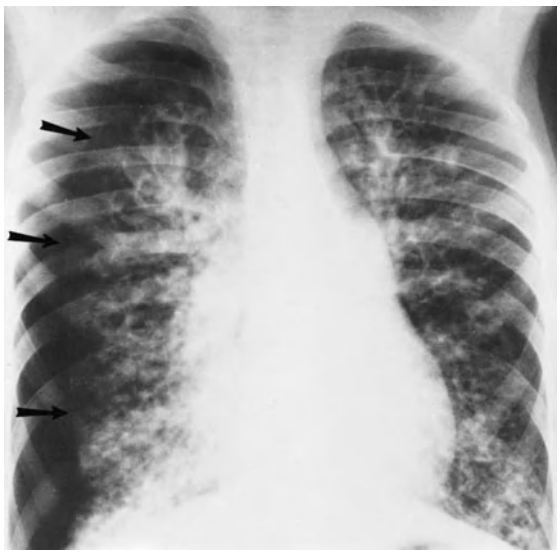

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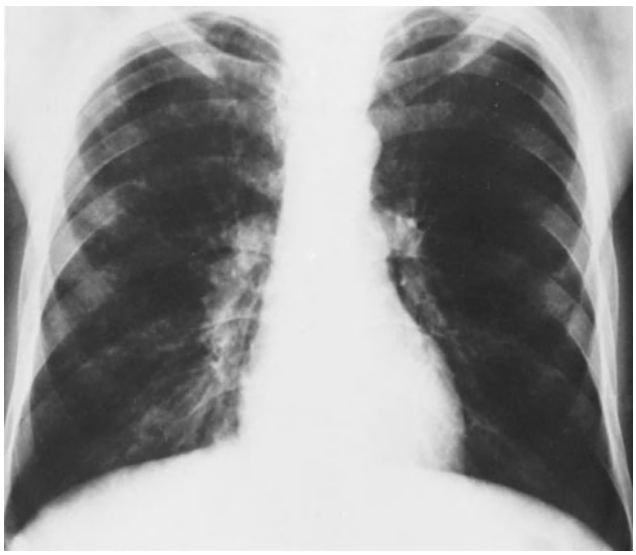

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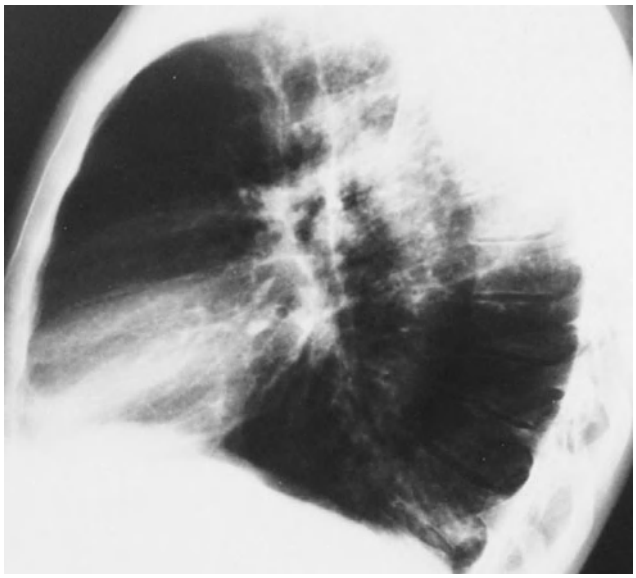

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Figure 51-11 Chest radiographs of patients with pulmonary complications of CF. *A*. Atelectasis of the right upper lobe in a 4-month-old boy. The atelectasis resolved with antibiotics and chest physiotherapy. *B*. The same patient at 9 years of age with mild hyperinflation, central bronchiectasis, resolving right upper lobe infiltrate. The diagnosis of allergic bronchopulmonary aspergillosis was made, and the patient improved after treatment with prednisone. *C*. Pneumothorax of the right lung (arrows) in a 13-year-old boy. The pneumothorax resolved after tube thoracostomy and tetracycline sclerosis. The patient died 3 years later from respiratory failure with congestive heart failure. There were no recurrences of the pneumothorax. *D* and *E*. A 43-year-old man showing hyperinflation and diffuse peribronchial thickening. The radiograph was taken during an episode of significant hemoptysis, and no acute changes were seen on the radiograph. He works full-time and has not had another episode of hemoptysis in the last 12 years.

Pneumothorax

Recurrent pneumothorax is common in CF, particularly in older patients (Fig. 51-11*C*). Tension pneumothorax occurs in up to 30 percent of patients with CF who develop pneumothorax. Tube thoracostomy is indicated when the pneumothorax occupies more than 10 percent of the area of the hemithorax seen on the posteroanterior chest radiograph. Because the frequency of recurrence of pneumothorax is high, attempts are often made at the time of the initial event to achieve chemical or surgical pleurodesis. Surgical pleurodesis is more effective at preventing recurrence of a pneumothorax and is no longer considered a contraindication to lung transplantation.

Hemoptysis

Expectoration of a small amount of blood-streaked sputum is a fairly common occurrence in CF and is generally managed by intensifying home therapy for pulmonary infection. In contrast, hemoptysis (the expectoration of at least 30 to 60 ml of fresh blood) requires hospitalization, even with a chest radiograph that is virtually unchanged (Fig. 51-11*D*). The probable mechanism underlying most instances of hemoptysis in CF is the erosion of an area of localized infection into a bronchial vessel. Massive hemoptysis (blood loss of 300 to 2500 ml) is uncommon in CF. However, it represents a potentially life-threatening situation. Bronchoscopy, and sometimes thoracic surgery, may be required to control the hemorrhage. Bronchial artery embolization has been used successfully in patients with CF and is now the treatment of choice when a physician experienced in the procedure is available.

Infection with Unusual Organisms

CF produces central bronchiectasis, even though the disease initially is in the small bronchioles. Bronchiectatic airways are frequently colonized with unusual organisms, including *Aspergillus* and atypical mycobacteria. As is the case with pathogenic bacteria, eradication of these organisms from the airways is virtually impossible. The focus of therapy is directed toward verifying that the organisms are resulting in worsening of the disease and controlling the infection, rather than effecting a microbiologic cure.

Mycobacteria

The prevalence of infection with mycobacteria in CF is approximately 12 to 15 percent. Frequently, the sputum culture is overgrown with pathogenic bacteria; accordingly, the culture should be handled specially to enhance isolation. Patients with CF should be screened for *Mycobacterium tuberculosis* infection with yearly PPD skin tests. Prophylaxis and treatment of *M. tuberculosis* in CF are the same as for patients without CF. A decision about therapy for isolation of atypical mycobacteria is based on the likelihood that the organism is contributing to airway infection and a decline in pulmonary function. Isolation of the same organism on several occasions, positive smears, presence of progressive chest radiographic changes, further decline in pulmonary status despite vigorous antipseudomonal (or antistaphylococcal) therapy, persistent night sweats, and fever are clinical clues that the atypical mycobacteria are contributing to disease. Demonstration of tissue infection with transbronchial lung biopsy is rarely recommended. A clinical database has been established by the CF Foundation to track results of treatment for atypical mycobacterial infections in patients with CF.

Aspergillus

In an analogous fashion, molds, especially *Aspergillus,* are occasionally isolated from patients with CF. Approximately 5 to 15 percent of patients have allergic bronchopulmonary aspergillosis (ABPA). The diagnosis of ABPA in CF is difficult because of overlapping symptoms between the two disorders. Diagnostic criteria for ABPA are (1) reversible airway obstruction, (2) proximal bronchiectasis, (3) history of pulmonary infiltrates, (4) skin test positivity to aspergillus antigens, (5) precipitating serum antibodies to *A. fumigatus,* (6) elevated total serum immunoglobulin E (IgE), (7) elevated specific serum IgE and serum immunoglobin G (IgG) to *Aspergillus,* and (8) peripheral eosinophilia. A negative skin test for *Aspergillus* effectively rules out the diagnosis of ABPA. During the active phase of ABPA, elevations in total IgE and eosinophil count are seen. Rises in *Aspergillus*-specific titers (IgE and IgG) are more specific for ABPA than are serum precipitins. ABPA in patients with CF is treated with corticosteroids and itraconazole.

Gram-Negative Bacteria

In the late 1970s and early 1980s, the importance of *Burkholderia cepacia* (formerly *Pseudomonas cepacia*) was recognized. *B. cepacia* is a gram-negative, oxidase-positive rod that is uniformly resistant to polymyxin and, frequently, panresistant. Isolation of *B. cepacia* requires plating on special OFPBL (oxidative fermentive polymyxin B bacitracin lactose) or PC (*P. cepacia*) agar plates to retard growth of other gram-negative rods and enhance growth of *B. cepacia.* The plates must be maintained for a minimum of 4 days. *B. cepacia* colonization has been associated with septicemia, which is very rarely seen with *P. aeruginosa.* The clinical course after acquisition of *B. cepacia* may be fulminant, with death occurring in a matter of months. However, most patients' disease follows a more benign course. Carefully controlled epidemiologic studies are needed to better define risk factors and to establish the true virulence of *B. cepacia.* Experimental evidence exists that at least one strain of *B. cepacia* may be transmitted in an epidemic fashion. The combination of a poor clinical course after acquisition of *B. cepacia* and the evidence supporting epidemic transmission has led to cohorting or isolation of patients with CF infected with *B. cepacia,* as recommended by the CF Foundation and the Centers for Disease Control (CDC).

In addition to being colonized with *Pseudomonas* and *Burkholderia* species, patients with CF may be colonized with

other gram-negative, oxidase-positive organisms, such as *S. maltophilia, Pseudomonas oryzihabitans,* and *A. xylosoxidans.* These are pathogenic organisms, similar in importance to *P. aeruginosa.* Antibiotic therapy should be directed toward these bacteria when they are isolated from the patient with CF who is experiencing an acute exacerbation. The prolonged, prophylactic, aggressive use of antibiotics in CF has led to emergence of resistant organisms. A multiply resistant *Pseudomonas* is an organism that is resistant to all agents in at least two different classes of antibiotics. Resistance to oral fluoroquinolones occurs after about 3 weeks of therapy; if the agent is withheld, the organism occasionally becomes sensitive again.

Respiratory Failure

As the pulmonary disease of CF progresses and the degree of hypoxia increases, patients are at risk to develop pulmonary hypertension and cor pulmonale. An increase in hypoxia often occurs during exacerbations of the pulmonary disease. During the acute episode, antibiotic treatment for the underlying pulmonary disorder is intensified and supplemental oxygen is added. Expectant monitoring and aggressive treatment of nocturnal hypoxemia (maintaining $Sa_{O_2} \geq 95$ percent) prevent the onset of cor pulmonale. When respiratory failure develops in CF—i.e., hypercarbia (Pa_{CO_2} at least 55 mmHg) in addition to hypoxemia—management becomes extremely difficult. Noninvasive mechanical ventilation using bilevel positive airway pressure has been used successfully in patients with end-stage CF awaiting lung transplant; it improved oxygenation, reduced respiratory rate, and was successfully transitioned to home nocturnal use.

Mechanical ventilation is generally instituted when an acute episode, such as viral pneumonia or status asthmaticus, thrusts the patient into acute respiratory failure. This approach is particularly indicated in the patient who has had good pulmonary function before the acute episode. Mechanical ventilation is less apt to be successful if the patient has previously experienced a bout of respiratory failure. When respiratory failure marks the end of a chronic course of progressive pulmonary insufficiency despite adequate medical therapy, mechanical ventilation is usually unhelpful. None of the indications or contraindications for mechanical ventilation are absolute, however, and the clinical outcome depends, to a large extent, on the availability of a dedicated and skilled intensive care team experienced in caring for patients with CF.

Complications Related to Lung Transplantation

Lung transplantation has emerged as an option for patients with end-stage CF. Despite initial concerns about immunosuppression in patients with suppurative lung disease, the outcome for those with CF who undergo lung transplantation is among the best reported for this procedure. Two major problems prevent lung transplantation from becoming widely recommended for CF. One is the lack of suitable organs for transplantation. Forty percent of patients with CF who are awaiting transplantation die before an organ is made available. The attrition is due, in part, to the allocation of lungs on the basis of wait-list time *alone,* rather than on the basis of severity of disease; this practice has changed to permit the most severely ill patients access to transplant. The median waiting time is currently more than 12 months, but wide variability exists. The organ shortage, especially from pediatric donors, has driven the development of living related-donor transplants.

The second major problem with lung transplantation for CF is the occurrence of obliterative bronchiolitis following transplantation. Obliterative bronchiolitis is a progressive occlusion of the bronchiolar lumina by inflammatory cells and submucosal fibrosis. The cause is probably chronic allograft rejection; transient improvement in airflow is seen following augmentation of immunosuppression. About 50 percent of transplant patients develop obliterative bronchiolitis after the second year following the procedure. The disease pursues a relentless downhill course, with a median survival of about 2 years following the initial diagnosis.

The poor prognosis associated with obliterative bronchiolitis has several important implications for patient selection and timing of referral for transplantation. First, the main reason for seeking lung transplant is to improve the quality of life, rather than to improve survival. Second, the timing of referral for lung transplantation necessitates weighing the risks of dying while on the waiting list against the possibility of developing obliterative bronchiolitis.

Appropriately timed referral for transplantation includes consideration of (1) the average length of waiting time, (2) the natural history of the disease, (3) the natural history of lung transplantation, and (4) the requirement that the patient be fully ambulatory. Therefore, ideal candidates for lung transplantation are those who have less than 2 years to live and have significant functional impairment but are capable of participating in a pulmonary rehabilitation program.

Results from clinical studies may aid with proper timing of referral for lung transplantation in CF. A study of 673 patients with CF revealed that patients with an FEV_1 less than 30 percent of predicted have a 50 percent 2-year mortality. Other important clinical parameters useful in determining the timing of transplantation are the presence of hypoxemia (Pa_{O_2} under 55) and hypercarbia (Pa_{CO_2} above 50). Of interest, in both single and multivariate analyses, female gender is associated with an increased relative risk, suggesting that for female patients, referral for lung transplantation should be considered at an even earlier stage.

Because CF is a multisystem disorder, both management and proper selection of patients are more complicated than for other diseases managed with lung transplantation. Among the most difficult challenges presented by patients with CF before transplantation is the microbiology of their lower airways. As discussed previously, colonization with multidrug-resistant *B. cepacia*, specifically the genotype, genomovar III, has been associated with a poor clinical outcome. For poorly understood reasons, patients with CF

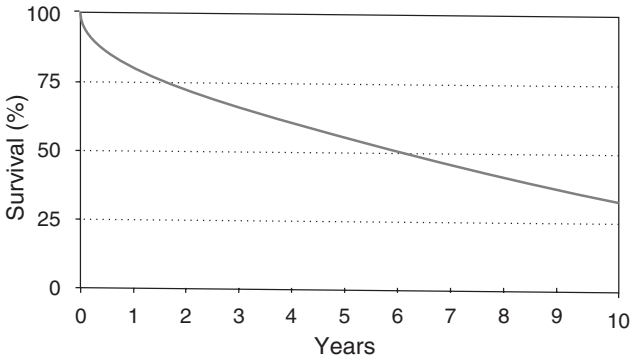

Figure 51-12 Kaplan-Meier survival for CF adult lung transplantation recipients (n = 1934) performed between January 1994 and June 2003. The CF lung transplant recipients had better survival outcomes than patients transplanted for idiopathic pulmonary fibrosis or primary pulmonary hypertension. *(From Trulock EP, Edwards LB, Taylor DO, et al: Scientific registry of the International Society for Heart and Lung transplantation: Twenty-second official adult lung and heart-lung transplant report—2005.* J Heart Lung Transplant *24:956–967, 2005.)*

metabolize drugs differently from those without CF, complicating the dosing of medications, including cyclosporine. The difficulties in achieving an optimal drug dose may be related to malabsorption or enhanced excretion of the drug. Nutritional issues also complicate the posttransplantation management of patients with CF. About 50 percent of all patients with CF over 30 years of age are overtly diabetic, and administration of corticosteroids induces diabetes in another 10 percent. Maintenance of proper nutrition is important in CF, especially for rapid postoperative recovery. Finally, gastroesophageal reflux may negatively impact pulmonary outcomes following transplantation. Despite all the special challenges to successful lung transplantation posed by patients with CF, their actuarial survival is quite good (Fig. 51-12). The 5-year survival is about 59 percent, reinforcing the tenet that lung transplantation is done principally to improve quality of life.

PSYCHOSOCIAL ISSUES

A number of psychosocial issues are important in the management of patients with CF. Special circumstances should be recognized for adults with the disorder.

General

Careful attention to the emotional, social, and financial well-being of the patient with CF and his or her family has considerable value in favorably influencing the course of the disease. At the time of diagnosis, it is important to strike an optimistic note while educating the patient about the illness and its management. As part of the early encounter with the patient, the importance of identifying and reinforcing the emotional and financial strengths of the family, as well as weaknesses that will need buttressing, should be recognized. Medical care for CF patients is costly, especially if hospital admissions are required. Many states have programs for children with disabilities that provide support for patients and families. Several states have also established special programs for adults with CF.

As the disease runs its course, counseling and feedback about disease progression are essential. As the patient and family go about setting educational, career, and family goals, they need guidance in realistic planning. It is vital that the physician develop and maintain a positive attitude. The patient who gives up hope is liable to undergo rapid deterioration. Conversely, even patients with severe pulmonary disease can continue to function well and be productive. At the stage when medical therapy is of no further avail, however, the patient and family require considerable emotional support to accept the inevitable. In recent years, many CF centers have allowed patients to die at home, rather than in the hospital. The family requires specific instructions about how to provide physical and emotional comfort for the patient in the home. Usually, home visits by some members of the CF team are required. Not all families have the strength or resources to care for the patient dying at home.

Special Considerations in Adult Patients

In 2004, the median life expectancy for patients with CF was about 35 years. Managing a chronic illness becomes more complicated when patients must also begin to manage their independence and make life decisions regarding education, marriage, children, careers, insurance, and self-care. Intense support for both patients and their families is required. Patients with a relatively mild clinical course of disease form healthy and satisfying relationships in a manner similar to that of their healthy, age-matched peers. With advanced disease, patients with CF have more difficulty in forming intimate relationships. Disturbances in body image, decreased mobility, and lack of opportunity to meet suitable partners are cited as reasons for the decreased ability to form intimate relationships in the severely affected young adult with CF.

The adult patient with CF faces unique problems with self-care. Families of patients with CF provide a tremendous amount of care that is expensive and time-consuming to replace for the independently living adult. When the disease flares, patients must "step up" their level of care at precisely the time when they are least able to do so. Judicious use of hospitalization and home care must be provided if the patient is to recover. The trend toward home management of a pulmonary exacerbation using intravenous antibiotics alone ignores the obvious contributions of nutrition, airway clearance, and rest toward resolution of the problem.

REPRODUCTIVE ISSUES

More than 98 percent of male patients with CF are sterile, secondary to bilateral absence of the vas deferens. Microsurgical

epididymal sperm aspiration (MESA), coupled with in vitro fertilization, has been successful in producing pregnancies in a few carefully selected patients. Not all males with CF are sterile, however. In addition to counseling, these men should be offered semen analysis.

Pregnancy for women with CF is increasingly common, and several important issues remain unsolved. In 2004, 191 women with CF were pregnant. This stands in marked contrast to the total of 13 pregnancies in 10 patients recorded from 1960 to 1966 (data from the 1994 CF Foundation Data Registry).

Maternal clinical status before pregnancy is the most important prognostic factor of maternal outcome. In a study of 25 women with 38 pregnancies, no significant difference was seen between pre- and postgravid gas exchange or nutritional status. A small but statistically significant decline in spirometry was noted. However, the decline was not outside the range of expected decline for the natural progression of the disease. More severely affected women suffer an irreversible decline in clinical status during pregnancy. Without an appropriately matched control group of nongravid women with CF, it is impossible to determine whether pregnancy per se is responsible for the decline or whether the decline is a reflection of the natural history of the disease.

Recommendations about pregnancy for women who are either mildly affected or severely affected is straightforward. For the woman with moderately compromised pulmonary status (i.e., FVC under 50 to 60 percent of predicted), an overall assessment of the clinical situation is recommended, although no firm guidelines can be given. Increased incidence of fetal prematurity is noted in women with a pregravid FVC below 50 percent of predicted, lending additional weight against recommending pregnancy to women with moderate to severe airflow obstruction. In any woman with CF who is contemplating pregnancy, thorough evaluation and treatment of nutritional deficiencies and pulmonary exacerbations are required. Frequent use of antibiotics is unavoidable, and the teratogenic risk of many antibiotics is unknown. Despite this theoretical risk, good maternal and fetal health depend on aggressive management of pulmonary exacerbations, including use of antibiotics. Management of the gravid patient with CF is best accomplished in a CF center that has a program in high-risk obstetrics.

For men with CF who opt for MESA and for women with CF who are contemplating pregnancy, all offspring are obligate heterozygotes for CF. These offspring need to be counseled that their risk of having a child with CF is about 1 in 50 if the genotype of the spouse is not known. Although genetic testing of children from affected parents is not recommended, they should receive genetic counseling on reaching adolescence. Parents with CF also need to consider the ethical issues of a premature parental death and its effect on the family.

Discovery of the CF gene in 1989 led to the hope that prenatal diagnosis would eventually decrease the incidence of the disease. However, affected families either are choosing not to test at-risk pregnancies or, if tested and found to be affected, are choosing to continue the pregnancy. Similarly, there has not been a large increase in the number of therapeutic abortions of fetuses with CF among women with the disorder who have a good clinical status. Obviously, the expected survival and quality of life for the child with CF must be sufficiently promising to explain these parents' decisions.

FUTURE DIRECTIONS

Concern exists that the marked improvement in survival of patients with CF noted over the past two decades is approaching a plateau. To further enhance survival in CF, physicians must look to insights gained from basic research. Although much work needs to be done, much has already been accomplished, warranting a realistic expectation that major breakthroughs will soon occur in the treatment of the disorder. Important areas for future development include new pharmacologic approaches and gene therapy.

Pharmacologic Approaches

Infection with *Pseudomonas* organisms is a critical aspect of CF that has attracted a great deal of attention. To date, *Pseudomonas* species have demonstrated a remarkable capacity to change expression of phenotype and to develop resistance to new antibiotics. One management strategy that is being employed more frequently is performance of synergy testing on isolates of *Pseudomonas* that are resistant to multiple antibiotics. Frequently, such testing directs the use of nontraditional combinations and doses of antibiotics with good therapeutic results. However, this strategy may be successful for only a limited period before panresistance develops.

Pharmacologic approaches to the basic defect in CF may offer treatment alternatives or additional benefit to the anticipated use of directed gene therapy (see below). As described earlier, many of the mutations in CF have been classified into five categories, depending on the functional consequences of the mutation on the gene product, which is an integral membrane glycoprotein. A CFTR mutation in the first category with a premature stop codon, G542X, can be activated by treating patients with intravenous gentamicin; this approach produced changes in nasal potential difference consistent with some improvement in chloride efflux. The most common mutation, ΔF508, is a class II or processing mutation in which most of the gene product remains in the endoplasmic reticulum, with only a very small amount localized to the surface membrane prior to degradation. Since CFTR has been shown to interact with several chaperones during processing, these molecules provide an attractive theoretical target for pharmacologic intervention, although, to date, there has been no functional correction with this approach. However, two agents, 4-phenylbutyric acid and glycerol, have been shown to increase cell surface localization of CFTR in vitro by an unknown mechanism. Since analogs

of 4-phenylbutyric acid have been employed clinically in treatment of sickle cell disease, a phase II clinical trial was performed. Other agents which have the property of "correcting" CFTR processing and localization to the apical membrane are being sought by the technique of high-throughput screening.

Other classes of compounds shown to "potentiate" or increase the chloride conductance of cells with the ΔF508 mutation are also being sought. Since infection and inflammation play a critical role in the pathophysiology of the lung disease of CF, efforts have been directed at decreasing airway inflammation. The approaches are both pharmacologic (e.g., use of ibuprofen and prednisone) and physiological (e.g., prevention of *Pseudomonas* binding to airway cells and immunization against *Pseudomonas*). The insufficient antioxidant capacity in CF airways is also being addressed by studies to evaluate antioxidant augmentation with nacystelyn and glutathione.

Gene Therapy

Improvements in gene transfer technology represent an important future direction in CF. Because the disease is inherited as an autosomal-recessive trait, only one normal copy of the gene needs to be provided to cells. Vectors proposed thus far for carrying the normal CFTR gene include adenovirus, adeno-associated virus, cationic liposomes, and DNA-protein complexes.

Several human clinical trials of gene therapy in CF have been initiated, based on use of adenoviral vectors, adeno-associated viral vectors, and nonviral vectors. Results have been remarkably similar among the trials. In a few patients, patchy expression of the transgene has been demonstrated in both the nose and lung using immunohistochemistry or in situ hybridization; overall efficacy has been poor. Dose-dependent inflammation has been encountered; in one study, a patient became acutely ill for several days following instillation in the lung of a high titer of replication-deficient adenovirus. Physiological correction of cyclic adenosine monophosphate (cAMP)-mediated chloride secretion in the nose has not been convincingly demonstrated after gene transfer, although a trend toward correction of the basal potential difference has been observed.

Finally, because the immune response to viral vectors constitutes a significant impediment to successful gene transfer, several approaches are currently being developed. These include production of less immunogenic viral vectors, immune suppression, development of nonimmunogenic, nonviral vectors, and using smaller molecules for gene repair inhibition of gene expression.

Progress toward cure of CF will require a multidisciplinary approach. Management of the lung disease in CF will probably be based on combined methods. However, the momentum gained from recent improvements in our understanding of basic pathogenetic mechanisms provides a basis for realistic optimism that specific therapy will result in better outcomes for patients with CF.

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Bronchiolitis

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Bronchiolitis is a fibrotic lung disease that primarily affects the small conducting airways, often sparing a considerable portion of the interstitium. Commonly occurring diseases with prominent involvement of the small airways (asthma, bronchitis, bronchiectasis) are described elsewhere in this book. However, several additional, uncommon small-airway diseases are important to recognize and treat. These "bronchiolar syndromes" frequently accompany infections, drug reactions, connective-tissue diseases, toxic gas or fume exposure, and organ transplantation. Bronchiolitis is an intellectual challenge to clinicians and pathologists. The "gold standard" approach is a multidisciplinary one, including clinical, radiological, and histopathological expertise, to establish the final diagnosis. This chapter reviews the clinical, radiographic, and histopathological findings of the bronchiolar syndromes.

DEFINITION AND CLASSIFICATION

Although bronchiolitis has been recognized since the 1800s, it was not until 1901 that the first detailed description of the clinicopathological syndrome appeared and the phrase *bronchiolitis obliterans* was applied. Bronchiolitis is an inflammatory reaction that follows damage to the bronchiolar epithelium of the small conducting airways. Subsequent

healing leads to excessive proliferation of granulation tissue within the airway walls, lumen, or both. Depending on disease stage, the repair process may cause narrowing and distortion of the small airways (constrictive bronchiolitis) or complete obliteration (bronchiolitis obliterans). Alveoli adjacent to the injured small airways are almost always affected, but a considerable portion of the pulmonary interstitium is often spared. Repair occurs in numerous clinical settings, with a variable clinical course and histological appearance. Consequently, a clear understanding of pathogenesis is lacking.

The nomenclature applied to the bronchiolar syndromes has been confusing. The following terms have been used: bronchiolitis obliterans, bronchiolitis fibrosa obliterans, bronchiolitis obliterans and interstitial pneumonia, bronchiolitis obliterans-organizing pneumonia (BOOP), cryptogenic-organizing pneumonia, and follicular bronchiolitis. Unfortunately, the terms are often used interchangeably to describe what are now believed to be separate and distinct clinical entities. Before the description of BOOP in 1985, most cases described as idiopathic bronchiolitis obliterans were actually cases of BOOP. Since some degree of inflammation, narrowing, and obliteration of the small airways is present in most patients, we have chosen the term *bronchiolitis* to refer to the broad spectrum of histopathological processes. Bronchiolitis obliterans refers to a histological lesion characterized by polypoid obliteration of the lumen of bronchioles, without involvement of the distal lung parenchyma by inflammation or organizing pneumonia—i.e., constrictive bronchiolitis. BOOP refers to disorders characterized histologically by intraluminal polyps in the respiratory bronchioles, alveolar ducts, and alveolar spaces, accompanied by organizing pneumonia in the more distal parenchyma. Bronchiolitis obliterans syndrome (BOS) is a clinical term that refers to the progressive airflow limitation secondary to small-airway obstruction which commonly complicates lung transplantation that is defined not by histology, but by lung function changes.

In BOOP, the alveolar walls show a mild to moderate chronic inflammatory infiltrate, type II cell hyperplasia, and foamy macrophages in the alveolar spaces; a "proliferative" bronchiolitis is present. Since only a minority of cases showing the "BOOP pattern" represent the idiopathic syndrome described in 1985, and since patients with idiopathic BOOP manifest a distinctive clinical syndrome, this group is referred to as "cryptogenic-organizing pneumonia," in order to distinguish the syndrome from other causes of the BOOP pattern.

Three classification schemes appear useful in defining cases of bronchiolitis: (1) a clinical classification based on the etiology; (2) a histopathological classification that includes two major morphologic types: proliferative bronchiolitis and constrictive bronchiolitis; and (3) a radiologic classification based on the findings of thin-section, high-resolution computed tomography (HRCT). The histopathological-radiologic classification appears most useful, since histopathological-radiologic changes correlate best with clinical manifestations.

Clinical Classification

The clinical classification of bronchiolitis is based on etiology (Table 52-1): inhalation injury, infections, drug reactions, and idiopathic causes. The first three categories are frequently recognized from their association with an acute illness or known exposure before the onset of disease. Idiopathic cases often have a more insidious onset, characterized by cough or dyspnea; initially, they may be confused with more common problems, such as chronic obstructive pulmonary disease or interstitial lung disease, depending on the predominant histopathological pattern.

Radiologic Classification

HRCT is an excellent way to examine the morphology of small-airway diseases. Consequently, it has become the method of choice for assessing these airways, often replacing the need for surgical lung biopsy. Several studies have examined the patterns found on computed tomography (CT) scans and correlated the patterns with histopathological findings. Based on radiologic features, investigators have classified bronchiolar diseases into three predominant CT patterns: (1) nodules and branching lines; (2) ground glass opacification (hazy increased attenuation, i.e., increased density of the lung with preservation of bronchial and vascular margins) and consolidation (hazy increased parenchymal attenuation in which the bronchial and vascular margins are obscured); and (3) low attenuation (i.e., decreased density of lung or "black lung") and mosaic perfusion (a patchwork of regions of varied attenuation, interpreted as secondary to regional differences in perfusion). The mosaic perfusion pattern appears to be most helpful in suggesting the presence of bronchiolitis obliterans.

Histopathological Classification

The histopathological classification (Table 52-2) of bronchiolitis includes proliferative and constrictive varieties. Each type, including the presumed pathogenesis, is described below.

Proliferative Bronchiolitis

Proliferative bronchiolitis—the "BOOP pattern"—is characterized by an organizing intraluminal exudate and is found, to some degree, in a variety of pulmonary disorders. It is particularly extensive and prominent in cryptogenic-organizing pneumonia (also called idiopathic BOOP). The intraluminal fibrotic buds (Masson bodies) are seen in respiratory bronchioles, alveolar ducts, and alveoli (Fig. 52-1). Proliferative bronchiolitis most frequently is associated with diffuse infiltrates on chest radiograph and a restrictive defect on pulmonary function testing, especially when cryptogenic organizing pneumonia is present.

Constrictive Bronchiolitis

Constrictive bronchiolitis is characterized by alterations in the walls of membranous and respiratory bronchioles which

Table 52-1

Clinical Syndromes Associated with Bronchiolitis

- *Inhalational injury*
  - Toxic gases (e.g., oxides of nitrogen)
  - Grain dusts
  - Irritant gases (e.g., chlorine)
  - Mineral dusts
  - Organic dusts (hypersensitivity pneumonitis)
  - Cigarette smoke
  - Free-base cocaine
  - Fire smoke
  - Flock worker's lung (fine nylon fiber)
  - Volatile flavoring agents
- *Postinfectious (mostly in children)*
  - Acute bronchiolitis
    - Common
      - Respiratory syncytial virus
      - Parainfluenza (types 1, 2, and 3)
      - Adenovirus (types 1, 2, 3, 5, 6, 7, and 21)
      - *Mycoplasma pneumoniae*
    - Uncommon
      - Coronavirus
      - Rubeola
- *Drug-induced reactions*
  - Penicillamine
  - Hexamethonium
  - L-Tryptophan
  - Busulfan
  - Gold
  - Cephalosporin
  - Sulfasalazine
  - Amiodarone
  - Acebutolol
  - Sulindac
  - Paraquat poisoning
- *Idiopathic*
  - No associated disease
    - Cryptogenic constrictive bronchiolitis
    - Respiratory bronchiolitis-associated interstitial lung disease
    - Cryptogenic-organizing pneumonia (also called idiopathic bronchiolitis obliterans-organizing pneumonia, BOOP)
    - Diffuse panbronchiolitis
    - Primary diffuse hyperplasia of pulmonary neuroendocrine cells
  - Associated with other disease
  - Associated with organ transplantation
    - Bone marrow
    - Heart-lung
    - Lung
  - Associated with connective-tissue diseases
    - Rheumatoid arthritis
    - Sjögren's syndrome
    - Systemic lupus erythematosus
    - Polymyositis dermatomyositis
  - Distal to bronchial obstruction ("obstructive pneumonitis")
  - Ulcerative colitis
  - Chronic eosinophilic pneumonia
  - Other rare associations
    - Radiation pneumonitis
    - Aspiration pneumonitis
    - Idiopathic pulmonary fibrosis
    - Malignant histiocytosis
    - Acute respiratory distress syndrome
    - Vasculitis, especially Wegener's granulomatosis
    - Chronic thyroiditis

cause concentric narrowing or complete obliteration of the airway lumen (Fig. 52-2). Often these lesions occur without extensive changes in alveolar ducts or alveolar walls. The changes of constrictive bronchiolitis may be extremely subtle, and frequently they are identified only after step-sectioning and special staining (e.g., use of stains to identify remnants of airway walls) of the lung biopsy. The range of histopathological changes includes: (1) subtle cellular infiltrates around the small airways; (2) extensive cellular infiltrates and smooth-muscle hyperplasia; (3) bronchiolectasia with mucus stasis, distortion, and fibrosis; and (4) total obliterative bronchiolar scarring. These lesions are seen most often in patients with progressive obstructive lung disease. A normal chest radiograph may be present. Cases of constrictive bronchiolitis are very rare.

Pathogenesis

A similar sequence of events may lead to both histopathological patterns of bronchiolitis. However, differences appear to relate to the type of insult, extent and severity of the initial insult, and predominant site of the injury (bronchioles, alveolar ducts, or both). In some diseases associated with bronchiolitis, varying degrees of both proliferative and constrictive bronchiolitis can be found on histological examination.

The initial lesion in constrictive bronchiolitis usually involves airway epithelial injury and destruction (Fig. 52-3). An inflammatory response follows, with accumulation of neutrophils at the site of injury. Neutrophils cause further injury to the airway epithelium and matrix by release of inflammatory mediators. Persistence of the injury

Table 52-2

Comparison of Key Pathological, Radiologic, and Physiological Features in Proliferative and Constrictive Bronchiolitis

Feature	Proliferative Bronchiolitis	Constrictive Bronchiolitis
Histopathological manifestations	Common finding Nonspecific reparative reaction to bronchiolar injury Organizing intraluminal exudate Most prominent in alveolar ducts Inflammatory changes in surrounding alveolar walls Foamy macrophages in alveoli	Very uncommon finding Obliterans not a constant feature Variety of histological changes: bronchiolar inflammation to progressive concentric fibrosis; smooth-muscle hyperplasia, bronchioloectasia with mucous stasis; distortion and fibrosis of small-airway walls with bronchial metaplasia extending onto peribronchiolar alveolar septa Follicular bronchitis (lymphoid hyperplasia) Cellular bronchiolitis Diffuse panbronchiolitis
Radiographic abnormalities	Bilateral patchy airspace opacities Interstitial opacities Small rounded opacities Opacities may be recurrent and migratory	May be normal Progressive increase in lung volume on serial radiographs HRCT scan may show marked heterogeneity of lung density
Pulmonary function	Restrictive defect (a mixed pattern may be seen)	Obstructive defect with hyperinflation
Clinical syndromes	Cryptogenic-organizing pneumonia (idiopathic BOOP) Collagen vascular disease (e.g., rheumatoid arthritis, dermatomyositis, SLE) Organizing acute infection (especially influenza or *Nocardia asteroides, Mycoplasma, Pneumocystis carinii, Legionella pneumophila*, cytomegalovirus, or HIV infection) Chronic eosinophilic pneumonia Hypersensitivity pneumonitis Organizing diffuse alveolar damage/(ARDS) Vasculitides, especially Wegener's granulomatosis Organ transplantation (rare) Drug-induced reactions (hexamethonium, L-tryptophan, busulfan, free-base cocaine, gold, cephalosporin, sulfasalazine, amiodarone, acebutolol, sulindac) Other uncommon associations: chronic thyroiditis, ulcerative colitis, irradiation pneumonitis, aspiration pneumonitis, distal to bronchial obstruction, "obstructive pneumonitis," chronic heart or renal failure, common variable immunodeficiency syndrome	Allograft recipients (bone marrow, heart-lung, lung) Collagen vascular disease (especially rheumatoid arthritis) Postinfectious (especially respiratory syncytial virus, adenovirus, influenza, parainfluenza, *Mycoplasma*) Inhaled toxins (e.g., nitrogen dioxide, sulfur dioxide, ammonia, chlorine, phosgene) Drugs (e.g., penicillamine, lomustine) Cigarette smoke Mineral dust airway disease (asbestosis, silica, iron oxide, aluminum oxide, talc, mica, and coal) Idiopathic Hypersensitivity reactions

(*Continued*)

Table 52-2

(*Continued*)

Feature	Proliferative Bronchiolitis	Constrictive Bronchiolitis
Natural history	Corticosteroid responsive and usually reversible	Relatively corticosteroid unresponsive and usually progressive with the development of irreversible airflow obstruction and air trapping. May respond to macrolide antibiotics.

HRCT, high-resolution computed tomography; BOOP, bronchiolitis oblitevans-organizing pñeumonia; SLE, Systemic lupus erythematosus; HIV, human immunodeficieny virus; ARDS, acute respiratory distress syndrome.

may determine whether there is resolution and recovery or progression to a less reversible state, manifested by intramural and intraluminal fibrosis. The repair process results in the characteristic obliterative bronchiolar lesions.

In general, "proliferative" bronchiolitis appears to be a common "early" lesion that may resolve completely or partly. Intermediary steps in the development of intraluminal, extracellular matrix synthesis have been clarified. First, a florid alveolitis with edema occurs as a result of damage to the alveolar lining. The degree of alveolar lining destruction and disruption of the basal lamina, with resulting gaps on the basement membrane, appears to determine the extent of intra-alveolar fibrosis. Although the alveolar basement membrane is most frequently damaged, minor changes are also noted in the endothelial basement membrane. The alveolitis coincides with the presence of inflammatory proteins in the airspace, including immunoglobulins (IgG, IgA, and IgM), fibronectin, and procoagulant factors (fibrinogen and factors VII and X). The cellular response includes neutrophils, eosinophils, macrophages, and lymphocytes. Many mast cells are also present in the septal and intra-alveolar compartments.

After development of the alveolitis, fibroblasts migrate into the lesion, proliferate, and secrete matrix proteins. This results in the formation of Masson bodies, polypoid buds of fibroblasts, and extracellular matrix projecting into the lumina of respiratory bronchioles, alveolar ducts, and alveoli. The matrix of the Masson bodies stain positive for type III collagen and fibronectin (cell and plasma in origin). The fibroblasts in the Masson bodies also stain strongly for procollagen type I. Delicate fibrils within the matrix of some Masson bodies contain type IV collagen. Inflammatory changes in surrounding alveolar walls, including prominent foamy

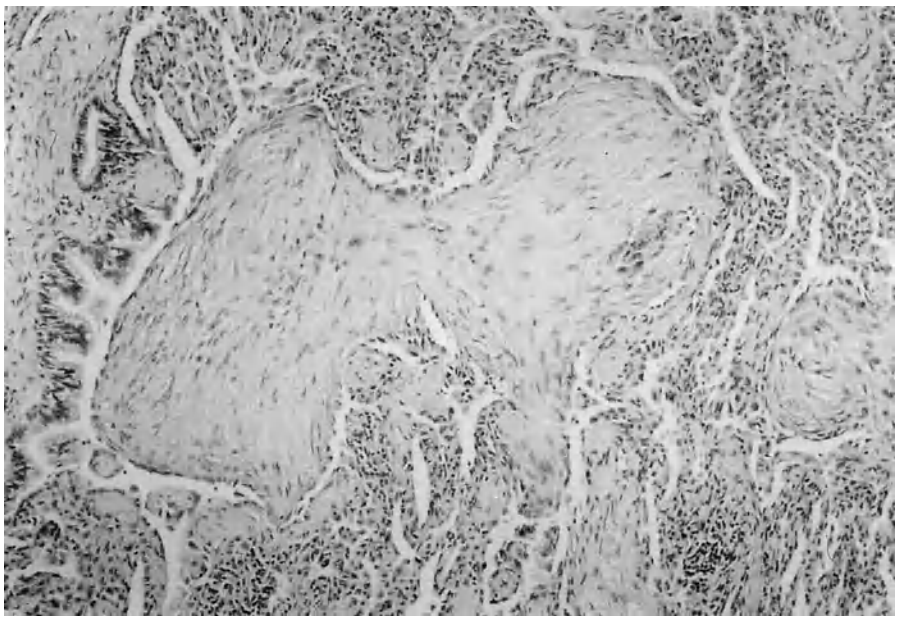
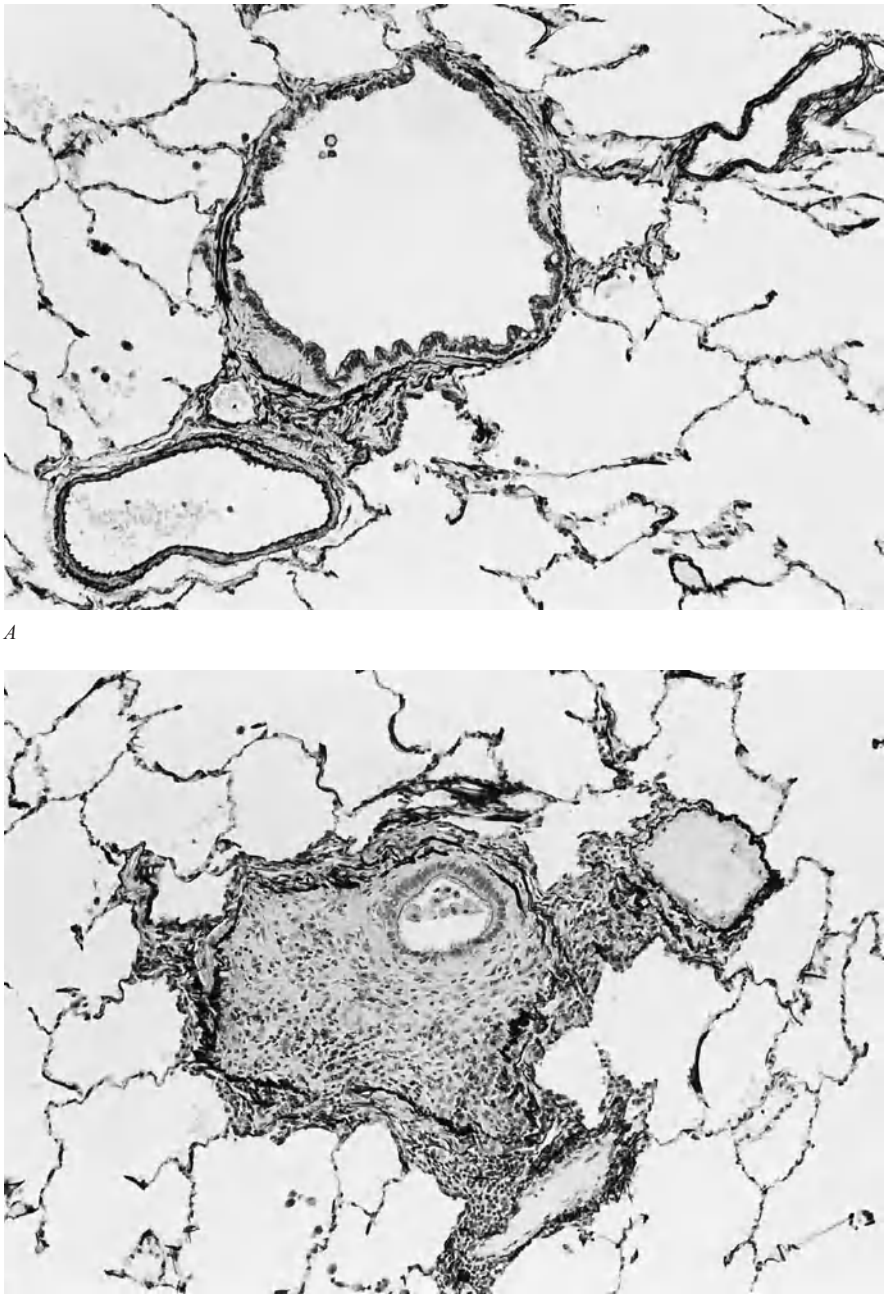


Figure 52-1 Bronchiolitis obliterans-organizing pneumonia (BOOP). Photomicrograph of open lung biopsy from a patient with cryptogenic-organizing pneumonia (COP). Polypoid masses of granulation tissue fill the lumens of a respiratory bronchiole and alveolar ducts. Adjacent alveolar interstices are broadened by a lymphoplasmacytic inflammatory infiltrate. (Pentachrome stain, ×156.)



A

B

Figure 52-2 Constrictive bronchiolitis. Photomicrograph of open lung biopsy from a patient with constrictive bronchiolitis following toxic gas exposure. *A*. Slightly dilated but otherwise normal bronchiole with normal intervening lung. (Pentachrome stain, ×156.) *B*. Step-section of specimen. Marked concentric narrowing of the bronchiolar lumen due to fibrosis is apparent. (Pentachrome stain, ×156.)

macrophages in alveoli spaces (i.e., organizing pneumonia) are commonly present.

INHALATIONAL LUNG INJURY CAUSING BRONCHIOLITIS

The inhalation of fumes, gases, mists, mineral dusts, or organic material constitutes a significant industrial and environmental hazard in many settings (Table 52-3). Exposure can result in subtle or severe clinical illness, usually associated with immediate development of pulmonary edema and late development of constrictive bronchiolitis with airflow limitation.

Toxic Gases

The inhalation of gases or fumes (i.e., fine particulates) is a rare cause of bronchiolitis, with or without obliterans. Oxides of nitrogen are the most common and best-described agents leading to acute and chronic lung injury. Silo filler's disease is a well-studied example (Fig. 52-4). The estimated annual incidence of silo filler's disease is 5 cases per 100,000 silo-associated farm workers per year. Most cases occur during the harvest period (September and October).

Mechanism of Injury

The distribution and extent of the lung injury are determined by the concentration of the agent, duration of exposure, route

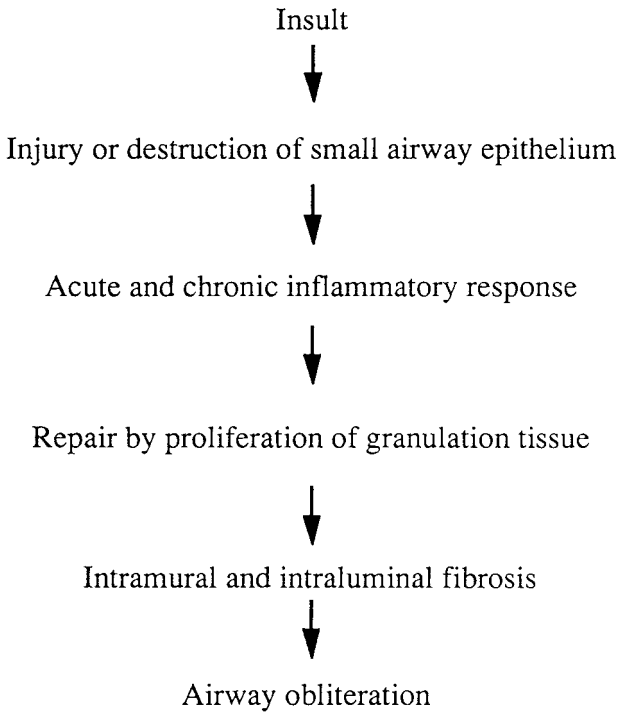


Figure 52-3 Proposed pathogenetic mechanism for airway injury in constrictive bronchiolitis. (See text for details.)

and pattern of breathing, solubility and biologic reactivity of the agent, and biologic susceptibility of the individual.

Nitrogen dioxide (NO_2) and nitrogen tetroxide are responsible for the injury. NO_2 is relatively insoluble. After inhalation, the gas reaches the periphery of the lung, where it combines with water to form nitric and nitrous acids and nitric oxide, which are powerful oxidants capable of causing severe tissue injury. Unlike highly water-soluble gases, such as chlorine, ammonia, and sulfur dioxide, NO_2 is less irritating to the mucous membranes of the nasal and upper airways. The gas produces a yellow to brown haze and an acrid, ammonia-like odor that is irritating.

Clinical Findings

Clinical manifestations of exposure to NO_2 depend on the concentration of the inhaled gas and the duration of exposure. Three clinical patterns or phases may follow exposure. All phases may not appear in an individual patient. Progression to death may be an outcome at any stage.

Acute Phase

Acutely, during milder exposures, people may develop upper-airway and visual disturbances, cough, dyspnea, fatigue, cyanosis, vomiting, hemoptysis, hypoxemia, vertigo, somnolence, headache, emotional difficulties, and loss of consciousness. These findings usually resolve within hours, but they may persist for several weeks; complete recovery without obvious sequelae is usually observed.

At higher concentrations of exposure, pulmonary edema (so-called, "chemical pneumonitis") is a frequent

Table 52-3

Toxic Exposures Associated with Bronchiolitis, with or without Obliterans

- Nitrogen dioxide ("nitrous fume")*
  - Spillage of nitric acid (component of jet and missile fuels)
  - Metal pickling
  - Silo gas
  - Chemical manufacturing (explosives, dyes, lacquers, celluloid)
  - Detonation of explosives
  - Electric arc or acetylene gas welding
  - Contamination of anesthetic gases (nitrous oxide gas cylinder)
  - Nitrocellulose combustion
  - Tobacco smoke
  - Fire smoke (firemen, astronauts, others exposed to burning materials)*,†
- Sulfur dioxide†
  - Burning of sulfur-containing fossil fuels
  - Bleaching of wool, straw, wood pulp
  - Sugar refining, fruit preserving
  - Fungicides
  - Refrigerants
  - Ore smelting
  - Acid production
- Ammonia†
  - Fertilizer and explosives, production, refrigeration
- Chlorine‡
  - Bleaching, disinfectant and plastic making
- Phosgene*
  - Chemical industry, dye and insecticide manufacturing
- Chloropicrin
- Trichlorethylene
- Ozone
  - Arc welding and air, sewage, and water treatment
- Cadmium oxide
  - Ore smelting, alloying, and welding
- Methyl sulfate
- Hydrogen sulfide
  - Natural gas retrieval, paper pulp, sewage treatment, tannery work
- Hydrogen fluoride
  - Etching, petroleum industry, silk working
- Talcum powder (hydrous magnesium silicate)
- Stearate of zinc powder
- Oxygen toxicity
- Asbestos (chrysotile and amphibole)
- Iron oxide§
- Aluminum oxide§
- Silica§
- Sheet silicates (talc, mica, etc.)§

(*Continued*)

Table 52-3

Toxic Exposures Associated with Bronchiolitis, with or without Obliterans

Coal[§]
Activated charcoal
Talc
Free-base cocaine*
Chemical weapons (mustard gas and the nerve gases, sarin, VX, and tabun)[†]

* *These agents have been associated with development of bronchiolitis obliterans (intraluminal polyps).*
† *These agents have been associated with development of constrictive bronchiolitis.*
‡ *These agents have been associated with development of histological focal bronchiolitis without significant clinical disease.*
§ *These agents have been associated with development of respiratory bronchiolitis.*

complication in the early stages. Patients may be asymptomatic at the time of exposure, only to later develop (in 3 to 30 h) the clinical picture of severe acute respiratory distress syndrome. During this acute phase, patients who develop pulmonary edema and acute respiratory distress syndrome have significant pulmonary dysfunction. Hypoxemia is secondary to ventilation-perfusion mismatching as a result of altered airway dynamics and interstitial and alveolar edema, impaired diffusing capacity, and methemoglobinemia that occurs when nitrate ions react with hemoglobin. Severe metabolic acidosis occurs because of the dissolution of NO_2 in body fluids, resulting in formation of nitrous and nitric acid, as well as the lactic acidosis resulting from tissue hypoxia. Systemic hypertension may be present. Recovery without long-term sequelae is usual, but death may occur at this stage.

The radiographic manifestations during this stage include pulmonary edema (i.e., alveolar filling). In survivors, these changes clear rapidly. Physiological studies reveal the simultaneous occurrence of restrictive and obstructive ventilatory defects; the former is manifest as a shift in the static pressure-volume curve downward and to the right. These abnormalities gradually resolve in survivors. Histopathological findings, as determined from autopsy studies, include marked intra-alveolar edema and exudation, as well as thickening of the alveolar walls with lymphocytic cellular infiltrates.

Subacute Phase

In patients who progress to the second phase, physiological disturbances include hypoxemia at rest or with exercise and associated restrictive or obstructive pulmonary function abnormalities. The radiographic pattern in this late stage may be variable. A normal chest film may be seen; however, a miliary, or discretely nodular, pattern is thought to be characteristic of bronchiolitis obliterans. Occasionally, only pulmonary hyperinflation is seen, usually accompanied by a progressive and irreversible obstructive ventilatory defect noted on lung function testing.

Chronic Phase

After recovery from the acute illness, or in patients with no symptoms following exposure, recurrence or new onset of clinical illness may be seen 2 to 6 weeks later. This phase is characterized by the progressive onset of cough and dyspnea. These patients may be identified in an early, asymptomatic stage from the appearance of mild hypoxemia. Tachypnea is present, and crackles are usually heard. Widespread proliferative bronchiolitis with marked intraluminal fibrous tissue proliferation arising in the bronchiolar wall (without organizing pneumonia) is found, especially in those with preceding pulmonary edema; however, these findings may occur as the initial manifestation of previous exposure.

Management

The treatment of patients exposed to NO_2 or other toxic gases or fumes should include observation in the hospital for 48 h, followed by weekly or biweekly evaluations for 6 to 8 weeks. When dysfunction occurs, treatment with corticosteroids should be started immediately. Corticosteroid therapy has been demonstrated to be useful in the management of both the acute phase (pulmonary edema) and the late phase (bronchiolitis obliterans). Corticosteroids should be continued for a minimum of 8 weeks, since relapses have been reported with the earlier cessation of therapy. Bronchodilators are occasionally helpful, but antibiotics should be used only when clinically indicated; they should be directed at a specific pathogen. If methemoglobinemia is present, methylene blue should be administered at a dose of 2 mg/kg intravenously, followed by doses titrated according to the concentration of methemoglobin in the blood. For patients in whom this diagnosis is suspected, and for whom open lung biopsy or general anesthesia is planned, some have suggested that nitrous oxide not be used as an anesthetic because of concern that it might lead to disease progression.

Prognosis

In general, the prognosis for survivors of toxic gas or fume inhalation (fewer than one-third die acutely) is good. Some authors have suggested that lasting pulmonary disability is uncommon in silo filler's disease; others have identified a wide variety of functional derangements. What functional abnormalities result from chronic, low-level exposure to NO_2 are not clear. Education is key in preventing this disease, since simple measures to reduce the NO_2 levels and use of approved respiratory protection equipment will eliminate the risk of injury.

Other Irritant Gases

A number of irritant gases have occasionally been associated with bronchiolitis, with or without obliterans (Table 52-3). Since lung biopsies have not been performed in all cases, it is not always clear that the pulmonary injury associated with these inhalation exposures is only bronchiolitis obliterans. However, sulfur dioxide, chlorine gas, "smoke inhalation" or inhalation burns, hydrogen chloride, ammonia, phosgene,

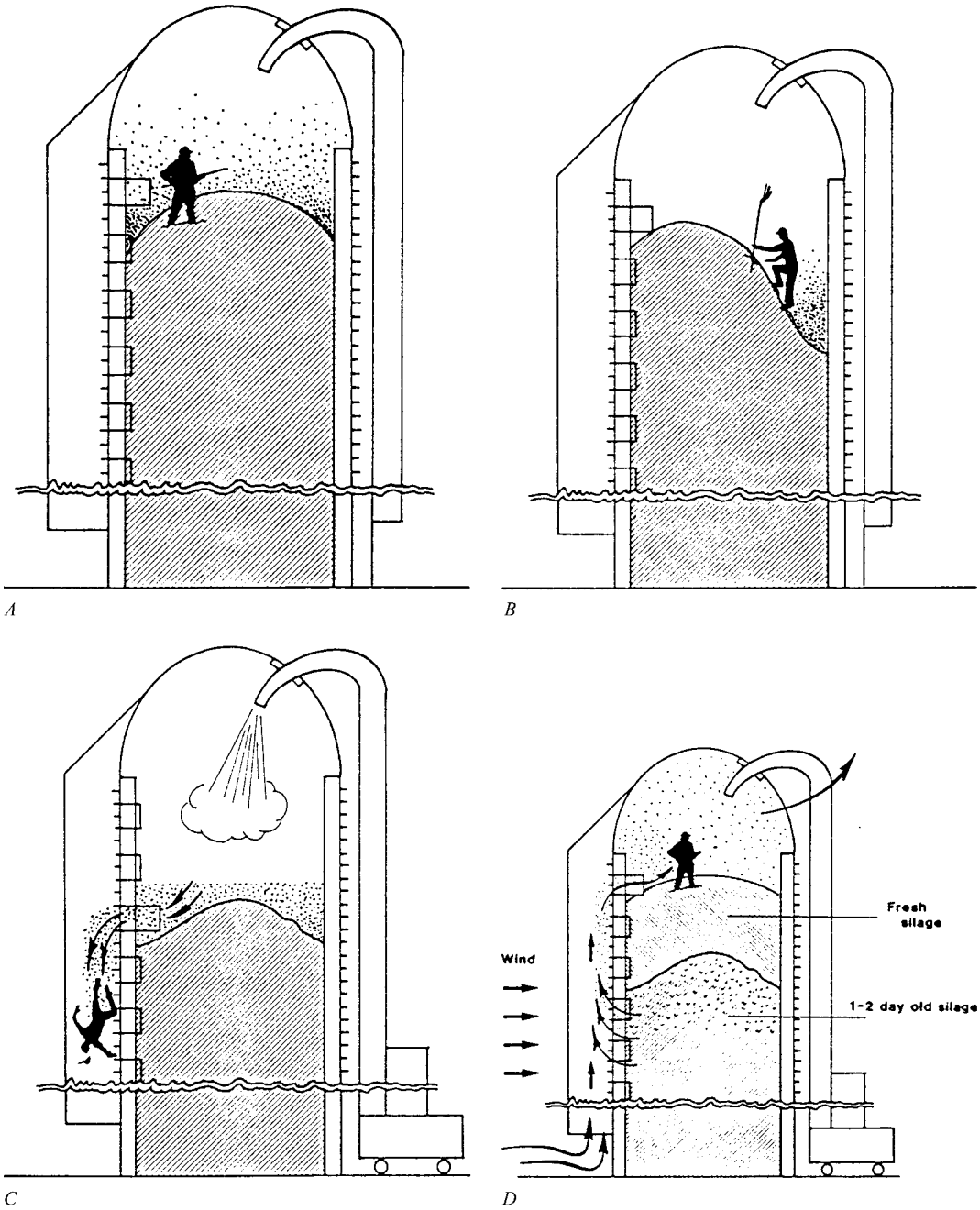


Figure 52-4 Exposure to nitrogen oxides and silo filler's disease. The upright concrete stave silo is the most common type of silo. Chopped silage is blown through the filling pipe (on right of silo) to the top of the silo and dispersed evenly. *A*. Exposure usually occurs 1 to 4 days after silo filling, when the farmer enters to level the silage, to prepare for unloading, or to spread a plastic sheet over the top. *B*. Silo gas is heavier than air and accumulates in low places within the silo. Descent into these areas may be fatal. *C*. Opening a door just above the silage may result in concentrated exposure, causing rapid loss of consciousness and a fall down the silo chute. *D*.Entry immediately after completion of silo filling may not be safe, since gas from 1- to 2-day-old silage may leak out through the silo doors and be drawn into the working spaces by a chimney-like updraft. *(Based on data from Douglas WW, Colby TV: Fume-related bronchiolitis obliterans, in Epler GR (ed)*, Diseases of the Bronchioles. *New York: Raven Press, 1994, pp 187–213, with permission.)*

and chloropicrin produce a disease with clinical, physiological, and radiographic manifestations similar to those described for NO_2 exposure. Respiratory bronchiolitis after exposure to photochemical air pollutants, ozone, and NO_2, has been reviewed.

Mineral Dusts

Pathological changes in the small airways (respiratory bronchiolitis) may be found secondary to exposure to inorganic mineral dusts, including asbestos, silica, iron oxide, aluminum oxide, several different sheet silicates, and coal.

Clinical relevance of the changes remains to be better defined. Nonetheless, development of an obstructive, rather than restrictive, pattern is increasingly recognized in subjects with inorganic mineral dust exposure.

Pathologically, these lesions are characterized by marked abnormalities in the small airways, particularly in the membranous and respiratory bronchioles. The principal finding is fibrosis in small-airway walls and, occasionally, in alveolar ducts. The lesions appear to extend down into the airway and often are accompanied by pigment deposition. Abnormalities are seen in nonsmokers, but occur most commonly in heavily exposed workers who are cigarette smokers. The pathogenesis is unclear, but a synergistic role for cigarette smoking appears likely. The injury appears to result from the inflammatory response that follows deposition of mineral particles or fibers in the walls of the small airways.

Organic Dusts

Numerous agents are associated with the development of hypersensitivity pneumonitis, a topic discussed elsewhere (see Chapter 69). Interstitial pneumonitis is seen in virtually 100 percent, and granulomas in approximately 70 percent, of patients with hypersensitivity pneumonitis; unappreciated is that bronchiolar lesions are also seen in essentially all cases. The bronchioles contain granulomas within the walls or lumina—or show tufts of granulation tissue, as seen in bronchiolitis obliterans. A reversible restrictive process is the most common physiological abnormality in hypersensitivity pneumonitis. However, small-airway dysfunction may be present in patients with early hypersensitivity pneumonitis. As the disease progresses, either obstructive or restrictive physiology may arise, depending on the predominant histopathological process present.

Volatile Flavoring Agents

A recent report described development of severe, fixed obstructive lung disease in nine former employees of a microwave popcorn factory. Four of the patients were on lung transplant lists. All had a respiratory illness resembling bronchiolitis obliterans, with symptoms of cough and dyspnea on exertion. Their median duration of employment was 2 years (range, 1 to 17 years). Each of the workers first became symptomatic between 1993 and 2000, while employed by the factory, after a median of 1.5 years of employment (range, 5 months to 9 years). Cough, shortness of breath, and wheezing were the presenting symptoms. Most patients identified had normal results on pre-placement spirometry. These values subsequently fell precipitously, with development of moderate to severe, nonreversible airway obstruction. HRCT scans showed evidence of air trapping.

The presumed inciting exposure was to a mixture of soybean oil, salt, flavorings, and coloring agents that was mixed in a large heated tank. This process produced visible dust, aerosols, and vapors with a strong buttery odor. More than 100 volatile organic compounds were identified in the air samples from the mixing room area of the plant. Diacetyl (2, 3)-butanedione, a ketone with butter-flavor characteristics, was the predominant compound isolated. The highest incidence of illness occurred in workers who worked nearest the mixing tank and who were more likely to have inhaled mixing tank substances.

Preliminary animal studies at the Division of Respiratory Disease Studies, National Institute for Occupational Safety and Health (NIOSH), suggested severe damage to airway epithelium after inhalation exposure to high air concentrations of butter-flavoring vapors (diacetyl) used at one of the worksites. After removal from exposure, patients did not recover, but they did appear to have no further loss of lung function. However, NIOSH has been investigating whether similar cases have occurred in workers at other microwave popcorn factories or who work with food-flavoring agents that might be heated and aerosolized. The general population using microwave popcorn products does not appear to be at any risk.

INFECTIOUS CAUSES OF BRONCHIOLITIS

Infection is the most common cause of acute bronchiolitis, although infectious causes are more frequent in children than adults. The usual agents include viruses and Mycoplasma pneumoniae—organisms that have a propensity to infect and injure epithelial cells of the respiratory tract. Constrictive bronchiolitis is the most common histopathological pattern observed after bronchiolar infection.

Infectious Bronchiolitis in Children

Acute bronchiolitis is a common illness in infants and young children, occurring primarily as a result of a viral infection. Pathogens include respiratory syncytial virus (approximately 34 percent of cases), parainfluenza virus types 1, 2, and 3 (approximately 30 percent of cases), adenoviruses (approximately 7 percent of cases), influenza A and B, and *Mycoplasma pneumoniae* (approximately 11 percent of cases) (Table 52-1). Males are more commonly affected with respiratory syncytial virus than are females (1.5 to 1.8:1 male-to-female ratio).

Reviews of bronchiolitis in children have been published previously. Infectious bronchiolitis obliterans is rarely seen in persons older than 2 years. Adenovirus types 3, 7, and 21 are the most common etiological agents. Other causes are measles, whooping cough due to *Bordetella pertussis*, *M. pneumoniae*, and influenza A. Severe infectious bronchiolitis obliterans leading to hospitalization and death is rare.

Clinical Findings

The usual presentation is an acute viral-like illness with mild coryza and sneezing occurring during the winter months. Several days later, cough, dyspnea, tachypnea, tachycardia, fever, chest wall retractions, sibilant and sonorous crackles,

expiratory wheezing, and, in severe cases, cyanosis, develop. Prostration and respiratory failure are unusual.

Radiographic Findings

The radiographic pattern of childhood bronchiolitis is variable. The chest radiograph may be normal or show hyperinflation with increased bronchial markings. Subsegmental consolidation and collapse may be seen. A pattern similar to that of diffuse interstitial pneumonia, often in association with hyperinflation, is seen. Some patients demonstrate a diffuse nodular or reticulonodular pattern, whereas others may show patchy alveolar or ground glass opacities. Those with a nodular pattern frequently have "pure" bronchiolitis obliterans on lung biopsy; those with a reticulonodular pattern are likely to have more interstitial inflammation and scarring. The role of HRCT has not been adequately defined, but it is thought to be important in ruling out other diagnoses, especially bronchiectasis. Ventilation-perfusion lung scans may be very helpful, since a markedly abnormal pattern of patchy, matched ventilation and perfusion defects is often seen, even when the plain chest film is unremarkable. Bronchography may reveal saccular bronchiectasis and ballooning of the airways at the blind end when the airways are distended by positive pressure; passage of contrast medium into the alveoli does not occur. Bronchography has largely been abandoned with the advent of HRCT.

Physiological Findings

Tests of lung function may be normal. However, obstructive changes with air trapping can often be documented. Pulmonary function testing has not been well studied in infants with this disease. Resting hypoxemia is frequently present.

Histopathological Findings

In this setting, open lung biopsy is the gold standard for the diagnosis of bronchiolitis obliterans. The earliest change is necrosis of the respiratory epithelium, followed by epithelial proliferation. Dense plugs of alveolar debris and strands of fibrin are seen within small bronchi and bronchioles, causing partial or complete obstruction. These findings may develop as soon as 8 days after the onset of the illness. A lymphocytic infiltrate, including collections with germinal centers, may be seen in the airway wall. Severe and widespread destruction of the respiratory epithelium may cause denudation and a pronounced inflammatory response that involves the adjacent peribronchial space and alveolar walls. Depending on the stage at which the biopsy is obtained, findings consistent with proliferative bronchiolitis ("early"), constrictive bronchiolitis ("late"), or both may be seen. The pathogenetic mechanisms in development of obliterative bronchiolitis secondary to infections and the reason for the predilection in infants are unknown.

Treatment

Treatment is symptomatic, including administration of supplemental oxygen and adequate hydration. Bronchodilators, antibiotics, antiviral agents, and corticosteroids are frequently used in management, but few controlled clinical trials on their efficacy have been performed. Mechanical ventilation is rarely required; it may be necessary if progressive respiratory failure ensues. Lung transplantation has been performed in severe cases.

Prognosis

Recovery is usual and occurs in days or weeks. Whether or not bronchiolitis in infancy predisposes to asthma or chronic obstructive pulmonary disease (COPD) in later life remains unproved.

Swyer-James (MacLeod) syndrome—unilateral hyperlucent lung—is a long-term complication of bronchiolitis in children, especially after adenoviral infection occurring in infancy. The affected child may be asymptomatic, but more often he or she has recurrent pulmonary infections and eventually develops bronchiectasis. Dyspnea on exertion, hemoptysis, and chronic productive cough are seen. Patients may have localized, unilateral, or bilateral involvement. The chest radiograph demonstrates lobar or unilateral hyperlucent lung; normal or reduced volume of the affected lung is noted on full inspiration. Severe airway obstruction occurs during expiration. The affected lung has a diminished pulmonary vascular bed, decreased pulmonary blood flow, and reduced peripheral vascular markings. Bronchography demonstrates diffuse bronchiectasis with absence of filling of the terminal bronchioles ("pruned tree" appearance). HRCT is the procedure of choice for identifying the characteristic changes in Swyer-James syndrome.

The final size of the affected lung in Swyer-James syndrome relates to the age of the patient at the time bronchiolitis occurs. If it occurs early in life, the lung fails to grow normally and appears smaller than the opposite lung. If the bronchiolitis occurs later in childhood, the lung may be of normal size. Pulmonary function tests reveal airflow obstruction and a reduced total lung capacity in cases where concomitant pulmonary fibrosis exists. The syndrome has been reported with a number of etiological agents and must be distinguished from congenital absence of the pulmonary artery, pulmonary artery occlusion, partial obstruction of a lobar or main bronchus, and congenital lobar emphysema. CT and pulmonary angiography are helpful in distinguishing among these conditions.

Infectious Bronchiolitis in Adults

Acute bronchiolitis in older children and young adults has been associated primarily with *M. pneumoniae*; however, a number of other viruses (e.g., respiratory syncytial virus, especially in the elderly) and bacterial agents have been identified (Table 52-1). Only sporadic cases of bronchiolitis obliterans secondary to infections have been reported in adults (Fig. 52-5).

The clinical presentation of infectious bronchiolitis in adults is ill defined; no systematic study has been reported. Most patients have a history of an upper respiratory tract

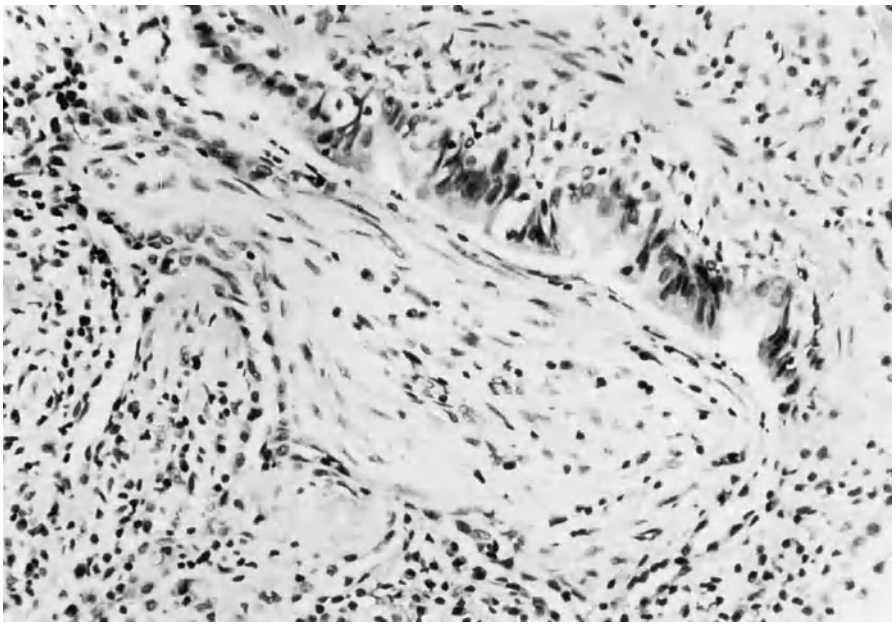


Figure 52-5 Acute infectious bronchiolitis. Photomicrograph showing acute bronchiolitis in a patient with adenovirus infection. An intraluminal infiltrate associated with epithelial necrosis (lower left) is present. In addition, a peribronchiolar infiltrate of acute and chronic inflammatory cells is demonstrated. (H&E stain, ×156.)

illness that precedes the onset of dyspnea with exertion, cough, tachypnea, fever, and wheezing. Measles, varicella-zoster, and pertussis have been reported to cause bronchiolitis obliterans in adults. A number of adults have developed an acute or subacute diffuse ventilatory obstruction that has occasionally been fatal.

IDIOPATHIC FORMS OF BRONCHIOLITIS

Several clinicopathological syndromes associated with prominent bronchiolar impairment have been reported recently. Although no specific origins have been identified, the constellation of findings in reported cases suggests that these syndromes are unique and must be distinguished from more common problems, including COPD, pneumonia, and pulmonary fibrosis. In the discussion below, three syndromes are highlighted: cryptogenic adult bronchiolitis, respiratory bronchiolitis-associated interstitial lung disease (RB-ILD), and cryptogenic-organizing pneumonia (COP) or idiopathic BOOP.

Cryptogenic ''Adult'' Bronchiolitis

Cryptogenic adult bronchiolitis is a rare clinicopathological syndrome that must be distinguished from asthma, chronic bronchitis, emphysema, cystic fibrosis, bronchiectasis, and α_1-antitrypsin deficiency. Few cases have been reported, and it is not entirely clear that all of those reported are the same entity. For example, many patients have had a significant cigarette smoking history and may have smoker's bronchiolitis. Despite these concerns, the constellation of findings in reported cases is unique and suggests that adult bronchiolitis represents a distinct, definable clinicopathological entity that is a diagnostic challenge to clinicians and pathologists.

The pathogenesis of cryptogenic adult bronchiolitis is unknown. The true incidence of the disease is also unknown, but has been estimated to be approximately 4 percent of all causes of obstructive lung diseases. The disorder is diagnosed largely by exclusion and requires a high index of suspicion, along with an awareness of its unique clinical features.

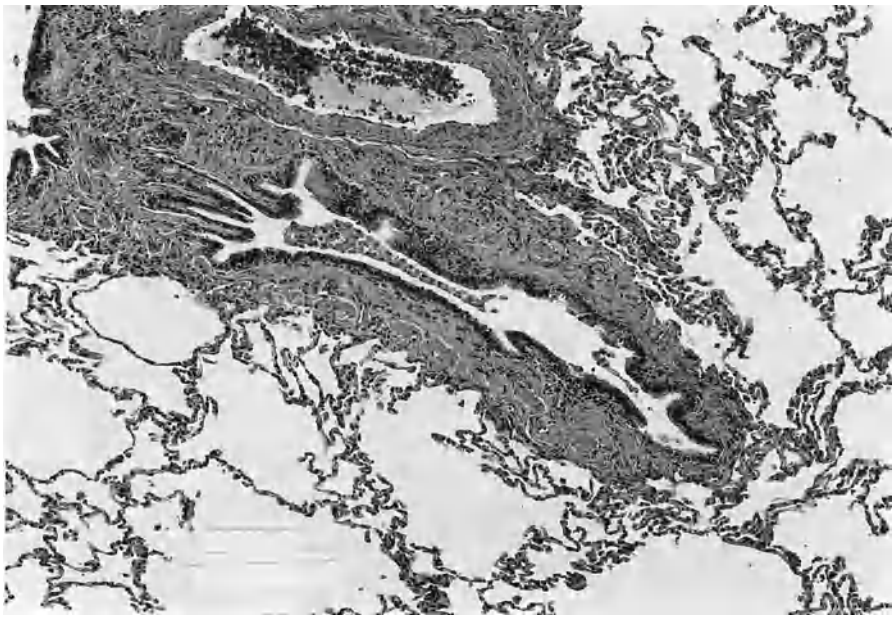
Clinical Findings

Most patients are middle-aged women who have a nonproductive cough, shortness of breath, or other nonspecific chest complaints, usually of relatively short duration (6 to 24 months). Most are identified because of an accelerated, severe obstructive respiratory disorder that is clinically distinct from the more commonly encountered obstructive disorders. A history of cigarette smoking, chronic sputum production, frequent chest infections, wheezing, known connective-tissue disorder, and immunoglobulin deficiency are absent. No association with inhalation injury or viral infection has been identified. Physical findings are unremarkable, although wheezing or crackles may be heard.

Diagnostic Studies

The chest radiographic findings are normal or nonspecific. Increased bronchial wall thickening may be seen. Hyperinflation (without marked flattening or hyperlucent areas) may be the only abnormality noted. HRCT scanning is normal or shows airway dilatation.

Pulmonary function testing yields a variety of results. Most patients have increased lung volumes and airflow limitation. A few patients who have had pressure-volume curves performed show an upward shift and a normal slope, consistent with airflow limitation. The diffusing capacity is reduced, and resting hypoxemia may be present. Exercise testing shows gas exchange abnormalities associated with an abnormal [dead space/tidal volume ratio (V_D/V_T)].



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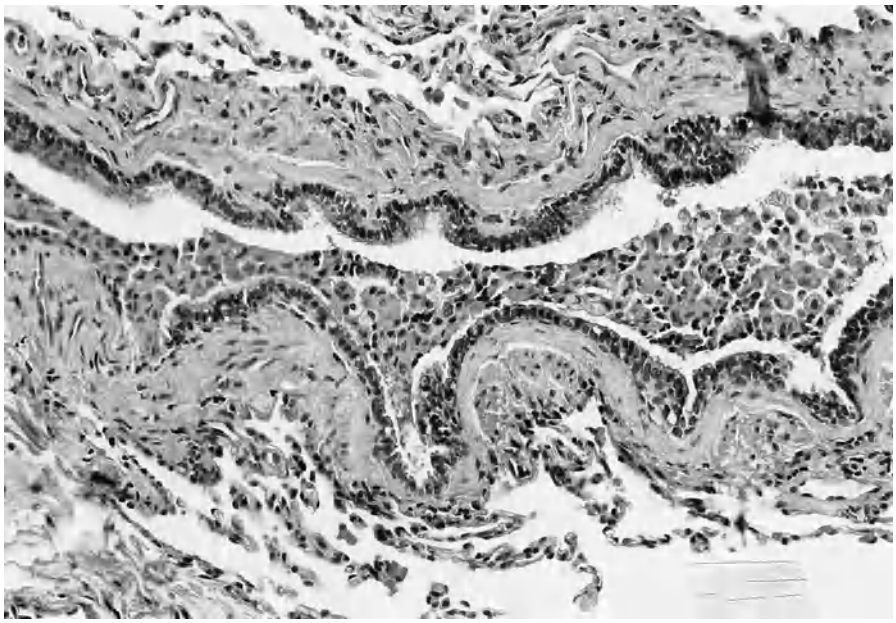


B

Figure 52-6 Cryptogenic constrictive bronchiolitis. *A*. Constrictive bronchiolitis with bronchiolar smooth-muscle hyperplasia and mild submucosal and adventitial bronchiolar scarring. Alveolar parenchymal architecture is preserved; no significant interstitial inflammation or fibrosis is present (H&E stain). *B*. Histiocytes in the lumen of some bronchioles. While intraluminal histocytes are common in smokers, their presence in nonsmokers suggests airway pathology analogous to mucus stasis (H&E stain).

Bronchoalveolar lavage (BAL) studies demonstrate marked neutrophilia associated with an increase in the specific neutrophil products, collagenase, and myeloperoxidase. Most patients have a neutrophil level over 25 percent (normal for nonsmokers is under 4 percent); some have levels exceeding 90 percent.

Pathological Findings

Lung biopsies reveal a cellular constrictive bronchiolitis, often quite subtle, with both acute and chronic inflammatory changes, primarily in the membranous bronchioles (Fig. 52-6). Few cases examined have shown airway obliteration and mucus stasis. The pulmonary parenchyma is normal or shows only mild hyperinflation. Mild focal interstitial fibrosis has been identified in a few subjects. No vascular lesions have been described.

Treatment

Steroids may be of benefit in many patients with adult bronchiolitis. Early treatment may be important, since irreversible structural changes and persistent, progressive breathlessness may develop, often with recurrent bouts of respiratory infection. BAL neutrophilia returns toward normal in patients who respond to treatment. Thus, recognition of these cases and distinction from other small-airway disorders (e.g., RB-ILD, asthma, chronic bronchitis, emphysema, bronchiolitis associated with connective-tissue disease, and diffuse panbronchiolitis) are possible and important.

Respiratory Bronchiolitis-Associated Interstitial Lung Disease

Bronchiolitis has been demonstrated in patients exposed to cigarette smoke. The inflammation and fibrosis lead to distortion and narrowing of small airways. Because respiratory bronchiolitis was initially found at autopsy in young cigarette smokers without known disease, the lesions were considered to be clinically insignificant. Later, it was hypothesized that the lesions in respiratory bronchioles could explain the mild abnormalities in lung function seen in cigarette smokers—so-called small-airway disease (i.e., elevated airflow resistance, airway hyperresponsiveness, and subsequent airflow limitation). More recently, RB-ILD has been recognized as a distinct clinical syndrome found in current or previous cigarette smokers. This disease may be confused with chronic diffuse interstitial fibrosis, desquamating interstitial pneumonitis (DIP), and eosinophilic granuloma of the lung (pulmonary histiocytosis X). The last two disorders also develop almost exclusively in cigarette smokers.

Clinical Findings

The male-to-female ratio is 1.6:1. Most are current or former smokers in the fourth or fifth decade of life. The average exposure is more than 30 pack-years of cigarette smoking. The incidence of RB-ILD is unknown. Patients commonly present with dyspnea (70 percent) and cough (58 percent). Coarse crackles are often heard (33 percent) and occur throughout inspiration; sometimes they continue into expiration. Finger clubbing has not been reported. Routine laboratory studies are usually normal.

Diffuse, fine reticulonodular interstitial infiltrates are found on the chest radiograph in most patients (80 percent), usually with normal lung volumes. Bronchial wall thickening, prominence of peribronchovascular interstitium, small regular and irregular opacities, and small peripheral ring shadows are distinctive features of respiratory bronchiolitis. Diffuse or patchy ground glass opacities or fine nodules are found on HRCT (Fig. 52-7). Mild emphysema, atelectasis, or linear and reticular interstitial abnormalities are also detected. In a study correlating pathological findings with CT abnormalities, areas of ground glass attenuation were related to three main histological features: (1) accumulation of pigmented macrophages and mucus in alveolar spaces, associated with mild interstitial inflammation or fibrosis; (2) thickening of alveolar walls by inflammatory cells; and (3) presence of organizing alveolitis. The parenchymal micronodules corresponded to bronchiolectases with peribronchiolar fibrosis.

Pulmonary function may be normal; however, a mixed obstructive-restrictive pattern is most commonly found. Normal total lung capacity (TLC) and functional residual capacity (FRC) are commonly present, but the residual volume (RV) is usually increased. A normal or slightly reduced diffusing capacity (D_{LCO}) is frequently present. Hypoxemia may be present at rest or with exercise.

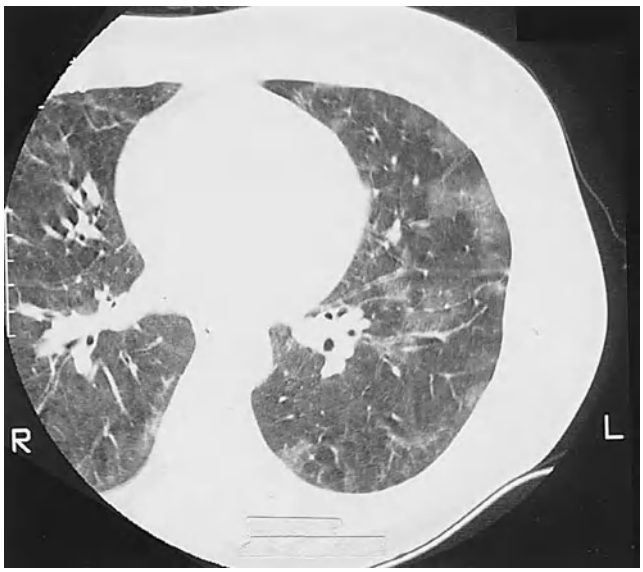


Figure 52-7 Respiratory bronchiolitis-associated interstitial lung disease. High-resolution computed tomography (HRCT) in a 35-year-old woman with a heavy smoking history and progressive dyspnea with exertion. Extensive ground glass opacities are demonstrated. The plain chest film was normal. The diagnosis was confirmed by open lung biopsy. Symptoms improved after smoking cessation.

Histopathological Findings

An inflammatory process in the membranous and respiratory bronchioles is the characteristic histopathological feature of RB-ILD. Tan-brown pigmented macrophages within respiratory bronchioles, neighboring alveolar ducts, and alveoli dominate the pathological findings (a "DIP-like" reaction) (Fig. 52-8). These macrophages stain strongly with diastase-predigested periodic acid–Schiff. The bronchiole may be ectatic with mucus stasis; the walls are mildly thickened. Frequently evidence of extension of the bronchiolar metaplastic epithelium into the immediately surrounding alveoli is observed. Most of the interstitium is usually normal; alternatively, it may demonstrate mild hyperinflation. The findings are sometimes so subtle as to be missed during routine evaluation. On occasion, examination of multiple-step sections may be required. Many cases of respiratory bronchiolitis have actually been misclassified as DIP. Similar pathological findings have been demonstrated in other conditions.

Treatment

The clinical course and prognosis of RB-ILD are unknown. Most studies suggest a favorable response to corticosteroids, with documented improvement in the chest radiograph and in lung function. Since smoking appears to play a role in pathogenesis, smoking cessation is considered to be important in management.

Cryptogenic-Organizing Pneumonia

Cryptogenic-organizing pneumonia (COP), or idiopathic BOOP, is a distinct clinical entity that was described in 1901

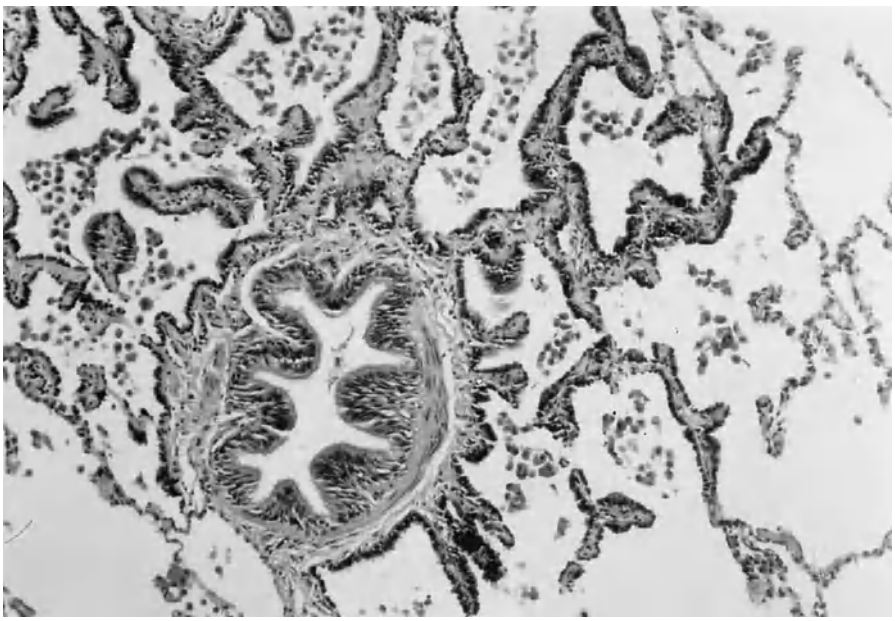


Figure 52-8 Respiratory bronchiolitis-associated interstitial lung disease (RB-ILD). Photomicrograph shows inflammatory process in the membranous and respiratory bronchioles. Bronchiole wall is thickened, and bronchiolar metaplastic epithelium extends into immediately surrounding alveoli. Macrophages are present within the peribronchiolar alveolar spaces (desquamating interstitial pneumonitis ["DIP"]-like reaction) (H&E stain).

by Lange. However, recognition of COP increased in the early 1980s, as several investigators highlighted the characteristic clinical course and suggested that COP is a distinct entity with features of pneumonia, rather than a primary airway disorder. The true incidence and prevalence of COP are unknown; a prevalence of 6 to 7 per 100,000 admissions has been reported.

Clinical Findings

Disease onset is usually in the fifth or sixth decade, with a mean age of 58 years; men and women are affected equally. Almost three-fourths of patients have symptoms for less than 2 months; few have symptoms for more than 6 months before diagnosis. Cigarette smoking is not a precipitating factor, since approximately 50 percent of subjects are never-smokers, 25 percent are ex-smokers, and only 25 percent are current smokers.

The clinical presentation may mimic that of community-acquired pneumonia. A persistent and usually nonproductive cough is the most common presenting symptom (72 percent of subjects). Frequently, patients experience dyspnea with exertion (66 percent). Disease onset is usually described as a flulike illness, with fever (51 percent), malaise (48 percent), fatigue, and cough. Weight loss of greater than 10 lb is a common complaint (57 percent). Physical examination reveals inspiratory crackles (74 percent); wheezing is rare and is usually present in conjunction with crackles. Clubbing is rare (fewer than 5 percent of patients). Twenty-eight percent of patients in one series had normal pulmonary function.

Laboratory Findings

Routine laboratory studies are nonspecific. A leukocytosis is seen in approximately half of patients. The initial erythrocyte sedimentation rate is elevated, frequently reaching or exceeding 100 mm/h; a positive C-reactive protein is observed in 70 to 80 percent of patients. Autoantibodies are usually negative or only slightly positive.

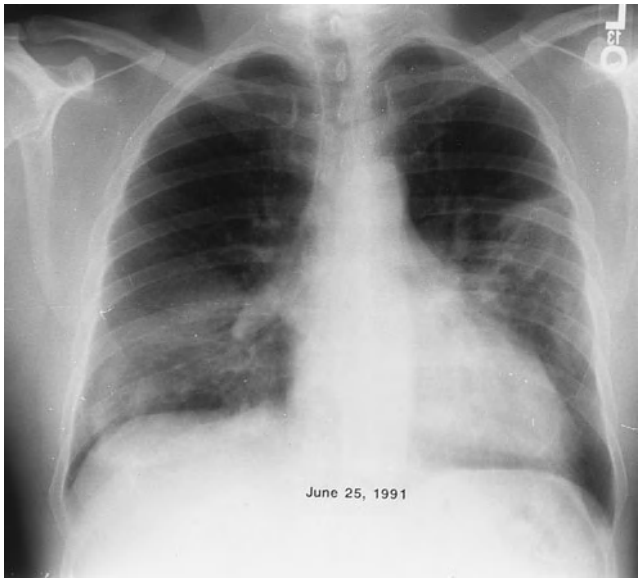
Chest Imaging Studies

The radiographic manifestations of COP are quite distinctive: bilateral, diffuse alveolar opacities in the presence of normal lung volume (Fig. 52-9). This pattern was present in 79 percent of reported subjects for whom the radiographic appearance was detailed. A peripheral distribution of opacities, very similar to that thought to be "virtually pathognomic" for chronic eosinophilic pneumonia, is also seen. The alveolar opacities may be unilateral. In addition, recurrent and migratory pulmonary opacities are common. Fifty percent of Japanese patients with idiopathic BOOP demonstrated migration of radiographic shadows. Irregular linear or nodular interstitial infiltrates were rarely present as the sole radiographic manifestation. Honeycombing is rarely seen at presentation and is discussed only as a late manifestation in the few patients who have progressive disease. Other radiographic abnormalities—such as pleural effusion, pleural thickening, hyperinflation, and lung cavities—seldom occur. Severity of the radiographic abnormalities correlates with the extent of histological involvement of the respiratory bronchioles and alveolar ducts, but not of the larger terminal bronchioles.

CT of the lung reveals patchy airspace consolidation, ground glass opacities, small nodular opacities, and bronchial wall thickening and dilation. These patchy opacities occur more frequently in the periphery of the lung and are often in the lower lung zones (Fig. 52-9). CT may reveal much more extensive disease than is expected from review of the plain chest radiograph.

Physiological Findings

Pulmonary function is usually impaired; a restrictive defect is the most common finding. An obstructive defect (ratio of forced expiratory volume in 1 second to the forced vital



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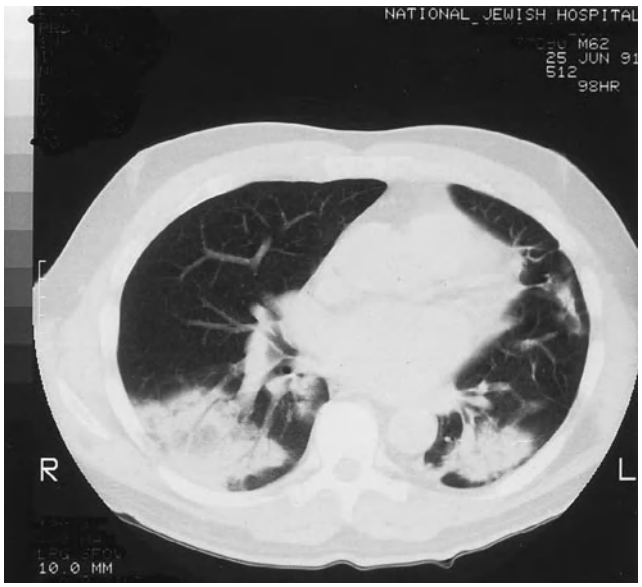

B

Figure 52-9 Cryptogenic-organizing pneumonitis (COP) in a 62-year-old man with a 1-month history of dyspnea with exertion, fatigue, and weight loss. *A*. Posteroanterior radiograph reveals bilateral patchy alveolar opacities. *B*. Computed tomography shows bilateral patchy airspace consolidation in the right and left lower lobes. Air bronchograms are present on the right. Corticosteroid therapy resulted in complete resolution.

capacity percent [FEV_1/FVC%] less than 70 percent) is found uncommonly (in fewer than 21 percent of cases) and is seen mostly in patients who are current or former smokers. Lung function is occasionally normal. The pressure-volume curve is shifted downward and to the right, consistent with noncompliant lungs. The maximal transpulmonary pressure and the coefficient of elastic recoil (maximal transpulmonary pressure divided by TLC) are increased. Gas exchange abnormalities are extremely common. The D_{LCO} is reduced in most patients (72 percent). Widening of the resting alveolar arterial oxygen gradient (greater than 20 mmHg) and exercise-related hypoxemia are common abnormalities (83 percent).

Bronchoalveolar Lavage Cellular Findings

Bronchoalveolar lavage (BAL) studies have been reported in only a few subjects with COP. The percentage of instilled fluid recovered from patients with COP is lower than that from healthy volunteers. However, the total number of cells recovered is greater in patients with COP. The proportion of macrophages is lower, while the proportion of lymphocytes, neutrophils, and eosinophils is higher in COP. Patients with COP tend to have higher lymphocyte counts than those with idiopathic pulmonary fibrosis. Other BAL abnormalities in COP include presence of foamy macrophages and, occasionally, mast cells and plasma cells; decreased ratio of CD4 to CD8 cells; normal percentage of CD57+ cells; increased activated T cells, as reflected in human HLA-DR expression; and, occasionally, interleukin-2 (IL-2) receptor (CD25) expression. The findings are similar to those in hypersensitivity pneumonitis; in hypersensitivity pneumonitis, however, CD25 expression is normal, and CD57+ cells are increased. This "mixed pattern" of increased cellularity is thought to be characteristic of COP, especially when associated with multiple alveolar opacities on the chest radiograph.

Histopathological Findings

The histopathological lesion characteristic of COP is an excessive proliferation of granulation tissue within small airways (i.e., proliferative bronchiolitis) and alveolar ducts, along with chronic inflammation in surrounding alveoli. This organizing pneumonia is the most important basis for the clinical and radiographic manifestations of COP. Several additional key features are notable: (1) the distribution of lesions is usually patchy and peribronchiolar; (2) the lesions are usually located predominantly within the airspace; (3) there is a uniform, recent temporal appearance to the changes in that all the lesions look similar, with an inflamed, edematous-appearing stroma with little collagen deposition; (4) the intraluminal buds of granulation tissue consist of loose, collagen-embedding fibroblasts and myofibroblasts that extend through the pores of Kohn from one alveolus to another, giving rise to the characteristic "butterfly" pattern; (5) the bronchiolar lesions are usually secondary to intraluminal plugs of granulation tissue occurring in association with plugs in the alveolar ducts and alveolar spaces; (6) severe fibrotic changes (honeycombing) are unusual at the time of diagnosis; (7) foamy macrophages are very common in alveolar spaces, presumably secondary to the bronchiolar occlusion; (8) giant cells are rare or absent, and no granuloma or vasculitis is present; and (9) the lung architecture is not severely disrupted.

Diagnosis

The clinical and histopathological features of COP may be present in other disorders, such as bacterial pneumonia, hypersensitivity pneumonitis, chronic eosinophilic pneumonia,

viral infection, drug reactions, and connective-tissue disorders. Thus, the diagnosis of COP depends on both the clinical setting and characteristic pathological features, including the prominent finding of the BOOP pattern in the absence of features suggestive of an underlying process.

An open or thoracoscopic lung biopsy is recommended to confirm the diagnosis. Ample lung tissue must be obtained and carefully reviewed to rule out other diseases, especially idiopathic pulmonary fibrosis, hypersensitivity pneumonitis, chronic eosinophilic pneumonia, and diffuse alveolar damage seen in the acute respiratory distress syndrome.

Transbronchial lung biopsies are generally inadequate in confirming COP and ruling out other disorders. The histopathological features of bronchiolitis obliterans associated with areas of organizing pneumonia can be seen in a number of settings; therefore, small biopsies increase the chance of missing the central diagnosis. Step-sectioning of transbronchial biopsies is useful in identifying the lesions of COP.

The biopsies must be reviewed by an experienced lung pathologist who has been given adequate clinical information to guide the search for specific lesions supporting the diagnosis. Once the characteristic findings of proliferative bronchiolitis are confirmed, the clinician must ensure that a thorough search has been performed to rule out the many other diagnostic considerations. Indeed, the clinicopathological syndrome of COP is a diagnosis of exclusion.

Treatment and Clinical Course

Corticosteroid therapy is the most common treatment. Complete clinical recovery, physiological improvement, and normalization of the chest film are seen in two-thirds of patients. Approximately one-third demonstrate persistent disease.

In general, clinical improvement is rapid, within several days or a few weeks. Occasionally, recovery is quite dramatic. Relapses occur commonly when corticosteroids are withdrawn after 1 to 3 months. Most patients who relapse show improvement when re-treated with corticosteroids. Spontaneous improvement in a few patients appears to occur over 3 to 6 months.

Patients with airspace opacities on the chest radiograph have a much better outcome than those with interstitial opacities. The overall prognosis for COP is much better than for other interstitial lung diseases (e.g., idiopathic pulmonary fibrosis). Rapidly fatal COP is uncommon.

Based on our clinical experience and that of others, high-dose oral corticosteroid therapy should be used to treat COP. Therapy is usually initiated with prednisone in a dose of 1 to 1.5 mg/kg per day (using ideal body weight), not to exceed 100 mg daily. The drug is given as a single oral dose in the morning, and the dose is maintained for 4 to 8 weeks. If, after 5 to 8 weeks, the patient's condition is stable or improved, the dose is gradually tapered to 0.5 to 1 mg/kg per day for the ensuing 4 to 6 weeks. High-dose parenteral corticosteroid therapy (e.g., methylprednisolone, 125 to 250 mg intravenously every 6 h for 3 to 5 days) has been recommended as initial treatment for patients with rapidly progressive COP.

For the patient in stable or improved condition, the prednisone is gradually tapered off after 3 to 6 months of therapy. A chest radiograph and pulmonary function tests should probably be performed every 6 to 8 weeks during the first year, and therapy should be reinstituted aggressively with any sign of recurrence. Although therapy with corticosteroids is usually well tolerated, side effects are common; some patients develop side effects more readily than others. If the patient's condition deteriorates despite corticosteroid therapy, a cytotoxic agent should be considered while low-dose (0.25 mg/kg per day) therapy with prednisone is continued. Cyclophosphamide and azathioprine have both been used successfully, although the optimal dose in COP is unknown.

Localized Bronchiolitis Obliterans-Organizing Pneumonia

Occasionally, localized areas of BOOP are found at open lung biopsy, usually performed to rule out carcinoma. These lesions present radiographically as irregular nodules or irregular sublobar areas of airspace consolidation. Surgical resection usually resolves this problem. The origin of the lesions is unknown and may be secondary to resolving pneumonia.

CONNECTIVE-TISSUE DISEASES

Pulmonary impairment is common in many of the connective-tissue disorders. In most cases, the pulmonary dysfunction is related to alveolar, rather than airway, pathology. Bronchiolitis appears to occur infrequently and varies in its manifestations among the connective-tissue diseases. Further, most of the current understanding of bronchiolar disease in this setting is based largely on anecdotal case reports or small case series. Bronchiolitis, both constrictive and follicular, is most common in patients with rheumatoid arthritis. This section reviews the characteristics of bronchiolitis in rheumatoid arthritis, Sjögren's syndrome, systemic lupus erythematosus, progressive systemic sclerosis, polymyositis, and dermatomyositis.

Rheumatoid Arthritis and Constrictive Bronchiolitis

Obstructive pulmonary disease is remarkably prevalent in rheumatoid arthritis. In particular, bronchiolitis obliterans with airway obstruction is an increasingly recognized complication of this connective-tissue disorder. The basic lesion is fibrous narrowing and obliteration of the bronchioles and smallest bronchi. The role of prior penicillamine therapy as a potential etiological factor remains to be confirmed.

Clinical Findings

Most patients are middle-aged women with long-standing seropositive rheumatoid arthritis. This finding is consistent with the increased incidence of rheumatoid arthritis in women, but it is inconsistent with the increased frequency of pulmonary disease in rheumatoid arthritis reported among men. The clinical manifestations of bronchiolitis obliterans associated with rheumatoid arthritis help to distinguish it from other pulmonary processes associated with this disorder. Clinical findings include the rather abrupt onset of dyspnea and dry cough, often associated with inspiratory crackles and a mid-inspiratory "squeak."

The chest radiograph is typically normal, but it may show signs of air trapping. HRCT usually excludes the presence of bronchiectasis. Expiratory CT often shows multiple scattered areas of air trapping consistent with small-airway obstruction.

Pulmonary function studies reveal airflow obstruction and normal pulmonary compliance. Arterial blood gases show moderate hypoxemia and a respiratory alkalosis. The rapid rate of progression in airflow obstruction is atypical for COPD.

Histopathological Findings

A "constrictive" bronchiolitis is most common. Lymphoplasmacytic infiltration of small-airway walls is noted. The lumina are gradually obliterated, and the bronchiolar wall is destroyed by granulation tissue. Lesions are usually confined to the small bronchi and bronchioles. Parenchymal involvement is generally localized to areas surrounding the bronchiolitis. Lesions may be at different stages of development or may appear uniform. Immunofluorescence studies show granular depositions of IgM and a striking linear deposition of IgG in the alveolar wall, suggesting possible direct immune-mediated lung injury.

Treatment and Prognosis

Treatment with antibiotics and bronchodilators is ineffective. Corticosteroid therapy appears effective in some patients. The use of intravenous cyclophosphamide and oral prednisone has been suggested. One case report has described improvement of refractory rheumatoid arthritis-associated bronchiolitis in a patient treated with etanercept (tumor necrosis factor [TNF]-α inhibitor) and methotrexate. The prognosis is poor, with early deaths reported. In most patients, the disease runs a chronic course.

Rheumatoid Arthritis and Bronchiolitis Obliterans-Organizing Pneumonia

Occasionally, in rheumatoid arthritis, patchy organizing pneumonia with granulation tissue plugs extending into the alveolar ducts (BOOP) is the predominant lesion. Rheumatoid arthritis with BOOP appears to have a worse prognosis than does rheumatoid arthritis with constrictive bronchiolitis. In fact, patients with rheumatoid arthritis and BOOP are prone to development of a rapidly progressive, fatal form of pneumonia.

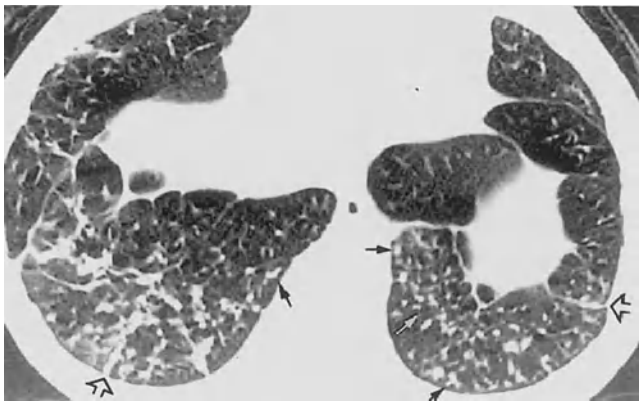

Figure 52-10 Follicular bronchiolitis. Thin-section (1.5-mm-collimation) computed tomography scan through the lower zones in a 61-year-old man with a mixed collagen vascular disease demonstrates multiple well-defined nodules. Several nodules (solid arrows) are clustered and located a few millimeters from the pleura or interlobular septa, which indicates centrilobular distribution. Mild interlobular septal thickening (open arrows) is also present. *(From Howling SJ, Hansell DM, Wells AU, et al: Follicular bronchiolitis: Thin-section CT and histologic findings*. Radiology *212:637–642, 1999.)*

Rheumatoid Arthritis and Follicular Bronchiolitis

Follicular bronchitis and bronchiolitis may occur in patients with rheumatoid arthritis, Sjögren's syndrome, juvenile rheumatoid arthritis, immunodeficiency syndromes, familial lung disorders, chronic infection, and hypersensitivity-type reactions.

Patients with rheumatoid arthritis always present with dyspnea; fever and cough occur occasionally. A positive rheumatoid factor is present, often at high levels (rheumatoid factor titers of 1:640 to 1:2560). The chest film is abnormal, showing bilateral reticular or nodular opacities (Fig. 52-10). Arterial blood gases demonstrate hypoxemia, hypocapnia, and a widened alveolar-arterial oxygen gradient. Both obstructive and restrictive patterns have been identified by spirometry, but the restrictive pattern appears to be more common. Immunofluorescence studies are negative.

The lesions of follicular bronchiolitis produce obstruction by external compression of bronchioles, rather than by direct luminal occlusion, as is characteristic of proliferative bronchiolitis obliterans (Fig. 52-11). In almost all cases, a concentric inflammatory infiltrate of lymphocytes and plasma cells surrounds the bronchiole. Abundant germinal centers in the peribronchiolar regions are present and are characterized by hyperplastic follicles located between bronchioles and pulmonary arteries. The bronchiolar lumen is often compressed into a slitlike or fish-mouth shape. Some have suggested that follicular bronchiolitis may be the precursor of interstitial lymphoid pneumonia or pseudolymphoma. Treatment with

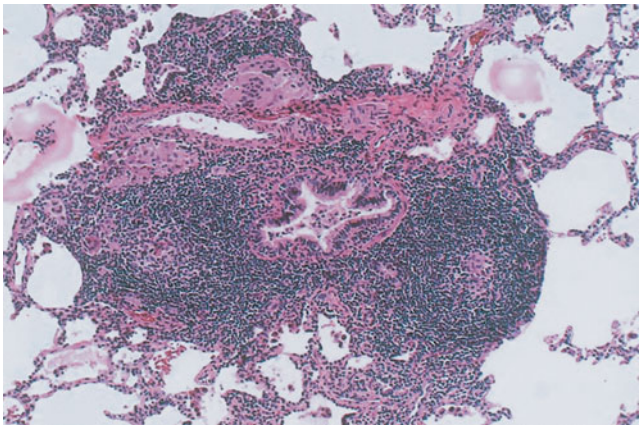

Figure 52-11 Proliferation of lymphoid follicles with germinal centers along the airways and infiltration of the epithelium by lymphocytes (H&E stain). *(Slide courtesy of Jeffrey L. Myers, M.D., Mayo Clinic, Rochester, MN.)*

corticosteroids has yielded variable results. Erythromycin may be useful for the management of this process.

Sjögren's Syndrome

Obstructive airway disease has been reported in patients with Sjögren's syndrome, often in association with other connective-tissue diseases, particularly rheumatoid arthritis. Desiccation of the tracheobronchial tree is very common in Sjögren's syndrome and no doubt accounts for the obstructive findings. Atrophic rhinitis, xerostomia, xerotrachea (manifested by chronic, dry cough), chronic bronchitis (with cough and production of tenacious sputum), atelectasis (with frequent middle-lobe collapse), and recurrent bronchopneumonia are manifestations of the severe mucosal dryness that can occur within the tracheobronchial tree. Secondary BOOP has been reported as a rare complication of Sjögren's syndrome.

The clinical impact of the obstructive airway dysfunction in Sjögren's syndrome is rarely severe. Most symptomatic patients complain only of a dry cough and mild dyspnea. Adequate studies addressing pulmonary function and pathology are limited. However, lung biopsy has revealed a mononuclear cell infiltration around narrowed small airways (i.e., constrictive bronchiolitis).

Systemic Lupus Erythematosus

Fewer than 5 percent of patients with systemic lupus erythematosus (SLE) have airflow obstruction. A patient with SLE who developed rapidly progressive airway obstruction and demonstrated early obliterative bronchiolitis on open lung biopsy has been reported. Hence, this lesion may account for the obstructive dysfunction occasionally seen in SLE. BOOP has also been reported in two patients with SLE. Although one patient responded to corticosteroid therapy, the other died, despite treatment with corticosteroids and cyclophosphamide.

Progressive Systemic Sclerosis

Clinically significant small-airway disease is not often found in nonsmokers with progressive systemic sclerosis, even in the presence of interstitial pulmonary involvement. Focal lymphoid hyperplasia (follicular bronchiolitis) was identified in 23 percent of the open lung biopsies from patients with progressive systemic sclerosis. Interstitial lung disease is the most important pulmonary complication of this disorder.

Polymyositis and Dermatomyositis

BOOP, usual interstitial pneumonia, and diffuse alveolar damage are the most common histological patterns identified in patients with polymyositis and dermatomyositis. BOOP may occur de novo. Patients with polymyositis or dermatomyositis and BOOP present with cough, fever, and dyspnea, in addition to the proximal muscle weakness, malaise, and rash commonly found in this disease. The pulmonary lesion is responsive to corticosteroid therapy.

DRUG-INDUCED CAUSES OF BRONCHIOLITIS

Bronchiolitis, usually with organizing pneumonia, has been reported in association with a number of drugs (Table 52-1). Most reports are of single cases or small case series.

Bronchiolitis Associated with Gold Compounds

Several forms of pulmonary disease occur among patients treated with gold, including chronic interstitial pneumonitis, organizing pneumonia, and bronchiolitis obliterans. Pure bronchiolitis obliterans with airflow obstruction has been associated with gold therapy, especially in patients with rheumatoid arthritis. Since patients with rheumatoid arthritis are prone to develop bronchiolitis obliterans, determination of whether the cases resulted from gold-induced airway injury is difficult.

Amiodarone-Induced Bronchiolitis

An organizing pneumonia with or without bronchiolitis obliterans (BOOP-pattern) is seen in approximately 25 percent of cases of amiodarone-induced lung disease. This presentation is acute and characterized by cough, fever, dyspnea, and patchy alveolar opacities on the chest radiograph. Findings mimic an infectious pneumonitis. Pleuritic chest pain and nonproductive cough are common. Crackles and pleural rub are typically evident on auscultation.

Treatment consists primarily of stopping the drug, provided that alternative treatment options are made for potentially life-threatening arrhythmia. Corticosteroid therapy (prednisone 40 to 60 mg a day, tapering over 2 to 6 months)

can be life-saving for severe cases and for patients in whom withdrawal of amiodarone is not advisable.

Because of the drug's accumulation in fatty tissues and its long elimination half-life (approximately 45 days), pulmonary toxicity may progress despite drug discontinuation; furthermore it may recur upon steroid withdrawal.

Sauropus Androgynus-Induced Bronchiolitis

An outbreak has been reported in Taiwan of rapidly progressive respiratory distress associated with consumption of uncooked Sauropus androgynus, a vegetable claimed to be effective in weight control. Most patients were young or middle-aged women who consumed the juice of uncooked Sauropus androgynus, generally mixed with guava or pineapple juice, for a mean duration of 10 weeks. Progressive dyspnea and persistent cough were the main symptoms on presentation.

Pulmonary function testing uniformly revealed moderate to severe airflow obstruction. Hypoxemia was also present. The chest radiographs were essentially normal. HRCT showed bilateral bronchiectasis and patchy low attenuation of lung parenchyma with mosaic perfusion. The radiographic presence of air-trapping was better correlated with changes in pulmonary function than was bronchiectasis. Findings on ventilation-perfusion lung scans were compatible with obstructive lung disease. Open lung biopsy specimens confirmed the presence of bronchiolitis obliterans. No effective treatment has been reported; the clinical response to prednisolone is limited.

ORGAN TRANSPLANTATION

Pulmonary disease is a common complication of organ transplantation and, consequently, it is a significant source of morbidity and mortality in transplant recipients. Bronchiolitis, manifested by progressive airflow obstruction, is increasingly becoming one of the most frequent noninfectious posttransplant respiratory complications. The BOOP pattern has also been reported in transplant recipients.

Bone Marrow Transplantation

Pulmonary disease is a common complication of bone marrow transplantation, occurring in 40 to 60 percent of patients. Furthermore, pulmonary complications are a significant source of morbidity and mortality in transplant recipients. The disease usually results from an infectious pneumonia (bacterial, fungal, or viral, especially cytomegalovirus) or idiopathic interstitial pneumonitis. Lymphocytic bronchitis and lymphoplasmacytic infiltrates of the trachea and large bronchi are among the earliest pulmonary problems encountered after bone marrow transplantation. Progressive airflow obstruction secondary to bronchiolitis obliterans is one of the most frequent noninfectious posttransplant respiratory complications. Cases appear after the first 100 days following transplantation, usually in the setting of chronic graft-vs.-host disease (GVHD). GVHD has been postulated to play a role in the development of this lung disease. Bronchiolitis obliterans is most prevalent in patients after allogeneic transplantation, but it has been recently reported with autologous bone marrow transplantation, as well.

Clinical Findings

Approximately 10 to 17 percent of long-term survivors with chronic GVHD develop severe obstructive pulmonary disease. Risk factors include older age, recurrent sinusitis, chronic GVHD, methotrexate prophylaxis for GVHD, and acquired hypogammaglobulinemia. Patients usually present with nonproductive cough (60 percent), dyspnea with exertion (51 percent), and nasal congestion. Scattered wheezes are heard in 40 percent of patients; expiratory "squeaks" are also frequently noted. Bibasilar crackles are uncommon.

Radiographic Findings

The chest radiograph may show diffuse interstitial infiltrates; in approximately 80 percent of cases, the lung fields are normal. Hyperinflation may also be seen. Pneumothoraces may complicate the course of advanced disease. HRCT can be helpful in supporting the diagnosis. In established bronchiolitis obliterans, the most striking CT feature is lobular or segmental areas of lung attenuation, associated with narrowing of pulmonary vessels. The attenuation is presumed to represent areas of air trapping and oligemia.

Physiological Findings

The finding of a new obstructive pattern on pulmonary function testing is a significant signal that bronchiolitis obliterans is developing, especially when noted in the presence of GVHD. Reduced flow, often with hyperinflation and air trapping, is the most common manifestation. Bronchial hyperreactivity also has been identified in some patients after transplantation, but most have fixed obstruction unresponsive to bronchodilators. The presence of bronchial hyperreactivity before transplantation has not been associated with the subsequent development of either clinical or pathologically proven posttransplantation bronchiolitis obliterans. The diffusing capacity is reduced, and hypoxemia is common.

Histopathological Findings

Lung biopsy findings are quite variable. The major changes are in and around the bronchioles. In most patients with rapidly progressive obstruction, marked lymphocytic, plasmacytic, or neutrophilic infiltration of the walls of the terminal respiratory bronchioles and obliteration of the bronchiolar lumina with fibrous tissue and surrounding interstitial fibrosis (i.e., "pure" bronchiolitis obliterans) are found. A moderate lymphocytic infiltrate may invade the adjacent pulmonary parenchyma. Other changes characteristic of constrictive bronchiolitis are frequently noted. The BOOP pattern has also been found after bone marrow transplantation.

Transbronchial lung biopsies are usually inadequate for definitive diagnosis. An open or thoracoscopic lung biopsy is

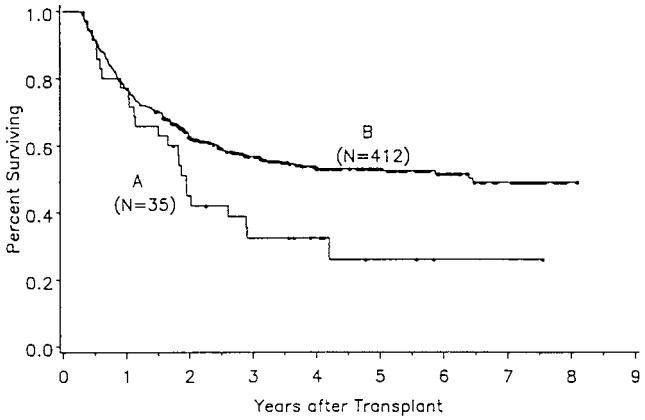

Figure 52-12 Bronchiolitis obliterans associated with bone marrow transplantation. Curve A shows posttransplant survival of 35 patients who developed obstructive lung disease. Curve B shows posttransplant survival of 412 concurrent patients (age 16 years or over) with chronic graft-vs.-host disease who survived at least 80 days after transplantation and who had no evidence of obstructive lung disease. *(Based on data from Clark JG, Crawford SW, Madtes DK, et al: Obstructive lung disease after allogeneic marrow transplantation. Clinical presentation and course.* Ann Intern Med *111:368–376, 1989, with permission.)*

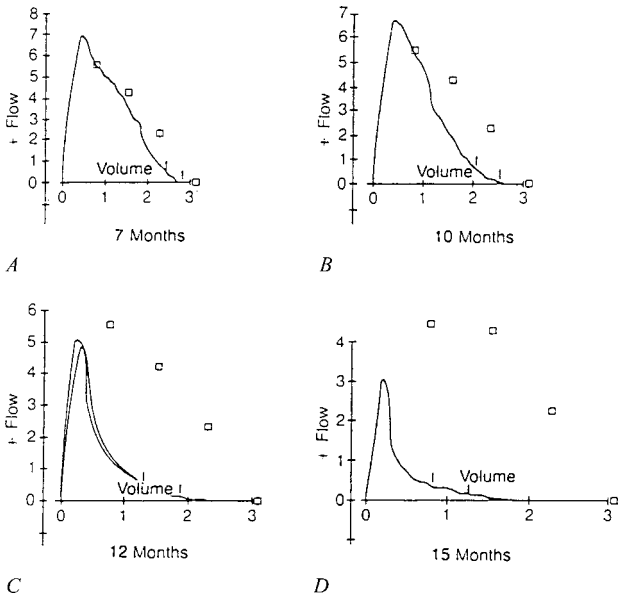

Figure 52-13 Segmented changes in flow-volume loops in bronchiolitis obliterans associated with heart-lung transplantation. Curves are from a 33-year-old woman 7, 10, 12, and 15 months after transplantation. *A*. Upper left figure is essentially normal curve. *B*. Upper right curve shows early ''coving" of the expiratory flow limb over the middle 50 percent of the forced vital capacity. *C* and *D*. Progressive obstruction is present at 12 (lower left) and 15 months (lower right). Small boxes in each panel represent normal flow. Flow is expressed in L/s; volume is expressed in L. *(Based on data from Theodore J, Starnes VA, Lewiston NJ: Obliterative bronchiolitis*. Clin Chest Med *11:309–321, 1990, with permission.)*

often necessary. Since infections are frequent, they should be diagnosed and treated promptly. In this setting, BAL analysis is useful only in ruling out infections. A lymphocytic (i.e., 30 to 50 percent lymphocytes in BAL fluid) or mixed lymphocyte-neutrophil predominance is usual.

Management

The appropriate treatment of bronchiolitis obliterans associated with bone marrow transplantation is unclear. In most cases, bronchodilators and corticosteroids have not improved airflow limitation. Furthermore, use of immunosuppressive agents for the treatment of chronic GVHD has had no consistent beneficial effect on pulmonary function. Consequently, early recognition and management are required if treatment is to be successful.

The prognosis is variable. A significant number of reported patients have had progressive or persistent disease; many have died secondary to respiratory failure (40 to 65 percent of subjects) (Fig. 52-12). Increasing recognition, early treatment, and the introduction of cyclosporine have resulted in a reduction of the incidence of posttransplantation obstructive airway disease.

Heart-Lung Transplantation

The main pulmonary complication in long-term survivors of heart-lung transplantation is a life-threatening obstructive ventilatory defect—bronchiolitis obliterans. The incidence of obliterative bronchiolitis in this setting has declined in recent years from 50 percent to 10 to 23 percent. However, in a recent study, 65 percent of lung transplant recipients (including 48 heart-lung, 18 single lung, and 8 bilateral-lung recipients) who survived longer than 90 days, and who underwent transplantation more than 15 months before data analysis, developed bronchiolitis obliterans.

Clinical Findings

Bronchiolitis obliterans is noted clinically several months to several years after heart-lung transplantation. Cough productive of mucopurulent sputum is most often seen. Progressive dyspnea follows. Most patients experience repeated upper respiratory tract infections, both viral and bacterial in origin. Occasionally, disease onset is identified only from abnormalities in routine pulmonary function testing (Fig. 52-13). With advanced disease, wheezing on exertion is common.

The development of bronchiolitis obliterans frequently is preceded by acute organ rejection. Often, patients have a history of prior lung infection with cytomegalovirus, *Pneumocystis carinii*, or Epstein-Barr virus. Chest examination reveals diffuse, coarse crackles, inspiratory squeaks, and expiratory rhonchi. The classic signs of severe airflow obstruction and hyperinflation are seen in advanced, end-stage disease.

Radiographic Findings

The chest radiograph may be normal in early stages of the disease, but frequently it reveals diffuse, nonspecific peribronchial and interstitial infiltrates and variable pleural thickening. Bronchography and CT reveal central bronchiectasis.

Physiological Findings

Pulmonary function tests show largely irreversible airflow obstruction; however, TLC is reduced. The D_{LCO} is moderately depressed. Hypoxemia and hypocapnia are universally present.

Histopathological Findings

Histopathological changes affect all areas of the lung, but they are frequently patchy. Inspissated mucus and distal obstructive airway changes are often noted. Diffuse increases in peribronchial and interstitial fibrosis are present in most biopsies. Pleural, venous, and arteriosclerotic vascular changes are common. These changes are different from those in acute pulmonary rejection, which is characterized by perivascular lymphocytic cuffing and diffuse alveolar damage. Clinical acute rejection predisposes to subsequent development of bronchiolitis obliterans.

Occasionally, classic BOOP, with patchy organizing pneumonia and granulation tissue plugs extending into the alveolar ducts, is observed as the predominant lesion. The clinical and radiographic features are those seen with BOOP (discussed previously). Usually, known causes of this lesion are identified—e.g., infection, aspiration, drug reaction, etc.

Pathogenesis

Increasing evidence suggests that the key pathogenetic factor is a form of alloreactive injury to the bronchial epithelium. Donor-specific alloreactivity of BAL lymphocytes, manifested by a proliferative response to donor spleen cells, appears to be a useful marker for this process. A number of other possible causes or associations of bronchiolitis obliterans in heart-lung transplantation have been described: (1) recurrent, persistent bacterial or viral infections; (2) immunoreaction to the transplanted lung (e.g., GVHD or transplant rejection); (3) altered mucociliary clearance and impaired ciliary function from injury to the pulmonary nerve supply or from abnormal mucus chemistry and viscosity; (4) bronchial artery ligation and resulting alteration in repair of injured bronchi and bronchioles; (5) reaction to immunosuppressive drugs (especially cyclosporine, which has been shown to have fibroproliferative properties that could cause progressive narrowing and obliteration of affected bronchioles); and (6) loss of cough reflex and aspiration, creating a milieu favorable to continued growth of infectious agents.

Diagnosis

Open or thoracoscopic lung biopsy is required to confirm the diagnosis of bronchiolitis obliterans and to rule out other causes of pulmonary dysfunction in patients who have undergone heart-lung transplantation. With increased recognition of this potential complication, early detection of the disorder through use of serial pulmonary function tests, BAL, and repeated transbronchial lung biopsies can be achieved and may decrease the need for surgical lung biopsy to confirm the diagnosis. The value and role of serial surveillance transbronchial lung biopsies in the absence of clinical symptoms and signs remain unknown. Unsuspected rejection or infection requiring therapy may be seen in 25 percent of surveillance bronchoscopy procedures performed after lung transplantation. Most episodes (68 percent) of unsuspected rejection or infection appear in the first 6 months following transplantation.

Management

No clearly useful treatment protocol has been established. Efforts at preventing repeated episodes of rejection seem most important. Prompt diagnosis and treatment of acute rejection and any infectious complications are paramount. Routine serial lung function testing and fiberoptic bronchoscopy with transbronchial biopsy and BAL are helpful.

The best medical regimen for prevention of bronchiolitis obliterans remains to be defined. Nonetheless, experience suggests that optimal maintenance of immunosuppression requires a regimen that includes azathioprine and cyclosporine. Prednisone is also commonly included. Use of corticosteroids, bronchodilators, antibiotics, antithymocyte globulin, or OKT3 monoclonal antibody has resulted in documented stabilization or reversal of disease in some patients. Retransplantation has been successful. Spontaneous improvement does not occur.

Lung Transplantation

Lung transplant recipients were initially thought not to develop bronchiolitis obliterans. However, this complication is now recognized as the major factor limiting long-term success with this procedure. The incidence of bronchiolitis obliterans among single-lung recipients is approximately 20 percent; in double or bilateral, sequential single-lung recipients, the incidence is 12 percent. Risk factors include recurrent episodes of acute rejection, severe acute rejection, inadequate or fluctuating levels of maintenance immunosuppression, recurrent infections, and ischemic airway injury occurring early after transplantation.

Bronchiolitis Obliterans Syndrome

Progressive airflow limitation secondary to small-airway obstruction is the hallmark of the bronchiolitis obliterans syndrome (BOS). This syndrome has a variable clinical course. Some patients experience rapid loss of lung function and respiratory failure. Others experience either slow progression or intermittent loss of function with plateaus, during which pulmonary function is stable for prolonged periods of time. BOS likely reflects more than one process.

Clinical Findings

The clinical presentation is similar to that described in heart-lung transplantation. Nonproductive cough, mild malaise, and fatigue are common symptoms. Eventually, all subjects develop dyspnea. Results of physical examination are usually normal, but inspiratory squeaks may be heard. Crackles are uncommon.

Radiographic Findings

Decreased peripheral vascular markings, slight volume loss, and subsegmental atelectasis may be early changes. A common radiographic finding in long-standing disease is the gradual progression of pleural-based densities in the middle and upper lung zones. Biopsy reveals subpleural parenchymal fibrosis without active inflammation. The scarring may result from relative ischemia in areas of affected lung. HRCT shows lobular or segmental areas of lung attenuation and narrowing of pulmonary vessels, representing regions of air trapping and oligemia.

Histopathological Findings

Three major kinds of airway injury may be seen in lung allografts: acute rejection, bronchiolitis obliterans, and lymphocytic bronchitis or bronchiolitis. The lesions of bronchiolitis obliterans affect the membranous and respiratory bronchioles. They are characterized by the features of constrictive bronchiolitis (see above). If a submucosal mononuclear cell infiltrate is present, the lesions are considered "active." Their absence may indicate "inactive" disease. Vascular changes are often found and usually consist of fibrointimal thickening of arteries and veins, with or without an active inflammatory component.

A BOOP pattern, with patchy organizing pneumonia and granulation tissue plugs extending into the alveolar ducts, has been reported in some lung transplant recipients. The clinical and radiographic features are progressive respiratory failure, acute or subacute alveolar opacities noted on chest radiograph, and a restrictive pattern of pulmonary function tests. Usually, known causes of this lesion are identifiable, especially infection. Patients respond well to corticosteroid therapy.

Management

Several recent trials have demonstrated significant functional improvement in BOS with treatment of macrolide antibiotics. Prevention of repeated episodes of acute rejection appears important. Prompt diagnosis and treatment of acute rejection and infectious complications are important. A regimen of immunosuppression that includes azathioprine, cyclosporine, and prednisone is most commonly employed. This regimen appears to slow the rate of decline in lung function; however, the overall prognosis remains poor. Approximately 50 percent of all deaths after the first year following transplant are due to bronchiolitis obliterans. Retransplantation has been successfully employed in some patients.

DIFFUSE PANBRONCHIOLITIS

Diffuse panbronchiolitis is a distinctive form of small-airway disease that is relatively common in Japan, China, and Korea; it is rare in other parts of the world. A few case reports of the disease in non-Asians have appeared in the literature. A familial occurrence has been described, with a significant increase in HLA Bw54 (63 percent frequency). The genetic and ethnic background observed with this unique syndrome may be explained on the basis of HLA Bw54 or its related haplotype being confined primarily to some Asian races—e.g., Japanese, Chinese, and Koreans. HLA Bw54 may also be a useful marker in the differential diagnosis of diffuse panbronchiolitis, since the frequency of this haplotype in the general population is very low (11.8 percent). A similar pulmonary lesion has been demonstrated in ulcerative colitis and adult T-cell leukemia. Environmental factors also appear important, since the disorder is very uncommon in persons of Asian ancestry living abroad.

Clinical Findings

Diffuse panbronchiolitis is more prevalent in men, with a 2:1 male-to-female ratio. The peak incidence occurs between the fourth and seventh decades of life; mean age at presentation is 50 years. Chronic sinusitis is present in 75 to 100 percent of cases. Sinus symptoms often precede chest symptoms by years or decades. Chronic cough with expectoration of copious purulent sputum, exertional dyspnea, and wheezing are the most common clinical manifestations. Cigarette smoking or occupational exposures have not been shown to be predisposing factors. Physical examination reveals coarse crackles; clubbing is not a feature.

The most characteristic laboratory abnormality is persistent, marked elevation of serum cold agglutinins; mycoplasmal antibody titers are negative. Rheumatoid factor may be elevated. Immunoglobulin levels are usually normal. BAL studies reveal marked neutrophilia.

Radiographic Findings

The chest radiograph often reveals small nodular opacities up to 2 mm in diameter; the opacities are seen diffusely throughout the lung fields. A reticular "airway" pattern may be evident with more advanced disease. Hyperinflation may also be present. HRCT yields more information about the location and distribution of the pulmonary disease than do conventional radiographic techniques. HRCT also better reflects the clinical stages and pathology. On HRCT, the nodular shadows are distributed in a centrilobular fashion, often extending to small, branching linear areas of attenuation. The nodular and linear densities correspond to thickened and dilated bronchiolar walls with intraluminal mucus plugs. Inhomogeneity in lung density may be apparent as a result of peripheral air trapping. Bronchiectasis may be prominent in advanced disease.

Physiological Findings

Pulmonary function tests reveal marked obstruction. Arterial blood gases show hypoxemia, with or without hypercapnia. In rare instances, a restrictive ventilatory defect is present. The diffusing capacity is variably reduced. In general, patients with diffuse panbronchiolitis exhibit less bronchodilator responsiveness than do patients with COPD.

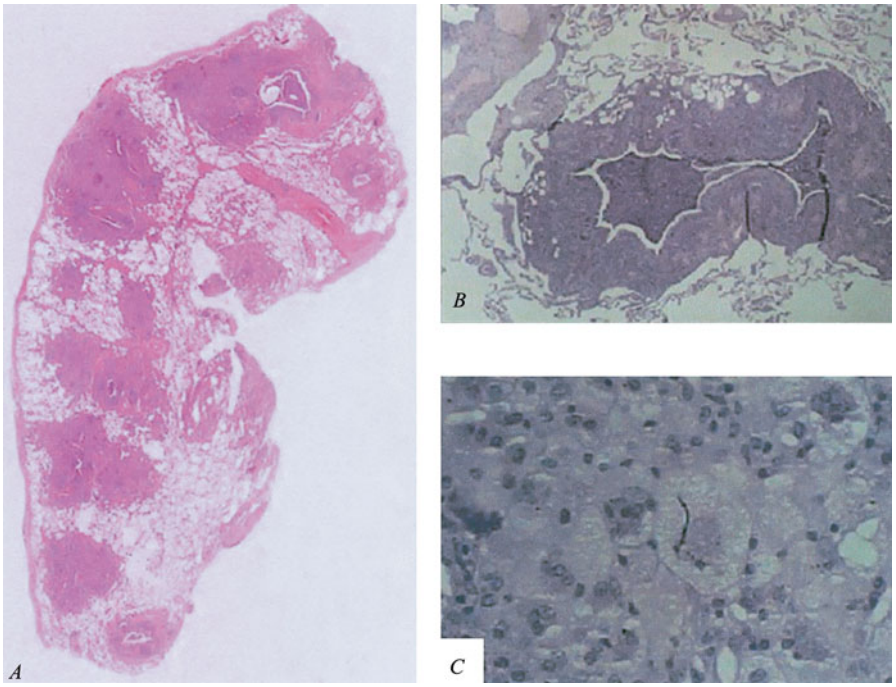

Figure 52-14 *A*. Scanning power microscopy shows the inflammatory process has a predilection for bronchioles (H&E stain). *B*. Inflammatory process characterized by mononuclear cell inflammation of the respiratory bronchioles. Acute inflammation in the lumen of the respiratory bronchiole and chronic inflammation in the wall, including numerous interstitial foam cells, are noted (H&E stain). *C*. Foamy macrophages in the bronchiolar lumina and adjacent alveoli (H&E stain). *(Slide courtesy of Jeffrey L. Myers, M.D., Professor of Pathology, Mayo Clinic, Rochester, MN.)*

Histopathological Findings

Thickening of the walls of the respiratory bronchiole, infiltration with lymphocytes, plasma cells and histiocytes, and extension of the inflammatory changes into peribronchiolar tissue are noted on biopsy (Fig. 52-14). Advanced disease is manifested by secondary ectasia of proximal bronchioles.

Management and Outcome

Optimal therapy for diffuse panbronchiolitis is unclear. Low-dose erythromycin (200 to 600 mg a day) is adequate for most patients. Erythromycin impairs neutrophil chemotaxis, neutrophil superoxide production, and neutrophil-derived elastolytic activity, and it decreases the number of neutrophils in BAL fluid following challenge with gram-negative bacteria. In addition, erythromycin may cause a reduction in mucus production by decreasing glycoconjugate secretion. Finally, erythromycin has been shown to reduce the circulating pool of T lymphocytes bearing HLA-DR, a marker of cellular activation.

Corticosteroids are commonly used in treatment regimens, but evidence supporting their efficacy is lacking. Nonsteroidal anti-inflammatory drugs (NSAIDs) may have a role in controlling the bronchorrhea associated with this disease by altering airway epithelial ion and water transport. No controlled trials with NSAIDs have been performed. Routine use of β_2-agonists or ipratropium bromide should be encouraged to promote mucociliary clearance and bronchodilation in patients with a component of reversible airway disease and as a part of routine pulmonary toilet. In addition, treatment of coexisting sinus disease may help in control of airway disease.

Prompt treatment of bronchial infections is also important. The choice of antibiotics should be guided by results of sputum Gram's stain and culture. The disease progresses insidiously, and the prognosis is often poor, with fatalities due to repeated respiratory infections (particularly with *Pseudomonas aeruginosa*) that result in respiratory failure.

PRIMARY DIFFUSE HYPERPLASIA OF PULMONARY NEUROENDOCRINE CELLS

Primary diffuse hyperplasia of pulmonary neuroendocrine cells is a clinicopathological entity characterized by diffuse hyperplasia and dysplasia of neuroendocrine cells primarily affecting the distal bronchi and bronchioles. The disorder is seen primarily in women in their fifth or sixth decade. Clinical findings include nonproductive cough and long-standing dyspnea (usually of more than 10 years' duration). All reported cases are in never-smokers. The chest examination is unrevealing. Chest radiographs show diffuse reticulonodular opacities in most; multiple nodules are seen in a few cases. HRCT demonstrates diffuse small-airway thickening, with patchy areas of hyperlucency, suggesting air trapping. The most common physiological abnormality is irreversible airflow obstruction. Open or thoracoscopic lung biopsy is required for diagnosis. The spectrum of histopathological changes includes diffuse hyperplasia and dysplasia of neuroendocrine cells, numerous neuroepithelial bodies, prominent carcinoid tumorlets, and even typical carcinoid tumors in the distal bronchi and bronchioles. Pathogenesis, treatment, and prognosis of the syndrome are unknown. Most patients have a relatively benign course characterized by many years of symptoms.

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53

Bullous Disease of the Lung

David M. F. Murphy • Alfred P. Fishman

DEFINITION

A *bulla* is an air-containing space within the lung parenchyma that arises from destruction, dilatation, and confluence of airspaces distal to terminal bronchioles (Fig. 53-1). By definition, a bulla is larger than 1 cm in diameter, and its walls are composed of attenuated and compressed parenchyma.

Bullae occur in several different clinical contexts: (1) with emphysema ("bullous emphysema"), particularly with the acinar (paraseptal) variety; (2) with pulmonary fibrosis, as in the late stages of sarcoidosis or complicated pneumoconiosis; (3) in so-called "vanishing lung," in which the parenchyma is rapidly replaced by multiple bullae; and (4) in lungs that are otherwise normal ("bullous lung disease") and therefore likely secondary to a mechanism different from that of bullae occurring in conjunction with emphysema (Table 53-1).

Distinctions are drawn between bullae, blebs, and cysts (Table 53-2). A *bleb* is an accumulation of air between the two layers of the visceral pleura that arises when the thin covering of the bleb ruptures and permits entry of air (Fig. 53-1). In contradistinction, *cysts* are epithelial-lined cavities that may resemble bullae on the chest radiograph. Many fall into the category of developmental anomalies and include mixtures of mesenchymal and epithelial components that are normally present in the lung. The pathological nature of these cystic lesions is reflected in their names: "cystic adenomatoid malformations," "peripheral bronchogenic cysts," "congenital polycystic disease," and "atypical bronchopulmonary sequestration."

The designation *bullous disease* is reserved for multiple bullae in lungs that are otherwise normal. This entity is different in etiology and pathogenesis from that in which bullae occur in conjunction with underlying chronic obstructive pulmonary disease (COPD).

Confusion occasionally arises between the two entities because some pathologists are inclined to regard bullous disease as a subset of panacinar emphysema. However, this view is not useful clinically on at least three accounts: (1) panacinar emphysema tends to occur in the lower lobes, whereas bullous disease favors the upper lobes; (2) the natural history of the two disorders is quite different; and (3) panacinar emphysema has certain distinctive features not shared by bullous disease (e.g., a "winter tree" appearance on angiography). Bullae may occur not only as part of obstructive lung disease, but also as a complication of fibrotic lung disease (Table 53-1).

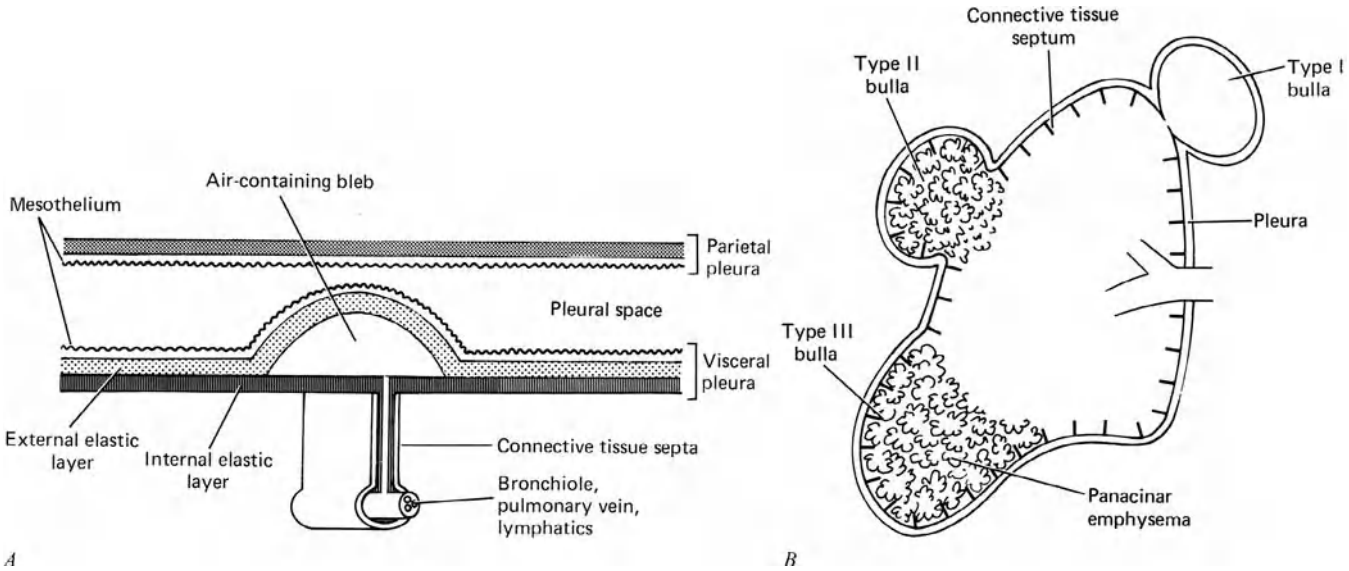


Figure 53-1 Blebs and bullae. *A.* Development of a bleb. A bleb is an accumulation of air within the pleura that is not confined by connective-tissue septa within the lung. Air that escapes within the substance of the lungs makes its way to the surface, separating the internal from the external elastic layers on the visceral pleura. *B.* Different types of bullae. In contrast to a bleb, a bulla is confined by connective-tissue septa of the lung and is deep to the internal elastic layer of the visceral pleura. Three different types of bullae are shown arising from a lung that has been removed from within the chest wall. A type I bulla is shown at the apex, a type II is in the middle zone, and a type III is arising at the base. The short dark lines denote connective-tissue septa. Panacinar emphysematous parenchyma is present within the types II and III bullae. *(Based on data from Reid L:* The Pathology of Emphysema. Chicago, Year Book, 1967, pp 211–240, *with permission.)*

ETIOLOGY OF BULLAE

Bulla may originate in a variety of clinical and pathogenetic settings: (1) with emphysema of distal acini (Fig. 53-2); (2) in the setting of cigarette smoking; (3) in conjunction with scar tissue formation, which "traps" areas of normal lung, enlarges airspaces by traction on surrounding intact alveoli, or produces retraction or shrinkage of intact walls of adherent alveoli; (4) in the setting of intravenous drug abuse; (5) as a result of chronic inflammation and destructive changes in terminal and first-order respiratory bronchioles, resulting in airspace distention from delayed emptying; and (6) with α_1-antitrypsin deficiency in the elderly.

CLASSIFICATION

Bullae are classified anatomically into three main types (Fig. 53-1*B*).

Type I bullae are characterized by a narrow neck that connects the bullae with the pulmonary parenchyma. This type of bulla may be caused by over-inflation of a volume of flawed lung tissue. The bullae behave like a paper bag that is extremely compliant until full, when it then becomes tense. The walls of type I bullae are thin, and their interiors are empty. Type I bullae are usually found at the lung apices and along the edges of the lingula and middle lobes. They often occur in association with paraseptal emphysema. Scanning electron microscopy has demonstrated that the thin neck is a consistent feature and that pleural mesothelial cells on the external surface are either reduced in number or completely absent; bundles of collagen fibers lie naked and separated from one other by small pores or crevices.

In contrast, type II bullae arise from the subpleural parenchyma and are characterized by a neck of panacinar emphysematous lung tissue. Also, the interior of these airspaces consists of emphysematous lung in which blood vessels are still present. In contrast to type I bullae, the outer wall is formed by pleura covered with intact mesothelial cells. Although connective-tissue septae are present within the bullae, they are not found in the wall. Type II bullae may occur anywhere in the lung, but they are most frequent in the upper lobe, at the anterior surface of the middle lobe, and over the diaphragm.

Type III bullae consist of slightly hyperinflated lung connected to the rest of the lung by a broad base extending deep into the parenchyma. This type is believed to represent an atrophic form of emphysema.

PATHOGENESIS

It is unclear how bullous lung disease develops. Several hypotheses have been proposed over the years, but none have

Table 53-1

Classification of Bullae

Primary
- Vanishing lung syndrome
- Single giant bulla
- Bullous lung disease

Secondary
- Emphysema
  - Paraceptal
  - Panacinar
  - Centriacinar

Pulmonary fibrosis
- Sarcoidosis
- Idiopathic pulmonary fibrosis
- Progressive massive fibrosis
- Conglomerate silicosis
- Fibrotic tuberculosis
- Other fibrotic lung disorders

Familial disorders
- α_1-antitrypsin deficiency
- Ehlers-Danlos syndrome
- Salla disease
- Marfan's syndrome
- Fabry's disease
- Cutex laxa

been proved. Among these are the following: (1) Weakness of the alveolar walls predisposes to the formation of bullae, particularly at the apices of the lungs, where pleural pressures are most negative. This theory underscores the proclivity of bullae for the upper lobes and stresses the influence of mechanical forces acting upon flawed tissue. (2) Inflammatory disease of a bronchiole leads to progressive air trapping and "tension airspaces." (3) Disordered collateral ventilation in some way produces the findings. (4) The same mechanisms responsible for generalized emphysema are operative in the formation of bullae. (5) Underlying paraseptal emphysema produces bullous disease.

Of all the hypotheses, that of underlying paraseptal emphysema is the most popular. The hypothesis envisages destruction of alveoli adjacent to connective septae or the pleura, with small "bubbles" developing along the edges of the lung. The pattern relates to the fact that capillaries in alveolar walls that abut connective-tissue septa are less numerous than elsewhere because of a sparse network of arterioles and arteries in peripheral alveoli. Consequently, these regions of the acinus have less vascularity and greater compliance.

Small bullae rarely become visible on the chest radiograph, but they are usually easily visible by computed tomography (Fig. 53-3). As a rule, small bullae usually produce no symptoms, signs, or discernible alterations in pulmonary function. However, rupture of one or more bullae may lead to spontaneous pneumothorax.

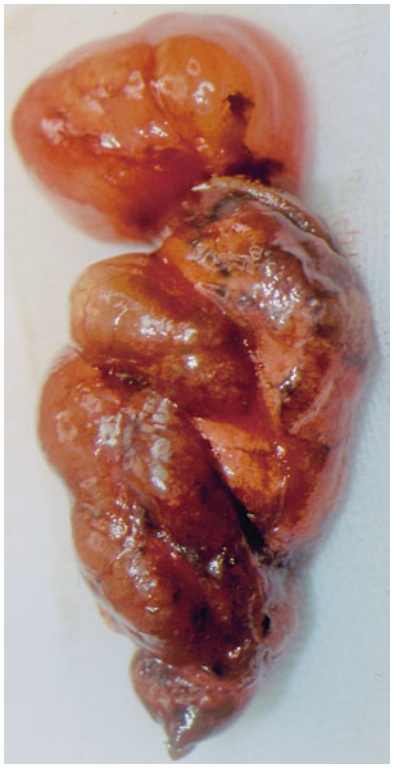
Dynamic computerized tomography and intra-bulla pressure measurements have raised questions about the theory that bullae are formed by positive pressure within the airspace. The lung surrounding a bulla is less compliant than the bullae itself; accordingly, the pressure necessary to inflate the surrounding lung is greater than that necessary to inflate the bulla. The pressure within a giant bulla has been found to be the same as pleural pressure. Therefore, when a bulla and its surrounding lung are exposed to the same negative pleural pressure, the bulla fills preferentially and completely like an inflated paper bag, prior to the surrounding lung inflating. Further inspiration increases the elastic recoil pressure, thereby exerting a greater retractive force on the lung parenchyma and enlarging the airspace. Nevertheless, bullae can be removed from within the lung while still maintaining their volume, indicating a positive intra-bulla pressure.

Bullae within the intact chest are molded and compressed to fit adjacent anatomic configurations. However, if the lung is released from these constraints (e.g., when removed from the chest cavity), bullae project as shiny bubbles

Table 53-2

Characteristics of Blebs, Bullae, and Cysts

	Bleb	**Bulla**	**Cyst**
Site	Within visceral pleura	Arises within secondary lobule	Lung parenchyma or mediastinum
Size	1–2 cm	1 cm to 75% of a lung	2–10 cm
Lining	Elastic laminae of the pleura	Connective tissue septa	Epithelium
Associated condition	Spontaneous pneumothorax	Bronchogenic carcinoma	Respiratory infection



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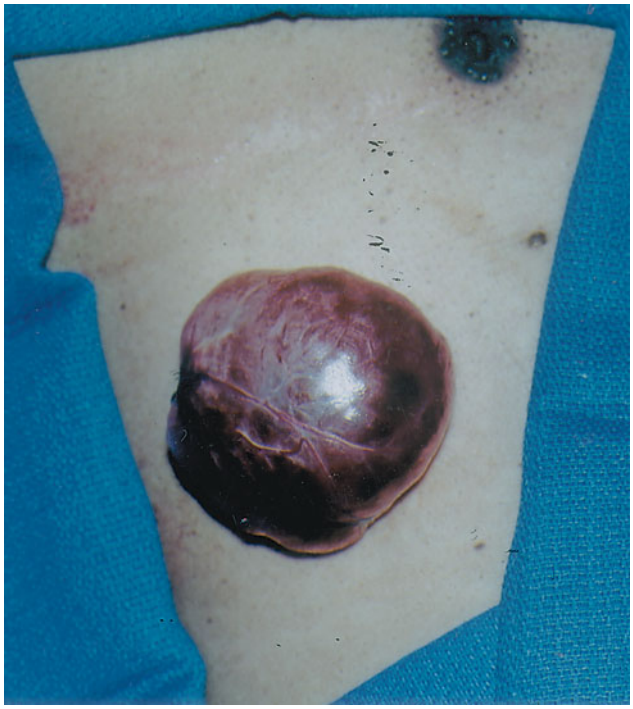
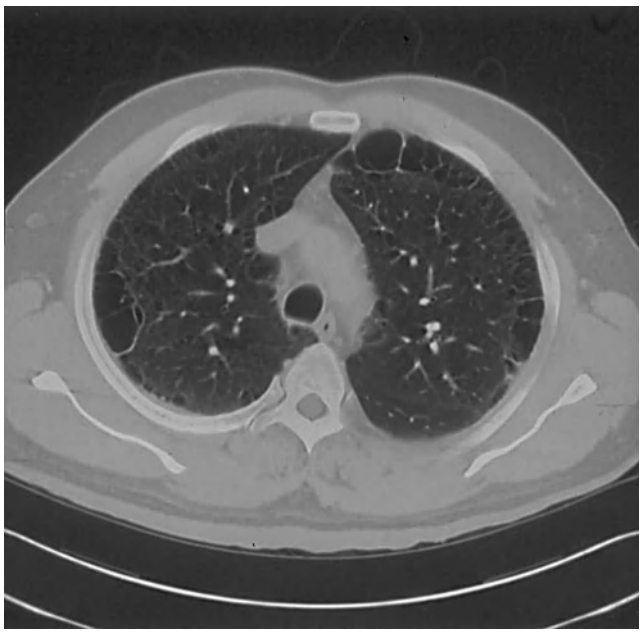


B

Figure 53-2 *A*. Surgically resected specimen with a bulla projecting from the lung surface. *B*. A bulla is shown projecting through a previous chest tube insertion site onto the surface of the skin.



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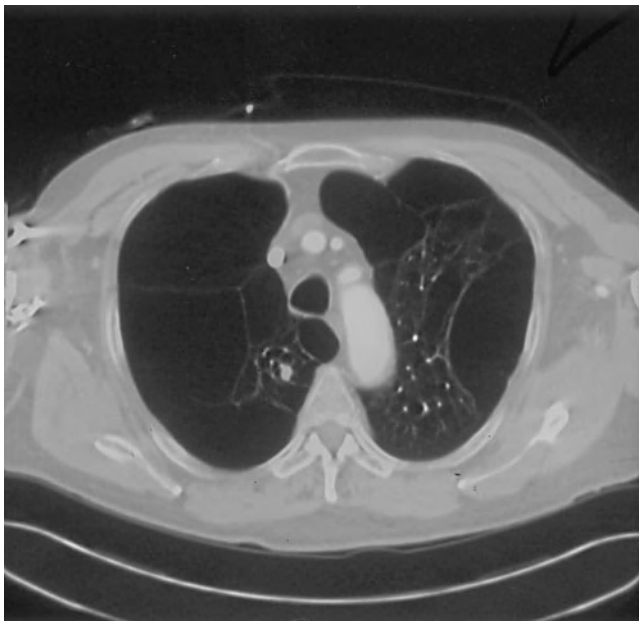


B

Figure 53-3 *A*. CT image of the lungs showing paraseptal emphysema visible beneath the visceral pleura and an associated bulla. *B*. CT image of the lungs showing severe bullous emphysema with hairline markings identifying the walls of several bullae.

at the lung surface (Fig. 53-2). Within the thoracic cavity, large bullae cause crowding of adjacent lung parenchyma, and structures such as bronchi are displaced, stretched, and narrowed over the bullae surfaces. Very large airspaces can expand across the midline or even extend into the neck. Bullae represent more than just over-expanded alveoli, because the remnants of bronchioles and their accompanying vessels sometimes persist as trabeculae within the bullae.

Interlobular septae can become incorporated into the wall as the airspace expands from within the secondary lobule.

Two important risk factors for bullous emphysema are cigarette smoking and α_1-antitrypsin deficiency. Many patients with bullous emphysema are cigarette smokers, and most bullous lesions are associated with paraseptal or centriacinar emphysema. Although bullous emphysema is typically found in young males, elderly patients with α_1-antitrypsin deficiency who are lifelong nonsmokers may develop bullous changes in later life. A hereditary predisposition to bullous emphysema is also suggested by its association with a variety of rare familial disorders, including Fabry's disease, Salla disease, cutix laxa, Ehlers-Danlos syndrome and Marfan's syndrome. Giant bullous emphysema has also been reported with histological changes of placental transmogrification of the lung. The tight skin mouse, which has a dominant mutation for the elastase gene and is characterized by multiple connective-tissue abnormalities, serves as a unique model for bullous emphysema. In addition, pups, which have weakness of bronchial cartilage, may constitute a valuable model.

DISTRIBUTION OF BULLAE

As noted previously, the tendency for bullae to occur in the upper lobes is usually attributed to the greater mechanical stresses imposed on the lung apices than bases. Because intrapleural pressure near the lung apices is more negative than at the bases, apical alveoli are subjected to greater expanding stresses than are basal alveoli. Radioactive gas studies and in situ freezing techniques have demonstrated that alveoli in the upper lung zones are considerably larger than those in the lower zones. Gravity also plays a role, as the upright lung behaves like a coiled spring, which, when allowed to dangle in the upright position, shows larger gaps between coils at the top than the bottom.

Engineering techniques used to study the distribution of stresses in aircraft have been applied to the analysis of stresses on the lung. These have shown that the larger expanding stresses at the apices are directed primarily in a vertical direction, and to a lesser extent, laterally. The stresses tend to increase with expansion of the lung, but they are present also when the lung volume decreases below functional residual capacity (FRC). The increase in apical stress at low lung volumes has been attributed to an increase in the rigidity of the lungs as residual volume is approached.

ATMOSPHERIC PRESSURE EFFECTS ON BULLAE

Changes in ambient pressure have effects on bullae size that may be of clinical importance. Bullae, blebs, and cysts increase or decrease in size with decreases (e.g., with ascent to high altitude) or increases (e.g., with diving) in atmospheric pressure, respectively. Boyle's law governs the changes: at constant temperature, the volume of a given mass of gas varies inversely with its pressure. Expressed mathematically,

$$P_1V_1 = P_2V_2 \quad (1)$$

where

V_1 = initial volume
V_2 = final volume
P_1 = initial pressure
P_2 = final pressure

Therefore, a twofold increase in pressure results in a 50 percent decrease in volume.

In addition, Charles's law, which states that at constant pressure, the volume of a gas is proportional to its absolute temperature, should be considered in predicting behavior of bullae:

$$V_1/V_2 = T_1/T_2 \quad (2)$$

where

V_1 = initial volume
V_2 = final volume
T_1 = initial temperature, absolute
T_2 = final temperature, absolute

Combining Boyle's and Charles's laws results in the general gas law, which indicates the relationships among pressure, volume, and temperature for an air-filled structure:

$$P_1V_1/T_1 = P_2V_2/T_2 \quad (3)$$

Finally, an additional relevant consideration is that within body cavities, gas is not "dry," but rather, it is saturated with water vapor, the partial pressure of which is related to body temperature. Since normal body temperature is fairly constant at 37°C, the partial pressure of water vapor is also constant at 47 mmHg. Furthermore, since water vapor is not compressible, "wet" gases respond to pressure changes differently than dry gases. Expressed mathematically,

$$V_1(P_1 - PH_2O) = V_2(P_2 - PH_2O) \quad (4)$$

where

V_1 = initial volume
V_2 = final volume
P_1 = initial pressure of gas in the cavity, mmHg
P_2 = final pressure of gas in the cavity, mmHg
PH_2O = water vapor pressure

Thus, for a given reduction in pressure, wet gas expands to a greater extent than does dry gas. The magnitude of relative gas expansion is the ratio of the final volume of the gas (V_2) to the initial volume (V_1), which can be expressed as:

$$V_2/V_1 = (P_1 - PH_2O)/(P_2 - PH_2O) = (P_1 - 47)/(P_2 - 47) \quad (5)$$

Ascent to 39,000 feet in an unpressurized cabin would result in a fivefold increase in the volume of dry air and a sevenfold increase in the volume of wet air.

With reductions in ambient pressure, a pressure differential develops between the inside of a bulla and the external environment. The pressure differential is relieved if air can escape from the bulla to the external environment. If not, the volume of the bulla increases as ambient pressure declines.

Normally, changes in bulla volume are limited anatomically by the magnitude of chest cavity expansion. However, with chest over-expansion, or with an inability to decompress, increases in bulla volume may lead to its rupture and air entry into the extraalveolar compartments, including the mediastinum (pneumomediastinum), soft tissues of the chest or neck (subcutaneous emphysema), pleural space (pneumothorax), or vascular system (air embolism). The magnitude of the effect is related to the ratio of pressure of the gas within the bulla to ambient pressure.

To some extent, this kind of expansion occurs during commercial air travel, since airplanes are not pressurized to atmospheric pressure but rather to a cabin pressure equivalent to an altitude of 6000 to 8000 feet. However, the incidence of barotrauma in commercial flight is low, probably because bulla volume changes are small. In studies performed in subjects with blebs or bullae who are taken to altitudes of 18,500 feet (at an ascent rate of 1000 feet per minute), little increase in bulla volume is noted, probably reflecting good communication between bullae and airways and adequate pressure equalization. The fact that so little volume change occurs supports the "paper bag" hypothesis for bulla formation, rather than a "ball valve" mechanism. In contrast, with space travel, since spacecraft are maintained at atmospheric pressure, as long as decompression does not occur, no changes in the size of bullae are observed.

CLINICAL FEATURES

In asymptomatic individuals, bullae may be detected in the course of routine chest radiography. However, in some patients, bullae give rise to progressive dyspnea or chest pain (Fig. 53-4). On occasion, a patient with bullous lung disease develops sudden, severe breathlessness secondary to development of a spontaneous pneumothorax (Fig. 53-5) or sudden increase in bulla size due to air trapping. Development of bullae in individuals with obstructive airways disease tends to aggravate existing breathlessness, presumably because of a further decline in expiratory flow rates (Fig. 53-6).

In patients with known bullous disease, the onset of fatigue, generally accompanied by an increase in coughing and sputum production, usually heralds the presence of infection in a bulla. Occasionally, pleuritic chest pain is part of the syndrome, while fever and leukocytosis are often not prominent. A Gram's stain of the sputum often shows only mixed flora, without a predominant organism. Radiographically, infection is usually identified by the appearance of an air-fluid level (Fig. 53-7). Alternatively, the accumulation of fluid may be attributed to impeded drainage of the contents of the bulla secondary to obstruction of microscopic communications between the airspace and pulmonary parenchyma. In some instances, infection of a bulla causes it to disappear completely. More often, the air-fluid level persists for weeks or months after the infection has cleared.

The physical findings in a patient with one or more bullae usually reflect the overall state of the lungs. Only infrequently do giant bullae reach a size sufficient to cause a localized decrease in regional air entry, with absent breath sounds and increased resonance to percussion.

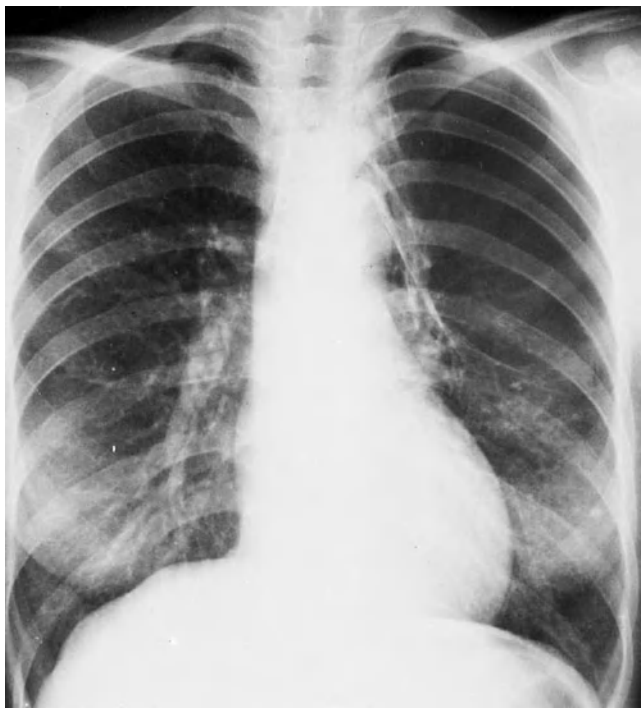
RADIOLOGIC FEATURES

Although routine chest radiography is the most practical method for identifying the presence of bullae, the technique discloses only about 15 percent of bullae identified at autopsy. In a given patient, serial radiographs taken over years are invaluable in tracing evolution of the disease. The presence of the condition is suggested by areas of increased radiolucency which are sharply delineated by fine radiopaque lines representing the walls of the bullae. These lines, or "hairline shadows," are composed of compressed and fused interlobular septae or pleura. Because the hairline shadows appear incomplete on the chest radiograph, they delineate only segments of the bulla wall (Fig. 53-5 *A* and *B*). Distinction between hairline shadows produced by a bulla, and thicker, sometimes irregular, walls of a cavity is usually not difficult. More troublesome is distinguishing bullae from cysts. The presence of other radiologic signs of emphysema or fibrotic lung disorders suggests that the cystic structure is a bulla. Similarly, distinguishing between a large bulla and pneumothorax may be challenging. Observation of "the double wall sign" (i.e., the presence of air on both sides of the bulla wall) may be helpful in identifying the findings as due to a bulla. The differential diagnosis of multiple, enlarged thin-walled airspaces on the chest radiograph in adults is shown in Table 53-3.

Fluid in Bullae

Although a localized air-fluid level on the chest radiograph raises the possibility of infection, the differential diagnosis includes lung abscess, tuberculosis, fungal disease, cavitary lung carcinoma, pulmonary hemorrhage within a bulla, congestive heart failure, and carcinoma arising from within a bulla (Fig. 53-8). The superimposition of a chronic infiltrate and an existing bulla raises the likelihood of concomitant fungal infection or tuberculosis.

The presence of a fluid level within a bulla, especially if the bulla is located subpleurally, occasionally prompts the mistaken diagnosis of a loculated hydropneumothorax. Computed tomography is helpful in separating these two conditions: when locules within the bulla fill with fluid, the



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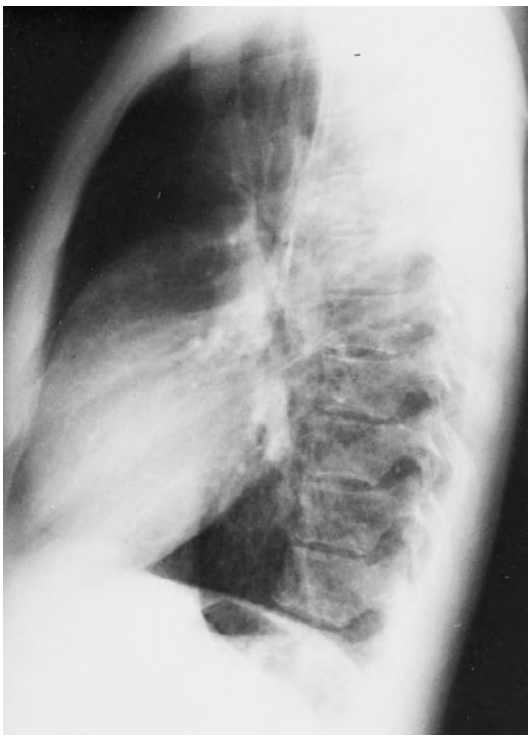

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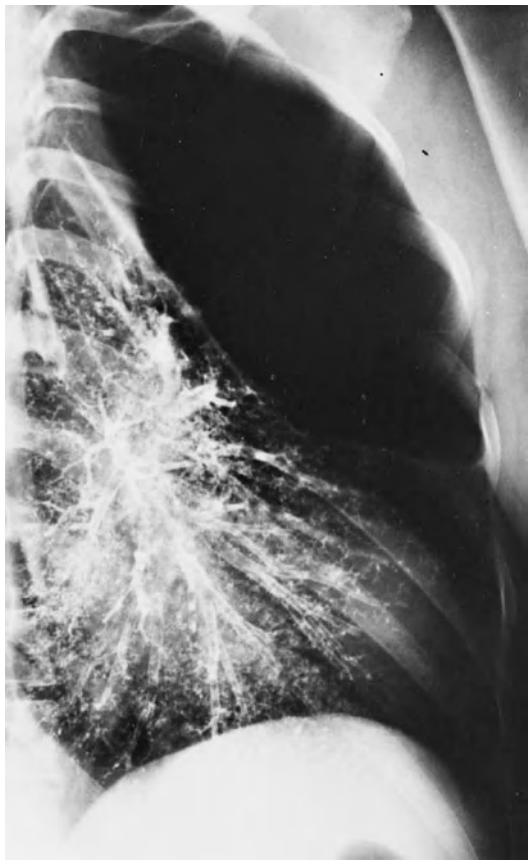
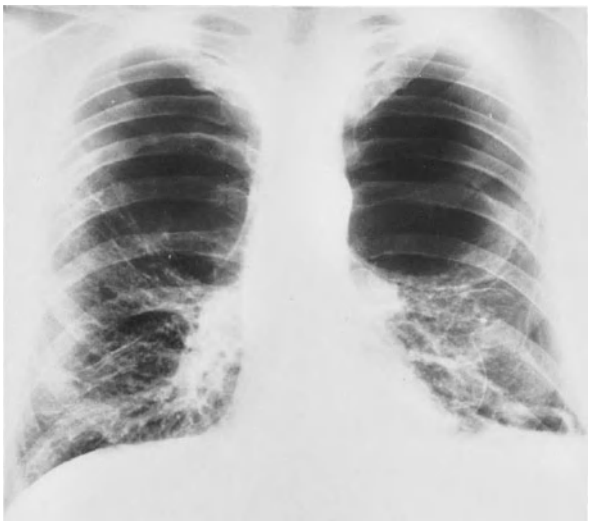


C

Figure 53-4 Large bulla in a 35-year-old woman admitted because of chest pain and increasing dyspnea. *A*. Chest radiograph (PA view). A large translucent area in the left upper lung represents a bulla that is causing compression of adjacent lung. *B*. Chest radiograph (lateral view). A hairline shadow outlines a large bulla in the left upper lobe. *C*. Bronchogram of left lung. Compression of the bronchial tree by the large bulla is evident.



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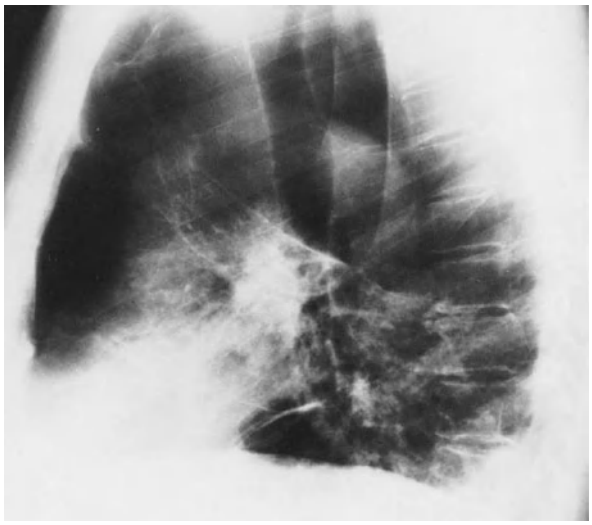

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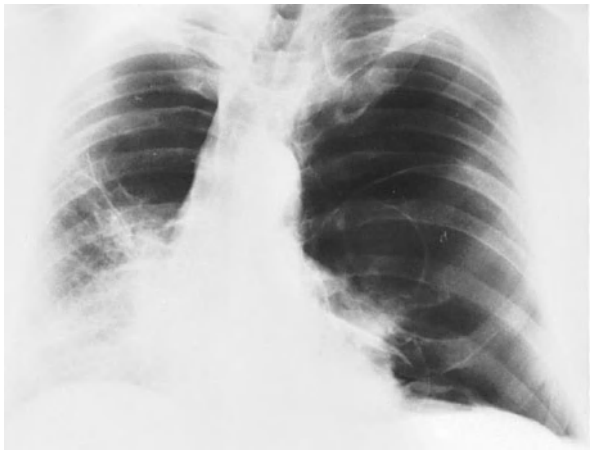


C

Figure 53-5 Bullous disease in a 53-year-old man. *A*. Chest radiograph (PA view) showing upper zonal areas of increased radiolucency. *B*. Chest radiograph (lateral view) showing hairline borders of multiple bullae. *C*. Chest radiograph showing a left-sided pneumothorax with residual inflated bullae. *(Courtesy of Dr. S. Flicker.)*

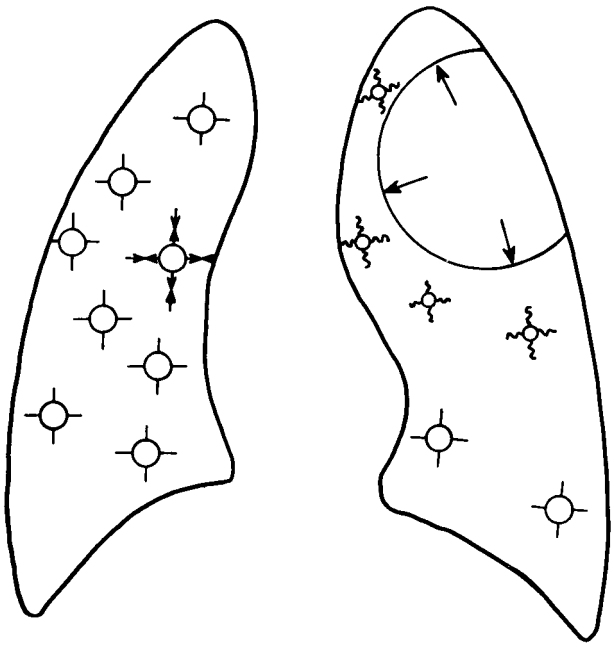


Figure 53-6 The effects of an enlarging airspace on radial traction exerted by elastic tissue on the airways. The reduction in lumen diameter is associated with an increase in airway resistance.

bulla shows characteristic strands or septae, sometimes in a "stepladder" configuration. In contrast, a loculated hydrothorax shows no septae.

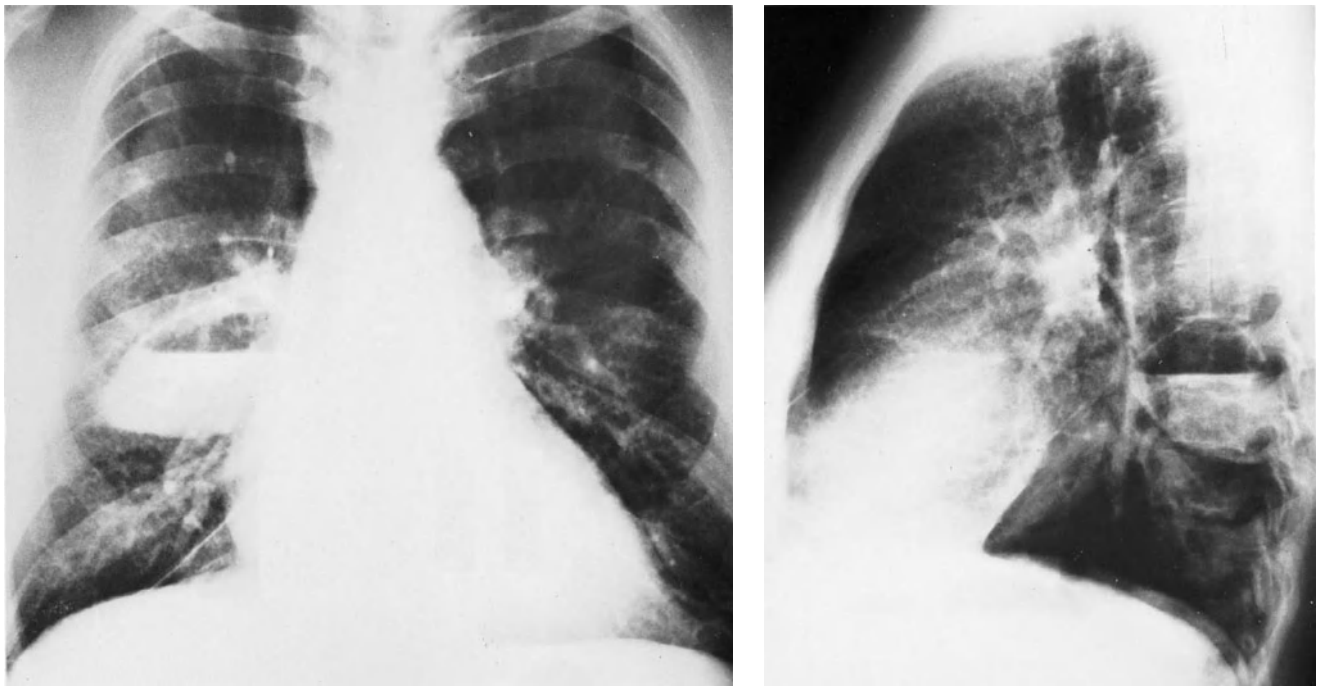
Special Techniques

A chest radiograph obtained after forced expiration is sometimes helpful in demonstrating the presence of bullae: air trapping during the expiratory maneuver accentuates their outline by preventing a decrease in their size as the surrounding lung empties. Large bullae sometimes displace the mediastinum contralaterally and may even compress the opposite lung.

Computed Tomography

Computed tomography (CT) provides valuable anatomic information about the size, number, and relationships of bullae, as well as crowding of adjacent lung and disposition of the pulmonary vasculature. Bullae are identified as areas of radiolucency that usually do not contain blood vessels and that are confined by visible walls. High-resolution computed tomography (HRCT) shows that large bullae are frequently associated not only with distal acinar (paraseptal) emphysema, but also with centri-acinar emphysema—the type of emphysema usually associated with cigarette smoking.

These observations are consistent with the hypothesis that peripheral airspaces in paraseptal emphysema may coalesce to form larger bullae that may crowd normal adjacent lung. In addition, CT has shown that when bullae occur in the context of generalized emphysema, the extent of bullous emphysema correlates poorly with measurements of pulmonary function, and that the main determinant of



A *B*

Figure 53-7 An infected bulla in a 44-year-old man with mitral stenosis. *A*. Chest radiograph (PA view). A translucent area is visible in the right midzone with a clearly defined air-fluid level. *B*. Lateral radiograph.

respiratory function is the severity of emphysema in the bullous-free parts of the lung (Fig. 53-9). In contrast, the severity of emphysema in nonbullous lung, as assessed by CT-density histograms of the lung, correlates well with measurements of air flow limitation and diffusing capacity.

CT has been used to create three-dimensional reconstructions of bullae, which can then be used to calculate bullae volumes.

Nuclear Medicine Techniques

Lung scanning using radionuclide-based techniques may provide useful preoperative information in evaluating patients with bullous lung disease (Figs. 53-10 and 53-11). A lung perfusion scan provides a semiquantitative assessment of regional blood flow; results of ventilation scans vary with the technique: a single-breath scan using ^{133}xenon often fails to demonstrate ventilation of a bulla, whereas a continuous ventilation scan often shows slow filling and emptying of the structure. Complete lack of communication between the airways and bulla is reflected in the absence of filling during all phases of the continuous ventilation scan.

Very occasionally, angiography may be necessary to provide additional information on the pulmonary vasculature (Fig. 53-11). Similarly, a regional bronchogram at the time of bronchoscopy is sometimes helpful in assessing the state of the airways in compressed lung.

Table 53-3

The Differential Diagnosis of Thin-Walled Enlarged Airspaces in the Lungs

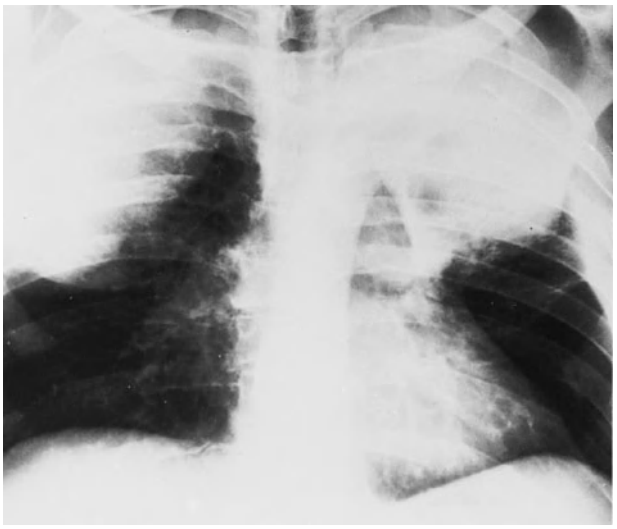
Cystic bronchiectasis
Pneumatoceles
Fungal infections (coccidioidomycosis)
Septic emboli
Parasitic disorders

PATHOPHYSIOLOGY

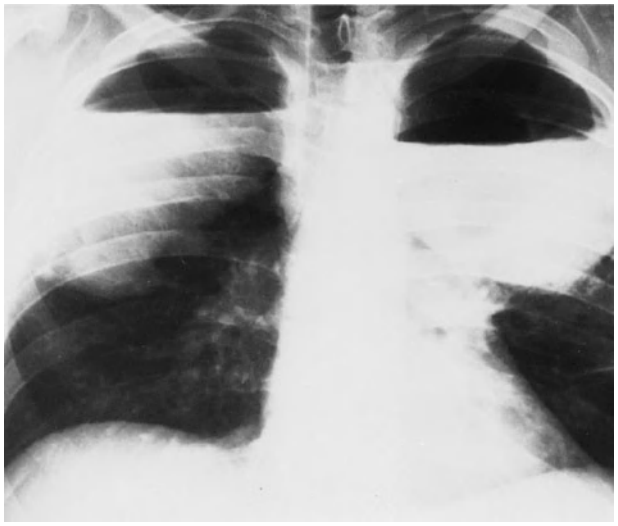
Clinical evaluation of bullous lung disease is aided by assessment of pulmonary function, pulmonary mechanics, exercise performance, and the pulmonary circulation.

Pulmonary Function Tests

Pulmonary function tests have considerable practical value in distinguishing between individuals with localized bullae in whom intervening lung is normal (bullous disease), and those in whom localized bullae are part of obstructive airways disease (bullous emphysema) (Tables 53-4 and 53-5). The distinction is important, since those with obstructive airways disease are generally poor surgical candidates because of impaired pulmonary function.



A



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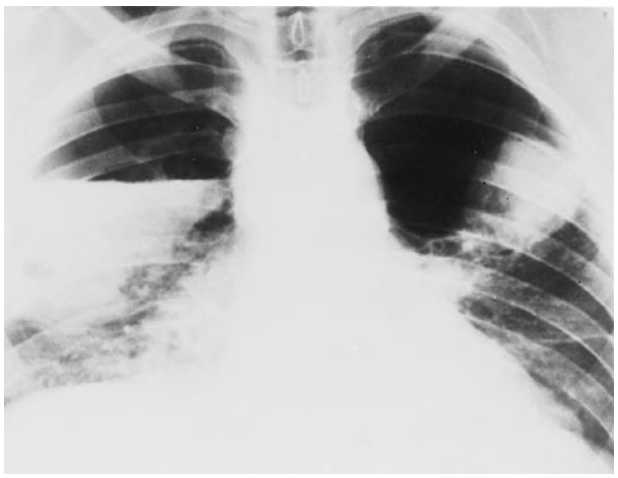


C

Figure 53-8 Infected bullae. *A*. Bilateral infected bullae in a 62-year-old man. *B*. Fluid levels in both bullae. *C*. Clearing of the infection revealed a bronchogenic carcinoma on the left. *(Courtesy of Dr. M. Feierstein.)*

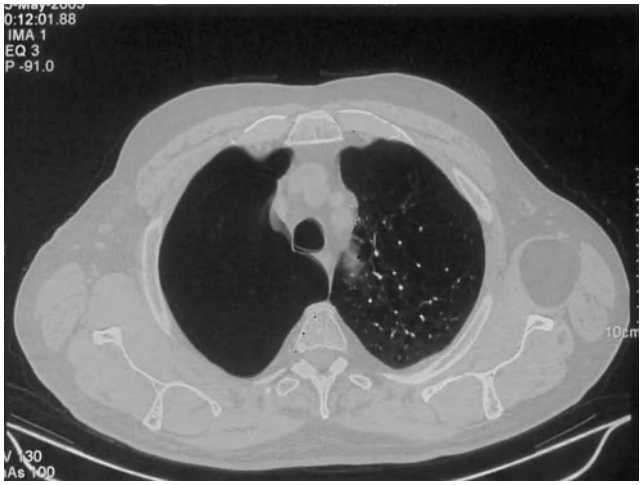


Figure 53-9 CT image showing a giant right upper lobe bulla compressing adjacent pulmonary parenchyma. The bulla was surgically resected with significant improvement in pulmonary function. See Table 53-7.

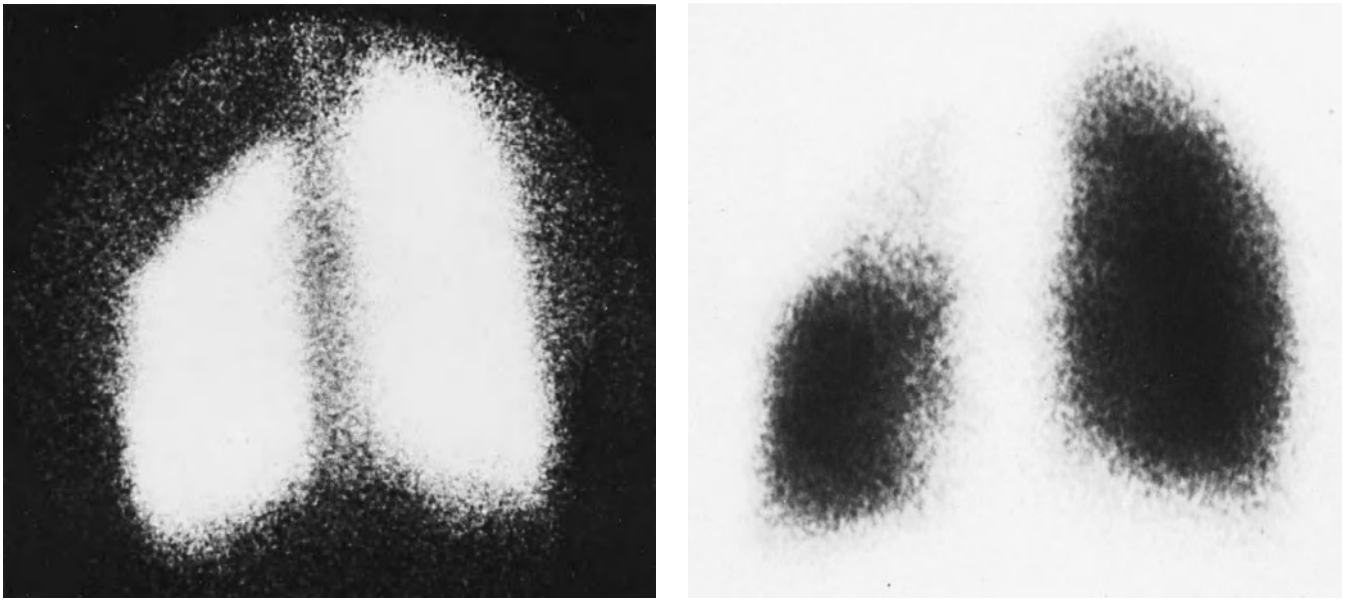
In individuals with bullous disease, the volume of air in the lungs can be estimated using plain radiography, CT, body plethysmography, or other pulmonary function test methods for determining lung volume, including closed circuit (helium dilution) and open circuit (nitrogen washout) techniques. The volume of air trapped in a bulla can be determined as the difference between the functional residual capacities determined plethysmographically and by open or closed circuit methods (Table 53-6). This difference is due to the relative inability of the inert gas used in the circuit methods to enter the bulla.

Although the nitrogen washout curve is usually normal, the concentration of N_2 in alveolar gas at the end of the test's 7-minute period of breathing 100 percent O_2 is often abnormal. Finally, somewhat counterintuitive is the observation that expansion of a large bulla may produce a restrictive pattern on pulmonary function testing—presumably as a result of the bulla compressing intervening normal lung.

Pulmonary Mechanics

Distinction between widespread obstructive airways disease with concomitant bullae and bullous lung disease has practical significance, since surgical lung resection in generalized emphysema offers a less certain therapeutic response than does resection of giant bullae in the absence of widespread obstructive lung disease.

As large bullae expand, they initially cause relaxation of adjacent elastic lung tissue; with continued expansion, adjacent lung is compressed. Relaxation of the surrounding pulmonary parenchyma results in a decrease in radial traction on airways, thereby increasing air flow resistance. The effects of bullectomy on respiratory mechanics are inconsistent. In some patients, removal of a large bulla increases lung static elastic recoil and decreases airways resistance (Table 53-7); in others, bullectomy decreases elastic recoil pressure.



A *B*

Figure 53-10 Lung scans in the preoperative evaluation of patients for bullectomy. *A*. Preoperative ventilation lung scan (^{133}Xe). Ventilation is absent in the left upper zone. *B*. Preoperative perfusion lung scan using ^{131}I-macroaggregated albumin. Blood flow is absent in the left upper zone while it is maintained at the left base. *(Courtesy of Dr. A. Alavi.)*

As a practical matter, the diffusing capacity, rather than lung elastic recoil, is usually determined to aid in distinguishing between widespread emphysema and localized bullae; indeed, the diffusing capacity correlates better with morphologic estimates of emphysema than do most other tests. Although the combination of a decreased diffusing capacity and reduced static elastic recoil pressure favors the diagnosis of widespread emphysema rather than localized bullae, both measurements may also be decreased by bullae that compress adjacent normal lung.

Respiratory muscle strength, assessed by measurements of maximal inspiratory and transdiaphragmatic pressures, improves after bullectomy in some patients with bullous emphysema.

Exercise Testing

In patients with a few circumscribed bullae and otherwise normal lungs, exercise testing reveals that the alveolar-arterial difference in Pa_{O_2}, ratio of dead space to tidal volume, diffusing capacity, and arterial oxygenation remain normal or near normal with exercise. On the other hand, in patients in whom bullae are associated with panacinar emphysema, the alveolar-arterial difference in Pa_{O_2} is widened at rest and during exercise. The latter group of patients also may develop arterial hypoxemia during exercise. The Pa_{CO_2} tends to hover around the upper limit of normal at rest and during exercise, and the ratio of dead space to tidal volume is higher than in patients with normal intervening lung. The steady-state diffusing capacity is also reduced and fails to increase normally during exercise.

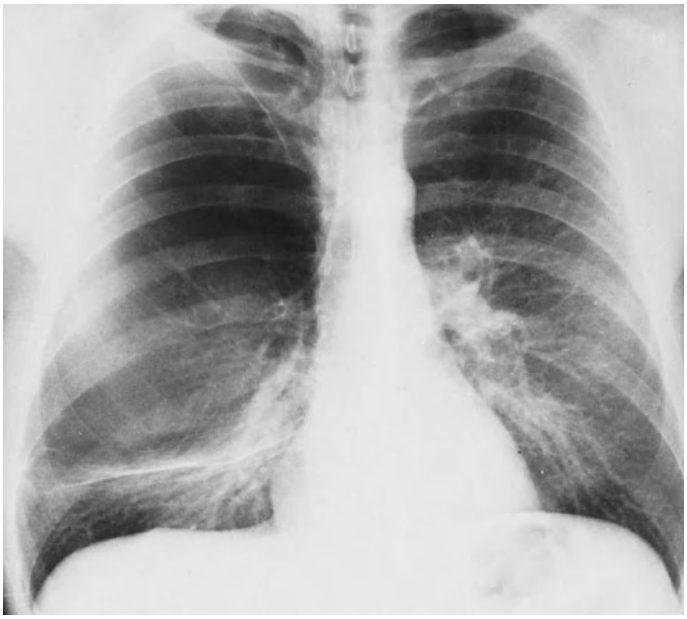
Patients in whom bullae are associated with chronic bronchitis also show a widened alveolar-arterial difference in Pa_{O_2} and an increase in the ratio of dead space to tidal volume at rest. However, in these patients the decrease in Pa_{O_2} during exercise is modest, even though the Pa_{CO_2} at rest is abnormally high and increases further during exercise (indicating progressive alveolar hypoventilation).

Pulmonary Circulation

As a rule, resting pulmonary arterial pressure and blood flow are within normal limits in patients with bullous lung disease (i.e., the bullae act like "amputated" segments of lung); the volume of the vascular bed available for recruitment as cardiac output increases is limited. However, in patients in whom bullous disease has severely reduced the extent of the pulmonary vascular bed, pulmonary arterial pressure may be elevated at rest and during exercise; in a few instances, pulmonary and cor pulmonale may be observed. Exercise in bullous lung disease is generally associated with an excessive increase in pulmonary arterial pressure as increases in pulmonary blood flow are not effectively accommodated by the restricted vascular bed. Underlying pulmonary disease further exaggerates the increase in pulmonary artery pressure during exercise.

COMPLICATIONS

The major complications of bullous lung disease are infection of the bulla, chest pain, hemorrhage, spontaneous pneumothorax, and lung cancer.



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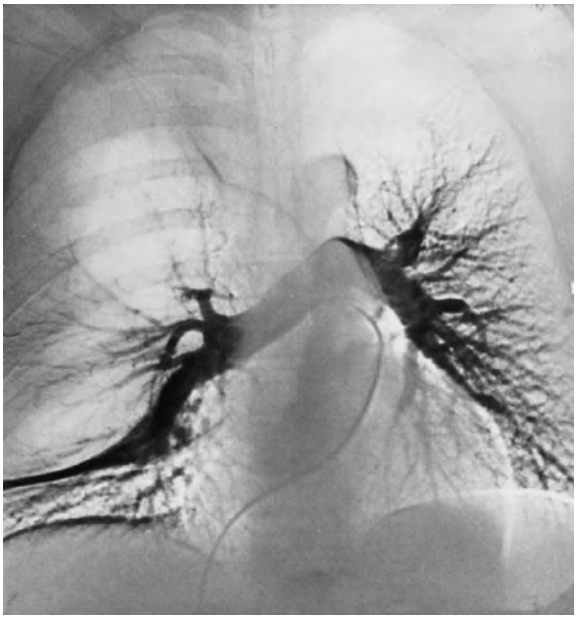

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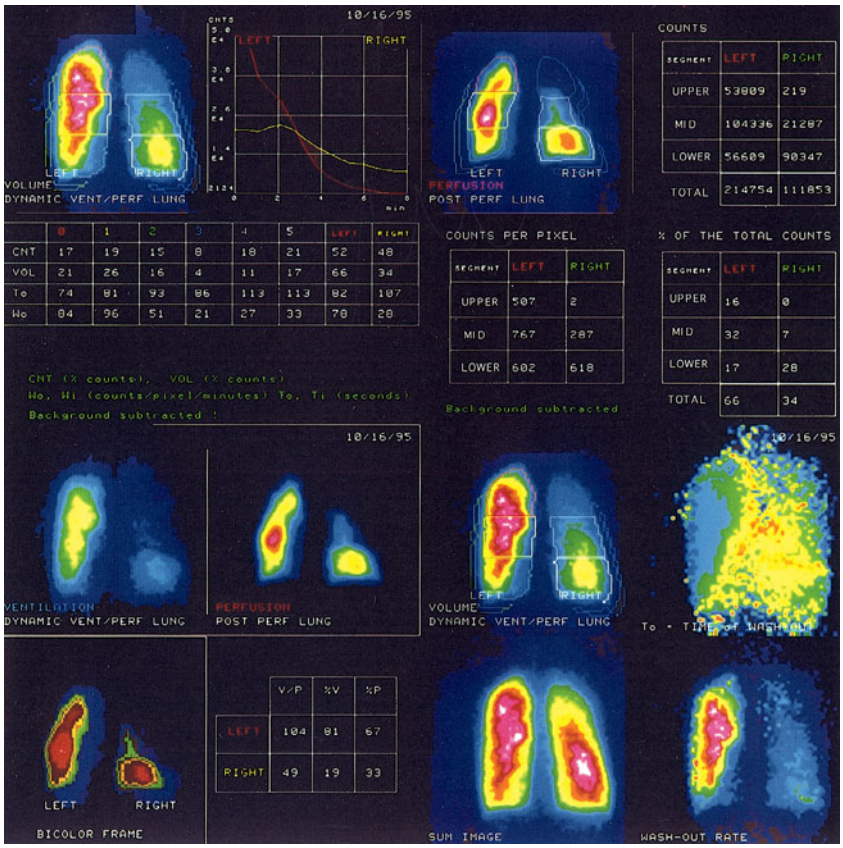

C

Figure 53-11 Large bulla in a 38-year-old man admitted because of increasing dyspnea. *A*. A chest radiograph (PA view). A large translucent area in the right upper lung represents an enlarging bulla that is causing compression of adjacent lung. *B*. Pulmonary arteriogram, subtraction technique. The pulmonary vasculature is compressed by the large bulla. *C*. Lung scans in the preoperative evaluation of patients for bullectomy. The ventilation lung scan (^{133}Xe) shows decreased ventilation to the left upper lung zone. The perfusion lung scan using ^{131}I-macroagglutinated albumin shows blood flow is decreased on the left upper zone while it is maintained at the left base. Quantitative regional ventilation and perfusion obtained from the lung scans of this patient. Ventilation is markedly reduced in the right upper zone. Perfusion is absent in the right upper zone while it is present at the base. *(A and B courtesy of Dr. M. Ora; C courtesy of Dr. B. Paczolt.)*

Table 53-4

Pulmonary Function Tests in a 65-Year-Old Black Man with Bullous Lung Disease

	Prebronchodilator		
Spirometry	**Actual**	**% Pred.**	**Pred.**
FVC, L	1.21	38	3.16
FEV_1, L	0.74	30	2.46
FEV_3, L	1.03	35	2.94
FEV_1/FVC%	61		80
FEV_3/FVC%	85		97
FEF_{25-75}, L/s	0.34	11	3.21
PEFR, L/s	3.05	46	6.57
FIF_{25-75}, L/s	1.30	23	5.67
SVC, L	1.42	38	3.72
IC, L	1.13	48	2.38
ERV, L	0.28	21	1.33
FRC, L	1.60	44	3.59
RV, L	1.31	58	2.26
TLC, L	2.73	47	5.85
RV/TLC%	48.11	123	39.00
D_{LCO}, single breath, ml/min/mmHg	10.06	40	25.18
Pulmonary vascular pressures			
Pulmonary artery, mmHg	60/22		30/16
Mean, mmHg	27		20

Table 53-5

Pulmonary Function Tests

Test	**Bullous Disease**	**Obstructive Airways Disease and Bullae**
TLC, L	N	N ↑
RV, L	N	↑
FRC, L	N	↑
FRC,* L	↑	↑
RV/TLC%	N	↑
FEV_1, L	N ↓	↓
FVC, L	N ↓	↓
FEV_1/FVC%	N	↓
MVV, L/min	N	↓
D_{CO}/V_A, (ml/min/mmHg)/L	N	↓
Raw, cmH_2O/L/s	N ↑	↑
Cst, exp, L/cmH_2O	N ↑	↑
Pst, TLC, cmH_2O	N ↓	↓

* *FRC determined by body plethysmography.*
Note: N = normal, ↑ = increased, ↓ decreased.

True infections within bullae are rare. The presence of an air-fluid level in a bulla usually is attributable to surrounding pneumonitis. Fluid within the airspace is usually sterile, is frequently resorbed, and may be associated with shrinkage and complete resolution of the bulla. Occasionally, a fungus (usually *Aspergillus* species) colonizes a bulla and may go on to form a mycetoma or "fungus ball" which can lead to hemoptysis.

Chest pain may occur with a bulla and is attributed to over-distention of the structure. The pain is angina-like and located retrosternally. The symptom is sometimes so severe as to constitute an indication for surgical intervention.

Hemoptysis, which is occasionally massive, can result from rupture of blood vessels within the walls of bullae. Pneumothorax secondary to bulla rupture into the pleural space can severely compromise a patient's ventilatory reserve in the setting of generalized emphysema. However, bullae per se do not appear to indicate a predisposition to recurrent pneumothoraces.

Recurrent spontaneous pneumothorax also may be a complication of paraseptal emphysema, particularly in patients who continue to smoke. Lung density measurements in spontaneous pneumothorax demonstrate air trapping, suggesting a ball-valve mechanism due to peripheral airway inflammation, rather than rupture of preexisting bullae. Patients with ruptured bullae also tend to have prolonged air leaks, along with pleural and parenchymal infections.

Table 53-6

Pulmonary Function Tests in a 43-Year-Old Man with Right-Upper-Lobe Bulla (see Fig. 53–12)

	Prebronchodilator Pulmonary Function Tests		
	Actual	**Predicted**	**% Predicted**
FVC (L)	4.79	4.69	102
FEV_1 (L)	3.39	3.57	95
$FEF_{25–75\%}$ (L/s)	2.24	3.73	60
PEFR (L/s)	8.74	8.92	98
FEV_1/FVC%	70.79	—	—
MVV (L/min)	116.75	131	89
SVC (L)	4.76	4.66	102
TLC (L)	7.09	6.63	107
FRC (L)*	2.86	2.70	106
FRC (L)†	3.83	2.70	142
RV (L)	2.34	1.90	123
RV/TLC (%)	32.98	28.92	114
Raw (cm H_2O/L/s)	4.30	0.5–2.0	—

** measured by helium dilution; † measured by body plethysmography.*

Primary lung cancer has been reported to be associated with bullous lung disease. In many instances, the bullae are detected only by CT. The increased incidence of lung cancer may be due to the fact that lung cancer occurs more frequently in fibrotic lungs which are, themselves, predisposed to development of bullae. Other explanations for the increased incidence of malignancy include dystrophic changes in lung parenchyma caused by bullous disease or persistence of carcinogens in poorly ventilated bullae.

TREATMENT

Many patients with bullous lung disease can be managed medically. Because the natural history of a bulla is unpredictable, patients with bullous disease should be monitored by chest radiography at regular intervals to ensure that the disease is stable. Occasionally, bullae enlarge suddenly and rapidly for no apparent reason; alternatively, they may shrink or disappear, usually as a result of infection.

Medical Management

The finding of a bulla in an asymptomatic patient calls for reassurance, a recommendation for annual chest radiography, advice to stop smoking, and an alert to the need for a prompt visit to a physician should symptoms develop. Activities that promote rupture of bullae (e.g., contact sports and scuba diving) should be proscribed. Chronic bronchitis, asthma, or emphysema associated with bullae require treatment in their own right. For patients with α_1-antitrypsin deficiency augmentation therapy with antiproteases may be appropriate.

Infection of a bulla requires sputum specimens for culture and Gram's stain. Fiberoptic bronchoscopy is usually performed if sputum samples fail to disclose the nature of the infection; sterile sheathed catheters may be helpful in obtaining noncontaminated respiratory tract secretions for culture. Direct sampling of fluid from within the bulla is rarely useful in making the diagnosis.

Once the diagnosis of an infected bulla has been established, treatment with antibiotics and chest physiotherapy is begun. The choice of antibiotic depends on the findings on Gram's stain and sputum cultures. Treatment is sometimes prolonged and may require parenteral administration, since poor drainage of the bulla inevitably slows resolution of the disease process. The course of the infection should be followed by interval chest radiographs. Most infections eventually respond to medical therapy, but radiographic evidence of an air-fluid level often persists after the infection has resolved. An infected bulla containing a very large amount of fluid may require surgical intervention in order to minimize the risk of the fluid being decanted into the adjacent or contralateral lung and airways.

Surgical Management

In patients with giant bullae who are selected carefully for the presence of localized disease and well-preserved pulmonary function, surgical intervention may provide symptomatic relief, extend exercise tolerance, and improve spirometry, diffusing capacity, and ventilation-perfusion matching.

In general, surgical outcome depends on the size and number of resected bullae, condition of compressed lung, status of the contralateral lung, and development of postoperative complications.

Radionuclide scanning and CT are helpful in preoperative assessment of the compressed lung. Pulmonary angiography is now rarely employed for this purpose.

Localized Bullae with Normal Intervening Lung (Bullous Lung Disease)

In patients with localized bullae and normal intervening lung, acute complications (e.g., spontaneous pneumothorax

Table 53-7

Preoperative and Postoperative Pulmonary Function Tests in Bullous Disease*

	Preoperative		Postoperative	
Test	**Actual**	**Predicted**	**Actual**	**Predicted**
FVC (L)	1.76	3.67	2.79	3.67
FEV_1 (L)	0.73	2.43	1.23	2.43
$FEF_{25-75\%}$ (L/s)	0.26	2.36	0.44	2.36
PEFR (L/s)	3.57	7.93	4.83	7.93
FEV_1/FVC%	41.76	>70	44.04	>70
MVV (L/min)	29.09	100.3	51.80	100.3
SVC (L)	2.54	3.97	3.71	3.97
TLC (L)	7.27	9.32	5.80	9.32
FRC (L)	5.25	3.41	3.62	3.41
RV (L)	4.73	2.34	2.09	2.34
RV/TLC%	65.05	38.72	36.09	38.72
Raw (cm H_2O/L/s)	35.60	0.5–2.0	5.46	0.5–2.0
D_{LCO} (ml/mm/mmHg)	7.20	23.2	9.78	23.2
D_{LCO}/V_A (ml/min/mmHg/L)	2.04	3.85	2.13	3.85

** Test for a 74-year-old man who underwent successful bullectomy after smoking cessation. Second study performed 4 months after surgery (see Fig. 53-9).*

or massive hemorrhage) may require urgent surgical intervention, even though the bullae may be small. In non-urgent circumstances, indications for surgical intervention include the following: (1) enlarging bullae that cause dyspnea; (2) enlarging bullae that compress surrounding lung tissue; (3) bullae that cause recurrent pneumothoraces; (4) bullae that become infected and fail to respond to medical treatment; (5) bullae causing acute respiratory insufficiency; (6) bullae that become acutely distended; (7) enlarging bullae that produce severe chest pain; (8) bullae associated with primary lung cancer; and (9) bullae containing very large fluid collections.

The surgical approach depends on the location of the bullae. Median sternotomy, which is associated with less postoperative morbidity than standard thoracotomy, may be appropriate for bilateral upper lobe bullae. As a rule, small wedge excisions or plications of large bullae produce larger increments in expiratory flow rate than lobectomy and may be performed with using video-assisted thoracoscopy (see below). Surgical techniques developed to reduce air leaks following resection of emphysematous lung include use of "buttressed stapling" and application of fibrin glues. Bullectomies are now sometimes combined with lung volume reduction surgery.

The best functional improvement after surgery occurs when the bulla comprises 50 to 100 percent of the hemithorax (Fig. 53-12), where postoperative increments in forced expiratory volume in 1 second (FEV_1) range from 50 to 200 percent. Better results may be anticipated when the involved lung contributes little to overall ventilation, when large volumes of trapped air exist, and when there is crowding and compression of normal lung parenchyma.

Surgical techniques involve buttressing staple lines using bovine pericardium and use of fibrin glues and pleural tents. Attention to postoperative management is critical to good surgical outcomes and includes underwater thoracostomy suction, early and vigorous chest physiotherapy, and early ambulation. Regular postoperative chest radiographs

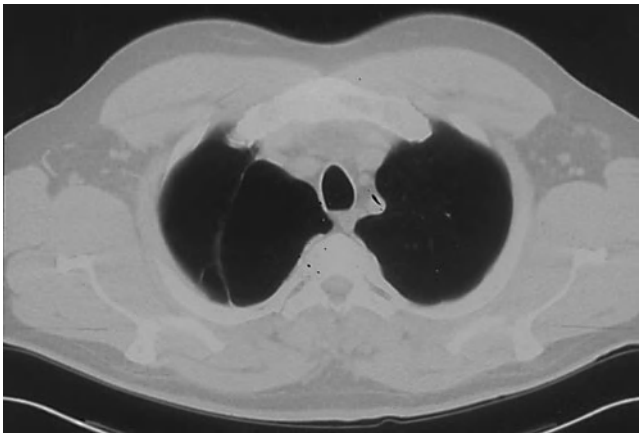

Figure 53-12 CT image showing a single right upper lobe bulla in the medial portion of the lung. See Table 53–6.

identify residual airspaces. Prolonged air leaks may be managed using Heimlich valves following patient discharge from the hospital.

Postoperative complication rates tend to be high (up to 80 percent). Not surprisingly, persistent air leaks and pleuropulmonary infections are common; atrial fibrillation, need for prolonged postoperative mechanical ventilation, massive subcutaneous emphysema, and retention of respiratory secretions also occur.

Overall surgical mortality may be as high as 9 percent, but it is usually approximately 2 to 5 percent. The most common causes of death are infection and respiratory failure; sudden development of a contralateral pneumothorax and herniation of a bulla across the mediastinum are uncommon causes.

Five-year survival is approximately 90 percent, and significant increments in FEV_1 persist in over 80 percent of patients. Residual volume usually returns to baseline. Improvements in dyspnea also persist at 3 years in over 80 percent of patients.

Localized Bullae with Abnormal Intervening Lung

As a rule, bullae that complicate either obstructive or fibrotic lung disease do not require surgical intervention unless a life-threatening complication arises.

When bullae occur in conjunction with widespread panacinar emphysema, usually, but not necessarily, little improvement is seen with bullectomy. This is particularly true in COPD when the FEV_1 is less than 35 percent of predicted. Elderly individuals in whom the bullae are associated with widespread emphysema frequently have a high surgical mortality. When bullae are associated with chronic bronchitis, improvement after surgery is generally short-lived (i.e., less than 6 months). A prolonged, productive cough and secondary pulmonary hypertension are associated with a poor prognosis. The outlook after surgery is better for those who stop smoking than for those who do not (Table 53-7).

Video-Assisted Thoracoscopy

Video-assisted thoracoscopy has become a common surgical approach in plication of bullae. Thoracoscopy requires careful general anesthetic management and introduction of a double-lumen endotracheal tube to permit collapse of one lung. Once a bulla has been identified, the lung is deflated and the bulla excised using a stapling device. Mortality and complication rates are usually lower than with other surgical approaches.

Laser Surgery

Current laser-based surgical techniques have evolved since 1990, when a low energy carbon dioxide laser was used to ablate pleural blebs in treatment of spontaneous pneumothorax. Subpleural bullae collapse when exposed to laser energy, as do multiple bullae occurring in the setting of widespread emphysema. Complications of the technique include postoperative air leaks, bleeding, and acute lung injury.

Patients with large bullae associated with crowding of adjacent lung structures, upper lobe predominance, and minimal underlying emphysema appear to experience the greatest improvement in FVC, FEV_1, maximal voluntary ventilation (MVV), specific airway conductance, and residual volume.

Both the argon beam coagulator and yttrium-aluminum-garnet (YAG) laser have been used in conjunction with video-assisted thoracoscopy in ablating bullae in treatment of bullous emphysema. Procedure-related mortality in using these two devices is 0 and 10 percent, respectively.

External Drainage: Monaldi Procedure

In 1938, Monaldi described a two-stage technique for the open intubation and external drainage of tuberculous cavities. The procedure was subsequently applied to treatment of pyogenic lung abscesses and bullae as a single-stage procedure—endocavitary aspiration with sclerosis and pleurodesis, known as the Brompton technique. The technique is sometimes useful in patients whose pulmonary function precludes thoracotomy. Data indicate a 28 percent improvement in FEV_1 and 12 percent improvement in total lung capacity following the procedure. The mortality rate is approximately 7 percent. Predictors of a poor prognosis are an FEV_1 less than 0.5 L and a Pa_{CO_2} greater than 49 mmHg.

Reduction Pneumoplasty and Lung Transplantation

Other potential treatments for giant bullae include reduction pneumoplasty, following which both symptomatic and functional improvements have been reported. Reduction pneumoplasty is most effective when bullae are larger than one-third of a hemithorax, adjacent lung is compressed, and the FEV_1 is less than 50 percent of predicted. However, the duration of improvement and the late morbidity and mortality are not well defined.

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PART

V

Occupational and Environmental Disorders

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54
CHAPTER

Occupational Lung Disorders: General Principles and Approaches

Mridu Gulati • Carrie A. Redlich

Hazardous exposures in the workplace and elsewhere in the environment continue to contribute to the burden of lung disease. With increasing concerns regarding the health effects of environmental and occupational exposures, such as exposures following the World Trade Center collapse, clinicians must be prepared to recognize, diagnose, and manage occupational and environmental lung diseases. As patient access to sources of information regarding such exposures expands, health care providers must also be prepared to provide preventive advice and to address patients' concerns regarding such exposures. Most respiratory diseases, including asthma, chronic obstructive pulmonary disease (COPD), interstitial lung disease, and lung cancer may be caused or exacerbated by factors in the workplace, but rarely are such disorders distinguishable pathologically or clinically from idiopathic or nonoccupational causes. Thus a high level of suspicion and knowledge of the basic approaches used in the diagnosis and management of occupational and environmental disorders is essential for all practitioners. This chapter provides an overview to these approaches. Since the last edition, a growing body of literature has expanded our understanding of several aspects of occupational and environmental lung diseases, including a substantial contribution of workplace exposures to the development of COPD and asthma, adverse health effects related to indoor and outdoor air pollution, and greater recognition that work-exacerbated asthma can be as disabling

as primary occupational asthma. Additional information can be obtained from several excellent recent texts on this topic.

CLASSIFICATION OF OCCUPATIONAL AND ENVIRONMENTAL LUNG DISEASE

Environmentally induced lung diseases can be classified according to several schemes. One useful approach is to classify them by clinical presentation or disease, as shown in Table 54-1. A given exposure (asbestos, cobalt, etc.) can cause more than a single disorder. When one is examining a patient, it can also be helpful to consider occupational lung diseases by types of exposures that can cause lung disease, such as mineral dusts (asbestos, silica, coal), biologic factors (animal exposures, microbial agents), metals (beryllium, cobalt, aluminum), or inorganic gases (carbon monoxide, chlorine, nitrogen oxides), or by the type of industry associated with selected respiratory problems, such as mining, agriculture, forestry, or welding. For patients presenting with interstitial lung disease, a classification scheme based on histological pattern, as shown in Table 54-2, may facilitate diagnosis and management.

Occupational and environmental exposures play an important role in many lung disorders. However, accurate estimates of the contribution of such factors to specific lung diseases can be difficult to find. It is generally believed that under recognition and under reporting of occupational lung diseases are widespread. Although historically the pneumoconioses have been the most commonly diagnosed occupational lung diseases, occupational airways diseases have become the most prevalent occupational lung disorder in developed countries. Worldwide, silicosis remains the most common occupational lung disease. In a few instances, such as the rare tumor mesothelioma, most cases can be attributed to occupational exposure to asbestos. However, the contribution of

Table 54-1

Classification of Occupational Lung Disorders

Major Disease Category	Representative Causative Agents
Upper respiratory tract irritation	Irritant gases, fumes, dusts
Airway disorders	
Occupational asthma	
Sensitization	
Low molecular weight	Diisocyanates, anhydrides, wood dusts
High molecular weight	Animal-derived allergens, latex
Irritant-induced, RADS	Irritant gases, smoke
Byssinosis	Cotton dust
Grain dust effects	Grain
Chronic bronchitis/COPD	Mineral dusts, coal, fumes, dusts
Acute inhalation injury	
Toxic pneumonitis	Irritant gases, metals
Metal fume fever	Metal oxides: zinc, copper
Polymer fume fever	Plastics
Smoke inhalation	Combustion products
Hypersensitivity pneumonitis	Bacteria, fungi, animal proteins
Infectious disorders	Tuberculosis, viruses, bacteria
Pneumoconioses	Asbestos, silica, coal, beryllium, cobalt
Malignancies	
Sinonasal cancer	Wood dust
Lung cancer	Asbestos, radon
Mesothelioma	Asbestos

Note: Abbreviations: RADS = reactive airway dysfunction syndrome; COPD = chronic obstructive pulmonary disease.

Table 54-2

Histologic Classification Lung Disorders

Selected Histologic—Clinical Descriptions	Selected Associated Occupational Exposures
Usual interstitial pneumonitis/idiopathic pulmonary fibrosis	Asbestos, radiation
Nonspecific interstitial pneumonitis	Organic antigens
Acute interstitial pneumonitis (diffuse alveolar damage)	Irritant inhalational injury—NO_x, SO_x
Hypersensitivity pneumonitis	Organic antigens (i.e. farmer's lung, wood worker's lung), Animal antigens (birds), Metal working fluids Chemicals—isocyanates, anhydrides
Sarcoid-like granulomatous lesions	Beryllium, organic antigens, aluminum
Giant interstitial pneumonitis	Cobalt (hard metal)
Bronchiolitis obliterans	Toxic fumes (nitrogen dioxide, sulfur dioxide, diacetyl-popcorn lung), painting textiles
Alveolar proteinosis	High level exposure to silica
Diffuse alveolar hemorrhage	Acid anhydrides

occupational and environmental factors to most other lung diseases is much harder to determine. For example, estimates of the proportion of lung cancers attributable to occupational exposures have ranged from 1 to over 40 percent. Occupational factors are estimated to account for 10 to 20 percent of cases of asthma in adults. A growing literature supports the conclusion that occupational exposures account for about 15 percent of COPD, and a higher proportion of COPD in nonsmokers. However, clinicians rarely diagnose occupational asthma, COPD, or lung cancer, especially in patients who smoke.

BASIC PRINCIPLES OF OCCUPATIONAL AND ENVIRONMENTAL LUNG DISEASE

Certain principles apply broadly to the full range of respiratory disorders caused by inhalation exposure to agents in the workplace or environment:

1. While a few environmental and occupational lung diseases may present with pathognomonic features, such as mesothelioma, most are difficult to distinguish from disorders of nonenvironmental origin. In addition, most lung disorders can be caused or exacerbated by environmental or occupational exposures. Thus, environmental and occupational triggers must be constantly sought in the evaluation and management of pulmonary disorders.
2. A given substance in the workplace or environment can cause more than one clinical or pathologic entity. For example, cobalt exposure can cause interstitial lung disease and airway disease.
3. The etiology of many lung diseases may be multifactorial, and occupational factors may interact with other factors. For example, the risk of developing lung cancer in asbestos-exposed workers who smoke is much greater than in those exposed to either asbestos or cigarettes alone.
4. The dose of exposure typically is an important determinant of the proportion of people affected and the severity of disease. Higher doses of exposure usually result in more affected individuals or greater disease severity. Dose generally correlates with severity in patients experiencing nonimmunologic direct toxicity, such as chemical toxic pneumonitis, asbestosis, or silicosis. In those with cancer or immune-mediated disorders, dose more commonly affects incidence than severity.
5. Individual differences in susceptibility to exposures exist. Adverse effects occur in some persons,

while others with similar exposure are spared. Host factors that determine susceptibility to environmental agents are poorly understood but probably include, genetic factors and also acquired factors such as diet, and the presence of other lung diseases and exposures. Occupational diseases, especially immune-mediated processes such as chronic beryllium disease or occupational asthma, can occur or progress at low levels of exposure, below government-set exposure standards.

6. The effects of a given exposure occur after the exposure with a predictable latency interval. For acute diseases such as toxic pneumonitis, there is a short and usually predictable period between exposure and resultant clinical manifestations, which facilitates recognition of a causal relationship between exposure and disease. When symptoms or signs are recurrent with repeated exposures, as with occupational asthma, this temporal relationship can help establish the diagnosis. For chronic diseases such as cancer or most pneumoconioses, long latency periods between the first exposure and subsequent clinical manifestations are common. Consequently, the patient's exposure to the offending agent(s) may have ceased long before the onset of disease, making the diagnosis of such diseases particularly challenging.

IMPORTANCE OF OCCUPATIONAL AND ENVIRONMENTAL LUNG DISEASES

There are several compelling reasons to search for an occupational or environmental cause in all cases of pulmonary disease. First, knowledge of cause may affect patient management and prognosis, and may prevent further disease progression in the affected person. Second, establishment of cause may have significant legal, financial, and social implications for the patient. Third, the recognition of occupational and environmental risk factors can also have important public health and policy consequences. For example, a larger population at risk may benefit from the initiation of preventive measures. In addition, new associations between exposure and disease may be identified, such as the growing recognition that occupational exposures contribute to COPD. Last, occupational and environmental lung diseases can also serve as important disease models. For example, chronic beryllium disease may serve as a model for sarcoidosis.

ESTABLISHING A CAUSE

Diagnostic Criteria

To establish whether a lung disease has an occupational or environmental origin, the disease should first be defined and characterized, and then the degree to which occupational or environmental exposures are causative or contributory should be determined. The following criteria are used to determine whether a disease is caused or exacerbated by agents in the workplace or environment:

1. The clinical presentation and work-up are consistent with the diagnosis.
2. A causal relationship between the exposure and the diagnosed condition has been previously established or strongly suggested in the medical, epidemiological, or toxicological literature (see below).
3. There is sufficient exposure to cause the disease (see below).
4. The details of the particular case, such as the temporal relationship between exposure and disease, are consistent with known information about the exposure-disease association.
5. There is no other, more likely diagnosis.

In addition, for acute diseases such as occupational asthma, improvement away from the exposure or reproduction of the disease manifestations by re-exposure to the suspected agent can provide additional evidence to support the diagnosis. The degree of uncertainty in diagnosing occupational illnesses is generally substantially greater than in other medical settings—a source of uneasiness for clinicians. For example, in the United States, for most workers' compensation systems, a disease is considered occupational if "more probably than not" (greater than 50 percent chance) it is work related.

Determination of Causal Relationship

Three main types of information have been used to support a causal relationship between an exposure and a respiratory condition: case series or reports, epidemiological studies, and toxicology animal studies. Clinical studies of similarly exposed patients have identified potential occupational causes of lung disease, which have then undergone further epidemiological investigation. The clinical practice of occupational and environmental lung disease relies heavily on the field of epidemiology, as well as toxicology to provide databases for diagnostic decision making.

Epidemiology and Toxicology

Epidemiology focuses on the causes of disease in populations. Occupational and environmental epidemiological studies (e.g., cohort or case-control studies) can demonstrate associations between certain exposures or jobs and adverse effects, using industrial hygiene (exposure) records and data such as medical surveillance. Occupational and environmental epidemiological studies may also provide useful information about the magnitude of the risk, the amount of exposure that can cause or exacerbate disease, and the latency between exposure and disease, and whether control measures are effective in reducing the risk of disease. There are three basic study designs of epidemiological studies: (1) cross-sectional observation of a population at one point in time; (2) longitudinal observation of a group (or cohort) over time; and (3)

case control studies comparing cases with the disease to controls. All give some measure of the relative risk of disease in the exposed group compared to the nonexposed group. A relative risk or odds ratio greater than 2 implies that, more probably than not, the abnormality observed can be attributed to the exposure in question.

Toxicology studies are especially relevant for the thousands of new chemicals introduced into production each year, in which human data are often limited. Toxicology studies use animal and in vitro data to characterize the toxicity of individual chemicals. Such studies elucidate dose-response relationships, and the primary organ of toxicity for a given exposure. Serious limitations include potential differences between species, and the use of single or high-dose exposures that do not simulate the long-term, chronic, lower-level mixed exposures seen with humans.

CLINICAL APPROACH TO THE PATIENT

General Approach

There are two important phases in the work-up of any patient with a potential occupational or environmental lung disease. First, as with any patient presenting with a potential disorder of the respiratory tract, its nature and extent should be defined and characterized, regardless of the suspected origin. Although knowledge of exposures may guide the order of the diagnostic work-up, it is important to establish the basic disorder before proceeding to investigate the etiology of the process. Second, the extent to which the disease or symptom complex is caused or exacerbated by exposure(s) at work or in the environment must be determined.

The initial approach to such patients includes a detailed history, physical examination, appropriate laboratory testing, chest radiograph, and spirometry. Initial exposure information can be used to direct the sequence of the work-up and obviate unnecessary procedures when the diagnosis is fairly straightforward. If the initial evaluation does not fully explain the patient's symptoms, other tests are available to better characterize the nature and extent of the respiratory disorder, including additional physiological testing, computed chest tomography, cardiopulmonary exercise studies, bronchoscopy, open lung biopsy, and immunological studies. However, few are specific for any given occupational or environmental diagnosis.

Prior medical records can be extremely helpful in the evaluation of a patient with a potential occupational or environmental lung disease. Such records can establish the patient's complaints at earlier points in time, may provide objective data such as prior pulmonary function testing or chest radiographs for comparison, and may clarify temporal relationships between exposure and effect and rate of progression of disease; factors which may help establish cause. Medical and spirometry surveillance records, if available, can be quite informative in the diagnostic work-up of occupational diseases.

The Occupational and Environmental History

The occupational and environmental history is the single most important tool to determine whether a respiratory problem may be related to an occupational or environmental exposure. A detailed occupational history includes a chronological list of all jobs, including job title, a description of job activities, potential exposures at each job, and an assessment of the extent and duration of exposure (Table 54-3). Given clinicians' time constraints, the history should focus on the jobs and exposures of greatest concern, which vary given the nature of the problem (i.e., cancer with latency vs. acute inhalation injury). The occupational history can provide essential information on whether exposure to one or more environmental agents has occurred, the magnitude and extent of the exposure, and the timing of the exposure in relationship to symptoms or the disease (Table 54-3). A thorough description of the job process or work done is imperative. The length of time (hours to years) of exposure to the agent, the nature and use of personal protective equipment such as respirators, and a description of the ventilation and overall hygiene are all helpful in estimating exposure from the patient's history. Patients should be asked whether they think their problem is related to anything in their home or work environments, and temporal relationships between exposures and symptoms, such as whether or not symptoms improve away from work. Historical and current exposure data in the form of material safety data sheets (MSDS) and industrial hygiene databases often kept for administrative purposes can further characterize an individual's exposure. Whether co-workers have similar symptoms should be clarified. Information about potential exposures outside the workplace, such as in the home or hobbies, should also be obtained.

Physical Examination

With occupational lung diseases, the physical examination is generally unrevealing about specific cause. It is most helpful in ruling out nonoccupational causes of respiratory symptoms or diseases such as cardiac problems or connective-tissue diseases.

Diagnostic Tests

A number of tests can be helpful in the diagnosis of occupational lung disorders, such as chest radiography and pulmonary function tests (PFTs). The use of these diagnostic tests in the occupational setting is discussed below.

Chest Radiography

The chest radiography is the most important diagnostic test for occupational pneumoconioses. It is critical that radiographs of high technical quality be obtained. Under certain circumstances, the chest radiograph can be unique or highly suggestive of an occupational disorder and may be sufficient, along with an appropriate exposure history, to establish a diagnosis. For example, silicosis, coal workers' pneumoconiosis, and asbestosis with pleural disease all have characteristic radiographic findings strongly suggestive of the specific

Table 54-3

Taking an Occupational and Environmental History

General health history
- Does the patient think symptoms/problem is related to anything at work?
- When was the onset of symptoms, and how are they related to work?
- Has patient missed days of work, and why?
- Prior pulmonary problems
- Medications
- Cigarette use

Current or most relevant employment
- Job/process: title and description
- Type of industry and specific work
- Name of employer
- Years employed

Exposure information
- General description of job process and overall hygiene
- Materials by worker used
- Ventilation/exhaust system
- Use of respiratory protection
- Are other workers affected?
- Industrial hygiene samples/OSHA data

Environmental nonoccupational factors
- Cigarettes
- Diet
- Hobbies
- Pets

Specific workplace exposures
- Fumes/dusts/fibers
- Gases
- Metals
- Solvents
- Other chemicals: plastics, pesticides, corrosive agents
- Infectious agents
- Organic dusts: cotton, wood
- Physical factors
- Noise
- Repetitive trauma
- Radiation
- Emotional factors, stress

Past employment
- List jobs in chronologic order
- Job title
- Exposures
- Military service

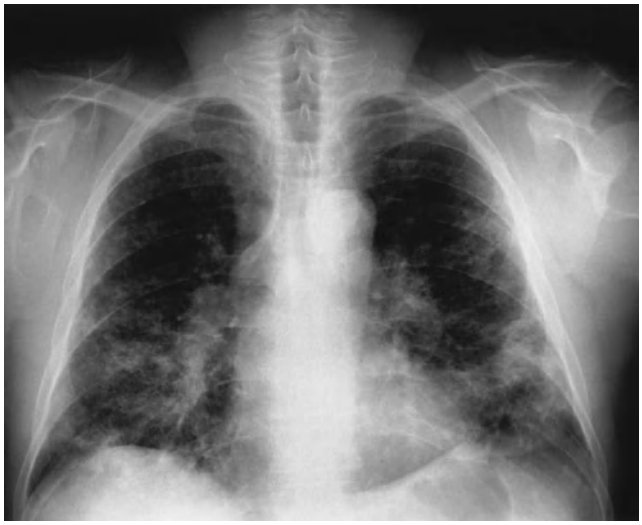

Figure 54-1 Posteroanterior chest radiograph of a patient with silicosis. Multiple small nodular densities are seen throughout both lungs. Bilateral conglomerate masses of progressive massive fibrosis are also seen. International Labour Office classification of the film is category 3/3 showing category C large opacities.

occupational diagnosis. The finding of small rounded opacities, progressive massive fibrotic lesions in the upper zones, and "eggshell" calcification is highly suggestive of silicosis (Fig. 54-1). Similarly, the finding of bilateral pleural plaques and diffuse small irregular linear opacities in the lower lung zones is highly suggestive of asbestosis (Fig. 54-2). However, the chest radiography findings can also be nonspecific, as with asbestosis without pleural plaques where linear shadows in the lower lobes and honeycombing resemble the findings

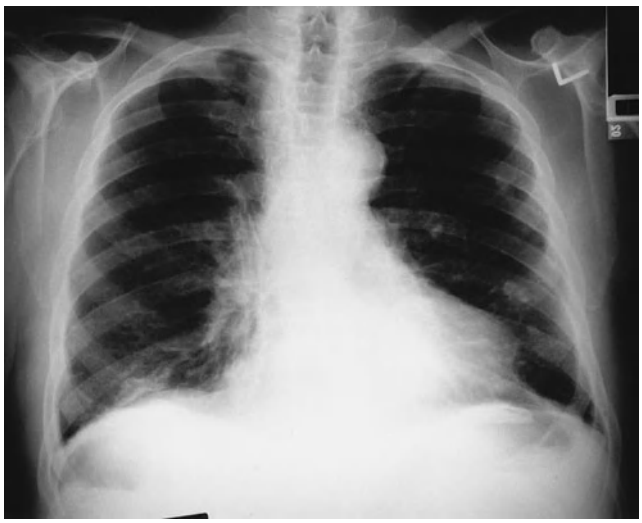

Figure 54-2 Posteroanterior chest radiograph of a patient with asbestosis and pleural plaques. Calcified pleural plaques are seen on the diaphragms bilaterally, *en face* in the left thorax, and on the right medial pleural surface. Increased reticular markings greatest at the lung bases are also seen. International Labour Office classification of the film is category 1/1 small irregular opacities predominantly in the lower lung fields.

of idiopathic pulmonary fibrosis, or the hilar adenopathy or diffuse nodules found in beryllium disease are identical to the features of sarcoidosis. Chest radiographs can also be normal in patients with symptomatic pneumoconiosis.

Under the auspices of the International Labour Office (ILO) in Geneva, Switzerland, a uniform classification system has evolved to evaluate chest radiographs for epidemiological studies, clinical evaluation, and screening. The system requires a posteroanterior radiograph and comparison to a standard set of radiographs. Parenchymal opacities are classified according to size, shape (rounded or irregular), extent, and profusion (concentration). Examples of ILO readings are shown in Figs. 54-1 and 54-2. Pleural changes are also graded according to site, pleural thickening, and pleural calcification.

Computed Tomography

There is a growing literature addressing the role of computed tomography (CT) scanning in the evaluation of patients with occupational interstitial lung disease, primarily asbestosis and hypersensitivity pneumonitis. Similar to the nonoccupational setting, conventional CT scanning (8- to 10-mm thick slices) and high-resolution computed tomographic (HRCT) scanning (1- to 3-mm thick slices) can be used to better evaluate pleural and parenchymal abnormalities (see Chapter 30). The use of CT scans for screening for lung cancer is also under investigation.

Conventional CT scanning is more sensitive than chest radiography for the diagnosis of pleural disease and is helpful in distinguishing subpleural fat from pleural fibrosis. HRCT scanning allows improved visualization of the lung parenchyma and is used in the evaluation of patients with suspected asbestosis and other occupational interstitial diseases. HRCT scanning is especially informative in patients with unrevealing chest radiographs and unexplained respiratory symptoms or abnormal physiology (restrictive lung function, abnormal gas exchange, or abnormal response to exercise). CT scan features have been shown to correlate with physiological and histological changes. For example, interlobular septal thickening represents interstitial fibrosis, as seen in asbestosis, and ground-glass opacities likely represent active alveolar inflammation, as seen in hypersensitivity pneumonitis. The specific features and distribution of HRCT changes may be suggestive of a specific cause and narrow the differential diagnosis. For example, centrilobular nodules, ground-glass opacities, and air trapping may suggest hypersensitivity pneumonitis. Additional imaging techniques may also be useful. Inspiratory and expiratory imaging may demonstrate air trapping seen in hypersensitivity pneumonitis, and prone imaging may distinguish lower lung zone reticulations seen in asbestosis from dependent changes. Although less commonly used, classification systems such as the ILO chest radiograph system have been proposed for CT scans.

Physiological Methods

PFTs—including spirometry, lung volumes, and diffusing capacity—are the most important tools to assess functional respiratory status in patients with occupational lung disease, as with nonoccupational diseases (see Chapter 34). PFT findings are generally not specific for a particular cause but are important for evaluating dyspnea, differentiating obstructive from restrictive airway defects, and assessing the degree of pulmonary impairment.

Although in clinical practice obstructive lung disease may be treated before objective physiological documentation, it is especially important to clarify the diagnosis in settings where work exposures may be causative or contributing factors, and management decisions may involve a worker's job. Spirometry with bronchodilator response can document airflow obstruction and reversibility (see Chapter 34). However, the increased use of inhaled steroids, which are effective at reducing airway inflammation, can make reversible airflow obstruction more difficult to confirm, especially in milder asthmatics. Testing can be repeated off inhaled steroids. Forced expiratory flow rates between 25 percent and 75 percent (FEFR 25 to 75) have also been used to determine the presence of small airways disease; however, caution must be used in relying upon FEFR 25 to 75 given the significant variability in the general population.

When spirometry is normal, nonspecific bronchial hyperresponsiveness (NSBH) such as methacholine challenge testing can be helpful in demonstrating the presence of hyperreactive airways. NSBH can also be used to estimate severity as well as to follow improvement away from work.

Peak expiratory flow rate (PEFR) diaries can be particularly useful in the diagnosis of occupational asthma. Use of a peak flow meter and diary for at least 2 to 3 weeks including periods at work and away from work, such as vacation or weekends away from work, can document work-related changes in lung function. The confounding effects of bronchodilator therapy, respiratory protection and patient effort may influence results, and should be noted on the diary.

Specific inhalation challenge with the suspected agent(s) is considered the gold standard for diagnosing sensitizer-induced occupational asthma. However, such testing requires specialized facilities and expertise, carries certain risks, is not widely available, and false-negatives can occur.

With occupational interstitial lung diseases, restrictive ventilatory impairments and reductions in the diffusing capacity of carbon monoxide (D_{LCO}) are highly suggestive of disease. Hence, obtaining full pulmonary function testing are important since screening spirometry and plain chest radiographs may not be sufficiently sensitive to explain the presence of respiratory symptoms. Reductions in D_{LCO} may often be the first sign of disease and present as an isolated abnormality.

Longitudinal testing may be particularly informative given the variation in testing in the population and is often available in working populations undergoing routine medical surveillance. Careful attention must also be paid to several factors that may affect the quality of the testing; these include that spirometry is performed according to ATS guidelines and that the equipment is routinely calibrated. Changes in

technicians and in the equipment can also affect spirometry results.

Cardiopulmonary Exercise Testing

Cardiopulmonary exercise testing can be used to assess functional impairment and disease progression in selected patients with occupational respiratory disorders (see Chapter 35). Exercise testing can help distinguish among cardiac, pulmonary, and deconditioning causes of dyspnea. In patients with significant interstitial lung disease, exercise results in an increase in the alveolar-arterial oxygen gradient and arterial hypoxemia. Cardiopulmonary exercise testing is helpful in evaluating a select group of patients with dyspnea and normal pulmonary function tests or dyspnea that appears out of proportion to the changes in lung function. However, cardiopulmonary exercise testing is not helpful in determining the specific origin of the pulmonary disease.

Bronchoscopy

The diagnosis of major pneumoconioses such as asbestosis, silicosis, or coal workers' pneumoconiosis usually can be made on the basis of the occupational history, chest radiograph, and PFTs, as noted. Under certain circumstances, such as the evaluation of chronic beryllium disease, bronchoscopy with transbronchial biopsy and bronchoalveolar lavage (BAL) may be helpful diagnostically (see Chapter 56). Transbronchial biopsies yield small tissue samples that are most helpful in identifying granulomatous interstitial processes such as sarcoidosis, beryllium disease, and hypersensitivity pneumonitis, or diffuse malignant processes. Sufficient tissue is usually not obtained for analyses for dust or metal content.

Under certain circumstances, BAL can be diagnostically helpful. A predominance of lymphocytes suggests certain diagnoses such as sarcoidosis, hypersensitivity pneumonitis, or chronic beryllium disease, but is not by itself diagnostic. The diagnosis of chronic beryllium disease can be established with the finding of a positive beryllium lymphocyte proliferation test (BeLPT) using BAL cells. Characteristic multinucleated giant cells may be seen in the BAL cells of patients with hard-metal lung disease. BAL cells may contain dust or mineral particles, such as asbestos, which can reflect current and past exposures. For example, asbestos bodies (asbestos particles coated with iron) have been quantitated in BAL, and have correlated variably with disease and symptoms.

Pathologic Examination of Tissues

Open lung biopsy techniques are usually not needed to make a diagnosis of the more common occupational interstitial lung diseases, as noted. However, when there is no clear cause, limited exposure history, atypical features, more than one causative agent, or potentially a newly recognized agent, lung biopsies can be very helpful. Certain histopathologic findings can suggest a specific disease such as hypersensitivity pneumonitis, asbestosis, or hard metal disease. Lung biopsies can also rule in or out certain nonoccupational causes of lung disease, such as pulmonary vascular disease or infection. Open lung biopsy enables sufficient amounts of tissue for histological and mineralogical (qualitative and quantitative) analysis.

Several methods have been used to analyze the dust content of lung tissue. Light microscopic evaluation with polarization is widely available and can provide a qualitative assessment of the presence of dust particles and ferruginous bodies. It does not, however, identify the specific dust particles or enable quantification. Bulk and microanalytic techniques that allow more definitive identification and quantification of minerals and dusts are also available. They include radiographic fluorescence scanning electron microscopy and energy dispersion radiographic spectroscopy. These methods can be used to identify and quantify specific minerals in sections or tissue digests. In a patient with interstitial lung disease of unclear origin in whom an occupational or environmental etiology is being considered, more extensive particle analysis should be considered if light microscopic histological examination is not diagnostic. There are limitations that should be remembered. Only substances that are insoluble and retained in tissue at sufficient concentration will be detected. More soluble agents, such as cobalt, can be underestimated with these techniques. The analytic methods can be tedious and standards to compare findings are limited. Most important, a positive finding documents biologically detectable exposure but does not demonstrate disease or establish a causal relationship.

Other Laboratory Tests

As noted, few laboratory tests exist that diagnose specific occupational lung diseases. Skin tests and detection of specific IgE to a suspected agent, such as large-molecular-weight antigens (i.e., animal or plant proteins) can demonstrate exposure and a specific immunological reaction, but does not confirm a clinical disease, and a negative finding does not rule out either exposure or disease. The BeLPT is quite sensitive and specific for beryllium sensitization, but does not distinguish asymptomatic sensitization from chronic beryllium disease.

Exposure Assessment

A careful occupational and environmental history is the single best way to evaluate a patient's exposures, as noted. Substantial information regarding work and home exposures can usually be obtained directly from the patient.

Other Sources of Exposure Information

There are a several other sources for additional workplace exposure information. In the United States, employers are required by federal law to provide employees with information about the potential toxicity of all materials used in the workplace, called Material Safety Data Sheets (MSDS). Patients should obtain an MSDS on any substances of concern. For recent or current exposures, a site visit is usually most helpful in providing information about the nature and extent of potential exposures and other exposed workers. A number of methods and sampling strategies exist to measure

particular exposures in either the work or home environment. They include personal and area sampling devices, and direct monitoring devices. It should be remembered that sampling variability and analytic errors can occur, and that the exposure information obtained usually reflects a narrow window of time during which monitoring was performed.

Another potential source of information is the results of inspections by health and regulatory agencies such as the Occupational Safety and Health Administration (OSHA). Unions, insurance groups, and community groups may also provide exposure information. In addition, epidemiological data on coworkers or workers with similar types of jobs can be used to assess the nature and extent of exposure for a given patient.

Compliance with established occupational exposure limits does not exclude the possibility of disease. Low levels of exposure can induce disease in susceptible individuals. Also exposures are often variable and high levels of brief exposure may not be noted in industrial hygiene records.

There has been great interest in developing biologic markers that attempt to more accurately identify and quantify exposure(s), or an early effect of the exposure, such as sensitization to a specific antigen. Such markers can be measured in the target organ, such as the lung or BAL fluid, or in blood or urine. In general, although of great research interest, most markers have relatively limited use in the clinical practice of occupational and environmental medicine and associations between these markers of exposure and disease is not always clear.

Once the available information is obtained, the clinician has to make a final determination about whether occupational or environmental exposures are causing or contributing to the patient's disease process. As noted, there are several criteria to determine whether work or environmental exposures are causative, including a consistent clinical picture, sufficient exposure, and appropriate temporal relationships. The diagnosis of an occupational lung disease frequently entails a greater degree of diagnostic uncertainty than physicians are generally used to in other settings. In most workers' compensation cases in the United States, the standard of certainty is greater than 50 percent likelihood that the disorder is related to an occupational or environmental exposure. Thus, occupational or environmental diseases are diagnosed even in the presence of a significant degree of uncertainty.

PREVENTION

Social, Economic, and Public Health Considerations

It is important for the clinician to remember that making the diagnosis of an occupational or environmental respiratory disease almost invariably has important social, economic, legal, and public health considerations. Many countries and selected states in the United States require reporting of occupational illnesses and injuries. For the individual patient, such a diagnosis can have a profound impact on the patient's work, income, and social situation.

Many countries, including the United States, have a workers' compensation no-fault system of insurance to provide medical, lost work time and other benefits for workers with injury or illness caused by work. Physicians are obligated to diagnose and treat work-related illness, inform the patient of such an illness, and assist with documentation to obtain benefits. Physicians are asked to determine the presence and severity of respiratory impairment, a loss of physical or physiological function (see Chapter 39). Disability refers to the impact of the impairment on the person's life and is determined by administrators based on the information provided by physicians, requirements of the job and other factors, discussed in Chapter 39.

Prevention

Prevention is central to the practice of occupational and environmental medicine. There are two main strategies for prevention: primary prevention, which entails removal or modification of the hazardous risk or exposure before disease has occurred, such as product substitution or engineering controls to reduce exposures. Secondary prevention depends on early detection, and prompt treatment after some adverse effect of the exposure has occurred. The physician can play an important role in both primary and secondary prevention. The physician should also consider the relevant public health issues when a patient is diagnosed with an occupational or environmental lung disease, such as whether others are currently or in the future similarly exposed and at risk of disease. Reporting of occupational illnesses is critical in identifying problem areas that need further investigation and improved preventive strategies. Physicians are essential for secondary prevention. With knowledge of workplace hazards and appropriate monitoring of patients, early abnormalities can be detected, and treatment instituted, typically with removal from further exposures. Reporting of occupational illnesses is critical in identifying problem areas that need further investigation and improved preventive strategies.

Regulatory Issues

In the United States, several federal and state laws and agencies regulate hazardous substances in the environment and workplace, including the Environmental Protection Agency and OSHA, which was established in 1970 by the Occupational Safety and Health Act to reduce the risk of injury and illness to workers. The National Institute for Occupational Safety and Health (NIOSH), also established in 1970, is charged with performing research and teaching, and evaluating occupational hazards. Several organizations recommend occupational exposure limits. OSHA establishes enforceable permissible exposure limits (PELs). In addition, the American Conference of Governmental Industrial Hygienists (ACGIH) and NIOSH recommend threshold limit values (TLVs) and recommended exposure limits (RELs), respectively.

Respirators

The best strategy for reducing inhalation exposures is to prevent or contain the exposure or substitute a less harmful material for a toxic one. Respiratory protective devices (respirators) are used to provide protection from exposure by inhalation when adequate engineering control of airborne contaminants is not feasible, or in an emergency or temporary situation. There are two main types of respirators: air-purifying respirators, which remove contaminants from the air using filters or chemical absorbents, and atmosphere supply respirators, which supply breathable air from another source, such as an air cylinder. Types of air-purifying respirators include dust masks, cartridge respirators, and high-efficiency particulate air (HEPA) filters. Physicians may be asked to determine a worker's fitness for respirator use. OSHA regulations require that a worker not be assigned to a job requiring use of a respirator unless the worker is able to perform the work with a respirator. It should first be determined whether appropriate engineering controls and an appropriate respiratory protection program are in place. No spirometry or other specific criteria exist to determine respirator fitness. The physician must use clinical judgment in determining whether a given worker will be able to use a respirator. Respirators can increase the work of breathing, and they can interfere with the worker's ability to perform the job (by reducing vision, range of motion, and hearings). Factors that can limit respirator use include facial hair, inability to tolerate the respirator, claustrophobic reactions, and particular medical conditions, such as pulmonary or cardiovascular disease. Reassessment after a brief trial of respirator use is indicated if the patient is having problems or concerns.

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Asbestos-Related Lung Disease

William N. Rom

EFFORTS AT ASBESTOS CONTROL

Asbestos is a fibrous hydrated magnesium silicate with more than 3000 commercial uses due to its indestructible nature, fire resistance, and spinnability. It has been used for centuries: the ancient Greeks called asbestos *amiantos*, and the Greek biographer Plutarch (A.D. 46–120) commented on its use in wicks for oil lamps and napkins that could be cleansed in a fire. Mining and milling that began in the late nineteenth century used asbestos in textiles and insulation materials. Cooke described the first case of asbestosis in 1924 in a 33-year-old textile worker with 25 years of exposure to asbestos and extensive pulmonary fibrosis.

Approximately 98 percent of the asbestos used in the United States has been chrysotile, a serpentine form of asbestos. Other asbestos types are the amphiboles—notably amosite, mined in South Africa, and crocidolite, mined in the Cape Province of South Africa and in Western Australia. Anthophyllite in minimal amounts has been used commercially in Finland. These asbestos fiber types have strikingly different physical characteristics: chrysotile tends to be wavy and long, and occurs in bundles; crocidolite is needle-shaped with many long fibers; and amosite is similar to crocidolite but generally thicker.

Initially, asbestos was widely used in fireproof textiles and later as insulation for boilers and pipes. Thereafter, asbestos was used in yarn, felt, paper, millboard, shingles, paints, cloth, tape, filters, and wire insulation. More recently, asbestos has been used in cement pipes for potable water, in gaskets, and in friction materials, including brake linings, and roofing and floor products. Asbestos was extensively used for ship construction during World War II. World consumption of asbestos declined in the 1990s to approximately 50 percent of the peak in 1973. In 1994, approximately 2.7 million tons

were produced, with the United States consuming less than 27,000 metric tons. Worldwide production by mining in 1994 was led, in order, by Russia, Canada, Kazakhstan, China, and Brazil.

TYPES OF EXPOSURE

Asbestos exposure has occurred in a variety of settings. Primary exposures occurred in miners and millers. Secondary exposures occurred in manufacturing plants using asbestos in the production of textiles, friction materials, tiles, and insulation materials. Epidemiological studies focused on cohorts in these plants, since asbestos fiber type was often specified and dust measurements were obtained. These studies demonstrated that intensity and duration of exposure play an important role in the prevalence of asbestos-related disease. In a study of 1584 insulation workers and 1330 sheet-metal workers, 83.5 percent of the insulators had abnormal chest radiographs (55 percent with parenchymal opacities), whereas 42 percent of the sheet-metal workers had abnormal chest radiographs (17 percent with parenchymal opacities).

Although measurements of airborne asbestos fibers were seldom made, the most significant exposures appear to have occurred in the construction trades. These trades included asbestos insulators (called "laggers" in the United Kingdom), who mixed asbestos cement on site to insulate joints and elbows on pipes; boilermakers and sheet-metal workers, who worked adjacent to the asbestos workers; and electricians, carpenters, plumbers, and others who worked in the vicinity of work requiring asbestos exposure. These exposures were mainly to chrysotile asbestos, since practically no crocidolite was imported into the United States, and only small amounts of amosite were admixed.

Asbestos workers and other construction workers wore their asbestos-covered clothes home, so their wives and children were exposed either upon greeting them or while washing their garments. These household contact exposures are often referred to as *indirect exposures,* and those exposed while working near asbestos workers are called *bystander exposures.* In the United States, approximately 14 million persons who were exposed to asbestos in the workplace between 1940 and 1979 were alive in 1980. From this cohort, estimates have been projected for the late 1990s of a peak incidence of approximately 3000 mesothelioma deaths and 5000 asbestos-related lung cancer deaths. Pleural fibrosis remains a relatively common finding among asbestos-exposed blue-collar workers, whereas asbestosis is becoming increasingly uncommon.

NONMALIGNANT PLEURAL MANIFESTATIONS

Pleural disease is the most common manifestation of asbestos exposure. The nonmalignant manifestations of asbestos exposure in the pleural space include circumscribed pleural plaques, diffuse pleural thickening, rounded atelectasis, and asbestos-related pleural effusions.

Pleural Plaques

Pathology

Pleural plaques are the most common manifestation of asbestos exposure. They are focal, irregular, raised white lesions found on the parietal and, rarely, the visceral pleura. The plaques may be small or extensive; commonly they occur in the lateral and posterior midlung zones, where they may follow rib contours and the diaphragm. They commonly enter lobar fissures and can invade the mediastinum or pericardium; rarely do they invade the apices or costophrenic sulci. Histologically, asbestos-related pleural plaques are characterized by a paucity of cells, extensive collagen fibrils arranged in a basket-weave pattern, and a thin covering of mesothelial cells. The parietal pleura is uniformly involved, with minimal thickening of the visceral pleura. The two pleural surfaces are free of adhesions. Pleural calcifications frequently develop in these fibrohyaline lesions as the length of time from exposure increases. Exposure to asbestos is the most frequent cause of pleural plaques. These plaques, although typical of asbestos, are not specific for asbestos exposure.

Pathogenesis

Two theories have been proposed for the pathogenesis of pleural plaques. The most plausible is based on the direct effects of fibers that reach the pleural space. Asbestos fibers—the short, thin ones in particular—have been shown to be transported by subpleural lymphatics to the pleural space. In the pleural space, it is believed that they scratch, injure, and irritate the pleural surface, leading to hemorrhage, inflammation, and eventually fibrosis. The plaques are submesothelial. Cell-cell interactions appear to play an important role in this response. In the absence of macrophages, pleural reactions tend to be disorganized and widespread. Mesothelial cells also appear to play an important role in the pathogenesis of these lesions: they internalize asbestos fibers via an integrin receptor that recognizes vitronectin; in vitro pleural mesothelial cells also can synthesize collagens (types I, III, and IV), elastin, laminin, and fibronectin. In keeping with the submesothelial location of the plaques, cultured mesothelial cells can organize these macromolecular connective-tissue components into an assemblage of extracellular matrix that is limited to the base of the cell.

Epidemiology and Natural History

In the 1960s, hyaline and calcified pleural plaques were noted to be an index of exposure to asbestos. In shipyard workers, the frequency of pleural abnormalities was approximately 10 times that of parenchymal disease. The greater the exposure, the more likely the worker was to have extensive calcified pleural plaques as well as parenchymal fibrosis. The intensity of the exposure has been noted to be an important

determinant of the prevalence of these abnormalities. For example, among British shipyard workers, 36 percent of those with continuous exposure as "laggers" developed pleural plaques, while extensive pleural thickening and pulmonary fibrosis were seen in 5 and 7 percent, respectively. In contrast, those with intermittent exposure had a 6 percent prevalence of plaques and no pulmonary fibrosis. On average, the latency time for the appearance of plaques is 30 years, but the time can vary greatly. This variation can also be appreciated from studies of British shipyard workers in whom the prevalence of pleural plaques increased from 17 percent at 10 years after the first exposure to 70 percent at 30 years among those with continuous exposure; for those with intermittent exposures, the prevalence increased from 1 percent at 10 years to 16 percent at 30 years.

All asbestos fibers are equally capable of inducing pleural plaques: pleural plaques are found in US insulators or shipyard workers exposed to chrysotile or amosite, as well as miners in Western Australia who were exposed to crocidolite. Circumscribed pleural plaques are not associated with pleural effusions. They increase in size slowly, usually over decades, and rarely, if ever, give rise to diffuse malignant mesothelioma.

In addition to occupational exposures, domestic and residential exposures have, on rare occasions, been implicated in the production of pleural plaques. Evidence for the latter is the remarkably high rates of pleural calcification (up to 30 percent) in some rural areas of Greece, Bulgaria, and Turkey.

Clinical and Physiological Features

In the absence of concomitant asbestosis or obliteration of the costophrenic angle, pleural plaques are usually asymptomatic. Most often they are incidental findings on chest radiographs. In addition, they do not cause significant abnormalities such as pleural rubs, rales, or rhonchi on auscultation of the chest.

Pleural disease has been recognized as a cause of reduced pulmonary function since the 1970s. Among 998 shipyard workers in Groton, Connecticut, who had 15 or more years of asbestos exposure, 17 percent of those with pleural changes had a forced vital capacity (FVC) under 80 percent of predicted; for those with normal chest radiographs, 9 percent had decreased vital capacities ($p > 0.05$). In those with normal chest radiographs, the values were significantly reduced only among smokers and ex-smokers. Recent studies that have applied stepwise regression analysis to data from insulation workers have disclosed a significant inverse relationship between FVC and an integrative pleural index for patients with circumscribed pleural plaques. Even among those with pleuroparenchymal abnormalities, the pleural index was found to make a significant contribution to decrements in FVC, independent of that due to parenchymal abnormalities.

In nonsmoking asbestos workers with circumscribed or diaphragmatic pleural plaques, flow rates (FEV_1, $FEF_{25–75\%}$, and $FEF_{75–85\%}$) have been reported to be reduced. In an epidemiological study of 1211 sheet-metal workers, pleural fibrosis was detected in 334 and was related to age, duration of exposure, more pack-years of smoking, and the presence and degree of interstitial fibrosis. After controlling for these confounders, multivariate regression analysis found that both plaques and diffuse thickening were independently associated with decrements in FVC, but not with decrements in the FEV_1/ FVC ratio. Furthermore, diffuse pleural thickening was associated with a decrement in FVC twice as great as that seen with circumscribed pleural plaques. After confounding variables such as age, height, smoking status, and the presence of parenchymal abnormality as assessed by chest radiography and gallium scintography were taken into account, there was a significant decrease in FEV_1 and FVC (222 and 402 ml, respectively) among workers who had pleural plaques or diffuse pleural fibrosis.

Radiographic Features

The visualization of plaques on routine chest radiography depends on their thickness, location, and the orientation of the radiographic beam. As a result, they can be viewed in profile along the lateral chest wall or on en face with a rolled or holly-leaf pattern, especially if calcified (Fig. 55-1). Only a modest proportion of plaques detected at autopsy can be seen on standard posteroanterior (PA) chest radiograph. Oblique views and computed tomographic (CT) scanning increase plaque detection.

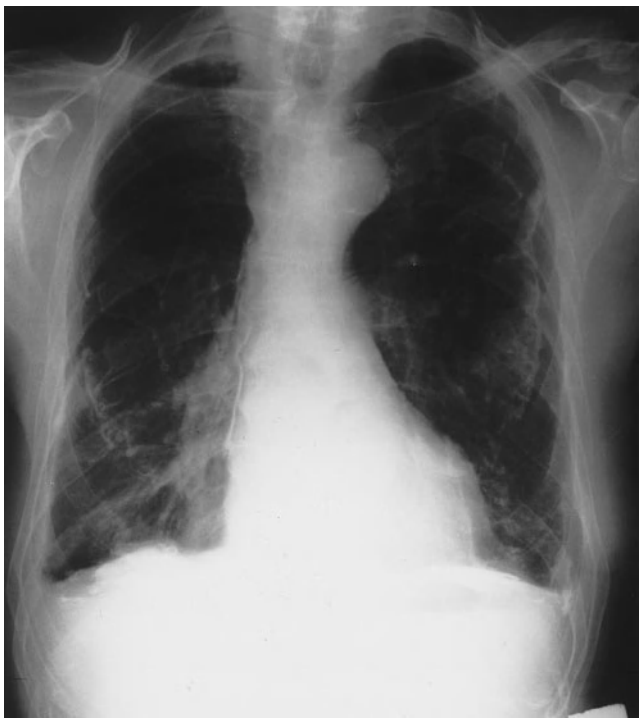


Figure 55-1 Posteroanterior (PA) chest radiograph of a 75-year-old man who worked in a shipyard during World War II insulating ships. The radiograph shows bilateral calcified pleural plaques en face and on top of the diaphragm. The pleura is diffusely thickened bilaterally and the costophrenic angles are blunted. Mediastinal pleural calcification is present on the right. *(Courtesy of Dr. Timothy Harkin.)*

The CT scan can recognize plaques at a much earlier and less well-defined state than the conventional chest radiograph. The CT scan is particularly useful for perivertebral and pericardiac plaques, and high-resolution CT scanning (HRCT) helps to establish the presence of diaphragmatic lesions. In all cases, the CT scan can help to differentiate plaques from extrapleural fat pads and can detect concomitant parenchymal abnormalities that may be difficult or impossible to see on the PA chest radiograph.

Diagnosis

Pleural plaques due to asbestos exposure are usually bilateral (80 percent of the time), whereas unilateral pleural plaques may be due to trauma, previous tuberculosis, or, rarely, other causes, such as collagen vascular disease. The lesions are usually stable and will remain the same size for months. This helps to differentiate plaques from pleural tumors. Histological tissue examination is not necessary for diagnosis the vast majority of the time.

Treatment

No specific treatment is required for asbestos pleural plaques. Since they are markers of asbestos exposure and identify patients at risk for other asbestos-related disorders, medical surveillance, including periodic chest radiographs, is recommended.

Diffuse Pleural Thickening

Pathology

Pleural fibrosis in persons who have been exposed to asbestos has been well described. The fibrotic responses can be localized or diffuse and either unilateral or bilateral. Macroscopically, the lesions vary in thickness from a whitish discoloration of the lung surface to a thick white peel that can encase significant pulmonary structures. Diffuse pulmonary thickening is most often seen as a continuous sheet that is 5 to 10 cm in craniocaudal extent, and in 90 percent of patients it affects the costophrenic angle. Interlobar and interlobular fissures are commonly involved. Whereas pleural plaques predominantly affect the parietal pleura, diffuse pleural thickening or fibrosis is a disease of the visceral pleura. Diffuse pleural fibrosis occurs most commonly as part of a fibrotic process of the visceral pleura and subadjacent interstitium. It may occur, however, and be quite severe, in patients with minimal pulmonary parenchymal fibrosis. Asbestos bodies or fibers are often found in the visceral pleura, the underlying parenchyma, or both.

Pathogenesis

Diffuse pleural thickening has been proposed to result from three different mechanisms. The first is the confluence of large pleural plaques. This is believed to account for 10 to 20 percent of the cases. The second is the extension of subpleural fibrosis to the visceral pleura. This probably accounts for 10 to 30 percent of cases. The most common pathogenic mechanism is thought to be the fibrotic resolution of a benign pleural effusion, producing diffuse pleural thickening. The importance of this mechanism is highlighted by the finding that about one-third of patients with diffuse pleural thickening have had a prior benign asbestos-related pleural effusion diagnosed by thoracentesis or on serial chest radiographs. The pathogenic mechanisms differentiating diffuse pleural thickening from circumscribed pleural plaques are not well defined. However, the fundamental irritative mechanism of asbestos fibers is likely to be important in both. In the case of diffuse pleural responses, these fibers are deposited mainly in the parenchymal subpleural areas of the lung.

Clinical and Physiological Manifestations

Diffuse pleural fibrosis most often occurs long after short-term heavy exposure to asbestos. When mild, diffuse pulmonary fibrosis can be asymptomatic and discovered as an incidental finding on a chest radiograph obtained for another reason. The diffuse nature of the lesion, however, often leads to pulmonary symptoms, including dyspnea on exertion, chronic dry cough, and chest pain. As noted above, diffuse pleural thickening can cause a restrictive physiological abnormality. The degree of physiological abnormality varies with the degree of fibrotic response. On rare occasions, in patients with severe bilateral disease, respiratory insufficiency and death have occurred. Diffuse pleural fibrosis can increase in severity over time. In miners heavily exposed to crocidolite asbestos, however, progression of diffuse pleural thickening has been noted to level off as much as 15 years after the initial exposure.

Radiographic Features

On the routine chest radiograph, diffuse pleural fibrosis presents as a continuous pleural opacity extending over more than 25 percent of the pleural surface of a lung, often blunting the costophrenic angle. It can be unilateral or bilateral and seen in the presence or absence of concomitant asbestosis and pleural calcifications. Rarely, the pleural fibrosis will produce a fibrotic pseudotumor with a pleural basis (rounded atelectasis) (see below). CT scanning is particularly useful in delineating the relationship between diffuse fibrosis and other pleural abnormalities and differentiating pleural fibrosis from fat deposits.

Diagnosis

The diagnosis of diffuse pleural fibrosis is usually based on the clinical presentation and chest radiograph. In more than 30 percent of cases, a history of asbestos-related pleuritis can be obtained. The lesions of diffuse pleural fibrosis are not unique to asbestos-exposed persons and can represent old inflammatory reactions from tuberculosis, thoracic surgery, hemorrhagic chest trauma, or drug reactions. Differentiation among these causes is frequently based on a careful clinical history. Radiographic patterns are also helpful, since bilateral interstitial changes in the lower lung zones in association with

pleural plaques or calcifications strongly support a diagnosis of asbestos exposure. A biopsy may be required when the thoracic lesion is progressing or when malignancy is in the differential.

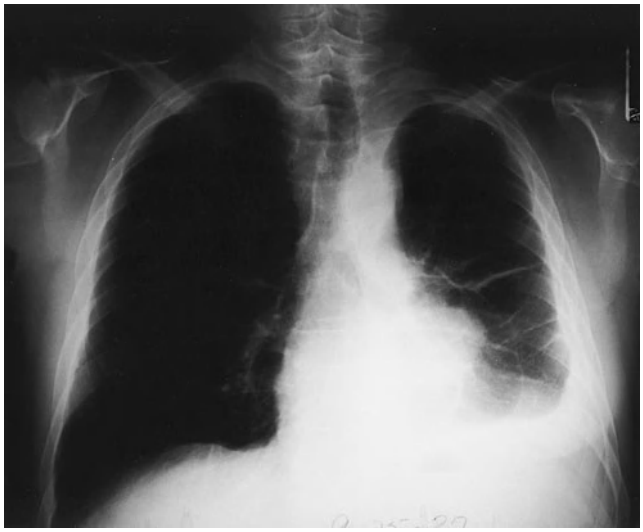
Treatment

As seen with circumscribed pleural plaques, there are no specific therapies for asbestos-related diffuse pleural fibrosis. Medical surveillance is required to detect disease progression and observe for other asbestos-related disorders. In the rare extremely severe case, pleurectomy may be required.

Rounded Atelectasis

Rounded atelectasis is a rare complication of asbestos-induced pleural disease. It is caused by scarring of the visceral and parietal pleura and the adjacent lung, with the pleural reaction folding over on itself. The pleural surfaces then fuse to one another, trapping the underlying lung and leading to atelectasis. As a result of this alteration, a mass lesion that mimics lung cancer can be seen on the PA chest radiograph (Fig. 55-2). This lesion is most easily appreciated to be a pseudotumor with use of CT scanning. HRCT can noninvasively demonstrate continuity to areas of diffuse pleural thickening, evidence of volume loss in the adjacent lung, or a characteristic comet tail of vessels and bronchi sweeping into a wedge-shaped mass (Fig. 55-2).

CT scanning can also demonstrate stability over time (from months to years), which supports the diagnosis of a benign lesion, and pleural plaques or parenchymal changes, which support a diagnosis of asbestos exposure. In one clinical series of 74 patients with rounded atelectasis, 64 had significant asbestos exposure, and the lingula or right middle lobe was affected in 49 of the patients. HRCT scans localized most cases of rounded atelectasis to the lower, posterior portion of the lung (Fig. 55-2); moreover, in one-third of the patients, the lesions were multiple. In most patients, rounded atelectasis occurs suddenly on a background of only plaques or a normal chest radiograph. In others, a slowly increasing pleural effusion may precede its appearance. If the benign nature of the lesion cannot be assured by chest radiography, the patient may require fiberoptic bronchoscopy with a transbronchial biopsy or transthoracic needle aspiration to rule out a malignant process.



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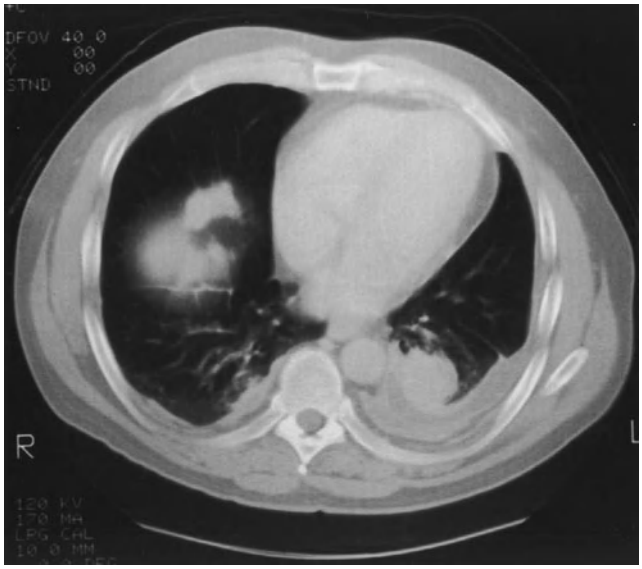

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Figure 55-2 Rounded atelectasis and other pleural abnormalities in an asbestos worker. The chest radiograph (*A*) shows a left-sided pleural effusion, bilateral pleural thickening, greater on the left than on the right, and a mass in the left midlung field. HRCT (*B*) demonstrates the mass to be rounded atelectasis, with bronchovascular structures entering the trapped lung. It also reveals the pleural effusion, bilateral pleural thickening, and pleural plaques, one of which is on the right hemidiaphragm. *(Chest radiograph and HRCT courtesy of Dr. Coralie Shaw.)*

Acute Benign Pleural Effusions

Acute benign pleural effusions are common pleural manifestations in asbestos-exposed persons between 20 and 40 years of age. The latency period for these effusions is shorter than for pleural plaques, malignant mesotheliomas, or pulmonary malignancies. Benign pleural effusions generally occur earlier after exposure than do other asbestos-related processes—12 to 15 years after the first asbestos exposure. However, benign effusions can also occur as long as 30 years after first exposure. The effusions may be small to moderate in size or may be manifested as an increase in the extent or severity of an existing pleural reaction.

About 50 percent of the patients with acute benign pleural effusions are asymptomatic. When patients are symptomatic, the manifestations may be those of a pleurisy (chest pain, chest tightness, dyspnea, cough, and fever). Physical examination reveals the signs of a pleural effusion; a pleural friction rub may be heard. The effusions are exudative and often bloody; glucose concentrations are normal. Mesothelial

cells are found in about 50 percent of patients. In about 25 percent of patients, the fluid is eosinophilic. Rarely are asbestos bodies found even though they may be present in underlying lung tissue.

The designation "benign" refers to the lack of evidence of malignancy. The collections may persist for 6 months or more. They frequently clear spontaneously, only to recur on the contralateral side. Benign asbestos pleural effusions do not presage the development of malignant mesotheliomas. Moreover, patients with effusions have the same risk of developing asbestosis as do patients with chronic pleural fibrosis. However, a benign asbestos pleural effusion is a risk factor for the development of pleural thickening, especially diffuse pleural fibrosis. The diagnosis of acute benign pleural effusions is one of exclusion. Thoracentesis is essential. Pleural biopsy is frequently required to rule out other causes of pleural effusions, including mesothelioma. The usual pathological findings are a chronic fibrous pleurisy with minimal cellularity. Long-term follow-up is also a diagnostic requirement, since the diagnosis of a benign pleural effusion cannot be fully established until a tumor-free interval of 3 years has elapsed.

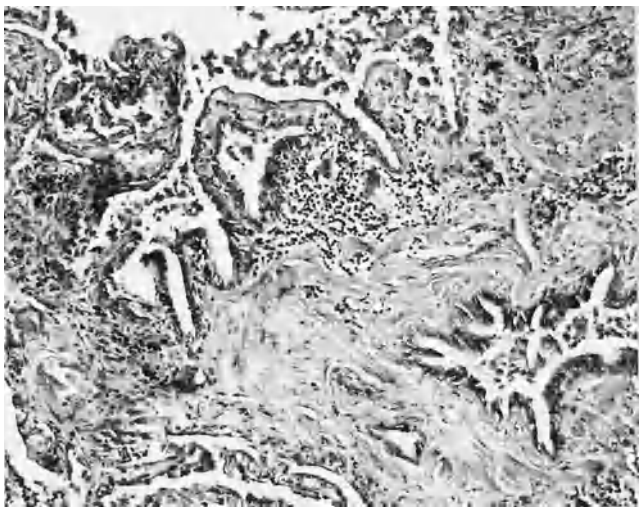

Figure 55-3 Lung tissue from a 64-year-old asbestos insulator with 46 years of exposure to asbestos while insulating pipes. His chest radiograph revealed extensive irregular opacities and bilateral pleural thickening. The figure illustrates peribronchiolar fibrosis, interstitial chronic inflammation, accumulation of macrophages in the airspaces, and proliferation of type II pneumocyte. *(Based on data from Rom WN, Travis WD, Brody AR: Cellular and molecular basis of the asbestos-related diseases: State of the art.* Am Rev Respir Dis *143:408–422, 1991, with permission.)*

ASBESTOSIS

Pathology

Asbestosis is the interstitial pneumonitis and fibrosis caused by exposure to asbestos fibers. Early lesions are characterized by discrete areas of fibrosis in the walls of respiratory bronchioles. The septi adjacent to the respiratory bronchioles are often thickened, and the fibrosis sometimes appears to spread outward from the bronchioles. In addition to the peribronchiolar fibrosis, there is an intense peribronchiolar cellular reaction that may narrow and obstruct the airway lumen. Macrophage accumulation is a prominent feature of this cellularity. Proliferation of type II alveolar epithelial cells is enhanced. The interstitium may contain collections of lymphocytes; smooth-muscle proliferation may be prominent in areas of remodeling; and buds of loose connective tissue may be seen within the alveoli (Fig. 55-3). Initially, the disease usually involves first-order bronchioles; subsequently, second- and third-order bronchioles are affected. As the disease progresses, the fibrosis becomes diffuse, the architecture of the lung undergoes extensive remodeling, and honeycombing supervenes. In contrast to other pneumoconioses, lymph node enlargement and progressive massive fibrosis do not occur. Pathologically, the alterations seen in asbestosis cannot be differentiated from many other interstitial fibrotic disorders except for the presence of asbestos bodies and uncoated asbestos fibers.

Pathogenesis

Asbestos fibers are deposited at airway bifurcations and in respiratory bronchioles and alveoli by impaction, sedimentation, and interception. Fibers then migrate into the interstitium, in part via an uptake process involving type I alveolar epithelial cells. This causes alveolar macrophages to accumulate in the alveolar ducts, peribronchiolar interstitium, and alveolar spaces, constituting an alveolar macrophage alveolitis. Following this initial macrophage alveolitis, most fibers are cleared, leaving the lungs unscarred. If clearance is incomplete, fibrosis can ensue. The degree of fibrosis in asbestosis relates, in general, to the lung dust burden. If the dust load is small, the tissue reaction may be limited and the disease may be mild and not progress. If the retained dust load is great, tissue reaction and macrophage alveolitis are proportionately more intense, greater injury occurs, and chronic and progressive lung disease can develop.

The macrophage alveolitis that is seen in early stages of asbestosis results from monocyte recruitment from the blood and in situ macrophage replication. These cells appear to play an important role in the pathogenesis of the inflammation and fibrosis seen in this disorder. Morphologically, they express an activated phenotype characterized by cellular multinucleation and a striking increase in membrane ruffling, surface blebbing, and lysosomes and phagolysosomes. These macrophages are presumably attempting to engulf and clear the asbestos fibers. This process is not uniformly successful, however. First, the fibers induce apoptosis in the cells. Although the coating of asbestos fibers to form asbestos bodies makes them less toxic, the vast majority of fibers in the lung remain uncoated. Second, the long fibers cannot be completely phagocytosed. Finally, chrysotile asbestos fibers tend to split longitudinally. This generates additional fibers that can multiply the asbestos effect even after exposure has ceased. As

a result, asbestos has a prolonged residence and surprising mobility and penetrates the interstition of the distal lung.

These characteristics probably contribute to the pathogenesis of the disease, since—in contrast to inert particles, which can be ingested by macrophages and cleared without generating a significant response—asbestos fibers stimulate macrophages to produce a variety of important moieties. These include cytokines, such as platelet-derived growth factor (PDGF), insulin-like growth factor-1 (IGF-1), interleukin-1β (IL-1β), tumor necrosis factor (TNF), and IL-8, the matrix molecule fibronectin, oxygen free radicals, and plasminogen activators. The oxygen radicals contribute to tissue injury via direct cell cytotoxicity and lipid peroxidation of membrane components. The IL-8 recruits granulocytes to sites of disease activity. The PDGF, IGF-1, IL-1, TNF, and fibronectin contribute to tissue fibrosis by stimulating fibroblast proliferation and chemotaxis and collagen biosynthesis.

Bronchoalveolar lavage (BAL) in asbestosis has demonstrated an alveolar macrophage alveolitis with a modest increase in neutrophils. This neutrophilia correlates with the finding of rales on physical examination and oxygenation parameters and is apt to be more pronounced in patients with advanced disease. In patients with asbestosis, ^{67}gallium lung scans may also be positive. Clinically apparent asbestosis occurs only after a significant latent period. However, studies using BAL, CT scanning, and ^{67}gallium scanning have demonstrated that inflammatory events occur well before the onset of clinical disease. Thus, it is likely that the initial exposure induces inflammation and injury that persist through the latent or subclinical phase and develops into the clinical disease diagnosed by classic radiography and other techniques. Current concepts of the pathogenesis of the disease link inflammation and fibrosis in a causal fashion.

Epidemiology

The prevalence of parenchymal asbestosis among asbestos workers increases as the length of employment increases. This is illustrated in an early report in which investigators analyzed the chest radiographs of 1117 New York and New Jersey asbestos insulation workers. They found asbestosis in 10 percent of the workers who had been employed for 10 to 19 years, in 73 percent of those who had worked for 20 to 29 years, and in 92 percent of those who had worked 40 or more years. A similar dose-response relationship was found in the asbestos cement industry. Among "bystanders" (i.e., among sheet-metal workers who worked in close proximity to insulation workers) the overall prevalence of asbestos-related changes was 31 percent, including 9 percent who had only pleural abnormalities and 12 percent who had parenchymal abnormalities. Among those who had been in the trade for 40 years or more, 41.5 percent had radiographic signs of asbestos-related disease.

Cigarette smoking can affect the expression of asbestosis. Smokers without dust exposure may have a few irregular radiographic opacities, probably representing acute or chronic bronchitis or bronchiectatic changes in the lung parenchyma. Both smokers and ex-smokers have a higher frequency of asbestos-related irregular opacities on their chest radiographs than do their nonsmoking colleagues. Among asbestos insulation workers, lower grades of radiographic small opacities predominated. Smoking does not alter the expression of asbestos-induced pleural fibrosis. The effects of smoking on asbestosis may be clinically important, since the mortality from asbestosis is higher in asbestos workers who have smoked than in their nonsmoking coworkers. This risk declines if the worker quits smoking. The mechanism of interaction of asbestos and cigarette smoking is poorly understood. However, cigarette smoking may interfere with the clearance of inhaled asbestos, thereby potentiating the effects of the dust in the lung.

Natural History

Following asbestos exposure, asbestosis becomes evident only after an appreciable latent period. The duration of exposure and its intensity influence the prevalence of radiographically evident parenchymal pulmonary fibrosis. Because work sites around the world increasingly meet recommended control levels, high-level exposure to asbestos is now uncommon and clinical asbestosis is becoming a less severe disease that manifests after a longer latent interval. In Western Australian crocidolite workers, a median of 14 years elapsed before asbestosis was detectable radiographically (range, 2 to 34 years). In retired Quebec chrysotile miners and millers, the frequency of pleuroparenchymal lesions was 31 percent, and progression of parenchymal opacities occurred in 9.3 percent; progression was confined to the more heavily exposed group.

One approach to the study of low-level exposure is to evaluate the outcome from short-term exposure. In such a study in an amosite asbestos factory, employment for even as little as 1 month resulted in a 20 percent prevalence of parenchymal opacities: one-third of the participants had pleural abnormalities after 20 years of follow-up; it is significant that both "first attacks" and progression of established radiographic abnormalities occurred 20 and more years after exposure had ceased.

Radiographic asbestosis, once established, may remain static or progress. Rarely has regression been recorded. The factors that determine the outcome are poorly understood. The level and duration of exposure (i.e., cumulative exposure) appear to be prognostic factors. Progression is also considerably more common in persons who already have radiographic abnormalities. This fact provides the basis for the advice that further exposure is to be avoided once the diagnosis of parenchymal asbestosis has been made.

Clinical and Physiological Features

Dyspnea on exertion is the earliest, most consistently reported, and frequently the most distressing symptom of asbestosis. Often dyspnea is accompanied by a persistent cough, which can be spasmodic, and sputum production. Chest tightness is not uncommon, and wheezing also can occur.

In a cross-sectional survey of 816 asbestos-exposed workers using the respiratory symptom questionnaire of the American Thoracic Society, cough, phlegm, wheeze, and dyspnea were inversely related to pulmonary function. Cough, phlegm, and chronic bronchitis were associated with a 2 to 8 percent reduction in FVC and FEV_1; the reduction in these measurements was more significant with wheeze and dyspnea, which caused an 11 to 17 percent reduction. Similarly, based on the British Medical Research Council questionnaire for dyspnea, the prevalence of grade 3 dyspnea among asbestos insulators increased in stepwise fashion from 19.4 percent in patients with category 1 chest radiographic abnormalities (1/0 to 1/2 abnormalities by International Labor Organization [ILO] classification) to 34.5 percent in patients with category 2 chest radiographs and to 49.4 percent in patients with category 3 radiographic abnormalities.

Rales are a distinctive feature of asbestosis. They are usually bilateral, late to paninspiratory in timing, heard best at the posterior lung bases, and not cleared by coughing. They differ in quality and timing from the crackles of bronchitis, which tend to be fewer and earlier. The crackles of asbestosis appear first at the bases in the midaxillary line and tend to spread toward the posterior bases. In prevalence surveys, approximately 83 percent of patients with higher radiographic categories of asbestosis have bilateral rales. In a study of 42 patients with a clinical diagnosis of asbestosis, in 40 the chest radiograph showed at least 1/0 profusion of irregular opacities, 36 had rales, 36 had dyspnea, and 22 had digital clubbing. Rales and clubbing were almost as common among those with less as those with more advanced categories of asbestosis.

In years past, asbestosis-induced respiratory failure was a frequent cause of death in patients with this disorder. In recent years, as the severity of asbestosis appears to have attenuated, cancer has become an increasingly common terminal event. It is important to appreciate that the clinical features of asbestosis and the findings on physical examination are not unique to this disorder and resemble those of a variety of other diffuse interstitial inflammatory and fibrotic processes.

The characteristic pulmonary function changes of asbestosis are a restrictive impairment with a reduction in lung volumes (especially FVC and total lung capacity), decreased lung diffusing capacity (D_{LCO}), and arterial hypoxemia. Large-airway function, as reflected in the FEV_1/FVC ratio, is generally well preserved. In one of the earliest studies, approximately 50 percent of asbestos workers had a reduced FVC and the vital capacity was decreased, on average, by 18 percent as predicted over the next 10 years. Among the 1117 asbestos insulators in New York and New Jersey, the frequency of an abnormal FVC increased to more than 50 percent as follow-up was prolonged. In a larger cohort of 2611 asbestos insulators, the FVC percent predicted decreased as the profusion of irregular opacities on the chest radiograph increased; pleural thickening exaggerated the decrease for each category of profusion. For each category of profusion, diffuse pleural thickening caused a further decrease (at least 10 percent) in FVC percent predicted compared to circumscribed plaques.

Mild airway obstruction can also be seen in nonsmokers with asbestosis. These patients usually have a restrictive pattern of lung function, increased isoflow volume, and increased upstream resistance at low lung volumes. Open lung biopsies from a limited number of these patients suggest that these obstructive findings may be due to peribronchiolar fibrosis, since they revealed peribronchiolar infiltrates with macrophages and fibrosis that extended into the adjacent interstitium. Therefore, it is not surprising that lesser grades of asbestosis can show a mixed restrictive and obstructive abnormality.

Long-term medical surveillance is recommended for all asbestos-exposed persons, especially those with radiographic abnormalities. Periodic physiological assessments play an important role in these evaluations. Although complex physiological abnormalities can be seen in these patients, for prospective assessments of asbestosis carried out in the clinical context, simple measurements of lung volume, such as the FVC, seem to be the most useful.

Radiographic Features

In asbestosis, the standard PA chest radiograph reveals bilateral diffuse reticulonodular opacities, predominantly in the lower lung zones. In 2000, the International Labor Organization (ILO) revised the International Classification of the Radiographs of the Pneumoconioses to make provisions for reading the radiographic features of asbestosis. It used the term *small irregular opacities* to describe the irregular linear shadows that develop in the lung parenchyma and obscure the normal bronchovascular branching pattern seen in disease-free lungs. This schema categorized the irregular rounded opacities found on PA chest radiographs according to size and expressed them on a 12-point scale. Category 0 was defined as a normal radiograph and category 1 as mild asbestosis. Typically, a profusion of irregular opacities at the level of 1/0 is taken as the break point between normal and abnormal. Moderate asbestosis and advanced asbestosis were defined as category 2 and 3 chest radiographs, respectively. As duration from onset and intensity of exposure increase, there is an increase in prevalence and severity of asbestosis as reflected in the chest radiograph.

CT scanning has improved the sensitivity for detecting asbestos-related lesions (Fig. 55-4). It eliminates a common problem with PA chest radiographs—i.e. the superimposition of pleural abnormalities over parenchymal lesions. It also enhances the attenuation discrimination for parenchymal opacities. As a result of more than 300 HRCT evaluations of persons with asbestos exposure, five HRCT features of asbestosis have been identified: (1) curvilinear subpleural lines, (2) increased intralobular septa, (3) dependent opacities, (4) parenchymal bands and interlobular core structures, and (5) honeycombing. These changes have recently been corroborated by histological examination. This spectrum of radiographic findings stands in contrast to the fine irregular opacities that are so prominent on the PA chest radiographs of these persons. In asbestos-exposed workers, abnormal HRCT

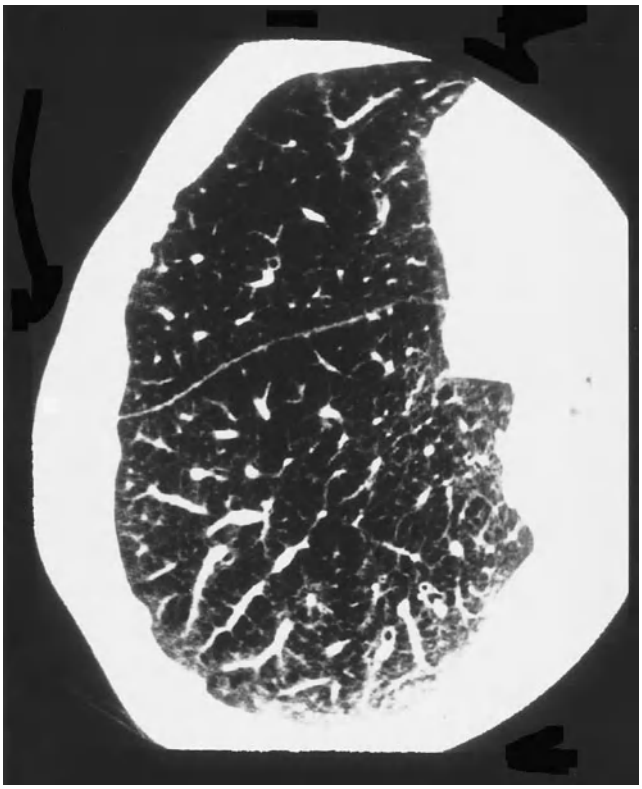

Figure 55-4 HRCT scan with irregular opacities of the lung parenchyma and interlobar structure. The PA chest radiograph was graded 2/1 on the ILO International Classification of the Radiographs of the Pneumoconioses. *(Courtesy of Dr. David Naidich.)*

has been shown to correlate with restrictive physiological abnormalities and abnormal diffusing capacities. HRCT is also extremely sensitive in documenting the asbestos-related pleural abnormalities discussed above. The presence of pleural plaques (particularly if they are bilateral) provides useful evidence that the parenchymal process is asbestos related. Hilar node enlargement is not a feature of asbestosis, and progressive massive fibrosis is also uncommon.

Diagnosis

Asbestosis is defined as parenchymal fibrosis, with or without pleural thickening, usually associated with dyspnea, bibasilar rales, and pulmonary function changes. To diagnose this disorder, one must establish the presence of pulmonary fibrosis and determine whether exposure has occurred of a duration and intensity sufficient to put the person at risk for developing this syndrome. The PA chest radiograph and its interpretation are the most important factors. As noted above, a profusion of irregular opacities at the level of 1/0 is used as the break point between normal and abnormal in the evaluation of lung fields on the chest radiographs of asbestos-exposed persons. When radiographic or lung function changes are marginal, CT scanning often reveals characteristic parenchymal abnormalities as well as pleural plaques and/or pleural fibrosis. These lesions, particularly when bilateral, are strongly suggestive of asbestos exposure.

The diagnosis of asbestosis must always be based on an appropriate exposure history. The features of the history that need to be defined include the duration, onset, type, and intensity of exposure experienced by the patient. Convincing occupational exposures include manufacture of asbestos products, asbestos mining and milling, construction trade worker (insulator, sheet-metal worker, electrician, plumber, pipe fitter, carpenter), power plant worker, boilermaker, and shipyard worker. In performing this evaluation, it is important to keep in mind that intensity of exposure can be heavy even if duration of exposure is short. For example, heavy exposures were experienced by shipyard workers engaged in insulation application or removal in contained areas for brief periods aboard ship and by asbestos insulators during their apprenticeship when they unloaded asbestos sacks into troughs and mixed asbestos cement. Short, intense exposures of this sort, which lasted from several months to 1 or 2 years, can be sufficient to cause asbestosis. Exposures over 10 to 20 years are, however, usually necessary. The timing of the exposure is also relevant. Industrial hygiene controls in the 1950s and 1960s, especially in the construction trades, were not widely applied or enforced. Thus, workers exposed during these periods may have received a heavy asbestos load. Time since onset of exposure is also crucial. Cohort studies have identified latency to be an important factor, with the prevalence of asbestosis increasing with time since the onset of exposure.

The specificity of the diagnosis of asbestosis increases as the number of clinical criteria (symptoms, signs, chest radiograph, pulmonary function) increase. In addition, as the accuracy of the diagnosis increases, the more significant the asbestos exposure. The more trivial the asbestos exposure, the less likely it is to be causal. Misclassification and diagnostic difficulty occur in patients with a heavy cigarette-smoking history and concurrent emphysema (which also reduces the diffusing capacity). Patients with idiopathic pulmonary fibrosis (IPF) may have a history of asbestos exposure. These patients tend to be younger, however, and their asbestos exposure is usually casual, brief, and recent and can often be discounted. Since patients with IPF require a lung biopsy for confirmatory diagnosis, an asbestos fiber count per milligram of dry lung can be helpful (see below). An open lung biopsy is not required in most cases when a significant exposure history can be identified.

In the absence of an adequate exposure history or in the presence of a confusing clinical presentation, biopsy material may be helpful in identifying the nature of the disease. It allows the pulmonary interstitial process to be compared to the known features of asbestosis and other interstitial disorders. It also allows the pathologist to look for the presence of asbestos materials. Asbestos fibers exist in the lung in two forms: uncoated or bare fibers, which, for practical purposes, are visible only on electron microscopy, and coated fibers, which are also called asbestos bodies. The latter are visible by light microscopy (Fig. 55-5). Uncoated fibers are much

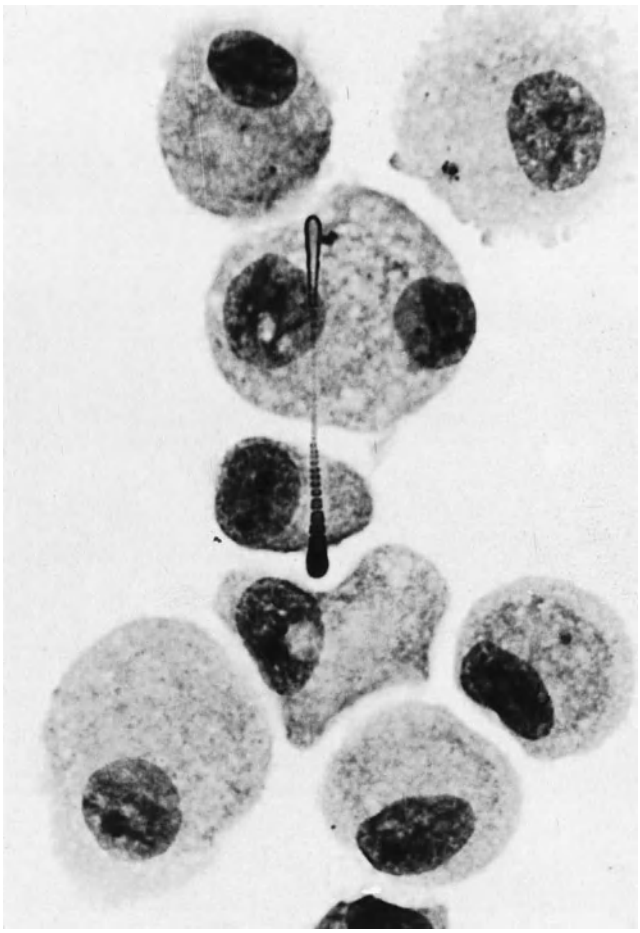

Figure 55-5 Light microscopic appearance of an asbestos body in a cytocentrifuged preparation of alveolar macrophages lavaged from a nonsmoking asbestos insulator (Wright-Giemsa stain, ×400). *(Courtesy of Dr. T. Takemura and Dr. V. Ferrans.)*

more common, exceeding the frequency of coated fibers by anything from 5- to 10,000-fold. Although other inhaled particles may also become coated, most coated fibers found in human lungs have an asbestos core. Thus, the presence of asbestos bodies or asbestos fibers is considered the hallmark of exposure, past or current. The presence of more than one coated fiber has been cited as a necessary criterion for the pathological diagnosis of asbestosis, even in a subject with an obvious exposure history. This may be inappropriate, however, since asbestos bodies may not be able to be detected even after heavy exposure. Cases have been described in which the load of uncoated fibers was high in the absence of asbestos bodies, and asbestos bodies have been noted in the tissues of people without significant asbestos exposure. Thus, although asbestos bodies probably reflect exposure, their absence by no means excludes it.

Asbestos bodies can also be detected in BAL samples. In some studies, these asbestos bodies correlate with heavy exposure and asbestosis. This is illustrated in a large series of 563 patients: those with asbestosis had a mean of 120 asbestos bodies per milliliter; those with pleural disease, 5 asbestos bodies per milliliter; and those with malignant mesothelioma or lung cancer, 8 asbestos bodies per milliliter of lavage fluid. Of 49 patients with more than 100 asbestos bodies per milliliter of lavage fluid, 30 had asbestosis, 8 had pleural disease, 13 had mesothelioma or lung cancer, and 3 had an exposure history only. Others have estimated that one asbestos body per milliliter of BAL fluid correlates with 1000 to 3000 asbestos bodies per gram of dry lung tissue. The problems inherent in counting asbestos bodies in an attempt to establish a diagnosis of asbestosis were noted above. Thus, the utility of BAL asbestos body counts in diagnosing asbestos awaits further definition.

Treatment and Prognosis

Major causes of morbidity and mortality in patients with asbestosis include the progression of the underlying lung disease and the development of lung cancers and malignant mesotheliomas. Longitudinal observations of asbestos-exposed trade workers have demonstrated accelerated declines in pulmonary function. In a study of 77 workers with a mean of 31 ± 1 years of occupational exposure, linear regression demonstrated a mean annual decline of 92 ± 28 ml per year in FVC, 66 ± 22 ml per year in FEV_1, and 14 ± 53 ml per year in total lung capacity. Although corticosteroids and colchicine have been used for the treatment of IPF, they have not been demonstrated to be beneficial in asbestosis. At present, there is no established treatment for this disorder. Because of the risk of lung cancer and mesothelioma, however, medical surveillance is recommended.

MALIGNANT MESOTHELIOMA

Pathology

Most instances of mesothelioma occur in persons who have been exposed to asbestos fibers. In its early stage, the mesothelioma appears as multiple, small, grayish nodules on the visceral and parietal pleura that evolve to coalesce and form larger masses of tumors. These tumors then invade thoracic and other structures by direct extension, causing the morbidity and mortality of disease. Fewer than 25 percent of malignant mesotheliomas are peritoneal in origin.

Mesotheliomas are conventionally classified into three histological patterns: epithelial, sarcomatous, and mixed or biphasic; these patterns account for 50, 20, and 30 percent, respectively. The epithelial variant—in which neoplastic cells are arranged in papillary, tubular, or solid nest configurations—is most easily confused with metastatic adenocarcinoma. The sarcomatous variant has spindle-shaped cells that may be pleomorphic, with considerable mitotic activity.

The pathological diagnosis of malignant mesothelioma may be difficult. In particular, the differentiation of malignant mesotheliomas, adenocarcinomas, and other tumors may be problematic. Histochemistry and immunohistochemistry

may be helpful in making the distinction. Thus, in contrast to mesotheliomas, adenocarcinomas contain neutral mucin that stains positive with the periodic acid–Schiff stain and is often resistant to diastase. Hyaluronic acid, the major acid mucopolysaccharide in mesotheliomas, can be identified with the Alcian blue or colloidal iron stain. Removal by prior digestion with hyaluronidase increases the specificity of the reaction. In contrast, adenocarcinomas are negative for Alcian blue and colloidal iron. Mesothelial cells contain cytoskeletal filaments, including cytokeratin and vimentin; staining for these structures is not specific, since other tumor types are also positive. Carcinoembryonic antigen is absent in malignant mesothelioma but is present in up to 90 percent of adenocarcinomas. Similarly, the monoclonal antibody B72.3, generated against a membrane fraction of human metastatic breast cancer, was positive in 19 of 22 pulmonary adenocarcinomas but none of 20 mesotheliomas. Monoclonal antibody Leu MI is frequently positive in lung carcinomas and nonreactive with mesotheliomas.

The ultrastructural features of malignant mesotheliomas are also noteworthy. Malignant mesotheliomas contain abundant tonofilaments, often organized into perinuclear bundles, and long, sinuous, slender surface microvilli. The microvilli sometimes show secondary and tertiary branching and may interdigitate with stromal collagen. Malignant mesothelial cells produce collagen, a prominent feature of the sarcomatous variant.

Malignant mesotheliomas are locally invasive, spreading along the pleural wall and invading the lung, mediastinal lymph nodes, and other thoracic and nearby structures. At autopsy, tumor may be found in the diaphragm, heart, liver, spleen, adrenals, gastrointestinal tract serosa, bone, pancreas, and kidneys. Between 50 and 80 percent of patients also have metastases.

About 10 percent of patients with a malignant mesothelioma are alive at 24 months. Survival is significantly longer for patients with an epithelial subtype or with a pleural rather than a peritoneal mesothelioma, and for those under 65 years of age.

The incidence of mesothelioma is increasing because of the cohort exposed to asbestos between 1940 and 1970. Incidence rates vary from a low of 11 to 13 per million per year in the United States to 33 per million per year in South Africa and to 66 per million per year in Western Australia. These rates reflect mining and manufacturing industries and the location of crocidolite mines. Although the peak incidence in the United States may have passed since imports decreased after 1945, imports of asbestos in the United Kingdom reached their peak in the 1960s to 1970s. Thus, the peak of mesothelioma deaths in the United Kingdom is expected to occur in 2020, when up to 1 percent of men may die of the disease. Chrysotile was the major asbestos import to the United Kingdom, and half of this material went into the construction industry. Amosite was the leading amphibole import, and most of it went into insulation board. Thus, workers in the construction industry in the United Kingdom seem to be at greatest risk.

Epidemiology

In 1960, Wagner and colleagues published a landmark paper demonstrating an association between malignant mesothelioma and asbestos exposure. They reported on 33 patients from South Africa, 28 of whom were exposed in the crocidolite mining region and 4 of whom were exposed in asbestos factories. They observed that mesotheliomas occurred 20 to 40 years after exposure to asbestos dust and found asbestos bodies in lung tissue from 8 of 10 patients from whom lung tissue was available for study. Subsequently, the importance of direct asbestos exposure was confirmed and the potential importance of indirect exposure to asbestos was recognized.

Evaluations of asbestos fiber content have shown a clear association between asbestos exposure and the occurrence of mesothelioma. Epidemiological studies have shown that crocidolite may be the more potent fiber type among asbestos miners. Most mesotheliomas have occurred from chrysotile-amphibole mixtures, since chrysotile is the most common fiber in commercial use. Few controversies in medicine are as intense as the disagreements concerning the relation between asbestos fiber type and carcinogenic risk. Nonetheless, associations between malignant mesothelioma and other (noncrocidolite) fiber types have been reported. For example, the incidence of malignant mesotheliomas among chrysotile workers who came before the Workers' Compensation Board of Quebec was similar to that in Western Australian crocidolite miners. Studies of Canadian cohorts have also indicated that high concentrations of chrysotile, or an amphibole contaminant, are required to cause mesothelioma, suggesting that chrysotile has weaker biopersistence than does tremolite, which is merely a contaminant in most ores. In the United States, amosite is the predominant amphibole found in lung tissue: in one study it was identified in 81 percent of 90 patients with mesothelioma; in this population, it accounted for 58 percent of all fibers at least 5 μm in length.

Cigarette smoking is a confounding variable in studies that relate asbestos-exposed persons to cancer risk. The contribution that cigarettes make to the risk of lung cancer is impressive (see below). It is universally accepted, however, that mesothelioma is not associated with cigarette smoke per se.

Pathogenesis

Insight into the pathogenesis of malignant mesothelioma has come from experiments in which asbestos fibers were introduced into the pleural space of animals. These studies have demonstrated that amosite, anthophyllite, crocidolite, and Canadian chrysotile can all cause these pleural malignancies. Studies of fiber size have shown that the most carcinogenic fibers in the pleural space are 1.5 μm or less in diameter and more than 8 μm in length. Inspection of electron micrographs of asbestos fibers has shown that crocidolite and amosite possess needlelike characteristics, whereas anthophyllite has a more boxlike appearance and chrysotile has a long, curly appearance. These variations in size are also consistent with epidemiological studies indicating that crocidolite and amosite

may have greater risk for mesothelioma than do other types of asbestos, although these studies are often confounded by intense exposures to these amphibole types.

One theory concerning the mechanism of asbestos-induced carcinogenesis focuses on the observation that asbestos fibers become entangled in the mitotic spindle during interphase, thereby causing chromosomal abnormalities. Electron microscopic evaluations have shown fibers penetrating between multiple lobes of the nucleus and associating, along their length, with the outer surface of the nuclear envelope. Structural chromosomal abnormalities in mesothelioma are clonal and complex, and include both chromosomal gains (chromosome 22) and losses (chromosome 7). Deletions of the short arm of chromosome 3, the break point 1p11 to p22, chromosome 17, and structural and numeric changes in chromosome 7 have been described. The last is quite interesting, since the tumor suppressor gene *p*53 is located in the region of 17p13. In asbestos insulators, sister chromatid exchanges in circulating lymphocytes are increased: larger chromosomes are more susceptible, and in the largest chromosome group, there is a significant interactive effect between asbestos exposure and cigarette smoking.

Cell lines established from malignant mesotheliomas have been shown to constitutively up-regulate the PDGF B-chain gene and, to a lesser extent, the PDGF A-chain gene. High levels of transforming growth factor-β_1 (TGF-β_1), TGF-β_2, and TGF-β_3 mRNA and bioactivity have been reported for cell lines derived from malignant mesotheliomas. These TGF-β moieties may be involved in the considerable matrix formation that accompanies mesothelial tumors. Mesothelioma cell lines also release IGF-1 and express mRNA for the IGF-1 receptor. This is consistent with an IGF-1–based autocrine loop for mesothelioma cell proliferation.

Clinical and Radiographic Features

Pleural mesotheliomas are found mainly in males (ratio, between 3 and 4 to 1) and are most commonly diagnosed in patients between 50 and 70 years of age. Chest pain is the most common symptom experienced by patients with mesotheliomas. Dyspnea is next in frequency. Less common symptoms are cough, weight loss, and fever. A pleural effusion is usually present and can be massive. The effusion is an exudate, can be hemorrhagic, and may have high levels of hyaluronic acid (Fig. 55-6). Malignant mesothelioma is locally invasive, spreading along the pleural wall and invading the lung and nearby structures. Metastases are less common but can give rise to symptoms due to tumor in the diaphragm, heart, liver, spleen, adrenals, gastrointestinal tract, bone, pancreas, and kidneys. The syndrome of inappropriate antidiuretic hormone secretion, clubbing, or hypoglycemia is rare. Thrombocytosis is common—in 90 percent of cases in one series—and thromboembolic complications can occur. Ascites and weight loss are characteristic features of peritoneal mesothelioma.

A variety of radiographic abnormalities are found in malignant mesothelioma. They include a thick pleural peel along the lateral chest wall that can extend to the apex with an irregular nodular surface, multiple pleural nodules or masses, plaquelike opacities, and pleural effusion(s). As the disease progresses, the lung parenchyma may be involved, the affected hemithorax may decrease in size, and the mediastinum or hilar may be invaded. Pericardial thickening or effusion, abdominal extension, and chest wall invasion are common. The HRCT can help in differentiating pleural effusion from tumor and in determining the extent of tumor progression. The presence of asbestosis or of pleural plaques on the opposite side can assist in establishing the diagnosis of malignant mesothelioma.

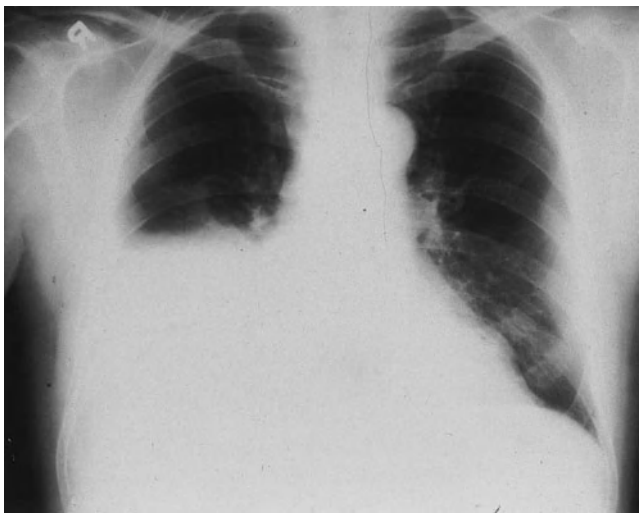

Figure 55-6 Large pleural effusion in an asbestos-exposed worker with an underlying malignant mesothelioma. *(Courtesy of Dr. J. Elias.)*

Diagnosis

The diagnosis of malignant mesothelioma requires cytological or histological validation. Obtaining a cytological diagnosis from the pleural exudate is difficult because reactive mesothelial cells and malignant cells are not easy to distinguish. Biopsy is required. Because mesothelioma has been shown to invade the track of the needle on about 20 percent of patients in whom biopsy was performed by transthoracic needle, open biopsy is preferable. Thoracoscopy is probably the procedure of choice in establishing the diagnosis of mesothelioma. Its diagnostic rates are greater than 80 percent—a value similar to that of open pleural biopsy. Local radiation after biopsy significantly reduces spread in needle tracks or incisions.

Treatment and Prognosis

Median survival time is approximately 8 to 12 months for all patients with malignant mesothelioma. Overall, fewer than 20 percent of patients are alive at 2 years. Pleurectomy or pneumonectomy, combined with radiation therapy, has failed to significantly influence survival rates. Chemotherapy

with doxorubicin (Adriamycin) has shown variable responses without prolonging survival.

Interventions, such as gene therapy or the use of cytokines, for the treatment of malignant mesothelioma are currently being investigated. Thus, in 89 patients, the intrapleural instillation of γ-interferon twice weekly for 8 weeks resulted in eight histologically confirmed complete responses and nine partial responses, with at least a 50 percent reduction in tumor size. The overall response rate was 20 percent, increasing to 45 percent in stage I disease. In 15 patients, a phase I clinical trial of continuous infusion into the pleural space of recombinant IL-2 for 5 days, when evaluated at 36 days after infusion, revealed one complete remission and six partial remissions. The main side effect was fluid retention, no greater than 10 percent, in one-third of the patients. In mice with severe combined immune-deficiency, gene therapy, using a replication-defective adenovirus carrying the herpes simplex–thymidine kinase gene followed by the antiviral drug ganciclovir, was used successfully to treat malignant mesothelioma. A significant antitumor effect occurred with clinically achievable dose ranges, even in bulky tumors. The virus did not spread from the serosal cavity following instillation. In mice with subcutaneously implanted mesothelioma, tumor regression occurred when only 10 percent of cells were infected—a result consistent with a *bystander effect.* A phase I clinical trial has shown this therapy to be safe. However, humoral and cell-mediated immune responses that developed against viral surface proteins compromised the therapeutic effectiveness of this approach. Also, the thymidine kinase gene in vivo had no effect on promoting regression of the tumor. These promising areas of research need further development before they can be applied as standard therapy.

LUNG CANCER

Epidemiology

The association between asbestos exposure and the development of lung cancer is based on a number of successive epidemiological investigations. Case reports of lung cancer and asbestos deaths occurred as early as 1935. Series of patients with asbestosis who went to autopsy were reported by 1947. In 1955, an epidemiological cohort study of 113 men exposed to asbestos for 20 years disclosed 11 deaths due to cancer (compared with 0.8 expected), all of which had evidence of asbestosis. In 1965, a retrospective cohort study in two asbestos insulator unions in the United States reported that deaths from lung cancer were 6.8 times the expected rate and that the incidence of lung cancer increased with time after exposure. In 1968, a follow-up of men in this cohort demonstrated an important synergy between asbestos exposure and cigarette smoking, since the risk of lung cancer was almost entirely borne by those who had a history of cigarette smoking.

The largest survey of asbestos-related deaths looked at a North American asbestos insulator cohort. This study demonstrated a threefold excess of cancer deaths that were due primarily to pulmonary malignancies. Comparatively few of these excess deaths were observed among those less than 25 years after the start of exposure. Lung cancer peaked at 40 years from exposure and mesothelioma at 45 years. In contrast, death rates from asbestosis increased progressively with time. This study confirmed the multiplicative effect of smoking plus asbestos exposure on the risk of lung cancer. Moreover, it showed that deaths from lung cancer dropped by almost two-thirds for asbestos insulators who subsequently stopped smoking.

Additional insights were provided by a study of amosite workers who were exposed to concentrations of 50 fibers per milliliter. These patients experienced a fivefold increase in lung cancer. Long-term follow-up showed: (1) a latency period of about 20 years before the increase in cancer occurred; (2) the greater the dose or the longer the exposure, the greater risk of developing lung cancer; and (3) the greater the dose or exposure time, the shorter the latency period before the tumor developed. Malignancies were also noted in the wives and children of these workers who were exposed to asbestos in the household, primarily on work clothes. In addition, men employed for less than 1 month between 1941 and 1945 developed lung cancer at an increased rate. Studies of a variety of other cohorts have confirmed the increased incidence of lung cancer in asbestos-exposed populations. They have also demonstrated an increased frequency of digestive cancers and cancer of the larynx; in the latter, asbestos has been found in laryngeal tissue. As in the case of cancer of the lung, cigarette smoking has a strong association with the occurrence of these laryngeal malignancies.

Epidemiological studies have also provided information about dose-response relationships and about the importance of asbestos-processing techniques and fiber type in the pathogenesis of pulmonary malignancies. A number of investigators have observed linear dose-response relationships for lung cancer. Different dose-response relationships have, however, been found in other studies. These differences may be the result of differences in processing techniques. For example, studies in a South Carolina plant demonstrated that the steeper dose-response relationship of miners vs. textile weavers was probably due to the manufacturing process, which resulted in high levels of brief exposure during the opening of asbestos bags and the sudden separation of the asbestos fibers. Similarly, differences in lung cancer mortality in asbestos cement product plants in Louisiana were found to be associated with the addition, in one of these plants, of crocidolite to the asbestos cement pipe mixture. Other risk factors in the work place—such as concomitant metals, ionizing radiation, and other chemicals—may also contribute to the differences that have been noted. It has been argued that there is a difference in lung cancer risk for different asbestos fiber types; however, the risk of lung cancer increases most clearly with cumulative asbestos exposure. Despite these uncertainties, however, it is clear that each of the asbestos fiber types causes lung cancer.

Pathology

Asbestos-related lung cancers are not distinct from lung cancers that occur in cigarette smokers and otherwise normal persons in type, nature, or location. All histological types of lung cancer occur with increased frequency, but adenocarcinoma has the highest incidence. In the vast majority of patients, there is histological evidence of asbestosis and asbestos bodies are frequently found. Asbestos-related lung cancer can occur in the absence of asbestosis.

Pathogenesis

Animal experiments using several types of asbestos have succeeded in reproducing pulmonary malignancies. In one study, approximately one-third of rats exposed by inhalation to asbestos (amosite, anthophyllite, crocidolite, Canadian chrysotile, or Rhodesian chrysotile) for periods ranging from 1 day to 24 months developed adenocarcinomas or squamous cell carcinomas of the lung. In these experiments, a clear dose-response relationship existed between asbestos dose and the occurrence of tumors. The mechanisms responsible for the induction of these malignancies are poorly understood. However, DNA injury and activation of nuclear transcription factors may play an important role. The former appears to relate to the physical properties of the asbestos fibers, which enable DNA, RNA, and chromatin to bind to asbestos. Reactive oxygen species may also play an important role in this process, since chrysotile asbestos, along with cigarette smoke, synergistically increases the number of breaks in DNA strands, and oxidant scavengers—such as mannitol, catalase, iron chelators, and dimethylsulfoxide—prevent this DNA damage. Asbestos also induces nuclear factor-κB (NF-κB) DNA binding in tracheal epithelial cells in vitro. NF-κB is an important transcription factor for cytokines, growth factors, and protooncogenes that could contribute in a variety of ways to malignant transformation.

Clinical Features

The patterns of presentation of lung cancer among asbestos workers are similar to those of high-risk patient populations: cough, chest pain, dyspnea, hemoptysis, recurrent bouts of pneumonia, and localized wheezing are major symptoms that frequently bring patients to medical attention. However, patients can also be asymptomatic at the time of initial discovery, the abnormality being noted on a routine or screening chest radiograph. Other manifestations of carcinoma—such as rib invasion, shoulder-arm pain, and paraneoplastic syndromes—can also occur in asbestos-related malignancies.

One of the most vexing questions in asbestos-related lung cancers is the relationship between the lung cancer and asbestosis. Asbestosis can be detected radiographically or histologically in the vast majority of patients with asbestos-related lung cancer. Most, but not all, patients with lung cancer in the Quebec asbestos mining district had small parenchymal opacities on the chest radiograph before death. In addition, in amphibole miners from South Africa with carcinoma of the lung who were evaluated by stepwise regression analysis for exposure variables, asbestosis was by far the most striking variable. Moreover, a dose-response relationship was found between the severity of asbestosis and the frequency of lung cancer. However, in keeping with the high frequency of asbestosis that cannot be seen on the chest radiograph (i.e., asbestosis that can be detected only in vivo by HRCT or biopsy) it is clear that radiographic evidence of asbestosis cannot be detected in all patients with asbestos-related lung cancer. Thus, in the North American insulator cohort, 18 percent of the patients who died of lung cancer did not have radiographic evidence of parenchymal fibrosis. Similarly, in a case control study of 271 patients with lung cancer, a small but definite increase in cancer risk was noted in patients whose chest radiographs were not definitely abnormal (0/1 or less by ILO classification). This study indicated that asbestos exposures that do not cause small opacities on the chest radiograph may nevertheless increase the risk of lung cancer.

Radiographic Features

The radiographic manifestations of asbestos-induced lung cancers do not differ, per se, from those of lung cancers associated with other carcinogens. Mass lesions, atelectasis, postobstructive pneumonia, and pleural effusions are all seen. As noted above, these lesions are frequently superimposed on a background of asbestosis or asbestos-induced pleural abnormalities. Confusion with lung cancer may arise from en face pleural plaques or rounded atelectasis. In contrast to lung cancer, however, these abnormalities are stable over time. Newer techniques, such as the helical CT scan, which can evaluate the chest in a single breath, may increase the early detection rate of lung cancer in this high-risk patient population.

Diagnosis

The principles employed in the diagnosis of lung cancer in asbestos workers are identical to those in the diagnosis of pulmonary malignancies in patients exposed to other carcinogenic agents. Appropriate cytological or histological specimens are required. This can be accomplished by sputum analysis or by bronchoscopy with brushings, biopsy, or lavage. Transthoracic needle aspirates, thoracoscopic parenchymal biopsies, or open lung biopsies may be required for definitive diagnosis.

Treatment and Prognosis

The therapeutic approaches utilized for asbestos-related lung cancers are similar to those employed for lung cancers induced under other circumstances. When one is dealing with non–small-cell malignancies, patient operability and resectability need to be evaluated and, if appropriate, surgical extirpation undertaken. The impact of other asbestos-related pulmonary processes must always be taken into account. For

example, severe asbestosis may limit operability, and diffuse pleural thickening may make surgical intervention problematic. Overall, however, lung cancer has a poor prognosis—15 percent survival at 5 years.

EFFORTS AT ASBESTOS CONTROL

In order to control the risk of exposure to asbestos, the US Occupational Safety and Health Administration regulates the usage of all types of asbestos fibers.

Industrial hygiene efforts to control exposure have focused on engineering controls, including enclosure of the process lines, especially all sites where asbestos is introduced into a system, increasing ventilation, and the use of wet manufacturing methods. Personal respirators are used as a last resort in achieving control of exposure in the workplace. Most of the insulation-manufacturing industry has switched to alternative materials, especially fibrous glass, rock and slag wool, and refractory ceramic fibers. Animal experiments have generally shown these asbestos substitutes to be safe, except that refractory ceramic fibers were able to produce mesotheliomas in hamsters. Asbestosis and asbestos-related cancers may occur at increased rates in the future, owing to the increased use of asbestos in developing countries.

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Chronic Beryllium Disease and Hard-Metal Lung Diseases

Mary Elizabeth Kreider • Milton D. Rossman

CHRONIC BERYLLIUM DISEASE

History

Beryllium is the lightest weight metal and has an atomic number of 4. Gem stones, such as aquamarine, emerald, and beryl, contain beryllium and have been recognized since ancient times. But beryllium as an element was first discovered in 1798 by the French chemist, Vauquelin, and reduced to its metallic form and named beryllium in 1828 by the German metallurgist, Wohler. Beryllium became a commercial product when it was used as an alloy first with aluminum and later with copper, nickel, and cobalt after World War I. The industry grew in the 1930s due to the increased use of beryllium-copper products during World War II and the use of beryllium oxide in the refractory and fluorescent lamp industries. During and after World War II, beryllium was used in the nuclear industry because of its ability to function as a neutron multiplier. Beryllium was used for both civilian nuclear reactors and for military weapons.

With an increased industrial need for beryllium, acute chemical pneumonitis was first described by Weber and Engelhardt in Germany in 1933 and in the United States by van Ordstrand et al in 1943. This condition was usually limited to the upper respiratory tract, though it could extend to the bronchi, bronchioli, and alveoli if there was sufficient exposure. This condition peaked in the 1940s and with the implementation of industrial hygiene standards will now only be seen if there are plant explosions or other serious lapses in procedures. The last reported possible case in the United States occurred in the early 1980s.

A second pulmonary complication of beryllium exposure was first described by Hardy and Tabershaw in 1946. This disease differed from the acute chemical pneumonitis because of the delayed onset, granulomatous response, and chronic course. Now known as chronic beryllium disease (CBD), this condition is a hypersensitivity reaction to beryllium and is the major hazard facing beryllium workers today.

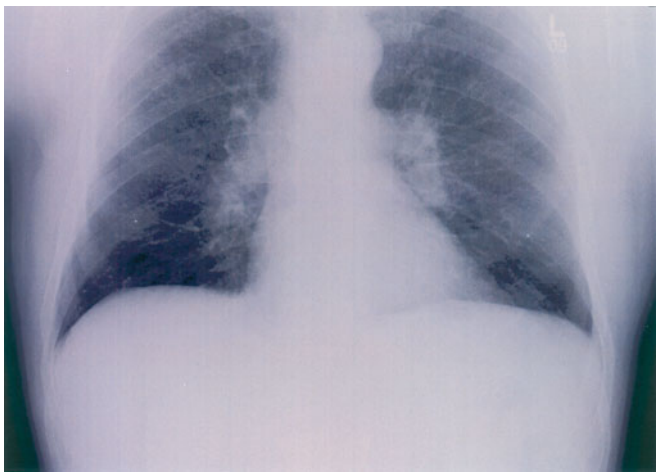
Clinical Presentation

CBD is primarily a pulmonary granulomatous disorder. Although involvement of other organ systems has been reported (e.g., lymph node, skin, and liver), the lungs are the principal organ affected and account for the morbidity and mortality of this disease. In the early stages, CBD may be asymptomatic. A positive blood proliferative response to beryllium (evidence for beryllium hypersensitivity) may be the earliest sign of

CBD. Radiologic changes can also be detected on routine chest radiographs. Symptomatic disease usually begins with nonspecific respiratory complaints, such as exertional dyspnea and cough. Early in the disease process, routine chest radiography may not be helpful. Pulmonary function testing early in the disease may be normal or have an isolated abnormality of the diffusing capacity (D_{LCO}). As the disease progresses, symptoms become more characteristic for chronic interstitial lung disease with a nonproductive cough, substernal burning pain, and progressive exertional dyspnea. At this stage dry bibasilar crackles are observed on physical examination. A rare patient may have asthmatic-type complaints and physical findings. With advanced disease progressive weakness, easy fatigability, dyspnea at rest, anorexia, and weight loss may occur and acrocyanosis and clubbing may be observed. As cor pulmonale develops, peripheral edema, hepatomegaly, and distended neck veins are seen. Fever is unusual but can be seen. Hypercalcemia and nephrocalcinosis, hyperuricemia, joint pains, and severe cachexia have been described. Severe liver involvement has not been seen, but liver granulomas with mild elevation of the liver function tests occur. Skin involvement may occur in 10 to 30 percent of cases and frequently involves small granulomatous nodules on the hands, arms, and chest.

Radiography

Radiographic changes in CBD are nonspecific and cannot be differentiated from sarcoidosis (Fig. 56-1). The most common radiographic abnormalities are diffuse round and reticular abnormalities. While most patients have both round and reticular nodules, opacities may be only round or only reticular. These opacities are usually present diffusely throughout the lung but may be confined to the upper lobes. Hilar adenopathy similar to what is commonly observed in sarcoidosis may also be seen in up to 50 percent of cases. However, the large "potato type" node involvement is not seen. As the disease advances, radiologic evidence of scarring and retraction can be seen. The hila are retracted upward and conglomerate mass and emphysematous bullae may be present. Gross architectural distortion can occur from severe fibrosis. Pleural thickening can be seen in the presence of long-standing disease. In early disease complete resolution of radiographic abnormalities can occur secondary to corticosteroid therapy and may recur as the corticosteroids are



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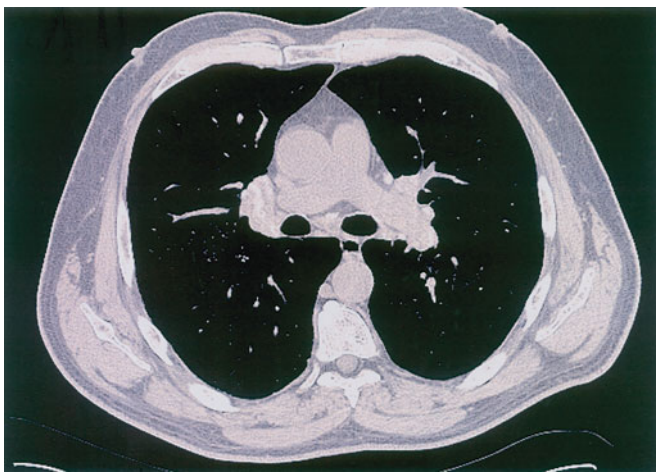

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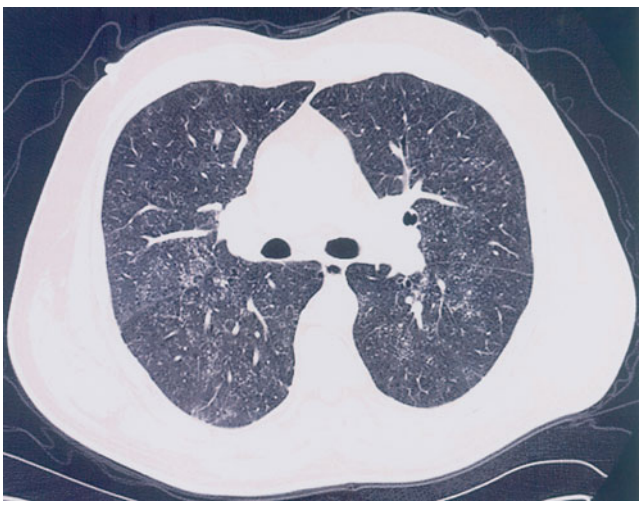

C

Figure 56-1 A 61-year-old male smoker who had worked at a beryllium processing facility for 20 years. He had a productive cough for 10 years but denied any shortness of breath. He had a positive response of both blood and bronchoalveolar lavage (BAL) cells to beryllium (SI for blood BeLPT = 13.8 [NI < 3.0], SI for BAL BeLPT = 306 [NI < 5.0]. His BAL also demonstrated a marked lymphocytosis (cell yield = 6×10^5 cells/ml [NI < 3.0×10^5 cells/ml], lymphocytes = 55.2% [NI < 20%]. *A*. Chest radiograph demonstrating nodular interstitial disease with adenopathy. *B*. Chest CT mediastinal window demonstrating calcified bilateral hilar and mediastinal lymph nodes. *C*. Chest CT lung window demonstrating a diffuse, fine-nodular pattern of interstitial lung disease that was most prominent in the mid and upper lung zones.

tapered. Complete spontaneous disappearance of the radiographic lesions has not been observed. The computed tomographic appearance of CBD includes upper lobe or diffuse fibrosis, pulmonary nodularity, and hilar and mediastinal adenopathy. However, in biopsy-proven CBD the computed tomographic findings may be normal or demonstrate ground-glass changes.

Immunopathogenesis

There are three important characteristics of CBD. First, this disease is usually associated with industrial exposure to beryllium. The only cases that have been described in nonindustrial workers have been in individuals who lived near beryllium plants and were either exposed to the airborne emissions from the plant or from family members who brought contaminated work clothes into the home. All other cases have been described in individuals who have been involved in the heating, grinding, abrading, or handling of beryllium metals, alloys, salts, or oxides. In addition, workers not directly handling beryllium may be exposed from processes occurring near them. Industrial hygienic practices today include efforts to remove potential airborne beryllium at the source to prevent beryllium from becoming airborne, limiting the number of workers with potential exposure to beryllium, limiting skin exposure, and trying to keep the airborne levels as low as possible. Recently the Department of Energy has used 0.2 $\mu g/m^3$ as an action level because of the repeated reports of CBD with possible exposure below the Occupational Safety and Health Administration (OSHA) recommended threshold level of 2 $\mu g/m^3$/8 h shift.

A second important characteristic of CBD is the long time interval or latency that occurs between initial exposure and the onset of disease. The average time to the onset of clinical symptoms is 10 years. This fact combined with the lack of a clear-cut dose-response relationship to CBD has hampered efforts to determine a safe level of beryllium. Thus, it is uncertain whether a peak exposure level or a total accumulated dose is more important for the development of CBD. Individuals have been described (i.e., secretaries with apparently little exposure) who have worked in industry for less than 1 year and yet still develop disease years to decades later.

A third important characteristic of CBD is that not all exposed workers will develop the disease. Only 1 to 8 percent of exposed workers will ever develop the disease. This percentage appears to have remained the same despite dramatic efforts by industry to reduce the potential exposure in their workers. This last characteristic of CBD may be due to a genetic predisposition (see below).

The suspicion that an immunologic reaction to beryllium caused CBD was based on the following observations. (1) Beryllium painted on the skin (patch testing) could elicit delayed-type hypersensitivity reactions in patients with CBD. However, because of the concern that patch testing could sensitize individuals to beryllium, skin testing has not been widely used. (2) CBD was associated with "immunologic granuloma." (3) Finally, animal studies demonstrated that a hypersensitivity could be demonstrated in animals and that this could be passed with cells.

In vitro studies that simulated patch testing were developed in the 1970s and applied to patients with CBD. The blood cells from a large percent of patients with CBD had positive proliferative responses to beryllium. In addition, after stimulation with beryllium, blood cells from many patients with CBD could release the lymphokine, macrophage inhibition factor. However, all patients with CBD did not have positive responses with their blood cells.

The confirmation that CBD was due to a cell-mediated response to beryllium came in the 1980s when cells harvested from the bronchoalveolar lavage fluid (BALF) from patients with CBD were examined. Not only was a marked increase in the number and percent of CD4+ T lymphocytes in the BALF noted, but also a positive proliferative response of bronchoalveolar lymphocytes to beryllium was observed. Positive proliferative responses to beryllium were observed in all cases of CBD and negative responses were noted in beryllium workers with biopsy-proven non-beryllium lung disease, patients with sarcoidosis and no history of beryllium exposure, and normal volunteers. Not only did all patients with CBD have a positive proliferative response of their bronchoalveolar cells to beryllium, but this response was more pronounced in their lung cells than their blood cells. Thus, there was the suggestion that there was an accumulation of beryllium-specific cells in the lungs of all patients with CBD. This has recently been confirmed using ELISPOT analysis.

The CD4+ T-cell response to beryllium suggested that specific HLA class II molecules might be involved in CBD since HLA class II molecules present antigenic peptides to CD4+ T cells. A strong association of CBD with the marker HLA DPB1-glu 69 was first shown by Richeldi and subsequently confirmed in three other laboratories. However, rather then just a marker for CBD, this marker appears to be associated with the ability to develop an immune response to beryllium. However, individuals homozygous for this marker may be more likely to develop CBD rather than just have sensitization with no apparent disease. For the 10 to 20 percent of individuals with beryllium sensitization who are DPB1-glu-69–negative, recent studies suggest that DR may be important in these individuals.

Recent studies suggest that HLA DPB1-glu 69 is not just a marker for beryllium sensitization, but is strongly associated with the ability of beryllium to cause T-cell proliferation. The beryllium-induced T-cell response is blocked by anti-DP antibodies but not by anti-DR or anti-DQ antibodies. Only DPB1-glu 69 containing B-cell lines are able to stimulate sensitized T cells in the presence of beryllium. In addition, beryllium was shown to stimulate the release of the CLIP molecule only from glu-69–containing DP molecules. Finally, the DPB1 molecules containing glu-69 are necessary not only for the T-cell proliferative response but also for these cells to secrete interferon-γ (IFN-γ), tumor necrosis factor-alpha (TNF-α), interleukin-2 (IL-2), and numerous surface markers.

The above studies suggest the following model for the pathogenesis of CBD. Beryllium is inhaled and deposited in

Table 56-1

Laboratories Performing Beryllium Proliferation Testing

Immunopathology Laboratory Cleveland Clinic Foundation Cleveland, OH
National Jewish Center for Immunology and Respiratory Medicine Denver, CO
Pulmonary Immunology Laboratories Hospital of the University of Pennsylvania Philadelphia, PA
Oak Ridge Institute for Science and Education Oak Ridge, TN
Specialty Laboratories, Inc. Santa Monica, CAL

the periphery of the lung. Beryllium, either alone as a crystal or combined with a normal lung protein(s), is bound by glu-69–containing DPB1 molecules and presented to beryllium-specific T cells. The beryllium protein or beryllium crystal is poorly digestible and cannot be removed by the immune response. Persistent inflammation leads to granuloma formation. The cells of the granuloma secrete enzymes that cause tissue destruction and fibrosis.

Diagnosis

Because of the frequent need for corticosteroid treatment of patients with CBD, all patients should have tissue confirmation of their diagnosis. A confirmed diagnosis of CBD requires demonstration of a granulomatous reaction secondary to beryllium hypersensitivity. The former requires biopsy material. The latter can be most convincingly demonstrated by testing the proliferative response of bronchoalveolar cells to beryllium. If bronchoalveolar lavage cells cannot be easily or safely obtained, testing of blood proliferative responses to beryllium is a reasonable alternative. Laboratories performing these tests are listed in Table 56-1. In cases where biopsy demonstration of granulomatous inflammation is not possible, radiologic evidence of granulomatous inflammation may substitute.

Because immunologic tests of beryllium hypersensitivity have been available only since the late 1980s, their use for screening worker populations is not clear. However, studies to date indicate that blood proliferative response to beryllium is the most sensitive screening test for CBD. The major difficulty with using the blood proliferative response to beryllium as a screening tool is that not all individuals with beryllium sensitization will go on to develop CBD. In addition, the number of workers with beryllium sensitization that ultimately develop symptomatic CBD that requires treatment is unknown. In addition, the justification for a screening test requires that there must be some action that will alter the course of the disease. While it is generally believed that early treatment of CBD will alter the natural course of this condition this is not certain. In addition, removal from further exposure, a prudent but unproven practice, is possible for current workers but would not be applicable to former workers. Thus, the strongest recommendation for use of the beryllium lymphocyte proliferation test as a screening test can be made for current workers. Recommendations for screening former workers and residents of communities with past beryllium exposure from the ambient air are less certain. Nevertheless, because the risk of developing CBD is lifelong, the question of appropriate screening for exposed individuals remains.

Differential Diagnosis

The major challenge to making the diagnosis of CBD is to think of the possibility of beryllium exposure. Most cases of CBD that are misdiagnosed are diagnosed as sarcoidosis because either the exposure to beryllium was not known by the patient or the physician failed to elicit an occupational history. Because the radiographic and clinical presentation of CBD (Table 56-2) is similar to sarcoidosis, the differential diagnosis includes upper-lobe fibrotic processes (Table 56-3). In addition, as for sarcoidosis, other causes of granulomatous disease must be searched for and eliminated. The differential between sarcoidosis and CBD is the result of proliferation testing to beryllium. Patients with sarcoidosis do not respond to blood proliferation to beryllium, while CBD patients do. Cases of sarcoidosis among beryllium workers can be diagnosed in this manner. However, caution should always be used and repeatedly negative blood and lung tests should be determined before accepting a case of granulomatous lung disease in a beryllium worker as sarcoidosis.

Treatment

No standard approach to the use of corticosteroids has been adopted in the treatment of CBD. Because of the side effects, corticosteroids should be reserved for patients with documented pulmonary impairment or those with progressive deterioration. Doses of corticosteroids should be tapered to the lowest dose that controls signs of active disease. Monitoring of patients with chest radiographs, pulmonary function tests, exercise tests, and serum angiotensin-converting enzyme may be useful. Most cases of CBD will be arrested with corticosteroid treatment. In cases of corticosteroid resistance or end-stage disease discovered at initial diagnosis, lung transplantation may be a reasonable approach.

The long-term prognosis for CBD is uncertain. Follow-up of cases that were diagnosed in the 1940s and 1950s suggest that the mortality of the disease might be as high as 30 percent. Whether a similar mortality will be present in patients with

Table 56-2

Comparision of Chronic Beryllium Disease and Sarcoidosis

Manifestations	Sarcoidosis	Chronic Beryllium Disease
Erythema nodosum	10–20%	Absent
Hilar adenopathy	50–75%	< 50%
Peripheral adenopathy	Occasional	Rare
Hypercalcemia	Occasional	Rare
Nephrocalcinosis	Rare	Rare
Bone changes	In chronic disease	Absent
Parotid involvement	Occasional	Absent
Posterior uveitis	Occasional	Absent
Liver involvement	Common	Frequent
Splenomegaly	Rare	Rare
Skin	Uncommon	Unusual
Central nervous system	Occasional	Absent
Response to steroids	Only active disease	Only active disease

disease diagnosed in the 1980s or 1990s is not certain. Newer techniques to diagnose CBD (immunologic testing) enable the disease to be detected earlier. The natural history of this condition detected at the presymptomatic stage is unknown.

Table 56-3

Differential Diagnosis of Chronic Beryllium Disease

Sarcoidosis
Hypersensitivity pneumonitis
Tuberculosis
Histoplasmosis
Silicosis
Talc granulomatosis
Eosinophilic granuloma
Idiopathic pulmonary fibrosis

The two major questions are whether or not the disease detected early is inevitably progressive and whether the disease will be more responsive to corticosteroid therapy.

Beryllium and Lung Cancer

Animal studies have clearly indicated that beryllium is carcinogenic. Whether beryllium is carcinogenic in humans is not clear. A National Institute for Occupational Safety and Health (NIOSH) study suggests that a small increase in lung cancer (SMR = 1.26) may occur in beryllium workers. However, this finding has been challenged because of the poor data with regard to cigarette smoking. This issue will remain controversial, as additional studies are not currently planned. Whatever the risk of cancer is in beryllium workers, the more significant medical concern is CBD.

HARD-METAL LUNG DISEASE

Introduction and Overview

Hard metal is an alloy of tungsten carbide in a matrix of cobalt into which smaller amounts of chromium, molybdenum, nickel, niobium, tantalum, titanium, and/or vanadium may be added. These components are milled to a fine powder, mixed together, pressed into the desired shape, and heated under pressure to between 800 and 1000°C, yielding a product with a chalklike consistency. The material may then undergo additional machining before being baked at 1500°C, which is above the melting point of cobalt and leads to the formation of an alloy that is 90 to 95 percent as hard as a diamond. Because of this property, hard metal is an important component in cutting tools, drill bits, armor plate, and jet engine parts.

Hard metal was developed in the 1920s, and interstitial lung disease was first reported in hard-metal workers in 1940. Lung disease has been noted to occur in those working in both the initial production of hard metal and the machining and maintenance of hard-metal tool components. In addition, although hard metal is not used in the diamond-polishing industry, a similar spectrum of disease has been reported in diamond polishers using steel polishing disks whose cutting surfaces consist of microdiamonds cemented into a fine cobalt mesh. In contrast, workers in the cobalt-producing industry, who are more likely to be exposed to cobalt alone, may develop occupational asthma but appear to be much less likely to develop interstitial lung disease.

The industrial processes associated with hard-metal lung disease produce respirable fine metallic dust particles. They also produce metallic ions that accumulate in the coolants used in the metalworking procedure and are absorbed through the skin or inhaled in vaporized coolant fluids. To counteract these exposures, the American Conference of Government Industrial Hygienists (ACGIH) have established current permissible exposure limits for cobalt metal, dust, and fumes at an 8-h threshold-weighted average (TWA) of 0.02 mg/m^3. NIOSH recommends an exposure limit of 0.05

mg/m^3 as a TWA for a 10-h workday and a 40-h workweek and OSHA requires an 8-h TWA of 0.1 mg/m^3.

Clinical Manifestations in Hard-Metal—and Cobalt—Exposed Persons

A variety of respiratory syndromes have been associated with exposure to hard metal, most commonly: (1) asthmatic reactions; (2) a form of hypersensitivity lung disease; and (3) interstitial pulmonary fibrosis. The last two forms may be a continuum of the same process with subclinical or unrecognized hypersensitivity alveolitis proceeding to the development of fibrotic lung disease. *Hard-metal disease* has been used to describe all types of lung disease but is most often used to reference the parenchymal or interstitial lung disease rather than the airway-related manifestations of hard-metal inhalations.

Interstitial Lung Disease

Interstitial lung disease has been seen in hard-metal workers and diamond polishers. Studies have attempted to determine the prevalence of interstitial lung disease (ILD) among hard-metal workers. The studies have been frequently limited by lack of appropriate control groups, loss of former workers who may have left the plant due to illness, inconsistent disease detection/definitions, and small numbers. However, despite these limitations it is clear that ILD develops in a small minority of exposed workers. Estimates range from 0.7 to 12.9 percent in cross-sectional studies. A more recent study found no ILD in its cohort but it was a small study with more recent exposure and may represent the effects of limiting exposure levels. Although ILD may occur after a short duration and low levels of exposure, longer duration or higher levels of exposure are associated with increased risk. Nonsmokers and former smokers also appear to be at higher risk. Interestingly, most studies suggest that workers exposed to cobalt alone without tungsten and other metals do not appear to develop ILD. A few cases of diamond polishers exposed to cobalt alone who have developed ILD have been reported, but this appears to be fairly rare.

In some patients, hard-metal disease presents as a hypersensitivity pneumonitis, or allergic alveolitis. These patients manifest fever, anorexia, cough, dyspnea, inspiratory crackles, and fine reticulonodular infiltrates on chest radiograph. Pulmonary function testing typically shows a restrictive pattern, with a reduced D_{LCO}. Symptoms may resolve when exposure is discontinued but may recur with re-exposure. Over time, progressive dyspnea, lung function impairment, and interstitial fibrosis may develop. Fibrosis may also occur in the absence of antecedent symptoms. Patients with advanced disease exhibit weight loss, hypoxemia, digital clubbing, pulmonary hypertension, and cor pulmonale.

The histopathological manifestations of the interstitial disease in these patients can be varied, with findings consistent with bronchiolitis, desquamative interstitial pneumonitis, usual interstitial fibrosis, and giant-cell interstitial pneumonitis (GIP). Granuloma formation does not occur. Lung biopsies may show heterogeneous patchy involvement, with foci of active alveolitis, fibrosis, and normal parenchyma. Bronchiolitis may be seen in areas with and without active alveolitis. GIP is characterized by lymphoplasmacytic infiltration, epithelial desquamation, and the presence of numerous multinucleated giant cells in the alveolar spaces. These giant cells are formed by both actively phagocytic alveolar macrophages and type II pneumocytes. Infiltration with eosinophils has also been described. Analysis of BALF may demonstrate hypercellularity, with increased numbers of macrophages and giant cells. A relative or absolute increase in the number of lymphocytes, with a reduced CD4/CD8 ratio as well as increased numbers of neutrophils, eosinophils, and mast cells, may also be seen. Additionally, the multinucleated giant cells can also be found in the BALF which can be diagnostic of hard-metal lung disease without requiring a surgical lung biopsy. Electron microscopy with energy dispersive x-ray analysis (EDAX) of the particulate material present in biopsy specimens may demonstrate the presence of the elements used to form hard metal. Because of its high solubility, significant amounts of cobalt may not always be present.

Few studies have looked at the radiography of hard-metal disease. Many of the screening studies of cobalt workers rely on plain chest radiographs and use the profusion score of the International Labour Office (ILO). However, a consistent description of the typical findings has not been offered. More recently, with the advent of computed tomography (CT) scans a few case reports have described the CT findings of patients with hard-metal disease. Like the pathology, these findings show a wide variability and can include end-stage honeycombing with cystic changes and traction bronchiectasis, to less impressive reticulation and even areas of ground-glass opacities. No pathognomonic finding has been described.

Treatment for this disease consists of discontinuation of exposure and administration of systemic corticosteroids. Although no clinical trials have been performed, dosage and duration of treatment similar to those used in other forms of active alveolitis or fibrosis should be considered. Patients with active alveolitis may show a dramatic response to steroids, whereas patients with more prominent fibrosis may show minimal response despite prolonged steroid treatment. Fibrosis can also progress despite cessation of exposure. GIP has been observed to recur after lung transplantation despite cessation of occupational exposure.

Occupational Asthma

In contradistinction from ILD, asthma can occur in workers exposed to cobalt alone without tungsten. The reported prevalence of asthma or wheezing related to cobalt or hard-metal exposure is also low and ranges from 6.6 percent to 10.9 percent. This variation may be attributed to different levels of exposure and the criteria used by various authors to define occupational asthma. As with other forms of occupational asthma, patients may note cough, wheezing, dyspnea,

chest tightness, conjunctivitis, and rhinitis. Throughout the workday, symptoms may increase in severity, and a progressive decline in peak flow may be demonstrated. Symptoms usually abate during weekends or vacations and often resolve when exposure is discontinued. Upper-airway symptoms may result from either direct airway irritation or atopic responses.

In addition to demonstrating an association between workplace exposure and symptoms, the diagnosis may be confirmed by bronchoprovocation testing (BPT) with cobalt or cobalt salts. Testing with cobalt salts is preferable, as it is much easier to control dosage and delivery of soluble ion solutions than those of particulate substances. Immediate or delayed airway reactivity to cobalt chloride may be observed after BPT. Tungsten carbide has not been shown to produce bronchoconstriction. A positive radioimmunosorbent test (RAST) to cobalt-conjugated human serum albumin has also been reported in some patients, suggesting a type I allergic response. Skin patch testing with cobalt salts does not appear to be of use in diagnosing hard-metal asthma.

Some studies have suggested a dose-response relationship between higher levels of cobalt exposures and lower forced expiratory volume in 1 second (FEV_1) on spirometry and symptoms of asthma. A twofold increase in the relative odds ratio for work-related wheezing was noted when cobalt exposure exceeded 0.05 mg/m^3. However, asthma and reductions in FEV_1 have been seen at levels below the allowable limit of 0.05 mg/m^3. This suggests that the current permissible exposure limit may not protect all workers against the development of cobalt-induced asthma. Because of findings of this sort, baseline evaluations and employee screenings should be performed in workers exposed to hard-metal dust. A reasonable strategy would include assessments for symptoms of rhinitis, conjunctivitis, wheezing, dyspnea, or chest tightness; the relationship of symptoms to work hours; smoking history; physical examination; pulmonary function testing; and chest radiography. In patients with symptoms or findings suggestive of occupational asthma, peak flow monitoring during working and nonworking hours should be performed and other causes of pulmonary function deterioration ruled out. Specific BPT and RAST results may provide additional positive criteria for diagnosis. Personal employee air sampling and measurement of urinary cobalt levels can provide information about ongoing exposure. The workplace should also be examined for levels of cobalt exposure and employee protective practices.

Treatment for occupational asthma related to cobalt includes control of exposure as well as medical therapy with bronchodilators and inhaled corticosteroids. Systemic corticosteroid treatment is usually not required.

Lung Cancer

Cobalt and cobalt-containing compounds have been shown to cause cancer in rats after local injection and intratracheal instillation. The International Agency for Research on Cancer reviewed the evidence for the carcinogenicity of cobalt in 1991 and concluded that although there was sufficient evidence for the carcinogenicity of cobalt metal powder and cobalt oxide in experimental animals, there was inadequate evidence for the carcinogenicity of cobalt and cobalt compounds in humans. Since that publication, however, there have been studies suggesting a relationship. One study of 709 French hard-metal workers found an excess of lung cancer mortality in their workers and the excess was greater in workers with the highest levels of exposures though no relationship with duration of exposure was found. However, this study was not powered to examine the effect of smoking as well so firm conclusions could not be drawn. A second study by the same group of researchers found a twofold higher risk of lung cancer among subjects exposed to both tungsten and cobalt and the odds ratio increased with cumulative exposure. This study was able to adjust for smoking and found the relationship between hard metal and lung cancer held.

Mechanisms of Injury

The pathogenesis of the hard-metal–associated lung diseases is poorly understood. There are two predominant, competing hypotheses for the pathogenesis of hard-metal lung toxicity: (1) hypersensitivity with lymphocyte-driven toxicity; and (2) free-radical and cytokine-mediated injury.

Several authors point out the similarities of hard-metal lung disease and hypersensitivity lung disease including the ability of cobalt to function as a hapten in complex with albumin and cause a contact dermatitis. Bronchoalveolar lavage (BAL) studies of both exposed workers and those with hard-metal disease have shown increased lymphocytes with reduction of the helper/suppressor T-cell ratios. Additionally, in at least one subject with hard-metal disease a lymphocyte transformation test was found to be positive in the presence of cobalt. Finally, a recent report suggests an association between a glutamic acid residue in position 69 of the HLA-DP beta chain and susceptibility to hard-metal disease. This is similar to CBD, a known hypersensitivity disorder.

However, there are features of this disease that do not suggest a hypersensitivity reaction as the mechanism for the disease. Perhaps most obviously is the fact that granulomas, the hallmark of chronic hypersensitivity pneumonitis, are not typically found on biopsy. Additionally, the finding that both cobalt and tungsten are required for most (though not all) cases of hard-metal lung disease requires explanation. In vitro studies using peritoneal and alveolar macrophages from rats and mice have demonstrated that the combination of tungsten carbide and cobalt is highly cytotoxic, while cobalt and tungsten carbide alone produce minimal or no cytotoxicity. Additionally, the acute lung toxicity of tungsten carbide plus cobalt is much higher than that of each component after intratracheal instillation in rats.

Lison has proposed a mechanism that might explain this interaction. He suggests that tungsten carbide can act as an electron carrier to transfer electrons from cobalt to oxygen. This then leads to the production of free radicals and reactive oxygen species which in turn causes pulmonary damage.

Differences in susceptibility to disease would therefore be due to differences in subjects' antioxidant defenses. Further research is required to elucidate the pathophysiology behind hard-metal lung disease.

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Coal Workers' Lung Diseases and Silicosis

Edward L. Petsonk • John E. Parker

COAL WORKERS' LUNG DISEASES

Introduction and History

Coal miners are at risk for developing several distinct clinical illnesses in relation to their occupational exposures. Historically, some names applied to these conditions were miners' asthma, phthisis, anthracosis, and in Scotland, miners' black lung. It was recognized early that these afflictions were related to the occupation of mining; however, it wasn't until the development of specialized techniques such as chest radiography, pulmonary function testing, the discovery of the tubercle bacillus, and sophisticated histological examination of tissue that respiratory diseases affecting miners could be separated and defined.

Coal workers' pneumoconiosis (CWP) is the parenchymal lung disease that results from the inhalation and deposition of coal mine dust, and the tissue's reaction to its presence. This occupational lung disease was first described in the early 1800s. In addition to CWP, coal mine dust exposures increase a miner's risk of developing chronic bronchitis, chronic obstructive pulmonary disease, and pathological emphysema. Radon gas exposures in coal mines may exceed recommended levels and represent a risk for cancers of the lung and larynx.

For a long time, the pneumoconiosis that affected coal miners was thought to be silicosis. In the 1930s, it was argued that silicosis, CWP, and bronchitis were distinct clinically and pathologically. Unfortunately, it was also suggested that coal dust was not harmful, in spite of reports of the adverse effects of coal dust among coal trimmers. It was not until washed coal, free of silica, was shown to produce a dust disease of the lungs in stevedores, who worked leveling coal in the holds of ships, that CWP was widely accepted as pathophysiologically distinct from silicosis.

In the United States, little attention was given to coal miners' respiratory diseases until the Public Health Service conducted a pilot prevalence study of CWP in the early 1960s. Since then, a large number of studies performed by

Figure 57-1 Roof bolting in underground coal mine. A potentially high-risk operation for respiratory exposures to airborne silica. *(Photo courtesy of U.S. Bureau of Mines.)*

the National Institute for Occupational Safety and Health (NIOSH) have greatly increased the knowledge and understanding of the nature and extent of lung diseases from coal mining in the United States.

Coal and Coal Mining

Coal is not a pure mineral. It is a spectrum of carbonaceous rocks derived from the accumulation of vegetation sedimented under swampy conditions and subjected to extreme pressure over long periods of time. Coals are characterized by rank, which relates to geologic age, hardness, carbon content, and the amount of heat released (BTUs) when they are burned. Thus, peat is the lowest rank (softest) coal, being geologically the newest, and anthracite is the highest rank (hardest) and oldest type of coal.

Coal may be found in outcroppings and in seams that vary from a few feet to several thousand feet below the surface. Surface or strip mining, which currently accounts for the majority of US coal production, involves removal of the overburden and mining the coal seams with large earth-moving equipment. In some areas of the eastern United States, mountaintop removal mining has become the dominant form of mining. Mountaintop mining involves first removal of all vegetation and soil, and then drilling and blasting through hundreds of feet of strata to access the coal seam. The excess rock and soil is placed in the steep stream beds along the mountainsides, creating areas called valley fills. Occasionally, surface mining is also performed by boring into coal outcrops with an auger. Dust levels in the air at surface mines are generally less hazardous than in underground mines, with a few notable exceptions (discussed below).

Deep mines produce somewhat less than half of the coal mined in the United States. Coal outcrops of sufficient size can be mined deep into the hillsides. Deep seams are accessed through vertical shafts drilled from the surface to the coal seam where the mining process then follows the seam through a series of more or less horizontal tunnels.

Not all coal mining jobs are equally exposed to respiratory hazards. In underground mines, airborne dust concentrations are highest at the coal-cutting face, where coal is removed from the intact seams. Face jobs include the loading of coal into transportation vehicles or train cars, and, depending on the techniques used in the mine, operation of continuous or long wall mining machines. Exposures to crystalline silica and thus risk of silicosis also occur in underground mines, particularly in miners involved in roof support, called roof bolting (Fig. 57-1), or drilling operations, and in motormen who operate underground coal trains and use sand for traction on the rails. Workers in some aboveground coal mining operations also may have important exposure to dusts. These include workers at tipples and preparation plants, where crushing, sizing, washing, and blending of coal is done, and coal is stored or loaded onto ships, railroad cars, or river barges. Workers at surface coal mines who work in or around the drilling rigs, to make holes in which explosives are placed, are exposed to silica and at risk for the development of silicosis rather than CWP.

Epidemiology of Lung Diseases in US Coal Miners

The first major survey of the health of American coal workers was conducted by the US Public Health Service from 1969 to

1971, evaluating symptoms, lung function, and chest radiographic findings. This study included over 9000 miners at 31 underground mines (2 were anthracite mines; 29 were bituminous mines). Participation in the survey was over 90 percent. The mines were chosen to represent different geographic areas, coal seams, and mining methods. After this initial study, subsequent surveys have been conducted to evaluate miners at these and other US mines.

Radiographic Findings

Radiographic data from the initial survey showed an overall prevalence of simple and complicated CWP of nearly 30 percent. There was variation by region of the country and the type (rank) of coal mined. Among eastern Pennsylvania anthracite (high rank) coal miners, 46 percent had simple and 14 percent had complicated CWP. In contrast, among the miners in the western plateau of Colorado and Utah mining a lower rank coal, only 5 percent had simple CWP, and none had the complicated form. Among underground miners, those working at the coal face and exposed to higher concentrations of coal mine dust, higher prevalences of CWP were found than among surface workers or those whose jobs caused them to enter the face area intermittently.

Results from multiple studies have clearly demonstrated that the prevalence of radiographic changes of simple CWP is related to the duration and intensity of dust exposure, and CWP can develop even at current dust levels. British studies also clearly showed that the attack rate (incidence of new cases) and the probability of progressing to a higher category of simple CWP were related to the mass of respirable dust to which the miner was exposed during his or her lifetime.

The same cannot be said for the complicated form of CWP, progressive massive fibrosis (PMF). Once an individual has inhaled sufficient coal mine dust into the lungs for the chest radiograph to be classified with at least International Labour Office (ILO) Category 2 pneumoconiosis (see below), the probability of progressing to the complicated form appears to be independent of any further dust exposure. The rate of progression to PMF appears to be influenced chiefly by the age at which the miner begins to show radiographic changes of CWP. Progression may also be influenced by the presence of a rheumatoid diathesis (see below for additional discussion of immunologic issues).

Enforcement of dust control measures in the United States, fully enacted in 1973, resulted in a declining pneumoconiosis attack rate. Subsequently, many miners with CWP retired, and follow-up studies have demonstrated a marked decline in the prevalence of CWP in active US miners. This was confirmed through the federally mandated chest radiograph surveillance program for underground US miners. Between 1973 and 1978, CWP was found in over one-third of the miners who participated in the program and had worked 25 years or more underground. By 1996–2002, only 1 in 20 (5.4 percent) of these miners showed radiographic evidence of CWP (Fig. 57-2). Between 1999 and 2002, chest radiographic surveillance examinations were also offered to many

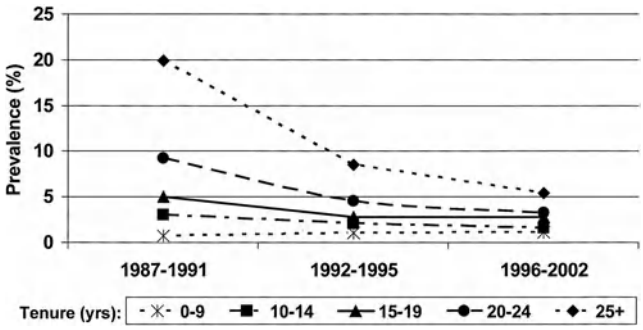

Figure 57-2 Trends in coal workers' pneumoconiosis (CWP) prevalence by tenure among examinees employed at underground coal mines, US Coal Workers' X-Ray Surveillance Program, 1987–2002.

surface coal miners, and 3.4 percent of miners with work tenure of 25 or more years demonstrated radiographic pneumoconiosis. In spite of the marked overall improvements in dust control in US underground coal mines, a recent evaluation of national surveillance data demonstrated onset of advanced CWP among miners who had worked their entire careers under the current dust enforcement regime. The authors of this report observed an increased risk of rapidly progressive pneumoconiosis among miners in smaller mines (less than 50 employees) and in certain geographic regions, and concluded that prevention measures in these settings were inadequate (Fig. 57-3).

Ventilatory Lung Function

Ventilatory function was also evaluated in the large studies of US miners mentioned above. Initial reports evaluated miners' lung function in comparison to the *radiographic findings* of CWP. Miners with complicated CWP were found to consistently show an important deficit in lung function. In contrast to the ventilatory findings associated with PMF, obstructive abnormalities were noted in miners with simple pneumoconiosis; however, the findings were not consistent, and with increasing category of simple CWP, the average functional decrement was small and variable. Subsequently, studies in the United States and Great Britain evaluated lung function with respect to the miners' *cumulative dust exposure*, and have helped to clarify the adverse effect of dust on coal miners' lung function. Miners show a progressively greater risk of lung function loss with increasing cumulative dust exposure, independent of the chest radiographic findings of CWP. The forced expiratory volume in 1 s (FEV_1) loss is most severe in those who work for many years at the dustiest jobs. Among smoking miners, the effects of tobacco smoke appear to be additive to the dust effect but no disproportionate dust effect has been noted in relation to tobacco use. Also, there is evidence that miners experience a more rapid loss in spirometric function parameters over their first few years of mining, with slower dust-related declines after that time.

In summary, the epidemiological evidence has shown that coal miners experience ventilatory lung function loss with increasing exposure to dust, either in the presence or

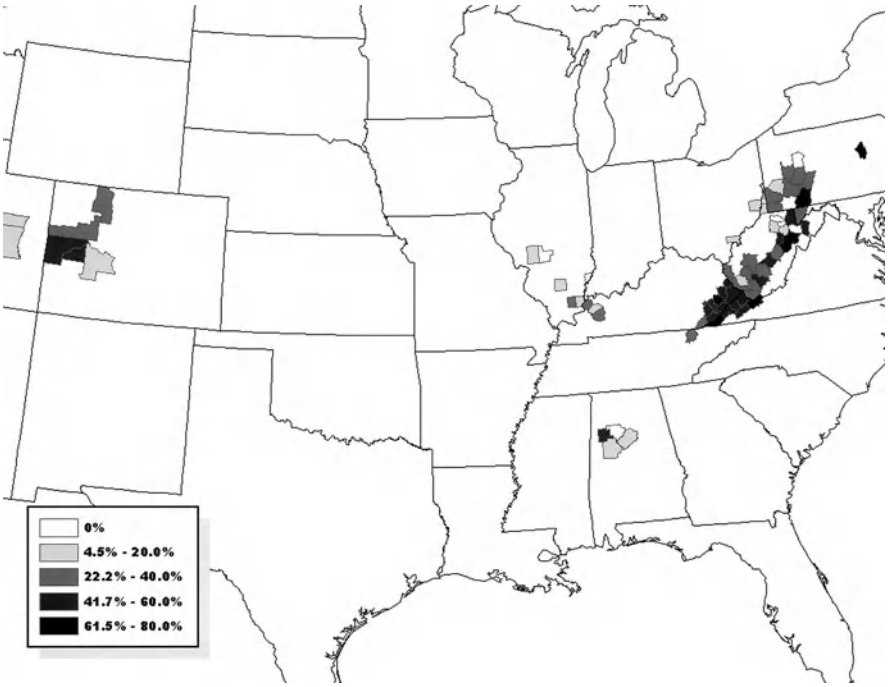

Figure 57-3 Proportion of miners with rapidly progressive CWP by county (not shown are counties with fewer than five miners evaluated).

absence of CWP. Among smoking miners, the effects of tobacco and dust appear to be additive. Although, on average, functional losses associated with dust are small, it is estimated that 35 years of work at the current dust limit will cause a clinically important FEV_1 loss in 8 out of 100 nonsmoking coal miners. When complicated CWP is present, an additional ventilatory deficit is likely.

Mortality

Studies of mortality in coal miners have been reported from the United States and Britain. Findings from both countries have been generally consistent, and reveal that the miners experience increased mortality attributable to pneumoconiosis, emphysema, and chronic bronchitis. Radiographic findings of advanced CWP (PMF) consistently affect mortality, especially in categories B and C, whereas among miners with simple CWP, decreases in survival were smaller. Accelerated FEV_1 decline is also associated with increased mortality from both cardiovascular and respiratory causes. Miners' risks of dying from the obstructive airway diseases of emphysema and chronic bronchitis exhibit a different geographic pattern than the mortality from CWP, suggesting that these dust effects have different mechanisms.

Pathology of Coal Miners' Lung Diseases

The coal macule is the primary lesion of simple CWP (Fig. 57-4). This lesion is essential for the pathological diagnosis of CWP. The lesion consists of a focal collection of coal dust in pigment-laden macrophages around the respiratory bronchioles and tapering off toward the alveolar duct. A fine network of reticulin is present in the early stages and may include a small amount of collagen depending upon the character of the dust. Centriacinar emphysema, the dilation and injury of lung gas exchange units, is observed with increased prevalence in the lungs of coal miners. The severity is proportional to the miner's cumulative dust exposure. Focal emphysema is the form of centriacinar emphysema that is seen as an integral part of the simple lesion of CWP. It is characterized by enlargement of the airspaces immediately adjacent to the dust macule. The pathological severity of the emphysema increases with increasing lung dust retention. Muscular thickening of pulmonary arteries, in conjunction with hypertrophy of the right ventricle, can be observed with both simple and complicated CWP, and is increasingly prominent when CWP is associated with other lung disorders. Pathological changes in the airways consistent with chronic bronchitis, including enlargement of mucous glands, have also been noted in miners' lungs.

With increasing dust exposure, due to the normal clearance mechanisms being overwhelmed, the lung lesions increase in size and number. These larger fibrotic lesions are called coal nodules and are palpable in lung specimens, whereas coal macules are not. Palpable coal nodules are classified as micronodular up to 7 mm in diameter and macronodular from 7 mm and larger.

Classic silicotic nodules have been found in the lungs of 12 percent of coal miners at autopsy. Other patterns of interstitial disease (usual interstitial pneumonia, UIP) have also been reported among coal miners either alone or in combination with the typical pathology of the pneumoconioses.

Complicated CWP or PMF is diagnosed when one or more nodules in a lung specimen are noted to attain a size of 2 cm or greater in diameter. The 2 cm is an arbitrary choice of a minimal diameter that permits better correlation with clinical and radiographic measurements. (In fact, when coal-induced radiographic shadows are >1 cm, PMF is said to be present.)

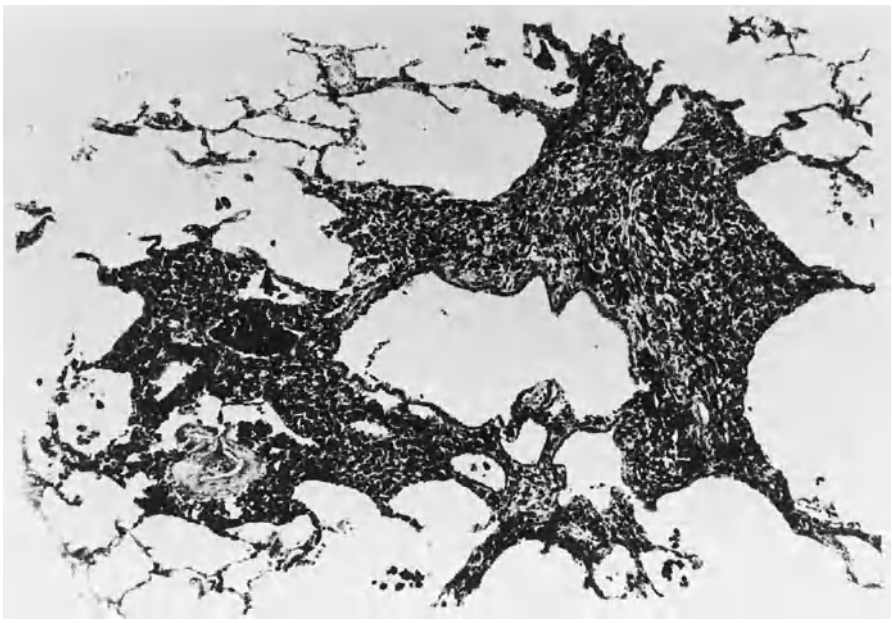

Figure 57-4 A coal macule, microscopic section. *(Courtesy of Dr. Val Vallyathan, National Institute for Occupational Safety and Health, Morgantown, WV.)*

Lesions are solid, heavily pigmented, rubbery to hard, and occur most commonly in the apical posterior portions of the upper lobes or the superior segments of the lower lobes. They tend to occur symmetrically, but may be asymmetrical, and may cavitate. Airways and vessels adjacent to the lesions may be distorted, and within the lesions, they are destroyed. PMF generally occurs in association with background pathological changes of simple CWP.

Clinical Features of Coal Workers' Lung Diseases

Chronic cough and sputum production are more common with increasing dust-exposure, regardless of the presence or absence of simple pneumoconiosis. These symptoms are likely related to bronchitic changes in the large airways, including thickening of the airway wall with mucous gland enlargement and hypersecretion that result from continued inhalation of dust particles presenting a chronic burden to the mucociliary escalator. Some miners with simple pneumoconiosis may have no related symptoms or physical signs, but with severe airflow obstruction or advanced pneumoconiosis, dyspnea, cough, and sputum production are frequent. Edema of the lower extremities, and findings consistent with cor pulmonale, may occur. Melanoptysis (expectoration of black sputum) occasionally results from excavation of a PMF lesion.

Clubbing and crackles are not generally considered features of coal miners' lung diseases, and if noted, should prompt further studies. However, a series of 38 cases of a chronic interstitial pneumonia among coal miners has recently been reported. The clinical findings in these atypical cases included crackles, finger clubbing, restrictive impairment, diffusion block, and neutrophilic bronchoalveolar lavage (BAL). CWP has not been associated with increased risk for development of coexisting mycobacterial infection, in contrast to silicosis. However, a minority of miners show classic silicotic nodules. Certainly, progressive infiltrates or cavitary lesions in PMF should prompt examination of the sputum for typical and atypical mycobacteria.

Radiology of Coal Workers' Pneumoconiosis

The diagnosis of CWP can be made with confidence, without histological confirmation, in the presence of an adequate history (at least 5 to 10 years) of coal mine dust exposure and a characteristic chest radiograph. The radiograph in simple pneumoconiosis shows small opacities, ranging in size from pinhead up to 1 cm in diameter. Rounded nodules predominate and tend to appear first in the upper zones and involve middle and lower zones as the number of opacities increase. PMF is characterized by one or more large opacities greater than 1 cm. Upper lobe predominance is also typical in complicated pneumoconiosis. High-resolution computed tomography (HRCT) scanning in coal miners may reveal parenchymal nodules and emphysema when standard radiographs are normal. In atypical cases, CT scans may show ground-glass opacities and honeycombing, at times without nodular findings typical of CWP. Radiographic evidence of bronchiectasis has also been reported in coal miners, particularly among those with CWP.

Several schemes have been used for classifying the radiographic shadows of pneumoconiosis in epidemiological studies; currently the ILO 2000 classification is the most widely accepted. When using the ILO system, simple pneumoconiosis is divided into major categories 1, 2, and 3 according to the profusion of small opacities in the lung fields. Each major category, including 0, is subdivided into 3 subcategories, providing a full range of 12 categories of simple CWP. A reading of category 1/0 indicates the definite presence of opacities consistent with pneumoconiosis. Complicated pneumoconiosis (PMF) is divided into categories A, B, and C, based on

the size of the large opacities. Findings of collapse, consolidation, and emphysema may be associated with the shadows of complicated pneumoconiosis.

The clinician may be presented with the diagnostic dilemma of distinguishing primary or metastatic lung neoplasia from an unusual presentation of PMF or Caplan's syndrome. When typical large opacities of PMF occur symmetrically and bilaterally on a background of simple CWP, one can be confident that the lesions are unlikely to represent neoplastic disease. Prior radiographs from medical screening programs are often obtainable, and can help confirm stability or progression over a long time interval. Positron emission tomography with fluorodeoxyglucose (FDG-PET) scanning may be useful in differentiating PMF lesions from malignancy when the mass lesion has a low level of glucose metabolism, although some massive pneumoconiotic lesions may demonstrate an uptake of fluorodeoxyglucose similar to neoplasms. On magnetic resonance imaging (MRI) with contrast enhancement, the pattern of change over time in signal intensity has been reported to be a differential criterion in this setting. When the imaging workup is equivocal, the differentiation of PMF from neoplasm may be impossible without a biopsy. Hemorrhagic complications may occur during biopsy of PMF lesions due to their vascular nature.

Lung Function and Respiratory Impairment in Coal Miners

Coal mine exposures may result in several pathological processes (simple and complicated CWP, silicosis, chronic bronchitis, mineral-dust airway disease, emphysema, and dust-related airflow limitation), each of which may contribute to adverse physiological consequences. In an individual miner, the pattern and severity of impairment found will be related to such recognized factors as the intensity and duration of respirable dust exposure, geologic factors (e.g., coal rank, silica content), residence time of dust in the lung, and exposure to other respiratory hazards (e.g., tobacco smoke). In miners with airway hyperresponsiveness, greater functional deficits and an increased risk of symptoms may be expected. Several other mining exposures may also contribute lung function loss in coal miners, including gases from underground explosive blasting and aerosols of potentially contaminated water used for dust control. Additional factors implicated in underground coal miners' accelerated lung function declines include weight gain, childhood pneumonia, and childhood exposures to environmental tobacco smoke.

Ventilatory Function

Epidemiological studies, as discussed above, have extensively documented the occurrence of exposure-related deficits in FEV_1 and forced vital capacity (FVC) in coal miners. The magnitude of the average dust effect has varied between studies. Over a working lifetime, average predicted losses in FEV_1 under current US dust standards ranged from 124 ml to 610 ml. Subgroups of miners experience a more severe effect, and from 6 to 8 percent of miners may be expected to develop clinically important airflow limitation. For example, a more severe effect of dust on loss of lung function was observed in a group 199 men who had chosen to leave coal mine work. These dust effects can be compared with those of another recognized respiratory hazard, cigarette smoking. For example, Attfield observed that when 1072 miners' lung function was followed over an 11-year period, a year of work at coal face jobs resulted in lung function loss essentially similar to that due to smoking for 1 year. When tenure in less dusty work was included in the analysis, mine dust exposure resulted in average lung function losses about 38 percent of that attributable to smoking (average 13 cigarettes per day).

Physiological findings consistent with small airways disease have been noted to develop in nonsmoking miners, consistent with the pathological findings with dust deposition.

Gas Exchange

Diffusing capacity has been studied in relation to radiographic changes of coal worker's pneumoconiosis. The small rounded opacities seen in miners with simple CWP have not generally been associated with measurable reductions in D_{LCO}. However, in subgroups of miners, abnormal diffusing impairment has been correlated with radiographic changes. Thus, gas transfer is often low when the large opacities of complicated CWP are present and may also be reduced in miners who show either predominantly pinpoint opacities ("p" type by the ILO classification) or small irregular opacities on their chest radiograph.

Gas exchange on exercise has also been investigated in coal miners. Many of the reports have been based in patients referred for disability evaluations, and thus suffer from ill-defined selection biases. Exposure-response relationships are also unclear with respect to findings in these series. Exertional hypoxia, pulmonary arterial hypertension, and excess ventilation have frequently been observed in miners, particularly those with complicated CWP or airflow obstruction. However, the proportion of miners who show exertional gas exchange abnormalities in the absence of either PMF or clinically important airflow obstruction is still a topic of investigation.

Immunology of Coal Workers' Pneumoconiosis

The potential role of immunologic factors in mineral dust pneumoconioses was noted by Caplan who observed the association between distinctive nodular radiographic opacities in the lungs of Welsh coal miners and rheumatoid arthritis. This observation was extended when similar radiographic appearances were described in miners without arthritis but with circulating rheumatoid factor (RF). Increased prevalence of circulating RF among miners with complicated pneumoconiosis (PMF) has also been reported.

Soutar et al reported on a study of serum antinuclear antibodies (ANA) and RF among 109 miners with radiographic evidence of pneumoconiosis attending the London

Pneumoconiosis Panel. They reported positive ANA in 17 percent and RF in 10 percent of the miners whereas about 2 to 3 percent positive ANA was expected in a healthy male population. The prevalence of ANA was 9 percent in simple CWP and 27 percent in those with category C (PMF). A similar trend was seen with RF, ranging from 6 percent in simple CWP to 18 percent in category C. Combining both ANA and RF resulted in prevalences of positive results in 13 percent of the miners with simple CWP and 45 percent of those with category C CWP.

In 1973 Lippmann et al reported a prevalence study of circulating ANA and RF among coal miners in the United States. Sera from 207 coal miners were examined. Of the 196 miners with radiographic opacities of pneumoconiosis, 9 were positive for RF, while 34 percent had positive ANA. There were regional variations in ANA that seemed to parallel the prevalences of radiographic changes; namely, prevalence was higher in anthracite miners and lower in bituminous miners.

Studies of serum immunoglobulins were conducted by Hahon et al among 155 US coal miners with chest radiographs demonstrating simple CWP, Caplan's syndrome, or PMF. They found significantly higher serum concentrations of C3, α_1-antitrypsin, IgA and IgG in anthracite miners than in bituminous miners with PMF. Compared to normal controls, the miners' C3, α_1-antitrypsin, and IgG and IgG values were elevated. There were few differences in these serum proteins among the miners with simple CWP. The authors did not find any association between the elevated immunoglobulins and FEV_1.

There have been few studies of the peripheral lymphocytes in coal miners. Dauber et al examined the lymphocyte function of 15 miners with pneumoconiosis. They found decreased numbers of both T and B lymphocytes in the peripheral blood in the miners compared to controls. They also found that cell function, as determined by response to stimulation by concavalin A, was lower in the miners with complicated CWP than in either miners with simple CWP or controls.

Autoantibodies directed at lung collagen and reticulin have been identified in the sera of coal miners. The lung autoantibodies tend to reside in the serum IgA. It is not clear whether these autoantibodies participate in the CWP reaction in the lungs or simply represent epiphenomena.

Special Studies

Bronchoalveolar lavage (BAL) has been used in studying mechanisms in the pulmonary reactions in CWP. Rom et al studied 15 symptomatic, nonsmoking coal miners with simple CWP by BAL. They found no significant difference between miners with CWP and controls in the number of cells recovered, the percentage distribution, and in the release of superoxide anion or hydrogen peroxide. This contrasted with the findings in subjects with asbestosis and silicosis whose values for spontaneous release of oxidant superoxide and hydrogen peroxide were significantly higher than controls. With regard to fibronectin and alveolar macrophage–derived growth factor, the miners with CWP had values that were elevated above controls and not different from the values obtained in subjects with asbestosis and silicosis.

Wallaert demonstrated significantly increased total number of lung cells recovered from miners with simple and complicated CWP, as well as increased percentages of alveolar macrophages, lymphocytes, and neutrophils. Alveolar cells from miners with simple and complicated CWP spontaneously released significantly more superoxide demonstrated by chemiluminescence than controls.

Management of Coal Workers' Lung Diseases

There is no specific therapy for CWP. The primary prevention of lung disease in miners must include continuing efforts at reducing coal mine dust exposure. Medical management is best directed at prevention, early recognition, and treatment of complications. The major clinical challenges are the recognition and management of airflow obstruction, respiratory infection, hypoxemia, respiratory failure, cor pulmonale, arrhythmias, and pneumothorax.

Improved mining methods and lower dust levels appear to be reducing exposures and new cases of both simple and complicated pneumoconiosis. Medical surveillance programs, using chest radiographs, allow early recognition of workers with simple pneumoconiosis. Workers with simple pneumoconiosis should be encouraged to exercise their rights to frequent dust measurements, and transfer to low dust jobs when necessary. Any worker with PMF should be carefully advised about the risks of further dust exposures.

Workers presenting with respiratory symptoms should have careful evaluation. Initial history and examination should be supplemented by chest radiograph, spirometry with bronchodilators, diffusing capacity, electrocardiogram, and resting arterial blood gas measurement as indicated. A thorough initial database allows accurate assessment of the worker's respiratory health and serves as a starting point for observing the response to therapy or progression of disease.

For miners who smoke, cessation is important regardless of symptoms, radiographic abnormalities, or functional status. Physician encouragement to stop smoking should be supplemented by support from smoking cessation groups, use of nicotine replacement, pharmacologic aids, and behavior modification techniques.

Symptomatic reversible airflow obstruction may benefit from treatment with inhaled and oral bronchodilators. Patients with severe obstruction and inadequate improvement from the usual measures should be considered for a monitored trial of corticosteroids. If improvement is objectively documented, continuation of inhaled and, rarely, oral steroids may be of benefit.

Hypoxemia can be a serious complication in advanced pneumoconiosis. It may be present at rest, with exercise, or during sleep. Chronic hypoxemia can lead to additional complications including polycythemia, pulmonary hypertension, cor pulmonale, and cerebral dysfunction. Therapy with low flow oxygen is indicated when arterial oxygen tension is less

than 55 torr. Oxygen therapy in this setting may improve exercise tolerance, reduce dyspnea, and prevent arrhythmias, polycythemia, and heart failure.

Patients with significant airflow obstruction or PMF should receive appropriate immunization with influenza and pneumococcal vaccines. Bacterial and viral episodes of bronchitis or pneumonia should be promptly recognized and appropriately treated.

Patients with complicated pneumoconiosis, especially those who have been exposed to silica as well as coal mine dust, deserve special attention with regard to mycobacterial infection. Patients with a history of weight loss, fever, sweats, or malaise should be promptly investigated with chest radiographs and sputum examination for acid-fast bacilli stains and cultures. Occasionally, the sputum may be negative and mycobacterial infection can only be documented by fiberoptic bronchoscopy with brushings and washings. Active tuberculosis in patients with CWP can, in general, be successfully treated with the usual drug regimens provided rifampin is one of the drugs used. However, some authorities would recommend that in coal miners with a significant history of concurrent silica exposure (such as motormen, roof bolters, drillers, and shaft development workers), the treatment for tuberculosis may need to be more aggressive, and long-term follow-up is indicated in view of several reports of recurrent pulmonary tuberculosis in patients with PMF after completion of apparently adequate therapy.

Respiratory failure may complicate advanced disease in coal miners, as it does in other chronic obstructive respiratory diseases. Ventilatory support measures are indicated when the failure is precipitated by a treatable complication. The application of ventilatory support measures should be clarified in advanced directives before the need arises.

Clinicians need to assess the contribution of occupational dust exposures to ventilatory impairments in their patients with a history of coal mine exposure. Factors which can assist in this include a careful work history with documentation of the mining region, duration and categories of coal mine employment, as well as the duration and intensity of any tobacco smoking. Factors associated with an increased risk of a clinically important dust effect are a history of prolonged exposures in dusty jobs, exposures to higher rank coals, a younger age at first employment, and the finding of radiographic changes of CWP. Physicians should assist their patients with job-related impairments in obtaining appropriate compensation through local and national programs.

SILICOSIS

Introduction

Silicosis is a fibrosing disease of the lungs caused by the inhalation, retention, and pulmonary reaction to crystalline silica. Despite knowledge of the cause of this disorder (inhalation of dust containing respirable crystalline silica), this serious and potentially fatal occupational lung disease remains prevalent throughout the world. Silica, or silicon dioxide, is the predominant component of the Earth's crust. Occupational exposure to silica particles of respirable size (aerodynamic diameter of 0.5 to 5 microns) is associated with mining, quarrying, drilling, tunneling, and abrasive blasting with quartz-containing materials (sandblasting). Silicosis risk is also recognized in masonry and refractory operations, cement and concrete production, and highway repair, and as well as during work in potteries, foundries, and dental laboratories. Among ornamental stone carvers in Brazil, the prevalence of disease remains over 50 percent. Because crystalline silica exposure is so widespread, and silica sand is an inexpensive and versatile component of many manufacturing processes, millions of workers throughout the world are at risk of disease. The disease is often unrecognized and underreported, and thus its true prevalence is substantially underestimated. In the United States, fatal cases of silicosis and multiple cases from the same worksite continue to be recognized.

Definition

Silicosis is an occupational lung disease attributable to the inhalation of silicon dioxide, commonly known as silica, in crystalline forms, usually as quartz, but also as other important crystalline forms of silica (i.e., cristobalite and tridymite). These forms are also called "free silica" to distinguish them from the silicates. The silica content in different rock formations, such as sandstone, granite, and slate, varies from 20 percent to nearly 100 percent.

Workers in High-Risk Occupations and Industries

Although silicosis is an ancient disease, new cases are still reported in both the developed and developing world. In the early part of the twentieth century, silicosis was a major cause of morbidity and mortality. Contemporary workers are still exposed to silica dust in a variety of occupations. When new technology lacks adequate dust controls, exposures may be more hazardous and dust levels higher than in nonmechanized work settings. Whenever the Earth's crust is disturbed and silica containing rock or sand is used or processed, there are potential respiratory risks for workers. The development of silicosis is continuing to be reported among workers from industries and work settings not previously recognized to offer a risk of this disease, reflecting the nearly ubiquitous presence of silica. The type of silica exposure appears to affect the risk of disease—settings such as drilling or sandblasting in which silica is freshly fractured, represent an increased risk of silicosis. Even brief periods of exposure to high levels can result in a clear increased lifetime risk for disease. The development and progression of silicosis frequently occurs after exposures have ceased. In countries throughout the world, mining, quarrying, tunneling, abrasive blasting, construction, and foundry work continue to present major risks

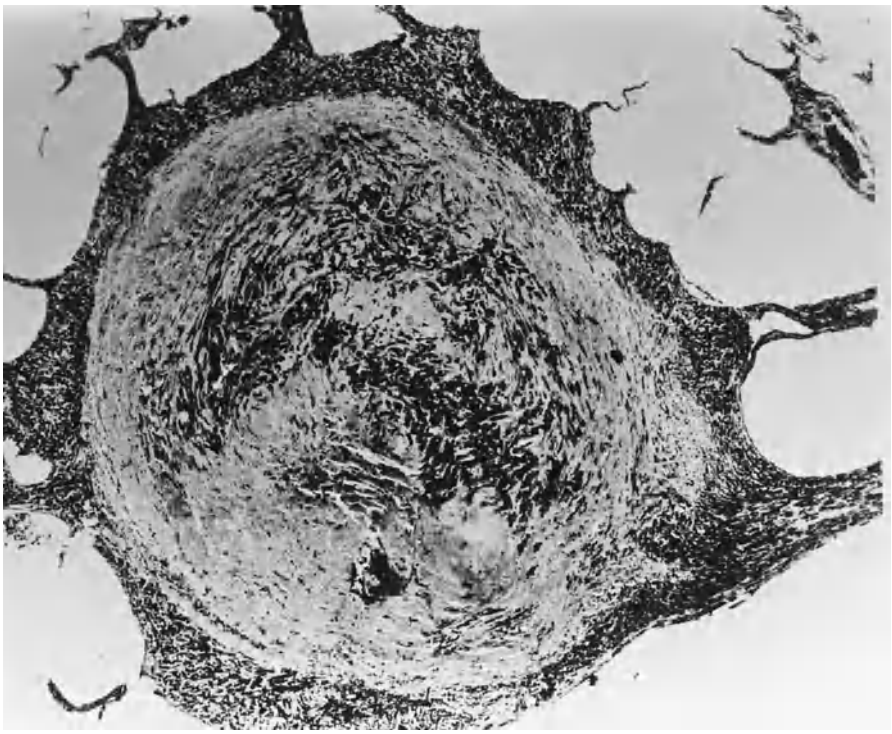

Figure 57-5 Lung pathology showing classic silicotic nodule. (See text for description.) *(Courtesy of Dr. Val Vallyathan, National Institute for Occupational Safety and Health, Morgantown, WV.)*

for silicosis, and important exposures continue to occur, even in developed nations.

Forms of Silicosis: Exposure History and Clinicopathological Descriptions

Chronic, accelerated, and acute forms of silicosis have been well characterized. These clinical and pathological expressions of the disease reflect differing exposure intensities, latency periods, and natural histories. The chronic or classic form usually follows one or more decades of exposure to respirable dust containing quartz. The accelerated form results from heavier exposures, often with a latency of 5 to 10 years. Accelerated silicosis develops more rapidly than the chronic form and generally progresses inexorably even after silica exposure is interrupted. The acute form of silicosis is a consequence of intense exposures to high levels of respirable dust which contain a significant proportion of silica. The reported exposure period is usually from several months up to about 5 years, and the clinical course is usually one of rapid progression.

Chronic (or classic) silicosis may be asymptomatic or result in insidiously progressive exertional dyspnea or cough (often mistakenly attributed to the aging process). A latency of 15 years or more since onset of exposure is common. Radiographically, it presents with small (less than 10 mm) rounded opacities predominantly in the upper lung zones. The pathological hallmark in the lungs of patients with the chronic form is the silicotic nodule. The lesion is characterized by a cell-free central area of concentrically arranged, whorled hyalinized collagen fibers, surrounded by cellular connective tissue with reticulin fibers (Fig. 57-5). When examined under polarized light, birefringent particles are typically seen most prominently in the periphery of the silicotic nodule. Electron microscopy using specialized techniques can identify the specific mineral content of the particles, but is rarely needed for routine diagnostic purposes. Silicotic nodules in the visceral pleura, regional lymph nodes, and occasionally in other organs, may also result from silica exposure. One or more groups of the small lung nodules of chronic silicosis may coalesce and result in larger shadows on the chest radiograph (greater than 10 mm), heralding the onset of complicated or conglomerate silicosis (often referred to as progressive massive fibrosis). This progressive illness may occur even after exposure to silica-containing dust has ceased.

Progressive massive fibrosis (*PMF*) is frequently associated with a clinically important compromise of lung structure and function, and as a consequence, symptoms of exertional dyspnea and reduced functional status. This form of silicosis is characterized by nodular opacities greater than 1 cm on the chest radiograph (Fig. 57-6). Common laboratory findings include a diminished carbon monoxide diffusing capacity, reduced arterial oxygen tension at rest or with exercise, and a demonstrable restrictive pattern on spirometry and lung volume measurement. Concomitant dust-induced bronchitis or distortion of the bronchial tree may also result in productive cough or airflow obstruction. Recurrent bacterial infection, not unlike that seen in bronchiectasis, may occur. Weight loss and cavitation of the large opacities should prompt concern for tuberculosis or other mycobacterial infection.

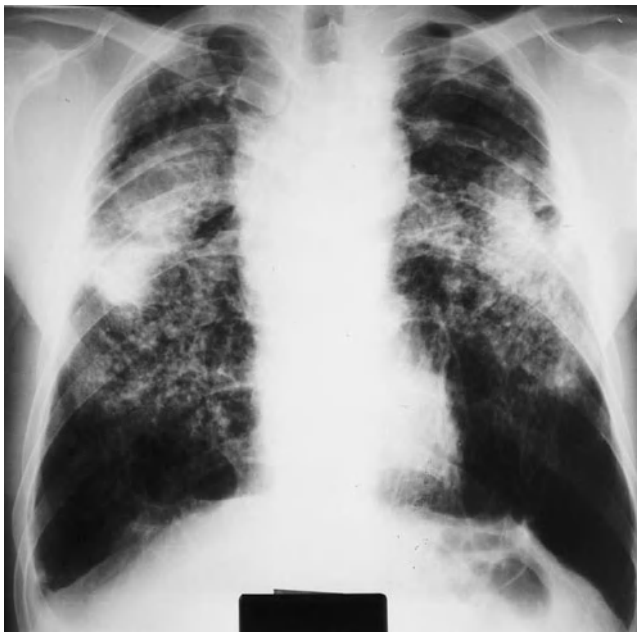

Figure 57-6 Complicated silicosis demonstrating progressive massive fibrosis.

Pneumothorax may be a life-threatening complication, since the fibrotic lung may be difficult to re-expand. Hypoxemic respiratory failure with cor pulmonale and congestive heart failure are common terminal findings.

Accelerated silicosis results from exposures that are more intense and of shorter (5 to 10 years) duration than in the chronic form, while symptoms, radiographic findings, physiological measurements, and lung pathology are similar. Deterioration in lung function is more rapid, and many workers with accelerated disease develop superimposed mycobacterial infection. Findings consistent with autoimmune diseases, including scleroderma, rheumatoid arthritis, or systemic lupus, may be seen in association with silicosis, more often in the accelerated type. The progression of radiographic abnormalities and functional impairment can be very rapid when autoimmune disease occurs with silicosis.

Acute silicosis may develop within a few months up to about 5 years after a massive inhalation of silica. Dramatic dyspnea, weakness, and weight loss are often presenting symptoms. The radiographic findings differ from those in the more chronic forms of silicosis, and are dominated by a diffuse alveolar filling pattern, with a lower lung zone predominance. Air bronchograms may be present. Histological findings similar to pulmonary alveolar proteinosis have been described, and extrapulmonary (renal and hepatic) abnormalities are occasionally reported. The usual clinical course is rapid progression to severe hypoxemic ventilatory failure and death.

Tuberculosis may complicate all forms of silicosis, but people with acute and accelerated disease may be at higher risk. Silica exposure alone, even without silicosis may also predispose to this infection. *Mycobacteria tuberculosis* is the usual organism, but nontuberculous (atypical) mycobacteria are also seen.

Even in the absence of radiographic silicosis, silica-exposed workers may also develop other diseases associated with occupational dust exposure, such as chronic bronchitis and the associated emphysema. Progressive declines in lung function have been documented in workers from inhalation of silica and other occupational mineral dust exposures.

Pathogenesis and the Association with Tuberculosis

The precise mechanism of silica toxicity is uncertain, but it is thought to be mediated by generation of reactive oxygen species, both by the surface of silica particles themselves and by activation of alveolar macrophages. The nature and the extent of the biologic response are in general related to the intensity of the exposure; however, there is growing evidence that freshly fractured silica may be more toxic than aged silica-containing dusts, perhaps related to reactive oxidant radical groups on the surface cleavage plane. An abundance of evidence implicates the interaction between the pulmonary alveolar macrophage and silica particles deposited in the lung. Release of chemotactic factors and inflammatory mediators result in recruitment of polymorphonuclear leukocytes, lymphocytes, and additional macrophages. Fibroblast-stimulating factors are released that promote hyalinization and collagen deposition. The resulting pathological lesion is the silicotic nodule, containing a central acellular zone with silica particles surrounded by whorls of collagen and fibroblasts, and an active peripheral zone composed of macrophages, fibroblasts, plasma cells, and additional free silica (Fig. 57-5).

The initiating toxic insult may occur with minimal immunologic reaction; however, a sustained immunologic response may be important in some of the chronic manifestations of silicosis. For example, ANA are noted in accelerated silicosis occurring with scleroderma, as well as in other collagen diseases among workers who have been exposed to silica. The susceptibility of silicotic workers to infections, such as tuberculosis and *Nocardia asteroides*, is likely related to the toxic effect of silica on pulmonary macrophages.

The link between silicosis and tuberculosis has been recognized for nearly a century. Again, people with acute silicosis appear to be at considerably higher risk.

Clinical Picture of Silicosis

When silicosis is symptomatic, the primary symptom is usually dyspnea, first noted with activity or exercise and later, as the functional reserve of the lung is lost, also reported at rest. However, in the absence of other respiratory disease, shortness of breath may be absent and the presentation may be an asymptomatic worker with an abnormal chest radiograph. The radiograph may at times show quite advanced disease with only minimal symptoms. The appearance or progression of dyspnea may herald the development of complications including tuberculosis, airways obstruction, PMF, or cor pulmonale. Productive cough is often present, secondary to chronic bronchitis from occupational dust exposure, tobacco use, or both. Cough may at times also be attributed to

pressure from large masses of silicotic lymph nodes on the trachea or mainstem bronchi.

Other chest symptoms are less common than dyspnea and cough. Hemoptysis is rare and should raise concern for complicating disorders, such as pulmonary neoplasms or mycobacterial infection. Wheeze and chest tightness may occur in the presence of silicosis, but usually as part of associated obstructive airways disease or bronchitis. Chest pain and finger clubbing are not features of silicosis. Systemic symptoms, such as fever and weight loss, suggest complicating infection or neoplastic disease. Advanced forms of silicosis are associated with progressive respiratory failure with or without cor pulmonale. Few physical signs may be noted unless complications are present.

Radiographic Patterns in Silicosis

The earliest radiographic signs of uncomplicated silicosis are generally small, rounded opacities. These can be categorized using the ILO International Classification of Radiographs of Pneumoconioses by size, shape, and profusion category. In silicosis, rounded opacities of the "q" and "r" type dominate. Other patterns have also been described, including linear or irregular shadows. The opacities seen on the radiograph represent the summation of pathological silicotic nodules and associated changes. They are usually found to predominate initially in the upper lung zones and may progress to involve other zones. Hilar lymphadenopathy is also noted, sometimes in advance of nodular parenchymal shadows. Eggshell calcification of the lymph nodes is strongly suggestive of silicosis, although this feature is uncommon. PMF is characterized by the formation of large opacities. These are categorized by size using the ILO classification as categories A, B, or C. The large fibrotic lesions of PMF tend to contract to the upper lung zones, leaving areas of compensatory emphysema at their margins and in the lung bases. As a result of this process, small, rounded opacities that previously were evident on the radiograph may become less visible or at times disappear. Pleural abnormalities are not common on routine chest radiographs with silicosis, however, CT scanning often documents localized pleural thickening, particularly in association with conglomerate lesions. Pleural effusions are less frequently noted. Large opacities may pose a concern regarding neoplasm. The radiographic distinction between PMF lesions and lung malignancies may be difficult, particularly if previous radiographs are unavailable for comparison. As in complicated CWP, FDG-PET scanning may sometimes be helpful in this distinction. Although ischemic necrosis may occur in large silicotic lesions, the onset of cavitation or a rapid change in the radiographic appearance should prompt a search for active mycobacterial disease. Acute silicosis may present with a radiologic alveolar filling pattern with rapid development of PMF or complicated mass lesions.

Lung Functional Abnormalities in Silicosis

Pulmonary function tests, such as spirometry and diffusing capacity, are helpful for the clinical evaluation of people with suspected silicosis. Spirometry may also be of value in early recognition of the health effects from occupational dust exposures, as it can detect physiological abnormalities that may precede radiographic changes. No specific or characteristic pattern of ventilatory impairment is present in silicosis. Spirometry may be normal, or when abnormal, the tracings may show obstruction, restriction, or a mixed pattern. Obstruction may indeed be the more common finding. Silica and mixed dust exposures may lead to clinically important airflow limitation independent of radiographic abnormality. Functional changes tend to be more marked with advanced radiologic categories. However, no good correlation exists between radiographic abnormalities and ventilatory impairment, and workers experience lung function loss proportionate to the duration and intensity of silica dust exposure. Diffusing impairment may also occur in the absence of ventilatory impairment. In acute and accelerated silicosis, functional changes generally occur earlier, are more marked, and the progression is more rapid. In acute silicosis, radiographic progression is accompanied by increasing ventilatory impairment and gas exchange abnormalities, which leads to respiratory failure and eventually to death from intractable hypoxemia.

Complications and Special Diagnostic Issues in Silicosis

With a history of sufficient exposure and a characteristic radiograph, the diagnosis of silicosis is generally not difficult to establish. Challenges arise only when the radiologic features are unusual or the history of exposure is not recognized. Lung biopsy is rarely required to establish the diagnosis. However, tissue samples are helpful in some clinical settings when complications are present or the differential diagnosis includes tuberculosis, neoplasm, or PMF. Biopsy material should be sent for culture, and in research settings, dust analysis may be a useful additional measure. When tissue is required, open or thoracoscopic lung biopsies are generally necessary for adequate material for examination, and to assure satisfactory hemostasis.

Vigilance for infectious complications, especially tuberculosis and other mycobacteria, cannot be over-emphasized, and symptoms of change in cough or hemoptysis, and fever or weight loss should trigger a workup to exclude this treatable problem. Nocardia and fungal infections are also reported in association with acute silicosis.

The International Agency for Research on Cancer has classified crystalline silica as a 2A carcinogen based on "sufficient" evidence of carcinogenicity in laboratory animals and "limited" evidence of carcinogenicity in humans. Uncertainty over the pathogenic mechanisms for the development of lung cancer in silica-exposed populations exists, and the possible relationship between silicosis (or lung fibrosis) and cancer in exposed workers continues to be studied. Regardless of the mechanism that may be responsible for neoplastic events, there is ample evidence of the link between occupational exposure to silica and lung cancer.

Prevention of Silicosis

Prevention remains the principal goal in dealing with this occupational lung disease. Effective exposure controls are available for most processes, and include process enclosure, wet abrasive techniques, and local exhaust ventilation, combined with a comprehensive approach to personal protection. Where possible, less hazardous industrial agents should be substituted for silica. The education of workers and employers regarding the hazards of silica dust exposure and measures to control exposure is also important.

If silicosis is recognized in a worker, termination of any continuing exposures is advisable. Unfortunately, the disease often will progress even without further silica exposure. The finding of a case of silicosis is a "sentinel health event" and should prompt a thorough evaluation of workplace exposures and control measures by a competent authority, with the goal of recognizing the sources of the hazard and protecting other workers who may continue to be at risk.

Medical Screening and Surveillance in Silicosis

Workers exposed to silica and other mineral dusts should be monitored on a regular basis for adverse health effects as a supplement to, but not a substitute for, exposure monitoring and control. Health screening commonly includes evaluation of respiratory symptoms, spirometric abnormalities, and radiographic changes. There is evidence that, if silicosis subsequently develops, workers who have participated in periodic health monitoring experience reduced severity of disease. Evaluation for tuberculosis infection with intradermal skin testing should also be performed. In addition to reporting of results to the individual workers, health data from all workers at a plant or operation should be periodically analyzed to assess the adequacy of prevention activities.

Therapy, Management of Complications, and Control of Silicosis

When prevention has been unsuccessful and silicosis has developed, therapy is directed largely at complications of the disease. Therapeutic measures are similar to those commonly used in the management of airflow obstruction, infection, pneumothorax, hypoxemia, and respiratory failure complicating other pulmonary disease. Historically, the inhalation of aerosolized aluminum was attempted, unsuccessfully, as a specific therapy for silicosis. Polyvinyl pyridine-N-oxide, a polymer that has protected laboratory animals, is not available for use in humans. Laboratory work with tetrandrine has shown in vivo reduction in fibrosis and collagen synthesis in silica-exposed animals treated with this drug. However, evidence of human efficacy is currently lacking, and there are concerns about the potential toxicity, including mutagenicity, of this drug. Because of the high prevalence of disease in some countries, investigations of combinations of drugs and other interventions continue. Currently, no successful approach has emerged, and the search for a specific therapy for silicosis has to date been unrewarding.

For workers with a diagnosis of silicosis, further exposure to silica-containing dusts is undesirable. If the disease is advanced, or has occurred after a relatively short exposure (i.e., less than 15 years), then further dust exposure should be assiduously avoided. Advice on job reassignment should be considered in the context of the worker's age, symptoms, functional status, and the current working conditions and measured silica exposures. Patients with silicosis may have few symptoms early in the disease; however, physicians should be aware that many states have a strict time limit dating from the physician's diagnosis of silicosis regarding application for workers' compensation and reimbursement of medical costs.

In the medical management of silicosis, vigilance for complicating infection, especially tuberculosis, is critical. The use of bacillus Calmette-Guérin (BCG) vaccine in the tuberculin-negative silicotic patient is not recommended, but the use of preventive isoniazid (INH) therapy in the tuberculin-positive silicotic patient is advised. The diagnosis of active tuberculosis infection in patients with silicosis can be difficult. Clinical symptoms of weight loss, fever, sweats, and malaise should prompt radiographic evaluation and sputum acid-fast bacilli stains and cultures. Radiographic changes with infection may be subtle and atypical. Enlargement or cavitation in conglomerate lesions or nodular opacities is of particular concern. Bacteriologic studies on expectorated sputum may not always be reliable in silicotuberculosis. Fiberoptic bronchoscopy for additional specimens for culture and study may be helpful in establishing a diagnosis of active disease. The use of multidrug therapy for suspected active disease in silicotics is justified at a lower level of suspicion than in the nonsilicotic patient, due to the difficulty in firmly establishing evidence for active infection. To obtain satisfactory results in the presence of silicosis, antituberculous treatment must be more prolonged, with regimens lasting at least 8 months. A multiplicative increase in risk of mycobacterial infection is associated with the combination of silicosis and human immunodeficiency virus (HIV) infection, as has been encountered in South African gold miners. These infections represent major clinical and public health challenges. Prolonged treatment is essential, and there is potential for both adverse drug reactions and interactions between antiretroviral and antituberculous therapy. Recommended approaches continue to evolve, and clinicians should consult the latest authoritative recommendations.

Ventilatory support for respiratory failure is indicated when precipitated by a treatable complication. Pneumothorax, spontaneous and ventilator-related, is usually treated by chest tube insertion. Bronchopleural fistula may develop, and surgical consultation and management should be considered.

Acute silicosis may rapidly progress to respiratory failure. When this disease resembles pulmonary alveolar proteinosis and severe hypoxemia is present, aggressive therapy has included massive whole-lung lavage with the patient under general anesthesia in an attempt to improve gas exchange and remove alveolar debris. Although appealing in concept,

the efficacy of whole lung lavage has not been established. Glucocorticoid therapy has also been used for acute silicosis; however, it is also of unproven benefit.

Some young patients with end-stage silicosis may be considered candidates for lung or heart-lung transplantation by centers experienced with this expensive and high-risk procedure. Early referral and evaluation for this intervention may be offered to selected patients.

The discussion of an aggressive and high-technology therapeutic intervention such as transplantation serves to dramatically underscore the serious and potentially fatal nature of silicosis, as well as emphasize the crucial role for primary prevention. The control of silicosis ultimately depends upon the control of workplace dust exposures. This is accomplished by rigorous and conscientious application of fundamental occupational hygiene and engineering principles, with a commitment to the preservation of worker health.

PREVENTION STRATEGIES FOR COAL WORKERS' LUNG DISEASES AND SILICOSIS

The control of coal workers' lung diseases and silicosis in both the developed and developing world requires comprehensive prevention strategies, including exposure control, medical surveillance, research, and education. Example approaches include:

- Major efforts must be directed to installation of effective engineering controls and improvements in work practices to progressively reduce dust exposures to acceptable levels. These efforts are labeled primary prevention. Personal respiratory protection should also be used, particularly during short-term operations or unusual/emergency conditions, and while engineering controls are being modified or improved. The use of respirators will only be effective when part of a professionally managed comprehensive respiratory protection program, and should never be relied upon outside of such a program.
- Primary prevention should involve ongoing dust exposure monitoring, and include mechanisms for feedback to modify and improve working conditions if exposures are measured above mandated levels. Even exposure at currently permissible levels has been reported to represent a risk of disease.
- Secondary prevention through medical screening and surveillance should be designed to benefit the individual worker and other potentially exposed workers. Illness identified through medical screening represents a failure of primary prevention, and thus should trigger feedback to those involved in environmental monitoring and work practice evaluations.
- Education about the respiratory health hazards from uncontrolled exposures to silica and coal mine dust must be available to workers, employers, managers, and health care providers.
- Information on the cumulative burden of disease should be monitored over time for both silica and coal mine dust.
- Research into mining-related lung diseases should be encouraged, to improve recognition, monitoring, exposure reduction, and therapy, and to increase understanding of pathogenesis. Research efforts should supplement, not displace, attention to dust control.
- Clinicians who recognize coal-related diseases or silicosis in their patients should attempt to determine whether ongoing workplace exposures present a continuing risk to current workers, while maintaining the confidentiality of the patient-physician relationship. Assistance in this can often be obtained through local or state health departments, occupational medicine groups, and federal agencies. Reporting of occupational diseases is required in many states.

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58

Occupational Asthma, Byssinosis, and Industrial Bronchitis

J. Allen D. Cooper, Jr.

Inhalation of foreign material at the workplace can cause a number of pulmonary syndromes. Among the organs affected by occupational exposures, the lungs are secondary only to the skin with respect to organs commonly affected by occupational exposures. The lung parenchyma and airways, as well as the pleura, can be affected by inhalation of toxic material. This chapter discusses reactions of the airway to inhalation of toxic substances present in the workplace. Lung parenchymal and pleural reactions as well as obliterative bronchiolitis in response to inhaled materials are discussed elsewhere in this text. Occupational airway disease can manifest itself as chronic bronchitis, with variable airway hyperreactivity (industrial bronchitis or asthmalike syndrome), or with asthma accompanied by persistent hyperreactivity of the airways (occupational asthma). Four major differences exist between these syndromes: (1) Industrial bronchitis occurs most often without a latent period whereas occupational asthma commonly develops after a period of exposure. (2) Occupational asthma occurs after the airway has become sensitized to a substance, so that re-exposure to a very small amount of the substance will induce bronchospasm; in contrast, patients with industrial bronchitis may show attenuation of the response over time. (3) Compared to occupational asthma, industrial bronchitis is more often associated with systemic symptoms. (4) Industrial bronchitis is associated with a neutrophilic bronchitis whereas the bronchial inflammation that is associated with occupational asthma is made up predominantly of eosinophils, much like that seen in nonoccupational asthma. Some occupational exposures can cause both industrial bronchitis and asthma while others cause only one or the other. Cotton dust is the most common cause of industrial bronchitis without occupational asthma. Grain dust can cause both industrial bronchitis and asthma. In this chapter general and specific issues regarding industrial bronchitis and occupational asthma are discussed.

INDUSTRIAL BRONCHITIS

Byssinosis

History

Adverse pulmonary reactions in cotton workers have been recognized for more than 100 years. In 1831, Kay described chest tightness and fever that commonly occurred on Monday after workers had been off work over the weekend. It was because of this observation that the term *Monday morning fever* was coined. The term *byssinosis* was proposed by the French physician Proust and is derived from the Greek word meaning linen or fine flax. Over the years, as cotton mills appeared in

more and more countries, the association of chronic bronchitis with cotton dust exposure was confirmed.

Epidemiology

There is no doubt that recurrent exposure to cotton dust results in chronic bronchitis. In a prospective study, 16 percent of cotton mill workers in South Carolina developed symptoms of chronic bronchitis, as compared to only 1 percent of appropriate controls in the region. In another study, 4.5 percent of 2000 cotton workers screened by questionnaires and pulmonary function testing complained of Monday morning chest tightness and showed physiological impairment. The percentage of subjects with symptoms varied with the work area and was as high as 26 percent in certain areas. Another recent study of cotton textile workers in China found that the frequency of symptoms of byssinosis increased from 7.6 percent at baseline to 15.3 percent after 15 years of working in the textile mill. In this study, airway flow rates decreased significantly over time in textile workers when compared to silk workers. The appearance of symptoms during work or worsening of pulmonary function tests during the work shift predicted this accelerated loss of pulmonary function.

There are over 800,000 textile workers in the United States. These individuals are predominantly at risk for developing symptoms due to inhalation of cotton dust. Flax and hemp workers are also at risk for developing the disease. Clinical studies suggest that approximately 65 percent of the general population will react significantly to de novo inhalation of components of cotton dust. Therefore, the majority of individuals who begin employment that entails the processing of cotton, flax, or hemp are at risk for developing respiratory symptoms. Why some individuals are more susceptible than others to the effects of cotton dust is unclear.

Certain jobs in the textile mill are associated with a higher risk for development of bronchitis. Ginning, opening, or carding work carry a higher degree of risk. In addition, workers who clean out or maintain the various machines that divide up and clean the cotton are especially prone to develop symptoms. These are particularly high-risk jobs because of the high levels of cotton dust generated during the cleaning procedure. Strippers and grinders, who maintain the carding machinery that cleans and aligns the cotton, are particularly at risk for development of symptoms. Indeed, in the past, byssinosis was called "strippers' asthma."

Clinical Presentation, Risk Factors, and Stages of Byssinosis

Shortness of breath often occurs on the day back to work at the textile mill after several days off, as on a Monday after being off over the weekend. Over time, workers can develop more persistent symptoms. These have been graded by Schilling (Table 58-1) to allow comparison of symptomatology with physiological parameters. Using this grading system, it has been established that workers with a higher grade of symptoms tend to have a more rapid decline in pulmonary function. Risk factors for developing higher grades of byssinosis include (1) length of employment in a cotton mill and (2) level of dust exposure. Tobacco smoking has been shown to be synergistic with exposure to cotton dust in producing chronic bronchitis. Although it is controversial whether exposure to cotton dust without cigarette smoking causes chronic pulmonary disability unless associated with cigarette smoking, it appears that 7 percent of exposed individuals will develop irreversible airway obstruction that cannot be explained by smoking. Cross-shift pulmonary function tests that show a decrease in flow rates after work also predict chronic effects.

Table 58-1

Clinical Grading of Byssinosis as Proposed by Schilling

Grade 0	No symptoms on first day of work
Grade 1/2	Occasional chest tightness or irritation of respiratory tract on the first workday of week
Grade 1	Chest tightness on every first day of workweek
Grade 2	Chest tightness on first and other days of workweek
Grade 3	Chest tightness on first and other days of workweek and physiological evidence of permanent disability

PULMONARY FUNCTION TEST ABNORMALITIES

Characteristically, byssinosis is associated with a reduction in the forced vital capacity (FVC) and forced expiratory volume in 1 s (FEV_1) on the day of return to work after an absence. The degree of reduction in these parameters increases over the workday. This change is generally more severe on the first day of work after an absence than on subsequent days. The mechanism by which this developed tolerance occurs is unknown. Whether subjects with byssinosis have airways that are hyperreactive to methacholine challenge is controversial. One study has shown a significant decrease in arterial oxygen tension after exposure to hemp dust.

Pathology and Pathogenesis of Byssinosis

The histopathology of byssinosis is similar to that of the bronchitis that is induced by tobacco smoke—with hyperplasia of mucous glands and infiltration of the bronchi with polymorphonuclear neutrophils. Several animal studies have demonstrated that different components of cotton dust can recruit

Table 58-2

Evidence That Bacterial Endotoxin Is the Causative Agent in Byssinosis

1.	Measurable levels of endotoxin can be detected in cotton dust.
2.	Inhaled endotoxin can include airway inflammation in animals and humans.
3.	In a controlled setting, ambient levels of endotoxin correlate with degree of airflow reduction occurring in a simulated carding room.
4.	Repeated inhalation of endotoxin results in an attenuation of the airway response similar to that noted in patients with byssinosis.
5.	Measures that reduce levels of ambient endotoxin reduce the incidence of byssinosis.

neutrophils into bronchi. In addition, components of cotton dust can also stimulate resident pulmonary cells, such as mast cells and macrophages, to release molecules that attract neutrophils.

There is now a large amount of information that points to a lipopolysaccharide (endotoxin) produced by bacterial contaminants of cotton as the causative agent of byssinosis. The evidence for this is listed in Table 58-2. The most compelling study that examines this issue was presented by Castellan and colleagues, who demonstrated that ambient concentrations of endotoxin in a simulated carding room correlated with reduction in airway flow rates in a time frame similar to that which occurs after exposure to cotton dust in the workplace. An interesting related finding is that byssinosis is less prevalent in Australia, probably because of the lower level of endotoxin on cotton grown in this drier climate. The acquired tolerance during the workweek displayed by patients with byssinosis can be simulated by administration of multiple aerosols of endotoxin in animals. Because airborne levels of endotoxin appear to be directly related to the pathogenesis of byssinosis, mechanisms to control the levels of endotoxin and other airborne components of cotton dust have been implemented in the textile industry. This intervention has met with success in controlling industrial bronchitis in this setting.

There have also been reports implicating other components of cotton dust in the pathogenesis of byssinosis. An extract of cotton bract has been shown to induce bronchoconstriction in approximately 60 percent of normal volunteers. The level of this low-molecular-weight (MW) compound parallels the endotoxin level in certain cotton dust preparations, but it is not a component of endotoxin. Other reports have documented significant levels of histamine in cotton dust extracts. In addition, clinical studies have suggested that workers with byssinosis have elevated serum histamine levels. The role(s) that cotton bract or histamine play in the pathogenesis of byssinosis is not clear, since none have held up under scrutiny as a cause of this disorder as convincingly as has endotoxin.

Treatment and Prevention

The most important treatment for byssinosis is removal of the individual from the offending work environment. Screening pulmonary function testing at the workplace is important to identify susceptible individuals who exhibit airflow abnormalities. In addition, since the 1970s, measures have been taken in developed countries to control cotton dust levels in textile mills. One measure has been to steam-clean cotton while it is still in the bale. In 1970, Burlington Industries began a program for dust control and annual medical surveillance. With this program, the incidence of symptoms of byssinosis dropped from 4.5 percent in 1970 to 0.6 percent in 1979. In addition, the number of employees who had a significant decrease in FEV_1 over the work shift decreased from 18 percent in 1971 to 3.5 percent in 1979. Similar measures have been taken in other textile plants, with good success in controlling byssinosis. Unfortunately these measures have not been implemented worldwide, and there remains a significant prevalence of byssinosis outside of the United States.

Grain Dust—Induced Industrial Bronchitis

Exposure to grain dust can also result in the development of chronic bronchitis. Between 4 and 11 percent of grain workers show a reduction in FEV_1 of 10 percent or greater over the work shift. This reduction in flow rates is directly related to the amount of dust in the air. Studies have suggested that the component of grain dust responsible for causing airway symptoms is endotoxin, the apparent active component of cotton dust (see above). Grain dust extract, possibly its endotoxin contaminant, can activate complement, and this may be a mechanism by which grain dust induces inflammation in bronchi. However, in contrast to cotton dust, grain dust can, in sensitive individuals, also precipitate an acute drop in airway flow rates rather than only the slow reduction in flow rates similar to that precipitated by cotton dust. This finding suggests that airway reactions to grain dust may be heterogeneous. Grain dust also tends to produce skin abnormalities in affected individuals, in contrast to cotton dust, which generally does not cause skin reactions.

OCCUPATIONAL ASTHMA

Definition and List of Offending Agents

Occupational asthma is characterized by variable airway obstruction resulting from exposure to ambient dusts, vapors, gases, or fumes incidentally present at a workplace. Bronchial

Table 58-3

ACCP Case Definition of Occupational Asthma

A. Physician diagnosis of asthma
B. Onset of asthma after entering workplace
C. Association between symptoms of asthma and work
D. One of the following: 1. Workplace exposure to agent known to cause occupational asthma 2. Work-related changes in FEV_1 or PEF 3. Work-related changes in bronchial responsiveness 4. Positive response to specific inhalation challenge test 5. Onset of asthma with a clear association with a symptomatic exposure to an inhaled irritant agent in the workplace
Definite occupational asthma requires A, B, C, and D(2) or D(3) or D(4) or D(5)
Likely occupational asthma requires A, B, C, and D(1)

Abbreviations: FEV_1 = forced expiratory volume in 1 s; PEF = peak expiratory Flow.

hyperresponsiveness to nonspecific agents, such as methacholine or histamine, is usually present in these patients. In this setting, asthma may be caused de novo by the offending agent, as in the case of isocyanate-induced asthma, or underlying asthma may be exacerbated by the offending agent. The American College of Chest Physicians (ACCP) consensus statement for the diagnosis of occupational asthma includes several criteria that can be used for the definitive or probable diagnosis of the disease (Table 58-3).

Agents that have been associated with induction of occupational asthma can be conveniently grouped into categories of high- and low-MW compounds (Table 58-4). All of these agents tend to sensitize the individual, so that low ambient concentrations of the substance can ultimately cause significant bronchoconstriction. In addition, certain agents can cause direct irritant-related bronchoconstriction and airway hyperreactivity.

Risk Factors

Atopy appears to be the major risk factor for developing occupational asthma, particularly when the inciting agent is a high-MW compound. Family or personal history of atopy appears to put the subject at risk. Because low-MW agents can induce asthma through nonallergic as well as allergic mechanisms, atopy may not be as important. Smoking is also a risk factor for the development of occupational asthma, particularly in workers exposed to platinum salts and anhydride compounds. There have been several studies documenting that workers who smoke have a higher incidence of asthmatic reactions to specific airborne agents, possibly due to overall higher immunoglobulin E (IgE) levels in smokers as compared with nonsmokers. Recent studies have also suggested that there are genetic factors that predispose to occupational asthma. Major histocompatibility complex class II proteins are important for development of occupational asthma due to acid anhydrides, diisocyanates, western red cedar, platinum salts, latex, and animal proteins. Certain glutathione S-transferase and N-acetyltransferase genotypes also predict development of occupational asthma in certain settings.

Clinical Presentations

Occupational asthma presents in a similar manner as other forms of asthma. If the physician does not maintain a high index of suspicion, symptoms will be treated but the inciting agent will not be identified. Two general forms of occupational asthma have been identified. Most commonly patients develop symptoms after a period of exposure to the inciting agent (occupational asthma with latency) and less commonly they develop immediate symptoms with exposure to the agent (occupational asthma without latency or irritant-induced asthma). In general the former syndrome is associated with a true allergic reaction to the offending agent while the latter is generally mediated nonimmunologically.

Occupational Asthma with Latency

Most commonly patients who develop occupational asthma do so after a period of exposure to the inciting agent. Agents that induce this sort of pattern include high- and low-MW molecules. Individuals are usually exposed to the agent for weeks to months before developing symptoms. With the appearance of symptoms, nonspecific airway hyperreactivity, determined by methacholine or histamine challenge, is present. Also with appearance of symptoms, the individual develops hypersensitivity to low ambient concentrations of the offending agent. Therefore exposure to very low concentrations of the material in the workplace precipitates severe bronchoconstriction in these patients. Controlled exposure with the offending agent will elicit bronchoconstriction in patients with this syndrome, especially when asthma is due to a high-MW molecule.

Occupational Asthma without Latency (Irritant-Induced Asthma)

This syndrome is less common. Symptoms develop within hours of exposure. Pathological changes are generally similar to those occurring in the syndrome of occupational asthma with latency, although epithelial changes such as desquamation and subepithelial fibrosis may be more prominent. Agents that commonly cause this syndrome are irritant gases or fumes such as chlorine or ammonia. In addition, certain agents such as acid anhydrides and isocyanates can cause occupational asthma with and without latency. Cough and airway hyperreactivity occurring in emergency responders to the

Table 58-4

Categories of Agents That Commonly Cause Occupational Asthma

Categories	Occupations at Risk	Major Putative Component
High-molecular-weight compounds		
Animal products	Animal handlers Veterinarians	Pelt or urinary proteins
Seafoods	Crab or prawn processors Oyster farmers	Water-extractable proteins
Insects	Entomologists Grain workers Laboratory workers River workers Flight crews	Insect proteins
Plants	Grain handlers Bakers Tea workers Brewery chemists Tobacco manufacturers	Extractable plant proteins
Biologic enzymes	Detergent industry workers Pharmaceutical workers	*Bacillus subtilis*, trypsin, pancreatin, papain, pepsin Bakers
Latex	Health care workers Doll manufacturers Glove makers	Latex rubber extract
Gums	Printers Gum manufacturers	Gum acacia Gum tragacanth
Low-molecular-weight compounds		
Diisocyanates	Polyurethane workers Plastic workers Foundry workers Spray painters	Isocyanate-protein complex
Anhydrides	Epoxy resin workers Plastics workers	Phthalic anhydride-protein complexes
Wood dust	Carpenters Sawmill workers	Plicatic acid (western red cedar) Wood dust extracts
Fluxes	Aluminum solderers Electronics workers	Aminoethylethanol amine
Pharmaceuticals	Pharmaceutical manufacturers	Antibiotics, psyllium, piperazine
Fixatives	Hospital workers	Formaldehyde, glutaraldehyde

World Trade Center collapse are probably due to this form of asthma.

Mechanisms and Pathology

High-Molecular-Weight Compounds

Most commonly, high-MW compounds, usually proteins produced at the workplace, induce asthma through IgE-dependent classic immediate hypersensitivity reactions. Specific serum IgE antibodies to the protein can usually be demonstrated and skin tests using extracts of the substance show positive results. Atopic individuals are more at risk for developing the syndrome. Because specific IgE antibodies must be produced in this setting, the latent period for developing the reaction can be long, sometimes several months or years. Pathologically, asthma due to high-MW compounds is associated with bronchial infiltration of lymphocytes and eosinophils, indistinguishable from other forms of allergic asthma. Specific IgE antibodies to occupation-related allergens trigger mast cell degranulation in a similar manner as in the nonoccupational setting. In severe cases, bronchial epithelial desquamation and subepithelial fibrosis are exhibited pathologically.

Low-Molecular-Weight Compound

These agents also tend to cause IgE-dependent bronchoconstriction. However, in contrast to higher-MW agents, specific IgE or IgG antibodies produced in these individuals are directed at the low-MW compound coupled to a protein within the serum. There is also some evidence that low-MW compounds induce asthma through IgE-independent mechanisms, possibly by affecting T lymphocytes directly, as shown for cobalt and nickel salts as well as isocyanates. Interestingly, the bronchial pathology is similar whether or not the response is an IgE-dependent reaction. In addition, certain low-MW compounds can directly affect chemical pathways that are involved in airway tone. For example, organophosphates have been shown to induce bronchoconstriction through anticholinergic effects. Other agents may cause asthma simply through irritation of the airways.

Diagnosis

History

A high index of suspicion for occupational causes must always be present when patients with new-onset asthma are being evaluated. Because asthma can be induced by remote exposure to a substance, the current and previous occupational history is very important. Computerized lists of exposures that occur at various workplaces are available, and these facilitate this process. Included in the history should be documentation of specific jobs of the individual at the specific workplace as well as potential exposures during performance of those jobs. The history can be verified through the use of material safety data sheets (MSDS) as well as industrial hygiene data and employee health records from the workplace. Clinical history that suggests occupation-related asthma includes symptoms that occur at work and improve when the patient is away from work for a period of time, as during vacations. The duration of symptoms prior to removal from the offending environment is important for predicting prognosis. Those individuals who have had symptoms for a longer period of time are more likely to develop chronic symptoms that do not remit after exposure has been discontinued. It should be noted that many compounds induce a late reaction, several hours after exposure. Therefore the relationship between the exposure and symptoms may not be entirely apparent to the patient.

Questions should also be asked regarding other causes of obstructive pulmonary disease. Questions regarding a history of tobacco use are important. A past history or family history of asthma may suggest that the patient's symptoms are not occupation-related. Therefore, questions to establish the degree of respiratory symptomatology prior to beginning a particular job are important. Questions aimed at assessing cardiac or upper-airway abnormalities are also very important.

Physical Examination

Signs of atopy should be assessed. As in cases of asthma due to other causes, the pulmonary examination may be entirely normal when the patient is seen outside of the workplace. However, wheezing, either during quiet respiration or on a forced maneuver, suggests airflow obstruction. Signs of dermatitis may support the diagnosis of work-related disease.

Skin and Immunologic Tests

General atopy is a risk factor for developing certain forms of occupational asthma when it is due to high-MW compounds. Therefore routine skin testing, using a panel of allergens, for wheal-and-flare reactions can be useful. In addition, extracts of a compound that is suspected to cause occupational asthma in a particular patient can be used for skin testing. Extracts from flour, animal by products, coffee, and other sources have been used for skin testing in various studies. Specific IgE antibodies to extracts that contain high-MW compounds or to low-MW compounds coupled to a serum protein, such as albumin, can also be detected by the radioallergosorbent test (RAST) or enzyme-linked immunoadsorbent assay (ELISA). In addition, specific IgE antibodies to low-MW compounds have been detected in patients with asthma due to these compounds. However, positive results in all of these tests do not necessarily indicate that disease is due to the specific agent; they simply suggest sensitization. All of these tests must be evaluated in the context of the individual patient.

Pulmonary Function Tests

Patients with workplace-induced asthma may present with normal pulmonary function tests when they are away from the inciting agent. For this reason pulmonary function tests should be assessed in the light of the time that has elapsed since the patient was exposed to a suspected agent. Pulmonary

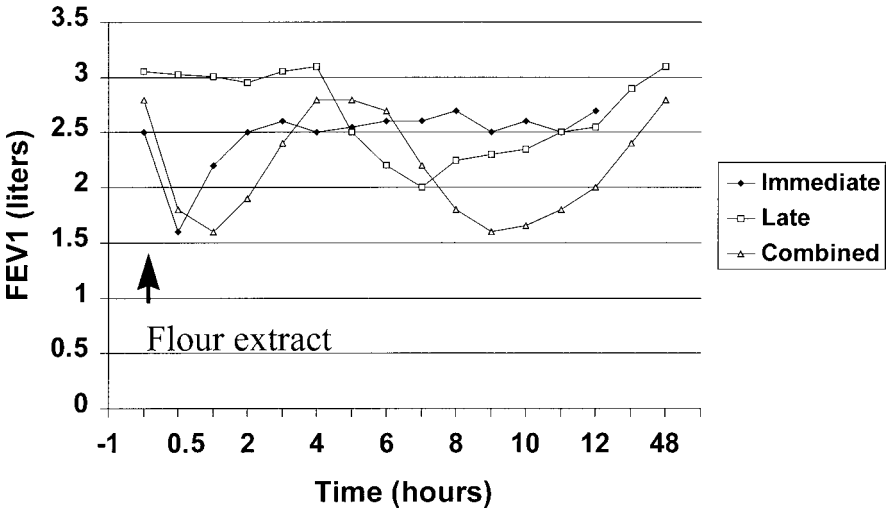

Figure 58-1 Examples of early, late, and combined reactions to inhalation of a specific agent (in this case, flour extract) implicated in causing occupational asthma. Flow rates are plotted vs. time after inhalational exposure.

function tests pre- and postwork can be very helpful in objectively evaluating respiratory function in relation to work.

Peak-flow monitors are useful in the assessment of workplace-related symptoms because they can be used on the job. Initially, peak-flow measurements should be determined at least four times per day: on awakening, at the beginning and end of work, and before bed. Similarly timed measurements should also be performed on days that the subject is off work. Three measurements at each time period should be made and recorded; two of these should be within 20 L/min of each other to demonstrate reproducibility. Measurements should be performed each day over at least 4 weeks. In addition to this regimen, a more intense regimen of peak-flow measurements every 2 h has been proposed by Burge, but this schedule may be too cumbersome to be practical, and studies have suggested that a protocol using measurements performed four times a day is as predictive.

Because peak-flow measurements are very effort-dependent, they should be supplemented by other methods for assessing the degree of impairment. It is always important to document that patients who are being evaluated for occupational asthma are not malingering in order to obtain compensation. When pulmonary function is assessed in these patients, technicians should be alerted that a work-related disorder is suspected, so that they can evaluate the patient's effort. In addition, reproducibility of the repeated maneuvers can be useful in determining degree of effort. If peak-flow measurements suggest that there is an airway reaction to a substance at the workplace, a technician with a portable spirometer can be sent to the workplace to measure FVC and FEV_1 at hourly intervals during work.

Bronchial Provocation Tests

Patients who develop occupational asthma invariably develop bronchial hyperreactivity to nonspecific agents such as methacholine and histamine. An arbitrary cutoff of a provocative concentration producing a 20% decline in FEV_1 (PC_{20}) of 8 to 16 mg/ml has been chosen. In patients with normal spirograms at presentation, a bronchial challenge with either of these agents may be necessary for diagnosis. Such a challenge can also be used to choose the concentration(s) of specific allergen that should be employed in a specific bronchial provocation test, since studies have shown a good correlation between the degree of nonspecific bronchial reactivity and responses to specific allergens.

Specific bronchoprovocation can be a valuable tool to determine whether a patient's symptoms are due to a particular agent. This maneuver should be performed only by an experienced physician because it carries some risks. Bronchodilator and anti-inflammatory medication should be withheld prior to the exposure, which should be performed, if possible, in a whole-body chamber that allows more reproducibility of the work situation. Exposure levels should start low and gradually increase to levels that are consistent with ambient levels in the subject's workplace.

Patterns of bronchoconstriction after exposure to specific agents can differ. The two most common patterns are an immediate reaction, occurring within a few minutes of challenge and peaking at 10 to 15 min after challenge, and a late reaction, occurring several hours after challenge and peaking at 5 to 8 h (Fig. 58-1). These responses can be seen individually or together in a given patient. Less frequent patterns have also been noted. One of these involves a reduction in flow rates 1 h after challenge, with resolution 3 to 4 h after exposure. In another, a reduction in flow rates occurs much later, the day after the exposure, and occasionally recurrent abnormalities can be manifest for several days. Recurrent symptoms of nocturnal asthma for several days have also been reported after exposure to a number of agents.

Management

Once it has been determined that an individual has developed asthma due to exposure in the workplace, he or she should be removed from the offending environment. In some instances reduction in exposure at the workplace can allow the worker to continue gainful employment without having progressive respiratory symptoms. Although some studies have suggested the use of certain therapeutic agents, such as inhaled

cromolyn for bakers' asthma, which can inhibit physiological changes triggered by the offending agent, protection is not complete. Because it is sometimes difficult to convince the patient to change jobs, an alternative to this is the use of a protective mask to prevent airway exposure to the offending agent. The inciting agent dictates the type of protective headgear employed. For example, subjects working with low-MW compounds require helmet respirators with an isolated air source to prevent exposure. If the subject continues to work in the implicated environment, pulmonary function tests should be done frequently to rule out progressive physiological impairment.

Disability Determination

Documentation of impairment associated with objective physiological changes that occur predominantly in the workplace suggests an occupation-related disorder. Patients with asthma due to an occupational exposure should be referred to the appropriate compensation or review board. The American Thoracic Society has developed guidelines for the evaluation of impairment and disability due to this disorder. Determination of initial impairment should be made after optimal treatment of the asthma has been delivered. Impairment should be assessed using lung function tests, or measurements of airway hyperresponsiveness using: (1) methacholine or histamine; (2) documentation of the type and amount of medication required to treat the patient; and (3) observation of the effect of the disease on the patient's life-style.

Specific Examples

Animal Handlers' Asthma

For several years it has been known that there is a high incidence of asthma and rhinitis among workers in animal care facilities. Development of symptoms tends to occur following months or years of exposure. Symptoms of asthma are often preceded by rhinitis, conjunctivitis, or urticaria that occur primarily at work. In one study, 56 percent of individuals who had been exposed to laboratory animals for 3 months or more complained of respiratory symptoms. Skin testing to animal-associated allergens may be helpful in determining individuals at risk for developing this syndrome. In addition, a prior history of atopy, elevated serum IgE levels, and positive skin tests against non-animal environmental allergens also predict the development of asthma in animal handlers. Approximately one-third of individuals with a history of atopy develop asthma when exposed to laboratory animals for more than 3 months. Although multiple allergens—including molecules found in the pelt, serum, and urine of the animal—may be involved, a major allergen is the rat urinary allergen. In one study, specific IgE antibody to this protein correlated very well with reported asthmatic symptoms in animal handlers. Serum IgG antibody to this protein was also present in animal handlers with symptoms, but it was additionally present in a significant number of asymptomatic subjects as well. Anti-rat urinary protein IgG antibody appeared to be simply a marker of exposure, while IgE antibody was integrally associated with onset of asthma.

Avoidance of exposure to laboratory animals is the best treatment for this condition. Although one study has documented that airway reactivity does not tend to worsen in these individuals even if they remain on the job, chronic exposure probably perpetuates airway inflammation. If the individual cannot avoid the exposure, use of a helmet respirator, enabling him or her to completely avoid inhalation of the protein allergen, can prevent symptoms. Worker education regarding avoidance of airborne allergens can also be useful in controlling symptoms.

Asthma in Crab Processors

Approximately 16 percent of workers who process snow crab meat will develop asthma due to work exposure. The majority of individuals who develop this problem exhibit nonspecific airway hyperreactivity at the time of diagnosis. Studies have suggested that asthma in this setting is due to an immediate hypersensitivity reaction to a component of the crab. One study showed that immediate hypersensitivity skin reactivity, or the appearance of specific IgE antibody to crabmeat extracts or the cooking water used in crab processing, correlated with the development of asthma. Water extracts were more potent than the meat extract.

Much as in other forms of occupational asthma, the syndrome in crabmeat processors can become chronic even after removal of the individual from the implicated work environment. In one study, 19 of 31 subjects with the syndrome continued to have symptoms of asthma after being removed from exposure for an average of 1 year. The propensity to develop chronic symptoms appeared to correlate with the duration of employment in the crab-processing plant. As with other causes of occupational asthma, it is important to identify susceptible individuals early, so that they can be removed from the offending environment.

Bakers' Asthma

Cereal flours induce a specific IgE reaction in a high percentage of exposed subjects. Epidemiological studies of bakers' asthma have been most complete in Germany, where it has been shown that IgE-mediated immediate skin test reactivity in bakers is directly related to their time in service. One study has shown that 20 percent of bakers' apprentices develop positive skin tests after 5 years of service. However, exposed individuals can develop specific IgE antibodies and skin test reactivity to flour antigens without developing asthma, suggesting these tests are mainly a parameter of exposure. In one study, however, the percentage of bakers with documented occupation-related airway disease had a much higher concentration of IgE antibody than did unselected bakers who had been employed for a similar period of time. Overall, 7 to 20 percent of bakers develop allergic symptoms, including asthma, that occur predominantly in the workplace. Symptoms can be minimized by using properly occlusive masks, although most subjects find these devices difficult to wear

during the entire work shift. Airway reactions to inhaled flour dust allergens can also be reduced by pretreatment with cromolyn sodium. However, no studies have documented that cromolyn can reduce symptoms at the workplace or prevent chronic respiratory abnormalities from developing.

Biologic Enzyme—Induced Asthma

Detergents containing proteolytic enzymes from bacteria were first noted to cause asthma in 1966. Enzymes associated with asthma include trypsin, pancreatin, papain, pepsin, flaviastase, and bromelain. These proteins induce an immediate hypersensitivity reaction; specific IgE antibodies have been demonstrated in some instances. Attempts to reduce this problem have included changes in detergent preparations so that the molecules will be less readily inhaled.

Asthma Due to Latex

Urticaria and asthma occur in a small number of individuals who are exposed to rubber latex by wearing gloves or working in doll factories. Risk factors for developing sensitization to latex are (1) frequent use of disposable gloves, (2) the presence of prior atopic disease, and (3) prior or current hand dermatitis. Approximately 80 percent of patients with asthma due to latex develop contact urticaria upon wearing gloves, a large percentage of patients also report rhinitis and conjunctivitis upon exposure to latex. Skin tests using extracts of latex are usually positive in affected individuals. Treatment is limited to avoidance of latex-based products. One study has shown that measures implemented to reduce exposure while working, such as use of powder-free gloves, can allow a sensitized individual to continue to remain on the job.

Asthma Due to Acid Anhydrides

These low-MW compounds are used in numerous industries, including the curing of epoxy and alkyl resins, production of plasticizers and adhesives, and the manufacture of drugs. Specific acid anhydride compounds used include trimellitic acid (TMA), phthalic acid (PA), tetrachlorophthalic acid (TCPA), and malic acid (MA). All of these compounds have been associated with induction of asthma. TMA exposure has been associated with several different syndromes: (1) an irritant syndrome, (2) early asthma and rhinitis, (3) late-onset dyspnea with systemic symptoms ("TMA flu"), and (4) pulmonary infiltrates with hemoptysis. The irritant syndrome does not require a latency period, while the other three syndromes require a period of exposure to the acid anhydride prior to development. Asthma caused by these compounds appears to be due to the development of specific antibodies to the acid anhydride coupled to a body protein. Specific IgE and IgG antibodies to TMA coupled to human serum albumin have been noted. In one study, total IgE levels were a good parameter of exposure, while specific IgE levels correlated with symptoms of asthma and skin test positivity. The absence of a specific IgE antibody to TMA strongly argues against TMA as the cause of asthma in a particular patient. Another study has shown that IgG in serum from sensitized patients can trigger histamine release by basophils. In contrast to asthma caused by high-MW compounds, atopy does not appear to be a definite risk factor for development of asthma due to acid anhydrides. However, a history of smoking may be a risk for the development of asthma due to these agents. Removal of the employee from the environment is the best form of therapy for the disorder. Employee education regarding exposure can also be useful. Even with removal from the offending environment, affected subjects may continue to have symptoms for as many as 5 years after changing work. Specific IgE antibody may also be detected several years after discontinuation of exposure.

Isocyanate-Induced Asthma

Isocyanates are highly reactive chemicals used in a number of industries. Prominent in this regard is their use in the production of polyurethane, which is found in paints, varnishes, flexible foams, and adhesives. Major forms of isocyanates include toluene diisocyanate (TDI), diphenyl methane diisocyanate (MDI), and hexamethylene diisocyanate (HDI). Exposure to TDI has been most often associated with the development of asthma, and TDI is also the most chemically reactive isocyanate. Overall 5 to 30 percent of workers exposed to TDI develop airway symptoms. There is some evidence that HLA class II alleles are associated with increased risk for the development of isocyanate-induced asthma. In addition, asthma due to toluene diisocyanates is associated with the Ile^{105}/Ile^{105} phenotype of glutathione-S-transferase enzyme protein whereas the Val^{105}/Val^{105} protects against asthma in this setting. Also, slow acetylator genotypes of the N-acetyltransferase gene have an increased risk of diisocyanate-induced asthma.

Isocyanates can cause an irritation syndrome similar to that due to acid anhydrides, occurring without significant time latency. In one reported case, a patient was exposed to large concentrations of TDI and developed airway symptoms within hours of the exposure. Twelve years after exposure, the patient continued to manifest hyperactivity to TDI as nonspecific airway hyperreactivity. More commonly, isocyanates induce an asthma syndrome that develops after exposure to the substance for weeks to years. When subjects develop asthma due to these agents, they also manifest bronchoconstriction after exposure to the substances in a controlled setting, such as an exposure chamber; usually these individuals will also manifest nonspecific airway reactivity to methacholine or histamine. Isocyanates may also induce chronic airway abnormalities in the absence of symptoms. One study, which examined the decremental fall in flow rates in workers exposed to TDI, predicted a 2-L greater loss in FEV_1 over 40 years in these workers as compared with controls.

Isocyanates cause asthma by inducing intense airway inflammation. Bronchoalveolar lavage studies have demonstrated increased numbers of neutrophils and eosinophils in the airways of subjects with asthma due to isocyanates, particularly those who manifest a late airway reaction upon controlled exposure. Bronchial biopsies of affected patients also

show intense inflammation, much of which is lymphocytic. Why inflammation is induced by these agents is controversial. There are studies suggesting that isocyanates may interact directly with elements that modulate inflammation. Because these compounds are very reactive, they may affect membrane receptors or enzymes involved in inflammatory pathways. However, because of the latency period that is commonly required prior to the development of isocyanate-induced asthma, an immunologic mechanism is likely. Lymphocyte-mediated and humoral responses have been proposed. One study has demonstrated specific IgE and IgG antibodies to isocyanates coupled to human serum albumin in sera of individuals with symptoms and positive inhalation challenge tests with isocyanates. Although the levels of both of these subclasses of immunoglobulins tend to correlate with airway responsiveness to the isocyanate, the IgG level tends to be more predictive.

As with other forms of occupational asthma, the most efficacious treatment for individuals affected with isocyanate-induced asthma is removal from the offending environment. Once the individual has become sensitized, very low concentrations of the particular agent can induce bronchospasm, so that transfer of the individual to an area that is in close proximity to an area of isocyanate use is not effective management. Bronchoconstriction following controlled isocyanate exposure can be attenuated by inhaled or oral corticosteroids. However, use of these agents should not replace removal of the patient from exposure at work. Use of respirators prophylactically in areas with high concentrations of isocyanates is important to prevent the development of asthma. There have been reports of persistent isocyanate-induced asthma even after removal of the subject from the offending environment. One study reported persistent respiratory symptoms in 83 percent of workers who had been away from isocyanate exposure for 4 years. Another study demonstrated that 7 of 12 subjects with TDI-induced asthma continued to have nonspecific airway hyperreactivity 2 years after removal from the work environment.

Asthma in Emergency Responders at the World Trade Center

Approximately 25 percent of firefighters who responded to the World Trade Center collapse developed airway hyperreactivity to methacholine from exposure to respirable particles, possibly because of high alkalinity of the dust. The predominant symptom associated with this exposure was cough. One study showed that airway hyperreactivity shortly after the disaster predicted airway hyperreactivity 6 months later. This syndrome is most consistent with occupational asthma without latency (irritant-induced asthma).

Asthma Due to Western Red Cedar Wood Dust

Workers are at risk for developing asthma due to wood dust exposure. Although a number of woods are associated with this problem, the syndrome due to western red cedar is best characterized and the causative agent within the dust has been identified. Overall 5 percent of workers who are exposed to western red cedar dust develop symptoms of wheezing and cough after a latency period of months to years. The mean latency period prior to development of symptoms is 50 months. Workers who develop the syndrome usually have nonspecific airway hyperreactivity to methacholine or histamine. In addition, a specific airway reaction to plicatic acid, a component of the wood dust, is usually present and manifested by an early or late reduction in flow rates after exposure.

Mechanisms of western red cedar–induced asthma are not totally defined. Plicatic acid, which makes up approximately 50 percent of the total extractable fraction of the wood dust, induces bronchoconstriction in affected subjects. Those subjects who manifest an early and late airway response to inhalation of plicatic acid generally have had a longer exposure to the western red cedar dust. Specific IgE antibodies to plicatic acid coupled with human serum albumin have also been detected in 28 to 40 percent of subjects with the syndrome.

Like other forms of occupational asthma due to low-MW compounds, subjects with asthma due to western red cedar can continue to have symptoms even when they are removed from the offending environment. In one study, 60 percent of affected individuals continued to have symptoms after leaving the industry. For this reason, the identification of individuals and specific jobs that place individuals at risk is important. Use of protective devices may reduce exposure and subsequent development of asthma due to this dust, but this has not been systematically addressed.

Asthma Due to Metal Salts

Platinum used in electroplating, platinum refinery, and jewelry making has been noted to cause asthma. Smoking is a risk factor for development of asthma due to this metal. Airway responses to preparations of complex salts of platinum have been documented in affected workers. In addition, positive skin-prick tests and specific IgE antibodies to platinum conjugated to albumin have been found. There has been one report that hyposensitization is useful for prevention of symptoms, but this has not been verified. Exposure to nickel, chromium, cobalt, vanadium, and tungsten carbide has also been associated with development of asthma. Welders are commonly exposed to nickel fumes when welding stainless steel.

Soldering Flux Asthma

Various fluxes—including aluminum solder flux, which contains aminoethylethanolamine, and colophony—have been associated with, and thought to cause asthma. One study documented occupational asthma in 21 percent of workers in the plant of a manufacturer of consumer electronics. Colophony fumes can also induce bronchoconstriction in affected individuals when given as a controlled exposure. However, skin tests and RAST evaluations using extracts of colophony have failed to show positive results in affected workers. Thus, the mechanism(s) of these reactions is unknown. They may very well be secondary to the irritant properties of the fumes.

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Acute and Chronic Responses to Toxic Inhalations

Robert P. Dickson • David A. Schwartz

The lungs and airways are in constant contact with the outside world and thus are especially vulnerable to toxic substances present in the environment. Within seconds of exposure to an inhaled toxin, pathological events occur that may cause immediate distress, systemic illness lasting days, or even lead to the development of chronic lung disease. This chapter discusses the pathology and pathophysiology that can result from various inhaled toxins, and also highlights the role of several common and medically significant toxic inhalants that are known to cause acute and chronic pathophysiological responses in the lung. The chapter also discusses several systemic syndromes caused by acute toxic inhalations. The scope of this chapter does not include chronic exposure to low levels of toxins.

DETERMINANTS AND MECHANISMS OF IRRITANT-INDUCED PULMONARY INJURY

Inhaled toxins exist in many forms and may be categorized by taking into account their physical properties. General categories include gases, vapors, fumes, aerosols, and smoke. A variety of factors determine the pathological results of a toxic inhalation: the size of inhaled particles, solubility of the inhaled substance in water, concentration of the inhalant in ambient air, duration of exposure, presence or absence of ventilation, and a variety of host factors (age, smoking status, co-morbid diseases, use of respiratory protection, and perhaps even genetic susceptibility). While toxic inhalants provoke a broad range of chemical and biologic activities that contribute to pathogenesis, their physical properties, namely their particle size and water solubility, are of fundamental importance in determining the site and severity of pulmonary injury. Tables 59-1 to 59-3 summarize the physical properties of the discussed inhalants that substantially affect the resulting pathogenesis of these agents.

The size of aerosolized particles is of critical importance in inhaled toxin pathogenesis. In general, larger aerosolized particles are more likely to deposit on the nasopharynx via impaction and not gain access to the lower airways, while smaller particles are able to penetrate smaller airways and effect toxicity at the level of the alveolus. Aerosolized

Table 59-1

Definitions of Types of Inhaled Substances

Gas: A formless state of matter in which molecules move freely about and completely occupy the space of enclosure.

Aerosol: A relatively stable suspension of liquid droplets or solid particles in a gaseous medium.
Coarse particles: Particles between 1 and 10 μm.
Fine particles: Particles between 0.1 and 1 μm.
Ultrafine particles: Particles smaller than 0.1 μm.

Vapor: The gaseous form of a substance that normally exists as a liquid or solid and that generally can be changed back to a liquid or solid by either increasing ambient pressure or decreasing the temperature.

Fume: An aerosol of solid particles, generally less than 0.1 μm in size, that arises from a chemical reaction or condensation of vapors, usually after volatilization from molten materials.

Smoke: The volatilized gaseous and particulate products of combustion; the particles are generally less than 0.5 μm in size and do not settle readily.

SOURCE: *Data from Kizer KW: Toxic inhalations.* Emerg Med Clin North Am *2: 649–666, 1984.*

particles larger than 30 to 80 μm are not inhalable through the nose, and particles larger than 5 μm typically do not reach the alveoli. Ultrafine particles (those smaller than 0.1 μm) have been specifically implicated in the toxicity due to the agents of polymer fume fever. Inhaled particles may have direct toxic effects themselves, or they may function as vehicles for adsorbed gaseous agents that are toxic to terminal bronchioles and alveolar cells.

In addition to particle size, the relative solubility of an inhalant in water determines where along the respiratory tract toxicity will occur. Substances with high water solubility, such as ammonia, sulfur dioxide, and hydrochloric acid provoke immediate and evident injury to the conjunctiva and mucosal surfaces of the upper airways; they are largely absorbed by the mucus lining the pharynx and larynx and often react there to form caustic acids and alkalis. The provoked symptoms quickly prompt exposed individuals to flee the area or contain the source of exposure, reducing the duration of exposure. These compounds also can activate irritant receptors in the upper airways, provoking a bronchoconstrictor reflex that may further limit access of the inhalant to lower airways. In contrast, compounds such as phosgene and ozone have low

Table 59-2

Water Solubility and Mechanisms of Lung Injury of Gaseous Respiratory Irritants

Irritant Gas	Water Solubility	Mechanism of Injury
Ammonia	High	Alkali burns
Chlorine	Intermediate	Acid burns, reactive oxygen species, reactive nitrogen species
Hydrogen chloride	High	Acid burns
Oxides of nitrogen	Low	Acid burns, reactive oxygen species, reactive nitrogen species
Ozone	Low	Reactive oxygen species, reactive nitrogen species
Phosgene	Low	Acid burns, reactive oxygen species, protein acetylation
Sulfur dioxide	High	Acid burns, reactive oxygen species

SOURCE: *Data from Schwartz DA: Acute inhalational injury, in Rosenstock L (ed),* Occupational Medicine: Occupational Pulmonory Disease. *Philadelphia, Hanlay Belfus, 1987, pp 297–318.*

Table 59-3

Water Solubility and Site of Initial Impact of Toxic Irritants

Water Solubility	Initial Level of Impact	Inhalant
High	Nose Pharynx Larynx	Ammonia Chlorine Sulfur dioxide
Medium	Trachea Bronchi	Ozone
Low	Bronchioles Alveoli	Nitrogen dioxide Phosgene

SOURCE: *Data from Balkissoon R: Occupational upper airway disease.* Clin Chest Med *23:717–725, 2002.*

water solubility and thus fail to cause immediate irritation, promoting longer exposure to the inhalant and deeper penetration of the lower airways. Compounds of intermediate solubility (e.g., chlorine gas) typically have pathological effects throughout the respiratory tract. These differences in solubility can be overcome by differences in concentration and duration of inhalant exposure: Virtually any inhaled toxin (even the most soluble agents) can cause diffuse damage of the respiratory tract by overwhelming the absorptive capacity of the upper respiratory tract. Furthermore, adsorption of a toxic gas on particulate matter may permit a toxin access to otherwise unreachable airways.

Host factors also play a significant role in predicting an individual's response to a toxic inhalation. Underlying pulmonary or extrapulmonary disease may worsen a patient's response to an exposure. Children deposit a smaller fraction of inhaled particles in their nasopharynx than adults and thus may be at elevated risk of lower airway exposure and pathology. Moreover, as some gases (e.g., chlorine, sulfur dioxide) are heavier than air, children may be subjected to a longer duration and higher concentration of gas than adults near the same site of toxin release. With particles greater than 0.5 μm, breathing through one's nose increases upper airway particle deposition compared with mouth-breathing; this difference is absent with particles smaller than 0.5 μm. Tobacco smoking impairs ciliary clearance and cellular defense, limiting the exposed patient's ability to clear inhaled particles and prolonging exposure. Patients with increased minute ventilation (e.g., those panicking at the scene of an irritant gas release) are at elevated risk of increased exposure and toxicity. An emerging literature in experiments with inbred strains of mice suggests that genetic variants may alter the risk of responding to various inhaled toxins.

Injury from toxic inhalation may occur via a number of mechanisms. If the concentration of the inhalant is high enough and if ventilation is inadequate, simple asphyxiation due to displacement of atmospheric oxygen may occur. The reflex bronchoconstriction triggered by upper-airway irritant receptor activation may itself cause inadequate oxygen inhalation. Cell injury from acute toxin exposure typically occurs via nonimmunologic mechanisms of injury and inflammation, generally via formation of an acid (chlorine, oxides of nitrogen, phosgene, sulfur dioxide), an alkali (ammonia), or reactive oxygen or nitrogen species (ozone, oxides of nitrogen, chlorine). Acid formation results in coagulation of underlying tissue, while alkali exposure causes a liquefaction of mucosa and characteristically deep lesions within the airways. Reactive oxygen and nitrogen species and their derivatives achieve local tissue damage via lipid peroxidation and protein oxidation, and may cause similar toxicity systemically. Free radicals may be direct derivatives of inhaled substances, or they may be released by alveolar macrophages that are activated by inhalant exposure. All three types of tissue damage generally lead to an increase in expression of proinflammatory cytokines that can perpetuate the acute injury and may be responsible for the development of later sequelae. Disruption and repair of injured airway epithelial tissue may compromise the host's defenses against further infectious or irritant substances. A role played by the innate immune system in disease progression is evident in the case of endotoxin exposure in organic dust toxin syndrome (ODTS), and may be a host factor in the response to ozone and nitrogen dioxide.

PATHOGENESIS AND CLINICAL PRESENTATION OF TOXIC INHALATION INJURY

Upper Airway

Effects of toxins on the upper airways are typically sudden and short-lived compared with those more distal along the respiratory tract; thus, chronic pathology in this region is unusual. Compounds that provoke a response in the nose, pharynx, and larynx tend to be particulate with relatively large average particle size or gases with high water solubility. Acids, alkalis, and reactive oxygen and nitrogen species may all cause tissue injury in this region, depending on the inhaled compound and its reactions along airway epithelium. Characteristic tissue injury depends on dosage and ranges from slight edema of the nasopharynx and larynx to epithelial ulceration and frank hemorrhage. Once the airway epithelium is compromised, it fails to function as a protective barrier against the environment. Underlying inflammatory cells, nerves, muscles, and blood vessels become exposed, which may further the inflammatory response. An obstructive response to some irritants starts to occur at concentrations only barely perceivable as irritating.

The typical presentation of patients with acute exposure of irritant substances to the upper airways includes burning sensations of the nasal passages and throat, copious sputum production, coughing, and sneezing. Extrapulmonary

manifestations include burning of the eyes, profuse lacrimation, headache, and dizziness. The most serious risk in the exposed patient is airway obstruction due to reflex bronchoor laryngospasm, mucosal edema, increased secretions, and sloughed epithelial cells. Patients presenting with hoarseness or stridor should be carefully observed for further evidence of airway compromise. Although inhalational injury confined to the upper airways tends to be self-limited with no or few long-term sequelae, a chronic rhinitis following irritant exposure, *reactive upper airway dysfunction syndrome* (RUDS) has been described, and was observed among World Trade Center rescue workers following the attacks of September 11, 2001.

Patients with acute toxic exposure to the upper airways should be immediately removed from the source, which may require removal of the patient's clothes. The patient's airway should be secured and monitored; racemic epinephrine may be used, but it should not delay endotracheal intubation if necessary. Frequent suction may be required. Profuse amounts of water should be irrigated over exposed surfaces. Supplemental oxygen should be provided if appropriate. Patients with extensive upper airway edema may benefit from corticosteroids,[14] although this is unsupported by clinical trials. Ophthalmological consultation should be sought for management of eye exposure.

Conducting Airways

Acute Injury

As is the case with the upper airways, the conducting airways protect their submucosal structures with epithelia that may be compromised by acute inhalational injury. The resulting edema, inflammation, and bronchoconstriction may be life threatening if it results in an obstructed airway, and without its epithelial barrier the airway is vulnerable to infections and other environmental pathologies. This damage to the epithelium appears to occur at the tight junction interface between cells, resulting in increased epithelial permeability to other irritants, which gain direct access to effector cells within the subepithelial mucosa. Resulting bronchospasm may cause ventilation-perfusion mismatch. The smooth muscle of the airways can be hyperresponsive in the hours and days following irritant exposure, an effect probably mediated by the neutrophilic and eosinophilic inflammatory response inhalational injury provokes.

Conducting airway injury may manifest as intrathoracic airflow obstruction hours after the initial insult. Patients with histories of exposure who present with any evidence of respiratory compromise should be hospitalized for observation, even if asymptomatic. Findings of concern include expiratory wheezing, decreased airflow on peak expiratory flow measurement or spirometry, and abnormalities of gas exchange or an abnormal chest x-ray. Likewise, patients with complaints of dyspnea or chest tightness should be observed carefully and treated symptomatically with inhaled steroids and bronchodilators, even in the absence of objective findings. When significant airflow obstruction is present, systemic steroids may be of some utility.

Chronic Injury

Reactive Airways Dysfunction Syndrome

A persistent asthma-like disease following acute exposure to an irritant inhalant, known as reactive airway dysfunction syndrome (RADS, or "Brooks syndrome")was named in 1985, but observed among World War I soldiers exposed to war gases. Investigation and diagnosis of the disease is generally limited by the absence of spirometry results in patients prior to exposure and the presence of confounding factors (e.g., cigarette smoking), but numerous reports exist of previously asymptomatic patients experiencing hyperreactive airway disease presenting soon after a single toxic exposure and persisting for months or years. RADS is distinguished from immunologic occupational asthma in that it follows a single exposure and does not follow a latency period of sensitization to the offending substance.

The pathogenesis of RADS likely begins with the initial injury to and desquamation of the epithelium, which results in hemorrhage and edema followed by inflammatory changes, and finally long-term structural changes of the airways involving epithelial regeneration and fibrosis. Ensuing airway narrowing may be due to mucosal edema, inflammation, or structural changes to the architecture of the bronchial wall.

RADS typically presents abruptly within 24 hours following exposure with the classic symptoms of obstructive airway disease: wheezing, chest tightness, dyspnea, and cough. The symptoms and obstructive findings on examination and spirometry are relieved by bronchodilators, although not as effectively as in other types of reactive airway disease (perhaps due to chronic fibrotic remodeling of the conducting airways). The disease can persist for months and may be permanent in some instances. Anecdotally, inhaled corticosteroids have shown benefit in relieving airflow obstruction. Systemic corticosteroids have been proven beneficial in an animal model of RADS.

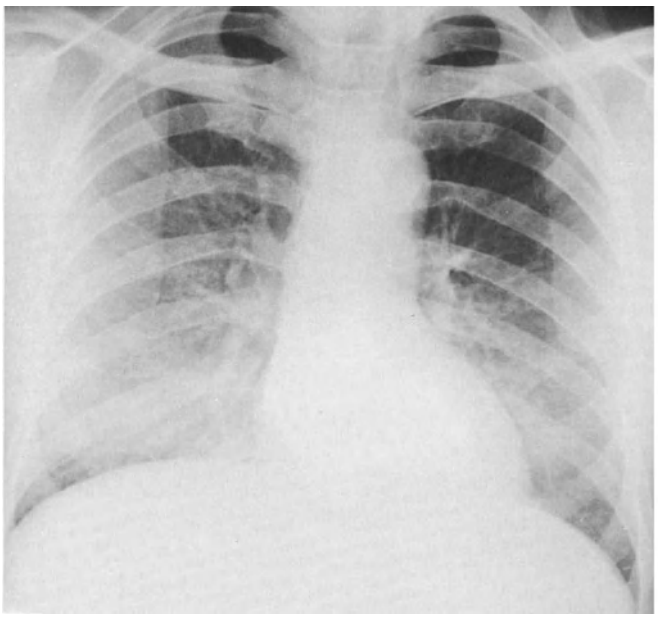
Vocal Cord Dysfunction

Vocal cord dysfunctionmay also follow a single acute irritant exposure and may be confused with RADS. The disorder may be caused by reflex response to nerve stimulation by irritants. Patients suspected of having RADS who do not respond appropriately to bronchodilators should be evaluated for vocal cord dysfunction; direct laryngoscopy is the gold standard of diagnosis.

Lower Airways and Pulmonary Parenchyma

Acute Injury

Although all toxic inhalants are capable of producing distal airway disease at extreme concentrations and durations, the gases most likely to do so are those with low water solubility such as phosgene and nitrogen dioxide, which bypass reflex bronchoconstriction and absorption by upper airway mucous (Fig. 59-1). The initial pathological events in distal



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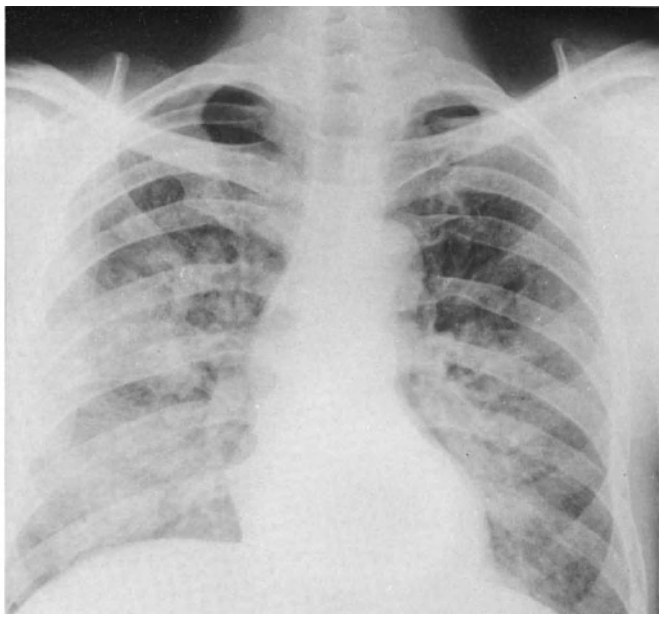

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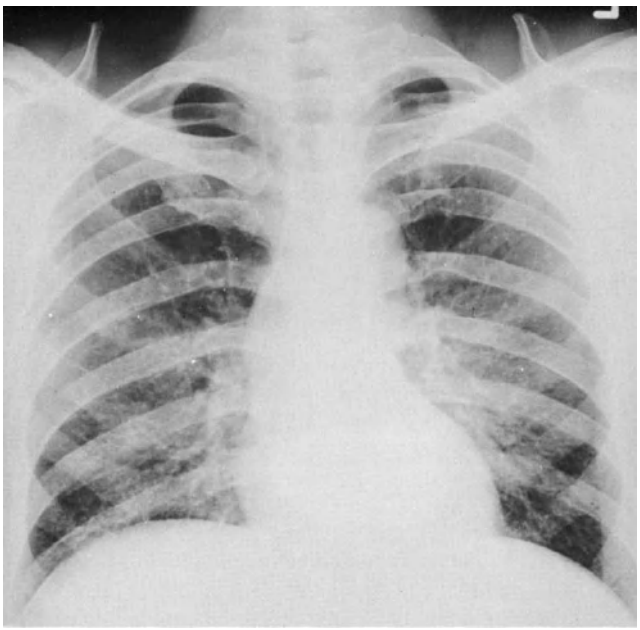


C

Figure 59-1 Accidental exposure of 55-year-old mechanic to spill of liquid Cl_2, followed immediately by coughing and dyspnea. *A*. Day of exposure. Bilateral alveolar infiltrates, most marked on right. *B*. Two days later. Progression of alveolar infiltrates. *C*. Seven days later. Incomplete resolution of infiltrates associated with persistent shortness of breath.

airways are caused by the cellular toxicity of the inhaled agent and its derivatives, which compromise the impermeability of the alveolar-capillary interface. Some of this cytotoxicity may be derived indirectly from reactive oxygen species released from activated inflammatory cells. In the absence of an intact alveolar-capillary interface, profound pulmonary edema may develop that impairs gas exchange and can prove fatal. The severity of this pulmonary edema, which typically presents after a latent period of several hours following the initial insult, is likely dose related. This process may cause no more than slight dyspnea and cough with a mild alveolar infiltrate, or may progress via diffuse alveolar damage to adult respiratory distress syndrome (ARDS). For this reason, patients with exposure to gases capable of causing distal airway disease should be hospitalized and monitored for symptoms of respiratory distress and with serial chest x-rays for at least 24 hours following exposure. Development of ARDS from toxin exposure likely shares a common pathway with other causes of acute lung injury, and management is similar: supportive care with mechanical ventilation, careful control of blood glucose, surveillance for infection, and deep venous thrombosis prophylaxis. Diuresis, IV corticosteroids, prone positioning, nitric oxide inhalation, and exogenous surfactant are all unsupported by clinical trials but are potentially of some benefit. Diffuse bronchiolitis also has been reported following acute exposure.

Chronic Injury

Bronchiolitis Obliterans

Bronchiolitis obliterans (BO) is a well-documented but infrequent long-term sequela of toxic gas exposure, especially of nitrogen dioxide, but also to ammonia, mercury, and sulfur dioxide. The disease typically presents 1 to 3 weeks following the initial lung injury and pulmonary edema (Fig. 59-2). The interim is often free of symptoms. When BO does develop, patients may present with dyspnea on exertion or obstructive findings on spirometry. Physical examination may be either unremarkable or remarkable only for early inspiratory crackles. Chest x-ray is either normal or demonstrates hyperinflation. Pulmonary function tests typically demonstrate airflow obstruction that may in some cases also be associated with restrictive defects. On biopsy, granulation tissue is seen in the lumen of small airways and bronchiole walls may be obliterated by fibrous scarring. Corticosteroids may be of benefit in preventing or alleviating BO if administered early in the course of the disease, although this is controversial.

Bronchiolitis Obliterans Organizing Pneumonia

Bronchiolitis obliterans organizing pneumonia (BOOP) is another observed delayed sequela of toxic inhalation. Patients present in the weeks following exposure with fever, a persistent and nonproductive cough, sore throat, and malaise. Late inspiratory crackles may be observed. Chest x-ray may reveal bilateral patchy "ground glass" densities that start as focal lesions but may coalesce with time. Pulmonary function tests generally reveal a restrictive process with decreased diffusion capacity. Histologically, granulation tissue extends past the terminal bronchioles and into the alveolar spaces, sometimes with interstitial scarring. BOOP and BO are probably both chronic results of the initial inflammatory response to the toxic insult and the ensuing proliferative process. BOOP responds well to corticosteroids, although a small number of patients may develop progressive fibrosis. Duration of therapy should be guided by the patient's clinical status.

EFFECTS OF SPECIFIC INHALED TOXINS ON THE RESPIRATORY SYSTEM (TABLE 59-4)

Ammonia

Ammonia (NH_3) is a water-soluble nitrogen-containing compound that ranks among the most commonly spilled hazardous substances. Familiar to all as a household cleaner, it also has countless uses in industry: as a chemical coolant used for refrigeration, a fertilizer, a fixative in photocopiers, and in the manufacture of polymers and explosives. Small amounts are naturally present in the atmosphere as products of the putrefaction of vegetable and animal proteins. The smell of concentrated ammonia is immediately recognizable due to the prevalence of ammonia in household cleaners and its use in smelling salts (which exploit the noxious effect of ammonia on nasal membranes to arouse consciousness). Ammonia is frequently dissolved into water for storage and transportation, and vaporizes readily on exposure to air. Most inhalation exposures are the result of accidental releases, including tank leaks and transportation mishaps, and most exposures occur in the industrial workplace. A recently reported source of exposure is via fumes produced in clandestine methamphetamine laboratories.

Ammonia tends to affect the proximal airways, where it reacts rapidly with the water present on mucosal surfaces to form ammonium hydroxide, causing tissue liquefaction. This necrosis liberates formerly intracellular water, which serves as further reactant for ammonia, perpetuating the reaction. In addition to the alkali burns caused by the generated ammonium hydroxide, thermal burns can result from the heat generated by this exothermic reaction. The resulting injury, typical of alkali burns, penetrates deeply. The initial injury to the mucosa of the oropharynx can cause edema, hemorrhage, sloughing of tissue, and increased secretions that can bring about fatal upper airway obstruction. Ammonia is directly caustic to airways at concentrations of 1000 ppm and higher.

Although concentrated at the proximal airways, the effects of ammonia have been observed at all levels of the respiratory tract. The penetration of the gas to the smaller airways and alveoli is a function of its concentration and the duration of exposure. Reported acute conditions associated with ammonia exposure include pulmonary edema, laryngitis/tracheobronchitis, bronchiolitis, and bronchopneumonia; reported chronic sequelae include bronchiectasis, bronchospasm/asthma (termed reactive airways dysfunction syndrome), and chronic obstructive pulmonary disease. There are several reports of interstitial lung disease following a single exposure to ammonia. A biphasic pattern of pulmonary response to ammonia inhalation has been reported, characterized by initial, acute pneumonitis that may clear over the next 2 to 3 days, followed in some individuals by the gradual development of airway obstruction and respiratory failure. There may be a correlation between the contraction of a bacterial superinfection after exposure with the ensuing development of bronchiectasis. In one review of published case reports, 21 percent of patients with acute ammonia inhalation died within 60 days of exposure. The most common causes of death were laryngeal edema and obstruction, noncardiogenic pulmonary edema, and extensive pneumonic complications.

Management of a patient who has experienced ammonia inhalation requires removing him or her from the source of the irritant, securing the airway, and immediately irrigating all exposed surfaces (especially the eyes) with copious amounts of water. Airway management should be aggressive, given the frequency of laryngeal edema in exposed patients. Rales detected on physical exam are predictive of the subsequent hospital course, even in the absence of hypoxemia and chest x-ray abnormalities. Medical management is largely supportive. Corticosteroids and antibiotics are both frequently used, but both are unproved in human trials.

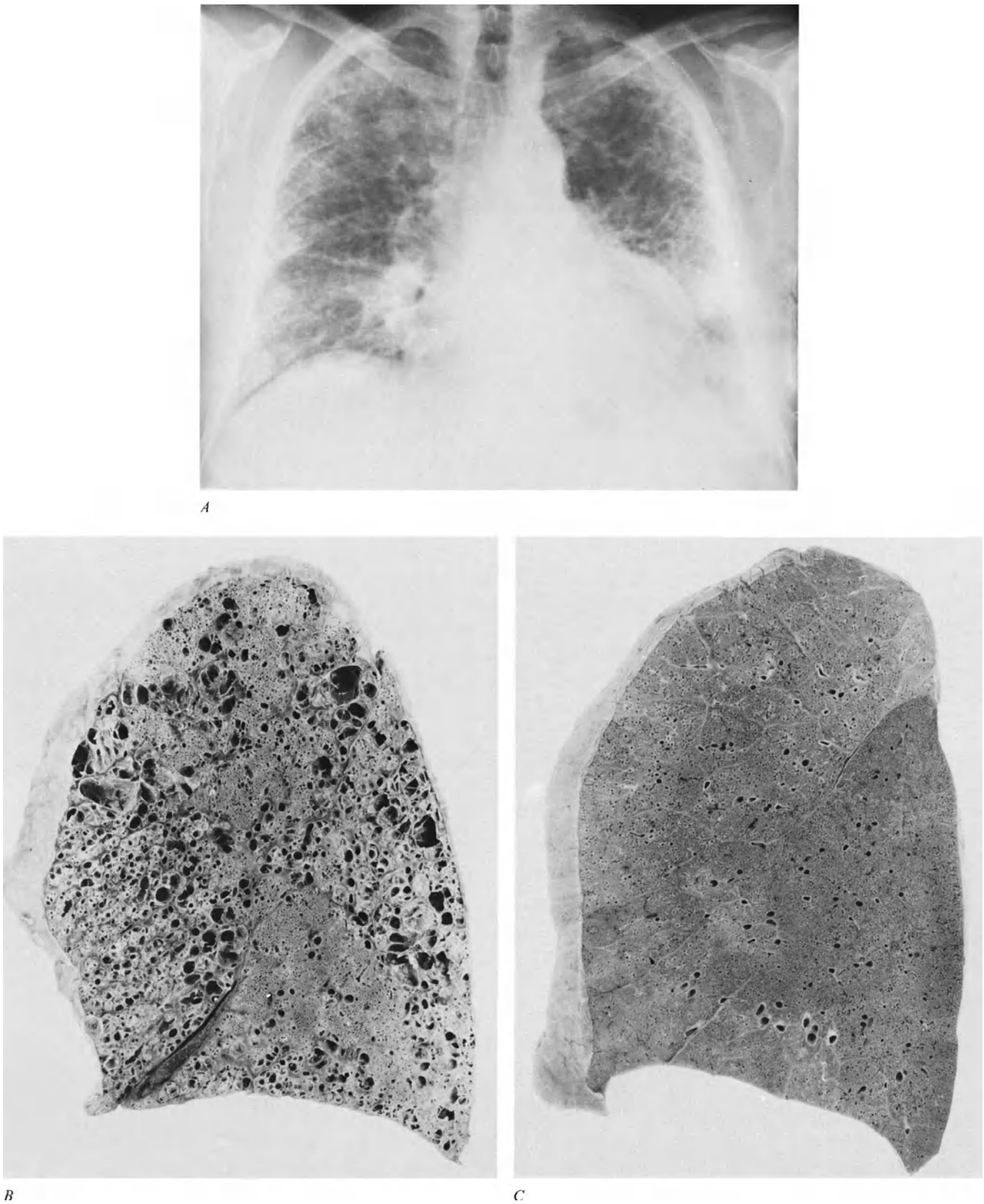


Figure 59-2 Bronchiolitis obliterans in a 63-year-old man who had been exposed to a wide variety of unidentified fumes in his jobs, which included welding. *A*. Chest radiograph. Diffuse pulmonary fibrosis and honeycombing, most marked in the peripheral portions of the lungs. *B*. Sagittal section of lung from same patient showing markedly dilated airspaces. Microscopic sections revealed bronchiolitis obliterans and chronic interstitial pulmonary fibrosis. *C*. Normal lung from a 43-year-old man who died suddenly. The difference between *B* and *C* in the alveolar portions of the lungs is striking. *(Courtesy of Dr. R. Ochs.)*

Table 59-4

Pulmonary Manifestations of Toxin Inhalation

	Acute Clinical Manifestations			Chronic Clinical Manifestations	
Substance	**Onset**	**Upper Airway Irritation**	**Pneumonitis, ARDS**	**Bronchiolitis Obliterans, BOOP**	**RADS**
Irritant gases					
Ammonia	Minutes	Severe	+	+	+
Chlorine	Minutes to hours	Moderate	+	−	+
Hydrogen chloride	Minutes	Severe	+	−	+
Oxides of nitrogen	Hours	Mild	+	+	+
Ozone	Minutes to hours	Mild	+	−	−
Phosgene	Hours	Mild	+		+
Sulfur dioxide	Minutes	Severe	+	+	+
Metals					
Cadmium	Hours	Mild	+	−	−
Mercury	Hours	Mild	+	+	−
Zinc chloride	Minutes	Mild	+	−	+
Zinc oxide	Hours	Mild	+	−	−

Note: Abbreviations: + = exposure reported to be associated with clinical entity; − = exposure as yet not reported to be associated with clinical entity.

Chlorine, Chloramines, and Hydrochloric Acid

Chlorine (Cl_2) is a common gas of intermediate water solubility. The first reports of its toxicity followed its use as an agent of chemical warfare in World War I, and war gassings remain the largest historical source of chlorine gas exposure. Most exposures since then have occurred in the industrial setting, where chlorine is used in the manufacture of paper, cloth, antiseptics, and other products. More common in the household is the liberation of chloramines and other toxic chlorine derivatives from the reaction of chlorine-containing products (e.g., hypochlorite bleach) with ammonia or products containing hydrochloric or phosphoric acid. Numerous exposures to chlorine gas have occurred near swimming pools, where chlorine-releasing agents (e.g., calcium hypochlorite and chlorinated isocyanuritic acids) are used in water purification. Chlorine gas is greenish-yellow in color and is heavier than air. Although its odor is distinct, patient exposure to it may be prolonged compared with other toxic gasses due to its delayed irritation of mucosal surfaces and its high density, which keeps it low to the ground.

The pathogenicity of chlorine gas derives directly from elemental chlorine's effects on the respiratory tract and indirectly from its reaction with water to form hydrochloric acid (HCl) and hypochlorous acid (HOCl). The character and distribution of injury from chlorine exposure varies according to duration of exposure and the relative concentrations of elemental chlorine and its derivative compounds. HCl and HOCl possess considerable water solubility and are responsible for the tissue damage sustained by the upper airways and ocular conjunctivae. Irritation to trigeminal nerve endings caused by these compounds can cause a reflex bronchoconstriction that may contribute to compromise airway diameter. In addition to causing the tissue coagulation typical of acid exposures (described above), these compounds ionize and enter cells, where they may form reactive oxygen species. HOCl has been shown to react with nitrite (NO_2^-) to produce reactive nitrogen-containing compounds able to nitrate, chlorinate, and dimerize phenolic amino acids. As nitrite and nitric oxide (its parent compound) levels are elevated at sites of tissue inflammation, this potentially is another mechanism of injury. Although lower respiratory tract irritation has been reported following high-level exposures, less than 5 percent of inhaled chlorine gas penetrates beyond the upper airways. Fatal dosages from chlorine inhalation have ranged from 50 to 2000 ppm.

The immediate clinical manifestations of acute chlorine exposure are typical of irritants of its solubility: rhinitis, cough, dyspnea, wheezing, and chest tightness, along with conjunctivitis and skin irritation. When chlorine gas exposure has resulted acutely in death, autopsies have revealed diffuse ulcerative tracheobronchitis, pulmonary edema, thrombi within pulmonary vessels, and denudation of respiratory tract epithelium. Acute respiratory symptoms are more prevalent and severe among patients who already have chronic respiratory disease.

The lasting respiratory sequelae of chlorine gas exposure have been described since the years following use of the gas in World War I. Reported long-term pulmonary diseases following exposure have included both restrictive and obstructive processes, frequently resolving to normal function within a month and almost always before two years

following exposure. Reactive airways dysfunction syndrome may be an infrequent sequela of high-level exposures to chlorine.

Patients who have been exposed to chlorine gas should be managed according to the severity of their presenting symptoms similarly to other victims of irritant inhalation. Nebulized sodium bicarbonate has shown promise as a useful treatment, but lacks supporting clinical trials and showed no outcome benefit in a relatively large observational study of chloramine gas exposure. Beta agonist bronchodilators and humidified oxygen are frequently used and are probably of benefit. The reported benefit of corticosteroid administration is anecdotal and unconfirmed by clinical trial.

Sulfur Dioxide

Sulfur dioxide is a heavy, colorless, and highly water-soluble gas that has the distinct, pungent odor of burnt matches. It is generated in the combustion of coal and petroleum and is often used as a preservative in alcoholic beverages and fruit. Industrial exposures have occurred around ore smelting, sugar refining, and the bleaching of wool and wood pulp. Sulfur dioxide is among the most harmful gases released to the atmosphere during volcanic eruptions. In 1986 the gases emitted from one eruption killed nearly 2000 people in Cameroon. Sulfur dioxide's great density keeps it low to the ground and slow to dissipate from sites of release; thus, children may be at an increased risk of exposure.

Sulfur dioxide reacts with water present on mucous membrane to form sulfuric acid, which causes tissue coagulation in underlying exposed surfaces. Sulfuric acid also further dissociates into hydrogen ions, sulfite, and bisulfite, which can then react with oxygen to produce reactive oxygen species; ensuing lipid peroxidation may be a contributing mechanism of injury to immediate tissues and elsewhere.

Exposures of high enough intensity can irritate both upper and lower airways. Patients exposed typically present with dyspnea, burning of the nose and throat, rhinorrhea, cough, and airway obstruction. Proximal airway injury is characterized by acute denudation of the airway mucosa without inflammatory cell infiltrates. When lower airways are exposed, alveoli fill with fluid due to noncardiogenic pulmonary edema and the clinical picture is consistent with ARDS. Alveolar architecture is generally preserved. Extremely high-intensity acute exposures can lead within minutes to death from respiratory failure due to a combination of alveolar hemorrhage and edema, possible reflex vagal stimulation, and the asphyxiating effect of high concentrations of sulfur dioxide. Reactive airways dysfunction syndrome has been reported following single sulfur dioxide exposure. Bronchitis has also been observed. One pattern of postexposure progression reported is a rapid recovery followed several weeks later by the onset of irreversible airflow obstruction due to bronchiolitis obliterans. Sulfur dioxide is detectible to humans at 3 to 5 ppm and is lethal at levels exceeding 400 ppm for 1 minute.

Care for patients who have been exposed to sulfur dioxide is supportive: humidified supplemental oxygen, bronchodilators, and intubation and ventilation if necessary. The use of corticosteroids in the setting of ARDS following sulfur dioxide exposure has not been shown to be of benefit, but a trial is not unreasonable. Antibiotics may be reserved for use upon evidence of infectious complications.

Nitrogen Oxides

Nitrogen oxides are ubiquitous air pollutants, released from automobile engines and the combustion of coal and petroleum and present in cigarette smoke. High-level acute exposure is most likely to occur in industrial settings, including mining, acetylene welding, and explosives manufacturing. A well-known form of exposure occurs in "Silo-filler's disease," in which farmers inhale concentrated nitrogen dioxide gas released within silos by decomposing nitrogenous biomaterial. Exposures to high levels of nitrogen dioxide have been attributed to blast furnaces, anesthetic gases, military incidents, and ice hockey arenas. Nitrogen dioxide is a liquid at room temperature and a reddish-brown gas above 70°F.

Nitrogen dioxide is hydrolyzed by the water on mucosal surfaces to form nitric and nitrous acid, although much of its toxicity is explained via the free radical activity of nitrogen dioxide itself and the nitrites and nitrates that derive from it. Although the predominant site of toxicity from nitrogen dioxide exposure is the interface of the terminal bronchioles and alveolar membranes, the relative insolubility of nitrogen dioxide in water ensures that enough gas penetrates the upper airways such that injury can occur virtually anywhere along the respiratory tract. Nitrogen dioxide itself is a reactive nitrogen species that, along with other reactive derivatives, is capable of lipid peroxidation and protein oxidation, both of which may be significant contributors to the gas's toxicity via disruption of the cell membrane. Mice with defective Toll-like receptor 4 expression exhibit a lessened response to nitrogen dioxide exposure compared with normal strains, suggesting that the patient's innate immunity may play a role in disease development. There is also evidence that nitrogen dioxide exposure is mutagenic to lung cells.

The initial effects of nitrogen dioxide exposure are relatively benign at all but very elevated concentrations: cough, fatigue, and occasionally nausea. With high-intensity exposure, patients also may experience headache and chest tightness, although even these symptoms tend to resolve promptly. Nitrogen dioxide is less irritating to mucosal surfaces than other toxic inhalants. Symptoms typically abate for a period of hours before an intense pulmonary edema consistent with ARDS occurs due to increased capillary permeability following extensive damage to vascular and airway epithelium. Patients who survive this are at risk for the development of bronchiolitis obliterans and bronchiolitis obliterans organizing pneumonia 1 to 4 weeks following exposure.

This clinical course of nitrogen dioxide toxicity demands vigilant monitoring on the part of medical personnel. Patients who are relatively asymptomatic following exposure may rapidly progress to ARDS within hours or severely obstructive bronchiolitis obliterans within weeks. Treatment is largely supportive. In animal studies, antioxidant administration has proved protective against lung injury following

nitrogen dioxide exposure, suggesting that aerosolized antioxidant medications are potentially of some utility in humans. Interestingly, nitric oxide (NO) has been used successfully as a pulmonary vasodilator in the treatment of ARDS following acute nitrogen dioxide toxicity. Individuals who survive the initial lung injury still require close following with serial assessment of pulmonary mechanics and gas exchange over the ensuing several weeks. Patients exhibiting evidence of progressive airflow obstruction may benefit from corticosteroids to prevent or decrease the severity of bronchiolitis obliterans.

Phosgene

Phosgene (carbonyl chloride, $COCl_2$), like nitrogen dioxide, has relatively low water solubility and penetrates deeply to the alveolar spaces. It is colorless, lacks a strong odor (in high concentrations it is reported to smell like moldy hay) and is not irritating to the nasal and oral mucosa. These traits were notoriously exploited in World War I, when phosgene was used by both sides of the conflict as a weapon, resulting in tens of thousands of fatalities. Modern uses include the production of pesticides, polyurethane resin, toluene diisocyanate, pharmaceutical products, and dyes. It also can be produced accidentally via the heat decomposition of various solvents, paint removers, dry cleaning fluids, and methylene chloride.

Phosgene reacts with water to form hydrochloric acid and carbon dioxide, but its limited solubility results in little hydrolysis in the upper airways. In the relatively moist alveolar air spaces, however, the resulting acid is destructive of alveolar walls and small vessels, resulting in epithelial necrosis. Phosgene's lack of irritability in the upper airways precludes the reflex bronchoconstriction provoked by other toxic gases, ensuring open passage of the gas to the alveoli. Phosgene also causes tissue damage by rapidly acetylating the amino, hydroxyl, and sulfhydryl groups of proteins, resulting in protein denaturation and structural compromise of cell membranes, leading to a breakdown of the blood-air interface. Lipid peroxidation has also been shown to occur, and antioxidant therapy has been shown to attenuate phosgene's effects in animal models.

On exposure to phosgene, patients may experience chest tightness, wheezing, or cough; some victims experience no immediate symptoms. Following exposure, the patient experiences a latent period of 30 minutes to 8 hours before the onset of symptoms. The duration of this latent period is thought to be inversely proportional to both the severity of exposure and the ensuing severity of disease. The latent period is typically followed by pulmonary edema: The patient experiences dyspnea, cough and respiratory distress, and rales and cyanosis are appreciable on physical examination. Although survival for patients with acute phosgene exposure is good, numerous long-term sequelae have been reported, including prolonged exertional dyspnea, chronic bronchitis, and emphysema.

During the latent period following exposure, numerous therapeutic options exist that may prevent or lessen the severity of pulmonary edema. Corticosteroids are frequently used but of unproven benefit. Ibuprofen, *N*-acetylcysteine, aminophylline, and isoproterenol have all proven beneficial in animal models.

Ozone

Ozone (O_3) is a colorless, odorless gas of low water solubility. It is found throughout the atmosphere and occurs in greatest concentrations in the stratosphere, where it is protective against ultraviolet radiation. It is the main oxidant pollutant in smog and can reach hazardous levels at ground levels on days with elevated atmospheric temperature. Atmospheric levels are known to aggravate chronic lung diseases such as asthma[99] and chronic obstructive pulmonary disease. Acute toxic exposures are associated with its uses in industry, including bleaching of fabrics, disinfecting water and surfaces, and the manufacture of plastics. Reports of acute ozone exposure have been reported in an airplane cabin on a high-altitude flight.

Ozone is extremely reactive, and is almost entirely consumed before crossing a single bilayer membrane. It results in the formation of reactive nitrogen species and probably causes toxicity via the oxidation of membrane lipids. It induces epithelial necrosis and airway inflammation and in severe exposures can cause dyspnea, cyanosis, and pulmonary edema. A genetic component to the response to ozone has been reported. Treatment is supportive and no specific therapies have been shown to be beneficial.

Cadmium

Cadmium is a highly corrosion-resistant metal with many industrial applications. Most cadmium is used in nickel-cadmium batteries, although it is also found in alkaline accumulators, electroplating, bearings, solder, and as a barrier around nuclear fission generators. It is present in many metal ores, and cadmium-containing pigments are used in paints, artists' colors, rubber, plastics, printing inks, wallpaper, leather, glass, and enamels. Most inhalations occur to workers who are involved with soldering, brazing, smelting, and refining. The heating of sheet metal electroplated in a cadmium cyanide bath has been reported to cause cadmium toxicity.

The mechanisms involved with the acute lung injury due to cadmium inhalation are not well defined. Postmortem examinations of individuals who died after accidental acute inhalation exposure have revealed tracheobronchitis, consolidated lungs, denuded bronchial epithelium, intra-alveolar hemorrhage, and the presence of macrophages in the alveolar spaces. It is known that cadmium inhibits the synthesis of plasma alpha 1-antitrypsin, which may explain the correlation between cadmium exposure and the later development of emphysema. Rats exposed to cadmium fumes and cadmium chloride aerosols develop pulmonary edema and on necropsy show increased numbers of alveolar type II cells.

When cadmium-containing materials are heated, cadmium vapors and cadmium oxide fumes are released. Patients who are exposed initially present similarly to those with metal fume fever (see below): They are asymptomatic for several hours before developing fever, malaise, and myalgias. These constitutional symptoms are often accompanied by or shortly followed by respiratory distress, including cough, chest tightness, and dyspnea. Cadmium may be detected in the urine if the identity of the toxin is uncertain. Fatal cases have been remarkable for initial pneumonitis that relentlessly progresses to ARDS and eventual death from respiratory failure. Management is supportive; there are no specific treatments for cadmium inhalation.

Mercury

Although mercury has a low solubility in distilled water, its solubility increases in contact with plasma or whole blood, as at the blood-air interface. Sources of mercury gas exposure are primarily industrial and include ore smelting, cement production, fur and felt hat manufacture, fossil fuel combustion, and gold extraction. Mercury is found within the silver amalgam used by dentists, and a number of exposures, including several with fatal outcomes, have occurred in the home during amateur attempts to extract precious metals from amalgams that also contain mercury.

Like phosgene and cadmium, mercury vapor has little or no immediate upper airway or mucosal surface irritant effects, and as a result exposed individuals may inadvertently remain in an area where the harmful vapors are present. Typical clinical presentations include symptoms of cough, dyspnea, and respiratory distress that develop 12 to 24 hours postexposure. Sometimes these initial symptoms are accompanied by fever, nausea, vomiting, diarrhea, and a metallic taste in the mouth, similar to what is often experienced by individuals with metal fume fever and associated transient pneumonitis. In fact, mercury vapor inhalation can be mistaken for metal fume fever or influenza. However, symptoms of mercury vapor inhalation do not spontaneously resolve as with metal fume fever. Instead, the pneumonitis may progress to ARDS; death has been preceded in several reports by tension pneumothorax. The toxicity of mercury vapors within the lung is thought to be due in part to the irritant effects of oxidized mercurous and mercuric ions and the disruption of enzyme systems containing sulfhydryl groups. Mercury coagulates protein, blocks cellular metabolism of carbohydrates at the pyruvic oxidase level, and as a result produces a metabolic acidosis. Lung pathology following acute exposure reveals pulmonary edema, capillary damage, and the desquamation and proliferation of airway epithelium followed by an obliteration of airspaces. Inhaled mercury vapor is absorbed rapidly into the blood, where it can achieve systemic toxicity; renal, hepatic, and nervous system pathology have been reported. Patients surviving the acute injury typically experience resolution of their symptoms within 1 week following onset, but have also progressed to develop interstitial fibrosis. Mortality due to exposure may be increased in children.

Blood levels of mercury may reflect acute uptake, and urine levels can monitor chronic stores. Treatment of mercury inhalation is supportive and addresses the acute lung injury. Mechanical ventilation, including positive pressure and high-frequency oscillating ventilation, may be beneficial in the treatment of mercury-induced ARDS. Corticosteroids have no proven benefit. Chelating agents, such as dimercaprol and d-penicillamine, are frequently used to increase the rate of mercury excretion after ingestion, but have not been shown to affect the outcome of the acute lung injury.

Zinc Chloride

Zinc chloride ($ZnCl_2$, or hexite), a major ingredient of smoke bombs and smoke-generating devices, has been responsible for numerous toxic and fatal exposures. The compound forms when zinc oxide is ignited with hexachloroethane. Toxic inhalations have occurred in settings in which individuals have inhaled smoke in confined spaces, in most instances without functional protective breathing apparatus (Fig. 59-3). The smoke effect tends to contribute to the duration of exposure by obscuring vision, sometimes resulting in directional disorientation and the inability to quickly escape the area of exposure.

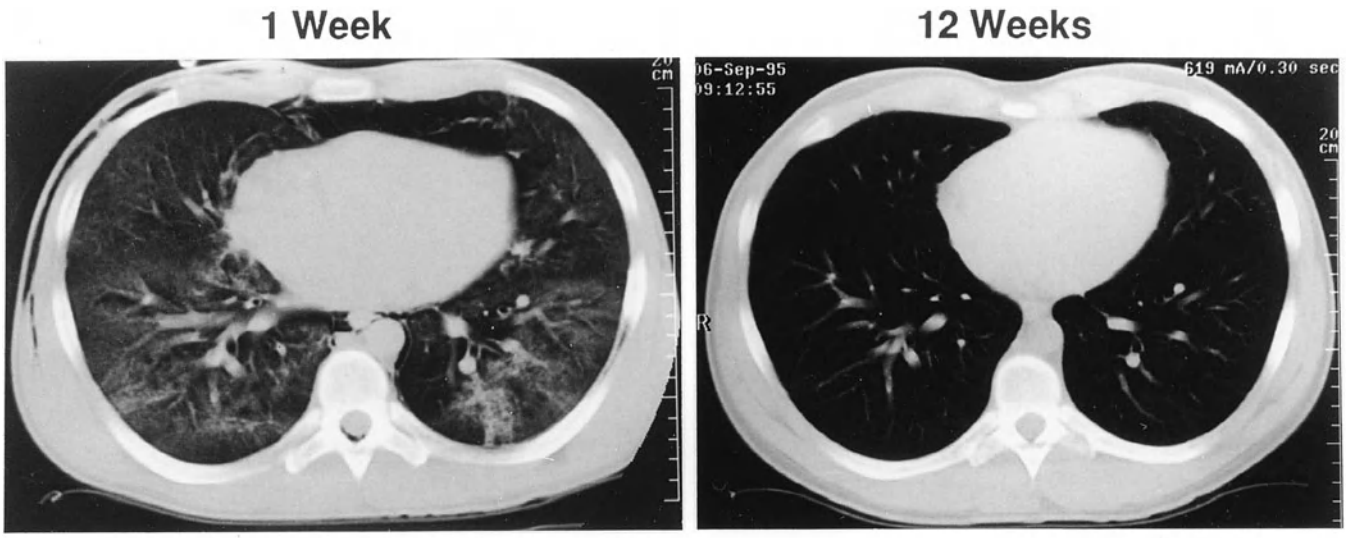
When inhaled, zinc chloride is in particulate form with an average particle size of 0.1 μm, small enough to allow large amounts of it to penetrate through to the lower respiratory tract. After depositing on the airway and alveolar surfaces, zinc chloride reacts with water to form hydrochloric acid and zinc oxychloride. This directly causes irritation of exposed mucosal surfaces and is the probable mechanism behind the diffuse lung injury observed on exposure.

Zinc chloride inhalation is commonly followed by tracheobronchitis and pneumonitis, reflecting the sites of particle deposition. Patients experience cough, dyspnea, and chest tightness followed by a period of relative stabilization before progressing to ARDS. Chest imaging may be normal initially but can reveal pleural effusions, pneumomediastinum, and bilateral infiltrates consistent with pneumonitis. There is evidence that prominence of ground glass opacities observed on high-resolution CT imaging is predictive of both severity of exposure and length of hospital stay.

A urine zinc level may confirm the diagnosis of zinc inhalation toxicity. Patients should be monitored for progression to ARDS and treated with supplemental oxygen and mechanical ventilation if indicated. The administration of high doses of *N*-acetylcysteine may accelerate systemic zinc clearance, and thereby spare some oxidant-induced lung injury, although this is unsupported by clinical experience. Corticosteroid use is similarly controversial.

Mace and Tear Gas

"Tear gas" is the name collectively given to chloroacetophenone (CN or "chemical mace"), *ortho*-chlorobenzylidene malonitrile (CS) and oleoresin capsicum (OC or "pepper spray"). All three agents are used by military and law



	1 week	3 weeks	12 weeks
FVC	2.5 (54%)	3.2 (68%)	5.7 (119%)
FEV_1	2.2 (52%)	3.0 (69%)	4.7 (107%)
FEV_1/FVC	88%	75%	83%
TLC	3.6 (61%)	4.9 (82%)	6.9 (114%)
RV	1.1 (90%)	1.3 (106%)	1.2 (94%)
DLCO	14 (44%)	19.1 (58%)	48.7 (141%)

Figure 59-3 Chest computed tomography (CT) scan and pulmonary function tests obtained on a person with inhalation injury after a smoke bomb was ignited in an underground cave. The CT scans were obtained 1 week and 12 weeks after the accident and demonstrated extensive interstitial lung disease, which resolved on radiographs. The pulmonary function tests obtained 1, 3, and 12 weeks after the exposure demonstrated marked restrictive lung function and abnormal gas exchange, which also resolved within 3 months of exposure.

enforcement agencies to control crowds and individuals, making use of their intense and immediate irritant effects on mucous membranes and lacrimal glands. Exposure to any of them results in immediate rhinorrhea, mucositis, chemical conjunctivitis, and profuse lacrimation. Immediate pulmonary effects include an intense burning sensation in the upper airways, reflex airway constriction, chest tightness, dyspnea, and cough. Exposure also may provoke nausea, headache, and photophobia. Severity of response depends on the concentration of the agent used, duration of exposure, and presence or absence of ventilation and protective breathing apparatus.

The effects of tear gas are predominantly due to its upper airway irritant effects, and thus lower airway injury and parenchymal disease is rarely observed. Auscultation of the chest is typically clear, and the chest radiograph is usually without abnormality. Case reports of severe pulmonary disease exist, describing pneumonitis, pulmonary edema, reactive airways dysfunction syndrome, and acute bronchospasm in an asthmatic. These cases have in common prolonged periods of exposure with poor ventilation. A fatal hypersensitivity reaction to CS has been reported.

The most immediate concern in the treatment of tear gas exposure is maintenance of a patent airway. Mucosal surfaces should be irrigated profusely, and suction may be useful in clearing the copious oral and nasal secretions that may compromise the airway. Humidified O_2 should be administered and beta agonists should be used in the presence of bronchospasm. No benefit from corticosteroids has been observed. Patients with prolonged or intense exposure should be monitored carefully for evidence of progression to significant respiratory disease.

SYSTEMIC ILLNESS FROM INHALED TOXINS

Systemic, flulike illness lasting under 2 days has been observed in patients exposed to organic dusts and fumes of heated

metals and fluorocarbons. The disease course is self-limited and in all cases appears to be cytokine mediated.

Metal Fume Fever

Since its first description by Potissier in 1822, metal fume fever has been known by a number of other names: brazier's disease, smelter shakes, brass chills, zinc chills, welder's ague, copper fever, foundry fever, and Monday morning fever. It is a self-limited syndrome characterized by the delayed onset of fever, chills, myalgias, and generalized malaise following exposure to fumes that contain metal oxides. Specific fumes that have been blamed include those of beryllium, cadmium, copper, magnesium, nickel, silver, and zinc. Welders are at the highest risk for metal fume fever contraction, although it has been reported in other metalworking occupations including soldering, brazing, cutting, metallizing, forging, melting, and casting. Episodes of varying severity of metal fume fever may be experienced by between 20 percent and 35 percent of all welders. Exposure is typically associated with confined spaces and poor ventilation. An estimated 2000 cases of metal fume fever are reported each year in the United States.

The typical course of metal fume fever begins with sensations of dry throat and a sweet or metallic taste. Fever, chills, and myalgias develop 4 to 8 hours after exposure and spontaneously resolve within 48 hours. Respiratory-related symptoms of chest tightness, nonproductive cough, and dyspnea are sometimes observed. Laboratory findings are remarkable for transient leukocytosis. Chest x-ray is typically normal, although findings consistent with pneumonitis have been observed. Pulmonary function tests are usually normal, although obstructive and restrictive deficits, as well as abnormalities of diffusion, have been reported. Repeated exposure appears to lead to tachyphylaxis; the name "Monday morning fever" refers to the recurrence of acute disease on return to exposure following a short period of absence. The disease has been mistaken for influenza, atypical or community-acquired pneumonia, and a malaria-like illness because of overlapping presenting symptoms. Metal fume fever is generally thought to have no long-term sequelae. An association between it and the later development of occupational asthma has been observed, but a prospective study failed to show that a history of metal fume fever is predictive of later bronchial hyperresponsiveness.

The pathogenesis of metal fume fever appears to involve an increase in proinflammatory cytokine activity in the lung; increased bronchoalveolar lavage fluid concentrations of tumor necrosis factor (TNF), interleukin-6 (IL-6), and interleukin-8 (IL-8) have been reported in subjects exposed to zinc oxide fumes, probably produced by pulmonary macrophages. Following exposure, bronchoalveolar lavage TNF-α levels peak earlier than other cytokines, suggesting that its role may be central to disease progression. Of the numerous components of metal fumes, it appears to be the soluble transition metal particles, which generate reactive oxygen species and deplete glutathione stores, that are responsible for the fumes' cytotoxicity. A proposed mechanism of the observed tolerance to metal fumes involves the increased synthesis of toxic metal-binding protein metallothionein in exposed patients.

The treatment of metal fume fever is supportive, and includes antipyretics and analgesics. Metal fume fever must be distinguished from acute metal fume toxicity, as with cadmium or mercury, which can present similarly to metal fume fever but fails to resolve and instead progresses to respiratory distress. Prevention of metal fume fever involves provision of adequate ventilation, fume removal devices and respiratory protection for workers in environments in which metal oxide fumes are generated.

Polymer Fume Fever

A syndrome similar to but less common than metal fume fever, polymer fume fever, was first reported in 1951. Fluorocarbon polymers are a class of compounds that are commonly used as nonstick coatings on cooking equipment (polytetrafluoroethylene [PTFE, or Teflon] is a famous example) but are also used as mold-release sprays, lubricants, and fabric or leather treatments. When fluorocarbon polymers are heated, fumes are produced that include carbonyl fluoride, perfluorinated alkanes, hydrofluoric acid, and carbon dioxide; extremely small particles capable of reaching alveolar sacs also may contribute to disease progression.

Polymer fume fever presents similarly to metal fume fever: Initial symptoms include dry throat, rhinitis, chest tightness, and conjunctivitis. Constitutional symptoms (fever, chills, myalgias) typically follow exposure by about 4 to 8 hours and spontaneously resolve within 1 day. As with metal fume fever, a leukocytosis is observed concurrent with the patient's constitutional symptoms. Individuals with preexisting obstructive lung disease may experience worsening obstruction after recurrent exposures to polymer fumes. Pneumonitis is more frequently observed than with metal fume fever, perhaps due to release of hydrofluoric acid. Tachyphylaxis, a hallmark observation of metal fume fever, is not observed in polymer fume fever, suggesting that different mechanisms are responsible for the two diseases. As with metal fume fever, the systemic response to particle inhalation appears to be cytokine mediated.

Although exposure to pyrolized fluoropolymers occurs in industrial settings where it may be immediately suspected in the context of respiratory complaints, it also occurs in homes and via less obvious means of exposure. In one report, within an hour of an empty PTFE-coated pan being heated on a stove, five exposed pet birds died and their owner contracted polymer fume fever. Numerous reports have suggested that workers with skin exposed to fluoropolymers may have contracted polymer fume fever via smoking their self-contaminated tobacco. Another may have contracted the disease via igniting his marijuana with cotton that had previously been impregnated with hairspray. Several recent episodes of polymer fume fever have occurred following exposure via the waterproofing spray used on horse rugs.

Treatment of polymer fume fever is supportive. Workers exposed to fluoropolymers should both be provided adequate ventilation and also instructed of the risk of indirect exposure via skin contamination. Strict hand-washing should be required and tobacco smoking should be especially discouraged after exposure.

Organic Dust Toxic Syndrome

Another systemic illness caused by inhalational exposure is organic dust toxic syndrome (ODTS), also known as silo unloader's syndrome, atypical farmer's lung, pulmonary mycotoxicosis, and toxic pneumonitis. As with metal fume fever and polymer fume fever, ODTS is a self-limited disease that presents with fever, chills, and myalgias several hours after exposure to the offending agent, in this case organic dusts. As with the other systemic diseases discussed, ODTS typically resolves spontaneously within 48 hours following exposure. Agricultural workers are at the highest risk for contracting ODTS, as it commonly follows exposure to hay or corn silage-containing silos, spoiled animal feed, and swine confinement facilities. Other settings of ODTS have included a college fraternity party in which hay was laid on the floor, a storehouse containing moldy oranges, a waste-sorting plant, a print-shop in which an air humidifier was colonized with gram-negative bacteria, fungi, and amoebae, and following exposure to wood chip mulch. Lifetime risk of contracting ODTS may be around 19 percent for farmers with exposure to organic dust.

The specific agent or agents within organic dust responsible for ODTS have not been fully characterized, but bacterial cell wall components endotoxin and peptidoglycan are thought to play prominent roles. Fungal spores and actinomyces also are likely contributors to pathogenicity, and an ODTS-like response can be provoked with endotoxin-free grain extracts. The disease process is likely initiated or provoked by activation of the patient's innate immune system by organic dust components, such as endotoxin's activation of Toll-like receptor 4. Cytokine expression increases following organic dust exposure, especially of proinflammatory cytokines such as TNF-α and interleukin-6 (IL-6), suggesting a means by which local activation of innate immunity may provoke the observed systemic manifestations. Interleukin-1 (IL-1) is also thought to play a critical role in ODTS development. An intriguing correlation has been observed between patients with celiac disease and the development of ODTS, suggesting that some underlying disorder, perhaps a hyperactivity of innate immunity, may increase a patient's susceptibility to both.

Patients with ODTS frequently present with no findings on chest examination, although bibasilar crackles and scattered wheezes may be appreciated. A neutrophil-predominant leukocytosis is frequently found, and mild hypoxemia and bilateral infiltrates on chest x-ray have been reported. Although bronchoalveolar lavage may initially reveal a predominance of neutrophils, a lymphocytic response may come to dominate the BAL cellular population.

ODTS needs to be clinically distinguished from hypersensitivity pneumonitis (HP), which is also provoked by inhaled organic dust. HP typically follows low levels of exposure after a period of sensitization, while ODTS is an acute reaction to high levels of organic dust, potentially on first exposure. HP is a restrictive process detectable by pulmonary function testing, while ODTS sometimes presents with transient airflow obstruction and often with no appreciable functional abnormality. The early BAL findings in ODTS are overwhelmingly neutrophilic, unlike the lymphocytic findings in HP.

Treatment of ODTS is symptomatic. Unlike with HP, corticosteroids appear to be of only marginal benefit in the treatment of ODTS.

SUMMARY

Toxic inhalations may be due to numerous agents and produce a broad spectrum of pulmonary and systemic injuries. Treatment is largely supportive and should be guided by the patient's clinical status. Specific attention should be paid to the patency of the airway following acute upper airway exposures, and providers should be aware of the risk of the development of severe pulmonary disease following an asymptomatic latent period. Given the unpredictable clinical course of these exposures, cautious monitoring of exposed patients is prudent. Materials safety data sheets and the National Library of Medicine's TOXNET (http://toxnet.nlm.nih.gov/) are excellent information resources for specific toxins.

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60
CHAPTER

Indoor and Outdoor Air Pollution

Jonathan M. Samet • Mark J. Utell

Both indoor and outdoor air pollution are of concern to pulmonary physicians. Exposures to indoor and outdoor air pollutants may both exacerbate and cause respiratory diseases and also increase the population's risk for morbidity and mortality from malignant and nonmalignant diseases. This chapter provides a broad introduction to indoor and outdoor air pollution. It begins with a brief review of the emergence of indoor and outdoor air pollution as clinical and public health issues. The chapter then considers general principles and concepts related to inhalation injury, exposure, and health outcomes. The health consequences of indoor and outdoor air pollution are covered separately, although this distinction is artificial, given the penetration of outdoor pollutants into indoor environments and the overlap between the pollutants found in indoor and outdoor locations. The chapter concludes by considering two issues of direct concern to clinicians: susceptible populations and control strategies.

OVERVIEW

Air pollution has probably had adverse effects on health throughout history. The use of fire for heating and cooking brought exposure to smoke, and the rise of cities concentrated the emissions of pollutants from dwellings and manufacturing facilities within restricted locales. Industrialization and electric power generation brought new point sources of pollution; that is, localized sources such as power plants, and sometimes immense emissions of combustion byproducts, particles, nitrogen oxides, and sulfur oxides into adjacent areas where people lived and worked. During the twentieth century, mobile sources, including cars, trucks, and other fossil fuel–powered vehicles, created a new type of pollution—photochemical pollution, or "smog"—first recognized in the Los Angeles air basin. The unprecedented growth of some urban areas to form "megacities," such as Mexico City, São Paulo, and Shanghai, has led to unrelenting air pollution from massive vehicle fleets and snarled traffic and from polluting industries and power plants. During the twentieth century, there also has been increasing recognition that the problem of air pollution extends into indoor environments. In the less-developed countries, exposure to smoke from biomass fuel combustion is widespread, as it was in past centuries. In the more developed countries, indoor pollutants are generated by human activities and released from the materials used for construction and in furnishings, and often maintained at unhealthy concentrations by building designs that seal pollutants within.

Health effects of air pollution have long been of concern. During the reign of Edward I (1272–1307), the pollution of London by coal smoke prompted a royal proclamation banning burning of "sea-coal" in open furnaces. In 1661, John Evelyn published *Fumifugium or the Aer and Smoake of London Dissipated*, describing an approach to the control of air pollution in London. However, air pollution was not regulated in England until approximately two centuries later with the passage of the Smoke Nuisance Abatement Act and the Alkali Act, directed at industrial pollution. In the United States, recognition of the public health dimensions of air pollution began in the middle of the twentieth century, driven by the rising problem of smog in southern California and the 1948 air pollution episode in Donora, Pennsylvania, which caused 20 excess deaths and thousands of illnesses. The first national legislation, the Air Pollution Control Act, was passed in the mid-1950s; the original Clean Air Act was passed in 1963 and most recently revised in 1990.

The modern era of air pollution research and control dates to the episodes in Donora and other cities, during which extremely high levels of pollution caused clearly evident excess deaths. The most dramatic episode was the London Fog of 1952, which caused thousands of excess deaths. These episodes led to regulations for the control of outdoor air pollution and to the conduct of research designed to develop evidence on the health effects of outdoor air pollution as a foundation for control measures. The research included characterization of the pollutants in outdoor air as to their sources, concentrations, and chemical and physical properties; toxicological investigation on the injury caused by air pollutants and the underlying mechanisms; and epidemiological studies of the health effects of air pollution in the community. These approaches remain fundamental to research on air pollution. We now have a large body of evidence on the health effects of air pollution gained over nearly 60 years of investigation and complex regulations that limit emissions and control concentrations of key pollutants in outdoor air.

The health effects of indoor air pollution are a more recent concern. Only limited measurements were made of indoor air contaminant levels before the 1970s, and the findings of the first large-scale studies of the health effects of indoor air pollution were not reported until the late 1960s and early 1970s. Pollutants of initial interest included secondhand tobacco smoke (SHS) or environmental tobacco smoke (ETS), the mixture of side-stream smoke and exhaled mainstream smoke inhaled involuntarily by nonsmokers, and nitrogen dioxide (NO_2) generated by gas cooking stoves and ranges and by space heaters. Research soon broadened to biologic agents, volatile organic compounds, and two respiratory carcinogens—radon and asbestos. Concern about the potential health effects of indoor air pollution was heightened by the design and construction of buildings with reduced exchange of indoor with outdoor air for the purpose of energy conservation; the reduction of air exchange was anticipated to diminish dilution and thereby increase indoor air pollutant concentrations. Beginning in the 1970s, outbreaks of nonspecific complaints started to occur among workers, who attributed their symptoms to the indoor environments in which they worked. Now referred to as *sick-building syndrome,* these outbreaks continue—but seemingly in smaller numbers than 10 years ago. Another recently described syndrome, *multiple chemical sensitivity*, has also been linked to indoor air pollution; persons with this syndrome, who may obtain consultation from pulmonary specialists, often report debilitating symptoms after exposure to indoor air contaminants, even at levels that may be considered generally safe. One new concern is disease resulting from potential exposure to mold in homes, particularly following water damage. The flooding of many homes in New Orleans and Houston by catastrophic hurricanes has served to reinforce the potential for chronic exposure to mold.

Control of indoor air pollution has been enacted primarily through nonregulatory approaches, as the Environmental Protection Agency (EPA) does not directly regulate the levels of pollutants in indoor air. The cornerstone of the control of indoor air pollution has been education of the public, manufacturers, and employers on approaches for reducing exposures and for reducing emissions from indoor sources. The EPA has given a guideline value for an acceptable indoor radon concentration; it has also proposed that all homes be tested for radon and the homes modified if the concentration is above the guideline. The handling of asbestos in schools was regulated under the Asbestos Hazard Emergency Reduction

Table 60-1

Criteria Pollutants, Sources, and National Ambient Air Quality Standards (NAAQS)

Pollutant	Sources	Primary Standards	Averaging Time
Sulfur dioxide	Coal and petroleum combustion, smelting, and other manufacturing	0.14 ppm (365 $\mu g/m^3$) 0.03 ppm (80 $\mu g/m^3$)	24 h Annual (arithmetic mean)
PM_{10}	Coal and petroleum combustion, vehicles, industry, surface dust	150 $\mu g/m^3$ 50 $\mu g/m^3$	24 h Annual (arithmetic mean)
$PM_{2.5}$	Fuel combustion from automobiles, power plants, wood burning, industrial processes, and diesel powered vehicles	65 $\mu g/m^3$ 15.0 $\mu g/m^3$	24 h Annual (arithmetic mean)
Nitrogen dioxide	Coal and petroleum combustion, vehicles, industry	0.053 ppm (100 $\mu g/m^3$)	Annual (arithmetic mean)
Carbon monoxide	Coal and petroleum combustion, vehicles	35 ppm (40 $\mu g/m^3$) 9 ppm (10 $\mu g/m^3$)	1 h 8 h
Ozone	Secondary formation from NO_2 and hydrocarbons	0.08 ppm	Maximum daily 1-h average
Lead	Gasoline, lead-containing dust	1.5 $\mu g/m^3$	Maximum quarterly average

Act, and the agency has classified ETS as a class A carcinogen. In the United States and some other countries, a substantial proportion of households have banned smoking in the home in the absence of any regulatory policy. The Occupational Safety and Health Administration published Proposed New Rules on indoor air quality in 1994, but later withdrew the proposal.

The literature on air pollution is now voluminous and has been published in a broad array of journals and technical reports. Of necessity, this chapter is selective in its review; emphasis has been placed on the most relevant findings for clinicians and on the newer literature. The documents prepared by the EPA on the six "criteria" pollutants (sulfur dioxide [SO_2], particulate matter, NO_2, carbon monoxide [CO], ozone [O_3], and lead) offer encyclopedic reviews that are updated periodically (Table 60-1). The American Thoracic Society (ATS) has occasionally published summary statements for health professionals on the health effects of outdoor air pollution, with several published in 1996. Several books address the topic of indoor air pollution generally or address specific aspects of indoor air pollution. The EPA has published an introductory primer on indoor air pollution. Key documents on specific pollutants are cited within the appropriate sections of this chapter.

GENERAL PRINCIPLES AND CONCEPTS

Adverse responses to air pollutants reflect exposure and the delivery of the dose of the injurious agent to the target site within the respiratory tract. Air pollutants cause disease through various mechanisms. This section of the chapter covers principles of inhalation injury and the related spectrum of adverse health effects; it also covers principles of exposure assessment. The research methods used to characterize the effects of air pollutants are also detailed.

Principles of Inhalation Injury

Atmospheric pollutants, whether indoors or outdoors, exist in both gaseous and particulate forms. In evaluating clinical consequences of specific exposures, the clinician should recognize that penetration into and retention within the respiratory tract of toxic gases can vary widely, depending on the physical properties of the gas (e.g., solubility), the concentration of the gas in the inspired air, the rate and depth of ventilation, and the extent to which the material is reactive. Gases that are highly water soluble, such as SO_2, are almost completely extracted by the upper airways of healthy

subjects during brief exposures at rest. In contrast, removal of less water-soluble gases, such as NO_2 or O_3, is much less complete, and these gases may penetrate to the airways and alveoli of the respiratory tract. CO is poorly soluble in water and is not removed in the upper airways. On reaching the lung, CO diffuses across the alveolar-capillary membrane and then binds avidly to hemoglobin.

Exercise greatly augments penetration of gases into the deep lung and, thus, the total dose of pollutants delivered to targets in the airways. Exercise increases the dose directly by increasing minute ventilation; also, because many people switch from the nasal to the oral breathing route during moderate to heavy exercise, the more efficient pollutant removal in the nasal passages is replaced by the less efficient removal in the oral airway.

Particulate pollutants usually occur in nature as aerosols. Small liquid droplets or solid particles are dispersed in the atmosphere with sufficient stability to remain in an aerosol suspension. Examples of common aerosols are sulfuric acid mists and sulfate and nitrate salts formed from SO_2 and NO_2, respectively. Deposition of inhaled particles depends on many factors, including the aerodynamic properties of the particle (primarily size), airway anatomy, and breathing pattern. Particles larger than 10 μm are effectively filtered out in the nose and nasopharynx, where these relatively large particles are deposited efficiently because of impaction against surfaces and gravitational forces. Particles trapped in the nose and nasopharynx are cleared in secretions and coughed out or swallowed. Particles less than 10 μm in aerodynamic diameter (PM_{10}) may be deposited in the tracheobronchial tree; deposition in the lung's alveoli is maximal for particles less than 1 to 2 μm in diameter. Particles smaller than 0.5 μm move by diffusion to the alveolar level, where they collide with gas molecules by Brownian movement and are impacted on alveolar surfaces. Recent interest has focused on both environmental and man-made particles in the so-called "ultrafine" range, that is, particles less than 100 nanometers in size; despite their extremely small size, high deposition has been found in the respiratory tract and total deposition increases as the particles get smaller. Removal of particles from the larger airways by the mucociliary apparatus is efficient and occurs within hours of deposition; clearance from the deep lung by alveolar macrophages is much slower, requiring days to months.

The mechanisms by which inhaled gases and particles injure the lung are diverse and not yet fully understood. Oxidant gases, O_3 and NO_2, cause inflammation of the respiratory epithelium, presumably through the production of toxic oxidant species and release of potent mediators. SO_2 is also an irritant gas. The response to particles likely depends on the chemical and physical nature of the particles. Oxidizing compounds on particles may dissolve into tissue fluids and induce an inflammatory response. Organic materials on particles may also produce inflammation or act as initiators or promoters of cancer. The respiratory track, of course, is exposed to multiple pollutants, and interactions among them may synergistically increase effects. Exposure to oxidant gases, for example, enhances responses to inhaled allergens.

Adverse Health Effects of Air Pollution: Clinical and Public Health Concerns

The spectrum of adverse effects of air pollution is broad, ranging from the consequences of acute and dramatic exposures, which may cause death, to far more subtle and chronic effects on disease risk and well-being. This spectrum has been conceptualized as a pyramid with mortality at its tip and an increasingly common set of morbidities as the base. Perhaps the most common "adverse" effect is a loss of well-being from the diminished aesthetic value of a polluted environment. Clinicians are more likely to be concerned with the less common, more acute effects with clinical consequences—acute responses, often in asthmatics, for which a link to air pollution exposure may be made by history or challenge testing; the more subtle and long-term consequences are typically a focus for public health researchers and regulators. Nevertheless, clinicians may be asked to assess risks of long-term exposures or to estimate the contribution of exposures to disease causation in a particular patient. They may also be asked to guide their communities in evaluating air pollution as a local public health problem.

To interpret the scientific evidence on the effects of air pollution, clinicians need a framework for determining whether an effect is "adverse." Judgment on the adversity of responses is societal and reflective of prevalent valuations and perceptions of risk. The Clean Air Act uses the term "adverse" without definition. If a broad construct of health is used that includes a state of well-being as a component, adverse effects of air pollution include not only clinically evident disease but also more subtle symptom responses and physiological effects that may compromise well-being or increase the risk of disease. In a report issued in 2000, a committee of the ATS offered guidelines for defining adverse respiratory health effects in epidemiological studies of outdoor air pollution. The committee turned to a medical basis for this determination, defining adverse respiratory health effects as medically significant physiologic or pathologic changes.

Indoor air pollution has a broad range of effects as well (Table 60-2). Cases of clinically evident disease caused by indoor air pollution occur, and an unquestionable causal link can often be established for specific persons from a careful history or appropriate diagnostic testing, as with hypersensitivity pneumonitis. Indoor air pollution can also exacerbate chronic respiratory diseases—e.g., house dust mite antigen and asthma in house-dust mite–allergic persons. More subtle effects have become of increasing concern as we have learned that indoor air pollution can adversely affect comfort and increase risk for future disease; consequently, even the perception of exposure to indoor pollutants may adversely affect well-being. Radon and asbestos, for example, are respiratory carcinogens, which are presumed to increase risk of lung cancer.

Concepts of Time-Activity and Total Personal Exposure

Definitions of concentration, exposure, and dose are fundamental to considering the health effects of air pollution.

Table 60-2

A Classification of the Adverse Effects of Indoor Air Pollution

Clinically evident diseases: Diseases for which the usual methods of clinical evaluation can establish a causal link to an indoor air pollutant
Exacerbation of disease: The clinical status of already established disease is exacerbated by indoor air pollution
Increased risk for diseases: Diseases for which epidemiological or other evidence establishes increased risk in exposed persons; however, the usual clinical methods indicative of injury typically cannot establish the causal link in an individual patient
Physiological impairment: Transient or persistent effects on a measure of physiological functioning that are of insufficient magnitude to cause clinical disease
Symptom responses: Subjectively reported responses that can be linked to indoor pollutants or are attributed to indoor pollutants
Perception of unacceptable indoor air quality: Sensing of indoor air quality as uncomfortable to an unacceptable degree
Perception of exposure to indoor air pollutants: Awareness of exposure to one or more pollutants with an unacceptable level of concern about exposure

SOURCE: Data from Samet JM: Indoor air pollution: A public health perspective. *Indoor Air* 3:219–226, 1993.

Concentration refers to the amount of material present in air. *Exposure* constitutes contact with a material at a portal of entry into the body—the respiratory tract, gastrointestinal tract, and skin. For the lung, exposure would constitute time spent in contaminated air. Exposure is the unit of concentration multiplied by time. *Dose* refers to the amount of material that enters the body; *biologically effective dose* is the amount of material reaching target sites for injury—e.g., the mass of respirable particles delivered to the small airways. For example, the concentration of particles less than 10 mm in aerodynamic diameter (PM_{10}) might be 100 mg/m^3; a person spending 10 h at this concentration would have an exposure of 10 h times 100 mg/m^3, or 1000 mg/m^3– h. Assuming lung deposition to be 50 percent of the total mass and a minute volume of 10 L/min, the dose of PM_{10} would be 600 mg. For most inhaled pollutants, dose will vary with activity level as ventilation rises and falls with the demands imposed by activities.

With regard to impact on health, *total personal exposure* to a pollutant is the relevant index of exposure, not the exposures received separately within indoor and outdoor environments. The total personal exposure of a person to a pollutant can be conceptualized as the time-weighted average pollutant concentration in the "microenvironments" in which the person spends time (Fig. 60-1). The microenvironments are locations having relatively constant concentration of the pollutant during the time spent there. The principal microenvironments contributing to total personal exposure are those with relatively high concentrations or in which relatively large amounts of time are spent. For example, for exposure to particles, key microenvironments might include an office in which smoking is allowed and an urban environment in which a home is located and time is spent outdoors and indoors.

Studies of time-activity patterns indicate that residents of more developed countries spend most of their time indoors and, consequently, personal exposures to many pollutants take place largely in indoor microenvironments. However, pollutants generated by outdoor sources do penetrate indoors, so indoor microenvironments can contribute to exposures to pollutants typically considered outdoor pollutants, such as particles and CO. Data on time use in a number of countries showed that people spend an average of 65 to 75 percent of their time inside their residences and more than 90 percent of time indoors, counting time at home, work, and elsewhere. Data from a 1987 to 1988 survey of Californians show a similar pattern, with employed adults averaging 15 h per day indoors at home and 6 h per day in other indoor settings. In the California study, school-age children spent an average of 18 h indoors at home. While these data emphasize the predominance of indoor microenvironments in determining exposures to many pollutants, exposure outdoors may be the predominant determinant of dose for some pollutants. For example, the dose of O_3 (which generally has low indoor levels) received by the lung's airways may be dominated by exposure received outdoors, particularly for people exercising outdoors.

Research Approaches to Air Pollution

Our understanding of the health effects of air pollution derives from a tripartite research approach: characterization of atmospheric pollutants and exposures, toxicological studies, and epidemiological studies. These approaches are complementary. There has long been research on the physical and chemical properties of air pollutants, and more recently, exposure assessment has emerged as a separate research discipline.

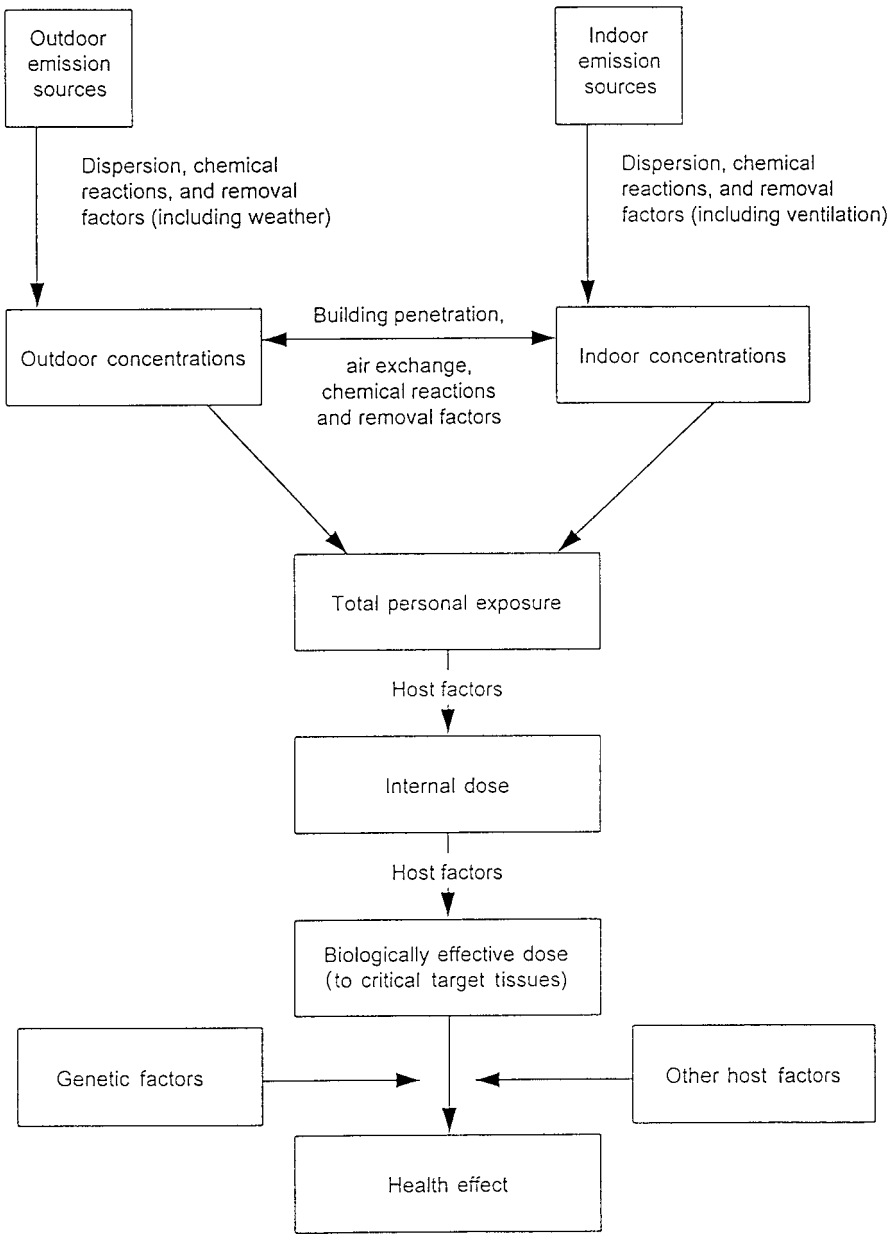

Figure 60-1 Framework for conceptualizing exposure, dose, and health effects from outdoor and indoor air pollution. *(Based on National Research Council data.)*

The tools of the exposure assessor include questionnaires that capture activities and time use, personal and area monitors, statistical models for estimating exposures, and biomarkers of exposure and dose.

Toxicological studies are often conducted to characterize the hazards of air pollutants; research may entail exposures of animals to one or more pollutants to assess patterns of injury and disease risk. Increasingly, toxicological approaches are used to characterize the relationship between exposure and dose and the mechanisms underlying injury. This mechanistic information addresses the appropriateness of extrapolating from animal studies to humans, particularly if parallel data from humans are available on dosimetry and mechanisms. Toxicological studies in which volunteers are exposed to pollutants, often referred to as *clinical studies,* have proved to be an informative approach for investigating the acute consequences of pollution exposure. In addition to healthy volunteers, groups in the population considered susceptible to the effects of the pollutant(s) of concern may be selected for investigation—e.g., persons with asthma, chronic obstructive pulmonary disease (COPD), or coronary artery disease. Of necessity, exposures in clinical studies are of brief duration and ethically limited to levels that will have limited, transient effects. In addition to monitoring symptoms and physiological measures, clinical studies may be strengthened by more invasive collection of biologic specimens, using phlebotomy, nasal lavage, or fiberoptic bronchoscopy with biopsy of the mucosa or bronchoalveolar lavage, to elucidate mechanisms of injury. Molecular approaches using microarrays to analyze changes in gene expression are now being applied to cells (e.g., macrophages and blood monocytes) removed from humans following controlled exposure to pollutants.

Table 60-3

Steps in Risk Assessment

Hazard identification: The determination of whether an agent is causally linked to the health effect of concern
Dose-response assessment: The determination of the relation between level of exposure and risk of the health effect
Exposure assessment: Description of the extent of human exposure
Risk characterization: Description of the human risk, including uncertainties

SOURCE: Data from National Research Council (NRC), Committee on the Institutional Means for Assessment of Risks to Public Health. *Risk Assessment in the Federal Government: Managing the Process.* Washington, D.C., National Academy Press, 1983.

Clinical studies are also incorporating analyses to identify genetic polymorphisms that determine susceptibility to air pollutants.

Epidemiological studies provide an assessment of the adverse effects of pollution exposures under the circumstances of "real world" exposure. The principle epidemiological study designs used for air pollution research include cross-sectional studies or surveys, short-term cohort studies with intensive measurements of exposures and outcomes, "panel studies," which are longer-term cohort studies directed at mortality and chronic disease risk, and time-series studies that assess short-term changes in outcomes, e.g., mortality counts, in relation to air pollution. The findings of epidemiological studies of air pollution have direct public health and regulatory relevance. The exposures are inherently representative of those received in the community, and the pollutants are inhaled in the form of the complex mixtures that actually exist in indoor and outdoor air. Additionally, the community members in a study can be selected from the full spectrum of potentially susceptible subjects. There are, however, weaknesses to the epidemiological approach. Exposures to pollutants may be difficult to measure accurately, particularly past exposures that may have determined current health; hence, exposure estimates in epidemiological studies are subject to substantial error. The effects of other exposures relevant to the health outcome of interest, termed *confounding factors,* may not be sufficiently controlled, and these extraneous exposures may artifactually increase or decrease the apparent effect of air pollution exposure. Epidemiological studies having inadequate sample size and, therefore, limited statistical power may supply imprecise and uninformative estimates of risk and not precisely answer public health questions.

The technique of quantitative risk assessment has been increasingly applied to estimate the burden of disease associated with air pollution, particularly carcinogens. The 1990 Clean Air Act amendments include specific provisions on the use of risk assessment, particularly in regard to the hazardous air pollutants regulated under Section 112 of the Act. This process integrates the information on exposure and dose response to provide a characterization of the impact of an environmental agent on the population's health; as the evidence is systematically reviewed in the conduct of a risk assessment, gaps in the evidence and attendant uncertainties are identified, and assumptions are made to fill the gaps. The approach was also used by the World Health Organization in its Global Burden of Disease estimates, which covered indoor and outdoor air pollution.

Risk assessment can be conceptualized as comprising the four steps outlined in the seminal 1983 report of the National Research Council (Table 60-3). A full risk assessment can be a large undertaking, requiring review of all relevant data and mathematical modeling to characterize the risk. In a risk assessment, gaps in the scientific evidence, which are sources of uncertainty, are catalogued and used to estimate the level of confidence attached to the risk characterization. The findings of risk assessment guide *risk management*, the process by which decisions are made about the need for risk reduction and the approaches to be implemented to reduce risks. Risk management means choosing among the options to control risk and balancing risk reduction, costs, and technological capability for reducing exposure. Uncertainties in the scientific information that have been catalogued in the risk assessment process may cloud risk management and introduce ambiguity regarding the optimum strategy. Nevertheless, risk managers need to make decisions in the face of uncertainty.

Understanding the effects of complex mixtures of pollutants in indoor and outdoor air has proved particularly daunting for researchers. Exposures to pollutants rarely occur singly, without simultaneous exposures to other pollutants in the relevant microenvironments. Many outdoor sources inherently produce complex pollutant mixtures; for example, power plants release particles, nitrogen oxides, and sulfur oxides, and vehicle exhaust contains CO, nitrogen oxides, particles, and hydrocarbons. Indoor air is inevitably contaminated by complex mixtures, reflecting the multiplicity of sources in indoor environments. Synergistic or antagonistic interactions between components of complex pollutant mixtures can produce unanticipated effects, based on the toxicity of individual components. While this problem is well recognized, epidemiological and toxicological research approaches have provided

little understanding of the interactions that may determine the toxicity of complex mixtures.

OUTDOOR AIR POLLUTION

Outdoor air pollutants have diverse sources, both man-made and natural. This section begins with a review of the sources and then considers the effects of the principal man-made outdoor pollutants. The pollutants are grouped according to their designation by the EPA.

Overview: Sources and Classification of Outdoor Air Pollution

Many pollutants, from both man-made and natural sources, can be found in outdoor air. Some naturally occurring pollutants in outdoor air are well documented as causing or exacerbating pulmonary diseases—e.g., pollens and fungi. This chapter does not address these biologic agents but considers the man-made pollutants. Researchers have focused more attention on the effects of man-made pollutants, which may reach potentially hazardous levels in urban areas or near point sources, such as power plants, smelters, or manufacturing facilities. In the United States, the principal outdoor pollutants are generally classified within the framework provided by the Clean Air Act, which identifies two sets of air pollutants, "criteria" pollutants (Table 60-1) and "toxic" air pollutants. The term *criteria* refers to the standard-setting process for these pollutants, which requires preparation of a criteria document reviewing all relevant evidence every 5 years. The criteria pollutants include primarily combustion-related pollutants (SO_2, NO_2, CO, and particles), the secondary pollutant O_3, and lead. The toxic pollutants are predominantly carcinogens; the sources are diverse but principally comprise industrial emissions and waste products. Examples of these pollutants are benzene, chlordane, ethylene oxide, hydrochloric acid, methane, parathion, propylene oxide, toluene, and vinyl chloride.

These two groups of pollutants are regulated through different mechanisms. For the criteria pollutants, National Ambient Air Quality Standards (NAAQS) are set after extensive review of all relevant evidence; the standards must afford protection to the entire population, including those with heightened susceptibility, and offer an "adequate margin of safety." The hazardous pollutants are predominantly carcinogens, such as asbestos and radionuclides, and standards for maximum concentrations are also intended to provide a margin of safety. The Clean Air Act includes mechanisms for achieving levels within the standards and enforcement. In spite of existing federal standards for ambient air quality, excesses are common in many areas of the country, particularly for O_3. Although the pollutants are considered in the following section on an individual basis, it should be re-emphasized that exposures of the population occur most often to mixtures, and synergism among individual pollutants may increase the effects of the mixture beyond the expected effect based on the components.

Outdoor Air Pollutants: Exposures and Health Effects

The pollutants covered in this section are of public health significance throughout the world. Sulfur oxides, particles, nitrogen oxides, and CO are generated by combustion and are typically found together in the complex air pollutant mixtures in outdoor environments. O_3 is a secondary pollutant. While the pollutants are considered individually, exposures to them typically occur in the form of inhaled mixtures.

Sulfur Dioxide

Sulfur oxides are produced by combustion of fuels containing sulfur, such as coal from the eastern United States and crude petroleum. Smelting of ores containing sulfur is also a prominent source in some regions, such as the southwestern United States. In the past, scientific research and regulatory concern in relation to the sulfur oxides were directed primarily at the health effects of SO_2, the criteria pollutant regulated by the EPA. SO_2 is a water-soluble gas that is effectively scrubbed from inspired air by the upper airway; exercise, however, may increase the inhaled dose by its effect on minute ventilation and the switch to the oral breathing route. This pollutant has been shown to have adverse effects without concomitant exposures to other pollutants. In fact, exposures of volunteers to SO_2 alone show that the gas may have adverse respiratory effects; asthmatics are particularly sensitive, with some showing particular sensitivity. Significant exposures to SO_2 alone might result from plumes released by smelters processing sulfur-containing ores or from other industrial processes.

Exposures to SO_2 in outdoor air occur primarily with simultaneous exposures to other combustion-related pollutants, including nitrogen oxides and particles. Heavy industry and coal-burning power plants are predominant sources for this type of pollutant mixture. Tall smokestacks for power plants, used to control local pollutant concentrations, release sulfur oxides and nitrogen oxides high into the atmosphere, where residence time is prolonged. Through a series of chemical reactions, the sulfur oxides and nitrogen oxides form acidic sulfate and nitrate particles, which may undergo long-range transport. These acidic particles represent a regional air pollution problem—blanketing, for example, the central and northeastern United States and portions of Canada. Fortunately, concentrations of SO_2 have fallen in the United States, in part due to controls implemented under the Environmental Protection Agency's Acid Rain Program, and from changing patterns of fuel use and energy generation. From 1983 through 2002, the average annual concentration fell about 50 percent. The effects of particulate air pollution and acidic aerosols are considered separately below; this section considers the effects of gaseous SO_2.

Asthmatics are particularly susceptible to SO_2, responding to exposure in chambers with increased airway resistance and reduced levels of lung function. With exercise and hyperventilation, which increase the dose delivered to the respiratory tract, some asthmatics are adversely affected at levels common in ambient air and well below those that might occur transiently with direct exposure to the plume from a

power plant or factory. Inhalation of SO_2 produces an immediate response and does not provoke delayed reactions or repetitive nocturnal attacks. The decrements in lung function on breathing of SO_2 may be sufficient to produce symptoms of dyspnea, wheezing, and chest tightness. The bronchoconstriction resolves within an hour of exposure, and peak bronchoconstrictor responses may lessen on repeated challenge after a short recovery period. Responses to SO_2 can be partly blocked by pretreatment with cromolyn sodium and anticholinergics and can be reversed by β-adrenergic agonists. Sequential exposures to SO_2 and oxidant gases (O_3 and NO_2) have been performed in asthmatics; these clinical studies have provided little evidence of synergistic interactions in reducing airway function. Although some asthmatics have been shown to be affected by SO_2 with exposure at low concentrations in the laboratory, complementary epidemiological data have not been reported that document parallel community morbidity.

Recent epidemiological studies from Hong Kong have examined the consequences of a major reduction in sulfur content in fuels over a very short period of time. The investigators found an associated substantial reduction in health effects (childhood respiratory disease and all age mortality outcomes). Daily SO_2 was significantly associated with daily mortality in 12 Canadian cities with an average concentration of only 5 $\mu g/m^3$. Nevertheless, there is still considerable uncertainty as to whether SO_2 is the pollutant responsible for the observed adverse effects or, rather, a surrogate indicator for ultrafine particles (UFP) or some other correlated substance. For example, in Germany and the Netherlands a strong reduction of SO_2 concentrations occurred over a decade. Although mortality decreased with time, the association of SO_2 and mortality was judged as noncausal and attributed to a similar time trend of particulate matter.

Nitrogen Dioxide

Nitrogen oxides, like sulfur oxides, are produced by combustion processes and contribute to the formation of aerosols. Even though NO_2 is regulated by the EPA as a criteria pollutant, substantial personal exposure in the United States occurs in indoor microenvironments contaminated by unvented gas stoves and space heaters. The principal source of NO_2 in outdoor air is motor vehicle emissions, but power plants and industrial sources may also contribute. There have been few locations where point sources were strong enough to make NO_2 alone a source of concern. The health effects of NO_2 released into outdoor air probably arise principally from the formation of secondary pollutants. NO_2 is an essential precursor of O_3, and one of the principal pathways by which NO_2 in outdoor air adversely affects respiratory health may be through the formation of O_3. The nitrogen oxides also secondarily form acidic nitrate particles.

NO_2 is an oxidant gas of low solubility that penetrates to the small airways and alveoli of the lung. The toxicological evidence at exposures far greater than typically sustained in indoor and outdoor environments suggests that NO_2 exposure can impair lung defenses against respiratory pathogens and cause airway inflammation, with associated effects on lung function and respiratory symptoms. In animal models, exposure to NO_2 increases mortality after challenge with bacterial respiratory pathogens. Therefore, a wide range of health effects are of concern, including increased risk for respiratory infections, respiratory symptoms, reduced lung function, and exacerbation of chronic respiratory diseases. However, there have been only limited epidemiological data, largely derived from studies of children exposed to indoor sources of NO_2; these studies and other evidence on indoor exposures are considered separately in the section on indoor air pollution. Several more recent studies link NO_2 to indicators of morbidity, but the findings are inconsistent and are unlikely to reflect NO_2 acting by itself.

A number of clinical studies have been performed to investigate the acute effects of NO_2 by itself on the status of persons with asthma. These studies were performed to assess the need for a short-term standard for outdoor NO_2 concentration, as the present NAAQS provide only an annual standard for NO_2. NO_2 could plausibly affect airway responsiveness by causing airway inflammation. The findings of the clinical studies have been inconsistent, and the discrepancies between the "positive" and "negative" studies have not been readily explained. One study showed consistent responses to NO_2 of some asthmatics, suggesting that there might be a susceptible group among persons having asthma in general, but this susceptibility has not been found in other studies. The epidemiological evidence remains inconclusive, largely because of methodological problems arising in attempting to separate the effects of NO_2 from those of other pollutants. Persons with COPD may represent a group with increased susceptibility to short-term exposure to NO_2 outdoors.

Particles

Particles in outdoor air have numerous natural and man-made sources, including the same combustion processes that produce SO_2 and NO_2. Particles are suspended in air by the action of wind on crustal material and road dust. The man-made sources are diverse and include power plants, industry, and motor vehicles, including diesel-powered vehicles that emit particles in the inhalable size range. Particles, of course, are present in indoor and outdoor air; consequently, personal exposures to particles reflect both indoor and outdoor microenvironments. Additionally, outdoor particles, particularly those of smaller size, penetrate indoors.

The man-made particles are primary, i.e., emitted directly by combustion or other processes, or secondary, i.e., formed through chemical and physical transformation of gaseous pollutants, such as NO_2 and SO_2. Because of the diversity of sources, particles comprise a rich mixture that may be quite variable, spatially and temporally. The toxicity of particles in a particular place thus reflects the source mix, which includes both local sources and those contributing to the regional background pollution. In the eastern United States, for example, much of the regional background of $PM_{2.5}$ comes from transport of power plant emissions from the central portion of the country. Hypotheses proposed on determinants of

particle toxicity have focused on issues related to particle acidity, particle content of transition metals, organic compounds on particles (e.g., diesel particles), bioaerosol, and UFP, i.e., particles smaller than 100 nm in aerodynamic diameter. Metals associated with particulate matter are capable of causing pulmonary inflammation and injury and the same chemical properties that allow metals to function as catalysts in reactions with molecular oxygen can generate oxygen-based free radicals and cause oxidative stress. UFP have a high specific surface area and carry an increased burden of reactive oxygen species and may be particularly important with regard to cardiovascular effects because of their potential for evading clearance mechanisms, and for entering the lung interstitium and vascular space.

Historically, particle concentrations in outdoor air have been measured with several different techniques and over recent decades these technologies have been refined and directed at biologically relevant size fractions. Until 1987, the EPA specified the measurement of total suspended particulates (TSP), which included particles well above the inhalable size range. In 1987, the reference method for the NAAQS was changed to particulate matter less than 10 μm in aerodynamic diameter (PM_{10}), and in 1997 24-hour and annual standards were added for $PM_{2.5}$. The PM_{10} standard, challenged in court, was set aside in a Supreme Court decision, and in 2005, the EPA proposed a standard for coarse mixes in urban areas, $PM_{10–2.5}$. This set of standards makes no provision with regard to the chemical composition of the particles. Equivalent mass concentrations of particles are hypothesized to have differing toxicity, depending on acidity, content of metals, or carcinogenic potency. The characteristics of particles that determine their toxicity is a focus of current research. The size distribution below the 10 and 2.5 μm cutoffs may also affect toxicity through its consequence for sites of deposition. In addition, the ultrafine component contributes little to the mass and the number count or surface area may turn out to be an important metric.

Nationally PM_{10} concentrations have decreased 31 percent since 1988, mainly in regions of the country that had higher concentrations such as the Northwest (39 percent), the Southwest (33 percent), and southern California (35 percent). Since 1999, $PM_{2.5}$ concentrations have decreased 10 percent nationally. $PM_{2.5}$ has decreased the most in regions with the highest concentrations to start with, such as the Southeast (20 percent), southern California (16 percent), and the industrial Midwest (9 percent). Except for the Northeast, most regions of the country have had at least modest declines from 1999 to 2003.

There has been extensive epidemiological and toxicological investigation of the effects of particles on health since the air pollution disasters at mid-century. The toxicological studies have used a range of approaches, from exposing volunteers to generated particles or concentrated air particles, to animal exposures, and to diverse in vitro assays. This extensive body of evidence shows that particles are injurious and indicates mechanisms by which particles could cause adverse effects on the respiratory and cardiovascular systems.

The epidemiological studies have addressed the relationship between exposures to particles and short- and long-term variations in mortality, both from all causes and from cardiovascular and respiratory causes. The studies have also addressed the relationship between exposures to particles and diverse indicators of respiratory morbidity, including the frequency of respiratory symptoms and illnesses, level of lung function and rates of lung function growth and decline, and outpatient visits and inpatient admissions. In the studies of particulate air pollution during the 1950s and 1960s, the measures of exposure were general; some studies included only surrogate measures of exposure, such as location of the place of residence. In spite of such crude exposure measures, these studies found adverse effects of exposure to particulate air pollution and became the basis for establishing air quality standards for particles. The standards were generally considered to be sufficiently protective of public health. Studies linked particulate air pollution to a number of adverse health effects.

As levels of air pollution were reduced in the United States and other Western countries, excess mortality at times of higher concentrations was not readily evident and, since the 1970s, the focus of research and of public health concern has generally shifted to morbidity. However, studies of air pollution and daily variations in mortality, facilitated by new techniques for longitudinal data analysis, have shown statistically significant, positive associations between measures of particle concentration and daily mortality counts for cities in the United States and elsewhere. Several analyses have combined data for multiple cities in the United States and in Europe. These analyses pool the information from many locations to estimate precisely the effect of particulate matter and also to examine the variations in risk among the contributing locations. These analyses show a statistically significant effect of airborne particles on mortality, independent of the possible contributions of other pollutants or weather. In interpreting these findings, the extent to which life is lost from these short-term effects is critical. Several prospective studies indicate that life-shortening from air pollution may be substantial.

Many complementary studies of morbidity have also been reported. These studies have been directed at clinical indicators, such as hospitalization or the triggering of arrhythmias, myocardial infarction, or sudden death. They have also examined biomarkers and electrocadiographic parameters. A review in 2004 by the American Heart Association compiled a substantial body of evidence linking particulate air pollution to adverse cardiovascular effects. Additionally, in some studies, airborne particles have been shown to adversely affect persons with asthma and COPD. These findings suggest that the present NAAQS for particulate matter may not protect against adverse health effects with the "adequate margin of safety" mandated by the Clean Air Act. They also call into question other national and international standards and have led to tightening of the standards. It remains premature to offer specific clinical recommendations with regard to particulate air pollution until mechanisms of toxicity are better understood and the role of outdoor exposures

in contributing to morbidity and mortality is further characterized.

Carbon Monoxide

Carbon monoxide (CO) is an invisible gas formed by incomplete combustion of fossil fuels and other organic materials. The most prominent outdoor source is vehicle exhaust; consequently, outdoor concentrations are highly variable in place and time, changing with vehicle density and traffic patterns. Urban locations with high traffic density tend to have the highest concentrations. CO also has indoor sources, such as cooking stoves and tobacco smoke. Exposures to CO can be conveniently assessed by using the level of carboxyhemoglobin as a biomarker of exposure or by measuring the concentration of CO in an end-tidal breath sample, following a breath hold.

In regard to outdoor air, acute effects of CO on susceptible persons have been of particular concern, and the current U.S. standard is intended to protect susceptible persons with coronary artery disease. Inhaled CO binds to hemoglobin with high affinity (more than 200 times greater than for oxygen) to form carboxyhemoglobin (COHb) (see Chapter 12). The COHb complex is very stable; depending on ambient levels of CO, level of activity, and lung function, the half-life of CO in the body ranges from about 2.5 to 4 h. The rate of accumulation of ambient CO in the body above endogenous levels is affected by ambient CO concentrations, alveolar ventilation, lung diffusivity, total hemoglobin mass, and COHb level. People with impaired gas exchange (e.g., persons with COPD) have compromised ability to excrete CO.

The binding of CO to hemoglobin reduces oxygen transport by red blood cells to tissues. The binding also displaces oxygen and causes an allosteric change in the hemoglobin molecule, which increases the affinity of heme groups for oxygen. Persons with cardiovascular disease are considered to be at greatest risk from CO exposure. Standard exercise tests on subjects with ischemic heart disease have demonstrated a decreased time interval to the onset of angina at COHb levels ranging from 2 to 6 percent. The 1-h 35-ppm and 8-h 9-ppm federal standards for outdoor air (Table 60-1) were selected to prevent COHb levels from rising above 1.5 percent, thereby protecting persons with ischemic heart disease from aggravation of myocardial ischemia with onset of angina and attendant loss of exercise capacity. Recent evidence indicates that controlled CO exposure during exercise of patients with stable coronary artery disease can induce subjective and objective evidence of myocardial ischemia earlier in the exposure than during exercise without CO. This effect can be induced at COHb levels as low as 2 to 4 percent. These studies are relevant to the urban environment, where people may be exposed to sufficient CO to reach blood COHb levels in this range. Furthermore, moderate exercise results in even greater CO uptake. In addition, at a COHb level of 6 percent, patients with coronary artery disease have an increased frequency of arrhythmias. Fetuses, as well as persons with COPD, may also be harmed by CO, and normal persons may have reduced oxygen uptake during exercise at low levels of CO exposure.

Ozone

Photochemical pollution, or "smog," is a complex oxidant mixture produced by the action of sunlight on hydrocarbons and nitrogen oxides in vehicle exhaust. Ozone (O_3) is invariably present in photochemical pollution, and its concentration serves as an index of the level of this mixture. The problem of tropospheric O_3 pollution, i.e., ground-level, is distinct from the problem of depletion of the stratospheric ozone layer. Photochemical pollution was first recognized over 50 years ago in southern California, where the combination of sunlight and heavy vehicle travel promotes its formation. O_3 has now become a problem in many other locations, including Western cities with similar sprawling growth and heavy vehicle traffic and the Eastern United States during the summer. O_3 is also produced naturally, but the exposure of concern for health almost exclusively reflects the O_3 created by human activities.

Since 1990, NOx emissions have decreased approximately 25 percent and VOC emissions have dropped by about 35 percent. National ozone levels in 2004 were 11 percent lower than in 1990 and 21 percent lower than in 1980 for the 8-hour standard (3-year average of the annual fourth highest daily maximum 8-hour average concentration is less than 0.08 ppm). Between 1990 and 2004 the most significant improvements in air quality were in the Northeast (17 percent decrease) and Southwest (16 percent decrease) regions of the country.

The toxicology of O_3 has been extensively investigated. Low-level exposures cause damage to the small airways of experimental animals; the demonstration of subtle fibrosis in one animal model has raised concern about permanent structural alteration in exposed populations. Volunteers exposed to O_3 at concentrations in the range of the present standard—which are often present during pollution episodes—experience transient reductions in lung function; normal subjects have a range of responsiveness that is broad but repeatable for individuals. Evidence of an inflammatory response and biochemical changes in BAL fluid has been detected 18 h after an experimental exposure to O_3 at levels that are commonly found. Taken together, the progressive decrements in pulmonary mechanics during exposure, coupled with the persistent biochemical changes many hours after cessation of exposure, indicate the potential for chronic effects from repeated inhalation. Surprisingly, in clinical studies, asthmatics have not been shown to have increased susceptibility to O_3 compared with nonasthmatics. The evidence for short-term effects of O_3 exposure on the lung function of normal volunteers has raised concern about possible long-term effects of living in southern California and other locations with sustained photochemical pollution. Relevant epidemiological data suggest that O_3 may have chronic effects, but these data are not definitive, and a long-term study of southern California children found that ozone was not associated with

reduced lung growth. The same study found evidence that ozone might contribute to the onset of asthma. Some time-series studies have linked short-term exposure to ozone to increased risk of mortality.

Lead

Exposure to lead may occur through many environmental media, including ambient air. At present, ingestion is the principal pathway of concern in the United States. Fortunately, in the United States the importance of ambient air as a source of exposure of the population to lead has diminished with the removal of lead from gasoline. Children are particularly vulnerable to lead exposure. Even levels previously considered safe have been associated with adverse neurological effects, and there has been a progressive tightening of recommendations of blood lead levels by the Centers for Disease Control and Prevention.

Toxic Air Pollutants

The toxic air pollutants are predominantly carcinogens, but they demonstrate a variety of other toxicities. Approximately 200 "hazardous pollutants" are listed as air toxics in the 1990 Clean Air Act amendments. Examples of the hazardous pollutants are asbestos, benzene, cadmium compounds, chlorine, formaldehyde, and nickel. Although the sources are diverse, emission releases tend to be localized, often at industrial sites, or from municipal incinerators or waste sites.

Only a small proportion of lung cancers can be attributed to air pollution, even though carcinogens are found widely in outdoor air. For example, polycyclic aromatic hydrocarbons (PAHs), in diesel exhaust, are widely dispersed and present in urban air throughout the world. The PAHs possess mutagenic and carcinogenic activity. But, to date, only limited epidemiological data on risks in humans are available. Analyses of occupational cohorts exposed to diesel exhaust for years are suggestive of a small excess risk of lung cancer. Given the difficulties of measuring exposure, confounding by cigarette smoke and by other occupations, and the small excess numbers of lung cancers, it is difficult to reach any definitive conclusion on the role of diesel exhaust in causing lung cancer in the general population. Nevertheless, as the percentage of light-duty vehicles powered by diesel fuel in the United States increases, there will be an increasing imperative to determine the carcinogenicity of the PAHs and diesel exhaust. There is also current concern that new types of fuels may introduce additional carcinogens into outdoor air. Some recent experimental and epidemiological evidence indicates that diesel particles may increase risk for allergic sensitization and asthma.

INDOOR AIR POLLUTANTS AND HEALTH EFFECTS

Indoor environments are contaminated by numerous air pollutants, including outdoor air pollutants that have penetrated indoors and indoor air pollutants generated by the numerous indoor sources. This section reviews exposures and health effects of the principal indoor pollutants. The organic compounds and biologic agents include myriad individual agents that may adversely affect health. As for outdoor air pollution, clinicians should consider that exposures to indoor air pollutants typically occur as exposures to mixtures, rather than as single agents.

Overview: Sources and Classification of Indoor Air Pollution

Indoor air pollution has myriad sources, including the materials from which the space is constructed, its furnishings, processes operating within the environment, biologic agents, and even the occupants. Outdoor air pollutants can also penetrate indoors, as can soil gas. The broad source headings are combustion, evaporation, abrasion, biologic, and radon (Table 60-4). The principal combustion sources are gas cooking stoves, burning cigarettes, fireplaces and wood stoves, and unvented space heaters. Evaporation of volatile organic compounds from materials and products leads to ubiquitous contamination by these agents. Abrasion of friable asbestos is a principal source of this indoor contaminant. The biologic agents are heterogeneous, extending from infectious organisms to pets and the occupants themselves. Radon comes primarily from soil gas.

The concentration of an indoor contaminant depends on the strength of its source, the rate of removal, the volume of the space, and the rate of exchange of air between the space and outdoors. This *mass-balance* formulation indicates that the concentration of a contaminant might be reduced by limiting source strength, increasing removal rate, or increasing exchange between indoor and outdoor air.

In the typical modern building, the exchange of indoor with outdoor air is accomplished by a central heating, ventilating, and air-conditioning (HVAC) system. These systems are diverse, although all have the same purpose: the delivery of air of acceptable quality to building occupants. The volume of air to be delivered follows the recommendation of standards set by the American Society of Heating, Refrigerating, and Air-Conditioning Engineers. In most new buildings, occupants can no longer control the temperature of the work environment and cannot open windows to increase air exchange. Most residences, however, still rely on natural ventilation.

Carbon Monoxide

Carbon monoxide, a byproduct of combustion of fuels, is released indoors by cooking and heating devices and also by smoking. Surveys conducted several decades ago of urban population exposures in Denver, Colorado, and Washington, D.C., indicate that residential concentrations of CO are typically low, ranging from 2 to 4 ppm during the winter, when windows of homes are generally closed and the homes heated. People living in homes with gas cooking ranges and those living with smokers have slightly higher levels of personal exposure. Measurements in the surveys of CO in

Table 60-4

Sources of Common Air Contaminants

Contaminant	Source
Asbestos	
Chrysotile	Some wall and ceiling insulation installed between 1930 and 1950
Crocidolite	Old insulation on heating pipes and equipment
Amosite	Old wood stove door gaskets
Tremolite	Some vinyl floor tiles
	Drywall joint-finishing material and textured paint purchased before 1977
	Cement-asbestos millboard and exterior wall shingles
	Some sprayed and troweled ceiling finishing plaster installed between 1945 and 1973
	Sprayed onto some structural steel beams as fire retardant
Combustion byproducts	
Carbon monoxide	Gas ranges
Nitrogen dioxide	Wood and coal stoves
Sulfur dioxide	Gas and propane engines
Particulate soot	Fireplaces
Nitrogenated compounds	Backdrafting of exhaust flues
	Candles and incense
Tobacco smoke	
Carbon monoxide	Cigarettes
Nitrogen dioxide	Pipes
Carbon dioxide	Cigars
Hydrogen cyanide	
Nitrosamines	
Aromatic hydrocarbons	
Benzo[a]pyrene	
Particles	
Benzene	

(*Continued*)

Table 60-4

(*Continued*)

Contaminant	Source
Formaldehyde	
Nicotine	
Formaldehyde	Some particle board, plywood, pressed board, paneling
	Some carpeting and carpet backing
	Some furniture and dyed materials
	Urea-formaldehyde insulating foam
	Some household cleaners and deodorizers
	Combustion (gas, tobacco, wood)
	Some glues and resins
	Tobacco smoke
	Cosmetics
	Permanent-press textiles
Biologic organisms	
Fungal spores	Mold, mildew, and other fungi
Bacteria	Humidifiers with stagnant water
Virus	Water-damaged surfaces and materials
Pollens	Condensing coils and drip pans in HVAC systems
Arthropods	Drainage pans in refrigerators
Protozoa	Some thermophilics on dirty heating coils
	Animals
	Rodents
	Insects
	Humans
Radon	
Radon gas and radon progeny	Radon gas emanating from soil, rocks, and water that diffuses through cracks and holes in the foundation and floor
	Radon in well water

Table 60-4

(*Continued*)

Contaminant	Source
	Radon in natural gas used near the source wells
Volatile organic compounds	Some building materials such as granite
Alkanes	Solvents and cleaning compounds
Aromatic hydrocarbons	Paints
Esters	Glues and resins
Alcohols	Spray propellants
Aldehydes	Fabric softeners and deodorizers
Ketones	Combustion
	Dry-cleaning fluids
	Some fabrics and furnishings
	Stored gasoline
	Outgasing from water
	Some building materials
	Waxes and polishing compounds
	Pens and markers
	Binders and plasticizers

SOURCE: Data from Turner WA, Bearg DW, Brennan T: Ventilation, in: Seltzer JM (ed), *Effects of the Indoor Environment on Health.* Philadelphia, PA, Hanley & Belfus, 1995, pp 41–58.

commercial and institutional buildings showed concentrations in the same range as in residences. The CO in residences and public buildings without combustion sources primarily reflects entry of motor vehicle exhaust from outdoor air into buildings through natural and mechanical ventilation. Intake vents at street level bring co-contaminated air into buildings. Elevated levels have been measured in commercial buildings with drive-in window operations (e.g., banks), buildings with underground parking garages, and enclosed ice rinks with ice-resurfacing machines without emission controls.

Acute and chronic health effects may be caused by CO exposure. About 500 accidental deaths in the United States are attributed annually to asphyxiation by CO inhalation and approximately 15,000 people are treated each year in emergency departments for CO exposure. The majority of the non-fatal cases occur in residences, with about 20 percent associated with faulty furnaces. A small proportion of cases occur in public buildings having faulty, unvented, or improperly ventilated combustion sources, such as charcoal stoves. The most common symptoms are nonspecific and include headache, nausea, and dizziness.

The level of CO in the blood is a useful biomarker of dose, and the health effects of exposure to CO can be related to COHb levels. In nonsmokers who are not exposed to CO in the environment, COHb levels are approximately 0.5 percent. This endogenous COHb comes from catabolism of hemoglobin and heme-containing enzymes of the liver. In comparison, COHb levels of cigarette smokers average about 4 percent and may be much higher. Frank CO poisoning, as manifest in headache, loss of motor control, and

coma, generally occurs with COHb levels above 20 percent. Clinicians have proposed the concept of "occult" CO poisoning, arising from persistent exposure to low levels of CO in indoor environments. Headache and dizziness, early symptoms of CO poisoning, have been associated with COHb levels greater than 10 percent. Increased levels of COHb resulting from indoor exposures may, at times, extend to values at which clinical testing has demonstrated cardiovascular and neurobehavioral effects. The Centers for Disease Control and Prevention recommend use of battery-powered CO detectors in homes to avoid CO exposure.

Nitrogen Dioxide

In the United States, with the exception of a few urban areas where outdoor NO_2 levels are high, indoor environments are the predominant determinant of total individual exposure. Residential exposures from unvented gas cooking stoves and kerosene space heaters are the major sources contributing to total individual exposure. Although vented to the outside by building codes, gas furnaces and water heaters may pollute residences because of flue-gas spillage and backdrafting caused by improper installation, maintenance, and weather conditions.

Levels in residences and the determinants of these levels have been characterized in many regions of the United States. Indoor NO_2 levels are generally increased during the winter, when homes are closed; they may also be high in the summer, when homes are closed for air conditioning. During cooking, concentrations may reach 1000 ppb while the stove is in use, resulting in substantial, but brief, exposures for persons near the stove. High indoor NO_2 concentrations have been documented in small inner-city apartments and when an oven is used for heating. Data on NO_2 levels in commercial and institutional buildings are very limited, but they generally show low levels consistent with the lack of indoor sources. High concentrations of NO_2 have been measured in ice-skating rinks, contaminated by emissions from resurfacing machines without emissions controls.

Oxidant injury has been postulated to be the principal mechanism by which NO_2 damages the lung. Inhaled NO_2 is thought to combine with water in the lung to form nitric acid (HNO_3) and nitrous acid (HNO_2). At high concentrations, NO_2 causes extensive lung injury in animals and humans. Fatal pulmonary edema and bronchopneumonia have been reported at extremely high concentrations; lower concentrations are associated with bronchitis, bronchiolitis, and pneumonia.

Experimental evidence indicates that NO_2 exposure adversely affects lung defense mechanisms. In experimental models, NO_2 effects mucociliary clearance, the alveolar macrophage, and the immune system. In animal experiments employing challenge with respiratory pathogens, exposure to NO_2 reduces clearance of infecting organisms and increases the mortality of the experimental animals. Adverse effects in these animal experiments have been demonstrated at concentrations that are an order of magnitude greater than those typically found in indoor environments.

The health effects of indoor NO_2 have been investigated primarily in studies directed at the consequences of indoor exposures for children. The toxicology of NO_2 implies that a wide variety of health effects are of potential concern, including reduced efficacy of host defenses against infectious organisms and the consequent increased risk of infection, exacerbation of asthma and chronic obstructive pulmonary disease, and respiratory tract inflammation with respiratory symptoms and a reduction in lung function. In spite of extensive investigation using laboratory and epidemiological approaches, the evidence still remains inconclusive with respect to each of these health outcomes.

The hypothesis that NO_2 increases the risk for respiratory infection has received the most intensive investigation. A number of epidemiological studies have compared the occurrence of respiratory infections in children in homes having gas stoves and higher concentrations of NO_2 with the occurance in children in homes with electric stoves and lower concentrations of NO_2. In a cohort study of infants at risk for asthma, NO_2 exposure during the first year of life was associated with respiratory symptoms including wheeze, cough, and shortness of breath. The findings of these studies have been inconsistent, largely because of the methodological complexities of investigating this association. Experimental exposures also have failed to provide consistent evidence that NO_2 increases infectivity in humans.

Inflammation of the airways by NO_2 could plausibly be associated with increased respiratory symptoms and reduced lung function. These potential adverse effects of NO_2 have been examined using data from epidemiological studies of children and adults. Many of these studies have included large numbers of participants studied cross-sectionally. The health outcome measures (e.g., reports of symptoms and levels of spirometric lung function) have been compared for participants living in homes with NO_2 sources, such as gas stoves and space heaters, and participants living in homes without such sources. Despite the number of such studies, there is no clear pattern of results. A meta-analysis using data from 11 studies found that a long-term increase in NO_2 exposure of approximately 15 ppb, consistent with the presence of a gas stove in the home, is associated with a 20 percent increase in the risk of respiratory illness in children.

Inflammation of airways would be expected to worsen the health status of persons with asthma. Short-term effects of NO_2 exposures on asthmatics have been studied by exposing volunteers and following the level of pulmonary function and nonspecific airway responsiveness. The evidence has been conflicting, and the findings are of limited generality because of the inclusion of relatively mild asthmatics in most studies.

The NO_2 exposures typically found in indoor and outdoor environments are not likely to cause clinically relevant effects for most persons with asthma. However, recent studies indicate that exposure to NO_2, in combination with allergens, may adversely affect persons with asthma. Studies have shown that exposure to NO_2 increases the response to challenge with specific allergen at levels as low as 0.40 ppm. A study of asthmatic children in the United Kingdom showed that exposure

to NO_2 increased the severity of virus-caused exacerbations. An experimental study in Australia of reduction of NO_2 exposures in schools showed that symptom rates in asthmatic children dropped following reduction of NO_2 concentration in the classroom. Thus, for persons with asthma, indoor NO_2 from unvented combustion sources could increase the adverse effects of exposure to common indoor allergens, such as those associated with house dust mites, cats, and cockroaches, and to viral pathogens. Little information is available on the effects of NO_2 exposure on persons with COPD.

Secondhand Smoke

Although the prevalence of smoking in the United States has decreased among adults to 20.9 percent, smoking remains common in public places and homes. *Secondhand smoke* (SHS) is a term now widely used to refer to the combination of side-stream smoke that is released from the cigarette's burning end and the mainstream smoke exhaled by the smoker. Survey and biomarkers data on SHS exposure for nonsmokers and children have documented widespread exposures, but the most recent evidence shows substantial declines in exposure to secondhand smoke. Blood levels of cotinine, the nicotine biomarker, dropped sharply from 1988 to 1989 to 2000 among nonsmoking participants in the National Health and Nutrition Survey (NHANES). In the first survey, most participants had a detectable cotinine value, but a majority did not in the more recent report. If smokers are present, exposure received indoors at home may dominate total personal exposures of involuntary smokers for particles and some gaseous pollutants, such as benzene.

Hundreds of chemical compounds have been identified in cigarette smoke; the indicators most often used to quantify its presence in the environment are respirable suspended particles (RSP), particles of mean aerodynamic diameter of less than 2.5 μm, CO, and nicotine, which is in the vapor phase of SHS. Nicotine is a highly specific marker for the presence of tobacco smoke; it can be monitored with both active and passive techniques. Largely because RSP can be readily monitored with area and personal sampling methods, levels of RSP have been widely used as a marker for SHS. The data show that smoking in the home approximately doubles the 24-h average indoor RSP concentration. Much higher short-term exposures, not reflected in these longer-term integrated measurements, must occur in homes when smoking is actually taking place. Data on SHS levels in public buildings have shown high short-term measurements in bowling alleys, at cocktail parties, in bars, and in other locations with a high density of smokers.

The adverse effects of environmental tobacco smoke (ETS) have been assessed in the context of the voluminous evidence on active smoking and health and of the detailed characterizations that have been made of the composition and toxicology of mainstream and sidestream cigarette smoke. Associations of SHS with disease and other adverse outcomes have been demonstrated (Table 60-5). The evidence has been reviewed by a number of expert panels, with the repeated conclusion that ETS causes both malignant and nonmalignant diseases in nonsmokers.

Table 60-5

Established Health Effects of Involuntary Exposure to Tobacco Smoke

Decrement in pulmonary function growth in childhood
Increased frequency of acute lower respiratory illness in early childhood
Increase in respiratory illness in children
Increased frequency of middle ear disease
Increased severity of asthma episodes and symptoms
Onset of asthma
Sudden infant death syndrome
Lung cancer in nonsmokers
Coronary heart disease
Reduced birth weight

Studies of children of smoking parents provided the first warning of the adverse effects of SHS on nonsmokers. Maternal smoking was found to increase risk of infants for lower respiratory tract illnesses, and smoking by household members, particularly the mother, was shown to increase the incidence of chronic respiratory symptoms and reduce the rate of lung growth in children. Children with asthma whose parents smoke have heightened airway responsiveness and increased morbidity, as documented by indexes of medical care utilization. Exposure to SHS is also a suspected cause of asthma, and infants of smoking parents have increased airway responsiveness shortly after birth. Epidemiological studies show that parental smoking is associated with persistent middle-ear effusions and other ear problems.

Exposure to SHS was first linked to lung cancer in never-smokers in two reports published in 1981. Numerous epidemiological studies have addressed this association, and the weight of the evidence shows a consistent positive association between living with a smoker and the risk of lung cancer. By 1986, the evidence led to conclusions of the International Agency for Research on Cancer, the U.S. Surgeon General, and the U.S. National Research Council that SHS causes lung cancer in never smokers. The risk of lung cancer is increased by approximately 20 percent for never-smoking women married to smokers. Based on review of the epidemiological evidence, as well as the supporting toxicological data, the EPA classified SHS as a class A carcinogen, a designation applied to agents causally linked to cancer.

Additional health effects of SHS have now been identified. A number of epidemiological studies have shown that marriage to a smoker increases risk for ischemic heart disease.

Although the evidence is not as extensive as for the respiratory consequences of SHS exposure, the American Heart Association, the United Kingdom's Scientific Committee on Tobacco, and the Environmental Protection Agency of the State of California have concluded that SHS exposure is a cause of cardiovascular disease and death. Estimates have been made that SHS causes between 22,669 to 69,553 cardiovascular disease–related deaths annually. Cited mechanisms include promotion of atherosclerosis, increased platelet aggregation, endothelial cell damage, and the consequences of CO exposure. SHS exposure at home and in the workplace has been linked to reduced lung function in some studies.

Wood Smoke

The presence of wood smoke indoors can be assessed by measurements of particles, organic compounds, and CO. Available data for developed countries suggest that the routine operation of a properly installed and maintained wood stove does not greatly affect indoor air quality, and outdoor air contaminated with wood smoke of neighbors can enter and pollute the interior air of homes without wood stoves. By contrast, in developing countries, biomass fuel combustion for cooking and space heating leads to very high exposures for large numbers of households around the world and also contributes to outdoor air pollution.

Wood smoke is a complex mixture, both in its physical and chemical characteristics and in its toxicological properties. The toxicology of some components of wood smoke, such as benzo[*a*]pyrene, other polycyclic organic compounds, and nitrogen oxides, has been extensively studied. Little research, however, has addressed the toxicology of wood smoke as a complex mixture.

Most of the available epidemiological evidence on the health effects of wood smoke is derived from investigations in developing countries, where intense smoke exposure results from the use of cooking fires in poorly ventilated dwellings. Studies from less developed countries suggest that smoke exposure adversely affects children and adults, increasing the occurrence of acute respiratory illness in children and chronic respiratory morbidity in children and adults. The occurrence of COPD in never-smoking women exposed to wood smoke has been described as well. Data from more developed countries are sparse and do not clearly indicate adverse effects at the lower concentrations of wood smoke generally present. Several studies indicate an association with childhood asthma.

Organic Compounds

Organic compounds are ubiquitous indoors, where they are released from furnishings and equipment, construction materials, and consumer and office products (Table 60-6). The organic compounds found in indoor air can be grouped by boiling point range as volatile (0 to 240°C), semivolatile (240°C to 380°C), and particulate (greater than 380°C). The volatile and semivolatile organic compounds are most relevant to human health. Volatile organic compounds exist as vapors over the normal range of air temperatures and pressures, whereas semivolatile organic compounds are liquids or solids but also evaporate.

Hundreds of organic compounds have been identified in indoor air. Although many of these agents are also released by outdoor sources such as chemical plants, indoor concentrations and sources have been shown to determine personal exposures to most of the organic compounds. The Total Exposure Assessment Methodology (TEAM) study conducted by the EPA showed the dominant contributions of indoor sources to personal exposures, even in locations with outdoor air polluted by industry. For example, benzene, a human carcinogen, may be emitted into outdoor air by industry and from gasoline. Among cigarette smokers in the TEAM study, however, the main source of personal exposure was benzene in mainstream cigarette smoke; passive smokers are also exposed to benzene.

Formaldehyde, used in hundreds of products, is one of the most ubiquitous indoor organic compounds. The largest use of formaldehyde is in preparation of urea and phenol-formaldehyde resins, which are used to bond laminated wood products and to bind the wood chips in particle board. Formaldehyde-containing wood products are used as shelving, counters, bookcases, cabinets, floors, and wall coverings in homes, offices, and public buildings. Formaldehyde resins are also used to treat paper products and fabrics and are constituents of numerous other consumer products. In 2004, on the basis of sufficient evidence in humans and sufficient evidence in experimental animals, the International Agency for Research on Cancer (IARC) concluded that formaldehyde is carcinogenic to humans (Group 1), a higher classification than in previous IARC evaluations.

The health risks of the organic compounds are diverse; the organics found in indoor air include several dozen carcinogens and mutagens (e.g., benzene), irritants (e.g., formaldehyde and terpenes), and neurotoxins (e.g., aromatic compounds). Despite the potential risks of the organic compounds in indoor air, few studies have shown specific exposure-disease associations, largely because of the difficulty of characterizing exposures and identifying effects of components of complex mixtures in indoor air. Indoor exposures to organics may contribute to the risks for several cancers, although few epidemiological studies have been directed specifically at assessing cancer risk in relation to indoor exposures to organics.

Radon

Radon-222, a noble gas, is in the decay chain of naturally occurring uranium-238. It decays with a half-life of 3.8 days into a series of short-lived progeny: polonium-218, lead-214, bismuth-214, and polonium-214. Irradiation of respiratory epithelial cells by alpha particles released by polonium-218 and polonium-214 damages cellular DNA and causes lung cancer. The principal source of radon in buildings is naturally occurring gas in soil. The driving pressure for entry of soil gas into a building is the pressure gradient established by a structure across the soil. The soil gas enters through openings,

Table 60-6

Common Organic Chemicals and Their Sources

Chemicals	Measured Peak Nonoccupational Exposure ($\mu g/m^3$)	Major Sources of Exposure
Volatile chemicals		
Benzene	1000	Smoking, auto exhaust, passive smoking, driving, pumping gas
Tetrachloroethylene	1000	Wearing or storing dry-cleaned clothes, visiting dry cleaners
p-Dichlorobenzene	1000	Room deodorizers, moth cakes
Chloroform	250	Showering (10-min average)
	50	Washing clothes, dishes
Methylene chloride	500,000	Paint stripping, solvent usage
1,1,1-Trichloroethane	1000	Wearing or storing dry-cleaned clothes, aerosol sprays, fabric protectors
Trichloroethylene	100	Unknown (cosmetics, electronic parts)
Carbon tetrachloride	100	Industrial strength cleansers
Aromatic hydrocarbons Toluene, xylenes, ethylbenzene, trimethylbenzenes	1000	Paints, adhesives, gasoline, combustion sources
Alphatic hydrocarbons Octane, decane, undecane	1000	Paints, adhesives, gasoline, combustion sources
Terpenes Limonene, *a*-pinene	1000	Scented deodorizers, polishes, fabrics, fabric softeners, cigarettes, food, and beverages
Semivolatile chemicals		
Chlorpyrifos (Dursban)	10	Insecticide
Chlordane, heptachlor	100	Termiticide
Diazinon	100	Insecticide
Polychlorinated biphenyls (PCBs)		Transformers, fluorescent ballasts, ceiling tiles
Polycyclic aromatic hydrocarbons (PAHs)	1	Combustion products (smoking, wood burning, kerosene heaters)

SOURCE: Data from Wallace LA: *The Total Exposure Assessment Methodology (TEAM) Study: Summary and Analysis.* Washington, D.C., U.S. Environmental Protection Agency, Office of Research and Development, 1987.

such as sump pump wells, drains, cracks, and utility access holes. In most locales, building materials and water used in the home do not contribute significantly to concentrations of radon indoors. Because radium, the parent radioisotope for radon, is ubiquitous, radon is present in outdoor air and in higher concentrations in indoor environments.

Extensive data on radon concentrations in homes in the United States show that the average value is about 1.5 picocuries per liter (pCi/L). Homes with high concentrations have been identified in all states, although the proportion exceeding the EPA's action guideline of 4 pCi/L is variable among the states. In a national survey conducted from 1988 through

1991, the EPA measured radon concentration in 6000 randomly selected homes in the United States. About 4 percent of homes were estimated to exceed the guideline of 4 pCi/L annual average.

Exposure to radon progeny, the short-lived decay products of radon, has been causally linked to increased risk of lung cancer in uranium miners and other underground workers. Measurements made since the 1970s in the United States and elsewhere have shown that radon is present in most homes and can reach high concentrations—as high as those in underground mines—with a documented excess of lung cancer. Current risk models that assume that the risk follows a linear nonthreshold relationship imply that even values under current guidelines cause a significant number of lung cancer cases. Thus, any exposure is assumed to convey some risk, an assumption supported by experimental data. Additionally, epidemiological studies of indoor radon confirm that indoor radon concentration is positively associated with radon risk.

The hazard posed by exposure to radon progeny in indoor air has been characterized primarily through risk estimation procedures. In the most widely applied risk assessment approach, the risks for the general population are projected by extrapolating risks observed in the studies of miners to the general population. The risk of radon indoors has also been directly estimated by carrying out case-control studies in the general populations. Estimates obtained by pooling the results of these studies are consistent with the extrapolated risks from studies in miners. Use of such models leads to the conclusion that radon contributes significantly to the incidence of lung cancer in the population. The burden of radon-related lung cancer in the general population reflects, in part, the synergism between radon and cigarette smoking assumed in the models.

One risk model is based on a pooled analysis of data from 11 epidemiological studies of male miners, including 68,000 who accounted for more than 2700 cancer deaths. The analysis showed a positive linear relationship between the risk of lung cancer and occupational radon exposure, down to exposures only a fewfold greater than average lifetime exposure from indoor radon. Lung cancer risk was found to decline with increasing age and time since exposure; the risk was also found to increase as the rate of exposure decreased—the so-called inverse-dose rate effect. When the model was applied to the U.S. population, indoor exposure to radon at home was estimated to be responsible for about 12 percent of lung cancer deaths in the United States. Of the 15,000 to 22,000 lung cancer deaths attributed to radon in 1995, about 85 percent were assigned to smokers and 15 percent to never-smokers.

The substantial lung cancer burden attributed to indoor radon has led to programs for reduction of exposure. The program in the United States, conducted by the EPA, calls for voluntary measurement of radon levels in single-family homes and modification if the annual concentration exceeds the agency's guideline level of 4 pCi/L. Two types of passive measurement devices are available: short-term devices, which make measurements for a few days, and long-term devices, which make measurements for periods of months up to a year. The short-term devices, primarily charcoal canisters, are often used when a measurement is quickly needed during a real estate transaction; the longer-term devices incorporate a piece of plastic that is etched by alpha particles released by progeny.

Fortunately, increased radon concentrations can be lowered, often by such simple measures as sealing basement cracks and sump holes. Approaches also include ventilating the basement to the outside and, for homes built on concrete slabs, by providing a system to exhaust the soil gas from beneath the slab. In areas having a high potential for indoor radon problems, radon-resistant construction techniques can be applied in anticipation of high levels.

The success of the EPA's program for managing the indoor radon problem rests on voluntary action by the public. To engage the public, the Agency has developed a risk communication strategy that uses the media, voluntary health agencies (e.g., the American Lung Association), and health-care providers. Its pamphlet, "A Citizen's Guide to Radon," informs readers about the risks and the recommended approaches for managing them.

Asbestos and Man-Made Fibers

Asbestos, comprising several fibrous inorganic materials characterized by chemical formulation and crystalline structure, has been used extensively in building materials since the beginning of the century because of its high tensile strength and thermal properties. The broad categories of use are thermal and acoustic insulation, fire protection, and reinforcement of building products. In addition to its use in acoustic ceiling tiles and vinyl floor tiles, asbestos has been used in paints and wall and ceiling plaster; until banned in the late 1970s, asbestos materials were used to coat pipes, boilers, and steel structural beams.

Asbestos-containing materials are present in homes, offices, and schools. The EPA has estimated that 20 percent of the nation's buildings, or about 733,000 buildings (not including schools and residential dwellings with fewer than 10 units), contain some asbestos materials.

Asbestos had been used widely in ceiling tiles, pipe wrap, plaster, floor tiles, shingles, and sprayed-on insulation, among other applications. Release of fibers from these materials may result from impact, abrasion, fallout, vibration, air erosion, and fire damage. Water damage and the normal aging of binders, leading to the friability of the material, increase the likelihood of release. Asbestos-contaminated surface dust may contribute to airborne concentrations in buildings.

Man-made mineral fibers are now used increasingly as substitutes for asbestos in building materials. These are fibrous inorganic substances made primarily from rock, clay, slag, or glass; the principal types are glass fibers (comprising glass wool and glass filaments), rock wool, slag wool, and ceramic fibers. Fiberglass and glass wool refer to silica-based vitreous fibers manufactured by a number of different processes. The different types of fibers vary in their chemistry

and dimensions, as well as in their durability in vivo. Because they are physically fibrous, there is concern about the same health effects as for asbestos.

An enlarging database on airborne asbestos concentrations in buildings demonstrates extremely low average values under the conditions of normal building use. Occupant risk is determined by exposures to airborne fibers, rather than the presence of asbestos-containing materials in the building. Surveys of asbestos concentrations in commercial buildings demonstrate very low fiber concentrations under normal conditions. The Literature Review Panel Report published by the Health Effects Institute, Asbestos Research Committee, compiled all published data, as well as previously unpublished information, on buildings sampled for litigation and for other purposes. The total data set included 1,377 measurements made by transmission electron microscopy in 198 buildings. For fibers greater than 5 mm in length, which are considered most relevant to disease risk, the mean and median concentrations were low, at approximately 0.001 fiber per milliliter, or three or more orders of magnitude lower than concentrations in the occupational settings of the past. Individual buildings with levels much higher than the typical values in the data assembled by the Health Effects Institute, Asbestos Research Committee, have been reported.

For office workers, visitors to buildings, and schoolchildren and teachers, mesothelioma and lung cancer are the principal health effects of concern; asbestosis would not be expected at usual exposures for these building occupants. The risks of indoor asbestos for the general population have been estimated by extrapolation of risks for occupationally exposed persons. Uncertainty is inherent in this approach, but the risks cannot be directly investigated by epidemiological methods. The Literature Review Panel Report of the Health Effects Institute, Asbestos Research Committee, has estimated risks for various scenarios of exposure (Table 60-7).

Table 60-7

Estimated Lifetime Cancer Risks for Different Scenarios of Exposure to Airborne Asbestos Fibers*

Conditions	Premature Cancer Deaths (Lifetime Risks) per Million Exposed Persons
Lifetime, continuous outdoor exposure	
0.00001 fiber/ml from birth (rural)	4
0.00001 fiber/ml (high urban)	40
Exposure in a school containing ACM, from age 5 to 18 years (180 days/year, 5 h/day)	
0.0005 fiber/ml (average)†	6
0.005 fiber/ml (high)†	60
Exposure in a public building containing ACM, from age 25 to 45 years (240 days/year, 8 h/day)	
0.0002 fiber/ml (average)†	4
0.002 fiber/ml (high)†	40
Occupational exposure from age 25 to 45	
0.1 fiber/ml (current occupational levels)‡	2000
10 fiber/ml (historical industrial exposures)	200,000

ACM = asbestos-containing material.

*This Table represents the combined risk (average for males and females) estimated for lung cancer and mesothelioma for building occupants exposed to airborne asbestos fibers under the circumstances specified. These estimates should be interpreted with caution because of the reservations concerning the reliability of the estimates of average levels and of the risk assessment models.

†The "average" levels for the sampled schools and buildings represent the means of building averages for the buildings reviewed herein. The "high" levels for schools and public buildings, shown as 10 times the average, are approximately equal to the average airborne levels of asbestos recorded in approximately 5 percent of schools and buildings with asbestos-containing materials. If the single highest sample value is excluded from calculation of the average indoor asbestos concentration in public and commercial buildings, the average value is reduced from 0.00021 to 0.00008 fiber/ml, and the lifetime risk is approximately halved.

‡The concentration shown (0.1 fiber/ml) represents the permissible exposure limit proposed by the U.S. Occupational Safety and Health Administration. Actual worker exposure, expected to be lower, will depend on a variety of factors, including work practices and use and efficiency of respiratory protective equipment.

SOURCE: Data from Health Effects Institute, Asbestos Research Committee, Literature Review Panel. *Asbestos in Public and Commercial Buildings: A Literature Review and a Synthesis of Current Knowledge.* Cambridge, MA, Health Effects Institute, 1991.

Custodial and maintenance workers in buildings with asbestos-containing materials may be exposed to higher levels of asbestos than other building occupants, since their activities disturb the materials and release fibers. These workers may be at particular risk if they are unaware that asbestos-containing materials are present or are untrained in dealing with these materials. Several studies have shown that custodial and maintenance workers may have pleural plaques and possibly asbestosis, causing concern that a "third wave" of asbestos-caused disease could occur in such workers.

Because of the morphological and toxicological comparability of asbestos and man-made mineral fibers, there has been concern that exposure to man-made mineral fibers could produce the same diseases caused by asbestos. The relevant epidemiological data from exposed workers are less extensive than for asbestos. Animal studies have shown the fibers that are long and thin to be carcinogenic. Some have concluded from epidemiological evidence and toxicological properties of the materials that the health risk of man-made mineral fibers is likely to be negligible for exposures of building occupants.

Recently, the IARC re-evaluated the carcinogenic risk of airborne man-made vitreous fibers. Epidemiological studies, published since a review in 1988, as well as research conducted on newer fibers, were evaluated. The IARC concluded that only the more biopersistent materials, such as refractory ceramic fiber (RCF), remain classified as possible human carcinogens. Continuous glass filaments and the more commonly used vitreous feber wools, such as insulation glass wool, rock wool, and slag wool, are now considered not classifiable as to their carcinogenicity to humans. Nevertheless, to date, no data are available linking RCF with tumors in humans.

Table 60-8

Sources of Biologic Air Pollutants

Acarids
Dust mites and spiders
Insects
Cockroaches, crickets, beetles, fleas, moths, flies, and midges
Domestic animals
Cats, dogs, other mammals, and birds
Rodents
Wild
Mice and rats
Pets
Mice, gerbils, and guinea pigs
Fungi
Indoors (growing on interior surfaces or in air-conditioning systems)
Penicillium, Aspergillus, Rhizopus, and *Cladosporium*
Outdoors
Numerous species entering with incoming air
Pollens
Derived from outdoor plants or plant materials brought inside
Bacteria
Legionella (introduced into ventilation systems by cooling towers and standing water reservoirs)

Biologic Agents

Indoor allergens and microbes—the principal biologic agents in indoor air relevant to human health—have diverse sources, both indoors and outdoors (Table 60-8). Indoor levels of allergens and microbes may be increased by accumulation of materials indoors, such as human and animal dander, and growth of fungi and bacteria on interior surfaces or in air conditioning systems. Indoor pollen is derived almost entirely from outdoor plants, and fungus spores from outdoors may also enter the indoor environment on air infiltration or inadvertently on people, animals, or objects.

Some of the most severe and prevalent indoor biologic pollution problems result from the growth of microorganisms on interior surfaces that are wet and moist. Substrates which provide a source of both carbon and water can support the growth of microorganisms. High relative humidity, in excess of 70 percent, promotes condensation on interior surfaces (e.g., cool exterior walls or windowsills). Leaks from water pipes and roofs can also provide consistent sources of moisture. Other moisture sources are humidifiers, vaporizers, and air conditioners; once contaminated, these devices can distribute fungal fragments, spores, and dissolved allergens into room air. Mold has been a problem in homes flooded by storms.

In recent years, the growth of molds in home, school, and office environments has been cited as the cause of a wide variety of human ailments and disabilities. So-called "toxic mold" has become a prominent topic in the lay press and is increasingly the basis for litigation when individuals, families, or building occupants believe they have been harmed by exposure to indoor molds.

Molds and other fungi may adversely affect human health through allergy or infection. Some species of fungi, including some molds, are known to be capable of producing secondary metabolites, or mycotoxins and, possibly, of causing respiratory disease via a toxic syndrome. A controversial issue regarding mold in the home is that of "idiopathic pulmonary hemorrhage" associated with *Stachybotrys chartarum.* Following an initial report of 10 cases in Cleveland in 1994, additional case reports followed, linking mold exposure or mycotoxins with pulmonary hemorrhage in infants. Recent critical reviews of the literature have concluded that indoor

airborne levels of microorganisms are only weakly correlated with human disease or building-related symptoms and that a causal relationship has not been established between these complaints and indoor exposures to *S. chartarum.*

Limited information exists on levels of microbial particles in air. Indoor levels and, hence, personal exposure are highly variable and are probably affected by activities such as vacuuming, sweeping, dusting, making beds, scrubbing contaminated surfaces, and using electric fans. Further, airborne and dust concentrations of allergens probably have limited value for assessing the contribution of a particular allergen in causing disease. Factors such as aerodynamic behavior, respirability, solubility, and cross-reactivity with other allergens are also important in the process of immunological sensitization and the development of allergic disease.

Dust mites (*Dermatophagoides pteronyssinus, D. farinae*, and *Euroglyphus maynei*) are commonly found in houses and are important sources of allergens, particularly for persons with asthma. These mites are approximately 0.3 mm in length and live in carpets, upholstered furniture, mattresses, and bedding, where they eat skin scales. Two major dust mite allergens have been identified, *Der p* I and *Der p* II. These proteins are derived from digestive enzymes in the gut of the mite and are found in high concentrations in the fecal pellets. Vacuum sampling and immunologic assays indicate that in the home, the highest levels of allergen occur in the bedroom in carpeting, mattresses, and bedding.

Domestic cockroaches, including the German cockroach, *Blattella germanica*, are commonly found indoors and represent another source of allergen in residences, particularly in infested inner-city housing. Fecal material and saliva contain large amounts of the allergens *Bla g* I and *Bla g* II. In inner-city homes, mice infestations may contaminate residences with the mUS antigen.

Cats and dogs are prevalent sources of allergen exposures. *Fel d* I is the most significant allergen associated with cats, and high levels of this protein are found in cat dander and fur and also in saliva and urine. The median level of *Fel d* I in samples of settled household dust in homes with a cat are reported to range from 2 to 130,000 ng/g of dust, with a median level of 90 ng of *Fel d* I/g of dust. In homes without a cat, much lower levels are observed, ranging from 2 to 7500 mg of *Fel d* I/g of dust; the antigen is persistent in indoor environments for long periods after a cat is no longer indoors. The presence of the allergen in the dust of homes and buildings in which cats are not kept suggests that the allergen can be transported on clothing. The major dog allergen, *Can f* I, is present in dog fur and saliva and is a relatively stable protein that may persist in dust for a long time. The content of *Can f* I in household dust from homes with a dog ranges from 10 to 10,000 mg/g of dust, compared with 0.3 to 23 ng/g of dust in homes without a dog.

Mouse allergen, a cause of asthma in laboratory workers, is prevalent in homes. A national study of inner-city childhood asthma found widespread contamination with this allergen and frequent positivity to the allergen on skin testing.

Fungi are present in the air of virtually all homes and public buildings. Commonly isolated genera include *Cladosporium, Penicillium, Alternaria, Epicoccum, Aspergillus,* and *Drechslera.*

Biologic agents in indoor air may cause disease through various mechanisms, including direct toxicity, infections, and immune hyperresponsiveness. A complete review of these diverse effects is beyond the scope of this chapter. Selected examples of diseases caused by biologic agents are given; more extensive information is available in published reviews.

The presence of dampness and mold, determined by questionnaire, has been associated with upper respiratory symptoms and eye irritation in large studies of children in the United States and elsewhere. These associations were adjusted for known determinants of respiratory symptoms, including maternal smoking, city, child's age and sex, and parent education. There are also similar findings in adults. A recent systematic review concluded that dampness in buildings contributes to adverse health effects in persons with and without atopy, but a specific causal agent cannot be identified. The evidence on dampness was reviewed by an Institute of Medicine committee which did not find the evidence to be sufficient to conclude that dampness causes respiratory symptoms or asthma.

Allergic rhinitis, or "hay fever," is common, affecting approximately 20 percent or more adults in the United States. Identification of the specific indoor allergen associated with the symptoms may be accomplished by skin testing and in vitro measurement of antibody [radioallergosorbent test (RAST)]. Many persons with asthma are sensitive to specific antigens from pollens, animal fur, fungi spores, and house dust. The risk of acute or severe attacks of asthma is increased in residences with levels of *Der p* I in excess of 10 μg/g of house dust, and asthmatic patients have been reported to show a 25 percent prevalence of skin test positively to cat or dog allergen extracts. Building-related allergic respiratory disease and epidemic asthma have been reported in office buildings in association with air-handling systems and humidifiers contaminated with bacteria and fungi.

Avian proteins are present in bird excreta (e.g., the droppings of pet birds such as parakeets), and fungal spores of thermophilic actinomycetes, *Aspergillus* species, *Penicillium* species, and *Aureobasidium* species may contaminate the indoor environment and cause hypersensitivity pneumonitis. A careful review of symptom pattern in relation to home and work environments and site evaluation may be needed to identify the source of exposure.

The bacterium *Legionella pneumophila,* the agent of legionnaires' disease, causes an often fatal pneumonia associated with exposure to the bacterium in aerosols of cooling towers and air-handling systems and in humidifiers and spas. It exemplifies a respiratory pathogen associated primarily with indoor environments, in both source and transmission. Of course, indoor environments are the locus of transmission of many infectious respiratory diseases, including influenza

and tuberculosis. The risk of diseases depends on the strength of sources and the level of ventilation. A low air exchange rate increased the risk for pneumococcal infection among inmates in a large county jail.

CLINICAL SYNDROMES ASSOCIATED WITH INDOOR ENVIRONMENTS

During the last 20 years, complaints attributable to indoor environments have generally been classified into one of two broad groups: specific building-related illnesses and sick building syndrome (SBS).

Building-related illnesses have a number of etiologies, but the specific agent responsible for causing the disease is present in the indoor environment, e.g., hypersensitivity pneumonitis caused by fungi in the ventilation system or Legionnaires' disease resulting from transmission of the organism that grows in cooling-tower water.

Sick building syndrome refers to nonspecific health problems related to indoor air quality in nonindustrial buildings. Irritation of mucosal surfaces and neurotoxic effects may contribute to the nonspecific symptom complex that often include headache, fatigue, and difficulty concentrating. Atopic individuals have been shown to have lower irritant thresholds than nonatopics. Multiple factors, including specific exposures, inadequate ventilation, and poor building maintenance have been linked to SBS. Panel studies in Denmark have found that complaints were most often attributed to the ventilation system, SHS, office machines, and other sources.

SUSCEPTIBLE POPULATIONS

The legislative history of the Clean Air Act mandated that the primary NAAQS were to be set low enough to protect the health of all susceptible groups within the population except those requiring life-support systems. Only two diseases, asthma and emphysema, were specifically identified in the Clean Air Act as associated with increased susceptibility. Other groups in the population, accounting for large numbers of people, are also considered to be at increased risk from air pollutants: persons with coronary artery disease and, possibly, peripheral vascular disease; infants and the elderly in general; and children with chronic pulmonary ailments such as cystic fibrosis and bronchopulmonary dysplasia.

In this section, we consider the evidence concerning these susceptible groups (Table 60-9). Pulmonologists are likely to be asked about the consequences of pollution exposures by persons with chronic lung diseases. Patients may report being adversely affected by exposures and may request guidance concerning control measures—e.g., purchase of an air-cleaning device or additional medication use when exposed.

Clinical Studies in Asthma and COPD

Clinical studies have provided much of the evidence on the effects of pollutants on persons with chronic respiratory diseases. Controlled laboratory studies of volunteers have attempted to identify specific effects of individual pollutants, as assessed primarily by pulmonary mechanics;

Table 60-9

Populations Considered Susceptible to Air Pollution

Population	Potential Mechanism	Consequences
Asthmatics	Increased airway responsiveness	Increased risk for exacerbation and respiratory symptoms
Cigarette smokers	Impaired defense and clearance, lung injury	Increased damage through synergism
Elderly	Impaired respiratory defenses	Increased risk for respiratory infection
	Reduced functional reserve	Increased risk for clinically significant effects on function
Infants	Immature defense mechanisms of the lung	Increased risk for respiratory infection
Persons with coronary heart disease	Impaired myocardial oxygenation	Increased risk for myocardial ischemia
Persons with chronic obstructive pulmonary disease	Reduced level of lung function	Increased risk for clinically significant effects on function

however, other end points, including symptoms, have been assessed.

The most striking effect of acute exposure to SO_2 at concentrations under 1.0 ppm is the induction of bronchoconstriction in asthmatics after exposures lasting only 5 min. In contrast, inhalation of concentrations of SO_2 in excess of 5 ppm causes only small decrements in airway function in normal subjects. Lung function responses to SO_2 in asthmatics are greater when SO_2 exposure is accompanied by increased ventilation, usually stimulated by exercise. SO_2-induced bronchoconstriction can be exacerbated by breathing cold or dry air and oral (versus nasal) breathing. The SO_2 bronchoconstrictor response can be reduced or inhibited in asthmatics by anticholinergic agents, mast cell stabilizers, or beta agonist bronchodilators.

Inhalation of acidic aerosols generally produces little alteration in pulmonary function in normal subjects, even Permissible Exposure Limit of 1 mg/m^3 in the workplace. As with SO_2, asthmatic subjects have been found to be susceptible to the effects of acidic aerosol exposure, although different laboratories have found differing concentrations for threshold exposure. Adult asthmatics exposed to aeorsols of 450 and 1000 $\mu g/m^3$ of H_2SO_4 demonstrate decrements in specific airway conductance. Adolescent asthmatics appear to be more sensitive to the effects of acidic aerosols than adult asthmatics. Functional decrements have been observed in adolescents at levels as low as 70 $\mu g/m^3$, concentrations occasionally noted in outdoor air and an order of magnitude lower than the level at which effects are observed in normal subjects. The apparent difference in sensitivity of adult and adolescent asthmatics may also be due to differences in the research protocols. In these studies, young asthmatics showed functional decrements at exposure levels that corresponded to near-peak outdoor levels in the northeastern United States. Field studies in summer camps of both normal and asthmatic children reported decrements in pulmonary function during pollution episodes that included exposure to increased levels of acidic aerosols, supporting the concern that children and adolescents may be particularly susceptible to effects of acidic atmospheres.

Although several controlled human studies have found asthmatics to be responsive to low levels of NO_2, the findings have not been consistent. The conflicting results among these studies are probably related to the differences in subject selection and exposure protocols. Persons with COPD may represent a group with increased susceptibility to short-term exposure to NO_2. Further study of the issue is needed.

Consonant with the provisions of the Clean Air Act and with its legislative history, a group that appears to be at potential risk from exposure to ozone consists of those characterized as having pre-existing respiratory disease. In the case of asthmatics, however, emerging data from controlled studies indicate no greater responsiveness to ozone in mild asthmatics than in normal, healthy populations. Pretreatment of healthy volunteers with β-adrenergic agents before O_3 exposure and exercise does not prevent bronchoconstriction, whereas pretreatment with atropine or indomethacin reduces the decrement in lung function. Since exercise greatly potentiates the response to ozone, the best strategy for clinical management includes avoiding outdoor exercise during periods of high O_3 pollution.

Clinical Studies in Heart Disease

Persons with coronary heart disease have also been identified as a group at risk from increased levels of air pollution. In the presence of coronary artery disease, there is limited ability to increase coronary blood flow in response to increased myocardial oxygen consumption during exercise. When myocardial blood flow is not sufficient to meet oxygen demand, the myocardium becomes ischemic, resulting in angina pectoris, ECG changes, or both. Several recent studies conducted at relatively low COHb levels have investigated the effects of CO exposure on exercise capacity and the occurrence of myocardial ischemia. These studies found a decrease in the time to the occurrence of myocardial ischemia in persons with coronary artery disease during exercise after CO exposure. The lowest CO dose to produce a decrease in time to the onset of angina was associated with a 2 percent COHb level. In this study, there was a mean decrease of 4.2 percent in the time to angina and a mean decrease of 5.1 percent in the time to ECG changes, indicative of myocardial ischemia at 2 percent COHb compared to control (air exposure) days; greater effects were noted at 3.9 percent COHb. Clinical studies have shown a significant dose-response relationship for the individual differences in time to the onset of ECG changes at increasing COHb levels. In addition, at a COHb level of 6 percent, patients with coronary artery disease experience an increase in the frequency of arrhythmias. Of note, at the same low levels of COHb, adverse effects have been observed in humans but not in animals.

CONTROL STRATEGIES

Controlling the health effects of indoor and outdoor air pollution requires strategies oriented toward populations and toward individual patients. Clinicians can make practical recommendations to their patients in order to reduce risk for disease and for exacerbation of established disease. Clinicians may serve as consultants or as advocates in seeking to reduce the effects of indoor and outdoor air pollutants through population-oriented control approaches.

Patient-Oriented Strategies

Approaches for limiting the health risks of breathing polluted ambient air have received little investigation. Present understanding of the determinants of exposure suggests that modifying time-activity patterns to limit time outside during episodes of pollution represents the most effective strategy. The levels of some reactive pollutants tend to be lower indoors than outdoors. O_3 levels in buildings are lower than outdoor levels, but they can be driven upward by increasing the rate

Table 60-10

Questions and Answers About Indoor Air Pollution

Question	Answer
Do air cleaners work?	Air cleaners have not yet been shown to have direct health benefits.
Should the radon concentration in my home be measured?	Yes, radon can be readily measured at relatively low cost, and mitigation is feasible.
Should the air ducts in my home be cleaned?	There is no evidence on health benefits of cleaning air ducts.
Will controlling mites be beneficial?	Controlling mite levels is beneficial for persons with mite-sensitive asthma.
Should my home be humidified?	Humidification may increase allergen levels.

of exchange of indoor with outdoor air. Fine acid aerosols can penetrate indoors, but neutralization by ammonia produced by occupants, pets, and household products may reduce concentrations. Other types of particles in outdoor air may also enter indoor air. Nevertheless, health care providers can reasonably advise patients to stay indoors during pollution episodes. Vigorous exercise outdoors, which increases the dose of pollution delivered to the respiratory tract, should also be avoided at such times.

Susceptible patients should be counseled concerning the nature and degree of their susceptibility. The use of medication should follow the usual clinical indications, and therapeutic regimens should not be adjusted because of the occurrence of a pollution episode without evidence of an adverse effect on symptoms or function. In the laboratory, inhalation of cromolyn sodium and bronchodilating agents blocks the response to some pollutants, but use of these drugs solely because of exposure to air pollution cannot be advised.

Respiratory protective equipment has been developed for use in the workplace to minimize exposure to toxic gases and particles. Many of these devices, particularly those likely to be most effective, add to the work of breathing and cannot be tolerated by persons with respiratory disease. Under most circumstances, health care providers should not suggest respiratory protection as a method for reducing the risks of ambient air pollution. Similarly, air cleaners have not been shown to have health benefits, whether directed at indoor pollutants generated by indoor sources or at those brought in with outside air.

Pulmonologists may be concerned with diverse issues related to the control of indoor air pollution, ranging from answering patients' questions about pollutant health effects and control, to management of complex problems in large buildings. Some commonly asked questions and answers that reasonably reflect the state of the evidence are provided in Table 60-10. The clinically relevant microenvironments are numerous, including the home, the workplace, public buildings, and places where leisure time is spent.

Workplace problems, such as the "sick-building syndrome," may be particularly challenging. The health care provider needs to establish the connection between the workplace and the occurrence of symptoms and then seek a solution that includes identifying and remediating the responsible factors in the workplace. The diagnostic task requires a sufficient awareness of the possible causal role of the indoor environment (Fig. 60-2). Resolution may require an evaluation and intervention by indoor air quality professionals. The physician may be unable to resolve the patient's symptoms without motivating a building evaluation and resolution of underlying problems. Guidance for the clinician has been offered by the ATS.

Community-Oriented Strategies

Frequently, communities become concerned about the effect of particular local sources—e.g., a power plant or manufacturing facility or vehicle depot. Exposures to air pollutants and other environmental contaminants may dispropotionately affect disadvantaged communities. The term "environmental justice" is used in addressing inequities between poorer and more well-to-do communities. Concern about the health risks may quickly lead to controversy and litigation. Thus, understanding the health risks posed by local sources may be difficult and may require skills in community health, as well as in epidemiology and toxicology. Local physicians may become active through concerns about the health of their patients or as advocates for the community's environment or for the polluting facility. Most often the dimensions of such complex problems exceed the skills of local physicians. Involvement may be appropriate, but guidance should be obtained from appropriate public health and environmental agencies.

In 1976, the EPA proposed cautionary statements for public reporting of outdoor air quality—the Pollutant

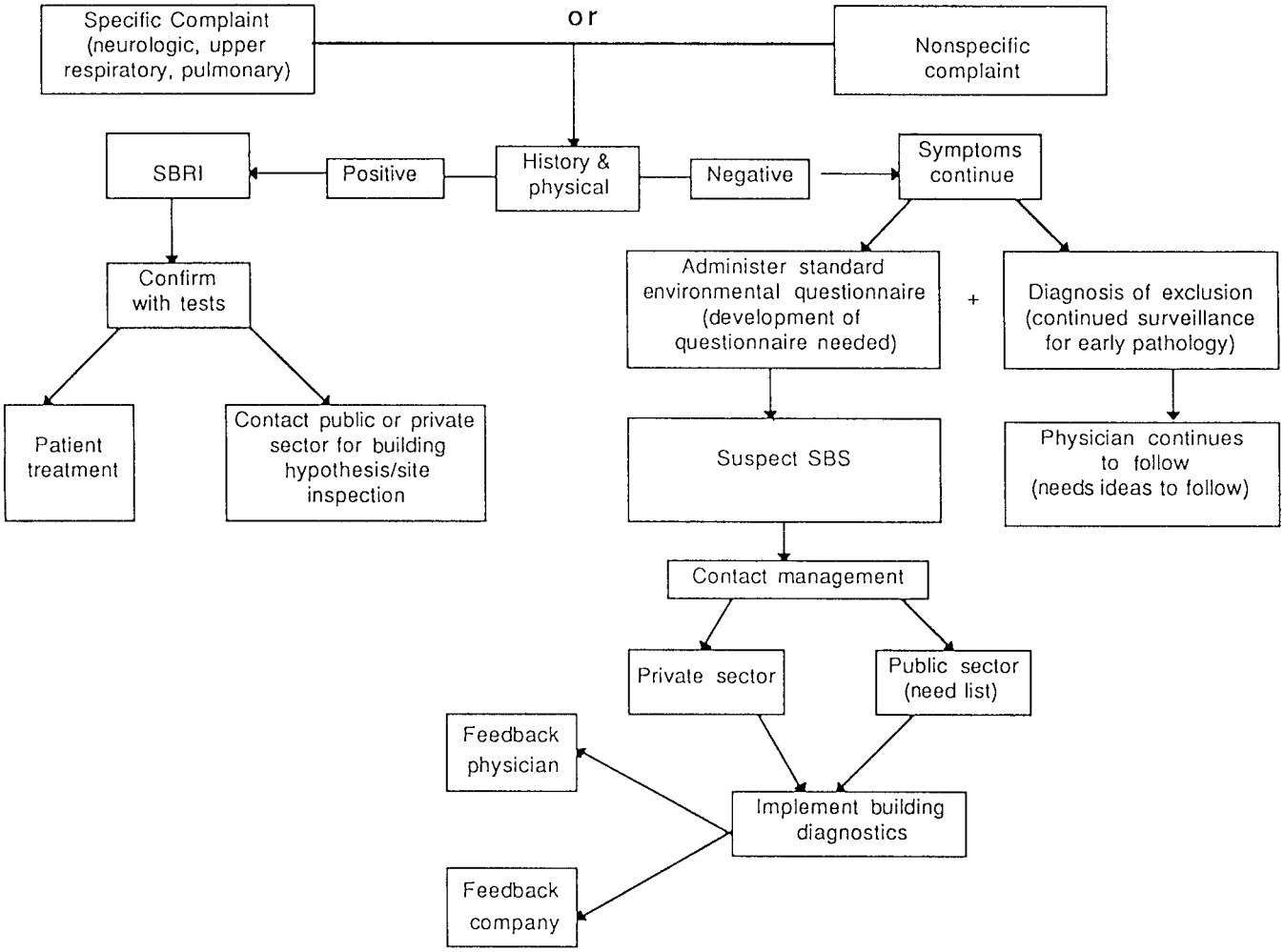

Figure 60-2 Medical approach to patient with complaints possibly related to indoor air pollution without an antecedent diagnosis. SBRI = Specific building-related illnesses; SBS = sick building syndrome. *(Based on American Thooracic Society data.)*

Standards Index—for criteria pollutants. In the 1999 revision, the name was changed to the Air Quality Index (AQI). The index provides AQI levels, descriptors of air quality, and guidelines for cautionary statements. The actions taken when "alert levels" are reached or expected to be reached include the issuance of health advisories (or cautionary statements) to the public. The EPA's advice is intended to be applied by local air pollution agencies in preparing daily air quality summaries to be disseminated to the media. Although the cautionary statements require some revisions, especially as related to ozone exposures, useful guidelines are offered for the physician and public health officials.

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High-Altitude Physiology and Clinical Disorders

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ARTERIAL CHEMORECEPTORS AND CONTROL OF RESPIRATION

The responses of oxygen-sensing organs lie at the core of adaptations that take place with ascent to high altitude. This chapter focuses on these physiological adaptations and clinical disorders, including acute mountain sickness, high-altitude pulmonary edema, high-altitude cerebral edema, and chronic mountain sickness.

Only since the late 1920s has it been recognized that the ventilatory response to hypoxia originates from peripheral chemoreceptors situated in the carotid and aortic bodies. Previously, the central chemoreceptors, as CO_2-sensing organs, were the focus of investigation of the respiratory control system. Even Haldane believed that hypoxia acted centrally by producing acid. Eventually, the basis of the hypoxic stimulus to breathing was discovered using simple cross-circulation experiments in dogs.

Acute Responses to Hypoxia

The carotid body is composed of highly aerobic tissue that depends primarily on mitochondrial oxidative phosphorylation for adenosine triphosphate (ATP) production. Synthesis of ATP by mitochondria is tightly coupled to oxygen consumption; that is, mitochondria respire only fast enough to replenish ATP as it is used. Decreased availability of oxygen first affects the ability of mitochondria to maintain the ratio [ATP]/[ADP][Pi], a measure of energy available when ATP is hydrolyzed to adenosine diphosphate (ADP) and inorganic phosphate (Pi). Respiration is stimulated by decreasing the ratio and, as a result, the rate of respiration does not decrease until oxygen deprivation is severe enough to exhaust the capacity of the control system.

Inhibitors of mitochondrial function have been known for decades to transiently stimulate afferent activity of the carotid body, and many studies have used inhibitors of mitochondrial respiration and phosphorylation in both isolated carotid body preparations and glomus cells. Among the compounds causing a transient increase in afferent activity are reparatory chain inhibitors (e.g., cyanide); inhibitors of energy coupling (e.g., oligomycin); and uncouplers of oxidative phosphorylation (e.g., dinitrophenol [DNP]). Each can cause a transient increase in afferent activity in the carotid body and a significant increase in intracellular calcium concentration in glomus cells.

In thin slices of the carotid body, catecholamine release increases with decreasing glucose concentration. Thus, a deficiency in the substrate for the citric acid cycle and oxidative

phosphorylation mimics hypoxia. High levels of mitochondrial inhibitors abolish the oxygen chemosensory response in the carotid body, although carotid body afferent activity can still be stimulated, at least transiently, by changes in carbon dioxide or hydrogen ion concentrations. Collectively, inhibitor-uncoupler studies infer that oxygen sensing occurs through phosphorylation.

Two main hypotheses regarding the oxygen sensor responsible for the rapid response to hypoxia have been advanced. One is that the oxygen sensor is mitochondrial cytochrome oxidase, which, through its effects on oxidative phosphorylation, transmits information to the rest of the cell. The other is that glomus cells have oxygen-sensitive potassium channels, the conductance of which are lowered with decreasing oxygen pressure. Although mitochondrial cytochrome oxidase is recognized as the primary oxygen sensor, it is possible that oxygen-dependent ion channels help to modulate sensitivity to changes in oxygen tension.

In order for cytochrome oxidase to act as the oxygen sensor for rapid changes in oxygen pressure, mitochondrial oxidative phosphorylation must be sensitive to cellular oxygen tension in vivo. Blood flowing through the carotid body comes from the carotid artery, where the oxygen pressure is typically 80 to 100 mmHg. Carotid body afferent activity rises significantly when arterial oxygen pressure falls below 60 mmHg. However, oxygen pressure in the mitochondria is much lower, because as blood enters the carotid body, oxygen is extracted by cells. By the time an aliquot of arterial blood reaches the microvessels of the carotid body, its average oxygen pressure is about 50 mmHg; minimal values are likely near 20 mmHg. Although diffusion of oxygen from blood in the microvessels to the mitochondria is expected to further decrease the oxygen pressure, it is reasonable to expect an average mitochondrial oxygen pressure of about 40 mmHg and a minimum of about 15 mmHg. Thus, a significant portion of the mitochondria of glomus cells is exposed to an oxygen pressure of less than 20 mmHg when arterial oxygen pressure is 80 mmHg.

Changes in ventilation due to changes in alveolar (PAC_{O_2}) or alveolar P_{O_2} (PA_{O_2}) are described in Figure 61-1. In the acute phase of hypoxia (e.g., the first 10 min), at a given rate of oxygen consumption, as PA_{O_2} is decreased to below 60 mmHg, ventilation increases, resulting in a decrease in PA_{CO_2}. In the chronic phase, ventilation is increased with reductions in PA_{O_2} at all levels of PA_{O_2}, and the curve is shifted downward, reflecting increased sensitivity of carotid chemoreception and restoration of pH after a period of hypocapnia-induced alkalemia. The diagram is particularly useful for describing the acclimatization process in response to altitude-associated chronic hypoxia.

Hypoxemia is often accompanied by alterations in PA_{CO_2}. In the carotid body, low PA_{O_2} and high PA_{CO_2} interact synergistically to stimulate glomus cells; i.e., the ventilatory effects of concurrent hypoxia and hypercapnia are greater than the sum of the two stimuli when they are applied separately. As the PA_{O_2} level declines, the relationship between the sensory afferent nerve activity and PA_{CO_2} becomes increasingly steeper (Fig. 61-2), leading to enhanced ventilatory drive.

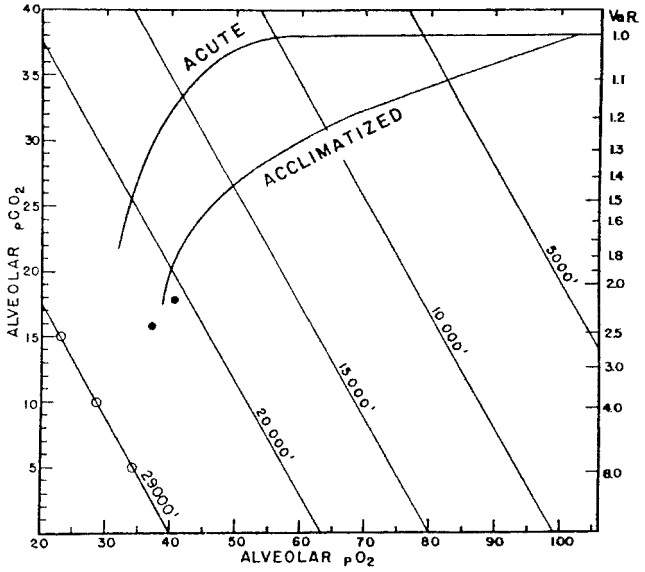

Figure 61-1 Alveolar P_{O_2}-P_{CO_2} relationship in acute and acclimatized subjects. In acute hypoxia, a drop in alveolar P_{CO_2} (due to hyperventilation) is observed when alveolar P_{O_2} decreases below 60 mm Hg. However, with acclimatization, even at an alveolar P_{O_2} above 60 mm Hg, arterial P_{CO_2} decreases because of increased drive from the chemoreceptors. *(From Rahn H, Otis AB: Man's respiratory response during and after acclimatization to high altitude.* Am J Physiol *157:445–462, 1949.)*

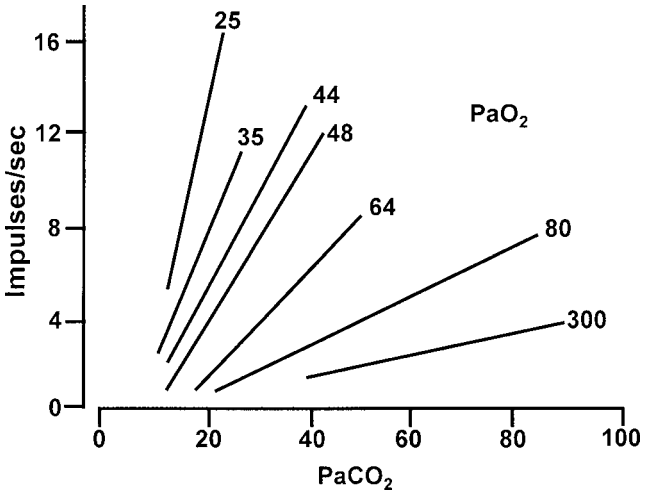

Figure 61-2 Relationship between afferent chemosensory nerve discharge and P_{CO_2} levels recorded from carotid body sinus nerve preparation in a cat. P_{CO_2} levels were varied at different prevailing levels of P_{O_2}. Note the increased slope of the relationship as O_2 levels decline. *(From Lahiri S, Delaney RG: Stimulus interaction in the responses of carotid body chemoreceptor single afferent fibers.* Respir Physiol *24:249–266, 1975.)*

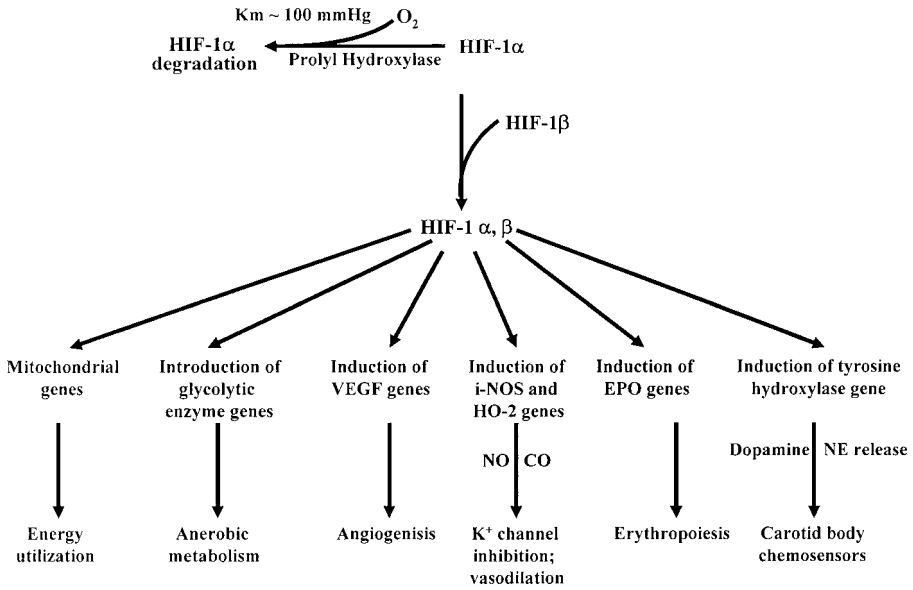

Figure 61-3 The HIF-1 hypoxia response pathway. With decreases in oxygen tension, the rate of proline hydroxylation decreases, leading to accumulation of HIF-1α. HIF-1α binds to HIF-1β to form a heterodimer that binds to, and activates expression of, various genes, including those encoding glycolytic enzymes (for anaerobic metabolism), VEGF (for angiogenesis), inducible nitric oxide synthase and heme-oxygenase-2 (for NO and CO production and vasodilatation), erythropoietin (for erythropoiesis), and possibly, tyrosine hydroxylase (for dopamine production and resultant effects on carotid body chemoreception). The gene products promote cell survival at low oxygen tension or act to restore normal oxygen levels. Some gene targets of HIF-1 are induced in most hypoxic cells, while others, like erythropoietin, are induced only in specific tissues, and, hence, require tissue-specific regulators. Mitochondrial inhibitors suppress HIF-1α, indicating that HIF-1α signaling is coupled to function of the mitochondrial respiratory chain. *(Modified from Wilson DF, Roy A, Lahiri S: Immediate and long-term responses of the carotid body to high altitude.* High Altitude Med Biol *6:97–111, 2005.)*

Chronic Responses to Hypoxia

The carotid body chemoreceptors are minimally sensitive to hypoxia at birth and become more sensitive over the first few days or weeks of life. The observation that chronic hypoxia increases hypoxia sensitivity applies to the carotid body of *adult* animals.

In a state of chronic hypoxia (after 2 min of hypoxia), hypoxia-inducible factor (HIF-1α) becomes elevated (Fig. 61-3). Under normoxic conditions, HIF-1α is formed continuously and degraded in the cytoplasm. HIF-1α combines with a constitutively expressed component, HIF-1β to form HIF-1, which moves into the nucleus to produce gene transcription. HIF-1α is hydroxylated by the enzyme prolyl hydroxylases prior to its degradation. The prolyl hydroxylases have a relatively high Km for oxygen; hydroxylation leads to degradation under physiological conditions. Decreased oxygen pressure results in significant accumulation of HIF-1α in less than 2 min; HIF-1α is rapidly degraded upon reoxygenation.

Recent studies reported that mice partially deficient in HIF-1α had a marked decrease in carotid body chemosensory response to acute hypoxia, but that the in vivo ventilatory response was not compromised. Furthermore, wild-type mice exposed to hypoxia for 3 days manifested an augmented ventilatory response to a subsequent acute hypoxic challenge. In contrast, chronic hypoxia resulted in a diminished ventilatory response to acute hypoxia in the partially HIF-1α–deficient mice. Thus, partial HIF-1α deficiency has a significant effect on carotid body neural activity and ventilatory adaptation to chronic hypoxia.

In the 1960s, Lahiri and Milledge working in the Himalayan high altitude, and Severinghaus et al. working in the South American altiplano found that adult natives showed a blunted ventilatory response to an acute reduction in inspired P_{O_2}, both at rest and during exercise. The age at which this pulmonary adaptation occurred was not known; neither was it known whether it was acquired or genetic. The conclusion was that the responses to chronic hypoxia were determined by environmental rather than genetic factors. Recent investigations on the adaptive responses to hypoxia have demonstrated that increased expression of HIF-1α, VEGF, and iNOS normally present in young animals are less evident as animals age. Hence, oxygen-sensing mechanisms appear to decline with aging.

PHYSIOLOGICAL CHANGES AT HIGH ALTITUDE

While a variety of physiological changes have been described during ascent to high altitude, several are particularly notable and are described briefly below.

Pulmonary Circulation

In contrast to the systemic circulation, the pulmonary circulation is a high-flow, low-pressure system. Based upon a balance of hydrostatic and oncotic pressure gradients across pulmonary capillary microvessels, as represented in the Starling equation, the pulmonary interstitium and alveolar spaces are maintained "dry." However, a disruption in hemodynamics, as may seen in hypoxic pulmonary vasoconstriction, may result in formation of excess lung water and overwhelming of the so-called "edema safety factors" (see Chapters 144 and 145). At high altitude, while respiratory mechanics do not change appreciably, changes in hemodynamics due to pulmonary hypertension may be dramatic.

Pulmonary blood vessels are extensively supplied with sympathetic (vasoconstrictor) fibers and, to a smaller extent, parasympathetic (vasodilator) fibers. Despite this innervation, regulation of vasomotor tone is largely dictated by the local effects of P_{O_2} and P_{CO_2}. Alveolar hypoxia results in contraction of vascular smooth muscle, vessel narrowing, and shunting of pulmonary blood flow away from the hypoxic area. Furthermore, local CO_2 accumulation leads to a decline in pH and resultant vasoconstriction (unlike the CO_2-induced vasodilation seen in other tissues).

The presence of pulmonary hypertension (both systolic and diastolic) at high altitude is well documented. It is more prominent in younger individuals than in older individuals and is related to the state of pulmonary vasoconstriction. Exercise accentuates pulmonary hypertension. Acute hypoxia causes a rise in pulmonary arterial pressure that falls when hypoxia is relieved if the hypoxia is present for only a few hours. Pulmonary artery pressure does not decline immediately if hypoxia is present for several days. After resolution of hypoxia, regression occurs in pulmonary hypertension and muscularization of the pulmonary arteries. The right ventricular hypertrophy associated with pulmonary hypertension also regresses upon return to sea level.

The entire cardiac output passes through the lungs. At sea level, the low-pressure pulmonary circulation easily accommodates an exercise-related increase in blood flow, with little increase in pulmonary artery pressure and pulmonary vascular resistance. During acute hypoxemia, the relationship between pulmonary blood flow and pulmonary pressure is altered. During chronic hypoxia, structural remodeling of pulmonary arterioles results in increases in resting pulmonary arterial pressure and pulmonary vascular resistance.

High-altitude residents show a widened pressure gradient from pulmonary artery to left atrium during exercise (as reflected in pulmonary artery occlusion or pulmonary capillary "wedge" pressure measured using a Swan-Ganz catheter). These findings suggest that at high altitude, vasomotor control of the pulmonary circulation resides in the lung arterioles, whereas at sea level it resides in the left heart. Altitude "resets" the regulatory mechanism, and exercise makes the difference obvious.

Sleep and Periodic Breathing

Sleep depresses ventilation, resulting in decreases in alveolar and arterial P_{O_2} and increases in alveolar and arterial P_{CO_2}. At altitude, these changes become critically important, stimulating breathing, increasing P_{O_2}, and decreasing P_{CO_2} which, in turn, decreases ventilation and initiates periodic breathing.

At altitudes above 3000 m, subjects typically manifest periodic breathing, particularly during sleep. The quality of both REM and non-REM sleep becomes impaired. With acclimatization, the sleep pattern tends to become more normal. However, periodic breathing during non-REM sleep persists over time at higher altitudes.

Erythropoiesis

Erythropoietin levels are increased at high altitude because of chronic hypoxia, resulting in increased numbers of erythrocytes. Hypoxia also increases ventilation, resulting in decreases in alveolar and arterial P_{CO_2} and arterial $[H^+]$; concomitantly, serum levels of 2,3-diphosphoglycerate (2,3-DPG) are increased. While the reductions in Pa_{CO_2} and $[H^+]$ increase hemoglobin affinity for O_2, increases in 2,3-DPG diminish the affinity. Loading and unloading of O_2 from hemoglobin depends upon the balance of these factors.

As described previously, with chronic hypoxemia at high altitude, decreased hypoxic ventilatory drive is followed by decreases in arterial P_{O_2}. Consequently, polycythemia and pulmonary hypertension arise, resulting in right ventricular hypertrophy, and eventually, in right heart failure and death. This syndrome of chronic mountain sickness (see below) is relieved only by descent to sea level.

Fluid Homeostasis and Renal Function

In healthy individuals, ascent to high altitude normally results in a diuresis that persists during the stay. In addition, suppression occurs of voluntary sodium and water intake. Lung edema, cerebral edema, and peripheral edema may be seen (see below), with elevated levels of aldosterone and antidiuretic hormone.

COMMON CLINICAL DISORDERS OF HIGH ALTITUDE

A variety of altitude-related clinical disorders are well recognized, including acute mountain sickness, high-altitude pulmonary edema, high-altitude cerebral edema, and chronic mountain sickness. While these entities may be observed at altitudes as low as 8000 feet (2500 m), their frequency increases with increasing altitude.

Acute Mountain Sickness

Acute mountain sickness (AMS) affects previously healthy individuals who ascend rapidly to high altitude. After a delay of

a few hours to 2 days, symptoms develop, including headache (usually frontal), nausea, vomiting, irritability, malaise, insomnia, and poor climbing performance. The simple or benign form of the condition is self-limiting, lasting 3 to 5 days. Typically, symptoms, once resolved, do not recur at a given altitude, although recurrence may be experienced if the subject ascends to higher altitude. In a small proportion of individuals, progression to the malignant forms of AMS—high-altitude pulmonary edema (HAPE), high-altitude cerebral edema (HACE), or a mixture of the two—may be seen (see below). If not treated, these conditions are frequently fatal in a matter of hours.

Incidence

The incidence of AMS depends upon the altitude attained and rate of ascent. With increased accessibility of high-altitude resorts and the feasibility of rapid ascent to high mountain locations in a very few days, the incidence of AMS has probably increased in recent years. A survey of alpine hut dwellers noted an incidence of 9 percent at 2850 m, 13 percent at 3050 m, 34 percent at 3650 m, and 53 percent at 4559 m. Among trekkers en route to an Everest base camp, the incidence was 43 percent at 4300 m; it was higher in those who had flown into an airstrip at 2800 m (49 percent) than those who had walked all the way (31 percent).

Mechanism

Although hypoxia appears to be a trigger in the genesis of AMS, it is not the immediate cause, since symptoms are delayed by several hours after arrival at high altitude, despite the fact that hypoxia is most severe in the first few minutes. Symptoms are similar to those associated with increased intracranial pressure; in patients with high-altitude cerebral edema, evidence of increased intracranial pressure has been demonstrated. The most popular view is that even in simple AMS, a degree of cerebral edema (and, often subclinical pulmonary edema) causes the symptoms of AMS. In addition, a generalized disturbance of fluid balance or capillary permeability throughout the body is likely, accounting for other findings in AMS, including dependent or periorbital edema.

Prevention

A slow rate of ascent is the best way to prevent AMS. A suggested rule is that above 3000 m (10,000 ft), ascent should be at a rate less than 300 m (1000 ft) per day, with a "rest" day (i.e., no additional ascent) every 3 days. However, even this rate will be too fast for some and unnecessarily slow for others. An additional rule is, "If symptoms of AMS develop, go no higher. If they become severe, go down." Individuals who ascend to high altitude should be advised to limit their activity for the first few days upon ascent. Adequate hydration should be encouraged. Although theophylline may be useful, and benzodiazepines have been investigated as prophylactic agents, acetazolamide, and dexamethasone constitute the principal preventative pharmacologic measures; their benefits may be additive.

Use of acetazolamide (250 mg at bedtime) for several days after arrival may improve sleep and ability to function during the day. Alternatively, the drug may be started 2 to 3 days before arrival at a dose of 250 to 500 mg twice daily. Prophylactic administration of acetazolamide is advisable for anyone with a prior history of AMS. Corticosteroids (e.g., dexamethasone at a dose of 4 mg every 6 hours) may be a suitable alternative for individuals unable to take acetazolamide (e.g., those with sulfa allergy). The drug is continued until acclimatization occurs after a few days.

Treatment

Simple or benign AMS is self-limiting and usually lasts about 3 days, so treatment is not essential; aspirin or paracetamol can be used to relieve headache, but they are not very effective. In a placebo-controlled trial, ibuprofen has been demonstrated to be useful. If the condition progresses to HAPE or HACE, urgent treatment is warranted, as described below. Acetazolamide and dexamethasone can alleviate symptoms of AMS. Acetazolamide is generally considered first-line treatment; dexamethasone can be used in sulfa-allergic individuals. A combination of the two agents can be used for rapidly evolving symptoms, particularly when descent may be delayed.

High-Altitude Pulmonary Edema

In the great majority of cases, AMS is a minor affliction that resolves in a few days. However, in a small proportion of individuals ascending to high altitude, one or a combination of potentially lethal conditions may develop: acute pulmonary edema (HAPE) or cerebral edema (HACE). Their incidence depends on the rate of ascent and the population studied. Estimates are 0.5 to 2.0 percent. Individuals who have a previous history of HAPE are at greater risk of subsequent altitude-related disorders. Some demonstrate a "threshold" effect in which repeated ascents to a particular altitude are associated with development of HAPE at that altitude.

In addition to lowlanders, individuals who normally reside at high altitude, but who descend and then return to high altitude are susceptible. Men and women of all ages may fall victim, although young males appear to be more at risk than others. Athletic fitness affords no protection.

The typical patient is a previously fit young man who has climbed rapidly and is energetic on arrival. Moderate symptoms of AMS may be present initially as the individual becomes more breathless. A cough develops, which is initially dry, then productive of frothy white sputum, and later, blood-tinged. The climber may complain of chest discomfort. The pulse and respiratory rate are increased, and auscultation of the chest reveals crackles at the bases. An elevated jugular venous pressure and peripheral edema may be seen, and a right ventricular heave and accentuated pulmonary component of the second heart sound may be detected. Over a few hours, the

patient's condition may deteriorate further, with additional increases in pulse and respiratory rate. As breathing becomes "bubbly" due to pulmonary edema, cyanosis develops. In the absence of definitive treatment, coma and death ensue.

Mechanism

The mechanism underlying development of HAPE is unclear. Despite the clinical similarity to congestive heart failure, acute left ventricular failure does not appear to be the basis. Hemodynamic studies universally demonstrate a normal left atrial (pulmonary artery occlusion or "wedge") pressure.

The most popular hypothesis, originally proposed by Hultgren in the 1960s, is that susceptible subjects experience a brisk hypoxic pulmonary artery vasoconstrictor response that is uneven throughout the lung. In some areas, where there is a greater degree of vasoconstriction, blood flow is reduced and the areas are protected from development of pulmonary edema. In those areas in which vasoconstriction is less marked, increased blood flow is associated with edema formation, perhaps through flow-related capillary damage, or sheer stress on vessel walls, or increased intracapillary pressure. In addition, various kinins which have been identified in the edema fluid are likely to increase permeability further and to recruit additional leukocytes.

Prevention

Use of nifedipine prophylactically (slow-release formulation, 20 mg twice daily prior to ascent, then three times daily) appears to lower significantly the incidence of HAPE. Mean systolic pulmonary artery pressure is lowered with prophylaxis. The drug appears to be ineffective in preventing AMS. Prophylactic use of an inhaled beta agonist also reduces the risk of HAPE.

Treatment

Descent is critical for survival. Initial treatment while the subject awaits descent includes strict rest, supplemental oxygen, and, if available, use of a portable hyperbaric chamber. Although not yet studied in a well-controlled trial, nifedipine (10 mg sublingually) may be used. If clinically significant hypotension does not occur with the first dose of nifedipine, its administration can be repeated every 15 to 30 min. Future studies may establish a role for use of sildenafil and related compounds as prophylactic treatment in individuals at risk for HAPE.

High-Altitude Cerebral Edema

The other malignant form of AMS is HACE. In its early stages, HACE is indistinguishable from simple AMS. Initially, headache, nausea, and vomiting are prominent symptoms. When ataxia develops, "benign" AMS has become "malignant." Truncal ataxia (unsteadiness when sitting), hallucinations, clouding of consciousness, extensor plantar reflexes, and papilledema may follow. Concurrent signs of pulmonary edema may also be noted. In the absence of treatment, coma arises.

As for HAPE, descent is critical. While awaiting evacuation, supplemental oxygen should be given. Several hours in a portable hyperbaric chamber may be a useful and life-saving measure while descent is arranged; however, the beneficial effects of the portable chamber may develop more slowly in HACE than in HAPE, especially in severe cases. Administration of dexamethasone (4 to 8 mg), intramuscularly in severe cases, or orally in less severe cases, helps reduce cerebral edema and should be given while awaiting evacuation; doses can be repeated every 6 h.

Chronic Mountain Sickness

In the 1920s, Carlos Monge reported cases of polycythemia in high-altitude residents of the Andes (Monge's disease), and in 1942, Hurtado published detailed observations of eight cases, including symptomatology and hematological changes. The condition—chronic mountain sickness (CMS)—is quite different from AMS.

CMS affects residents of high altitude, is more common in males, and develops in middle and later life. Its defining feature is extreme polycythemia, with hemoglobin concentrations as high as 23 gm/dL and hematocrits as high as 83 percent. Patients typically have rather vague neuropsychological complaints, including headache, dizziness, somnolence, fatigue, difficulty in concentration, and loss of mental acuity. Irritability, depression, and even hallucinations, may be observed. Dyspnea on exertion is not common, but poor exercise tolerance is; weight gain may also be seen. Characteristically, symptoms disappear on descent to sea level and reappear on return to high altitude.

Although normal individuals are mildly cyanotic at an altitude of 4000 m, patients with CMS stand out with elevated hemoglobin concentrations, low oxygen saturations, and hence far higher concentrations of reduced hemoglobin. In Andean Indians, who have the highest prevalence of the disorder, signs may be florid, including black lips and wine-red mucosal surfaces. The conjunctivae are congested, and the fingers may be clubbed. In whites, the appearance is less striking, since it occurred at lower altitudes (e.g., in Leadville, CO, elevation 3100 m). Under these circumstances, affected individuals appear similar to patients with polycythemia secondary to hypoxic lung disease. Some patients show very few signs.

As noted, symptoms and signs usually disappear upon descent to sea level, which is the definitive form of treatment. However, for many patients who wish to remain at altitude for family or economic reasons, phlebotomy and administration of supplemental oxygen are beneficial. Phlebotomy lowers the raised hematocrit and improves many of the neuropsychological symptoms. Pulmonary gas exchange and exercise performance are also improved in some subjects.

An alternative to phlebotomy for residents at high altitude is the long-term use of respiratory stimulants. Medroxyprogesterone has been employed with some success; side

effects, including loss of libido, limit its use. Although acetazolamide has been used in prevention of acute mountain sickness, trials addressing its use in CMS are lacking. However, the drug may be useful in improving oxygen saturation during sleep and in reducing the hematocrit. Further studies are necessary in establishing the role, if any, of sildenafil and related compounds in patients at risk for CMS.

ACKNOWLEDGMENT

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Diving Injuries and Air Embolism

James M. Clark

Current estimates of active divers in the United States range from 1.6 to 2.9 million. The most accurate available statistics of diving related injuries are published online by the Divers Alert Network (DAN) in an Annual Review of Recreational Scuba Diving Injuries and Fatalities. Annual numbers of diving injuries treated at participating hyperbaric chamber facilities and reported to DAN America range from about 600 in 1987 to peaks of about 1160 in 1994 and 1999 to the most recent value of 1063 in 2002. During the period from 1970 to 2002, annual numbers of recreational diving fatalities in the United States and Canada range from a peak of 147 in 1976 to a low value of 66 in 1988 with an overall average of 99 per year. Of the 89 fatalities reported in 2002, 47 (53 percent) were attributed to drowning, 16 (18 percent) to air embolism, another 18 percent to cardiovascular problems, and only 1 (1 percent) to decompression sickness. It is likely that some of the drowning fatalities were precipitated by air embolism. Of all the possible causes of diving related injuries, this chapter will discuss only those caused by dissolved or embolic gas. The central role of gas in the pathogenesis of these injuries has been emphasized by referring to them collectively as gas lesion diseases. Although the incidence of arterial air embolism caused iatrogenically is not reported annually, it is likely that such statistics, if available, would add significantly to the morbidity and mortality of gas lesion diseases related to diving accidents.

The adverse effects of diving-related gas lesions upon the lung and other vital organs originate from two major sources: (1) compression of gas within the lungs and other body spaces as ambient pressure is increased, with later expansion of that gas upon return to normal atmospheric pressure; and (2) solution of excess quantities of inert gas in blood and body tissues during exposure to increased ambient pressures, followed by evolution of venous and tissue bubbles when decompression occurs too rapidly. The former condition can cause pulmonary barotrauma, with arterial gas embolism as its most serious sequela, while the latter can result in decompression sickness with manifestations ranging from localized pain in a joint to massive neurological deficits from spinal cord infarction.

PULMONARY BAROTRAUMA

If a diver were to descend while holding his or her breath, the gas within the lungs would be compressed progressively while maintaining a volume that is inversely proportional to the increasing pressure (Fig. 62-1). In order to prevent collapse of the lung to less than residual volume, with tearing of pulmonary parenchyma and blood vessels, the diver is obliged to breathe an oxygen-containing gas mixture at a pressure equal to that of the surrounding water. During return to normal atmospheric pressure, compressed gas within the lungs expands exponentially and must be exhaled if alveolar rupture is to be avoided.

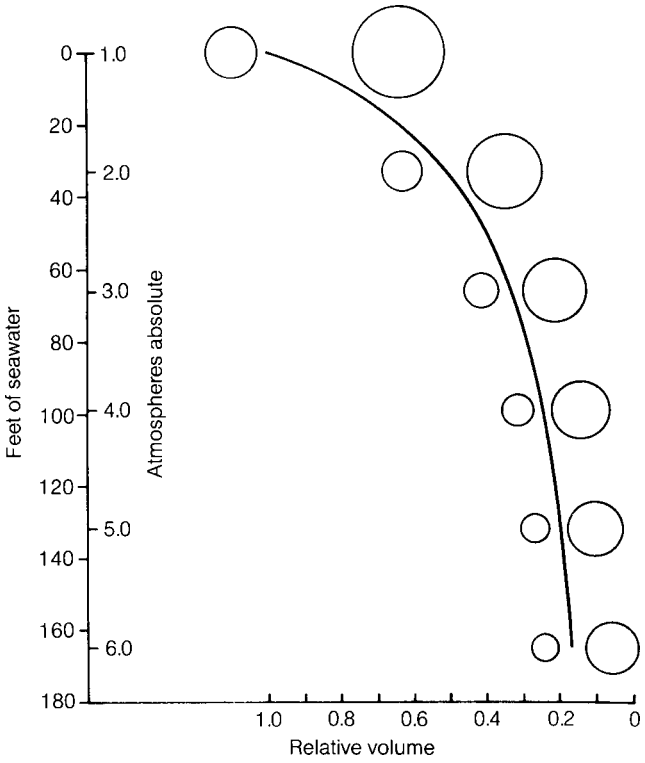

Figure 62-1 Relationship of relative gas volume to ambient pressure during compression from 1.0 to 6.0 atm (surface to 165 ft of sea water). Boyle's law states that, at constant temperature, the volume of a gas is inversely proportional to its pressure. Bubbles on the left show the decrease in diameter that would occur during compression without access to a gas source at ambient pressure. Bubbles on the right show expansion that would occur during decompression after restoration of unit volume at a depth of 165 ft. Similar lung volume changes during diving are prevented by inhalation of compressed gas during descent and exhalation of expanding gas during ascent.

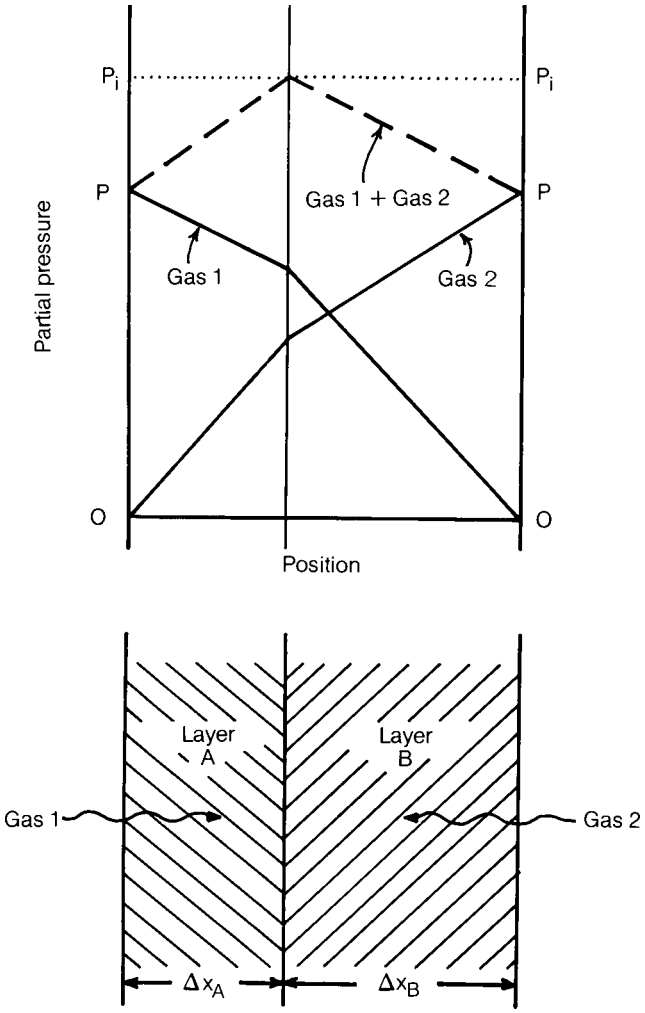

Figure 62-2 Supersaturation and bubble formation by countercurrent diffusion at the interface of a two-layer system. The two gas reservoirs are large, and their contents are well mixed. In this model, gas 1 (helium) diffuses more rapidly than gas 2 (nitrogen) through layer A (water), and the relative diffusivities of gases 1 and 2 are reversed in layer B (oil). Total gas pressure at any point in the system is the sum of partial pressures of both gases. Bubbles will form at the interface if suitable nuclei are present and if at least one of the two layers is a liquid. *(From Graves DJ, Idicula J, Lambertsen CJ, Quinn JA: Bubble formation in physical and biological systems: A manifestation of counter-diffusion in composite media.* Science *179:582–584, 1973, with permission.)*

The greatest danger of alveolar bursting occurs within the last 33 ft of ascent to the surface, because the relative gas volume doubles during that transition (Fig. 62-1). Theoretically, a critical threshold for alveolar rupture could be reached by ascent from as shallow a depth as 4 ft (1.2 m) after full inspiration at that depth. Fatal arterial gas embolism has occurred following ascent from a depth of 7 ft (2 m).

Possible Sequelae of Alveolar Rupture during Decompression

The sequelae of pulmonary overpressure accidents are determined by the nature and severity of associated tissue trauma as well as by the volume of expanding extra-alveolar gas. Following rupture of alveolar septa, expanding gas enters the interstitial spaces and dissects along perivascular sheaths to enter the mediastinum. Gas also may enter the pleural space to cause pneumothorax. Mediastinal gas may further dissect into the pericardial sac, the retroperitoneal space, or the subcutaneous tissues of the neck.

Mediastinal emphysema is often associated with mild substernal discomfort that may be described as a dull ache or a feeling of tightness. Deep inspiration, coughing, or swallowing may exacerbate symptoms, and mild pain may radiate to the shoulders, neck, or back. Unless extensive, mediastinal emphysema is usually not associated with dyspnea, tachypnea, or other signs of respiratory distress. Clinically significant volumes of mediastinal gas have a distinctive appearance on the chest radiograph.

Subcutaneous emphysema from pulmonary barotrauma causes swelling and crepitance in the neck and supraclavicular fossae. These signs may be associated with sore throat, dysphagia, or a change in voice tone. Subcutaneous gas can also be demonstrated radiographically. Recompression therapy is not needed for uncomplicated cases of mediastinal

or subcutaneous emphysema. If symptoms are bothersome, resolution of gas can be hastened by breathing 100 percent oxygen at normal atmospheric pressure. Gas volumes within the pericardial sac or retroperitoneal space are seldom large enough to be clinically significant.

Pneumothorax is not a frequent complication of pulmonary barotrauma. In one series of submarine escape ascents, pneumothorax occurred in 5 to 10 percent of the divers who had lung overinflation syndromes with arterial gas embolism. Recompression of an individual who is known to have a pneumothorax should be avoided if at all possible. Nevertheless, it must be carried out if neurological symptoms or any other manifestations of arterial gas embolism are present.

Conversion from a simple to a tension pneumothorax will occur if a tear in the visceral pleura remains open during descent, thereby allowing compressed gas to enter the pleural space, and then becomes effectively sealed prior to ascent. Upon decompression, the gas in the pleural space will expand to compress the lung and interfere with venous return. Severe dyspnea, cyanosis, and hypotension may occur, especially if the inferior vena cava is kinked at the diaphragmatic hiatus. This is an emergency that will require immediate recompression to relieve symptoms and insertion of a chest tube before decompression is resumed. Smaller pneumothoraxes can be managed by inserting a large, 10- to 14-gauge catheter (Angiocath) through the appropriate intercostal space and attaching it to a flutter valve made from a Penrose drain or some other suitable material.

Arterial Gas Embolism

When expanding extraalveolar gas is forced down a pressure gradient into torn septal vessels, it traverses the pulmonary veins to the left atrium and left ventricle, from which it is ejected into the systemic circulation as foamy particles or discrete bubbles. Distribution of the gas emboli is determined by their buoyancy relative to blood and orientation of the body with respect to gravity. It may also be influenced by local factors such as blood flow and vessel size. With the body in the head-up, erect position, most of the embolic air travels to the brain.

Cerebral air embolism is a relatively frequent component of lung overinflation syndromes. In a series of 88 divers with pulmonary barotrauma, the incidence of neurological signs and symptoms was about 75 percent. Electroencephalographic evidence of abnormal neuronal activity after submarine escape training ascents in the absence of associated clinical manifestations indicates that the true incidence of cerebral gas embolism may be even higher than that established on the basis of positive historical and physical findings.

Clinical manifestations of dysbaric arterial gas embolism have been grouped into two or three categories, based on the initial presentation and response to treatment. About 5 percent of the divers who experience arterial gas embolism are critically injured and often die even when recompression is initiated within minutes. These individuals develop apnea, unconsciousness, and cardiac arrest during ascent or immediately after surfacing from a dive. Possible causes of this frequently lethal condition include massive volumes of air in the central circulation, cerebral embolism, and/or direct embolization of the coronary arteries.

The majority of patients with dysbaric arterial gas embolism present with neurological signs and symptoms, but spontaneous respiration and heart rate are maintained. Just as in the more seriously injured divers, onset of symptoms occurs during ascent or within minutes after surfacing. The clinical spectrum of neurological disturbances ranges from focal signs, such as monoparesis or discrete sensory deficits, to diffuse brain dysfunction, as manifest by confusion, stupor, or coma. In response to prompt recompression, most patients have complete resolution of all neurological deficits. For reasons that are not well understood, a subgroup of these patients fail to respond completely or experience initial improvement followed by recurrence of the presenting signs and symptoms. The probability of incomplete response or recurrence is increased as the time between onset of symptoms and initiation of definitive therapy is prolonged.

Iatrogenic Arterial Gas Embolism

Accidental arterial gas embolism is a serious and sometimes lethal complication of many procedures that are widely used in modern medicine. It is often misdiagnosed or recognized only after a delay of several hours. Even when the diagnosis of arterial gas embolism is correctly made, many physicians who are not specifically trained in diving medicine are apparently unaware that hyperbaric oxygenation is the definitive and highly efficacious therapy for this condition.

Arterial gas embolism has been reported in association with a variety of procedures including cardiac surgery; intravenous therapy, especially with the use of central venous catheters; neurosurgery; pulmonary diagnostic or surgical procedures; surgery of the aorta or cervical arteries; surgical procedures involving the head and neck; hemodialysis; arterial catheterization, especially for arteriography; mechanical ventilation; abdominal or retroperitoneal gas insufflation; liver transplantation; and uterine catheterization or insufflation, usually during criminal abortion (i.e., if performed under nonmedical, unsterile conditions). Most cases of accidental arterial gas embolism present with focal or diffuse manifestations of brain ischemia. Management is often made more difficult by the existence of concurrent medical or surgical complications. In many patients, hyperbaric oxygen therapy, if administered promptly, completely reverses all neurological deficits. It is generally remarkably efficacious even when initiated after a delay of several hours.

DECOMPRESSION SICKNESS

Decompression sickness, which is characterized by a broad clinical spectrum with multiple manifestations, occurs when ambient pressure is reduced too rapidly to allow the inert gas dissolved in blood and body tissues to remain in

physical solution. It usually occurs in the diver after inadequate decompression from prolonged exposure to increased ambient pressures, but it can also occur in the aviator or astronaut who is exposed to high altitude or space with blood and body tissues that are saturated with inert gas at normal atmospheric pressure.

Although the precipitating cause of decompression sickness is the evolution of dissolved inert gas from body fluids, neither the physical mechanisms nor the locations of bubble formation are completely understood. Both intravascular and extravascular bubbles have been found in animals exposed to severe decompression stress. Intravascular bubbles are more likely formed in veins than in arteries, due to the greater hydrostatic pressure in the latter vessels. Primary effects caused by the physical presence of undissolved gas in vivo include the obstruction of blood vessels and the mechanical disruption of tissue. In addition, there are secondary effects, caused by tissue reactions to intravascular or extravascular bubbles, which include the concurrent activations of cellular components, such as leukocytes and platelets, and biochemical pathways, such as the complement, coagulation, and kinin systems. It is also possible during or after decompression from a dive to have circulating venous bubbles, as detected by Doppler ultrasonography, without precipitating the onset of decompression sickness.

Clinical Manifestations of Decompression Sickness

Musculoskeletal pain in one or more extremities is the most common symptom of decompression sickness in military divers, commercial divers, and caisson workers. Sport divers, in contrast, more commonly present with neurological symptoms or signs. These apparent patterns may reflect both the reluctance of professional divers to report neurological symptoms due to the related occupational penalties and the tendency of many recreational divers to delay seeking medical assistance until neurological symptoms occur. However, neurological and pain-only manifestations of decompression sickness also appear to have different latencies. Among divers who present with neurological involvement, about 50 percent become symptomatic within 10 min of surfacing, and over 90 percent are symptomatic within 3 h. In about 90 percent of divers who present with musculoskeletal pain only, symptoms occur within 6 h after the dive. Onsets of decompression sickness 36 h or more after the dive have been reported, but delays exceeding 24 h are extremely rare. Relatively long delays prior to symptom onset sometimes occur during flights in commercial aircraft that are not pressurized to 1.0 atm and may have cabin altitudes as high as 8000 ft. It is generally recommended that flying should be delayed for at least 24 h after diving.

Clinical manifestations of neurological decompression sickness usually reflect involvement of the spinal cord at the lower thoracic or upper lumbar levels. Paresthesias and sensory deficits may occur with or without associated weakness or paralysis. Transient or persistent abdominal pain may be present. Bladder or bowel dysfunction may occur alone or with associated signs. A form of decompression sickness that is characterized by vestibular involvement may present with the sudden onset of vertigo and severe impairment of balance. Associated symptoms often include nausea, vomiting, nystagmus, tinnitus, and sometimes hearing loss. Vestibular decompression sickness can be unusually difficult to treat, as manifest by a slow or incomplete response to aggressive hyperbaric oxygen therapy.

Pulmonary Decompression Sickness

This relatively rare form of decompression sickness occurs most frequently after short, deep dives or altitude decompressions. This condition, known to divers as the "chokes," is manifest by substernal pain, cough, and dyspnea, often associated with extreme malaise. The onset of symptoms is often within minutes after decompression, but it may be delayed for several hours. In some instances, there is only a mild sensation of chest "tightness" that resolves spontaneously. Patients who are more severely affected characteristically manifest a progressive exacerbation of symptoms, entailing rapid, shallow breathing to avoid substernal pain and paroxysmal coughing whenever deep inspiration is attempted. If untreated by hyperbaric oxygenation, pulmonary decompression sickness can terminate in hypoxemia, pulmonary hypertension, shock, and death.

The pathogenesis of pulmonary decompression sickness apparently involves accumulation in the lung of embolic bubbles along with entrapped aggregates of platelets, fibrin, leukocytes, and erythrocytes. These events may be accompanied by release of vasoactive substances, thromboxanes, and leukotrienes. Endothelial damage with increase in vascular permeability may also occur. Although these potential mechanisms were demonstrated in animal models that were subjected to extreme decompression stress or direct venous gas infusions, divers who remained asymptomatic after exposure to a single air decompression dive had significant reductions in arterial P_{O_2} and pulmonary diffusing capacity for carbon monoxide concurrently with the detection of venous bubbles by precordial Doppler monitoring.

CONTINUOUS PULMONARY EMBOLISM AS A MODEL OF PULMONARY DISEASE

Development of a unique experimental model of lung disease was stimulated by a series of unexpected observations during deep diving research in human subjects exposed in a hyperbaric chamber to ambient pressures equivalent to depths up to 1200 ft of seawater. When the respired inert gas was nitrogen or neon, with helium as the ambient inert gas at constant ambient pressure, the subjects experienced intense itching in association with maculopapular skin lesions and, on some occasions, developed severe vestibular derangements, with vertigo and nystagmus. The skin lesions were found to be caused by gas bubbles in the skin and subcutaneous tissues.

The vestibular derangements were attributed to counterdiffusion of inert gases through the eardrum and middle ear to the inner ear.

Subsequent experiments in pigs and in vitro systems revealed that the development of skin and subcutaneous tissue gas bubble lesions at constant pressure was caused by the more rapid inward diffusion of helium from the ambient atmosphere into skin capillaries than outward diffusion of nitrogen or neon from capillaries to atmosphere. The process has been designated "isobaric counterdiffusion gas lesion disease," and Fig. 62-2 illustrates schematically its probable pathogenetic mechanism. In vivo systems are obviously much more complex than the simple two-layer system shown in Fig. 62-2.

Continuous, steady-state venous gas embolism can be produced in an anesthetized pig by administration of a normoxic nitrous oxide–oxygen inspired gas mixture with all or part of the pig's body enclosed in a helium-filled bag. This inert gas counterdiffusion model can be used to study adverse effects of gas embolization, interactions of bubble surfaces with blood and vascular constituents, and various methods of therapeutic intervention.

HYPERBARIC OXYGEN THERAPY

The oxygen environment of any organ or tissue depends on several interacting factors that influence the balance between oxygen supply and its metabolic utilization. Arterial oxygen content is determined by oxygen partial pressure, hemoglobin concentration, and oxyhemoglobin percent saturation. Oxygen supply to any organ is also highly dependent on the blood flow. Diffusion distance between any individual cell and the nearest capillary is determined by the density of the capillary network. Finally, at the mitochondrial end of the oxygen pathway, tissue requirements for oxygen are determined by the level of metabolic activity.

Many of the therapeutic benefits of hyperbaric oxygenation are associated with its capacity for increasing oxygen delivery to hypoxic tissues (Fig. 62-3). Although little additional oxygen can be combined with hemoglobin, which is 97 to 98 percent saturated at normal arterial P_{O_2}, the quantity of physically dissolved oxygen increases linearly with arterial P_{O_2} elevation (about 2.4 ml O_2 per 100 ml blood per atmosphere-inspired P_{O_2}). This important increment in arterial oxygen content is associated with a much larger elevation of the oxygen partial pressure gradient from capillary blood to metabolizing cell. The combined increments in oxygen content and diffusion gradient facilitate oxygen delivery to tissues that, due to ischemia or some other cause, remain hypoxic during air breathing. In many of these states, oxygen breathing at 1.0 atm would also be beneficial, but the associated increments in oxygen content and P_{O_2} are often insufficient to ensure resumption of normal metabolic function in ischemic tissues.

Medical uses of hyperbaric oxygen therapy now extend considerably beyond its initial applications in diving. Several conditions in which there is a physiological and/or experimental basis for its use and in which its clinical efficacy has been demonstrated are listed in Table 62-1. A comprehensive review of clinical experience with all of the medical

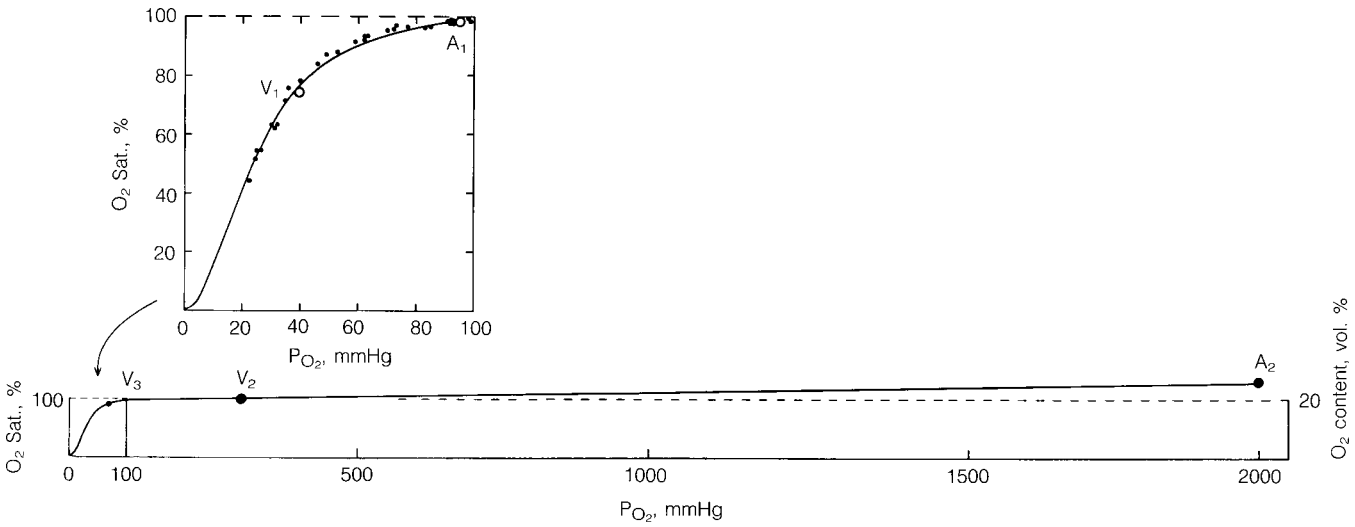

Figure 62-3 Hemoglobin-bound and physically dissolved oxygen in the arterial blood of normal men. *Top:* A typical range of arterial to mixed venous P_{O_2} (A_1 to V_1) during air breathing and its relationship to oxyhemoglobin percent saturation. The points through which the curve is drawn represent measurements in arterial blood of normal men breathing air or low oxygen/gas mixtures. Hemoglobin is an important source of oxygen transport at this level of P_{O_2}. *Bottom:* The increase in arterial P_{O_2} and the additional oxygen uptake over that bound to hemoglobin when inspired P_{O_2} is increased to 3.5 atm. The additional oxygen is transported as gas physically dissolved in blood water. Fall in P_{O_2} from A_2 to V_2 indicates the decrement across brain capillaries predicted on the basis of same oxygen extraction that occurs during air breathing. Direct measurement shows that brain venous P_{O_2} actually falls to V_3, because brain blood flow is reduced prominently during oxygen breathing at 3.5 atm. Lambertsen CJ: Effects of hyperoxia on organs and their tissues, in Robin ED (ed): Extrapulmonary Manifestations of Respiratory Disease. New York, Marcel Dekker, 1978, pp 239–303.

Table 62-1

Current Indications for Hyperbaric Oxygen Therapy Approved by the Hyperbaric Oxygen Therapy Committee of the Undersea and Hyperbaric Medical Society

Gas lesion diseases
Decompression sickness
Gas embolism
Infections
Clostridial myonecrosis
Necrotizing soft tissue infections
Chronic refractory osteomyelitis
Vascular insufficiency states
Radiation necrosis of bone or soft tissue
Healing enhancement in problem wounds
Compromised skin grafts or flaps
Acute traumatic ischemias
Thermal burns
Postischemic reperfusion injury
Carbon monoxide poisoning

SOURCE: Modified after Clark JM. Hyperbaric oxygen therapy, in *The Lung: Scientific Foundations*, 2nd ed. Crystal RG, West JB, Weibel ER, et al (eds), Philadelphia, Lippincott-Raven, 1997. pp. 2667–2676.

applications of hyperbaric oxygen therapy and what is currently known about mechanisms for the observed beneficial effects is beyond the scope of this chapter. Succinct summaries of therapeutic applications of hyperbaric oxygenation are updated and published every 3 or 4 years by the Hyperbaric Oxygen Therapy Committee of the Undersea and Hyperbaric Medical Society.

Hyperbaric Oxygen Therapy of Arterial Gas Embolism and Decompression Sickness

Although arterial gas embolism and decompression sickness have different etiologies and clinical presentations, similar therapeutic principles are applied in both conditions. Primary aims of therapy in both cases are reduction in bubble size, acceleration of bubble resolution, and maintenance of tissue oxygenation. Resolution of bubbles in decompression sickness and air embolism is greatly hastened by breathing oxygen at increased pressure, because the associated elimination of nitrogen from all body tissues and concurrent bubble compression combine to maximize the outward diffusion gradient for bubble nitrogen. The pressure-oxygenation profile used to accomplish these aims in arterial gas embolism is shown in Fig 62-4.

The rationale for initial compression to 165 ft is that reduction in bubble size to one-sixth of their original volume will allow at least some bubbles to traverse capillaries

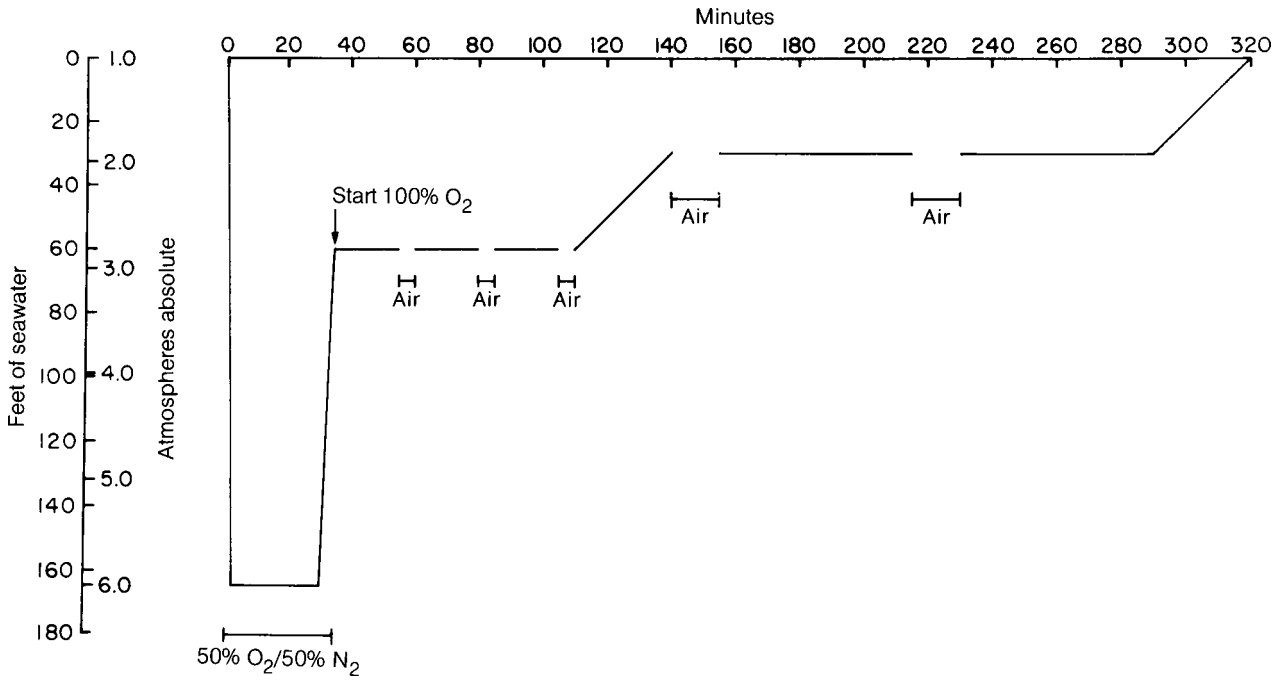

Figure 62-4 Pressure-time profile for hyperbaric oxygen therapy of arterial gas embolism and severe decompression sickness. During the initial period of compression to a pressure equivalent to a depth of 165 fsw, 50 percent O_2 in N_2 is administered to the patient for up to 30 min. Upon decompression to 60 fsw over a 4-min interval, the patient breathes 100 percent O_2 and chamber air intermittently for at least 75 min. After a 30-min period of decompression on oxygen to 30 fsw, the patient breathes oxygen and air intermittently for at least 150 min, followed by another 30-min decompression on oxygen to normal ambient pressure. *(Modified from* U.S. Navy Diving Manual, *vol 5. Flagstaff, AZ, Best, 1999. with permission.)*

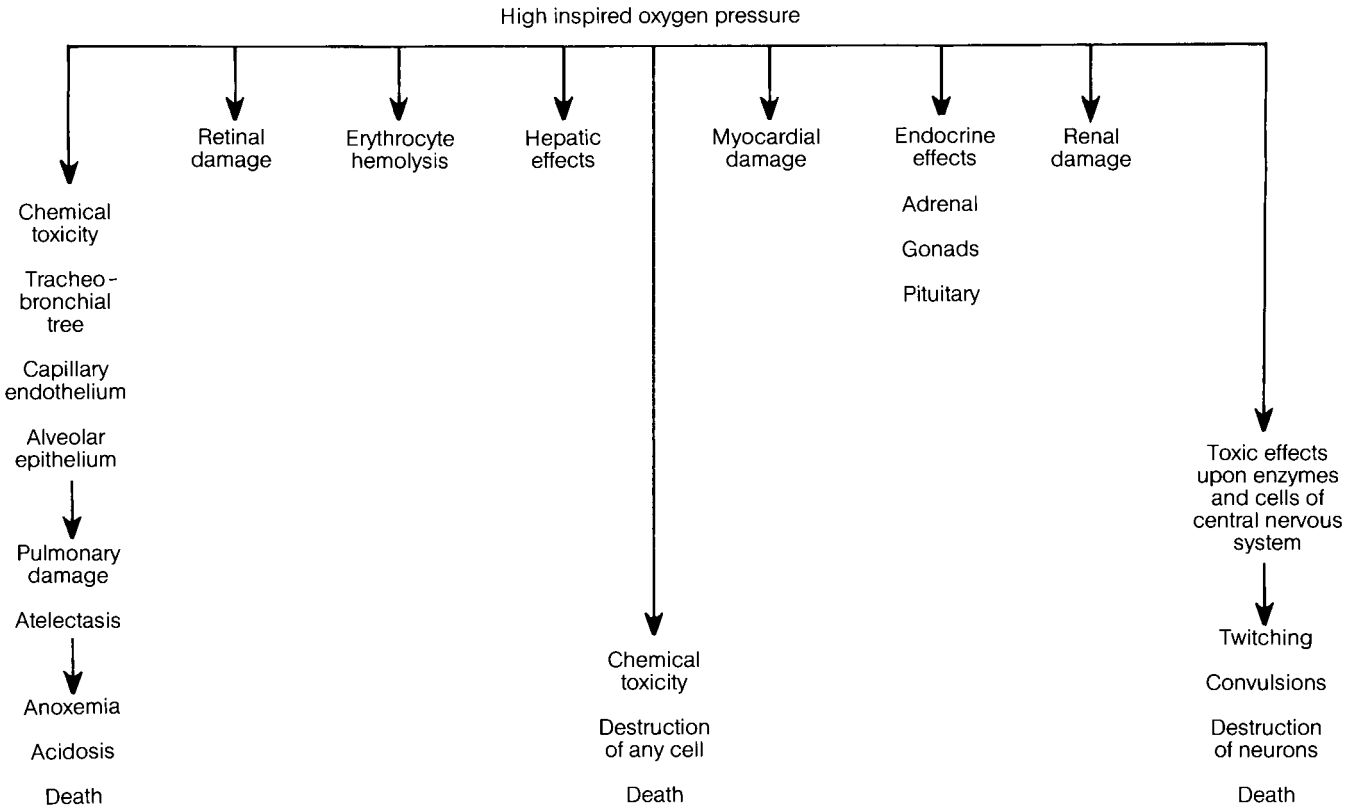

Figure 62-5 Manifestations of oxygen poisoning in specific organs and functions. *(Modified from Clark JM, Thom SR: Oxygen under pressure, in Brubakk AO, Neuman TS (eds):* Bennett and Elliott's Physiology and Medicine of Diving, *5th ed. Philadelphia, Saunders, 2003, pp 358–418, with permission.)*

and enter the venous circulation to be trapped in the lung. Although the patient cannot safely breathe 100 percent oxygen at 165 ft, administration of 50 percent oxygen throughout this phase will provide hyperoxygenation at a level slightly greater than that afforded by breathing 100 percent oxygen at 60 ft. Oxygen is administered intermittently throughout the remainder of the therapy to accelerate bubble resolution and maintain tissue oxygenation, while avoiding harmful effects of oxygen toxicity by allowing partial recovery during the air intervals. The profile in Fig. 62-4 may be extended in severe cases by adding oxygen intervals at 60 and 30 ft. Hyperbaric oxygen therapy of decompression sickness, which seldom involves cerebral gas embolism, is usually performed by compressing directly to 60 ft without prior pressurization to 165 ft.

In both arterial gas embolism and decompression sickness, increased blood viscosity, hypovolemia, and other systemic effects of bubble interactions with blood components and vessels occur concurrently with the localized tissue ischemia caused by mechanical vascular obstruction. Isotonic fluids are administered intravenously to oppose at least some of these secondary effects. If the patient has other conditions that require medical or surgical intervention, such care is provided concurrently with the administration of hyperbaric oxygenation.

LIMITATIONS IMPOSED BY OXYGEN TOXICITY

During oxygen breathing at increased ambient pressures, rate of intoxication increases progressively in proportion to inspired P_{O_2} elevation. Duration of oxygen exposure at 1.0 to 2.0 atm is limited primarily by pulmonary effects of oxygen toxicity. At oxygen pressures of 3.0 atm or higher, visual impairment and convulsions usually occur before development of prominent pulmonary intoxication.

Although the toxic effects of oxygen are numerous and varied (Fig. 62-5), they can be avoided by appropriate administration of hyperbaric oxygen therapy. Early stages of intoxication, even when associated with symptoms and detectable functional alterations, are fully reversible upon termination of exposure. The onset of toxic effects is delayed effectively by periodic interruption of oxygen exposure with scheduled "air breaks" (Fig. 62-4).

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63

Thermal Lung Injury and Acute Smoke Inhalation

Daniel L. Traber • Perenlei Enkhbaatar

OVERVIEW AND EPIDEMIOLOGY

Inhalation injury is a serious medical problem. In the case of smoke, more than 30 percent of thermally injured patients admitted to burn centers in the United States have a concomitant smoke inhalation injury. Similar percentages of fire victims who have sustained smoke inhalation appear in several other countries. Despite effective management of fluid resuscitation and early surgical excision of burned tissue, the mortality rate of patients who have combined burn and smoke inhalation injury is still high. In patients with combined injury, the lung is a critical organ and the progressive respiratory failure associated with pulmonary edema is a pivotal determinant of mortality. Although not as lethal, smoke inhalation alone is a serious problem. It is estimated by the World Health Organization that there are over 1 billion people who develop airway and pulmonary inflammation as a result of inhaling smoke from indoor cooking fires, forest fires, and burning of crops.

The inhalation of smoke has been of interest for a number of years, especially as the result of the use of gas warfare. In the 1940s there were two very large fires that focused interest on the inhalation of smoke in fire victims. The first was a fire at a nightclub in Boston called the Cocoanut Grove, where a large number of people were trapped in a burning building and consequently sustained severe inhalation injury. It is interesting that in recent times a similar fire occurred in a nightclub near Boston in Rhode Island. The second occurred in Texas City across the bay from Galveston, Texas. Here a ship exploded in a harbor and set off a chain of explosions and fires among some 50 refineries and chemical plants, resulting in over 2000 hospital admissions of patients with smoke inhalation alone, those with burn injuries, many of whom who had simultaneously inhaled smoke as well. In many ways the burn victims of the 9/11 disaster were similar to these individuals, since the burns and inhalation involved combustion of petroleum products. At any rate, these two disasters led to the establishment of centers for the care of burn victims and research into the pathophysiology of burn injury.

THE FIRE ENVIRONMENT

Toxic Smoke Compounds

Inhalation injury is caused by steam or toxic inhalants such as fumes, gases, and mists. Fumes consist of small particles dispersed in air with various irritants or cytotoxic chemicals adherent to the particles. Mists consist of aerosolized irritant or cytotoxic liquids. Smoke consists of a combination of fumes, gases, mists, and hot air. Heat, toxic gases, and low oxygen levels are the most common causes of death in fire

Table 63-1

Origin of Selected Toxic Compounds

Gases and Chemicals	Material	Source
Carbon monoxide	Polyvinyl chloride Cellulose	Upholstery, wire/pipe coating, wall, floor, furniture coverings Clothing, fabric Wood, paper, cotton
Cyanide	Wool, silk Polyurethane Polyacrylonitrile Polyamide Melamine resins	Clothing, fabric, blankets, furniture Insulation, upholstery material Appliances, engineering, plastics Carpeting, clothing Household and kitchen goods
Hydrogen chloride	Polyvinyl chloride Polyester	Upholstery, wire/pipe coating, wall, floor, furniture coverings Clothing, fabric
Phosgene	Polyvinyl chloride	Upholstery, wire/pipe coating, wall, floor, furniture coverings
Ammonia	Wool, silk Polyurethane Polyamide Melamine resins	Clothing, fabric, blankets, furniture Insulation, upholstery material Carpeting, clothing Household and kitchen goods
Sulfur dioxide	Rubber	Tires
Hydrogen sulfide	Wool, silk	Clothing, fabric, blankets, furniture
Acrolein	Cellulose Polypropylene Acrylics	Wood, paper, cotton jute Upholstery, carpeting Aircraft windows, textiles, wall coverings
Formaldehyde	Melamine resins	Household and kitchen goods
Isocyanates	Polyurethane	Insulation, upholstery material
Acrylonitriles	Polyurethane	Insulation, upholstery material

Source: Data from Prien T, Traber DL: Toxic smoke compounds and inhalation injury: A review. Burns *14:451–460, 1988.*

scenes. A large variety of toxic gases and chemicals can be generated depending on the fire environment (Table 63-1).

Many of these compounds may act together to increase mortality, especially carbon monoxide and hydrogen cyanide, in which a synergism has been found to increase tissue hypoxia and acidosis and perhaps also decrease cerebral oxygen consumption and metabolism. Hydrogen sulfide would also be predicted to synergize with carbon monoxide since both cyanide and hydrogen sulfide are inhibitors of mitochondrial cytochrome oxidase. Victims may be incapacitated by the blinding and irritating effects of smoke, as well as the decreasing oxygen concentration that occurs with combustion and results in progressive hypoxia.

Inhalation injury can be classified: (1) upper airway injury, (2) lower airways and pulmonary parenchyma injury, and (3) systemic toxicity. The extent of inhalation damage depends on the fire environment: the ignition source, temperature, concentration, and solubility of the toxic gases generated. For instance, thermal and chemical compounds usually cause upper airway injury. The water-soluble materials such as acrolein and the other aldehydes damage the proximal airways and set off reactions that are inflammatory to the bronchi and parenchyma, whereas agents with lower water solubility, such as chlorine, phosgene, and nitrogen oxide, nitrogen dioxide, or N_2O_3 or even N_2O_4 are more likely to cause insidious injury. Toxic gases such as carbon monoxide and cyanide rarely damage the airway but affect gas exchange, producing more systemic effect. Thus, it is important to obtain information relative to the source of the fire and combustion products generated when treating a fire victim (Table 63-1). It is also

important to know the duration of exposure and the extent to which the fire victim was in an enclosed area because this relates to the dose of toxic materials presented.

Carbon Monoxide

Carbon monoxide (CO) is an odorless, colorless gas that is produced by incomplete combustion of many fuels, especially cellulolytic (cellulose products) such as wood, paper, and cotton. Carbon monoxide toxicity remains one of the most frequent immediate causes of death following smoke-induced inhalation injury. The predominant toxic effect of CO is its binding to hemoglobin to form carboxyhemoglobin (COHb). The affinity of CO for hemoglobin is approximately 200 to 250 times higher than that of oxygen. Inhalation of a 0.1 percent carbon monoxide mixture may result in generation of a carboxyhemoglobin level as high as 50 percent. The competitive binding of CO to hemoglobin reduces delivery of oxygen to tissues, leading to severe hypoxia, especially of the most vulnerable organs such as the brain and heart. The oxygen-hemoglobin dissociation curve loses its sigmoid shape and is shifted to the left, thus further impairing tissue oxygen availability. In addition, the ability of CO to bind to intracellular cytochromes and other metalloproteins contributes to CO toxicity. This competitive inhibition with cytochrome oxidase enzyme systems (most notably cytochromes a and P-450) results in an inability of cellular systems to use oxygen. Shimazu and colleagues have shown that extravascular binding of CO to cytochromes and other structures accounts for 10 to 15 percent of total body CO stores, which explains the two-compartment elimination of CO from the circulation. Miro and colleagues reported that CO inhibits cytochrome c oxidase activity in lymphocytes. The electron chain dysfunction by CO may cause electron leakage, leading to superoxide production and mitochondrial oxidative stress.

Symptoms and Diagnosis

The symptoms may predominantly manifest in organ and systems with high oxygen utilization. The severity of clinical manifestations is varied depending on the concentration of CO. For instance, central nervous system symptoms such as headache, confusion, and collapse may occur when the blood COHb level is 40 to 50 percent. Symptoms such as unconsciousness, intermittent convulsions, and respiratory failure may occur if the COHb level exceeds 60 percent, and eventually leading to death if exposure continues. The cardiovascular manifestations may result in tachycardia, increase in cardiac output, dysrhythmias, myocardial ischemia, and hypotension depending on severity of poisoning. The correlation of clinical manifestation and severity of CO poisoning is summarized in Table 63-2.

The diagnosis should be based on direct measurement of COHb levels in arterial or venous blood by co-oximetry. Portable breath analyzers may be used at the scene. Inability to differentiate oxyhemoglobin from COHb limits the use of pulse oximeters. The use of blood gas analyzers that estimates S_{O_2} based on measurement of dissolved P_{O_2} should be avoided also. The measurements of acid-base balance, plasma lactate levels, and bicarbonate are helpful in management of CO poisoning with accompanying lactic or metabolic acidosis. It is important to note that high oxygen concentrations are usually administered to the victim in transit to the hospital, and some delay from cessation of exposure to measurement of CO may limit evaluation of the true extent of exposure. A nomogram has been developed that can relate the carboxyhemoglobin levels of a patient to the values that may have been present at the time of smoke inhalation; this can be used to estimate the true degree of inhalation injury.

Table 63-2

Symptoms and Signs at Various Concentrations of Carboxyhemoglobin

COHb%	Symptoms
0–10	None
10–20	Tightness over forehead, slight headache, dilation of cutaneous blood vessels
20–30	Headache and throbbing in the temples
30–40	Severe headache, weakness, dizziness, dimness of vision, nausea, vomiting, collapse
40–50	As above; greater possibility of collapse, syncope, increased pulse and respiratory rate
50–60	Syncope, increased pulse and respiratory rate, coma, intermittent convulsions, Cheyne Stokes respirations
60–70	Coma, intermittent convulsions, depressed cardiac and respiratory function, possible death
70–80	Weak pulse, slow respirations, death within hours
80–90	Death in less than 1 h
90–100	Death within minutes

Source: Data from Einhorn IN: Physiological and toxicological aspects of smoke produced during the combustion of polymeric materials. Environ Health Perspect *11:163–189, 1975; Schulte JH: Effects of mild carbon monoxide intoxication.* Arch Environ Health *7:524–530, 1963.*

Treatment

The half-life of carboxyhemoglobin is 250 min (adult male) in room air and 40 to 60 min in a person breathing 100 percent oxygen at 1 atmosphere (atm). Those values are 30 percent

shorter in females. Therefore, all fire victims should be isolated from fire site and given 100 percent oxygen en route to the hospital. This allows delivery of an inspired oxygen concentration of 50 to 60 percent, which is usually adequate. To adequately treat CO poisoning it is important also to establish COHb level as early as possible. In a patient with loss of consciousness, cyanosis, or an inability to maintain the airway, 100 percent oxygen should be delivered via mechanical ventilation through endotracheal tube until the COHb levels drop below 10 to 15 percent. The alternative method to rapidly decrease COHb is hyperbaric oxygen therapy. The hyperbaric oxygen therapy allows CO to dissociate from cytochrome a, a_3, and to increase P_{O_2} despite impaired hemoglobin function. Chou and colleagues reported that children with CO poisoning alone who are treated with hyperbaric oxygen therapy (HBOT) are at low risk for dying regardless of initial COHb level. However, there is some debate on use of HBOT especially in patients with burn injury. Because of the difficulty of physiological monitoring and providing emergency procedures in small chambers, unstable hemodynamic conditions and other complications such as seizures or aspiration of severely burned patients limit the use of hyperbaric oxygen therapy.

Hydrogen Cyanide

Hydrogen cyanide is a colorless gas with the odor of bitter almonds. However, it is difficult to detect it on the site of fire. Cyanide is a likely weapon for terrorists because of its notoriety, lethality, and availability. Hydrogen cyanide is produced in fires involving nitrogen-containing polymers (upholstery, furniture, nylon, wool, silk, and acrylics) and may produce rapid and lethal incapacitation of a victim at the fire source. Toxicity of cyanide is produced by inhibition of cellular oxygenation with resultant tissue anoxia, which is caused by reversible inhibition of cytochrome c oxidase. It is toxic to a number of enzyme systems. The mechanism includes combination with essential metal ions, formation of cyanohydrins with carbonyl compounds, and the sequestration of sulphur as thiocyanate. However, the main target enzyme is cytochrome c oxidase, the terminal oxidase of the respiratory chain, and involves interaction with the ferric ion of cytochrome a_3.

Symptoms and Diagnosis

Diagnosis at the fire scene may be difficult. Poisoning results in central nervous system, respiratory, and cardiovascular dysfunction, resulting from inhibition of oxidative phosphorylation. It may include dyspnea, tachypnea, vomiting, bradycardia, hypotension, coma, and seizures. Electrocardiographic S-T segment elevation, which mimics an acute myocardial infarction, may be suggestive. Laboratory findings of anion gap metabolic acidosis and lacticacidemia aid in confirming the diagnosis. The lactic acidosis that is not rapidly responsive to oxygen therapy may be good indicator for cyanide poisoning. Also, elevated mixed venous saturation is suggestive of cyanide toxicity. Cyanide increases ventilation through carotid body and peripheral chemoreceptor stimulation. Increasing ventilation may augment toxicity in the early stages. Correlation of blood cyanide concentrations with clinical symptoms is summarized in Table 63-3.

Table 63-3

Hydrogen Cyanide Concentrations in Air and Associated Symptoms in Humans

HCN Concentration ppm	Symptoms
0.2–5.0	Threshold of odor
10	(TLV-MAC)
18–36	Slight symptoms (headache) after several hours
45–54	Tolerated for 1/2–1 h without difficulty
100	Death in 1 h
110–135	Fatal in 1/2–1 h
181	Fatal in 10 min
280	Immediately fatal

Source: Data from Einhorn IN: Physiological and toxilogical aspects of smoke produced during the combustion of polymeric materials. Environ Health Perspect *11:163–189, 1975; Kimmerle G: Aspects and methodology for the evaluation of toxicological parameters during five exposure, in* Polymer Conference Series: Flammability characteristics of materials. *Salt Lake City, University of Utah, 1973.*

Hydrogen cyanide is found routinely in low levels in the blood of healthy individuals at levels of 0.02 μg/ml in nonsmokers and 0.04 μg/ml in smokers. Toxicity occurs at a level of 0.1 μg/ml, and death is likely at 1.0 μg/ml.

Treatment

Fire victims suspected to have cyanide poisoning should be removed from exposure and fully decontaminated. All victims should be given pure (100 percent) oxygen and resuscitated properly if cardiopulmonary failure is present. Oxygen therapy appears to have strong positive effect; however, hyperbaric oxygen therapy is not recommended for the reasons previously mentioned. Cyanide is metabolized by hepatic rhodanese, which catalyzes the donation of sulfur from the sulfone pool to cyanide to form nontoxic thiocyanate. The half-life time of cyanide is approximately 1 to 3 h in humans. Although there is still controversy surrounding the treatment of cyanide poisoning, a few antidotes are available that can be used by first responders. Kelocyanor (dicobalt edentate) may be useful, but it is dangerous, and requires experts to

administer it. The following agents may be considered in an intensive care setting.

Methemoglobin Generators

The therapeutic goal is to convert the ferrous ion of hemoglobin to ferric ion. The resultant methemoglobin chelates cyanide to form cyanmethemoglobin. The drugs of choice in this group are sodium nitrite (intravenously) and amyl nitrite (inhaled). These drugs reduce oxygen-carrying capacity; therefore, they should be used with caution, especially in patients with concomitant CO poisoning, which induces COHb that may further compromise oxygen transport. These drugs should be used with precaution in patients with burn shock, because they are also vasodilators and can cause hypotension. In addition, there is little evidence to suggest these measures are effective, and cardiac toxicity in people with heart disease may be problematic.

Sulfur Donors

The therapeutic goal is to convert cyanide to thiocyanate. The drug of choice in this group is sodium thiosulfate (intravenously). Toxicity is minimal other than an osmotic diuretic action, which may be beneficial. However, the onset of action is quite slow.

Direct Binding Agents

These are based on cobalt chemistry and chelate the cyanide ion directly. Hydroxocobalamin is the precursor of vitamin B_{12} and has very little toxicity. However, this drug is not available in the United States for treatment of cyanide poisoning.

Other Toxic Chemicals

These may also contribute substantially to the morbidity and mortality in a burn victim. Hydrogen chloride is produced by polyvinyl chloride degradation and causes severe respiratory tract damage and pulmonary edema. Nitrogen oxides may also cause pulmonary edema and a chemical pneumonitis and may contribute to cardiovascular depression and acidosis. Aldehydes such as acrolein and acetaldehyde, which are found in wood and kerosene, may further contribute to pulmonary edema and respiratory irritability. Toxic industrial chemicals such as chlorine, phosgene, hydrogen sulfide, and ammonia are of central importance. Because of their wide spread availability and high toxicity, there is certain concern that these chemicals may be used as a weapon by terrorists.

Phosgene is colorless, nonflammable, heavier-than-air gas at room temperature with an odor of newly mown hay. Under 8°C phosgene is an odorless and fuming liquid. Phosgene's inadequate warning properties and delayed symptoms make it a potential terrorist weapon. Phosgene is only slightly soluble in water; hence, its deeper penetration in the pulmonary system. On contact with water it hydrolyzes into carbon dioxide and hydrochloric acid, resulting in direct caustic damage. It also undergoes acylation reactions with amino, hydroxyl, and sulfhydryl groups of cellular macromolecules, resulting in cell damage and apoptosis. As mentioned, phosgene has delayed effects from 20 min up to 48 h, depending on the intensity of exposure. Phosgene inhalation produces severe pulmonary edema. Initially victims develop upper airway irritant symptoms (eye irritation, rhinorrhea, cough); then they develop lower respiratory symptoms such as shortness of breath, substernal burning, and chest tightness. The development of overt pulmonary edema within 4 h of exposure portends a poor prognosis.

Chlorine is a greenish yellow gas, an oxidizing agent that is very reactive with water. It has a pungent odor. Upon contact with water, chlorine liberates hypochlorous acid, hydrochloric acid, and oxygen free radicals. It causes irritant effects throughout the respiratory tree but mostly nasal mucosa and upper airways. Cell damage is caused by its strong oxidizing capability. Phosgene and chlorine were used extensively during World War I.

Ammonia is a colorless gas at room temperature with a very pungent odor. Ammonia readily dissolves in water to form ammonium hydroxide, a very caustic alkaline solution. It causes cutaneous, ocular, and pulmonary injuries. When inhaled, ammonia can rapidly produce laryngeal injury and obstruction. It also causes upper tracheobronchial mucosal necrosis with sloughing and severe pulmonary edema.

There are no specific antidotes against irritant gases (phosgene, chlorine, and ammonia) toxicity. Depending on the severity of exposure, supportive therapy such as airway management and ventilation should be provided. Early intubation is required if any significant upper airway symptoms such as stridor are present.

PATHOPHYSIOLOGY

Tracheobronchial Area

With rare exceptions, such as the inhalation of steam, injury to the airway is usually from the chemicals in smoke. The heat capacity of air is low and the bronchial circulation is very efficient in warming or cooling the airway gases so that most are at body temperature as they pass the glottis. Flames must be in almost direct contact with the airway to induce thermal injury. The chemicals in smoke are dependent on the materials that are being burned; however, for the most part the host response is similar. In most instances biologic materials such as cotton fabric, wood, or grass, or the products of these such as cattle feces (commonly used as fuel in third world countries) are fuel for the fire. These contain caustic materials such as reactive oxygen (ROS) and nitrogen species (RNS) organic acids and aldehydes. These chemicals interact with the airway to induce an initial response to trigger an inflammatory response.

Many of the studies concerning bronchial circulation following smoke inhalation injury have been performed in sheep, because these animals have a single bronchial artery and a single lymphatic draining the lung that allows the

measure of pulmonary transvascular fluid flux. There was a tenfold increase in bronchial blood flow within 20 min of smoke inhalation. These same animals demonstrate a sixfold increase in pulmonary transvascular fluid flux and a fall in $Pa_{O_2}/FiO_2 \leq 300$, but these were delayed to 24 h. Similar findings have been reported in patients with smoke inhalation alone or the combination of a large cutaneous thermal injury and smoke inhalation.

Hyperemia of the airway is such a consistent finding in smoke inhalation that it is used to diagnose the injury. Other variables used include injury in an enclosed space, singed nasal hair, and soot in sputum. However, these latter injuries may be present but the subject may still not develop the signs of low Pa and pulmonary edema characteristic of inhalation injury. Airway inflammation plays a major role in the overall response to inhalation injury.

As noted, there is a large sustained increase in blood flow in the airway following smoke inhalation. These changes in blood flow are associated with increased bronchial microvascular permeability to protein and small particles and pressure. Simultaneous with the changes in the function of the bronchial microvascular, there is a loss or shedding of the bronchial columnar epithelium. These changes result in a perfuse transudate with a protein content similar to an ultrafiltrate of the plasma. There are also copious secretions from the goblet cells. Early in the response these secretions are fluid and form a foamy material in the airway that many mistake for severe pulmonary edema in human patients. After several hours this transudate/exudate solidifies or clots forming obstructive materials in the airways. The mechanism of airway obstructive cast formation is illustrated in Fig 63-1. These obstructive materials formed in the upper airway may appear in the lower airway and alveoli. The presence of fibrin

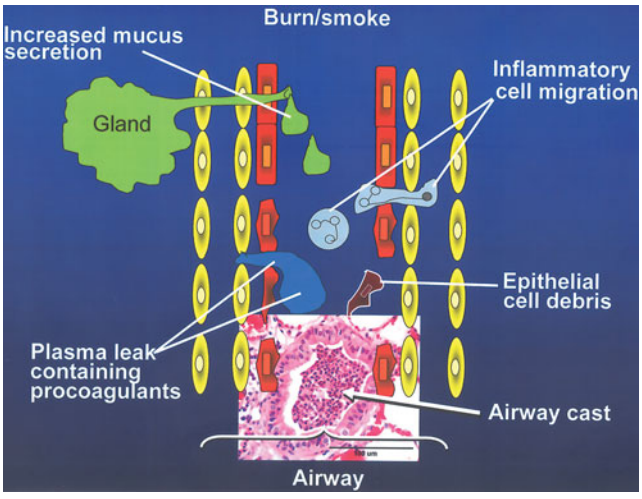

Figure 63-1 The pathophysiological processes involved in the formation of the airway obstructive material following injury. The bottom is a microscopic picture of a bronchiole almost completely blocked by airway obstructive material containing mostly mucus/fibrin and inflammatory cells. Sheep lung tissue was taken for histological analysis 48 h after combined burn and smoke inhalation injury.

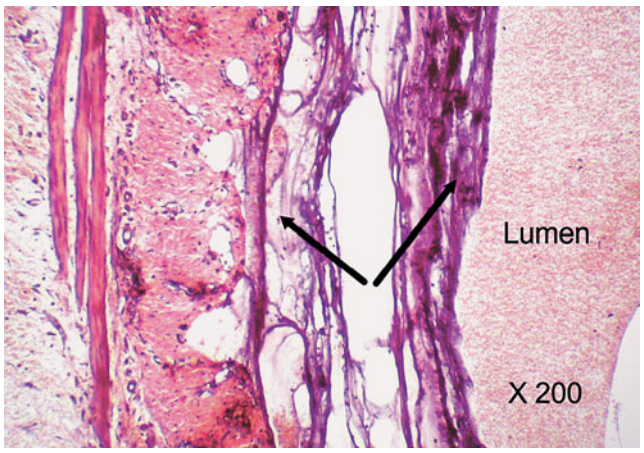

Figure 63-2 Light micrograph showing the presence of fibrin (arrows) lining the lumen of a bronchus in sheep subjected to combined burn and smoke inhalation injury. Lung tissue for histological analysis (Formalin fixation, Zenker postfixation, modified Masson trichrome stain) was taken 48 h after the injury.

makes the removal of airway obstructive cast extremely difficult (Fig. 63-2). This obstructive material is problematic from several stand points. In some rare instances of severe airway injury these materials can induce total obstruction and cause a life-threatening problem (Fig. 63-3). Occlusion of some of the bronchi or bronchioles in high NO production can lead to a loss of hypoxic pulmonary vasoconstriction and thus increased shunt fraction. Loss of hypoxic pulmonary vasoconstriction with inhalation injury has been reported. Lastly, if single bronchi are occluded while the patient is on a volume-limited-ventilated ventilator, there could be over stretch and barotrauma to the alveoli of the nonoccluded portion of the lung.

The airway is richly innervated with vasomotor and sensory nerve endings. It is also known that these fibers release neuropeptides in response to caustic materials. Neuropeptides release can cause activation of nitric oxide synthase, have chemokine activity, and change microvascular permeability. The resultant activities lead to the formation of reactive oxygen and nitrogen species. Some of the latter are very potent oxidants that can damage DNA. Damage to DNA causes the activation of a repair enzyme poly(ADP-ribose) polymerase (PARP). This enzyme depletes the cell of high-energy phosphates and causes the activation of nuclear factor κB (NF-κB). Activation of the nuclear factor causes the upregulation of iNOS and IL-8, thus creating accelerated production of reactive oxygen and nitrogen species (Fig. 63-4). NO and 3-nitrotyrosine, an index of ROS, iNOS mRNA, and protein have been reported to be in the airway after smoke inhalation. Poly(ADP-ribose) [PAR], the product of the constitutive enzyme PAR polymerase, was identified in the airway tissues following smoke inhalation. Inhibition of PARP prevented the formation of PAR, the up-regulation of NF-κB, and the formation of 3-nitrotyrosine. It is interesting to note that airway inflammation is not seen in a typical asthma model in

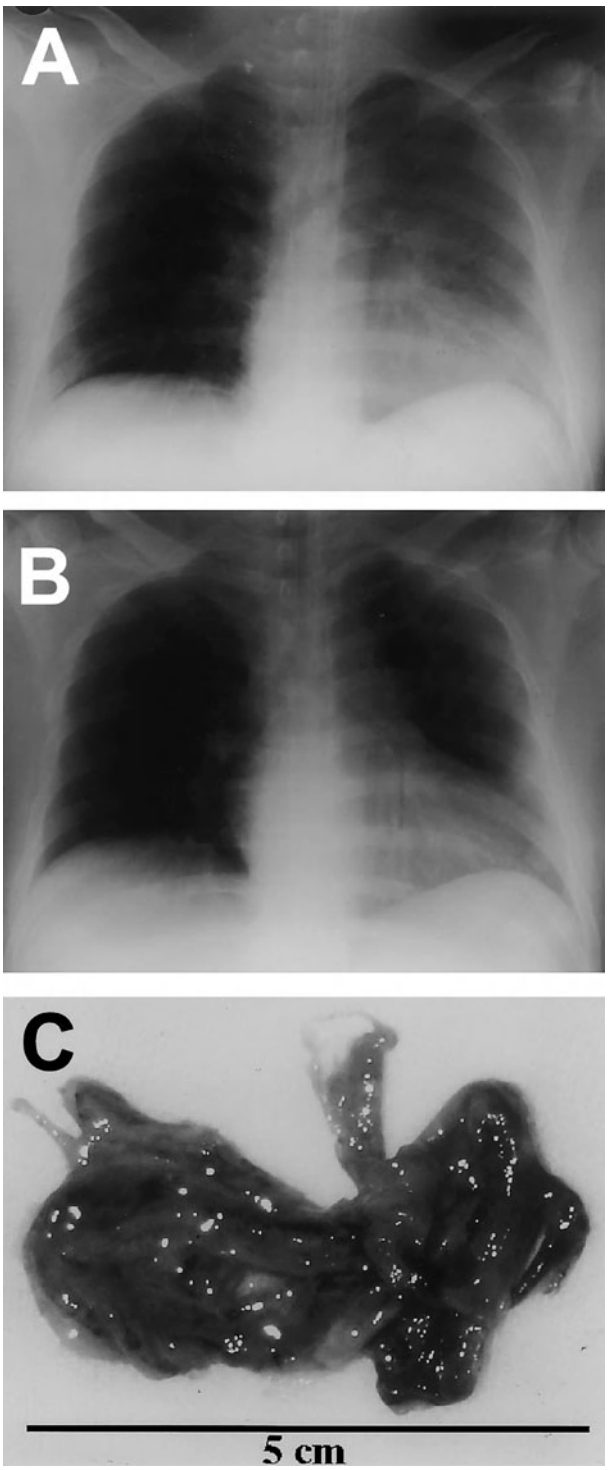

Figure 63-3 A chest radiograph of patients suffering from smoke inhalation taken at the time of admission and after removal of solid airway obstructive cast. *A*. There was decreased transmission of the entire left pulmonary area, elimination of the heart shadow, and elevation of the left diaphragm before the removal of cast. *B*. Radiograph taken 30 min after removal shows improved transmission; also, the heart shadow became visible. *C*. The cast was removed with basket forceps from the main left bronchus to the bifurcation of the upper and lower lobe bronchi. *(From Nakae H, Tanaka H, Inaba H: Failure to clear casts and secretions following inhalation injury can be dangerous: Report of a case.* Burns *27:189–191, 2001, with permission.)*

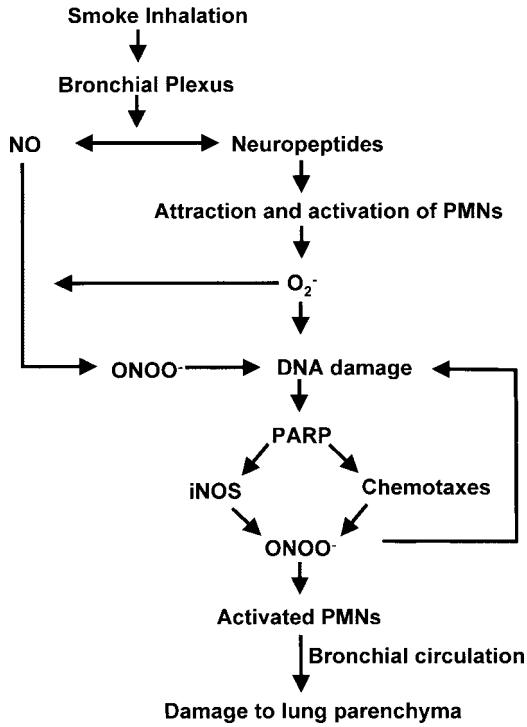

Figure 63-4 The mechanism of lung parenchyma damage in smoke inhalation injury. NO, nitric oxide; iNOS, inducible nitric oxide synthase, PMNs, polymorphonuclear cells; PARP, poly(ADP-ribose) polymerase.

the presence of a PARP inhibitor or mice lacking the PARP gene.

Lung Parenchyma

As noted, the lung parenchyma changes, as reflected by reduced Pa_{O_2}/Fi_{O_2}, and reduced compliance and increased edema formation are delayed. The delay depends on the severity of airway injury. Lung injury is associated an increased pulmonary transvascular fluid flux. The degree of transvascular fluid is proportional to the duration of smoke exposure and is independent of the levels of CO in the inhalant gas. The factors responsible for fluid leak are codified in the Starling-Landis equation. The variables of this equation relate fluid movement to pressure and permeability variations. With inhalation of smoke there is a reduction in refection coefficient (permeability to protein), increase in filtration coefficient (permeability to small particles), and increase in pulmonary microvascular pressure. Figure 63-5 demonstrates that pulmonary transvascular fluid flux in sheep following smoke inhalation is due to changes in both microvascular permeability and pressure. It appears that microvascular changes may be responsible for early events.

Animals that were exposed to smoke inhalation injury were also noted to have reduced Pa_{O_2}/Fi_{O_2}. The change in this variable showed a good relationship to the histology injury scores and the changes in transvascular fluid flux. In addition, there was a loss of hypoxic pulmonary vasoconstriction in the injured animals that helps to explain the loss of oxygenation.

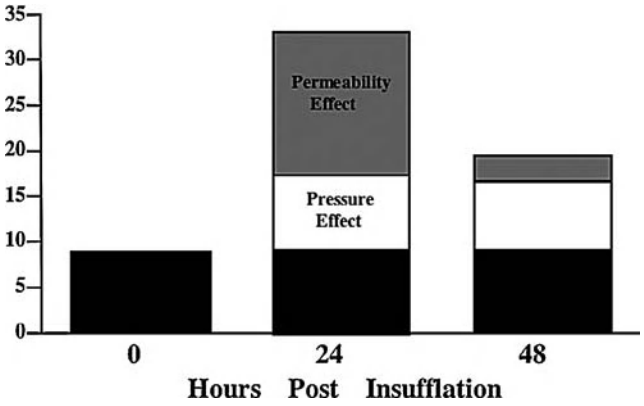

Figure 63-5 Diagram showing portion of edema resulting from either changes in pulmonary microvascular permeability or pressure at 24 and 48 h after inhalation injury. *(From Isago T, Fujioka K, Traber LD, et al: Derived pulmonary capillary pressure changes after smoke inhalation in sheep.* Crit Care Med *19:1407–1413, 1991, with permission.)*

As in the airway, the injury is markedly reduced by the administration of iNOS or PARP inhibitors and is associated with the reduction of PAR and 3-nitrotyrosine.

The venous outflow of the bronchial circulation drains into the pulmonary microcirculation at the precapillary level. The fact that initial damage to the airway appeared to drive the pathophysiology of the parenchyma led investigators to hypothesize that the bronchial blood might deliver cytotoxic materials or cells into the pulmonary microcirculation. To test this hypothesis, several investigators tied off the bronchial artery of sheep and then exposed the animals to smoke. The hypothesis was affirmed in these studies; lung parenchymal changes were reduced.

What could be the linkage among the airway, bronchial venous drainage, and parenchymal injury to the lung? Neutrophils activated in the bronchial circulation flow out into the bronchial venous drainage. Activated polymorphonuclear cells (PMN), especially neutrophils, are stiff. The diameter of neutrophils that have been fixed is approximately 7 μm. Since these cells have been dehydrated in alcohol as part of the fixation process, unfixed cells are much larger, on the order of 12 μm. The pulmonary capillary is small, with an average diameter of 6 μm. Normally the large neutrophil can traverse the pulmonary capillary by changing shape. However, many neutrophils have been activated in the bronchial areas. Their F-actin is activated and the cells are stiff and cannot deform. These stiff cells are carried to the pulmonary microvasculature, where they are impaled by the narrow pulmonary capillaries. The activated neutrophils release ROS and proteases that damage the parenchyma. The following evidence supports this concept of neutrophil cytotoxicity. Oxidative processes are well known following inhalation injury. There is lipid peroxidation and release of proteolytic enzymes following injury. Administration of protease inhibitors or scavengers of ROS reduces the response to smoke inhalation when activated PMNs lose the L-selectin on their surface. This L-selectin shedding is prevented by treatment with an L-selectin antibody. Treatment of the cells with an antibody to L-selectin prevents the changes in transvascular fluid flux and other aspects of parenchymal damage. The final proof of this hypothesis was to deplete the animals of their neutrophils and determine how this affected the response to inhalation injury. In these studies of sheep depleted of their leukocytes, a high percentage of the response to smoke inhalation was blocked.

In addition to the depletion of antioxidants, it also has been reported that burned patients are depleted of arginine. When arginine levels are low the NOS produces superoxide rather than nitric oxide. Administration of arginine may assist in reducing the oxidation that occurs with inhalation injury. However, the necessity of administering the arginine as arginine hydrochloride (because of solubility) limits the amount that may be given intravenously without producing acidosis.

Treatment

Some pretreatment for smoke inhalation can be accomplished. Some people are chronically exposed to smoke, such as farmers who burn crops, individuals with fires in their huts, and firefighters. There are reports that individuals who are chronically exposed to smoke are depleted of antioxidants. Consequently, antioxidant supplementation should be considered.

The airway is a major concern in the post-inhalation period. This is very difficult to manage in patients with combined inhalation and burn injuries. Intubation is very difficult in patients with burns of the soft tissues of the face, oral pharynx, and neck. Burn injury to these soft tissues results in almost immediate and severe edema and swelling. Intubation in such an individual requires great skill. Securing the tube is difficult. Accidental removal of the endotracheal tube is easy and lethal. Often burns and/or the chemicals in smoke damage the larynx, and placement of the tube can cause damage and delay healing of such a wound. Tracheostomy is performed sometimes, but also can be difficult if it has to be placed through burned skin on the neck. For information on this, the reader is referred to the chapters of Fitzpatrick and Gioffi as well as Mlcak and Herndon, in Herndon's *Total Burn Care*.

To counter obstruction, vigorous toilet should be performed. The cast material contains fibrin. Experimentally, the use of heparin has been reported to be effective in reducing airway obstruction. However, heparin requires the presence of antithrombin to be effective, and this factor has been reported to be deficient following burn injury. Consequently, antithrombin has been reported to be effective in these situations in animal studies. Antithrombin and activated protein C also may act as anti-inflammatory agents. Once obstructive materials have formed in the airway, heparin and antithrombin are ineffective in removing them. Animal studies have demonstrated that tissue plasminogen activator might be effective in removing these materials. Aerosolized tissue plasminogen activator has been reported to be effective in

removing bronchial obstructive material in patients who have had Fontan procedures. Many burn units nebulize heparin into the airway of their patients with inhalation injury.

Many drugs have proved effective in reducing injury to the lung parenchyma of animal models of inhalation injury, including cyclooxygenase inhibitors, iNOS inhibitors, PARP inhibitors, and oxygen scavengers, as well as the anticoagulant factors mentioned in the preceding. However, only the latter are in clinical use and/or clinical trial.

In many instances conventional methods of ventilation can no longer sustain the pulmonary function of burned patients. Extracorporeal membrane oxygenation has been used in these patients with some success. Techniques have now been developed in animal models of inhalation injury that involve a unique form of CO_2 removal called arterial venous CO_2 removal (AVCOR). Off the shelf CO_2 removal devices, used in extracorporal bypass and cardiopulmonary bypass, have been modified to be driven by the subject's own arterial pressure. These were tested in animal models and shown to be very successful in reducing pathophysiology, morbidity, mortality, and days of ventilatory support of inhalation injury models. AVCO2R is now in clinical trials for the treatment of severe ARDS associated with inhalation injury.

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PART

VI

Drug-Induced Lung Diseases

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64

Pulmonary Toxicity Associated with Chemotherapeutic Agents

Lynn T. Tanoue • John R. McArdle

Toxicities related to medications comprise a major category of iatrogenic illness. Many chemotherapeutic agents are known to have potential for pulmonary toxicity. With an expanding understanding of biologic mechanisms fundamental to neoplasia, the horizons for treatment options broaden. As new therapeutic modalities become available, patients with cancer are living longer, and may in their long-term survivorship display delayed toxicities related to their treatment. For the pulmonologist, drug-induced lung disease is therefore necessarily an area of growing concern. Chemotherapeutic agents, therapeutic radiation, and biologic response modifiers are used in a wide range of regimens further complicated by the use of hematopoietic support and bone marrow or stem cell transplantation. Many can directly or indirectly be associated with pulmonary toxicity. An estimated 5 to 10 percent of patients undergoing chemotherapy will ultimately develop therapy-related pulmonary complications.

APPROACH TO THE PATIENT WITH SUSPECTED CHEMOTHERAPY-INDUCED PULMONARY TOXICITY

The diagnosis of drug-induced pulmonary toxicity is one of exclusion. Patients most often present with nonspecific constitutional or respiratory complaints. In many cases, symptoms and physical signs may be minimal or even absent. In these situations, the only evidence of an ongoing pulmonary process may be an abnormal chest radiograph (Table 64-1). The diagnosis of lung disease caused by chemotherapeutic agents poses a particular challenge to the clinician, as there are several complicating features inherent to the oncology patient population. First, treatment may be given in multidrug regimens or in combination with other modalities such as radiation therapy, bone marrow transplantation, or stem

Table 64-1

Differential Diagnosis of Radiographic Abnormalities in Cancer Patients

Infection
Primary malignancy
Lymphangitic tumor, metastatic disease, leukemic infiltration
Drug toxicity
Radiation injury
Pulmonary edema
ARDS
Pulmonary hemorrhage
Pulmonary emboli
Leukoagglutinin reaction
Pulmonary fibrosis

cell transplantation. Assigning pulmonary toxicity to a single drug or modality within such a regimen is often impossible. Moreover, the combined toxicity of two or more drugs or a single drug with radiation therapy may exceed the individual toxicities of those drugs. Second, patients undergoing chemotherapy are often immune suppressed, either from the malignancy itself or from myelosuppressive or immunosuppressive effects of their treatment. These patients are therefore susceptible to opportunistic infection, which may be indistinguishable radiographically from drug toxicity. It should be remembered that the lung is the most common site of serious infection in patients with cancer. It has been estimated that a relative minority (5 to 30 percent) of pulmonary complications in the immunocompromised host are actually due to drug toxicity. Since changing a treatment regimen may affect the chance for prolonging survival or cure, reasonable certainty of drug-related complications necessarily involves exclusion of infection as the cause of pulmonary disease. Third, cancers themselves may mimic lung disease. This is particularly true in cases of lymphangitic tumor spread or metastases to the lung parenchyma or pleura. Fourth, toxicity from some drugs appears to be related to cumulative dosage levels. However, adverse reactions may occur even with a low cumulative dose, when clinical suspicion for toxicity is low. Finally, pulmonary toxicity due to a single chemotherapeutic agent may present with several different syndromes that vary clinically, radiographically, and temporally. While a severe pulmonary reaction acutely following drug administration usually raises suspicion of drug toxicity, as patients survive for longer periods of time it is becoming increasingly clear that toxicity due to some chemotherapeutic agents may be delayed by months to even years after treatment. In such situations, clinical suspicion of drug toxicity may be low. Monitoring for potential pulmonary toxicity in the patient undergoing chemotherapy requires ongoing clinical vigilance. Symptoms such as cough, dyspnea, or chest discomfort may be mild or even absent. Radiographic findings may be equally subtle. Even if clinical symptoms and radiographic abnormalities are present and severe, they are usually nonspecific. The possibility of adverse drug effects must be considered within the complex medical context inherent to the patient with cancer undergoing physically challenging or immunosuppressive treatment.

PULMONARY PHYSIOLOGICAL TESTING

Pulmonary physiological testing has received significant attention as a potential screening tool for drug-induced pulmonary disease. A multitude of investigations studying the utility of the pulmonary function test (PFT) in monitoring pulmonary effects related to administration of chemotherapy have been reported. Various physiological abnormalities have been described, the most common of which are decreases in lung volumes and diffusing capacity for carbon monoxide (D_{LCO}). The application of these findings to clinical management has been a subject of much debate. Monitoring patients receiving chemotherapy with pulmonary function testing frequently demonstrates physiological abnormalities in the absence of clinical signs of toxicity. Abnormalities in D_{LCO} in particular have been felt in some studies to be indicative of early onset drug-related pulmonary injury. Most such studies have been performed in patients receiving bleomycin, busulfan, or carmustine. Discontinuation of drug with or without initiation of treatment including corticosteroids in such situations typically results in improvement. Whether such early intervention based on D_{LCO} abnormalities in the absence of clinical symptoms does indeed diminish the likelihood of long-term pulmonary impairment related to toxicity is unclear. In such cases, consideration would have to be given to the knowledge that discontinuation of drug because of potentially unfounded concern for progressive pulmonary disease might lead to alteration of otherwise preferred therapy. In contrast, in situations of clinically evident drug toxicity accompanied by PFT abnormalities, clinical recovery may not necessarily be paralleled by improvement in physiological measurements. For example, in a study examining pulmonary function in 116 long-term (5 to 13 years after treatment) survivors of Hodgkin's disease in Norway, nearly 30 percent of patients had exertional dyspnea with associated pulmonary function abnormalities. Multivariate analysis of these patients identified chemotherapy with a combination of bleomycin

and anthracyclines as the sole significant predictor of lung function impairment.

A number of factors further complicate the practice and interpretation of pulmonary function testing in the oncology population. Many physiological parameters are effort dependent. The ability of a patient to consistently perform test maneuvers may be affected by weakness, pain, or the use of analgesic or sedating medication. Reproducibility of results therefore is a significant issue in patients whose functional status and strength are potentially impaired by their malignancy or its treatment. Many patients will have anemia induced by malignancy, medication, or chronic illness. Since D_{LCO} is affected by hemoglobin concentration, it is critical that appropriate corrections for anemia be made. Patients with cancers may also be subject to processes other than drug toxicity that will affect PFT results. Primary pulmonary malignancy, metastatic lung disease, infection, thoracic or abdominal surgical procedures, and a host of other clinical situations may all independently cause variation in physiological measurements. Therefore, identifying pulmonary physiological abnormalities specific to drug effect may be extremely difficult.

Ultimately, despite the uncertainties in interpretation of physiological abnormalities, most clinicians will continue to rely on pulmonary function testing as a screening and monitoring tool in the hope of identifying toxicity early enough to prevent serious pulmonary disease. Unfortunately, the predictive value of baseline or serial pulmonary function testing remains unclear. Moreover, there are no definitive data that toxicity can be averted by serial monitoring. The presence of subclinical abnormalities does not imply that patients will develop irreversible lung disease, yet these abnormalities often dictate the withdrawal of drug. Conversely, normal physiology cannot predict abrupt toxicity that may produce profound pulmonary injury. As always, medical decisions based on pulmonary physiological findings must be made in the context of the patient's clinical situation as a whole.

Diagnostic Evaluation

Given the potential impact of pulmonary drug toxicity on a patient's present and future treatment, it is important to establish this diagnosis as firmly as possible. The thoughtful and judicious use of invasive procedures plays an important role in that evaluation.

The approach to the cancer patient in whom drug toxicity is suspected should parallel the approach to any immunocompromised patient with diffuse or localized lung disease. Because clinical features are usually not specific, sampling of respiratory tract secretions and/or lung tissue may be critical to this evaluation. Direct sputum examination or culture may suggest specific pathogens or may be diagnostic of infections such as invasive fungal disease, *Pneumocystis jiroveci* pneumonia, or tuberculosis. In the absence of diagnostic sputum findings, invasive procedures may be necessary. Fine-needle aspiration of the lung may be useful with focal lesions. However, the utility of this procedure in diffuse lung disease is relatively low. This is particularly problematic for patients with drug-induced pulmonary toxicity, which typically presents with a diffuse interstitial pattern on chest radiograph. Fiberoptic bronchoscopy with bronchoalveolar lavage and transbronchial biopsy has become central to the evaluation of both diffuse and localized lung disease in the immunocompromised host. The procedure is associated with a low rate of major complications (less than 1 percent) and with a diagnostic yield ranging from as low as 37 percent to as high as 72 percent. This broad variation in yield is probably reflective of the wide range of disease processes that can involve the lung in the immunocompromised patient. Highest diagnostic yields are obtained in patients with infections; lower yields are seen in interstitial inflammatory processes, which may include toxicity from drugs. However, even in situations in which a specific etiology is not identified, exclusion of infection by bronchoscopy often provides clinically useful information. Open or thoracoscopic lung biopsy is associated with the highest diagnostic yield and can be performed with low complication rates even in critically ill patients. If drug-induced pulmonary injury is suspected, surgical biopsy may be necessary to definitively exclude other causes of lung disease.

The evaluation of a patient in whom chemotherapy-related pulmonary toxicity is a consideration clearly presents significant challenges. Clinicians must be vigilant in the evaluation and management of patients receiving chemotherapeutic regimens. An awareness of potential iatrogenic complications related to drug therapy is therefore essential. This chapter reviews the major pulmonary toxicities associated with various chemotherapeutic agents.

CYTOTOXIC ANTIBIOTICS (TABLE 64-2)

Bleomycin

Bleomycin is a cytotoxic antibiotic produced by *Streptomyces vermiculus*, and is used in the treatment of various malignancies, including lymphomas, germ cell tumors, and cancers of the head and neck. Bleomycin is concentrated in skin and lung, with its major toxicities manifested in these organs. Limitation of its use usually hinges on its known potential for pulmonary toxicity. The incidence of bleomycin-induced lung injury varies from 6 to 18 percent. Published data suggest that 1 to 2 percent of bleomycin-treated patients will succumb to pulmonary toxicity, although this rate may increase to as high as 10 percent in those receiving more than 550 units.

The pulmonary toxicities of bleomycin have been studied extensively in animal models. Endothelial and epithelial injuries are noted in the most common form of bleomycin-induced injury. Type I pneumocyte destruction is followed by type II pneumocyte hyperplasia and dysplasia leading to activation of fibroblasts, collagen deposition, and fibrosis (Fig. 64-1). A variety of mediators have been implicated in murine models of bleomycin-induced lung injury. In vitro

Table 64-2

Cytotoxic Antibiotics

Drug	Pulmonary Syndrome	Treatment	Comments
Bleomycin	Chronic pneumonitis/ pulmonary fibrosis	Corticosteroids Discontinue drug	Most common syndrome of bleomycin toxicity "Radiation recall" effect Risk factors: Cumulative dose >400 u Oxygen therapy Therapeutic radiation Renal insufficiency Older age ? Concurrent use of other cytotoxic drugs
	Hypersensitivity-type lung disease	Corticosteroids Discontinue drug	Dyspnea, cough, skin rash, eosinophilia May not recur with rechallenge
	Chest pain syndrome	Discontinue drug	Associated with intravenous infusion of drug
Mitomycin-C	Chronic pneumonitis/ pulmonary fibrosis	Corticosteroids Discontinue drug	Most common syndrome of mitomycin-induced lung toxicity Risk factors: Oxygen therapy Therapeutic radiation Concurrent use of other cytotoxic drugs
	Acute dyspnea/ bronchospasm Noncardiogenic pulmonary edema	Supportive care Discontinue drug Corticosteroid	Occurs in patients also receiving vinca alkaloids Risk factor: Concurrent use of vinca alkaloids
	Hemolytic uremic syndrome	Supportive care Discontinue drug	Microangiopathic hemolytic anemia thrombocytopenia, renal insufficiency, noncardiogenic pulmonary edema
Actinomycin-D	Exacerbation of radiation-induced injury	Discontinue drug	Radiosensitizing effect may be long-standing Risk factor: Therapeutic radiation

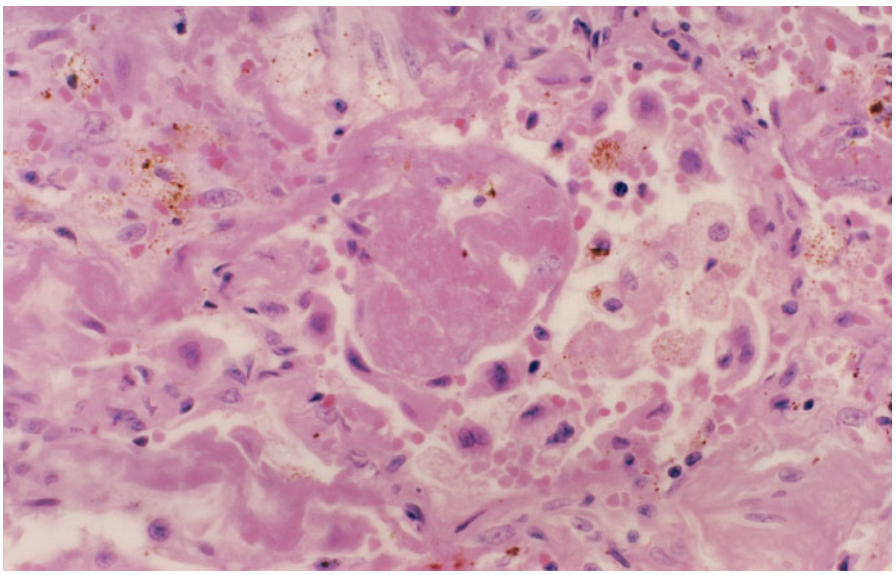


Figure 64-1 Lung biopsy specimen from a patient with clinical and radiographic evidence of bleomycin-induced pulmonary toxicity shows drug effect with acute and chronic changes. The alveolus contains an exudate of fibrin, which is undergoing organization and is surrounded by alveolar macrophages. The large and atypical cells are markedly reactive alveolar type II pneumocytes. The alveolar wall itself is scarred with collagen deposition by the spindle-shaped fibroblasts. *(Courtesy of Dr. Darryl Carter, Professor of Pathology, Yale University School of Medicine.)*

data demonstrate that pulmonary microvascular endothelial cells exposed to bleomycin demonstrate a rapid up-regulation of interleukin-8 (IL-8) and intercellular adhesion molecule-1 (ICAM-1). This early response may lead to the development of an acute neutrophilic inflammatory response. Interleukin-1 (IL-1), interleukin-6 (IL-6), and tumor necrosis factor (TNF) are all present in increased quantities in bronchoalveolar lavage fluid (BALF) from mice treated with intratracheal bleomycin. TNF and IL-6 levels in BALF are elevated within 6 hours of instillation. These increases are followed by release of macrophage-inflammatory protein-1α (MIP-1α) from alveolar macrophages. MIP-1α is a member of the C-C chemokine family and mediates the recruitment of mononuclear phagocytes. Blockade of TNF and IL-6 are associated with a decrease in the early expression of MIP-1α, which has been implicated as an important mediator of fibrosis. One theory holds that TNF, IL-6, and IL-1 are released from alveolar epithelial cells and macrophages after exposure to bleomycin. A resultant increase in MIP-1α release from alveolar macrophages then leads to an expansion of the inflammatory response by recruiting mononuclear cells. The continued expression of TNF and IL-1 may ultimately predispose to the production of transforming growth factor-β (TGF-β), with the promotion of dysregulated collagen production and fibrosis. The importance of several of these mediators to the development of bleomycin pulmonary toxicity has been demonstrated by abrogation of the fibrotic response by neutralization of specific mediators. Antibodies against TGF-β, IL-1, and MIP-1α as well as neutralization of TNF via soluble receptors have all been demonstrated to reduce the development of fibrosis in rodent models.

Several risk factors have been identified for the development of bleomycin-induced pulmonary toxicity. These include the following: (a) Toxicity appears to correlate with higher cumulative dosages. While injury has been observed after administration of as little as 20 units, there is a significant escalation in toxicity with total doses over 400 units. (b) Supplemental oxygen therapy is a synergistic toxin in patients previously treated with bleomycin. This is particularly problematic for those exposed to high oxygen concentrations in the setting of general anesthesia and in the postoperative period. The duration of this relationship is not well characterized, but exposures to bleomycin within the past 6 months are generally considered a significant risk in those treated with high inspired oxygen concentration. (c) Thoracic irradiation prior to, concomitant with, or subsequent to bleomycin administration has been associated with an increase in toxicity. This "radiation recall" may extend outside the original port of irradiation, and may last for years after bleomycin therapy. (d) Impaired renal function has been identified as a risk factor for the development of pulmonary toxicity. Bleomycin is excreted by the kidneys, and its half-life increases when creatinine clearance decreases below 35 mL per minute. (e) The risk for pulmonary toxicity rises in patients over 70 years of age. (f) Concurrent use of other cytotoxic agents may result in synergistic toxicity. Uncontrolled studies have suggested that toxicity is enhanced with coadministration of bleomycin and cyclophosphamide, doxorubicin, vincristine, or methotrexate. These synergistic effects have not been clearly reproducible, although convention has been to reduce bleomycin dosage in drug regimens in which this synergy is a concern.

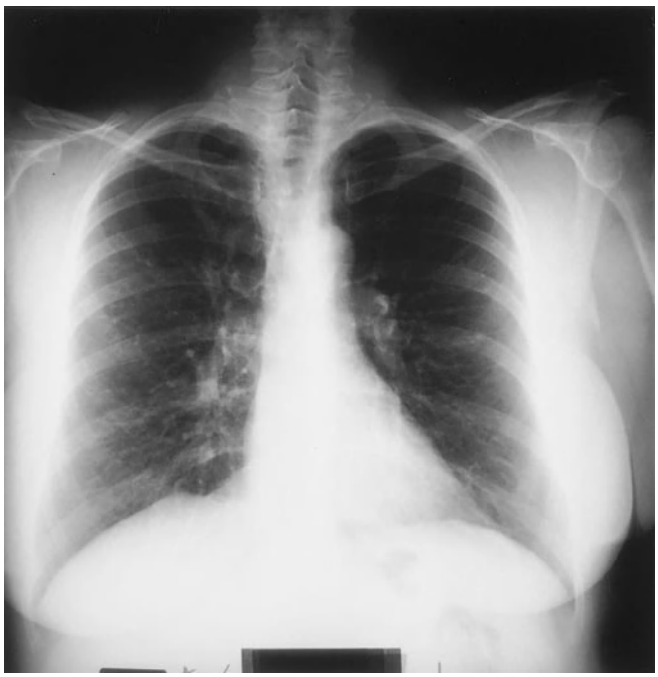
The clinical presentation of bleomycin toxicity is usually subacute and insidious, occurring within a few weeks to 6 months after treatment. A more fulminant presentation with acute respiratory failure has been reported but is less common. Patients generally present with dyspnea, nonproductive cough, and low-grade fever. Substernal or pleuritic chest pain occurs, but is infrequent. Up to 20 percent of patients may be asymptomatic. Chest radiograph usually shows bilateral reticular or fine nodular infiltrates with a basilar predominance, often beginning at the costophrenic angles (Fig. 64-2*A,B*). Loss of lung volume with diaphragmatic elevation is also commonly seen. However, various radiographic patterns including alveolar infiltrates, lobar consolidation, asymmetric lung involvement, and even lung nodules have been described. Computed tomographic (CT) scanning is more sensitive in the evaluation of radiographic abnormalities and may be useful in patients who have spirometric or clinical evidence of toxicity but negative chest x-rays (Fig. 64-3).

Bleomycin also has been described to cause an acute syndrome of dyspnea, cough, and rash immediately following administration of drug. Lung biopsy in these cases shows eosinophilic infiltration, and changes consistent with hypersensitivity pneumonitis. Of interest, rechallenge with drug does not necessarily result in recurrence of the syndrome, suggesting that this is not a true hypersensitivity reaction. Bleomycin may also present with an acute chest pain syndrome. In one series of 286 patients, the incidence of severe chest pain was 2.8 percent. Chest pain in these patients was concurrent with bleomycin infusion and resolved after termination of drug. Clinical and radiographic evidence of pleuropericarditis are often observed.

Overall mortality due to drug toxicity in patients receiving bleomycin is 1 to 2 percent. In patients who develop pulmonary toxicity, mortality rates are substantially increased. Discontinuation of drug alone in patients with mild toxicity may lead to reversal of abnormalities but treatment with corticosteroids is generally recommended for patients with clinically significant bleomycin-induced toxicity. Doses of corticosteroids are usually given in the range of 60 to 100 mg of prednisone per day, with tapering done slowly and according to the clinical stability of the patient. Improvement often occurs within weeks but complete resolution may take up to 2 years and patients may be left with residual radiographic and/or physiological abnormalities.

Mitomycin C

Mitomycin-C is an alkylating cytotoxic antibiotic generally used in multidrug regimens for solid organ malignancies including breast, gastrointestinal, and gynecological cancers. The incidence of pulmonary toxicity due to mitomycin is variably reported between 3 and 39 percent. This variation may



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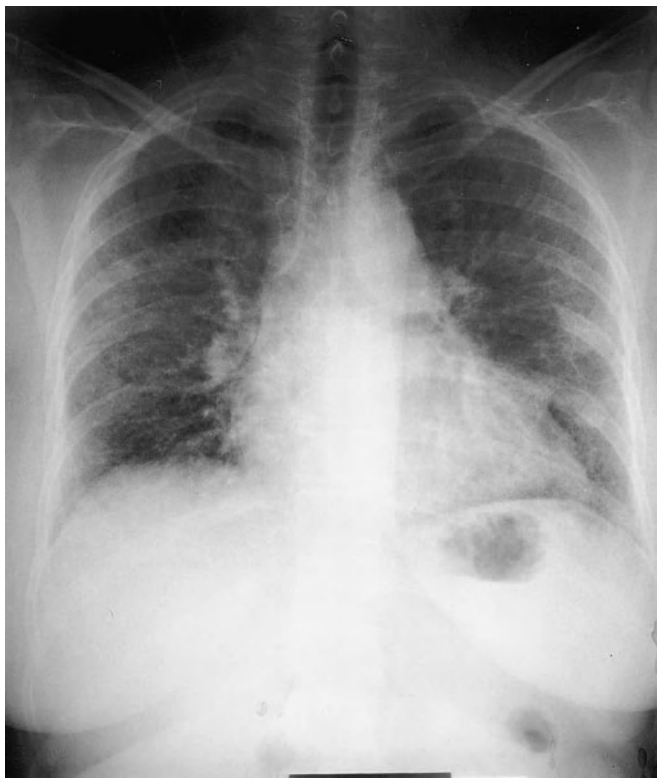


B

Figure 64-2 Posteroanterior chest radiographs of a 56-year-old woman with cervical carcinoma (*A*) before and (*B*) after chemotherapy with a bleomycin-containing regimen. Note the decrease in lung volume and diffusely increased interstitial lung markings in the postchemotherapy radiograph.

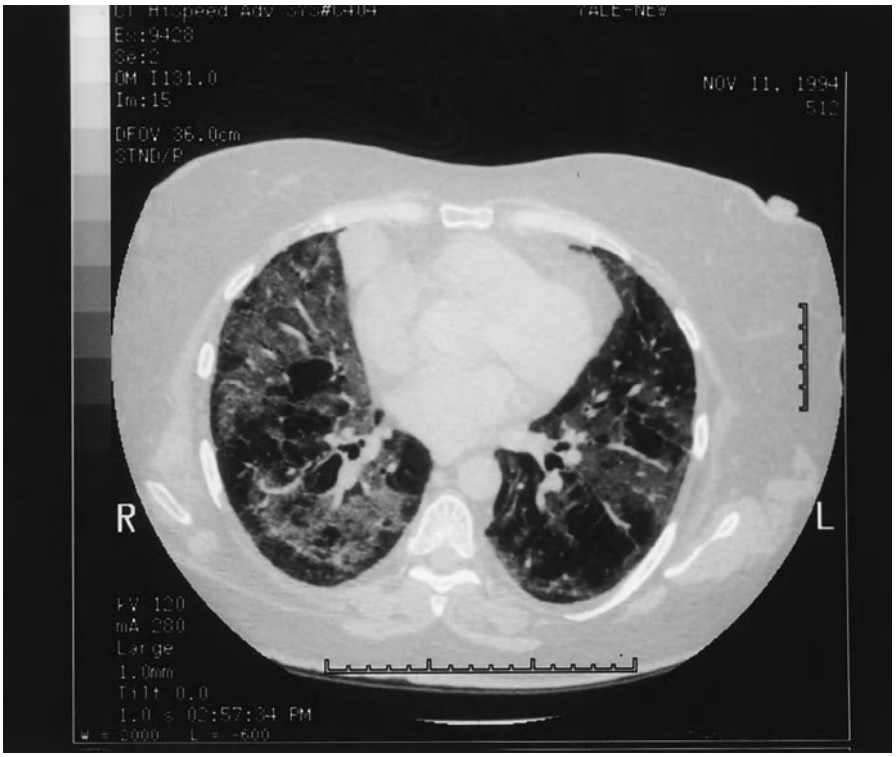


Figure 64-3 Chest computed tomography (CT) scan of same patient as in Fig. 64-2, taken at the time of radiograph in Fig. 64-2. Note the patchy distribution of bilateral infiltrates, whose extent is clearly delineated by CT.

be in part due to two factors. First, the drug is rarely given alone and toxicity seems dependent to some extent on concurrent administration of other agents or therapies. Though agreement about synergistic toxicity is not universal, pulmonary toxicity may be potentiated when mitomycin is used in conjunction with bleomycin, vinca alkaloids, cis-platinum, 5-fluorouracil, cyclophosphamide, and doxorubicin. Therapeutic thoracic irradiation and oxygen may also be co-toxins. Second, mitomycin-induced lung injury presents with at least three clinically distinct syndromes. The most common form of mitomycin-induced lung toxicity is a chronic pneumonitis with pulmonary fibrosis similar to that seen with bleomycin. The mechanism of injury is unknown though several have been proposed, including lipid peroxidant injury, hypersensitivity reactions, or immune complex mediated disease. Toxicity is felt to be potentiated by oxygen supplementation and therapeutic radiation. Toxicity does not appear to be dose related. Though it has been suggested that patients receiving doses greater than 30 mg/m^2 are at increased risk of pulmonary injury, this dose dependency has not been substantiated. Pulmonary toxicity usually occurs after 2 to 12 months of therapy but may occur after a single dose. Clinically, patients present with a subacute syndrome of cough and progressive dyspnea, often with fatigue and sometimes with pleuritic chest pain. Fever is less common. Chest radiograph usually shows bilateral interstitial infiltrates, occasionally with alveolar or fine nodular patterns. Histologically, biopsy specimens show mononuclear cell infiltration, alveolar lining cell hypertrophy, collagen deposition, and alveolar septal thickening. Type II pneumocyte enlargement and lymphocytic or eosinophilic infiltration have also been described. Patients develop a clinical picture of interstitial pneumonitis and fibrosis. This syndrome may respond to discontinuation of drug and institution of corticosteroids.

The second syndrome of mitomycin-induced pulmonary toxicity is seen in patients who have also received vinca alkaloids. While drugs of this latter category confer little in the way of risk of pulmonary toxicity when used as single agents, vinblastine, vinorelbine, and vindesine given concurrently or subsequent to administration of mitomycin have been described to precipitate a syndrome of acute pulmonary toxicity. Clinically, patients present with rapid onset of dyspnea or bronchospasm within hours after administration of vinca alkaloid. Pulmonary symptoms may be associated with hypoxia and bilateral interstitial infiltrates on chest radiograph. In a series of 126 patients, 6 percent developed this syndrome. A smaller number may go on to develop respiratory failure and noncardiogenic pulmonary edema. While the acute dyspnea syndrome usually subsides with supportive care, withdrawal of drug, and corticosteroids, long-term impairment of clinical and physiological parameters may persist. Re-challenge with vinca alkaloid will result in similar symptoms in most patients.

The third syndrome of mitomycin toxicity is an association with the hemolytic uremic syndrome. A number of cases of microangiopathic hemolytic anemia, thrombocytopenia, and renal failure following mitomycin administration have been reported. Approximately one-half of these patients develop noncardiogenic pulmonary edema. Additionally, pulmonary alveolar hemorrhage in this setting has been described. The mechanism of toxicity appears related to endothelial injury in the pulmonary vasculature. Prognosis for patients with this syndrome is poor. In a series of 39 patients, overall mortality was 72 percent. In patients who also developed pulmonary edema, mortality increased to 95 percent. A variety of therapies have been tried in attempts to reverse the toxicity including administration of corticosteroids, plasmapheresis, heparin, and cytotoxic agents without clear benefit, although the removal of circulating immune complexes via immunoadsorption correlates with temporal improvement in renal function, and should be considered in patients with this disorder.

Additionally, mitomycin has been implicated in two cases of fatal pulmonary venoocclusive disease in patients with lung cancer treated with mitomycin C prior to surgical resection.

Actinomycin D

Actinomycin D is an antitumor antibiotic used in the treatment of sarcomas, Wilson's tumor, and gestational choriocarcinoma. While this drug is most often associated with primary lung toxicity, like bleomycin and mitomycin, it may exacerbate radiation-induced injury. Of note, this radiosensitizing effect may be long-standing.

ALKYLATING AGENTS (TABLE 64-3)

The chemotherapeutic properties of the alkylating agents result from the formation of covalent linkages (alkylation) of DNA components. Nitrogen mustards are the prototypic alkylating agents and were the first drugs to be used as modern cancer chemotherapy, but many other drugs also exert antineoplastic effects by alkylation. Alkylating agents that have been associated with pulmonary toxicity include derivatives of nitrogen mustards (cyclophosphamide, melphalan, chlorambucil, ifosfamide), alkyl sulfonates (busulfan), and the nitrosoureas (carmustine/BCNU, lomustine/CCNU). The nitrosoureas are considered in a separate section below.

As single drugs, the nitrogen mustard derivatives and busulfan are associated with less pulmonary toxicity than many other classes of chemotherapeutic agents. Increased pulmonary toxicity may occur in the setting of radiation therapy, oxygen supplementation, or combination treatment with other cytotoxic agents. Toxicities related to combination treatments are often difficult to specifically attribute to individual drugs or interactions between drugs. Further, the role of underlying pulmonary disease in predisposing to toxicities from drugs is difficult to discern in this patient population.

Table 64-3

Alkylating Agents

Drug	Pulmonary Syndrome	Treatment	Comments
Cyclophosphamide	Chronic pneumonitis/ pulmonary fibrosis	Discontinue drug	Toxicity may occur several years after treatment Risk factors: Use of very high drug doses Concurrent use of other cytotoxic drugs Therapeutic radiation
Busulfan	Chronic pneumonitis/ pulmonary fibrosis	Discontinue drug	Toxicity may occur within weeks and as long as several years after treatment
Chlorambucil Melphalan Ifosfamide	Chronic pneumonitis/ pulmonary fibrosis	Discontinue drug Consider corticosteroids	Clinical pulmonary toxicity is rare

Cyclophosphamide

Cyclophosphamide is widely used in the treatment of many malignancies, including lymphomas, breast and ovarian cancers, and a variety of other solid tumors. It is commonly used as part of myeloablative conditioning regimens prior to bone marrow or peripheral blood stem cell transplantation. Cyclophosphamide is also used in the treatment of nonneoplastic inflammatory disorders including autoimmune diseases and systemic vasculitides. While the incidence of pulmonary toxicity is reportedly less than 1 percent, these broad indications for its use make it likely that cyclophosphamide-induced lung injury will be encountered by the practicing pulmonologist. Cyclophosphamide appears to have an increased incidence of toxicity when used in multidrug regimens or when used in the setting of therapeutic thoracic irradiation.

Cyclophosphamide is administered as an inactive prodrug that is metabolized by the liver to the active compound, phosphoramide mustard, and the bladder-toxic metabolite acrolein. The pharmacokinetics of both the inactive parent compound as well as its active alkylating derivative can be affected by variations in the cytochrome P450 superfamily of enzymes as well as by interactions with other drugs. Though the exact mechanism of cyclophosphamide-induced injury to the lung is unknown, cyclophosphamide has been shown in animal studies to deplete hepatic glutathione stores, which may render cells more susceptible to oxidant injury. Intratracheal or intraperitoneal administration of cyclophosphamide in animals causes lung injury manifested by type II cell abnormalities, inflammatory pneumonitis, and progressive interstitial fibrosis. While no definite dose-response relationship has been established for cyclophosphamide, higher exposure to active drug may occur in the setting of concurrent treatment with drugs that induce hepatic enzyme activity, such as rifampin, phenytoin, and alcohol. Since the drug is excreted by the kidneys, renal dysfunction may result in increased exposure.

As with a number of other chemotherapeutic agents, cyclophosphamide-induced pulmonary toxicity may present early on during the course of treatment, or in a delayed fashion even years after treatment is completed. Clinically, patients usually present insidiously with symptoms of cough and progressive dyspnea, often accompanied by fever. As noted, the timing of onset of pulmonary toxicity can be highly variable and may occur 2 weeks to as many as 13 years after initiation of treatment. When patients present in the acute treatment setting, an association with exposure to cyclophosphamide may be evident. However, in cases in which pulmonary symptoms occur long after exposure to the drug, such an association may be more difficult to identify. Chest radiograph usually shows evidence of bilateral interstitial lung disease, often accompanied by pleural thickening. This latter radiographic finding may be helpful in distinguishing cyclophosphamide-associated interstitial lung disease from the idiopathic interstitial pneumonias. Histologic findings in the lung, as with pulmonary toxicity from other cytotoxic drugs, are not specific. Lung biopsy in these patients is primarily useful for exclusion of other identifiable causes of interstitial lung disease in immunocompromised patients, including infection and malignancy.

Cyclophosphamide-induced lung injury can cause significant morbidity. When used to treat nonneoplastic lung disease, concern is often raised that the underlying pulmonary disease may be exacerbated by superimposed drug toxicity. The distinction between the two processes is often very difficult to delineate. When used as a chemotherapeutic agent, identifying cyclophosphamide as the specific etiology of lung injury may be difficult as it is rarely used alone. As with all

multi-drug or multi-modality regimens, pinpointing specific toxicity to a single agent may be impossible. Moreover, it appears that cyclophosphamide may have synergistic toxicity with therapeutic thoracic radiation as well as with other chemotherapeutic agents. For patients actively receiving cyclophosphamide, a high suspicion for pulmonary toxicity should result in discontinuation of the drug. Whether corticosteroids have a role in treating early toxicity is unclear. Prognosis in the setting of late-onset symptomatic pulmonary toxicity ascribed to cyclophosphamide is poor, as disease tends to progress to respiratory failure. Many authors recommend treatment with corticosteroids, though there is no definitive evidence of disease reversal with this intervention. As is often the case in such situations, randomized clinical trials addressing whether corticosteroids are effective would be difficult to conduct, and, thus, clinical experience typically guides the decisions about such interventions.

While cyclophosphamide administered at conventional dosage confers relatively low risk for pulmonary injury, treatment with high doses may cause significant toxicity. In one study of patients with small cell lung cancer, treatment with radiation therapy and very high doses of cyclophosphamide was complicated by a 74 percent incidence of pulmonary fibrosis. By extrapolation, new dose-intensive regimens using drugs generally felt to be "safe" from a pulmonary standpoint at conventional doses merit careful follow-up and prompt evaluation at any sign of pulmonary toxicity.

Busulfan

Busulfan has historically been used in the treatment of chronic myeloproliferative disorders. Because of the nature of these hematopoietic malignancies, patients may require therapy for months to years. Busulfan in this situation is usually well tolerated, but cumulative dosage is of concern because of the duration of treatment. While a threshold dose for toxicity has not been determined, cumulative doses above 500 mg appear to be associated with increased risk of pulmonary toxicity. In older series, up to 46 percent of patients treated with busulfan had evidence of pulmonary fibrosis, but the majority had no clinically significant disease.

Busulfan is also used in conditioning regimens prior to bone marrow and stem cell transplantation. Total body irradiation combined with cyclophosphamide has historically been the standard myeloablative therapy for patients undergoing bone marrow transplantation for hematopoietic malignancy, but an alternative regimen of busulfan with cyclophosphamide has also been widely used since the mid-1980s. Concern has been raised that busulfan-based conditioning regimens may be associated with late onset post-transplant pulmonary toxicity, including bronchiolitis obliterans (BO). In a report of over 6000 patients receiving allogeneic transplants for leukemia and followed by the International Bone Marrow Transplant Registry, multivariate analysis identified use of a busulfan-based conditioning regimen as a factor associated with an increased risk for BO. Of note, only 1.7 percent of all patients in this report had BO at 2 years after transplantation, and other factors associated with increased risk for development of BO included the presence of graft-vs.-host disease (GVHD), peripheral blood stem cell transplant (as opposed to bone marrow transplant), female donor to male recipient, and a prior episode of interstitial pneumonitis.

Symptoms of busulfan lung injury usually present insidiously, often within weeks, but sometimes years after initiation of therapy. Symptoms include cough, fever, fatigue, weight loss, and progressive dyspnea. Chest radiograph usually shows bilateral interstitial infiltrates with a basilar predominance. Pathological findings are consistent with other cytotoxic drug–induced pulmonary injury, with type II pneumocyte hyperplasia, dysplasia, and desquamation into alveolar spaces. Fibroblast proliferation, collagen deposition, and fibrosis are usually evident. Scattered cases of pulmonary ossification and pulmonary alveolar proteinosis have also been reported.

There is no specific treatment for busulfan-induced pulmonary injury, except withdrawal of the drug. When clinically evident busulfan-induced pulmonary toxicity occurs, prognosis for recovery is poor. Corticosteroids have anecdotally been reported to be of benefit but as with most chemotherapeutic agents, no prospective studies are available. Given the possibility of late-onset pulmonary toxicity, it seems prudent that long-term follow-up of recipients of bone marrow or peripheral blood stem cell transplants with busulfan-based conditioning regimens should include pulmonary evaluation. However, guidelines for identification or treatment of pulmonary toxicity in this situation are lacking.

Other Alkylating Agents

Chlorambucil and melphalan are slow acting nitrogen mustards. Chlorambucil has an important role in the treatment of lymphoreticular malignancies including chronic lymphocytic leukemia. Like cyclophosphamide, this drug has also been used in the treatment of nonneoplastic diseases, including sarcoidosis. Pulmonary toxicity is rare, occurring in less than 1 percent of patients. As with busulfan, chlorambucil as treatment for chronic hematologic disorders may be given over long spans of time. However, there does not appear to be an association of pulmonary toxicity with cumulative dosage. Since the number of cases of reported chlorambucil pulmonary toxicity are small, no distinct clinical patterns have emerged. In cases of interstitial pneumonitis thought related to chlorambucil, bronchoalveolar lavage has demonstrated a T-lymphocytic alveolitis with a CD8 predominance and the presence of eosinophils, suggesting the possibility of hypersensitivity. In cases in which interstitial pneumonitis is thought to be related to administration of chlorambucil, drugs should be discontinued. Given the possibility of drug hypersensitivity based on bronchoalveolar lavage findings, administration of corticosteroids should be considered in patients with progressive pulmonary disease.

Table 64-4

Antimetabolites

Drug	Pulmonary Syndrome	Treatment	Comments
Methotrexate	Chronic pneumonitis/ pulmonary fibrosis	Corticosteroids Discontinue drug	Most common syndrome of methotrexate-induced lung toxicity
	Hypersensitivity-type lung disease	Corticosteroids Discontinue drug	May resolve even if drug is continued, but can progress to fibrosis
	Acute chest pain syndrome	Discontinue drug	Often accompanied by pleural effusions
	Noncardiogenic pulmonary edema	Supportive care Discontinue drug	Associated with intrathecal administration
Cytosine arabinoside	Noncardiogenic pulmonary edema	Supportive care Discontinue drug	Onset of symptoms usually occurs within days of initiation of treatment Risk factor: Cumulative dose
Fludarabine	Hypersensitivity reaction	Discontinue drug	Associated with increased incidence of opportunistic infections
	Interstitial pneumonitis	Discontinue drug	Toxicity is uncommon
Gemcitabine	Dyspnea	Usually self-limited, occurring within hours of dose	Occurs in up to 8% of patients
	Bronchospasm	Bronchodilators, corticosteroids	Occurs in <1% of patients
	Noncardiogenic pulmonary edema	Discontinue drug, corticosteroids	May resolve, but respiratory failure and death reported

Melphalan has been used in the treatment of multiple myeloma as well as solid tumors including ovarian cancer, rhabdomyosarcoma, and osteogenic sarcoma. Melphalan-induced pulmonary toxicity is rare; when it occurs it has typically manifested as interstitial lung disease. However, like other alkylating agents, melphalan is being used now in novel treatments for a variety of cancers. High-dose melphalan (greater than or equal to 200 mg/m^2) used in conditioning regimens prior to stem cell transplantation has been reported to be associated with pulmonary toxicity. High-dose melphalan delivered by isolated lung perfusion is also being evaluated as a treatment for pulmonary metastatic disease. Since large series of such patients are not available, the incidence of pulmonary toxicity associated with high-dose melphalan given in these situations is not known. As these types of treatments become more widely available, new data should define whether pulmonary toxicity related to melphalan or other alkylating agents is indeed more prevalent than has been historically appreciated.

Ifosfamide is an alkylating agent that is structurally related to cyclophosphamide. It is used in the treatment of lymphoma and acute and chronic leukemias, as well as in solid tumors including sarcomas, ovarian cancer, and breast cancer. Dose limitation is usually related to bladder toxicity. Clinically evident ifosfamide-induced pulmonary toxicity appears to be rare, and typically presents as interstitial pneumonitis.

ANTIMETABOLITES (TABLE 64-4)

Methotrexate

Methotrexate is a folate antagonist used as a chemotherapeutic agent as well as in the treatment of nonneoplastic inflammatory diseases. When used in high doses for the treatment of cancers, the incidence of pulmonary toxicity is estimated at 7 percent. Toxicity does not appear to have dose dependency but may be related to frequency of administration. In one study, daily or weekly treatment carried more risk of pulmonary injury than treatment every 2 to 4 weeks. Synergistic toxicity has been reported with combination therapy using cyclophosphamide. Tapering of corticosteroid therapy or adrenalectomy may also increase the risk of methotrexate-induced toxicity.

The mechanism of methotrexate-induced lung injury is unknown. Clinically, toxicity presents with several

syndromes. The most common of these is the development of a symptom complex characterized by fever, dyspnea, cough, malaise, and myalgias, usually within weeks after initiation of therapy. Chest radiograph usually shows diffuse interstitial infiltrates. Occasionally, chest radiograph may show unilateral or bilateral effusions, a nodular appearance, or may even be normal. Additionally, hilar and mediastinal adenopathy have been observed. Skin rash is present in up to 17 percent of patients and peripheral blood eosinophilia in up to 40 percent of patients. Bronchoalveolar lavage in this setting may show a lymphocytic alveolitis, suggestive of a hypersensitivity reaction. However, illness may resolve even with continuation of the drug, and rechallenge does not necessarily result in relapse. These findings suggest that hypersensitivity may not be the true mechanism of injury. This presentation of methotrexate-induced pulmonary toxicity parallels the hypersensitivity-type syndrome that is sometimes observed with bleomycin. As some patients may go on to develop chronic pneumonitis and pulmonary fibrosis, the drug is generally withdrawn when toxicity occurs.

Pulmonary toxicity from methotrexate may also present as a more insidious subacute syndrome of interstitial lung disease. Symptoms including cough, fever, dyspnea, headache, and malaise typically occur within 4 months after the initiation of treatment. Radiographically and clinically this syndrome more closely resembles the type of chronic pneumonitis seen with other cytotoxic drugs and has been described as complicating all routes of methotrexate administration (oral, intravenous, intrathecal). In contrast to many other chemotherapeutic agents, the pneumonitis caused by methotrexate appears in general to be responsive to corticosteroids.

Pathological findings in the lung parallel those seen with lung injury due to other cytotoxic drugs, with interstitial and alveolar inflammation and fibrosis. Additionally, eosinophilic infiltration of the interstitium as well as granulomatous inflammation may be observed. These latter findings are again suggestive of a potential hypersensitivity-type mechanism of inflammation.

Methotrexate-induced lung injury may also appear as an acute syndrome with pleuritis and pleural effusion. Respiratory distress progressing to noncardiogenic pulmonary edema has been described after intrathecal administration of the drug and may be neurogenic in origin.

In patients with rheumatoid arthritis, polymyositis, and other collagen vascular diseases, the potential for a variety of pulmonary manifestations related to the underlying disease can make the diagnosis of methotrexate-induced pneumonitis challenging. The diagnostic criteria of Searles and McKendry (Table 64-5) are frequently employed in an effort to determine whether pulmonary involvement is related to methotrexate. Though they have not been validated in a prospective cohort, these criteria are commonly used to assist with this diagnosis. In a multicenter case-control study of methotrexate-induced lung toxicity in patients with rheumatoid arthritis, Alarcon and colleagues identified risk factors associated with the development of pneumonitis, including age greater than 60 years (associated with a sixfold increase in risk of pneumonitis compared with those less than 50 years of age), prior history of rheumatoid pleuropulmonary disease, diabetes, previous use of disease-modifying antirheumatic drugs, and hypoalbuminemia.

Table 64-5

Diagnostic Criteria of Searles and McKendry for Methotrexate Pneumonitis

Diagnostic criteria:
Acute onset of shortness of breath
Fever (>38.0°C)
Tachypnea (≥28 breaths per minute) with nonproductive cough
Radiographic evidence of interstitial or alveolar infiltrates
WBC ≤15,000
Negative blood or sputum cultures for pathogenic organisms (required)
Pulmonary function tests demonstrating restrictive disease with low diffusion capacity
Pa_{O_2} < 55 mmHg on room air (at presentation)
Biopsy histopathology consistent with bronchiolitis or interstitial pneumonitis with giant cells and without evidence of pathogenic microorganisms
Presence of methotrexate pneumonitis:
Definite: at least 6 of 9 criteria
Probable: 5 of 9 criteria
Possible: 4 of 9 criteria

The prognosis with methotrexate-associated lung toxicity is generally felt to be favorable. As noted, symptoms and radiographic abnormalities may resolve even with continuation of treatment. The use of corticosteroids is generally recommended though prospective trials of this intervention are not available. The overall mortality rate with methotrexate-induced pneumonitis is approximately 10 percent.

Cytosine Arabinoside

Cytosine arabinoside (Ara-C) is a pyrimidine nucleoside analog that rapidly inhibits DNA synthesis. It is important in the treatment of acute leukemias and nonHodgkin's lymphoma. Pulmonary toxicity parallels intensity of treatment. High-dose regimens have been associated with a 5 to 44 percent incidence of acute or subacute respiratory insufficiency. Symptoms include fever, cough, dyspnea, and tachypnea and may coincide with chemotherapeutic treatment or may be delayed for up to several weeks after treatment is initiated. Hypoxemia may be present. Chest radiograph generally shows a diffuse interstitial or alveolar pattern. The pathogenesis of pulmonary toxicity due to Ara-C is unknown but appears to result in a syndrome of noncardiogenic pulmonary edema. In

an autopsy series of 181 patients who died of acute leukemia, Haupt and colleagues described a group of 42 patients who had received Ara-C within 30 days of death and had moderate to severe pulmonary edema. Lung pathology showed highly proteinaceous infiltrates in both alveoli and interstitium. Twenty-eight of these 42 patients had no identifiable cause of their pulmonary edema. In these cases, Ara-C was felt to be the most likely precipitant.

Cytosine arabinoside has also been associated with cryptogenic organizing pneumonia when administered with anthracyclines or interferon-α. The pulmonary manifestations typically occur within a few weeks to 2 months after drug exposure and are characterized by fever, shortness of breath, and radiographic infiltrates that may be either lobar or nodular. All patients reported to date have achieved resolution of their pulmonary disease, either spontaneously or with the use of corticosteroids

Treatment for Ara-C lung toxicity is standard supportive care for noncardiogenic pulmonary edema. Administration of corticosteroids has been recommended by some authors but is of unclear benefit. Clinical and radiographic resolution may take 7 to 21 days. Overall mortality associated with Ara-C induced pulmonary toxicity ranges from 6 to 13 percent.

Fludarabine

Fludarabine monophosphate is a purine nucleotide analog used in the treatment of chronic lymphocytic leukemia (CLL), low-grade non-Hodgkin's lymphoma, and a variety of other lymphoproliferative disorders. Pulmonary toxicity from fludarabine, including interstitial pneumonitis and acute eosinophilic pneumonitis, has been described. Helman and colleagues reported the largest series to date, which included nine patients with fludarabine-related pulmonary toxicity out of a total of 105 patients (8.6 percent) treated with fludarabine over an 11-year period at a single institution. Toxicity did not correlate with age, prior treatment regimens, or history of prior lung disease, but occurred more frequently in patients with CLL compared with patients being treated for other lymphoproliferative disorders. The onset of symptoms ranged from 3 to 6 days after therapy, with radiographs notable for new interstitial or mixed interstitial and alveolar infiltrates. BAL fluid revealed increased cellularity without a consistently predominant cell type. Multifocal nodular pulmonary infiltrates have also been described. Biopsy specimens most commonly reveal diffuse, chronic interstitial inflammation and fibrosis, although in some cases granulomas have been observed, suggesting the possibility of a hypersensitivity reaction. In the report by Helman and colleagues, patients with fludarabine-associated pulmonary toxicity generally demonstrated subjective and objective improvement with corticosteroid therapy. Most patients responded within days, although more delayed responses were possible.

Therapy with fludarabine is associated with profound immunosuppression, which may persist for months after treatment. The risk of opportunistic infections, including *Pneumocystis jiroveci* pneumonia is increased by the use of corticosteroids in this setting. Symptomatic pulmonary disease in patients treated with fludarabine within this time frame is most likely therefore to be related to infection. However, recrudescence of noninfectious pulmonary infiltrates has been described with fludarabine retreatment; thus fludarabine should be avoided in future regimens in patients who have developed drug-related pulmonary toxicity.

Gemcitabine

Gemcitabine is a pyrimidine analog which is structurally similar to cytosine arabinoside and used in the treatment of cancers of the lung, pancreas, ovary, and uroepithelium. The drug is generally well tolerated, with myelosuppression as the major toxicity. Drug-related dyspnea has been reported to occur in 8 percent of treated patients. This dyspnea may occur within hours to days of treatment, and is generally self-limited. Bronchospasm has been rarely described. Severe pulmonary toxicity has been reported, with development of noncardiogenic pulmonary edema characterized radiographically by mixed interstitial and alveolar infiltrates. Though responses to corticosteroids have been noted, this syndrome can be fatal. Histologic evaluation most commonly reveals type II pneumocyte hyperplasia, interstitial inflammation, and hyaline membrane formation consistent with acute lung injury. Some patients with ultimately fatal outcome have demonstrated premonitory symptomatology including dyspnea, hypoxemia, and radiographic infiltrates to a milder degree with prior doses of gemcitabine. Such symptoms should raise consideration to discontinue gemcitabine.

NITROSOUREAS (TABLE 64-6)

The nitrosourea group includes carmustine or BCNU (1,3-bis-(2-chloroethyl)-1-nitrosourea), lomustine or CCNU (1-(2-chloroethyl)-3-cyclohexyl-1-nitrosourea), semustine or methyl-CCNU, and chlorozotocin. These cytotoxic drugs are active against a variety of neoplasms. BCNU and CCNU are highly lipophilic and can cross the blood-brain barrier, which makes them particularly useful in the treatment of central nervous system malignancies. BCNU is also being increasingly used in high-dose conditioning regimens prior to bone marrow or stem cell transplantation for a variety of malignancies, including breast cancer, Hodgkin's and non-Hodgkin's lymphomas, multiple myeloma, and gliomas.

Carmustine (BCNU)

Of the nitrosoureas, BCNU has been most extensively studied. Like bleomycin, this drug has been used in animal models of lung injury, but the mechanisms by which injury occurs are not well understood. Intraperitoneal injection of BCNU

Table 64-6

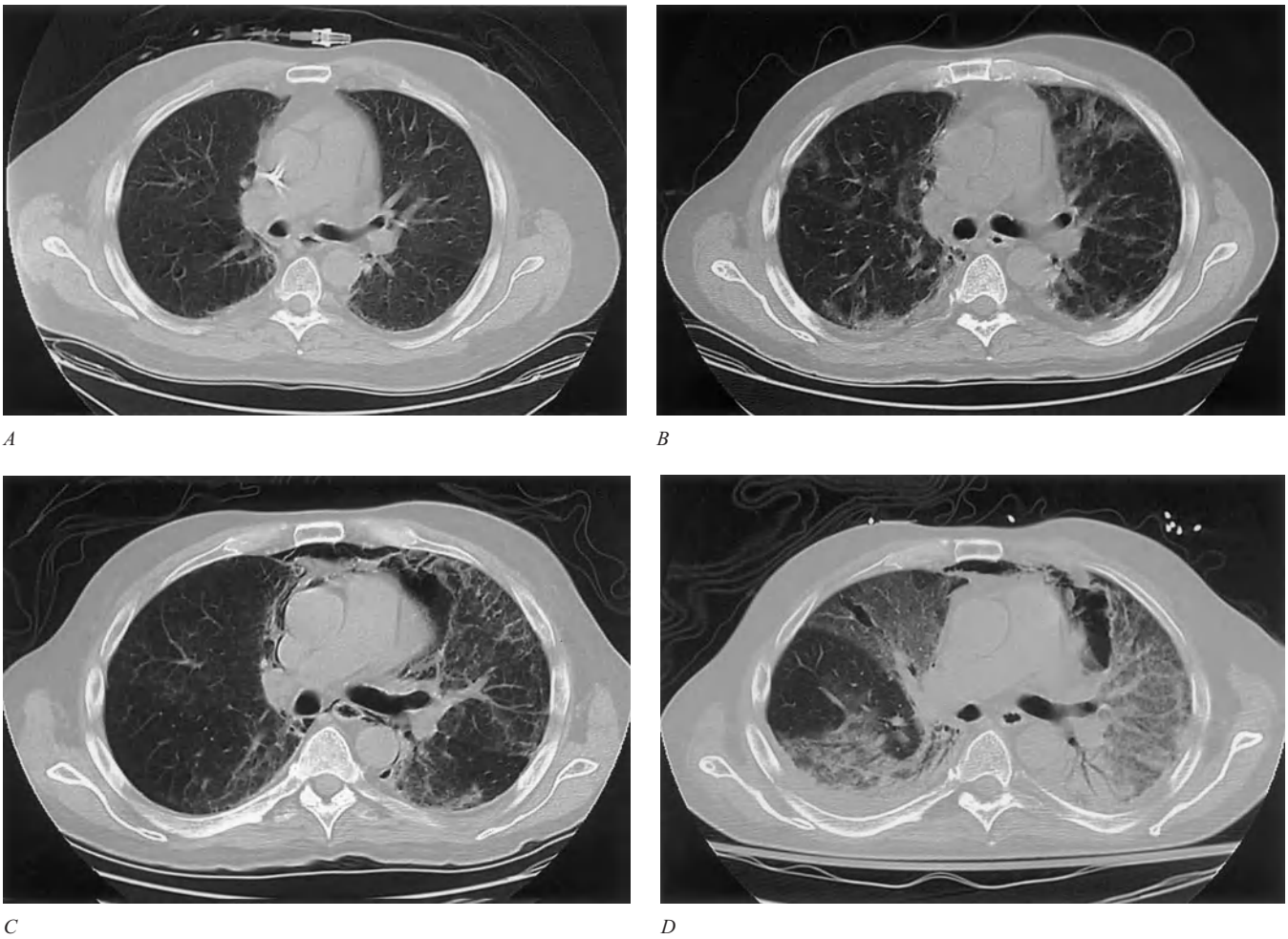
Nitrosoureas

Drug	Pulmonary Syndromes	Treatment	Comments
BCNU	Early onset pulmonary physiologic abnormalities and/or interstitial lung disease	Supportive care Discontinue drug ? Corticosteroids for early onset pulmonary physiological abnormalities	Toxicity may appear years after therapy Risk factor: Cumulative dose >1200 mg/m^2
	Late-onset pulmonary fibrosis		Possible risk factors: Female sex Concurrent use of other cytotoxic drugs Underlying pulmonary disease
CCNU Semustine Chlorozotocin	Chronic pneumonitis/ pulmonary fibrosis	Supportive care Discontinue drug	By extrapolation, toxicities and risk factors probably parallel BCNU

in rats results in granulomatous inflammation and interstitial fibrosis, which progresses even after withdrawal of drug. Oxidant lung injury may play a role in the pathogenesis of toxicity as BCNU is known to inhibit glutathione reductase in pulmonary macrophages and reduces lung glutathione stores. Like bleomycin, the toxicity of BCNU appears to be dose related. In a study of 94 patients with Hodgkin's disease who received chemotherapeutic regimens including BCNU, doses less than 475 mg/m^2 were associated with a 15 percent incidence of pulmonary toxicity; doses ranging between 475 and 525 mg/m^2 with a 32 percent incidence; and doses in excess of 525 mg/m^2 with a 47 percent incidence of pulmonary toxicity. Treatment of intracranial gliomas can result in substantially higher cumulative BCNU doses. Very high doses (greater than 1200 to 1500 mg/m^2) result in pulmonary toxicity in as many as 20 to 50 percent of patients. Risk factors contributing to the development of pulmonary toxicity with BCNU may include underlying lung disease, a history of smoking, previous or simultaneous treatment with other chemotherapy agents (including cyclophosphamide or bleomycin), chest radiotherapy, and female sex.

Pulmonary toxicity related to BCNU may occur within days to weeks after treatment, but may also present years later. Early onset pulmonary injury appears to be an underappreciated event. In a study of 152 patients treated for breast cancer with a regimen of BCNU (600 mg/m^2), cyclophosphamide, and cisplatin followed by stem cell transplantation, 59 percent developed a significant decrease in D_{LCO} at a median time after treatment of 45 days. The vast majority of these patients had subclinical disease and appeared to have improvement in their pulmonary status with initiation of corticosteroid therapy. Early-onset toxicity can also present as fulminant lung injury with progression in some cases to fatal pulmonary fibrosis. Late-onset pulmonary toxicity, typically presenting as pulmonary fibrosis, can occur years after BCNU treatment. O'Driscoll and colleagues in 1990 first reported their observations on this phenomenon in survivors of childhood brain tumors. Of 31 original patients, 14 died of their tumors. In their last report in 2004 of a 25-year follow-up of the 17 survivors, nine (53 percent) had died of complications related to pulmonary fibrosis. Two patients died within the first 3 years after chemotherapy, four died between 6 and 13 years after chemotherapy, and three died between 13 and 25 years after chemotherapy. Furthermore, of the remaining eight patients still surviving, seven had radiographic and physiological evidence of pulmonary fibrosis. Thus, in this population of children treated with high-dose BCNU, late toxicity in the lung was extremely common and of severe clinical consequence.

The clinical presentation of BCNU-induced lung toxicity is variable. As noted, it may present fulminantly as acute respiratory failure but more commonly presents insidiously with asymptomatic physiological abnormalities or radiographic evidence of pulmonary fibrosis. Symptoms of this latter subacute course include cough, fatigue, and progressive dyspnea. Chest radiograph is rarely normal in symptomatic patients, usually showing bilateral interstitial infiltrates with a basilar predominance. However, in O'Driscoll's series of patients with childhood brain tumors treated with high-dose BCNU and who developed late-onset pulmonary fibrosis, patients demonstrated an upper lobe predominance to the distribution of fibrotic changes. Patients with an acute presentation may present with confluent alveolar infiltrates. Pneumothorax has been described in a number of cases and may be bilateral (Fig. 64-4). Pulmonary physiology generally shows a restrictive ventilatory defect with diffusion abnormalities and eventually hypoxia. As with bleomycin, D_{LCO} may decrease without radiographic or clinical evidence of



A *B*

C *D*

Figure 64-4 Serial chest computed tomography scans of a 54-year-old man with a history of Hodgkin's lymphoma, treated with a BCNU-containing regimen. The dates of the examinations span 6 months from (*A*) to (*D*). Note the progression of diffuse interstitial patchy infiltrates, starting with the baseline normal study in (*A*). Pneumomediastinum and left pneumothorax are seen in (*C*) and (*D*). Bronchoscopy was performed between examinations (*B*) and (*C*), and demonstrated no evidence of infection. The patient had progressive dyspnea and respiratory insufficiency and eventually died of respiratory failure.

disease. While it has been suggested that a decrease in D_{LCO} may be the earliest sign of pulmonary toxicity, prospective evaluation of screening pulmonary function studies in the diagnosis of BCNU-induced lung toxicity has not been adequately studied. However, in light of the frequency and severity with which BCNU-associated pulmonary injury appears to occur, pulmonary function testing may be helpful in identifying patients at risk and in whom administration of corticosteroids might be considered.

Pathological changes in the lung from BCNU parallel those seen with other cytotoxic agents. Type II pneumocyte hyperplasia and dysplasia, fibroblast proliferation, and deposition of proteinaceous material in alveoli have been described. However, inflammation tends not to be a prominent histological feature, and the cardinal feature of BCNU-induced lung toxicity appears to be interstitial fibrosis. In some cases, angiocentric necrotizing granulomatous inflammation or, more rarely, pulmonary veno-occlusive disease have been described.

The prognosis for patients with BCNU-induced lung injury is poor. For patients with early-onset lung toxicity, treatment with corticosteroids may be effective. One study of patients with breast cancer for whom BCNU was administered as part of treatment with high-dose chemotherapy followed by stem cell transplantation suggested that inhaled corticosteroid might be helpful in preventing pulmonary toxicity. Late-onset pulmonary fibrosis related to BCNU does not appear to respond to corticosteroid therapy. The primary approach to BCNU toxicity should be to administer the lowest possible effective dose and monitor closely for signs of toxicity. Long-term treatment remains supportive. With the known long potential delay in the onset of signs of toxicity, long-term follow-up is also warranted.

Other Nitrosoureas

The other nitrosoureas used as chemotherapeutic agents, lomustine (CCNU), semustine (methyl CCNU), and

chlorozotocin have also been described to cause pulmonary toxicity. In general, these drugs have been used less widely than BCNU and in smaller cumulative doses. Their described lower incidence of pulmonary toxicity is likely due to these factors. As with BCNU, toxicity tends to present insidiously with interstitial pneumonitis and pulmonary fibrosis. However, given their close chemical relation, the potential for severe lung toxicity as seen with BCNU must be taken into consideration when using other drugs of this class.

BIOLOGIC RESPONSE MODIFIERS (TABLE 64-7)

All-*trans* Retinoic Acid

All-*trans* retinoic acid (ATRA) is a vitamin A derivative that has proved beneficial in the treatment of acute promyelocytic leukemia. Activity of ATRA occurs through the induction of maturation of malignant cells into mature neutrophils. The "retinoic acid syndrome" was first described in 1991 in a series of 35 patients treated with ATRA, nine of whom developed the constellation of symptoms and signs defining the syndrome. Similar incidence (44 of 167 patients) was noted during Intergroup Study 0129. The retinoic acid syndrome usually occurs from 2 to 21 days after drug initiation and is characterized by fever, edema, weight gain, interstitial or alveolar infiltrates, pleural or pericardial effusions, diffuse alveolar hemorrhage, and renal insufficiency. The syndrome is frequently, although not universally, seen coincident with the development of a pronounced leukocytosis. Radiographic features of the syndrome include pleural effusions, cardiomegaly, increased pulmonary blood volume, and widened vascular pedicle. Less frequently seen are prominent septal lines, nodules, ground-glass opacities, or parenchymal consolidation with air bronchograms. In the setting of diffuse alveolar hemorrhage, high-resolution computed tomography (CT) reveals poorly defined centrilobular nodules and diffuse ground-glass opacification.

Histological examination of lung tissue most commonly reveals infiltration of the lung parenchyma with maturing myeloid cells, with or without pulmonary hemorrhage. Fibrinoid necrosis and pulmonary capillaritis have also been described. The syndrome is thought to result from endothelial damage resulting in edema, hemorrhage, fibrinous exudates, and infiltration of neutrophils. The mechanism of ATRA-mediated pulmonary toxicity is poorly understood, but increased expression of cell adhesion molecules on leukemic cells has been demonstrated after ATRA administration,

Table 64-7

Biologic Response Modifiers

Drug	Pulmonary Syndrome	Treatment	Comments
All-*trans* retinoic acid	"Retinoic acid syndrome"	Corticosteroids Discontinue drug Supportive care	Treatment regimens using all-*trans* retinoic acid should include corticosteroids
Interleukin-2	Pleural effusions Focal or diffuse radiographic abnormalities	Supportive care Discontinue drug	Radiographic abnormalities uncommon Usually reversible Risk factors: Increasing cumulative dose Administration of LAK cells IL-2-induced cardiac toxicity may contribute to pulmonary edema
	Noncardiogenic pulmonary edema	Supportive care Discontinue drug	
Gefitinib	Diffuse alveolar damage	Supportive care Discontinue drug	Preexisting lung fibrosis a risk factor
Bevacizumab	Pulmonary hemorrhage	Supportive care Discontinue drug	More common with cavitary tumor, squamous cell histology, hemorrhage is usually from site of tumor
Rituximab	Interstitial pneumonitis/ cryptogenic organizing pneumonia	Corticosteroids Discontinue drug	Toxicity extremely rare

as have increased endothelial expression of intracellular adhesion molecule-1 (ICAM-1) and vascular cell adhesion molecule-1 (VCAM-1). In addition, elevated levels of interleukin-1β (IL-1β), interleukin-6 (IL-6), and tumor necrosis factor α (TNFα) have been observed, and may promote leukocyte activation, contributing to tissue injury.

The incidence of the retinoic acid syndrome varies between 5 and 27 percent in the published literature. Several series suggest that coadministration of idarubicin may reduce the incidence, although this is not a universal finding. The mortality rates vary from 5 to 29 percent, with prompt initiation of corticosteroids seemingly associated with improved outcome. The continuation of ATRA does not appear to be absolutely contraindicated as long as corticosteroids are administered in a timely fashion. In cases with severe manifestations, discontinuation of ATRA seems reasonable, although reintroduction of drug on resolution of the syndrome is only infrequently met with recurrence.

Interleukin-2

Interleukin-2 (IL-2) is a glycoprotein secreted by activated lymphocytes. IL-2 therapy alone or in conjunction with lymphokine activated killer (LAK) cells has proved beneficial in patients with metastatic renal cell carcinoma or melanoma. However, significant treatment-related pulmonary toxicities have been observed. In a series of 54 patients who received high dose IL-2 and LAK therapy, 80 percent of patients were noted to have focal or diffuse parenchymal lung opacities. Pleural effusions were also a common finding. The spectrum of pulmonary toxicities range from subclinical restrictive and obstructive physiological abnormalities often associated with a decline in the D_{LCO}, to more severe clinically evident cases of respiratory insufficiency. The latter generally presents as a syndrome of noncardiogenic pulmonary edema and may be associated with hypotension and renal insufficiency. Several mechanisms have been identified that may explain the increase in capillary permeability. IL-2 activated lymphocytes produce a variety of cytokines, including tumor necrosis factor and IL-1. These may alter endothelial permeability and are thought, for example, to contribute to the septic shock syndrome. IL-2 also may promote the adhesion of natural killer cells to the capillary endothelium, thus altering vascular integrity. Furthermore, IL-2 is also associated with toxicity in multiple other organs, including the heart. Therefore, IL-2–induced cardiac dysfunction may contribute to the development of pulmonary interstitial edema.

IL-2 appears to have a cumulative dose-dependent lung toxicity that seems to be compounded by LAK cell administration. Lung toxicity does appear to be reversible. In most cases, clinical and radiographic abnormalities resolve within several days after cessation of therapy. IL-2 has also been administered via inhalation to treat pulmonary metastases in patients with renal cell carcinoma and melanoma. The inhalational route of IL-2 appears to abrogate the risk of pulmonary toxicity, while demonstrating efficacy against intrapulmonary metastatic disease.

EGFR Inhibitors

Gefitinib

Gefitinib is a selective inhibitor of epidermal growth factor receptor (EGFR) tyrosine kinase, and has been used in the treatment of non–small-cell lung cancer (NSCLC). Toxicities most commonly associated with gefitinib administration include skin rash and diarrhea. Postmarketing experience with this agent was notable for reports of acute pneumonitis in patients exposed to this agent. The incidence of this side effect has been reported to be 1 percent in 50,500 patients treated worldwide, although reported incidence in single institution series is as high as 10.9 percent. In patients with preexisting pulmonary fibrosis, this complication has been noted in 33 to 56 percent of patients.

Gefitinib-induced pulmonary toxicity may occur within days of initiation of therapy, though median exposure times vary from 24 to 42 days prior to the development of toxicity. The clinical syndrome is marked by the development of rapidly progressive dyspnea and hypoxemia with diffuse ground-glass opacities noted on chest CT scan. Progression to respiratory failure and death has been noted in one-third of patients. It is unclear whether corticosteroids modulate this disease process. Histologic evaluation in patients who have succumbed to this illness has revealed diffuse alveolar damage.

The mechanism of gefitinib-induced lung injury remains a subject of investigation. EGFR is known to be upregulated in response to lung injury, and may be important in promoting type II pneumocyte hyperplasia in response to injury. In murine models, gefitinib has been demonstrated to result in more severe lung fibrosis in animals exposed to bleomycin. The increased frequency of this toxicity in patients with preexisting pulmonary fibrosis lends credence to the hypothesis that gefitinib impairs the regeneration of alveolar epithelial cells in response to injury.

Erlotinib

Interstitial lung disease has also been described with erlotinib, another agent with activity against the EGFR tyrosine kinase. However, the incidence is similar to that seen in placebo-treated patients, and thus a specific risk of interstitial pulmonary diseases associated with erlotinib has not been defined.

Bevacizumab

Bevacizumab is a monoclonal antibody directed against vascular endothelial growth factor (VEGF) that has demonstrated activity against breast, colon, renal, and NSCLCs. Increased response rates for locally advanced and metastatic NSCLC are observed when bevacizumab is added to traditional chemotherapy. In a series including 99 patients with newly diagnosed stage IIIB or IV or recurrent NSCLC, six patients developed serious bleeding complications including hemoptysis or hematemesis. Four of the six patients died as a result of the hemorrhage. All six cases of hemorrhage appeared to be tumor related, with four of the six patients having

Table 64-8

Miscellaneous Agents

Drug	Pulmonary Syndrome	Treatment	Comments
Doxorubicin	Noncardiogenic pulmonary edema	Supportive care Discontinue drug	Increases risk of radiation pneumonitis Risk factor: Therapeutic radiation
Procarbazine	Hypersensitivity-type pneumonitis Chronic pneumonitis/ pulmonary fibrosis	Discontinue drug Discontinue drug	Pulmonary toxicity uncommon
Vinca Alkaloids Vindesine Vinblastine Vinorelbine	Noncardiogenic pulmonary edema, interstitial pneumonitis, bronchospasm	Supportive care Discontinue drug Corticosteroids	Risk factor: Concurrent treatment with mitomycin-C
Taxines Paclitaxel	Dyspnea, bronchospasm	Discontinue drug Supportive care	Pretreatment with histamine antagonists and corticosteroids reduces incidence of toxicity
Docetaxel	Noncardiogenic pulmonary edema	Discontinue drug Supportive care	Toxicity is related to cumulative dose

squamous cell histology. Radiographically visible cavitation or necrosis was seen in five of the six cases of hemorrhage. Current clinical investigations of regimens including bevacizumab generally exclude patients with cavitary pulmonary disease or squamous cell histology.

Rituximab

Rituximab is a monoclonal antibody directed against the CD-20 antigen on B lymphocytes, and has demonstrated activity against B-cell nonHodgkin's lymphoma as well as refractory immune thrombocytopenic purpura. Cases of acute interstitial pneumonitis have been reported with rituximab use alone or in combination with cytotoxic chemotherapy. The incidence of rituximab-induced interstitial lung disease is estimated to be extremely low, on the order of 0.03 percent.

The clinical syndrome typically begins insidiously with cough and dyspnea, which may progress with subsequent exposure to rituximab. The development of hypoxemia in association with parenchymal ground-glass opacification on CT scan has been noted. Histological examinations have revealed reactions typical of cryptogenic organizing pneumonia/bronchiolitis obliterans-organizing pneumonia as well as interstitial inflammation with T lymphocytes and extensive arterial thrombosis. While fatal outcome has been reported, generally this entity has responded well to withdrawal of rituximab and administration of corticosteroids.

MISCELLANEOUS AGENTS (TABLE 64-8)

Procarbazine

Procarbazine is a cytotoxic drug used primarily in the treatment of lymphoma. Though uncommon, procarbazine has been associated with hypersensitivity pneumonitis. This syndrome typically is seen after the second or third cycle of chemotherapy, although toxicity can occur after the first cycle or after later cycles. Cough, dyspnea, and fever are the most common symptoms with the development of interstitial and/or alveolar infiltrates. Patients have a variable response to corticosteroids in published cases, and rechallenge with procarbazine is associated with recurrence of the syndrome in the majority of patients.

Taxines

Paclitaxel is a member of the taxane family, which functions through inhibition of microtubule disassembly and disruption of the G2 and M phases of the cell cycle. Paclitaxel has activity against a variety of carcinomas, including breast, ovarian, and NSCLC. There is a high incidence (up to 30 percent) of acute hypersensitivity reactions associated with paclitaxel administration, with symptoms including dyspnea, bronchospasm, urticaria, and hypotension. The administration of corticosteroids and histamine antagonists with paclitaxel greatly reduces the frequency of this reaction to 1 to

2 percent. Paclitaxel has also been associated with the development of corticosteroid responsive hypersensitivity pneumonitis occurring several days to weeks after paclitaxel administration, and should be suspected in those who develop interstitial infiltrates following paclitaxel therapy.

Docetaxel has a much lower incidence of acute hypersensitivity reactions when compared to paclitaxel. Docetaxel is associated with a syndrome of fluid retention related to capillary leak. This syndrome is associated with the development of peripheral edema, pleural effusions, or ascites, and is lessened in frequency by pretreatment with corticosteroids. Interstitial pneumonitis has been associated with docetaxel administration, and may progress to respiratory failure and death. This syndrome occurs 1 to 2 weeks after administration of the drug. Biopsies have been reported to reveal histologic changes consistent with drug-induced hypersensitivity pneumonitis or diffuse alveolar damage. As opposed to many cases of drug-induced hypersensitivity, this reaction may have a protracted course prior to recovery.

Vinca Alkaloids

The vinca alkaloids given as sole agents are rarely associated with pulmonary toxicity. However, the combination of vinblastine, vindesine, or vinorelbine with mitomycin C has been reported to be associated with noncardiogenic pulmonary edema, interstitial pneumonitis, and bronchospasm, often in conjunction with more diffuse endothelial dysfunction. This synergistic toxicity is discussed in more detail in the preceding section on cytotoxic antibiotics. Vinorelbine as a sole agent has been associated with dyspnea in less than 5 percent of cases, which is usually acute in origin, occurs within hours of dosing, and generally responds to bronchodilators and corticosteroids. Respiratory distress with pulmonary edema and interstitial pneumonitis has also been described.

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Drug-Induced Lung Disease Due to Nonchemotherapeutic Agents

Hilary C. Cain

Drugs have been recognized as having the potential to cause pulmonary disease at least since the report of opiate-related pulmonary edema published by Osler in 1890. In recent decades, numerous authoritative reviews have addressed this topic. As the number of therapeutic drugs continues to increase, so do case reports of well-established and suspected drug reactions. Web-based databases are devoted to the topic and can serve as useful tools for the clinician (www.pneumotox.com).

APPROACH TO THE PATIENT WITH SUSPECTED DRUG-INDUCED LUNG DISEASE

The diagnosis of drug-induced pulmonary toxicity may be challenging to confirm. For most drugs, there are no definitive diagnostic criteria by which to establish the diagnosis. Recognition of the patient's risk of disease is the first step in diagnosis

because the clinical presentation of drug-induced lung injury may be similar to that of other disorders, including infection, hypersensitivity pneumonitis due to environmental antigens, eosinophilic lung disease, collagen vascular disease, and idiopathic interstitial pneumonitis. Drug-induced lung disease occurs not only with prescribed drugs, but also with over-the-counter preparations, herbal or alternative medicine preparations (many of which can contain a variety of substances that could be implicated as the culprit agents), and illicit drugs. Patients may be reluctant to offer accurate information about their use of these agents, and thus the history must be skillfully elicited by the clinician.

A diagnosis of drug-induced lung toxicity is also difficult to establish, because patients with this condition typically come to medical attention with nonspecific symptoms, radiological findings, and laboratory data. Even among those who have lung tissue obtained by biopsy, histopathological patterns similar to those of other disorders may be seen. The challenge of diagnosis is further compounded by the fact that the latency from the onset of drug use to development of a toxic reaction can be highly variable, such that the temporal relationship between the pulmonary findings and the culprit drug is not readily apparent. Furthermore, many drugs (e.g., amiodarone and nitrofurantoin) can cause acute, subacute, or chronic pulmonary toxicity. In many cases, drug reactions are idiopathic, rather than dose-dependent reactions, and risk factors that predispose individuals to the development of pulmonary toxicity are not well characterized.

A common challenge in the diagnostic work-up is that the underlying disease can produce pulmonary findings similar to drug-induced lung disease. For example, rheumatoid arthritis can cause pulmonary infiltrates with similar radiographic appearance and histology to toxic reactions induced by methotrexate, gold, and penicillamine used to treat the rheumatoid arthritis itself.

Finally, new drugs will continue to come on the market, some of which will inevitably cause lung disorders. Often the potential for drugs to cause toxic reactions will only be recognized once the drug has been in use for a sufficient length time to allow a low frequency event, such as drug-induced toxicity, to be recognized.

As a result of these various factors, the diagnosis of drug-induced lung disease may only be established once other etiologies of disease are excluded.

RISK FACTORS FOR DISEASE

Several observations can be made that are relevant to understanding drug-induced pulmonary toxicity. One is that the lung has an enormous surface area on which blood-borne substances (e.g., therapeutic medications, nutritional supplements, illicit drugs, or toxins), may exert their effects. Despite this, pulmonary toxicity is a rare event, which occurs in the smallest minority of individuals exposed to a given agent. In addition, while certain histological patterns of lung injury may occur more frequently than others, there is no single clinical presentation, nor pathognomonic histological pattern of injury induced by a given drug. Furthermore, for most drugs the histological pattern of injury is unrelated to the pharmacologic properties of the drug. Most nonchemotherapeutic drugs cause pulmonary toxicity idiosyncratically, rather than in a dose-dependent reaction. Exceptions include: (1) amiodarone, for which there is increased risk of toxicity with higher daily maintenance dosages and for which the associated histopathology is related to amiodarone's pharmacologic properties; and (2) heroin, methadone, aspirin propoxyphene, ethylchorvynol, and colchicines that cause pulmonary toxicity only in the setting of overdose.

Thus, for most drugs neither dose, duration of exposure, the patient's clinical demographics, nor the pharmacologic nature of the drug determines toxicity. Based on these observations, it may be inferred that there are likely host-specific risk factors that influence the development of pulmonary toxicity. The factors influencing individual susceptibility may be: (1) genetically determined; (2) due to concurrent exposures to medications or environmental factors; (3) related to the individual's co-morbid disease; or (4) a function of some or all of these.

The specifics of the host-drug interaction are not fully characterized, but may include host-specific enzyme polymorphisms affecting drug metabolism. Drug biotransformation occurs predominantly in the liver, largely through the cytochrome P450 family of enzymes, but the lung is a site of active drug metabolism as well. The lung has cytochrome P450 enzymes levels estimated at 10 to 15 percent of that of the liver. In addition, there are lung specific cytochrome P450 isoenzymes, which imply lung-specific metabolism of drugs.

Exogenous inhalational exposures may exert a harmful effect through a variety of mechanisms. The harmful effect of concurrent oxygen administration in association with the chemotherapeutic agent, bleomycin, has been well established. It has been suggested that the apparent increased risk of amiodarone toxicity in patients who have had thoracic surgery (see below) may be a result of the impact of intraoperative high oxygen tensions. However, high oxygen tension does not substantially increase the risk of toxicity for most nonchemotherapeutic agents. It is plausible that the additive effect of oxidant injury may be more relevant for some individuals than others. There are evolving data that other exogenous factors, such as cigarette smoke, may influence lung injury through induction of cytochrome P450 enzymes.

It also has been hypothesized that leukocyte transfusions increased the risk of toxic injury to the lung in the setting of amphotericin use. Acute onset of respiratory symptoms accompanied by interstitial infiltrates has been reported in a series of 14 of 22 patients (64 percent) receiving amphotericin B (non-liposomal) concurrently with daily leukocyte transfusions in the setting of profound neutropenia. In half of the cases, respiratory failure began acutely after amphotericin infusion and it contributed to the death of five affected

patients. The deleterious effect of leukocyte transfusions has not been observed for other drugs.

MECHANISMS OF PULMONARY INJURY

In general, specific mechanisms of lung injury due to nonchemotherapeutic drugs are less well defined that those associated with chemotherapeutic agents. This topic has been recently reviewed by Delaunois and earlier by Cooper and colleagues. It appears evident that drugs affect lung homeostasis, but the effect may vary from individual to individual. Proposed mechanisms of lung injury include oxidant injury, immunological and inflammatory cell-mediated injury (including immune complex–mediated injury), and interference with cellular repair processes and matrix formation.

The role of drug-induced oxidant injury is best established for nitrofurantoin, paraquat (a herbicide used as a defoliant), and bleomycin, but may have relevance for other drugs as well. Biotransformation of these drugs results in generation of reactive oxygen species, including hydrogen peroxide, the hydroxyl radical, and superoxide anion, all of which promote lipid peroxidation and consequently cellular dysfunction. Immunologically mediated injury is undoubtedly important as well. Lymphocytic or neutrophilic alveolitis and inflammatory cell interstitial infiltrates are present in many cases of drug-induced lung injury and the elaboration of chemokines and proteases by these cells may lead to cellular injury. Complement mediated injury has bee implicated for drugs causing noncardiogenic pulmonary edema or ARDS, particularly opiates and beta agonists.

Amphiphilic compounds, such as amiodarone, quinidine and some beta blockers are passively sequestered in the lung within macrophages and type II alveolar cells. The role of disruption of phospholipid metabolism as a consequence of this sequestration has been well established for amiodarone-mediated lung injury as is discussed below.

HISTOPATHOLOGICAL PATTERNS OF INJURY AND CLINICAL SYNDROMES

The entire respiratory system, including the muscles of respiration, is susceptible to the adverse effects of drugs. Drugs may induce disease in the lung parenchyma, airways, pleura, pulmonary vasculature, and lymph nodes. Of these areas, the parenchyma is most commonly affected, and the tissue injury may manifest itself as interstitial disease, alveolar disease, and/or vasculitis. Pulmonary disease may occur as the sole effect of drug toxicity or it may be one manifestation of a systemic syndrome. For example, systemic lupus erythematosus (SLE) may occur, with or without pulmonary involvement, from exposure to beta blockers, amiodarone, ACE inhibitors, hydralazine, procainamide, isoniazid, methyldopa, minocycline, and tetracycline, among others. Systemic hypersensitivity syndromes are commonly induced by drugs, particularly the aromatic anticonvulsants. In addition, drugs (e.g., phenytoin) can cause the clinical picture of a pulmonary-renal syndrome, with evidence for pulmonary and renal vasculitis and renal failure.

Interstitial Lung Disease

Of the processes affecting the lung parenchyma, interstitial involvement is among the most common. All the major histopathological forms of interstitial disease have been reported to occur as a result of drugs. It should be recognized that among the many case reports citing the presence of interstitial lung disease (ILD), many have no tissue confirmation of the precise histological pattern of ILD, and older case reports were published before the current guidelines for classification of ILDs were published. However, it seems likely that much of the previously reported drug-induced ILD would now be classified as either cellular or fibrotic NSIP. Virtually all histopathological types of ILD have been reported to occur in association with drugs, including organizing pneumonia (with and without obliterative bronchiolitis), usual interstitial pneumonitis, eosinophilic pneumonia, desquamative interstitial pneumonitis, and hypersensitivity pneumonitis. Alveolar disease occurs in the form of pulmonary edema, diffuse alveolar damage/ARDS, and diffuse alveolar hemorrhage (both bland and vasculitic). It is important to recognize that few drugs have been reported to cause a single histopathologic pattern of parenchymal injury and in the cases of many drugs, several patterns of injury can occur (Table 65-1).

Organizing Pneumonia and Bronchiolitis Obliterans

Organizing pneumonia (OP) with or without histopathological evidence of obliterative bronchiolitis is a frequently reported pulmonary reaction to medications. Many of the drugs that have been reported to cause bronchiolitis obliterans organizing pneumonia (BOOP) are commonly used medications, and therefore knowledge of their potential toxicity is advisable. Among the antimicrobials implicated are cephalosporins, minocycline, nitrofurantoin, amphotericin B, and interferons. One of the most utilized antiarrhythmic agents, amiodarone, is know to cause BOOP; as are the anticonvulsants carbamazepine and phenytoin; and the anti-inflammatory agents gold, penicillamine, and sulfasalazine. In patients treated for rheumatoid arthritis (RA) with gold or penicillamine, it is important to distinguish between drug-induced OP and infiltrates reflecting a pulmonary manifestation of the underlying RA itself. A variety of other agents reported to cause obliterative bronchiolitis are listed in Table 65-1.

The clinical presentation of drug-associated OP or BOOP is similar to that of the idiopathic disease, which is now referred to as cryptogenic organizing pneumonia (COP). Symptoms include shortness of breath, nonproductive cough, and in some cases low-grade fever and/or pleuritic chest pain.

Table 65-1

Major Histopathological Diagnoses and Syndromes Associated with Drug Toxicity

Histopathological Diagnosis	Drug	Strength of Association
Interstitial Infiltrates/Fibrosis (acute, subacute, or chronic)	Amiodarone	+++
	β-adrenergic blockers	+
	Carbamazepine	+
	Gold salts	++
	Hydralazine	+
	Interferon-α	++ (Sarcoidosis)
	Methotrexate	+++
	Nitrofurantoin	+++
	Penicillins	++
	Phenytoin	++
OP/BOOP	Amiodarone	++
	Amphotericin B	+
	β-Adrenergic blockers	+
	Carbamazepine	++
	Cephalosporins	+
	Cocaine	++
	Interferon-α	++
	Minocycline	++
	Nitrofurantoin	+
	Phenytoin	+
Eosinophilic lung disease	ACE inhibitor	+
	Anti-TB	+
	Carbamazepine	+
	Cephalosporins	
	Erythromycin	++
	Gold salt	+
	Minocycline	+++
	NSAIDS	++
	Penicillins	++
	Sulfonamides	++
	Tetracycline	++
	L-tryptophan (OTC preparation)*	+++
Pulmonary or systemic hypersensitivity	Aspirin	+
	Carbamazepine	+++
	Minocycline	++
	NSAIDs	++
	Phenytoin	+++
	Sulfonamides	++
Systemic lupus erythemtosus	ACE inhibitor	+
	Amiodarone	+
	β-Adrenergic blockers	++
	Isoniazid	+++
	Methyldopa	++
	Minocycline	++
	Procainamide	+++
	Tetracycline	++

Table 65-1

(*Continued*)

Histopathological Diagnosis	Drug	Strength of Association
Airways disease	Aspirin	++
	ACE inhibitor	+++
	Adenosine	++
	β-Adrenergic blockers	+++
	NSAIDs	++
Noncardiogenic pulmonary edema/ARDS	Amiodarone	++ (ARDS)
	Amphotericin	++
	Aspirin/NSAID overdose	++
	HCTZ	+++
	Heparins	+
	Methotrexate	+
	Prostacyclines	++
	Opiate overdose	+++
	Radiographic contrast	++
	Tocolytic agents (e.g., terbutaline, ritodrine)	+++
	Tricyclic antidepressants	+
DAH/vasculitis	Amiodarone	+ (bland)
	Cocaine	++ (bland)
	LTRAs	++ (vasculitis)
	Methotrexate	+ (bland)
	Minocycline	+ (vasculitis)
	Nitrofurantoin	++ (vasculitis)
	Penicillamine	++ (bland)
	Propylthiouracil	+++ (vasculitis)
	Sulfonamides	++ (vasculitis)
Pulmonary hypertension	Anorexigens	+++
	L-tryptophan (OTC preparation)*	+++
Alveolar hypoventilation	Aminoglycosides	+
	Corticosteroids	++
	Opiates	+++
	Sedative/hypnotics	+++

*, *withdrawn from the market*

ACE, angiotensin converting enzyme; ARDS, acute respiratory distress syndrome; BOOP, bronchiolitis obliterans organizing pneumonia; INH, isoniazid; LTRA, leukotriene receptor antagonist; OTC, over the counter; NSAID, nonsteroidal anti-inflammatory drug; PAS, para-aminosalicylic acid; TB tuberculosis.

The chest radiograph typically shows bilateral patchy infiltrates that may be migratory over serial radiographs, with interval normal chest radiographs despite continuous drug exposure. As with other interstitial lung disease, the utility of bronchoalveolar lavage (BAL) is primarily to exclude an infectious etiology of the infiltrates; there is no specific BAL cellular profile characteristic of OP or BOOP. Lung biopsy reveals characteristic histopathology, identical to that of COP. Patients with drug-induced OP or BOOP may have spontaneous resolution of disease when the offending drug is discontinued, but oral corticosteroids may be used to accelerate disease resolution if the patient is more profoundly symptomatic.

Eosinophilic Lung Disease

Drug-induced eosinophilic lung disease can mimic other eosinophilic pulmonary syndromes including: simple eosinophilic pneumonitis (Loeffler's syndrome), chronic eosinophilic pneumonia, acute eosinophilic pneumonia, pulmonary infiltrates, peripheral eosinophilia (PIE), and Churg-Strauss syndrome. Suspicion of a drug-induced condition is

warranted in all cases of eosinophilic lung disease and a search for a culprit drug is an integral part of the evaluation. While the presentation of drug-induced eosinophilic pneumonia may be identical to idiopathic conditions, several distinctions can be made between idiopathic eosinophilic processes and drug-induced conditions. In idiopathic eosinophilic pneumonia, symptoms affect the lung exclusively, while in drug-induced eosinophilic pneumonia, respiratory symptoms may be accompanied by systemic symptoms such as rash and fever. Marked peripheral blood eosinophilia (>1000 cells/ml) suggest drug-induced pneumonitis rather than acute idiopathic eosinophilic pneumonia in which the eosinophilia is more modestly elevated or normal.

Laboratory tests may support the diagnosis of drug-induced eosinophilic pneumonia. Specific testing for drug allergies, such as the lymphocyte transformation test, have been used to implicate a culprit drug; however, the clinical utility of such tests is uncertain, as negative test results may be obtained even when there is high suspicion of a drug reaction. The diagnosis of drug-induced eosinophilic pneumonia is supported by peripheral blood and/or pulmonary eosinophilia in a setting of exposure to a suspect drug and may be established when other eosinophilic lung diseases are excluded. Pulmonary eosinophilia is a common finding among patients with drug-induced lung disease. Drugs are a significant cause of BAL eosinophilia; 12 percent of patients with eosinophilia of >5 percent on BAL had drug-induced lung disease. Of 19 patients undergoing BAL for suspected drug-induced lung disease, 42 percent had elevated BAL eosinophil counts and 95 percent had elevated lymphocytes on lavage, so the presence of eosinophilia does not imply a drug-induced process.

When evaluating a patient with pulmonary eosinophilia, it is particularly important to exclude infectious causes of eosinophilia so as to avoid promoting progressive infection and/or death by use of corticosteroid treatment for presumptive drug-induced eosinophilic pneumonia. Tropical pulmonary eosinophilia caused by filarial infection should be suspected if the patient has a consistent travel history; *Schistosoma* and *Paragonimus westermani* are other potential pathogens to be excluded. *Strongyloides, Ascaris,* and *Toxocara* are indigenous to the United States and are known to cause pulmonary infiltrates and peripheral blood eosinophilia. Missing the diagnosis of a fungal infection can be particularly catastrophic. *Aspergillus* is a ubiquitous fungus that can be difficult to diagnose as a pulmonary pathogen. BAL eosinophilia may be present without definitive evidence of invasive fungal infection, which may require a tissue biopsy for diagnosis. *Coccidioides immitis* is endemic in the southwestern United States and infection can result in peripheral blood eosinophilia and pulmonary infiltrates. Serological testing for antibodies to *Coccidioides* and sputum or BAL cultures are useful studies to exclude coccidioidomycosis.

Successful management of drug-induced eosinophilic lung disease is achieved by identification and discontinuation of the inciting drug. Typically, resolution of symptoms in drug-induced eosinophilic lung disease occurs with discontinuation of the culprit drug, and frequently without the need for treatment with corticosteroids. In contrast, idiopathic chronic eosinophilic pneumonia can require months of treatment with corticosteroids and relapse may occur as steroids are tapered. Relapse of the disease as the steroids are tapered is rare in drug-induced eosinophilic lung disease and recrudescence of the infiltrates should suggest an alternate diagnosis.

Hypersensitivity Syndromes

Systemic hypersensitivity syndromes may be caused by a number of drugs, most commonly the aromatic anticonvulsants, phenytoin and carbamazepine, as well as nonsteroidal anti-inflammatory drugs (NSAIDs), minocycline, and sulfonamides, among others. Drug rash with eosinophilia and systemic symptoms (DRESS) has been reported primarily with the anticonvulsants, and is in some cases accompanied by pulmonary disorders such as BOOP, ILD, or granulomatous inflammation.

Not all cases of pulmonary hypersensitivity are accompanied by rash or other systemic symptoms. The clinical presentation of drug-related pulmonary hypersensitivity is typically acute onset of dyspnea, cough, and fever. The radiographic pattern is one of diffuse reticular or peripheral alveolar infiltrates, sometimes accompanied by pleural effusion. In most cases, drug withdrawal with or without oral corticosteroids, results in disease resolution. A minority of individuals (10 percent) show persistent radiographic abnormalities after several months, and rarely, progressive disease may occur despite drug withdrawal.

Diffuse Alveolar Hemorrhage, Vasculitis, and Pulmonary-Renal Syndromes

Drug-induced diffuse alveolar hemorrhage (DAH) is infrequently reported in the literature on drug-induced pulmonary disease. Mechanistic classification of DAH is based on histopathological findings, and includes: (1) capillaritis; (2) bland hemorrhage; and (3) bleeding due to drug-induced coagulopathies caused by anticoagulants, thrombolytic agents, and drug-induced thrombocytopenia.

Pulmonary capillaritis is induced by relatively few drugs. In the case of propylthiouracil, the DAH can be a manifestation of a systemic vasculitic syndrome characterized by leukocytoclastic vasculitis, glomerulonephritis, and pulmonary capillaritis, with antibodies to neutrophil cytoplasmic myeloperoxidase (p-ANCA). The presence of leukocytoclastic vasculitis appears to be more common in cases of drug-induced vasculitis (63 percent of 14 cases), than it is in idiopathic vasculitis (25 percent of 57 cases).

Numerous cases of pulmonary or systemic vasculitis also have been reported for sulfonamides, nitrofurantoin, and leukotriene receptor antagonists. In the latter case, there has been considerable discussion as to whether the vasculitis was a toxic effect of the leukotriene antagonists or

whether withdrawal of oral steroids leads to identification of pre-existing Churg-Strauss granulomatous vasculitis. At least some reported cases of Churg-Strauss syndrome are unrelated to steroid withdrawal and appear to represent a rare complication of leukotriene antagonists.

Bland hemorrhage, without capillaritis, can occur in the setting of drug-induced diffuse alveolar damage (DAD). DAH accompanying DAD has been reported for amiodarone, nitrofurantoin, minocycline, methotrexate, gold, cocaine, and chemotherapeutic agents, but may occur with other drugs that cause DAD as well.

Noncardiogenic Pulmonary Edema and ARDS

Noncardiogenic pulmonary edema can be precipitated by numerous drugs, including aspirin, opiates, calcium channel blockers, some diuretics (e.g., hydrochlorothiazide and acetazolamide), intravenous and inhaled pulmonary vasodilators (e.g., epoprostenol and nitric oxide), methotrexate, TNF-α, radiographic contrast media, tocolytics, and oxytocin. Although the mechanisms of pulmonary edema may vary for these drugs, frequently the resolution of symptoms is prompt within days of drug discontinuation. ARDS is an infrequent pulmonary reaction to drugs, but has been reported as an uncommon toxic reaction to amiodarone and nitrofurantoin.

Airways Disease

Cough and bronchospasm may be induced by the ingestion of a number of therapeutic drugs. Bronchospasm can be triggered by use of β-adrenergic blockers, aspirin, and nonsteroidal anti-inflammatory drugs (NSAIDs). The effects of these agents can range from mild chest tightness and dyspnea on exertion to respiratory failure in susceptible individuals. Aspirin and NSAIDs induce bronchoconstriction by diverting arachidonic acid metabolites toward the lipoxygenase metabolic pathway, thereby leading to enhanced leukotriene-mediated airway inflammation and bronchoconstriction. Airway irritation manifested as nonproductive cough is an adverse effect of angiotensin converting enzyme inhibitors as a class, and can limit use of the these agents in affected individuals. Inhalation of illicit drugs, especially "crack" cocaine, can precipitate bronchoconstriction and thermal injury of the upper and lower airways.

Pulmonary Hypertension

Pulmonary hypertension is a relatively infrequent complication of drug therapy, but because of the subtlety of the onset of disease, paucity of symptoms until significant vascular compromise has occurred, and potential for vascular collapse and death, it is critical to recognize drug-induced pulmonary hypertension. Among the drugs known to cause pulmonary hypertension are cocaine, other illicit stimulants, anorexigens, and toxic contaminants of food and additives to nutritional supplements (e.g., tryptophan).

The history of the association of appetite suppressants and pulmonary hypertension dates to the late 1970s when reports of unexplained "primary" pulmonary hypertension were first published. The "epidemic" of pulmonary hypertension was linked the use of aminorex fumarate, an amphetamine-derived appetite suppressant that came into use because its potential for addiction and abuse was lower than that of amphetamine. The mechanism of action on the pulmonary vasculature is through the release of catecholamines, including dopamine. The use of aminorex was associated with a significant rise in the incidence of pulmonary hypertension, primarily among women in Germany, Austria, and Switzerland. The development of disease occurred as early as weeks to months from the onset of use of the drug, with a dose-dependent risk as high as 2 in 100. The epidemic subsided as the drug's use declined.

This was followed by the introduction of fenfluramine, which, like amphetamine and aminorex, is a phenylethylamine. It had been shown to be equally effective for weight reduction as an amphetamine, without the potential for abuse. Satiety is normally accompanied by the release of serotonin, which acts on central serotonin 2_C receptors. Fenfluramine and the racemic dexfenfluramine effectively mimic normal satiety through competitive inhibition of the serotonin transporter, leading to release of serotonin from intracellular stores. These agents were used primarily in Europe throughout the 1980s. Case reports of users with pulmonary hypertension were published in Britain as early as 1981, but use of these agents persisted through the decade of the 1980s. Two landmark reports supported a causal relationship between the use of fenfluramine and dexfenfluramine and pulmonary hypertension. The first of these was published in 1993, describing a cohort of young to middle-aged users of the anorexigens who developed pulmonary hypertension indistinguishable from idiopathic primary arterial pulmonary hypertension. This was followed in 1996 by the findings of the International Primary Pulmonary Hypertension Study Group, which published a case-control series of 192 patients with pulmonary arterial hypertension. An eightfold increased risk of development of the disease was found among those who had used and anorexigen for >3 months, with an estimated incidence of one to two cases per million users per year. Further support for a causal link is contained in the surveillance study of pulmonary hypertension among anorexigen users in the United States. Fenfluramine was withdrawn from the market in 1995 due to its association with increased risk of pulmonary hypertension, as well as its role in the development of valvular heart disease in users of the fenfluramine-phentermine combination anorexigen, known as fen-phen.

Epidemics of pulmonary hypertension also have been reported due to contaminants in a specific manufacturer's rapeseed oil in Spain, and from use of an over-the-counter L-tryptophan preparation that resulted in the eosinophilic myalgia syndrome, characterized by a systemic syndrome, which included acute lung injury and pulmonary hypertension.

The reason(s) that some individuals develop drug-related pulmonary hypertension while others do not has not been clearly defined. One putative risk may be polymorphisms of a cytochrome P450 enzyme, CYP 2D6, which is the primary enzyme to metabolize fenfluramine. Reports have suggested that as many as 21 percent of subjects who develop anorexigen-related pulmonary hypertension may be abnormal metabolizers. Other risk factors are yet to be characterized.

DRUGS USED TO TREAT CARDIOVASCULAR DISORDERS

Amiodarone

Amiodarone is an iodinated, benzofuran-derivative antiarrhythmic used for management of life-threatening supraventricular and ventricular arrhythmias. Both amiodarone and its major metabolite, desethyl-amiodarone are cationic, amphiphilic compounds with high lipid solubility causing the drug to accumulate in, and clear slowly from, a variety of tissues. The elimination half-life of amiodarone is between 30 to 60 days. The concentration of amiodarone in lung tissue can be 100- to 500-fold higher than serum levels, and the drug has been found in lung tissue as long as 1 year after discontinuation of therapy. These pharmacokinetic characteristics of amiodarone contribute to its potential to cause toxicity and have an impact on treatment strategies for amiodarone pulmonary toxicity, as discussed in the following.

As with many other medications, the radiographic and histological findings associated with amiodarone pulmonary toxicity are not stereotypic. While the most common histological pattern observed over the decades has been that of a subacute ILD, there are also many reports of organizing pneumonia, pulmonary fibrosis, fewer reports of nodules (which can be fluorodeoxyglucose [FDG]-avid on PET imaging), ARDS, and systemic lupus erythematosus (SLE), and rare reports of PIE and diffuse alveolar hemorrhage.

Amiodarone toxicity may involve a number of etiological mechanisms. One of amiodarone's biochemical effects is to impair normal phospholipid catabolism by phospholipases. The accumulation of phospholipids in the cell may cause direct cellular injury and tissue inflammation, and some evidence supports tissue injury as a result of immunological mechanisms. The impairment of phospholipid metabolism results in the histopathological findings of lamellar inclusions and lipid-laden foamy macrophages that characterize the amiodarone effects seen on lung biopsy and bronchoalveolar lavage (BAL).

Adverse reactions to amiodarone have been reported in a variety of tissues, including the lung, liver (liver function abnormalities and increased tissue attenuation on radiographic imaging), thyroid (thyrotoxicosis), skin (discoloration), and cornea. The first reports of amiodarone pulmonary toxicity were published in 1980 and were followed subsequently by larger series of patients as amiodarone was tested in the United States in early to middle 1980s. Based on two trials published in 1987, the clinical picture of amiodarone pulmonary toxicity emerged as a syndrome of respiratory symptoms, most often cough and dyspnea of subacute or chronic onset, accompanied by pulmonary infiltrates. In one series, 11 of 171 patients (6.4 percent) treated with 400 to 1200 mg of amiodarone developed pulmonary disease and in the second series, 15 of 154 subjects (9.7 percent) developed disease. The duration of therapy before onset of symptoms was reported as 61 to 465 days in one series and 30 to 720 days in the other. Approximately one-half of the patients in each series had fever and malaise, and one-third had chest pain. Many subjects had underlying lung disease. Subsequent reports have further refined these initial observations, as discussed in the following.

Risk Factors for Toxicity

Predisposing risk factors for the identification of amiodarone pulmonary toxicity include the daily dose and pre-existing lung disease. A less firmly established risk factor may be high concentrations of inhaled oxygen. Duration of therapy or cumulative dose does not appear to confer increased risk.

The risk of pulmonary toxicity is daily dose dependent; 0.1 to 0.5 percent of patients on 200 mg per day typically develop amiodarone pulmonary toxicity, and as many as 50 percent of those using the highest dosages (e.g., 1200 mg/day) become affected. Most reports of amiodarone toxicity have been in subjects receiving >400 mg day. Although lower doses of amiodarone are considered to be safer than higher doses, toxicity has been reported at doses as low as 200 mg/day, with symptom onset ranging from 3 months to 5 years into therapy. While the tendency to use lower doses of amiodarone has resulted in a lower incidence of disease, it is felt that the severity of disease, when it occurs, has been unchanged by this dosing strategy.

Several authors have suggested that the onset of amiodarone pulmonary toxicity may be triggered by high concentrations of oxygen or that oxygen may act in synergy with amiodarone to enhance cellular injury. A high index of suspicion for amiodarone toxicity, therefore, should be maintained in the postoperative setting, especially if high concentrations of oxygen were used intraoperatively or high loading doses of amiodarone were used in the management of perioperative cardiac arrhythmias. A less substantiated risk factor may be use of intravenous iodinated contrast media; two cases of rapidly progressive fatal ARDS attributed to amiodarone toxicity have been reported following pulmonary angiograms.

Pre-existing lung disease was identified as a risk factor for pulmonary toxicity in the earlier publications, but not all subsequent studies have identified it as a risk. It is not clear that the incidence of toxicity is actually higher or if pre-existing lung disease results in earlier perception of symptoms and a focused attention to pulmonary rather than cardiac causes of dyspnea. The recent AFFIRM (Atrial Fibrillation

Follow-up of Rhythm Management) trial reported that there was a higher risk of diagnosis of amiodarone lung toxicity if the patient had pre-existing pulmonary disease; however, there was no higher risk of either pulmonary death or all-cause mortality. Based on the literature to date, it is acceptable to use amiodarone in the setting of pre-existing lung disease if vigilance is maintained for the development of symptoms suggesting amiodarone toxicity. Prospective studies have suggested that a decrement in diffusing capacity from baseline is a poor predictor of amiodarone toxicity. Therefore, there are no formal recommendations for screening pulmonary function tests, but a reasonable approach would be performance of a baseline pulmonary function test, including diffusing capacity and symptom-driven testing thereafter.

Clinical Presentation

The clinical presentation of amiodarone pulmonary toxicity is typically nonproductive cough and dyspnea, sometimes accompanied by pleuritic chest pain, fever, malaise, and/or weight loss. The onset of symptoms is unpredictable, but most cases occur within the first 1 or 2 years of therapy. Most subjects have an insidious onset of symptoms over several months, but fatal amiodarone-induced pulmonary toxicity occurring 2 weeks into therapy has been reported. The earliest abnormality identifiable on pulmonary function testing of affected individuals is impairment in diffusing capacity for carbon monoxide (D_{LCO}). There may be an accelerated decline in the D_{LCO} as the disease progresses, accompanied by mild restrictive physiology. Since a low D_{LCO} is not specific for amiodarone toxicity, a decline should not necessarily prompt discontinuation of the drug, but should trigger evaluation for possible cause(s) of the impairment.

Radiographic Findings

Typical radiographic findings in patients with subacute or chronic onset of disease are diffuse or patchy, interstitial, or mixed alveolar-interstitial infiltrates, which are either bilateral or unilateral. Chest x-ray may underestimate the extent of disease apparent on high resolution CT (HRCT) imaging. Mild cases of toxicity may be characterized by a diffuse ground-glass pattern on HRCT, often in a peripheral, subpleural distribution. Focal and patchy areas of higher attenuation may be superimposed on the ground-glass opacification. Alveolar opacities may correspond to areas of organizing pneumonia that are indistinguishable from idiopathic BOOP. Amiodarone toxicity should be considered in cases of migratory infiltrates consistent with BOOP that are unresponsive to steroids. The infiltrates of BOOP resolve after discontinuation of amiodarone. Amiodarone-induced fibrosis occurs in 5 to 7 percent of patients diagnosed with amiodarone pneumonitis and may be present at disease presentation. A coarse interstitial pattern in the periphery of the lung, accompanied by traction bronchiectasis, is characteristic, but honeycombing is rare.

Laboratory Data

The earlier trials of amiodarone identified elevated sedimentation rates (ESR) (i.e., range of 39 to 150 mm/hour) in 9 of 11 patients with pulmonary toxicity, but nonspecificity of the ESR makes this test only marginally useful in the clinical setting. Identification of a brain naturetic peptide (BNP) value that is normal, or at a patient's baseline, may be useful in distinguishing pulmonary causes of dyspnea from congestive heart failure, but is nonspecific for amiodarone toxicity. Other common laboratory abnormalities include mild leukocytosis and serum LDH elevation. Laboratory findings that are investigational and do not yet have a place in routine clinical evaluation are elevated serum levels of KL-6, a mucinlike glycoprotein secreted by proliferating type II pneumocytes, and surfactant protein SP-D. Elevations of the latter may be an early marker of amiodarone pulmonary toxicity, but the sensitivity and specificity of these tests is uncertain.

Diagnostic Evaluation and Therapeutic Management

The challenge to the practitioner considering the diagnosis of amiodarone pulmonary toxicity is that the differential diagnosis of acute and subacute dyspnea with pulmonary infiltrates in the patient with known cardiac disease is extensive. Cardiogenic and noncardiogenic etiologies must be excluded. Consideration must be given to cardiac conditions, including ischemic and nonischemic cardiomyopathies, diastolic dysfunction, mitral valve disease, aortic stenosis, and atrial fibrillation. Noncardiogenic causes may include infections; the broad range of idiopathic interstitial pneumonitides; malignant causes of infiltrates (e.g., lymphangitic spread of tumor or lymphoma); systemic diseases such as sarcoidosis, amyloidosis, or autoimmune disease; and exposures to inhaled agents (e.g., occupational inorganic dust exposures, or organic inhalations with subsequent development of hypersensitivity pneumonitis), in addition to exposures to drugs other than amiodarone.

The risk of invasive work-up must be weighed against the risks of empiric therapy, which may include oral corticosteroids. Bronchoalveolar lavage may reveal a lymphocytosis, often with a predominance of CD8+ lymphocytes, reflective of a lymphocytic alveolitis. This finding is not consistently reported, and some affected individuals may have elevated BAL neutrophils as well. Significant BAL eosinophilia is rare. Abundant alveolar macrophages with a "foamy" cytoplasm, indicative of undigested phospholipids, is found is all subjects chronically exposed to amiodarone and is not indicative of pulmonary toxicity per se. Hemosiderin laden macrophages are infrequently found, since alveolar hemorrhage is rare. As the BAL findings are neither sensitive nor specific for pulmonary toxicity, the role of BAL in the diagnosis in controversial.

Lung biopsy findings, however, may be diagnostic of amiodarone toxicity. The earlier reports of amiodarone pulmonary toxicity describe diffuse alveolar damage (DAD) of variable severity in all affected subjects. The more severely

affected had evidence of acute DAD, with abundant hyaline membranes and reactive type II pneumonocytes lining the alveoli, while others showed organizing DAD with interstitial and intraalveolar proliferation of fibroblasts and prominent type II pneumocytes. All cases had abundant "foamy" macrophages, both singly and in clusters in the alveolar spaces. The foamy appearance of the cytoplasm is due to the presence lamellar bodies (~1 μm in diameter) containing lipid particles, reflecting the disrupted lipid metabolism caused by amiodarone. The foamy macrophages or histiocytes are not indicative of toxicity, in fact similar vacuolated histiocytes and parenchymal cells may be found in thyroid, liver, and skin of treated individuals without clinical evidence of cellular dysfunction.

The diagnosis of amiodarone pulmonary toxicity is supported by the presence of lamellar bodies in macrophages, pneumocytes, bronchiolar epithelium, and/or endothelial cells, but the diagnosis cannot be made unless there is also evidence of interstitial lymphocytic infiltrates or fibrosis and alveolar distortion. Histological findings may also fit the description of fibrotic NSIP or bronchiolitis with organizing pneumonia, and combinations of the above histological findings may occur. Despite the early reports, few patients have DAD pathologically unless they fit the clinical picture of ARDS. Alveolar hemorrhage may be present but is not a common feature of amiodarone toxicity.

In contrast to the treatment of many other types of drug-induced pulmonary toxicity, the treatment of amiodarone-induced toxicity may require more than discontinuation of the drug alone. Depending on the severity of respiratory symptoms, practitioners may often need to treat affected patients with oral corticosteroids. Specific dosages of prednisone have not been studied for efficacy, but 0.5 to 1 mg/kg is a reasonable starting point in most cases requiring steroids. Amiodarone becomes sequestered in tissues and the clearance of drug is typically prolonged. Due to these pharmacokinetic characteristics, the required duration of therapy is often as long as several months and recrudescent disease is common.

Procainamide

Procainamide, used in the treatment of supraventricular and ventricular arrhythmias, is frequently cited as a cause of drug-induced systemic lupus erythematosus (DI-SLE). Of patients using procainamide for over 2 months, as many as 50 to 90 percent will develop serum antinuclear antibodies (ANA), and of these, 10 to 20 percent may develop symptomatic DI-SLE. Symptoms associated with drug-induced disease are indistinguishable from those of idiopathic SLE, and may include fever, rash, arthralgias, Raynaud's disease, myositis, vasculitis, and serositis. Among these subjects, 40 to 80 percent will exhibit pulmonary manifestations of SLE, such as pleuritis with pleural effusion and/or diffuse parenchymal infiltrates. Of these two findings, pleural disease is more common, while parenchymal infiltrates are present in less than half of affected individuals. The more severe myositis also may affect respiratory muscle function and result in ventilatory insufficiency, perhaps contributed to by competitive blockade of the acetylcholine receptor by procainamide. The pleuritis of DI-SLE may produce pleural fluid with characteristics indistinguishable from those of spontaneous SLE: high pleural fluid ANA (≥1:160), high pleura to serum ratio of ANA (≥1), and LE cells. The absence of renal or central nervous system involvement may suggest DI-SLE, but it is otherwise difficult to differentiate drug-induced disease from other SLE on clinical grounds. Serological markers may be useful, however. The absence of anti–double-stranded DNA and normal complement levels and identification of antibodies to histone complex H2A-H2B support the diagnosis of DI-SLE.

Unlike idiopathic SLE, DI-SLE may resolve over several weeks simply with discontinuation of the drug, without use of corticosteroids or immunosuppressants. More severely affected patients may benefit from oral corticosteroids, which appear to accelerate the speed of symptom resolution. A positive ANA without signs or symptoms of local or systemic disease need not warrant discontinuation of procainamide. Relapse after symptom resolution does not occur unless the drug is reintroduced.

Angiotensin Converting Enzyme (ACE) Inhibitors

Airway irritation presenting as dry cough occurs to varying degrees in 5 to 25 percent of individuals using ACE inhibitors and is not accompanied by pulmonary parenchymal disease. Bronchial irritation is likely due to a direct effect of the drug, inducing kinin and substance P accumulation in the airway. Therefore, cough is a class effect of ACE inhibitors and typically recurs if one type is substituted for another. The cough can be severe enough to warrant discontinuation of the medication. Discontinuation of the offending drug typically results in symptom resolution in 10 days. Angiotensin II receptor antagonists may be substituted for ACE inhibitors without recurrence of symptoms. Much less common pulmonary side effects of ACE inhibitors include PIE, SLE, and subacute ILD.

β-Adrenergic Receptor Blockers

The most common adverse effect of β-adrenergic blockers on the respiratory system is precipitation of bronchospasm in asthmatics and patients with COPD and reactive airways. The high frequency of clinically significant bronchospasm in hypertensive asthmatics treated with nonselective β-adrenergic blockers, such as propranolol, requires that these agents generally be avoided in asthmatics. β1 Receptor–selective agents and the mixed α and β receptor blocker labetalol are better tolerated, but should be used with considerable caution in these subjects. The use of β-adrenergic blockers for patients with COPD is not contraindicated; many of these individuals tolerate initiation of β-adrenergic blockers without significant decrement in their lung function. Patients with COPD who have clinical or spirometric evidence of variable airflow obstruction responsive to bronchodilators should be

observed carefully for bronchospasm upon initiation of these agents, but the cardiac benefit of β blockade may be substantial in these subjects, who have a high likelihood of having concomitant coronary artery disease as a result of smoking.

Pulmonary parenchymal injury associated with the use of β-adrenergic blockers is not common, but it warrants mention because of the ubiquitous use of these agents. Subacute interstitial infiltrates, PIE, and pulmonary edema have been reported in conjunction with the use of acebutolol, propranolol, labetalol, nadolol, and/or pindolol; thus, the clinician should be vigilant for these reactions from β-adrenergic blockers as a class. Systemic lupus erythematosus (SLE) has reported with the use of acebutolol, propranolol, labetalol, and pindolol.

Hydralazine

Hydralazine-induced pulmonary disease is not common, but can be associated with systemic toxicity. The most commonly reported complication of the use of hydralazine is systemic lupus erythematosus (SLE), but subacute ILD/NSIP, organizing pneumonia, and diffuse alveolar hemorrhage also have been documented infrequently in the literature.

Hydrochlorothiazide

The most commonly reported pulmonary side effect of the diuretic hydrochlorothiazide (HCTZ) is noncardiogenic pulmonary edema or ARDS. Pulmonary edema was first reported in 1968 as a potentially life-threatening complication of HCTZ use. The onset of symptoms be acute or may occur later in the course of use. Typical symptoms are acute dyspnea and hypoxemia, but fever, tachycardia, hypotension, and shock may accompany the dyspnea. Immunologically mediated capillary leak has been suggested as a possible mechanism of action by several authors. IgG deposition in the alveolar membrane and elevated serum IgM have been reported. Management is supportive care and symptom resolution typically occurs in a few days. Rechallenge with HCTZ can cause recrudescent pulmonary edema and is not recommended. Since HCTZ is a widely used diuretic, frequently used in patients with cardiovascular disease and prone to pulmonary edema, the true incidence of noncardiogenic pulmonary edema may be underreported.

ANTICONVULSANTS

Diphenylhydantoin/Phenytoin and Carbamazepine

Numerous types of pulmonary injury can result from exposure to phenytoin. Among the reported patterns of injury are pulmonary hypersensitivity reactions, which may be a component of systemic hypersensitivity (see the discussion of DRESS), and two fatal cases of apparent polyarteritis nodosum and necrotizing vasculitis have been reported. The histological findings in subacute phenytoin lung toxicity have most often been consistent with NSIP, but lymphocytic interstitial pneumonitis and BOOP are described as well. In some cases, the parenchymal findings are accompanied by peripheral blood eosinophilia, suggesting PIE syndrome, and the presence of cold hemagglutinins has been reported. Carbamazepine, similarly to phenytoin, has been reported to cause systemic and pulmonary hypersensitivity syndromes.

ANTI-INFLAMMATORY AND IMMUNOSUPPRESSIVE AGENTS

Aspirin

The most common pulmonary reaction associated with aspirin use is bronchospasm, which may occur in aspirin-sensitive individuals at therapeutic dosing. Less common reported pulmonary complications include PIE syndrome, diffuse alveolar hemorrhage, pulmonary hypersensitivity, vasculitis, and ARDS.

Acute salicylate poisoning produces symptoms of central nervous system toxicity ranging from tinnitus, vertigo, nausea, vomiting, and hyperventilation in mild to moderate overdose, to coma, severe metabolic acidosis, and noncardiogenic pulmonary edema in more critical overdose. Risk factors for salicylate toxicity are age and chronic aspirin ingestion. Pulmonary edema occurs in as many as 30 percent of patients with severe salicylate poisoning, and may result in respiratory failure, often exacerbated by severe metabolic acidosis. Management of severe toxicity includes supportive intensive care and sodium bicarbonate infusion to promote drug excretion.

Methotrexate

Methotrexate is a dihydrofolate reductase inhibitor used as an anti-inflammatory and immunosuppressant as well as a chemotherapeutic agent. Despite the availability of newer antirheumatic drugs, methotrexate has retained its position as a first-line disease-modifying agent for the management of rheumatoid arthritis (RA). Methotrexate affects cell replication through inhibition of dihydrofolate reductase, which serves to reduce tetrahydrofolates, allowing them to serve as one-carbon carriers in the synthesis and repair of DNA. The major nonpulmonary side effects of methotrexate correlate with the degree of folate deficiency. In contrast, pulmonary toxicity does not correlate with folate deficiency and may be seen at doses as low as 7.5 mg/week, a conventional starting dose for treatment of RA. Methotrexate-induced pulmonary toxicity typically occurs within the first 2 years of treatment and can occur as early as 1 month into therapy. Conditions that have been identified as risk factors for toxicity include diabetes (odds ratio [OR] 35.6), hypoalbuminemia (OR 19.5), rheumatoid pleuropulmonary disease (OR 7.1), previous use of other disease-modifying agents (e.g., gold, sulfasalazine, or penicillamine), and older age (OR 5.1).

Methotrexate-induced reactions may be acute in onset, presenting clinically as an acute hypersensitivity pneumonitis with dyspnea, cough, and fever, or as a subacute hypersensitivity with development of symptoms over several weeks. Radiographic changes are interstitial and bilateral in 50 percent of cases, but may also include a mixed alveolar-interstitial pattern that may appear as ground-glass opacities on high-resolution CT imaging. Fibrotic changes are less common.

Diagnosis is challenging in cases of suspected methotrexate-induced pulmonary toxicity and RA, because similar clinical presentations may occur as a manifestation of RA itself. A diagnosis of methotrexate-induced lung disease is suggested by lymphocytosis on bronchoalveolar lavage (BAL) in contrast to the neutrophilic lavage, which characterizes pulmonary infiltrative disease associated with RA. The lymphocytic lavage of methotrexate-induced pneumonitis typically has CD8 predominance (low CD4:CD8 ratio). Histopathology is varied and may demonstrate ill-formed granulomas suggestive of hypersensitivity pneumonitis, changes of chronic interstitial pneumonitis, BOOP, and/or DAD. PIE syndrome has also been reported due to methotrexate.

As with other pulmonary toxicities, prompt drug withdrawal is critical and resolution follows in the majority of patients. Corticosteroids may accelerate recovery in those with severe disease and/or symptoms refractory to drug withdrawal alone. Fatalities have been reported in subjects rechallenged with methotrexate, but rechallenge has been tolerated in others, arguing against hypersensitivity as the mechanism of injury in some subjects.

D-Penicillamine

D-Penicillamine is used as an anti-inflammatory agent in the management of rheumatoid arthritis. Although it is now used less frequently than methotrexate, its pulmonary manifestations are important to recognize, as mortality is as high as 50 percent. It is one of relatively few drugs that causes a pulmonary-renal syndrome. Penicillamine is a heavy metal chelating agent that has inhibitory effects on T-lymphocytes, impairs fibroblast proliferation, and decreases rheumatoid factor and immune complex levels. DAH and subacute interstitial infiltrates are the two most frequently reported histological patterns of penicillamine-induced lung toxicity. Other patterns of pulmonary injury associated with use of penicillamine are chronic alveolitis, PIE, and hypersensitivity pneumonitis.

A pulmonary-renal syndrome similar in clinical presentation to Goodpasture's syndrome is associated with penicillamine use. It occurs infrequently among patients with RA on penicillamine therapy and also has been reported in patients prescribed penicillamine as a chelating agent in Wilson's disease, supporting the hypothesis that the pulmonary findings are not simply a manifestation of the underlying collagen vascular disease. Symptoms at disease presentation include cough, dyspnea, hemoptysis, and hematuria. The syndrome may progress to include respiratory and/or renal failure. Symptom onset has been reported after a wide range of duration of exposure from 10 months to 20 years. No definitive dose-response relationship has been defined; there are reports of toxicity at doses as low as 300 mg/day and as high as 3.5 g/day. No specific risk factors have been identified for penicillamine-induced pulmonary-renal syndrome.

Coalescing, bilateral alveolar infiltrates characterize the radiographic findings, resulting in severe hypoxia. Diagnosis is supported by high serum titers of antinuclear antibodies (ANA), but anti-glomerular basement membrane (anti-GBM) antibodies are typically absent from the serum, although rare reports of positive anti-GBM antibodies exist. Bronchoalveolar lavage reveals an increase in red blood cell count on serial lavage and the presence of hemosiderin-laden macrophages, both of which characterize DAH. Pulmonary vasculitis, however, is absent. Renal histopathology is that of crescentic glomerulonephritis similar to that of Goodpasture's syndrome, but linear anti-GBM immunofluorescence is rare.

Mortality from penicillamine-induced pulmonary-renal disease has been reported to be as high as 50 percent. Survivors in one series were all left with residual radiographic abnormalities and many patients are hemodialysis dependent despite treatment. Therefore, prompt identification and treatment are warranted. Drug withdrawal accompanied by high-dose corticosteroids is the cornerstone of therapy, and adjunctive treatment with cyclophosphamide or azathioprine is often offered, although studies definitively supporting their use do not exist. In the absence of anti-GBM antibodies, plasmapheresis is probably not warranted.

Penicillamine can also induce interstitial lung disease characterized by and hypersensitivity and/or bronchiolitis obliterans, in some cases accompanied by alveolitis. A sister drug, bucillamine, has also been reported to cause centrilobular, ground-glass opacities and thickening of interlobular septae.

Gold Salts

The immunomodulatory properties of gold have been recognized since the 1920s when the first cases of rheumatoid arthritis treated with chrysotherapy were first reported. The first reports of gold-induced pulmonary toxicity followed in 1948. Gold remains a therapeutic option for the treatment of rheumatoid arthritis that is refractory to other agents, and it also has a role in the management of juvenile RA, ankylosing spondylitis, and pemphigus. As with methotrexate and penicillamine, the toxic reaction must be distinguished from pulmonary disease related directly to the underlying rheumatoid arthritis. One of the largest reviews of 140 patients treated with gold therapy who developed pulmonary toxicity, identifies distinguishing features of this gold toxicity. The pattern that emerges from this review is that cough and dyspnea are

the most common presenting symptoms, with half of the patients exhibiting fever. More than one-third of patients had an erythematous skin rash, and peripheral blood eosinophilia is a common finding. The onset of symptoms is typically early in the course of treatment, usually within the first 4 months of therapy. Gold-induced pulmonary toxicity affects women more than men, at a ratio of 4:1, and the mean age of onset of disease is in the sixth decade of life. A restrictive ventilatory defect characterizes the disease and the diffusing capacity is reduced in over 90 percent of affected individuals.

Diagnostic evaluation may include BAL, which typically shows a lymphocytic predominant fluid with a CD8+ lymphocyte predominance. This finding, in conjunction with a positive in vitro gold lymphocyte proliferation assay, strongly supports the diagnosis of gold-induced pulmonary toxicity. These diagnostic features provide evidence that the gold-induced toxicity is a hypersensitivity reaction.

Treatment necessitates discontinuation of the drug. Longitudinal data reveal that gold-induced impairments in diffusing capacity may take months to resolve. Rarely, disease progression may occur after discontinuation of the gold. Refractory or progressive symptoms may be treated with prednisone at 30 to 60 mg/day.

Sirolimus

Sirolimus is a potent immunosuppressive agent used in the management of patients with solid organ transplant. It serves to suppress organ rejection through its inhibition of growth factor–induced smooth muscle cell proliferation and migration, and inhibits T- and B-cell activation as well.

Sirolimus was introduced into clinical use in the late 1990s. Case reports of sirolimus-induced pulmonary toxicity began to appear in the literature in 2000, when it was implicated as the cause of biopsy-proven BOOP in a renal transplant recipient. A recent case series of 24 patients further characterizes the drug reaction. In that series, most patients exhibited a radiographic pattern of patchy peripheral consolidations consistent with BOOP, while four patients had reticular and ground-glass opacities. The BAL was lymphocytic in 19 subjects with $\geq$5 percent eosinophilia in four. Neither lymphocyte subsets nor biopsies were reported in this series, but other authors have reported CD4+ predominance in one case. Several authors have described both BOOP and granulomatous interstitial pneumonitis, characterized by noncaseating granulomas in the bronchial wall with surrounding granulomatous inflammation.

Discontinuation of sirolimus is necessary for syndrome resolution, and complete recovery is typically achieved in all patients by 6 months. A dose-response relationship is suggested by this series, in which dose reduction appeared to ameliorate the pneumonitis. However, toxicity can occur despite therapeutic serum sirolimus levels and can occur as early as 2 weeks into therapy, although it more often occurs after at least 6 weeks. Sirolimus-induced pneumonitis in solid organ transplant recipients is an important consideration in the differential diagnosis of dyspnea with interstitial infiltrates.

ANTIMICROBIAL DRUGS

The most commonly reported clinical syndrome reported for all classes of antimicrobials is pulmonary infiltrates with peripheral eosinophilia (PIE). Among the reports of antibiotic-associated PIE syndrome are many cases of minocycline- and erythromycin-induced PIE, and fewer cases associated with penicillins, tetracycline, sulfonamides, and cephalosporins. Cases of PIE have also been reported with the use of antituberculous drugs, including isoniazid, rifampin, and ethambutol.

Nitrofurantoin

Nitrofurantoin is one of the most commonly implicated antimicrobial agents that cause pulmonary toxicity. Although its peak usage worldwide was probably in the 1980s, it remains a widely used antibiotic for the management of chronic urinary tract infections. Pulmonary toxicity may have significant clinical impact if the affected patient has underlying cardiopulmonary disease. Since the drug is used primary in the elderly population, in whom cardiopulmonary disease is common, recognition of its potential contribution to a patient's respiratory decline is important. In addition, the clinical spectrum of respiratory disease caused by nitrofurantoin is wide: The onset of symptoms is highly unpredictable, the severity of disease is variable, and the histopathology is diverse.

Ninety percent of cases in the earliest reports of nitrofurantoin pulmonary toxicity have been reported to be acute in onset, within days to weeks of treatment initiation. These patients presented with fever (80 percent), cough, dyspnea, rash (20 percent), arthralgias, and peripheral eosinophilia. As reports of toxicity have continued to fill the literature, it has become clear that subacute and chronic presentations are common as well. It is inevitable that many cases may be missed due to the long latency between the first dose of drug and the onset of clinical onset of symptoms. The median time to diagnosis in one series was 4 months and as long as 5 years. Among those with chronic symptoms, the most common histopathological pattern is that of chronic interstitial pneumonitis, with fewer reported cases of BOOP. In one recent publication, high-resolution CT findings in 18 patients with chronic nitrofurantoin lung injury showed bilateral ground-glass opacities seen in all subjects (diffuse in 30 percent and exhibiting a middle to upper lung zone predominance in 40 percent), irregular linear opacities in 30 percent, consolidation in 30 percent, and traction bronchiectasis in 10 percent (one subject).

Many other histopathological patterns and clinical syndromes have been reported, including pulmonary edema, ARDS, vasculitis, DAH, SLE, PIE, and nodules.

Interferon-alpha and Pegylated Interferon-α_2b

The rising prevalence of chronic hepatitis C worldwide and its treatment with interferon-alpha, and more recently with the longer-acting pegylated interferon-α_2b, has brought with it reports of pulmonary toxicity, most commonly interstitial infiltrates and BOOP. Systemic side effects are common among patients using interferon, and typically include flulike symptoms, with fatigue, headache, anorexia, and myalgias, whereas pulmonary symptoms occur infrequently. Ribavirin, a synthetic nucleoside analog is often used in conjunction with either interferon-alpha or pegylated interferon-α_2b, to enhance the antiviral activity of the interferons. Ribavirin is associated with dyspnea and cough, but has not been reported to cause pulmonary toxicity when used alone. The reported rate of significant pulmonary interstitial disease and/or BOOP is as high as 6 percent among patients receiving high-dose daily interferon for hepatitis C, and <1 percent among patients on conventional three-times-weekly dosing schedules of interferon-alpha and ribavirin. The occurrence of interstitial disease among users of interferon-alpha is not exclusive to those with hepatitis, and has been reported in patients on interferon therapy for chronic myelogenous leukemia and myelofibrosis as well. Most cases of pulmonary toxicity occur within several weeks of initiation of therapy and resolve with discontinuation of the medications.

Several case reports or small series of cases characterize the association of de novo sarcoidosis and recrudescent sarcoidosis with interferon-α and interferon-α_2a use for chronic hepatitis C. The incidence of sarcoidosis among patients receiving interferon is not well established, but has been reported to be as high as 5 percent (three cases) in a reported series of 60 patients receiving treatment with interferon-α_2a for hepatitis C. Although most of the reports of sarcoidosis have been of patients undergoing treatment for hepatitis C, it also can occur in the setting of treatment of hematological malignancy. Pulmonary manifestations of sarcoidosis occur along with other sites of disease involvement, including cutaneous, parotid, liver, ocular, and cardiac disease. The spectrum of sarcoidosis in the setting of interferon has been reviewed recently (Celik et al.).

Vigilance for pulmonary symptoms among patients treated with interferon is warranted, and prompt withdrawal of the drug in cases of documented toxicity is indicated.

OPIATES AND ILLICIT DRUGS

Complications of illicit drug use are numerous and encompass toxic injury to the lung related to use of the drug itself, and conditions associated with infectious sequelae of venous cannulation, such as endocarditis, septic embolization, and HIV-associated opportunistic infection. The prevalence of tuberculosis among drug users puts these individuals at high risk of active tuberculosis as well. Opiates or other sedatives may cause altered mental status and impairment of the gag reflex, substantially increasing the risk of aspiration pneumonia. Pulmonary parenchymal disease may also be caused by talc or other inert substances used to "cut" the drugs. Recognition of these conditions unrelated to direct toxicity of the drug will broaden the differential diagnosis of pulmonary symptoms in users of illicit drugs.

Heroin

Overdoses of heroin and other narcotics have long been known to cause pulmonary edema. One of the earliest reports of drug-induced lung disease was by Osler in 1880, in which he described pulmonary edema in an opiate addict, and ascribed the edema to the opiate use. The frequency with which heroin-induced pulmonary edema (HIPE) occurs appears to have decreased in recent decades for unknown reasons. In one series of patients compiled between 1968 and 1970, 48 percent of 149 patients with heroin overdose had pulmonary edema on presentation. The presence of pulmonary edema was associated with increased mortality (18.3 percent vs. 8.7 percent if pulmonary edema was absent). A more recent case series describes a much lower incidence of pulmonary edema: 2.1 percent of cases of heroin overdose. It is unclear whether the change in the epidemiology of HIPE relates to a change in the additives to illicit heroin or other factors. In the latter series, one-third of the patients required intubation and mechanical ventilation, but the hypoxia of HIPE resolved within 48 hours of presentation.

The literature does not conclusively indicate the mechanism of HIPE. Some studies have reported higher protein levels in pulmonary edema fluid of HIPE than in cardiogenic pulmonary edema, supporting increased capillary permeability as the mechanism, while other investigators have suggested that HIPE is the result of an anaphylactoid reaction based on high serum levels of tryptase and eosinophilic cationic protein in subjects who died of heroin overdose. Other reactions associated with heroin use include acute bronchospasm.

Pulmonary disease associated with illicit injection drug use can be unrelated to the drug itself. Talc used to cut heroin or inert substances used in pills that are crushed and injected produce foreign-body granulomatous reactions in the pulmonary vasculature and interstitium. A longitudinal study of six patients with pulmonary talcosis describes characteristic radiographic findings, consisting initially of a diffuse, micronodular pulmonary infiltrate that evolves into coalescent conglomerates, often in the upper lobes, similar in appearance to those of progressive massive fibrosis. These changes may be accompanied by emphysematous changes in the lower lobes, which may result in pneumothoraces. Other pulmonary

complications of injection drug use include septic emboli, abscess formation, bronchiectasis, and bullae independent of apical fibrotic reactions.

Cocaine

Cocaine may be injected intravenously, inhaled nasally, or smoked. It is the latter route of ingestion that is most frequently associated with respiratory symptoms and pulmonary injury. Cocaine is typically smoked as "crack" cocaine, an alkaloid derivative of cocaine hydrochloride that is mixed with ether or alcohol. Respiratory symptoms typically develop acutely within hours of use, and include cough, hemoptysis, chest pain, and shortness of breath. Bronchospasm, which may be severe enough to precipitate respiratory failure, has been reported with and without a prior history of asthma.

TREATMENT AND DISEASE RESOLUTION

Prompt recognition of drug-induced lung disease before irreversible lung injury occurs, affords patients the greatest chance of clinical and radiographic recovery. In most cases of drug-induced pulmonary injury, discontinuation of the culprit drug is sufficient for regression of clinical symptoms along with most or all of the radiographic findings. The decision to accompany this strategy with corticosteroid treatment must be individualized based on the severity of the clinical picture, and the expected rapidity of symptom resolution. For example, amiodarone pulmonary toxicity frequently requires oral corticosteroid administration, unless the symptoms are very mild, because of the long serum half-life of the drug. Moreover, recrudescent disease has been reported during steroid tapers in the case of amiodarone toxicity, presumably due to the tissue sequestration of this drug. Recrudescence is rare among other implicated drugs. Overall, corticosteroids are used with apparent success, but controlled studies to determine therapeutic efficacy are lacking, and the infrequent occurrence of most drug toxicities will never allow this treatment to be convincingly studied in clinical trials.

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PART

VII

Interstitial and Inflammatory Lung Diseases

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66
CHAPTER

Interstitial Lung Disease: A Clinical Overview and General Approach

Michael A. Nead • David G. Morris

The interstitial lung diseases are a clinically challenging and diverse group of over 150 disorders characterized by varying degrees of fibrosis and inflammation of the lung parenchyma or interstitium. The interstitium of the lung spans the region between alveolar epithelium and pulmonary vascular endothelium. This region includes a variety of cell types (fibroblasts, myofibroblasts, and macrophages) and matrix components (collagens, elastin, and proteoglycans). The interstitium extends from the alveolar space proximal to the terminal and respiratory bronchioles. However, for clinical purposes, some disorders that primarily affect the alveolar space (e.g., pulmonary alveolar proteinosis or cryptogenic organizing pneumonia) also typically fall under the heading of interstitial lung diseases. The classification, prognosis, and treatment of interstitial lung diseases continue to evolve as our understanding of them improves. With this improved understanding has come an increased complexity of the field with new and altered terminology now used to characterize each disease (Table 66-1). This chapter provides a framework by which to evaluate patients with suspected interstitial lung disease.

EPIDEMIOLOGY

The actual incidence of interstitial lung diseases remains unknown. Current estimates of the incidence and prevalence of interstitial lung disease are higher than historical estimates. The higher numbers stem from increased

Table 66-1

Current and Historical Terminology of Select Interstitial Lung Diseases

Current Clinical Terminology	Current Histopathologic Terminology	Historical Terminology
Idiopathic pulmonary fibrosis (IPF) Cryptogenic fibrosing alveolitis (CFA)	Usual interstitial pneumonia (UIP)	Hamman-Rich syndrome Chronic interstitial pulmonary fibrosis Cryptogenic fibrosing alveolitis (CFA) Lone cryptogenic fibrosing alveolitis (lone-CFA)
Acute interstitial pneumonia (AIP)	Diffuse alveolar damage (DAD)	Likely the original Hamman-Rich cases
Nonspecific interstitial pneumonia (NSIP)	NSIP pattern	
Desquamative interstitial pneumonia (DIP)	DIP pattern	
Lymphoid interstitial pneumonia (LIP)	LIP pattern	
Respiratory bronchiolitis interstitial lung disease (RB-ILD)	Respiratory bronchiolitis	
Cryptogenic organizing pneumonia (COP)	Organizing pneumonia	Bronchiolitis obliterans organizing pneumonia (BOOP) Bronchiolitis obliterans with usual interstitial pneumonia (BIP)
Langerhans' cell granulomatosis *aka* Pulmonary histiocytosis X *aka* Eosinophilic granuloma		
Obliterative bronchiolitis *aka* Constrictive bronchiolitis		
Hypersensitivity pneumonitis *aka* Extrinsic allergic alveolitis		
Hard metal pneumoconiosis		Giant-cell interstitial pneumonia

awareness, improved imaging modalities, changing disease definitions, and prior incomplete data collection. Estimates of the prevalence of one subset of interstitial lung disease, idiopathic interstitial pneumonia, from one county in New Mexico, are 81 per 100,000 for males and 67 per 100,000 for females. The prevalence of all interstitial lung disease is estimated at 1 in 3000 to 4000 in the United Kingdom.

Different interstitial lung diseases show specific age predilections. Unique forms of interstitial lung disease occur in infancy and childhood. These include follicular bronchitis, cellular interstitial pneumonia, and acute idiopathic pulmonary hemorrhage of infancy. After adolescence and before age 40, familial idiopathic pulmonary fibrosis (IPF), metabolic storage disorders, Hermansky-Pudlak syndrome, and other inherited interstitial lung diseases need to be considered. Collagen vascular disease-associated interstitial lung disease is more likely to occur in this age group, as are lymphangioleiomyomatosis and pulmonary Langerhans' cell granulomatosis. Sarcoidosis can present at any age, but tends

to be a disease of young to middle-aged people. IPF is more common after age 50, and is present in nearly 1 in 500 people over the age of 75. Gender also impacts disease prevalence for some interstitial lung diseases. Traditional occupational roles have placed men at greater risk of pneumoconiosis, which are scarring lung diseases that develop after particular environmental exposures. Women are more likely to have collagen vascular disease–associated interstitial lung disease, due to increased risk of autoimmune disease. Women are also almost exclusively affected by lymphangioleiomyomatosis and tuberous sclerosis–associated interstitial lung diseases. Particular ancestry also increases the likelihood of some interstitial lung diseases. For example, sarcoidosis occurs 10- to 12-fold more often in blacks than their white counterparts in the United States, United Kingdom, and South Africa. Hermansky-Pudlak syndrome occurs in 1 in 1800 people of Puerto Rican descent.

CLINICAL APPROACH TO PATIENTS WITH INTERSTITIAL LUNG DISEASE

Combining clinical, radiologic, and pathological information is pivotal to accurate diagnosis in interstitial lung diseases (Fig. 66-1). A working differential diagnosis requires review and adjustment as the results of diagnostic studies become available for each patient. However, the cornerstone upon which the initial differential rests is a comprehensive history. Diseases outside of the classic realm of interstitial lung disease should not be overlooked, although they do not receive extensive discussion in this overview. Infectious causes, such as community acquired and atypical pneumonias, can be confused with acute interstitial lung diseases. Chronic or remote mycobacterial infections, which are both associated with a significant postinflammatory fibrotic response, can be confused with idiopathic interstitial lung disease. Immunodeficiency necessarily broadens consideration of other infectious etiologies that can mimic the radiographic appearance of interstitial lung diseases, such as *Pneumocystis jiroveci (carinii)* pneumonia, and other noninfectious possibilities, such as lymphoproliferative disorders. Cardiac pathology, acute respiratory distress syndrome from a variety of causes, and neoplastic disorders are also possibilities. A systematic approach is important to avoid missing a progressive but eminently treatable disease that, left untreated or incompletely treated, could result in significant morbidity or even death (e.g., polymyositis, acute interstitial pneumonia, etc.). The following paragraphs include a discussion of the most common interstitial lung disease considerations for each sign and symptom. Several excellent resources are available that provide a more encyclopedic discussion.

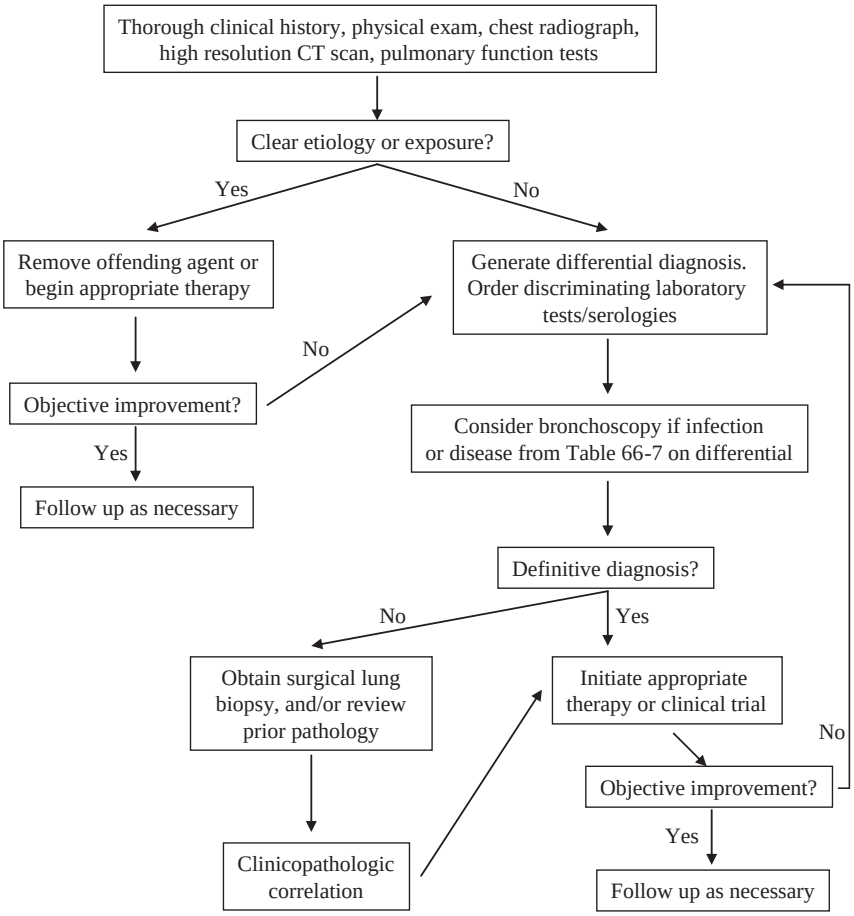

Figure 66-1 Diagnostic evaluation of a patient with interstitial lung disease.

Table 66-2

Interstitial Lung Diseases by Duration of Symptoms

Acute onset: days to weeks
Acute interstitial pneumonia
Acute pneumonitis from collagen vascular disease (especially SLE)
Cryptogenic organizing pneumonia
Drugs
Diffuse alveolar hemorrhage
Eosinophilic lung disease
Hypersensitivity pneumonitis
Subacute: weeks to months
Collagen vascular disease–associated ILD
Cryptogenic organizing pneumonia
Drugs
Subacute hypersensitivity pneumonitis
Chronic: months to years
Chronic hypersensitivity pneumonitis
Collagen vascular disease–associated ILD
Idiopathic pulmonary fibrosis
Nonspecific interstitial pneumonia
Occupation-related lung disease (e.g., silicosis, asbestosis)

Note: Abbreviations: ILD = interstitial lung disease; SLE = systemic lupus erythematosus.

Clinical History

Dyspnea

The majority of patients with interstitial lung diseases complain of difficulty in breathing. A detailed history of the onset and duration of symptoms may help frame the differential diagnosis. Depending on the nature of the underlying disease, the difficulty in breathing may be acute (hours to days), subacute (2 weeks to months), or chronic (Table 66-2). Travel to an unaccustomed altitude or an increase in activity level may unmask a chronic disease previously insidious in onset.

Cough

A substantial percentage of patients with interstitial lung diseases complain of cough, making it a very nonspecific initial finding. Unfortunately, cough in these patients can be disabling, particularly in idiopathic pulmonary fibrosis and diseases that primarily affect airways, such as bronchiolitis, cryptogenic organizing pneumonia, and sarcoidosis. Lymphangitic carcinomatosis can also cause an irritating cough that stems from submucosal lymphatic involvement. Gastroesophageal reflux is one of the most common causes of chronic cough, and gastric aspiration should be considered in a patient with cough and interstitial lung disease. Hemoptysis occurs in one-third of patients with diffuse alveolar hemorrhage, and should raise the possibility of pulmonary capillaritis due to pulmonary vasculitis or interstitial lung disease associated with collagen vascular disease. Hemoptysis is the presenting complaint in about 20 percent of patients with lymphangioleiomyomatosis.

Fever

With most interstitial lung diseases, constitutional complaints such as fevers, chills, and weight loss are absent. The presence of complaints often suggests either an underlying collagen vascular disease or a more acute disease, such as cryptogenic organizing pneumonia or acute interstitial pneumonia. Up to one-third of patients with sarcoidosis present with fever and systemic symptoms. Some types of hypersensitivity pneumonitis, such as farmer's lung, may present with fevers, chills, and shortness of breath. Patients with tropical pulmonary eosinophilia often experience fever and a nocturnal hacking cough, and patients with chronic eosinophilic pneumonia may have fevers and night sweats.

Chest Pain/Pleurisy

Some forms of pulmonary vasculitis and collagen vascular diseases affect the pleural surface and give rise to pain. Chest pain is most common in systemic lupus erythematosus, but occurs sometimes in such diseases as mixed connective tissue disease, Wegener's granulomatosis, and rheumatoid arthritis. Sarcoidosis may present with symptoms ranging from vague chest discomfort to outright pleurisy. Pneumothorax is also a possibility in a patient with suspected interstitial lung disease and chest pain.

Smoking History

Two-thirds of patients with idiopathic pulmonary fibrosis are current or former tobacco smokers at the time of diagnosis. Respiratory bronchiolitis-associated interstitial lung disease (RB-ILD), desquamating interstitial pneumonitis (DIP), and eosinophilic granuloma (EG, or Langerhans' cell granulomatosis) all occur nearly exclusively in smokers. Goodpasture's syndrome occurs most frequently in patients with a smoking history. Sarcoidosis and hypersensitivity pneumonitis occur less often in smokers. An interstitial lung disease may also aggravate the health effects beyond those that accompany tobacco use. Examples include worsened lung function in smokers with coal workers' pneumoconiosis, and the increased risk of bronchogenic carcinoma in patients with silicosis.

Exposure and Occupational History

A detailed history of past and present employment may reveal a specific etiology for a patient's interstitial lung disease. Identifying the offending agent is imperative in order to limit contact by both the patient and others who may be at risk. For most agents, the minimal exposure needed to produce interstitial lung disease remains unknown. Accordingly, an astute clinician is needed to seek out information in individuals who are only temporarily employed. Respirable materials capable of inducing interstitial lung

Table 66-3

Selected Occupational and Recreational Exposures Associated with Interstitial Lung Disease

Exposure	Associated Lung Disease
Bird breeders and fanciers	Hypersensitivity pneumonitis
Automotive mechanics Electricians Pipefitters Shipyard workers	Asbestosis
Electronic and computer industry workers	Berylliosis
Farmers	Farmer's lung (hypersensitivity pneumonitis)
Hot tub, sauna, humidifiers	Hypersensitivity pneumonitis
Metal workers (tool and die)	Metal-induced pneumoconioses
Miners Sandblasters Ceramic workers	Silicosis
Miners (specifically coal)	Coal workers' pneumoconiosis
Bark strippers Woodworkers	Hypersensitivity pneumonitis

disease are common. Selected exposures along with their associated diseases are listed in Table 66-3. Recreational activities may also cause interstitial lung disease and are included in Table 66-3. Part V provides a more thorough discussion of occupational and environmental causes of interstitial lung disease.

Medication and Drug Use History

As with occupational exposures, the list of medications associated with pulmonary reactions continues to expand. A complete history of prescription and nonprescription medications, including both current and prior medications, is part of the routine clinical assessment of these patients. Some of the more common offenders are listed in Table 66-4. Recreational drugs and contaminants (i.e., talc) should also be considered. Continuously updated, comprehensive resources that catalogue drug-induced pulmonary side effects are available.

Family History

A family history of lung disease or connective tissue diseases is important to consider during the evaluation of a patient with interstitial lung disease. Familial pulmonary fibrosis is associated with an autosomal dominant pattern of inheritance, and studies from the United Kingdom and Finland suggest that the familial form accounts for 0.5 to 3.7 percent patients with pulmonary fibrosis. Sarcoidosis also has a significant genetic association. Similarly, a family history suggestive of tuberous sclerosis (hamartomas, epilepsy, or mental retardation) may suggest lymphangioleiomyomatosis or multifocal micronodular pneumocyte hyperplasia.

Miscellaneous

Symptoms of chronic sinusitis occur in diffuse panbronchiolitis and Wegener's granulomatosis. Esophageal reflux occurs more frequently in patients with idiopathic pulmonary fibrosis, but may also be a sign of otherwise occult systemic sclerosis. Some specific clinical syndromes are virtually pathognomonic of particular diseases. One example is the syndrome of uveitis, parotiditis, and erythema nodosum that may occur as an initial presentation of typically self-limited sarcoidosis. Such syndromes, while diagnostically helpful, are relatively rare. A careful travel history may suggest a parasitic infection as the cause of an eosinophilic pneumonia. Close questioning may also uncover symptoms suggestive of a possible collagen vascular disease. Among such manifestations are Raynaud's phenomenon, proximal muscle weakness, and joint swelling/pain.

Physical Examination

Many of the interstitial lung diseases may show dermatologic or systemic signs detectable by the astute clinician. Some of these are mentioned in the following paragraphs. Any unexplained abnormalities discovered during a comprehensive review of systems and physical examination should be pursued as potential clues to the cause of the patient's interstitial lung disease. These clues are often extrapulmonary. In contrast, the lung examination, per se, is quite nonspecific in patients with interstitial lung disease. The classical "Velcro rales," or inspiratory crackles, occur not only in most patients with idiopathic pulmonary fibrosis, but also in many other interstitial lung diseases. The crackles last throughout inspiration and usually predominate at the lung bases initially. As the disease progresses, the crackles eventually may extend to the apices. In only a minority of patients with sarcoidosis or other granulomatous interstitial lung disease are rales chronically audible (5 to 20 percent). Mid inspiratory squeaks suggest airway-centered diseases, including cryptogenic organizing pneumonia, constrictive bronchiolitis, or hypersensitivity pneumonitis. Squeaks may occur with nonspecific interstitial pneumonia. Patients with constrictive bronchiolitis may have an expiratory wheeze that is refractory to inhaled bronchodilators.

Eighty percent of patients with clubbing have a respiratory disorder. Among patients with interstitial lung disease,

Table 66-4

Selected Medications Associated with Interstitial Lung Disease

Medication	Pulmonary Fibrosis	Acute Hypersensitivity Pneumonitis	Infiltrate + Eosinophilia	Organizing Pneumonia	Desquamative Interstitial Pneumonia	Lymphocytic Interstitial Pneumonia	Lung Nodules	Diffuse Alveolar Damage	Mineral Oil Pneumonia	Alveolar Hemorrhage
Acetylsalicylic acid			X							X
Amiodarone	X		X	X			X	X		X
ACE inhibitors			X							
Anticoagulants										X
Beta blockers	X	X	X	X						
Bleomycin	X			X			X			
Bromocriptine	X									
Busulfan	X				X					
Carbamazepine		X	X	X				X		X
Carmustine (BCNU)	X									
Cyclophosphamide	X			X			X			
Ergots	X			X						
Fenfluramine/dexfenfluramine		X	X							
Hydrochlorothiazide			X							
Iodine (contrast material)			X						X	X
L-tryptophan			X							
Methotrexate	X	X	X							X
Minocycline		X	X			X				
Mitomycin C	X									X
Nilutamide		X	X	X						
Nitrofurantoin	X	X	X	X	X					X

(*continued*)

Table 66-4

(*Continued*) Selected Medications Associated with Interstitial Lung Disease

Medication	Pulmonary Fibrosis	Acute Hypersensitivity Pneumonitis	Infiltrate + Eosinophilia	Organizing Pneumonia	Desquamative Interstitial Pneumonia	Lymphocytic Interstitial Pneumonia	Lung Nodules	Diffuse Alveolar Damage	Mineral Oil Pneumonia	Alveolar Hemorrhage
Nitrosoureas	X									
NSAIDs			X							
Paraffin (mineral oil)									X	
Penicillamine	X		X	X						X
Phenytoin			X	X		X				X
Practolol	X									
Propylthiouracil		X				X				X
Sulfamides-sulfonamides		X								
Sulfasalazine	X	X	X							
Vinblastine										X

Source: Adapted from: Foucher P, Camus P, Geppi T. www.pneumotox.com; Abbreviations: ACE = angiotensin converting enzyme; NSAIDs = nonsteroidal anti-inflammatory drugs.

clubbing is found in 25 to 50 percent of patients with idiopathic pulmonary fibrosis, and 50 percent of patients with desquamative interstitial pneumonia. Patients with sarcoidosis, cryptogenic organizing pneumonia, and collagen vascular disease–associated interstitial lung disease rarely have clubbing. However, clubbing occurs in up to 75 percent of patients with interstitial lung disease from rheumatoid arthritis.

An insidious onset of proximal muscle weakness before the onset of interstitial lung disease, with or without muscle tenderness, should raise the concern of polymyositis/dermatomyositis. Myositis may also occur with sarcoidosis, Sjögren's syndrome, scleroderma, and mixed connective tissue disease.

Laboratory Evaluation

Laboratory tests are insufficiently specific and sensitive to be diagnostic in the patient with interstitial lung disease. In individual patients, even serologic markers, which are helpful when markedly abnormal, require substantial clinical correlation before a final diagnosis can be rendered. However, laboratory tests can provide important supporting evidence for a suspected clinical diagnosis. The routine tests that should be ordered in all patients in whom interstitial lung disease is suspected include a complete and differential blood count, a blood chemistry panel including calcium, liver function tests, and a urinalysis. The clinical picture should dictate additional laboratory testing, such as a hypersensitivity panel, or complement levels in suspected cases of systemic lupus erythematosus, rheumatoid arthritis, hypersensitivity, or vasculitis. Table 66-5 provides data concerning the sensitivity of immunologic tests with respect to the diagnosis of rheumatic diseases. However, sensitivity may vary when patients with interstitial lung disease, per se, are considered. For example, anti-Jo1 antibodies, directed against histidyl-tRNA synthetase, are present in only 13 percent of patients with systemic polymyositis-dermatomyositis without

Table 66-5

Sensitivity of Some Immunologic Tests Associated with Rheumatic Disorders That May Cause Interstitial Lung Disease

Disease	dsDNA	ssDNA	RF	anti-RNP	anti-Sm	anti-Scl-70	anti-Jo-1	anti-Ro	anti-La	cANCA	pANCA
RA	1–5	Mod	72–85	10	1	0	0	10	5	0	
SLE	60–70	80	20	30–50	25–30	0	0	25–35	15	0–1	
Drug LE	Rare	80		5–20	1		0	<5	<5	0	
Sjögren's syndrome	5	Mod	75	15	1–5	5	0	8–70	14–60	0	
Diffuse scleroderma	0		25–33	30	<1	15–50	0	0	0	0	
PM/DM granulomatosis	0		33		<1	Low	20–50	Low	0	0	
Wegener's	0		50		0	0	0	0	0	75–95	20
Goodpasture's syndrome										Rare	10–38
MPA										10–50	80
Churg-Strauss syndrome										80	

Source: Adapted from: Laboratory Assessment. Primer on the Rheumatic Diseases, *11th ed. Atlanta, Arthritis Foundation, 1997; Hellmann D: Arthritis and musculoskeletal disorders,* in *Tierney LM, Papadakis MA (eds),* Current Medical Diagnosis and Treatment. *East Norwalk, CT, Appleton & Lange, 1997, pp. 750–799; Reichlin M. Measurement and clinical significance of antinuclear antibodies.* UpToDate, *2005; Schwarz MI, King TE (eds):* Interstitial Lung Disease, *4th ed., Hamilton, Ontario, BC Decker, 2003.*
Note: Abbreviation: Mod = moderate.

interstitial lung disease, but 50 percent of those with pulmonary manifestations. Both the erythrocyte sedimentation rate (ESR) and angiotensin converting enzyme (ACE) level are too nonspecific to warrant inclusion in a standard diagnostic panel.

Chest Radiographic Patterns: Computed Tomography and High-Resolution CT Images

With rare exception, patients with clinically significant interstitial lung disease have abnormalities detectable by radiologic imaging of the chest. Unfortunately, plain chest radiographs can be misleadingly negative in up to 10 percent of all patients with clinically significant interstitial lung disease and up to 90 percent of patients with hypersensitivity pneumonitis. Conventional computed tomography (CT) of the chest is a better but still relatively insensitive supplement. Consequently, high-resolution computed tomographic (HRCT) imaging of the chest is the current gold standard for imaging patients with interstitial lung disease. Diagnostic certainty is associated with particular patterns of abnormality on HRCT scans of the chest and can obviate the need for lung biopsy in selected diseases. Among these diseases are idiopathic pulmonary fibrosis, sarcoidosis (Fig. 66-2), and some forms of hypersensitivity pneumonitis (Fig. 66-3). Several diseases manifest classic findings that are highly suggestive of a diagnosis, including pulmonary alveolar proteinosis (Fig. 66-4), lymphangioleiomyomatosis (Fig. 66-5), and eosinophilic granuloma (pulmonary Langerhans' cell histiocytosis) (Fig. 66-6). The features of an HRCT for the radiographic diagnosis of definite usual interstitial pneumonia include a reticular pattern with associated honeycombing and/or traction bronchiectasis in a basal, predominantly subpleural distribution (Figs. 66-7 and 66-8). Nodules and consolidation should be absent. The diagnostic utility of HRCT is often substantially augmented by combining both inspiratory and expiratory imaging to increase the detection of coexisting airways disease as manifested by regional air-trapping

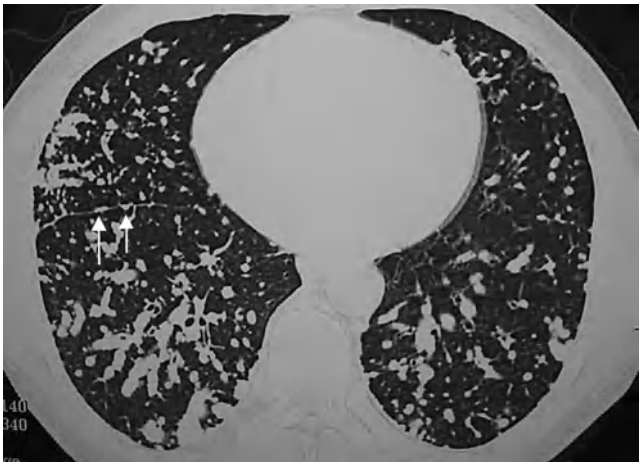

Figure 66-2 Sarcoidosis. High-resolution computed tomography of the chest of a patient with sarcoidosis, demonstrating septal beading (arrows) and nodules abutting bronchovascular bundles.

during exhalation. Nevertheless, the value of careful review of all prior chest radiographs in patients with interstitial lung disease cannot be overstated. Information from these studies offers invaluable insight into the time of onset, clinical course, and current trajectory of a given patient's pulmonary disease.

Tables 66-6 and 66-7 summarize helpful radiographic patterns that may guide formulation of the differential diagnosis and ensuing work-up. The value of a skilled thoracic radiologist on the interstitial lung disease team has been demonstrated repeatedly in the literature (see Clinicopathological Correlation in the Diagnosis of Interstitial Lung Diseases).

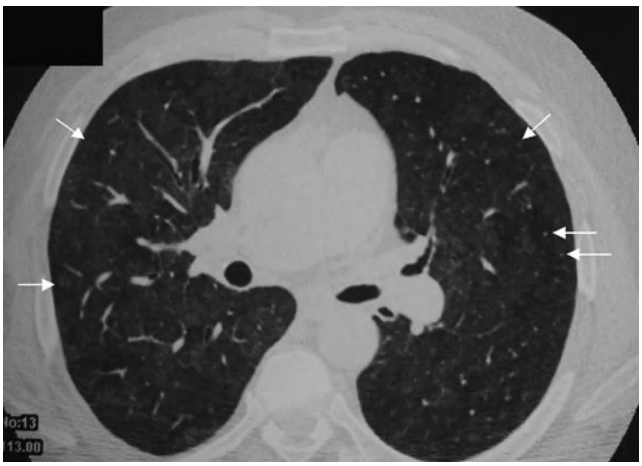

Figure 66-3 Hypersensitivity pneumonitis. High-resolution computed tomography of the chest of an individual with hypersensitivity pneumonitis from the pigeons he raised. Subacute hypersensitivity classically has ground-glass opacities, lymphadenopathy, and centrilobular nodules, which are identified by the sparing of pleural surfaces. Ground-glass and nodules (arrows indicate representative nodules) are visible in this frame. *(Image courtesy of Dr. Erica Herzog.)*

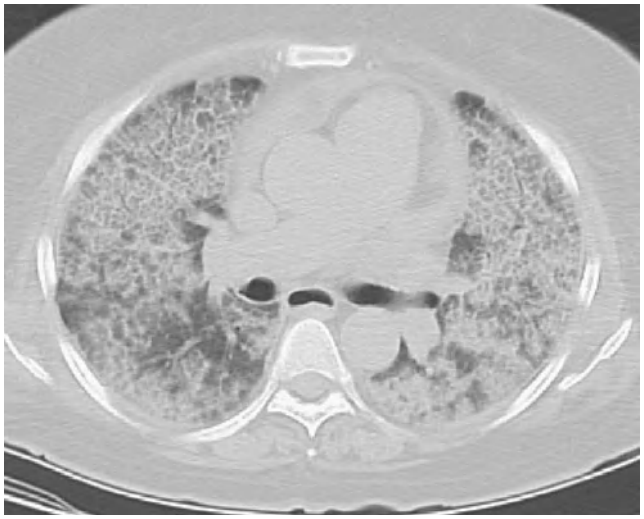

Figure 66-4 Pulmonary alveolar proteinosis. Standard resolution (5 mm) computed tomography of a 53-year-old patient with pulmonary alveolar proteinosis demonstrates ground-glass opacities demarcated by thickened interlobular septae. The findings are bilateral and symmetric in this patient, but may occur unilaterally or asymmetrically. *(Image courtesy of Dr. John McArdle.)*

Pulmonary Physiology Testing

Interstitial diseases alter mechanical and gas exchange properties of the lungs. In general, the hallmarks of interstitial lung diseases are restrictive changes in pulmonary physiology (i.e., reduced total lung capacity, reduced residual volume, decreased static compliance, and a reduced VC, often with an increased FEV_1/FVC ratio), and a reduced diffusing capacity for carbon monoxide (D_{LCO}). A few diseases also manifest substantial components of airflow obstruction. Among these diseases are sarcoidosis, lymphangioleiomyomatosis, Langerhans' cell histiocytosis (eosinophilic granuloma), constrictive

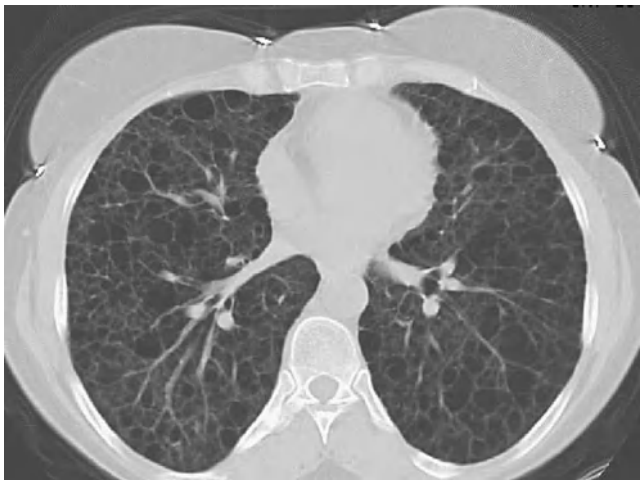

Figure 66-5 Lymphangioleiomyomatosis. Standard resolution (5 mm) computed tomography of the chest demonstrates the diffusely distributed, bilateral, thin-walled cysts that are typical of lymphangioleiomyomatosis. *(Image courtesy of Dr. Richard Matthay.)*

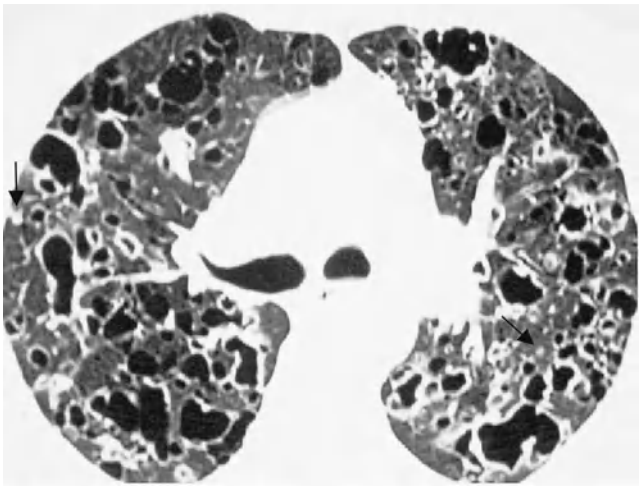

Figure 66-6 Eosinophilic granuloma (pulmonary Langerhans' cell histiocytosis). The high-resolution computed tomogram demonstrates the irregular cysts and centrilobular nodules (arrows) typical of eosinophilic granuloma. Changes occur predominantly in the upper and mid lung zones, and pneumothoraces may be seen. *(Image courtesy of Dr. Michael Gotway.)*

bronchiolitis, respiratory bronchiolitis–interstitial lung disease, and hypersensitivity pneumonia. In some patients, the coincidence of both restrictive and obstructive components, as occurs in interstitial lung disease associated with asthma or chronic obstructive pulmonary disease, can lead to normalization of lung volumes. As such, a careful examination of the flow-volume loop should be made for each patient, and chest imaging studies should be checked for correlation with pulmonary function tests. Respiratory muscle weakness may cause low maximal voluntary ventilation and decreased maximal inspiratory pressure, suggesting possible systemic lupus erythematosus, polymyositis, or scleroderma. Formal measures of lung compliance may be necessary to differentiate respiratory muscle weakness from the physiological effects of interstitial fibrosis.

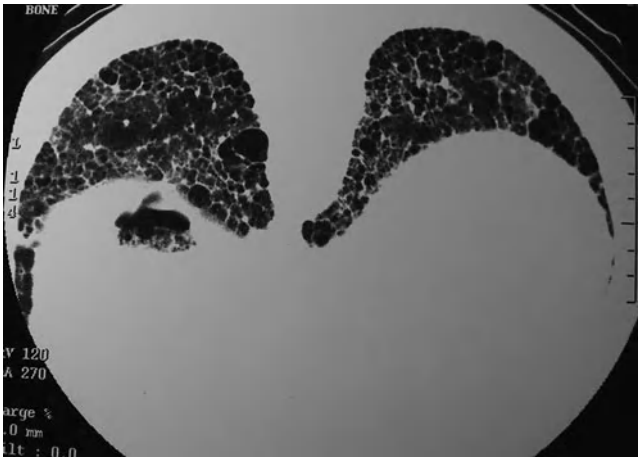

Figure 66-7 Idiopathic pulmonary fibrosis. This high resolution computed tomogram of the chest demonstrates classic bilateral honeycombing.

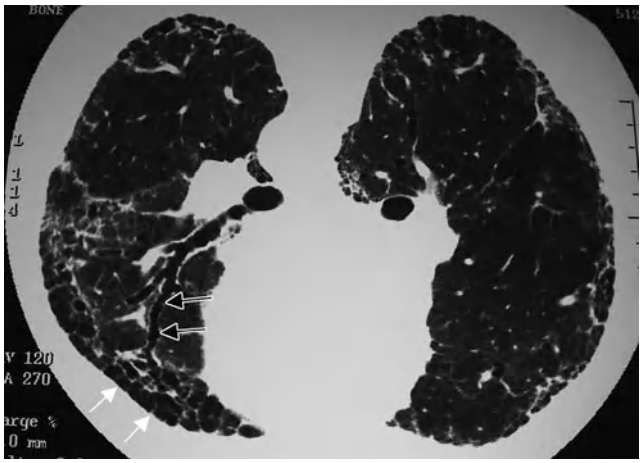

Figure 66-8 Idiopathic pulmonary fibrosis. Traction bronchiectasis (dark arrows) and bilateral, basal honeycombing (white arrows) are demonstrated on this high-resolution computed tomogram of the chest. In addition, a confident radiographic diagnosis of usual interstitial pneumonia requires the absence of nodules and consolidation.

The diffusing capacity for carbon monoxide (D_{LCO}) may be the first and only abnormality found in the early stages of interstitial lung disease. In diseases such as idiopathic pulmonary fibrosis, the diffusing capacity for carbon monoxide is often decreased out of proportion to the restrictive defect. A D_{LCO} less than 35 to 40 percent predicted for idiopathic pulmonary fibrosis and less than 40 percent for systemic sclerosis has been shown to predict worse outcomes.

Quantitative studies suggest that virtually all of the hypoxemia at rest in patients with interstitial lung disease is due to ventilation-perfusion inequality. In patients in whom gas exchange is apparently normal at rest, exercise testing may be helpful in unmasking these defects and therefore useful in understanding patients' dyspnea on exertion. In sarcoidosis, a 6-minute bicycle test detected pulmonary dysfunction sooner than did standard investigative methods. The 6-minute walk test (6MWT) has been used extensively in obstructive lung diseases, and is gaining favor in assessing interstitial lung diseases and the outcomes of therapeutic interventions. Performance in the 6MWT has been shown to correlate with disease severity and prognosis in patients with idiopathic interstitial pneumonias, and it appears to provide information beyond pulmonary function studies in predicting injury due to radiation.

Bronchoalveolar Lavage

Beyond radiologic imaging and physiological testing, most patients with suspected interstitial lung disease require invasive studies to establish a final diagnosis. These studies range from bronchoscopy with bronchoalveolar lavage (BAL) to surgical lung biopsy. Whether a patient should undergo bronchoscopy prior to a surgical lung biopsy hinges on the assembled clinical and radiographic information. A poor candidate for the operative risks of a surgical biopsy might undergo

Table 66-6

Common Computed Tomography Findings of Interstitial Lung Diseases

Peripheral disease	Asbestosis Collagen vascular disease–associated Interstitial Lung Diseases Eosinophilic pneumonia Organizing pneumonia Usual interstitial pneumonia
Upper lobe predominance	Berylliosis Coal workers' pneumoconiosis Cystic fibrosis Eosinophilic pneumonia Hypersensitivity pneumonitis Langerhan's cell histiocytosis Sarcoidosis Silicosis
Lower lobe predominance	Asbestosis Collagen vascular disease associated ILD Nonspecific interstitial pneumonia Organizing pneumonia Usual interstitial pneumonia
Peribronchovascular disease	Lymphangitis carcinomatosis Lymphoproliferative disorders Nonspecific interstitial pneumonia Organizing pneumonia Sarcoidosis Usual interstitial pneumonia
Small nodules	Bronchiolitis obliterans Cryptogenic organizing pneumonia Hypersensitivity pneumonitis Panbronchiolitis Pneumoconiosis Respiratory bronchiolitis Silicosis Vasculitis (Infection: fungal, tuberculosis; malignancy)
Large nodules/ masses	Amyloidosis Churg-Strauss syndrome Langerhans cell histiocytosis Rounded atelectasis, asbestos Sarcoidosis Silicosis Wegener's granulomatosis (Lymphoma metastatic cancer, infection: fungal)
Pleural nodules	Lymphangitic carcinoma Pneumoconiosis (coal workers' silicosis) Sarcoidosis (Infection: fungal, tuberculosis; hematogenous metastatic disease)
Cystic disease	Desquamative intersititial pneumonia Langerhan's cell histiocytosis Lymphangiomyomatosis Lymphoid interstitial pneumonitis (rule out emphysema)
Honeycombing	Asbestosis Collagen vascular disease–associated ILD End-stage ARDS Hypersensitivity pneumonitis (chronic) Sarcoidosis Usual interstitial pneumonia
Consolidation	Acute interstitial pneumonia ARDS Cryptogenic organizing pneumonia Eosinophilic pneumonia Lipoid pneumonia Pulmonary alveolar proteinosis (Bronchoalveolar cell carcinoma)
Ground-glass opacities	Acute interstitial pneumonia ARDS Bronchioloalveolar carcinoma Churg-Strauss syndrome Cryptogenic organizing pneumonia Desquamative interstitial pneumonia Diffuse alveolar hemorrhage Eosinophilic pneumonia (acute, chronic) Nonspecific interstitial pneumonia Pulmonary alveolar proteinosis Radiation pneumonitis Respiratory bronchiolitis interstitial lung disease Sarcoidosis (Infection, pulmonary edema)
Lymphadenopathy (hilar or mediastinal)	Amyloidosis Asbestosis Berylliosis Collagen vascular disease–associated ILD Hypersensitivity pneumonitis Sarcoidosis Silicosis Systemic sclerosis with ILD Usual interstial pneumonia (Infection lymphoma)
Pneumothorax	Ankylosing spondylitis Langerhans' cell granulomatosis Lymphangioleiomyomatosis Neurofibromatosis Tuberous sclerosis (Cystic fibrosis)

Note: Abbreviations: ARDS = Adult respiratory distress syndrome; ILD = interstitial lung disease.
Diseases in parenthesis are not classically cateroized as interstitial lung diseases but should be considered.
Sources: Adapted from Lynch DA, Travis WD, Muller NL, et al: Idiopathic interstitial pneumonias: CT features. Radiology *236:10–21, 2005; Lynch DA: Imaging of diffuse parenchymal lung diseases,* in *Schwarz MI, King TE Jr (eds.), Interstitial Lung Disease, 4th ed. Hamilton, Ontario, BC Decker, 2003, pp 75–113; Webb RW, Muller NL, Naidich DP:* High-resolution CT of the Lung, *3rd ed. Philadelphia, Lippincott Williams & Wilkins, 2001.*

Table 66-7

Clinical, Radiographic, and Treatment of the Idiopathic Interstitial Pneumonias

Feature	IPF	NSIP	COP	AIP	DIP, RB-ILD	LIP
Clinical pearls	Chronic. Age >50 y. Velcro rales, clubbing.	Subacute to chronic. Age 30–70. CVD associated in some cases.	Subacute. Age 50–60s. NS to smokers 2:1. Many assoicated conditions. Restriction on PFTs.	Acute. Most >40 y. Fever, cough, SOB, rales. May have family history or prior episode.	Subacute. Most 30–40s. Smokers >90%. Dyspnea and cough.	Chronic. Any age, most >30 y, female. Autoimmune or systemic disorder–associated.
HRCT: Range of findings	Peripheral, subpleural, basal. Reticular opacities. Honeycombing. Traction bronchiectasis. Architectural distortion. Rare focal ground glass.	Peripheral, subpleural, basal, symmetric. Ground-glass opacities. Rare consolidation. Lower lobe volume loss. Subpleural sparing may occur.	Subpleural or peribronchial. Patchy consolidation. Nodules.	Diffuse, bilateral. Ground-glass opacities, often with lobular sparing.	*DIP*: Diffuse ground-glass opacity in middle and lower lung zone. *RB-ILD*: Bronchial wall thickening, centrilobular nodules, patchy ground glass opacity.	Diffuse. Centrilobular nodules. Ground-glass opacity. Septal and bronchovascular thickening. Thin-walled cysts.
Histology	UIP pattern	NSIP (cellular, fibrotic, mixed)	Organizing pneumonia, Masson bodies	Diffuse alveolar damage	DIP pattern respiratory bronchiolitis	LIP pattern
Treatment	Poor response to corticosteroids or cytotoxic agents.	*Cellular:* Corticosteroid responsive. May require additional immunosuppressants. *Fibrotic:* Similar to IPF.	Corticosteroid responsive. May require additional immunosuppressants, particularly with underlying collagen-vascular disease.	Corticosteroid responsiveness unknown, but high-dose "pulse" therapy often used.	Corticosteroid responsive. Smoking cessation is primary therapy.	Corticosteroid responsive. HAART if HIV positive.

Table 66-7

(*Continued*) Clinical, Radiographic, and Treatment of Collagen Vascular–Associated Interstitial Lung Diseases

Feature	SLE	Rheumatoid Arthritis	Scleroderma	Polymyositis-Dermatomyositis	Sjögren's Syndrome	Ankylosing Spondylitis
Clinical pearls	60% with pleuropulmonary disease Pleurisy +/− effusion, acute pneumonitis, DAH, interstitial disease, thromboembolism, pulmonary HTN.	Cough, dyspnea, clubbing. Pleural involvement most common. Interstitial disease, nodules, bronchiolitis obliterans, pulmonary HTN. Restriction with low diffusing capacity.	Dyspnea and cough. Pulmonary fibrosis, vascular disease, and pleural disease. Pulmonary HTN. Esophageal disease.	Proximal muscle weakness/pain. Heliotrope rash, Gottren papules, finger ulcerations, dyspnea, cough. First, 50s–60s.	Xerostomia and keratoconjunctivitis, with cough and dyspnea. *Primary:* Postmenopausal women. *Secondary:* In-presence of connective tissue disease.	Whites: 30s–40s. Males 50× more likely to have ILD. PFTs: decreased TLC and VC, increased FRC and RV.
HRCT: Range of findings	Interlobular septal thickening, honeycombing. Ground glass opacities. Bronchiectasis. Pleural thickening.	Nodules Bronchiectasis. Pleural thickening. Ground-glass opacities. Honeycombing.	Honeycombing initially basilar. Basal and paravertebral cysts. Pleural thickening. Pneumothorax. Bronchiectasis. Pleural effusion.	Patchy consolidation. Reticular changes. Scattered ground-glass opacities.	Bronchial wall thickening. Ground-glass opacities. Small nodules.	Apical fibrobullous disease, with thickening of pleura, linear septa, interlobular septa.
Histology	NSIP pattern, interstitial fibrosis, foci of organizing pneumonia, inflammation of arterioles.	Diffuse fibrosis with lymphocytic infiltration. Follicular bronchiolitis.	NSIP pattern, often fibrotic. Intimal thickening.	Lymphocytic infiltrate with lymphoid aggregates. Diffuse alveolar damage possible.	Organizing pneumonia, LIP or UIP pattern, bronchiolitis obliterans. Focal clumps of mononuclear cells ("pseudolymphoma")	Fibrosis of pleura and parenchyma. Bronchiectasis. Pneumothorax.
Treatment	Corticosteroids. Azathioprine, cyclophosphamide, methotrexate, pheresis have been used.	Corticosteroid and immunosuppressant responsive.	Not corticosteroid responsive. Cyclophosphamide with significant disease.	Corticosteroids generally insufficient alone with ILD.	Corticosteroids or immunosuppressive therapy.	

(*continued*)

Table 66-7

(*Continued*) Clinical, Radiographic, and Treatment of Miscellaneous Interstitial Lung Diseases

Feature	Sarcoidosis	Hypersensitivity Pneumonitis	Wegener's Granulomatosis	Churg-Strauss	Microscopic Polyangiitis	Goodpasture's Syndrome
Clinical pearls	Rare crackles. Smoking protective. May have fever, constitutional symptoms. Any organ, including uveitis, cardiac, neurologic.	Smoking protective. *Acute:* Dyspnea, cough, fever. *Chronic:* Fatigue, weight loss, dyspnea, cough.	Upper and lower respiratory tracts, glomerulonephritis, and small-vessel vasculitis. >90% white. Mean age 45. Initially fevers, arthralgias, myalgias, malaise, weight loss.	Allergic background or asthma. Peripheral eosinophilia.	Pulmonary hemorrhage and focal segmental glomerulonephritis.	Anti-glomerulo-basement membrane antibodies. Pulmonary hemorrhage and renal disease. Onset usually 17–27 years old.
HRCT: Range of findings	Upper and mid lung. Nodular opacities along septae, peribronchovascular bundles, pleura. Ground-glass opacities. Honeycombing possible. Hilar and/or mediastinal adenopathy.	May be normal. *Acute:* noncardiac pulmonary edema, adenopathy. Upper and mid lung. *Subacute:* Poorly defined, centrilobular, micronodules. Ground-glass opacities, with air trapping. *Chronic:* mid/upper lobe, UIP pattern.	Rounded nodules up to several centimeters, 50% cavitary. Solitary or bilateral. May have diffuse alveolar infiltrate.	Parenchymal consolidation. Varying ground-glass opacities.	Alveolar filling. Interstitial thickening with repeat hemorrhage. Often perihilar.	Alveolar filling. Interstitial thickening with repeat hemorrhage. Often perihilar.
Histology	Tightly formed, noncaseating granulomas.	Poorly formed granulomas, some giant cells. Lymphocytic infiltrate.	Granulation tissue surrounding necrotic area.	Granulomatous lesions with eosinophils, giant cells, and necrosis involving arteries and capillaries.	Hemosiderin-laden macrophages. Evidence of vasculitis.	Hemosiderin-laden macrophages. Alveolar capillaritis. Linear deposits of immunoglobulin alveolar basement membranes.
Treatment	Corticosteroid responsive, but indications for use are controversial.	Eliminate exposure. Corticosteroids if chronic.	Corticosteroids and cyclophosphamide.	Corticosteroids insufficient. Consider cyclophophamide, corticosteroids, and plasma exchange.	Corticosteroids and cyclophosphamide.	Corticosteroids, cyclophosphamide/ azathioprine, and plasmapheresis.

Feature	Langerhan's Cell Granulomatosis	LAM	PAP	Acute Eosinophilic Pneumonia	Chronic Eosinophilic Pneumonia
Clinical pearls	Smokers. Age 20–50. Mainly whites. Recurrent pneumothorax. Constitutional symptoms in 15%–30%.	Women. Mean age 30–36 years old. Progressive obstruction. Present with pneumothorax, hemoptysis, or chylothorax.	Progressive dyspnea, cough. May have thick sputum. Elevated shunt fraction and LDH. Associated with GM–CSF deficiency.	Dyspnea, fever, myalgias, rapidly progressive respiratory failure. Eosinophils in BAL but not serum.	90+% nonsmokers. 2:1 female:male. Peak age 30–45. Peripheral eosinophilia common.
HRCT: Range of findings	Upper and mid lung. Nodules, usually <5 mm. May cavitate. Cysts, thin or thick-walled, esp. upper zones, may be irregular. Some ground glass in up to 20%. Mediastinal or pretracheal adneopathy in one-third.	Diffuse, but apical sparing. Regular shaped, thin-walled cysts. Pneumothorax. Pleural effusion. Renal angiomyolipomas.	Often central and symmetric. Intra- and interlobular septal thickening. Ground-glass opacities. "Crazy paving."	Intralobular septal thickening. Poorly defined nodules. Ground-glass opacities. Majority with pleural effusions.	Upper zones and peripheral. Irregular airspace consolidation. Ground-glass opacities. Mediastinal nodes in up to 50%. Rare effusions, usually small.
Histology	Granulomatous inflammation. S100 and CD1a positive cells.	Smooth muscle nodules in walls of cysts, vessels, airways. HMB45 staining.	PAS-positive material filling alveoli, distal airways.	Diffuse alveolar damage with interstitial edema. Eosinophilic infiltration of alveoli, bronchioles, and bronchial walls.	Infiltration by eosinophils, lymphocytes, and macrophages. May have giant cells. Intraluminal fibrosis. Granulomas may be seen.
Treatment	Smoking cessation. Consider steroid trial.	Avoid pregnancy. Consider oophrectomy, progesterone, antiestrogens, clinical trials.	Corticosteroid unresponsive. Lavage, GM-CSF therapy.	Dramatically corticosteroid responsive.	Dramatically corticosteroid responsive.

Note: Abbreviations: AIP = acute interstitial pneumonia; COP = cryptogenic organizing pneumonia; CVD = collagen vascular disease; DIP = desquamative interstitial pneumonia; HIV = human immunodeficiency virus; HAART = highly active antiretroviral therapy; HTN = hypertension; ILD = interstitial lung disease; IPF = idiopathic pulmonary fibrosis; NS = nonsmokers; NSIP = nonspecific interstitial pneumonia; PFTs = pulmonary function tests; RB-ILD = respiratory bronchiolitis–interstitial lung disease.

Table 66-8

Diffuse Parenchymal Diseases Diagnosable by Bronchoscopy with Lavage and/or Biopsy

Disease	Diagnostic Bronchoscopic Findings
Berylliosis	Granulomatous or mononuclear cell interstitial inflammation AND positive beryllium lymphocyte proliferation test (BAL for blood)
Chronic eosinophilic pneumonia	Eosinophils >50% on BAL with typical clinical history and radiographs
Diffuse alveolar hemorrhage	Increasing red cell count on sequential BALs, >20% hemosiderin-laden macrophages
Infections	Postive stains/cultures
Langerhans' cell granulomatosis	Langerhans' cells >3% total BAL cell count (CD1a and S100 positive)
Lymphangitic carcinomatosis	Malignant cells.
Pulmonary alveolar proteinosis	Milky BAL fluid with debris and foamy macrophages
Sarcoidosis	Noncaseating granulomas

bronchoscopy with BAL in search of specific diagnostic features or a typical BAL cell pattern to strengthen the clinical-radiographic diagnosis. Any significant concern for infection necessitates a bronchoscopy, with specific consideration given to mycobacterial and fungal diseases, as well as *Pneumocystis jiroveci* (*carinii*) pneumonia. A bronchoscopy may also be pursued if the differential diagnosis includes diseases with pathognomonic findings likely to be discovered by bronchoscopy (Table 66-8). Included on this list are the infections mentioned in the preceding, alveolar hemorrhage, and pulmonary alveolar proteinosis. An eosinophil count higher than 25 percent suggests Churg-Strauss or eosinophilic pneumonia, even though diseases from idiopathic pulmonary fibrosis to asthma to allergic bronchopulmonary aspergillosis may, on rare occasion, present with such an elevated eosinophil count. Although the lack of specificity limits the diagnostic utility for diseases other than those listed in Table 66-8, cellular profiles that may be found with other interstitial lung diseases are depicted in Table 66-9. Although some interstitial lung diseases occasionally are associated with bronchoscopically obvious airway abnormalities (e.g., sarcoidosis, lung cancer with lymphangitic spread, Kaposi's sarcoma in HIV infected patients), most are not. The absence of finding on BAL may also be helpful. A normal differential on a technically sound BAL largely excludes eosinophilic pneumonia and Churg-Strauss syndrome.

In general, bronchoalveolar fluid analysis in patients with interstitial lung disease should include total and differential cell counts (with particular attention to eosinophilia); cytologic examination both for neoplasia and microorganisms such as *Pneumocystis jiroveci (carinii)*; culture and stains for bacterial, fungal, and mycobacterial pathogens; and assays for viral and other "atypical" pathogens such as *Mycoplasma pneumoniae*. Specific clinical concerns warrant more specialized testing, such as cytologic analysis for hemosiderin-containing alveolar macrophages in cases of suspected acute or chronic alveolar hemorrhage; PAS staining of the proteinaceous debris and vacuolated alveolar macrophages from the opalescent, milky lavage fluid of pulmonary alveolar proteinosis (Fig. 66-9); cultures for unusual viral pathogens; flow-cytometric analysis of lymphocyte subsets in cases of suspected hypersensitivity pneumonitis, sarcoidosis, or lymphoid malignancy; staining for anti-CD1a for Langerhans' cell histiocytosis; or fat staining (oil red O or Sudan III) of the lipid-laden macrophages in aspiration. In general, in cases of interstitial lung diseases, BAL is substantially more useful in ruling out particular conditions such as infection, than in determining a specific noninfectious cause.

Bronchoalveolar lavage has a limited utility in assessing the prognosis of interstitial lung disease and response to treatment. One exception is that an increased percentage of BAL neutrophils appear to portend a worse prognosis in sarcoidosis, idiopathic pulmonary fibrosis, and hypersensitivity pneumonitis.

Bronchoscopy with Transbronchial Biopsy

Endobronchial and transbronchial biopsies (TBB) may augment the visual inspection and BAL of bronchoscopy. In general, bronchoscopic biopsies are of limited utility in the evaluation of interstitial lung diseases. The notable exception to this generalization is sarcoidosis. In sarcoidosis, endobronchial biopsy has a sensitivity of up to 90 percent in patients in whom bronchial abnormalities are seen, and "blind" TBBs have a sensitivity of 80 percent or greater in patients in whom no bronchial abnormalities are seen. Depending on the stage, 6 to 10 TBBs are required to achieve this sensitivity. Instead, surgical biopsies are preferable in most cases of interstitial lung disease because the amount of tissue obtained is substantially larger, allowing a vastly improved visualization of the pattern and nature of the pathological abnormalities.

Surgical Lung Biopsy: Thoracoscopy-Guided and Open Lung Biopsy

Combining clinical information with an HRCT that depicts 'definite usual interstitial pneumonia' can provide a diagnosis of idiopathic pulmonary fibrosis that is sufficiently certain

Table 66-9

Bronchoalveolar Lavage Cellular Profile

Normal Adults (nonsmokers) **Total Cell Count (10^6)*** **Cell Types**	**Never Smokers** **18** **(Mean Percent)**	**Current Smokers** **60** **(Mean Percent)**
Alveolar macrophages	85%	93%
Lymphocytes	12%(T4:T8 ratio 0.9–2.5)*	5%
Neutrophils	≤1%	2%
Eosinophils	≤1%	≤1%
Elevated T Lymphocytes	**Elevated Eosinophils**	**Elevated Neutrophils**
Sarcoidosis†	Sarcoidosis (±)	Sarcoidosis (±)
Berylliosis		
Hypersensitivity pneumonitis		Hypersensitivity pneumonitis (±)
Collagen vascular diseases	Systemic lupus erythematosus	Collagen vascular diseases
Idiopathic pulmonary fibrosis†	Idiopathic pulmonary fibrosis§	Idiopathic pulmonary fibrosis
Drug induced	Drug induced	
Radiation pneumonitis	Eosinophilic pneumonias	Aspiration pneumonia
Lymphoma/pseudolymphoma	Hodgkin's disease	
Silicosis		
Lung rejection	Bone marrow transplant	
AIDS	AIDS	
Infection: tuberculosis, viral	Infection: bacterial, fungal helminthic, pneumocystis	Infection: bacterial, fungal
	Bronchitis	Bronchitis
	Asthma	
	Churg-Strauss syndrome	
	Allergic bronchopulmonary aspergillosis	Asbestosis Adult respiratory distress syndrome

* *Individual laboratories should have their own reference values.*
† *Both increased and decreased CD4:CD8 T-cell ratios have been described. The increased ratio is most common in sarcoidosis.*
‡ *Associated with favorable prognosis.*
§ *Associated with poor prognosis.*
BAL values for smokers and never smokers derived from Anonymous: Bronchoalveolar lavage constitutents in healthy individuals, idiopathic pulmonary fibrosis, and selected comparison groups. The BAL Cooperative Group Steering Committee. Am Rev Respir Dis *141:S169–202, 1990.*

Figure 66-9 Bronchoalveolar lavage (BAL) fluid from a patient with pulmonary alveolar proteinosis. The patient underwent 25 L of sequential lavage with concomitant chest physiotherapy. The first three and last three liters of BAL fluid are demonstrated from left to right. Note the decreasing amount of precipitant, which represents protein- and lipid-rich material, including large amounts of surfactant proteins, and some foamy macrophages.

that a tissue diagnosis is not required (Table 66-10). For most other situations, a surgical biopsy is required. Multiple well-designed studies have shown conclusively that video-assisted thoracoscopic (VATS) biopsies are equivalent in diagnostic yield to open lung biopsies, resulting in improved morbidity and mortality rates. As a result of these improvements, lung biopsies have become outpatient surgical procedures in some centers. Sampling multiple lobes increases both the diagnostic yield and the prognostic utility of surgical lung biopsies. The thoracic surgeon should avoid merely sampling regions of severe honeycombing, but instead, obtain tissue from the spectrum of disease based on gross appearance and CT findings. Concerns about the diagnostic utility of biopsies from the lingula and right middle lobe, where nonspecific fibrotic and vascular changes are often found, led initially to avoidance of biopsying these lobes. More recent data from both immunocompromised and immunocompetent patients suggests that this is no longer a concern.

Clinicopathological Correlation in the Diagnosis of Interstitial Lung Diseases

A multidisciplinary collaboration is strongly encouraged prior to beginning therapy on any patient with interstitial lung disease because of the complexity and inter-relatedness of the clinical, radiographic, and pathological manifestations of illness and the lack of a truly diagnostic "gold standard." This approach has been incorporated into the recommendations of the American Thoracic Society/European Respiratory Society in their consensus statement on idiopathic interstitial pneumonias. Such collaboration typically necessitates person-to-person, real-time interaction between a radiologist who has an interest in diseases of the chest, a consulting pulmonologist, and a pathologist who is expert in the interpretation of non-neoplastic lung pathology. Considerable motivation

Table 66-10

ATS/ERS Criteria for Diagnosis of IPF in Absence of Surgical Lung Biopsy

Major criteria*
Exclusion of other known causes of ILD such as certain drug toxicities, environmental exposures, and connective tissue diseases
Abnormal pulmonary function studies that include evidence of restriction (reduced VC, often with an increased FEV1/FVC ratio) and impaired gas exchange [increased $P(A\text{-}a)_{O_2}$, decreased Pa_{O_2}, with rest or exercise or decreased D_{LCO}]
Bibasilar reticular abnormalities with minimal ground glass opacities on HRCT scans
Transbronchial lung biopsy or BAL showing no features to support an alternative diagnosis
Minor criteria
Age >50 y
Insidious onset of otherwise unexplained dyspnea on exertion
Duration of illness >3 mo
Basilar, inspiratory crackles (dry or "Velcro"-type in quality)

In the immunocompetent adult, the presence of all of the major diagnositic criteria as well as at least three of the four minor criteria increases the likelihood of a correct clinical diagnosis of IPF.

** Reprinted with permission from: American Thoracic Society and European Respiratory Society: American Thoracic Society/European Respiratory Society. International Multidisciplinary Consensus Classification of the Idiopathic Interstitial Pneumonias. This joint statement of the American Thoracic Society (ATS), and the European Respiratory Society (ERS) was adopted by the ATS board of directors, June 2001 and by the ERS Executive Committee, June 2001. [Erratum appears in* Am J Respir Crit Care Med *166:426, 2002].* Am J Respir Crit Care Med *165:277–304, 2002.*

is required to develop, coordinate, and nurture such high-intensity multispecialty collaboration. Nevertheless, collaborative efforts of radiologists and pathologists interacting with clinicians increase the accuracy of the diagnosis as well as patient survival. As noted in the ATS/ERS consensus statement, further revision and refinement of the "final" clinical diagnosis is to be expected as additional history or laboratory studies are obtained. Although the pathological or radiologic diagnosis may be tempting, it is the responsibility of the clinician to determine the final diagnosis and management. The clinician must be familiar with the myriad of radiographic and histopathological patterns associated with each of these diseases.

TREATMENT

The optimal therapy for interstitial lung diseases is an area of intense investigation. Supportive care, providing oxygen

to hypoxemic patients, and pulmonary rehabilitation should be considered in all patients. Pulmonary rehabilitation is underutilized in patients with interstitial lung disease and should be considered earlier and more frequently than is done at present. Pneumococcal and influenza vaccination should not be overlooked. National and local organizations exist for many diseases that provide support and information for patients and their families. Patients require counseling concerning the removal of offending environmental agents, such as tobacco smoke in desquamative interstitial pneumonia and respiratory bronchiolitis–interstitial lung disease, specific antigens in hypersensitivity pneumonitis, and medications in drug-induced pulmonary reactions. If possible, disease modifying therapies should be withheld until diagnostic lung tissue has been obtained. Table 66-7 includes information on the steroid-responsive nature of some of the interstitial lung diseases. Since the field continues to evolve, readers are directed to other chapters in this text as well as current literature for specific treatment guidelines once a diagnosis has been made. Even the optimal dose and duration of prednisone for steroid-responsive diseases is often based on case series and clinical experience rather than controlled trials. Clinicians also should consider enrolling patients in relevant clinical trials.

Care should be taken to minimize the iatrogenic effects of medical therapy. Patients should be carefully monitored for symptoms or serologic evidence of adverse drug reactions. Prophylactic measures should be taken, such as giving calcium, vitamin D, and bisphosphonate therapy to appropriate patients on prednisone, and folic acid to appropriate patients on methotrexate. Opportunistic infections such as *Pneumocystis jiroveci (carinii)* appear to occur less often with iatrogenic immunosuppression in patients with interstitial lung disease than in patients with hematologic or central nervous system malignancies. Nevertheless, opportunistic infections have been reported, particularly in patients with Wegener's granulomatosis, but also in patients with a range of interstitial lung diseases. Consideration should be given to prophylaxis in patients receiving immunosuppression.

The clinician should consider lung transplantation as an option once the diagnosis of an interstitial lung disease with an unfavorable prognosis has been rendered. The time required for a transplant center to evaluate a candidate combined with a shortage of available lungs and age limitations makes early consideration mandatory.

SUGGESTED READING

American Thoracic Society and the European Respiratory Society: American Thoracic Society/European Respiratory Society International Multidisciplinary Consensus Classification of the Idiopathic Interstitial Pneumonias. This joint statement of the American Thoracic Society (ATS), and the European Respiratory Society (ERS) was adopted by the ATS board of directors, June 2001 and by the ERS Executive Committee, June 2001. [Erratum appears in *Am J Respir Crit Care Med* 166:426, 2002.] *Am J Respir Crit Care Med* 165:277–304, 2002.

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67

Systemic Sarcoidosis

David R. Moller

Sarcoidosis is a multisystem disorder of unknown origin characterized by noncaseating granulomatous inflammation at sites of disease. Although any organ can be involved, the disease most commonly affects the lungs and intrathoracic lymph nodes. Since the cause of sarcoidosis is uncertain, a diagnosis is most securely established from compatible clinicoradiologic findings, together with histologic evidence of noncaseating epithelioid granulomas in more than one organ and the exclusion of granulomatous disorders of known cause. Clinical, epidemiologic, and family studies support the hypothesis that sarcoidosis is triggered by exposure to microbial agents in individuals with a genetic susceptibility to the disease. The clinical course is highly variable, with a mortality rate of 1 to 5 percent. Corticosteroids remain the mainstay of treatment for patients with threatened organ failure or progressive disease.

HISTORICAL PERSPECTIVE

Jonathan Hutchinson was the first to describe a case of sarcoidosis in 1887; he called it Mortimer's malady, after one of his patients who presented with face and limb skin lesions. In 1889, Besnier of Paris described a 34-year-old man with violaceous skin lesions of the nose, ear lobules, and central face; he proposed that the lesions were a variant of lupus erythematosus leading to its designation as "lupus pernio." In 1899, Caesar Boeck first described the characteristic noncaseating granulomas in a patient with peripheral lymphadenopathy and skin nodules. He proposed the term *multiple benign sarcoids of the skin* because he thought the granulomatous changes resembled sarcomatous tissue. Subsequently, descriptions of sarcoid-type lesions in the eyes, bones, lungs, and salivary glands were made, but the systemic and unifying nature of sarcoidosis was not recognized for almost 20 years.

The view that sarcoidosis is a systemic disorder is largely based on the work of Jorgen Schaumann, a Swedish dermatologist, who in 1914 presented the view that Besnier's lupus pernio and Boeck's multiple sarcoids were manifestations of the same disease termed "lymphogranulomatose benigne," thought to represent a variant of tuberculosis. In 1935, Williams and Nickerson reported that intradermal inoculation of a suspension of sarcoidosis tissue resulted in firm papules in patients with suspected sarcoidosis. Ansgar

Kveim, a dermatologist in Oslo, demonstrated in 1941 that these papules contained sarcoidlike granulomas on biopsy. Louis Siltzbach and others would demonstrate in worldwide studies that this "Kveim" reaction was positive (showed granulomas) in up to 80 percent of sarcoidosis and was highly specific for the disease.

The next major breakthrough in understanding sarcoidosis was based on the pioneering observations of Sven Löfgren of Sweden in the 1940s and 1950s, who noted that sarcoidosis frequently begins with asymptomatic bilateral hilar adenopathy or with acute erythema nodosum. In the 1950s, corticosteroids were reported to be successful in treating sarcoidosis. The development of bronchoalveolar lavage (BAL) as a research tool in the 1970s allowed the study of local cellular mechanisms in pulmonary sarcoidosis and led to the paradigm shift that sarcoidosis is associated with compartmentalized, enhanced T-cell immunity at sites of inflammation. More recently, the tools of cell and molecular biology have advanced our understanding of the immunologic, genetic, and etiologic basis of sarcoidosis, but have not yet led to breakthroughs in the development of safe, effective therapies.

EPIDEMIOLOGY

Sarcoidosis is found worldwide, although the frequency of the disease varies among different geographic regions. Estimates of disease prevalence are not known with certainty because many people with sarcoidosis are asymptomatic, and there is no sensitive nor specific diagnostic test. Prevalence rates of between 10 and 40 cases per 100,000 population are reported in North America, southern Europe, and Japan. Higher prevalence rates are noted in Sweden, Denmark, and US blacks. The lifetime risk for developing sarcoidosis has been estimated as 1.4 and 1.0 percent in women and men of Scandinavian countries, respectively, whereas one US study calculated a lifetime risk of 2.4 percent for blacks and 0.85 percent for whites living in a midwestern city. Worldwide, the disease is reported to be slightly more frequent in women. More than 80 percent of cases occur in persons between 20 and 40 years of age, with a second peak in women more than 50 years of age. Sarcoidosis is rare in the preadolescent period.

The frequency of different clinical manifestations of sarcoidosis also varies among geographic regions and ethnic groups. Erythema nodosum is common in Scandinavian countries and Ireland, but found in less than 5 percent of black or Japanese patients. In contrast, lupus pernio appears more frequently among black populations. In Japan, over 50 percent of patients may have cardiac sarcoidosis. Several studies suggest that race is an important determinant of disease severity with black populations more likely to have persistent disease and greater mortality than white populations. In the United States, 40 to 80 percent of mortality from sarcoidosis is from advanced pulmonary disease. In Sweden and Japan, cardiac involvement is the leading cause of death from sarcoidosis. Overall, mortality rates directly related to sarcoidosis approximate 1 to 5 percent according to hospital statistics.

ETIOLOGY

The cause of sarcoidosis remains uncertain. Since sarcoidosis was first described, investigators as early as Boeck in 1905 have postulated an infectious cause of the disease based on the clinical similarities to tuberculosis. Environmental exposures are linked to sarcoidosis due to seasonal clustering of the disease with a predilection for winter and early spring months in both northern and southern hemispheres. Geographic variation and time–space clustering also support a role for environmental triggers in sarcoidosis. Occupational associations have been described for health care professionals, firefighters, military personnel, and workers involved in the lumber industry. Chronic beryllium disease causes a granulomatous pneumonitis histologically identical to pulmonary sarcoidosis in less than 5 percent of exposed workers following immunologic sensitization to beryllium. However, there is no evidence that beryllium is a cause of systemic sarcoidosis.

A recent US-based multicenter study of sarcoidosis etiology called ACCESS (A Case Control Etiologic Study of Sarcoidosis) compared 706 newly diagnosed, biopsy-proven sarcoidosis cases to age-, sex-, and race-matched controls. Results from the study showed an absence of environmental or occupational associations positively linked to sarcoidosis risk that carried an odds ratio (OR) greater than 2.0 and an exposure prevalence of greater than 5 percent (prestudy goal). Weak positive associations (OR approximately 1.5) were found for insecticide use at work, mold/mildew exposures at work, and musty odors, suggesting possible links to microbial-rich environments. Sarcoidosis was not associated with exposure to heavy metals including beryllium, wood dusts, or rural residence as previously hypothesized. The ACCESS study found a robust negative association of smoking and sarcoidosis risk, confirming earlier studies. The lack of a single, dominant exposure associated with sarcoidosis risk is consistent with the concept that gene-environmental interactions are important in causing disease.

Many studies over decades have directly examined a role for infectious agents in sarcoidosis. Investigators in the 1960s reported the presence of a transmissible agent in sarcoidosis tissue, but these studies could not be reproduced, and despite many attempts, no mycobacterial or other infectious organisms have been reproducibly cultured from sarcoidosis tissue. More recently, US, European, and Japanese investigators report the presence of mycobacterial DNA in 0 to 80 percent of biopsy specimens, but also in 0 to 30 percent of control tissues using highly sensitive polymerase chain reaction techniques. Japanese investigators find *Propionibacterium acnes* DNA in 80 to 98 percent of sarcoidosis tissues from Japan and Europe but also in 0 to 60 percent of control tissues. Other microbial agents, such as *Borrelia burgdorferi*, *Chlamydia pneumonia*, or *Rickettsia helvetica* have been implicated in sarcoidosis from

tissue or serologic studies, but these latter studies all lack wider confirmation. High titers of antibodies against lymphotropic DNA viruses (Epstein-Barr virus, cytomegalovirus, and human herpesvirus type 6) and HTLV1 have been described in patients with sarcoidosis but may reflect generalized B-cell activation in sarcoidosis, since a viral origin has not been substantiated by viral cultures or tissue analysis. Despite a lack of consistent results, reports of systemic sarcoidosis developing in naïve transplant recipients receiving organs from known or suspected sarcoidosis patients support a transmissible agent as a cause of sarcoidosis.

Some investigators hypothesize an etiologic association with autoimmunity, perhaps triggered by an infectious agent through molecular mimicry. In support of this concept, sarcoidosis is associated with features of autoimmunity, such as antinuclear antibodies, rheumatoid factor, hypergammaglobulinemia, and immune complexes.

Recently the author and his colleagues used a limited proteomic approach to identify potential pathogenic antigens in sarcoidosis tissues based solely on the biochemical properties of the Kveim reagent and not on a priori hypotheses regarding specific infectious or autoimmune causes. This approach detected the mycobacterial catalase-peroxidase protein (mKatG) in over 50 percent of sarcoidosis tissues. IgG responses to mKatG were detected in approximately 50 percent of sarcoidosis patients, supporting the premise that mKatG is a pathogenic antigen and that mycobacterial organisms trigger a subset of sarcoidosis. Although direct demonstration of an infectious etiology remains unproven, many investigators favor the hypothesis that certain classes of microbial organisms trigger sarcoidosis in those with genetic susceptibility.

GENETICS

Family and case control association studies provide strong evidence for a genetic influence on the risk of developing sarcoidosis and in determining clinical expression of the disease. Familial clustering of sarcoidosis occurs in 3 to 14 percent of patients, with a greater frequency among black compared with white populations. The US ACCESS study found siblings of sarcoidosis cases have a higher relative risk (OR approximately 5.8) than parents (OR approximately 3.8). The significantly higher adjusted familial relative risk (RR) estimates reported for whites in both the US ACCESS study (RR approximately 18) and in a UK study with mostly whites (RR approximately 36 to 73) and blacks (RR approximately 2.8), suggest that genetic factors have a greater influence in susceptibility to sarcoidosis in whites than blacks.

Early studies examined the role of HLA class I alleles using serologic techniques. The HLA-B8 allele has most consistently been associated with disease susceptibility, increasing sarcoidosis risk in whites from the United States and Europe but not in blacks or Japanese. A recent Scandinavian study found HLA-B*07 and B*08 increased risk of sarcoidosis independent of class II alleles.

The role of HLA class II alleles has been intensively studied in sarcoidosis. HLA-DR3 has been associated with sarcoidosis susceptibility, while HLA-DR1 and -DR4 alleles have been associated with disease protection in Scandinavian and European populations. Using molecular genotyping, the ACCESS study found a significant association between HLA-DRB1*1101 in both blacks and whites, while HLA-DRB1*1501 was associated with sarcoidosis risk only in whites. Other studies find the class II HLA-DR17 (DR3) haplotype and specifically HLA DRB1*0301 or the closely linked DQB1*0201 alleles to be associated with favorable outcomes (Löfgren syndrome, acute arthritis, stage I chest radiograph, or remission within 2 years) in European and Japanese populations. The DRB1*1501 or the closely linked DQB1*0602 alleles were associated with more severe or chronic disease in a Danish cohort. HLA-DPB1 and DQB1 alleles have been associated with disease susceptibility in some studies, although linkage disequilibrium makes it difficult to separate from effects of HLA-DR alleles. These data support a consensus view that MHC class II alleles are the major contributor to disease susceptibility across different ethnic populations in sarcoidosis.

Non-HLA genes have also been the subject of multiple case control studies (Table 67-1). The tumor necrosis factor (TNF) gene located inside the MHC locus is associated with sarcoidosis outcome in some studies. Two studies report associations with sarcoidosis and the CC chemokine receptors (CR), CCR2 and CCR5. Only one of several studies report the angiotensin converting enzyme, complement receptor 1 or macrophage inhibitory factor to be associated with sarcoidosis risk.

Family linkage studies employing genomewide microsatellite analysis confirm the importance of genes from the MHC locus in determining susceptibility to sarcoidosis. A German study found strongest linkage to the MHC class II locus on chromosome 6p with minor linkage peaks on chromosomes 1, 3, 9, and X. A US-based study of blacks called SAGA (Sarcoidosis Genetic Analysis Consortium) found the highest linkage peak on chromosome 5q and minor peaks on chromosome 1, 2, 9, 11, and 20. No significant linkage to the MHC region on chromosome 6 was found, possibly due in part to the influence of white gene admixture among blacks in the United States.

More recently, using fine mapping of the MHC locus in both families and case control samples, German and US investigators report that the butyrophilin-like 2 (*BTNL2*) gene is associated with sarcoidosis risk in white and to a lesser extent, black populations. Since *BTNL2* is a member of the B7 receptor family that functions in T-cell costimulation, a plausible hypothesis links the *BTNL2* gene with T-cell immunity and sarcoidosis susceptibility.

PATHOLOGY

The pathological hallmark of sarcoidosis is the presence of discrete, noncaseating, epithelioid cell granulomas (Fig. 67-1).

Table 67-1

Major Clinical Manifestations of Sarcoidosis

Organ System (Percent Clinical Disease)	Major Clinical Features
Pulmonary (>90%)	Restrictive and/or obstructive disease, fibrocystic disease, bronchiectasis
Upper respiratory tract and oral cavity (5–10%)	Hoarseness, laryngeal or tracheal obstruction, nasal congestion, sinusitis
Ocular (20–30%)	Anterior and posterior uveitis, chorioretinitis, conjunctivitis, optic neuritis
Skin (20–30%)	Erythema nodosum, chronic nodules and plaques, lupus pernio, alopecia
Hepatic/Abdominal (10–20%)	Hepatosplenomegaly, jaundice, cirrhosis, abdominal/retroperitoneal lymphadenopathy
Cardiac (5–10%)	Arrhythmias, heart block, cardiomyopathy, sudden death
Neurologic (5–10%)	Facial and other cranial neuropathies (e.g., Bell's palsy) aseptic meningitis brain mass, seizures, obstructing hydrocephalus, hypothalamic hypopituitarism, myelopathy, polyneuropathy
Exocrine gland (10–20%)	Salivary, lacrimal, and parotid gland enlargement, sicca syndrome
Hematologic (20–30%)	Peripheral or retroperitoneal lymphadenopathy, splenomegaly, hypersplenism, anemia, lymphopenia
Joints and musculoskeletal (10–20%)	Polyarthritis, Achilles tendinitis, heel pain, polydactylitis, bone cysts, myopathy
Endocrine (10–30%)	Hypercalciuria, hypercalcemia, hypopituitarism, diabetes insipidus
Renal (<5%)	Renal calculi, nephrocalcinosis, renal failure
Genitourinary (<5%)	Ovarian or uterine mass, dysmenorrhea, testicular mass, epididymitis
Psychosocial manifestations (30–60%)	Depression

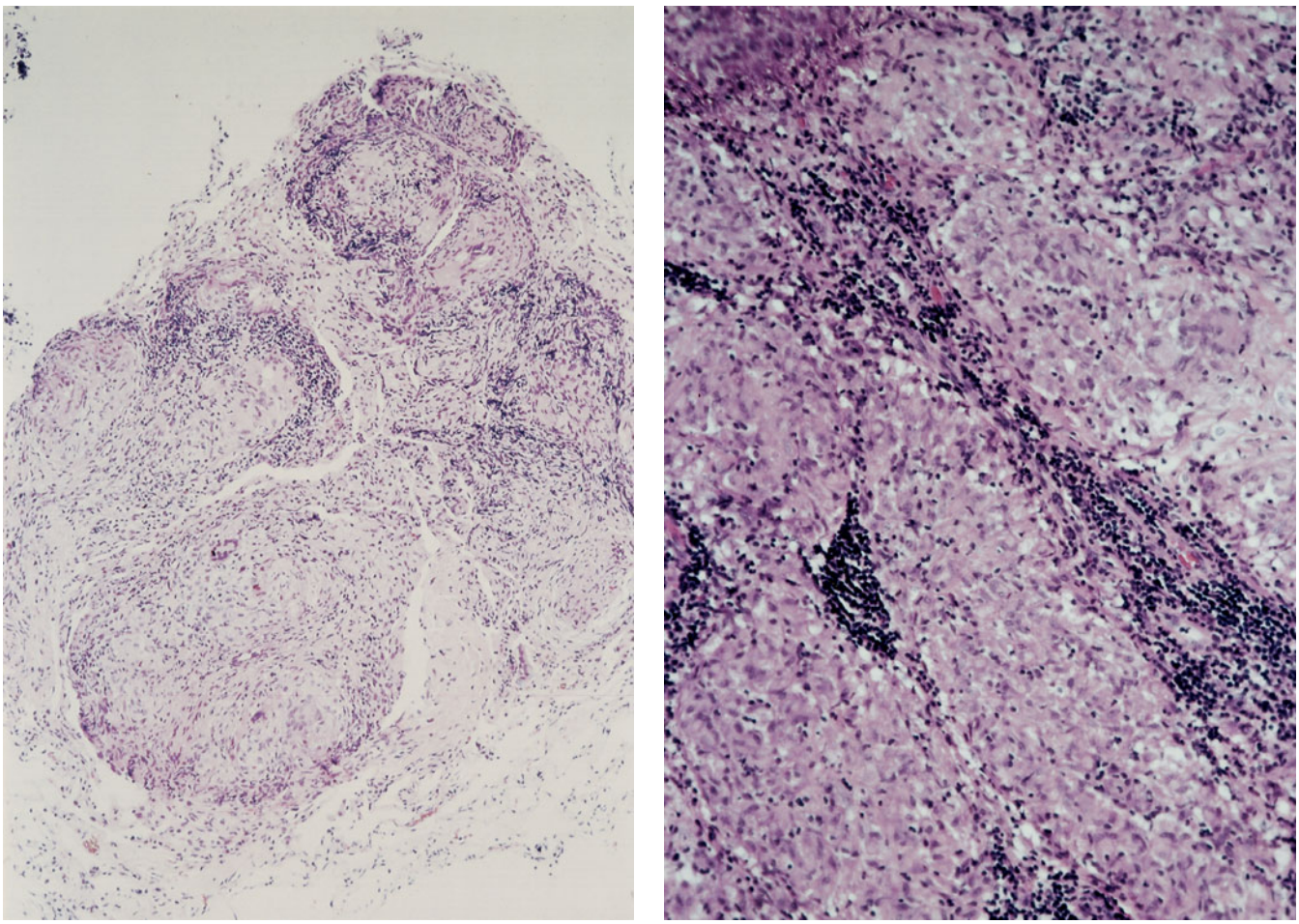
The dominant cell in the central core is the epithelioid cell, thought to be a differentiated form of a mononuclear phagocyte. CD4 lymphocytes and mature macrophages are typically interspersed throughout the epithelioid core, whereas both CD4+ and CD8+ lymphocytes may be seen in the periphery of the granuloma. Occasionally, focal fibrinoid but not caseating necrosis may be seen. Giant cells, often containing cytoplasmic inclusions such as calcium and iron-laden Schaumann bodies, are scattered throughout the inflammatory locus. These features are not specific for sarcoidosis, as similar histopathologic findings can be seen in infections, berylliosis, Crohn's disease, and local "sarcoid reactions" that occur near neoplastic, foreign body, or chronic inflammatory areas.

In the lung, granulomas tend to form along perivascular, peribronchial, and septal regions, areas rich in lymphatic vessels. In the lung, a mononuclear cell infiltration composed predominantly of lymphocytes is often present in the adjacent interstitium. Granulomas in sarcoidosis may resolve or undergo fibrosis, leaving a stellate scar or hyalinized ghost of a former granuloma.

PATHOPHYSIOLOGY

Immunopathology

Experimental models indicate that the first step in granuloma formation involves the tissue deposition of poorly soluble antigenic material. This material is phagocytosed by antigen presenting cells such as macrophages or dendritic



A *B*

Figure 67-1 Photomicrographs of noncaseating granulomatous inflammation in sarcoidosis. *A*. Thoracoscopic lung biopsy showing extensive parenchymal involvement with granulomas, multinucleated giant cells, and mononuclear cell inflammation (×80). *B*. Extensive granulomatous inflammation of the myocardium in a fatal case of cardiac sarcoidosis (×100).

cells that degrade proteins and display peptide:class II MHC complexes on the cell surface for analysis by CD4+ T cells. Immune-mediated granulomatous inflammation can be driven by either Th1 cytokines (IFNγ) or Th2 cytokines (IL4, IL5, IL13) depending on the nature of the inciting agent in association with the release of critical cytokines such as TNF and chemokines. Granulomatous inflammation is down-regulated with clearance of antigen; persistent stimulation from a lack of clearance of antigens is associated with chronic inflammation and fibrosis.

The immunopathology of sarcoidosis can be modeled in this experimental context (Fig. 67-2). Sites of granulomatous inflammation such as the lung contain activated T cells and mononuclear phagocytes that express the same proinflammatory cytokines and chemokines that have been shown experimentally to be critical in granuloma formation. Lung T cells are predominantly of the CD4 T helper, CD45R0 "memory" phenotype, express the activation markers, VLA-1 (very late activation antigen-1, CD49a) and HLA-DR molecules. Sarcoidosis alveolar macrophages (AMs) spontaneously produce TNF, interleukin-6 (IL-6), IL1α, IL15, osteopontin and the Th1 regulatory cytokines, IL-12 and IL18 as well as increased amounts of lysozyme, angiotensin-converting enzyme (ACE), and reactive oxygen species. Sarcoidosis AMs express increased density of the costimulatory molecules, CD80, CD86, and CD40, consistent with their enhanced antigen presenting capability. Sarcoidosis AMs also release increased amounts of transforming growth factor-β (TGF-β), fibronectin, insulinlike growth factor-1 (IGF-1), and laminin that are important in fibroblast recruitment and replication. TNF is considered to be a major effector cytokine of granuloma formation in sarcoidosis (and therapeutic target) as enhanced release of TNF by BAL cells, is associated with persistent disease.

Studies of T-cell receptor (TCR) gene expression provide direct evidence that sarcoidosis is an antigen-driven disorder. Oligoclonal expansions of T cells expressing specific Vβ- or Vα-specific TCR gene segments have been found in the lung (BAL T cells), skin (Kveim biopsy sites), and blood. The best studied example involves the remarkable expansion

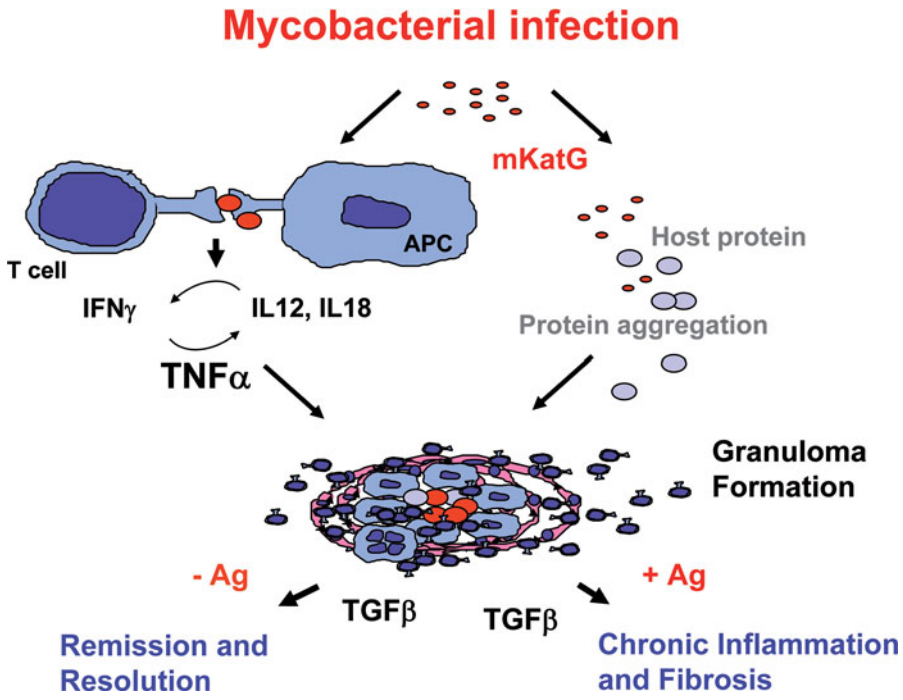


Figure 67-2 Hypothetical model of the pathogenesis of sarcoidosis. Mycobacterial proteins such as mKatG from an occult mycobacterial infection induce antigen-driven granulomatous inflammation orchestrated by Th1 cytokines, IFNγ, and IL-2. Macrophages and dendritic cells (antigen presenting cells, APC), activated directly by the microbial derived components, produce the Th1-promoting cytokines IL12 and IL18. Both APCs and T cells produce enhanced amounts of TNFα and other cytokines and chemokines that orchestrate the complex process of granuloma formation surrounding poorly soluble aggregates of microbial and host proteins. Removal of the inciting antigens in association with the immunosuppressive effects of TGFβ results in granuloma regression and disease remission. Failure to remove the microbial antigens or possibly the induction of autoimmunity, results in persistent inflammation, tissue injury, and resultant fibrosis mediated in part by the profibrotic effects of TGFβ.

of Vα2.3 (AV2S3)+ BAL T cells from HLA-DR17(3) Scandinavian patients with sarcoidosis. Together, these studies provide evidence that oligoclonal T-cell expansions in sarcoidosis are driven by conventional antigens. The specific antigens driving these clonally expanded T cell populations remain unknown.

Th1 Immunity

There are compelling data that sarcoidosis is characterized by dominant Th1 cytokine production at sites of inflammation. Multiple studies confirm that pulmonary sarcoidosis is associated with enhanced expression of Th1 associated IFNγ, IL12, and IL18 in the lung but low or undetectable levels of IL4 or IL5. Characteristic of a Th1 response, most sarcoidosis BAL T cells express a functional, high affinity IL12 receptor and the chemokine receptors CXCR3 and CCR5. This dominant Th1 polarization is characteristic of sarcoidosis at time of diagnosis and in some patients after years of known disease. There are no data on cytokine profiles in fibrotic sarcoidosis to know whether this Th1 polarization persists or whether there is a later evolution to a more profibrotic Th2 profile in chronic, fibrotic disease, a possibility supported by findings of increased IL13 expression in some patients with sarcoidosis. The role of humoral immunity in sarcoidosis pathogenesis is uncertain. Older studies indicate that acute sarcoidosis is associated with circulating immune complexes in almost 100 percent of patients. Whether immune complexes and humoral immunity play a role in disease remission remains speculative.

CLINICAL FEATURES

Classification

The clinical manifestations and course of sarcoidosis vary greatly (see Table 67-1). Although any organ of the body can be affected, the lungs or intrathoracic lymph nodes are involved in more than 90 percent of patients with sarcoidosis. Patients may manifest with no symptoms or develop acute, subacute, or indolent manifestations. Systemic constitutional symptoms such as fever, fatigue, malaise, and weight loss are seen in over 20 percent of patients and may be disabling. One classification scheme with prognostic information categorizes patients based on their initial manifestations as follows: asymptomatic, acute sarcoidosis with or without erythema nodosum, intermediate sarcoidosis with symptoms or signs of pulmonary disease for less than

Table 67-2

Rare Manifestations of Sarcoidosis Based on Organ Systems

Organ System	Rare Clinical Features
Pulmonary	Pulmonary vasculitis
	Mycetomas
	Cavitating nodules
	Lobar atelectasis
	Tracheal, bronchial stenosis
	Superior vena cavae syndrome
	Pleural disease
	Pneumothorax
Upper airway	Saddle nose deformity
	Respiratory failure from upper airway obstruction
	Sleep apnea
Oropharynx	Tonsillar sarcoidosis
	Pharyngeal sarcoidosis
	Periodontal disease
	Tongue mass
Skin	Subcutaneous sarcoidosis
	Ichthyosis
	Alopecia
	Scar granulomas
Ocular	Optic neuritis
	Retinal vasculitis
	Granulomatous orbital inflammation
Hepatic	Massive hepatomegaly
	Jaundice with pruritus
	Cirrhosis with portal hypertension
	Massive splenomegaly
Gastrointestinal	Pancreatic mass
	Gastric involvement
	Small or large intestine involvement
	Appendicitis
Nervous system	Optic chiasmal involvement
	Aseptic meningitis
	Cerebritis (white matter involvement)
	Cerebral vascular occlusion
	Encephalitis
	Hypothalamic/pituitary involvement
	Corpus callosum involvement
	Hydrocephalus
	Horner's syndrome, Argyll Robertson or Adie's pupil
	Cerebellar involvement
	Pseudotumor cerebrei
	Brain stem involvement
	Transverse myelitis, intraspinal mass
	Cauda equina or spinal root involvement
	Mononeuritis multiplex
	Peripheral neuropathies
	Small fiber neuropathy (common?)
Cardiac/vascular	Valvular disease
	Pericardial disease
	Ventricular or atrial mass
	Sudden death (not rare?)
Joints/ musculoskeletal	Polymyositis
	Bone cysts—Long bones, skull, vertebrae
Hematologic	Hypogammaglobulinemia
	Lymphedema
	Idiopathic thrombocytopenic purpura (ITP)
Endocrine/ exocrine gland	Heerfordt's syndrome
	Hypopituitarism, diabetes insipidus
	Thyroid mass, thyroiditis
	Parotid mass
	Lacrimal gland, dacryoadenitis
	Sicca syndrome
Renal/ genitourinary	Renal failure
	Uterine mass
	Ovarian involvement
	Menometrorrhagia
	Testicular mass
	Epididymitis
	Intermittent azoospermia

Source: Adapted with permission from Moller DR: Rare manifestations of sarcoidosis, in Drent M, Costabel U (eds), Sarcoidosis. Eur Respir Monog *32: 233–250, 2005.*

2 years, chronic pulmonary sarcoidosis of more than 2 years, and dominant extrapulmonary sarcoidosis. Two years represent an arbitrary but useful reference point for distinguishing patients who usually, but not always, have long-term disease.

Rare manifestations of sarcoidosis include unusual patterns of organ involvement, the result of granulomatous inflammation developing in unusual locations for sarcoidosis, or when sarcoidosis is associated with a second disorder (Table 67-2). In general, rarer manifestations reflect the known pathophysiology and clinical behavior of more common organ involvement.

Asymptomatic Sarcoidosis

Up to two-thirds of patients are asymptomatic but have sarcoidosis diagnosed after an incidental radiographic finding of bilateral hilar adenopathy. Occasionally, interstitial

infiltrates are seen in association with intrathoracic adenopathy in asymptomatic patients, most commonly in whites.

Acute Sarcoidosis with or without Erythema Nodosum

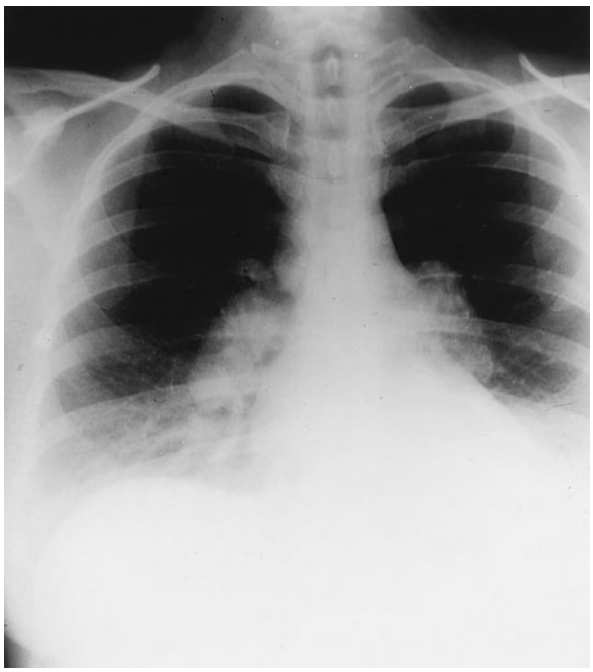
Sarcoidosis may manifest with the acute onset of erythema nodosum associated with bilateral hilar adenopathy, fevers, polyarthritis, and often uveitis, known as Löfgren syndrome. Erythema nodosum is characterized by tender reddish nodules several centimeters in diameter, usually located on the lower extremities; histologic examination shows panniculitis, not granulomas. The polyarthritis is often severe and incapacitating, typically involving the ankles, feet, knees, and occasionally, wrists, and elbows. Approximately 10 percent of patients with this syndrome have a normal chest radiograph. Löfgren syndrome is more common in European and white populations, but found in less than 5 percent of blacks with sarcoidosis. Some patients manifest acute arthritis, bilateral hilar lymphadenopathy, and constitutional symptoms without erythema nodosum. In either case, the prognosis is excellent for remission in 70 to 80 percent of patients. Resolution of symptoms usually occurs within weeks to several months.

Pulmonary Sarcoidosis

Respiratory symptoms occur in 40 to 60 percent of patients. The most common symptoms are cough and shortness of breath, usually of a progressive, insidious nature. The cough is usually nonproductive and may be severe. Dyspnea is typically worse with exertion. Sputum production and hemoptysis are frequent in patients with fibrocystic sarcoidosis that is often associated with bronchiectasis. Ill-defined chest pain is a frequent complaint, possibly caused by nerve irritation from inflammation, scarring, or lymph node enlargement in the chest. Chest tightness and wheezing are common with endobronchial disease or fibrocystic changes. These symptoms are usually poorly responsive to bronchodilators, except in those with reversible airway hyperreactivity. Segmental atelectasis and bronchial or tracheal stenosis are rare. Physical findings are infrequent, with lung crackles heard in less than 20 percent of patients; clubbing is rare.

Chest Imaging

The chest radiograph is abnormal in more than 90 percent of known cases and carries prognostic information. By international convention, the chest radiograph is divided into stages or types. A normal chest radiograph, or stage 0, is found in 5 to 10 percent of patients with sarcoidosis, often those with extrapulmonary manifestations. A stage I chest radiograph is characterized by hilar adenopathy without evidence of interstitial infiltrates and is found in approximately 40 percent of patients. Often, hilar adenopathy has a discrete, symmetric "potato node" appearance, and is accompanied by right paratracheal adenopathy. A stage II chest radiograph is characterized by bilateral hilar adenopathy and pulmonary infiltrates and is seen initially in 30 to 50 percent of patients (Fig. 67-3 *A*). Commonly, the infiltrates demonstrate fine linear markings



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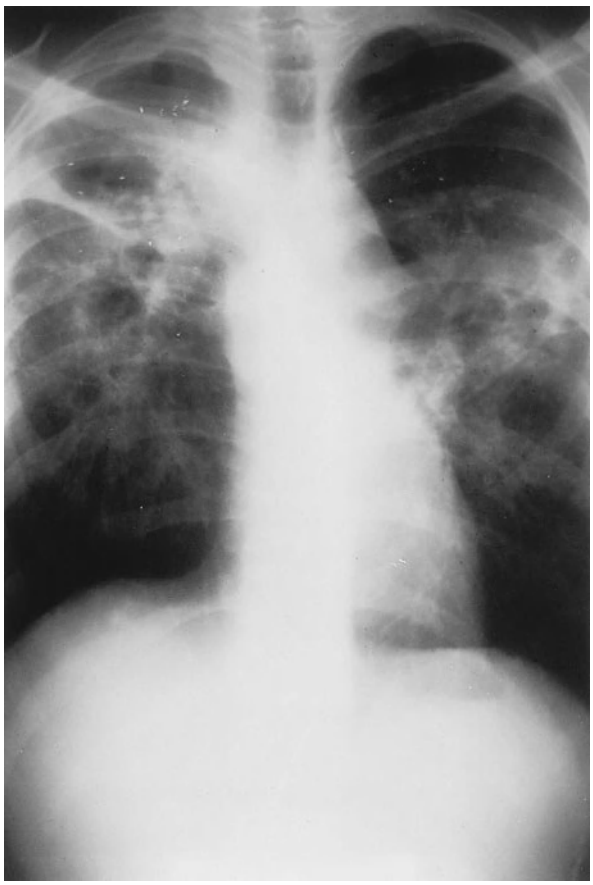


B

Figure 67-3 Chest radiographs of pulmonary sarcoidosis. *A*. Stage II sarcoidosis pattern with prominent, discrete "standaway" hilar nodes, right paratracheal adenopathy, and fine reticulonodular infiltrates. *B*. Fibrocystic sarcoidosis with extensive scarring, bullous and cystic changes, hilar retraction, and parenchymal infiltrates.

and small reticulonodules, particularly in mid- and upper lung zones. Occasionally, the infiltrates consist of discrete nodules or areas of fluffy "alveolar" consolidation that can mimic eosinophilic pneumonia, tumor, Wegener's granulomatosis, or infection. A miliary pattern can also be seen in sarcoidosis that resembles miliary tuberculosis, hypersensitivity pneumonitis, chronic beryllium disease, or lymphangitic carcinomatosis. Calcification of hilar lymph nodes is uncommon, but can occur with long-standing disease. When interstitial infiltrates are seen without evidence of hilar adenopathy, the chest radiograph is designated as stage III and is seen in approximately 15 percent of patients. Patients with extensive fibrocystic changes and scarring on chest radiograph are often grouped separately (stage IV) because of their poor prognosis. Characteristic features include cephalad hilar retraction, volume loss, coarse fibrous strands, small and large bullae, cystic changes, and honeycombing (Fig. 67-3 *B*). Unusual radiographic signs of sarcoidosis include pneumothorax, mycetoma, isolated nodule or mass, lobar atelectasis, or pleural effusions.

Chest computed tomography (CT) demonstrates that infiltrates tend to be central, following bronchovascular structures, but may also reveal ground-glass infiltrates or honeycombing. CT of the chest is often useful in the evaluation of patients with suspected sarcoidosis and to help plan bronchoscopic biopsy of enlarged lymph nodes, define unusual radiographic features, fibrocystic disease or bronchiectasis.

Pulmonary Function Tests

Pulmonary function may be normal even when the chest radiograph demonstrates pulmonary infiltrates. However, restrictive impairment with reduction in lung volumes, forced vital capacity (FVC) and forced expiratory volume in 1 sec (FEV_1), is common, particularly when pulmonary infiltrates are present on chest radiograph. Reduction in diffusing capacity can be seen in association with restrictive impairment or as an isolated deficit. Obstructive impairment is as common as restrictive impairment, particularly in advanced fibrocystic disease or endobronchial disease. A subgroup of patients have bronchial hyperresponsiveness and airway obstruction that may respond to bronchodilators. Resting hypoxemia and exercise O_2 desaturation are typical when there is severe obstructive or restrictive impairment. CO_2 retention is unusual except in advanced pulmonary disease.

Pulmonary Hypertension

Findings of pulmonary hypertension or cor pulmonale are seen in 1 to 4 percent of patients, usually from advanced fibrotic lung disease. Rarely, a granulomatous pulmonary vasculitis is seen that is not explained by the degree of interstitial lung disease.

Necrotizing Sarcoid Granulomatosis

This disorder is characterized by large, confluent, noncaseating granulomas involving both pulmonary arteries and veins but without systemic vasculitis, and is often considered a variant of pulmonary sarcoidosis. Patients may be asymptomatic or have cough, dyspnea, fever, chest pain, or constitutional symptoms. Chest radiographs typically demonstrate multiple, usually noncavitating, nodules. Pleural disease with pleurisy or pleural effusions occurs in the majority of patients and may be a clue to the diagnosis. Most patients have spontaneous improvement or a rapid response to corticosteroid therapy.

Extrapulmonary Sarcoidosis

Many patients have manifestations of granulomatous inflammation in one or more organ systems either in addition to pulmonary involvement or without evidence of pulmonary disease (see Table 67-1). More common manifestations are discussed below.

Sarcoidosis of the Upper Respiratory Tract and Oral Cavity

Sarcoidosis of the upper respiratory tract (SURT) occurs in 5 to 10 percent of patients, usually involving the nasal sinuses or laryngeal structures. Symptoms of nasal congestion, sinusitis, and intermittent epistaxis are often chronic, unresponsive to decongestants or inhaled steroids. Chronic disease or surgical intervention may result in destruction of the nasal septum and a "saddle nose" deformity. Laryngeal sarcoidosis may manifest with severe hoarseness, stridor, or acute respiratory failure secondary to upper airway obstruction. Frequently, laryngeal sarcoidosis is associated with chronic skin lesions, lupus pernio, or sinus disease. Oral and pharyngeal sarcoidosis is rare, but may manifest with macroglossia, tongue mass, or palatal mass with cartilaginous or bone destruction.

Ocular Sarcoidosis

Ocular involvement is detected in approximately 20 to 30 percent of patients, more frequently in black populations. Uveitis is the most common manifestation and is often associated with bilateral hilar adenopathy. The uveitis is more commonly anterior, and may be unilateral or bilateral, with either granulomatous or nongranulomatous features. Granulomatous conjunctivitis is less common. Optic neuritis, or severe chorioretinitis, may present dramatically with blindness.

Cutaneous Sarcoidosis

Chronic skin sarcoidosis is seen in approximately 25 percent of patients, usually manifesting as plaques or subcutaneous nodules and is more common and severe in blacks. Typically, the plaques are located around the hairline, eyelids, ears, nose, and extensor surfaces of the arms and legs. Lupus pernio is a disfiguring form of cutaneous sarcoidosis of the face, with violaceous plaques and nodules covering the nose, nasal alae, malar areas, and areas around the eyes.

Hepatic Sarcoidosis

Liver biopsies show granulomatous inflammation in over 50 percent of patients, but clinical manifestations are much less frequent. Active hepatic inflammation may be associated with fever, tender hepatomegaly, or pruritus that may mimic

primary biliary cirrhosis except that antimitochondrial antibodies are absent. Characteristically, the serum alkaline phosphatase and γ-glutamyltransferase are elevated proportionately higher than the transaminases or bilirubin, although all patterns can be seen. Elevated serum liver function frequently reverts to normal spontaneously or after treatment with corticosteroids. Progressive cirrhosis occurs in a subset of patients if not treated.

Gastrointestinal Sarcoidosis

Sarcoidosis involvement of the gastrointestinal tract is rare. Occasionally, direct esophageal involvement may cause dysphagia, but more commonly this symptom may be caused by extensive mediastinal lymphadenopathy that impinges esophageal motility. Gastric sarcoidosis may manifest as dyspepsia, abdominal pain, or gastric nodule. Although autopsy studies show scattered granulomas in the gut, clinically symptomatic intestinal sarcoidosis is rare.

Abdominal Sarcoidosis

A variant of sarcoidosis, often called abdominal sarcoidosis, manifests with liver, spleen, and often bone marrow involvement with hypercalcemia or abdominal lymphadenopathy. Constitutional symptoms are frequent with fevers and fatigue. This "triad" pattern may be seen with or without pulmonary involvement; in the latter instance, intra-abdominal malignancy must be excluded.

Cardiac Sarcoidosis

Although myocardial sarcoidosis is clinically apparent in less than 5 to 10 percent of cases in the United States, autopsy studies suggest the prevalence may be greater than 20 percent in the United States and greater than 50 percent in Japan. Arrhythmias, heart block, or sudden death may be the initial manifestation due to involvement of the conduction system. Myocardial inflammation can lead to dilated cardiomyopathy and congestive heart failure, local akinesia, or aneurysms. Myocardial mass, valvular dysfunction from papillary muscle dysfunction, pericarditis, and myocardial ischemia are rarer manifestations.

Neurosarcoidosis

Neurologic manifestations occur in approximately 5 to 10 percent of patients with sarcoidosis. The most common manifestation are cranial neuropathies with bilateral or unilateral seventh nerve (Bell's) palsy most common. Often the palsies resolve spontaneously or with corticosteroids, but may recur years later. Optic neuritis may result in sudden blindness. Spinal cord involvement is rare but can cause paraparesis, hemiparesis, back and leg pains either from a transverse myelitis, or tumorlike granulomatous involvement. Peripheral neuropathies account for about 15 percent of cases of neurosarcoidosis, typically presenting as mononeuritis multiplex or a predominant sensory deficit. Small fiber neuropathy is found in many patients with diffuse musculoskeletal pain and fatigue.

Hematologic Sarcoidosis

Persistent, bulky, painful, or disfiguring adenopathy is seen in less than 5 percent of patients, most commonly involving the cervical, supraclavicular, axillary, or epitrochlear lymph nodes. Splenomegaly occurs in less than 10 percent of patients, and may be massive and associated with hypersplenism. Peripheral blood lymphopenia is common in sarcoidosis; probably more often as a result of altered trafficking of lymphocytes than splenic trapping. Granulomas in the bone marrow are found in about 20 percent of patients who come to autopsy but usually do not cause symptoms. A known feature of sarcoidosis is the impaired cutaneous response to common antigens that elicit delayed-type hypersensitivity reactions, seen in 30 to 70 percent of patients. The mechanism is unknown.

Joint and Musculoskeletal Sarcoidosis

Arthralgias are a frequent complaint in sarcoidosis. A short-lived polyarthritis is typical of acute sarcoidosis, usually associated with erythema nodosum. Chronic joint disease is found in less than 5 percent of patients. Joint cartilaginous erosion is rare, but "punched out" bony lesions with cystic changes and loss of bony trabeculae may be seen in subchondral locations. Cystic lesions of the long bones, pelvis, sternum, skull, and vertebrae are uncommon. Symptomatic myopathy with weakness and tenderness is uncommon. Rarely, a polymyositis with profound weakness associated with marked elevation of serum creatine phosphokinase and aldolase occurs in sarcoidosis.

Exocrine Gland Sarcoidosis

Granulomatous inflammation of salivary, parotid, and lacrimal glands results in enlarged, tender glands, and/or sicca syndrome with dry mouth and dry eyes in less than 5 percent of patients with sarcoidosis. The association of fever, parotid enlargement, facial palsy, and uveitis is known as uveoparotid fever, or Heerfordt syndrome, and is usually accompanied by bilateral hilar adenopathy.

Endocrine Sarcoidosis

Abnormal calcium metabolism is found in sarcoidosis; hypercalciuria is more frequent than hypercalcemia. Evidence supports the concept that these abnormalities are due primarily to increased conversion of vitamin D metabolites to active 1,25(OH)2 vitamin D by tissue macrophages and epithelioid cells at sites of granulomatous inflammation. Hypothalamic/pituitary insufficiency may be a manifestation of neurosarcoidosis.

Renal Sarcoidosis

Kidney stones are the most frequent manifestation of renal sarcoidosis, usually related to abnormal calcium metabolism. Renal failure due to nephrocalcinosis may result from chronic, often asymptomatic hypercalcemia or hypercalciuria. Granulomatous involvement of the kidneys occurs but is rarely the cause of significant renal dysfunction.

Genitourinary Sarcoidosis

Sarcoidosis of the reproductive system has been estimated to occur in less than 1 percent of clinically diagnosed cases and in 5 percent of autopsy cases. Genitourinary manifestations of sarcoidosis in men include testicular masses and acute epididymis-orchiditis. In women, sarcoidosis may manifest with uterine or ovarian involvement that may cause dysmenorrhea or mimic malignancy or fibroids.

Psychosocial Manifestations

A Dutch study found the prevalence of depression was 4 percent in asymptomatic patients and 30 percent in symptomatic patients with sarcoidosis. The prevalence of depression was found to be 60 percent in a US study of both white and black patients with sarcoidosis. In this latter study, depression was associated with the female sex, lower socioeconomic status, poor access to care, and increased disease severity, but not race. The prevalence of pain in sarcoidosis is unclear, but clinical experience suggests it is common and multifactorial with frequent reports of arthralgias, myalgias, headache, chest pain, and fatigue. A subset of patients meets diagnostic criteria for fibromyalgia.

Associated Conditions

Sarcoidosis and Pregnancy

There is usually little long-term effect on the course of sarcoidosis from pregnancy. Spontaneous improvement in chronic sarcoidosis is seen in some patients during pregnancy, although exacerbations often follow several months after delivery. The reasons for the temporary clinical improvement are not known but might be related to suppressed Th1 immunity during pregnancy.

Altered Th1 Immunity

Sarcoidosis is associated with several clinically disparate situations associated with altered, enhanced Th1 immunity. The clearest example involves the administration of Th1-promoting therapeutics such as IFNα, IFNγ, IL2, and IFNβ that may be associated with initiation or recrudescence of sarcoidosis.

Common Variable Immunodeficiency

There is a well-established association of sarcoidosis with common variable immunodeficiency (CVID). Since CVID occurs at any age, a high index of suspicion must be maintained, particularly in sarcoidosis patients who have recurrent infections or in any child with sarcoidosis given the low frequency of sarcoidosis in this age group.

Human Immunodeficiency Virus

Sarcoidosis may develop in HIV-infected patients with immune reconstitution following initiation of highly active antiretroviral therapy, perhaps from reconstituted Th1 immunity. Granulomatous inflammation of the lungs or skin is most often reported.

Autoimmune Disorders

Sarcoidosis is associated with a variety of disorders of the immune system, such as Crohn's disease, ulcerative colitis, primary biliary cirrhosis, scleroderma, Sjögren's syndrome, autoimmune hemolytic anemia, and autoimmune endocrinopathies (Table 67-3). Given the rarity of some of these disorders, it is reasonable to postulate that these associations are the result of a common immune disturbance, with altered Th1 immunity that may predispose to both disorders.

Cancer

Noncaseating granulomas may be seen in or nearby 3 to 10 percent of tumors and in approximately 4 percent of regional draining lymph nodes. Much less commonly, multisystem granulomas consistent with systemic sarcoidosis develop in patients with a recent or past diagnosis of cancer or following chemotherapy treatment. Often the diagnosis is established by biopsy of enlarged lymph nodes or lung where the presurgical diagnosis is recurrent malignancy. There is usually little functional lung impairment from pulmonary sarcoidosis in these instances, and treatment is often unnecessary with eventual remission. A possible link involves dysregulated Th1/Th2 immunity, a premise supported by several cases of sarcoidosis developing in patients with 5q-myelodysplasia that results in deletion of several Th2 genes (IL4, IL13, CSF2).

DIAGNOSTIC APPROACH

A diagnosis of sarcoidosis is established on the basis of a compatible clinical picture, evidence of noncaseating granulomas on biopsy, and exclusion of other granulomatous disorders of known cause. Although histologic evidence is needed from only a single site, clinical involvement of more than one system helps exclude local granulomatous reactions to foreign bodies, infections, or tumor. In general, the easiest accessible biopsy site is used to confirm a diagnosis of sarcoidosis. Biopsy of a skin or conjunctival nodule, enlarged superficial lymph node, or lacrimal gland may help to establish a diagnosis. Noncaseating granulomas on a liver or bone marrow biopsy are nonspecific and support a diagnosis only when competing diagnoses such as infection, drug reaction, or malignancy are excluded. In the absence of clinical involvement of an easily accessible site, biopsy by fiberoptic bronchoscopy is usually performed because of its high yield and relative safety. The diagnostic yield from transbronchial biopsy (TBB) ranges from 40 to 90 percent if at least four biopsies are taken, and is higher when there are pulmonary infiltrates on the chest radiograph or chest CT scan. Sampling intrathoracic lymph nodes by transbronchoscopic needle aspiration biopsy can increase the diagnostic yield when technically feasible, with greater than 90 percent sensitivity in combination with TBB for stage I or II disease. Several studies find that bronchial mucosal biopsies show noncaseating granulomas in 40 to 60 percent of patients even in the absence of endobronchial nodules or

Table 67-3

Rare Associations of Sarcoidosis with Other Systemic and Organ-Specific Diseases

Organ System	Clinical Disorder
Pulmonary	Scleroderma
Oropharyngeal	Melkersson-Rosenthal syndrome
Skin	Pyoderma gangrenosum Scleroderma Porphyria cutanea tarda Vitiligo
Ocular	Idiopathic granulomatous orbital inflammation?
Abdominal	Primary sclerosing cholangitis Primary biliary cirrhosis Celiac disease Crohn's disease Ulcerative colitis
Neurologic	Progressive multifocal leukoencephalopathy
Joint/ musculoskeletal	Rheumatoid arthritis Lupus erythematosis Scleroderma Mixed connective tissue disease and overlap syndromes Marfan syndrome
Hematologic	Common variable immunodeficiency HIV with immune reconstitution Autoimmune hemolytic anemia Thrombocytopenia
Exocrine gland	Sjögren's syndrome Hashimoto thyroiditis
Renal	Membranoproliferative glomerulitis Amyloidosis
Systemic diseases	Autoimmune diseases Vasculitis Granulomatous vasculitis overlap with sarcoidosis
Malignancy	Lymphoma GU cancers—renal, testicular, bladder, ovarian, prostate Myeloproliferative disorders Thyroid cancer

Source: Adapted with permission from Moller DR: Rare manifestations of sarcoidosis, in Drent M, Costabel U (eds), Sarcoidosis. Eur Respir Monogr. *32:233–250, 2005.*

cobblestoning. Transbronchial lung biopsy in advanced fibrocystic sarcoidosis has a low yield, owing to extensive fibrotic changes. Some studies suggest an elevated BAL T cell CD4:CD8 ratio greater than 3.5 to 4.0 supports a diagnosis of sarcoidosis with a test specificity of approximately 95 percent and sensitivity of greater than 50 percent. Other studies find wide variability in this parameter with overlap of infectious, inflammatory, and malignant diseases.

When bronchoscopy is nondiagnostic, mediastinoscopy is generally recommended for patients with mediastinal lymphadenopathy, particularly in cases in which lymphoma, metastatic disease, or infection must be excluded. In patients with pulmonary infiltrates, a video-assisted thoracoscopic surgical lung biopsy or open lung biopsy establishes a diagnosis of pulmonary sarcoidosis with greater than 90 percent diagnostic yield.

Most experts agree that a confirmatory biopsy in Löfgren syndrome is usually not needed. Bronchoscopy is recommended prior to initiation of corticosteroid therapy in patients with Löfgren syndrome in areas where histoplasmosis is endemic or when mycobacterial or fungal infection cannot be reasonably excluded. There is controversy over the need for tissue confirmation in persons manifesting with isolated asymptomatic bilateral hilar adenopathy. Some authorities recommend biopsy for all cases of bilateral hilar adenopathy to exclude malignancy, while others cite evidence from studies that suggest these manifestations almost always are due to sarcoidosis if not accompanied by symptoms or abnormal physical findings.

A diagnosis of neurosarcoidosis is usually confirmed by biopsy of a non-CNS site. Rarely, brain biopsy is needed to exclude infectious or malignant disease. Similarly, a diagnosis of cardiac sarcoidosis is usually established by a noncardiac biopsy confirming systemic sarcoidosis along with consistent myocardial imaging studies or rhythm disturbances (Figs. 67-4 and 67-5). Endomyocardial biopsy is positive in less than 10 to 25 percent of cardiac sarcoidosis owing to sampling inefficiencies and the infrequency of right ventricular involvement.

For organs that are rarely involved in sarcoidosis or rare manifestations in commonly affected organs, directed biopsy of the involved tissue is often recommended to exclude alternative causes, even when there is documentation of a prior biopsy that confirmed an original diagnosis of sarcoidosis. For organs that are difficult to biopsy, imaging techniques such as gallium 67 scans or more recently, ^{18}F-fluorodeoxyglucose-positron emission tomography (FDG-PET) scanning may help to define sites of clinically occult inflammation that could provide an alternative biopsy approach. One case series suggests that a gallium 67 scan demonstrating the combination of uptake in the bilateral hilar and right paratracheal node region (lambda sign) as well as the parotid, salivary, and lacrimal gland region (panda sign) is pathognomic for sarcoidosis. Other patterns are not specific for sarcoidosis. PET scanning is replacing gallium scanning as the preferred method to detect active inflammatory sites as the test has much less radiation exposure and greater resolution, although has a similar lack of specificity.

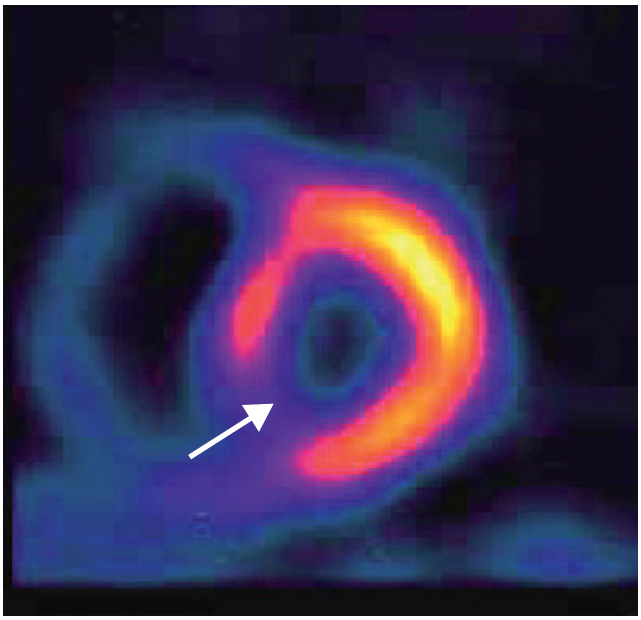


Figure 67-4 Images of cardiac sarcoidosis. Single-photon emission computed tomography (SPECT) image of a technetium ^{99m}Tc sestamibi myocardial scan in a patient with corticosteroid responsive cardiomyopathy secondary to systemic sarcoidosis. A fixed defect in myocardial uptake of technetium ^{99m}Tc sestamibi is seen in the myocardial septum (arrow).

Laboratory tests are generally not helpful in confirming a diagnosis of sarcoidosis but may assist in establishing an alternative diagnosis. Serum angiotensin-converting enzyme (SACE) levels are elevated in 30 to 80 percent of patients with clinically active disease, probably originating from activated epithelioid cells and macrophages at sites of inflammation. Although SACE was originally proffered as a diagnostic marker, elevated levels are seen in infectious granulomatous diseases, lymphoma, hepatitis, diabetes, and thyroid disease among others; thus, SACE is not recommended as a diagnostic tool.

CLINICAL ASSESSMENT

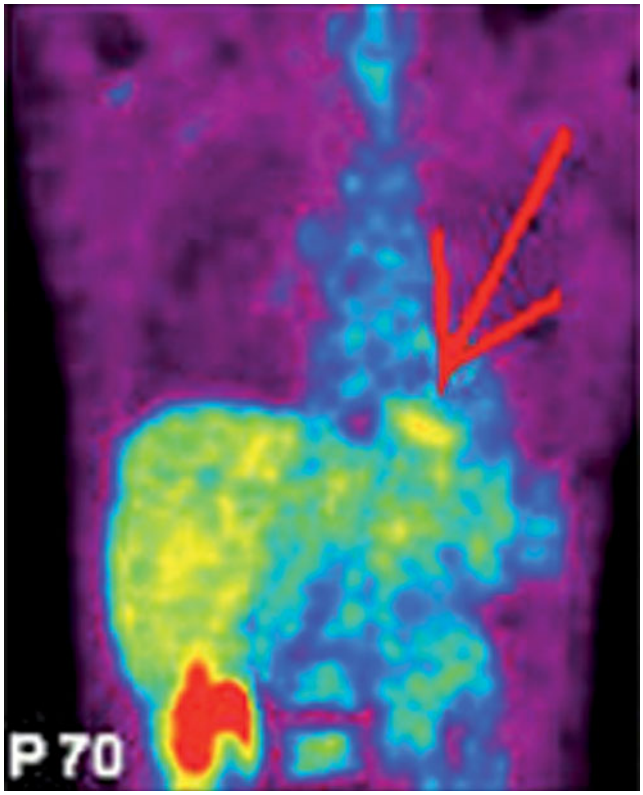
Once a diagnosis is established or suspected, an initial evaluation should consist of tests to evaluate the presence and extent of pulmonary involvement and screen for extrathoracic disease (Table 67-4).

Specialized testing is indicated when symptoms or signs suggest extrapulmonary involvement. Guidelines for when and how to screen for potential cardiac involvement remain uncertain. Given the risk for sudden death and the potential for underdiagnosis, screening for cardiac sarcoidosis is recommended whenever symptoms such palpitations, unexplained chest pain, or dyspnea are reported. Most authorities screen with echocardiography to assess cardiac function and Holter monitoring to exclude serious arrhythmias. Thallium or sestamibi myocardial scanning is more sensitive than echocardiography for detecting patchy defects consistent with myocardial inflammation or fibrosis. Cardiac MR with gadolinium enhancement or cardiac PET scanning offers greater resolution if uncertainty persists, although experience remains limited with the latter technique. Electrophysiological testing may be indicated to exclude arrhythmias undetected by routine studies and assess indications for prophylactic cardiac pacemaker or implantable defibrillator to reduce the risk of sudden death.

Evaluation for possible CNS and spinal sarcoidosis should include MRI with gadolinium enhancement, now considered the optimal test to detect characteristic inflammatory lesions. The distribution of inflammatory loci has a propensity for periventricular and leptomeningeal areas, although the images are nonspecific, and can be produced by infectious, malignant, or occasionally demyelinating disease. A normal scan does not exclude neurosarcoidosis, particularly for cranial neuropathies or in the presence of corticosteroid therapy. Examination of the cerebrospinal fluid is less often performed today, but may be useful by demonstrating characteristic lymphocytic pleocytosis and/or elevated protein levels. In suspected cases of peripheral neuropathy or myopathy, EMG or nerve conduction studies or rarely, tissue biopsy, may help to establish a link to sarcoidosis.

CLINICAL COURSE AND PROGNOSIS

A clinical framework can be constructed to assist in decisions regarding monitoring and planning treatment strategies. First, organ involvement usually defines itself early in the disease. For example, only 23 percent of patients in the ACCESS study were found to have one or more new organ systems involved with sarcoidosis during a 2-year follow-up evaluation; the presence of extrapulmonary involvement at presentation was a risk factor for new organ development. Second, patients who undergo remission usually do so within the first 2 to 3 years. Clinical experience suggests sarcoidosis rarely recurs after a prolonged period of remission, with exceptions most often involving neurological or ocular manifestations. Third, patients with chronic sarcoidosis comprise 30 to 50 percent of all known sarcoidosis cases, and generally have progressive, unremitting organ impairment. In these patients, the rate of progression varies from individual to individual, as does their response to treatment. A waxing-waning clinical course is uncommon except for a subset of patients with neurological or ocular manifestations or occasionally recurrent erythema nodosum. Fourth, prognosis in sarcoidosis is strongly influenced by the initial manifestations of disease. Patients with Löfgren syndrome have remission rates of 70 to 80 percent. An initial stage I chest radiograph is associated with a 60 to 90 percent remission rate. Patients manifesting with type II chest radiographs have a poorer outcome, with spontaneous remission occurring 40 to 70 percent of the time. A stage III chest radiograph is associated with remission in



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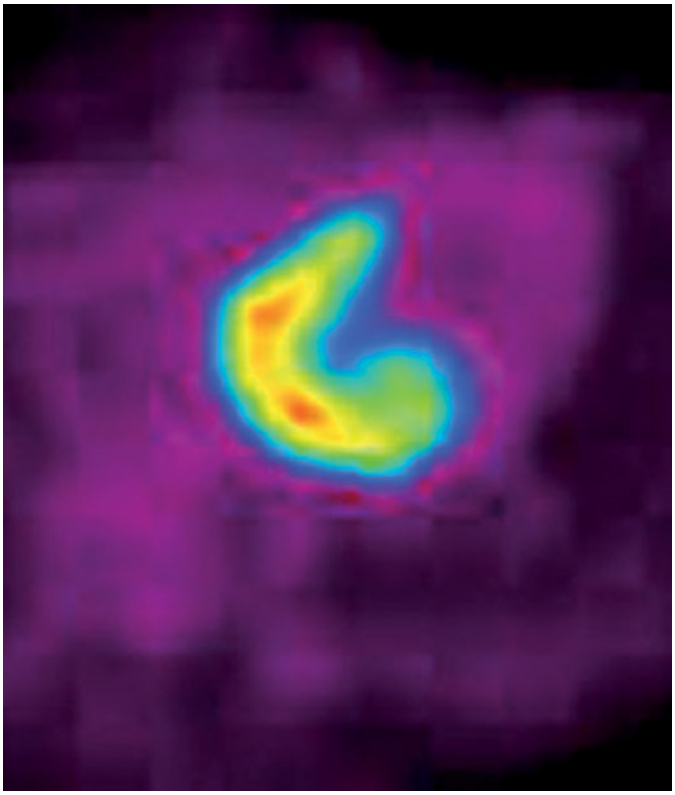

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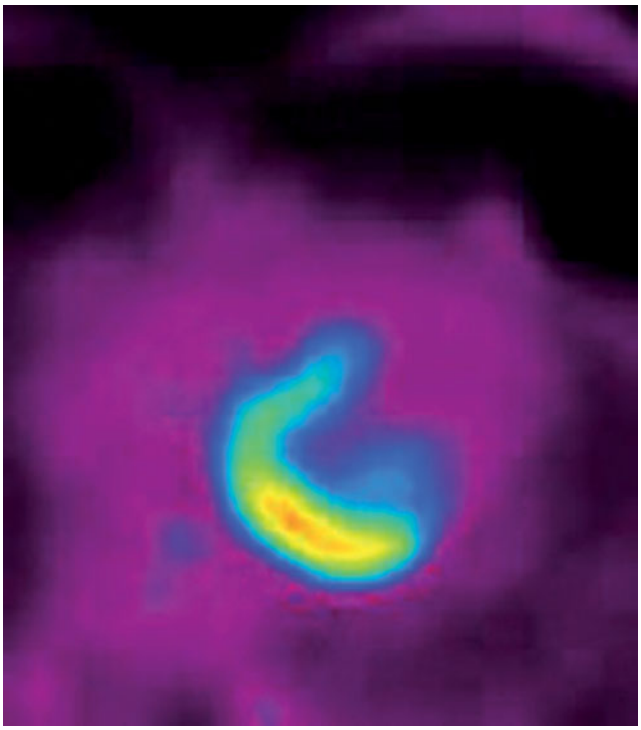

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Figure 67-5 *A,B.* ^{18}F-Fluorodeoxyglucose (FDG)-PET scanning shows ^{18}F-FDG uptake in the inferior myocardium (red arrow). *C*. ^{18}F-FDG uptake level is reduced by more than 50 percent after 1 month of corticosteroid therapy. *(Images courtesy of Jens Sorensen, MD of Uppsala University, Sweden.)*

only 10 to 20 percent of patients. Patients with extensive pulmonary fibrosis (stage IV) rarely undergo remission.

Currently, a consensus recommendation is that treatment decisions are best based on repeated clinical examinations and direct measurement of organ function and not on laboratory markers of disease "activity." SACE levels tend to correlate with the extent of granulomatous inflammation throughout the body and usually decrease in response to corticosteroids or with disease remission, but the test is highly variable and has no prognostic value. Similarly, BAL

Table 67-4

Recommended Tests for Clinical Evaluation of Systemic Sarcoidosis

All Patients	Organ-Specific Testing for Suspected Organ Involvement
Chest radiograph	Cardiac: Echocardiogram, Holter monitoring, thallium or sestamibi myocardial scan, cardiac MR, cardiac PET
Pulmonary function tests: Spirometry, diffusion capacity, lung volumes	Neurological: Brain or spine MRI with gadolinium enhancement, cerebrospinal fluid examination, nerve conduction studies
Ophthalmologic examination	Upper respiratory tract: Flow-volume loop, ENT evaluation
Complete metabolic panel	Endocrine: Pituitary function tests; thyroid function tests
Complete blood count with differential count	
Electrocardiogram	
Purified protein derivative (PPD) skin test	

parameters such the proportion of CD4 lymphocytosis or the CD4:CD8 ratio of BAL T cells have been inconsistent in predicting outcomes. Monitoring for at least 3 years following presumed "disease remission" is recommended; longer periods of observation are indicated for patients with serious pulmonary or extrapulmonary manifestations.

TREATMENT

Indications

Indications for treatment must take into account the overall excellent prognosis for most patients with sarcoidosis, particularly for patients with stage I disease, for whom systemic therapy is usually not required. Symptomatic or local therapy is recommended whenever possible. Löfgren syndrome is usually managed with bed rest and nonsteroidal anti-inflammatory drugs; corticosteroids are recommended when

Table 67-5

Indications for Treatment of Sarcoidosis

Threatened organ failure—severe ocular, cardiac, or neurological disease
Progressive or persistent pulmonary disease
Uveitis unresponsive to topical corticosteroids
Persistent hypercalcemia, renal or hepatic dysfunction
Palpable splenomegaly or hypersplenism
Severe myopathy
Disfiguring skin disease
Painful lymphadenopathy
Severe fatigue and weight loss

symptoms, particularly arthritis, are disabling and persistent. Most physicians agree that corticosteroid or other systemic therapy is indicated for the manifestations listed in Table 67-5. Typical dosing regimens and side effects for the drugs listed below are provided in Table 67-6.

Systemic Treatment

Corticosteroid Therapy

Corticosteroids remain the cornerstone of therapy for sarcoidosis. Although controversy exists regarding the overall effectiveness of corticosteroids in altering the long-term course of the disease, there is no disagreement that corticosteroids provide prompt symptomatic relief and reverse organ dysfunction in most patients with the degree of reversibility dependent on the extent of preexisting fibrosis. Case series and several but not all clinical trials support the view that corticosteroids favorably affect disease outcome in chronic pulmonary sarcoidosis. One large study by the British Thoracic Society found long-term improved lung function in patients with stage I or II pulmonary disease treated with daily corticosteroid therapy compared with a group treated intermittently with corticosteroids based on symptoms.

Optimal dosing of corticosteroid therapy has not been established by clinical trials. Most authorities suggest that initial treatment of pulmonary sarcoidosis usually does not require more than 20 to 40 mg per day of prednisone followed by a slow taper to a maintenance dose of 5 to 15 mg per day of prednisone. A qod regimen of prednisone in patients may be effective in some but not all patients. Treatment is usually continued for a minimum of 8 to 12 months, since premature attempts to taper off steroids are likely to result in relapse of disease. Inhaled steroids appear to have limited effectiveness in chronic pulmonary sarcoidosis and are not

Table 67-6

Therapies for Systemic Sarcoidosis

Drug	Typical Dose/Regimen	Major Adverse Effects
Corticosteroids	Prednisone 20–40 mg/d for 2 wk; decrease by 5 mg every 2 wk until 10–15 mg/d; maintain for 8–12 mo, then taper 2.5 mg/d every 2–4 wk; reinstitute for relapse	Weight gain, hypertension, hyperglycemia, osteoporosis, cataracts, psychosis
Antimalarial drugs		
Hydroxychloroquine	200 mg once or twice daily	Ocular toxicity (rare), gastrointestinal upset, rashes
Chloroquine	500 mg every other day for 6 mo followed by 6 mo drug holiday	Ocular toxicity, gastrointestinal upset
Anti-inflammatory drugs		
Minocycline, doxycycline	100 mg twice daily	Gastrointestinal upset, skin hyperpigmentation, headaches, dizziness, pseudotumor cerebri
Pentoxifylline	400 mg 3 or 4 times a day	Gastrointestinal upset, headaches
Thalidomide	100–200 mg once at bedtime	Teratogenicity, peripheral neuropathy, sedation
Immunosuppressive therapies		
Methotrexate	10–20 mg per week + folate 1 mg daily	Hepatic, pulmonary, bone marrow toxicity
Mycophenolate mofetil	1000–2000 mg per day	Bone marrow and hepatic toxicity, gastrointestinal upset, ?oncogenic potential
Azathioprine	100–200 mg per day	Bone marrow and hepatic toxicity, gastrointestinal upset, ?oncogenic potential
Antitumor necrosis factor agents	Infliximab, adalimumab; dosing varies	Hypersensitivity reaction, severe infection, reactivation TB, autoimmune phenomena, malignancy (rare)

recommended as sole therapy. Overall, recurrent progressive pulmonary disease occurs in 16 to 74 percent of patients as oral corticosteroids are tapered or discontinued.

Alternative Agents

Several classes of drugs have been reported to be beneficial in subgroups of patients with sarcoidosis (Table 67-6). None of these drugs has been proved effective by rigorous clinical trials.

Nonimmunosuppressive Drugs

Case series suggest hydroxychloroquine is effective in many patients with mucocutaneous sarcoidosis, hypercalcemia and occasionally, as a steroid-sparing agent in systemic sarcoidosis. Ocular toxicity is rare, and its overall safety profile provides a rationale for an early trial of this drug. Chloroquine may be efficacious in treating lupus pernio, SURT, or sinus disease, which is often recalcitrant to other therapies, although ocular toxicity has limited its use.

The tetracyclines, minocycline, and doxycycline, may be effective in a subgroup of patients with cutaneous sarcoidosis and occasionally as a steroid sparing drug in systemic disease. These antibiotics have mild anti-inflammatory effects, which probably account for their mechanism of action given that other antibiotics with similar antimicrobial activity have not been found effective in sarcoidosis.

Pentoxifylline is a phosphodiesterase inhibitor with anti-inflammatory effects that was found to be effective in early pulmonary sarcoidosis in one study. Other experiences have not been as favorable with responses in less than 10 percent of patients, generally those with mild pulmonary or systemic sarcoidosis. Melatonin was found to be beneficial in a small case series of patients with generally mild disease.

Thalidomide was found in one study to be beneficial in over 80 percent of patients with severe skin sarcoidosis (lupus pernio unresponsive to other therapies), but was not effective in pulmonary sarcoidosis. Given the drug's well-known teratogenicity and potential to cause peripheral neuropathy and sedation, the drug is recommended only in patients refractory to other treatments.

Immunosuppressive Drugs

Methotrexate is often the first immunosuppressive therapy used as an alternative therapy for refractory pulmonary or systemic sarcoidosis when corticosteroid and antimalarial therapies are ineffective or poorly tolerated. Studies suggest methotrexate is effective in 50 to 70 percent of patients, although responses may take longer than 6 months and low-dose corticosteroids may be needed. Hepatic, pulmonary, and renal toxicities limit the use of the drug. Clear advantages of methotrexate over low-dose corticosteroids in the routine management of sarcoidosis have not been established.

Other immunosuppressive agents, such as azathioprine or cyclophosphamide, have been found beneficial in a small series of patients with severe manifestations of sarcoidosis refractory to corticosteroids. More recently, mycophenolate mofetil has been used with anecdotal effectiveness for serious neurologic, ocular, pulmonary, and hepatic sarcoidosis. Several studies have shown that cyclosporine, a drug known to inhibit T-cell activation, is not effective in sarcoidosis, with the possible exception of a few patients with treatment resistant, severe neurosarcoidosis.

Anti-TNF Therapies

The scientific basis for the use of TNF inhibitors in sarcoidosis is firmly established based on the role of TNF in experimental models of granuloma formation. Preliminary reports from a recent multicenter study found infliximab to be effective in one of several primary end points (improved FVC after 24 weeks of therapy), although the effect was modest. Etanercept was not shown to be effective in a smaller clinical trial of pulmonary sarcoidosis. Anecdotal cases suggest adalimumab may be effective in some patients with sarcoidosis, although larger studies are lacking. Given the risk profiles of current immunosuppressive drugs, additional clinical trials of these agents are anticipated.

Special Circumstances

Fibrocystic Sarcoidosis

Advanced pulmonary sarcoidosis may be complicated by mycetomas, usually from *Aspergillus fumigatus* that colonize preexisting cystic spaces. The fungi rarely cause invasive disease, spontaneous resolution may be seen and the benefit of antifungal agents has not been established. Massive hemoptysis associated with mycetomas or bronchiectasis may be life-threatening, requiring therapeutic embolization of the appropriate bronchial or collateral artery for control. Surgery is usually not feasible because of the severe restrictive lung disease.

Pulmonary Hypertension

Moderate or severe pulmonary hypertension is an independent predictor of reduced survival in patients with advanced lung disease awaiting lung transplantation. A role for drugs used to treat primary pulmonary hypertension is under investigation.

Cardiac Sarcoidosis

Several large case series find prognosis in cardiac sarcoidosis, and response to treatment is related to the degree of cardiac dysfunction. Treatment of cardiac sarcoidosis consists of antiarrhythmic therapy, diuretics, and afterload-reducing agents for specific cardiac abnormalities. Although randomized trials are lacking, studies from Japan, Europe, and the United States consistently report that corticosteroids in moderate doses are associated with improved cardiac function and outcomes. Maintenance doses often range between prednisone 10 to 25 mg a day, although higher doses may be needed for intractable arrhythmias. Immunosuppressive drugs are frequently used as steroid-sparing agents since treatment often must be maintained for years. Automatic implantable cardioverter-defibrillators (ICDs) may prevent sudden death in patients with serious arrhythmias; guidelines for prophylactic placement of ICDs or pacemakers have not yet been established.

Neurosarcoidosis and Ocular Sarcoidosis

High doses of oral corticosteroids or high-dose pulse intravenous therapy are often indicated for serious ocular or CNS disease, such as optic neuritis or encephalitis followed by maintenance corticosteroid or immunosuppressive therapy. Anterior uveitis can usually be treated with topical ophthalmologic steroid drops.

Pregnancy

Corticosteroids are the only drugs recommended for use during pregnancy because of the potential of other steroid-sparing drugs to cause fetal toxicity or teratogenicity. In general, pregnancy has little effect on the long-term course of sarcoidosis. Sometimes, spontaneous abatement of chronic sarcoidosis occurs in pregnant patients, allowing a temporary reduction in steroid dosage. After pregnancy, however, an exacerbation often occurs, requiring a return to the original maintenance dose.

Quality of Life

There is increasing recognition of the need to treat depression and pain to improve quality of life in patients with these manifestations. The utility of nonpharmacologic treatments, such as exercise training or rehabilitation, merit investigation because of the impact of these problems in sarcoidosis patients.

Lung and Heart Transplantation

Successful lung, heart-lung, and heart transplantations have been performed in patients with advanced pulmonary sarcoidosis or cardiomyopathy. Although noncaseating granulomas have been found in some transplanted lungs or hearts, these findings do not appear to significantly affect outcome, although experience remains limited.

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68

Idiopathic Pulmonary Fibrosis

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Idiopathic pulmonary fibrosis (IPF) is a distinctive type of interstitial lung disease (ILD) of unknown cause that has come to be recognized by a unique compilation of clinical, radiographic and pathological abnormalities leading to progressive breathlessness and death in most instances. While there are many causes of ILD, IPF is one of the more common forms and certainly the most serious. IPF is characterized by an inexorable progression of interstitial fibrosis resulting in restrictive lung disease and worsening gas exchange leading to death from respiratory failure within 5 years of diagnosis in the majority of patients.

IPF typically comes to medical attention later in life, beginning in the sixth decade. IPF is rarely the cause of ILD in patients under the age of 40. The predominant presenting symptoms of IPF are exertional breathlessness and a dry, harassing cough. These are nonspecific complaints shared by a variety of pulmonary and cardiac diseases. In particular, exertional breathlessness is often attributed to advancing age by patients in their sixties and seventies, leading to delays in seeking medical evaluation. In addition, many patients are poorly conditioned and overweight and attribute their symptoms of breathlessness to these circumstances. In addition to the nonspecific clinical symptoms the nonspecific plain chest radiographic findings in IPF do not often trigger prompt medical evaluation. Fine peripheral linear opacities predominantly in the lower lung zones may be interpreted as chronic and nonspecific pulmonary fibrosis, which often does not elicit an alarming concern in primary care physicians reading a radiology report. Coupled with subtle clinical symptoms, the result is often a failure to refer for a pulmonary evaluation. The unknown etiology of IPF and the lack of a therapy of proven efficacy have generated a culture of nihilism that further promulgates a delay in diagnosis. However, in recent years there have been important advances in the understanding of the pathogenesis of IPF and new therapeutic trials are being performed that have increased the enthusiasm for early diagnosis of IPF. This chapter describes the recent advances in improving the accuracy of the diagnosis of IPF and describes new insights into pathogenesis that are prompting a multitude of attempts to find new treatments for patients who suffer from this devastating disease.

HISTORICAL PERSPECTIVE

A brief review of the evolution in our understanding of IPF will illustrate the contributions made by earlier investigators and account for much of the confusion that many clinicians have regarding IPF. One of the challenges in defining IPF has been the variety of antiquated terms formerly used to describe pulmonary fibrosis. While there are many causes of ILD in general, and pulmonary fibrosis in particular, it is important to note that IPF is a unique disease, although it had not been formally codified until recently when a group of expert pulmonologists, radiologists, and pathologists collaborated on a classification of ILD. Reviewing the history of IPF will both clarify the present terminology and distinguish contemporary nomenclature from the outmoded terms encountered in earlier literature.

Fibrosis of the lung was long recognized in association with infection or dust inhalation. In the nineteenth century, pulmonary fibrosis was known as "cirrhosis" of the lung. Yet little attention was paid to this form of respiratory illness. Interest in pulmonary fibrosis was ignited in 1944 when Louis Hamman and Arnold Rich published a seminal paper describing "acute diffuse interstitial fibrosis of the lungs." Hamman and Rich reported a series of unusual cases that shared a unique clinical presentation featuring idiopathic subacute respiratory failure followed by death. Their report was complete with pathological findings from autopsy. They described thickening of the alveolar interstitium and areas of dense fibrotic scar tissue within the lung. This was the first pathological depiction of pulmonary fibrosis and, to this day, is considered an accurate portrayal. In retrospect, the cases of Hamman and Rich best fit a diagnosis of the fibrosing interstitial pneumonia known as acute interstitial pneumonitis (AIP). Yet in the 1940s, the "Hamman-Rich syndrome" became synonymous with IPF. So it remained for the next three decades.

Over the years, clinical reports of pulmonary fibrosis suggested a number of alternate presentations that were referred to as "variants" of the Hamman-Rich syndrome. This included cases that exhibited a rather protracted duration of illness compared to the "classic" Hamman and Rich cases. It was also noted that pulmonary fibrosis occurred in patients who suffered from the "rheumatoid group of collagen diseases." An assortment of abnormal patterns was noted under the microscope. Eventually, the breadth of the Hamman-Rich syndrome encompassed a heterogeneous mixture of clinical manifestations and a variety of histological forms of pulmonary fibrosis with no distinction made between systemic and limited illness, nor any concession to the prognostic implications of an acute versus chronic presentation.

In the 1960s authors began to regularly substitute the term idiopathic pulmonary fibrosis for acute diffuse interstitial fibrosis. A debate began concerning the chronicity of this disease, with some authors suggesting a slow course punctuated by "terminal complications," while others reported an average illness of no more than 2 years.

The term fibrosing alveolitis was introduced in England in 1964. Cryptogenic fibrosing alveolitis (CFA) became the preferred term for pulmonary fibrosis in the European literature and it is essentially synonymous with IPF. This term was originally meant to improve upon its predecessor by capturing pathological features in a manner that was more precise and descriptive. CFA refers to the inter-alveolar location of the inflammation in pulmonary fibrosing as compared with the intra-alveolar inflammation of infectious pneumonia. This inter-alveolar septal inflammation was dubbed alveolitis. It was maintained that alveolitis was responsible for the subsequent development of fibrosis and it was first suggested that corticosteroids be used to treat alveolitis and therefore pulmonary fibrosis.

The most important advance came in 1964 with the publication of an improved and safe technique for performing open lung biopsy. With this procedure, it became possible to carry out a widespread analysis of lung tissue from patients with suspected pulmonary fibrosis. Before long there were new insights into the pathology associated with fibrotic lung disease.

In 1969 Liebow and Carrington heralded the modern era of interstitial lung disease histopathology with the notion that idiopathic interstitial pneumonia (IIP) could be split into separate pathological subtypes. They described distinct patterns of IIP, which were identified by examination of lung biopsy specimens with light microscopy. Moreover, these subtypes were found to predict prognosis and response to treatment. Based on their research findings, Liebow and Carrington produced the first detailed histopathological classification of IIP. They created five categories termed usual interstitial pneumonia (UIP), desquamative interstitial pneumonia (DIP), bronchiolitis obliterans interstitial pneumonia (BIP), lymphoid interstitial pneumonia (LIP), and giant-cell interstitial pneumonia (GIP). More recent observations have led to a modification of this classification of IIP subtypes. New categories have been added such as respiratory bronchiolitis-associated interstitial lung disease (RB-ILD) and nonspecific interstitial pneumonia (NSIP).

Simultaneously, a revolution in thinking about the pathogenesis of IPF affected the way in which experts talked about the disease. Researchers at the National Heart, Lung and Blood Institute (NHLBI) were major proponents of an "inflammatory theory" of pathogenesis as originally proposed by European investigators. This theory was based on studies at the NHLBI throughout the 1970s during which excessive amounts of inflammatory cells were identified in bronchoalveolar lavage fluid obtained from IPF patients. The NHLBI agreed with European researchers who had coined the term "alveolitis" and the NHLBI also endorsed corticosteroid treatments. The inflammatory theory has since fallen from favor, mostly as a consequence of corticosteroid inefficacy, and the term alveolitis has also fallen out of vogue.

A new hypothesis has replaced the inflammatory theory of IPF. This new concept proposes that IPF is the result of alveolar epithelial injury which is then followed by

aberrant repair mechanisms. This theory emerged from landmark ultrastructural studies performed in the mid-1980s. Using electron microscopy, it was discovered that the alveolar epithelial cells were injured in IPF. In addition, foci of subepithelial fibrosis were first described. This concept of injury and repair was modified and expand on by subsequent investigators.

In 1997 a modified version of Liebow's pathological classifications were proposed. The new classification scheme reinforced acceptance of certain categories within the context of an updated understanding of interstitial lung disease pathogenesis. For instance, DIP and UIP categories were retained in the new classification scheme. Some original categories were discarded and two modern categories were added. RB-ILD was recognized in the spectrum of smoking-related lung diseases and a provisional category, NSIP, was also added. This modern pathological classification became the basis for a consensus statement that finally standardized the nomenclature of ILD and IPF for the very first time.

In 2002 a panel of experts convened sponsored jointly by the American Thoracic Society and the European Respiratory Society. This panel released an official statement for the purpose of providing a new and comprehensive classification of IIP that considered all clinical, radiographic, and pathological features. This statement offers strict definitions for each subtype of IIP with practical guidelines for diagnostic purposes. The benefit of utilizing precise definitions is a uniformity of diagnostic decisions in both clinical practice and future research. The current classification system relies upon an assumption that each specific IIP is a discrete clinical entity, to an extent sufficient for its designation as a separate disease.

The diseases recognized by the 2002 ATS/ERS classification of IIP are idiopathic pulmonary fibrosis (IPF), nonspecific interstitial pneumonia (NSIP), cryptogenic organizing pneumonia (COP), acute interstitial pneumonia (AIP), respiratory bronchiolitis–associated interstitial lung disease (RB-ILD), desquamative interstitial pneumonia (DIP), and lymphocytic interstitial pneumonia (LIP). These diseases are each associated with a distinct pathological pattern upon surgical lung biopsy. IPF is associated with the UIP pattern.

DEFINITIONS

PF is defined as a specific form of chronic fibrosing interstitial pneumonia that is limited to the lung and associated with the histological appearance of UIP on a surgical lung biopsy. The diagnosis of IPF can only be made after the exclusion of other known causes of interstitial lung disease such as drug toxicities, environmental exposures, and collagen vascular diseases. Within the hierarchical structure of the interstitial lung diseases (ILD), IPF belongs to the subset of diseases known as the idiopathic interstitial pneumonias (IIP). ILD is a collection of non-neoplastic lung disorders, both acute and chronic, that present with variable degrees of inflammation and fibrosis. ILD is also termed diffuse parenchymal lung diseases (DPLD), which highlights the focus on the interstitium but does not exclude some involvement of airway abnormalities. DPLD can be subdivided into four groups. IIP includes the subset of DPLD that are of unknown etiology. DPLD can also be associated with identifiable causes of lung disease, such as environmental exposures or systemic illnesses such as the collagen vascular diseases. Granulomatous diseases, such as sarcoidosis and hypersensitivity pneumonitis, comprise another group of DPLD. Finally, a few rare forms of DPLD are recognized by their distinctive pathology. These include pulmonary Langerhans' cell histiocytosis (PLCH) and lymphangioleiomyomatosis (LAM).

The IIPs are defined by the ATS/ERS consensus classification as seven distinct disease entities. IPF is the most common IIP and its diagnosis is reserved for patients whose biopsy reveals the UIP pathology or in whom the clinical presentation and high-resolution computed tomography (HRCT) reveal a characteristic pattern. It is important to maintain this strict definition of IPF. Historically, several forms of IIP were grouped under the heading of IPF. This has made it difficult to assess the scientific literature. Misclassification has also contributed to confusion concerning the responsiveness of IPF to corticosteroids since some IIP such as COP and NSIP are more responsive than IPF. The latest investigations of IPF, using the strict definition of IPF, have reported a natural history and response to treatment that differs from those reported in older studies. This is likely explained by the change in definitions.

EPIDEMIOLOGY

Incidence, Prevalence, and Vital Statistics

The epidemiology of IPF is difficult to determine and the available data are of limited value. The epidemiology has been principally assessed by large population studies. The main criticism of these studies is that surgical lung biopsy was rarely performed, although biopsy remains the gold standard of diagnosis. Studies from the United Kingdom and the United States suggest that IPF is widely underreported. Studies that have examined the accuracy of diagnostic coding on death certificates have identified discrepancies among patients who otherwise carried a diagnosis of pulmonary fibrosis. Most experts agree that the currently reported epidemiologic figures underestimate the magnitude of the problem of idiopathic pulmonary fibrosis.

The precise incidence and prevalence of IPF cannot be known but the best estimates are based upon a few studies performed in the United States and have been supported by case series from around the world. The yearly incidence of IPF is estimated at 10.7 cases per 100,000 persons for males, and 7.4 cases per 100,000 persons for females. The prevalence of IPF is slightly higher at 20.2 cases per 100,000 men and 13.2 cases per 100,000 women. Mortality data are scant and

vary by country as well as race. This likely reflects differences in reporting practices rather than an actual disease pattern.

Risk Factors

Idiopathic pulmonary fibrosis has been reported worldwide. There are no apparent preferences for urban or rural settings. Neither is there a predilection toward any particular race or ethnicity. Age-adjusted rates of mortality appear to differ among blacks and whites in the United States, but these differences are likely related to inadequate reporting.

The incidence of IPF undoubtedly increases with age. Patients with IPF are usually between 40 and 70 years old. Two-thirds of IPF cases present in patients over the age of 60 years, with a mean age of 66 years at the time of diagnosis. IPF occurs infrequently among those younger than 40 years and rarely affects children, if at all. In one U.S. population–based study the prevalence was stratified by age. Among adults aged 35 to 44 years the prevalence was 2.7 cases per 100,000 persons. In contrast, the prevalence for individuals older than 75 years was greater than 175 cases per 100,000.

Besides age, several other risk factors have been identified by case-control studies. A strong association has been demonstrated between cigarette smoking and pulmonary fibrosis. An odds ratio of 2.3 (95 percent confidence interval, 1.3 to 3.8) was reported for those with a history of smoking between 21 to 40 pack-years. Another study associated antidepressants with an increased risk of developing IPF. A number of papers have implicated environmental exposures to such particulate materials as metal and wood dusts. In a related finding, an increased incidence of IPF was noted in industrial centers of the southeastern United States and central regions of the United Kingdom.

Several articles have implicated a variety of viruses, such as the Epstein-Barr virus, influenza virus, cytomegalovirus, and hepatitis C. All are found with higher incidence among patients with IPF. The significance of these findings is unclear. No evidence exists for a pathogenic mechanism involving viruses or involving any of the other aforementioned risk factors. However, a recent report made the intriguing observation of a marked high prevalence of HSV in biopsies from IPF patients.

Familial and Genetic Factors

Familial cases of IPF have been described in dozens of reports. The clinical features of familial IPF are indistinguishable from those of the non-familial form, except that the familial form may have an earlier age of onset. Familial IPF or familial interstitial pneumonia (FIP) is defined by at least two members of a primary biologic family (parent, child, siblings) presenting with a characteristic appearance of IPF that is confirmed by biopsy. Evidence of lung inflammation has also been reported in unaffected family members of those with FIP. Familial IPF seems to account for 0.5 to 2 percent of all cases of IPF.

In 2000, a report was published describing 25 families and comprising 67 cases of familial IPF. In this report the mean age at time of diagnosis was 56 years. Only half of the patients were smokers. The male-to-female ratio was 2:1 in contrast to earlier reviews of FIP, which suggested an inverted male-to-female ratio. One shortcoming of this particular study was the lack of biopsy confirmation for 68 percent of the cases.

A more recent study of FIP was published in 2005. This impressive report described a much larger cohort of 111 families with 309 affected family members. Most of these subjects were identified as having probable or definite IPF by the American Thoracic Society/European Respiratory Society diagnostic criteria. This study revealed a mean age at diagnosis of 68.3 years, with a slight male predominance (55 percent) and an increased association with cigarette smoking (even after controlling for age and gender differences). Analysis of pedigrees confirmed vertical transmission and provided strong evidence for an autosomal-dominant inheritance pattern of this disease.

These accounts of FIP provide compelling evidence for the existence of genetic factors that predispose to the development of IPF. However, specific hereditary markers for IPF have yet to be identified. The difficulty in identifying such genes is due to several factors, including the rarity of FIP in the general population. Several candidate genes have been selected, because of their bearing on proposed mechanisms of the disease, and these genes are currently under investigation.

Genes that code for a variety of inflammatory cytokines have been examined for genetic polymorphisms. These studies have been uninformative mainly because of small sample sizes. Limited data have suggested a role for the HLA loci, as well as genes encoding surfactant proteins.

Clinical Presentation

Diagnosis

Differential

In the setting of exertional breathlessness, the hallmark of IPF is a predominance of radiographically visualized lower lung zone reticular opacities that spread out over time to involve an ever-enlarging area of lung parenchyma (Fig. 68-1). The differential diagnosis of IPF frequently includes the other IIP, connective tissue diseases (principally scleroderma and rheumatoid arthritis), environmental exposures, chronic aspiration, and chronic hypersensitivity pneumonitis. The aforementioned disorders have in common symptoms of dyspnea on exertion coupled with radiographic abnormalities indicative of an interstitial pulmonary disorder.

High-resolution computed tomography (HRCT) has emerged as the single most important diagnostic modality in ILD. A number of diseases share a radiographic pattern that is similar to IPF, in other words, reticular abnormalities are demonstrated by HRCT with a tendency to involve the lower lobes. Examples include asbestosis, chronic aspiration, radiation pneumonitis, chronic hypersensitivity pneumonitis, end-stage sarcoidosis, and congenital disorders such as Gaucher's disease, Niemann-Pick disease, and tuberous

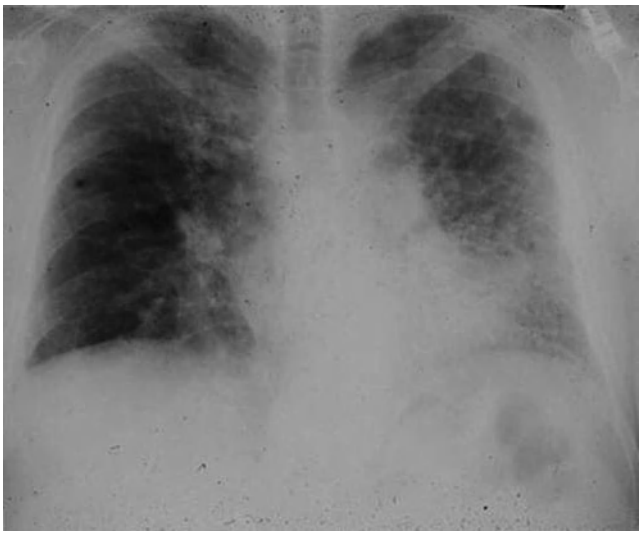

Figure 68-1 Posteroanterior chest radiograph of a 67-year-old man with progressive dyspnea revealing bilateral reticular infiltrates with lower lobe predominance.

sclerosis–lymphangioleiomyomatosis. The presence of extensive ground-glass opacities on HRCT should prompt the consideration of an alternative diagnosis, such as desquamative interstitial pneumonia, cellular nonspecific interstitial pneumonia, or acute hypersensitivity pneumonitis. Other IIP that are included in the differential diagnosis of IPF are fibrotic NSIP and COP.

History

Patients with IPF typically present with exertional dyspnea and a nonproductive cough. The dyspnea begins insidiously and is usually progressive. Dyspnea is the most prominent symptom in IPF. Associated systemic symptoms can occur but are not common. Systemic symptoms may include weight loss, low-grade fevers, fatigue, arthralgias, or myalgias.

Patients often have symptoms longer than 6 months before seeking a medical evaluation. It is not unusual for symptoms to be present for up to 2 years before an initial consultation is arranged with a pulmonary specialist. Patients are frequently evaluated and treated for other ailments, such as asthma or heart failure before IPF is identified as the diagnosis. Because most patients present over the age of 60, in which coronary artery disease is highly prevalent, most primary care physicians refer patients for a cardiology evaluation before a pulmonary evaluation for the exertional breathlessness.

The patient's age is an essential clue to the recognition of IPF. While IPF mostly occurs in patients beyond 50 years of age, several other interstitial lung diseases commonly present in the young or middle-aged (e.g., sarcoidosis, lymphangioleiomyomatosis, and pulmonary Langerhans' cell histiocytosis).

A history of cigarette smoking is a vital piece of information. While IPF, DIP, and PLCH are diseases found in former and current smokers, other diseases such as hypersensitivity pneumonitis are rare among a smoking population.

It is critical to obtain a detailed occupational history with particular attention paid to the identification of exposures to asbestos, silica, or any other respiratory toxins. This history is necessary to exclude the presence of pneumoconiosis. It is equally important to inquire about exposure to molds and/or pets in the home environment as this information may provide evidence suggesting a diagnosis of hypersensitivity pneumonitis.

A general health history, including an accounting of all medications, can be revealing. A review of systems may uncover photosensitivity, Raynaud's phenomenon, dry eyes or dry mouth that implies a connective tissue disorder. Certain drugs have been associated with pulmonary fibrosis, most notably nitrofurantoin, bleomycin, and amiodarone.

Physical Examination

In most patients the physical examination reveals fine, bibasilar inspiratory crackles, known as "Velcro rales." As the disease progresses, rales can extend toward the upper lung zones. Clubbing is found in up to 50 percent of patients with IPF. Resting arterial oxygen saturation may be normal but frequently falls with exercise. Extrapulmonary involvement does not occur in IPF. Thus, the physical examination is otherwise unremarkable in the early stages of the disease.

Later in the course of disease weight loss, cyanosis, and signs of pulmonary hypertension with cor pulmonale may become apparent. Findings at this stage include an accentuated pulmonic second heart sound, presence of a third heart sound, a right ventricular heave, and edema of the lower extremities.

Routine Laboratory Evaluation

A routine laboratory evaluation is not helpful except for its role in ruling out other causes of diffuse parenchymal lung disease. Polycythemia is a rare finding despite the frequency of chronic hypoxemia. Elevation of systemic inflammatory markers (i.e., erythrocyte sedimentation rate or C-reactive protein level) or the presence of hypergammaglobulinemia is found in IPF, yet such findings are nondiagnostic. The lactate dehydrogenase activity is often elevated but is also nonspecific. Up to 30 percent of patients with IPF may have positive tests for antinuclear antibodies or rheumatoid factor. These titers generally are not high. The presence of a high titer of autoantibodies suggests connective tissue disease, while an elevated angiotensin-converting enzyme level or antineutrophil cytoplasmic antibodies indicate alternative diagnoses.

Pulmonary Function and Physiology

Pulmonary function tests in IPF normally identify a restrictive ventilatory defect with reductions of total lung capacity (TLC), functional residual capacity (FRC), and residual volume (RV). These changes are the result of diminished lung compliance. Pressure-volume studies will yield a curve that is shifted downward and to the right, indicative of lost lung compliance. As the disease progresses, compliance decreases

further. Forced expiratory volume in one second (FEV_1) and forced vital capacity (FVC) also are decreased.

Unless a complicating airways disease is present (e.g., chronic obstructive pulmonary disease), isovolume flow rates are preserved. While functional alterations associated with small airways disease have been reported in IPF, this description is exclusive to smokers and likely represents a concurrent smoking-related airways disorder.

Impaired gas exchange is demonstrated by the measurement of a lowered diffusing capacity. The decline of diffusion capacity may even precede the development of abnormal lung volumes. Resting arterial blood gases are usually normal in IPF or else they will reveal mild hypoxemia with a respiratory alkalosis. Patients with IPF have tachypnea and often develop a pattern of rapid shallow breathing. The work of breathing is increased in IPF. While no chemical changes can explain the observed hyperventilation, it is felt that rapid respiratory rates are secondary to altered mechanical reflexes resulting from an increase in elastic recoil and elastic load. The major cause of hypoxemia is ventilation and perfusion (V/Q) mismatching, not anatomic shunting or reduced oxygen diffusion, as was previously suspected.

Patients with IPF have been shown to develop sleep disturbances, highlighted by fragmented sleep phases and REM-related cyclical hypoxemia. These disturbances are present even in the absence of sleep apnea. As a result, the Joint Statement of the ATS/ERS on the diagnosis and treatment of IPF recommends the use of supplemental oxygen for all patients with IPF who demonstrate nocturnal hypoxemia.

During exercise, patients with IPF and may exhibit evidence of pulmonary hypertension, even in early cases that have preserved lung function at rest. Pulmonary hypertension can also be present at rest, and is an expected finding, once the vital capacity drops below 50 percent of predicted or the diffusing capacity falls below 45 percent of predicted. The presence of pulmonary hypertension may be a predictor of poor outcome yet may not correlate with lung function.

Exercise Testing

The alveolar-to-arterial oxygen gradient (A-a gradient) is wide in patients with IPF reflecting V/Q mismatching. With exercise the A-a gradient widens further. Diffusion impairment also becomes a relevant factor during exercise. As a result, arterial oxygen pressure (Pa_{O_2}) and arterial oxygen saturation (Sa_{O_2}) fall during exercise. It is important to note that measures of blood oxygen tension at rest do not accurately predict the magnitude of abnormality seen during exercise. The most sensitive method for monitoring gas exchange abnormalities in IPF is formal cardiopulmonary exercise testing.

Normal persons will increase their minute ventilation during exercise by means of increased tidal volume (V_T). Persons with IPF can only increase their minute ventilation during exercise through an increase in respiratory rate. In IPF, the fraction of dead space-to-tidal volume (V_D/V_T, dead space fraction) is elevated at baseline yet remains stable during exercise due to subsequent increases in perfusion. An increase of the dead space fraction during exercise should raise concern for concurrent pulmonary vascular disease.

Radiology

Conventional Chest Radiograph

The chest radiograph is abnormal in nearly all patients with IPF (Fig. 68-1). Yet, in up to 10 percent of patients with histologically proven IPF, the chest film might be normal. In most of these cases, the use of HRCT uncovers evidence of the disease.

The most common abnormalities seen on a conventional chest film are reticular opacities. In other words, there is an appearance of net-like linear and curvilinear densities. These markings are found bilaterally, asymmetrically at times, and have a predilection for the lower lobes. A course reticular pattern, which takes the form of translucent "honeycombing," will emerge late in the course of disease and portends a poor prognosis.

The chest radiograph lacks specificity for the diagnosis of IPF. The correct diagnosis is made on the conventional radiograph in fewer than 50 percent of cases. In addition, the interpretation of conventional radiographs with an interstitial pattern shows poor interobserver agreement. Studies have examined this particular characteristic and report that concordance between radiologists is only 70 percent.

High-Resolution Computed Tomography

The development of the high-resolution CT scanner has revolutionized the diagnostic evaluation of the interstitial lung diseases. HRCT allows a detailed examination of the lung parenchyma by creating 1- to 2-mm-thin slices of the chest. HRCT uses a computerized reconstruction algorithm that maximizes spatial resolution. This generates much improved image clarity such that the specificity of interpretations is increased, interobserver variability is reduced, and the overall accuracy of diagnosis is enhanced. HRCT scanning allows for the earlier diagnosis of IPF and permits the identification of alternate patterns of disease. The primary role of HRCT in the diagnostic evaluation of ILD is the discrimination of typical IPF from the other interstitial lung diseases.

The appearance of IPF on HRCT is characterized by patchy, predominantly peripheral, predominantly subpleural, and bibasilar reticular opacities (Fig. 68-2). Ground-glass opacities can be found, but should occupy no more than a limited amount of territory. Areas that are severely involved with reticular markings may also demonstrate traction bronchiectasis. The presence of subpleural honeycombing (small, round translucencies with a density equal to that of air), traction bronchiectasis and thickened interlobular septae will increase the specificity of the CT scan for diagnosing IPF. These findings constitute the HRCT pattern that defines a "confident" or "certain" radiographic diagnosis of IPF.

Several studies have examined the diagnostic accuracy of HRCT scans in IPF. Studies were conducted in which observers were asked to determine a radiographic diagnosis that was then compared with the histopathology of UIP as

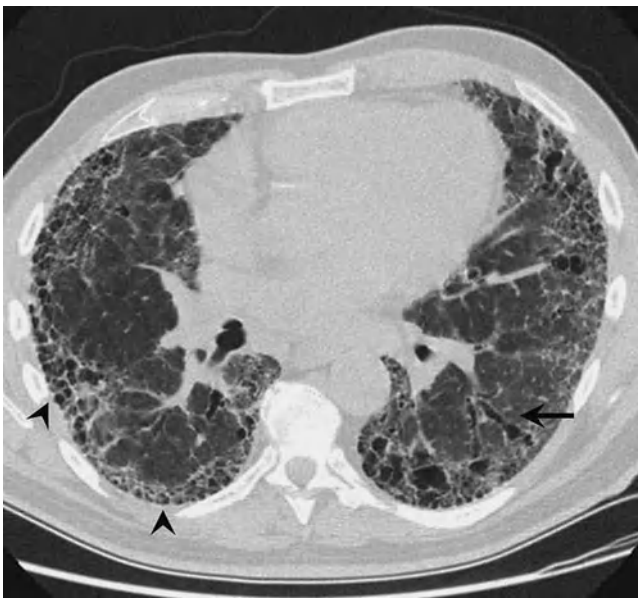

Figure 68-2 Computed tomography scan illustrates the "classic" features of idiopathic pulmonary fibrosis (IPF). Bilateral, peripheral, and subpleural reticular infiltrates are evident. The presence of advanced fibrosis is indicated by honeycomb changes (arrowhead) and traction bronchiectasis (arrow). These features permit experienced clinicians to make a confident radiographic diagnosis of IPF.

the "gold standard." In the hands of experienced observers, the "confident" radiographic diagnosis of IPF has a reported specificity for IPF histology, which exceeds 90 percent. Therefore it has become apparent that, in the right clinical setting, an experienced radiologist can diagnose IPF by the HRCT with considerable accuracy, obviating the need for biopsy.

However, the "confident" HRCT is not a sensitive tool for the diagnosis of IPF. The full spectrum of a "confident" radiographic pattern will only be seen in two-thirds of biopsy proven IPF. One-third of IPF cases will not show a "confident" CT pattern and would be missed if the HRCT was relied upon exclusively (Fig. 68-3). HRCT patterns other than the "confident" pattern should proceed to surgical lung biopsy for further evaluation. Some of these biopsies will identify an alternative disease.

Some features of the HRCT have been identified that suggest a diagnosis other than IPF. These features include ground-glass opacities, multiple nodules, the presence of significant lymphadenopathy, or a predominance of lesions in the upper lobes. The appearance of ground glass on a HRCT invokes a differential diagnosis that includes heart failure, NSIP, COP, DIP, RB-ILD, and hypersensitivity pneumonitis. Fine nodules are suggestive of hypersensitivity pneumonitis, granulomatous infection, or metastatic malignancy. Upper lobe disease is the predominant pattern in PLCH, hypersensitivity pneumonitis, a variety of pneumoconioses, sarcoidosis, and eosinophilic pneumonia. Lymphadenopathy is associated with sarcoidosis and other granulomatous diseases. These atypical features may yet represent IPF when seen in conjunction with reticular opacities. The specificity as regards

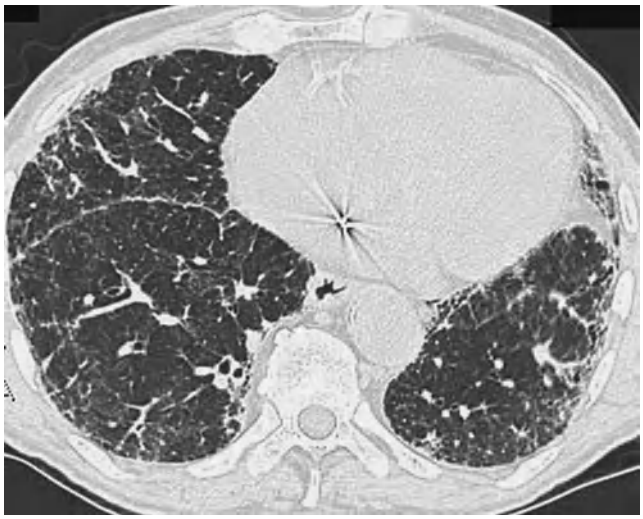

Figure 68-3 Computed tomography scan of an 81-year-old man with biopsy-proven idiopathic pulmonary fibrosis. A peripheral distribution of reticular opacities is demonstrated. Honeycombing and traction bronchiectasis are notably absent. In the absence of specific findings, a surgical lung biopsy was needed to make a diagnosis.

the diagnosis of IPF is markedly reduced when an atypical pattern is found on HRCT. Expert observers have described such equivocal CT scans using terms such as "probable IPF," "possible IPF," and "likely IPF." The specificity of "likely IPF" is estimated to be around 75 percent. Patients with a "likely" CT scan should be referred for biopsy.

Bronchoalveolar Lavage

An enormous amount of scientific information has been obtained by analyzing the content of bronchoalveolar lavage (BAL) fluid from patients with IPF. Notable increases of immune cells (neutrophils, eosinophils, and activated alveolar macrophages) are present in BAL fluid from IPF. In addition, BAL has aided in the identification of cytokines, growth factors, and other cellular products that are now implicated in the pathogenesis of IPF. As a research tool, BAL has been immensely valuable.

The role of BAL in the clinical diagnosis of IPF remains limited. Though much effort has been invested in evaluating the clinical utility of this modality, study results have been contradictory and generally disappointing.

Increased numbers of neutrophils are found in the BAL in 70 to 90 percent of all patients with IPF. Increased numbers of BAL eosinophils are found in 40 to 60 percent of IPF patients. A lymphocytosis of the BAL fluid is noted in 10 to 20 percent of IPF. Most samples of BAL from IPF demonstrate simultaneous increases of several effector cell types. Other fibrosing lung diseases exhibit similar increases of inflammatory cells. Unfortunately, studies have failed to demonstrate a clear distinction among pulmonary diseases based upon the predominant type of cell in the BAL fluid.

The diagnosis of IPF calls for the exclusion of alternative diagnoses and, in this regard, BAL fluid analysis can

be helpful. Appropriate laboratory studies of the BAL fluid may demonstrate the presence of tumor, infection, Langerhans' cells, or occupational dusts. Any of these findings may substantiate a diagnosis other than IPF.

The presence of a lone increase in BAL lymphocytes is unusual for IPF as this occurs in less than 10 percent of IPF patients. Lone BAL lymphocytosis should suggest a differential diagnostic list that includes mycobacterial infection, sarcoidosis, hypersensitivity pneumonitis, NSIP, COP, LIP, and drug-induced alveolitis.

Pathology

A surgical lung biopsy is recommended to confirm all cases of suspected IPF. A biopsy may not be necessary in cases with a "confident IPF" HRCT pattern in which the diagnosis is already clear. Biopsy may be achieved by either open thoracotomy or by video-assisted thoracoscopy (VATS). VATS is preferred as it has been associated with less morbidity and shorter hospital stays compared with open biopsy. A surgical lung biopsy provides the best sample from which to distinguish UIP form other forms of IIP. Transbronchial biopsies are not helpful in identifying IPF lesions because of the small size of the sample.

The decision to perform a surgical lung biopsy can be difficult. Relative and absolute contraindications to surgery must be considered before electing to perform a surgical lung biopsy. The decision to obtain a surgical biopsy requires a balance of the cost and complications of surgery against the benefit of an accurate diagnosis. While a biopsy provides vital information in all cases of ILD, the biopsy is particularly useful in the setting in which clinical or radiographic features are not typical for IPF. In this situation, it is possible to uncover a different diagnosis with resultant change in the prognosis and approach to therapy.

The gross appearance of an IPF sample may be normal but often has a distinctive nodular pleural surface that has been likened to cirrhosis. The histopathological lesion associated with IPF is usual interstitial pneumonia (UIP). This lesion is defined by a variegated structure. Normal lung alternates with patchy collagen fibrosis (Figs. 68-4 and 68-5). The fibrosis takes the form of alveolar septal thickening with a predominantly subpleural distribution. Whirls of fibroblasts embedded in a loose extracellular matrix embody the fibroblastic foci that are found in numerous quantities at the leading edge of dense scar (Figs. 68-4 and 68-5). Interstitial inflammation is present but remains scant and confined to areas of fibrosis. This limited inflammation consists of lymphocytes and plasma cells. Associated hyperplasia of the type 2 pneumocytes is found within areas of active inflammation. Areas that contain dense collagen may develop cystic structures that may be filled with mucin or lined by bronchiolar epithelium. These cysts are referred to as microscopic honeycomb change. Hyaline membranes and organized alveolar exudates are absent. Occasionally alveolar macrophages are present.

The UIP pathological pattern exhibits a wide range of severity with regard to the extent of honeycomb change and the extent of involved lung. A history of smoking may alter the histopathological appearance of UIP. Emphysematous change can be superimposed upon UIP. Pigmented alveolar macrophages, the hallmark feature of RB-ILD and DIP pathological patterns, may be present in small number in UIP lesions from former or current smokers.

The UIP pattern can be found in other diseases besides IPF. The presence of granulomas in a UIP lesion favors a diagnosis of fibronodular sarcoidosis or chronic hypersensitivity pneumonitis. Asbestos bodies found within a UIP pattern suggest the diagnosis of asbestosis. The histopathological

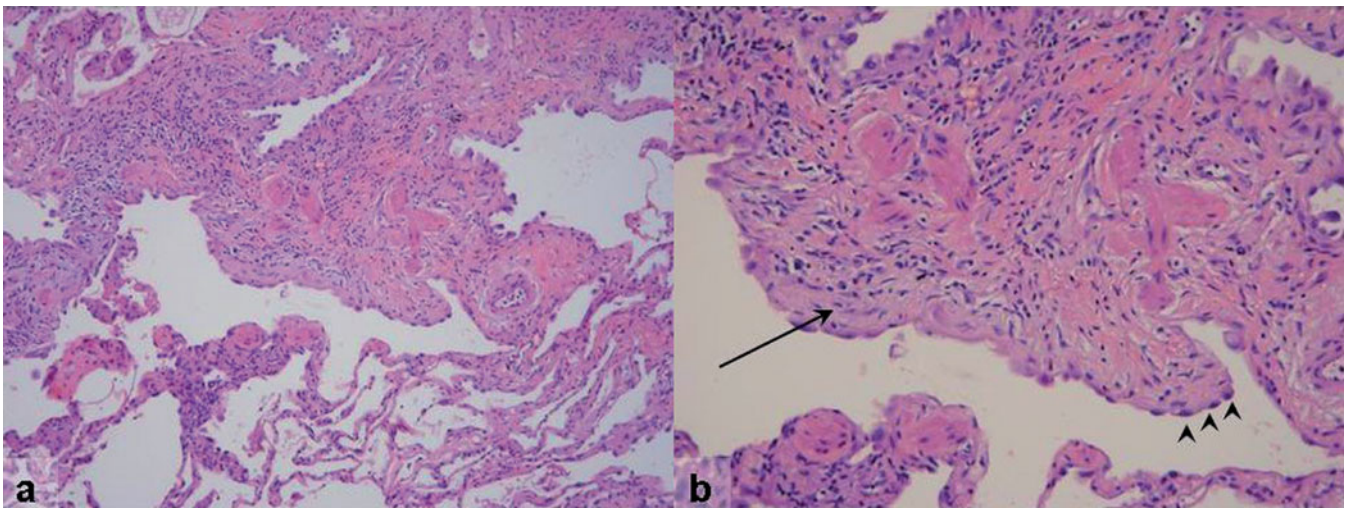

Figure 68-4 *A*. Low-magnification photomicrograph of usual interstitial pneumonia (UIP) showing the characteristic heterogeneous involvement of the parenchyma. Zones of interstitial fibrosis are seen alternating with areas of normal lung. *B*. Higher magnification demonstrates enlarged cystic airspaces lined with hyperplastic alveolar epithelium (arrowheads). Beneath the mucosal layer is an advancing region of young fibrosis containing loose extracellular matrix (pale pink staining) and fibroblasts (arrows).

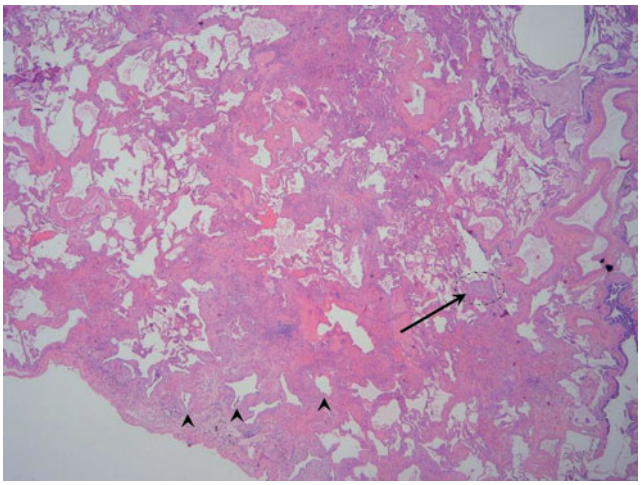

Figure 68-5 Scanning view of usual interstitial pneumonia (UIP) demonstrates the characteristic variegated appearance of UIP. Note the honeycomb change (arrowheads) present in the region of dense fibrosis adjacent to the pleural surface. A fibroblast focus (arrow) is seen at the leading edge of advancing fibrosis.

pattern of UIP can also be found in several conditions other than IPF. UIP can be found in association with connective tissue diseases, asbestosis, chronic hypersensitivity pneumonitis, the Hermansky-Pudlak syndrome, neurofibromatosis or in the setting of a toxic drug reaction (typically after administration of either bleomycin, methotrexate, nitrofurantoin or amiodarone [this is a partial list]). The identification of these conditions is largely a matter of correlation with the clinical history. It is important to note that the presence of honeycombing on biopsy is a nonspecific finding with a broad differential. Honeycombing is a common end point for a myriad of pathological processes. Although honeycombing carries the connotation of end-stage fibrosis it can also occur in a focal distribution after any lung injury. Seen alone, honeycombing is not indicative of idiopathic pulmonary fibrosis.

Diagnostic Criteria and Algorithm

Definite Diagnosis

The definite diagnosis of IPF can only be made in the presence of a surgical (thoracoscopic or open) lung biopsy. Criteria for the definite diagnosis of IPF include: (a) a biopsy with the histologic appearance of UIP; (b) exclusion of other known causes of interstitial lung disease such as connective tissue disease, radiation, drug, or environmental exposures; (c) abnormal pulmonary physiology with evidence of restriction and/or impaired gas exchange (at rest or with exercise); (d) bibasilar reticular abnormalities with minimal appearance of ground-glass opacities seen by either conventional chest radiography or HRCT. In the very early stages of disease the pulmonary function tests or imaging studies may be nearly normal.

The "Probable" or "Likely" Diagnosis

In the absence of a surgical biopsy, the diagnosis of IPF remains uncertain. However, a set of clinical criteria are recommended by the consensus opinion of a panel of experts who are endorsed by the American Thoracic Society and the European Respiratory Society. These guidelines were published in the year 2000. According to these guidelines the diagnosis of IPF is considered "likely" if the patient is an immunocompetent adult and all four major criteria are satisfied in addition to three out of the four minor criteria. Although these criteria have not been prospectively analyzed, they are useful in situations where a surgical lung biopsy is not possible. The criteria are as follows:

- Major criteria
  - Exclusion of other known causes of ILD, such as certain drug toxicities, environmental exposures, and connective tissue diseases
  - Abnormal pulmonary function studies that include evidence of restriction (reduced VC often with an increased FEV_1/FVC ratio) and impaired gas exchange [increased $AaPO_2$ with rest or exercise or decreased D_{LCO}]
  - Bibasilar reticular abnormalities with minimal ground glass opacities on HRCT scans
  - Transbronchial lung biopsy or bronchoalveolar lavage (BAL) showing no features to support an alternative diagnosis
- Minor criteria
  - Age greater than 50 years
  - Insidious onset of otherwise unexplained dyspnea on exertion
  - Duration of illness greater than or equal to 3 months
  - Bibasilar, inspiratory crackles (dry or "Velcro" type in quality)

Since the publication of these criteria, several studies have demonstrated the poor predictive value of BAL fluid concerning the diagnosis of ILD. Without a history to suggest a diagnosis other than IPF, the yield of a BAL examination or a transbronchial biopsy specimen is inherently low. Meanwhile, additional data have accumulated to highlight the accuracy of HRCT. It seems that bronchoscopy may no longer be warranted as a routine part of the evaluation for IPF. Until more research is done, this remains a matter of opinion.

Natural History and Prognosis

The natural history of IPF has never been fully defined. It is has been demonstrated that physiological function declines over time. Studies utilizing the modern definition of IPF have reported median survival between 2 to 5 years from the time of diagnosis. There are few, if any, reports of long-term survival with biopsy proven IPF/UIP.

Early studies identified older age, male sex, significant dyspnea, severe physiological abnormalities, advanced fibrosis and a poor response to therapy as factors predictive of shortened survival. One limitation of these earliest studies was their retrospective design. In addition, the first studies of IPF prognosis did not adhere to the modern, pathologically based definition of IPF.

Additional factors have combined to create barriers preventing the further, more rigorous description of the natural history of IPF. First, the diagnosis of IPF can be challenging and, not infrequently, the presence of "early" disease gets overlooked. Patients develop IPF in the later decades of life and often attribute their symptoms to old age. When their disease eventually comes to medical attention, there may be further delay in diagnosis because the symptoms are nonspecific. Most patients with IPF are evaluated for other diseases before a diagnosis of pulmonary fibrosis is considered. Moreover, the interstitial markings found on a chest radiograph are subtle and tend to go unnoticed or else simply get disregarded as clinically unimportant. Experts in IPF agree that patients usually have symptoms for 2 or more years prior to receiving a definitive diagnosis. Therefore it is apparent as to why most cases of known IPF present with an advanced disease state. The epidemiologic and prognostic data that describe IPF have been derived from such cohorts of "late" disease. "Early" disease is infrequently encountered and information describing the course of "early" disease has come from retrospective analyses of cohorts with "late" disease. A cohort of patients with "early IPF" has never been followed prospectively. However, the advent of CT scanning to search for cancer has had the secondary benefit of identifying patients with IPF in the "preclinical" stage of the disease, during which the symptom of breathlessness has yet to surface. In addition, clinical trials are now enrolling patients with preserved lung function in prospective studies that will provide valuable new insights into the natural history of IPF.

Pathological Predictors

One of the most important features of the spectrum of illness encompassed by IIP is the fact that pathological patterns predict survival. In the late 1990s it was recognized that the UIP pathological pattern had a precise correlation with clinical parameters and with outcome. Survival is significantly worse among patients whose biopsy contains a UIP pattern as compared to either NSIP or other patterns of fibrosis.

Within biopsy specimens, specific traits have also been correlated with survival. The degree of cellularity does not seem to affect survival nor does the degree of fibrosis. However, the presence of "young" connective tissue, characterized by multiple fibroblastic foci, is predictive of shorter survival. Fibroblastic foci have been linked to high mortality and large declines in physiological measures such as the forced vital capacity and diffusion capacity.

Physiological Predictors

Recently, three groups of researchers working independently made similar observations concerning the relationship between physiological changes and survival in IPF. Interestingly, it was observed that physiology might be a stronger predictor of outcome than histopathological pattern.

One study examined a cohort of patients with fibrotic lung disease who underwent surgical biopsy. Half of these patients had a UIP pattern, while the other half had fibrotic NSIP. The goal was to determine the prognostic significance of pathological patterns compared with the predictive value of baseline pulmonary function or 1-year trends in pulmonary function. It was found that trends in pulmonary function were the only significant prognostic determinant. Neither pathology nor baseline pulmonary function was predictive of outcome.

Another study exclusively examined patients with biopsy-proven IPF. It was discovered that a change in physiological parameters predicts survival. Specifically, at 6 and 12 months, a 10 percent decline in forced vital capacity or a 5 mmHg increase in $AaPO_2$ were associated with a poor prognosis. This observation was unrelated to baseline pulmonary function that exhibited no predictive value of its own.

Yet another group looked at patients with UIP and NSIP pathologies. In a multivariate regression analysis examining the prognostic contribution of several factors, a 6-month decrease in forced vital capacity was found to be an independent risk for mortality. The regression model controlled for pathological diagnosis, gender, smoking history, and the baseline vital capacity. None of these other factors yielded significant prognostic information.

An issue that affects the predictive value of physiological variables in IPF is the confounding influence of coexistent emphysema. This problem is addressed by the composite physiological index (CPI), which corrects for emphysema by combining several physiological measures into a single weighted score. The formula for the CPI includes diffusion capacity, FVC and FEV_1 in its calculations. The CPI was validated by comparison to HRCT. In addition, it was shown that the CPI is a more accurate prognostic determinant than any individual test of pulmonary function.

Radiographic Predictors

The utility of HRCT in predicting the outcome of IPF has been demonstrated. When biopsy-proven IPF patients were followed for 3 years it was found that HRCT honeycombing predicts the worst survival. Fibrosis measured by HRCT and fibrosis seen on histology were equivalent with respect to ensuing death or disease progression.

This finding is supported by another study comparing HRCT patterns to biopsy patterns and outcomes. Patients who had both a HRCT and a biopsy were analyzed and it was found that a HRCT pattern consistent with UIP correlated pathologically with the UIP pattern. However, an indeterminate HRCT pattern could be a manifestation of either UIP or NSIP. Patients with combined pathological UIP and radiographic "confident UIP" had a worse outcome compared to patients with pathological UIP and an indeterminate HRCT.

Composite Scores

Some authors have proposed that a composite scoring system for IPF would have better predictive value than measuring individual disease-related factors. The first clinical, radiological and physiological (CRP) scoring system was developed in 1986 and employed seven variables that accounted

for parameters such as dyspnea, specific radiographic findings, and physiological function. This CRP score was validated through comparison to histopathology in a group of 26 patients. No single component of the CRP score had a better correlation than the composite score.

In 2001, a new CRP score was derived to predict death rather than just histopathology. A large cohort of patients was followed prospectively to devise the new CRP score, utilizing multivariate statistical models to identify significant disease-related parameters. The new CRP score accounts for age, smoking status, the presence of clubbing, total lung capacity, arterial oxygen during maximal exercise, radiographic infiltrates, and radiographic findings consistent with pulmonary hypertension. The total score is calculated on a scale from 0 to 100, with higher scores indicating more severe disease. Five-year survival can be predicted in individual patients by calculating a CRP score employing the published formulas and then referencing published survival curves. An abbreviated version of the CRP score was simultaneously derived using a similar statistical model. Yet the abbreviated CRP score offers simplicity by omitting the exercise test, which may be impractical for patients with advanced disease. The abbreviated CRP score provides prognostic information comparable to the complete score and has a practical advantage. An abbreviated CRP score can be calculated for any patient following a single office visit.

Acute Exacerbation of IPF

Japanese investigators made the initial observation that patients with IPF can experience episodes of sudden decline, which they characterized as acute exacerbations. Recent observations from the placebo arm of two randomized clinical trials have suggested that acute exacerbations may be more common that previously appreciated. The acute exacerbation of IPF (AE-IPF) is characterized by a sudden worsening of symptoms and has been associated with hypoxemia and new radiographic infiltrates. It is important in making the diagnosis of AE-IPF to rule out infection, congestive heart failure, and pulmonary embolism. AE-IPF typically occurs in patients with established IPF; however, it has been recognized that AE-IPF can form the initial presentation of IPF as well, mimicking AIP. Patients with established IPF satisfy the criteria for an acute exacerbation if they have: (a) acute worsening of dyspnea within the last month; (b) deterioration from baseline in measures of pulmonary function or gas exchange; (c) new infiltrates on plain chest film or CT; and (d) the absence of other identifiable causes for decline. The initial presentation of IPF as AE-IPF is recognized when a patient with acute respiratory failure meets the ATS/ERS diagnostic criteria for definite IPF (biopsy reveals UIP) or presumptive IPF (satisfies major and minor diagnostic criteria, including a confident HRCT). The radiograph in AE-IPF demonstrates ground-glass opacification superimposed on the usual subpleural linear opacities. Histopathological examination of AE-IPF commonly reveals a UIP pattern with superimposed diffuse alveolar damage (DAD) characterized by diffuse alveolar septal thickening within a pale matrix that includes hyaline membranes and fibrin. UIP with superimposed organizing pneumonia has also been reported in AE-IPF. The prognosis of AE-IPF is poor. Series of patients with AE-IPF reported in-hospital mortality rates between 78 and 96 percent. Mortality is strongly associated with the need for mechanical ventilation.

PATHOGENESIS

IPF is a complex disorder and many pathogenic events have been observed. No unifying hypothesis explaining all of the abnormalities has yet emerged. The inciting event for lung injury is still unknown. In fact, it is not certain that the inciting event is exogenous or endogenous. Although more questions than answers currently exist, great strides are being made in elucidating new mechanisms in pathogenesis. We seem to be entering a new era in the understanding of the biology of IPF.

Inflammation

The concept that dominated the field in the 1970s and 1980s has been described as the "inflammatory theory" of pulmonary fibrosis. This paradigm was based largely on the observation that bronchoalveolar lavage fluid from patients with IPF had increased numbers of inflammatory cells (mostly neutrophils and eosinophils) relative to normal individuals. The concept that permeated the literature in that era was that IPF resulted from an unremitting inflammatory response to an exogenous insult, culminating in progressive fibrosis. By targeting the inflammatory response, the belief was that fibrosis could be limited or prevented. Unfortunately, it now appears that the data are more likely explained by structural abnormalities in lung architecture (traction bronchiectasis) such that inflammatory cell trafficking is altered. That is to say, the airway inflammation is likely a result, rather than a cause, of the fibrosis. Although the importance of chronic inflammation in the pathogenesis of IPF remains controversial, one should be cautious in omitting its contribution to disease progression.

Epithelial Cell Apoptosis

An emerging body of literature suggests that alveolar epithelial cell injury and apoptosis are important features of pulmonary fibrosis. Studies of human IPF tissue using electron microscopy have demonstrated injury and apoptosis of alveolar epithelial cells. Bronchoalveolar lavage from patients with IPF has established the presence of pro-apoptotic proteins. In the bleomycin model of lung injury and fibrosis in animals, fibrosis can be abrogated by various approaches to inhibit epithelial cell apoptosis. Studies have observed a decrease in experimental fibrosis by inhibiting the Fas-Fas ligand pathway. Inhibitions of angiotensin production and caspase activation have also been shown to reduce experimental fibrosis.

Evidence suggests that fibroblasts produce angiotensin peptides that lead to epithelial apoptosis. Other researchers have demonstrated that transforming growth factor-β (TGF-β) is involved with promoting epithelial cell apoptosis. Oxidant injury may also promote epithelial cell death and several studies of IPF patients have confirmed excessive oxidant production as well as glutathione deficiency.

Tumor necrosis factor-β (TNF-β) has been shown to promote alveolar epithelial cell apoptosis in vitro. In a mouse model, knockout of the TNF-β receptor confers resistance to bleomycin-induced lung fibrosis; while overexpression of TNF-β in the mouse has been associated with an increase in experimental fibrosis. Patients with IPF are known to exhibit an exaggerated expression of TNF-β which may contribute to epithelial injury.

Basement Membrane Injury

A unique feature of the UIP pathological pattern is a loss of integrity of the subepithelial basement membrane. This has been definitively demonstrated through the use of electron microscopy. Basement membranes in IPF are denuded of the usual type I pneumocytes. It is theorized that loss of this protective epithelial barrier results in further oxidative injury that degrades basement membranes. At the same time it appears that hyperplastic type II pneumocytes are abundantly present. This likely represents an attempt at epithelial cell regeneration. While the exposed basement membrane may provide the signal for epithelial growth, new epithelial cells cannot attach to a damaged membrane. The result is a "frustrated" epithelial cell response with failure to signal a termination of epithelial cell proliferation. Further examination of tissue from patients with IPF has confirmed an irregular pattern of alveolar epithelial cell proliferation, concurrent with dysregulation of the proteins that control the cell cycle.

An accumulation of growth factors in IPF may originate from the persistent proliferative response of epithelial cells. A downstream consequence of "frustrated" epithelial cell regeneration would be recruitment of fibroblasts and myofibroblasts, through the release of such growth factors. In essence, the signal to recruit and maintain a pool of mesenchymal cells (fibroblasts) might originate from an inability to successfully re-epithelialize the alveolar lining surface.

Growth Factors

Various growth factors that influence fibroblast function have been shown to be produced in the lung tissue of patients with IPF and also shown to mediate the pathogenesis of experimental fibrosis. Examples include keratinocyte growth factor, TGF-α, TGF-β, insulin-like growth factor-1 (IGF-1), platelet-derived growth factors (PDGF-A and PDGF-B), fibroblast growth factor-2, and hepatocyte growth factor. Many of these growth factors activate tyrosine kinase signaling pathways that promote fibroblast proliferation and matrix production. Growth factors such as IGF-1 may also promote fibroblast survival. IGF-1 has been shown to inhibit apoptosis by activating the Akt survival pathway, which may have important consequences for maintenance of a profibrotic environment.

TGF-β is a critical mediator of lung fibrosis in animal models and has attracted the attention of researchers attempting to control fibrogenesis. Several studies have shown that antagonizing TGF-β prevents the development of lung fibrosis. Targeted overexpression of TGF-β been shown to produce progressive pulmonary fibrosis. Recent evidence suggests that TGF-β has the capacity to promote epithelial cell transformation into a mesenchymal phenotype.

Th1 and Th2 Cytokines

Data suggest that a cytokine imbalance may exist in IPF. The link between Th2 cytokines and tissue fibrosis has been established in animal models. Overexpression of interleukin-13 (IL-13) in the lung using transgenic mice has been shown to result in accumulation of active TGF-β and increased tissue fibrosis. Human data demonstrating a cause and effect relationship for Th2 cytokines are lacking. However, studies have shown that there is increased expression of mRNA for Th2 cytokines (IL-4, IL-5, and IL-13) in lung tissue of patients with IPF. In addition, data have been reported suggesting that IPF may represent a relative Th1 deficiency (e.g., IFN-γ). In a small study, patients with IPF who received IFN-γ for 12 months were found to have an improvement in lung function. However, a phase 3 randomized, double-blinded, placebo-controlled trial evaluating the efficacy of IFN-γ1b found no effect on either the forced vital capacity or the resting alveolar–arterial oxygen gradient after 48 weeks. This same phase 3 trial observed an unanticipated trend toward a survival benefit from IFN-γ1b. A survival benefit must still be confirmed through prospective study before any conclusions can be made regarding the efficacy of IFN-γ in the treatment of IPF.

Angiogenesis and Angiostasis

Parallels have been drawn between the biology of IPF and the biology of cancer. The unremitting recruitment and maintenance of an altered fibroblast phenotype with generation of myofibroblasts that fail to die is reminiscent of the transformation of cancer cells. A hallmark of tumorigenesis is the production of new blood vessels that facilitate tumor growth. An important aspect of progressive fibrosis is increased angiogenic activity, which has been established in studies done on animals and humans. An imbalance between angiogenic chemokines (e.g., IL-8 and ENA-78) and angiostaxic chemokines (e.g., IP-10) has been suggested as a possible mechanism promoting angiogenic activity in IPF. IP-10 is induced by IFN-γ and this may partially explain the beneficial effects of IFN-γ described above.

In addition to reports of increased angiogenesis in IPF, there are conflicting reports suggesting that angiogenesis is hampered in IPF by decreased expression of VEGF and a reduction of endothelial cell proliferation. The fibroblast foci

are particularly lacking in the expression of angiogenic proteins. This is most evident when a direct comparison is made to protein expression within the granulation tissue of organizing pneumonia. It is possible that enhanced angiogenesis may occur during some stage of the development of UIP, whereas angiostaxis is dominant during other stages.

Matrix Turnover

The hallmark of IPF is an exorbitant production of extracellular matrix molecules, including collagen, hyaluronan, and a variety of proteoglycans. There is clearly an imbalance between the production of extracellular matrix and its subsequent degradation. Fibroblasts isolated from IPF tissue demonstrate an increased production of TIMPs (tissue inhibitor of metalloproteinases). TIMPs are inhibitors of matrix degradation. One property of TGF-β is to promote the production of TIMPs. It is unclear what role matrix degradation plays in the pathogenesis of progressive fibrosis. On the one hand, matrix degradation is essential for removal of scar tissue. Meanwhile, a recent study suggests that matrix degradation products are the stimulus for inflammation that promotes progressive fibrosis. One possibility is that matrix degrading enzymes are involved in the destruction of basement membranes, triggering a cascade of events beginning with "frustrated" epithelial cells and resulting in a fibroproliferative response. Gene expression profiles, measured by microarray analysis, provide further evidence for the involvement of matrix degrading enzymes in IPF. One microarray study implicated matrilysin, a novel matrix degrading enzyme, in the pathogenesis of IPF.

The Fibroblast

The concept that fibroblasts from patients with IPF have a unique phenotype is generally accepted, although the specifics of this phenotype differ from one study to the next. Two groups have observed that a large number of fibroblast foci within lung biopsy correlates with a poor prognosis, highlighting the importance of fibroblasts in IPF.

Phenotypes

First, it was observed that fibroblasts from different regions of the lung had dissimilar growth rates. Subsequently other properties of IPF fibroblasts have been found which differentiate them from normal lung fibroblasts. These properties include altered rates of proliferation and apoptosis, different expression of TNF-α receptors, and differing rates of production of TIMPs, prostaglandins, hyaluronan, and other mediators. Some discrepancy exists as to whether IPF fibroblasts proliferate more or less rapidly in comparison to normal lung fibroblasts. Studies have also suggested increased apoptosis consistent with rapid turnover of fibroblast populations.

Much attention has been focused recently on the role of the myofibroblast in the pathogenesis of IPF. Myofibroblasts have been described in a contractile phase in fibroblastic foci from IPF lung biopsies. The defining characteristic of the myofibroblast is the production of new collagen while simultaneously staining positive for α-smooth muscle actin. Myofibroblasts have contractile properties and, in normal wound healing, myofibroblasts appear transiently. Mechanisms that regulate the phenotype and maintenance of myofibroblasts in IPF are largely unknown. Myofibroblasts have been shown to accumulate in bleomycin-induced lung fibrosis. Immunohistochemical studies have suggested that they are important in the production of newly synthesized collagen. In the bleomycin model, however, myofibroblasts are present transiently and largely vanish from the lung within 21 days.

Telomerase-expressing fibroblasts have been described in an animal model of pulmonary fibrosis. It has been demonstrated that this fibroblast phenotype differentiates in vitro under the influence of basic fibroblast growth factor. Telomerase catalyzes the addition of telomeric DNA, which has been associated with increased cellular life span and cellular immortality. Some evidence suggests that telomerase-expressing fibroblasts may represent an intermediate cell that can further differentiate to the myofibroblast. The role of telomerase-expressing fibroblasts in human disease is unclear.

Fibroblast Recruitment and Maintenance

Differentiation from Normal Fibroblasts

TGF-β has been shown, in vitro, to induce the expression of α-smooth muscle actin in normal lung fibroblasts and promote contractile activity. TGF-β has also been shown to inhibit apoptosis of myofibroblasts that are challenged with IL-1. It is not known whether normal fibroblasts can differentiate into myofibroblasts in vivo. PDGF-A has been shown to be required for lung alveolar myofibroblast development during mouse embryogenesis. PDGF-A is important for fibroblast migration in vitro. The role of PDGF-A, in vivo, is less well characterized. In addition to growth factors, thrombin has been shown to differentiate normal lung fibroblasts to a myofibroblast phenotype in vitro.

Bone Marrow–Derived Precursors

Evidence is accumulating that suggests that bone marrow–derived cells may contribute to the pool of lung fibroblasts in IPF. In an animal model it has been shown that bone marrow–derived cells migrate to the lung and assume a fibroblast phenotype after injury. These bone marrow–derived cells do not express α-smooth muscle actin, nor do they express α-smooth muscle actin when stimulated in vitro with TGF-β. These fibroblasts do not seem capable of acquiring the myofibroblast phenotype. Another group of researchers observed that fibrocytes migrate into the lungs of animals following bleomycin injury. The fibrocyte is a recently recognized cell type of hematopoietic origin which circulates in the peripheral blood and has been shown to play a role in wound repair. Fibrocytes have been implicated in the pathogenesis of hypertrophic scars, scleroderma, and airway fibrosis in asthma. Recent evidence suggests that fibrocytes may play a similar role to the fibroblast in IPF.

Epithelial-Mesenchymal Transformation

Another possibility is that the fibroblasts in IPF are derived from the alveolar epithelium. A transformation of cell type from epithelium to mesenchyme is a well-documented phenomenon that takes place during embryogenesis. Epithelial-mesenchymal transition (EMT) has been demonstrated in tissue culture in response to stimuli with various growth factors. Recently, researchers have observed EMT occurring in adult cells in fibrotic kidney tissue. A new study has described lung tissue from patients with IPF that expressed both epithelial and fibroblast markers, suggesting that EMT plays a role in IPF. A unifying theory might suppose that "frustrated" epithelial regeneration could lead to activation of aberrant signaling pathways, i.e. growth factors, which triggers mesenchymal transformation. Evidence to support this phenomenon has been provided by the finding of Wnt/β-catenin signaling in IPF epithelium. The Wnt/β-catenin pathway is present in early lung development and its presence in adult disease suggests recapitulation of morphogenesis.

Progression through Various Pathological Patterns (NSIP to UIP)

The natural history of IPF is not well understood. In the absence of longitudinal studies of biopsy specimens from IPF patients, controversy exists concerning the difference between "early" and "late" disease. Leading pathologists have promoted the concept that "early" and "late" IPF manifest the same UIP pathological pattern, only "late" disease has more of it. Several observations suggest that the UIP pattern cannot represent an "early" stage of disease but rather corresponds to the intermediate or possibly end-stage of illness.

For example, a UIP specimen contains heterogeneous areas of lung. Normal lung is juxtaposed with areas of active fibrosis while other regions comprise end-stage honeycomb fibrosis. This has often been described as "temporal" heterogeneity with the connotation that the variegated pathological patterns are of different ages. Therefore UIP is an advanced lesion with evidence in the histopathology that a disease process has been underway for some considerable amount of time. This "temporal" heterogeneity has never been proved, since a biopsy specimen can only represent a single point in time. The time course of the UIP lesion has never been described, largely because serial lung biopsies are never obtained. However, a hint of this time course was suggested by analyzing the pathological patterns of multiple biopsy specimens obtained at a single time from patients with fibrotic lung disease. One such study examined biopsies from 109 patients and found that 26 percent had a UIP pattern in one lobe coexistent with an NSIP pattern in another lobe. Eight out of 11 patients who had two biopsies from a single lobe had coexistent UIP and NSIP in that lobe. This illustrates that IPF, even when defined by ATS/ERS diagnostic criteria, can frequently contain more than one histologic pattern. This has prompted some authors to suggest that NSIP could represent an "early" IPF lesion, which progresses over time to an "intermediate" stage comprising coexistent UIP and NSIP patterns, as areas of NSIP transform to UIP. This is an important concept because, if true, it would suggest that early intervention with immunosuppressive therapy to treat NSIP may be beneficial after all for IPF, albeit with a short window of opportunity.

Multiple Hits and Host Defense

A report suggests that herpesvirus DNA is consistently detected in lungs of patients with IPF. Viral DNA is detected in airway epithelial cells. This observation raises the possibility that epithelial injury occurs in response to viral infections, and repeated episodes of infection could be a source of recurrent injury or "multiple hits."

Another observation emerges from analysis of the placebo arm of a large prospective treatment trial involving IPF patients. It was noted that while physiological variables remained stable during the course of the study, a significant number of patients suffered a sudden and fatal deterioration. This suggests that such sudden exacerbations must represent renewed injury or another "hit."

Abnormalities in host defense could predispose to "multiple hits" and may be an underappreciated aspect of pathogenesis in IPF. One endogenous mediator of host defense is prostaglandin E2 (PGE2), which has also been shown to have antifibrotic properties. Evidence points to a reduction of PGE2 in IPF. Fibroblasts from patients with IPF have been shown to have diminished capacity to produce PGE2.

IFN-γ is a pleiotropic cytokine that plays an important role in host defense against infection. The intriguing observation that there may be a survival advantage conferred by IFN-γ, if confirmed, suggests that augmenting host defense mechanisms may be a novel approach to therapy for IPF. The concept of targeting the next "hit" is an important notion in devising future treatments for IPF.

Gastroesophageal Reflux Disease

It has been observed that IPF patients have a high prevalence of gastroesophageal reflux disease (GERD). The contribution of this observation to the pathogenesis of the disease is unknown as no rigorous prospective studies have been performed. Nevertheless, pursuing the diagnosis of GERD in patients with IPF appears warranted and, when identified, treatment according to established practice guidelines is appropriate.

TREATMENT

Pharmacotherapy

The management of IPF presents several challenges, namely, (a) whom to treat; (b) when to treat; and (c) how to select treatment. The third issue remains the most contentious since there is no evidence to date conclusively demonstrating that any drug or drugs unequivocally confers either survival benefit, physiological improvement, or quality of life benefit. However, a number of promising treatments are in various stages of investigation.

Historically, treatment strategies have been directed at suppressing the inflammatory processes of IPF. This strategy was employed despite histologic evidence demonstrating that inflammation is but a meager component of this disease. Alternative therapeutic agents were then developed to inhibit cytokines, proteases, oxidants, and mesenchymal growth factors. The new target for treatment has become the fibrotic processes, including the effector cell of these processes, the fibroblast. Then again, there remains little evidence to support the notion that mature fibrosis can ever be reversed.

In selecting patients for treatment, the ATS/ERS consensus statement on IPF suggests that careful consideration be paid to the risk-to-benefit ratio. The ATS/ERS statement asserts that therapy is not indicated for all patients. Patients should understand the substantial risk of side effects from treatment alongside any potential merits of therapy before deciding upon a course of action. Furthermore, treatment should be reserved for patients who possess clinical features suggesting a more favorable outcome. Meanwhile, treatment should be withheld from patients with unfavorable prognostic indices and a negative net benefit. Patients of older age with worse dyspnea, impaired physiology and advanced fibrosis on HRCT are the least likely to receive benefit. Patients with concomitant chronic diseases (e.g., heart failure, diabetes, or osteoporosis) are most likely to suffer the complications of treatment.

For the patient with favorable prognostic features and for whom therapy may be indicated, the exact time to initiate therapy is unknown. Theoretically, it would be ideal to start treatment during an early phase of disease before pathological changes become irreversible. Still, it is difficult to justify the risks of treatment in physiologically stable patients, asymptomatic or well-compensated patients who have little to gain in terms of a treatment benefit. Such patients require frequent monitoring to identify the onset of impairment or physiological decline. At the first sign of decline, therapy is warranted and should then be considered. The advent of placebo-controlled clinical trials in IPF represents an extraordinary advance in the approach to managing patients with IPF. Since there is no drug of proven benefit, the placebo arm is of critical importance. However, not all patients will have access to clinical trials or desire to participate. A recent study employed a panel of experts to rate the evidence of treatment options in IPF. This study concluded that it was most appropriate to either enroll eligible patients in clinical trials or refer them for a lung transplant evaluation. For patients without access to clinical trials, a corticosteroid as the sole agent was considered inappropriate. Corticosteroids used in conjunction with azathioprine were considered acceptable. With progressive disease interferon γ-1b was recommended. These recommendations based on expert opinion provide guidance for discussion with patients.

Conventional Therapy, Corticosteroids, and Immunosuppressants

In 2000, the ATS/ERS consensus statement on IPF produced treatment guidelines despite several reservations and misgivings. This statement acknowledges the lack of evidence to support any treatment benefit. Unfortunately, corticosteroids have never been studied in a head-to-head trial against placebo to determine their benefit in treating IPF. Nonetheless, first-line recommendations by the ATS/ERS are to use a combination of corticosteroids (prednisone or equivalent) and an immunosuppressant agent (azathioprine or cyclophosphamide). This recommendation is qualified by a statement suggesting that therapy be reserved "for those patients who have been given adequate information regarding the merits and pitfalls of treatment and who possess features consistent with a more likely favorable outcome."

The following regimen is advised: (a) prednisone at a dose of 0.5 mg/kg lean body weight (LBW) per day orally for 4 weeks, 0.25 mg/kg LBW per day for 8 weeks, then tapered to 0.125 mg/kg LBW daily (or 0.25 mg/kg LBW every other day); and (b) azathioprine or cyclophosphamide starting at a dose of 25 to 50 mg per day orally, increasing by 25-mg increments every 7 to 14 days until a maximum dose of 150 mg daily is achieved.

Although corticosteroids are usually tolerable, adverse effects are common and can be serious. Approaches to reduce the risk of steroid-induced osteoporosis are recommended, even during short-term therapy, and should constitute calcium supplementation plus a bisphosphonate drug as necessary. Corticosteroid therapy may suppress the immune response; therefore, tuberculin skin testing is advised before the initiation of therapy. Routine use of trimethoprim/sulfamethoxazole as prophylaxis against *Pneumocystis carinii* may be considered.

Cytotoxic therapy is also associated with numerous adverse effects. Cyclophosphamide and azathioprine use can lead to leukopenia and thrombocytopenia. If the white blood cell count decreases to less than or equal to 4000/mm^3 and the platelet counts fall below 100,000/mm^3, then the dose of azathioprine or cyclophosphamide should be stopped or lowered immediately by 50 percent of the current dose until these hematologic abnormalities recover. Both drugs have oncogenic potential and are also associated with gastrointestinal irritation and alopecia. Cyclophosphamide can lead to hemorrhagic cystitis. Forced diuresis is recommended with this prescription. Cyclophosphamide use poses a risk of cardiotoxicity with higher doses. Azathioprine is considered less toxic than cyclophosphamide as it does not induce bladder injury and has less oncogenic potential. It can, however, induce hepatocellular injury and rash. Azathioprine should be stopped if hepatic enzymes climb to three times the normal level. Monthly blood tests (complete blood count and hepatic function) and urinalysis are required during treatment with cytotoxic agents.

N-Acetylcysteine

Previous studies have demonstrated both an increased oxidant burden in the epithelial lining fluid from patients with IPF as well as diminished antioxidant capacity. These studies formed the basis for a controlled study comparing prednisone and azathioprine with prednisone, azathioprine, and

N-acetylcysteine (NAC). The results of this study showed that NAC slowed the deterioration of forced vital capacity and diffusion capacity after 1 year to a statistically significant extent. There was a high dropout rate in both arms and there was no difference in mortality. Interestingly, there was a significant reduction in bone marrow toxicity in the NAC group. This suggests that NAC may confer protection from the toxic side effects of azathioprine.

Interferon-γ1b

IFN-γ1b is the agent that has drawn the most interest over the last 5 years as a potential therapy for IPF due to the results of several promising clinical trials. The first trial was a small randomized pilot study involving 18 patients with progressive IPF who had already failed treatment with corticosteroids. Patients in this study received either IFN-γ1b and low-dose prednisolone or low-dose prednisolone alone. They were followed prospectively for 1 year. It was found that patients in the interferon group had significant improvement in physiological parameters such as total lung capacity, oxygenation, exercise desaturation, and dyspnea. This pilot study motivated a large multicenter randomized controlled trial to further evaluate IFN-γ1b in IPF. The results of the large study failed to confirm findings from the pilot study; there was no apparent physiological benefit in patients receiving IFN-γ1b. In the multicenter study, 330 patients with steroid-unresponsive IPF were randomized to receive either IFN-γ1b or placebo. Patients were treated for 48 weeks and some received concurrent therapy with up to 15 mg of prednisone daily. The primary endpoint of progression-free survival (a composite end point including death and physiological decline) showed no significant difference. Yet, an unanticipated benefit of IFN-γ1b was suggested by analysis of secondary end points. The study revealed a trend toward improved survival in the interferon group with an absolute reduction in risk of death equaling 7 percent, approaching statistical significance ($p = 0.08$). Furthermore, post hoc analysis indicated that the survival effect may be even more pronounced in the subgroups of treatment-adherent patients and patients with less severe baseline pulmonary function. A second interferon trial, enrolling 800 patients to be followed over 2 years, will examine the primary endpoint of mortality. This trial is currently ongoing and will determine if interferon-γ1b is efficacious in the treatment of IPF.

Pirfenidone

Pirfenidone is an oral antifibrotic compound that has been evaluated in phase I and II trials in IPF. A study from Japan examined the role of pirfenidone in 105 patients with IPF using a 2:1 randomization and a physiological end point incorporating gas exchange with exertion. The study was discontinued prematurely due to concern over excess morbidity in the placebo group and failed to demonstrate efficacy as measured by the primary end point. However, there were differences in forced vital capacity at the end of the study that have stimulated interest in additional clinical trials.

Etanercept

A phase II placebo-controlled trial was performed with the anti-TNF compound etanercept that has shown efficacy in the treatment of rheumatoid fibrosis. The results of this study were presented at the American College of Chest Physicians meeting in Montreal in November 2005. The primary end points of the study involving physiological parameters were not met. However, there may have been some subsets of patients showing benefit that could warrant further study.

Imatinib Mesylate

Imatinib mesylate is a tyrosine kinase inhibitor that has provided a major advance in the treatment of chronic myelogenous leukemia. This wide-ranging inhibitor has activity against the PDGF receptor pathway. Data from animal models suggest that blockade of this pathway could be a promising approach to limit the formation of fibrosis. A randomized and placebo-controlled phase II trial is underway.

Bosentan

Bosentan is an endothelin receptor antagonist that has been an important advance in the treatment of pulmonary arterial hypertension. There is evidence that endothelin expression is increased in lung tissue from IPF patients and experimental evidence that endothelin may be a profibrotic molecule. A randomized and placebo-controlled phase II trial was completed in patients with IPF that has not yet been published in the peer-reviewed literature. Preliminary disclosure of the results revealed that the primary end point of an improvement in 6-minute walk distance was negative. However, subset analysis suggested that there may be a benefit in physiological parameters in some patients and the results were encouraging enough to propose a larger study.

Anticoagulation

Previous studies demonstrated that augmenting the fibrinolytic cascade may inhibit the development of fibrosis. A Japanese trial randomized IPF patients in hospital to receive either prednisolone or prednisolone plus warfarin. Warfarin therapy was managed according to established clinical practice guidelines. Patients were followed for approximately 3 years and a survival advantage was found in favor of warfarin treatment. These results warrant further investigation.

Nonpharmacological Therapy

Lung Transplantation

Lung transplant remains the only therapeutic intervention of proven benefit in IPF. Transplant has been reserved for patients at the advanced stages of IPF and the 5-year survival data approach 50 percent. However, complications of lung transplant remain common and severe. Among the most important complications and the major cause of long-term mortality following lung transplant is bronchiolitis obliterans syndrome (BOS). BOS is an enigmatic process characterized by progressive fibrosis of terminal and respiratory bronchioles

leading to an inexorable decline in transplant function. New therapeutic approaches are sought to control BOS. Therapy for BOS is limited at this time.

Supplemental Oxygen

Patients with hypoxemia (Pa_{O_2} less than 55 mmHg or Sp_{O_2} less than 88 percent) at rest or during exercise can be managed with supplemental oxygen. There is evidence in patients with chronic obstructive pulmonary disease, which suggests that supplemental oxygen relieves exercise-induced hypoxemia and improves exercise performance. Studies examining quality of life (QOL) in patients with IPF emphasize the importance of maintaining a patient's independence and participation in physical activities. In one study that examined QOL in IPF patients, no difference was found between patients receiving supplemental oxygen compared to those who were not receiving oxygen. Thus, any concern can be put to rest that supplemental oxygen would have a deleterious effect on QOL domains such as self-esteem, dependence on therapy, and body image.

Pulmonary Rehabilitation

Patients with IPF should be encouraged to enroll in pulmonary rehabilitation programs. Although pulmonary rehabilitation has not yet been shown to be effective in the IPF population, recent evidence suggests the possibility of benefit from a tailored exercise program. Exercise capacity in the IPF population has been correlated with quadriceps strength, which implies that training of the lower extremities would increase exercise capacity in IPF much the same as it does in COPD. Furthermore, it has been shown that overall quality of life is impaired in IPF, with specific defects in areas of physical health and perceived social independence. Therefore, it has been suggested that pulmonary rehabilitation programs for IPF be designed to include education and psychosocial support elements with the goal of improving coping skills affecting a better quality of life.

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Hypersensitivity Pneumonitis

Richard I. Enelow

EPIDEMIOLOGY AND ETIOLOGIES

Hypersensitivity pneumonitis (HP), or extrinsic allergic alveolitis, is a spectrum of interstitial, alveolar, and bronchiolar lung diseases resulting from immunologically induced inflammation in response to inhalation of a wide variety of different materials that are usually organic or low-molecular-weight chemical antigens (or haptens) that may lead to irreversible lung damage. Despite the terms *hypersensitivity* and *allergic,* HP is not an atopic disease and is not associated with increased IgE or eosinophils. The prevalence of HP is quite variable in different populations, presumably because of differing intensity, frequency, and duration of inhalation exposure, and also probably because of host factors that have yet to be identified. Once thought to be a relatively rare disease, it is becoming more frequently recognized as awareness of the limitations of classical diagnostic criteria has increased. Among pigeon breeders, 8 to 30 percent of pigeon-breeding clubs members who participated in surveys exhibited evidence of HP, so-called pigeon breeder's disease. Among farmers, 0.5 to 5 percent have symptoms compatible with HP, so-called farmer's lung disease. The prevalence of symptoms is lower in farms that use hay-drying methods that decrease exposure to the responsible antigens and increased after a wet summer season.

The population at risk and the season of exposure vary with the type of HP. For example, most cases of farmer's lung disease occur in cold, damp climates in late winter and early spring, when farmers (usually male) use stored hay to feed their livestock. Pigeon breeder's disease occurs chiefly in men in Europe and the United States but predominantly in women in Mexico, owing to differing patterns of exposure, but without a seasonal preference in either population. Bird fancier's disease in Europe and the United States occurs in subjects who keep domestic birds and does not exhibit a predilection to either sex. Japanese summer-type HP occurs mostly in women without an occupation outside the home in June to September in warm, moist parts of the country. The disease has been reported in children as well, although rarely.

In contrast to other pulmonary diseases, there is a curious predominance (80 to 95 percent) of nonsmokers in all examples of HP, which is substantially higher than the proportion of nonsmokers in similarly exposed individuals without HP. The mechanisms of this phenomenon are unknown, but could include anti-inflammatory effects of nicotine. This clinical finding suggests that the presence of active smoking may be evidence against the diagnosis of HP, although this has not been consistently observed.

An important feature of HP is the great variability of susceptibility among exposed populations and the apparent resistance to illness of most exposed persons. Possible reasons include differences in exposure, or differences in the host response to exposure, which may be inborn and/or acquired. There are no differences in the prevalence of atopy or HLA-A, B, or C haplotypes in exposed subjects with and without HP, although there may be an alteration in the prevalence of several HLA-DR and -DQ alleles. An increased prevalence of a particular polymorphism in the TNF-α (tumor necrosis factor-α) promoter has also been reported in patients with

pigeon breeder's disease compared with exposed subjects without pigeon breeder's disease, as well as protective variants in the TIMP3 (tissue inhibitor of metalloproteinase-3) promoter in exposed subjects without pigeon breeder's disease, the possible significance of which is discussed below (see Immunopathogenesis).

A large number of agents are associated with HP, as shown in Table 69-1. Some types of HP have apparently disappeared from their originally described clinical settings (e.g., bagassosis in Louisiana), but presumably exist in areas with similar agricultural or industrial settings. In addition, other forms of HP are being newly recognized (e.g., potato riddler's lung and machine operator's lung). Both the disappearance of previously described examples of HP and the appearance of new examples are due to changing agricultural or industrial practices that result in changes of exposure of subjects to antigenic material that can cause HP. At the present time farmer's lung disease, bird fancier's disease, ventilator lung, and Japanese summer-type HP are the most commonly recognized forms of HP.

Recognition of new examples of HP usually requires a cluster of new cases with a unifying exposure history. Since complete occupational and avocational histories are at times not obtained from patients presenting with "pneumonia," it is likely that there are substantially more examples of HP that have not yet been recognized and described. For example, introduction of a new metalworking fluid led to recognition of machine operator's lung in an auto parts–manufacturing facility due to clustering of cases and a common unusual exposure (*Pseudomonas* in cooling fluid).

CLINICAL FEATURES

The manifestations of the disease may be acute, subacute, or chronic. The stereotypical acute clinical presentation includes transient fever, hypoxemia, myalgias, arthralgias, dyspnea, and cough that occur 2 to 9 h after exposure and resolve in 12 to 72 h without specific treatment (sometimes longer after a particularly intense exposure). Patients exhibit tachypnea, bibasilar rales, and occasionally cyanosis. There is usually peripheral blood leukocytosis with neutrophilia and lymphopenia (without eosinophilia), and bronchoalveolar lavage (BAL) neutrophilia. Subacute or intermittent disease may result from repeated exposures, and manifest as productive cough, dyspnea, fatigue, and weight loss. There may be BAL lymphocytosis, frequently (although not always) with a predominance of CD8+ T lymphocytes.

The chronic form is clinically more insidious, and patients may lack a history of acute episodes, but present with a gradual onset of cough, dyspnea, fatigue, and weight loss. Symptoms are usually present for months to years. There is typically no fever, but tachypnea and bibasilar dry rales are usually present. This form of the disease may be difficult to distinguish from idiopathic pulmonary fibrosis. Symptoms and signs of cor pulmonale are not uncommon at presentation.

The reasons for the different clinical presentations (i.e., acute, subacute, and chronic) of HP are not clear, but could include differences of intensity and duration of exposure (low-intensity long-duration exposure tending to cause chronic HP; high-intensity short-duration exposure tending to cause acute HP). This is most clearly demonstrated in HP due to bird exposure. Long-term exposure to low amounts of bird antigens is associated with chronic HP. Pigeon breeder's disease has different presentations in different geographic areas, manifesting as an acute HP in some and chronic HP in others. Intermittent exposure of pigeon breeders to large amounts of pigeon antigens in the United States and Europe is associated with acute disease and a good prognosis, whereas chronic exposure to a few household pigeons in Mexico is associated with chronic disease and a much poorer prognosis. In the United States and Europe, pigeon breeders keep their animals in an enclosure separate from their living areas, which they visit periodically so that exposure is intermittent. In Mexico, birds are often kept in living quarters so that exposure is constant. It is of interest that bird antigens can persist in a room for substantial lengths of time (more than 18 months) after removal of the birds, so Mexicans with pigeon breeder's disease might be exposed to pigeon antigens for prolonged periods even after removal of the pigeons. Therefore, pigeon breeder's disease in Mexico resembles bird fancier's disease in the United States and Europe in type of exposure, clinical presentation, and prognosis. It differs greatly from the acute HP that characterizes the pigeon breeder's disease in the United States and Europe. Since the relevant antigens are similar in these two examples of bird-associated HP, it is likely that the type of exposure, and not the antigen characteristics, determines clinical presentation and prognosis. The recognition of a new example of HP is usually associated with the acute form, which is likely related to the relative ease in making the association of acute disease and an acute exposure.

The preceding discussion indicates that HP, and particularly chronic HP, may be more prevalent than is readily apparent and may often be confused with other diseases, such as chronic bronchitis or idiopathic pulmonary fibrosis (IPF). The latter may be particularly important because detailed histories are not always obtained from patients with IPF, the serum antibody levels to the agents responsible for HP tend to wane after cessation of exposure, and chest high-resolution computed tomography (CT) scans of chronic HP can resemble those of IPF.

RADIOGRAPHIC FEATURES

The chest radiographs of patients with acute and chronic HP differ significantly. In acute HP, chest radiographs demonstrate diffuse poorly defined nodular radiodensities, often with areas of ground-glass radiodensities or occasionally even consolidation. These radiodensities tend to occur in the lower

Table 69-1

Etiologies of Hypersensitivity Pneumonitis

Disease	Antigen Source	Probable Antigen
Farmer's lung disease	Moldy hay	*Thermophilic actinomycetes* *M. faeni* (*S. rectivirgula*) *T. vulgaris* *Aspergillus spp.*
Bagassosis	Moldy pressed sugarcane (bagasse)	*Thermophilic actinomycetes* *T. sacchari* *T. vulgaris*
Mushroom worker's disease	Moldy compost and mushrooms	*Thermophilic actinomycetes* *M. faeni* *T. vulgaris* *Aspergillus* spp. Mushroom spores
Suberosis	Moldy cork	*Penicillium* spp.
Malt worker's lung	Contaminated barley	*Aspergillus clavatus*
Maple bark disease	Contaminated maple logs	*Cryptostroma corticale*
Sequoisis	Contaminated wood	*Graphium* spp., *redwood dust*, *Pullularia* spp.
Soybean lung	Soybeans in animal feed	Soybean hull antigens
Wood pulp worker's disease	Contaminated wood pulp	*Alternaria* spp.
Wood dust HP	Contaminated wood dust	*Bacillus subtilis* *Alternaria*
Compost lung	Compost	*Aspergillus* spp. *T. vulgaris*
Cheese worker's disease	Cheese or cheese casings	*Penicillium* spp.
Wood trimmer's disease	Contaminated wood trimmings, at times in sawmills	*Rhizopus* spp. *Mucor* spp.
Thatched roof disease	Dried grasses and leaves	*Saccharomonospora viridis*
Greenhouse lung	Greenhouse soil	*Aspergillus* spp., *Penicillium* spp., *Cryptostroma corticale*
Coffee worker's lung	Green coffee dust	Unknown
Potato riddler's lung	Moldy hay around potatoes	*Thermophilic actinomycetes,* *M faeni, T. vulgaris, Aspergillus* spp.
Tobacco worker's disease	Mold on tobacco	*Aspergillus* spp.
Wine grower's lung	Mold on grapes	*Botrytis cinerea*

(*Continued*)

Table 69-1

(*Continued*)

Disease Antigen	Source	Probable Antigen
Woodman's disease	Mold on bark and fuel chips	*Penicillium* spp.
Soy sauce brewer's lung	Fermentation starter for soy sauce	*Aspergillus oryzae*
Domestic allergic alveolitis	Decayed wood	*Fungi Serpula lacrymans, Leucogyrophana pinastr, Paecilomyces variottiii, Aspergillus fumigatus*
Riding school lung	Hay in horse stall	*Thermophilic actinomycetes, M. faeni (S. rectivirgula), T. vulgaris*
Stipatosis	Esparto grass (Stipa tenacissima), used to make plaster	Esparto grass antigens
Pigeon breeder's disease	Avian droppings, feathers, serum	Altered serum/feather proteins
Turkey handler's disease	Turkey products	Turkey proteins
Chicken breeder's lung	Chicken feathers	Chicken feather proteins
Bird fancier's lung	Domestic and wild bird products	Bird proteins
Duvet lung	Duvet and pillow	Goose proteins
Laboratory worker's HP	Rat fur	Rat urine protein
Pituitary snuff taker's disease	Pituitary powder	Vasopressin
Shell lung	Oyster or mollusk shell	Shell proteins
Miller's lung	Grain weevils in wheat flour	*Sitophilus granarius* proteins
Sericulturist's lung	Silkworm larvae	Silkworm larvae proteins
TDI HP	Toluene di-isocyanate	Altered proteins (albumin + others)
MDI HP	Diphenylmethane di-isocyanate	
HDI HP	Hexamethylene di-isocyanate	
TMA HP	Trimetallic anhydride	Altered proteins
Ventilator lung	Contaminated humidifiers, dehumidifiers, air conditioners, heating systems	*Thermophilic actinomycetes, T. candidus, T. vulgaris, Penicillium* spp., *Cephalosporium* spp. *Amoebae Klebsiella* spp. *Candida* spp.
Basement lung	Contaminated basement (sewage or mold)	*Cephalosporium spp.* *Penicillium* spp.
Sauna taker's disease	Sauna water	*Aureobasidium* spp.

Table 69-1

(*Continued*)

Disease Antigen	Source	Probable Antigen
Detergent worker's disease	Detergent enzymes	*Bacillus subtilis*
Japanese summer house HP	House dust, bird droppings(?)	*Trichosporon cutaneum*
Hot-tub lung	Mold on ceiling	*Cladosporium* spp.
Tractor lung	Contaminated tractor, cab air conditioner	*Rhizopus* spp.
Machine operator's lung	Contaminated metal working fluid	*Pseudomonas* spp.
Fertilizer lung	Contaminated fertilizer	*Streptomyces albus*
Sax lung	Saxophone mouthpiece	*Candida albicans*

lobes and spare the apices. Linear radiodensities (presumably representing areas of fibrosis from previous episodes of acute HP) may also be present. The nodular and ground-glass densities tend to disappear after cessation of exposure, so the chest radiograph may be normal after resolution of an acute episode of HP (Fig. 69-1). High-resolution CT scans often demonstrate ground-glass densities better than chest radiographs and at times reveal diffusely increased pulmonary radiodensities. They may also become normal after resolution of an acute episode. Pleural effusions or thickening, calcification, cavitation, atelectasis, localized radiodensities (coin lesions or masses), and intrathoracic lymphadenopathy are rare.

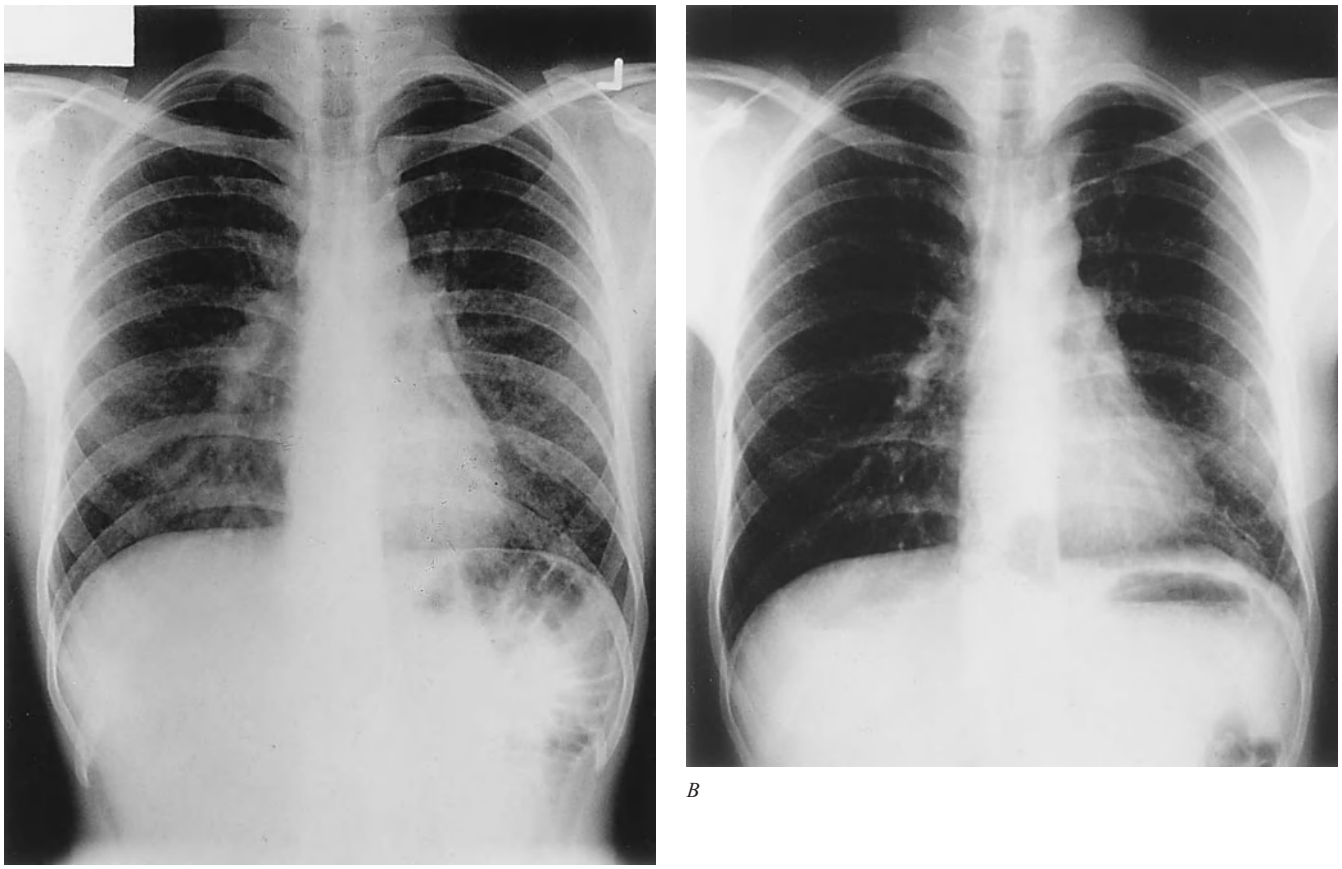
In chronic HP, chest radiographs are notable for diffuse linear and nodular radiodensities, with sparing of the bases and upper-lobe predominance, and volume loss (Fig. 69-2). Pleural effusions and thickening are very unusual, although subcutaneous emphysema (presumably as a consequence of pleural rupture due to bronchiolitis and lobular overinflation) has been reported.

High-resolution CT scans of patients with chronic HP demonstrate several patterns. Most commonly there are multiple centrilobular nodules 2 to 4 mm in diameter throughout the lung fields, with some areas of ground-glass radiodensities, especially in the lower lobes (Fig. 69-3). Unlike sarcoidosis, the nodules are seldom attached to the pleura or bronchovascular bundles, and the border between the nodules and the surrounding lung is well demarcated. There are also well-delineated areas of increased radiolucency, which are presumably overinflated pulmonary lobules subserved by partly occluded bronchioles. The ground-glass densities and micronodules tend to resolve after cessation of exposure. Although these findings are suggestive of HP, they are found in only a subset (50 to 75 percent) of patients with HP, and high-resolution CT scans of the lungs of patients with HP can resemble those of patients with IPF. Emphysematous abnormalities are also commonly detected by high-resolution CT scans in nonsmoking patients with farmer's lung disease.

LABORATORY FINDINGS

Patients with acute HP often have a peripheral blood leukocytosis with neutrophilia and without eosinophilia. Prominent cellular abnormalities may also seen in their BAL fluid, which may be useful in supporting the diagnosis of HP. At time points greater than 5 days after the last exposure, a two- to fourfold increase in BAL fluid leukocytes and lymphocytosis (typically 30 to 70 percent of total cells) are frequently noted. In most instances of HP, the BAL fluid lymphocytes are virtually all CD3+ (T lymphocytes), with a relative increase of CD8+ cells, so that the CD4:CD8 ratio is usually less than 1 (normally 2 to 2.5, as in peripheral blood). This profile varies significantly with the stage of disease. Furthermore, BAL lymphocytosis may persist for years following clinical improvement and apparent removal from antigen exposure. Conversely, exposed asymptomatic individuals may exhibit BAL lymphocytosis, further limiting its utility in diagnostic evaluation. After recent (less than 48 h) exposure, as well as in advanced disease, the lavage is frequently characterized by BAL fluid neutrophilia. The concentrations of IgG, IgM, IgG, and albumin are increased in BAL fluid, presumably a nonspecific manifestation of pulmonary inflammation.

Many patients with HP have easily demonstrable antibodies (typically IgG, IgM, and IgA) to the offending material



A

B

Figure 69-1 *A*. Chest radiograph of a patient with pigeon breeder's disease with fever, dyspnea, and bibasilar rales. The patient had kept pigeons for 5 years and presented with fever, dyspnea, and myalgias approximately 8 h after cleaning the pigeon coop. He had serum antibody to pigeon dropping extract. Note bilateral lower lobe 2- to 3-mm nodules. *B*. Chest radiograph of the same patient 2 weeks later without specific treatment. Note clearing of the lower-lobe nodules and the staples in the left chest from the open lung biopsy.

in the serum, detectable by a variety of methods. Since antigen preparations are not standardized, it is difficult to be confident of the meaning of a negative result; therefore, negative "hypersensitivity pneumonitis panel" does not exclude the diagnosis of HP. Furthermore, since serum antibody is also present in many exposed, but not ill, subjects in virtually the same amounts as in patients with HP, the presence of antibody should be considered supporting data in the proper clinical context.

In asymptomatic pigeon breeders, the prevalence of antibody to pigeon antigens is 30 to 60 percent. In farmers, the prevalence of anti–*Micropolyspora faeni* serum antibody is 2 to 27 percent. The occurrence of serum antibody is not consistently related to apparent exposure (i.e., hours of exposure or intensity of exposure) in most instances of HP. This may be related to a threshold effect, so that most exposures are above the minimum required to induce antibody and increases above that threshold are not associated with increases of the prevalence of antibody. In addition, serum antibody tends to wane after cessation of exposure, so patients with chronic HP who have not been exposed for some time may not have demonstrable antibody. In farmer's lung disease, approximately 50 percent of patients with initially positive serum antibody to *M. faeni (Saccharopolyspora rectivirgula)* lose demonstrable antibody 6 years after cessation of exposure. Farmers who continue to farm also lose detectable antibody (35 to 50 percent in 5 years), and some asymptomatic farmers who were initially negative later develop antibody without farmer's lung disease. In pigeon breeder's disease and bird fancier's disease, approximately 50 percent of patients with initially positive serum antibody to avian antigens lose demonstrable antibody 2 to 3 years after cessation of exposure. Therefore, it is possible that patients with HP will have no detectable serum antibody owing to either use of an inappropriate antigen in the assay or the waning of antibody in time since the last exposure.

Serum markers of systemic inflammation, such as increased sedimentation rate and C-reactive protein, are often elevated during an acute episode of HP, although they are quite nonspecific. There is increased uptake of gallium-67 in the lungs of patients with active HP, which declines with resolution of the disease, although this is also nonspecific.

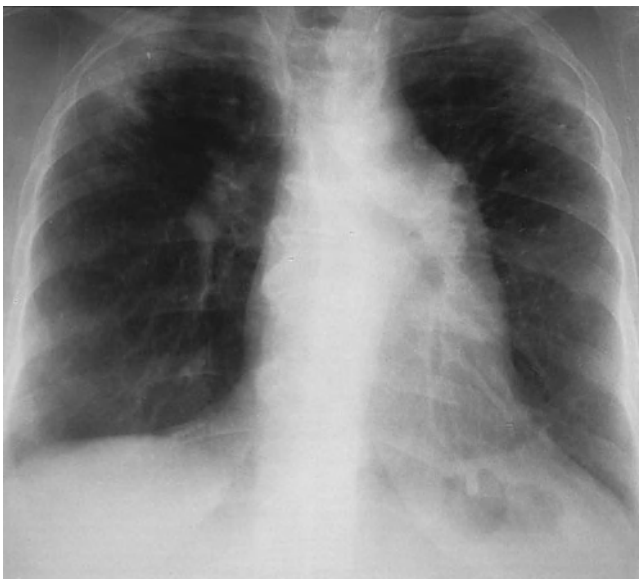


Figure 69-2 Chest radiograph of a patient with bird fancier's disease who presented with progressive dyspnea and weight loss. She had kept two to three parakeets in her home for 15 years and did not notice episodic fever or acute dyspnea. She had positive serum precipitins to parakeet serum, severe restrictive disease, and resting hypoxemia. Note the diffuse radiodensities, loss of volume of the upper lobes, and pulmonary hypertension.

In contrast to sarcoidosis, the serum angiotensin-converting enzyme levels are usually not elevated. Skin tests (either immediate or delayed type) to detect sensitization to the suspected antigens are not useful, since extracts of agents that cause HP produce nonspecific reactions that do not indicate sensitization and do not discriminate between sensitized and nonsensitized subjects.

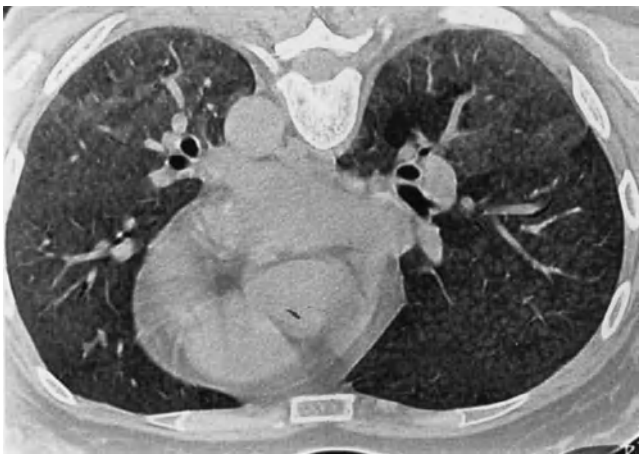


Figure 69-3 High-resolution computed tomography scan of a nonsmoking patient with exposure to both birds and shells who presented with progressive dyspnea and weight loss and had hypoxemia and a restrictive ventilatory defect. Note the diffuse nodular radiodensities in the lower lobes, with areas of ground-glass densities posteriorly.

Pulmonary function tests may be restrictive, obstructive, or mixed. There is an increased lung elastic recoil, and usually decreased diffusing capacity. Arterial hypoxemia with hypocapnia reflecting an increased A-a oxygen gradient either at rest or after exercise is common. Many patients with HP (20 to 40 percent) exhibit increased nonspecific airway reactivity, and 5 to 10 percent also develop clinical asthma. The increased airway reactivity and asthma tend to diminish after cessation of exposure.

DIAGNOSIS

The symptoms, signs, and laboratory findings of acute HP can resemble those of many other lung diseases, including pulmonary edema, organic dust toxic syndrome, inhalation fever, chronic bronchitis, and some pneumoconioses. Acute HP is also often confused with infectious pneumonia (viral, mycoplasma, or chlamydia in subjects exposed to birds). Subacute HP is characterized by a more gradual onset of cough, fatigue, dyspnea, and weight loss, and such symptoms may also develop with intermittent acute attacks. There is considerable overlap in the presentations of acute and subacute HP, in contrast to chronic progressive HP (discussed in the following).

Chronic bronchitis in nonsmoking farmers and bird breeders is more common than HP, and may share overlapping immunopathogenic mechanisms with HP. The finding of serum precipitins is more frequent in farm workers with chronic bronchitis than those who are asymptomatic. Organic dust toxic syndrome (ODTS) has been seen in some of the same populations exposed to materials that cause HP, although its cause is likely mycotoxins from bioaerosols contaminated with toxin-producing fungi. ODTS can occur in a larger proportion of the exposed population than HP and is characterized by transient fever, dyspnea, nonproductive cough, peripheral blood leukocytosis, and BAL fluid neutrophilia. The manifestations commonly include diffuse opacities on chest radiograph, restrictive ventilatory defects, reduced D_{LCO}, and bronchiolitis obliterans without granulomas on lung biopsy. Diffuse alveolar damage may occur in severe cases. In contrast to HP, prior sensitization is not required (as indicated by the absence of serum antibodies). Patients presenting with ODTS tend to have more intense exposure of shorter duration than those who present with farmer's lung disease. Another disease caused by exposure to the some of the same agents associated with HP is inhalation fever. This is manifest as fevers, chills, malaise, headaches, and myalgias without prominent pulmonary findings, although mild dyspnea and cough may occur. The onset usually occurs 4 to 12 hours after exposure. Usually there are normal lung volumes and diffusing capacity. The clinical syndrome remits after 12 to 24 h without specific therapy. Symptoms and signs are exaggerated following an exposure that occurs after a period of nonexposure (such as

vacations or weekends), but then become blunted despite continued exposure ("Monday illness"). All signs and symptoms of inhalation fever remit after cessation of exposure, and there are no permanent physiological or radiographic changes.

In contrast to acute and subacute HP, the classic or typical clinical findings are usually not present in chronic HP. The chronic form of HP often resembles IPF, and these entities may be extremely difficult to distinguish. The differential diagnoses also includes other causes of pulmonary fibrosis (e.g., drug reactions, rheumatologic disease, asbestosis, radiation). Further complicating matters is the frequent lack of clear history of acute episodes. In addition, removal from the presumptive offending agent may result in little or no clinical improvement at this stage.

A thorough and complete occupational and avocational history is essential to the diagnosis of all forms of HP. The history should seek to establish a link between a particular exposure (at work, at home, or elsewhere) and previous episodes of "pneumonia." Knowledge of other exposed persons with similar symptoms should be sought. Evidence of repetitive appropriate symptoms and laboratory and radiologic abnormalities associated with exposure to a particular environment is also highly suggestive of HP. In questionable instances, a "natural exposure" (i.e., documentation of appropriate symptoms and laboratory abnormalities after exposure to a suspect environment) can be used to diagnose HP. A "natural exposure" challenge should not be considered positive unless there is objective evidence of a change in temperature, total peripheral white blood cell count, chest radiograph (or high-resolution CT scan), or a decrease in diffusing capacity (or arterial P_{O_2}). If the history suggests a relationship between exposure and pulmonary symptoms, evidence of sensitization and the nature of the pulmonary inflammatory response should be determined. Sensitization is indicated by the presence of serum antibody to an agent known to cause HP. A large proportion of lymphocytes in BAL fluid (usually over 40 percent) is highly suggestive of, although not specific for, HP.

A variety of tools exist that have utility in the diagnosis of HP, all having certain advantages and disadvantages (summarized in Table 69-2). One of the difficulties in assessing the value of diagnostic methods in HP is the vagueness of the "gold standard." Although most would agree that the presence of poorly formed, airway-centered non-necrotizing granuloma on lung biopsy in a patient with exposure to a known offending agent is supportive enough to be "diagnostic," these features are commonly absent, and a number of histologic variants have been described. Since the utility of lung biopsy, absent classic features, is largely supportive, several prediction rules have been devised to determine the probablility of a diagnosis of HP based upon clinical features. One such model, developed by the Hypersentitivity Pneumonitis Study Group, examined a cohort of 400 patients with suspected HP and found six significant predictors retrospectively (116 were ultimately diagnosed with HP). These were then validated prospectively in 261 patients (83 of whom were eventually given the diagnosis). It should be noted that the ultimate determination, or gold standard, was the consensus of experts, in many cases without tissue. Although not ideal, at the current level of understanding of the nature of HP, this may be the best method available. The criteria used in this study were: (a) exposure to a known offending antigen; (b) positive precipitating antibodies to the offending agent; (c) recurrent episodes of symptoms; (d) inspiratory crackles on physical examination; (e) symptoms occurring 4 to 8 hours after exposure; and (f) weight loss. The probability of having HP was determined based upon the presence or absence of these predictors (Table 69-3). The probability of HP ranged from 0 percent in those patients with none of the predictors to 98 percent in patients with all six of these features. Exposure to a known offending antigen was the strongest clinical predictor with an odds ratio of 38.8; absent this critical feature the diagnosis was made only after further investigation and supportive findings on lung biopsy (discussed in the following). It should be emphasized that these clinical prediction rules are of little value in chronic HP, which is usually a more difficult diagnostic problem (often even when histopathology is available). Of course, in the evaluation of individual patients, the threshold for further investigation clearly depends upon the clinical setting and the consequences of the diagnosis.

HISTOPATHOLOGY

A lung biopsy specimen is generally required when there is significant doubt about the diagnosis. Transbronchial lung biopsies often do not provide sufficient material to fully establish the presence and interrelationships of granulomas, bronchiolitis, and interstitial inflammation, so either open or thoroscopically obtained lung biopsies may be necessary. These often reveal chronic interstitial and alveolar inflammation with infiltration of plasma cells, mast cells, macrophages, and lymphocytes, usually with poorly formed nonnecrotizing granulomas (Figs. 69-4 and 69-5). The inflammation usually extends from the terminal bronchioles into the parenchyma. Foamy macrophages are usually evident in the alveoli. There is often bronchiolitis as well as bronchiolitis obliterans. Organizing pneumonia is also present in up to 50 percent of patients with HP (Fig. 69-6). Conversely, patients with recognized bronchiolitis obliterans with organizing pneumonia (BOOP) may have underlying HP, whether or not other histologic manifestations are evident. Varying degrees of interstitial fibrosis are also often present. The granulomatous interstitial inflammatory responses of HP and sarcoidosis can be difficult to differentiate, although in HP they are usually smaller, poorly differentiated, loosely arranged, and contain more lymphocytes and fewer multinucleated giant cells. In contrast to sarcoidosis, the interstitial inflammatory cell infiltrate in HP occurs distal as well as proximal to the granulomas. The granulomas of HP also tend not to occur in groups and tend not to occur near bronchi or in subpleural locations.

Table 69-2

Advantages and Disadvantages of Methods Used in the Diagnosis of Hypersensitivity Pneumonitis

Method	Advantages	Disadvantages
Clinical history	Simple, sensitive	Low specificity
Precipitins	Relatively sensitive	False negatives (lack of standardized extracts)
IgG ELISA	More sensitive	Identifies IgG production not disease
Radiologic evaluation Chest x-ray CT scan	 Simple affordable More sensitive	Can be normal, nonspecific
Pulmonary spirometry	Relatively simple, affordable	Not specific for HP; HP not ruled out by a normal test
Gas exchange (D_{LCO})	Simple sensitive	Not specific for HP; HP not ruled out by a normal test
Lymphocyte proliferation test with specific antigens	More reliable in distinguishing disease from mere exposure	Few specialized centers, lack of adequate reagents (antigens), not validated yet
Bronchoalveolar lavage	Assess inflammation, normal lymphocyte count rules out active HP	Different stages of inflammation; affected by time lapse since last antigen exposure; typical but not specific
Lung biopsy	Histopathology highly suggestive	Different stages of disease; not pathognomonic
Specific inhalation challenge in the laboratory	If positive, confirmatory	If negative diagnosis not ruled out; few specialized centers; not standardized
"Natural challenge" with clinical and functional monitoring	If negative under usual exposure conditions rules out diagnosis; but if positive, is confirmatory	Difficult to differentiate from ODTS; requires collaboration (patient and staff)

Note: Abbreviations: HP = hypersensitivity pneumonitis; ODTS = organic dust syndrome.
Source: From: Fink Y, Ortega H, Reynolds H, et al: Needs and opportunities for research in hypersensitivity pneumonitis. Am J Respir Crit Care Med *171:792, 2005; Copyright © 2005 American Thoracic Society, with permission.*

Instead, they are usually adjacent to bronchioles and are often single. In the absence of granulomas, the pattern may remble that of nonspecific interstitial pneumonitis, although the bronchiolocentric nature of the lesions and the presence of giant cells or organizing pneumonia may be clues suggesting underlying HP.

The specific histologic changes of HP, when present, are quite helpful in making the diagnosis. However, the granulomas and respiratory bronchiolitis may not be present years after cessation of exposure, so only interstitial inflammation and fibrosis remain in many subacute and most chronic cases. Although these findings might be useful in supporting the clinical diagnosis of HP, they would be insufficient to confirm it.

IMMUNOPATHOGENESIS

Although poorly understood, the bulk of the evidence obtained in the past 25 years suggests a primary role for T-cell–mediated events in the pathogenesis of HP; however,

Table 69-3

Clinical Probability of Having Hypersensitivity Pneumonitis

Exposure to a Known Offending Antigen	Recurrent Episodes of Symptoms	Symptoms 4–8 h After Exposure	Weight Loss	Crackles, %			
				+		−	
				Serum Precipitins		Serum Precipitins	
				+	−	+	−
+	+	+	+	98	92	93	72
+	+	+	−	97	85	87	56
+	+	−	+	90	62	66	27
+	+	−	−	81	45	49	15
+	−	+	+	95	78	81	44
+	−	+	−	90	64	68	28
+	−	−	+	73	33	37	10
+	−	−	−	57	20	22	5
−	+	+	+	62	23	26	6
−	+	+	−	45	13	15	3
−	+	−	+	18	4	5	1
−	+	−	−	10	2	2	0
−	−	+	+	33	8	10	2
−	−	+	−	20	4	5	1
−	−	−	+	6	1	1	0
−	−	−	−	3	1	1	0

All the predictors are dichotomous variables: − = absent; + = present.

Source: From: Lacasse Y, Selman M, Costabel U, et al. Clinical diagnosis of hypersensitivity pneumonitis. Am J Respir Crit Care Med *168:952, 2003; Copyright © 2003 American Thoracic Society, with permission.*

a contribution of humoral immunity, especially in acute HP, has not been excluded. The presence of serum antibody in patients with HP and the timing of symptoms after exposure (2 to 9 h) led to the hypothesis that HP represents an example of immune complex–mediated lung disease. Therefore, it is possible that immune complexes initiate the injury upon antigen exposure, which is then perpetuated and amplified by T-cell activities. By the time the disease is clinically evident,

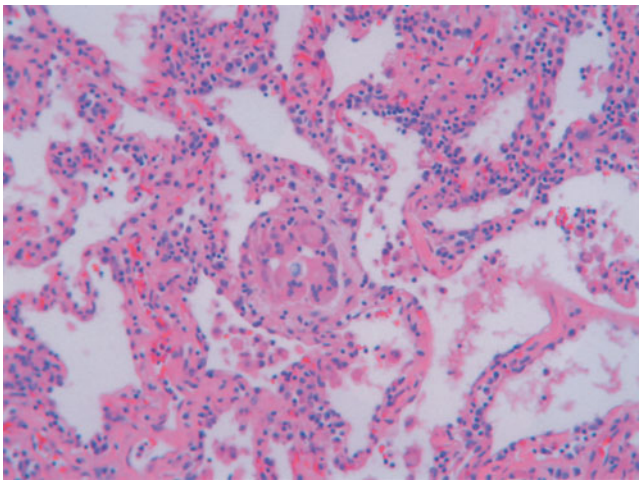


Figure 69-4 Low power view (20×) of H&E-stained section of surgical lung biopsy from a patient with bird fancier's disease. There is nonspecific interstitial mononuclear inflammation and loosely formed granulomatous lesions.

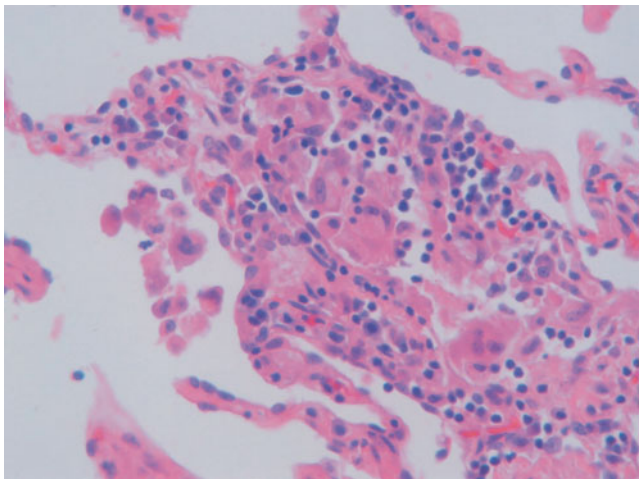


Figure 69-5 Higher-power view (40×) of the section shown in Fig. 69-4.

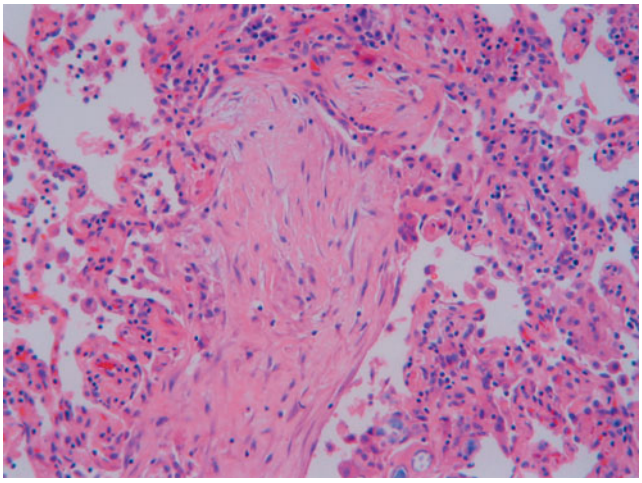


Figure 69-6 Organizing pneumonitis in a patient in a patient with bird fancier's disease.

lung tissue gene expression profiles indicate T-cell–driven inflammation (in contrast to the profiles of IPF and NSIP). The T cell responses evident in HP are notable for the predominance of CD8+ cells and the expression of interferon-γ, the prototypic cytokine of type 1 inflammatory processes. Expression of interferon-γ–dependent chemokines, such as CXCL9 and CXCL10, is also observed in HP lungs, which undoubtedly serves to amplify the type 1 inflammation. Not unexpectedly, CD8+ T cells in BAL of HP patients strongly express CXCR3, the receptor for both of these chemokine.

In animal models of HP, macrophage-derived cytokines such as IL-1, IL-6, IL-12, and TNFα (as well as a variety of chemokines) play a central role in models that entail intrapulmonary administration of various antigenic substances. TNF-α, produced by activated macrophages as well as CD8+ T cells, likely participates both in the amplification of the inflammation and the activation/degranulation of neutrophils recruited to the alveolar space. Interestingly, polymorphisms in the TNF-α promoter have been reported in a group of patients with farmer's lung disease, which correlated with higher serum levels of TNF-α after challenge with hay dust, compared with a group of sensitized asymptomatic controls. Two small genetic susceptibility studies in Mexican and Dutch patients with bird fancier's disease found protective polymorphisms in the tissue inhibitor of metalloproteinase-3 (TIMP-3) gene, which is involved in the inhibition of metalloproteinases associated with extracellular matrix turnover. TIMP-3 has also been identified recently as the primary inhibitor of TNF-α–converting enzyme (TACE/ADAM-17), and this enzyme is responsible for processing TNF-α to its soluble form, which is intensely proinflammatory. The TIMP-3 polymorphism was not found in patients with IPF or NSIP. Therefore, it is reasonable to speculate that the expression and/or proteolytic processing of TNF-α is important in the pathogenesis of HP, although clearly this leaves much to be explained concerning the varying clinical pictures of the disease.

PROGNOSIS AND TREATMENT

Prognosis varies considerably with the type of HP and even the geographic location. For example, farmer's lung disease has a good prognosis in Quebec, even in farmers who continue to farm. However, farmer's lung disease in Finland often results in significant physiological impairment and even death. Pigeon breeder's disease has a good prognosis in the United States and Europe, whereas the same disease in Mexico has a 30 percent 5-year mortality. The reasons for these differences are not clear but may include differences in the nature of the antigen and the exposure.

Identification of the offending antigen is critical to effective avoidance, which is the primary intervention in all forms of HP. This is not always practical when the exposure is occupational, such as in farmer's lung disease. In addition most farmers who continue to be exposed may fare no worse than those who leave their farms. Nevertheless, removal from exposure to the offending antigen(s) is usually sufficient to resolve symptoms and physiological abnormalities. Measures to reduce antigenic burden may include protective equipment and reducing microbial contamination of the home or work environment. Elimination of excess moisture, reduction in humidity, repair of water damaged materials, regular cleaning of humidifiers, ventilation, and air conditioning equipment all contribute to reduction in mold and other microbial colonization that may predispose to sensitization. Removal of birds from the home of patients with bird fancier's disease is a critical aspect of treatment, but antigens may persist for extended periods despite thorough cleaning of the home environment.

Systemic glucocorticosteroids are usually required to treat severely symptomatic patients, although there is no formal evidence that such treatment is associated with long-term abatement of symptoms or radiologic or pulmonary function test abnormalities. The usual treatment is prednisone or prednisolone, 40 to 60 mg a day for 2 weeks, followed by a gradual decrease over 2 to 4 weeks. Patients with farmer's lung disease treated with prednisolone, compared to those not treated with prednisone, demonstrated slightly more rapid resolution of some radiologic (ground-glass opacities) and some physiological abnormalities than untreated patients (slight improvement of diffusing capacity, no difference in lung volumes or arterial P_{O_2}). However, there were no differences between the groups 6 months after the diagnosis of HP. The above evidence suggests that systemic steroids may slightly increase the rate of resolution of acute pulmonary inflammation but have little or no effect on chronic residue of HP.

If patients are removed from exposure before there are permanent radiologic or physiological abnormalities, the prognosis is excellent, with little evidence of long-term ill effects. If removal from exposure is impossible, the use of efficient masks during exposure can result in prevention of acute HP and an excellent prognosis. The prognosis varies considerably with different types of HP. In general, bird fancier's disease carries a worse prognosis than other forms of HP,

although even this varies considerably depending on the specific nature of the exposure. It appears that long-term low-level exposure is associated with a poorer prognosis, whereas short-term intermittent exposure is associated with a more favorable one. Unfortunately, many patients with chronic HP present with pulmonary fibrosis and physiological abnormalities that are only partly reversible after cessation of exposure. The specific nature of histopathologic findings on biopsy in these patients at the time of diagnosis may help predict subsequent clinical course of the disease. Not surprisingly, patients with organizing pneumonia/BOOP or cellular NSIP have a better prognosis than those with fibrotic NSIP or other patterns of fibrosing pneumonitis.

In conclusion, HP is an immunologically mediated lung disease likely mediated primarily by T-cell responses to inhaled antigens. The diagnosis requires careful history, appropriate laboratory tests, and lung biopsy in selected cases. Avoidance of exposure is usually associated with a good prognosis, and corticosteroids are indicated in severely symptomatic patients. Because of constantly changing environmental exposures, new examples of HP are continually being described, and represent an ongoing challenge in patients presenting with undefined interstitial lung disease.

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70

Radiation Pneumonitis

Kenneth B. Roberts • Sara Rockwell

The discovery of x-rays by Roentgen in 1895 and the discovery of radium by the Curies in 1898 revolutionized medicine at the turn of the twentieth century. Roentgen's first paper on x-rays illustrated the power of diagnostic imaging with a radiographic image of Frau Roentgen's hand. As researchers around the world built vacuum tubes and acquired radioactive sources for their studies, it rapidly became apparent that these invisible radiations could produce dangerous and even lethal injuries. Erythema, chronic dermatitis, ulceration, loss of hair, and eye injuries were soon reported in patients who received large doses of radiation during prolonged fluoroscopy procedures. Even greater injuries were reported among the physicians, technicians, and scientists who performed diagnostic procedures or laboratory studies using unshielded x-ray generating equipment and highly radioactive sources. The development of these radiation injuries suggested that radiation might be useful in the treatment of cancer, and cancer patients were treated with radiation therapy as early as 1896. Radiation was found to inhibit the growth of tumors, but this benefit came with the cost of injury to the normal tissues within the irradiated area. Because of the very low energy of the early x-ray and gamma-ray sources, radiotherapy in its early days was limited to using poorly penetrating radiations, which delivered much higher doses of radiation to skin than to even very superficial tumors. As a result, severe early radiation reactions in the skin limited the doses of radiation that could be delivered to tumors. Studies of these skin reactions led to the development of the concept of normal tissue tolerance and an appreciation of the benefits of "fractionated" radiotherapy, using multiple treatments with small doses of radiation. The relative sensitivity of the lung to injury from radiation became apparent early in the development of radiation oncology. The clinical syndromes of dyspnea, cough, fever, and radiographic infiltrates occurring weeks to months after irradiation of the thorax were dramatic enough to be described as early as 1922.

The field of radiation oncology has matured immeasurably over the last century and has incorporated significant advances from fields as diverse as theoretical and applied physics, radiation biology, pathology, cell biology, and immunology. The importance of advances in physics and engineering to the maturation of radiation oncology is especially notable. These advances have led to the development of modern linear accelerators capable of delivering very high-energy, deeply penetrating radiations, which can be used to deliver high radiation doses with great precision to tumors deep within the body. Precise systems for radiation dose measurement, or *dosimetry,* rapid computers and precise algorithms for the rapid computerized three-dimensional planning of individualized radiotherapy treatments based on computed

tomography (CT) scans and magnetic resonance imaging (MRI) studies have been developed. These advances have changed the dose-limiting toxicities of radiation therapy from painful early reactions in the skin to life-threatening late reactions in the normal tissues invaded by and surrounding the tumors, including the lung.

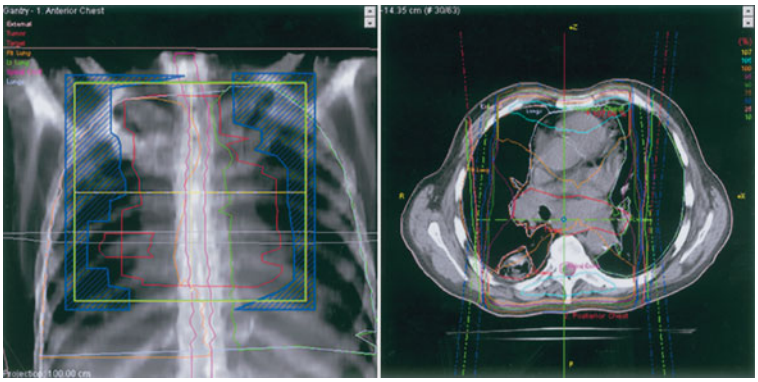
To the readers of this book, understanding radiation pneumonitis is important for two reasons. First, an understanding of radiation injury to the lung can be useful in understanding other lung diseases. Because the chemical mediators of radiation effects, both beneficial and harmful, are free radicals, the pathway leading to radiation injury overlaps with those leading to many other lung injuries. Second, understanding radiation pneumonitis has practical value to physicians in many areas of medicine. Approximately one in three people in the United States will be diagnosed with cancer at some point in their lifetimes. Over half of these patients will be permanently cured of their malignancies. Approximately 65 percent of all cancer patients now receive radiotherapy at some point in the treatment of their malignancies, and radiotherapy seems destined to remain an important component of cancer treatment for the foreseeable future. Because of this, every physician can expect to care for many patients who are receiving radiotherapy or have received radiotherapy at some point in the past. In addition, recent studies of plutonium workers have shown an excess incidence of pulmonary fibrosis. These findings, which are supported by data from a large number of studies in experimental animals, show that lung injury can be produced by inhalation of insoluble particulate radionuclides that are deposited in lung tissue and produce long-term irradiation of the tissue. Therefore, radiation injury to lung is possible in cases in which people are exposed to high levels of inhaled radionuclides through their occupations, accidents, or acts of war or terrorism. A working knowledge of the basics of radiobiology and radiation oncology is important to every physician and health care provider. An understanding of the potential toxicities of radiotherapy, including radiation pneumonitis, can be critical to patient care.

Many neoplasms involving the thorax are treated with regimens that include the use of radiotherapy to produce either cure or palliation. Radiotherapy is principally a localized, anatomically based modality. The success of radiotherapy hinges on delivering radiation selectively to the sites of malignant disease, while sparing to the maximal extent possible the uninvolved normal tissues. To plan radiotherapy treatments effectively, the radiation oncologist must have a sophisticated appreciation of the malignancy being treated and must understand its biologic behavior, its patterns of local and metastatic spread, its radiosensitivity, and the factors that influence the responses of individual patients to therapy. The radiation oncologist must also consider the effects of radiation on the normal tissues within the treatment volumes. Many factors, including the radiation dose, the fractionation pattern of the radiotherapy, the volume of the tumor and involved margins, the prior or planned use of other therapies such as surgery or systemic chemotherapy, and the presence of other diseases, influence both the probability of controlling the neoplasm and the probability of producing toxic reactions. For cancers of the lung, esophagus, pleura, breast, and chest wall, as well as for lymphomas involving the thorax, optimal treatment frequently involves the use of multiple overlapping x-ray beams and possibly electron beams, planned to encompass all of the cancer-containing tissues. Although treatments are carefully planned to include the smallest possible amount of healthy normal tissue, some normal tissue will necessarily be included in the radiation fields. The radiation sensitivity of the specific tissues in the irradiated fields and the acceptable level of risk for complications combine to limit the dose of radiation that can be administered. The planning of radiotherapy always involves a balance of benefit and risk, because the probabilities of controlling the malignancy increase with increasing radiation dose, but the probabilities and severities of the potential complications increase with dose as well.

To illustrate the mechanisms involved in planning radiotherapy treatments, a relatively straightforward treatment plan is depicted in Fig. 70-1*A*, which shows the isodose distribution for treatment of a stage IIIB non–small-cell lung cancer. Such intrathoracic tumors are often treated initially using daily irradiations through both anterior and posterior portals. The volume of normal tissue, in particular the lung, within the region receiving a full dose of radiation can be readily appreciated. After reaching the maximum dose that could be delivered safely to the spinal cord, boost fields using obliqued x-rays beams were then delivered, as shown in Fig. 70-1*B*. The radiation dose delivered both to the tumor and to the lungs is summarized by a "dose-volume histogram," shown in Fig. 70-1*C*, which integrates the proportion of the targeted organ or tumor receiving a certain cumulative radiation dose. While this dose-volume relationship loses important spatial and functional information, this formalism has become important in analyzing radiation dose delivery to correlate dosimetry with treatment outcome. In this illustration, the volume of lung receiving greater than 20 Gy is referred to as the V_{20}. In this case it is greater than 30 percent, which roughly predicts for an increased risk of pneumonitis. In fact, a follow-up chest radiograph (Fig. 70-2*A*) and CT scan (Fig. 70-2*B*) reveal a pattern of radiation-induced inflammatory changes corresponding to the high-dose region of the radiotherapy. In a case such as this, if the malignancy is cured or the patient experiences the desired improvement in the symptoms from the malignant disease with minimal or manageable toxicity from the radiotherapy, then the treatment has produced a desirable result even if it produces radiographic changes or measurable clinical damage to the lung or other organs. Overt pulmonary toxicity is, however, a potential consequence of thoracic radiotherapy, which sometimes overshadows the benefits of treatment.

BRIEF OVERVIEW OF RADIOLOGIC PHYSICS

External-beam radiotherapy is generally delivered using x-rays or gamma rays. Both of these radiations are high-energy electromagnetic waves or photons that are able to



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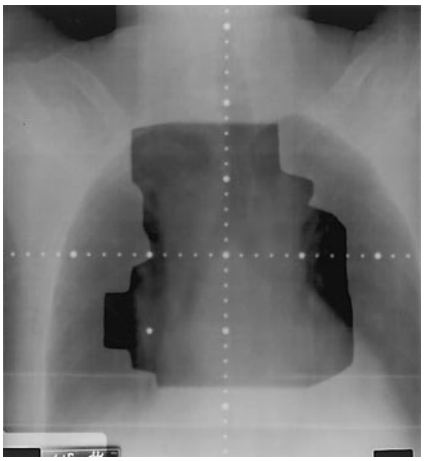

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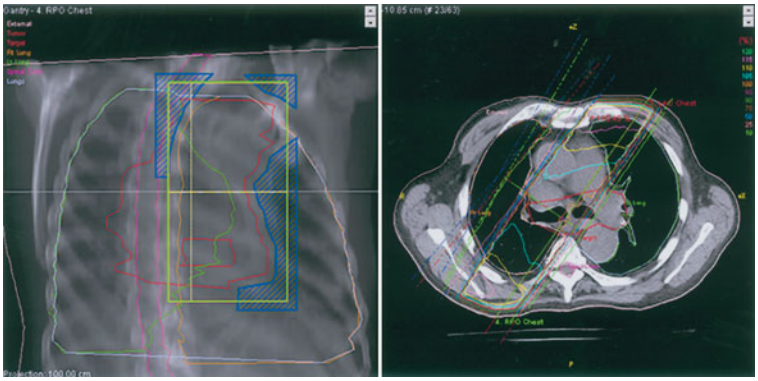

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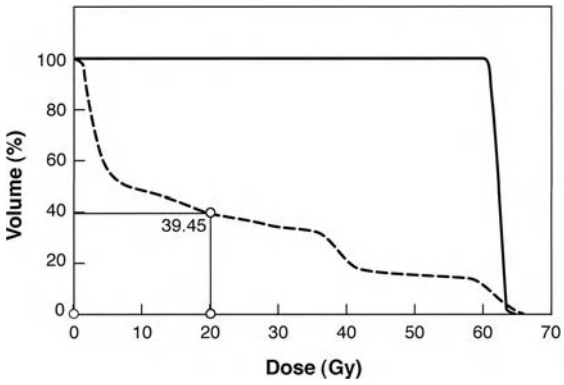

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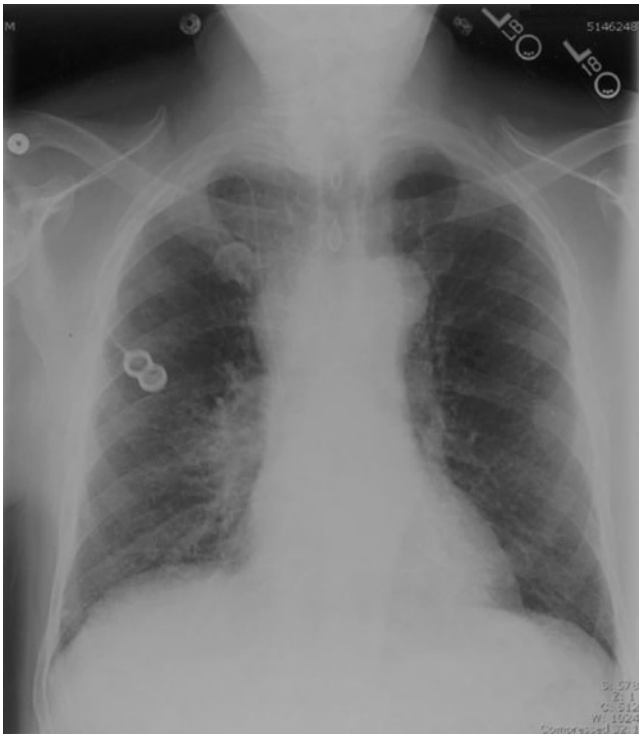
Figure 70-1 A 73-year-old man with stage IIIB non–small-cell lung cancer was treated with radical radiotherapy and concurrent cis-platinum chemotherapy. The plans for his radiation treatments are summarized. *A*. Initial anterior and posterior x-rays beams with simulation film on left and isodose distribution overlaid on computed tomography scan on right. *B*. Anterior port (i.e., treatment) film. *C*. Oblique boost fields with simulation film on left and axial view of radiation dose distribution off the spinal cord on right. *D*. Dose-volume histogram of the entire treatment course, for tumor (solid line) and lung (dashed line). The V_{20} (39.45) is derived from the lung histogram.

cause ionizations when interacting with matter. The only difference between them lies in the manner in which they are produced: Gamma-ray photons are emitted from atomic nuclei during the decay of radioactive atoms and x-rays are produced when high-energy electrons strike a target material and interact with the electron shells of atoms in that target, causing them to emit x-ray photons (i.e., the Bremsstrahlung effect). After its emission, an individual x-ray photon is indistinguishable from a gamma-ray photon. Thus, although our discussion uses x-rays for its examples, the discussions would be equally applicable to radiotherapy given using high-energy gamma rays, for example, from cobalt-60 teletherapy units.

The x-rays used for diagnostic imaging are in a relatively low energy range in which the dominant interaction of the photons with matter is through the photoelectric effect. In this process, absorption of an x-ray photon causes an electron to be ejected from the inner shell of an atom. The probability of photoelectric interactions increases as a function of the cube of the atomic number, that is as Z^3. Because of this, large, heavy atoms absorb low-energy diagnostic x-rays much more efficiently than smaller, lighter atoms. Diagnostic radiology capitalizes on the large differences between the absorption of these low-energy x-rays in materials with different compositions, e.g., air, soft tissue (which is 70 percent water and therefore comprised primarily of the small atoms hydrogen and oxygen), bone (with its high calcium content), and administered contrast agents containing barium, iodine, or other heavy atoms. The difference in absorption is used to image anatomical structures. In contrast, the high-energy x-rays used in radiotherapy interact with matter primarily by a phenomenon called the "Compton effect" in which x-rays cause ionization of atoms via interactions with their outer electron shells. The Compton effect is not dependent on the atomic number but is instead a function of the electron density. Because the electron densities of most biologic tissues are relatively uniform, it is a reasonable approximation for the purposes of most radiotherapy dosimetry to assume that a patient has a uniform density, equivalent to water.

An important caveat to radiation dosimetry relevant to this chapter involves the standard specification of doses in tissues that include a large proportion of air, such as the lung. As a single x-ray beam penetrates through water or tissue, the



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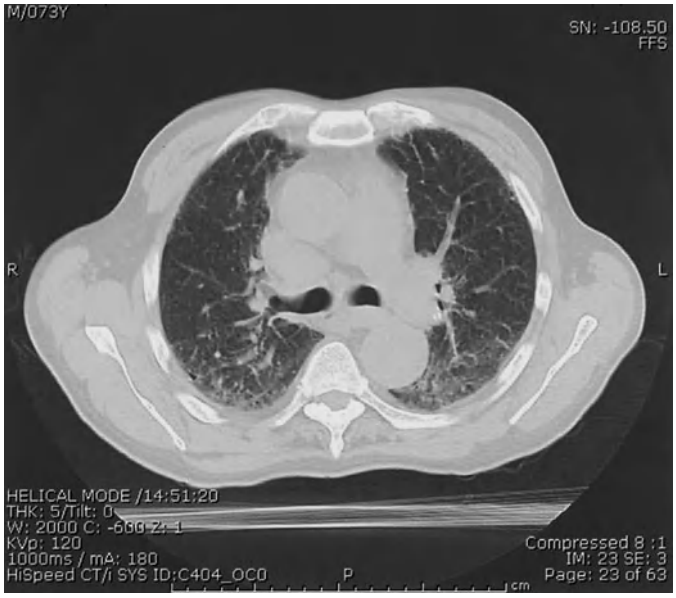

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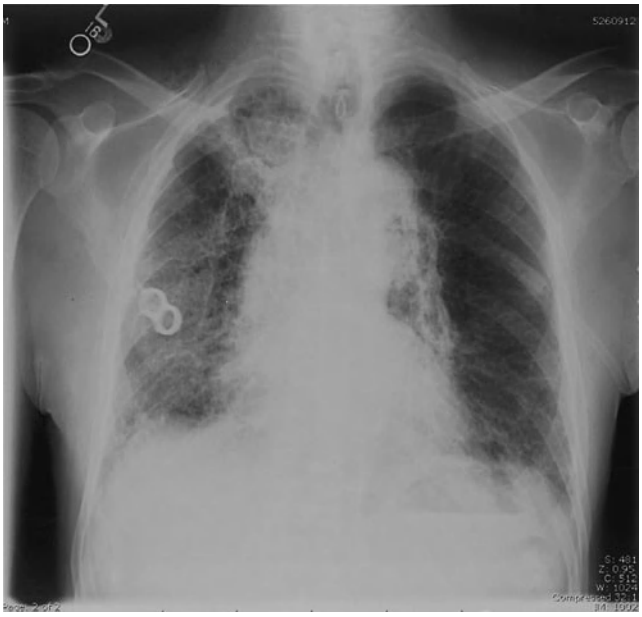

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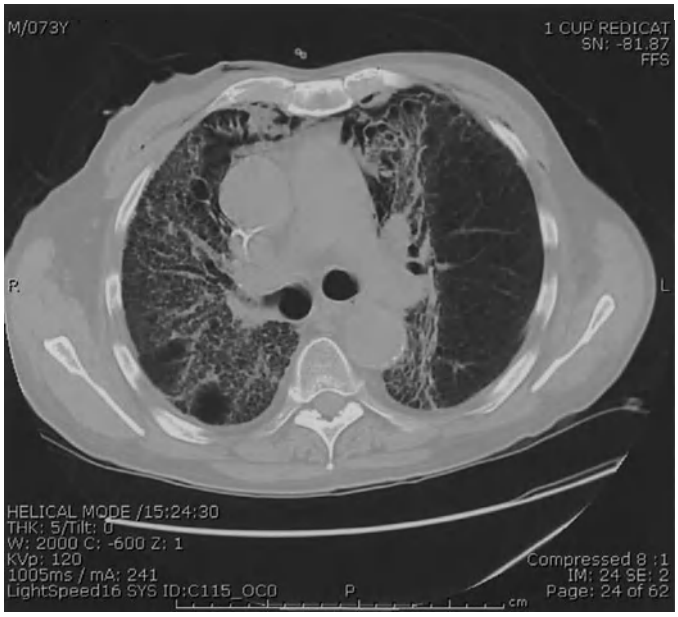

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Figure 70-2 Same patient as in Fig. 70-1, developed radiation pneumonits at 6 months following completion of radiotherapy. Baseline posterior chest x-ray (*A*) and computed tomography (CT) scan (*B*) are compared to follow-up chest x-ray (*C*) and CT scan (*D*) showing characteristic interstitial infiltrates corresponding to the radiation treatment portals.

dose received by the tissue falls progressively, generally as an exponential function of the depth. Because of its markedly lower density, air will absorb less radiation, and therefore attenuate the x-rays less than would tissue or water. With the quantitative knowledge of lung density that can now be derived from CT scanning, algorithms have been devised to estimate the inhomogeneity in the absorbed dose resulting from the differences in the density of lung and soft tissue. These heterogeneity corrections show that routine dosimetric calculations, which assume uniform density, underestimate the radiation doses to lung and tissues beyond the lung by factors that range from 5 to 25 percent. Although this is a very important consideration when quantifying the radiation dose delivered to the lungs, one must remember that

doses delivered to the thorax and the lungs historically have been reported in the medical literature *without* heterogeneity corrections. Moreover, because the preponderance of clinical data concerning lung tolerance have been determined and reported using older algorithms, which assume for dosimetric purposes that the lung has water-equivalent density, the impetus to change dose reporting is limited by a desire to avoid confusion between the new and older literature. Therefore, the reader should assume, unless explicitly stated otherwise, that the radiation doses given in this chapter, or for that matter any publication, are not corrected for lung density.

Radiation dose is currently reported using the unit of the System International (SI), the gray (Gy). The Gy is a measure of the energy absorbed by 1 kg of tissue; 1 Gy = 1 J/kg. The former unit of absorbed dose, called the "rad" (an acronym for "radiation absorbed dose") was measured with the cgs system; by definition, 1 rad = 100 ergs per gram. To compare old and recent literature, one must therefore recall that 1 Gy = 100 rad. Despite the fact that it is not an approved SI unit, some radiotherapy literature avoids this conversion by giving the dose in centigray (cGy), where 1 cGy = 0.01 Gy = 1 rad. Other measures of radiation dose seen in the literature include the roentgen, the Sievert, and the rem. The roentgen measures radiation *exposure,* rather than energy *absorption,* and refers specifically to the amount of ionization produced in air under standard conditions (1 R = 1 electrostatic unit/cc $= 2.58 \times 10^{-4}$ coulombs/kg of standard air given that air has a density of 1.29×10^{-4} g/cm^3 at 0°C and 760 torr). This unit is frequently encountered in the radiation dosimetry literature, not only because it was historically a measure of dose, but also because many widely used radiation monitors (e.g., ionization chambers) directly measure radiation exposure at the surface of the body. The dose absorbed by tissue is then calculated from this exposure. The radiation protection literature uses the unit of "equivalent dose," the Sievert (Sv), which is calculated as the absorbed dose (in Gy) multiplied by a "weighting factor" that considers the differing biologic effects of different radiations. Although the weighting factors for some radiations, such as neutrons and alpha particles, can be as high as 20, the weighting factors for x-rays, gamma rays, and electrons are defined as 1. For most purposes in diagnostic and therapeutic radiology, therefore, 1 Sv = 1 Gy. The Sv replaces the older unit of equivalent dose, the rem (1 Sv = 100 rem). Unfortunately, the literature on radiation-induced lung injury includes papers using all of these different units, creating great confusion for the casual reader. For simplicity, all doses given in this chapter have been converted to Gy.

RADIOBIOLOGY OF RADIOTHERAPY

When x-rays pass through tissue, a complex series of physical and chemical reactions occurs. As the x-rays interact with atoms along their path, as described, energy is absorbed, and energetic fast electrons are ejected. These fast electrons travel through tissue, producing secondary ionizations, which lead within milliseconds to the generation of a variety of highly reactive free-radical species. Because biologic materials are about 70 percent water, ions and free radicals derived from water (e.g., H·, OH·, H_2O^+, H_3O^+) are the main reactive species produced. These ions and radicals react with each other and other nearby molecules, creating a wide variety of chemically reactive species and producing many kinds of damage in biologic macromolecules. Because the DNA contains information that is critical to the cell while most other molecules can be replaced readily, damage to DNA is the most important biologic effect of irradiation. Radiation produces a wide variety of lesions in DNA, including single- and double-strand breaks, damaged bases and loss of bases, as well as chromosomal breaks and rearrangements. If these lesions are not repaired, the result can be permanent mutations or changes in chromosomal structure that lead to the death of the cell or changes in its behavior.

The cytotoxic effects of radiation are the basis for both the antineoplastic effects and the toxicities of radiotherapy. A theoretical concern is that radiotherapy may produce a mutation in a previously normal cell that leads to the development of a new malignancy. Although radiation-induced malignancies do occur, malignant transformation is, fortunately, a rare enough event at the doses used in radiotherapy that the risk of inducing a second cancer is acceptably small relative to the great benefit of curing the existing malignancy. The greater risk to the patient lies in the fact that radiation is not selectively toxic to the tumor cells but instead kills both normal and malignant cells within the treatment field.

Although the radiochemical reactions that lead to cytotoxic damage are complete within milliseconds after the end of irradiation, cells dying from radiation injury do not die immediately. In fact, soon after irradiation, radiation-sterilized cells are indistinguishable from cells that will ultimately survive irradiation in their appearance, metabolic activities, and even rates and patterns of proliferation. Most radiation-sterilized cells ultimately die during a mitosis but may first undergo one or even several divisions, producing an abortive clone of sterile cells, all of which ultimately die and disintegrate through apoptosis, necrosis, mitotic catastrophe, senescence, or other pathways of cell death. This delayed cytotoxicity underlies many of the effects seen in radiotherapy. Rapidly growing tumors, for example, generally begin shrinking sooner than slowly growing tumors, and many tumors continue to shrink progressively for months after radiotherapy. Analogously, radiation reactions in normal tissues reflect the normal patterns of cell turnover in the tissue. After irradiation, nonproliferating, terminally differentiated cells will continue to perform their differentiated functions throughout their normal life spans. Other cells that are not proliferating at the time of irradiation will likewise continue to function normally until they are recruited into proliferation, perhaps months or even years later; when they begin to proliferate their progeny will die. Rapidly proliferating cells such as epithelium or nucleated blood/marrow cells die within a few days of irradiation, leading to the familiar early radiation reactions of epilation, desquamation, mucositis, and hematologic

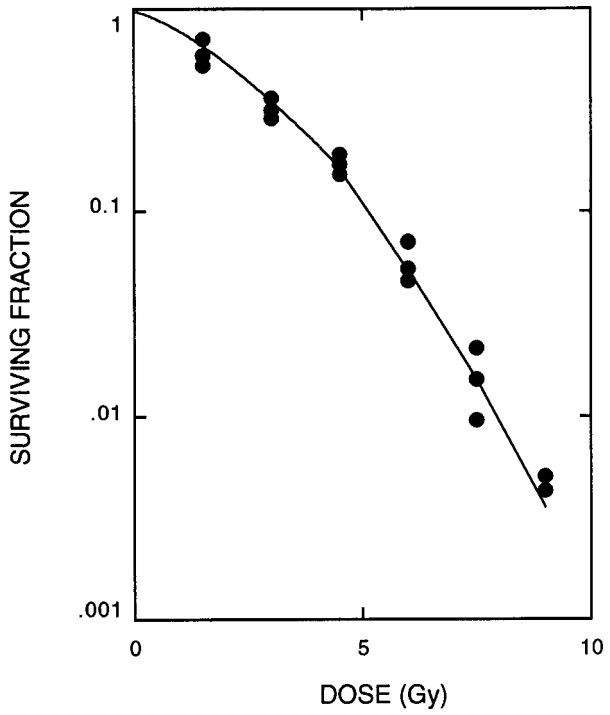


Figure 70-4 Survival of lung cells treated with different doses of radiation. Cells were explanted from mouse lungs, irradiated in vitro, and assayed for viability using a colony formation assay. *(Redrawn from Guichard M, Deschavanne PJ, Malaise EP: Radiosensitivity of mouse lung cells measured using an in vitro colony method. Int J Radiat Oncol Biol Phys 6:441–447, 1980 with permission.)*

depression. There is increasing evidence that some cell types, especially hematopoietic cells, can be induced by radiation-induced damage to enter a pathway of programmed cell death that leads to apoptosis; the role of early and delayed apoptosis in determining the response of tumors and normal tissues to radiotherapy is the subject of intensive investigation.

A typical survival curve for mammalian cells, obtained using mouse lung cells, is shown in Fig. 70-3. To a first approximation, cell survival falls exponentially as the radiation dose increases. Statistically, this implies that each incremental dose of radiation has the same cytotoxic effect; that is, each incremental dose kills the same proportion of the viable cells present in the population at the beginning of that irradiation. Very low doses of radiation have somewhat lesser effects; this shoulder on the cell survival curve reflects the ability of the cells to accumulate and tolerate or repair some of the damage produced by radiation.

The effect of the repair of radiation damage can be seen when the radiation dose is divided into two or more treatments separated by hours or days, rather than being delivered in a large single dose. Dividing, or "fractionating," the radiation dose allows cells to repair damage to their DNA between treatments. As a result, there is less cytotoxicity from a fractionated treatment regimen than from the same total radiation dose delivered as a large single fraction (Fig. 70-4). Smaller fractions produce less cytotoxicity than larger fractions. Similarly, the cytotoxic effects of radiation are diminished when the radiation is delivered continuously at a low dose rate, over hours or days, to allow repair and proliferation to occur during irradiation (Fig. 70-4). Fractionating therapeutic irradiations or delivering the radiation at low dose

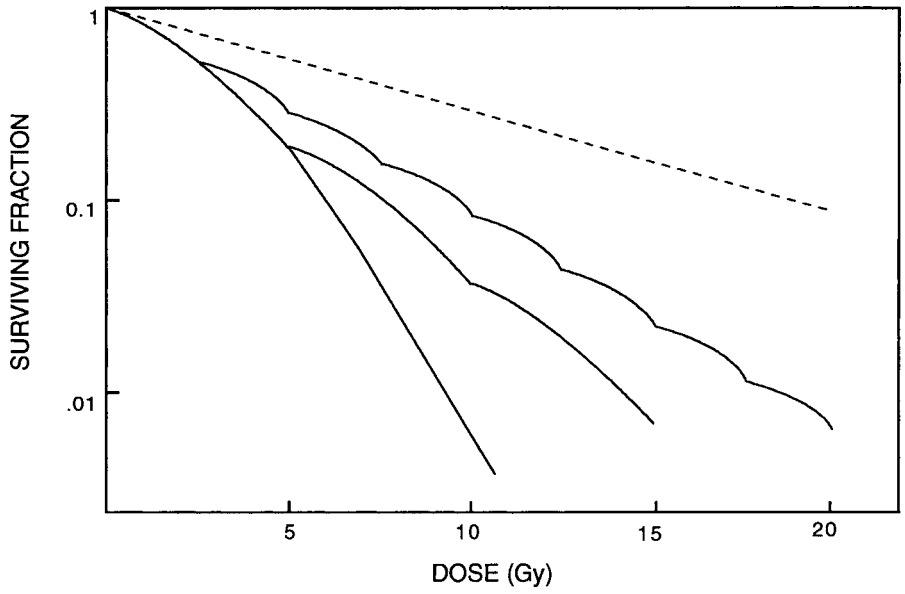


Figure 70-3 Effect of fractionated irradiation and low-dose rate irradiation on cell survival. The survival curve for lung cells treated with a single dose of radiation is redrawn from Fig. 70-3. The calculated effect of dividing the radiation dose into several daily treatments with 5 Gy/fraction or 2.5 Gy/fraction is illustrated. The dashed line illustrates the survival curve that would be expected for irradiation delivered continuously at a low dose rate over several hours, allowing repair and proliferation to occur during treatment. Changes in the cytotoxicity of radiation with fractionation and at low dose rates lead to decreased injury in lungs irradiated with analogous regimens.

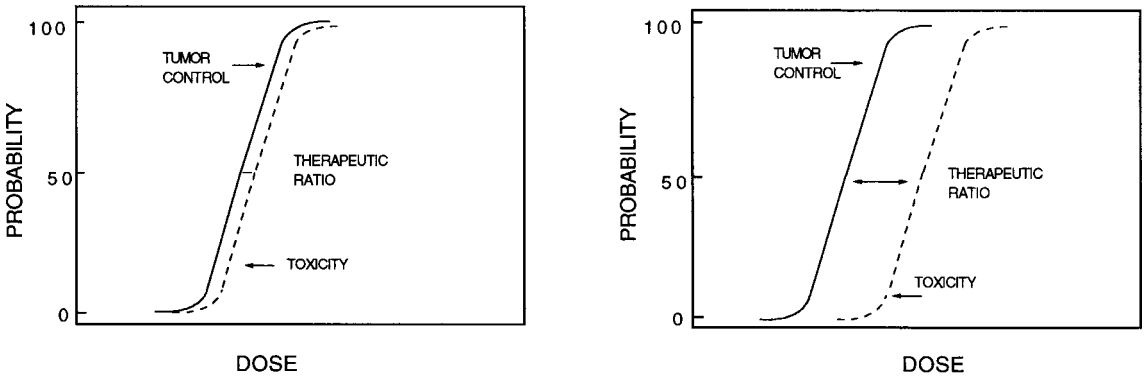


Figure 70-5 The therapeutic ratio is the critical factor determining the success of cancer therapy.

rates generally appears to increase the therapeutic ratio, by protecting normal tissues against radiation injury but producing a smaller increase in the relative radioresistance of the tumor, thereby improving the outcome of treatment. This increase in the therapeutic ratio is thought to reflect qualitative and quantitative differences between the normal and malignant cell populations, including differences in the intrinsic radiosensitivity of the critical cells and differences in the patterns of cell proliferation and cell loss, as well as differences in the ability of the normal and malignant cells to repair radiation damage. Empiric observations of patients treated with radiotherapy, laboratory experiments with tumors and normal tissues in rodents, and studies with cells in culture have all been used to guide the development of the clinical fractionation schedules now in use. This optimization process is ongoing and will undoubtedly continue, incorporating new information about the repair of radiation damage in normal and malignant cells and about the physiological factors that modulate the development of late radiation injuries in specific normal tissues. In this process, as in any change in cancer therapy, the parameter of critical importance is always the therapeutic ratio (Fig. 70-5). A new treatment regimen is superior only if it produces an increased effect on the tumor, without producing an equivalent increase in toxicities to critical normal tissues, thereby increasing the therapeutic ratio and producing therapeutic gain. The art of radiotherapy lies in the design of treatment fields that minimize radiation doses to normal tissues and in the development of treatment regimens that use all available information on the biology of the tumor and of the critical normal tissues to design treatment protocols that maximize the therapeutic ratio.

PATHOPHYSIOLOGY OF RADIATION PNEUMONITIS

Much of our current understanding of the pathophysiology of radiation injury to the lungs is derived from animal experimentation. Translation of animal data to human conditions is always problematic, because differences in the biology and physiology of different species may preclude direct and definitive extrapolation from animals to humans. Instead, studies with experimental animals must be designed to identify physiological factors and biologic mechanisms that can be used to interpret clinical data and suggest avenues for clinical investigations. Data on radiation pneumopathy in humans is fragmentary and complicated by the variability in the patients treated with thoracic irradiation. Most studies of radiation pneumonitis include patients with a variety of malignancies, treated with different irradiation regimens, often in combination with chemotherapy and surgery. Moreover, the patients vary widely in age and the presence of other diseases and risk factors. Therefore, our current understanding of radiation injury to the lung remains incomplete. What is known suggests a complex, multifactorial mechanism of injury and disease progression that reflects cytotoxic effects on both epithelial and endothelial tissues, inflammatory responses that include disordered cytokine and cellular signaling, and the induction of interstitial fibrosis. Similarities to lung injuries resulting from cancer chemotherapy, other drugs, inhaled chemicals, oxygen toxicity, and idiopathic pulmonary fibrosis are intriguing, especially when one considers that many of these diseases include pathological responses to free-radical chemical species and are likely to reflect similar underlying initial lesions.

Partial lung resection and localized irradiation have certain similarities, because their effects are largely localized to the treated areas and consequently depend on the number of pulmonary lobules or alveolar–capillary units functionally destroyed. Thus the volume of lung irradiated is an important determinant of toxicity. Consequently, the radiation oncologist plans the treatment to minimize the volume of lung receiving high radiation doses, just as the thoracic surgeon plans a lobectomy or pneumonectomy to consider the residual capacity of the lungs. Of course this simple analogy has its limitations. For example, inactivation of enough lobules by radiation increases the ventilatory dead space and could lead to shunting and ventilation-perfusion mismatching. However, in clinical practice, extensive

shunting generally is not observed. In fact, postradiation radionuclide ventilation-perfusion scans tend to show underperfusion rather than underventilation in the irradiated areas of partially irradiated lungs. In most cases, radiation injury in lung conforms to the radiation treatment fields, but in some instances effects outside the treated areas are observed, with localized radiation inducing a more generalized or diffuse hypersensitivity pneumonitis.

The effects of radiotherapy on the lung reflect the proliferation patterns of the different cellular components of the terminal capillary-alveolar units. Type I pneumocytes are the dominant epithelial cells of the lung, covering about 83 percent of the alveolar surface. Type I pneumocytes are normally nonproliferating and do not proliferate in response to injury. Because of this, they are thought to be relatively resistant to the cytotoxic effects of radiation. Type II pneumocytes, which comprise about 16 percent of the cells in the human lung, are the principal source for the surfactant that modifies alveolar surface tension to prevent atelectasis. Type II pneumocytes have turnover times of about 1 month. In response to certain injuries, these granular pneumocytes can be induced both to undergo rapid mitosis and to differentiate into type I pneumocytes. Endothelial cells comprise about 30 percent of the cells in human lungs and form a continuous layer between the blood and lung tissue. Although endothelial cells are classified in most tissues as stromal cells, endothelial cells in lung are actually parenchyma, because they are critical to the function of this organ. Capillary endothelial cells are a constantly renewing population. The turnover time of these cells has been estimated to be on the order of 2 months. Endothelial cells can be induced into rapid compensatory proliferation after injury; therefore, radiation can result in the depletion of both type II pneumocytes and endothelial cells.

Several lines of evidence suggest that radiation injury is related primarily to cytotoxic damage, especially to the surfactant-producing type II pneumocytes and vascular endothelial cells. Although clinical signs of pneumonitis require weeks to develop, laboratory studies reveal evidence of lung injury within hours after large single doses of radiation. Shortly after irradiation, electron microscopy can detect abnormalities in surfactant-containing lamellar bodies. There is an increase in surfactant in bronchoalveolar lavage specimens within hours of irradiation that persists for several weeks. Ultrastructural evidence of endothelial cell damage is also seen soon after lung irradiation, and a rapid increase in capillary permeability occurs, reflecting loss of integrity of cell junctions, intracellular vacuolization, cellular pleiomorphism, and sloughing of the basement membrane. Capillary occlusion by cellular debris and microthrombi may occur at high doses.

The clinical course of lung injury occurs later and includes a pneumonitic phase, developing weeks to months after radiation, followed by a fibrotic phase, developing months to years later. To explain the two clinical phases, Rubin and Casarett's original model of radiation lung toxicity suggested that the pneumocytes and endothelium represented two separate and distinct cellular targets and that damage to pneumocytes led to pneumonitis, while vascular damage led to fibrosis. This older model is now thought to be incorrect. The current weight of evidence from Rubin and others suggests that the pneumonitic and fibrotic processes both are manifestations of a common pathway of injury and response.

Histologically, one can recognize a typical sequence of events developing in the lung after large doses of radiation. Within days to weeks, vascular congestion and intra-alveolar edema and exudation occur, followed by infiltration of inflammatory cells and epithelial desquamation. Weeks later, collagen fibrils are deposited within areas of injury and interstitial edema, leading to a thickening of alveolar septa similar to that in hyaline membrane disease. The probability and severity of these changes are quite variable and depend on such factors as the radiation dose and treatment volume. The severity of the damage and volume of tissue affected determine whether a pneumonitic picture will become clinically evident. Resolution of inflammatory infiltrates and alveolar exudates, which can be improved by anti-inflammatory agents such as glucocorticoids, correlates with symptomatic improvement and resolution of radiographic opacities in the affected lung.

Inflammatory cells, particularly alveolar macrophages, migrate into areas of radiation injury. This induces an ensuing cytokine cascade and mediates the host response, similar to that which occurs in other inflammatory conditions, which can lead to pulmonary fibrosis. Rubin and his collaborators have detected a biphasic increase in mRNA expression for the proinflammatory cytokines IL-1α, IL-1β, and TNF-α at 2 and 8 weeks after radiation. Preliminary clinical trials also suggest that elevated serum levels of IL-6 before and during radiotherapy predict for an elevated risk of radiation pneumonitis. Beginning at 2 weeks, TGF-β, a cytokine that mediates fibrotic responses, increases. Clinical data implicating TGF-β as a predictive marker for pneumonitis, however, have been mixed. Collagen gene expression is also appreciably increased, corresponding to the fibrotic changes seen histologically. These studies suggest that early and persistent elevations of cytokine production and alterations of intercellular signaling are critical to the development of radiation reactions in the lung. There is increasing evidence from studies with inbred mice that genetic differences modulate the development and severity of fibrosis and hyaline membrane formation and thus determine the nature of the late toxic lesion and the time of development of radiation pneumotoxicity.

The processes described in the preceding lead to pathological changes that conform spatially to the areas in which localized radiation was administered. Interestingly, it has been discovered that radiation can also induce an allergic alveolitis. This is observed infrequently as a diffuse pneumonitis or even more rarely as patchy, transient pneumonitis occurring outside the treated fields. In its most severe form, this leads to adult respiratory distress syndrome. Morgan and Breit have suggested that this form of radiation pneumonitis be termed "sporadic"; however, the subclinical occurrence of this syndrome actually may be fairly common. Bronchoalveolar lavage in humans and in experimental animals frequently

shows a significant increase in activated T-helper (CD4+) lymphocytes, temporally related to irradiation and occurring equally in the irradiated lung and the contralateral, unirradiated lung. Gallium scanning in these subjects may also show bilateral uptake, not corresponding to the treated regions. Frequent reports of autoantibodies, including antibodies to collagen, in the sera of human cancer patients even before treatment suggest the possibility that malignancy-associated autoimmune reactions may be involved in this syndrome.

CONFOUNDING EFFECTS OF CHEMOTHERAPY

Many cytotoxic drugs employed as antineoplastic agents can produce pulmonary toxicity. Bleomycin, which kills cells by generating reactive free-radical species, can give rise to both pneumonitis and fibrosis. Mitomycin C and doxorubicin have both been associated with lung toxicity. As high-dose alkylating agent chemotherapy is used more frequently in the setting of bone marrow or peripheral stem cell transplantation, agents such as cyclophosphamide, BCNU, and busulfan have been associated increasingly with clinically significant pneumonitis. The direct toxicity of anticancer drugs to the lungs sounds a note of caution for those considering the development of treatment protocols combining systemic chemotherapy with lung irradiation.

Animal studies looking at changes in respiratory rates and/or death resulting from lung injury show that the severity of the lung injury can be increased when doxorubicin, bleomycin, cyclophosphamide, mitomycin C, dactinomycin, and vincristine are administered along with radiation. No enhancement has been documented in studies with 5-fluorouracil, cis-platinum, carboplatinum, hydroxyurea, vinblastine, or methotrexate, despite reports of lung toxicity from methotrexate alone. As a wide variety of cytokines are now available for pharmacologic administration, modulation of radiation injury by these biologic agents has received increasing study. Interferons have been shown both to increase and decrease radiation lung toxicity, whereas interleukins 1 and 2 may have protective effects. Some radiation-drug interactions in the lung have been shown to be schedule dependent, with the effect of the combination varying with the sequence and the time between treatments with the two agents. Additive, subadditive, and even supra-additive toxicities may be observed in rodents when single treatments with the same dose of radiation and drug are given over a 24-h period, but in different sequences and different times between treatments. Such findings highlight the complexities of combined modality therapy and the difficulty of using animal data to plan clinical treatment regimens.

Data from several specific clinical situations show that regimens combining radiation with particular chemotherapy agents can produce significant risks of pneumonitis. As summarized in a recent review of radiation pneumonitis in patients treated for lung cancer, cis-platinum, taxanes, mitomycin C, gemcitabine, and irinotecan concurrent with radiotherapy using a variety of fractionation regimens seem to elevate the risk of pneumonitis or lung toxicity. Older clinical data from pediatric trials strongly suggest that administration of concurrent doxorubicin or actinomycin D with thoracic radiotherapy generally should be avoided or, alternatively, that the radiation doses should be reduced significantly where these drugs are used. Sequential treatment with these drugs and radiation is less likely to produce lung injury. However, a phenomenon termed "radiation recall" has been well described, in which either of these two drugs given even several months after radiotherapy will produce an inflammatory reaction in the region corresponding to the radiation treatment fields. Although this reaction is best known in skin, it also has been well documented in the lungs in several case reports and has been produced in experimental animals. Radiation recall probably reflects the fact that the irradiated areas of the lung still retain residual, subclinical injury, which is exacerbated into clinical pneumonitis as a result of the additional injury from the drug. Therefore, the biologic basis of the recall phenomenon is analogous to that of the residual radiation injury, which decreases the ability of heavily irradiated lung tissue to tolerate a second course of radiotherapy delivered months or years later.

CLINICAL SYNDROMES

Radiation oncologists conventionally divide clinical toxicities into acute and late effects, with both radiation pneumonitis and fibrosis considered late toxicities. Several grading systems for pneumonitis have been developed for scoring lung injury during clinical trials (Table 70-1).

Acute Manifestations

It is relatively uncommon to observe acute pulmonary toxicity during the administration of fractionated radiotherapy. At relatively high therapeutic doses (50 to 60 Gy), however, acute radiation injuries to the tracheobronchial tree can be expected. Bronchoscopic examination of these patients is likely to reveal erythematous mucosa, with thickened secretions that can accumulate in and obstruct the airways. Although a majority of patients remain asymptomatic, occasional patients experience an irritative, dry cough. Antitussive agents such as codeine, adequate hydration, and reassurance are usually all that are required to manage this problem. Once the radiotherapy has been completed, the bronchial epithelium regenerates and heals over several weeks with a corresponding resolution of any symptoms.

Late Manifestations

The clinical course of late radiation injury to the lungs is biphasic with both inflammatory and fibrotic components.

Table 70-1

Toxicity Criteria for Pneumonitis

	Grade				
Scoring System	**1**	**2**	**3**	**4**	**5**
CTCAE	Asymptomatic; radiographic findings only	Symptomatic; not interfering with ADL	Symptomatic; interfering with ADL; O_2 indicated	Life-threatening ventilatory support indicated	Death
RTOG/EORTIC (LENT-SOMA)	Asymptomatic or mild symptoms (dry cough), with radiographic findings	Moderately symptomatic (severe cough fever)	Severely symptomatic	Severe respiratory insufficiency; continuous oxygen/assisted ventilation	Death
SWOG (33)	Asymptomatic or symptoms not requiring steroids with radiographic findings	Initiation of or increase in steroids required	O_2 required	Assisted ventilation necessary	Death

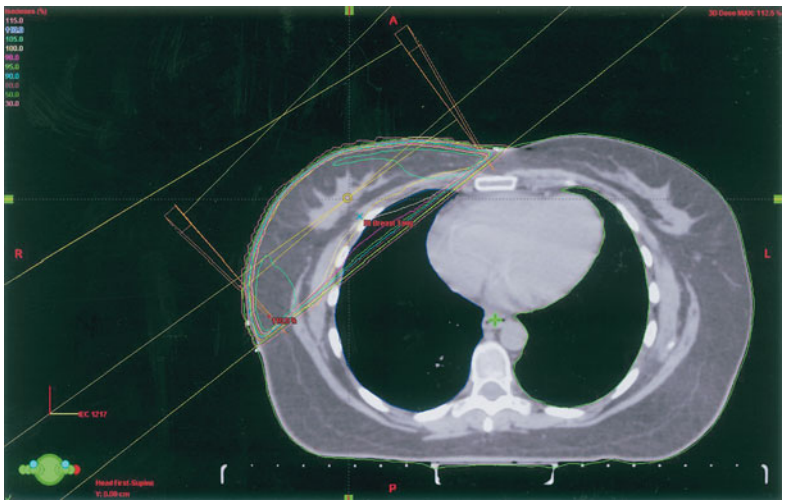
Notes: Abbreviations*: CTCAE = Common Terminology Criteria for Adverse Events; ADL = activities of daily living; RTOG = Radiation Therapy Oncology Group; EORTC = European Organization for the Research and Treatment of Cancer; LENT-SOMA = Late Effects on Normal Tissue-Subjective, Objective, Management and Analytic Scales; SWOG = Southwest Oncology Group.*

SOURCE: *Modified from Mehta V.:* Int J Radiat Oncol Biol. Phys *63:5–24, 2005, with permission.*

Radiation Pneumonitis

A pneumonitic process frequently becomes evident 6 weeks to 6 months following radiotherapy. At this time radiographs show alveolar opacities that generally conform to the treatment portals. The severity of radiation pneumonitis varies dramatically from patient to patient, even in those receiving identical therapeutic regimens. In most cases, the pneumonitis is asymptomatic, even though radiologic abnormalities are quite common, having been found in some prospective studies in as many as 50 percent of patients who have completed a course of thoracic radiotherapy. When symptomatic, this syndrome is often characterized by the abrupt onset of fever, cough, and dyspnea. The severity of symptoms depends on the extent of radiotherapy, increasing with the treated volume and the radiation dose. Symptoms in patients irradiated to limited lung volumes or to relatively low doses may consist of low-grade fever, cough, congestion, and chest fullness or discomfort. Any hemoptysis tends to be minimal. In more severe situations, dyspnea, high fever, and cough occur. When more than three-fourths of the total lung volume is irradiated to doses of 45 Gy—a situation to be avoided—acute radiation pneumonitis is highly likely and can be extremely severe, producing respiratory distress. The radiation oncologist is probably most likely to see clinically significant radiation pneumonitis that can be life-threatening when it occurs as a rare and unanticipated consequence of standard treatment, despite appropriate treatment planning designed to minimize the volume of lung treated with high doses of radiation. Fortunately, with well planned radiotherapy severe radiation pneumonits is a rare event, while milder forms are not uncommon and are manageable.

It is important to distinguish radiation pneumonitis from infection, recurrent tumor (particularly with lymphangitic spread), drug reactions, congestive heart failure, and other respiratory ailments. These distinctions may not be easy; one series from Duke suggested that up to 28 percent of patients with radiation associated lung toxicity have complex co-morbidities that make it difficult to assign a definitive diagnosis. Bacterial, fungal, viral, and pneumocystis pneumonias can be quite difficult to differentiate from pneumopathy induced by chemotherapy or radiation. Aids in the differential diagnosis include the clinical course and the temporal relationship between the irradiation and respiratory illness. Definition of the radiographic pattern of the infiltrate is also very useful, because radiation pneumonitis often conforms to the outline of the sharply demarcated radiation portal (Figs. 70-2 and 70-6). Bronchoscopy and lung biopsy can also be important diagnostic tools to direct therapeutic decisions. Ruling out infection is particularly important, because treatment of symptomatic radiation pneumonitis relies on supportive care



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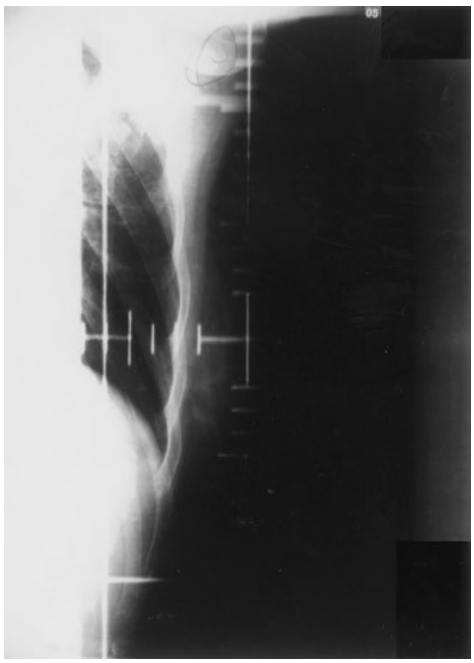

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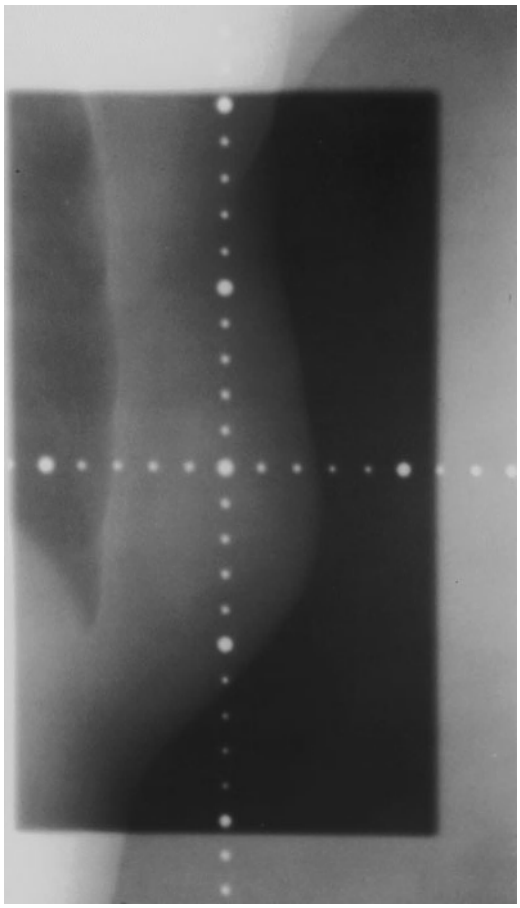

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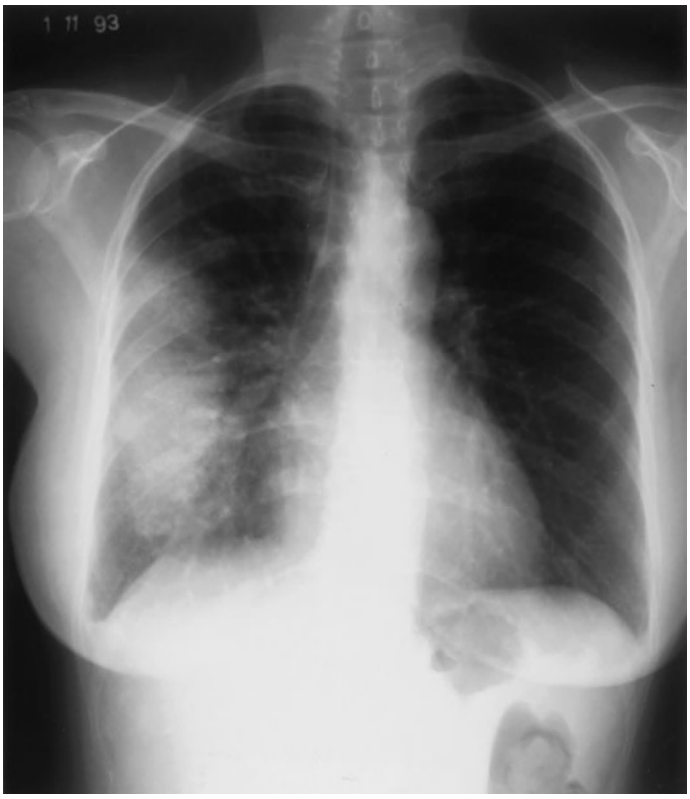
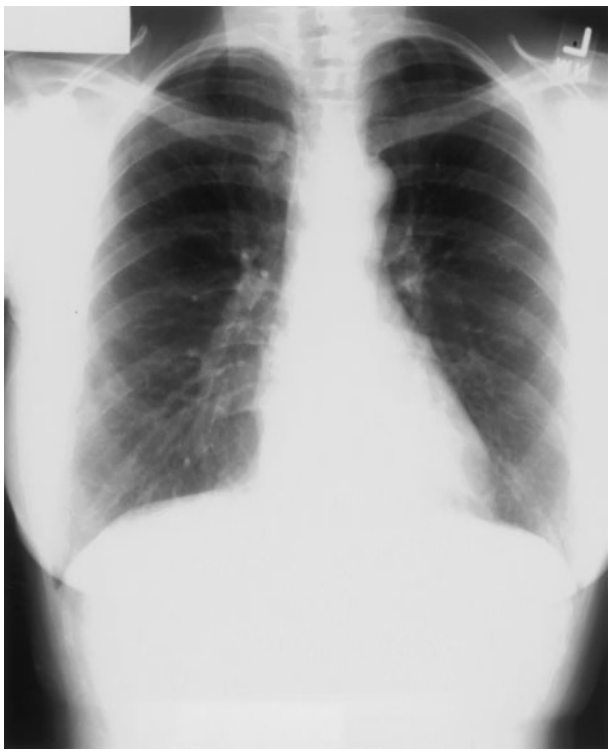


D

Figure 70-6 A 52-year-old woman found a nontender lump in her right breast and subsequently underwent a lumpectomy for a localized 1.4-cm diameter infiltrating ductal carcinoma. The axillary lymph nodes were negative. The patient was placed on Tamoxifen and underwent radiotherapy to the right breast, using tangential fields, to 50 Gy in 25 fractions over 36 days. *A*. A radiation dose distribution of the such photon fields overlying the right breast and chest wall.This was followed by boost radiation treatments to the surgical bed for an additional 14 Gy in 7 fractions. *B*,*C*. The simulation and port films, respectively, of the whole-breast treatments, again highlighting the different interactions of low-energy and high-energy x-rays with tissues. Four months after radiotherapy, the patient developed radiation pneumonitis characterized by fever, cough, and dyspnea requiring hospitalization. *D*. A right-lung opacity that does not correspond to normal anatomic structures but does correspond to her treatment fields. *E*. The patient responded dramatically to steroids, with resolution of radiographic findings on follow-up chest radiographs.



E

Figure 70-6 (*Continued*)

in conjunction with steroids, which is contraindicated with an active infection. Doses of glucocorticoids generally can be tailored to the severity of the symptoms. Asymptomatic pneumonitis can be managed with close observation. Severe cases generally warrant treatment with 0.5 to 1 mg/kg per day of prednisone (or its equivalent) in divided doses. Response rates to steroid therapy between 20 and 100 percent have been reported, and dramatic clinical and radiographic responses are not infrequently seen. Steroids should be tapered slowly after the patient is stabilized, because it is common to see a recrudescence of symptomatology when steroids are discontinued too rapidly. Failure to respond to steroid therapy is an adverse prognostic factor that suggests the prospect of rapid disease progression.

Radiation Fibrosis

A more indolent fibrotic process can follow either subclinical or symptomatic radiation pneumonitis. This begins several months after radiotherapy and peaks in radiographic severity several years later. Fibrosis tends to occur in or adjacent to areas of prior pneumonitis, but it can also occur in the absence of clinically overt radiation pneumonitis. Fibrotic changes and the retraction of the lung parenchyma from scarring occur in the irradiated regions (Fig 70-2). When the volume of lung irradiated is relatively small and the remaining lung parenchyma contains sufficient respiratory surface area, these changes tend to be asymptomatic. With increasing relative volumes of pulmonary fibrosis, a spectrum of symptomatology is possible, ranging from mild dyspnea on exertion to severe fibrosis with respiratory compromise, chronic cor pulmonale, cyanosis, and finger clubbing. At the severe end of the spectrum, the syndrome can be life-threatening. In general, in the absence of other underlying lung disease, symptoms are mild when less than 25 to 30 percent of total lung parenchyma is involved.

Radiation-induced Pleural Reactions

Pleuritis can also be seen 2 to 6 months following radiation. It can be associated with plueritic chest pain, a pleural friction rub, and an exudative pleural effusion. Large effusions are, however, distinctly unusual in the absence of other pathology. Like radiation pneumonitis, radiation-induced pleuritis can heal without significant residuae or can proceed through a fibrotic phase that generates pleural thickening.

Radiation-induced Bronchial Stenosis

With improvements in the technical delivery of radiotherapy, recent clinical trials for lung cancer have emphasized escalation of the administered radiation dose. As a result there is an increasing appreciation that radiation-induced fibrosis can result in bronchial stenosis, which can itself cause postobstructive atelectasis, volume loss, and functional impairments with respiration. Clinically, such fibrosis needs to be differentiated from recurrent tumor; bronchoscopy or positron emission tomography (PET) imaging may be of help in this process. One retrospective series in which radiation doses ranged from 60 Gy to as high as 86 Gy demonstrated that radiation-induced bronchial stenosis may occur in up to 25 percent of patients, with incidence directly correlating with radiation dose.

DEFINING THE RADIATION TOLERANCE OF THE LUNGS

Whereas we customarily speak of radiation doses that can be delivered safely either to the whole body or a particular organ, radiation tolerance is usually defined as the dose that will yield a 5 percent risk of late radiation injury. When discussing the tolerance of the lungs, one must consider several different therapeutic situations. The tolerance of the lung varies with the volume of lung tissue irradiated. In addition, single-dose irradiations, fractionated irradiations, and irradiations given at low dose rates pose different risks of injury and must be considered separately. Additional injury from surgery or chemotherapy or from a prior course of radiotherapy also must be considered, as must the confounding effects of injury to lung tissue from coexisting cardiopulmonary disease and the underlying malignancy. Infections and immunologic reactions are also important. The clinical endpoints used to define a case of radiation pneumonitis vary as well, because the severity of the lung injury spans a wide spectrum of diagnostic signs and clinical symptoms. Given the heterogeneity of clinical circumstances and biologic data in general, it is not

surprising that the medical literature that defines the risks for radiation pneumonitis and fibrosis is extremely complex and often difficult to interpret.

WHOLE-LUNG IRRADIATION

A good starting point when discussing lung tolerance is to consider the effects of irradiating the entire lung. This has direct clinical relevance because there are several circumstances in which the entire lung is irradiated. These include total body irradiation for bone marrow or hematologic stem cell transplantation, hemibody irradiation for palliation of widespread metastatic disease, and whole-lung irradiation electively or therapeutically for relatively radiosensitive tumors such as Wilms' tumor, Ewing's sarcoma, or Hodgkin's lymphoma. These are often circumstances in which chemotherapy is being administered as well.

Published experience from the Princess Margaret Hospital in Toronto provides some of the best data regarding whole lung tolerance. Investigators from that institution have an extensive experience with delivering upper hemibody irradiation to different doses and varying fractionation patterns. They reported in 1978 on a cohort of 245 patients, most with metastatic solid tumors, who received single-fraction upper hemibody irradiation at dose rates of 0.3 to 0.8 Gy/min to doses of up to 10 Gy. The actuarial incidence of acute radiation pneumonitis, defined as the sudden onset roughly 16 weeks after irradiation of cough, dyspnea, and opacities visible on chest radiographs, was strikingly dose dependent (Table 70-2). The doses shown in Table 70-2 were not corrected for heterogeneity in density. When doses were corrected for heterogeneity, producing an upward estimation of the doses actually received by the lungs, analysis yielded the sigmoid-shaped curve shown in Fig. 70-7.

Table 70-2

Actuarial Incidence of Radiation Pneumonitis after Single Fraction Whole-lung Irradiation

Uncorrected Dose	Patients	Pneumonitis
<6 Gy	49	2.7%
6 Gy	24	17.5%
8 Gy	149	35.6%
10 Gy	23	83.9%

Source: Data from Fryer Fitzpatrick PJ, Rider WD; CJH, et al: Int J Radiat Oncol Biol Phys *4:931–936, 1978. Doses are not corrected for heterogeneity in tissue density.*

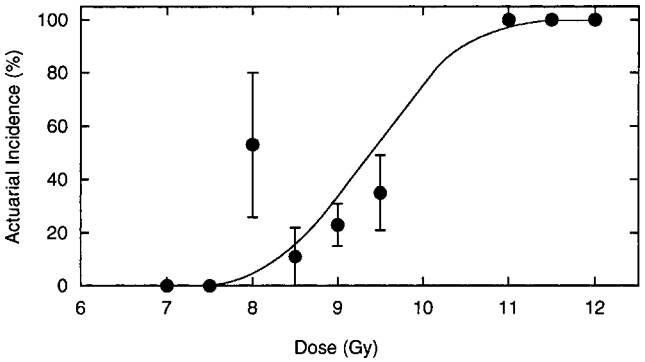


Figure 70-7 Incidence of radiation pneumonitis in patients receiving single-dose, whole-lung irradiation at dose rates of 0.3 to 0.8 Gy/min. Unlike most doses given in the text, doses on this figure *are* corrected for heterogeneity. The effect of this correction can be seen by comparing these data with those in Table 70-1, which were derived from an earlier analysis by the same group and are presented using uncorrected doses. *(Data are redrawn from Van Dyk, J, Keane TJ, Kan S, et al, Int J Radiat Oncol Biol Phys 7:461-467, 1981.)*

Using heterogeneity-corrected data, the incidence of pneumonitis is estimated to be negligible for single doses less than about 7.5 Gy. Other published data regarding upper hemibody single-fraction irradiation are in general agreement with these findings.

The careful reader would be struck by the fact that the single-fraction data might predict an unacceptable risk for pneumonitis when single-fraction, total-body irradiation (TBI) is utilized in the setting of bone marrow transplantation. The most important treatment factor making single-fraction TBI in the range of 8 to 10 Gy (uncorrected for heterogeneity) tolerable is that these treatments generally are given at a low dose rate (less than or equal to 0.1 Gy/min), so that the treatment is delivered over times of 1 to 2 h. In Seattle, where hundreds of patients with leukemia have undergone bone marrow transplantation (BMT) with total-body irradiation, using single fractions of 10 Gy (uncorrected) delivered at dose rates on the order of 0.08 Gy/min, the incidence of pneumonitis is roughly 25 percent. Review of transplant-related single-fraction TBI with variable dose rates shows incidences of clinical lung injury varying from 25 to 70 percent.

Studies in mice show that the toxicities of TBI can be improved further by fractionating the irradiation as well as by delivering radiation at a low dose rate. This concept is supported by a randomized clinical trial comparing low-dose rate single-fraction TBI (10 Gy) with low-dose rate fractionated TBI (12 Gy in 6 fractions over 3 days) for patients with acute myelogenous leukemia in first remission, which showed a significant improvement in event-free survival with fractionation, mainly because of an improvement in early mortality. Interstitial pneumonitis in these patients was decreased from 26 to 15 percent with fractionation. Ongoing trials are seeking to optimize irradiation regimens for TBI. Many fractionation patterns have been and are being tested, including daily fractions and 2 or 3 daily fractions with doses of 1.5 to 2.25 Gy per fraction. Other trials are testing different dose rates. At

many transplant centers it has become common practice to utilize lung transmission blocks to attenuate the lung dose and thereby reduce the risk of pneumonitis, in effect by compensating for the heterogeneity in tissue density due to the air within the lungs.

Pneumonitis in the BMT setting has a multifactorial etiology, reflecting not only the effects of radiation but also the effects of chemotherapy, graft-vs.-host disease (GVH), lung injury from tumor, opportunistic infections, and other risk factors. Cyclophosphamide is almost universally given with TBI. The addition of other drugs is based on institutional treatment policies. As described, many anticancer drugs are known to injure the lung. BMT conditioning regimens that do not use TBI (which tend to use high-dose busulfan in place of radiation) in fact have rates of interstitial pneumonitis comparable to regimens including TBI. The presence of GVH is also important, not only because GVH causes lung injury directly but also because the drugs used to control GVH injure the lung.

Whole-lung irradiation has been used in the treatment of widespread lung metastases. In two published series a combined total of 70 patients with osteosarcoma who received elective whole-lung irradiation to prevent pulmonary metastases (which is not currently a standard practice pattern) received 15 to 17.5 Gy in 10 fractions. None of these patients developed pneumonitis. Similarly, in a series of 40 patients who received 20 to 25 Gy of thoracic irradiation in 1.5-Gy fractions to treat pulmonary metastasis, no cases of pneumonitis were reported. This and other clinical experience with fractionated whole-lung irradiation in the nontransplant setting and in the absence of chemotherapy indicate that the following dose schemes should have a relatively low risk (less than 5 percent) for radiation pneumonitis: 25 Gy given in 20 fractions over 4 weeks or 20 Gy given in 10 fractions over 2 weeks. (As a reminder, all doses are given without heterogeneity corrections.)

Historically, radiotherapy for Hodgkin's disease has used whole-lung treatment in situations in which there is massive mediastinal adenopathy, hilar adenopathy, or overt pulmonary disease treated with chemotherapy. Risks of symptomatic pneumonitis ranging from 7 to 35 percent have been reported, with the risk highly dependent on the total radiation dose and the fractionation pattern. When the whole lung is to be irradiated, the available data suggest that the lungs should be treated through transmission blocks rather than using open fields. This reduces the total dose and the dose per fraction to the lungs, thereby reducing the risk of symptomatic pneumonitis to 4 to 7 percent, over a broad range of total lung doses of 10 to 20 Gy. There is a suggestion that the addition of mediastinal irradiation to fractionated whole-lung radiotherapy increases the risk of pneumonitis. To many oncologists, the risk of radiation pneumonitis from such treatment seems too great. As a result such patients are often treated primarily with chemotherapy (often with adjuvant low-dose radiotherapy), even though these regimens also produce significant risks for lung toxicity. In the setting of pulmonary metastases, the addition of low-dose radiotherapy to the whole lung after chemotherapy is controversial. There are few clinical data to quantify risks and benefits, but doses of 10 to 16 Gy, given in 0.7- to 1.5-Gy fractions, are associated with only modest risk.

Lung radiotherapy using 12 to 14 Gy for pulmonary metastases in pediatric patients with Wilms' tumor (who also receive sequential doxorubicin and actinomycin D) is associated with a 10 percent incidence of pneumonitis. Long-term follow-up in such children also shows restrictive lung disease, with total lung and vital capacities approximately 70 percent of the predicted values. In children receiving thoracic irradiation, inhibition of the normal growth and development of the lung parenchyma and bones as a result of radiotherapy also produces significant morbidity. The effects of radiation on growth and development and the radiosensitivity of growing tissues raise special concerns in the treatment of pediatric patients.

PARTIAL-LUNG IRRADIATION

Assessment of Risk

Estimating the risks of radiation pneumopathy for individual patients receiving fractionated external-beam radiotherapy is a daunting task, because so many confounding factors must be considered. With lung cancer, the tumor size and location influence the volume of adjacent normal lung that must be irradiated. The volume irradiated should determine the number of capillary-alveolar units destroyed and therefore influence the risk of symptomatic radiation pneumonitis and fibrosis. This qualitative prediction is borne out by clinical experience, but quantifying the risks is not straightforward. The location irradiated is also important because the upper lobe is less well perfused and therefore less important to gas exchange. Irradiation of this region produces less change in lung function than irradiation of areas lower in the lung. Treatment-related factors such as total dose, dose per fraction, and overall treatment time are also important, as are the other confounding factors described in the preceding sections.

Patients begin radiotherapy with a wide range of pulmonary functions, reflecting their age, smoking history, and the presence or absence of underlying cardiopulmonary disease. Because regional pulmonary fibrosis can be partially compensated by functional lung parenchyma, pretreatment lung status influences the severity of the symptoms. The clinical endpoints used to measure lung injury are quite varied and include symptom and quality-of-life scores, radiographic changes such as changes in CT-assessed lung density, pneumonitis, fibrosis, and other objective measures.

Pulmonary function tests are global organ measures that correlate quite crudely with symptomatology after partial-lung irradiation. A large tumor mass can cause localized obstructive or restrictive changes in lung function or phrenic nerve dysfunction, any of which may either improve or worsen as the tumor shrinks with treatment. These factors add to the variability produced by patient-to-patient

differences in the treatment volume, dose, fractionation, and so on. Thus the changes from radiotherapy in global lung function with regard to gas exchange, physiological dead space, shunting, V/Q mismatch, and respiratory surface area as measured by arterial blood gases, spirometry, and CO diffusing capacity (D_{LCO}) are complex and highly individualized. Several clinical studies have attempted to correlate predicted changes in FEV_1 from radiotherapy by superimposing radiation treatment portals on quantitative ventilation and perfusion scans. The simple notion that the proportion of lung irradiated should match the drop in FEV_1, akin to the highly useful preoperative assessment of predicted postresection lung function, unfortunately has not been verified. In fact, a report from the Massachusetts General Hospital examining global and regional pulmonary function in patients with lung cancer showed improvement in pulmonary function in 52 percent of patients, a mild decline in 37 percent, and the decline predicted from changes in radionuclide scans in only 11 percent. Similar observations have been made in nonoperative lung cancer patients. Whereas the mean pretreatment FEV_1 of 1.71 ± 0.67 L declined in these patients to an average of 1.15 ± 0.43 L after treatment, the posttreatment FEV_1 was improved in 19 percent of the patients, unchanged in 53 percent, mildly decreased in 22 percent, and decreased below predicted levels in 5 percent. Thus, the technique of superimposing radiation treatment portals over quantitative lung perfusion scans is of limited utility in predicting pneumonitis in individual patients. In fact it has been suggested that the diffusing capacity is a more sensitive indicator of tolerance to radiotherapy. Unfortunately, there are no firm tests or data to guide the development of tolerable regimens of radiotherapy for patients with borderline lung function, except we know that treatment volumes should be minimized. If the initial FEV_1 is below 1.0 L or D_{LCO} is less than 50 percent of normal, large-volume radiotherapy (e.g., elective nodal irradiation for lung cancer) may well be excessively hazardous. Despite the limitations described, quantitative perfusion scanning in selected patients may give a worst-case scenario to help the radiation oncologist decide on dose and volume of treatment.

The quantitative importance of the volume of lung irradiated to the toxicity has only recently been studied in any systematic fashion. An interesting set of mouse data published by investigators at MD Anderson showed a clear shift in dose-response curves for changes in respiratory rate and pulmonary death as a function of the volume of lung irradiated. As expected, the site irradiated was also important: Effects were more pronounced when the well-perfused base of the lung was irradiated, rather than the less well perfused apex. The response to lung irradiation was quite heterogeneous, even within mice of the same age and sex, from a single highly inbred mouse strain maintained in microbiological isolation under rigorously controlled environmental conditions. Histologic damage did not always predict morbidity in individual mice. In patients, preliminary dose-volume histogram analyses derived from detailed three-dimensional treatment evaluations and applied to an empirical normal-tissue complication model show only a fair correlation between volume and complication risk. Nevertheless, it is common practice to evaluate dosimetric parameters such as V_{dose} or mean lung dose. The V_{dose} (i.e., V_{20Gy} or V_{30Gy}) parameter is defined as the percent of total volume receiving equal to or greater than the threshold dose (i.e., 20 Gy or 30 Gy, respectively). The mean lung dose is defined as the average dose delivered to the whole lungs. Investigators at Duke and the Netherlands Cancer Institute have attempted to refine the correlation of dose-volume histograms with toxicity by factoring out nonfunctioning lung using lung perfusion scans. In lung cancer patients, particularly with chronic obstructive pulmonary disease (COPD), areas of hypoperfusion separate from tumor are seen frequently; irradiation of such irreversibly hypo perfused lung may not contribute additional toxicity. Such a "functional" dose-volume histogram analysis has not yet been shown to be of clinical value but it does provide an interesting and promising analytical framework. Nevertheless, there is a direct correlation between the change in ventilation, perfusion, or CT density regionally with increasing radiation dose (Fig. 70-8).

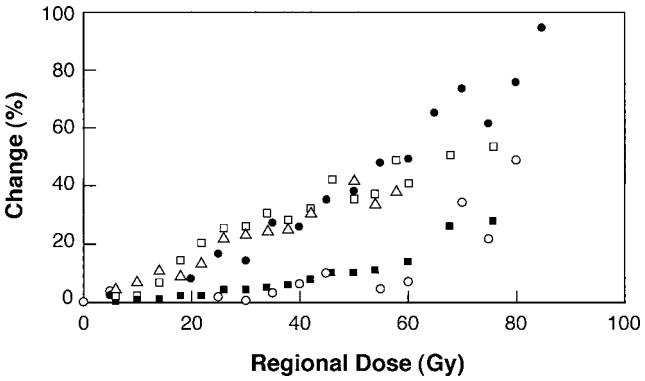


Figure 70-8 Regional changes in ventilation, perfusion, and computed tomography (CT) density from partial lung radiotherapy as a function of regional radiation dose: data from Duke University (Duke) and Netherlands Cancer Institute (NKI). Symbols in graph represent: (●) reduction in perfusion-Duke; (○) increase in CT density-Duke; (■) change in air-filled fraction-NK; (□) reduction in perfusion-NKI; and (△) reduction in ventilation-NKI. (*Redrawn from Marks LB, Yu X, Vujaskovic Z, et al: Semin Radiat Oncol 13:333-345, 2003*)

Perhaps the most accurate and clinically relevant means to estimate risks for radiation pneumopathy is to study a large group of patients who receive a relatively standard dose and fractionation scheme for a given disease. As described, the variability of the treatment volume for diseases such as lung cancer, as well as the frequent coexistence of other lung disease, especially COPD from tobacco use, makes this a difficult task. Increasing emphasis in prospectively evaluating the risk for pneumonitis involves the analysis of dosimetric parameters, especially V_{20} or V_{30}, i.e., the volume of lung receiving a threshold radiation dose of 20 or 30 Gy usually expressed as a percent of the total lung volume. A large series from Australia, for instance, found that V_{30} was a reasonable predictor of radiation pneumonits. The actuarial risk of pneumonits

was 16 percent at 6 months and 24 percent at 1 year follow-up in a series of 156 patients with non–small-cell lung cancer treated with primary radiotherapy with curative intent. Of several dosimetric parameters, V_{30} was the best predictor of pneumonits on both univariate and multivariate analysis. For instance a V_{30} greater than 22 percent was associated with a 30 percent risk of pneumonits at 1 year follow-up. Other data reviewed by Rodriguez et al. suggest trends of increasing risk of pneumonitis for V_{20} over 30 percent or mean lung dose over 20 Gy. More complex prediction models that factor in baseline D_{LCO}, serum cytokine levels, or tumor locations in upper versus low lobes have yielded variable improvements in prognostication. Similar data regarding the incidence of radiation fibrosis are quite difficult to obtain, largely because of the wide spectrum of severity in symptomatology. Clinical experience suggests that radiographic fibrosis is rare below 20 Gy and common above 40 to 50 Gy, with symptoms of respiratory insufficiency dependent on the volume of injured lung and the presence of coexisting lung disease.

Lung Cancer: Local Tumor Boosting

In the treatment of lung (and perhaps esophageal) cancer, it is quite standard to boost the primary tumor and a small volume of the lung to total cumulative doses beyond 50 Gy, commonly to 60 to 70 Gy. Clinical data, notably the dose-escalation lung cancer trials of the Radiation Therapy Oncology Group, suggest that increasing doses to small volumes from approximately 50 to approximately 65 Gy is not associated with a significant increase in lung toxicity, probably because the number of nonfunctional alveoli is not increased by this increase in dose. In most series of patients receiving radical thoracic radiotherapy, the risk of symptomatic radiation pneumonitis is usually around 10 to 20 percent, and some degree of radiographic fibrosis is almost universal.

Breast Cancer

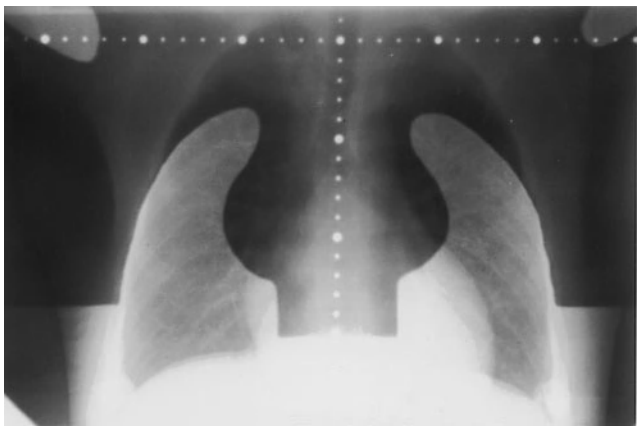
Breast cancer radiotherapy, whether after lumpectomy or mastectomy, typically uses opposed tangential beams, as depicted in Fig. 70-6, which irradiate a volume of lung anterolateral to a plane demarcating the mid chest to the lateral axillary line to doses of 45 to 50 Gy in 23 to 25 fractions. The volume of the ipsilateral lung irradiated can be estimated for individual patients from the simulator films and is typically about 20 percent of the lung volume. If supraclavicular and axillary nodes are irradiated as well, anterior treatment portals are matched to the tangential chest wall fields. As a result the apex of the lung (roughly another 10 to 15 percent of ipsilateral lung volume) is also irradiated. The incidence of symptomatic pneumonitis from tangential fields alone is roughly 0.5 percent, with some series documenting an increased risk with increasing lung volume. It is desirable to keep the irradiated volume below approximately 25 percent, if possible. Nodal irradiation increases the risk for pneumonitis to 0.5 to 1.5 percent. Risk further increases to as high as 9 percent when chemotherapy is given concurrently. The risk of pneumonitis is much lower when chemotherapy and radiation are given sequentially.

Early-Stage Hodgkin's Disease

Radiotherapy for early-stage Hodgkin's lymphoma, using moderate doses (40 to 45 Gy in 1.5 to 2 Gy fractions) and large volumes to treat lymph node–bearing regions, has represented a remarkable success story in oncology. Because it now has produced very high cure rates in a young patient population, allowing for extended follow-up over several decades, this experience also has produced considerable data regarding late radiation toxicities. In these protocols, the chest is irradiated with treatment portals, generically called "mantle fields," as depicted in Fig. 70-9. With modern radiation techniques that use sequential shrinking fields, the incidence of symptomatic radiation pneumonitis is 3 to 4 percent. The risk of pneumonitis increases to roughly 10 percent when full doses of both chemotherapy (MOPP or ABVD-type combinations) and radiation to a mantle field are given sequentially. Studies on pulmonary function in Hodgkin's disease patients suggest that a transient reduction in FEV_1 and vital capacity, on the order of 5 to 20 percent, occurs 3 to 9 months after radiotherapy, corresponding to the period of pneumonitis. There tends to be some recovery by roughly 1 year. Late follow-up of pulmonary function in Hodgkin's disease patients at Stanford further suggests that mantle field radiotherapy is associated with small, and for the most part clinically insignificant, reductions in vital capacity and D_{LCO}. These decreases in pulmonary function tests were associated with minor, if any, symptomatology, even for treatment regimens that included sequential chemotherapy with doxorubicin or bleomycin. Primary radiotherapy for Hodgkin's disease is now rarely practiced. Decades of follow-up in patients cured of their lymphomas show a steady increase in secondary cancers as well as cardiac complications. As a consequence, clinical trials have shown improved disease-free survival over 5 to 10 years with primary chemotherapy. In this setting in which lower-dose (20 to 30 Gy) involved-field radiotherapy is often delivered after chemotherapy, the incidence of clinical pneumonitis is quite low, although small changes in spirometric and diffusion capacity parameters can still be detected in up to 50 percent of the patients. Longer-term follow-up of toxicities from combined modality therapy in Hodgkin's disease is in progress.

PROGNOSTIC ASSAYS AND FUTURE TRENDS

Our understandings of the molecular and cellular mechanisms of radiation injury in general and radiation pneumonitis in particular are still evolving and improving. We hope increased understanding of these processes will lead to



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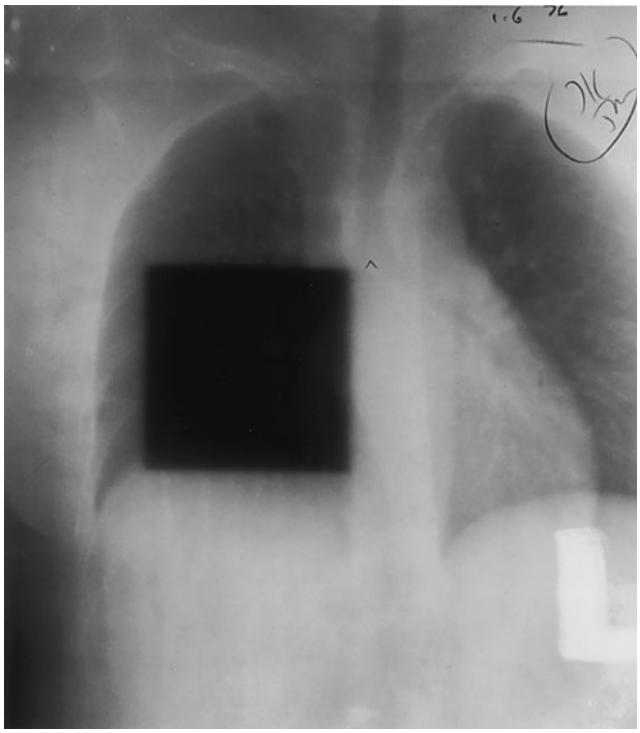

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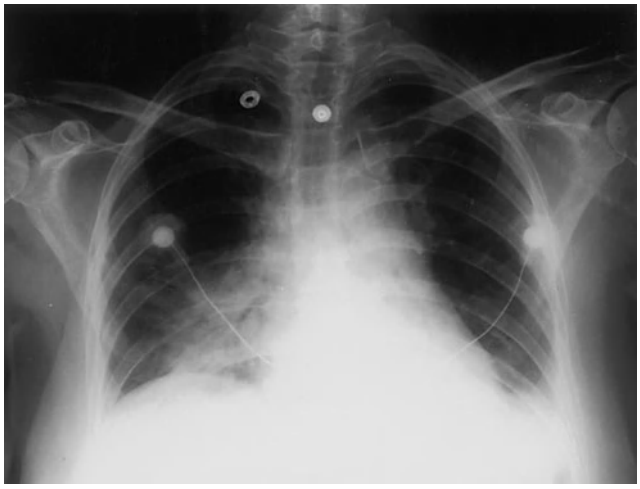

C

approaches for avoiding radiation injury to the lung, for modulating the development of injury or ameliorating its symptomatology, and for identifying patients at unusually high risk of injury. Several different lines of investigation leading to these ends are being pursued.

Innovations in radiation therapy techniques are under active investigation. These include modifications in the dose rates, fractionation patterns, and radiation dose distributions used in radiation therapy regimens for specific diseases. Improvements in diagnostic imaging that allow better identification of tumor-involved regions, computerized treatment planning and dosimetry systems, improved patient immobilization systems, the use of multiple "noncoplanar, noncoaxial" radiation portals (three-dimensional conformal radiotherapy), and the use of multiple radiation fields that have variable rather than uniform spatial intensities (intensity modulated radiotherapy) all are being explored in the hope that they will enable the radiotherapist to increase the dose to the tumor while decreasing the volume of surrounding normal tissue irradiated to high doses. Conformal radiotherapy will be more complex, and more costly, than current radiotherapy approaches. It may also be difficult to prove whether this technology results in improved clinical outcomes. Refinements in combined-modality therapy may lead to the development of regimens that decrease pulmonary toxicity and therefore increase the therapeutic ratio for the treatment of thoracic tumors. Consequently, improvements in the delivery of antineoplastic therapy may decrease the risk and severity of radiation pneumonitis.

The risk of developing radiation pneumonitis varies dramatically in different patients. To a certain extent, increased risk can be predicted from identifiable risk factors, such as prior treatment with thoracic radiotherapy, treatment with pneumotoxic drugs, or the existence of lung disease from other causes. However, even when the known risk factors are considered, the risk of symptomatic injury after radiotherapy varies dramatically from patient to patient. Studies with mice indicate that genetic factors contribute to individual variability in the development of late radiation injury in the lung. This raises the possibility that pretreatment measurements of enzyme or cytokine levels in the lung, analyses

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Figure 70-9 (*A*) shows the port film for a typical mantle used for treatment of a patient with Hodgkin's lymphoma. Note the effect of the lung blocks in reducing the dose to large volumes of the lung. (In this example, the whole heart/pericardium is not being treated.)

A 30-year-old female underwent mantle field and subdiaphragmatic radiotherapy (not shown) for early-stage Hodgkin's lymphoma. Ten years later, a recurrence in the right lower lobe and mediastinum was treated with MOPP-type chemotherapy and low-dose involved-field radiotherapy. The treatment field to the right lung, shown in (*B*), was irradiated to 15 Gy in 10 fractions, in addition to the 40 Gy given to the mantle field ten years previous. Radiation pneumonitis occurred 6 months later, as seen in (*C*). This responded to prednisone. Sixteen years later, the patient remains well and free of recurrence.

during treatment of changes in cytokine levels or of tissue response to cytokines, or some other relevant measure may be useful in predicting patients at high risk for the development for pneumotoxicity. Assays of surfactant levels shortly after irradiation predict radiation pneumonitis in some rodent studies but have not predicted radiation pneumonitis in individual patients in the clinical trials performed to date. TGF-β, a cytokine that mediates fibrosis, is currently the subject of intense investigation. Serum levels of TGF-β have been reported to predict pulmonary toxicity after high-dose chemotherapy for breast cancer, but its application to radiotherapy for lung cancer has been tenuous and controversial. Assays of other cytokines such as IL-6 are being explored clinically. Similarly, analyses of the intrinsic radiosensitivity in vitro of fibroblasts from patient biopsies have been suggested as a possible approach to measuring the general risks of individual patients for radiation injury. Such assays have proved useful in planning treatments for patients with the genetic disease ataxia telangectasia, which leads to unusual radiosensitivity. Prognostic assays predicting high or low risk for radiation pneumopathy could be used to guide clinical decision making and plan therapy to minimize risks for individual patients.

Insights into the physiology underlying the development of radiation pneumopathy may also lead to the development of regimens that prevent the development of disease or ameliorate its symptomology. The use of "radioprotectors" such as amifostine (Ethyol, WR2721) has been of variable benefit in reducing mucositis or xerostomia in head and neck cancer patients undergoing radiotherapy (without apparent effect on tumor control). This has led to analogous clinical investigations of amifostine to prevent pneumonitis, given its widespread distribution into most normal tissues and its activity as a free radical scavenger. Several small phase III trials in lung cancer suggested a benefit to amifostine during thoracic radiotherapy, in regard to the prevention of not only pneumonits, but also radiation esophagitis as well. A large multi-institutional trial sponsored by the Radiation Therapy Oncology Group involving 242 patients, however, failed to document a difference in pneumonits rates with amifostine. The trial has been criticized for its twice a day fractionation scheme in which amifostine was administered with only one fraction each day, an unusually high patient drop out rate of 19 percent due to toxicity, and the fact that 52 percent of patients did not receive their intended dose of amifostine. The development of radiation pneumopathy has not been appreciably altered by the use of prophylactic steroids, antibiotics, or anticoagulants. The use of gamma interferon in conjunction with radiation actually worsened pneumonitis in recent clinical trials. Beta interferon has been under clinical investigation. Nutritional factors merit further consideration, as subclinical vitamin A deficiency has been shown to increase radiation injury in the rat lung. Numerous other approaches are being investigated in laboratory studies, including the use of captopril, lovastatin, pentoxifylline, interleukin-11, and the modulation of TGF-β production. Captopril, which is an angiotensin-converting enzyme (ACE) inhibitor clinically used for the treatment of hypertension and heart failure, is of particular interest as it has several different potential mechanisms of action. As a thiol compound, it may act as a free radical scavenger. It can also forms copper complexes which has superoxide dismutase–like activity. Moreover, in animal studies captopril has vascular effects and can inhibit platelet aggregation perhaps mediated by IL-2 release that ameliorates radiation injury of pulmonary endothelium along with a decrease in pulmonary fibrosis. One retrospective review failed to demonstrate a benefit for ACE inhibitors but did not specifically evaluate captopril only. Lovastatin, a cholesterol-lowering drug that inhibits 3HMG coenzyme A reductase, also has potent anti-inflammatory effects. A murine model of whole-lung irradiation showed improved survival and reduced pulmonary infiltration of macrophages and lymphocytes by treatment with statins. This approach has not yet been investigated in the clinic.

All attempts to modulate the development of radiation pneumonitis must be pursued cautiously, however, because these therapeutic strategies are based on biologic epiphenomena and an incomplete understanding of the mechanisms by which radiation pneumopathies are produced. In testing such interventions, as with any alteration of cancer therapy, it will be critical to consider the effects of the intervention on the response of the malignancy, as well as its effects on normal tissue injury, because the intervention will be of value only if it increases the therapeutic ratio.

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Pulmonary Manifestations of the Collagen Vascular Diseases

Gregory P. Cosgrove • Marvin I. Schwarz

The pleuropulmonary complications associated with the collagen vascular diseases are frequent occurrences, and it would be the exception rather than the rule for an individual to avoid one of these during the course of such an illness. All the elements of the respiratory system may be affected, either separately or in combination. This includes the respiratory muscles, the pleura, the conducting airways, and the lung parenchyma—the small airways, the interstitium, or the pulmonary vessels. Moreover, these patients experience an increased incidence of community-acquired pneumonia as well as pneumonia associated with the immunosuppressive drugs employed for treatment. Anti-tumor necrosis factor-α (TNF-α) agents increase the risk for infections, particularly mycobacterial pathogens, both tuberculous and nontuberculous. Cytotoxic drugs, particularly methotrexate and gold, can also induce various noninfectious interstitial reactions, which are often difficult to distinguish from a primary interstitial complication of a collagen vascular disease.

Although most pulmonary complications appear in an established case of a collagen vascular disease, lung disease may precede the more typical systemic manifestations. For example, in both rheumatoid arthritis and polymyositis-dermatomyositis, the interstitial lung disease may precede the joint and muscle disease for several months to several years. This is also the case, but to a lesser extent, for scleroderma. In one study, 19 percent of patients initially diagnosed with idiopathic pulmonary fibrosis developed a collagen vascular disease over a period of 1 to 11 years, primarily rheumatoid arthritis or polymyositis-dermatomyositis. These individuals were younger and more likely to be women. Pleuritis with or without effusion sometimes heralds the onset of rheumatoid arthritis or systemic lupus erythematosus. An acute immunologic pneumonitis or diffuse alveolar hemorrhage has been reported to be the signal event in systemic lupus erythematosus, polymyositis-dermatomyositis, and mixed connective-tissue disease.

The actual incidence of the pleuropulmonary complications (Table 71-1) is variable. Interstitial lung disease is reported to be as high as 60 percent in premortem and 100 percent in postmortem studies in scleroderma. In contrast,

Table 71-1

Pulmonary Complications of the Collagen Vascular Diseases

	Relative Frequency (0–4)						
Manifestation	**SLE**	**RA**	**SS**	**PM-DM**	**MCTD**	**AS**	**Sjögren's**
Respiratory muscle dysfunction	2	1	0	2	1	0	0
Aspiration pneumonia	0	0	3	3	2	0	2
Primary pulmonary hypertension	2	1	4	1	2	0	0
Vasculitis	2	2	0	1	1	0	0
Interstitial lung disease	2	3	4	3	2	1	3
Capillaritis + DAH	2	1	1	1	1	0	0
Bland DAH	2	0	0	0	1	0	0
Diffuse alveolar damage	2	0	0	2	1	0	0
Nonspecific interstitial pneumonitis	2	3	3	3	3	0	1
Lymphocytic interstitial pneumonitis	1	2	1	0	0	0	3
Usual interstitial pneumonitis	2	3	2	2	2	1	1
Honeycomb lung	1	2	4	3	2	1	1
Bronchiolitis obliterans organizing pneumonia	1	3	1	3	2	0	1
Bronchiolitis	1	2	1	0	1	0	1
Obliterative bronchiolitis	0	2	0	0	0	0	1
Pleural effusion	2	3	1	0	2	0	1
Parenchymal nodules	0	2	0	0	0	0	1

Abbreviations: SLE = systemic lupus erythematosus; RA = rheumatoid arthritis; SS = systemic sclerosis (scleroderma); PM-DM = polymyositis-dermatomyositis; MCTD = mixed connective-tissue disease; AS = ankylosing spondylitis; Sjögren's = Sjögren's syndrome; DAH = diffuse alveolar hemorrhage.

interstitial lung disease in ankylosing spondylitis is an uncommon event. In general, the incidence of interstitial lung disease is increasing for most of the collagen vascular diseases, primarily due to increased recognition and more sensitive screening techniques such as high-resolution computed tomography and bronchoalveolar lavage, which will detect abnormalities in both asymptomatic as well as symptomatic patients with normal chest radiographs. Moreover, many of the earlier incidence studies relied on physiological testing, which included spirometry, lung volumes, and diffusing

capacity but did not measure rest and exercise gas exchange, which is the most sensitive physiological marker of interstitial lung disease as well as pulmonary vascular disease.

HISTOLOGICAL SPECTRUM OF PARENCHYMAL REACTIONS IN COLLAGEN VASCULAR DISEASE

Interstitial Lung Disease

Interstitial involvement is a common respiratory manifestation of the collagen vascular disorders, presenting with a number of different inflammatory responses within the lung. Each response may represent a different form of lung injury or response to injury. Defining which response is underlying a patient's interstitial lung disease has important prognostic and therapeutic significance.

Diffuse alveolar damage (DAD) is the underlying histological lesion that is also seen in the acute respiratory distress syndrome, idiopathic acute interstitial pneumonitis (Hamman-Rich syndrome), severe viral pneumonias, and cytotoxicity from some drugs. This damage consists of a mixed interstitial inflammatory infiltrate, interstitial edema and fibrin deposition, and the characteristic intra-alveolar hyaline membrane formation. Intra-alveolar red blood cells (diffuse alveolar hemorrhage) may be present in severe cases. With progression, there is intra-alveolar organization, intra-alveolar and interstitial fibrosis, alveolar collapse, and the development of an end-stage fibrotic or "honeycomb" lung. An acute immunologic pneumonia, seen in systemic lupus erythematosus (acute lupus pneumonitis) and in polymyositis-dermatomyositis, may demonstrate this underlying histological appearance.

Nonspecific interstitial pneumonitis (NSIP) refers to a spectrum of histological features with varying degrees of lymphoplasmacytic infiltration of the interstitium and collagen deposition (Fig. 71-1). In the cellular form, lymphoplasmacytic interstitial inflammation exists with associated type II alveolar epithelial cell hyperplasia. In the fibrosing form, the inflammation is accompanied by a temporally and spatially homogeneous deposition of collagen (fibrosis). Architectural distortion or honeycombing may occur in advanced cases and the presence of fibrosis dramatically changes the clinical course and prognosis to one resembling that seen in usual interstitial pneumonitis (see below). NSIP is most frequently seen in patients with rheumatoid arthritis, polymyositis-dermatomyositis, mixed connective-tissue disease, and scleroderma.

Lymphocytic interstitial pneumonitis refers to a monotonous infiltration of the interstitium by mature lymphocytes (Fig. 71-2). These lymphocytes tend to form germinal centers within the interstitium as well as displaying an angiocentric distribution. Other features of lymphocytic interstitial pneumonia include macrophagic giant cells, granuloma formation, and amyloid deposition. Lymphocytic interstitial pneumonitis can progress to usual interstitial pneumonitis and end-stage honeycomb lung. Among the collagen vascular diseases, this pneumonitis most commonly accompanies the primary form of Sjögren's syndrome and, to a lesser extent, the secondary form of Sjögren's syndrome appearing with other collagen vascular diseases, particularly rheumatoid arthritis.

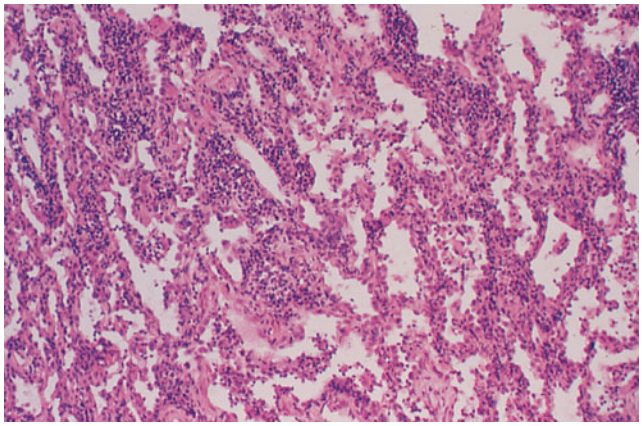


Figure 71-1 Nonspecific interstitial pneumonitis (NSIP) in rheumatoid arthritis. There is a lymphoplasmacytic infiltration of the interstitial compartment with minimal collagen deposition.

Usual interstitial pneumonitis (UIP) is the underlying lesion of idiopathic pulmonary fibrosis and can also appear in all the collagen vascular diseases. It consists of varying degrees of mononuclear cell infiltration and fibroblastic proliferation leading to collagen deposition within the alveolar interstitium (Fig. 71-3). With progression, this fibrotic reaction results in marked distortion of the lung architecture and what remains are 2- to 3-mm cystic spaces lined by metaplastic epithelium, the so-called honeycomb lung (Fig. 71-4). Other features of UIP include type II epithelial cell hyperplasia producing a "hob-nailed" appearance on the alveolar surface, collections

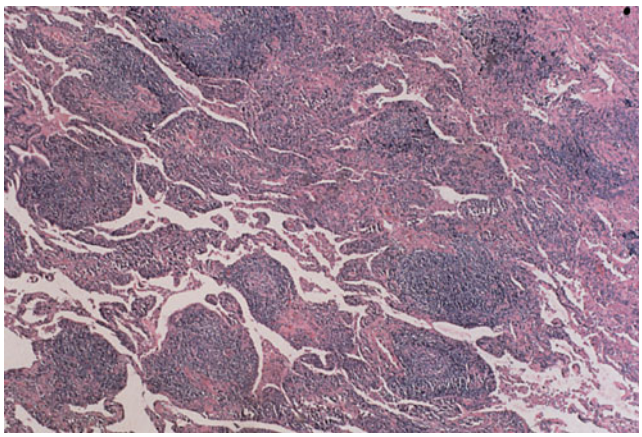


Figure 71-2 Lymphocytic interstitial pneumonitis in a patient with primary Sjögren's syndrome. There is a dense lymphocytic infiltrate, broadening the interstitium and lymphoid follicles.

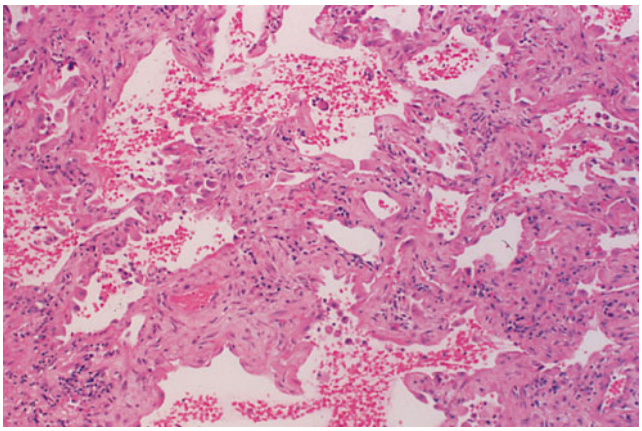


Figure 71-3 Usual interstitial pneumonia (UIP) in a patient with rheumatoid arthritis. There is broadening of the interstitium by varying degrees of mononuclear cell infiltration and collagen deposition.

of intra-alveolar macrophages, and smooth-muscle proliferation within the interstitium. Additional abnormalities seen in collagen vascular disease-associated UIP but not in patients with idiopathic pulmonary fibrosis may include: focal chronic pleuritis, lymphoid follicles with germinal center formation, perivascular collagen deposition, and an increase in CD4+ T lymphocytes, especially in rheumatoid arthritis.

Bronchiolitis obliterans organizing pneumonia is a distinctive histological lesion that follows a variety of insults to the alveolar structures including drugs, infection, radiation, and an idiopathic variety. Bronchiolitis obliterans organizing pneumonia can also complicate the collagen vascular diseases, particularly rheumatoid arthritis and polymyositis-dermatomyositis. Three features comprise the histological picture: (1) intra-alveolar space and intra-alveolar ductal fibroblastic proliferation with early collagen deposition (Masson bodies), (2) inflammatory polyps consisting of fibroblasts and mononuclear cells protruding into the lumens of respiratory and terminal bronchioles, and (3) alveolar septal lymphoplasmacytic infiltrate with type II pneumocyte hyperplasia within affected areas (Fig. 71-5). Bronchiolitis obliterans organizing pneumonia has the potential for being a completely reversible lesion; however, with continuing injury it may progress to end-stage fibrosis and honeycomb lung.

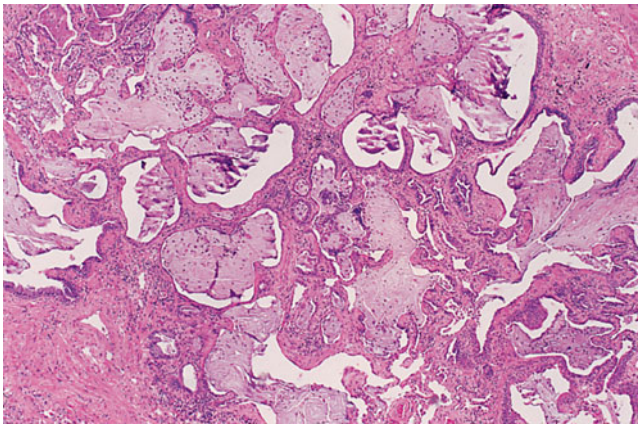


Figure 71-4 Advanced UIP in a patient with scleroderma (honeycomb lung). Normal alveolar tissue is replaced with broad bands of fibrous tissue lined by metaplastic epithelium and filled with inspissated mucus producing a cystlike network.

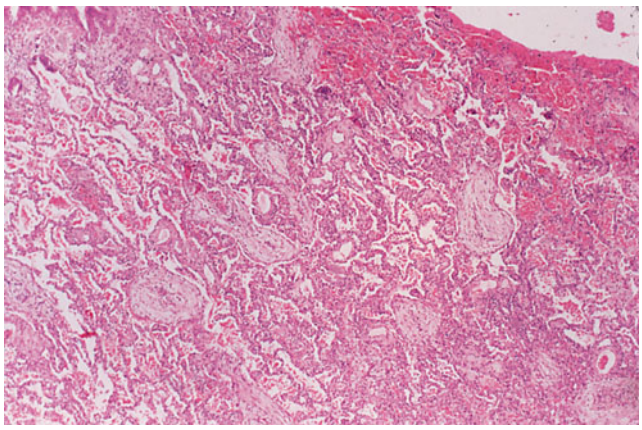


Figure 71-5 Bronchiolitis obliterans organizing pneumonia in a patient with rheumatoid arthritis. There is a mononuclear cellular infiltration of the interstitium without collagen deposition as well as alveolar duct and intra-alveolar fibroblastic proliferation and early collagen production.

Pulmonary Vascular Disease

A form of pulmonary artery hypertension, which most commonly appears in patients with scleroderma and is now being increasingly recognized in systemic lupus erythematosus, rheumatoid arthritis, and mixed connective-tissue disease, is histologically identical to the syndrome of idiopathic pulmonary artery hypertension (IPAH) seen in young women without collagen vascular disease, formerly known as primary pulmonary hypertension. This is a proliferative disorder (plexogenic arteriopathy) affecting the arterioles and small muscular pulmonary arteries. This form of pulmonary hypertension must be differentiated from secondary forms as a result of hypoxic vasoconstriction induced by interstitial lung disease or severe emphysema. In the plexogenic variety, there is endothelial cell intimal proliferation and smooth-muscle cell proliferation causing medial thickening with a resultant "onion ring" configuration and luminal obliteration. In the secondary forms of pulmonary hypertension due to hypoxia, medial hypertrophy is the primary finding. In patients with systemic lupus erythematosus and the antiphospholipid syndrome, pulmonary artery hypertension may develop as a result of recurrent pulmonary emboli and mimic the clinical picture of IPAH.

Vasculitis refers to an acute inflammatory angiodestructive process resulting in fibrinoid necrosis of the vascular wall. In the collagen vascular diseases, this is most often a small-vessel vasculitis involving arterioles and small muscular pulmonary arteries. Although uncommon, this is seen with greatest regularity in systemic lupus erythematosus and less frequently in rheumatoid arthritis,

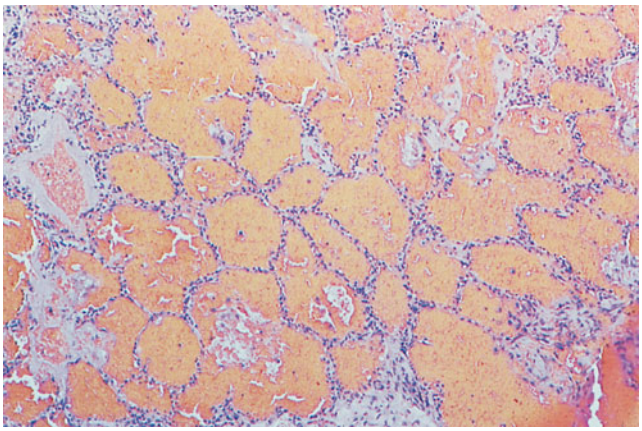


Figure 71-6 Bland diffuse alveolar hemorrhage in SLE. There is little if any interstitial reaction except for type II pneumocyte epithelial cell hyperplasia. The alveolar spaces are filled with red blood cells.

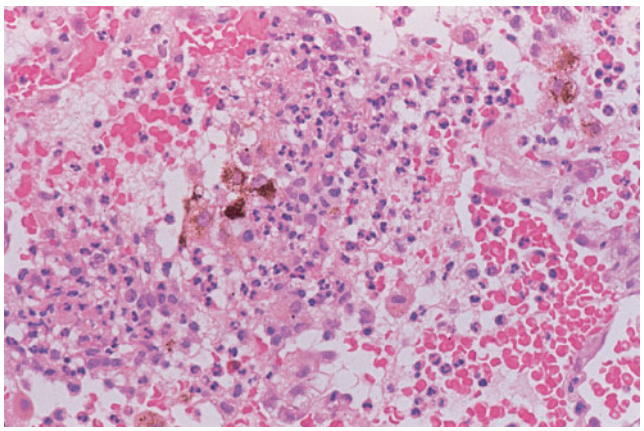


Figure 71-7 Low-power view of pulmonary capillaritis in a patient with SLE. There is marked thickening of the interstitial compartment and infiltration by acute and chronic inflammatory cells. The alveolar spaces are filled with red blood cells and neutrophils.

polymyositis-dermatomyositis, and mixed connective-tissue disease. Often accompanying the arteriolitis is the lesion of pulmonary capillaritis (see below).

Diffuse Alveolar Hemorrhage

Diffuse alveolar hemorrhage is recognized by the accumulation of red blood cells within the alveolar spaces, and with recurrent episodes, intra-alveolar and interstitial hemosiderin is deposited and fibrosis may result. There are two different histological subtypes seen in diffuse alveolar hemorrhage. One is devoid of inflammation and is referred to as *bland hemorrhage* (Fig. 71-6). It is therefore similar in histological appearance to idiopathic pulmonary hemosiderosis. The other, pulmonary capillaritis, is a unique neutrophilic infiltration of the alveolar interstitium, which results in necrosis and loss of integrity of the alveolar-capillary basement membrane, capillary destruction and thrombosis, and a leakage of red blood cells into the alveolar space (Fig. 71-7). A unique feature in pulmonary capillaritis is that many of the infiltrating neutrophils are undergoing fragmentation (leukocytoclasis), and others appear as densely staining apoptotic cells. Nuclear debris ("dust") subsequently accumulates within the necrotic, edematous interstitium and intra-alveolar compartments while red blood cells freely leak into the interstitial matrix due to capillary destruction. Capillary and arteriolar thrombosis, organizing pneumonia, and type II epithelial cell hyperplasia may also be seen.

Capillaritis is most commonly seen in the systemic vasculitides, particularly Wegener's granulomatosis and microscopic polyangiitis, the small-vessel variant of polyarteritis nodosa. Of the collagen vascular diseases, both bland pulmonary hemorrhage and diffuse alveolar hemorrhage secondary to pulmonary capillaritis appear most commonly in systemic lupus erythematosus. Cases of pulmonary capillaritis have also been reported to occur in rheumatoid arthritis, Sjögren's syndrome, polymyositis-dermatomyositis, and mixed connective-tissue disease.

Bronchiolitis

Bronchiolitis refers to an inflammatory-fibrotic process involving the terminal and respiratory bronchioles and possibly the surrounding alveolar structures. Respiratory bronchiolitis is primarily seen in smokers with or without an associated collagen vascular disease. There is also a primary form of cellular bronchiolitis that complicates the collagen vascular diseases, most often appearing in rheumatoid arthritis and Sjögren's syndrome. Histologically, there is a mononuclear cell infiltration of the wall of the bronchiole without impingement of the bronchiolar lumen. In contrast, in bronchiolitis obliterans, or obliterative bronchiolitis, there is a concentric fibrous obliteration of the bronchiolar lumen leading to a severe obstructive lung disease (Fig. 71-8). Bronchiolitis obliterans is most often reported as a complication of rheumatoid arthritis.

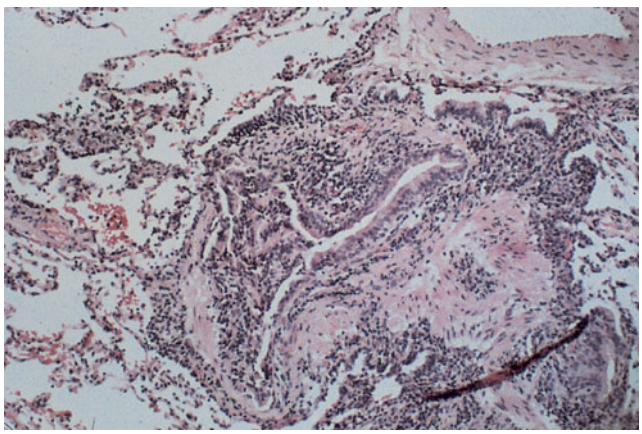


Figure 71-8 Obliterative bronchiolitis in rheumatoid arthritis. There is a marked reduction of the luminal diameter due to concentric fibrous obliteration and dense chronic inflammation. *(From Schwarz MI, Lynch DA, Tuder R: Bronchiolitis obliterans: The lone manifestation of rheumatoid arthritis.* Eur Respir J *7:817–820, 1994, with permission.)*

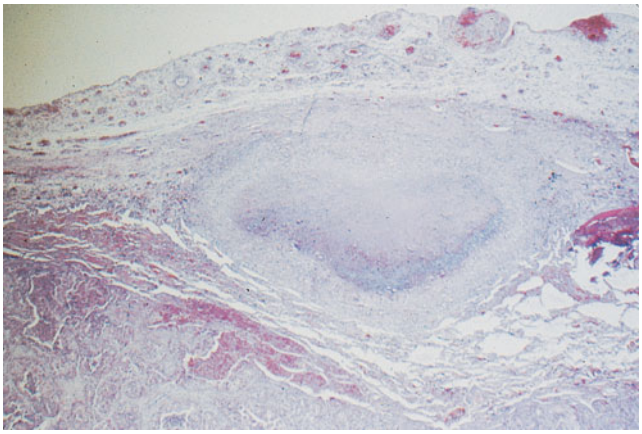


Figure 71-9 Typical subpleural location of a necrobiotic rheumatoid nodule. There is a central area of fibrinoid debris surrounded by palisading histiocytes.

Parenchymal Nodules

Noninfectious inflammatory parenchymal nodules occur in both rheumatoid arthritis and Sjögren's syndrome. In rheumatoid arthritis the nodules are referred to as the *necrobiotic* or *rheumatoid nodules*. These lesions are found both in the pleura and lung parenchyma and are identical in appearance to a subcutaneous rheumatoid nodule. In the lung parenchyma, these nodules are located in the interlobular septa and in the subpleural parenchyma. The necrobiotic nodule is comprised of palisading histocytes, giant cells, and other mononuclear cells surrounding an area of fibrinoid debris (Fig. 71-9). In Sjögren's syndrome, a rounded lesion known as pseudolymphoma can occasionally be detected on the chest radiograph. Pseudolymphoma is considered to be a localized form of lymphocytic interstitial pneumonia and is made up of a dense infiltrate of lymphocytes and histiocytes with occasional granuloma formation. There is a potential risk for malignant transformation in pseudolymphoma as well as in the other forms of lymphocytic interstitial pneumonia.

CLINICAL FEATURES OF THE COLLAGEN VASCULAR DISEASES

Systemic Lupus Erythematosus

Systemic lupus erythematosus (SLE) is characterized by the production of antibodies against various cellular antigens derived from the nucleus, cytoplasm, or cell membrane. Tissue injury appears to be associated with the development of immune complexes, the presence of low serum complement levels, and the production of antibodies to native DNA. The pulmonary complications are thought to be the result of an immune complex-mediated injury. A number of syndromes (Table 71-2) are associated with acute respiratory-type illness in SLE. A patient with SLE who presents with a febrile illness, cough with or without productive sputum,

Table 71-2

Acute Lung Syndromes in Systemic Lupus Erythematosus

Community-acquired or immunocompromised pneumonias
Pleurisy
Pulmonary embolization
Uremic pneumonitis
Cardiogenic pulmonary edema
Acute reversible hypoxemia syndrome
Acute lupus pneumonitis
Diffuse alveolar hemorrhage

and new pulmonary infiltrates must be considered to have an infectious pneumonia, although acute lupus pneumonitis and diffuse alveolar hemorrhage may have a similar presentation. Infection can be community-acquired or result from immunosuppressive treatment. Infectious pneumonia represents the most common cause of pulmonary disease in SLE, and infections in general represent the most common reason for death (33 to 77 percent) in these patients. Bronchoalveolar lavage is often helpful in excluding an infectious pneumonia in the immunocompromised SLE patient.

Another important consideration in an acutely dyspneic SLE patient is pulmonary embolization, a complication reportedly occurring in up to 25 percent of patients and a significant cause of mortality. The occurrence of thromboembolic disease correlates with the presence in the serum of acquired antiphospholipid antibodies (lupus anticoagulant or anticardiolipin). The most common epitope(s) to which antibodies exist in these patients is β_2- glycoprotein I. A more appropriate term may therefore be anti-β_2–glycoprotein syndrome. Up to a third of patients with SLE have the antiphospholipid syndrome. Thrombocytopenia, recurrent venous or arterial thrombosis, hemolytic anemia, leg ulcers, and recurrent fetal loss are also manifestations of antiphospholipid syndrome.

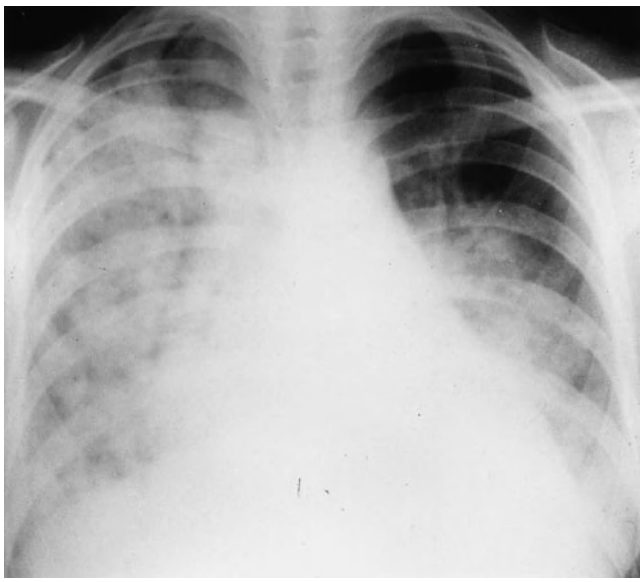
Other causes for acute respiratory failure in patients with SLE include a volume overload state, due either to renal failure or to congestive heart failure secondary to myocarditis. Uremic pneumonitis with underlying DAD is also a possible cause of an acutely dyspneic SLE patient with renal failure. A syndrome, *acute reversible hypoxemia*, occurring in acutely ill SLE patients who are experiencing systemic exacerbations has been described. These patients have hypoxemia and a

widened alveolar-arterial oxygen gradient, but both the chest radiograph and ventilation-perfusion lung scans are normal. It is postulated that there is complement-activated neutrophil aggregation in the pulmonary vasculature. The hypoxemia improves with immunosuppressive therapy. Given the high incidence of antiphospholipid syndrome in SLE, acute reversible hypoxemia should be considered only after excluding thromboembolic disease.

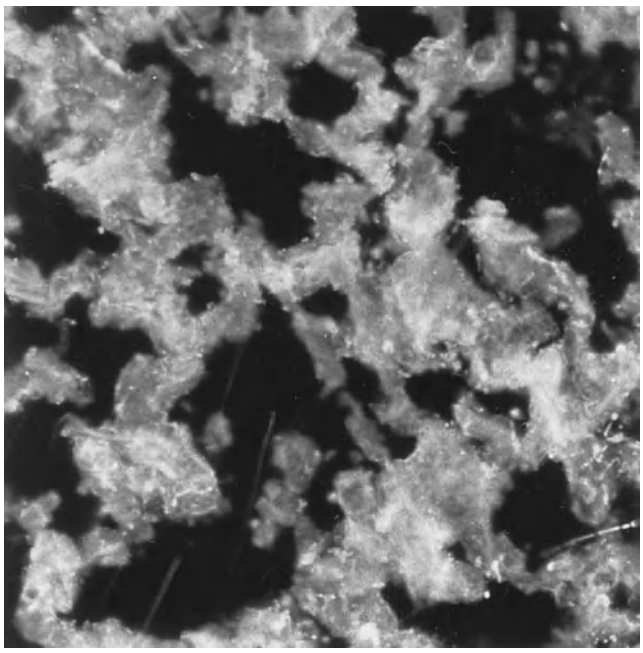
Acute Lupus Pneumonitis

Acute lupus pneumonitis is a clinical syndrome with an underlying histology of DAD, bronchiolitis obliterans organizing pneumonia, NSIP, or a combination of these. Acute lupus pneumonitis mimics an acute infectious pneumonia and may be the presenting manifestation of SLE in up to 50 percent of patients. In those with an established diagnosis, it also appears during a flare-up of the other systemic manifestations of SLE, particularly pleuritis, pericarditis, arthritis, and nephritis. Acute lupus pneumonitis is reportedly more common in the postpartum period. It frequently recurs and cases have been documented that have progressed to a more chronic interstitial lung disease (UIP). Fortunately, acute lupus pneumonitis is a relatively uncommon complication, occurring in less than 5 percent of patients.

Bilateral alveolar infiltrates, which can be patchy or densely consolidated and often accompanied by pleural effusions and cardiomegaly due to underlying pericardial effusion or myocarditis (Fig. 71-10 *A*), are present on chest radiographs at presentation. White blood cell counts and sedimentation rates are elevated and serum complement is often low. Immunopathologic studies reveal the presence of complement as well as antibodies to IgG and DNA in some patients, supporting the concept of an immune complex pathogenesis (Fig. 71-10 *B*). Because of the difficulty in distinguishing acute lupus pneumonitis from an infectious pneumonia, a bronchoalveolar lavage and sometimes an open (thorascopic) lung biopsy are indicated prior to instituting anti-inflammatory and immunosuppressive therapy. Acute respiratory failure in acute lupus pneumonitis often requires assisted mechanical ventilation. The mortality rate has been reported to be as high as 50 percent, with the causes of death in patients with acute lupus pneumonitis being either respiratory failure, another complication of SLE (nephritis, cerebritis), or a superimposed infection.



A



B

Figure 71-10 Acute lupus pneumonitis. The chest radiograph demonstrates diffuse alveolar filling with cardiomegaly (pericardial effusion vs. myocarditis). *A*. There is also a left pleural effusion. *B*. The immunofluorescent study demonstrates granular immune complex deposition in the alveolar interstitium.

Diffuse Alveolar Hemorrhage

Diffuse alveolar hemorrhage, although rare, may be a presenting manifestation of SLE. In several cases, recurrent diffuse alveolar hemorrhage was present for years prior to the diagnosis of SLE. The majority of cases, in contrast to acute lupus pneumonitis, first appear in a well-documented case of SLE. Diffuse alveolar hemorrhage accounts for 1 to 4 percent of SLE-related hospitalizations.

Diffuse alveolar hemorrhage can also present with symptoms reminiscent of an infectious pneumonia or acute lupus pneumonitis, and the additional symptom of hemoptysis raises the possibility of this diagnosis. Hemoptysis is present in 30 to 50 percent of patients during their initial presentation, but up to 90 percent will have hemoptysis during their subsequent course. Routine laboratory work demonstrates a falling hematocrit, and in 60 to 90 percent of patients an active glomerulonephritis is invariably present. A progressively serosanguineous bronchoalveolar lavage may be the first clue to this diagnosis. Diffuse alveolar infiltrates are present on chest radiography (Fig. 71-11), but in contrast

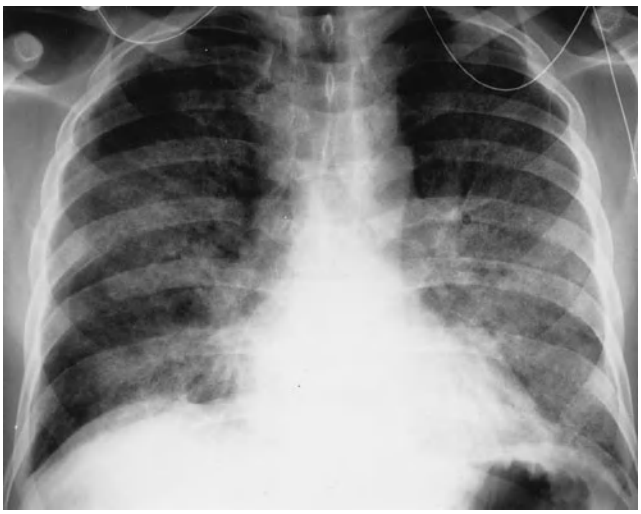


Figure 71-11 Diffuse alveolar hemorrhage in SLE. There are diffuse alveolar infiltrates without cardiomegaly or pleural effusions.

to acute lupus pneumonitis, pleuritis and pericarditis are not prominent features. Pathological changes that are reminiscent of both acute lupus pneumonitis (DAD and NSIP) and diffuse alveolar hemorrhage with or without pulmonary capillaritis are not unusual in a single biopsy specimen. The mortality rate is approximately 50 percent and is independent of the underlying histopathology (bland hemorrhage vs. pulmonary capillaritis). Recurrence is the rule rather than the exception.

There are no controlled clinical trials for the treatment of either acute lupus pneumonitis or diffuse alveolar hemorrhage. Once infection has been excluded, corticosteroids are the mainstay of therapy. Intravenous methylprednisolone, 1 to 2 grams daily in divided doses for 3 to 4 days prior to tapering, should be considered. Concomitant oral or parenteral cyclophosphamide or azathioprine is commonly administered, given the associated incidence of lupus nephritis. Plasmapheresis and immunoglobulin therapy, although logical in lieu of the proposed immune complex pathogenesis, have no proven efficacy to date.

Lupus Pleuritis

Pleurisy and pleural effusion are the most common primary pulmonary complications of SLE, occurring in 50 to 80 percent of patients. Pleurisy and/or a pleural effusion may also be the presenting and sole manifestation of the disease. They are usually recurrent and may accompany more severe complications such as acute lupus pneumonitis or nephritis. Patients complain of pleuritic pain, fever, and dyspnea. The chest radiograph may be normal (dry pleurisy) or demonstrate small to moderate pleural effusions (massive effusions are rare), which are bilateral in 50 percent of patients. When unilateral, there is no predilection for either side.

Effusions are serous or serosanguineous and exudative in nature. The white cell counts range from 5 to 10,000 cells/mm^3. Early on, neutrophils predominate, but with time mononuclear cells appear. These characteristics are nonspecific and are often seen with infectious parapneumonic effusions. In contrast to rheumatoid arthritis, the pleural fluid glucose concentration is not reduced. As in rheumatoid pleural effusions, the rheumatoid factor may be positive, and the pleural fluid complement, both the total levels and the individual components, is reduced. A positive double-stranded pleural fluid DNA titer is nonspecific as opposed to the serum test, since it has been found in pleural effusions due to malignancy and tuberculosis. The most helpful measurement is the pleural fluid antinuclear antibody titer. Levels greater than 1:160 are very suggestive of lupus pleuritis. Examination of the pleural tissue reveals infiltration with plasma cells and lymphocytes, and, with repeated episodes, pleural fibrosis supervenes. Occasionally, a vasculitis of the pleural vessels is detected, and immune complex deposition has been reported. Corticosteroid treatment is effective for relief of pleural pain, but time to resolution of the pleural effusion is quite variable and probably unaffected by this treatment. In the unusual case, recurrent lupus pleuritis may result in massive pleural fibrosis and lung entrapment, necessitating a pleural stripping procedure.

While pleural effusions and pleurisy are common in patients with SLE, a broad differential diagnosis should be considered. The increased incidence of infectious complications, thromboembolic disease, and pulmonary hypertension in SLE predisposes patients to parapneumonic effusions and empyema, congestive heart failure, and effusions secondary to thromboembolic disease.

Interstitial Lung Disease

Clinically significant interstitial lung disease is an uncommon pulmonary manifestation in SLE but UIP, lymphocytic interstitial pneumonitis, NSIP, and bronchiolitis obliterans organizing pneumonia have all been reported. UIP is known to appear following acute lupus pneumonitis and in some cases has been documented to appear as an independent insidious disease. In more recent studies using high-resolution computed tomography, 38 percent of patients with SLE patients with normal chest radiographs demonstrated pulmonary abnormalities consistent with some form of interstitial lung disease. In those who develop interstitial lung disease, a prior episode of acute lupus pneumonitis and an insidious onset of dyspnea are often noted. The prevalence of interstitial lung disease is increased in the subset of SLE patients with features suggestive of an mixed connective-tissue disease.

In patients who develop the insidious form of interstitial lung disease, the diagnosis of SLE is present for several years, and no other pattern of organ involvement predicts its appearance. These patients have progressive dyspnea and cough with interstitial infiltration on the chest radiograph. High-resolution computed tomography indicates combinations of ground-glass attenuation, inter- and intralobular septal thickening, and honeycomb change. Pulmonary function tests reveal a restrictive pattern with reduction in the diffusing

capacity and hypoxemia accentuated by exercise. Response to therapy, either corticosteroids alone or in combination with cyclophosphamide or azathioprine, depends upon the underlying histology. Those cases with underlying NSIP or organizing pneumonia are more likely to respond to treatment than those who demonstrate excess collagen deposition and cystic honeycomb formation.

Pulmonary Vascular Disease

Idiopathic pulmonary hypertension due to plexogenic arteriopathy was previously thought to be an uncommon complication of SLE. It is now estimated to occur in 1 to 9 percent of patients. This form of pulmonary hypertension is associated with Raynaud's phenomenon, digital vasculitis, serositis, antibodies to ribonucleoprotein, rheumatoid factor, antiphospholipid antibodies, and most recently anti-endothelial cell antibodies. Patients complain of dyspnea and fatigue but have normal chest radiographs. In advanced cases, pulmonary arterial enlargement appears. Spirometry and lung volumes are normal, but there is often an isolated reduction of the diffusing capacity for carbon monoxide as well as gas exchange abnormalities. Ventilation-perfusion lung scanning and, occasionally, pulmonary arteriography are indicated, particularly in those patients with the antiphospholipid syndrome who have a potential for recurrent small pulmonary emboli. Therapeutic options include vasodilator therapy, anticoagulation, immunosuppression with cyclophosphamide, and transplantation.

Vasculitis in SLE is more likely to be discovered in lung biopsy specimens, that demonstrate either diffuse alveolar hemorrhage or acute lupus pneumonitis as opposed to being an isolated finding. Autopsy series indicate small-vessel vasculitis in 20 percent of cases.

Bronchiolitis

Five percent of SLE patients are reported also to have obstructive physiology. Obliterative bronchiolitis has been documented in SLE, but is rare in contrast to rheumatoid arthritis. Bronchiolitis obliterans organizing pneumonia, with inflammatory polyps protruding into bronchiolar lumens, is one of the interstitial patterns that occurs in acute lupus pneumonitis and in chronic interstitial lung disease in SLE, but this entity causes restriction rather than obstructive lung disease. Bronchiectasis may occur in up 20 percent of patients but is often asymptomatic. Large airway involvement including tracheal and subglottic stenosis, vocal fold paralysis, epiglottitis, and necrotizing tracheitis have all been reported but are rare.

Respiratory Muscle Dysfunction

It is estimated that weakness of the diaphragm and other respiratory muscles is found in 25 percent of patients with SLE. This accounts for the previously unexplained findings of dyspnea without evidence of interstitial or pulmonary vascular disease. These patients have subsegmental atelectasis, an elevated diaphragm on chest radiograph (Fig. 71-12), and restrictive physiology. This has been referred to as *unexplained dyspnea and shrinking lungs syndrome.* Although there is a reduction in static lung volumes, the diffusing capacity, when corrected for alveolar volume, remains normal, thereby distinguishing respiratory muscle dysfunction from interstitial lung disease. The likely explanation for this is a reduction in the transdiaphragmatic pressure generated during maximal inspiration, which in turn reduces static lung compliance, producing the linear atelectasis seen on the chest radiograph. Moreover, in the patients with respiratory muscle weakness, no evidence for a generalized neuromuscular disease can be found. The pathogenesis of respiratory muscle dysfunction remains unexplained, although phrenic nerve conduction abnormalities have been excluded. Abnormal diaphragmatic activation, due in part to voluntary inhibition due to pleuritic pain, may contribute to diaphragmatic dysfunction in this disorder. Corticosteroids are not a frequently effective treatment modality. Progression is uncommon and most patients stabilize. Positive pressure ventilation (CPAP or BiPAP), particularly at night, may improve these patients' daytime symptoms, although there is limited evidence available to support noninvasive nocturnal ventilation.

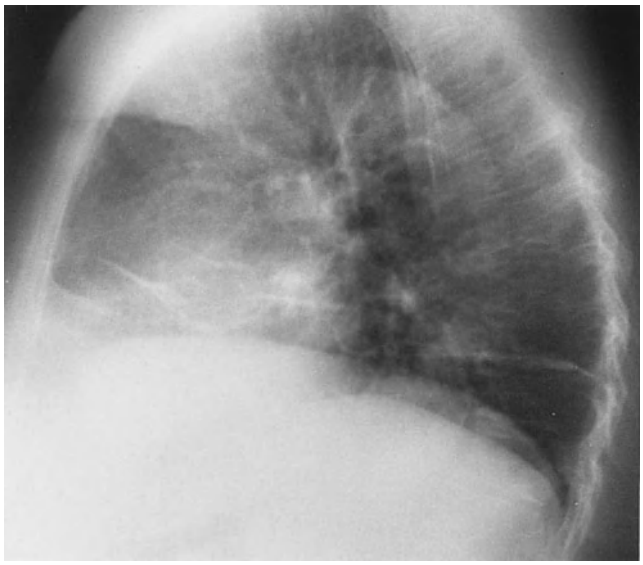


Figure 71-12 Diaphragmatic dysfunction in SLE. There is diaphragmatic elevation resulting in platelike atelectasis.

Rheumatoid Arthritis

Rheumatoid arthritis primarily affects the articular surfaces, but pleuropulmonary complications are responsible for an increased morbidity and mortality. Most often cited is a 50 percent incidence for these complications, but it is likely that this underestimates their frequency. Pleuropulmonary complications are more apt to occur in patients with more severe chronic articular disease, with high titers of rheumatoid factor, and in patients who have subcutaneous nodules, as well as other systemic complications such as cutaneous vasculitis, myocarditis, pericarditis, ocular inflammation, and Felty's syndrome. An association between smoking and an increased

risk for the development of pleuropulmonary disease, radiographic progression, and nodule formation in rheumatoid factor–seropositive patients has been reported. Pleuropulmonary disease may occur in seronegative patients and both methotrexate and gold compounds, commonly employed for treatment, can induce an interstitial lung disease, which is often difficult to distinguish from the primary forms complicating rheumatoid arthritis. Moreover, interstitial lung disease, pleuritis, and occasionally obliterative bronchiolitis may be the first and only manifestation of the rheumatoid state in up to 20 percent of patients, preceding the articular manifestations by months to years.

Pleurisy and Pleural Effusion

Pleural disease in a postmortem series was found in 40 percent of patients with rheumatoid arthritis. The incidence of clinically apparent pleural disease is closer to 5 percent, and the majority of patients experience mild symptoms. In approximately 20 percent of the patients who develop pleural complications, they do so prior to the onset of articular disease. In patients with rheumatoid arthritis, pleural complications are more common in men and occur most frequently during episodes of active articular disease and in patients with subcutaneous rheumatoid nodules.

Pleural disease is often first discovered on routine chest radiograph, and both pleural fibrosis and effusions have been reported to occur in asymptomatic patients. The pleural effusion can be unilateral or bilateral and coexist with interstitial lung disease or necrobiotic nodules. Symptomatic patients present with pleuritic pain, dyspnea, and occasionally fever. The effusion is an exudate by protein and lactic dehydrogenase criteria, and, if chronic, cholesterol concentrations are increased. Other characteristics include a low pleural fluid pH (less than 7.2), thought to be due to impaired carbon dioxide exit from the pleural space. The leukocyte counts can be as high as 15,000 cells per cubic millimeter and consist of a mixture of neutrophils and mononuclear leukocytes. As in SLE, the total and individual complement components are low, and the rheumatoid factor level is increased. The presence of rheumatoid factor in pleural fluid has also been reported with tuberculosis, malignancy, and other infectious diseases. A low pleural fluid glucose concentration, thought to be due to a defect in glucose transport, is characteristic of rheumatoid effusions. Up to 40 percent of patients have pleural fluid glucose levels less than 10 mg/dl, and 75 percent have levels under 50 mg/dl. It has been stated that cytologic examination of the pleural fluid, which demonstrates a background of necrotic debris, spindle-shaped macrophages, and multinucleated histiocytes, is characteristic of a rheumatoid effusion. Necrobiotic nodules are thought to be involved in the pathogenesis of the pleural effusions, but transthoracic pleural biopsy only occasionally will demonstrate this finding.

Treatment is not indicated for asymptomatic cases; however corticosteroids, when used for active articular disease, are also effective in hastening the resolution of the pleural effusion. Rarely, is any other form of intervention such as intrapleural corticosteroids necessary for these patients. In the unusual case, pleural fibrosis with resultant lung entrapment occurs, requiring surgical intervention. Spontaneous pneumothorax due to rupture of a necrobiotic nodule, another uncommon complication, necessitates tube thoracostomy, and with persistence of the bronchopleural fistula, surgical intervention is indicated.

Pulmonary Vascular Disease

In general, pulmonary vascular disease is the least common pleuropulmonary complication in rheumatoid arthritis. The fibroproliferative plexogenic arteriopathy typical of scleroderma and SLE is an infrequent complication. When it does occur, Raynaud's phenomenon is commonly present. The chest radiograph reveals normal lung fields and enlarged pulmonary arteries, and there is an isolated reduction of the diffusing capacity for carbon monoxide as well as hypoxemia.

Small-vessel vasculitis in rheumatoid arthritis occurs in the setting of diffuse alveolar hemorrhage due to pulmonary capillaritis and is a very rare event in rheumatoid arthritis. Several cases have been well documented and, in one, antineutrophilic cytoplasmic antibody to myeloperoxidase (p-ANCA) was present in the serum. Treatment with intravenous methylprednisolone, followed by oral corticosteroid preparations in addition to cyclophosphamide, is indicated for this complication.

Necrobiotic (Rheumatoid) Nodule

Radiographically visible lung parenchymal rheumatoid nodules are infrequently seen in a rheumatoid population (less than 1 percent). When they do occur, they are more common in men, particularly those who smoke, with active articular disease and high rheumatoid factors, and in those who have subcutaneous nodules. The nodules are primarily a chest radiograph finding, since most are asymptomatic. The major problem is differentiating the necrobiotic nodule from either malignant or infectious granulomatous diseases. Occasionally, cough and hemoptysis are the presenting symptoms. Radiographically, the nodules can be single or multiple with upper and midzone predilection, and approximately 50 percent will undergo cavitation due to the large amounts of proteolytic enzymes in these lesions. The size is variable, and nodules up to 7 cm have been reported. Spontaneous resolution and recurrence are to be expected. Continuous growth, although possible, should prompt a more aggressive diagnostic approach. In most cases, no treatment is required.

Caplan's syndrome refers to a radiographic picture that developed in Welsh coal miners with rheumatoid arthritis. It consists of the sudden appearance of discrete nodules primarily in the upper lobes that are histologically identical to the necrobiotic nodule (Fig. 71-13). The incidence of necrobiotic nodules is higher in rheumatoid patients with underlying pneumoconiosis, including coal workers' pneumoconiosis, silicosis, and asbestosis, than it is in a general rheumatoid population.

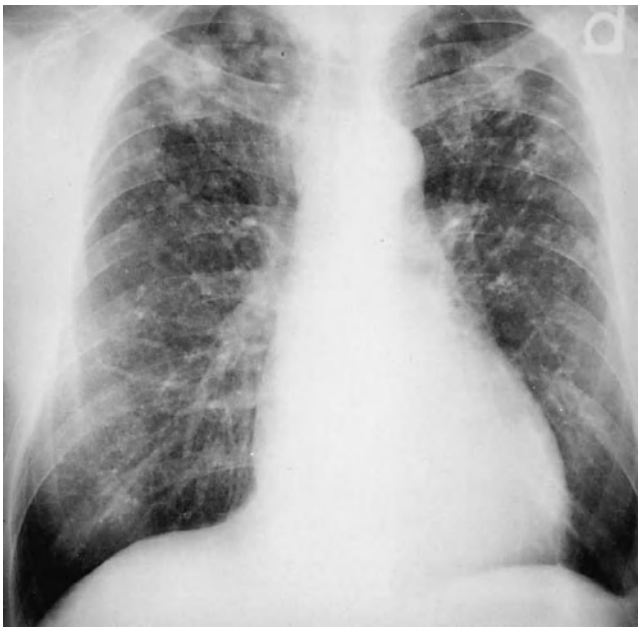
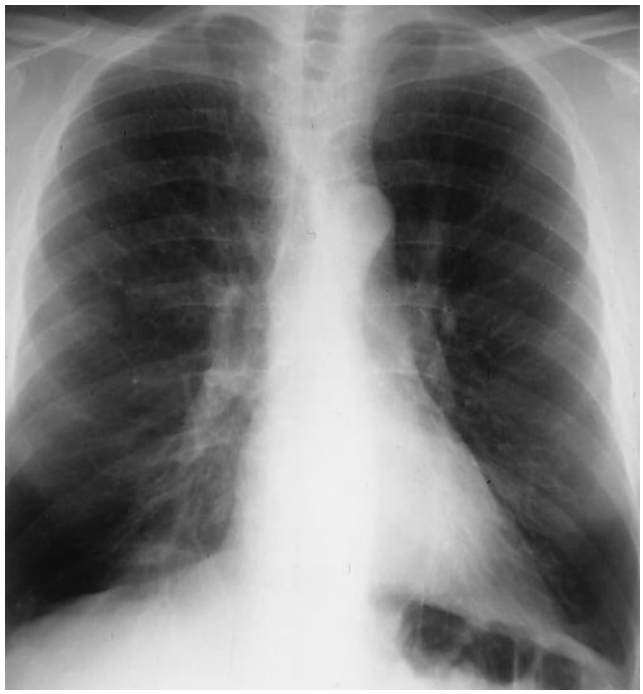


Figure 71-13 Caplan's syndrome in a patient with rheumatoid arthritis and silicosis (hard-rock miner). There are multiple small nodules in the middle and upper lung representing the silicosis. In addition, multiple upper-zone rheumatoid nodules are present.

Airway Disease

Upper-airway involvement by the rheumatoid process is most likely to involve the cricoarytenoid joint, causing difficulty with inspiration and occasionally resulting in stridor. A sore throat, hoarseness, and globus sensation are other common complaints. The prevalence of this complication, although asymptomatic in the majority of cases, approaches 50 percent when computed tomography screening is employed. Clinically significant disease can be detected by performing flow-volume loops, which indicate a variable extrathoracic obstruction of the inspiratory loop. Cricoarytenoid arthritis may further complicate endotracheal intubation and should be considered in all patients with rheumatoid arthritis requiring general anesthesia.

Bronchiolitis obliterans or obliterative bronchiolitis is a well-recognized cause of progressive and often severe obstructive lung disease in patients with rheumatoid arthritis. This complication was first thought to be a consequence of either penicillamine or gold therapy, but many cases have appeared in the absence of either treatment. The onset of obliterative bronchiolitis is insidious, with patients complaining of progressive dyspnea and cough while having a normal or hyperinflated chest radiograph (Fig. 71-14*A*). Initially, it was thought that this complication was limited to women, but this is not the case. Physical examination reveals a generalized reduction of breath sounds and occasionally an inspiratory squeak. Physiological testing reveals varying degrees of airflow limitation and hyperinflation, and the diffusing capacity may be normal or reduced. High-resolution computed tomography demonstrates adjacent areas of decreased and increased attenuation (geographic pattern), suggesting air trapping, which may be further identified by expiratory imaging (Fig. 71-14*B*). Some patients have responded to treatment with a combination of corticosteroids and cyclophosphamide, but the majority of cases progress to hypercapnic respiratory failure.



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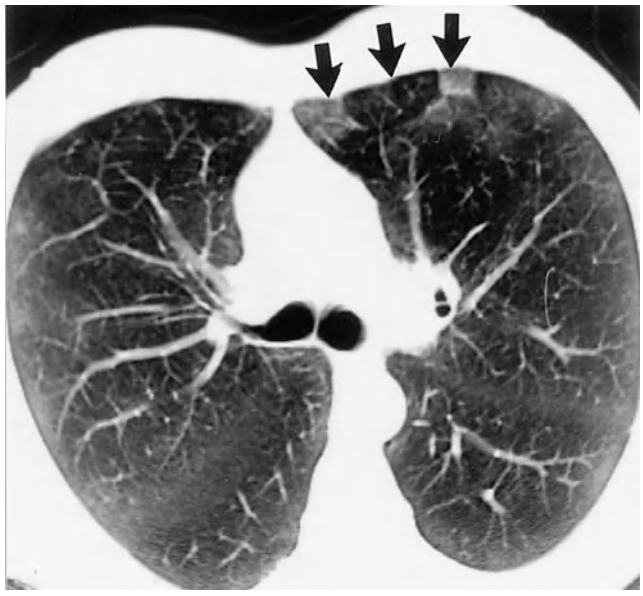


B

Figure 71-14 Obliterative bronchiolitis in a patient with rheumatoid arthritis. *A*. The chest radiograph is normal except for hyperinflation. *B*. A high-resolution computed tomography demonstrating areas of increased and decreased attenuation (arrows).

Another form of bronchiolitis seen in rheumatoid arthritis is a respiratory or follicular bronchiolitis, consisting

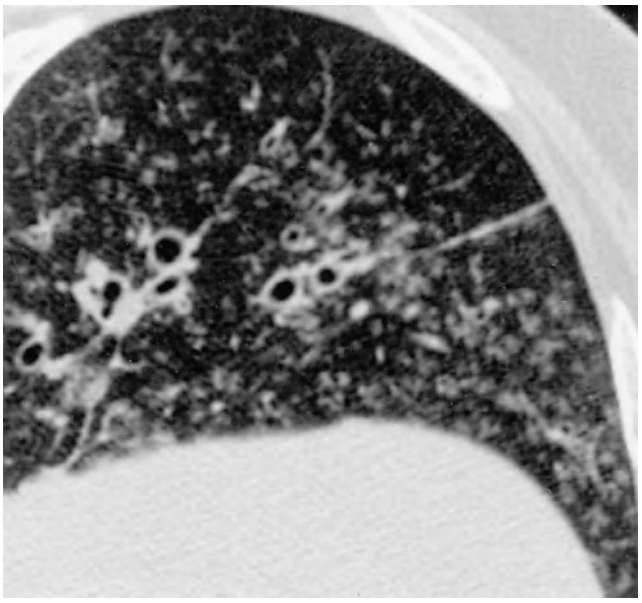


Figure 71-15 Follicular bronchiolitis in rheumatoid arthritis. High-resolution computed tomography demonstrating multiple centrilobular nodules.

of a dense infiltration of lymphocytes and plasma cells surrounding the terminal and respiratory bronchioles. Cough and dyspnea are common symptoms. Chest radiographs may be normal or demonstrate a fine nodular pattern more predominant in the middle and lower lung zones. High-resolution computed tomography demonstrates centrilobular nodules and bronchiectasis (Fig. 71-15). There is usually no physiological evidence for airflow limitation or reduced lung volumes, but rather gas exchange abnormalities dominate the physiological picture. Treatment with corticosteroids yields variable results.

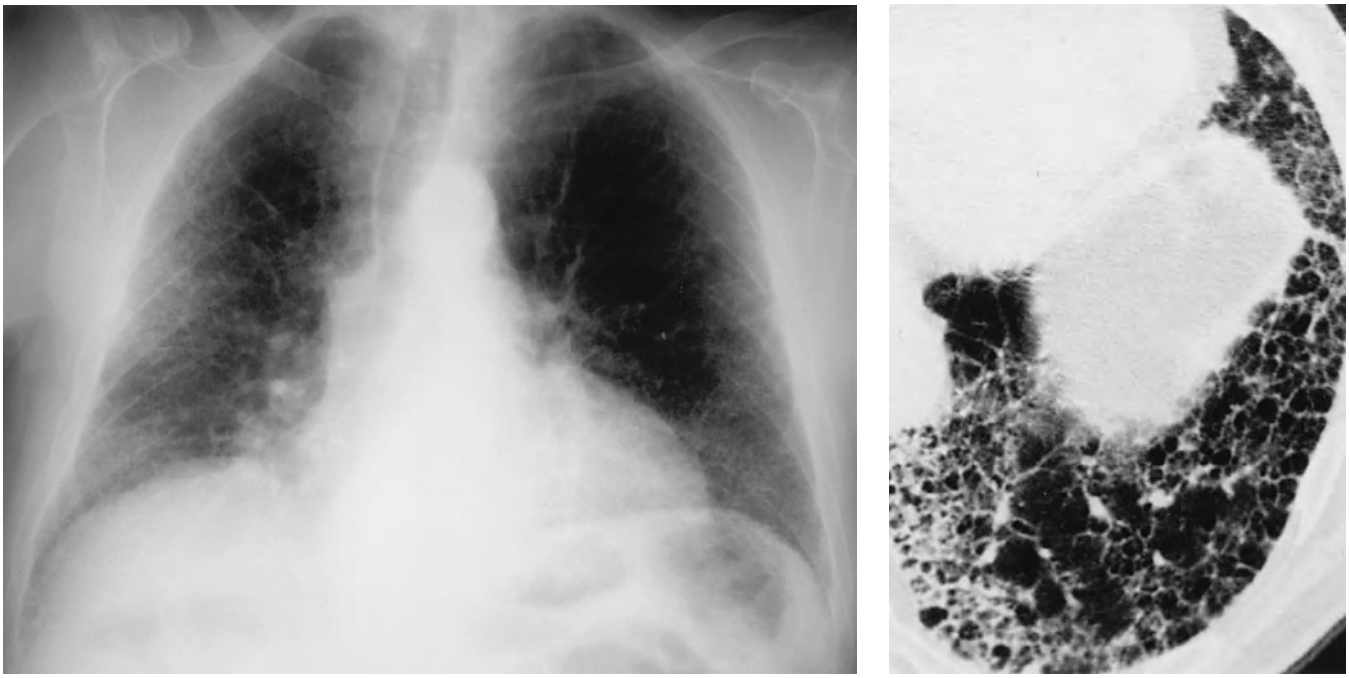
Diffuse panbronchiolitis has been reported in Japanese patients with rheumatoid arthritis. In both diffuse panbronchiolitis and rheumatoid arthritis, an association with HLA-DR4 and B54 haplotypes has been reported, suggesting a common genetic predisposition.

Interstitial Lung Disease

Interstitial lung disease is a relatively common complication in patients with rheumatoid arthritis. In contrast to most connective-tissue diseases, interstitial lung disease is more common in males than females (3:1), individuals who have late-onset disease, high-titer rheumatoid factors, and in those who smoke. It is not unusual for interstitial lung disease to precede the articular manifestations for a period of months to years. The incidence of this complication in a rheumatoid population is difficult to determine, being reported in 5 to 40 percent of patients depending upon the methods of detection. The use of bronchoalveolar lavage indicating alveolar inflammation and high-resolution computed tomographic scans indicating various interstitial changes, often in the face of a negative chest radiograph, are difficult to interpret. This is because follow-up studies determining whether these patients developed clinically apparent interstitial lung disease are lacking. Furthermore, some parenchymal changes described on computed tomography such as bronchiectasis have very little, if any, clinical significance. It is likely that clinically important interstitial lung disease occurs in 5 to 10 percent of patients with rheumatoid arthritis, the most common forms being UIP and degrees of NSIP. These patients are dyspneic and complain of cough. Physical examination reveals bibasilar crackles, clubbing of the digits in up to 75 percent, and evidence of cor pulmonale when pulmonary hypertension appears secondary to hypoxic vasoconstriction. The chest radiograph and computed tomographic scan demonstrate varying degrees of interstitial infiltrates with predilection for the lung bases and lung periphery (Fig. 71-16*A*). Other features include ground-glass attenuation on computed tomography with mixed alveolar-interstitial infiltrates on chest radiograph indicating a component of NSIP. Both imaging studies in advanced disease reveal the presence of honeycomb lung (Fig. 71-16*B*).

Several other interstitial reactions which produce subacute or chronic symptoms complicate rheumatoid arthritis. The first is bronchiolitis obliterans organizing pneumonia, which can present with identical symptoms to UIP and preempt the onset of the articular disease as well. The chest radiograph (Fig. 71-17) and computed tomography scan differ from that seen in UIP because the infiltrates are primarily alveolar and localized, patchy, or diffuse. The second interstitial reaction is lymphocytic interstitial pneumonia, which occurs when rheumatoid arthritis is complicated by Sjögren's syndrome. In addition to dyspnea and cough, these patients complain of dry mouth and eyes (xerophthalmia and xerostomia). The chest radiograph indicates patchy alveolar infiltrates primarily seen at the lung bases. Eosinophilic pneumonia has recently been reported as a pleuroparenchymal complication of rheumatoid arthritis and may be the primary presentation of the disease. Acute interstitial pneumonitis is a rare, acute form of interstitial lung disease in rheumatoid arthritis. While it may occur as a result of an immunologic injury to the lung, medication-related pulmonary toxicity and opportunistic infections should be considered. Lastly, fibrobullous disease, similar to that seen in ankylosing spondylitis, has been reported in rheumatoid arthritis and may precede the articular manifestations of the disease.

It is important to establish the underlying histology, since response to therapy and prognosis differs. Unless the imaging studies indicate end-stage honeycomb lung, which can also result from unresponsive or recurrent bronchiolitis obliterans organizing pneumonia, lymphocytic interstitial pneumonia, or UIP, further evaluation is indicated. Bronchoalveolar lavage will not necessarily help differentiate between these three histological pictures, but the finding of increased lymphocytic percentages as opposed to neutrophils and eosinophils indicates the potential for therapeutic responsiveness. Alveolar infiltrates and increased lymphocyte percentages are seen in lymphocytic interstitial pneumonitis. Bronchiolitis obliterans organizing pneumonia is associated with increases in neutrophil, eosinophil, and lymphocyte



A *B*

Figure 71-16 UIP in rheumatoid arthritis. *A*. Chest radiograph demonstrating lower zone and peripheral reticulonodular infiltrates. *B*. High-resolution computed tomography demonstrating a cystic network (honeycomb lung) at the lung base in a patient with advanced disease.

percentages as well as radiographic alveolar infiltrates. The finding of increased neutrophil and eosinophil percentages in suspected underlying UIP is an indicator of poor prognosis. Therefore, patients with lymphocytic interstitial pneumonitis and bronchiolitis obliterans organizing pneumonia are more treatment-responsive when compared to those with UIP. If imaging studies and bronchoalveolar lavage cellular analysis are not definitive, thorascopic open lung biopsy should be considered. Treatment consists of a corticosteroid preparation and often the addition of cytotoxic drugs in the nonresponsive cases. As opposed to the idiopathic variety of bronchiolitis obliterans organizing pneumonia, in which 66 percent of cases have favorable responses to corticosteroid medications, those associated with collagen vascular diseases are less responsive to treatment, often recur with tapering of the treatment regimen, and can progress to honeycomb lung. While the histopathology may be similar between rheumatoid arthritis and idiopathic pulmonary fibrosis, improved survival exists for those with rheumatoid arthritis–associated UIP but the long-term prognosis remains poor.

Gold-induced pneumonitis must be differentiated from the primary forms of interstitial lung disease in patients with rheumatoid arthritis, particularly since the underlying histology can be similar, indicating varying degrees of NSIP and bronchiolitis obliterans organizing pneumonia. Dyspnea and cough usually begin 4 to 6 weeks following initiation of therapy, and peripheral eosinophilia occurs in a minority of cases. Occasionally, the chest radiograph will demonstrate upper- as opposed to lower-zone mixed alveolar interstitial infiltration. Bronchoalveolar lavage indicates a predominance of lymphocytes, and differentiation from rheumatoid interstitial lung disease can only be made after withdrawal of the drug results in remission. In severe cases with marked gas

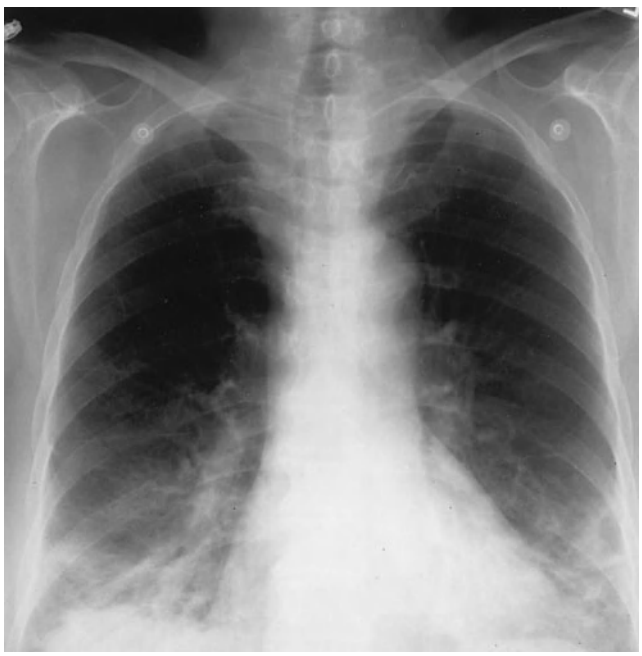


Figure 71-17 Bronchiolitis obliterans organizing pneumonia in rheumatoid arthritis. Chest radiograph demonstrating lower-zone mixed alveolar-interstitial infiltrates.

exchange abnormalities, corticosteroid therapy will occasion prompt reversal.

Methotrexate given in relatively low weekly doses (10 to 20 mg) is associated with the development of an interstitial disease in rheumatoid patients. No correlation with age, sex, duration of disease, or weekly or cumulative dose could be found. Conflicting data suggest that rheumatoid patients with underlying primary rheumatoid lung disease are predisposed to develop methotrexate pneumonitis. In rheumatoid patients treated with methotrexate, the incidence of methotrexate pneumonitis is 1 to 11 percent. The clinical onset is relatively acute with cough, fever, dyspnea, and new mixed alveolar and interstitial pulmonary infiltrates on chest radiograph. Increased white blood cell counts with mild eosinophilia, elevated sedimentation rates, and increased serum lactic dehydrogenase are nonspecific findings. Bronchoalveolar lavage indicates lymphocytosis and should be performed to rule out an infectious etiology. Lung tissue reveals an NSIP, organizing pneumonia, and granuloma formation reminiscent of a hypersensitivity pneumonitis. In patients who develop this clinical syndrome while on methotrexate, the drug should be discontinued since progression to end-stage fibrosis may occur. With life-threatening respiratory failure, corticosteroids given intravenously is an effective therapy.

The advent of TNF-α antagonists have revolutionized therapy for patients with rheumatoid arthritis. Their efficacy in the treatment of pleuroparenchymal complications remains unknown, with conflicting data having been reported. Of concern in those patients being treated with these agents should be the increased risk of infections, particularly both typical and atypical mycobacteria and fungi, as well as common bacterial pathogens.

Scleroderma

Scleroderma or systemic sclerosis is an inflammatory-fibrotic disease that results in deposition of excessive extracellular matrix in the skin and several visceral organs including the lungs, heart, kidneys, and gastrointestinal tract. Two subtypes of systemic sclerosis exist: diffuse and limited. In diffuse systemic sclerosis, extensive skin involvement of the extremities, face, and torso exists with accompanying marked visceral involvement that is progressive in nature. The limited form, or CREST variant (*c*alcinosis, *R*aynaud's phenomenon, *e*sophageal dysmotility, *s*clerodactyly, and *t*elangiectasias), has a more protracted course in most patients and usually affects an older subset of patients. Pulmonary disease contributes significantly to both the morbidity and mortality of patients. The pathogenesis, although not well understood, involves a complex interaction among immune cells, endothelial cells, and fibroblasts. In addition to the excessive extracellular matrix, which in the lung results in interstitial fibrosis, endothelial cell damage with intimal thickening of pulmonary and systemic arteries occurs, leading to luminal obliteration. This results in a form of idiopathic pulmonary hypertension.

The lung is involved in the great majority of cases, and postmortem series indicate a 70 to 100 percent incidence. Most patients with scleroderma develop dyspnea during the course of their illness due either to interstitial lung disease or pulmonary hypertension. Both bronchoalveolar lavage and high-resolution computed tomographic scans, in the face of normal chest radiographs, have indicated interstitial lung disease in both symptomatic and asymptomatic patients (Fig. 71-18). Although unusual, interstitial lung disease and pulmonary hypertension have preceded the dermatologic manifestations, defined as systemic sclerosis sine scleroderma. Despite the lack of skin involvement, the course in systemic sclerosis sine scleroderma does not significantly differ from the more common forms, with exception of a greater tendency toward the development of pulmonary hypertension.

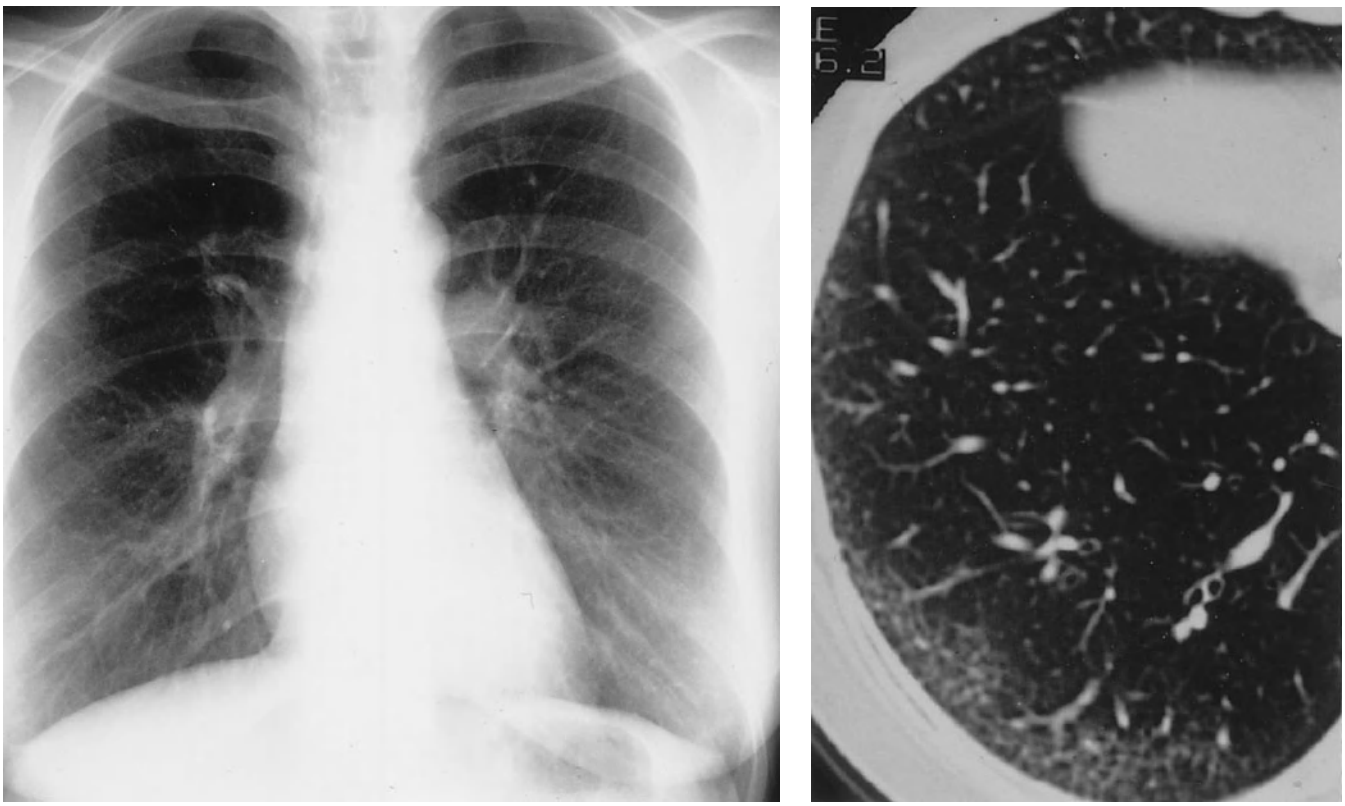
Pleural Disease

Although pleural fibrosis and adhesions are reported to be present in 40 percent of patients with scleroderma in postmortem studies, clinically apparent pleural thickening or pleural effusions on chest radiographs are considerably less frequent. The exception to this is pleural effusions secondary to congestive heart failure due to a scleroderma-associated cardiomyopathy.

Interstitial Lung Diseases

Interstitial lung disease, progressing to honeycomb lung, is the most common pulmonary complication of scleroderma, occurring in 30 to 100 percent of cases. A high-resolution computed tomographic study indicated a greater than 90 percent incidence of this abnormality with up to two-thirds of patients having normal chest radiographs. As many as 60 percent of patients who undergo bronchoalveolar lavage will demonstrate an abnormal inflammatory cell distribution. Chest radiographic and physiological screening indicate somewhat lower prevalence. The significance of the bronchoalveolar lavage and computed tomographic findings remain unclear, since no longitudinal follow-up is available. Following the histological reclassification of idiopathic interstitial pneumonias, the most common underlying histology in systemic sclerosis is NSIP with honeycomb lung. UIP, unclassifiable fibrosing interstitial lung disease, and rarely, organizing pneumonia and granulomatous lung disease resembling sarcoidosis have also been reported. It was previously thought that interstitial lung disease in scleroderma was primarily a fibrotic disorder. However, recent information derived from high-resolution computed tomography demonstrating ground-glass attenuation which indicates more cellular disease, bronchoalveolar lavage revealing increased inflammatory cell populations, and biopsy material demonstrating cellular infiltration of the interstitium indicates the presence of a cellular inflammatory response. This predates the development of fibrosis, consistent with the cellular subtype of NSIP. It is likely that the inflammatory phase in most cases is clinically silent.

Interstitial lung disease is more likely to occur in diffuse systemic sclerosis, although it may also complicate limited systemic sclerosis, formerly referred to as the CREST syndrome. Dyspnea on exertion progressing to dyspnea at rest



A *B*

Figure 71-18 *A*. Normal chest radiograph in a dyspneic patient with scleroderma. *B*. High-resolution computed tomography of the same patient demonstrating reticular interstitial infiltrates.

and cough are the predominant symptoms. Bibasilar crackles are heard, but clubbing is unusual due to the capillary destruction in the nail beds. Physical findings of cor pulmonale eventually appear. Bibasilar interstitial infiltrates followed by more diffuse changes, loss of lung volume, honeycomb cysts, and pulmonary hypertension are the typical radiographic features. Scleroderma was the first interstitial lung disease in which scar carcinoma (adenocarcinoma or alveolar cell carcinoma) was reported. Physiological testing eventually reveals restrictive lung disease, preserved flow rates, and a reduced diffusing capacity. Early on, the aforementioned measurements may be normal, and hypoxemia and a widened alveolar-arterial oxygen gradient at rest and heightened by exercise may be the only physiological abnormalities. A disproportionally greater reduction of the diffusing capacity, when compared to lung volumes, most likely indicates the presence of idiopathic pulmonary hypertension due to plexogenic arteriopathy, particularly in the limited form of systemic sclerosis.

Other forms of interstitial lung disease seen in scleroderma include lymphocytic interstitial pneumonitis in those cases associated with Sjögren's syndrome; rare cases of diffuse alveolar hemorrhage have been reported.

Immunosuppression is the mainstay of treatment, with corticosteroids and cyclophosphamide being the agents of choice. The recent NHLBI-sponsored Scleroderma Lung Health Study confirmed prior retrospective studies suggesting improved lung function in those patients treated with cyclophosphamide. Although the improvement in lung function is of questionable clinical significance, a therapeutic effect is expected in those with ground-glass attenuation on HRCT imaging, a lymphocytic or eosinophilic predominant bronchoalveolar lavage, and a cellular interstitial pneumonia on lung biopsy.

Pulmonary Vascular Disease

Pulmonary hypertension, due to a plexogenic arteriopathy involving the pulmonary arteries, occurs in approximately 10 percent of cases of scleroderma and is primarily seen in the limited form (CREST syndrome). In this form of scleroderma, pulmonary hypertension may coexist with interstitial lung disease. Patients present with a gradual onset of dyspnea and increasing fatigue. Physical examination and chest radiograph may initially be normal, and, with disease progression, physical and radiographic signs of pulmonary hypertension appear. Lung volumes and airflow parameters are maintained, unless there is concomitant interstitial lung disease. Typically there is an isolated reduction in the diffusing capacity as well as progressive hypoxemia. Prior to the use of vasodilator therapy, the mean survival following a diagnosis of pulmonary hypertension was approximately 2 years. Treatment with continuous intravenous prostacyclin, phosphodiesterase

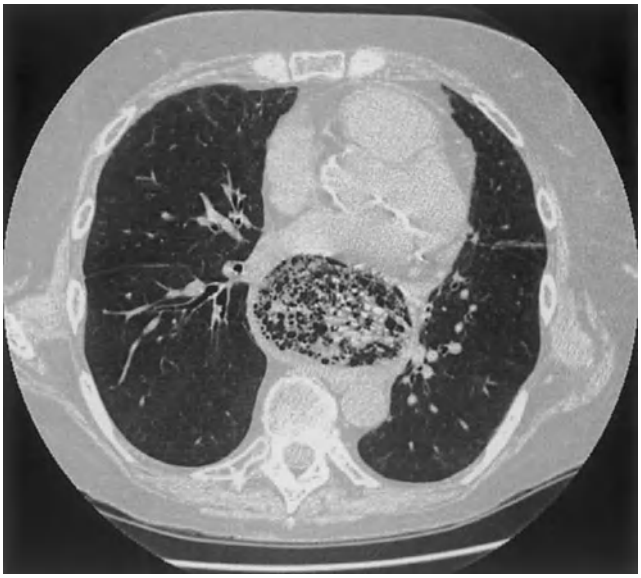


Figure 71-19 Mild peripheral, linear, ground-glass opacities in both lungs with marked thickening of the esophageal wall and severe dilatation of esophageal lumen with extensive debris filling the lumen in a patient with limited systemic sclerosis.

type 5 inhibitors, and endothelin antagonists have improved the quality of life and exercise performance. Improved survival has been suggested with the use of these agents but has not been adequately studied.

Aspiration Pneumonia

There is a high incidence of esophageal dilatation and decreased peristalsis (dysmotility) in patients with scleroderma, particularly in the limited variety (Fig. 71-19). This leads to dysphagia, heartburn, gastroesophageal reflux, and recurrent aspiration pneumonia. It has long been held that aspiration contributes to the development of interstitial lung disease. A definitive study has indicated that direct measurements of gastroesophageal reflux did not correlate with physiological impairment (low lung volumes and diffusing capacity) in these patients. Aggressive treatment to reduce the risk of aspiration is recommended despite conclusive evidence to suggest an association.

Polymyositis-Dermatomyositis

Polymyositis is a systemic autoimmune disorder characterized by an inflammatory myopathy. Dermatomyositis differs from polymyositis in that prominent skin involvement, characterized by a heliotropic rash and/or erythematosus scaling over the proximal interphalangeal joints, termed *Gottron's papules* or *rash*, occurs with less severe myositis. In polymyositis-dermatomyositis, pulmonary complications are common and important causes of morbidity and mortality and often predate or overshadow the muscle or skin manifestations. Pulmonary involvement has been reported in up to 40 percent of cases. In contrast to the other collagen vascular diseases, in polymyositis-dermatomyositis primary involvement of the airways and pleura do not occur. Pulmonary hypertension secondary to plexogenic arteriopathy has been reported on several occasions, most often in cases in which a crossover with scleroderma was suspected.

Aspiration Pneumonia

Aspiration pneumonia is a common pulmonary complication, occurring in 10 to 20 percent of patients with polymyositis-dermatomyositis; almost half of the patients complain of dysphagia as well. This complication results from an inflammatory myositis affecting the striated muscle of the hypopharynx and upper esophagus. As a result, there is loss of normal swallowing function and failure to protect the airway. Aspiration is more likely in those patients with extensive skin or muscle involvement.

Respiratory Muscle Dysfunction

Hypercapnic respiratory failure requiring assisted ventilation, due to extensive myositis involving the respiratory muscles and diaphragm, is an uncommon event (less than 5 percent prevalence). In those patients presenting with unexplained hypercapnic respiratory failure, polymyositis-dermatomyositis as well as demyelinating neuromuscular disorders should be considered. With less extensive involvement of these muscles, however, there is a reduction in cough generation and the potential for the development of hypostatic pneumonia and atelectasis due to mucous plugging. Weakness can also cause a restricted physiological defect with resulting tachypnea and dyspnea in the face of a normal diffusing capacity, normoxemia, and hyperventilation. Respiratory muscle dysfunction as the cause of restrictive lung disease can best be demonstrated by measurement of the maximal pressure generated during both phases of the respiratory cycle. Sequential measurements are useful for monitoring the disease course and response to treatment.

Interstitial Lung Disease

The prevalence of interstitial lung disease in polymyositis-dermatomyositis ranges from 5 to 30 percent. The incidence is significantly higher in certain populations. In Japan, it approached 40 to 80 percent in one series. As in the other collagen vascular diseases, the use of bronchoalveolar lavage and high-resolution computed tomography for screening increases the documented incidence.

Although UIP was previously reported to be the predominant histological type of interstitial lung disease seen in polymyositis-dermatomyositis, NSIP now appears to be most common, based on the revised classification system for idiopathic interstitial pneumonias. Diffuse alveolar damage (DAD), bronchiolitis obliterans organizing pneumonia, and diffuse alveolar hemorrhage secondary to pulmonary capillaritis may also occur. All forms of interstitial lung disease may precede, appear simultaneously with, or follow the muscle or skin manifestations. There is no relationship between interstitial lung disease and the extent of muscle or skin disease, the level of creatine phosphokinase elevation, or the presence of

serum rheumatoid factor or antinuclear antibodies. There is, however, a relationship between interstitial lung disease and a serum antibody directed against the cellular enzyme histidyl-tRNA-synthetase, known as anti-Jo-1. This antibody appears in 25 percent of patients with polymyositis-dermatomyositis in total, but in 50 percent of patients with interstitial lung disease and in 13 percent of patients without lung disease.

All forms of interstitial lung disease in polymyositis–dermatomyositis are more common in women. Several clinical syndromes occur and are associated with the underlying interstitial lung disease. The most common presentation is chronic cough and progressive dyspnea due to NSIP with varying degrees of fibrosis. Digital clubbing is rarely, if ever, seen. Chest radiographs demonstrate reticulonodular infiltrates, and with disease progression there is a reduction of the lung volume and the development of radiographic honeycomb lung and pulmonary hypertension. Physiological testing indicates a restrictive pattern with a low diffusing capacity. Response to treatment depends upon the underlying histology, the more cellular disease being more responsive. In corticosteroid-resistant patients, cyclophosphamide, cyclosporine, and tacrolimus have been used with efficacy.

In polymyositis-dermatomyositis, an acute pulmonary presentation with a clinical and radiographic picture reminiscent of a diffuse infectious pneumonia occurs. The underlying lesion is DAD. Severe respiratory failure occurs, and recovery is unusual in spite of aggressive anti-inflammatory and immunosuppressive therapy. Bronchiolitis obliterans organizing pneumonia may have either an acute or subacute presentation (Fig. 71-20). The differentiation from DAD becomes important because of the marked disparity in treatment outcome and survival. In bronchiolitis obliterans organizing pneumonia, corticosteroid responsiveness with or without an additional agent is the rule rather than the exception. Diffuse alveolar hemorrhage due to pulmonary capillaritis may also occur. This complication appears simultaneously with the onset of the muscle disease. Hemoptysis may or may not be present. As with other forms of pulmonary capillaritis, immunosuppression with corticosteroids and cyclophosphamide is efficacious.

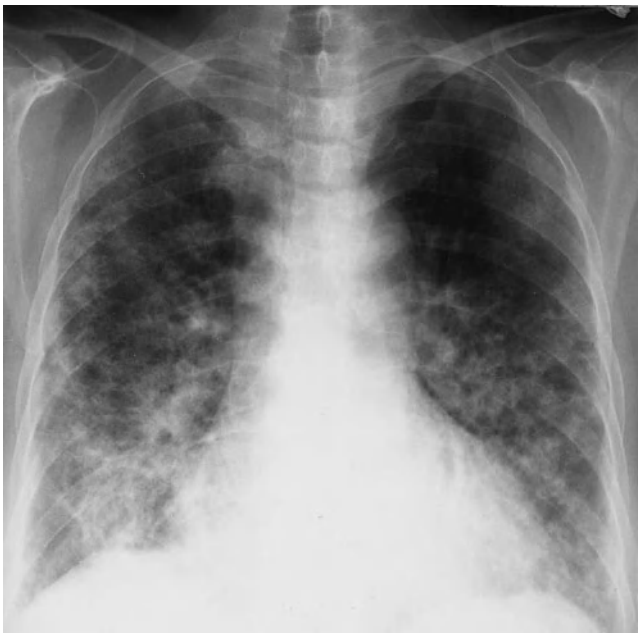


Figure 71-20 Bronchiolitis obliterans organizing pneumonia in a patient with polymyositis-dermatomyositis and acute symptoms. Chest radiograph demonstrating diffuse patchy alveolar infiltrates.

Mixed Connective-Tissue Disease

Patients with mixed connective-tissue disease have features of SLE, polymyositis-dermatomyositis, and scleroderma. Mixed connective-tissue disease is characterized by elevated titers of a specific antinuclear antibody directed against nuclear ribonucleoprotein (anti-RNP). Because of the similarity of mixed connective-tissue disease to the aforementioned collagen vascular diseases, pleuropulmonary complications are frequent, occurring in 20 to 80 percent of cases.

Pleural Disease

Although pleurisy has been reported to occur in 40 percent of cases, pleural effusions are uncommon, appearing in approximately 5 percent of cases. It is an exudative effusion, but very little information concerning its characteristics is available in the literature.

Pulmonary Vascular Disease

Pulmonary hypertension may be caused by recurrent pulmonary emboli, hypoxic vasoconstriction secondary to interstitial lung disease, or plexogenic arteriopathy, as occurs in SLE and scleroderma. This is a significant problem for these patients; however, the incidence is unknown. These patients, primarily women, present with dyspnea and fatigue. They have normal chest radiographs except for pulmonary arterial enlargement and an isolated reduction in the diffusing capacity for carbon monoxide. The prognosis in pulmonary hypertension secondary to mixed connective-tissue disease is similar to that noted in pulmonary hypertension seen in scleroderma and SLE.

Medium-size pulmonary artery vasculitis has been reported in mixed connective-tissue disease, with evidence suggesting immunologic-mediated injury with deposition (IgG, C_3) in the vascular walls. Circulating lupus anticoagulant (antiphospholipid syndrome) may also complicate the course of patients with mixed connective-tissue disease, predisposing them to thromboembolic disease. It is in these patients that recurrent small pulmonary emboli may mimic the clinical picture of idiopathic pulmonary hypertension.

Aspiration Pneumonia

Patients with mixed connective-tissue disease, presenting with predominant features of scleroderma or polymyositis-dermatomyositis, are predisposed to esophageal dysmotility and dilatation, which can be a significant problem leading to

reflux esophagitis and recurrent aspiration pneumonia. The incidence of abnormal esophageal manometry in one series was greater than 50 percent.

Respiratory Muscle Dysfunction

In those patients with features of polymyositis-dermatomyositis, an inflammatory myositis with respiratory muscle involvement may lead to hypercapnic respiratory failure or a restrictive lung disease with the development of hypostatic pneumonia.

Interstitial Lung Disease

The incidence of interstitial lung disease in mixed connective-tissue disease is increased in comparison to other collagen vascular diseases. If one applies physiological as opposed to radiographic criteria, the incidence approaches 80 percent. The histological pattern is NSIP and/or UIP, both of which may progress to honeycomb lung, particularly in those patients with the features of scleroderma. As with the other connective-tissue diseases, this interstitial lung disease manifests as progressive dyspnea, bibasilar reticulonodular infiltrates on chest radiograph, and physiological parameters, which indicate low lung volumes and a reduction in the diffusing capacity for carbon monoxide.

Diffuse alveolar hemorrhage has been reported in a few cases of mixed connective-tissue disease and is similar in presentation to that in SLE. It is assumed that the histology is one of either bland pulmonary hemorrhage or pulmonary capillaritis but remains unknown.

Sjögren's Syndrome

Sjögren's syndrome refers to a triad of xerophthalmia, xerostomia, and polyarthritis. This autoimmune exocrinopathy is characterized by lymphocytic infiltration of the lacrimal and salivary glands. A primary form, occurring in the absence of another collagen vascular disease, and a secondary form, associated with one of the other collagen vascular diseases, most frequently rheumatoid arthritis, exist. A strong female predominance exists in Sjögren's syndrome (greater than 90 percent). A positive rheumatoid factor (95 percent) and antinuclear antibodies in a speckled pattern (80 percent) are to be expected, as well as positive tests for antibodies to extractable nuclear antigens (anti-SSA, anti-SSB), which are specific for the primary form of the syndrome.

Airway Disease

Lymphocytic infiltration and destruction of airway mucous glands results in dessication of the tracheobronchial tree in Sjögren's syndrome. Patients may develop hoarseness, cough, inspissation of secretions resulting in atelectasis, recurrent pneumonias, and bronchiectasis. There is a high incidence of obstructive ventilatory dysfunction in these patients, secondary to follicular bronchiolitis. Obliterative bronchiolitis, constrictive bronchiolitis, and bronchiolectasis have also been reported.

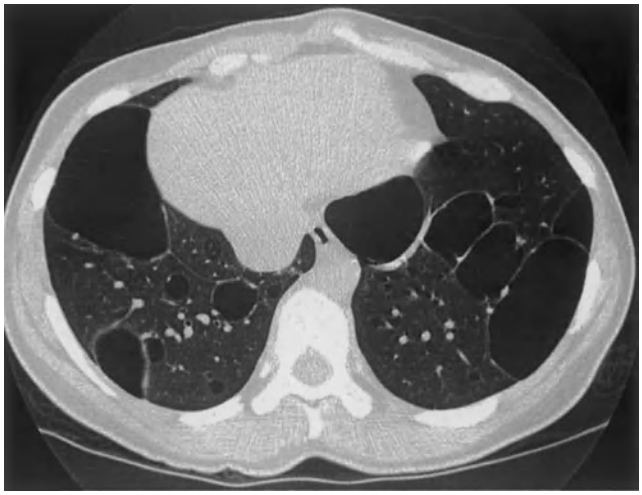


Figure 71-21 Multiple cysts of varying sizes scattered throughout both lungs in a patient with Sjögren's syndrome and lymphocytic interstitial pneumonia.

Interstitial Lung Disease

In primary Sjögren's syndrome, patients present with a nonproductive cough, dyspnea on exertion, or asymptomatic radiographic abnormalities. As occurs in the lacrimal and salivary glands, interstitial lung disease in these patients is the result of lymphocytic infiltration of the lung parenchyma. This occurs in two forms, lymphocytic interstitial pneumonitis and, less commonly, pseudolymphoma. Both of these lesions have the potential for lymphomatous conversion. Lymphocytic interstitial pneumonitis is an interstitial lung disease, and therefore cough, dyspnea, and a restrictive lung disease are to be expected. Because lymphocytes also infiltrate the alveolar spaces as well as the interstitium, the radiologic studies indicate mixed alveolar and interstitial infiltrates. In a subset of patients, variably sized cystic lesions with associated ground glass may be the only radiographic abnormality (Fig. 71-21). The development of pleural effusion or the appearance of hilar or mediastinal adenopathy often, but not always, indicates a malignant transformation to a lymphoma. Lymphocytic interstitial pneumonia is responsive to anti-inflammatory agents such as corticosteroids. Occasionally, cytolytic therapy, such as azathioprine or cyclophosphamide, is required but remains of unproven benefit. Cyclosporine has also been recommended as an additional agent in corticosteroid-resistant cases. While the majority of patients will respond to immunosuppressive therapy, a subset of patients progress to fibrotic lung disease with honeycomb change.

Pseudolymphoma is a tumorlike proliferation appearing as single or multiple masses on the chest radiograph. It is often difficult to distinguish from a malignant lymphoma and it has been suggested that pseudolymphoma, which is considered to be a localized form of lymphocytic interstitial pneumonitis, is a premalignant lesion. When associated with a monoclonal gammopathy, malignant transformation to lymphoma is likely.

Interstitial lung disease occurs more commonly in the secondary forms of Sjögren's syndrome and most likely represents a complication of the associated collagen vascular disease. The histological pattern in secondary Sjögren's syndrome mimics that seen in rheumatoid arthritis, with NSIP, UIP, and bronchiolitis obliterans organizing pneumonia reported. UIP, however, is uncommon in the primary form of Sjögren's syndrome.

Ankylosing Spondylitis

Ankylosing spondylitis is one of the seronegative spondyloarthropathies that may eventually result in fixation of the chest wall and a mild to moderate restrictive lung disease. Muscular involvement, in contrast to polymyositis-dermatomyositis, does not occur and diaphragmatic function is preserved. Ventilatory failure due to chest wall fixation does not occur given preserved respiratory muscle function.

The incidence of interstitial lung disease complication is reportedly less than 2 percent. In contrast to the other collagen vascular diseases that primarily affect the basilar portion of the lung, ankylosing spondylitis has a predilection for the upper lung zones, only appears late in the course of the chronic spondylitis, and never precedes it. Interstitial lung disease often appears as fibrocystic disease on the chest radiograph (Fig. 71-22) and is difficult to distinguish from tuberculosis. Histologically, it is a fibrosing process with cystic formation. Progressive dyspnea and cough are the predominant symptoms, and treatment with corticosteroids is ineffective and therefore not indicated. The most serious complication of this apical fibrocystic disease is infection with invasive aspergilla species as well as atypical mycobacteria. Further, saprophytic colonization of the cysts by aspergilla species (aspergilloma) may induce life-threatening hemoptysis.

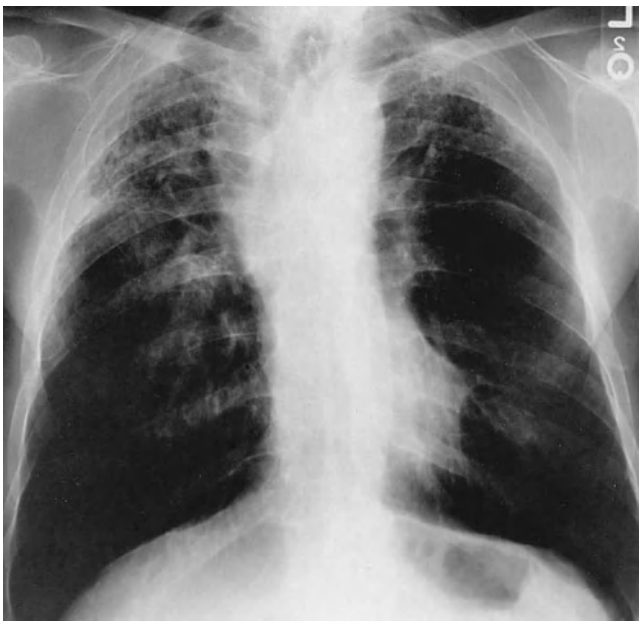


Figure 71-22 Ankylosing spondylitis. Chest radiograph demonstrating bilateral upper-zone fibronodular infiltrates.

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72

The Eosinophilic Pneumonias

Kristina Crothers • Carolyn L. Rochester

In 1932, Loeffler first identified the association between pulmonary infiltrates and eosinophilia. Subsequently, Crofton separated the eosinophilic pneumonias into five groups on the basis of clinical criteria: Loeffler's syndrome, prolonged pulmonary eosinophilia, pulmonary eosinophilia associated with asthma, tropical eosinophilia, and periarteritis nodosa. In 1952, Reeder and Goodrich coined the term *pulmonary infiltrates with eosinophilia* (PIE syndrome) to refer to these disorders. However, it was subsequently appreciated that pulmonary infiltration with eosinophils can occur in the absence of peripheral blood eosinophilia. As a result, in 1969, Liebow and Carrington broadened the description of the term *eosinophilic pneumonia* to include all disorders characterized by infiltration of the lungs with eosinophils, with or without an excess of eosinophils in the peripheral blood. Subsequent studies also demonstrated that in numerous disorders, peripheral blood eosinophilia can occur without tissue eosinophilic infiltration. As a result, the eosinophilic pneumonias are now recognized as a heterogeneous group of disorders characterized by varying degrees of pulmonary parenchymal or blood eosinophilia.

The precise role that eosinophils play in the pathogenesis of the different eosinophilic pneumonias is not clear. Our knowledge of the biology of eosinophils (see Chapter 21) does, however, suggest that they play a variety of roles, including initiation, perpetuation, and amplification of tissue inflammation and injury. These effector functions are no doubt the result of the ability of the eosinophils to release numerous soluble mediators, including granule-derived proteins, arachidonic acid metabolites, cytokines, superoxide anions, and hydroxyl radicals. The different roles of eosinophils in these disorders can be appreciated when comparisons are made of parasitic infections and disorders such as asthma or allergic bronchopulmonary aspergillosis. In the former, eosinophils play a crucial role in eradicating the infectious pathogen; in the latter, the eosinophils accumulate in the lung as a result of immune hypersensitivity and are prominent mediators of tissue injury.

The spectrum of diseases that can be primarily or secondarily associated with blood or pulmonary eosinophilia is shown in Table 72-1. It is beyond the scope of this chapter to discuss each of these disease entities in detail. Instead, discussion will focus on diseases of known or unknown causes in which eosinophilic infiltration of lung tissue is a characteristic feature, including acute eosinophilic pneumonias, tropical pulmonary eosinophilia, chronic eosinophilic pneumonia, allergic bronchopulmonary aspergillosis, Churg-Strauss syndrome, and idiopathic hypereosinophilic syndrome. Since eosinophilic granuloma of the lung is frequently seen in the absence of blood or tissue eosinophilia, it is considered separately in Chapter 74.

Table 72-1

Diseases Associated with Pulmonary Infiltrates and Eosinophilia

Pulmonary Eosinophilic Syndromes of Known Cause

Parasitic-induced eosinophilic pneumonias (including Loeffler's syndrome)
Drug-or toxin-induced eosinophilic pneumonias
Tropical pulmonary eosinophilia
Allergic bronchopulmonary mycosis

Pulmonary Eosinophilic Syndromes of Unknown Cause

Idiopathic acute eosinophilic pneumonia
Chronic eosinophilic pneumonia
Churg-Strauss syndrome (allergic granulomatosis and angiitis)
Idiopathic hypereosinophilic syndrome

Other Lung Diseases Variably Associated with Eosinophilia

Asthma/allergy
Bronchocentric granulomatosis
Bronchiolitis obliterans-organizing pneumonia
Infections
- Fungal (esp. coccidioidomycosis, *Aspergillus, Pneumocystis jirovecii*)
- Tuberculosis

Interstitial lung disease
- Idiopathic pulmonary fibrosis
- Collagen-vascular disease associated
- Sarcoidosis
- Eosinophilic granuloma (pulmonary histiocytosis X)

Malignancy
- Non–small-cell cancer of lung
- Non-Hodgkin's lymphoma
- Myeloblastic leukemia

Miscellaneous (e.g., lung transplantation, ulcerative colitis)

Table 72-2

Parasitic Infections Associated with Eosinophilic Pneumonia

Ancylostoma spp.	*Opisthorchis* spp.
Ascaris spp.	*Paragonimus westermani*
Brugia malayi	*Schistosoma* spp.
Clonorchis sinensis	*Strongyloides stercoralis*
Dirofilaria immitis	*Toxocara gondii*
Echinococcus spp.	*Trichinella spiralis*
Entamoeba histolytica	*Trichosporon terrestre*
Necator americanus	*Wuchereria bancrofti*

EOSINOPHILIC PNEUMONIAS WITH ACUTE PRESENTATIONS

Loeffler's Syndrome (Simple Pulmonary Eosinophilia)

In 1932, Loeffler first described a clinical syndrome characterized by mild respiratory symptoms, peripheral blood eosinophilia, and transient, migratory pulmonary infiltrates. The term *Loeffler's syndrome,* or *simple pulmonary eosinophilia,* has been used to define the numerous similar cases reported subsequently. Immune hypersensitivity to *Ascaris lumbricoides* has been recognized as the likely cause of most of the earliest reported cases, although several other parasitic infections and exposures to numerous drugs and other agents have also been recognized to induce a Loeffler's-like syndrome (see below and Tables 72-2 and 72-3). An identifiable etiologic agent may be lacking in up to one-third of patients.

Loeffler's syndrome affects people of all ages. It is characterized clinically by the presence of low-grade fever, nonproductive cough, dyspnea (mild to severe), and occasionally hemoptysis. The respiratory manifestations of Loeffler's syndrome are usually self-limited, typically resolving in 1 to 2 weeks. Laboratory examination of peripheral blood from patients reveals moderate to extreme eosinophilia, which may be at peak levels as respiratory symptoms resolve. Expectorated sputum, if present, frequently contains eosinophils. Transient, migratory, nonsegmental interstitial and alveolar infiltrates (often peripheral or pleural based) are evident on the chest radiograph. Pulmonary function evaluation typically reveals a mild to moderate restrictive ventilatory defect with a reduced diffusing capacity for carbon monoxide (D_{LCO}).

When Loeffler's syndrome is due to *A. lumbricoides,* the pulmonary manifestations are believed to result from a hypersensitivity reaction to the *Ascaris* larvae. Following ingestion of ova, larvae hatch within the small intestine, then cross the intestinal wall to enter the splanchnic and ultimately the pulmonary circulation. Subsequently, the larvae migrate across pulmonary capillaries into alveoli, mature into adult worms, ascend the large airways, and are swallowed into the gastrointestinal (GI) tract, where they complete their life cycle. The pulmonary manifestations of Loeffler's syndrome begin approximately 9 to 12 days following ingestion, and occur during the migration of larvae through the lung. *Ascaris suum,* a large roundworm endemic to pigs, can cause a nearly identical syndrome.

Table 72-3

Drugs and Other Exposures Causing Eosinophilic Pneumonia

Acetaminophen
Acetylsalicylic acid*
Aluminum
Amiodarone*
Ampicillin
Azathioprine

Beclomethasone dipropionate
Beryllium
Bleomycin*

Captopril*
Carbamazepine*
Chlorpromazine
Chlorpropamide
Clarithromycin
Clofibrate
Cocaine (inhalation)
Cromolyn (inhalation)

Dantrolene
Dapsone
Desipramine
Diclofenac

Ethambutol

Fenbarbamate
Fenbufen

Glafenine
Gold salts*
Granulocyte-macrophage colony-stimulating factor

Heroin (inhalation)

Ibuprofen
Imipramine
Indomethacin
Interleukins
Iodinated contrast agents*
Isoniazid

L-Tryptophan*

Maloprim
Mecamylamine
Mephenesin carbamate
Methotrexate*
Methylphenidate
Minocycline*

Naproxen
Nickel
Nilutamide*
Nitrofurantoin*
Nomifensine

Para-aminosalicylic acid
Penicillamine*
Penicillin
Pentamidine (inhaled)
Phenytoin*
Piroxicam
Procarbazine
Prontosil
Propylthiouracil*
Pyramethamine

Rapeseed oil
Red spider antigens

Salicylazosulfapyridine
Streptomycin
Sulfa-containing antibiotics*
Sulfasalazine*
Sulindac

Tamoxifen
Tetracycline
Thiazides
Tolazamide
Tolfenamic acid
Trazodone
Trichloroethane

Venlafaxine

Note: Drugs commonly or occasionally reported to cause pulmonary eosinophilia are marked with an asterix (*)

During the pneumonic stage of the illness, *Ascaris* larvae may be identified in sputum or gastric aspirates. In keeping with the life cycle of *Ascaris,* stool examination for ova and parasites is typically negative until 8 weeks after the onset of the respiratory syndrome. Histological evaluation of lung tissue is not required for confirmation of the diagnosis. When tissue has been obtained, a characteristic and striking eosinophilic infiltration of interstitium and alveolar-capillary units has been noted. Increased numbers of macrophages have also been appreciated. Tissue necrosis and vasculitis are not features of the disorder.

Since Loeffler's syndrome may be induced by a variety of exposures, a search for an etiologic agent (e.g., parasitic infection or drug reaction) should be undertaken. Bronchodilators and rarely corticosteroids may be used for alleviation of pulmonary symptoms, although these are usually self-limited. In cases due to *Ascaris*, treatment with oral mebendazole (100 mg twice a day for 3 days) should be given to prevent late GI manifestations of *Ascaris* infestation, which may include malnutrition, diarrhea, abdominal pain, and/or intestinal obstruction typically 8 weeks or more after onset of respiratory symptoms. Since stool specimens are negative for ova and parasites early in the illness, clinical follow-up over a 2- to 3-month period is indicated.

Parasitic Infections

Infections with parasites other than *Ascaris* species are also commonly associated with pulmonary infiltrates and blood or pulmonary eosinophilia. The parasites associated with the development of pulmonary eosinophilic syndromes are listed in Table 72-2. The prevalence of infection with each of these organisms varies with geographical location, socioeconomic status, and host immunity. In addition to *Ascaris* species, *Strongyloides stercoralis* (an intestinal nematode), *Ancylostoma brasiliensis* (cutaneous helminthiasis, "creeping eruption"), and *Toxocara canis* (dog roundworm, "visceral larva migrans") are the parasitic agents most commonly associated with pulmonary eosinophilia in the United States.

Strongyloides is widely distributed in the tropical and subtropical regions. Following initial transcutaneous infection, a Loeffler's-like syndrome may occur as larvae migrate through the lungs. Chronic strongyloidiasis occurs as a result of autoinfection, whereby the noninfectious rhabditiform larvae transform within the GI tract into infectious filariform larvae, penetrate the colonic wall or perianal skin, and reinfect the host. Chronic strongyloidiasis can be associated with recurrent asthma-like symptoms that may worsen with the administration of corticosteroids. The hyperinfection syndrome results from accelerated autoinfection, and usually occurs in persons with defects in cell-mediated immunity (such as lymphoma, human immunodeficiency virus [HIV] infection, and with chronic corticosteroid use) as well as in persons with underlying GI disease, but it may also occur in healthy persons. Respiratory manifestations include cough, dyspnea, chronic bronchitis, wheezing, hemoptysis, and pulmonary

infiltrates, in association with blood eosinophilia. Rarely, acute respiratory distress syndrome (ARDS) has been reported in patients with hyperinfection. GI manifestations are also common, including abdominal pain, paralytic ileus, nausea and vomiting, bowel perforation, and secondary sepsis from gram-negative bacteria. Central nervous system (CNS) manifestations such as meningitis have also been noted. The diagnosis of *Strongyloides* infection may be established by identification of larvae in sputum, bronchoalveolar lavage (BAL) fluid, bronchial brushings, or transbronchial biopsy specimens. Serologic testing, while sensitive but less specific, can also be used to establish a diagnosis. Thiabendazole or ivermectin may be used for the treatment of uncomplicated or disseminated strongyloidiasis; ivermectin is generally better tolerated in terms of side effects. Albendazole is an alternative agent. The hyperinfection syndrome associated with *Strongyloides* can be difficult to cure. Therapy should be continued until the clinical syndrome resolves and larvae are no longer detectable in the GI tract.

Ancylostomiasis is a nematodal infection endemic to the southeastern coastal regions of the United States, Mexico, and Central and South America. The organism is present in soil contaminated by stool from infected domestic animals. It penetrates human skin most commonly through the feet. This results in the development of the "creeping eruption" lesion—a raised, erythematous, serpiginous, tunnel-like, and often itchy lesion on areas of exposed skin. A Loeffler's-like syndrome occurs in up to 50 percent of cases of "creeping eruption." Specific treatment for pulmonary involvement is typically not required as illness is usually self-limited.

Infection with *T. canis* may occur throughout the world and leads to the clinical syndrome of "visceral larva migrans." This syndrome is characterized by hepatomegaly, leukocytosis, fever, hypergammaglobulinemia, and persistent blood eosinophilia. Because the disease most commonly affects young children, a high degree of clinical suspicion is necessary to establish the diagnosis in adults. Respiratory symptoms, including cough and wheezing, may occur after ingestion of substantial numbers of larvae. Laboratory evaluation reveals peripheral blood and BAL eosinophilia, elevated serum levels of immunoglobulin E (IgE), and poorly defined, diffuse nodular alveolar infiltrates on chest radiograph. Although the disease may be self-limited, treatment with albendazole, mebendazole, or corticosteroids may hasten recovery in patients who are severely ill.

Drug and Toxin-Induced Pulmonary Eosinophilic Syndromes

A vast number of drugs and toxic exposures have been associated with the development of pulmonary infiltrates and blood or pulmonary eosinophilia. A partial list of these medications and exposures is given in Table 72-3, and information regarding pulmonary drug toxicities may also be found on the Internet on the regularly updated web site www.pneumotox.com. Of the medications implicated, many are commonly used antibiotics, nonsteroidal anti-inflammatory agents, and selective serotonin-reuptake inhibitors. In addition to medications, a number of toxic exposures may also be associated with eosinophilic pneumonia. For example, eosinophilic pneumonia has been described following radiation therapy for breast cancer, exposure to iodinated contrast agents, and after inhalation of cocaine or heroin. The precise incidence of drug- or toxin-induced pulmonary eosinophilia is difficult to assess, considering that most of the literature pertaining to these syndromes is published in the form of case reports, rather than large series or controlled trials. For the same reason, the precise pathogenesis and the definition of the clinical syndromes associated with individual exposures are difficult to characterize.

In general, drug-induced pulmonary eosinophilic syndromes have an acute or subacute onset and are not always related to either the cumulative dose of drug used or the duration of treatment. Respiratory symptoms vary widely in severity, from a mild Loeffler's-like illness with dyspnea, cough, and fever to severe fulminant respiratory failure. Wheezing may be present, but obstructive physiology is not common on pulmonary function testing. Although radiographic findings are not specific, interstitial or alveolar infiltrates are typically evident on chest radiograph (Fig. 72-1), and common high-resolution chest computed tomographic (CT) findings include bilateral consolidation and ground-glass opacities, both of which are frequently peripherally located.

A diagnosis of drug- or toxin-induced eosinophilic pneumonia is based upon a careful review of drug and other exposures (including nonprescription drugs, herbal

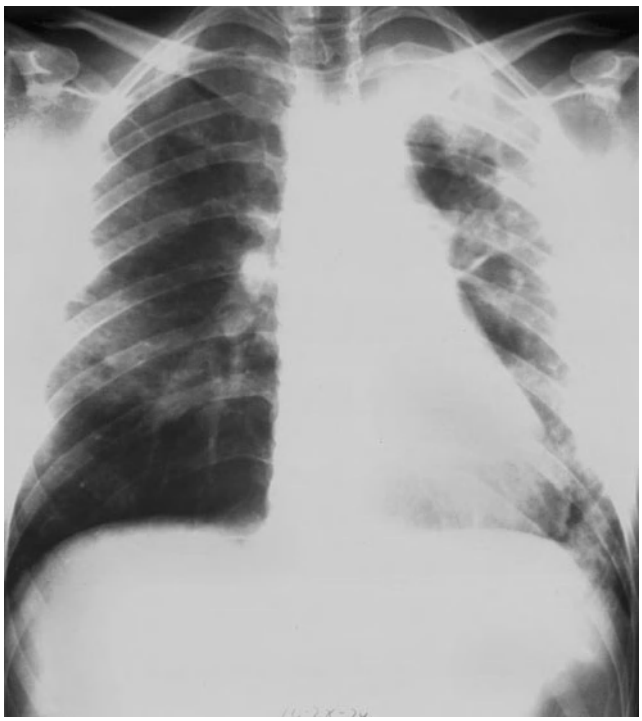


Figure 72-1 Chest radiograph of a 23-year-old woman with acute sulfasalazine-induced eosinophilic pneumonia. Bilateral interstitial and alveolar infiltrates are present.

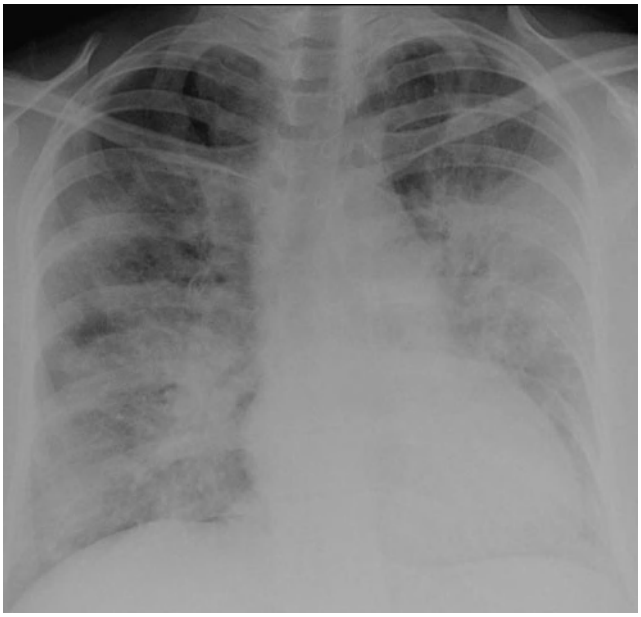
preparations, street drugs, and environmental exposures). Other causes of eosinophilic lung disease should be excluded. A concomitant skin rash and pleural effusion can support the diagnosis of drug-induced eosinophilic pneumonia. In some cases, testing with lymphocyte proliferation assays may reveal T-cell sensitization to specific drugs. However, the utility of such assays is limited as negative tests do not rule out a drug-induced disorder, and these assays are not widely available for routine clinical use. The prognosis is favorable in most cases. Elimination of exposure to the drug or other toxin usually leads to resolution of symptoms, eosinophilia, pulmonary infiltrates, and normalization of lung function within a month. Supplemental therapy with corticosteroids is not universally required, but it may hasten recovery in patients who are severely ill.

Idiopathic Acute Eosinophilic Pneumonia

In contrast to the typically benign Loeffler's syndrome, a more severe idiopathic form of eosinophilic pneumonia termed *acute eosinophilic pneumonia* (AEP) has been recognized as a distinct clinical entity. Although seen in patients of both genders and any age group, AEP tends to be slightly more common in younger men, with a mean age of approximately 30 years reported in two of the largest studies to date. AEP occurs commonly in previously healthy persons. Similar cases have been reported in persons with a history of chronic myelogenous leukemia or HIV infection. Although none of the patients in the original reported series had atopy or asthma, cases have since been described in persons with a history of atopy. In addition, cases have been reported in patients who have recently commenced smoking and who have been involved in activities with unusual exposures (such as cave exploration, plant repotting, woodpile moving, and indoor renovations). While no definite seasonal variation has been identified, a preponderance of cases have occurred during the summer.

Idiopathic AEP presents as an acute illness with fever, myalgias, cough, dyspnea, pleuritic chest pain, and hypoxemia (arterial P_{O_2} under 60 mmHg). Symptom duration is on average 3 days, although longer courses of up to 30 days have been described. Patients often have diffuse crackles on chest auscultation and develop overt respiratory failure requiring mechanical ventilation. A moderate leukocytosis is typical, but in contrast to other forms of AEP, blood eosinophilia is usually absent. Serum IgE levels may be moderately elevated. Striking eosinophilia (25 to 50 percent) is present in BAL fluid. Pulmonary function tests reveal a restrictive ventilatory defect with a reduced D_{LCO}.

Early in the course of illness, the chest radiograph reveals subtle, patchy infiltrates with Kerley B lines. Diffuse, symmetric alveolar and interstitial infiltrates resembling ARDS with a ground-glass or micronodular appearance (Fig. 72-2) develop within 48 hours. Historically, the presence of bilateral infiltrates is a defining feature of the disease, although a more recent study also described AEP with unilateral infiltrates. Small to moderate bilateral pleural effusions



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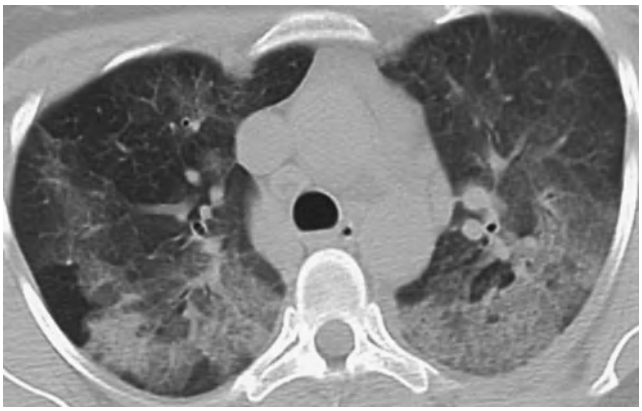


B

Figure 72-2 Radiographic appearance of idiopathic acute eosinophilic pneumonia (AEP). *A*. Diffuse bilateral alveolar and interstitial infiltrates apparent on chest radiograph. *B*. Diffuse parenchymal ground-glass opacity and consolidation evident on computed tomography scan.

are common. Fluid analysis typically reveals a high pH and marked eosinophilia. CT scanning confirms the presence of diffuse parenchymal ground-glass attenuation and consolidation (Fig. 72-2), with prominence along bronchovascular bundles and septae, as well as pleural effusion.

Light microscopic examination of lung tissue reveals prominent eosinophil infiltration in alveolar spaces, bronchial walls, and, to a lesser degree, the interstitium. The pathological pattern of diffuse alveolar damage with eosinophilic infiltrates should suggest the possibility of AEP. There is no evidence of vasculitis or extrapulmonary involvement.

The pathogenesis of idiopathic AEP is poorly understood. The occurrence of cases following unusual environmental exposures (such as plant repotting, cave exploration,

wood pile moving, smokehouse cleaning, gas tank cleaning, and indoor renovation work) and recent commencement of cigarette smoking as noted above suggests these exposures as possible disease-inciting events, perhaps as triggers for a hypersensitivity reaction to an unidentified antigen. Of note, elevated levels of the fungal cell wall component β-D-glucan have been described in the BAL fluid of patients with AEP, suggesting a possible association between exposure to fungus and development of disease.

However, the role of the eosinophil in this disorder has not been fully elucidated. Elevated levels of interleukin (IL)-5, a cytokine involved in activation and recruitment of eosinophils, have been described in the BAL of patients with AEP. Levels of vascular endothelial growth factor (VEGF), a cytokine induced by IL-5, have also been shown to be elevated and to correlate with number of eosinophils and levels of IL-5. Elevated BAL levels of IL-18, a cytokine capable of inducing several cytokines known to induce or enhance eosinophilia, have also been identified among patients with acute (and other) forms of eosinophilic pneumonia. It remains unknown, however, whether the eosinophils initiate the disease process or are a secondary manifestation of the disorder.

Idiopathic AEP is a diagnosis of exclusion and should be considered in a patient who presents with apparent acute lung injury (ALI) or ARDS without a typical antecedent illness. A careful search must be undertaken for other causes of pulmonary infiltrates. Specimens of blood, sputum, stool, BAL, and often transbronchial biopsy specimens should be obtained for stain and culture as well as serologic testing to rule out bacterial, mycobacterial, fungal, and parasitic infection.

Idiopathic AEP carries an excellent prognosis. Although fatalities have been reported, most patients demonstrate rapid dramatic responses to corticosteroid therapy, with abatement of fever and respiratory symptoms within hours and complete resolution of infiltrates usually within 1 month. The optimal steroid regimen for the treatment of AEP has not been determined. However, initial doses of methylprednisolone typically used range from 60 to 125 mg administered every 6 hours. After resolution of respiratory failure, oral prednisone (in doses of 40 to 60 mg per day) may be continued for 2 to 4 weeks with a subsequent slow taper over the next several weeks. Despite the apparent clinical success of steroid treatment, there is no definitive proof that steroids alter the natural history of the disease. Spontaneous disease regression has been reported, and absence of clinical relapse is characteristic. Follow-up pulmonary function testing is generally normal, although a small number of patients may demonstrate mild reductions in D_{LCO} or lung volumes.

TROPICAL PULMONARY EOSINOPHILIA

Tropical pulmonary eosinophilia (TPE) was first described in the early 1940s as a syndrome characterized by fevers, malaise, anorexia, weight loss, paroxysmal dry cough with dyspnea or wheezing, marked peripheral blood eosinophilia, and spontaneous resolution over several weeks' time. In the 1950s and 1960s, filarial infections were recognized as the cause of this disorder. TPE is most prominent in India, Africa, and Southeast Asia, but it may be seen worldwide in filarial-endemic regions. Disease may also present in nonendemic regions among immigrants or travelers. A rare manifestation of parasitic infection, TPE occurs in less than 1 percent of patients infected with lymphatic filariae and results from a hypersensitivity reaction to microfilariae from *Wuchereria bancrofti* and *Brugia malayi*. Illnesses resembling TPE have also been reported following infection with other parasites. Approximately 4 times more common in men, most patients with TPE manifest the disease between the age of 25 and 40 years, although children and older adults may also be affected. There is no known seasonal or genetic propensity to this disease, and it remains unclear why only such a small percentage of patients with filarial infection develop TPE.

The most common symptom of TPE is cough that usually occurs at night. Other typical symptoms include low-grade fevers, weight loss, fatigue, and malaise. Dyspnea and wheezing, which can be severe, are common, and the clinical presentation may resemble status asthmaticus. Chest pain, muscle tenderness, and cardiac, pericardial, and CNS involvement have also been reported. Rarely, patients remain asymptomatic. Physical examination of patients with TPE is notable for coarse rales or rhonchi and wheezing, although no abnormalities are found in approximately 20 percent of patients. Generalized lymphadenopathy and hepatosplenomegaly may be present, but they are far less common in adults than in children.

Laboratory findings in TPE include extreme peripheral blood eosinophilia (usually more than 3000 eosinophils per cubic millimeter and up to 90 percent of the leukocyte differential) that persists for several weeks, although the degree of eosinophilia generally does not correlate well with clinical disease severity or radiographic findings. Total serum IgE is usually elevated (more than 1000 U/ml), and high titers of filarial-specific IgE and IgG, measured by complement fixation or hemagglutination techniques, are crucial diagnostic findings. The erythrocyte sedimentation rate (ESR) may be moderately elevated, and patients may also have an abnormal electrocardiogram (ECG). Eosinophils may be identified in the sputum, and, in those with active disease, BAL may reveal intense eosinophilic alveolitis. Microfilariae are not found in blood or sputum, and examination of stool or urine for ova and parasites is negative (although patients from endemic countries may be simultaneously infected with other parasites). In contrast, microfilariae have been identified in lung and lymph node tissue, especially when lymphadenopathy is present.

Pulmonary function tests reveal an obstructive ventilatory defect in up to 30 percent of patients, particularly when symptoms have been present less than 1 month. A restrictive ventilatory defect and reduced D_{LCO}, with or without a concomitant obstructive defect, are typical of long-standing

disease. Ill-defined, diffuse reticulonodular infiltrates with a mottled appearance are characteristic radiographic findings in TPE. The mid- to lower lung fields are most commonly affected, but disease may appear anywhere in the lung. Bronchovascular markings may be prominent and hilar adenopathy and pleural effusions have occasionally been reported. The chest radiograph may be normal at the time of presentation in as many as 20 percent of patients. In rare cases where *Dirofilaria* is the causative agent, the chest radiograph may reveal solitary or multiple nodules thought to represent infarcts caused by parasitic emboli.

The histopathological findings in TPE depend on the tissue examined, as well as the stage and duration of the disease. Studies of lung pathology have shown that the early stage of the disease (within the first 2 weeks) is characterized by histiocytic inflammation in the alveolar, interstitial, peribronchial and perivascular spaces, with preservation of lung architecture. Tiny nodules may be palpable within the lung tissue. One to three months after symptom onset, eosinophilic infiltration with eosinophilic bronchopneumonia and microabscesses is present in lungs of untreated patients. Degenerating microfilariae may be present within the center of the microabscesses, and some destruction of alveolar walls may be evident. Local bronchial walls are also edematous and inflamed, with evidence of epithelial disruption. Longstanding untreated disease is associated with the presence of chronic mixed-cell inflammation in a nodular pattern and the development of pulmonary fibrosis. Foreign body–type granulomatous lesions are often present. Lymph node biopsies may reveal degenerating microfilariae or adult worms, surrounded by aggregates of eosinophils, their granule products, and giant cells.

The clinical features of TPE are believed to result from an intense hypersensitivity reaction to microfilarial antigens of *Wuchereria bancrofti* and *Brugia malayi*. Although a broad spectrum of clinical disease may be caused by filaria, patients with TPE rarely have other systemic features of filariasis. Canine filarial forms (e.g., *Dirofilaria immitis*) are rarely transmitted to humans but also may be recovered from lung and lymph node specimens. Disease occurs when larvae introduced into the body via insect bites develop into mature filariae. The adult worms, dwelling within the lymphatics, produce microfilariae, which are then trapped in the pulmonary vasculature. The release of antigens from degenerating microfilariae leads to an intense local and systemic inflammatory response. A striking antibody and eosinophilic response, similar to that seen in peripheral blood, is present within the lung. Increased numbers of total cells and eosinophils (up to 50 percent of differential), elevated levels of total IgE, and filarial-specific IgG, IgM, and IgE are present in fluid obtained by BAL.

Although little is known about the precise mechanisms by which filariae are cleared in patients with TPE, both antibody-dependent mechanisms and eosinophils probably play a role. In vitro, both granulocytes and macrophages can bind microfilariae in the presence of IgG, IgE, or complement, leading to the death of the organism. The finding of an intense lymphocytic- and plasma-cell infiltrate around microfilariae in tissues suggests that lymphocytes may be important for clearance of the organism. In vitro lymphocyte transformation in response to stimulation with microfilarial antigens can be demonstrated in some cases. The precise mechanisms by which eosinophils accumulate in the lung and contribute to tissue inflammation in patients with TPE are incompletely understood. Elevated levels of eosinophil-derived neurotoxin, an RNase capable of damaging the lung epithelium, have been observed in the BAL fluid of patients with TPE. IgE and eosinophil-, mast cell-, or basophil-derived products may contribute to the wheezing and airway hyperresponsiveness that can occur in this disorder.

The diagnosis of TPE is usually established on the basis of the clinical and laboratory findings described above. Lung or other tissue biopsies are not typically required. Biopsy of enlarged lymph nodes (e.g., scalene) may assist in establishing the diagnosis in some cases. A rapid treatment response may provide confirmatory evidence that the correct diagnosis has been made. The differential diagnosis includes Loeffler's syndrome, chronic eosinophilic pneumonia, allergic bronchopulmonary aspergillosis, drug reactions, other parasitic infections, hypereosinophilic syndrome, and lymphangitic spread of carcinoma. In nonendemic areas, the disease may also masquerade as asthma, atypical pneumonia, sarcoidosis, Churg-Strauss syndrome, Wegener's granulomatosis (WG), or tuberculosis (TB). Diagnosis in nonendemic regions is often delayed, and a careful review of travel history and a high index of suspicion are necessary to prompt the diagnosis.

Diethylcarbamazine, a piperazine derivative used widely in the treatment of filarial infections, is the therapy of choice for TPE, typically at a dose of 2 mg/kg three times daily for 14 to 21 days. Diethylcarbamazine acts by both direct and indirect mechanisms. It is directly filaricidal to both adult worms and microfilariae. It can also enhance the binding of granulocytes, macrophages, antibodies, and complement to the surface of microfilariae. A marked clinical improvement and decrease in eosinophil count usually occurs in the first 7 to 10 days of therapy. Clinical improvement following diethylcarbamazine treatment has been correlated temporally with the resolution of eosinophilic alveolitis. In addition, improvement in pulmonary function, reduction in BAL eosinophilia, a decrease in total and filarial-specific IgE and IgG, and radiographic clearing generally occur within 1 to 3 weeks of treatment.

The course and prognosis of the acute disease in patients treated with diethylcarbamazine are generally benign, and 3 weeks of diethylcarbamazine therapy is curative in most patients. However, acute relapses do occur in up to 20 percent of patients. Patients who experience acute relapses often respond to additional treatment with diethylcarbamazine at higher doses of 2 to 4 mg/kg three times a day for 21 to 30 days. Alternatively, mild, chronic inflammation may persist, causing chronic interstitial lung disease, with persistent respiratory symptoms, radiographic findings, and hematological and serologic abnormalities. Persistent clinical symptoms have been reported over 2- to 5-year follow-up periods in

up to 13 percent of patients with TPE treated with a standard course of therapy. BAL in these patients reveals a mild, persistent eosinophilia. Persons with symptoms of longer duration are less likely to have a favorable treatment response. Alternative antifilarial drugs (e.g., ivermectin) or a trial of corticosteroids may be useful therapies for the chronic variant of the disease, although controlled studies of these agents are lacking. A subset of patients with apparent TPE may fail to respond to diethylcarbamazine; whether these patients have diethylcarbamazine-resistant TPE or disease due to other parasites is unclear, as current serologic testing does not distinguish between human lymphatic filarial antigens and antigens on certain other parasites.

Untreated disease usually persists for weeks to months. Untreated TPE may remit spontaneously, but it commonly recurs within months to years. Although seldom fatal, untreated TPE often leads to the development of chronic interstitial lung disease.

CHRONIC EOSINOPHILIC PNEUMONIA

Chronic eosinophilic pneumonia (CEP) was first described as a clinical entity by Carrington and coworkers in 1969. Although CEP may develop in people of any age, the peak incidence occurs in persons 30 to 40 years of age. Women are affected approximately twice as often as men, and CEP has been reported during pregnancy. The female predominance is less obvious among patients whose disease begins after the age of 60. Most cases occur in Caucasians. Approximately one-third to one-half of patients have antecedent atopy, allergic rhinitis, or nasal polyps. In addition, up to two-thirds have adult-onset asthma preceding (by several months to years) or arising concurrently with the occurrence of CEP. Although prior data questioned an association with cigarette smoking, more recent analysis suggests that CEP is not associated with smoking; in fact, the prevalence of smoking among patients with CEP is generally quite low.

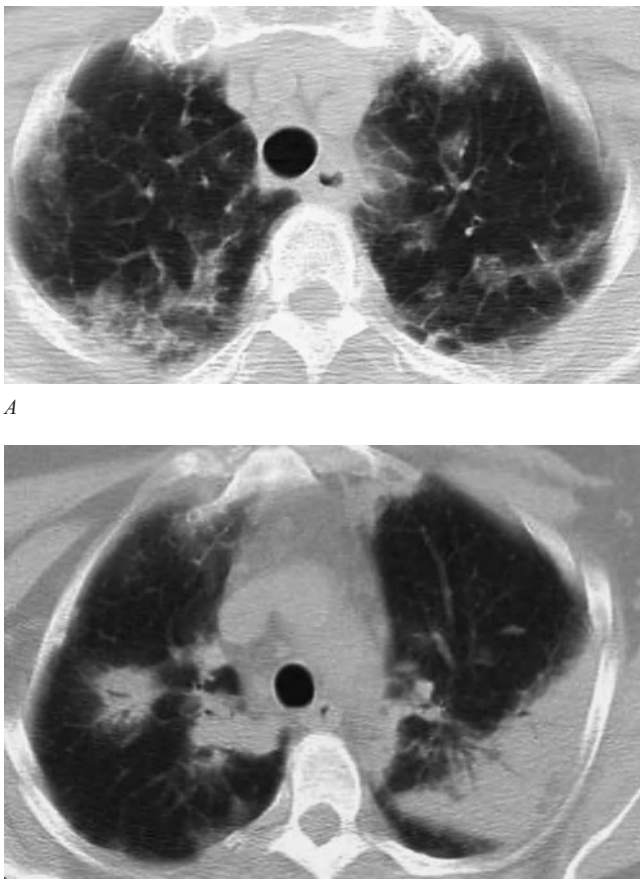
In contrast to idiopathic AEP, CEP typically has a subacute presentation, with symptoms present for several months before diagnosis. Common presenting complaints include low-grade fevers, drenching night sweats, and moderate (10- to 50-pound) weight loss. Cough, often dry initially and later productive of small amounts of mucoid sputum, is a virtually universal finding. Two of the nine patients described in Carrington's original series had minor hemoptysis. Patients ultimately develop progressive dyspnea, which may be associated with wheezing in those with adult-onset asthma. Infrequently, some patients with CEP may also have severe acute respiratory failure or ARDS, with severe hypoxemia requiring mechanical ventilation. There are no major extrapulmonary manifestations of CEP. Rarely, arthralgias, skin rash, pericarditis or unexplained heart failure have been described, raising questions as to whether there is a continuum between CEP and Churg-Strauss syndrome.

Patients with CEP frequently manifest a moderate leukocytosis. The majority (66 to 95 percent) have peripheral blood eosinophilia, with eosinophils constituting more than 6 percent of their leukocyte differential. Leukocyte differentials with up to 90 percent eosinophils have been noted in this disorder. However, a lack of peripheral blood eosinophilia does not rule out the diagnosis, since eosinophilia was absent in one-third of the cases originally described. A moderate normochromic, normocytic anemia and thrombocytosis may be present. The ESR is typically elevated (greater than 20 mm per hour), and IgE levels are elevated in up to one-half of cases. Analysis of BAL fluid reveals increased eosinophils, typically accounting for 40 percent or more of the white blood cell (WBC) differential, with a range from 12 to 95 percent reported. Blood and sputum cultures routinely fail to identify an infectious etiology in these patients.

The severity of pulmonary function abnormalities depends on the stage and severity of the disease. In the initial stage prior to treatment with corticosteroids, testing may reveal restrictive, obstructive, or normal physiology. Obstructive ventilatory defects, while more common in patients with a history of asthma, are also encountered in patients without preexisting asthma. Restrictive physiology may result from changes in lung compliance due to acute eosinophilic infiltration of lung parenchyma. Diffusing capacity may be reduced and the alveolar-arterial oxygen gradient may be mildly elevated.

In the original series, Carrington and colleagues described three radiographic features that are characteristic for CEP: (1) peripherally based, progressive dense infiltrates; (2) rapid resolution of infiltrates following corticosteroid treatment, with recurrences in identical locations; and (3) the appearance of infiltrates as the "photographic negative of pulmonary edema." In contrast to Loeffler's syndrome, the pulmonary infiltrates associated with CEP are typically nonmigratory and affect the outer two-thirds of the lung fields (Fig. 72-3). Infiltrates are most commonly bilateral, are located in the mid- to upper lung zones, and may mimic loculated pleural fluid. The areas of consolidation are patchy and dense and can have ill-defined margins. They are frequently nonsegmental, subsegmental, or lobar in distribution and apposed to the pleura. The characteristic "photographic negative of pulmonary edema" appearance (which occurs in less than 50 percent of cases) results if extensive infiltrates surround major portions of or the entire lung. Pleural effusions are not usually seen. Occasionally, the chest radiograph can be normal.

Common CT scan findings include ground-glass opacities without clear consolidation, as described in approximately half the cases of CEP in one series. In addition, apparent unilateral or isolated lower lung zone involvement noted on chest radiography may prove to be bilateral and diffuse on CT scanning. Mediastinal adenopathy, which may be evident on conventional chest radiograph, may also be identified on CT scan. Less typical radiographic findings include nodular infiltrates, linear oblique or vertical densities, and areas of fibrosis unassociated with anatomic divisions. Findings on CT



A

B

Figure 72-3 Radiographic appearance of chronic eosinophilic pneumonia (CEP). Variable computed tomography appearance of infiltrates in two patients with chronic eosinophilic pneumonia. Peripheral upper-lobe predominant infiltrates may have a ground-glass appearance (*A*) or may appear as regions of dense consolidation or nodular opacity (*B*).

scan may vary depending on the timing of the CT relative to the onset of symptoms. Typical areas of dense, peripherally located airspace consolidation are found in most cases within the first several weeks of disease onset. Streaky bandlike opacities may appear when symptoms have been present for more than 2 months.

The pulmonary lesions of CEP are characterized histopathologically by varying degrees of leukocytic infiltration of the alveolar airspaces and interstitium. These infiltrates are predominantly eosinophilic, with some associated macrophages, a small to moderate number of lymphocytes, and occasional plasma cells. They disrupt alveolar wall architecture, usually without causing wall necrosis. Focal edema of the capillary endothelium, focal type II epithelial cell hyperplasia, proteinaceous alveolar exudates, and multinucleated histiocytes within alveolar spaces can also be appreciated. Histological evidence of proliferative bronchiolitis obliterans may occur in up to one-third of cases, and a mild, nonnecrotizing microangiitis affecting predominantly the small venules may be seen. A small percentage of lesions (less than 20 percent) may have frank intra-alveolar necrosis, eosinophilic microabscesses, or noncaseating granulomas. Biopsy specimens of lymph nodes from patients with intrathoracic lymphadenopathy reveal lymphoid hyperplasia and eosinophil infiltration.

The cause of CEP is unknown. No specific genetic predisposition for the disease has been identified, although CEP has been reported in identical twins, raising the question of a familial tendency toward the disease. Although the precise immunopathogenesis of CEP is unknown, a variety of lines of evidence suggest that eosinophils play a primary pathogenetic role in the pulmonary tissue damage seen in this disorder. Increased numbers of eosinophils appear in the peripheral blood and bone marrow before the onset of clinical disease, and an eosinophilia is the predominant abnormality in BAL fluid. These eosinophils appear to be activated, since eosinophil-derived granule proteins (EDGP) have been identified microscopically within the pulmonary parenchyma and microvasculature, increased concentrations of EDGP are identified in BAL fluid from patients with CEP compared to controls, and BAL-derived eosinophils express activation markers including class II major histocompatibility (MHC) antigens. The processes that regulate eosinophil activation and degranulation in CEP are not clear. Evidence showing that class II MHC and other activation markers are expressed by BAL- but not blood-derived eosinophils suggests the presence of an immune inflammatory response compartmentalized within the lung. Data also suggest that eosinophils from the BAL fluid are more resistant to apoptosis than peripheral blood eosinophils in subjects with CEP. Of interest are the findings that immunoglobulins can augment eosinophil chemotaxis and degranulation in vitro, and that circulating immune complexes and elevated titers of IgE are noted in the context of clinical flares of the disease. To date, however, no clear causal relationship has been established between immunoglobulins and eosinophil activation in CEP.

The diagnosis of CEP is based on clinical, radiographic, and BAL findings, and on the inability to document pulmonary or systemic infection. The clinical signs and symptoms of CEP are nonspecific, however, and blood eosinophilia and typical radiographic features may be absent in some cases. In most reported series, open lung biopsy has been required only rarely to establish the diagnosis. Transbronchial biopsy, usually performed to rule out other diagnostic entities, may reveal eosinophil and mononuclear cell infiltrates. Because of the rapid and dramatic responsiveness of CEP to steroid treatment, a therapeutic trial of steroids is often useful in establishing the diagnosis. Failure to document rapid clinical improvement should alert the clinician to consider other diagnoses. The differential diagnosis of CEP includes infection (especially TB and fungal diseases like cryptococcosis), sarcoidosis, Loeffler's syndrome, desquamative interstitial pneumonitis, bronchiolitis obliterans-organizing pneumonia, chronic hypersensitivity pneumonitis, and eosinophilic granuloma.

Corticosteroids are the mainstay of therapy for CEP. Dramatic clinical, radiographic, and physiological improvements have been documented following steroid treatment in all series reported. Even patients presenting with severe respiratory failure may respond well to steroid treatment. In most cases, treatment with steroids leads to defervescence within 6 hours, reduced dyspnea, cough, and blood eosinophilia within 24 to 48 hours, resolution of hypoxia in 2 to 3 days, radiographic improvement within 1 to 2 weeks, complete resolution of symptoms within 2 to 3 weeks, and normalization of the chest radiograph within 2 months. No comparative studies exist to determine optimum treatment doses or duration of steroids, but one recommended regimen is prednisone (40 to 60 mg a day) continued until 2 weeks after resolution of symptoms and radiographic abnormalities. The dose of prednisone can then be tapered slowly. Treatment is usually maintained for at least 3 months and optimally for 6 to 9 months.

The prognosis of CEP is generally favorable. Spontaneous remissions seldom occur in untreated patients. In steroid-treated patients, morbidity and mortality directly related to CEP are low. Patients may require 1 to 3 years of initial steroid treatment to control the disease, and up to 25 percent may require long-term maintenance treatment (2.5 to 10 mg prednisone a day) to remain disease-free. The lowest possible dose of steroid that suppresses disease activity should be used. Some patients may respond to inhaled corticosteroids, allowing discontinuation of oral steroids, although inhaled steroids alone as initial therapy are inadequate.

Clinical, hematological, or radiographic evidence of relapse occurs in approximately one-third to one-half of patients when steroids are tapered or discontinued. Relapses may involve radiographic infiltrates in the same or different anatomic distribution compared to the original disease. Relapsing CEP must be distinguished from the development of new or worsening asthma. No obvious factors exist to identify persons who are likely to relapse or require long-term steroids, although relapses are more common in persons treated initially with a short course (less than 6 months) of steroids. Relapses may be less common in patients with asthma at the time of CEP, likely related to increased long-term inhaled steroid use in this population. Multiple recurrences may occur in anyone. The reinstitution of steroids generally leads to improvement, and relapses do not appear to indicate a worse prognosis, increased likelihood of treatment failure, or increased morbidity.

ALLERGIC BRONCHOPULMONARY ASPERGILLOSIS (MYCOSIS)

Allergic bronchopulmonary aspergillosis is a disorder caused by a complex hypersensitivity response to inhaled fungal antigens. Since the disease is most commonly induced by *Aspergillus* species, it is usually known as allergic bronchopulmonary aspergillosis (ABPA). When induced by non-*Aspergillus* species, the syndrome is called allergic bronchopulmonary mycosis. A comprehensive discussion of ABPA is provided in Chapter 49. ABPA complicates approximately 7 to 14 percent of cases of chronic steroid-dependent asthma and occurs in up to 15 percent of patients with cystic fibrosis. Rare cases lacking a history of asthma but meeting the other major diagnostic criteria (summarized in Table 72-4) have been reported. The diagnosis of ABPA is based on appropriate clinical features in combination with supporting serologic and radiologic findings. Greenberger and Patterson have proposed five minimal essential criteria needed to establish the diagnosis, including: (1) asthma, (2) positive immediate hypersensitivity skin test to *Aspergillus,* (3) serum precipitins to *Aspergillus fumigatus* (AF) or other relevant fungus, (4) total IgE greater than 1000 ng/ml, and (5) elevated serum anti-AF IgE and IgG. A history of current or previous pulmonary infiltrates and peripheral blood eosinophils (approximately 10,000 cells/ml), expectoration of brown mucous plugs, identification of *Aspergillus* (or other relevant fungus) in the sputum, and dual (immediate and delayed) cutaneous reactions to challenge with *Aspergillus* are also common clinical features of ABPA. Five clinical stages of ABPA have been recognized: acute illness (stage 1); remission (stage II); exacerbation (stage III); steroid-dependent asthma (stage IV); and fibrotic lung disease (stage V). The clinical features of these stages are shown in Table 72-5.

Typical radiographic manifestations of ABPA include transient, irregular pulmonary infiltrates with a predilection for the upper lobes (Fig. 72-4). Other common radiographic features include "finger-in-glove opacities," "tramline shadows," "toothpaste shadows," "ring shadows," and lobar consolidation (Fig. 72-4). These findings result from bronchial and bronchiolar wall inflammation, edema, and

Table 72-4

Diagnostic Criteria for Allergic Bronchopulmonary Aspergillosis

Major

Asthma
Positive immediate hypersensitivity skin-prick test to *Aspergillus*
Precipitating antibodies against *Aspergillus*
Elevated total IgE
Elevated serum *Aspergillus*–specific IgE, IgG
History of pulmonary infiltrates
Peripheral blood eosinophilia
+/− Proximal bronchiectasis

Minor

Mucous plugs containing *Aspergillus*
Dual cutaneous reaction to *Aspergillus*

Table 72-5

Clinical Stages of Allergic Bronchopulmonary Aspergillosis

Stage I: Acute

Acute asthma symptoms
Elevated serum IgE (typically > 1000 ng/ml)
Infiltrate on chest radiograph
Peripheral blood eosinophilia
Positive precipitating antibodies to *Aspergillus fumigatus*

Stage II: Remission

Resolution of symptoms
Radiographic clearing
Reduction or stabilization of IgE levels

Stage III: Exacerbation

Recurrence of elevated IgE levels
Development of a new pulmonary infiltrate on chest radiograph
+/− Escalation of asthma symptoms

Stage IV: Steroid-dependent Asthma

Difficult to control, steroid-dependent asthma
Persistently elevated total IgE, *Aspergillus* precipitins and *Aspergillus*-specific IgE and IgG despite corticosteroid therapy

Stage V: Fibrotic lung disease

Persistent steroid-dependent asthma
Fibrotic lung disease with gas exchange disturbances
Chronic sputum production and frequent infections common

remodeling, and from mucoid impaction of the bronchi with or without parenchymal involvement. Central (proximal) bronchiectasis, another characteristic radiographic manifestation of ABPA, occurs in many, although not all, patients, particularly when the disease has been present over an extended period of time.

Although lung biopsy is usually not required to establish the diagnosis, histopathological findings of ABPA include intense bronchocentric inflammation with eosinophils, lymphocytes, plasma cells, and monocytes, as well as mucoid impaction of bronchi. The features of ABPA are believed to result from a complex immunologic reaction to chronic airway colonization by *Aspergillus* (or other relevant fungal species) that includes features of type I, type III, and type IV immune responses. T-helper lymphocytes, neutrophils, eosinophils, and the fungus itself all also likely contribute to the pathogenesis of the disease.

The diagnosis of ABPA should be entertained in any patient with difficult to control asthma and/or the combination of asthma and eosinophilia, as well as patients with cystic fibrosis with progressive worsening of symptoms. However, ABPA may go unrecognized, due to overlap of clinical features with allergic, mold-sensitive asthma as well as other pulmonary eosinophilic disorders such as Churg-Strauss syndrome. ABPA may also be challenging to recognize due to the varying clinical presentations at different stages of disease.

Goals of treatment are to control symptoms, prevent exacerbations and preserve normal lung function. Systemic corticosteroids, with careful patient monitoring of clinical symptoms, IgE levels, and chest radiograph, are the mainstay of therapy. Corticosteroid doses that reduce IgE levels by at least half of acute stage levels and induce clearing of radiographic infiltrates must be used to control the disease; such doses are typically higher than those needed to control symptoms alone. Treatment with the antifungal agent itraconazole can also help control the symptoms and immunologic features of the disease. Bronchodilators and antibiotics help control bronchospasm and secondary respiratory infections.

CHURG-STRAUSS SYNDROME (ALLERGIC GRANULOMATOSIS AND ANGIITIS)

In 1939, Rackemann and Greene reported a subgroup of patients with polyarteritis nodosa and concomitant allergic disease. Similar findings were reported in the early 1940s by Harkavy. The histopathology and clinical features associated with this disease entity were first described in 1951 by Churg and Strauss, who reported a form of necrotizing vasculitis in several organs, associated with eosinophilic tissue inflammation and extravascular granulomas, occurring in asthmatics, with associated fever and peripheral hypereosinophilia. This disease entity, now recognized as Churg-Strauss syndrome (CSS), is an uncommon systemic disease. A case frequency of 2.4 to 6.8 cases per million persons per year is estimated among the general population, and 64 cases per million persons per year is estimated among patients with a history of asthma. The mean annual incidence has been estimated at 1 to 2.4 per million population across various countries. Approximately 10 percent of all patients with vasculitis prove ultimately to have CSS. Nevertheless, the precise incidence of CSS is unknown due to uncertainties regarding diagnosis and variable clinical presentation. The true incidence of CSS may be higher than is generally recognized, since the syndrome has many clinical, radiographic, and histological features in common with other vasculitic, eosinophilic, and granulomatous disease states. The diagnosis of CSS may be missed if not carefully entertained. CSS may occur in patients of any age, but it develops most commonly in patients between the ages of 38 to 50. There is no clear gender predominance. Among women, disease onset has been reported during pregnancy.

CSS tends to follow a subacute course, with symptoms ranging over months to years. Three distinct clinical phases

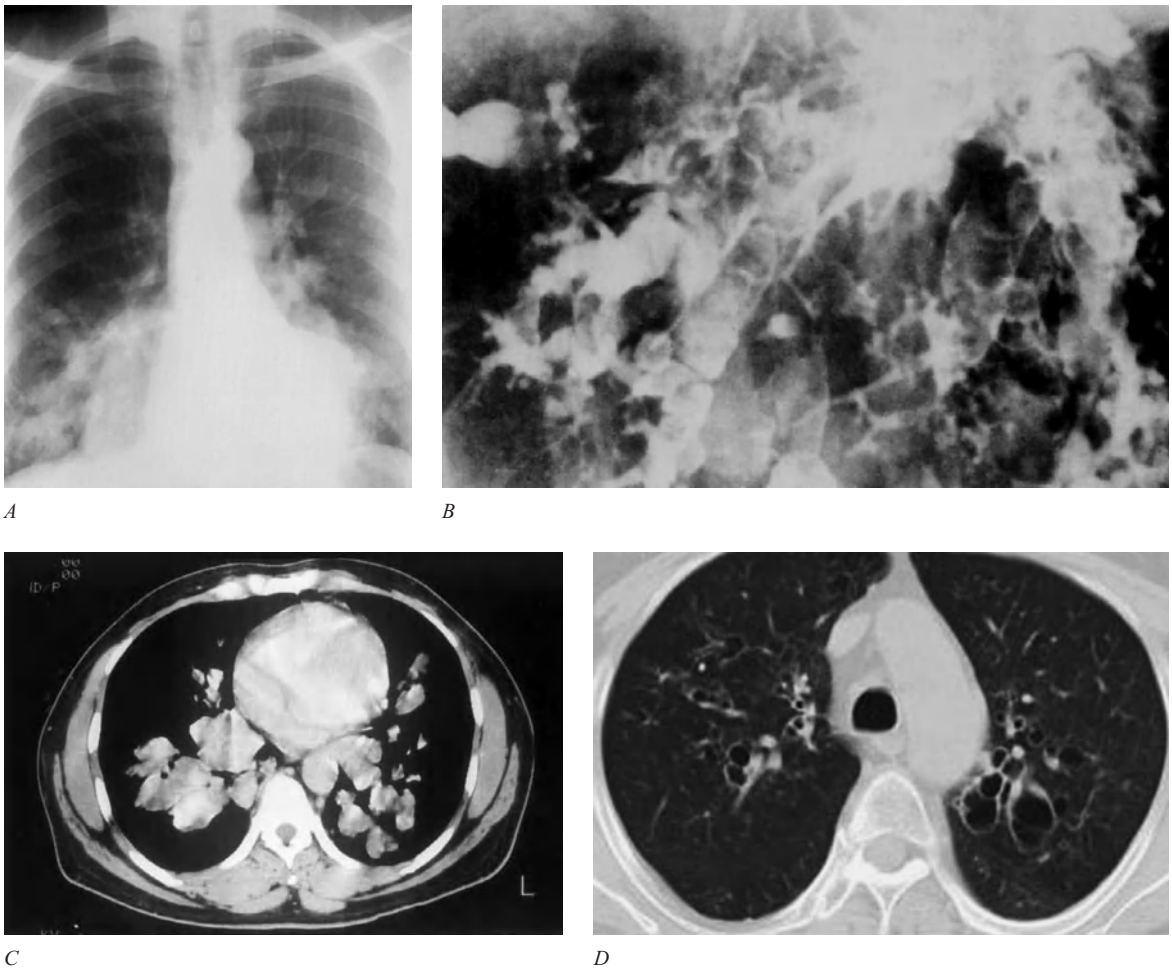


Figure 72-4 Radiographic appearance of allergic bronchopulmonary aspergillosis (ABPA). Extensive infiltrates with tubular configuration and "gloved finger" appearance are present, in this case predominantly in the lower lobes *(A)*. The bronchogram *(B)* and computed tomography (CT) of the chest *(C)* reveal extensive proximal bronchiectasis. Extensive mucoid impaction of the bronchi is evident on CT scan *(C)*. Central bronchiectasis and tram-track shadows in a patient with ABPA may also be present without mucoid impaction *(D)*.

of the disease have been recognized: the prodromal phase, the eosinophilic phase, and the vasculitic phase. The *prodromal phase* is characterized by "late-onset" (in the second or third decade) allergic rhinitis and atopy in persons often lacking a family history of atopy. Severe allergic rhinitis, sinusitis, drug sensitivity, and asthma are usually present for 8 to 10 years, and up to 30 years before CSS disease recognition. The *eosinophilic phase* is typified by the development of marked peripheral blood eosinophilia and eosinophilic tissue infiltration, most commonly of the lung, GI tract, and skin. The *vasculitic phase* is characterized by vasculitis of the small and medium vessels with vascular and extravascular granulomas. The onset of the vasculitic phase is often heralded by development of constitutional symptoms, including fever, malaise, weight loss, and increased allergic or asthmatic symptoms. Although the vasculitis tends to occur several years after the onset of allergic manifestations of the disease, in some cases it develops within months of, or concomitant with, the onset of asthma. A short duration between the onset of asthma and vasculitis is associated with increased severity of vasculitis. During the vasculitic stage, the asthma symptoms may persist and worsen, or they may diminish. When asthma dissipates, it often flares later in the course of illness and may require prolonged steroid treatment. Although CSS typically affects multiple-organ systems, limited forms of disease have also been described. Manifestations in the lungs, heart, skin, and nervous system are most common.

Most of the respiratory manifestations of CSS occur in the prodromal and eosinophilic phases of the disease. Nearly all patients have asthma at some point in the illness. Upper-airway allergic disease, including sinusitis, rhinitis, and polyposis, is seen in 75 to 85 percent of patients and may be the presenting symptom. Unlike WG, necrotizing granulomas involving the upper airway are unusual in CSS. The asthma and upper-airway disease usually are long-standing and often require steroid therapy (systemic or inhaled) to maintain control of symptoms. Spirometry may reveal an obstructive ventilatory defect. In rare instances, recurrent respiratory

infection leads to bronchiectasis. A Loeffler's-like syndrome with eosinophilic infiltration of the lung parenchyma is seen in 38 to 40 percent of patients. These patients may develop dyspnea, cough, and wheezing. Their chest radiographs have transient, migratory nonlobar, nonsegmental, often peripheral pulmonary infiltrates, with no regional predilection. Nodular lesions, interstitial lung disease, and hilar adenopathy are less common findings. In contrast to WG the CSS nodules rarely cavitate. Up to 30 percent of patients develop unilateral or bilateral pleural effusions, which may be associated with pleuritic chest pain. The chest radiograph may occasionally be normal. High-resolution CT scanning has demonstrated patchy peribronchial thickening, pulmonary artery enlargement (in comparison to the corresponding bronchi), irregular stellate configuration of some vessels, areas of septal thickening, and scattered patchy parenchymal opacities with ground-glass or consolidated appearance. These findings have been reported to correlate with pathological findings evident on open lung biopsy such as eosinophilic pneumonia, alveolar hemorrhage, eosinophilic infiltration of the bronchial wall, and septum. Further studies are necessary to determine whether high-resolution CT is useful to stage the disease or establish the diagnosis without tissue biopsy.

Cardiac manifestations generally are not present on initial presentation of CSS. However, they typically occur during the vasculitic phase of the disease and are a major source of morbidity and the principal cause of death (in up to 50 percent of cases) from the disorder. Progressive congestive heart failure (CHF) occurs in 47 percent of cases because of myocardial infiltration by eosinophils or ischemic cardiomyopathy resulting from necrotizing vasculitis of the coronary arteries. This coronary vasculitis is fatal up to 60 percent of the time. Acute pericarditis is present in approximately one-third of cases, and cardiac tamponade has been reported. Constrictive pericarditis may develop over time.

A wide array of neurological manifestations may develop in CSS. Mono- or polyneuropathy (most notably mononeuritis multiplex) is present in 69 to 75 percent of cases. CNS manifestations occur in approximately two-thirds of patients and include cranial nerve impairment (especially optic neuritis), seizure, subarachnoid hemorrhage, and cerebral infarction. Cerebral hemorrhage and infarction are common causes of patient death.

Skin, GI, renal, and other systemic alterations have been well described in CSS. Skin findings are present in approximately two-thirds of cases and may develop in localized crops. They can manifest as nonthrombocytopenic purpura, tender cutaneous or subcutaneous nodules (which may ulcerate), urticaria, a maculopapular rash, petechiae, ecchymoses, or livedo reticularis. GI manifestations of CSS are present in up to 60 percent of cases. They can include eosinophilic gastroenteritis or vasculitis that can lead to diarrhea, abdominal pain, intestinal obstruction, cholecystitis, pancreatitis, bleeding, liver function test abnormalities, and bowel perforation. GI disease is the fourth leading cause of death in patients with CSS (after cardiac, CNS, and renal impairment). Renal insufficiency occurs in up to 50 percent of patients with CSS. Interstitial nephritis, focal segmental glomerulonephritis (often with necrotizing features), hematuria, and albuminuria are common. Severe, difficult-to-control hypertension is also a major sequela of CSS (in 25 to 75 percent of cases) and may be due to recurrent renal infarction. In contrast to WG, overt renal failure is not commonly seen in CSS. Mild lymphadenopathy (in 30 to 40 percent), rheumatological manifestations (migratory polyarthralgias, myalgias, temporal arteritis), urological disease (ureteral, urethral, prostatic), and ocular manifestations have also been described.

Although there are no laboratory tests specific for a diagnosis of CSS, a majority of patients with CSS have a striking but fluctuating degree of peripheral blood eosinophilia (20 to 90 percent of the WBC differential), generally greater than that seen with asthma alone. The degree of eosinophilia may be suppressed by corticosteroid treatment of asthma. Serum total IgE levels are typically elevated (range, 500 to 1000 U/ml) and may parallel disease activity. Most patients have a normochromic, normocytic anemia and moderate elevation of their ESR. Some 70 to 75 percent of patients have positive antinuclear cytoplasmic antibody with a perinuclear staining pattern (pANCA). The majority of these are directed against myeloperoxidase (MPO-ANCA) and a minority against proteinase 3 (PR3-ANCA). As many as 50 percent of patients have low titers of rheumatoid factor; hypergammaglobulinemia and circulating immune complexes may also be seen. Laboratory examination of pleural fluid, if present, reveals an acidotic eosinophilic exudate with low glucose levels. Pleural biopsy shows chronic pleuritis with eosinophilic infiltration. BAL reveals an increased percentage of eosinophils, the magnitude of which is generally less than that seen with CEP or idiopathic hypereosinophilic syndrome. However, patients have been described whose BAL fluid leukocyte differential contained 81 percent eosinophils. ^{18}FDG/^{13}N ammonia positron emission tomography (PET) imaging may be useful to identify cardiac involvement in CSS.

The histopathological hallmarks of CSS vary depending on the stage of illness but include tissue (interstitial, blood vessel, and alveolar) infiltration by eosinophils; necrotizing vasculitis of small arteries, arterioles, and, to a lesser extent, small veins, venules, and capillaries and extravascular and interstitial eosinophilic granulomas (typically microscopic). Both pulmonary and systemic vessels may be affected. The precise histopathology of vascular impairment depends on the stage of the lesion. Early lesions demonstrate eosinophilic infiltration of the vessels and perivascular region (Fig. 72-5). Later lesions are characterized by necrotizing arteritis or vessel obliteration and scarring. The extent of vascular impairment varies from mild, eosinophilic perivascular cuffing to severe transmural inflammation with necrotization. Lesions may be sparse or widespread. Eosinophilic lymphadenopathy may also be present.

The pathogenesis of CSS remains poorly understood. The strong association with allergy, atopy, and elevated levels of IgE (especially during the vasculitic phase of the disease) has raised the question of immune hypersensitivity. As

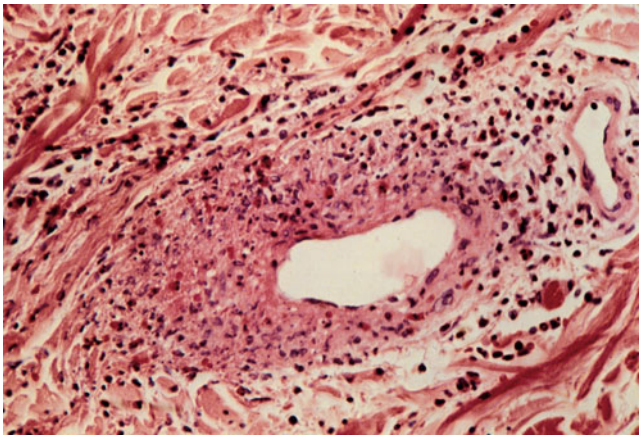


Figure 72-5 Pathological appearance of small arteriole in Churg-Strauss vasculitis. Intense perivascular inflammation with eosinophilia is present.

a result, it has been proposed that repeated antigenic stimulation in patients with a heightened T-cell and eosinophil response may be important in the development of the disorder. Heightened humoral immunity with immune complex disease may also play a role. The pathogenic role of antineutrophil cytoplasmic antibody (ANCA) remains uncertain. ANCA may contribute to tissue inflammation and injury by activation of inflammatory cells and generation of oxidative stress. Eosinophils likely also contribute significantly to the tissue injury. No genetic predisposition or HLA association with the disease has been identified.

The relationship between the pathophysiology of asthma in CSS to that of asthma without CSS also remains uncertain. A strong association has been noted between the use of leukotriene receptor antagonists (LTRA) and 5-lipoxygenase inhibitors and the development of CSS. The appearance of CSS following reduction in systemic corticosteroid dosing in many of these reports raises the possibility that preexisting, underlying CSS that was being treated with corticosteroids is unmasked by the administration of these agents and the reduction in corticosteroid dose. However, it remains uncertain whether these agents may be causally related to the onset of CSS. Patients with steroid-dependent asthma, in whom the diagnosis of CSS has not been demonstrated or entertained, should be monitored closely for evidence of CSS when steroid doses are tapered.

In 1990, the American College of Rheumatology published diagnostic criteria for CSS, based on assessments of the sensitivity and specificity of the diagnostic criteria used previously. The presence of at least four out of six of the following criteria yielded 85 percent sensitivity and 99.7 percent specificity in establishing the diagnosis: (1) asthma, (2) peripheral eosinophilia greater than 10 percent, (3) mono- or polyarthropathy, (4) migratory or transient pulmonary infiltrates, (5) paranasal sinus abnormality, and (6) extravascular eosinophils in a blood vessel on a biopsy specimen. The presence of asthma or allergy as well as more than 10 percent eosinophilia was 95 percent sensitive and 99 percent specific in distinguishing CSS among a subgroup of patients with well-documented systemic vasculitis. Subsequently, the Chapel Hill Consensus Conference recommended that diagnostic criteria for CSS include (1) appropriate clinical setting and histopathology and (2) eosinophil-rich and granulomatous inflammation involving the respiratory tract and necrotizing vasculitis affecting small and medium vessels with associated asthma and eosinophilia. However, these criteria require tissue biopsy and are less sensitive for CSS than others that have been proposed, hence they may be less useful to assist diagnosis in the routine clinical setting. Open lung biopsy is the gold-standard site for tissue biopsy. Transbronchial biopsy may reveal the diagnosis if there is alveolar involvement, but is often nondiagnostic. Biopsy of other sites (e.g., skin, pericardium, muscle, nerve, gut), with or without immunostaining, may assist in establishing the diagnosis in selected cases, although demonstration of characteristic histopathological changes are not essential for establishing the diagnosis.

The differential diagnosis of CSS includes polyarteritis nodosa, microscopic angiitis, WG, CEP, ABPA, idiopathic hypereosinophilic syndrome, Loeffler's syndrome, asthma, fungal or parasitic infection, drug-induced vasculitis, sarcoidosis, and Hodgkin's lymphoma. CSS can be distinguished from WG since compared with WG, patients with CSS have nasal polyps and allergic rhinitis but lack significant necrotizing upper-airway lesions and cavitation of lung nodules, and are more likely to have pANCA (in contrast to the c-ANCA seen in WG). Also, patients with CSS are less likely to develop renal failure, and vasculitic neuropathy and asthma/eosinophilia are not typical features of WG. CSS can be distinguished from MPO-ANCA–positive microscopic angiitis since patients with the latter syndrome have leukocytoclastic vasculitis without granulomas and do not have upper-airway involvement, asthma, and eosinophilia. Further, unlike CSS, cardiac involvement is rare in MPO-ANCA–positive vasculitis.

Patients in whom CSS goes untreated have a poor prognosis; up to 50 percent die within 3 months after the onset of vasculitis. As such, efforts at early recognition and treatment are important. No large randomized, controlled trials exist comparing various treatment methods, largely because of the rarity of the disorder. Thus, it is difficult to define the optimal treatment for the disease. Nevertheless, it is clear that corticosteroid treatment generally leads to dramatic clinical improvement, with disease stabilization or cure. Prednisone, 0.5 to 1.5 mg/kg/day (or 60 mg/day in adults) is given for 6 to 12 weeks, aiming to eliminate constitutional symptoms and cardiac, renal, neurological, or other vasculitic manifestations. Higher doses are occasionally required. Severe hypertension and mononeuritis multiplex often require prolonged steroid treatment, and may be difficult to eliminate. Once the vasculitic phase is controlled, steroids may be tapered, with doses titrated to maintain disease control. Low-dose prednisone is often given every day or every other day for up to 1 year. Although relapses are uncommon, patients should be followed closely for evidence of clinical deterioration, and should have periodic screening of total WBC and differential,

ESR, and IgE levels. Most reports suggest the pANCA is not useful to monitor disease activity or direct therapeutic intervention.

Treatment with cytotoxic immunosuppressive agents such as azathioprine, cyclophosphamide, high-dose methylprednisolone, or chlorambucil may prove effective and should be considered in patients whose condition fails to improve with steroid treatment or who have severe systemic involvement or poor prognostic features, including cardiac or GI involvement, renal insufficiency or proteinuria greater than 1 g/day. Cyclophosphamide (2 mg/kg/day orally or 0.6 g/m^2 intravenously per month) may be given concurrently with corticosteroids. Patients treated with cyclophosphamide should be monitored closely for hemorrhagic cystitis, renal insufficiency, bone marrow suppression, bladder fibrosis, and urological malignancies. Intravenous immunoglobulin may be beneficial for reducing symptoms and organ involvement and improving long-term disease control among persons with severe organ involvement. The immunoregulatory cytokine interferon-α (IFN-α) has led to improved pulmonary function tests, reduction in corticosteroid dose, and decreased WBC count and may be considered as another alternative treatment in persons with refractory disease. Plasma exchange may also be a successful adjunct treatment in some patients. Beta blockers should be avoided in the management of CSS-related hypertension, owing to the risk of bronchospasm and congestive heart failure (CHF).

Long-term overall remission can be achieved in approximately 81 to 92 percent of patients; relapses, if they occur, are most common within 1 year. In a series of 30 patients collected over the period 1950 to 1974, a median survival of more than 9 years was reported in patients treated with steroids; 1-year survival was 90 percent, 3-year survival was 76 percent, and 62 percent survival was noted at 5 years. A more recent study suggested 72 percent survival at 5 years. Patients with severe disease treated with corticosteroids and cyclophosphamide have better survival than those treated with corticosteroids alone.

IDIOPATHIC HYPEREOSINOPHILIC SYNDROME

Idiopathic hypereosinophilic syndrome (IHS) is a rare disorder first described in 1968 by Hardy and Anderson. Over the ensuing years, many case reports of severe peripheral eosinophilia and diffuse organ infiltration with eosinophils were described. Several names—including *eosinophilic leukemia, Loeffler's fibroplastic endocarditis,* and *disseminated eosinophilic cardiovascular disease*—were used to describe this disease entity. In 1975, Chusid and colleagues revised the definition of IHS to include only cases in which no other underlying cause of hypereosinophilia could be found. IHS is now recognized as a clinically heterogeneous syndrome with a wide range of disease severity. Whereas some patients experience a mild, limited form of the disease with minimal involvement of noncritical organs (e.g., skin), others have life-threatening multi-organ dysfunction. Emerging evidence suggests that IHS may indeed represent several diseases of distinct etiology that share several features in common.

IHS predominantly affects males, although the gender association is less prominent in older patients. Although persons of any age may be affected, disease onset is most common between 20 and 50 years of age. There is no known racial or ethnic predisposition. Symptoms vary according to the organ system(s) affected. Presenting complaints are often nonspecific and include weakness, fatigue, low-grade fevers, myalgias, cough, angioedema, rash, retinal lesions, and dyspnea. Involvement of virtually every organ system has been described. The three principal clinical features defining IHS are: (1) persistent blood eosinophilia greater than 1500/μl for more than 6 months; (2) symptoms and signs of end-organ dysfunction; and (3) no other identifiable underlying cause of eosinophilia.

The respiratory system is affected in an estimated 40 percent of patients with IHS. A majority of patients develop a predominantly nocturnal cough, which is either nonproductive or productive of small quantities of nonpurulent sputum. Wheezing and dyspnea are also common, without evidence of airflow obstruction on spirometric examination. Pulmonary hypertension, ARDS, and pleural effusions (which may be due to CHF) have been reported. In patients with pulmonary manifestations, the chest radiograph may reveal transient focal or diffuse pulmonary infiltrates (with no predilection for any particular distribution) and/or pleural effusion(s). Histopathological examination of affected lung specimens most commonly reveals intense interstitial infiltration with eosinophils. Less commonly, necrotic areas of parenchyma are found. These are believed to be due to pulmonary microemboli. In contrast to CSS, significant vasculitis is not present.

Cardiac disease, which occurs in most patients with IHS, is the major cause of morbidity and mortality. The most common cardiac manifestations are relentlessly progressive CHF due to eosinophilic myocarditis and endocarditis, intracardiac thrombi, and endocardial fibrosis. Cardiac involvement in IHS, which may be clinically silent, is believed to progress from an initial acute necrosis stage, followed by endocardial thrombus formation and eventually development of fibrosis which may lead to restrictive cardiomyopathy or valvular dysfunction such as mitral regurgitation. Bacterial endocarditis has also been noted. The cardiac damage is believed to be mediated at least in part by eosinophil-derived granule proteins. Disturbingly, cardiac involvement correlates poorly with the peripheral blood eosinophilia, hence echocardiographic follow-up at 6-month intervals is recommended.

Involvement of the central or peripheral nervous system, which occurs in up to 60 percent of patients, is also a major cause of morbidity. Neurological manifestations of IHS include encephalopathy with neuropsychiatric dysfunction, memory loss, gait disturbances with or without signs of upper motor neuron injury, visual changes, and sequelae

of thromboembolic events, including hemiparesis. Peripheral neuropathy with sensory and/or motor axonal loss (no vasculitic or eosinophilic infiltration) is extremely common in IHS. The bone marrow is universally affected with a striking eosinophilia (up to 25 to 75 percent of the differential). Other hematological manifestations are venous and arterial thromboembolism, anemia, thrombocytopenia, elevated vitamin B_{12} levels, hepatosplenomegaly, and lymphadenopathy (in 12 to 20 percent). GI (20 to 30 percent of patients), cutaneous (25 to 56 percent), renal (10 to 20 percent), musculoskeletal, ocular, and endocrine manifestations are all also well described.

Laboratory findings associated with IHS include an elevated total serum IgE (25 to 38 percent), hypergammaglobulinemia, circulating immune complexes (32 to 50 percent), and an ESR above 15 mm/h (68 percent). Elevated serum B_{12} and leukocyte alkaline phosphatase levels are also noted. Fungal and parasitic serologies, as well as aspirates of body fluids for ova and parasites, are negative. Of interest is that whereas blood and BAL eosinophilia are both prominent in persons with pulmonary involvement, blood eosinophilia is present and BAL eosinophilia is absent in persons lacking pulmonary manifestations of the disease. This finding has raised the question whether BAL eosinophilia may serve as a marker for the development of pulmonary disease associated with IHS.

The organ damage in IHS is believed to be due both to eosinophilic infiltration of tissues and to tissue injury caused by thromboembolic events. Eosinophils probably contribute to tissue damage via antibody-mediated cytotoxicity and the release of toxic granule products such as major basic protein and eosinophil cationic protein. Elevated serum levels of eosinophil cationic protein and major basic protein have been reported, but they do not correlate universally with clinical disease severity. The precise events inciting the extreme eosinophilia in IHS are unknown, but several mechanisms have been proposed, including overproduction or abnormal activity of cytokines leading to eosinophilia, and defects in cytokine signaling or signal transduction.

A variety of chromosomal abnormalities (including the Philadelphia chromosome) and immunologic abnormalities have been described in patients with IHS. Three major pathogenetic and clinical variants of IHS have been reported: (1) patients with clonal abnormalities in eosinophils; (2) patients with features of myeloproliferative disorder and chromosomal aberrations leading to abnormal constitutive production of tyrosine kinases; and (3) patients with dysregulation of T lymphocytes with overproduction of IL-5, a cytokine important for eosinophil growth, differentiation, and chemotaxis. The clinical presentation of IHS may vary, depending on the pathogenetic variant. Recognition of these variants also has potential implication for choice of therapy (noted below).

The diagnosis of IHS is established by demonstrating multi-organ dysfunction, severe peripheral blood eosinophilia (greater than 1500/μL) for at least 6 months (or with death before then), and an absence of any other known causes of peripheral blood eosinophilia. Occasionally, the disease presents with the incidental finding of blood eosinophilia before development of other complications. The total peripheral leukocyte count is typically elevated to above 10,000 (typical range, 10,000 to 30,000), with a preponderance of eosinophils (up to 70 percent). The leukocytosis may be progressive. Eosinophilic blast transformation was reported to occur at some time during the course of the disease in 28 percent of 51 patients in one series.

The differential diagnosis of IHS includes parasitic infection, acute eosinophilic leukemia, CSS, episodic angioedema with eosinophilia, tuberculous or fungal infection, allergic or autoimmune disease, other acute or CEPs, TPE, and other lymphoproliferative disorders. Patients with eosinophilic leukemia have immature eosinophils or blasts in the bone marrow and/or blood, whereas patients with IHS typically do not. Patients with IHS do not have asthma or vasculitis characteristically associated with CSS, and patients with episodic angioedema typically lack the multi-organ involvement associated with IHS.

Before the discovery of an effective therapy, the prognosis of IHS was poor. In one early series, 81 percent of 48 patients died within 1 year of diagnosis. Overall, without therapy, average survival was 9 months, and 3- to 4-year survival was estimated at 10 to 12 percent. The greatest mortality occurs within the first year after diagnosis. Death may occur from refractory CHF, azotemia, hepatic failure, venous thromboembolism, a perforated abdominal viscus, or infection. The advent of effective therapy for IHS has led to a marked improvement in median survival to more than 10 years.

Patients with the incidental finding of peripheral eosinophilia but without evidence of end-organ dysfunction can be followed closely at 3- to 6-month intervals without specific treatment, as they tend to follow a benign course. The mainstay of therapy for IHS with organ involvement includes corticosteroids such as prednisone at 1 mg/kg/day for several weeks, with taper of dose attempted to an every-other-day regimen once eosinophil levels are reduced. The mechanisms by which steroids are effective in this disorder are not fully clear. If the disease stabilizes or resolves, alternate-day corticosteroids should be continued for approximately 1 year at the minimal dose that effectively controls disease activity. Hydroxyurea (0.5 to 1.5 g per day) may be added to the regimen if there is evidence of further disease progression, with the aim of reducing the peripheral leukocyte count to the range of 5000 to 10,000. Vincristine may be used as a chemotherapeutic inducing agent in patients with extremely high peripheral WBC counts. Etoposide and chlorambucil are effective alternative agents for cases that prove refractory to standard treatment with corticosteroids. Cyclosporine may also be of benefit in controlling the disease, especially when used in combination with corticosteroids. IFN-α, a mediator that suppresses eosinophil function in vitro, has been beneficial in management of IHS, perhaps by inhibiting eosinophil proliferation and differentiation. IFN-α should be tried as a second-line agent among patients with IHS who fail to respond to corticosteroid treatment. Existing data suggest that another anti-eosinophil strategy, the anti–IL-5 antibody, may reduce symptoms and eosinophilic organ involvement associated with IHS, and may be particularly helpful in patients with

high IL-5 levels (e.g., persons with dysregulated T lymphocytes). Moreover, tyrosine kinase inhibitors such as imatinib mesylate (Gleevec) may also be beneficial for treatment of the myeloproliferative variant of IHS. Allogeneic bone marrow transplantation has also been reported anecdotally to be successful in selected severe cases of IHS in which end-organ damage is potentially reversible. Leukapheresis affords no clear benefit unless there is elevated blood viscosity with associated coagulation. Antiparasitic agents and radiation therapy are ineffective.

Favorable prognostic features include a rapid clinical response to treatment with reduction in blood eosinophilia and the presence of angioedema, an elevated IgE, and absence of findings associated with myeloproliferative disorder. Factors associated with a poor prognosis include presence of total blood WBC greater than 100,000/mm^3, myeloblasts in the peripheral blood, refractory CHF, basophilia above 3 percent, identifiable chromosomal abnormalities in bone marrow cells, and elevated serum B_{12} levels. The mechanisms by which these features are associated with a given prognosis are largely unknown.

APPROACH TO THE EVALUATION OF EOSINOPHILIC PNEUMONIAS

In approaching the patient with pulmonary infiltrates and eosinophilia, one must first establish whether the patient has one of the eosinophilic disorders described in this chapter or a disease process that is secondarily associated with eosinophilia (Table 72-1). A useful algorithmic approach to the evaluation of patients with pulmonary infiltrates and eosinophilia (blood or lung) is shown in Fig. 72-6. A careful search for the cause of the disease should be undertaken. A comprehensive medical history should be elicited, with particular attention paid to any antecedent illness (e.g., atopy, rhinitis, asthma, steroid use, immunosuppression), disease exposures, travel, and the duration and nature of the patient's symptoms. One should take special notice of the sequence and timing of events during the course of the illness. In addition to a careful chest examination, a search should be undertaken for physical findings suggestive of extrapulmonary disease (e.g., skin lesions, CHF, hypertension, neurological abnormalities, musculoskeletal disorders, or GI illness). The nature, distribution, and duration of infiltrates on chest radiograph should be noted. CT scanning of the chest can also provide additional information that may not be apparent on the chest radiograph.

The workup should include the following additional laboratory data: complete blood count (CBC) with differential, ESR, IgE level, ECG, blood urea nitrogen (BUN), creatinine, liver function tests, urinalysis, sputum cultures, and, when appropriate, sputum cytology. Serologies (e.g., *Aspergillus* precipitins, ANCA, antiparasitic antibodies) are indicated in selected cases. Bronchoscopy with BAL or transbronchial biopsy is important in the evaluation of pulmonary

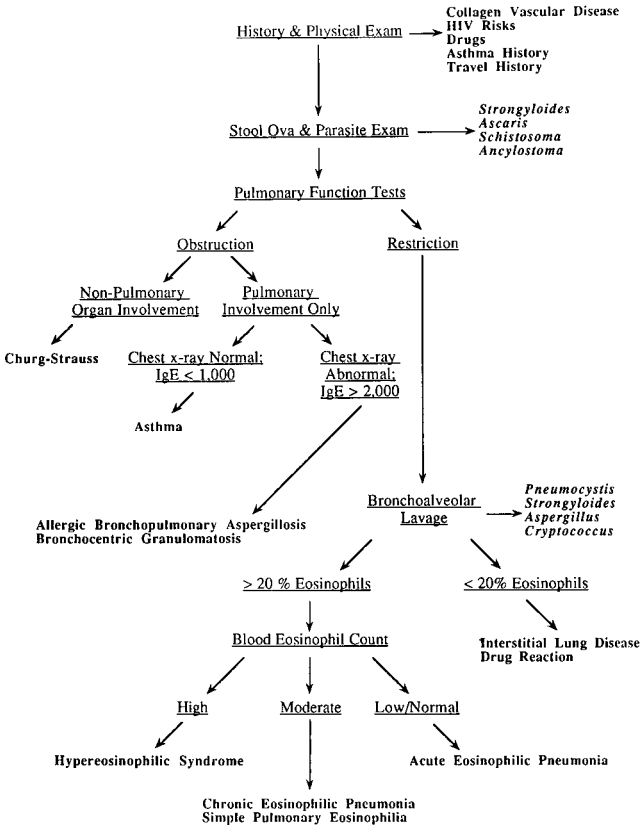


Figure 72-6 Algorithmic approach to evaluation of patients with pulmonary infiltrate and eosinophilia. *(Based on data from Allen JN, Davis WB: Eosinophilic lung diseases. Am J Respir Crit Care Med 150:1423–1438, 1994.)*

eosinophilic syndromes. The advent of BAL has allowed diagnosis of most cases of eosinophilic pneumonia without open lung biopsy. Normally, BAL fluid contains less than 2 percent eosinophils. In contrast to diseases associated secondarily with eosinophilia, all the primary pulmonary eosinophilic syndromes are characterized by striking BAL eosinophilia (more than 20 percent of the BAL leukocyte differential). The finding of more than 20 percent BAL eosinophils, viewed in combination with appropriate clinical and radiographic features, is strongly suggestive of the diagnosis of one of these syndromes. BAL and transbronchial biopsy are also useful in ruling out infections (bacterial, fungal, tuberculous, and parasitic), malignancies, and other causes of eosinophil-associated disease. It must be kept in mind that in the context of the overall list of pulmonary diseases associated with more than 5 percent BAL eosinophilia, the true pulmonary eosinophilic syndromes are rare.

The pulmonary eosinophilic syndromes are at times difficult to distinguish from one another, owing to the substantial amount of overlap among their clinical, radiographic, and histological features, as well as variable features at different stages of disease. The comparative features of the eosinophilic pneumonias described in this chapter, with regard to several key features, are shown in Table 72-6. The clinical presentation may be acute, subacute, or chronic. Disease may range from mild and self-limited to severe and

Table 72-6

Comparative Features of the Pulmonary Eosinophil Syndromes

	Loeffler's	**AEP**	**TPE**
Clinical course	Acute	Acute	Acute, subacute, chronic
H/o allergic disease/asthma	—	+/−	—
Blood eosinophilia	Extreme, transient	Absent	Extreme
Sputum/BAL eosinophilia	Prominent	Striking	Prominent
Elevated serum IgE	+/−	Moderate elev. in some	Highly elev.
Etiologic agent	*Ascaris* spp. or other parasites, drugs	Unknown	Filarial infection
Radiographic findings (CXR, CT)	Patchy, often peripheral unilateral or bilateral consolidation and GGO; usually transient, migratory	Diffuse, alveolar and interstitial GGO and airspace opacities, interlobular septal thickening, pleural effusion	Diffuse, reticulonodular
PFTs	RVD	RVD	OVD early, RVD late, or mixed pattern
Characteristic diagnostic findings	*Ascaris* larvae in sputum, gastric aspirate	None	*Filaria*-specific IgE, IgG, microfilaria in LN/lung
Vasculitis	None	None	None
Extrapulmonary manifestations	GI late, if untreated	None	Cardiac, CNS rare
Therapy	Mebendazole, if parasitic; removal of drug or toxin exposure +/− steroids	Corticosteroids	Diethylcarbamazine
Chronic/recurrent disease	None	None	Infrequent

Note: + = yes or present; − = no or not present; elev. = elevated; GGO = ground-glass opacity; h/o = history of; LN = lymph node; mod. = moderately; OVD = CXR = chest x-ray (radiograph); GI = gastrointestinal

Table 72-6

(*Contintued*)

CEP	ABPA	CSS	IHS
Subacute	Acute, subacute, chronic	Acute, subacute, chronic	Subacute, chronic
+ (30–60%)	Nearly 100%	100%	—
Mild–mod. in most	Typical	Extreme, fluctuating	Extreme, persistent
Striking	In some	Prominent	Striking
Mod.–elev. in 30%	Marked elev., fluctuates w/disease	Mod.–elev.	Mod.–elev. in some
Unknown	*Aspergillus* (or other fungus)	Unknown	Unknown
Predominately, peripheral consolidation and GGO; "photographic negative of pulmonary edema"	Upper lobe predominant proximal bronchiectasis	Transient, migratory peripheral, rarely diffuse; patchy peribronchial and septal thickening, patchy parenchymal GGO or consolidation	Transient, focal or diffuse
Normal, OVD, or RVD	OVD +/− RVD	OVD +/− RVD	Mild RVD in some
None	See Table 72-4	Histopathology plus appropriate clinical setting	Extreme persistent eosinophilia and multi-organ dysfunction (no other evident cause)
Occasionally mild, non-necrotic	None	Characteristic (see text)	None
Very rare reported	None	Typical of vasculitic phase	Cardiac, neurological, GI, hematological, other
Corticosteroids	Corticosteroids, bronchodilators, antibiotics, antifungals	Corticosteroids, other immunosuppressives (see text)	Corticosteroids, other immunosuppressives (see text)
Common	Typical	Infrequent after Rx	Chronicity typical

obstructive ventilatory defect; PFTs = pulmonary function tests; RVD = restrictive ventilatory defect; BAL = bronchoalveolar lavage; CT = computed tomograph;

life-threatening illness. To varying degrees in all the pulmonary eosinophilic syndromes, dyspnea, malaise, low-grade fever, cough, and wheezing are common presenting complaints. Of the diseases considered in detail in this chapter, only CSS and IHS are consistently associated with significant extrapulmonary manifestations. Radiographic infiltrates may be transient in Loeffler's syndrome, TPE, CSS, ABPA, and IHS. Blood eosinophilia is present in all the diseases discussed except idiopathic AEP and in a minority of cases of CEP. Variable degrees of elevation of serum IgE are also present. Pulmonary function abnormalities are not specific for these disorders. Except for the diseases caused by parasites, corticosteroids are the mainstay of therapy.

Although the eosinophilic pneumonias can, at times, pose diagnostic difficulties, it is crucial to establish an accurate diagnosis whenever possible. An accurate diagnosis is important because the dose and duration of steroid treatment, prognosis, and follow-up measures for each of these diseases vary widely, and initiation of other specific therapeutic interventions improves outcomes in selected situations. Furthermore, chronic fibrotic lung disease may result from failure to accurately diagnose and treat some of these disorders in a timely fashion, and misdiagnosis with resultant inappropriate therapy (e.g., high-dose steroid treatment of invasive fungal infection masquerading as CEP) may be catastrophic.

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73
CHAPTER

Depositional Diseases of the Lungs

Robert J. Homer

Deposits of endogenous body constituents or exogenous materials in amounts sufficient to deform structure and impair function can occur virtually anywhere in the body. Deposits of endogenous materials in the lungs or airways cause a variety of diseases (Table 73-1). These may have different clinical manifestations, depending on localization (i.e., pulmonary parenchyma or conducting airways). This chapter deals with a few of these manifestations: amyloidosis; diffuse pulmonary calcification; alveolar microlithiasis; diffuse alveolar hemorrhage syndromes; and idiopathic pulmonary hemosiderosis. Others are discussed elsewhere in this text.

AMYLOIDOSIS

Nature of Amyloid

Amyloidosis refers to the extracellular deposition of amyloid, a fibrillar proteinaceous insoluble material that has characteristic light, ultrastructural, and histochemical features (Fig. 73-1). Electron microscopic examination of amyloid reveals a dominant (95 percent) fibrillar component with distinctive periodicity, associated with a lesser (5 percent) pentagonal doughnut-shaped glycoprotein component, physically and chemically identical in all forms of amyloid, which is derived from a soluble plasma protein, *soluble amyloid P protein* (SAP). Amyloid also includes various glycosaminoglycans and certain apolipoproteins (E and J). Radiographic diffraction studies of amyloid show the fibrils to be arrayed in a β-pleated sheet configuration. This accounts for the ordered binding of the histochemical stain Congo red such that Congo red–stained amyloid appears apple-green under polarized light.

The main fibrillar component of amyloid can be derived from any one of 23 precursor proteins. In systemic disease, the most important sources of amyloid are immunoglobulin light-chain, serum amyloid-associated (SAA) protein and

Table 73-1

Depositional Diseases of the Lungs

Biological Material	Disease
Interstitium	
Amyloid	Amyloidosis
Water	Interstitial edema
Calcium	Metastatic calcification
Alveoli	
Surfactant	Alveolar proteinosis
Water	Alveolar edema
Calcium	Alveolar microlithiasis
Blood and hemosiderin	Alveolar hemorrhage syndromes

transthyretin. Less common sources of amyloid include β_2-microglobulin in patients with chronic renal failure on dialysis and various mutant amyloid precursor proteins. Finally, there are a number of organ-specific amyloid syndromes, the most important of which is Alzheimer's disease. A related entity to amyloidosis is light-chain deposition disease (LDCC) in which tissue deposits are also derived from immunoglobulin light chains and are similar to amyloid by light microscopy, but show granular deposition by electron microscopy and do not stain with Congo red. It seems likely that the biochemical properties of the light chain determine the nature of the deposit produced.

When amyloid is deposited in tissues it may produce atrophy of parenchymal cells (e.g., glomeruli), interference with mechanical function (e.g., heart and lungs), or impaired vasoconstriction of blood vessels, leading to hemorrhage (e.g., lungs and gastrointestinal tract). Amyloidosis may be a systemic disease with deposition of amyloid in multiple sites. In such cases, the amyloid is derived from a soluble-circulating plasma precursor. Localized amyloid deposition, involving a single body site, is thought to be derived from protein produced at the site of deposition.

Systemic amyloid light chain (AL) usually occurs in association with a clonal proliferation of B cells or plasma cells which produce a monoclonal immunoglobulin or immunoglobulin fragment (monoclonal gammopathy). The neoplastic clone may clinically manifest as multiple myeloma or lymphoma (generally lymphoplasmacytic lymphoma) or may be subclinical (formerly known as *primary amyloidosis*), causing bone marrow plasmacytosis. Most often the source protein is a λ-light chain, either intact or the amino terminal fragment.

AA amyloidosis is a far less common cause of symptomatic amyloidosis of the respiratory tract. The AA protein is derived from an acute-phase reactant found in normal plasma known as *serum amyloid associated* (SAA) *protein* and produced by the liver. Chronic increase in serum acute-phase reactants is an important precondition for the deposition of AA amyloid. AA amyloidosis (previously referred to as *secondary amyloidosis*) was formerly more common in patients with chronic infections (e.g., tuberculosis, leprosy, and chronic osteomyelitis) but is now seen more commonly with noninfectious chronic inflammatory diseases (e.g., rheumatoid arthritis, familial Mediterranean fever, Crohn's disease, and heroin abuse with "skin popping").

Amyloid derived from plasma transthyretin *(senile amyloidosis)* is not uncommon but only infrequently produces clinical disease. This most often takes the form of restrictive cardiomyopathy due to cardiac deposition, and dyspnea due to diffuse interstitial pulmonary deposition is quite rare.

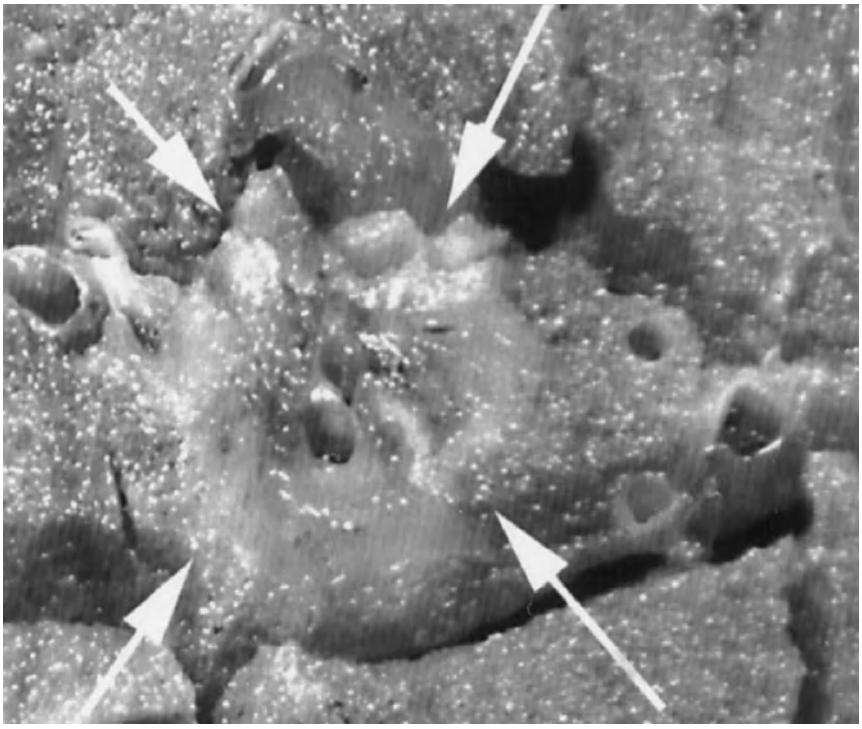
Pulmonary Involvement in Amyloidosis

Amyloidosis may involve any portion of the respiratory tract. For example, deposits in the tongue may be extensive enough to cause obstructive sleep apnea. Deposits in the tracheobronchial tree may cause signs of bronchial obstruction or hemorrhage. Persistent pleural effusions may be due to both pleural and cardiac disease. Diffuse interstitial pulmonary amyloidosis may lead to dyspnea or pulmonary hemorrhage. Diaphragmatic deposition may lead to respiratory failure. Pulmonary hypertension is a rare complication. Tracheobronchial amyloid deposition and nodular parenchymal amyloid deposition (amyloidoma) (Fig. 73-1*A*) most often occur as isolated phenomena, whereas diffuse interstitial deposition is more often seen in systemic amyloidosis. The vast majority of cases of pulmonary amyloidosis can be categorized as tracheobronchial amyloidosis, nodular parenchymal amyloidosis, and diffuse septal amyloidosis.

Nodular Parenchymal Amyloidosis

As a rule, solitary amyloid nodules *(amyloidomas)* are incidental radiographic findings in asymptomatic individuals (Fig. 73-1). When multiple, such nodules may be associated with cough, dyspnea, or hemoptysis. These nodules have no distinctive features, although occasionally, they may show radiographic evidence of calcification or cavitation. Usually the diagnosis of an amyloid nodule is made after surgical resection. Occasionally, the diagnosis has been made by transbronchial biopsy or percutaneous fine-needle aspiration. However, surgical excision of one or more nodules seems prudent, since, on rare occasion, amyloid deposition occurs within a pulmonary neoplasm (e.g., a primary neoplasm such as atypical carcinoid or a metastatic neoplasm such as medullary carcinoma from the thyroid).

Nodular parenchymal amyloidosis most often represents a localized abnormal immune response of bronchial-associated lymphoid tissue. Histologically, the amyloid deposit is often associated with an intense inflammatory reaction consisting of plasma cells, macrophages, and multinucleated giant cells. Only occasional chemical analyses are



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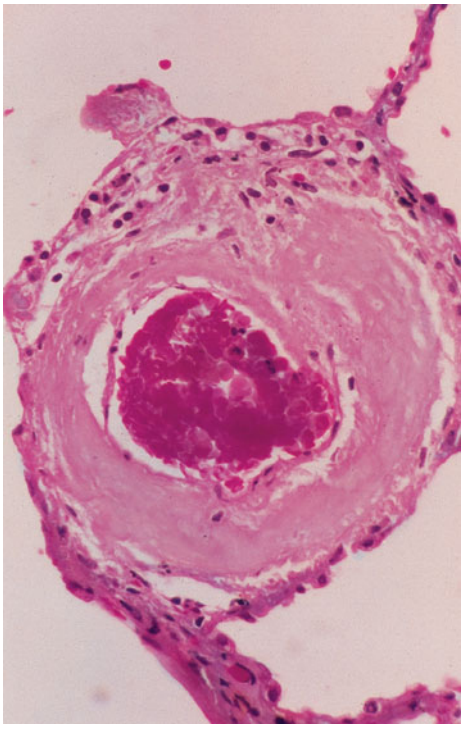

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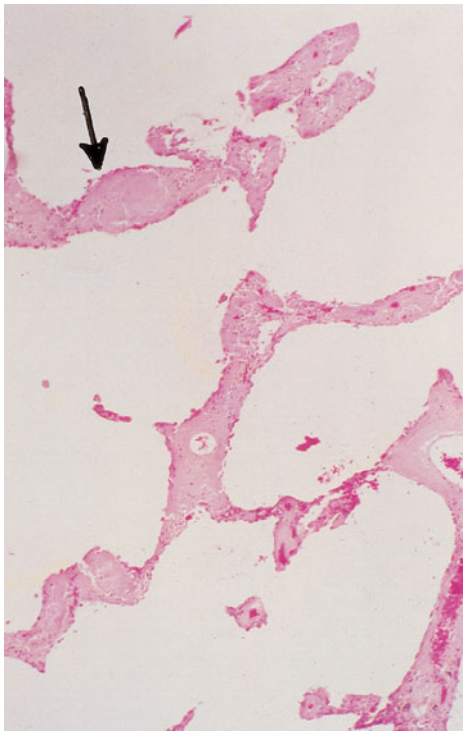

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Figure 73-1 Amyloid deposition. *A*. Amyloidoma. Cut surface of lung with white arrows indicating a dense, waxlike lesion that is characteristic of nodular amyloid. Incidental finding at autopsy. *(Courtesy of Leslie A. Litzky, M.D., Department of Pathology and Laboratory Medicine, Hospital of the University of Pennsylvania, Philadelphia.) B.* The typical amorphous appearance of amyloid is seen deposited within the wall of a pulmonary venule. Green birefringence on polarized light examination after staining with Congo red will confirm the amyloid nature of the deposit (H&E ×700). *C*. Amorphous amyloid in the alveolar interstitial space. Arrow indicates a thickened alveolar septum (H&E ×420).

available, and these have revealed that most nodular deposits are of light-chain derivation, although rare cases of amyloid-associated (AA) amyloid have been reported. Interestingly, when the accompanying plasma cells have been analyzed for clonality, they are more often polyclonal than monoclonal. In such cases, the inflammatory cells may therefore be a local reaction to the presence of amyloid, rather than the source of the amyloid precursor light chains. In a few instances, nodular amyloidosis has been associated with a low-grade pulmonary lymphoma. Clinical followup of nodular parenchymal amyloidosis unassociated with systemic or neoplastic disease is generally benign.

Tracheobronchial Amyloidosis

Amyloid deposition in the tracheobronchial tree can produce either plaques or tumoral masses. The more common presentation as plaques is diffuse, multifocal, and represents submucosal deposition of amyloid. Less commonly, deposition of amyloid in the tracheobronchial tree produces a solitary mass which mimics an endobronchial neoplasm. Tracheobronchial amyloid deposition is most often of light-chain derivation and a localized phenomenon, suggesting that this also represents a localized abnormal immune response of bronchial-associated lymphoid tissue rather than a systemic immune response. Like nodular amyloidosis, this form is virtually never associated with systemic disease.

Diffuse involvement of the airways is apt to be symptomatic, producing cough, stridor, or hemoptysis. In contrast, localized mass lesions are more likely to produce evidence of localized bronchial obstruction (i.e., atelectasis or air trapping), with or without hemoptysis. Both types of lesions can be readily identified by bronchoscopic examination. However, as is the case with amyloid deposition at all sites, with biopsy there is a risk of hemorrhage. Although localized tumoral masses may be treated by excision or observation, more diffuse involvement may be treated by laser ablation.

Diffuse Interstitial Amyloidosis

Widespread, *diffuse interstitial amyloidosis* of the pulmonary parenchyma may produce either a reticulonodular or miliary pattern on the chest radiograph. Such pulmonary involvement occurs most often in patients with systemic amyloidosis, derived from either immunoglobulin light-chain or amyloid-associated protein. Pulmonary interstitial amyloid deposition is rarely sufficiently severe to produce clinical manifestations but, uncommonly, it may produce progressive dyspnea, hemoptysis, or restrictive pulmonary function tests. The deposition of amyloid in the lungs is microscopic and may involve the alveolar septal interstitium, the walls of small blood vessels, or both (Fig. 73-1*B* and *C*). Transbronchial biopsy with Congo red staining is diagnostic, again bearing in mind the potential risk of biopsy-induced hemorrhage. It may be difficult in such cases to determine the relative contribution of pulmonary vs. concurrent cardiac amyloid deposition to the patient's symptoms.

Diagnosis of Amyloidosis

Diagnosis of amyloidosis requires tissue examination and Congo red staining and/or electron microscopy. Immunohistochemistry for amyloid precursor proteins including immunoglobulin light chains, amyloid-associated protein, and transthyretin among others can be used to classify patients, although AL disease may be technically difficult to document in this way. It has been shown that a significant number of patients with systemic amyloidosis and small light-chain clones do not necessarily have AL disease but rather have a hereditary form of amyloidosis. It has been suggested therefore that a genetic analysis be performed in any patient in whom a definitive diagnosis of AL cannot be reached. A similar analysis has not been done with patients with isolated pulmonary disease.

DIFFUSE PULMONARY CALCIFICATION

Calcification of the pulmonary parenchyma can occur by a variety of mechanisms. *Dystrophic calcification* refers to the deposition of calcium salts, most often crystalline hydroxyapatite, in dead tissue such as within the healing granulomas of tuberculosis. This type of calcification is usually localized; its distinctive radiographic features are sometimes diagnostically helpful.

Metastatic calcification refers to the deposition of calcium salts, usually amorphous, in normal tissues (Fig. 73-2). This latter type of calcification occurs in association with some derangement of calcium metabolism, such as primary hyperparathyroidism, secondary hyperparathyroidism of chronic renal failure, hypervitaminosis D, the milk alkali syndrome, sarcoidosis, or increased bone turnover due to multiple myeloma or metastatic carcinoma.

Although metastatic calcification can occur in almost any tissue of the body, it occurs most often in the lungs, kidneys, and the stomach (tissues with more alkaline pH), and the walls of blood vessels. Metastatic calcification in the lungs usually affects the interstitium of the alveolar septa and the walls of bronchioles and pulmonary vessels, sometimes localizing on elastic fibers.

Clinical manifestations of diffuse pulmonary calcification are unusual, occurring most often in patients who are in chronic renal failure, particularly in those on chronic hemodialysis.

Radiographically, metastatic calcification usually takes the form of a diffuse interstitial infiltrate, sometimes with fine nodularity. Less often, confluent patchy consolidation mimicking pneumonia may be seen. Although the calcific nature of the infiltrate is often apparent on routine chest radiograph, computed tomography (CT) scan is more sensitive both in detecting the interstitial deposits and in revealing their calcific

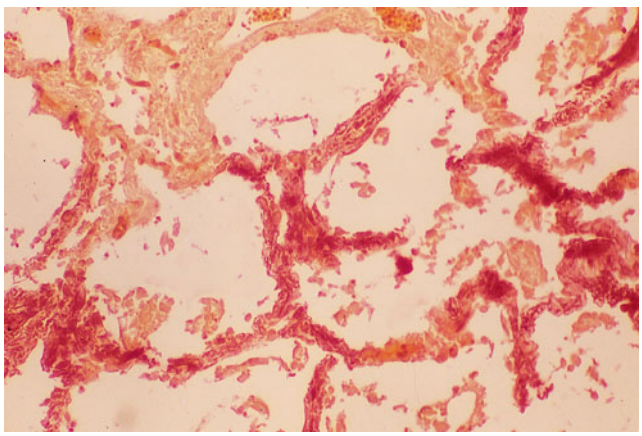


Figure 73-2 Metastatic calcification of alveolar septa in a renal dialysis patient. Photomicrograph shows calcium forming a dark red precipitate within the alveolar septa (Alizarin red ×280).

nature. Moreover, CT scan may also demonstrate calcification of chest wall blood vessels, circumstantially implicating calcification as the cause of pulmonary parenchymal abnormalities. Recognition of the calcific nature of the infiltrate is furthered by scanning with ^{99m}technetium.

Only rarely do the patients manifest dyspnea or arterial hypoxemia, and pulmonary function tests tend to not show signs of restrictive pulmonary disease. Unexplained dyspnea in a patient with chronic renal failure or hypercalcemia in the presence of a normal chest radiograph should lead to consideration of high-resolution computed tomography (HRCT) or technetium scanning.

The mechanism responsible for diffuse pulmonary calcification is unknown. Although high levels of parathyroid hormone or a marked increase in the calcium-phosphate solubility product occur in some patients, diffuse calcification can occur in the absence of either. Ultrastructural observations of minimal, presumably early, lesions show selective deposition of calcium on elastic fibers, suggesting that they may serve as the initial nidus. In contrast to their apparent role in alveolar microlithiasis, extracellular matrix vesicles do not appear to be involved.

ALVEOLAR MICROLITHIASIS

This rare disorder usually presents as an abnormal chest radiograph from an asymptomatic patient (Fig. 73-3). The chest radiograph is diagnostic, showing a sandlike micronodulation throughout the lung fields. This is caused by the presence of innumerable minute calcified spherules filling the alveolar spaces. The calcification is usually sufficiently dense as to constitute the signature of the disease on the routine radiograph. In some patients, concentration of the spherules in subpleural, paraseptal, and peribronchiolar alveoli can produce linear strands of calcification parallel to or perpendicular to the pleural surface, readily apparent on HRCT. The spherules also bind ^{99m}Tc, which can be a diagnostic adjunct. Although not usually required, bronchoalveolar lavage or biopsy can confirm the diagnosis. Biopsy shows calcified spherules filling alveolar spaces (Fig. 73-3). The spherules have a concentric lamellated appearance, suggesting that they grow by the addition of successive layers; the spherules contain both calcium and phosphorus. Although the microliths are intra-alveolar, one ultrastructural study has suggested that their formation is initiated in the pulmonary interstitium by the deposition in a collagenous matrix of hydroxyapatite crystals produced by extracellular matrix vesicles. These membrane-bound vesicles are derived from mesenchymal cells and can concentrate calcium ions and liberate phosphate from membrane phospholipids.

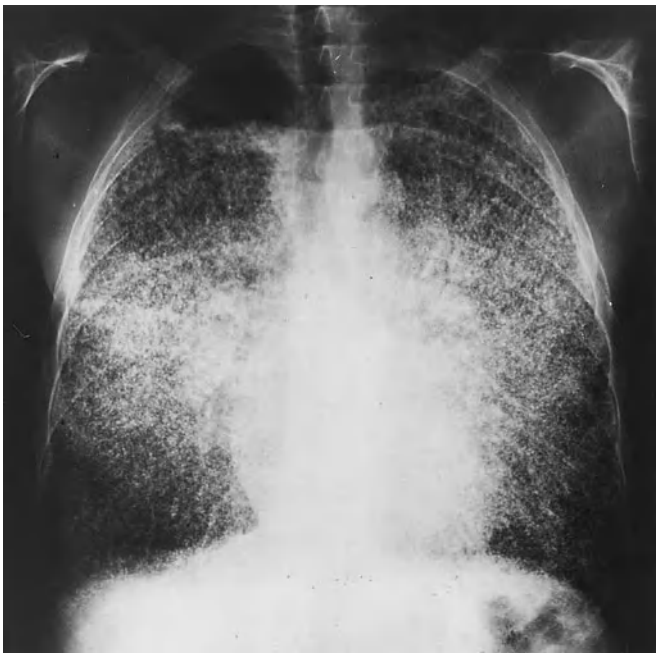
Although usually asymptomatic at the time of presentation, alveolar microlithiasis, on rare occasion, can produce functional abnormalities. When it does, the findings are those of restrictive pulmonary disease or exercise-induced pulmonary hypertension. In general, no therapy, including bronchoalveolar lavage, has proved effective, although one case report indicates improved oxygenation using nasal continuous positive airway pressure ventilation. Lung transplantation has also been performed in a few patients. The etiology of alveolar microlithiasis is unknown, but some cases appear to be familial.

ALVEOLAR HEMORRHAGE SYNDROMES

Pulmonary hemorrhage most commonly arises from endobronchial diseases (tumors, bronchiectasis, bronchitis). However, there is a subset of patients in whom bleeding originates at the level of the alveoli and who are referred to as having diffuse alveolar hemorrhage (DAH). Symptoms range from cough, fever, and dyspnea alone to respiratory failure. While hemoptysis is common, it is not universal, even when DAH is severe. In these cases, the diagnosis can be suspected due to a falling hemoglobin level. Evaluation of serial bronchoalveolar lavage aliquots in such patients may show a progressive increase in bloody return, as opposed to endobronchial disease, in which bleeding tends to clear. Bronchoalveolar lavage is also useful to exclude infection in patients with DAH.

The damage to alveolar septa may either be due to immunologic mechanisms (immune complex, antineutrophil cytoplasmic antibody [ANCA], antiglomerular basement membrane, antiphospholipid antibodies) or to nonimmunologic causes. This distinction is largely, although not perfectly, captured in the presence or absence of the pathological finding of capillaritis (Fig. 73-4 and Table 73-2). Capillaritis is characterized by infiltration of alveolar walls by inflammatory cells, usually neutrophils, but sometimes eosinophils or monocytes, with fibrinoid necrosis of the alveolar and vessel wall. However, due to the absence of supporting structures, alveolar necrosis leads to wall breakdown so rapidly that this latter feature may be hard to appreciate. In order to distinguish this process from simple margination of neutrophils, there should be evidence for neutrophils undergoing apoptosis (pyknosis and nuclear fragments). Distinction from infection requires determination that there is minimal accumulation of inflammatory cells within alveoli. The pathological diagnosis of pulmonary hemorrhage itself requires that there is either hemosiderin-laden macrophages or evidence of hemophagocytosis, since the blood that is commonly seen in lung biopsies may be due to surgery alone. If this evidence is absent, clinical criteria for DAH should be used.

Nonimmunologic mechanisms are quite diverse and include diffuse alveolar damage, inhalation of toxins, coagulopathy, and mitral valve disease, among others listed (Table 73-2). While the presence or absence of capillaritis is a useful way to think about these diseases, the decision about whether to actually perform a biopsy in these cases is challenging as interpretation of these biopsies is difficult, there is potential sampling error, and there is a significant risk of surgery to these patients. These problems limit this procedure's utility while alternative diagnostic schemes usually allow diagnosis in absence of biopsy.



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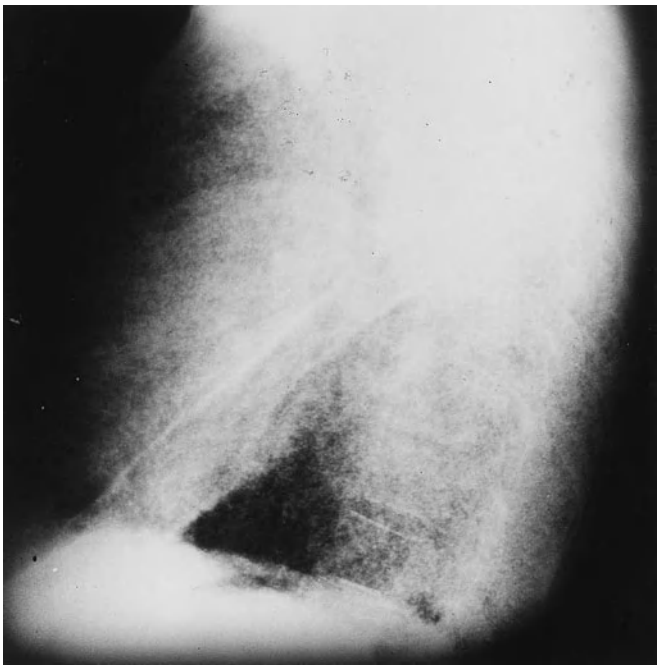

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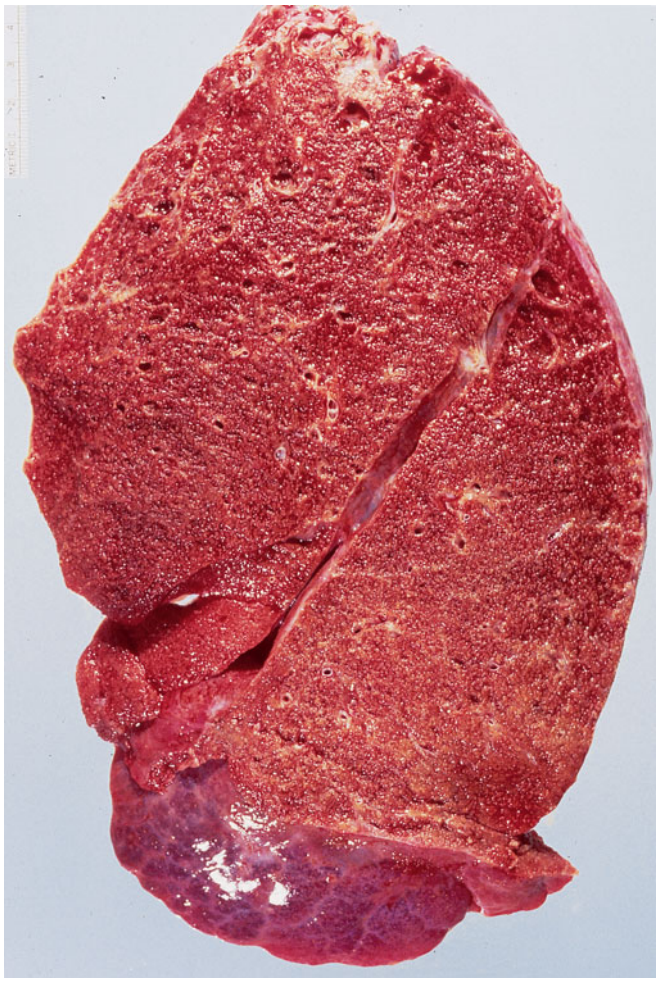

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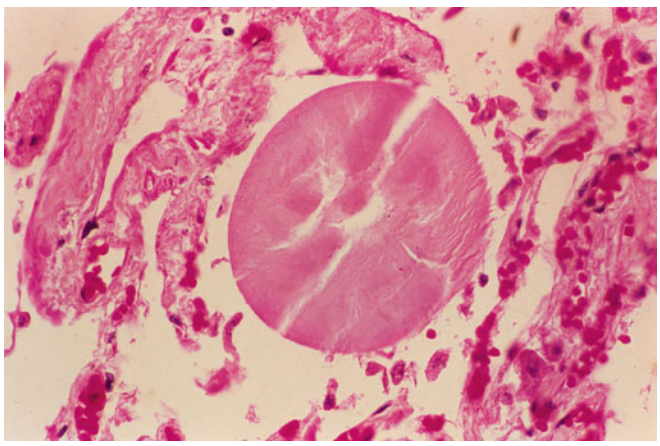

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Figure 73-3 Alveolar microlithiasis in a 46-year-old man admitted for nonpulmonary problems. History included slight dyspnea on exertion and previous episodes of "pneumonia" during 1947, 1950, and 1952. Clinical examination revealed severe restrictive lung disease, pulmonary hypertension, and cor pulmonale. Diagnosis confirmed by lung biopsy. *A* and *B*. Posterior-anterior and lateral chest radiographs demonstrate innumerable, tiny calcified nodules throughout both lung fields. Thin, lucent lines on each side represent normal pleura visualized between the calcified pulmonary parenchyma and the chest wall. Emphysematous blebs in the apices displace the calcifications. *C*. Cut surface of explanted lung from a patient undergoing lung transplantation for primary alveolar microlithiasis. Note the fine nodularity which correlated with the chest radiographs. *(Courtesy of Leslie A. Litzky, M.D., Department of Pathology and Laboratory Medicine, Hospital of the University of Pennsylvania, Philadelphia.) D*. Photomicrograph demonstrating a typical calcospherite in an alveolar space (H&E ×1120).

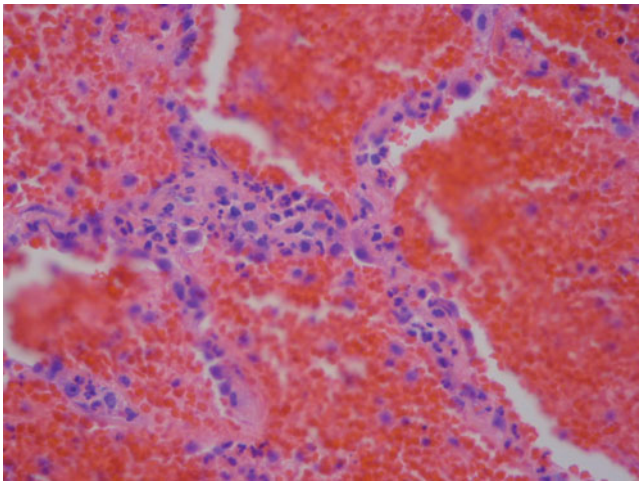


Figure 73-4 Capillaritis as a cause of pulmonary hemorrhage. Note the neutrophils in the alveolar septum (in center of image) and the blood and fibrin in the alveolar spaces (H&E ×100).

Goodpasture's Syndrome

This entity was originally described as an association of alveolar hemorrhage with glomerulonephritis. It was later determined that pulmonary and renal damage in many such patients was mediated by antibodies that are specifically directed against a component of glomerular and other capillary basement membranes, most often the α_3-chain of type IV (basement membrane) collagen. The anti-basement membrane antibodies cause pulmonary hemorrhage only in genetically predisposed individuals, after some injury such as cigarette smoke, viral respiratory infection, or hydrocarbon vapor inhalation exposes alveolar capillary basement membranes to the immune system. Although there are other causes of concomitant alveolar hemorrhage and glomerulonephritis, Goodpasture's syndrome is generally reserved for disease mediated by antiglomerular basement membrane antibodies (anti-GBM antibodies).

Goodpasture's syndrome can present with a broad spectrum of clinical findings. The "classic" patient presents with massive hemoptysis, dyspnea, diffuse alveolar infiltrates on chest radiograph (Fig. 73-5), and overt glomerulonephritis, often with acute renal failure. However, some patients present with only hemoptysis and subsequently develop overt renal disease months or even years later. On occasion, patients present with acute glomerulonephritis due to anti-GBM antibodies and either develop pulmonary hemorrhage subsequently or never develop pulmonary hemorrhage. Without pulmonary hemorrhage, the entity should not be called "Goodpasture's syndrome."

The histological findings on lung biopsy in Goodpasture's syndrome are not diagnostic. Routine light-microscopy reveals intra-alveolar hemorrhage, usually associated with intra-alveolar hemosiderin-laden macrophages (Fig. 73-5). There may be no evidence of vasculitis, capillaritis, interstitial or intra-alveolar inflammation, or necrosis. In some cases, subtle capillaritis may be present. In either case, nonspecific reparative proliferation of the alveolar-lining cells may be present.

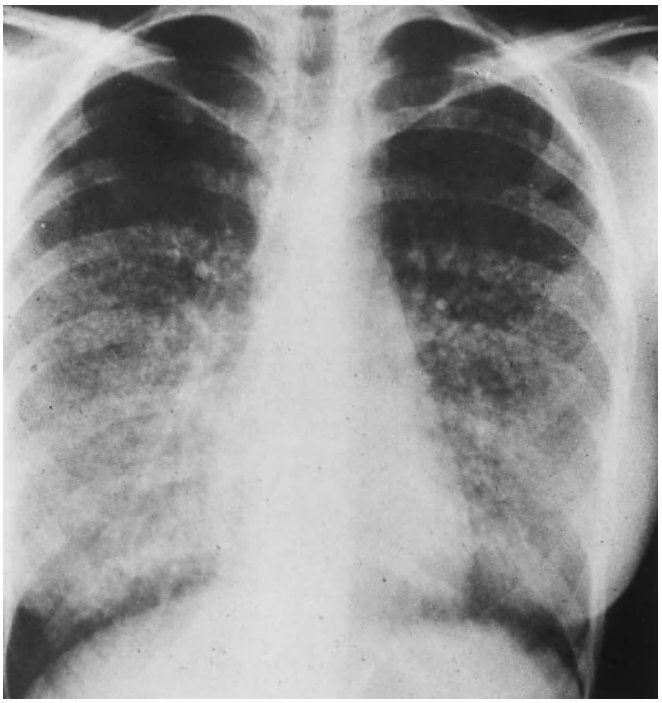
Table 73-2

Causes of Diffuse Alveolar Hemorrhage

Diffuse Alveolar Hemorrhage without Pulmonary Capillaritis
Inhalational toxins (trimetallic anhydride, crack cocaine)
Mitral stenosis
Severe coagulopathy (iatrogenic, renal failure, thrombocytopenia)
Nonspecific inflammation (diffuse alveolar damage, pulmonary gangrene, endocarditis)
Neoplasm/hamartomatous (angiosarcoma, lymphangioleiomyomatosis, tuberous sclerosis)
Pulmonary vascular disease (pulmonary venoocclusive disease, capillary hemangiomatosis)
Idiopathic pulmonary hemosiderosis
Diffuse Alveolar Hemorrhage with Pulmonary Capillaritis
ANCA-associated vasculitis (Wegener's granulomatosis, microscopic polyangitiitis, Churg-Strauss syndrome)
Immune complex–associated and collagen vascular disease (Behçet's disease, Henoch-Schönlein purpura, systemic lupus erythematosus, rheumatoid arthritis, mixed connective-tissue disease, polymyositis)
Isolated pauci-immune pulmonary capillaritis
Diffuse Alveolar Hemorrhage with or without Capillaritis
Goodpasture's syndrome
Systemic lupus erythematosus
Primary or secondary antiphospholipid syndrome
Drug-induced pulmonary hemorrhage

While the diagnosis of Goodpasture's syndrome can be made by detecting anti-GBM antibody in the patient's serum, the sensitivity and specificity of various methods to detect these antibodies varies considerably. The gold standard remains the detection of the linear pattern of immunofluorescence on a lung or kidney biopsy. However, only occasionally will immunofluorescence microscopy show diagnostic linear deposits of immunoglobulin and/or complement along alveolar capillary walls (Fig. 73-5 *D*). In contrast, kidney biopsy in Goodpasture's syndrome is usually diagnostic. Conventional light microscopy shows nonspecific focal or diffuse glomerulonephritis which may be crescentic and necrotizing.

When pulmonary hemorrhage due to Goodpasture's syndrome is life-threatening, plasmapheresis for rapid lowering of circulating levels of anti-GBM antibody and administration of intravenous corticosteroids and cyclophosphamide to suppress antibody synthesis can be life-saving. If the patient is not in advanced renal failure at the time of



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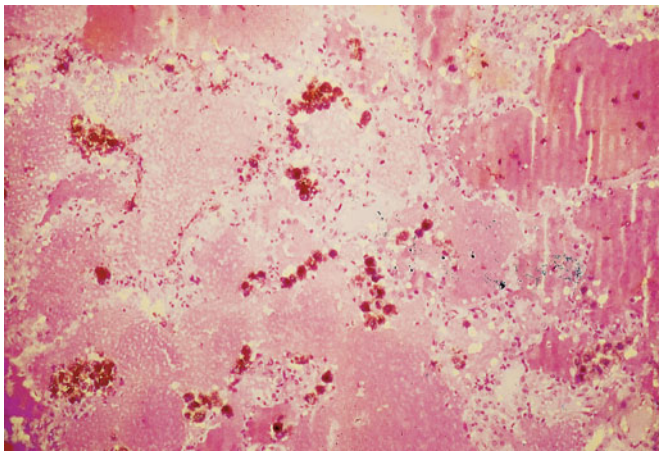

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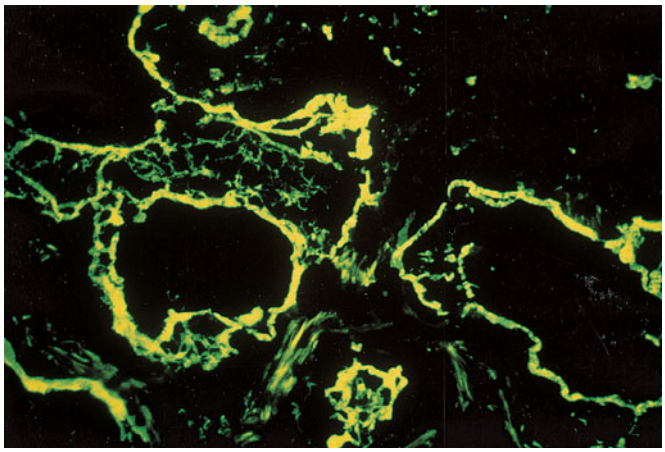

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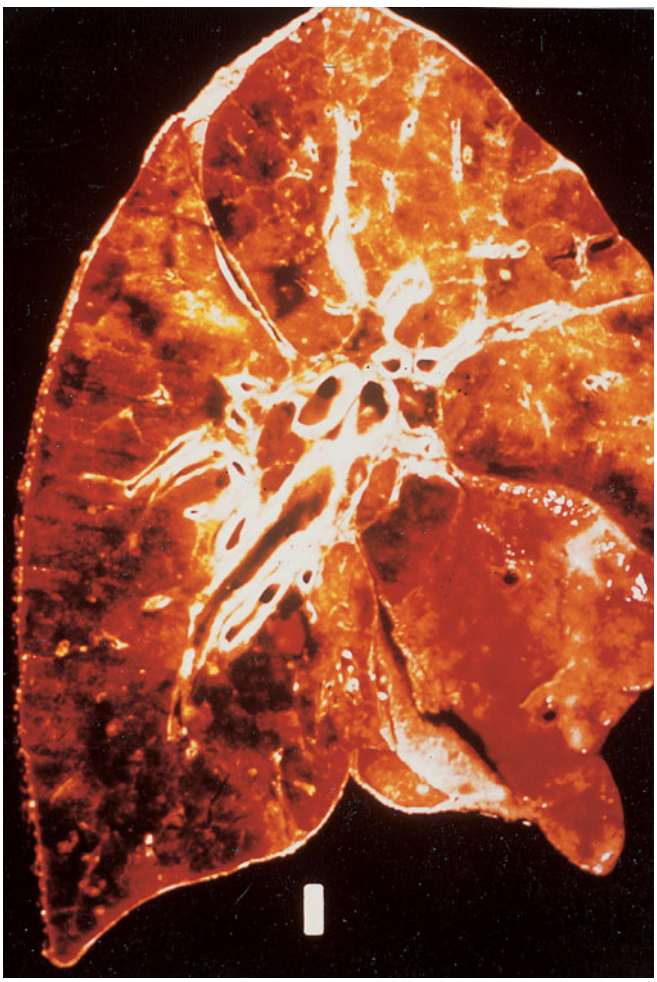

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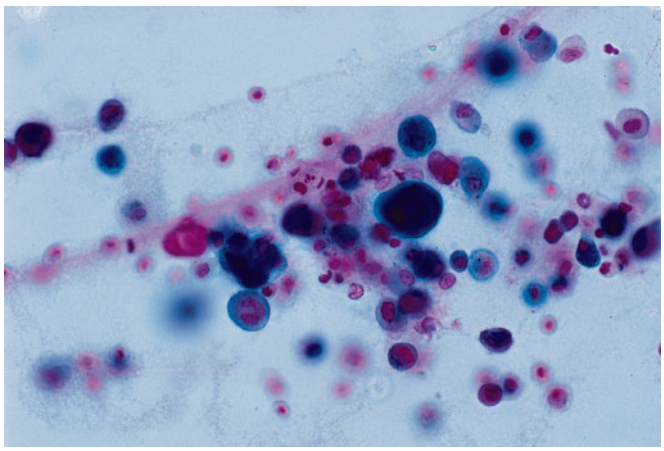

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Figure 73-5 Goodpasture's syndrome. *A*. Chest radiograph showing bilateral alveolar infiltrates, predominantly in the middle and lower lung fields. *B*. Autopsy specimen showing cut surface of lung with massive alveolar hemorrhage. *(Courtesy of Dr. Richard Garnett, Reid Memorial Hospital, Richmond, IN.) C*. Photomicrograph of intact alveoli, containing both red blood cells and hemosiderin-laden macrophages (H&E ×45). *D*. Immunofluorescent demonstration of immunoglobulin lining alveolar surfaces in a uniform distribution (fluoresceinated anti-IgG ×113). *E*. Smear of bronchoalveolar lavage demonstrating hemosiderin-laden macrophages (Prussian blue stain; original magnification ×132). *(Courtesy of Dr. David Lyon, Iankenau Hospital, Wynnewood, PA.)*

diagnosis, chronic immunosuppression with a combination of corticosteroids and cyclophosphamide can prevent progressive renal damage. If irreversible renal failure has already occurred, the patient can eventually be successfully transplanted once anti-GMB antibodies have disappeared from the serum. Elimination of the antibodies usually can be achieved by immunosuppression alone; in some instances, pre-transplant nephrectomy may be required.

ANCA-Associated Pulmonary Vasculitis

The ANCA-associated vasculitides, Wegener's granulomatosis (WG) and microscopic polyangiitis (MPA), represent the most common cause of immunologically mediated DAH. These have been associated with the development of autoantibodies directed against cytoplasmic components of neutrophils (and monocytes), the antineutrophil cytoplasmic antibodies (ANCAs). Detection of ANCAs entails the use of indirect immunofluorescence and heterologous antibodies against human immunoglobulin to detect autoantibodies bound to neutrophils of affected patients. Ethanol fixation of the neutrophils prior to antibody staining produces one of two patterns when autoantibodies are present: (1) a finely granular centrally accentuated cytoplasmic localization (c-ANCA) or (2) a perinuclear localization (p-ANCA). The usual targets of these antibodies have been identified as proteinase 3 for c-ANCA and myeloperoxidase for p-ANCA. Both antigens are found in the primary azurophilic granules of neutrophils. When ethanol is used as the fixative, the cellular granules are disrupted; the positively charged myeloperoxidase molecules then migrate toward the negatively charged nucleus to produce the perinuclear pattern, and the neutral proteinase 3 molecules remain dispersed in the cytoplasm to produce the cytoplasmic pattern. To maximize diagnostic accuracy, dual testing by fluorescence and an antigen-specific solid phase assay is required. Otherwise, a high degree of clinicopathological correlation is required for correct interpretation of these tests. Some patients with ANCA-associated alveolar hemorrhage also have anti-basement-membrane antibodies in the serum. These antibodies are directed against basement antigens other than those seen in Goodpasture's syndrome and are thought to be a secondary phenomenon, rather than of pathogenic significance.

Overt DAH occurs in approximately 15 percent of patients with WG or MPA. Depending on the specific syndrome present, alveolar hemorrhage may be isolated, associated with glomerulonephritis, or associated with widespread systemic vasculitis. In patients with ANCA-associated vasculitis, the occurrence of DAH is a poor prognostic indicator, although among survivors, complete recovery of lung function is common. Therapy does not depend on diagnosis of MPA vs. WG, and is based on immunosuppression with steroids and cyclophosphamide possibly augmented with plasmapheresis. Nevertheless, patients with WG/c-ANCA/proteinase 3 have worse outcomes with higher mortality and recurrence rate. While Churg-Strauss syndrome (CSS) is classified among the ANCA-associated vasculitides, DAH due to CSS is extraordinarily rare.

Rarely, patients have presented with isolated pulmonary capillaritis with no serologic or clinical evidence for a systemic disorder. These patients responded to immunosuppression but relapses did occur.

Antiphospholipid Antibody-Associated Alveolar Hemorrhage

Patients with serum antibodies directed against membrane phospholipid (antiphospholipid syndrome or APS) display hypercoagulability. Clinically, this manifests as peripheral arterial and venous thrombosis, fetal wastage in pregnant women, and thrombocytopenia. Pulmonary involvement can include pulmonary thromboembolism, pulmonary hypertension, diffuse alveolar damage, or rarely DAH. The latter produces fever, dyspnea, and diffuse pulmonary infiltrates on chest radiograph. Alveolar hemorrhage in APS has been associated with alveolar capillaritis with or without immune complex deposition and with microvascular thrombosis in the lungs. The combination of both thrombosis and hemorrhage greatly complicates therapy.

Antiphospholipid antibodies were first detected in patients with systemic lupus erythematosus (SLE) and were formerly known as the lupus anticoagulant because they prolong some laboratory test of clotting. APS can occur in the absence of SLE. How often these antibodies play a role in pulmonary hemorrhage due to SLE is unknown, as there are other possible mechanisms in that syndrome (see below). In patients with isolated APS and alveolar hemorrhage, corticosteroid treatment, sometimes supplemented by cyclophosphamide, can result in a favorable outcome.

Collagen Vascular Disease and Immune Complex—Associated Pulmonary Hemorrhage

DAH also occurs as a rare complication of certain connective-tissue disease syndromes, most often SLE but also rheumatoid arthritis, progressive systemic sclerosis, and mixed connective-tissue disease. Particularly in SLE, other causes of alveolar hemorrhage must be considered, including infection, uremia, and coagulopathy. When such causes have been eliminated, alveolar hemorrhage is sometimes found to be associated with capillaritis, with interstitial pneumonitis, or with immunofluorescent or ultrastructural evidence of immune complex deposition in alveolar septa. However, none of these disorders is consistently associated with pulmonary hemorrhage in SLE. Early diagnosis and treatment with corticosteroids and cytotoxic drugs is associated with favorable outcome, although relapse is not uncommon.

Drug-Induced Pulmonary Hemorrhage

There is a long list of drugs, both therapeutic and drugs of abuse, associated with vasculitis. The clinical spectrum ranges from isolated mild skin disease to severe multi-organ systemic disease, usually due to a small vessel vasculitis. Some of these drugs can induce an ANCA-associated vasculitis. DAH

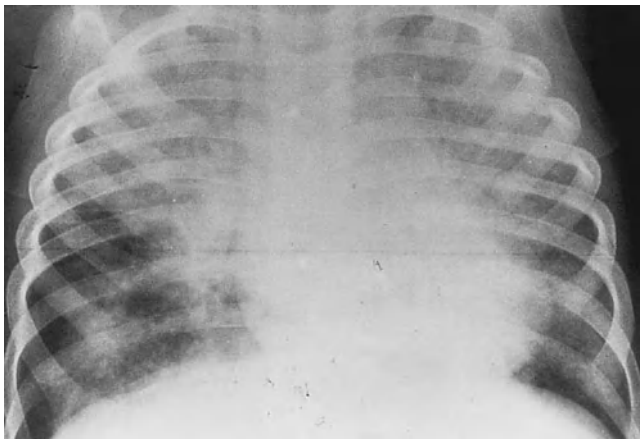
due to ANCA-associated pulmonary capillaritis is well documented for propylthiouracil, D-penicillamine, allopurinol, diphenylhydantoin, and minocycline. Drug-induced ANCA-associated vasculitis should be treated with cessation of all potential causative agents as well as immunosuppression. Once the offending drug has been eliminated, the possibility of relapse seems low.

Nonimmunologic Causes of Diffuse Alveolar Hemorrhage

There is a wide range of conditions that is associated with DAH with no capillaritis seen on biopsy and which are due to a wide variety of specific conditions, including toxins, neoplasms, nonspecific inflammation, infection, toxins, coagulopathy, and pulmonary vascular disease. When all the above diseases and syndromes have been excluded as likely possibilities, there still remains a small group of patients who develop recurrent DAH in the absence of extrapulmonary disease and with no evidence of an immune etiology. These patients are considered to have idiopathic pulmonary hemosiderosis, a diagnosis of exclusion (Fig. 73-6). Clinically, the patients form a heterogeneous group with respect to the onset and course of disease, which range from fulminant and fatal, to chronic relapse with eventual chronic pulmonary insufficiency due to interstitial fibrosis, to spontaneous remission with little or no residual deficit. The disease usually affects children and young adults. Pathological examination reveals nonspecific alveolar hemorrhage without evidence of inflammation, vasculitis, or immune complex deposition. Only a few observations on ultrastructure are available. These include focal disruption, smudging, or lamination of alveolar capillary basement membranes.

The pathogenesis of this condition remains unknown, and there are no associated antibodies or other serum markers in the idiopathic cases. However, the clinical and morphologic similarities to some cases of alveolar hemorrhage of known immune pathogenesis, the occasional responsiveness to immunosuppressive therapy, the occasional association with celiac sprue—a presumably immunologic disease of the small intestine—and frequent association with a nonspecific elevation of serum IgA all point to an as yet unelucidated immune pathogenesis. Rarely, children with hypersensitivity to cow's milk (Heiner's syndrome) can present with DAH.

If the diagnosis proves to be idiopathic pulmonary hemosiderosis, high-dose corticosteroid therapy with or without cyclophosphamide and plasmapheresis is useful in controlling acute bleeding, but the long-term effectiveness of these measures in preventing recurrence or progression of this disease is unknown.



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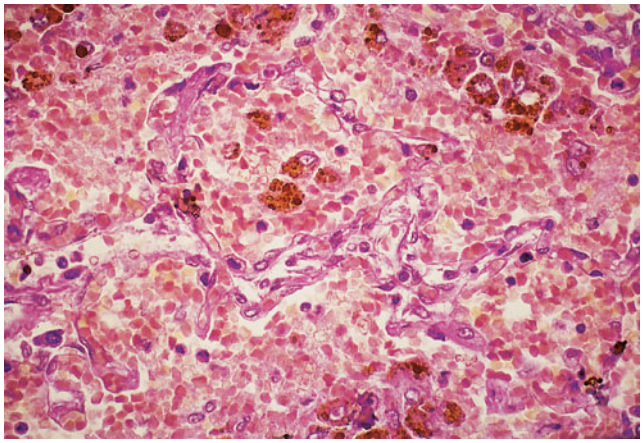

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Figure 73-6 Idiopathic pulmonary hemosiderosis in a 21-month-old child with anemia soon after birth. Iron stain of the sputum showed hemosiderin-laden macrophages. *A*. Chest radiograph showing extensive, bilateral, almost punctate densities throughout both lung fields, most prominent in the perihilar regions where an alveolar filling pattern appears. *B*. Photomicrograph of lung at autopsy, showing intact alveoli containing degenerating red blood cells and hemosiderin-laden macrophages. Immunofluorescence studies for immunoglobulin and complement deposition were negative (H&E ×131). *(Courtesy of Department of Pathology, St. Christopher's Hospital for Children, Philadelphia.)*

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74

Pulmonary Langerhans'-Cell Histiocytosis

Talmadge E. King, Jr.

Pulmonary Langerhans'-cell histiocytosis is also called pulmonary Langerhans'-cell histiocytosis, eosinophilic granuloma of the lung, and pulmonary Langerhans'-cell granulomatosis. Like Letterer-Siwe disease and Hand-Schüller-Christian disease, it is characterized by abnormal organ infiltration by Langerhans' cells. Langerhans' cells are highly differentiated cells in the monocyte-macrophage line that are also found in the dermis of the skin, the reticuloendothelial system, the pleura, and the lung. These related disorders have been grouped under the classification of histiocytosis X. However, the three disorders are clinically distinct.

Letterer-Siwe disease is an acute, often fulminant disease of children less than 2 years of age that is characterized by widespread infiltration of the reticuloendothelial system, bones, and lungs. Hand-Schüller-Christian disease is a more indolent disorder of children and young adults that also typically affects the bones and the lungs. Diabetes insipidus, exophthalmos, and osteolytic skull lesions form the classic clinical triad associated with this disorder. There is some overlap in the clinical manifestations of these diseases; some children present with isolated pulmonary manifestations, and some adults demonstrate more malignant-appearing, disseminated disease.

Pulmonary Langerhans'-cell histiocytosis is an uncommon, smoking-related, interstitial lung disease that primarily affects young adults. Less frequently, solitary osteolytic bone lesions are also seen. Rarely, multifocal or widely disseminated disease more closely approximating the pediatric histiocytoses is described. Advanced disease may mimic idiopathic pulmonary fibrosis but generally follows a more benign and protracted course. Although there is some similarity to other diffuse interstitial lung diseases, pulmonary Langerhans'-cell histiocytosis, as a specific disease entity, is distinct in its clinical, radiologic, and pathological manifestations.

EPIDEMIOLOGY

The true incidence and prevalence of pulmonary Langerhans'-cell histiocytosis are unknown. Pulmonary Langerhans'-cell histiocytosis is clearly an uncommon, if not rare, disease. No occupational or geographical predisposition has been reported. Among 28 patients seen by our group, we found higher than expected connections to farming (21 percent), woodworking (25 percent), and domestic exposure to animals (77 percent). Of note, nearly all affected persons report a prior smoking history. Thus, tobacco smoke is thought to be an etiologic factor. Other diffuse parenchymal lung diseases associated with cigarette smoking are respiratory bronchiolitis-associated interstitial lung disease and desquamative interstitial pneumonitis.

Most patients present to medical attention in young adulthood (20 to 40 years of age). Pulmonary Langerhans'-cell histiocytosis can, however, present in any age group. The older literature suggested a male preponderance; however, the recent literature suggests an equal sex distribution, with increasing presentations in middle age. In general, women tend to present at an older age than do men. If the demographics of pulmonary Langerhans'-cell histiocytosis have truly changed, as the literature would suggest, this may reflect the changing smoking habits of women in our society. Racial factors may also be important in the pathogenesis of the disease. Whites are affected much more commonly than are blacks or Asians, in whom this disease is very rare.

Pulmonary Langerhans'-cell histiocytosis has reportedly been associated with a number of malignancies and may be a premalignant condition. Lymphoma, both Hodgkin's and non-Hodgkin's, has been reported in association with pulmonary Langerhans'-cell histiocytosis. However, the evidence regarding this association is inconclusive. The carcinogenic effects of cigarette smoke are probably etiologic for some of these tumors; thus, the relative effects of tobacco in pulmonary Langerhans'-cell histiocytosis are difficult to discern.

NATURAL HISTORY AND CLINICAL PRESENTATION

Patients with pulmonary Langerhans'-cell histiocytosis come to medical attention in a variety of ways: as an incidental diagnosis that is suggested by a screening chest radiograph, after pneumothorax, or with respiratory or constitutional symptoms. Symptomatic patients most often have a nonproductive cough (56 to 70 percent) and, in decreasing order of frequency, dyspnea (40 percent; 87 percent of our patients had breathlessness with exertion on close questioning), chest pain (10 to 21 percent), fatigue (~30 percent), weight loss (20 to 30 percent), and fever (15 percent). In our clinic, a history of rhinitis has been elicited in 50 percent of the patients with pulmonary Langerhans'-cell histiocytosis.

Pleuritic pain and acute dyspnea with a spontaneous pneumothorax can be a recurrent problem in as many as 25 percent of patients. Pleural thickening or effusion is rarely seen in the absence of a history of pneumothorax. Hemoptysis (13 percent) is occasionally reported, and it should prompt consideration of superimposed infection (e.g., *Aspergillus*) or tumor.

Cystic bone lesions are present in 4 to 20 percent of patients with pulmonary Langerhans'-cell histiocytosis and may produce localized pain or a pathological bone fracture. The precise number of patients with bone lesions is not known because complete bone surveys are not routinely performed. Skeletal involvement may be either the sole symptomatic manifestation of pulmonary Langerhans'-cell histiocytosis or may precede the more typical pulmonary manifestations. The radiographic pattern is not diagnostic. In most instances, the lesions are solitary and affect the flat bones.

Central nervous system involvement with diabetes insipidus (approximately 15 percent of patients) is also seen with pulmonary Langerhans'-cell histiocytosis and is believed to portend a poor prognosis.

The physical examination is usually unremarkable. On chest examination, crackles are uncommon. Digital clubbing is also uncommon. Secondary pulmonary hypertension can occur and is probably under recognized. Manifestations of cor pulmonale are seen in advanced stages. Routine laboratory studies are usually unrevealing; the peripheral eosinophil count is normal.

RADIOLOGY

Chest Radiograph

The radiographic appearance of pulmonary Langerhans'-cell histiocytosis can be very characteristic if not diagnostic. The combination of ill-defined or stellate nodules (2 to 10 mm in size), reticular opacities, upper-zone cysts or honeycombing, preservation of lung volume, and costophrenic angle sparing are believed to be highly specific for this disorder. Typically, in keeping with the pathology, the reticular or nodular opacities are seen in the middle to upper zone (Fig. 74-1). The total lung volume is most often normal, although both hyperinflation and reduced volume have been described. In addition to pulmonary Langerhans'-cell histiocytosis, other interstitial diseases that may present with an increased lung volume are

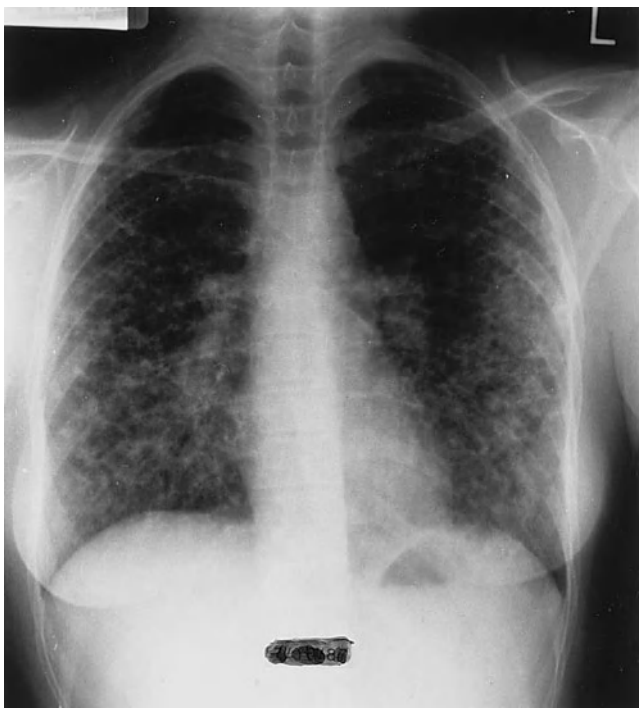


Figure 74-1 Pulmonary Langerhans'-cell histiocytosis in a 22-year-old woman. Chest radiograph demonstrates the classic features of profuse ill-defined nodules, reticulonodular opacities, cysts, costophrenic angle sparing, and preservation of lung volumes.

lymphangioleiomyomatosis, tuberous sclerosis, chronic hypersensitivity pneumonitis, stage III sarcoidosis, constrictive bronchiolitis, and any interstitial lung disease in an individual with emphysema.

Small cysts and nodules are the radiographic hallmark of pulmonary Langerhans'-cell histiocytosis (Fig. 74-2); occasionally miliary disease is seen. Hilar or mediastinal adenopathy in pulmonary Langerhans'-cell histiocytosis is rare and should prompt consideration of malignancy as a secondary diagnosis. Pleural thickening is most often due to treated pneumothorax, since pleural involvement by the primary disease process is uncommon. Bone lesions can occur in any bone, including the ribs. On rare occasions, patients come to medical attention with a solitary pulmonary nodule that, on biopsy, proves to be pulmonary Langerhans'-cell histiocytosis.

Computed Tomography

The combination of multiple cysts and nodules with a middle- to upper-zone predominance with interstitial thickening in a young smoker is so characteristic as to be diagnostic of pulmonary Langerhans'-cell histiocytosis (Fig. 74-2*B*). The nodules can be well or poorly defined. Occasionally they can be large and bizarrely shaped (Fig. 74-2*C*). Honeycombing can be seen in advanced disease.

Serial chest computed tomography (CT) scanning often suggests a sequence of progression from nodular to cavitating to cystic lesions over time. The degree of cyst formation is often underappreciated with routine chest radiography. Thus, this progression may explain a number of "spontaneous remissions" in the literature reported before the routine use of thin-section CT scanning.

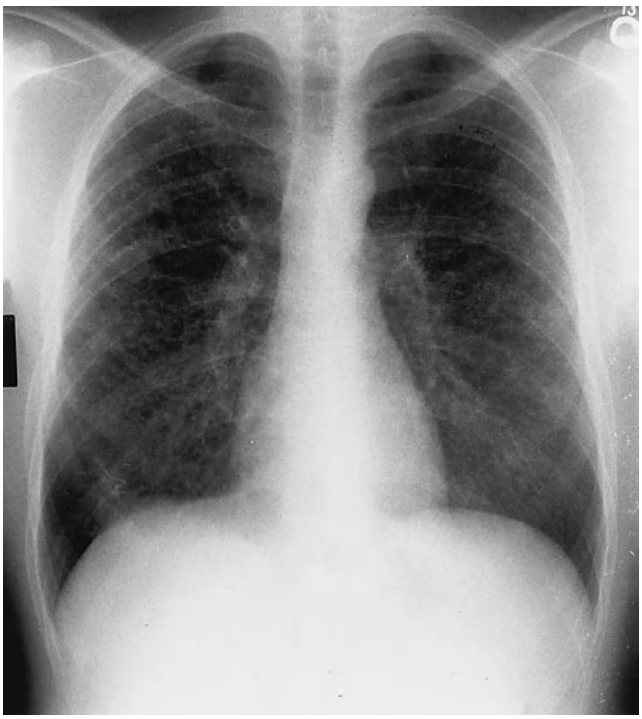
Magnetic Resonance Imaging

The role of magnetic resonance imaging in pulmonary Langerhans'-cell histiocytosis is limited to the evaluation of bony and central nervous system lesions.

PHYSIOLOGICAL TESTING

Pulmonary Function

Pulmonary function testing of subjects with pulmonary Langerhans'-cell histiocytosis can potentially demonstrate all



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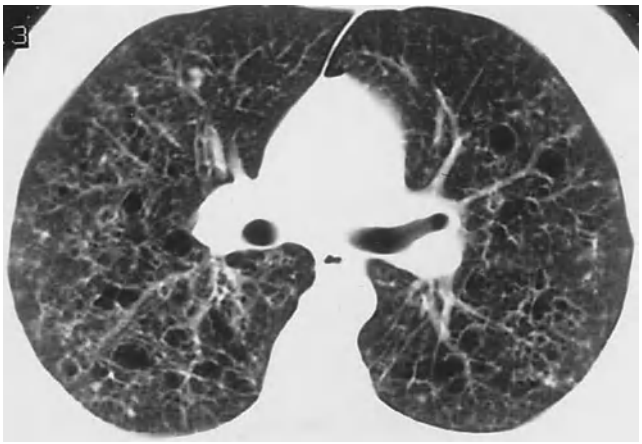

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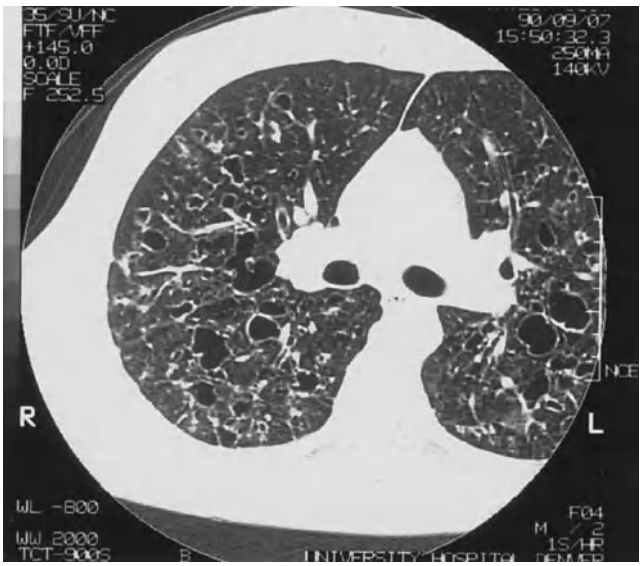

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Figure 74-2 Pulmonary Langerhans'-cell histiocytosis in a 33-year-old man. *A*. Chest radiograph reveals reticulonodular opacities in midlung zones, cysts, costophrenic angle sparing, and preservation of lung volumes. *B*. Conventional CT scan helps confirm the presence of bilateral reticulonodular opacities and cysts. *C*. High-resolution CT with thin section shows more clearly that the reticulonodular or emphysematous changes on chest radiography are actually cysts. In this instance, few nodules are present. The cysts vary markedly in size and may be larger than 10 mm. The cysts are bizarre in shape, and many are closely related to pulmonary arteries, often mimicking bronchiectasis.

possible patterns of function abnormality—normal, obstructive, restrictive, or mixed. In general, total lung capacity is well preserved, with nearly normal airflow. Most often, the diffusing capacity is disproportionately reduced. This pattern of pulmonary function abnormality suggests pulmonary vascular involvement by the disease process. Airflow limitation occurs in a minority of patients and is sometimes associated with reactive airways; significant improvement occurs after administration of a bronchodilator. When present, reactive airways disease may reflect coexisting chronic obstructive pulmonary disease (COPD). Classical manifestations of asthma are unusual in pulmonary Langerhans'-cell histiocytosis.

We recently reviewed our experience at the San Francisco General Hospital in 23 patients with pulmonary Langerhans'-cell histiocytosis we found two major subgroups. The first demonstrated a normal total lung capacity, with normal or near-normal airflow. In this group, testing of pulmonary mechanics revealed normal elastic recoil. The second group demonstrated predominantly restrictive disease, with reduced total lung volume and increased elastic recoil. In both groups, the diffusing capacity was markedly reduced. The patients in the restrictive group tended to have longer-standing disease. Only one subject demonstrated predominantly obstructive pulmonary dysfunction even though obstructive pathophysiology, with airflow limitation and hyperinflation, is well described in the literature.

The mean alveolar-arterial difference in P_{O_2} (AaP_{O_2}) was normal at rest in both subgroups but a subset of five subjects with more severe disease did have a markedly elevated AaP_{O_2} difference and required supplemental oxygen. The resting pH and Pa_{CO_2} were most often normal. Thus, the resting arterial blood gas was a very insensitive indicator of disease.

Exercise Physiology

Clinically, we have observed that patients with established pulmonary Langerhans'-cell histiocytosis generally demonstrate limitation in physical activity and intolerance for exercise that is out of proportion to their pulmonary function abnormalities. In our cross-sectional study of 23 subjects with pulmonary Langerhans'-cell histiocytosis, we found a marked decrease in exercise capacity as measured by either work achieved (54 ± 4 mean ± SEM percent of predicted) or oxygen utilization (V_{O_2}, 44 percent ± 3) at maximal exercise. The oxygen pulse at maximal exercise was reduced to 56 ± 3 percent. The anaerobic threshold was decreased to 33 percent ± percent of expected $V_{O_{2max}}$; specifically, it was less than or equal to 40 percent in all subjects in whom it was measured. The maximal ventilatory response ($V_{E_{max}}$, 83 ± 5 percent) was excessive for the maximal level of work. The maximal ventilatory response was not limiting, and the V_e was well below predicted ventilatory ceilings. Gas exchange abnormalities were reflected in increasing $AaPo_2$ differences as the level of exercise increased.

Alveolar dead space to tidal volume ratio (V_D/V_T), a parameter believed to reflect pulmonary vascular function, was either abnormally elevated or failed to decrease in most patients (Fig. 74-3). This abnormality suggested either pathological or functional involvement of the pulmonary vasculature by the disease process.

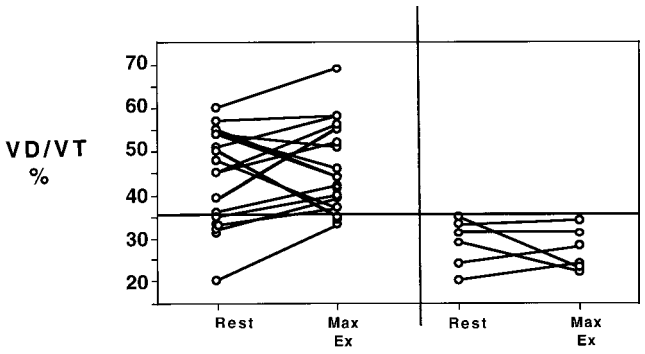

Figure 74-3 Dead space to tidal volume ratio (V_D/V_T%) at rest and maximal exercise (max ex) in patients with pulmonary Langerhans'-cell histiocytosis (n = 23). Seventeen patients demonstrated either an abnormal V_D/V_T at rest or response to exercise (left panel). Six patients had a normal V_D/V_T at rest and normal response to exercise (right panel). *(Based on data from Crausman RS, Jennings CA, Tuder R, et al: Pulmonary histiocytosis X: Pulmonary function and exercise pathophysiology. Am J Respir Crit Care Med 153:426–435, 1996, with permission.)*

Two linear regression models derived from pulmonary function indices predicted 73 percent ($r^2 = 0.73$) and 75 percent ($r^2 = 0.75$) of the variability in the maximal achieved workload and predicted oxygen consumption at maximal exercise (% $c_{max\,ex}$), respectively. The following equation was derived for the maximal achieved workload:

$$\text{maximal achieved workload} = 0.884 - (0.0088 * V_D/V_T \text{ baseline}) - (0.002 * RV) + (0.0044 * D_{LCO}).$$

Here the partial r^2 was V_D/V_T baseline ($r^2 = 0.40$, $p = 0.0007$), RV (0.19, 0.001), and D_{LCO} (0.15, 0.004). Figure 74-4 shows the regression model for the predicted oxygen consumption at maximal exercise.

Our analysis of the composite results concluded that exercise intolerance in subjects with pulmonary Langerhans'-cell histiocytosis was due to a combination of mechanical factors and pulmonary vascular involvement by pulmonary Langerhans'-cell histiocytosis.

HISTOPATHOLOGY

The pathological cell type of pulmonary Langerhans'-cell histiocytosis is the Langerhans' cell, a differentiated cell of the monocyte-macrophage line (Fig. 74-5). Langerhans' cells are normally found in the dermis, the reticuloendothelial system, the lung, and the pleura. They are distinguished by a pale-staining cytoplasm and large nucleus and nucleoli. Electron microscopy can demonstrate the classic pentilaminar cytoplasmic inclusion or Birbeck granule (X-body) (Fig. 74-6). Although this cell can be found in association with

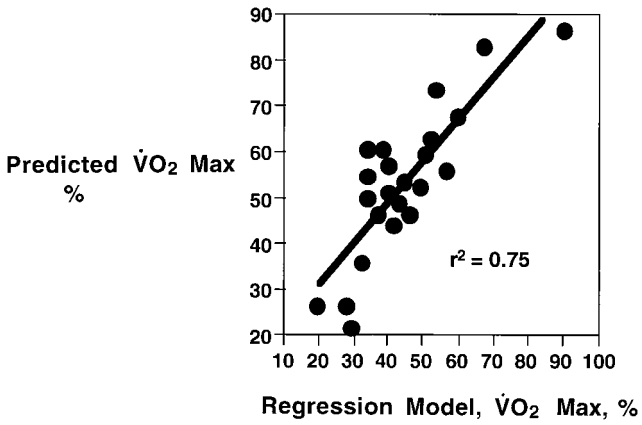

Figure 74-4 Correlation between predicted oxygen consumption at maximal exercise (Vo_{2max}) and predicted Vo_{2max} from the linear regression model: $Vo_{2max} = 0.062 - (0.0074 * \text{baseline } V_D/V_T) - (0.0014 * RV) + (0.0017 * \text{baseline } P(Aa)o_2) + (0.0011 * D_{LCO})$; r^2 0.75 *(Based on data from Crausman RS, Jennings CA, Tuder R, et al: Pulmonary histiocytosis X: Pulmonary function and exercise pathophysiology. Am J Respir Crit Care Med 153:426–435, 1996, with permission.)*

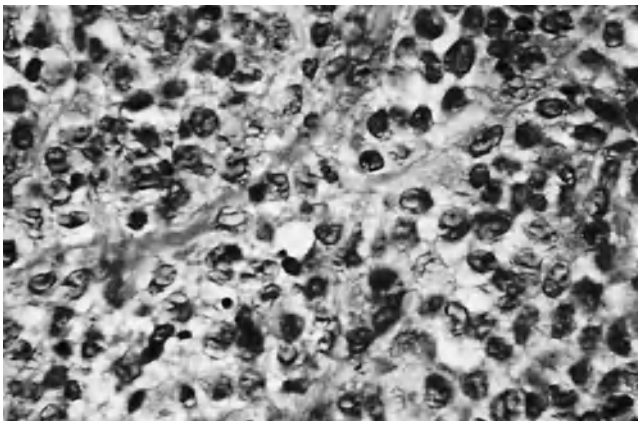

Figure 74-5 Lung tissue in pulmonary Langerhans'-cell histiocytosis . The histiocytosis X cells (Langerhans' cells) are typical. A characteristic longitudinal groove is seen along the center of some cells (×96.)

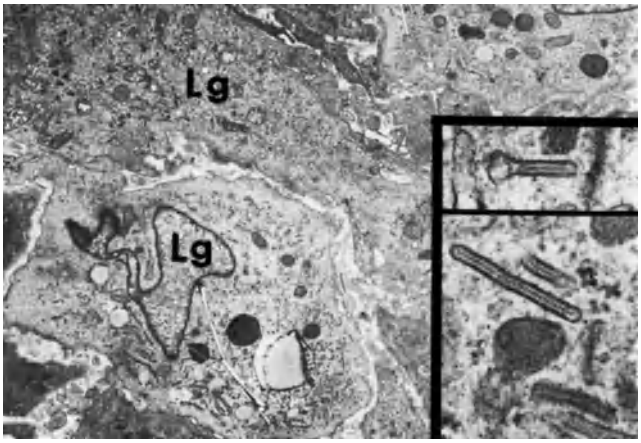

Figure 74-6 Electron micrograph of Langerhans' cell (Lg) of the lung. Typical X bodies (Birbeck granules) are seen in the two inserts.

cigarette smoking in otherwise healthy persons and with other pulmonary pathologies (e.g., idiopathic pulmonary fibrosis) or in normal lung, its presence is characteristic of pulmonary Langerhans'-cell histiocytosis. In pulmonary Langerhans'-cell histiocytosis, the Langerhans' cells are characteristically found in clusters and significantly outnumber those seen in other lung diseases. Absolute quantitative guidelines for diagnosis of pulmonary Langerhans'-cell histiocytosis have not been established.

Early inflammatory lesions center around the smaller bronchioles and usually contain a mixture of eosinophils, lymphocytes, and neutrophils. Pulmonary Langerhans'-cell histiocytosis is not a granulomatous disorder. Moreover, the lesions are often devoid of eosinophils. Thus, the older term, *eosinophilic granuloma,* is a misnomer. The lesions often affect pulmonary arterioles and venules so that the disorder can be described as having a bronchovascular distribution. Pseudo-desquamative interstitial pneumonia (characterized by the accumulation of alveolar macrophages in the alveolar parenchyma between pulmonary Langerhans'-cell lesions) and respiratory (smoker's) bronchiolitis (with pigmented macrophages filling the lumen of bronchioles and the surrounding alveolar spaces) have also often been found on lung biopsy. In addition, intraluminal fibrosis was often present (86 percent of specimens), the fibrosis was characterized by mural incorporation, alveolar obliteration, and intraluminal buds. It was mild in extent in 59 percent of specimens, moderate in 20 percent, and marked in 9 percent. These findings support the hypothesis that intraluminal fibrosis serves as a mechanism for alveolar collapse, with progression to interstitial fibrosis and lung remodeling.

Interstitial fibrosis and small cyst formation with a middle- to upper-zone predominance occur in advancing disease. This middle- to upper-zone predominance differs from that of idiopathic pulmonary fibrosis, which generally has a lower zone predominance. More advanced lesions extend widely into the parenchyma of the lung that surrounds the bronchovascular structures and produce the so-called stellate lesions that are characteristic of this disorder. Kambouchner and colleagues used three-dimensional reconstructions of serial histological sections to demonstrate that pulmonary Langerhans'-cell histiocytosis lesions are elongated, sheath-like structures of variable diameter that extend proximally and distally along bronchioles and do not necessarily have a spherical morphology (Fig. 74-7).

Older lesions are relatively acellular and produce a diffuse interstitial pathology that can be difficult to distinguish from other forms of end-stage pulmonary fibrosis, with extensive areas of fibrosis and honeycombing accompanying the cystic lesions. The mechanism for cyst formation is unknown. It may be a consequence of central necrosis of older stellate lesions. Alternatively, the cysts may occur as a result of secondary inflammatory foci in relatively avascular areas distal to more advanced bronchovascular lesions. Finally, these cysts may form, in part, because of obstruction of the more proximal airway by the stellate lesions.

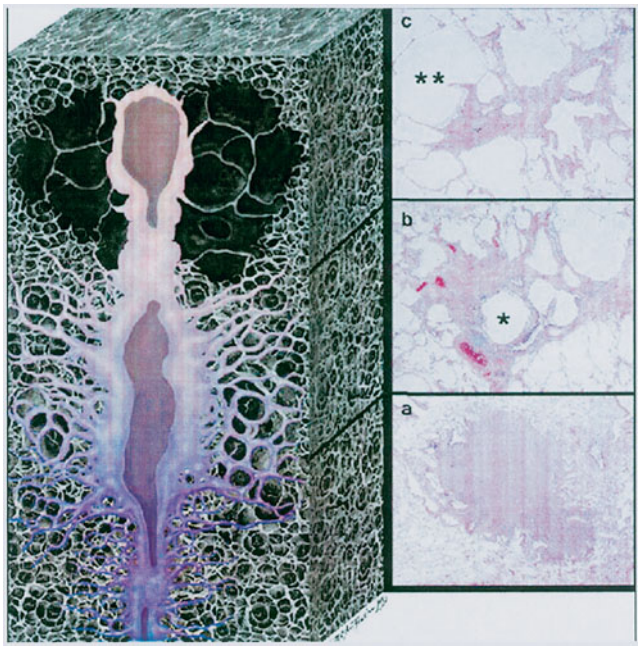

Figure 74-7 Three-dimensional appearance of a pulmonary Langerhans'-cell histiocytosis (PLCH) lesion. Artist's rendering, based on the reconstructions by Kambouchner et al, illustrates the elongated morphology and variable cellular and fibrotic composition of PLCH with correlative histological sections. As a PLCH lesion evolves, the nodule of densely packed cells (bottom, *a*) is centripetally replaced by fibrous tissue and ultimately becomes a stellate scar (top, *c*). This continuum of change may be evident within a single lesion. PLCH lesions are bronchiolocentric and propagate both proximally and distally along the small airways. The involved bronchiolar lumen may become either dilated or obliterated. The histological sections correspond to the early, middle, and late phases of PLCH. In the early phase (*a*), there is a densely cellular nodule with delicate stellate extensions along the adjacent alveolar walls (original magnification, ×12; H&E stain). As the disease progresses (*b*), cellularity diminishes as fibroblasts replace the lesion (original magnification, ×19.2; H&E stain). Note that the stellate extensions have become more prominent, the central bronchiole (*) is dilated, and adjacent alveolar spaces have coalesced because of focal destruction of alveolar walls (paracicatricial airspace enlargement). In the final phase (*c*), the characteristic Langerhans'-cell histiocytosis is absent and only a fibrous, stellate scar remains (original magnification, ×24; H&E stain). This phase is often accompanied by paracicatricial airspace enlargement (**). *(From Abbott GF, Rosado-de-Christenson ML, Franks TJ, et al: From the Archives of the AFIP: Pulmonary Langerhans cell histiocytosis. RadioGraphics 24:821–841, 2004, with permission.)*

PATHOGENESIS

The pathogenesis of pulmonary Langerhans'-cell histiocytosis is unknown. However, the nearly universal association with cigarette smoking strongly implies causation. One hypothesis of disease pathogenesis, the bombesin hypothesis, contends that increased bombesinlike peptide production plays a central role (Fig. 74-8). Bombesin is a neuropeptide produced by neuroendocrine cells, which are increased in the lungs of smokers. Bombesinlike peptides are chemotactic for monocytes, are mitogenic for epithelial cells and fibroblasts, and stimulate cytokine secretion. Thus, several attractive features support the hypothesis that these peptides contribute to the inflammation and fibrosis observed in pulmonary Langerhans'-cell histiocytosis. Tobacco glycoprotein and other regulatory glycopeptides (e.g., granulocyte-macrophage colony-stimulating factor) have been touted as being potentially important in the pathogenesis of this disease.

Attention has been focused on the processes that may regulate white blood cell traffic in this disorder. These studies suggest that the pathogenesis of pulmonary Langerhans'-cell histiocytosis entails alterations of the expression of the adhesion molecules that regulate interactions between white blood cells and endothelial cells. One important adhesion molecule for neutrophils that is expressed by endothelial cells is intercellular adhesion molecule-1 (ICAM-1). ICAM-1 expression by Langerhans' cells has been demonstrated in biopsy specimens of subjects with Langerhans'-cell histiocytosis. Expression of other leukocyte adhesion molecules, such as the $ß_1$ and $ß_2$ integrins, has also been noted. The significance of these findings and their relevance to pulmonary Langerhans'-cell histiocytosis remain to be elucidated.

Alternatively, a viral infection has been suggested as the underlying cause of generalized Langerhans'-cell histiocytosis. However, there are no convincing data to suggest a role for viral infection as a cause of pulmonary Langerhans'-cell histiocytosis.

Abnormalities in immune function, with a nonspecific increase in immunoglobulin G (IgG) in bronchoalveolar fluid, circulating and tissue-bound immune complexes, and abnormalities in T-cell function, have been observed in association with pulmonary Langerhans'-cell histiocytosis and may be important in the pathophysiology of this disorder. It is also possible, however, that these findings represent nonspecific consequences of a generalized activation of immune effector cells.

Although it is not a monoclonal disorder, the clinical similarities between pulmonary Langerhans'-cell histiocytosis and Langerhans'-cell histiocytosis and the frequent association with lymphoma do suggest a relationship with malignancy. At present, it is reasonable to think that pulmonary Langerhans'-cell histiocytosis may be a premalignant condition.

DIAGNOSTIC EVALUATION

The history and physical examination are the first steps in the diagnostic evaluation of a patient suspected of having pulmonary Langerhans'-cell histiocytosis. Unfortunately, the signs and symptoms of pulmonary Langerhans'-cell histiocytosis are generally nonspecific and often point to other, more common pulmonary diagnoses. For example, wheezing, cough, and dyspnea in a 50-year-old patient

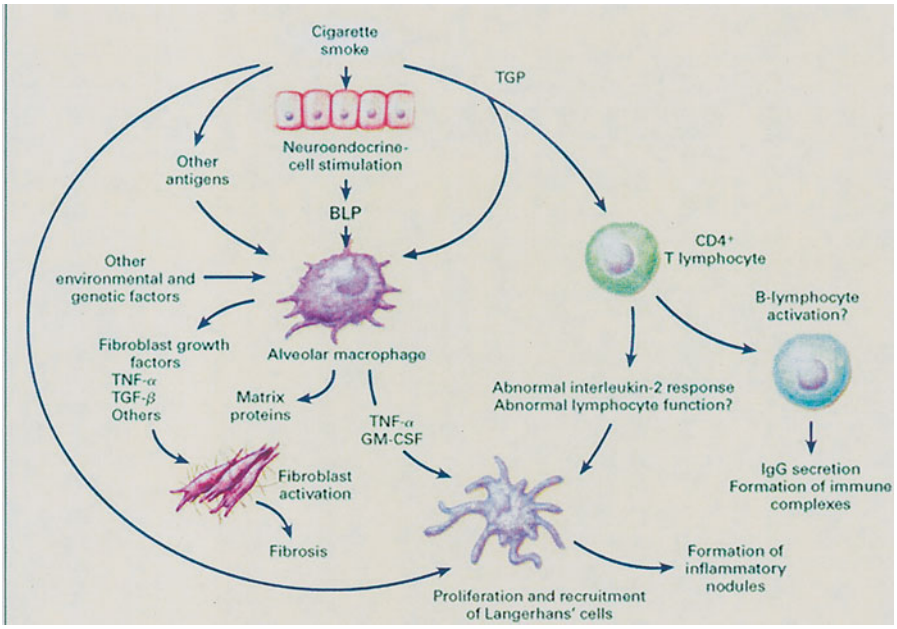

Figure 74-8 The primary event in the pathogenesis of pulmonary Langerhans'-cell histiocytosis probably involves cigarette-smoke–induced recruitment and activation of Langerhans' cells to the lung, a process that may result from a variety of potential mechanisms. Cigarette smoke may activate alveolar macrophages through bombesin-like peptides (BLP) released from airway neuroendocrine cells. Other antigens in cigarette smoke, including tobacco glycoprotein (TGP), may stimulate alveolar macrophages to produce cytokines (such as tumor necrosis factor [TNF-α] or granulocyte-macrophage colony-stimulating factor [GM-CSF]) or other factors that enhance recruitment and activation of Langerhans' cells. Cigarette smoke may also directly activate Langerhans' cells to secrete cytokines (such as TNF or GM-CSF) that mediate local accumulation of inflammatory cells, with resultant formation of nodules. Uptake of cigarette-smoke antigens by alveolar macrophages or Langerhans' cells may also promote local expansion of T lymphocytes and further inflammation. Through the action of tobacco glycoprotein, reduced interleukin-2 secretion by lymphocytes may occur, thereby enhancing local survival and proliferation of Langerhans' cells. T lymphocytes may further stimulate B-lymphocyte activation, promoting secretion of antibodies and immune-complex formation. Fibroblast activation and fibrosis may result from the local synthesis of tumor growth factor-ß (TGF-ß) and TNF by alveolar macrophages. *(From Vassallo R, Ryu JH, Colby TV, et al: Pulmonary Langerhans'-cell histiocytosis. N Engl J Med 342:1969–1978, 2000, with permission.)*

with a prominent smoking history are much more commonly due to COPD than to pulmonary Langerhans'-cell histiocytosis. However, when present, the history of recurrent pneumothorax, diabetes insipidus, or bone pain can be helpful. A smoking history is a consistent but not essential historical feature, since pulmonary Langerhans'-cell histiocytosis can occur without an antecedent history of smoking.

Most evaluations for pulmonary Langerhans'-cell histiocytosis are prompted by an abnormal chest radiograph. As previously noted, the chest CT, if classic, can be diagnostic, and should therefore be obtained in all who are suspected of having this disease. We recommend high-resolution chest CT as a prebiopsy step in the evaluation of any patient with diffuse interstitial lung disease suspected of having pulmonary Langerhans'-cell histiocytosis. A sufficiently characteristic chest CT in association with the appropriate history is believed by many to obviate the need for tissue confirmation. It should be noted that most often chest CT scans in pulmonary Langerhans'-cell histiocytosis are not diagnostic and can be confused with the chest CT scans of pulmonary lymphangioleiomyomatosis, tuberous sclerosis, hypersensitivity pneumonitis, sarcoidosis, or idiopathic pulmonary fibrosis. In these instances, further diagnostic evaluation is warranted.

Bronchoalveolar lavage (BAL) can be of diagnostic value in cases of suspected histiocytosis X. The total number of cells recovered is usually increased (as expected in smokers), and a modest increase in the concentration of neutrophils and eosinophils is common. In active disease, the total number of lymphocytes recovered may also be increased, and the CD4:CD8 ratio may be decreased. Langerhans' cells in BAL can be recognized by their characteristic staining for S-100 protein or peanut agglutination antigen. These cells are also OKT-6 (CD-1) positive, are identified by a specific monoclonal antibody (MT-1), and contain characteristic Birbeck or pentilaminar bodies on electron microscopic evaluation (Fig. 74-6). Quantitative criteria for the definitive diagnosis of histiocytosis X based on BAL Langerhans'-cell numbers have not been conclusively established. A BAL cell differential with more than 5 percent Langerhans' cells strongly suggests the diagnosis. Lesser proportions of Langerhans' cells can be seen in current smokers and in patients with other interstitial lung

disorders or bronchoalveolar carcinoma and even in normal subjects. Thus, the mere presence of Langerhans' cells is of little diagnostic value.

When tissue confirmation is sought, transbronchial biopsy can be sufficient to make the diagnosis. Sampling error and insufficient tissue may account for the substantial number of false-negative or nondiagnostic biopsies. Open, video-guided thoracoscopic lung biopsy, is generally definitive and can be done with a minimum of operative risk. Tissue immunostaining with the monoclonal antibody CD-1 (OKT-6) distinguishes Langerhans' cells from other histiocytes and can be a useful diagnostic adjunct. It can be performed on routinely fixed tissue and is less expensive than electron microscopy.

In patients with progressive disease and extensive fibrosis, the number of Langerhans' cells in either tissue specimens or BAL fluid decreases dramatically. Diagnosis at this stage can be difficult regardless of the laboratory methods used. In most cases, the combination of transbronchial lung biopsy and BAL, supplemented with the identification of CD-1–positive cells in tissue and BAL fluid, is highly likely to result in the correct diagnosis.

TREATMENT AND PROGNOSIS

The natural history of pulmonary Langerhans'-cell histiocytosis is extraordinarily variable, with some patients experiencing spontaneous remission of symptoms and others progressing to end-stage fibrotic lung disease (Table 74-1). Poor outcome in pulmonary Langerhans'-cell histiocytosis has been associated with an older age at the time of diagnosis, severe airway obstruction, reduced carbon monoxide diffusing capacity, and the need for corticosteroid therapy during follow-up.

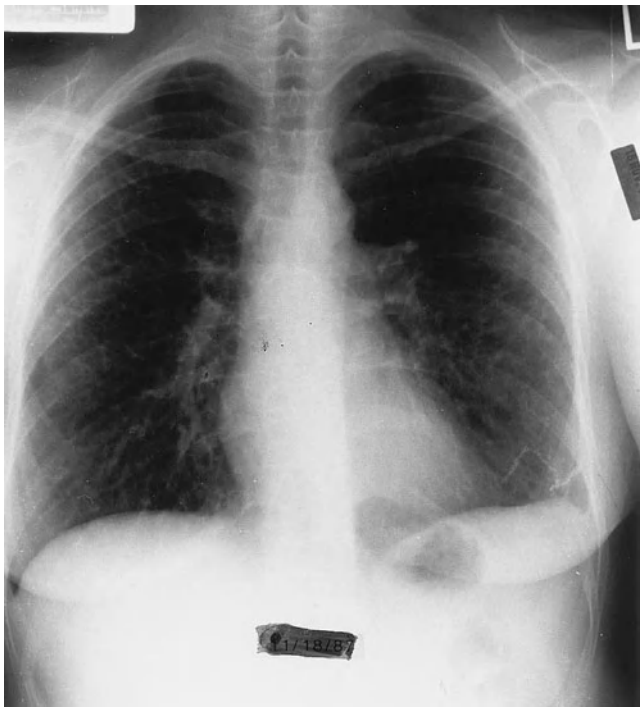

Figure 74-9 Follow-up chest radiograph in a 22-year-old woman taken 4 months after the initial film shown in Fig. 74-1. After an open lung biopsy performed on the left hemithorax, she was told to stop smoking and treated with prednisone. The chest radiograph shows marked clearing of the ill-defined nodules and preservation of lung volumes.

Most subjects who continue to smoke demonstrate gradual progression and regression of disease following smoking cessation. Therefore, it is important to stress smoking cessation (Fig. 74-9). The condition of patients with radiographic sparing of the costophrenic angle is more likely to remain stable or

Table 74-1

Clinical Course of Pulmonary Langerhans'-cell Histiocytosis

Reference	N	Years of Follow-Up	% Improved	% Stable	% Deteriorated	% Deaths
Basset, et al (1978)	67	1–3	13	40	21	25
Friedman, et al (1981)	60	Not stated	55*	37	7	2
Colby and Lombard (1983)	31	Not stated		74†	19	6
Lacronique et al (1982)	37	1–12‡	65	35		

** Forty patients had essentially no symptoms of residual disease at least 6 months after diagnosis; 13 of these had persistent radiographic abnormalities.*
† Stable or with partial or complete resolution.
‡ Twenty-six of 37 were followed for > 3 years; mean = 5.4 years.
Source: Data from Marcy TW, Reynolds HY. Pulmonary histiocytosis X. Lung *163:129–150, 1985.*

to improve than the condition of patients with involvement of the costophrenic angle.

Corticosteroids have not been shown to be of any value in the treatment of histiocytosis X. Nor has cytotoxic therapy, which may be of value in the treatment of disseminated disease. Reports of improved outcome with interleukin-2 and anti–tumor necrosis factor-α therapy in pediatric patients with disseminated histiocytoses may lead to similar trials in pulmonary Langerhans'-cell histiocytosis. Radiotherapy for symptomatic bone lesions can be palliative. Radiation is not useful in the treatment of the pulmonary manifestations. Lung transplantation has been successfully accomplished in a number of centers. It is a viable option for selected patients with end-stage disease. Recurrence of pulmonary Langerhans'-cell histiocytosis after lung transplantation has been reported, especially in patients who resumed smoking after lung transplantation.

Potential therapies that are apt to be of value in the future include gene therapy, monoclonal antibody therapy, and cytokine-based therapies. Given the vascular impairment seen with this disease and the occasional reports of pulmonary hypertension, it is also tempting to think about vasodilator therapy for symptomatic patients. However, these approaches remain speculative.

There is a high rate of recurrence of pneumothoraces in the absence of interventions to prevent additional episodes. Pleurodesis may be needed in patients with recurrent pneumothoraces.

See Fig. 74-10 for an analysis of expected and observed survival among adults with pulmonary Langerhans'-cell histiocytosis.

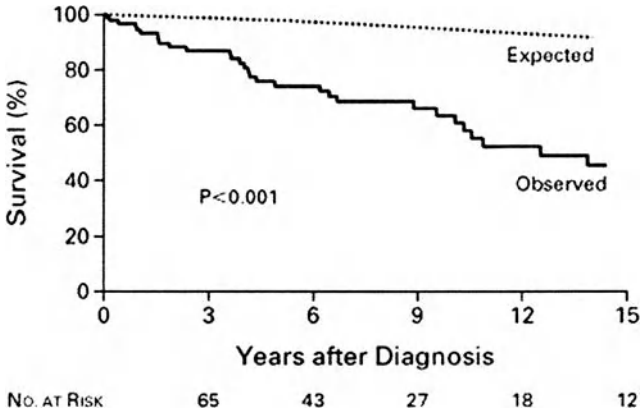

Figure 74-10 Kaplan-Meier analysis of expected and observed survival among 102 adults (40 men and 62 women) with pulmonary Langerhans'-cell histiocytosis. The expected survival was defined as that for age- and sex-matched members of the general US population. The median follow-up period after the diagnosis of pulmonary Langerhans'-cell histiocytosis was 4 years (range, 0 to 23). There were 33 deaths, 15 of which were attributable to respiratory failure. Survival was significantly shorter than that expected for healthy persons of the same sex and calendar year of birth ($p < 0.001$). *(From Vassallo R, Ryu JH, Schroeder DR, et al: Clinical outcomes of pulmonary Langerhans'-cell histiocytosis in adults. N Engl J Med 346:484–490, 2002, with permission.)*

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75

Pulmonary Lymphangioleiomyomatosis

Talmadge E. King, Jr.

LYMPHANGIOLEIOMYOMATOSIS

Pulmonary lymphangioleiomyomatosis is a rare, idiopathic, diffuse, progressive interstitial lung disease that afflicts young women of childbearing age. It occurs as a sporadic disease or with tuberous sclerosis complex, which can be inherited as an autosomal-dominant disorder involving multi-organ hamartomas. In the tuberous sclerosis complex, patients frequently develop lung and kidney lesions which are pathologically and genetically similar to those seen in lymphangioleiomyomatosis. Pathologically, the tuberous sclerosis complex is characterized by interstitial proliferation of smooth muscle and cyst formation that mimics pulmonary emphysema. It has been variously called myomatosis, angiomyomatosis hyperplasia, lymphangiomatous malformation, diffuse pulmonary leiomyomatosis, and muscular hyperplasia of the lung.

Although pulmonary lymphangioleiomyomatosis is commonly included among the diffuse interstitial lung diseases, lymphangioleiomyomatosis has more in common clinically, radiographically, and physiologically with pulmonary emphysema than with either idiopathic pulmonary fibrosis (IPF) or sarcoidosis. Like emphysema, lymphangioleiomyomatosis generally manifests with clinically significant airflow limitation and is often misdiagnosed as asthma or chronic obstructive pulmonary disease (COPD). Many subjects are evaluated for α_1-antitrypsin deficiency. However, lymphangioleiomyomatosis is an interstitial lung disease and should rightly be included with pulmonary histiocytosis X and (stage IV) cystic sarcoidosis as part of a subgroup of cystic interstitial lung diseases. Tuberous sclerosis can be associated with pulmonary disease that is indistinguishable pathologically from lymphangioleiomyomatosis.

Epidemiology

The incidence and prevalence of pulmonary lymphangioleiomyomatosis is unknown. It is a rare disease that presents almost exclusively in premenopausal women. Most patients (70 percent) are 20 to 40 years of age at the time of onset of symptoms or diagnosis. Until now, only 5 percent of patients have been more than 50 years of age at the time of presentation. However, currently more older women (usually without a history of pneumothorax) are being diagnosed with lymphangioleiomyomatosis. The few instances of the disease that have been reported in postmenopausal women have been associated most often with estrogen replacement therapy. Caucasians are afflicted much more commonly than are other racial groups. No features in the family history, perinatal events, or early life events have been associated with the occurrence of lymphangioleiomyomatosis.

Clinical Presentation

Women with lymphangioleiomyomatosis come to medical attention in various ways. Most often, the subjective complaint of dyspnea or fatigue prompts medical evaluation. Early in the course of the disease, patients are often misdiagnosed as having asthma. However, as the disease progresses inexorably, the

Table 75-1

Age and Clinical Manifestations of Patients with Pulmonary Lymphangioleiomyomatosis at Presentation or During Follow-up*

Reference	*N*	Mean Age at Onset (Range)	Cough (%)	Dyspnea (%)	Chest Pain (%)	Hemoptysis (%)	Pneumothorax (%)	Chylothorax (%)	Chylous Ascites (%)
Silverstein (1974)	32	39 (18–69)	9†	91†	18†	28	38	78	31
Corrin (1975)	28	33 (17–47)	64	86	7	36	43	39	7
Taylor (1990)	32	33 (range not reported)	41	94	34	44	81	28	6
Kitaichi (1995)	46	32 (20–63)	54	83	30	24	39	11	4
Crausman (1996)	16	32 (26–39)	56	100	—	13	69	—	—
Ryu (2006)	196	41.4 (18–76)	32	74	not reported	32	57	—	5

† *n = 22*

* *Wheezing was noted in only 92 of 309 subjects. Chyluria was noted in only 3 of 154. Chylopysis was noted in 16 of 350 subjects. Fatigue was reported in 72% of subjects in a recent survey (Cohen, 2005).*

disease is either correctly diagnosed or reclassified as having pulmonary emphysema.

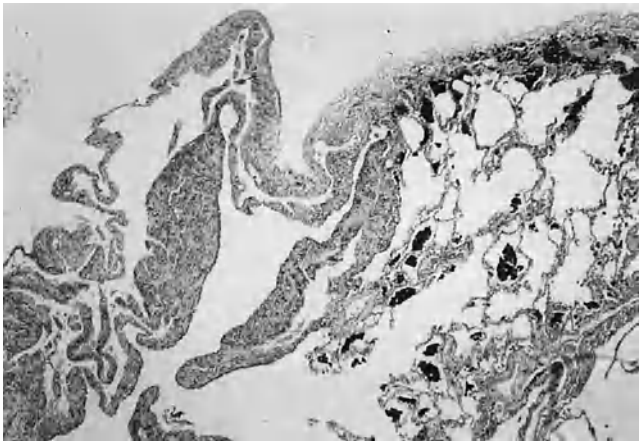
At the time of diagnosis, virtually all patients complain of dyspnea (Table 75-1). Spontaneous pneumothorax is common and occurs in almost two-third of cases. A history of pneumothorax is more common in younger patients (77 percent of women are under 40 years old at diagnosis) compared to only 50 percent of those who are more than 60 years of age. The disease is often recurrent, can be bilateral, and may necessitate pleurodesis. Barotrauma and cyst rupture can still occur after pleurodesis. Cyst rupture may be manifested as pneumomediastinum, pneumoretroperitoneum, pneumoretropharynx, and subcutaneous emphysema. Management of these complications after pleurodesis usually requires only observation since the complications are rarely associated with significant morbidity. In contrast, tension pneumomediastinum or pneumopericardium calls for decompression.

Although chylothorax, due to obstruction of the thoracic duct or rupture of the lymphatics in the pleura or mediastinum by proliferating smooth-muscle cells, is a characteristic feature of this disease, it is present in only a minority of patients at the time of diagnosis. Chyle can be recognized by its milky white appearance, high triglyceride level—usually greater than 110 mg/dl—and the presence of chylomicrons. Chylothorax, which is typically associated with nutritional wasting and some degree of immunocompromise, can be difficult to manage. Chyloperitoneum (chylous ascites) occurs in approximately 10 percent of patients. More rarely, chyluria (due to abnormal connections between dilated retroperitoneal lymphatics and the renal collecting system) and chylopericardium may also occur. Renal angioleiomyomata, a characteristic pathological finding in tuberous sclerosis, are also common in lymphangioleiomyomatosis (in as many as 50 percent of subjects). These lesions may grow to enormous size prior to clinical detection but uncommonly affect renal function. Hemoptysis of mild to moderate severity, a well-described clinical manifestation, may be life-threatening.

The physical examination can be unrevealing or may disclose end-expiratory rales (22 percent), hyperinflation, decreased or absent breath sounds, ascites, and intra-abdominal or adnexal masses. Clubbing is uncommon (less than or equal to 5 percent).

Pathology

In lymphangioleiomyomatosis, the predominant pathology, proliferation of atypical smooth muscle, occurs around the bronchovascular structures. However, this abnormal proliferation is not limited to the bronchovascular sheath but also progresses through the pulmonary interstitium. In addition, another unique pathological feature of lymphangioleiomyomatosis is the occurrence of diffuse cystic dilatation of the terminal airspaces (Fig. 75-1). Some degree of hemosiderosis is common and is thought to be a consequence of small amounts of hemorrhage that stem from the rupture of dilated and tortuous venules.



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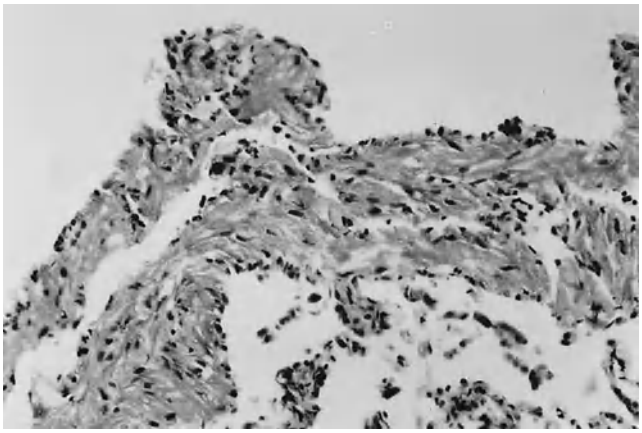


B

Figure 75-1 Histopathology of lymphangioleiomyomatosis. *A*. Smooth muscle is irregularly distributed throughout the pulmonary parenchyma. The muscle bundles are often found near blood vessels but extend into the alveolar walls. Intra-alveolar collections of macrophages and lymphocytes are also present (right side of figure). *B*. Higher-power view reveals the abnormal smooth-muscle proliferation. The cells appear shorter and more immature than normal smooth muscle. Mitotic figures are rarely encountered.

The atypical proliferating cells resemble vascular smooth-muscle cells but are often somewhat shortened and pleomorphic (Fig. 75-1*B*). The origin of the atypical cell is assumed to be a myocyte, but this is controversial. The cells are polyclonal in nature.

Grossly and microscopically, the normal architecture is distorted by multiple small cysts which range from 0.1 cm to several cm in diameter (Fig. 75-2). The interstitium is thickened by smooth-muscle-like proliferation around and within the pulmonary lymphatics, venules, and airways. The lymphatic and venous vessels can also be quite tortuous and dilated. Hilar, mediastinal, and retroperitoneal lymph nodes are often involved and enlarged. The thoracic duct is frequently thickened and dilated. Extrapulmonary involvement with renal, retroperitoneal, intra-abdominal, and pelvic angioleiomyomata is common.

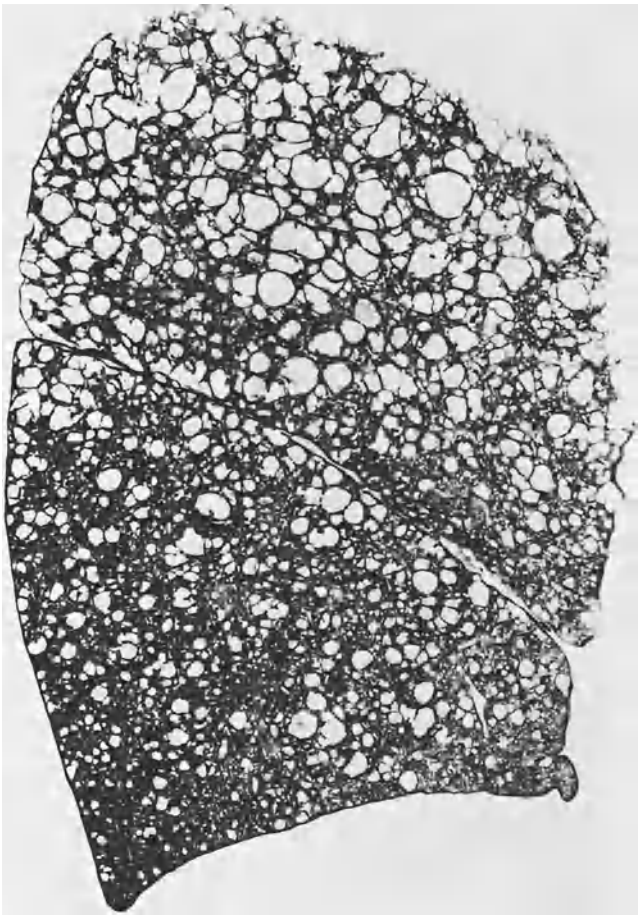


Figure 75-2 Pulmonary lymphangioleiomyomatosis causes thin-walled emphysematous spaces leading to the distinctive type of honeycombing. *(From Cornog JL Jr, Enterline HT: Lymphangiomyoma, a benign lesion of chyliferous lymphatics synonymous with lymphangiopericytoma. Cancer 19:1909–1930, 1966, with permission.)*

Pathogenesis

Lymphangioleiomyomatosis is primarily a disease of smooth-muscle-like cell proliferation throughout the interstitium of the lungs and within and around the lymphatics of the body. It is unknown whether the proliferation results from abnormality in the proliferating cells or if the abnormally proliferating cells are simply responding to abnormal stimulation from circulating mediators. The abnormal smooth-muscle-like cells have lost heterozygosity and inactivating mutations in one of the two tuberous sclerosis complex genes. Most mutations have been described in tuberous sclerosis complex-2 (16p13); mutations in the tuberous sclerosis complex-1 gene (9q34) have been less common. In the pulmonary lesions of lymphangioleiomyomatosis, loss of heterozygosity or other somatic mutations in either tuberous sclerosis complex gene have been reported. Renal angiomyolipomas contain abnormal blood vessels and adipose cells in addition to the smooth-muscle-like lymphangioleiomyomatosis cells. Based on loss of heterozygosity as the second genetic hit, all three types of renal angiomyolipoma cells appear to be neoplastic.

It is very likely that estrogen plays a central role in progression of the disease. The disease does not become manifest prior to menarche and only rarely after menopause. The few occurrences that have been reported in postmenopausal women have most often been in association with hormonal supplementation. The disease is known to accelerate during pregnancy and to abate after oophorectomy. In those patients in whom pulmonary disease is part of tuberous sclerosis, female preponderance is marked. Moreover, estrogen and progesterone receptors have been demonstrated in tissue biopsies. A recent study showed that estradiol and tamoxifen stimulated the growth of lymphangioleiomyomatosis-associated angiomyolipoma cells and activated both genomic and nongenomic signaling pathways.

The mechanism by which interstitial smooth-muscle proliferation causes cyst formation and emphysema-like disease is unknown. Although it has been proposed that the cysts and emphysema-like disease are due to compression of the conducting airways by the proliferating smooth muscle in the interstitium, this hypothesis is controversial. An alternate hypothesis is that smooth-muscle proliferation within the airways creates a "ball-valve" obstruction which leads to distention of the terminal airspaces. Finally, it has also been suggested that degradation of elastic fiber related to an imbalance in the elastase/α_1-antitrypsin system is a major mechanism leading to the emphysema-like changes. Some combination of these mechanisms probably affords the best explanation for the pathogenesis.

Pulmonary Physiology

Pulmonary function testing may be very helpful in providing a clue to the diagnosis of lymphangioleiomyomatosis. Lymphangioleiomyomatosis is one of the few interstitial lung diseases that presents with reticulonodular opacities on the chest radiograph, increased lung volumes, and an "obstructive" or "mixed" pattern on pulmonary function testing. Lymphangioleiomyomatosis patients are often hyperinflated with an increased total lung capacity (TLC) and increased thoracic gas volume (Vtg). Increased gas trapping is commonly manifested by an increase in the residual volume (RV) and in the RV/TLC ratio, even when TLC and Vtg are relatively normal. Often evidence of airflow limitation is manifested by a decrease in forced expiratory volume in 1 s (FEV_1) and vital capacity (FVC). Studies of pulmonary mechanics show that mean elastic recoil is decreased and that upstream resistance (Rus) is increased. A decrease in elastic recoil and an increase in pulmonary resistance contribute to the observed airflow limitation.

Gas exchange is often abnormal. A markedly reduced diffusing capacity (D_{LCO}) is a characteristic feature. The alveolar-arterial oxygen difference is also increased. In most patients exercise performance is decreased, with a reduced oxygen consumption and a low anaerobic threshold. Exercise causes an abnormal and excessive ventilatory response with high respiratory rate, excessive minute ventilation, and reduced breathing reserve. The baseline or exercise dead space to tidal volume ratio (V_D/V_T) is frequently abnormal

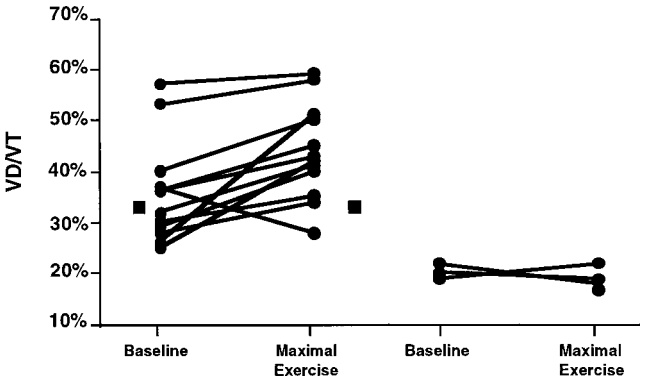


Figure 75-3 Pulmonary lymphangioleiomyomatosis. Dead space to tidal volume ratio- (V_{DS}/V_T) percent at rest and maximal exercise in patients with lymphangioleiomyomatosis (n = 15). *Left panel.* Twelve patients demonstrated an abnormal V_{DS}/V_T either at rest or in response to exercise. *Right panel.* The three subjects with a normal V_{DS}/V_T at rest and normal response to exercise are shown. *(Adapted from Crausman RS, Jennings CA, Mortenson RL, et al: Lymphangioleiomyomatosis: The pathophysiology of diminished exercise capacity. Am J Respir Crit Care Med 153:1368–1376, 1996, with permission.)*

(Fig. 75-3). Thus, the primary determinants of the exercise limitation are related to airflow limitation and mechanical factors (i.e., decreased breathing reserve, work of breathing) (Fig. 75-4). However, pulmonary vascular involvement also exerts a significant physiological effect upon the exercise performance, probably because the accompanying increase in physiological dead space can produce excessive ventilatory requirements. The interdependence between airflow limitation (which produces a decrease in the ventilatory ceiling) and pulmonary vascular dysfunction/destruction leads to severe impairment in exercise performance in many patients with pulmonary lymphangioleiomyomatosis.

Radiology

Chest Radiograph

The findings on the chest radiograph in lymphangioleiomyomatosis are variable, ranging from normal early in the course of the disease to severe emphysematous-like changes in advanced disease. Pneumothorax can be an early feature, and chylous pleural effusion can develop at any time during the course (Fig. 75-5). Initial reports of lymphangioleiomyomatosis described a pseudoreticular or nodular pattern of irregular opacities. These opacities result from the compression of smooth-muscle–rich interstitial tissue by more dilated cystic airspaces. Lymphatic obstruction, with the development of Kerley B septal lines, also contribute to the pattern. Cross-sectional studies show that the lungs of 33 to 62 percent of the patients are hyperinflated with cystic dilatation of the airspaces, resulting in relatively radiolucent lung fields.

Chest Computed Tomography

Chest computed tomography (CT) is very useful for demonstrating the cystic nature of this disease. High-resolution, thin-section CT scanning is much more sensitive than routine

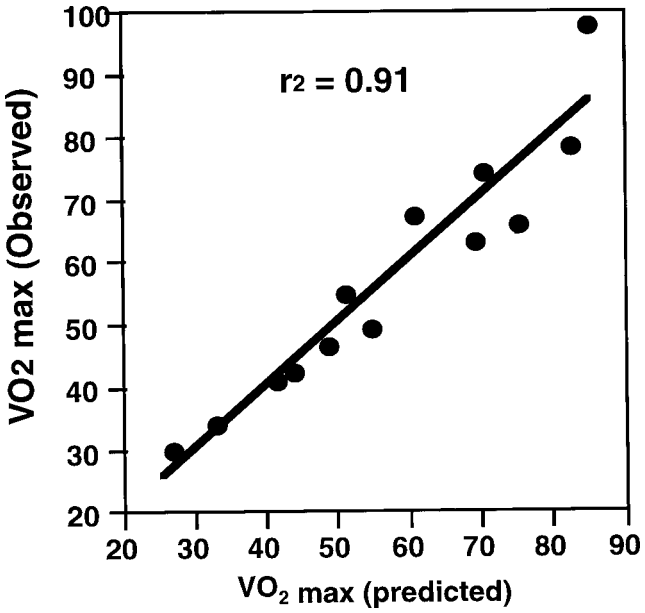


Figure 75-4 Linear stepwise regression model derived to determine the variability in exercise capacity. Correlation between percent predicted oxygen consumption achieved by the patients at maximal exercise ($V_{O_{2max}}$) and $V_{O_{2max}}$ predicted from the linear regression equation $V_{O_{2max}} = 0.40 - (0.0081^{*}\text{baseline } V_{DS}/V_T) (0.0070^{*}\text{sGaw})$, $r^2 = 0.91$. Both resting V_{DS}/V_T and sGaw are independent variables in this regression model. For this model, sGaw alone was able to predict 76 percent of the variability, and the addition of baseline V_{DS}/V_T predicted an additional 15 percent of the variability. None of the other airflow or gas exchange variables added significantly to this model's ability to predict maximal achieved oxygen consumption. The stepwise regression procedure determined that the best model for maximal achieved workload should include sGaw and baseline V_{DS}/V_T: maximal achieved workload $= 0.37 - (0.0081 * \text{baseline } V_{DS}/V_T) (0.0096 * \text{sGaw})$. This model was able to predict 76 percent of the variability in maximal achieved workload. (*From Crausman RS, Jennings CA, Mortenson RL, et al: Lymphangioleiomyomatosis: The pathophysiology of diminished exercise capacity. Am J Respir Crit Care Med 153:1368–1376, 1996, with permission.*)

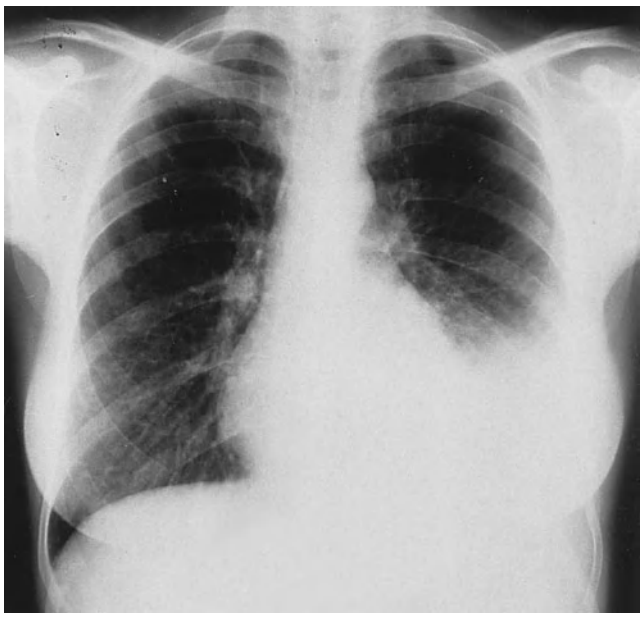


Figure 75-5 Posteroanterior radiograph of the chest showing minimal increase in markings in the lower lung zones. A chylothorax is present on the left.

chest radiography. Moreover, the findings of diffuse, homogenous, small (less than 1 cm diameter) thin-walled cysts can be pathognomonic in the appropriate clinical context (Fig. 75-6). Bilateral lung cysts (100 percent) and ground-glass opacities (59 percent) were the most frequent CT findings in 38 women in the Kyoto study. Nodular opacities (5 percent) were uncommon and linear densities were not seen.

The correlation is close between the extent of the cystic parenchymal replacement in patients with lymphangioleiomyomatosis (as measured by quantitative high-resolution chest CT) and the severity of the disease (as determined by spirometry, diffusing capacity, lung volume, or exercise performance). Thus, chest CT may be of both diagnostic and prognostic importance.

Abdominal CT and ultrasonographic findings are common in patients with thoracic lymphangioleiomyomatosis. The most common abdominal findings include renal angiomyolipoma (54 percent), enlarged abdominal lymph nodes (39 percent), lymphangiomyoma (16 percent), ascites (10 percent), dilatation of the thoracic duct (9 percent), and hepatic angiomyolipomatosis (4 percent). Diurnal variation in size of lymphangioleiomyomas may explain worsening of symptoms during the day.

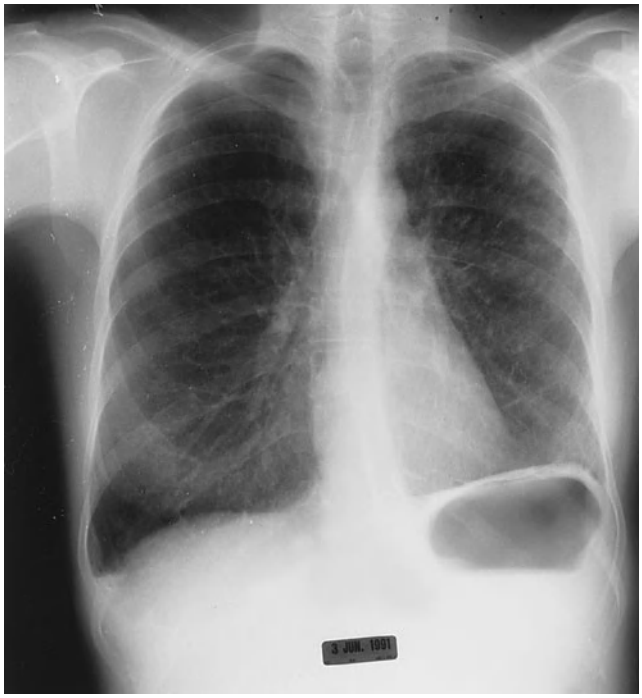
Diagnosis

Lymphangioleiomyomatosis can be readily diagnosed by its characteristic histological features on open lung or thoracoscopic biopsy. Often, transbronchial lung biopsy can yield an adequate sample for pathological evaluation especially when immunohistochemical stains specific for smooth-muscle components; actin or desmin and, more recently, HMB-45 have been employed to improve diagnostic sensitivity and specificity.

In general, the diagnosis should be strongly suspected in any young woman who presents with emphysema, recurrent pneumothorax, or a chylous pleural effusion. High-resolution chest CT can often confirm the diagnosis and tissue confirmation may not be necessary, although tissue confirmation is usually recommended because of the devastating nature of this disorder. The differential diagnosis includes: emphysema, α_1-antitrypsin deficiency, asthma, chronic extrinsic allergic alveolitis, pulmonary histiocytosis X, cystic sarcoidosis, and panacinar emphysema due to intravenous drug use.

Prognosis

The most common reasons for hospitalization are for the management of spontaneous pneumothorax, chylothorax, or renal angiomyolipomas that are acutely bleeding, or at risk for spontaneous hemorrhage. The natural history of this disorder is thought to be progressive with a median survival of 8 to 10 years after diagnosis. The prognosis for women with



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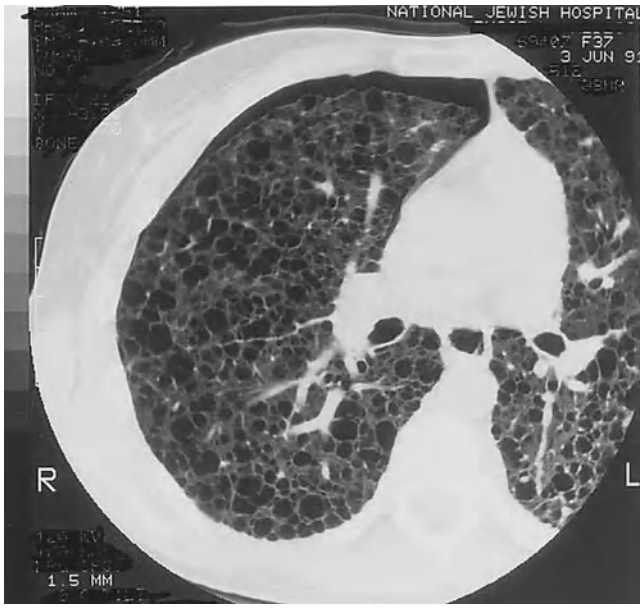

B

Figure 75-6 Same patient as in Fig. 75-5, 32 months later. *A*.The current posteroanterior radiograph of the chest shows increased lung volume and difficult-to-see cystic changes in the all lung zones. The pleural changes on the left are secondary to the prior effusion and to an open lung biopsy. *B*. The high-resolution CT scan demonstrates multiple thin-walled cystic airspaces.

lymphangioleiomyomatosis is variable but generally poor, with about 22 to 62 percent succumbing to progressive respiratory failure after 8.5 years after diagnosis (Fig. 75-7). Although uncommon, long-term survival 20 years after diagnosis has been reported. In the most recent large case series, there

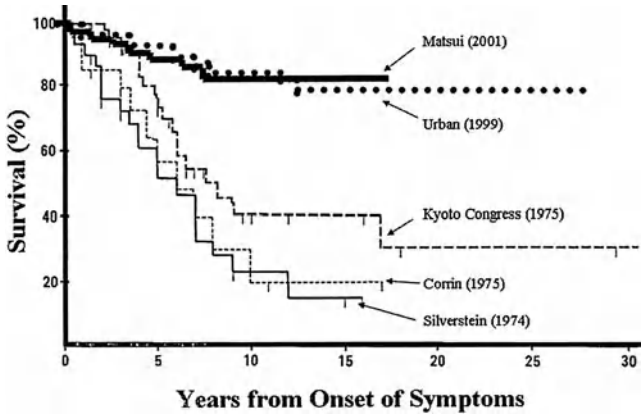

Figure 75-7 Kaplan-Meier plots of actuarial survival of patients with pulmonary lymphangioleiomyomatosis from the onset of symptoms. Five separate reports were analyzed: Silverstein and coworkers in 1974 described the outcome in 31 patients (solid line); Corrin and coworkers in 1975 described survival in 23 patients (dotted line); Kitaichi and colleagues in 1995 described the survival of 46 Asian women reported at the 1993 Kyoto Pulmonary Lymphangioleiomyomatosis Congress (dashed line). Urban and coworkers showed the survival probability of being alive was 91 percent after 5 years, 79 percent after 10 years, and 71 percent after 15 years of disease duration. Matsui and colleagues showed survival probabilities of 85 percent after 5 years and 71 percent after 10 years.

was an apparent improvement in survival. The reasons for this improved survival are unknown, but include the possibility of bias inherent in the methods, hormonal interventions, better supportive treatments, or a change in the natural history of the disease. These data also suggest that the rate of progression is quite variable and can occur many years after diagnosis and after menopause. Sudden onset of rapid deterioration is rare later in the course of the disease.

Pregnancy and the use of supplemental estrogen are known to accelerate the disease process. Interestingly, two-thirds of subjects enrolled in the Lymphangioleiomyomatosis (LAM) Registry had been pregnant. Of 353 pregnancies, 66.9 percent had resulted in live birth, 16.7 percent spontaneous abortion, 15.0 percent therapeutic abortion, and 1.4 percent in stillbirth. However, only 25 patients (21.7 percent of those who had been pregnant and able to recall symptoms) had experienced worsening of respiratory symptoms during pregnancy.

Pulmonary function and histological pattern of disease have been shown to be predictive of poor survival. An elevated total lung capacity (percent predicted TLC) and reduced FEV_1/FVC ratio were associated with poor survival 2 to 5 years after initial examination. Further, a predominantly cystic pattern of histopathology predicted a worse prognosis than a predominantly muscular pattern. It is unknown whether these patterns represent two distinct histopathologies or different stages in the evolution of the disease.

Treatment

Thus far, treatment regimens have been unsatisfactory. There is no role for either corticosteroids or cytotoxic agents and

there have been few advances since the early recognition that female hormones likely play an etiologic role in the pathogenesis. Oophorectomy, progesterone (10 mg/day), and more recently tamoxifen (20 mg/day) and luteinizing hormone-releasing hormone (LHRH) analogs have been employed with some anecdotal support. Alpha-interferon has also been tried, but in our experience has not been of any benefit, primarily because side effects limit its use. Only oophorectomy and treatment with progestational agents appear to provide reliable benefit. A recent meta-analysis summarized the results of 30 treated cases. Of patients treated early in the course of disease prior to widespread tissue destruction, five of seven stabilized or improved after oophorectomy; two patients who underwent both oophorectomy and treatment with progesterone stabilized or improved by objective criteria; only four of eight treated with progesterone alone stabilized or improved. Thus, combination therapy with oophorectomy and either progesterone and/or tamoxifen should be considered. Chemical oophorectomy with LHRH analogs may replace surgical oophorectomy as the primary treatment of this disorder; however, data are currently lacking.

To date, only lung transplantation offers any hope for cure and should be considered as definitive therapy for any failing patient. Compared with all lung transplant recipients, patients who have undergone lung transplantation for lymphangioleiomyomatosis experience increased morbidity and mortality due to complications related to their underlying disease (native lung pneumothorax, chylous pleural effusions and ascites, hemorrhagic renal angiomyolipomas, and recurrence of disease). Furthermore, reports of recurrent disease in transplanted lungs raise concern regarding this therapy. Recurrent lymphangioleiomyomatosis cells within donor lungs after transplantation were of recipient origin, suggesting metastatic spread.

TUBEROUS SCLEROSIS

Tuberous sclerosis (Bourneville's disease) is a rare (varies from 1 per 27,000 to 1 per 100,000 population) autosomal-dominant disorder, but up to 68 percent of cases may be new mutations. It affects men or women equally. Mental retardation, seizures, and facial angiofibroma (adenoma sebaceum) form the classic clinical triad. However, the features are variable and in some affected individuals intelligence is normal. Skin lesions are a prominent feature of tuberous sclerosis and are usually present in childhood. These lesions are characterized by hypopigmented spots on the trunk followed by adenoma sebaceum (wartlike lesions distributed in a butterfly pattern over the face and cheeks).

In less than 1 percent of cases, tuberous sclerosis can be associated with pulmonary manifestations that are indistinguishable from those of lymphangioleiomyomatosis (Table 75-2). The onset is generally in the fourth decade of life, rarely

Table 75-2

Features of Tuberous Sclerosis with and without Involvement of the Lungs

	Without Pulmonary Involvement	With Pulmonary Involvement
Age at onset, years	< 20	30–35
Sex incidence (male:female)	1:1	1:5
Family heredity	Yes	Yes
Presenting symptom	Central nervous system disorder	Dyspnea or spontaneous pneumothorax
Mental retardation	Frequent (~60 percent)	Uncommon (~40 percent)
Seizures	Frequent (70–90 percent)	Uncommon (~20 percent)
Facial angiofibroma	Frequent	Frequent
Pneumothorax	Not known (rare)	Frequent
Chylothorax	Not known (rare)	Rare
Angiomyolipoma	Frequent	Frequent

Source: Hauck RW, Konig G, Permanetter W, et al: Tuberous sclerosis with pulmonary involvement. Respiration *57:289–292, 1990, with permission.*

before age 20 years. Some have referred to lymphangioleiomyomatosis as a *forme fruste* of tuberous sclerosis. The complete triad of tuberous sclerosis is not commonly present in those who develop pulmonary involvement. In patients with pulmonary involvement female predominance is marked. Dwyer and colleagues reported that in 29 of 34 cases in their series the patients were female. Pulmonary lymphangioleiomyomatosis has been described in a phenotypically normal man with tuberous sclerosis complex and confirmed XY genotype.

Most patients with tuberous sclerosis present with dyspnea. In some, the onset is heralded by a spontaneous pneumothorax. Pneumothorax occurs in approximately one-third of patients. Hemoptysis and chest pain are other important features. The radiographic appearance is similar to that of pulmonary lymphangioleiomyomatosis described above. Chylothorax is a rare complication. The primary histological lesion is a hamartoma. Similar lesions occur in the brain and may calcify. A micronodular hyperplasia of type II pneumocytes has been described. The frequency of renal lesions, angioleiomyomata, is also high. Other associations include cardiac rhabdomyoma, sclerotic bone, and periungual fibromas.

Survival of patients with tuberous sclerosis is less than in the general population. Renal disease and brain tumors are the most common cause of death. Pulmonary involvement in tuberous sclerosis is associated with a poor prognosis. Progressive disease is common, and death usually occurs, secondary to respiratory insufficiency, within 5 years of the onset of symptoms. Long-term survivors have been described and may occur more often today because of improved management of the potential complications, especially cor pulmonale and pneumothorax. No effective treatment for tuberous sclerosis has been found. However, because of similarities to lymphangioleiomyomatosis, treatment with progesterone and/or oophorectomy in women is recommended.

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76

The Lungs in Patients with Inborn Errors of Metabolism

Masazuni Adachi • Francis A. Caccavo

A variety of diseases can be referred to collectively as being inborn errors of metabolism. As a result of increasingly sophisticated and complex biochemical and genetic approaches, our knowledge of these disorders has recently expanded greatly. Although many viscera and the central nervous system have been extensively studied in these disorders, comparatively little attention has been paid to the lungs. Most characterizations note that the "stored" material is sometimes deposited in the interalveolar septa or alveoli, that these pathological changes occasionally lead to pulmonary hypertension and severe pulmonary arteriosclerosis, and that, in some instances, characteristic alterations in the lungs can be demonstrated on radiographic examination. The manifestations of these diseases are diverse.

NIEMANN-PICK DISEASE

Niemann-Pick disease (NPD) is characterized by the excessive accumulation of sphingomyelin (types A, B and F) and cholesterol (types C, D, and E) in the cells of reticuloendothelial and parenchymal tissues of the viscera and/or the brain. The classification of NPD is based on the nature of the primary molecular defect. Types A, B, C, D, E, and F have distinct abnormalities. All types are autosomal-recessive disorders. Reticular or reticulonodular abnormalities are visible in chest radiographs of most patients with this disease.

Clinical Features

Type A NPD is an acute disorder that affects infants and involves viscera and the nervous system. Almost one-half of affected infants are of Jewish extraction. The onset is insidious, and the children manifest difficulties in feeding and fail to thrive during the early months. The infants experience progressive psychomotor deterioration and hepatosplenomegaly. The chest radiograph (Fig. 76-1) shows diffuse reticular infiltration. The infants generally die during the second year of life.

Type B is a chronic infantile form without neurological involvement. It is less common than types A and C. These infants often undergo hepatosplenomegaly and lymphadenopathy, which may develop as early as in infants with type A. However, most patients are in good health until late infancy. The children manifest increased susceptibility to pneumonia due to diffuse reticular infiltration by the lipids. They die during the juvenile stage.

In type C NPD the clinical manifestations are heterogeneous. Type C NPD involves viscera and the central nervous system. The initial symptoms usually occur after the first or second year and occasionally after the sixth year of life. Psychomotor deterioration is progressive. Hepatosplenomegaly is less striking than in types A and B. These patients occasionally survive to adolescence: most often they die between the fifth and fifteenth years of life.

In types C, D and E, NPD neurological symptoms progress slowly in late childhood (types C and D) and adulthood (type E).

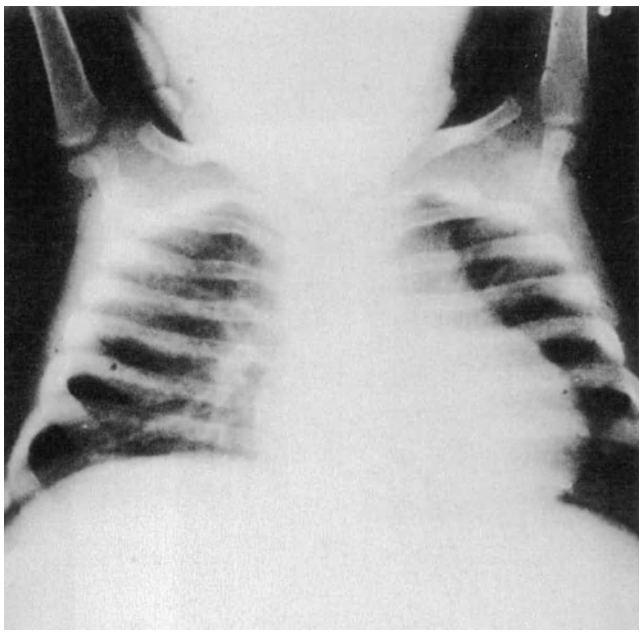

Figure 76-1 Chest radiograph of a patient with Niemann-Pick disease (type A) showing bilateral diffuse reticular infiltration.

Type F NPD patients have a heat-labile form of acid sphingomyelinase.

Genetics

The locus of the genes for types A and B NPD has been identified to be in chromosome 11p15.1 to p15.4. The molecular genetics have been derived from three cDNA (designated types 1, 2, and 3), and a total of 12 mutations have been identified as causing the type A and type B disorders. Nine were found to be single-base substitutions, and three were small deletions. Type 1 cDNA expressed catalytically active enzyme, and types 2 and 3 cDNA did not express catalytically active enzymes. In type C, the lesion has been mapped to chromosome 18p at genomic marker D18S40 (Fig. 76-1).

Pathological Features

Particularly in type A NPD, the lungs are frequently increased in weight, and their cut surfaces show yellow mottling. The liver is markedly enlarged and reaches two to three times its normal weight. Cut surfaces are diffusely yellow but the original architecture is usually preserved. The weight of the spleen is often 5 to 6 times normal, and sections show a yellow color with peculiar salmon-pink spots that represent malpighian bodies. The lymph nodes are also enlarged. The brains of the patients with types A and C NPD are uniformly reduced in size; on section, the cortex and the white and deep gray matters are atrophic.

Histology

Although some patients have no respiratory disturbances, foamy cells are usually contained in the pulmonary septa

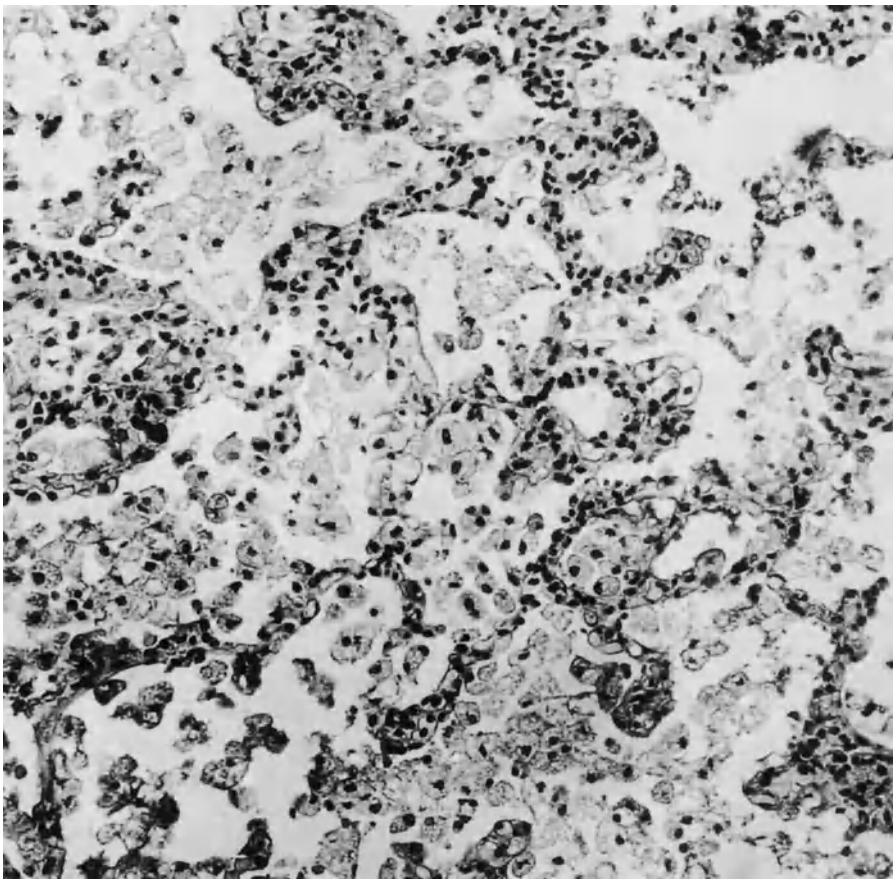

Figure 76-2 Sections from lung of a patient with Niemann-Pick disease (type A) exhibiting foamy cells in the alveoli (H&E, × 200).

and alveoli of most affected individuals (Fig. 76-2). These cells measure 15 to 90 μm in diameter and contain a single nucleus and cytoplasm with numerous fine vacuoles (Fig. 76-3). Similar foamy cells have been observed in other visceral organs and the nervous system. Although the foamy cells are characteristic of this disease, they are not diagnostic without histochemical proof of sphingomyelin (types A and B) or cholesterol (type C). Because the cytoplasmic vacuoles seen in routine sections represent a partly soluble material that is dissolved during histological preparation,

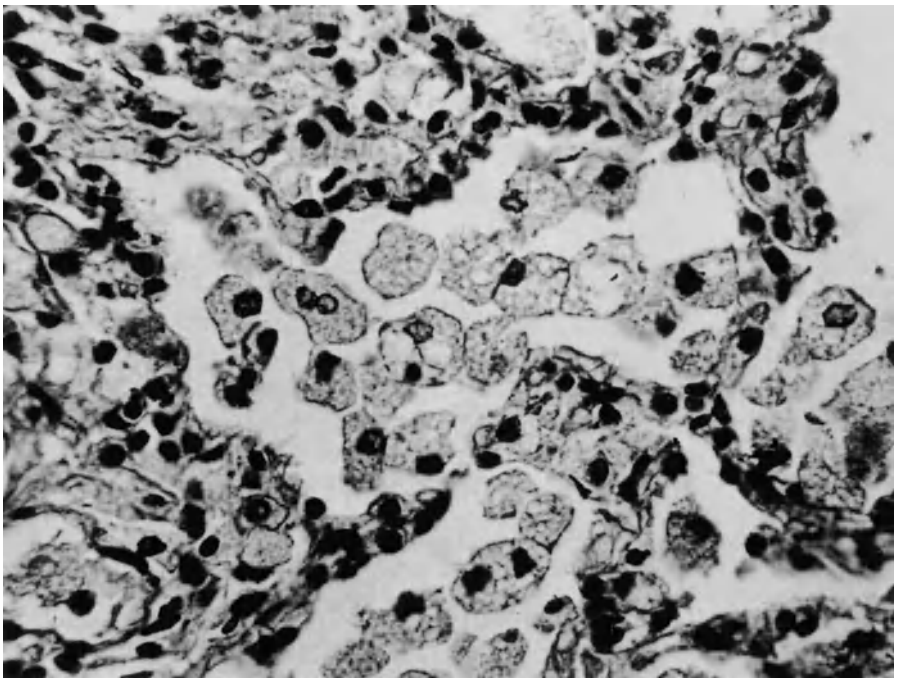

Figure 76-3 Under higher magnification, the foamy cells from a patient with Niemann-Pick disease (type A) contain one or two nuclei and numerous fine vacuoles (H&E, × 640).

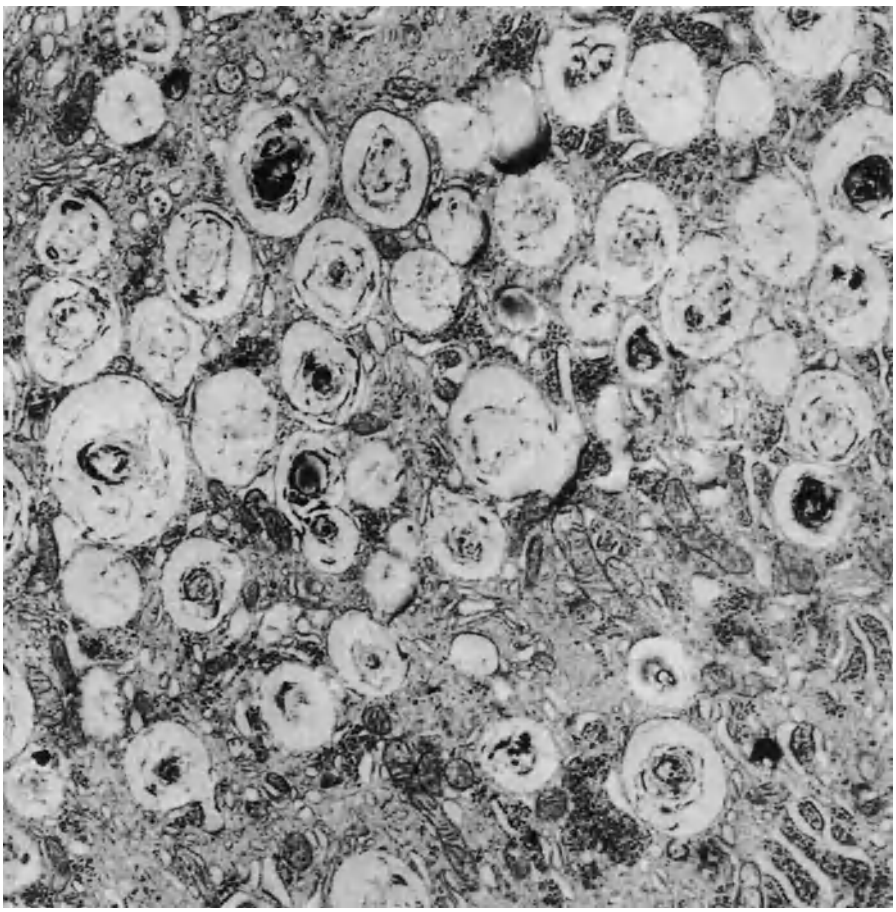

Figure 76-4 Electron micrograph of a portion of a foamy cell from a patient with Niemann-Pick disease containing cytoplasmic inclusion bodies which are membrane-bound and contain loosely arranged membranous structures (× 7200).

frozen sections are often required for this biochemical analysis (Fig. 76-2).

Ultrastructure

The foamy cells seen in the tissues of patients with NPD are filled with round to oval cytoplasmic bodies that range from 0.5 to 5 μm in diameter. These bodies are membrane-bound and contain loosely arranged membranous structures in types A and B NPD (Fig. 76-4). Electron-lucent vacuoles that are frequently accompanied by electron-dense membranes are seen in type C NPD. Histochemical preparations for lysosomal enzymes reveal reaction granules in the cytoplasmic inclusion bodies that are residua of a cellular effort to eliminate the accumulated lipid material.

Biochemical Features

An increase of 2 to 30 times normal in the sphingomyelin content of the viscera and/or brain is the basis for the diagnosis of types A and B NPD.

The esterified cholesterol content of the viscera is increased in type C. A deficiency of sphingomyelinase is the primary defect in types A and B, whereas impaired cholesterol metabolism occurs in types C, D, and E.

Type F shows heat-labile acid sphingomyelinase.

Diagnosis

Once suspicion of the disease is aroused types A and B NPD can be diagnosed by biochemical assays of sphingomyelinase in fresh blood samples and frozen tissue. The diagnosis of type C NPD requires analysis of cellular cholesterol esterification and the demonstration of filipin-cholesterol staining in cultured fibroblasts during low-density lipoprotein uptake. Enzyme analysis is not reliable for heterozygote studies, and molecular genetic identification is required. The peripheral smear, bone marrow, and/or lymph nodes or liver should be examined for foamy cells by special histochemical preparations. Types D and E also demonstrate abnormal cholesterol metabolism. Type F has heat-labile acid sphingomyelinase.

GAUCHER'S DISEASE

Gaucher's disease is a hereditary disorder which is transmitted as an autosomal-recessive trait. It is characterized by the accumulation of glucosyl ceramide in various organs in association with a deficiency of β-glucosidase.

Clinical Features

Three types of Gaucher's disease are usually recognized. Type 1, the "adult form," is the most common and usually

occurs in Ashkenazi Jews. It is a chronic disorder that may start soon after birth and usually lasts into childhood. It differs from the other types in its lack of neurological manifestations. Type 2 is the acute form. It occurs in infants and is characterized by progressive neurological deterioration. The incidence in Jewish families is less than in type 1. Type 3 is the subacute variety. It occurs in juveniles and undergoes a more protracted course of neurological deterioration than the type 2 disorder.

Some type 1 patients with the adult form of Gaucher's disease die early in life due to thrombocytopenia, severe anemia, and pulmonary infections. Hepatosplenomegaly and Gaucher's cells in the bone marrow are regular features. The concentration of acid phosphatase in serum is also markedly increased. Pulmonary hypertension and severe pulmonary arteriosclerosis occur in some patients. The reticular pattern of pulmonary infiltration that is characteristic of NPD is rare. Repeated episodes of bone pain are common, and fractures after minor trauma sometimes lead to permanent deformity. On radiologic examination, osteolytic changes are frequently seen.

In type 2 patients, the children develop normally until the age of 3 to 6 months. Thereafter, hepatosplenomegaly and lymphadenopathy become prominent, and Gaucher's cells are found in the bone marrow. High levels of serum acid phosphatase are sometimes found as early as at 3 months of age. Progressive psychomotor deterioration then sets in, and the patients die within 2 years.

In patients with the type 3 disorder, the course of neurological changes is more protracted. These patients also show splenomegaly and slowly progressive hepatomegaly. On radiologic examination, the children often display pulmonary infiltration. However, the typical reticular pattern is rare. Osteolytic lesions are frequent. About one-half of the patients with this variant have been reported from four interrelated families in the province of Norrbotten in northern Sweden. The mode of inheritance is also consistent with an autosomal-recessive trait. E-rosette–forming peripheral lymphocytes are defective in Gaucher's disease. This abnormality is caused by serum factors, one of which involves increased levels of ferritin, which have been found in these patients. The ferritin dysregulation may play a role in the high incidence of cancer in patients with Gaucher's disease.

Genetics

The gene coding acid β-glucosidase is located on chromosome 1 at q21. The gene for the enzyme is approximately 7 kb in length and contains 11 exons. A variety of mutations of this gene have been found to cause Gaucher's disease including missense mutations, frameshift mutations, a splicing mutation, deletions, gene fusions with a pseudogene, and gene conversions. The most common mutation in the Ashkenazi Jewish population is at nucleotide 1226, where an alteration in A-to-G causes an amino acid substitution in acid β-glucosidase.

Pathological Features

The spleen, liver, and lymph nodes of patients with this disease are markedly enlarged. Gaucher's cells are the histological hallmark of the disease (Fig. 76-5). They are round or polygonal in shape, measure 20 to 80 μm in diameter, and fibrils of varying sizes in their cytoplasm give the appearance of striation. Histochemically, Gaucher's cells show a characteristic reaction; they stain pink to red by the modified periodic acid–Schiff stain for cerebroside. These cells are primarily derived from the reticuloendothelial system. An unusual patient with Gaucher's disease has been reported: the patient is a 25-year-old black woman who had Gaucher's disease since 1 year of age with cardiac and renal involvement with pulmonary hypertension.

Although pulmonary infiltrates are typical on the chest radiograph, the infiltrates have not been extensively described in the literature. Severe involvement of the lungs in the adult disorder has been described in three patients with symptoms since infancy followed by the juvenile onset of dyspnea (Fig. 76-5). The lungs of these patients were heavy, and the cut surfaces revealed diffuse interstitial infiltrates. Gaucher's cells were found in the alveolar septa. The Gaucher's cells were located perivascularly and blocked gas exchange since they filled the alveoli. Also reported have been glomoid lesions in pulmonary arterioles with dilatation of postglomoid vessels which form angiomatoids typical of grade A3 hypertensive pulmonary vascular disease (Fig. 76-6), and

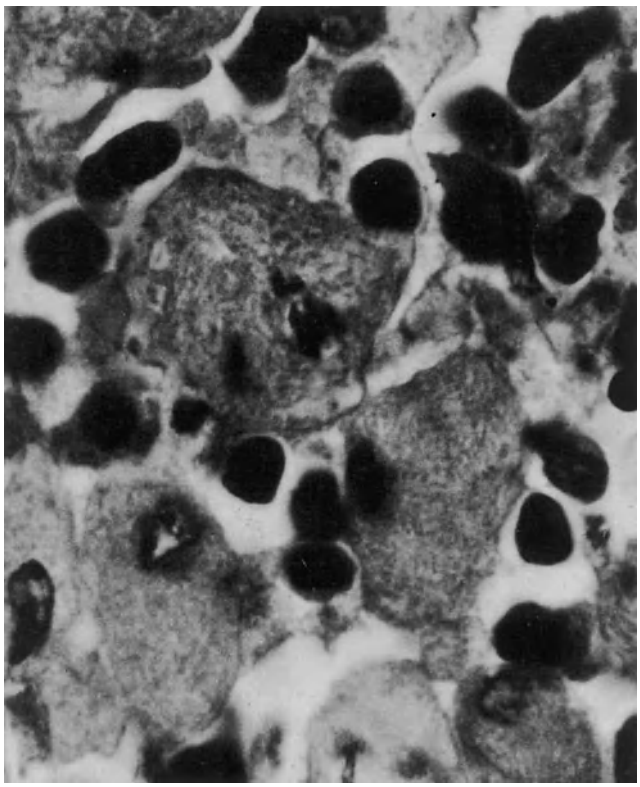

Figure 76-5 Gaucher's cells from an infant with Gaucher's disease. They contain numerous fibrils and appear striated (H&E, × 1090).

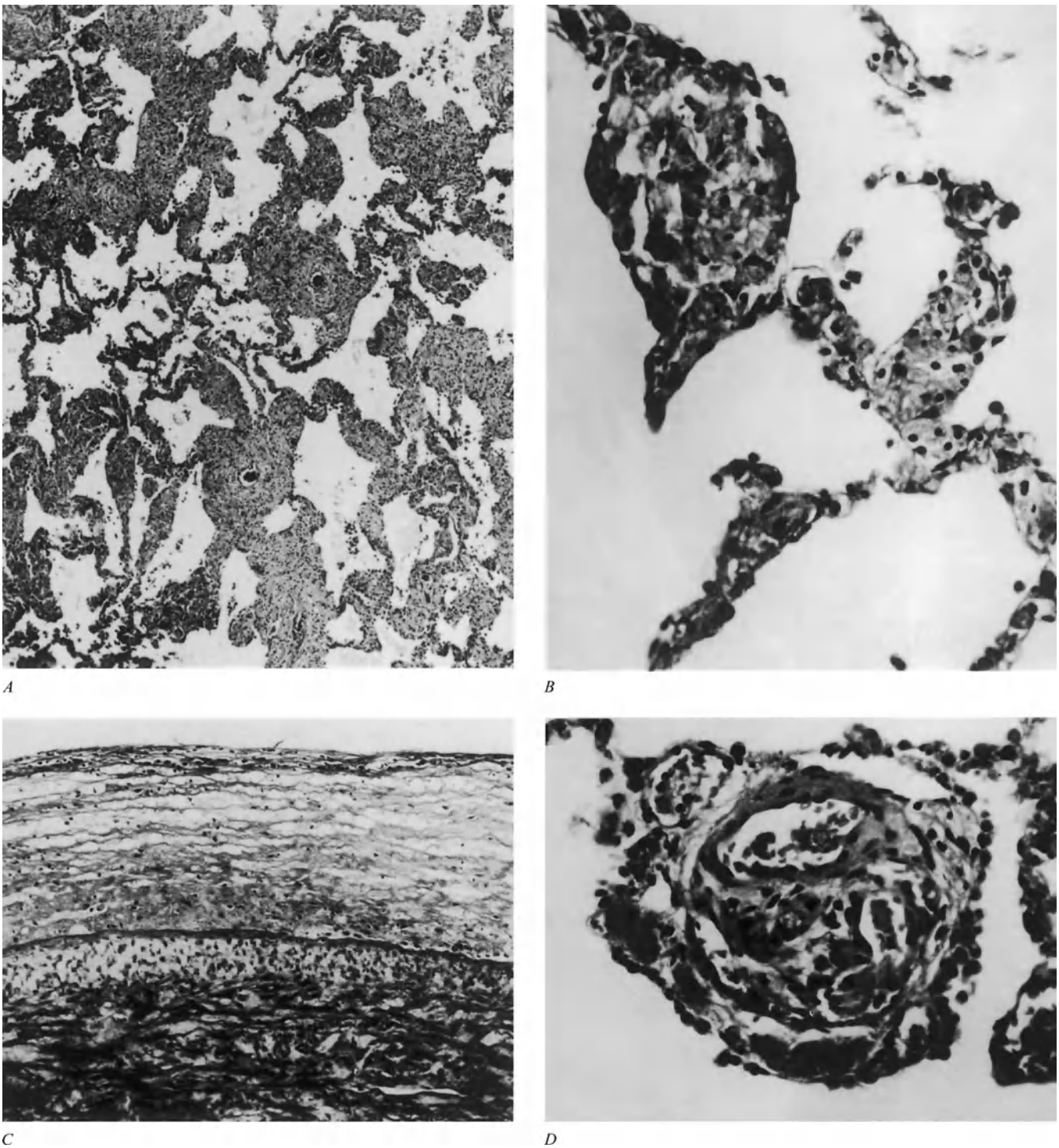

Figure 76-6 A & B. Low- and high-powered photomicrographs of pulmonary parenchymal infiltration by Gaucher's cells. The vascular bed appears to be absent in much of the tissue and what remains shows distension of capillaries with blood. *C*. Atherosclerotic lesion from the main pulmonary artery. *D*. Glomoid lesion in a pulmonary arteriole with dilatation of postglomoid vessels forming an angiomatoid, typical of grade A3 hypertensive pulmonary vascular disease. (*Courtesy of Dr. G.M. Hutchins,* Am J Med *65:356, 1978.*)

numerous marrow emboli of various ages containing Gaucher's cells.

In one series, malignant tumors associated with Gaucher's disease have been reported in 35 of 275 patients. The associated malignancies were myeloma, Hodgkin's disease, acute myelogenous leukemia, lymphatic leukemia, carcinoma of the lung, breast, kidney, liver, colon, pancreas, skin, mouth, larynx, prostate, and brain.

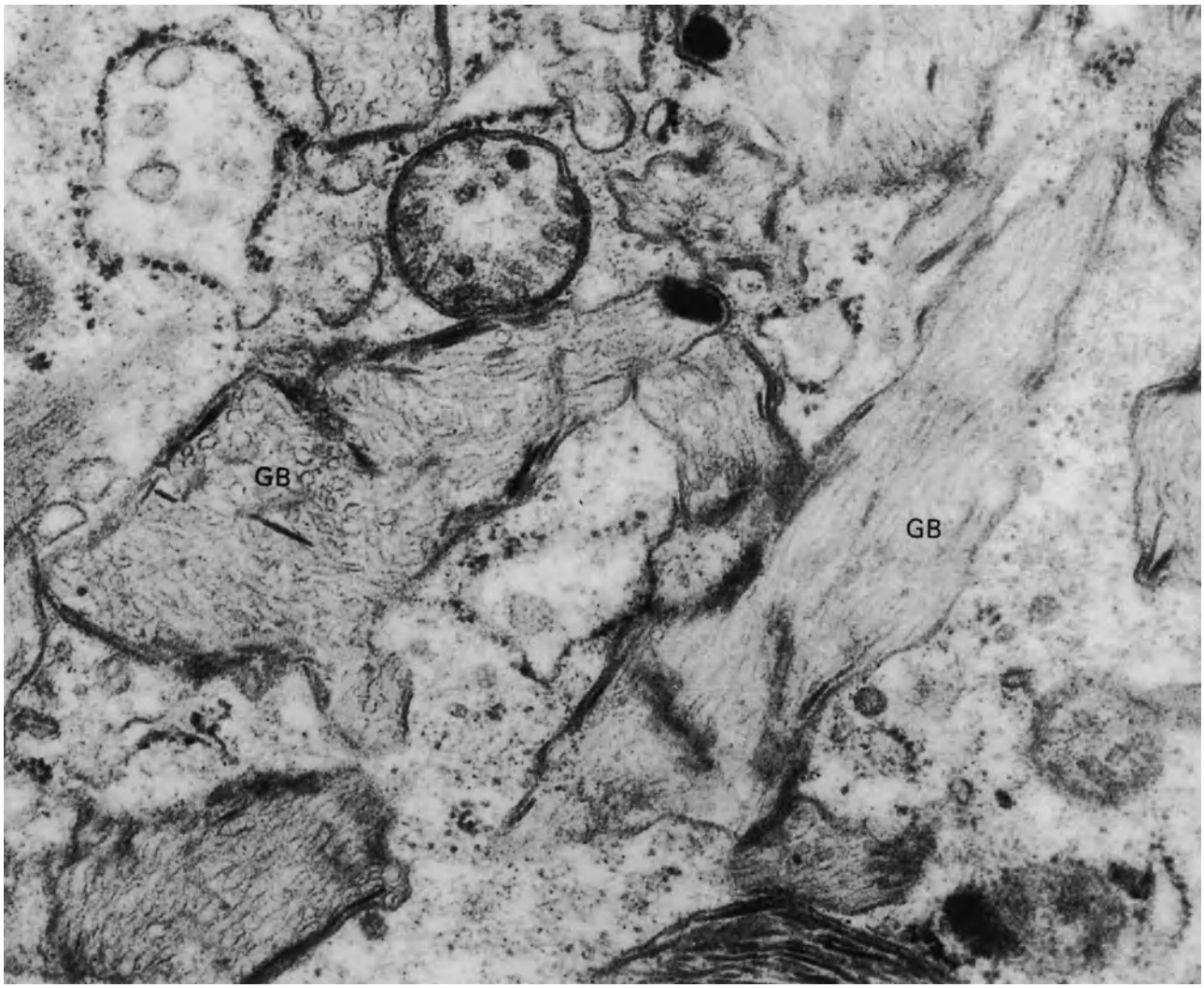

Figure 76-7 Electron micrograph of a portion of a Gaucher's cell showing pleomorphic Gaucher's bodies (GB) which contain tubular structures (× 43,000).

Ultrastructure

The Gaucher's cells contain pleomorphic cytoplasmic inclusion bodies enveloped in a single limiting membrane. These inclusions, called "Gaucher's bodies," contain tubular structures measuring 120 to 250 Å in diameter (Fig. 76-7), each of which consists of 10 to 12 fibrils in a characteristic arrangement. The inclusion bodies are derived from the cisternae of the endoplasmic reticulum. Acid phosphatase preparations disclose reaction granules within the Gaucher's bodies which indicate the lysosomal character of the inclusion material (Figs. 76-6 and 76-7).

Biochemical Features

The organs of patients with the three types of Gaucher's disease almost always have a marked increase in the concentration of glucose-1-ceramide, occasionally exceeding 100 times normal. The enzyme defect in Gaucher's disease is a deficiency of β-glucosidase which catalyzes the cleavage of glucose from glycosyl ceramide.

Therapy

Bone marrow transplantation has been employed in severe Gaucher's disease. It was successful in restoring β-glucosidase in mononuclear white blood cells and plasma with complete engraftment of the enzymatically normal donor cells. However, Gaucher's cells persisted in the bone marrow. The 8-year-old patient with type 3 Gaucher's disease died of sepsis 13 months after bone marrow transplantation.

Diagnosis

All suspected cases of Gaucher's disease should undergo a careful radiologic survey of the lungs and bones, identification of Gaucher's cells in smears from the bone marrow, and assays of β-glucosidase in leukocytes, or cultured fibroblasts. Should liver biopsy or splenectomy be undertaken, enough fresh frozen tissue (1.0 g) should be preserved for determination of the levels of glycosyl ceramide and β-glucosidase activity. Portions of these tissues should be studied histologically and

electron microscopically. For heterozygote studies, molecular genetic identification is required.

G_{M1} GANGLIOSIDOSIS (β-GALACTOSIDOSIS)

Three types of G_{M1} gangliosidosis have been recognized. The type 1 disorder is an infantile form with generalized gangliosidosis, accompanied by bone involvement and psychomotor retardation. Early in the disease, the lungs are unremarkable. Later, bronchopneumonia is common, and the patients usually die of bronchopneumonia before the age of 2 years. Radiologically, abnormalities similar to Hurler's disease are observed after 6 months. Foamy cells are demonstrable in smears of bone marrow. The type 2 disorder is a late infantile, juvenile form with milder bone abnormalities and progressive motor and mental deterioration. The average life span of children with this variant varies from 3 to 10 years. Visceral histiocytosis is less common, but neuronal lipidosis occurs more often than in type 1. The type 3 disorder is an adult, chronic form with juvenile onset of progressive cerebellar dysarthria and slow but progressive motor and intellectual impairment. Long-term survival is characteristic of this variant.

Genetics

The β-galactosidase gene has been mapped to chromosome 3p21-3q21. The cDNA coding for this enzyme has been cloned, and the genomic organization of the gene has been determined. Molecular genetic analysis has demonstrated heterogeneous genetic mutations in infantile G_{M1} gangliosidosis.

Pathological and Ultrastructural Features

Grossly, the liver, spleen, and kidneys of patients with this disease are usually increased in size and weight, but their lungs generally appear normal. The most striking histological finding is the presence of foamy histiocytes in many visceral organs. In the lungs, these cells are observed in the alveoli and septa. The material in their cytoplasmic vacuoles consists of complex proteolipid compounds. These cells also contain membrane-bound inclusions which consist of moderately electron-dense material mixed with fine granules (Fig. 76-8).

Biochemical Features

A deficiency of β-galactosidase is the underlying basis of this disorder. The deficiency causes ganglioside G_{M1} to accumulate in the different organs. The deficiency of β-galactosidase apparently also interferes with the degradation of mucopolysaccharides (Fig. 76-8).

Diagnosis

The diagnosis of β-galactosidosis can be confirmed by analysis of β-galactosidase activity in leukocytes, urine, and skin. Ultrastructural studies of biopsies of rectal mucosa can also be useful. Since enzyme studies are unreliable for heterozygotes, gene analysis is required for detection of carriers.

SULFATIDE LIPIDOSIS (METACHROMATIC LEUKODYSTROPHY)

Five categories of sulfatide lipidosis have been identified based on the age of onset of clinical manifestations: congenital, late infantile, early juvenile, late juvenile, and adult. In addition, two other types have been identified: multiple sulfate deficiency (MSD) and cerebroside 4-6 sulfatase activator deficiency. The clinical manifestations of these disorders predominantly reflect the striking changes in the white matter of the brain that occur during the course of the disease. MSD, however, begins with respiratory difficulty in early infancy followed by progressive psychomotor deterioration.

Genetics

The arylsulfatase A gene is located on chromosome 22 at q13. The mutations underlying the disorder have been identified in 60 to 70 percent of the arylsulfatase A gene. Therefore, carrier studies using genetic analysis are not feasible. The cerebroside sulfatase activator gene is located on chromosome 10 at q21-q22. Its mutations in patients with this disorder are incompletely understood.

Pathological and Biochemical Features

Grossly, the visceral organs from patients with sulfatide lipidosis are unremarkable. In contrast, microscopic changes are widespread and characterized by metachromatic cytoplasmic inclusion bodies, commonly affecting the lungs. These metachromatic granules are within histiocytes in the interalveolar septa but not in the alveolar spaces or in the vascular walls of the septa. Ultrastructural examination indicates that the cytoplasmic inclusion bodies are composed primarily of lamellar structures and irregular whorls.

Patients afflicted with this disease show a marked increase in the concentration of cerebroside sulfatides in their brain and viscera. This abnormality is secondary to the reduced activity of arylsulfatase A and to a lesser degree arylsulfatase B. Arylsulfatase C is affected only in MSD.

Diagnosis

The most important diagnostic procedure for β-galactosidosis is the quantification of arylsulfatase A activity levels in the leukocytes or cultured skin fibroblasts from patients who are suspected of having the disorder. Analysis for sulfatase A in the urine is rapid and simpler but less reliable. Heterozygotes can be identified by leukocyte

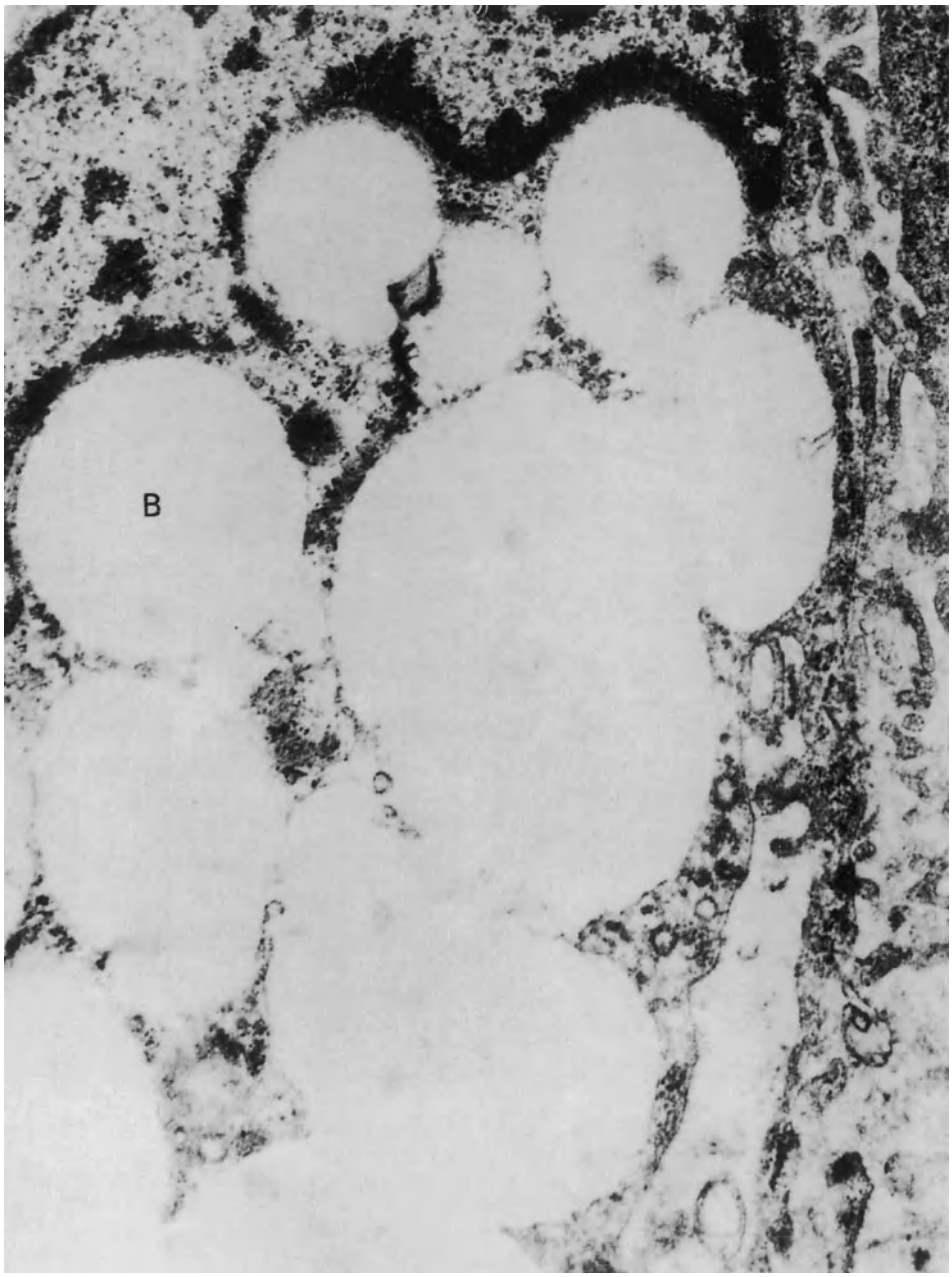

Figure 76-8 Electron micrograph of a portion of a foamy cell from a patient with G_{M1} gangliosidosis showing cytoplasmic membrane-bound inclusion bodies (B) which contain electron-lucent material mixed with fine granules (× 15,000).

and fibroblast assays for arylsulfatase A and cerebroside sulfatase.

GALACTOSYLCERAMIDE LIPIDOSIS: GLOBOID-CELL LEUKODYSTROPHY (KRABBE'S DISEASE)

Clinical Features

Three clinical forms of galactosylceramide lipidosis (GL) have been described based on the age of the patient at the onset of the disease. In most patients the disease occurs in early infancy, exhibiting its first clinical symptoms at 3 to 6 months of age. The disease is characterized by progressive psychomotor deterioration that generally culminates in death within 2 years. The late infancy form is rare and manifests as mental deterioration, pyramidal signs, and visual impairment in children 2 to 6 years old. The duration of this variant is approximately 1 to 5 years. In the adult form, the main clinical manifestation is visual impairment that starts between the ages of 10 and 35 years. Patients with this disease variant also exhibit slowly progressive motor deterioration and usually survive 2 to 10 years after presentation.

Genetics

GL is transmitted as an autosomal-recessive trait. The galactosylceramidase gene has been mapped to chromosome 14. The cDNA or the gene coding for the enzyme has not been cloned and the mutations underlying the disorder have not been characterized.

Pathological and Biochemical Features

In β-galactosidosis the gross pathological changes are generally confined to the brain. The white matter of all lobes of the brain is extensively affected whereas the cortices and deep gray matter are relatively preserved. Although the visceral organs appear normal, giant cells, similar to the globoid cells in the nervous system, also occur in the lungs, lymph nodes, spleen, and bone marrow. The globoid cells, which are derived from histiocytes, are characterized by large round cell bodies, several peripherally placed nuclei which are 20 to 50 μm in diameter, and fine cytoplasmic granules (Fig. 76-9). Similar lesions have been found in a variety of animal models of this disease in sheep, dogs, and the twitcher mouse (Fig. 76-9).

The primary defect in this disorder involves the enzyme galactocerebroside β-galactosidase. This leads to a marked increase in the galactosylceramide concentrations in the white matter of the brain and subsequent cerebral dysfunction.

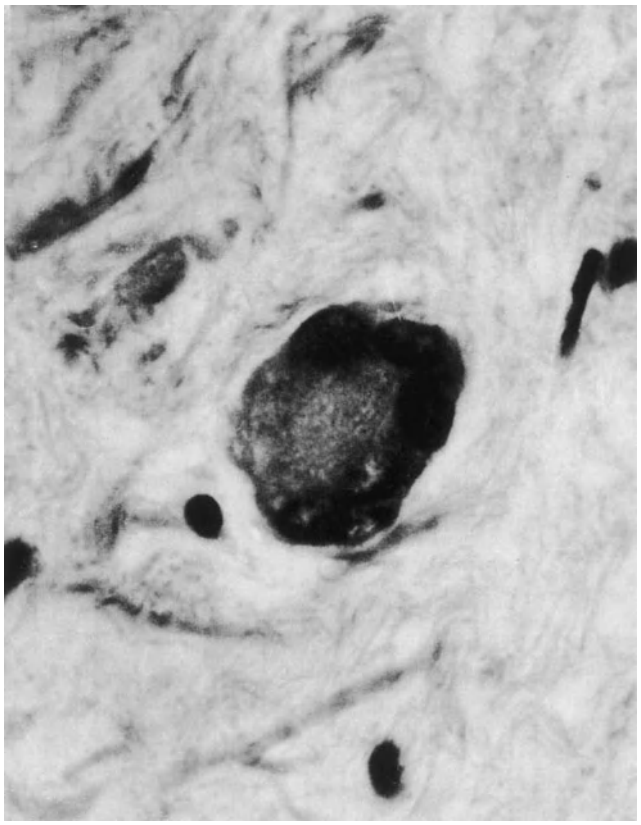

Figure 76-9 The globoid cell from a child with Krabbe's disease is characterized by large, round cell bodies containing several peripherally placed nuclei and many cytoplasmic fine granules (H&E, × 1100).

Diagnosis

In infants suspected of having GL serum, leukocytes or cultured fibroblasts should be studied to quantitate the activity of galactocerebroside β-galactosidase.

FABRY'S DISEASE (α-GALACTOSIDASE A DEFICIENCY)

Fabry's disease (FD) is the only sphingolipidosis that is transmitted by the gene on the X chromosome that controls the hydrolytic enzyme α-galactosidase A. The clinical picture results from the progressive accumulation of globotriaosyl (ceramide) in most visceral organs as well as the brain.

Clinical Features

The clinical manifestations of this disease most often occur in men but occasionally occur in heterozygote women. FD presents in childhood or adolescence with two types of symptoms: severe pain and telangiectasis. The pain is often in the form of a lightning or burning sensation in the fingers or toes that extends to the palms and soles, respectively. Attacks of abdominal or flank pain simulate those of appendicitis or renal colic. The telangiectases are symmetrical, involve the superficial layers of the skin, do not blanch on pressure, and are progressive. The oral mucosa, conjunctivae, hips, back, thighs, buttocks, penis, and scrotum are most commonly involved. The area between the umbilicus and the knees is involved less often but can be severely affected. Some patients with this disease develop abnormalities in the lungs. These abnormalities range from obstructive disease of the airways to diffuse interstitial abnormalities. Pulmonary function tests in older patients may reveal significant airflow obstruction, a reduced diffusing capacity, and a reduction in the V_{max25} values. Pulmonary complications are a frequent cause of death.

Genetics

The gene that is responsible for this disease has been localized to chromosome Xq22. The α-galactosidase A cDNA and genomic sequences have been isolated, characterized, and used to analyze the mutations that cause the disease. Partial gene rearrangements, splice-junction defects, and point mutations have been identified.

Pathological Features

Compared to appropriate controls, the lungs from patients with FD are increased in weight and have cut surfaces that are often congested and edematous. Multiple vacuoles also occur in the alveolar epithelium, airway, and vascular smooth-muscle cells and capillary endothelial cells. Ultrastructural examination shows that both the capillary endothelium and the alveolar type II cells contain laminated inclusions with a periodicity of 50 to 60 A. This pattern contrasts with the variable periodicity of the lamellar bodies contained within the type

II cells in the normal lung. The cytoplasmic inclusion bodies in the ciliated epithelial cells and goblet cells stain darkly with toluidine blue. Ultrastructurally, these inclusion bodies are limited by a single membrane and contain electron-dense lamellae arranged in either a parallel or concentric fashion. Alveolar macrophages are devoid of these inclusions.

Biochemical Features and Diagnosis

The primary enzyme defect in this disorder is the absence of α-galactosidase A activity. Affected males can be identified by demonstrating an increase in globotriaosylceramide and by assaying hydrolase activity in serum, leukocytes, tears, and cultured skin fibroblasts.

MUCOPOLYSACCHARIDOSIS

The term *mucopolysaccharidosis (MPS)* refers to a group of genetic diseases manifested by abnormal tissue deposition of acid mucopolysaccharide (glycosaminoglycans). Seven major forms of the disease have been recognized: Hurler's syndrome (MPS I), Scheie's syndrome (MPS IS, formerly V), Hunter's syndrome (MPS II), Sanfilippo's syndrome (MPS III), Morquio's syndrome (MPS IV), Maroteaux-Lamy syndrome (MPS VI), and Sly's syndrome (MPS VII). The most severely affected patients (except for those with type IS) commonly have respiratory involvement, particularly obstructive disease of the airways.

Genetics

The MPS diseases are transmitted in an autosomal-recessive pattern, except for MPS II, which is X-linked. The MPS I gene has been assigned to chromosome 22 at 4p16.3, the MPS II locus to Xq27-28, the gene of the very rare MPS III D (Sanfilippo D) to 12q14, the MPS IV A (Morquio A) gene to 16q24, the MPS VI gene to 5q13-q14, and the MPS VII gene to 7q21-q22.

Pathological Features

The visceral organs from patients with MPS can be grossly abnormal. However, the exact pattern of involvement varies with the type of disease that is manifested. Interestingly, in these patients, the lungs are rarely visibly abnormal. In type I, MPS histological alterations are seen in almost all organs, including the lungs. The characteristic feature is the presence of an abnormal deposited material in cells that are variously called clear cells, gargoyle cells, Hurler's cells, or balloon cells. The cells are large, oval or polygonal, measure 20 μm in diameter, and contain pale central nuclei. Frozen sections exhibit metachromatic material that stains with toluidine blue and gives a positive reaction in Alcian blue preparations. Characteristically the cells also contain round or oval inclusion bodies that are membrane-bound and display an electron-lucent or low electron-dense material, occasionally mixed with fine granules or lamellae. The histological changes in types II and III MPS are similar to those of type I. The histological findings in the other types are less well documented.

Biochemical Features

Patients with types I and IS MPS have a deficiency of α-L-iduronidase and increased urinary excretion of dermatan sulfate and heparin sulfate. The deficiency in type II MPS involves iduronate sulfatase. Dermatan sulfate and heparin sulfate are also excreted in abnormally large quantities in the urine of patients with this disorder. Although about 80 percent of the extracted mucopolysaccharide is dermatan sulfate in type I, in type II that portion is about 55 percent. In type III MPS, lesions have been found in the four enzymatic steps involved in the excretion and accumulation of heparin sulfate. The abnormalities are in heparin N-sulfatase in type III A; N-acetyl-α-D-glucosaminidase in type III B; acetyl CoA: α-glucosaminide-N-acetyltransferase in type III C; and N-acetyl-α-D-glucosaminide-6-sulfatase in type III D. The enzymatic defects in type IV MPS involve galactosamine-6-sulfate sulfatase in type IV A and β-galactosidase in type IV B. As a result these patients have increased levels of urinary keratan sulfate. Type VI MPS is due to a deficiency of arylsulfatase B activity, which results in increased urinary excretion of dermatan sulfate; type VII MPS is the result of the defective degradation of dermatan sulfate and heparin sulfate due to a deficiency of β-glucuronidase.

Diagnosis

The excretion of urinary mucopolysaccharides is markedly increased in many of these disorders. Although metachromatic material can be demonstrated in polymorphonuclear leukocytes and lymphocytes, the diagnosis can only be established by measuring urine mucopolysaccharides with precise identification of the substance excreted. The characteristic enzyme defect of each disorder should also be studied in leukocytes, serum, or fibroblasts from the patient.

GLYCOGEN STORAGE DISEASE

Among the major groups of glycogen storage disorders (GSD), Pompe's disease (GSD, type II) frequently shows cardiorespiratory disturbances. Hypotonia, which often develops by 2 months of age, is the cardinal feature of this disorder. The heart is markedly enlarged, and heart failure is common. Most patients die within the first year of life. However, a few survive up to 15 years.

Genetics

The disease is transmitted as an autosomal-recessive trait. It is believed to result from the dysfunction of the structural gene for acid α-glucosidase, which is located at chromosome 17 q23.

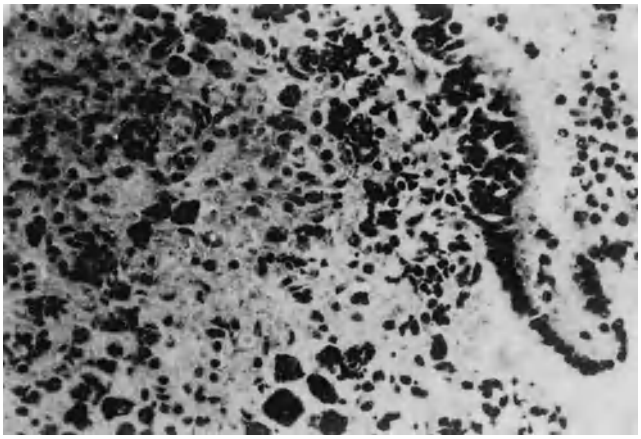

Figure 76-10 Intra-alveolar and interstitial macrophage laden with glycogen granules (black granules). (Best's glycogen stain.) *(From Spencer H: Pathology of the Lung. Oxford, Pergamon Press, 1985, pp 753–754, with permission.)*

Pathological and Biochemical Features

The lungs and brains of patients with GSD are grossly normal. In contrast, the heart is usually markedly enlarged and increased in weight (Fig. 76-10).

About one-fifth of the patients show thickening of the endocardium similar to that seen in endocardial fibroelastosis. Hepatomegaly is also frequent. Histologically, GSD is characterized by the massive accumulation of glycogen granules in the cytoplasm of the parenchymal cells of most organs including the lungs. Foamy alveolar macrophages filled with glycogen-like material also occur (Fig. 76-10). Glycogen is present in smaller amounts in cartilage cells and mucosal and bronchial epithelial cells. Ultrastructurally, the cytoplasmic inclusion bodies are membrane-bound and contain electron-dense glycogen granules. The massive accumulation in this disorder of tissue glycogen is due to a deficiency in acid maltase (acid α-glucosidase) activity.

Diagnosis

The diagnosis of GSD can be established by demonstrating increased concentrations in tissues of glycogen and a deficiency of α-glucosidase activity. Studies of urine, muscle tissue, and cultured fibroblasts are helpful in this regard.

DISORDERS OF AMINO ACID METABOLISM

Among the various types of amino acid metabolic disorders, only maple syrup urine disease (MSUD) (leucinosis, branched-chain ketonuria) is occasionally associated with bouts of respiratory difficulty for which there is no infectious explanation. In affected infants, respiratory distress develops within the first week of life. The infants often become apneic and require respiratory assistance. Severe psychomotor deterioration and episodes of seizures occur during the course of the disease, and the children usually die from intercurrent infections within the first year. However, with the help of a synthetic diet, some patients have survived for as long as 13 years.

Despite severe clinical symptoms in early life, at autopsy only the brain shows specific changes. Grossly, it exhibits microcephaly and microgyria. Histologically it shows a deficiency in myelin sheaths, presumably a result of reduced synthesis of proteolipids.

Genetics and Biochemical Features

MSUD is an autosomal-recessive disorder that is thought to result from abnormalities in the genes of the branched chain α-ketoacid dehydrogenase complex (E1-E3). These genes are on different chromosomes: E1α to chromosome 19q13.1-q13.2, E1β to 6p21-p22, E2 to 1p31, and E3 to 7q31-q32. The mutations in these enzymes cause a deficiency of branched-chain α-ketoacid dehydrogenase resulting in increased levels of urinary amino acids (leucine, isoleucine, and valine) and plasma branched-chain ketoacids.

Diagnosis

Patients with this disease classically have a maple-syrup-like odor of their urine which can be detected within the first weeks of life. Although the odor is clinically the most distinctive sign of this disease, the diagnosis should be verified by studies of the amino acids and ketoacids in blood and urine. The diagnosis is confirmed by enzymatic studies of leukocytes or cultured skin fibroblasts and lymphoblasts.

CYSTINE STORAGE DISEASE (LIGNAC-FANCONI DISEASE)

This disorder causes widespread pathological changes in many organs. It is inherited as a simple Mendelian recessive and manifests in children as severe rickets or dwarfism with marked photophobia, amino aciduria, and death from infection or renal dysfunction.

The disease affects the lungs, bones, kidneys, lymph nodes, spleen, and liver. The deposits provoke no cellular reaction and do not alter pulmonary function. The deposits may be mistaken for calcium with von Kossa's stain if they contain traces of cystine. The cystine is water-soluble, and thus sections are best fixed in absolute alcohol. In tissue sections, the crystals are birefringent and form clumps of radiating needlelike crystals when treated with concentrated sulfuric acid and phosphotungstic acid. The crystals in the lungs are mainly distributed within the peribronchial and periarterial reticuloendothelial cells in the alveolar septa.

CONCLUSIONS

Enzyme replacement therapy for these storage diseases is not totally successful at present. However, the birth of children

afflicted with inborn errors of metabolism can be prevented by prenatal diagnosis through amniocenteses and analysis of enzyme activity of cultured amniotic cells. Therefore, advice for genetic counseling seems to be one of the important functions of the physician if the parents are homozygotes or carriers and may produce a child afflicted with one of these disorders.

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PART

VIII

Alveolar Diseases

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77

Alveolar Hemorrhage Syndromes

Joseph P. Lynch, III • James W. Leatherman

Diffuse alveolar hemorrhage (DAH) is a potentially catastrophic complication of myriad immune and nonimmune disorders. Clinical features are broad, but hemoptysis, infiltrates on chest radiographs, hypoxemia, and progressive respiratory insufficiency are common to diverse etiologies. Nonimmune causes of alveolar hemorrhage include endobronchial tumors, arteriovenous malformations or aneurysms, ulcerative tracheobronchitis, hemorrhagic pneumonia, bronchiectasis, congestive heart failure, uremia, thrombocytopenia or coagulopathy, pulmonary venoocclusive disease, and massive pulmonary embolism. These nonimmune causes need to be excluded in patients with severe alveolar hemorrhage. Depending upon the clinical scenario, coagulation profiles and ancillary tests (e.g., echocardiogram, chest computed tomographic [CT] pulmonary angiography, fiberoptic bronchoscopy) may be required to establish a specific diagnosis. In addition, other causes of diffuse parenchymal infiltrates (but without severe alveolar hemorrhage) share features in common with DAH syndromes (e.g., cryptogenic organizing pneumonia, hypersensitivity pneumonitis, pulmonary alveolar proteinosis, and diverse interstitial or alveolar lung disorders). A discussion of these disorders is beyond the scope of this chapter, which focuses primarily on immune-mediated causes of DAH.

AUTOIMMUNE CAUSES OF ALVEOLAR HEMORRHAGE: DIFFERENTIAL DIAGNOSIS

Autoimmune DAH results from diffuse injury to the pulmonary microvasculature (termed *capillaritis* or *endotheliitis*) (Table 77-1). Systemic necrotizing vasculitides (principally microscopic polyangiitis [MPA] and Wegener's granulomatosis [WG]) account for the majority of cases of autoimmune DAH. Other causes of autoimmune DAH include antiglomerular basement membrane antibody (anti-GBM) disease, collagen vascular disorders (principally systemic lupus erythematosus [SLE]), exogenous agents (e.g., trimellitic anhydride, isocyanates), or drugs (e.g., D-penicillamine, propylthiouracil, etc.). In many of these disorders, rapidly progressive glomerulonephritis (RPGN) is present concomitantly. In most patients with autoimmune DAH and glomerulonephritis (GN), anti-GBM antibody and immune complexes are lacking. The term *pauci-immune glomerulonephritis* has been used to refer to this group of patients, who encompass a heterogenous group of disorders (discussed in detail below). Idiopathic pulmonary hemosiderosis, a rare cause of recurrent DAH with no renal or extrapulmonary component, occurs primarily in children and remains a diagnosis of exclusion.

Table 77-1

Etiology of Autoimmune Diffuse Alveolar Hemorrhage

Antiglomerular basement membrane antibody disease (Goodpasture's syndrome)
Antineutrophil cytoplasmic antibody (ANCA) mediated vasculitis (e.g., Wegener's granulomatosis, microscopic polyangiitis, Churg-Strauss syndrome, pauci-immune glomerulonephritis)
Idiopathic rapidly progressive glomerulonephritis
Collagen vascular disease (e.g., systemic lupus erythematosus)
Immunocompromised status (e.g., bone marrow transplant, AIDS)
Exogenous agents or drugs (e.g., trimellitic anhydride, isocyanates, D-penicillamine, cocaine)
Idiopathic pulmonary hemosiderosis (pathogenesis unknown)

Differentiation of these diverse syndromes can usually be accomplished by serological studies and by kidney biopsy. In such cases, lung biopsy is not required. GN can be demonstrated in the great majority of patients with DAH complicating WG or MPA. By contrast, the kidneys may be spared in DAH associated with collagen vascular disease, bone marrow transplant recipients, or immunocompromised patients. Urinalysis (to look for microscopic hematuria, red cell casts, and proteinuria) and measurement of renal function should always be done in the diagnostic evaluation of DAH. Findings consistent with GN warrant a prompt and aggressive evaluation that should include percutaneous needle biopsy of the kidney.

CLINICAL FEATURES OF AUTOIMMUNE ALVEOLAR HEMORRHAGE

Irrespective of etiology, the clinical, radiographic, and histopathological features of DAH may be similar. Classical findings are hemoptysis, diffuse alveolar infiltrates, hypoxemia, renal failure, and iron-deficiency anemia. However, the clinical spectrum is wide, and many of these features may be subtle or absent. In this context, the diagnosis of DAH may be difficult, as signs and symptoms overlap with diverse etiologies of diffuse alveolar infiltrates. Prompt diagnosis and institution of therapy is vital to avert early mortality from DAH and late sequelae from end-stage renal failure. Chest radiographs typically reveal bilateral alveolar infiltrates, often with a bat-wing appearance. However, focal, and even unilateral, patterns indistinguishable from pneumonia may occur. Following cessation of bleeding, infiltrates markedly improve or normalize within 24 to 72 h (Fig. 77-1). A presumptive diagnosis of DAH can often be made by a combination of clinical and serological findings and bronchoalveolar lavage (BAL) fluid. Grossly bloody BAL fluid (with progressively more blood with serial aliquots), large numbers of hemosiderin-laden macrophages, and the absence of purulent secretions or ancillary evidence for infection strongly support DAH as a cause of pulmonary infiltrates. Ancillary studies including serologies, renal function tests, and urinalysis may support the diagnosis.

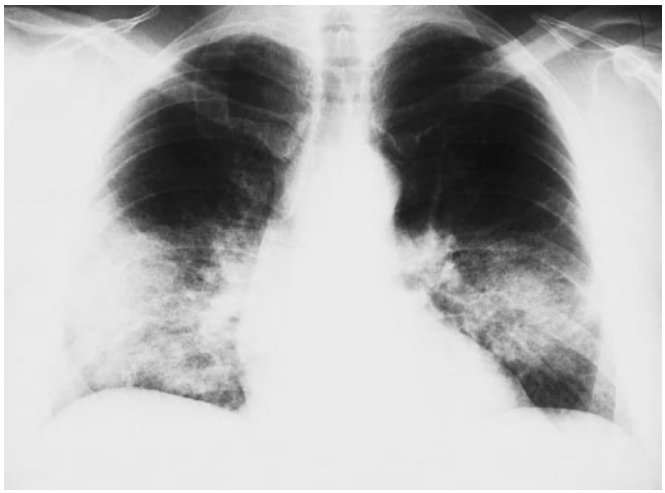
DIAGNOSIS

The Role of Lung Biopsy

The role of lung biopsy in the diagnosis of DAH and the determination of its etiology is controversial. We believe the risks of open or thoracoscopic lung biopsy are excessive in patients with severe DAH and respiratory failure. Postoperative complications such as infection and air leaks may be exacerbated by the corticosteroid or immunosuppressive agents used to treat many of these immune-mediated DAH syndromes. Furthermore, histological features are usually nonspecific. Predominant findings are extensive intra-alveolar hemorrhage and necrotizing pulmonary capillaritis (endotheliitis) (Fig. 77-2). Capillaritis is characterized by neutrophilic infiltration of capillaries, fragmented neutrophils (leukocytoclasis), and necrosis of the capillary walls (Fig. 77-3). Loss of the integrity of the alveolar-capillary basement membrane results in leakage of red blood cells and neutrophils into the alveolar space. Hemosiderin-laden macrophages (siderophages) accumulate within the alveolar spaces and interstitium; their presence is a clue to prior episodes of alveolar hemorrhage (Fig. 77-4).

Capillaritis was initially described as a marker of systemic vasculitis, but may also be observed in myriad disorders associated with DAH (e.g., SLE, collagen vascular disorders, anti-GBM disease, bone marrow transplant recipients, and drug-induced DAH). An associated venulitis and arteriolitis may sometimes be present, but larger vessels are spared. Capillaritis is subtle and often overshadowed by DAH filling the alveolar spaces.

Pulmonary capillaritis can be diagnosed by transbronchial biopsy, but this diagnosis is made with greater confidence when a larger biopsy specimen is obtained by video-assisted thoracoscopy or limited thoracotomy. Additional pathological features may be seen in patients with underlying granulomatous vasculitis (e.g., granulomas, necrosis, or eosinophils). Nongranulomatous inflammation in airways and lung interstitium, interstitial fibrosis, diffuse alveolar damage (DAD), fibrinous pleuritis, and cryptogenic



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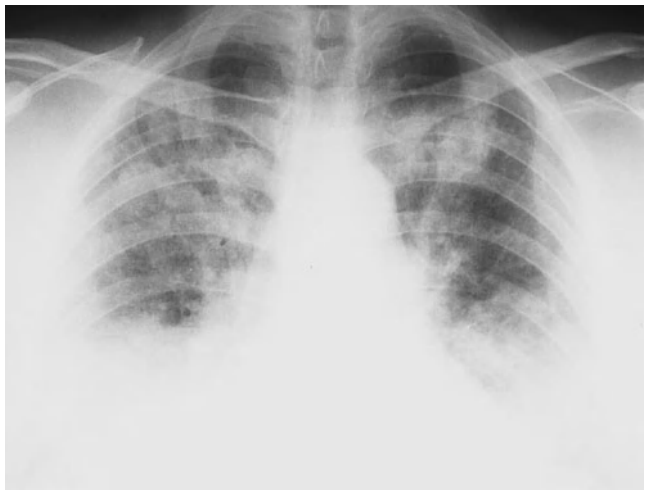

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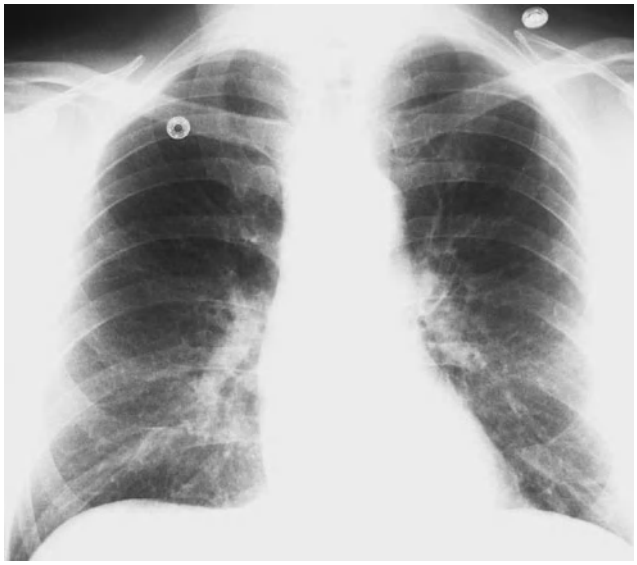


C

Figure 77-1 *A*. Idiopathic rapidly progressive glomerulonephritis. Posterior-anterior (PA) chest radiograph from a 52-year-old man with rapidly progressive glomerulonephritis, hemoptysis, and bilateral alveolar infiltrates, consistent with alveolar hemorrhage. Bronchoalveolar lavage demonstrated blood-tinged fluid and numerous hemosiderin-laden macrophages. *B*. Idiopathic rapidly progressive glomerulonephritis. PA chest radiograph from the same patient 18 months later with diffuse bilateral alveolar infiltrates representing recurrent massive alveolar hemorrhage. He was treated with pulse methylprednisolone (1 g daily for 3 days), followed by a gradual corticosteroid taper. *C*. PA chest radiograph from the same patient 3 weeks later demonstrating complete resolution of the alveolar infiltrates.

organizing pneumonia have also been described in DAH associated with antineutrophil cytoplasmic antibody (ANCA) vasculitic syndromes. Histological findings of alveolar hemorrhage and capillaritis, although distinctive, are nonspecific. Immunofluorescent stains (of lung or kidney) or serological markers (e.g., anti-GBM antibody or ANCA) are required to differentiate the various causes of autoimmune DAH (Table 77-2). Linear deposits of immunoglobulin G (IgG) along alveolar septa is pathognomonic for anti-GBM disease. A granular, or "lumpy-bumpy" pattern of immune complex deposits may be seen in SLE, systemic necrotizing vasculitis, or immune complex-mediated idiopathic RPGN. In patients with ANCA-associated capillaritis, immune complexes are usually lacking (hence the term *pauci-immune*). When immune DAH is suspected, a portion of the lung biopsy can be frozen for immunofluorescent (IF) stains, but IF stains of lung tissue are logistically difficult, and nonspecific background staining may lead to misinterpretation. When GN is present concomitantly, kidney IF stains are more sensitive and reliable.

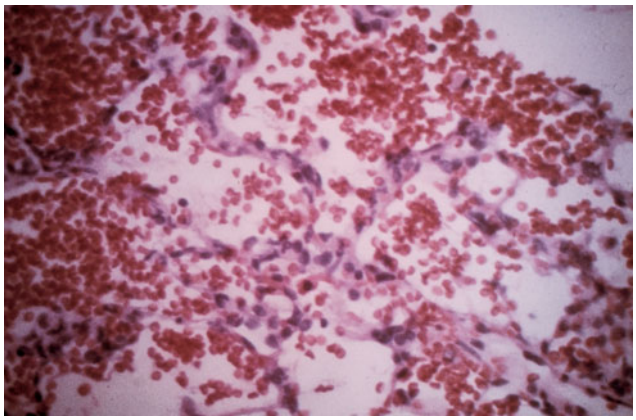


Figure 77-2 Postmortem lung biopsy demonstrates large numbers of red blood cells within alveolar spaces in a patient with alveolar hemorrhage due to Wegener's granulomatosis. There is no gross evidence for necrosis or granulomas. The alveolar architecture and septae are well preserved. These histopathological features are nonspecific (H&E). *(From Gravelyn TR, Lynch III JP: Alveolar hemorrhage syndromes, IM––Internal Medicine for the Specialist 8(1):63–83, 1987, copyright Medical Economics Company.)*

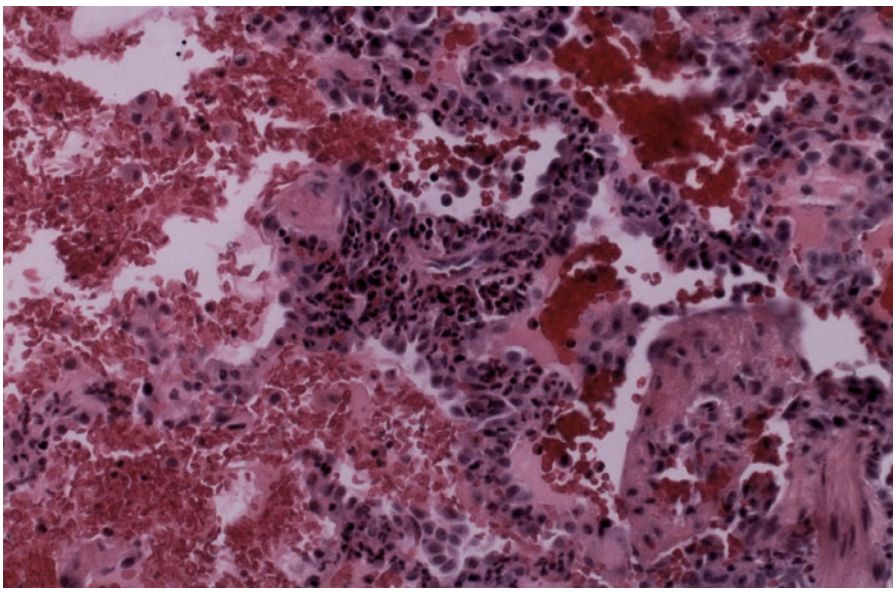


Figure 77-3 Pulmonary capillaritis. Intense inflammatory infiltrate involving pulmonary capillaries with intra-alveolar hemorrhage (H&E). *(Courtesy of Thomas Colby, M.D. From Leatherman J: Autoimmune diffuse alveolar hemorrhage. Clin Pulm Med 1:356–364, 1994, with permission.)*

Despite the greater accuracy of surgical lung biopsy in evaluating DAH, we believe fiberoptic bronchoscopy with BAL is usually adequate to exclude infectious etiologies and support the diagnosis of DAH. Bloody or serosanguineous BAL fluid (consistent with active or recent bleeding) or hemosiderin-laden macrophages (a clue to prior episodes of alveolar hemorrhage) may be sufficient to justify initiation of therapy provided clinical and serological features are consistent. Thoracoscopic lung biopsy may be useful in noncritically ill patients with suspected DAH when ancillary studies, kidney biopsy, and BAL are nondiagnostic.

The Role of Percutaneous Kidney Biopsy

Necrotizing GN is a cardinal (albeit nonspecific) feature of most immune-mediated DAH syndromes. The histological spectrum is varied, ranging from mild mesangial thickening to severe crescentic GN. Vasculitis of renal arterioles is rarely found, even in granulomatous vasculitides. Because of the strong association of autoimmune DAH and GN, percutaneous kidney biopsy should be performed in any patient with suspected DAH who has abnormalities on urinalysis or renal function tests. Conventional hematoxylin and eosin (H&E) stains are nonspecific, but the demonstration of glomerular inflammation with necrosis and crescents supports the diagnosis of an immune-mediated etiology (Fig. 77-5). IF stains may clarify the nature of the underlying disorder. Bright linear IF staining along glomerular basement membranes is pathognomonic for anti-GBM disease (Fig. 77-6). A lumpy-bumpy IF pattern, consistent with deposits of immune complexes, is found in collagen vascular disorders and in idiopathic immune complex-mediated GN. Negative

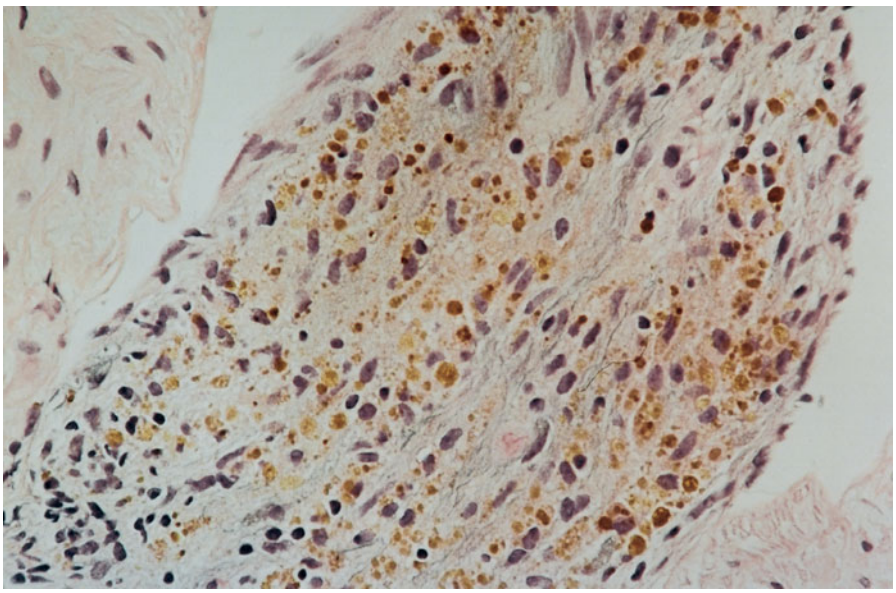


Figure 77-4 Hemosiderin-laden macrophages (siderophages) are prominent in the alveolar interstitium in a patient with recurrent alveolar hemorrhage (H&E). *(Courtesy of Joseph Fantone, M.D.)*

Table 77-2

Autoimmune Diffuse Alveolar Hemorrhage: Pathology and Serology

	Lung Pathology		Renal Pathology		
	Histopathology	**Immuno-fluorescence**	**Histopathology**	**Immuno-fluorescence**	**Serology**
ABMA disease (Goodpasture's syndrome)	±Capillaritis	Linear	Variable	Linear	ABMA (±p-ANCA)
Wegener's granulomatosis	Capillaritis (±granulomatous)	Negative	Segmental necrosis, crescents	Pauci-immune	ANCA (c-ANCA⋙ p-ANCA)
Microscopic polyangiitis	Capillaritis	Negative	Segmental necrosis, crescents	Pauci-immune	ANCA (p-ANCA or c-ANCA)
Systemic lupus erythematosus	Capillaritis	Granular	Variable	Granular	ANA
Idiopathic pulmonary hemosiderosis	±Capillaritis	Negative	Normal	—	Negative

ABMA = anti-basement membrane antibody; ANA = antinuclear antibody; ANCA = antineutrophil cytoplasmic antibody: p-ANCA = perinuclear antineutrophilcytoplasmic antibody; c-ANCA = cytoplasmic antineutrophil cytoplasmic antibody.

IF stains are characteristic of the pauci-immune GN of necrotizing vasculitis. Serologies are critically important in defining the underlying disorder responsible for DAH (particularly ANCA, anti-GBM antibody, and antinuclear antibodies). Recognizing the different pathogenetic mechanisms of these DAH syndromes is important, as the prognosis and treatment strategies differ.

THERAPY OF IMMUNE-MEDIATED ALVEOLAR HEMORRHAGE

Because of the rarity of the immune-mediated pulmonary-renal syndromes, controlled, randomized trials evaluating therapy are lacking. Corticosteroids are considered part of

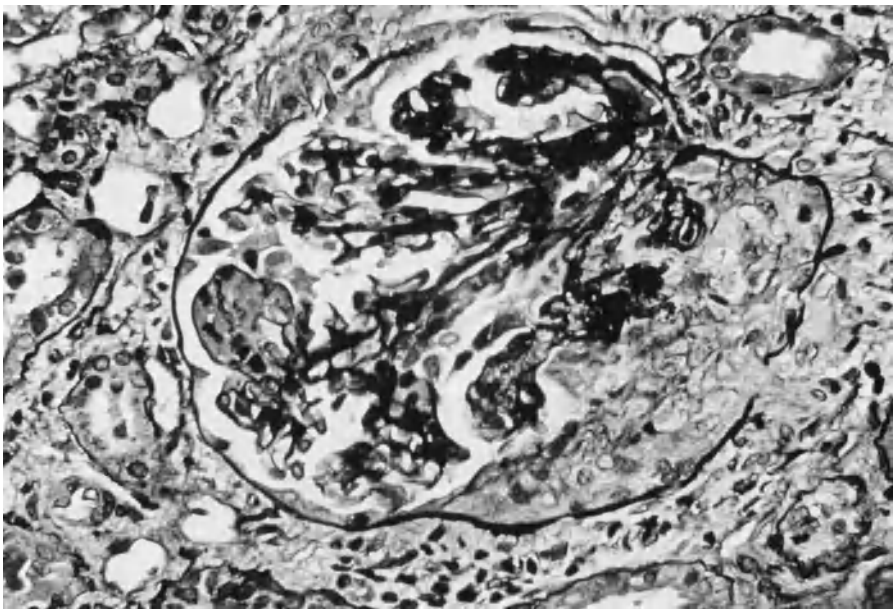


Figure 77-5 Segmental necrotizing and crescentic glomerulonephritis due to vasculitis (H&E). *(Courtesy of John Crosson, M.D. From Leatherman J: Autoimmune diffuse alveolar hemorrhage. Clin Pulm Med 1:356–364, 1994, with permission.)*

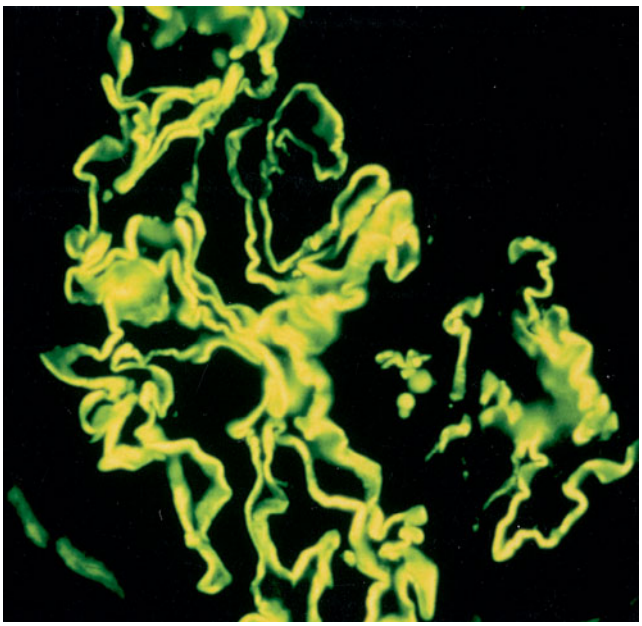
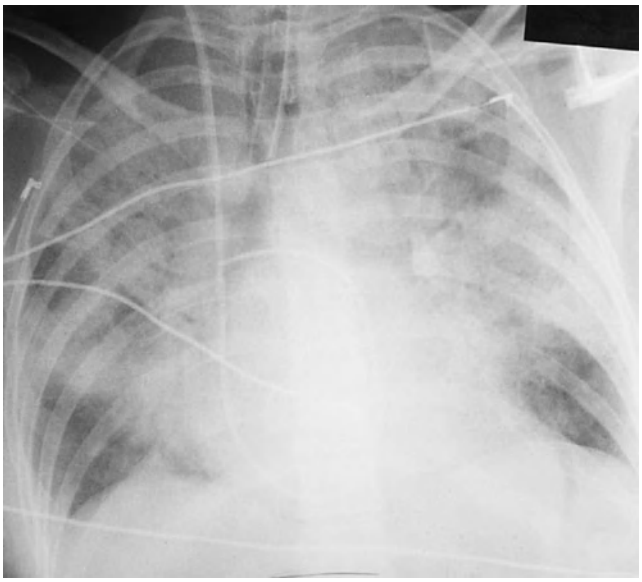


Figure 77-6 Linear immunofluorescent staining along glomeruli due to deposition of anti-basement membrane (anti-GBM) antibody. *(Courtesy of John Crosson, M.D. From Leatherman J: Autoimmune diffuse alveolar hemorrhage. Clin Pulm Med 1:356–364, 1994, with permission.)*

standard therapy for all the immune-mediated DAH syndromes (to be discussed in detail later in this chapter). For systemic necrotizing vasculitis, cyclophosphamide (or occasionally other immunosuppressive agents) are combined with corticosteroids. The role of cytotoxic agents in other immune-mediated DAH syndromes needs to be individualized. For severe, fulminant autoimmune DAH, high-dose intravenous (IV) ("pulse") methylprednisolone (1 g daily for 3 days) is advised (irrespective of underlying etiology), even while pursuing a diagnostic workup. Delaying pulse therapy in a critically ill patient for even a few hours may be catastrophic. Rapid resolution of bleeding can occur, often within 24 to 72 h of initiation of therapy (Fig. 77-7). Following the 3-day pulse, corticosteroids (dose of methylprednisolone 60 to 120 mg per day or equivalent) should be continued for a few days, until control of the bleeding and extrapulmonary manifestations has been achieved. The subsequent dose and rate of corticosteroid taper need to be individualized, based upon clinical, radiographic, and serological response. Cyclophosphamide or other immunosuppressive agents should be withheld until a specific diagnosis mandating treatment with these agents has been substantiated. The specific therapeutic regimen is dictated by the underlying disorder (discussed in detail below). Plasmapheresis is a central component of therapy for anti-GBM disease but has no *routine* role for other disorders. However, plasmapheresis may have an adjunctive role in patients with DAH and severe renal insufficiency (i.e., serum creatinine greater than 4 mg%) and in patients with severe or progressive DAH refractory to corticosteroids or immunosuppressive agents. Measures to ensure adequate oxygenation are also essential. Mechanical ventilatory support, often



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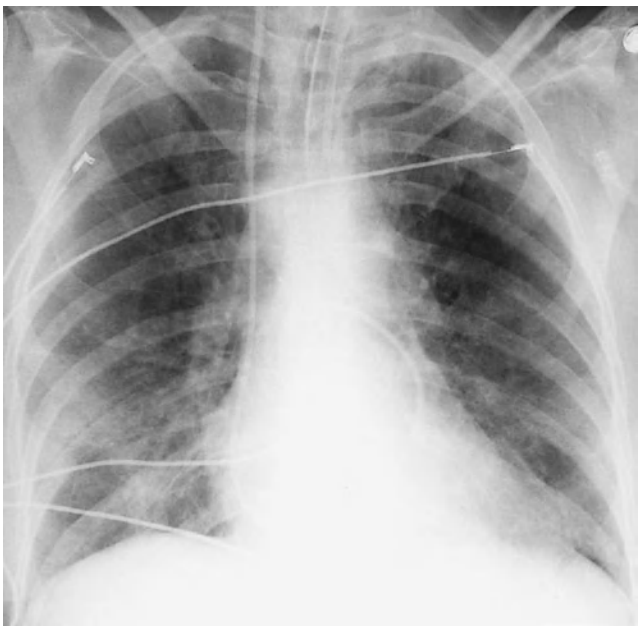

B

Figure 77-7 *A*. Alveolar hemorrhage due to microscopic polyarteritis (MPA). Posterior-anterior (PA) chest radiograph demonstrating massive alveolar infiltrates involving all lobes. Because of the severity of respiratory failure (requiring 16 cm H_2O of positive end-expiratory pressure to achieve acceptable oxygenation), no lung biopsy was performed. Urinalysis demonstrated numerous red cells and occasional red cell casts. Serum creatinine was 1.4 mg%. Pulse methylprednisolone (1 g daily × 3 days) was initiated, and renal biopsy was scheduled for the following morning. *B*. Alveolar hemorrhage due to MPA. PA chest radiograph from the same patient 12 h following initiation of pulse methylprednisolone. Marked improvement in alveolar infiltrates is evident. Renal biopsy demonstrated glomerulonephritis and a necrotizing vasculitis involving renal arterioles; no granulomas were present. Cyclophosphamide (2 mg/kg per day) was instituted, and corticosteroids were continued. Within 5 days, the infiltrates had cleared completely and serum creatinine was 0.6 mg%.

with positive end-expiratory pressure, may be necessary in fulminant cases of DAH, to prevent death due to refractory hypoxemia. Transfusion of red blood cells may be required to maintain an acceptable hematocrit (more than 25 percent) and adequate blood pressure. In the sections that follow, we will discuss each of the autoimmune DAH syndromes individually.

SPECIFIC SYNDROMES

Goodpasture's Syndrome

Clinical Features

Antiglomerular basement membrane (anti-GBM) disease (Goodpasture's syndrome), the prototype of pulmonary-renal syndromes, accounts for 18 to 32 percent of immune-mediated DAH. Classically, anti-GBM disease manifests as DAH and RPGN. Anti-GBM disease typically affects individuals between 20 and 45 years of age with a distinct male predominance. The incidence has been estimated as 0.3 cases per 100,000 population per year. The etiology is not known, but exposure to inhaled hydrocarbons and antecedent viral illnesses, particularly influenza, have been cited as risk factors. The demonstration of anti-GBM antibodies in tissue (typically kidney) or in serum is the cornerstone of the diagnosis.

The clinical expression of anti-GBM disease is highly variable. Most patients present with progressive dyspnea, widespread alveolar infiltrates, and hypoxemia; hemoptysis occurs in 80 to 94 percent. A cardinal feature of Goodpasture's syndrome is the presence of GN. Microscopic hematuria, red cell casts, or proteinuria are almost always present. Gross hematuria occurs in up to 41 percent of patients. Azotemia is noted in 55 to 71 percent of patients at presentation. Fatigue and weakness are common. In the absence of therapy, progressive renal insufficiency ensues, often resulting in end-stage renal failure within days to weeks of the onset of symptoms. Oliguria, severe renal failure, or greater than 50 percent crescents on renal biopsy are associated with a poor prognosis and low rate of recovery of renal function. The course may be fulminant, with severe renal failure and explosive, life-threatening DAH. In up to one-third of patients with anti-GBM disease, GN occurs without DAH; DAH alone is exceptionally rare. Chest radiographs typically reveal dense bilateral alveolar infiltrates, often with air-bronchograms. With cessation of bleeding, infiltrates may resolve within 24 to 36 h. Pleural effusions are rare and suggest an alternative diagnosis. Pulmonary function tests are rarely helpful in the acute setting of DAH. Increases in the diffusing capacity for carbon monoxide (D_{LCO}) occur, due to uptake of carbon monoxide by extravasated alveolar blood. Bloody or serosanguineous BAL fluid (that worsens with serial aliquots) suggests DAH but is nonspecific. Anemia is present in more than 90 percent of cases and may be profound. Serum iron and ferritin levels are usually decreased, reflecting diminished iron stores. Factors associated with a higher incidence of DAH include cigarette smoking, exposure to high concentrations of oxygen, upper respiratory tract infections, and increased hydrostatic (pulmonary capillary) pressures.

Serological assays for anti-GBM antibody are invaluable in confirming the diagnosis and monitoring the adequacy of therapy. Radioimmunoassays or enzyme-linked immunosorbent assays (ELISA) for anti-GBM antibody are highly sensitive (greater than 95 percent) and specific (greater than 97 percent) but are performed in only a few laboratories. Results are usually not available for several days. Since delay in institution of therapy may preclude a favorable outcome, percutaneous renal biopsy is usually performed while awaiting the results of serum assays. Although the height of serum anti-GBM antibody titer does not correlate with severity of disease, changes in titer over time may be a guide to efficacy of therapy. Rises in titer presage relapse; titers fall as the disease remits. Treatment can be tapered and discontinued after the antibody has disappeared from the circulation. Patients with circulating anti-GBM antibodies and ANCA have been described. Other serological studies are negative or nondiagnostic.

Histopathology

Percutaneous kidney biopsy is the preferred invasive procedure to substantiate the diagnosis of anti-GBM disease. Light microscopy demonstrates nonspecific features of a proliferative or necrotizing GN, often with cellular crescents. Over time, the crescents may fibrose, and frank glomerulosclerosis, interstitial fibrosis, and tubular atrophy may be observed. Although these microscopic features are nonspecific, IF stains are the cornerstone of the diagnosis. Bright linear deposits of immunoglobulin G (IgG) and complement (C3) along glomerular basement membranes are pathognomonic of anti-GBM disease (Fig. 77-6). All four subclasses of IgG are represented, but IgG1 predominates. Rare cases of linear deposits of IgM or IgA have been described. Lung biopsies are rarely necessary, as the histological features on renal biopsy are usually adequate to establish the diagnosis. When lung biopsy has been done, extensive hemorrhage predominates, with accumulation of hemosiderin-laden macrophages within the alveolar spaces. Foci of neutrophilic "capillaritis," hyaline membranes, and DAD may also be found. Interstitial or intra-alveolar inflammation is minimal or absent. Extensive necrosis or large-vessel vasculitis is not found. Similar histopathological features may be seen with a wide gamut of immune-mediated DAH syndromes. IF stains of lung tissue may be diagnostic, provided a clear linear pattern of immunofluorescence is present. However, IF stains are technically difficult in lung tissue, and autofluorescence may obscure the linear IgG deposits.

Pathogenesis

Antibodies are directed against the $\alpha 3$ chain of type IV collagen, an antigen highly expressed in both alveolar and glomerular basement membranes. The pathogenesis of anti-GBM disease remains speculative, but both genetic and environmental factors may play a role. Patients with anti-GBM

disease preferentially express certain immunoglobulin Gm allotypes and links between anti-GBM disease and the HLA DR2 histocompatibility antigen have been noted. Anecdotal cases of anti-GBM disease have been described in siblings, first cousins, and identical twins, suggesting that a genetic susceptibility may exist. Exposure to cigarette smoke, hydrocarbon-containing solvents, hard-metal dust, influenza A2 virus, chlorine gas, and D-penicillamine have been associated with anti-GBM disease. These exogenous factors may injure the basement membrane, resulting in increased capillary permeability, exposing the Goodpasture antigen (α3 chain) which is then recognized as foreign, eliciting a T-helper cell response. Immunoglobulin synthesis and deposits of IgG along the alveolar and glomerular capillary basement membranes then ensue. Anti-idiotypic (blocking) antibodies and activated T-suppressor (CD8+) cells may modulate the process, but this remains speculative.

Treatment

Before the availability of the current therapy and renal dialysis, mortality exceeded 90 percent, with a mean survival of less than 4 months. Currently, with the combination of plasmapheresis, corticosteroids, and cyclophosphamide, mortality has been reduced to less than 20 percent. Since its introduction as a therapeutic option for anti-GBM disease in the mid-1970s, plasmapheresis was quickly adopted worldwide and has been incorporated in all clinical trials. Because of the rarity of anti-GBM syndrome, only one randomized trial compared immunosuppressive therapy with the combination of immunosuppressive therapy plus plasma exchange. In that study, plasmapheresis together with immunosuppressive therapy was associated with more rapid disappearance of anti-GBM antibody and improved renal function than treatment with immunosuppressive agents alone. The optimal extent and duration of plasma exchanges have not been defined. Most investigators advocate plasma exchange daily or every other day for 2 to 3 weeks, until the clinical course has improved and serum anti-GBM antibodies are nondetectable. However, less frequent exchanges (i.e., every 3 days) for 30 days may be adequate. Immunosuppressive therapy is required to inhibit antibody production and rebound hypersynthesis which may occur following discontinuation of plasma exchange. Either cyclophosphamide (2 mg/kg per day) or azathioprine (2 mg/kg per day), combined with prednisone (1 mg/kg per day) have been used. Most investigators favor oral cyclophosphamide over azathioprine, but studies comparing these agents have not been performed. Treatment of acute, life-threatening DAH in Goodpasture's syndrome is similar to other autoimmune disorders. Pulse methylprednisolone (1 g daily for 3 days) is given, followed by a gradual corticosteroid taper. Cyclophosphamide can be initiated once the diagnosis of anti-GBM disease is substantiated by serologies or a pattern of linear immunofluorescence in tissue. This dose of cyclophosphamide is maintained for the duration of therapy, unless complications such as leukopenia necessitate dose reduction. The corticosteroid dose is gradually tapered over the next several weeks. Immunosuppressive or cytotoxic therapy may be discontinued within 3 to 6 months provided a sustained remission has been achieved and anti-GBM antibodies have disappeared.

With few exceptions, circulating anti-GBM antibodies clear within 8 weeks, irrespective of the initial titer. Early relapse (within the first 2 months) may occur when circulating antibodies are still present. This typically manifests as DAH. Risk factors for relapse include infection, volume overload, and cigarette smoking. Late recurrence, associated with renewed antibody synthesis following a remission, has only rarely been documented. In summary, aggressive therapy with plasmapheresis, corticosteroids, and immunosuppressive agents has dramatically improved prognosis. With this approach, 5-year survival exceeds 80 percent, and fewer than 30 percent of patients require chronic dialysis. Early recognition and treatment of this syndrome are critical, as the prognosis for recovery of renal function depends upon the initial extent of injury. Recovery of renal function can be expected in patients with minor functional impairment. By contrast, patients manifesting initial serum creatinine greater than 4 mg/dl, oliguria, or greater than 50 percent crescents on renal biopsy rarely recover and usually progress to end-stage renal failure requiring chronic dialysis. Renal transplantation has been successful in patients with irreversible renal failure, provided serum anti-GBM antibodies are undetectable.

Systemic Vasculitis

DAH is a well-recognized complication of microscopic polyangiitis (MPA) and Wegener's granulomatosis (WG) but rarely complicates Churg-Strauss syndrome (CSS), Behçet's disease, mixed cryoglobulinemia, and other systemic necrotizing vasculitides. Classic polyarteritis nodosa (PAN) rarely involves the lung. Necrotizing small-vessel vasculitis accounts for the majority of autoimmune DAH syndromes. RPGN is usually present in each of these DAH syndromes, but the disease is sometimes limited to the kidneys or lungs. Circulating antibodies directed against cytoplasmic components of neutrophils and monocytes (ANCA) have been detected in most patients with these "pulmonary renal syndromes," suggesting a common pathogenesis and mechanism of lung injury in these diverse vasculitic disorders.

ANCA-Associated Vasculitides

Goodpasture's syndrome (anti-GBM disease) was the first of the pulmonary renal syndromes to be immunologically characterized. Subsequent studies documented immune complexes in serum or renal tissue in subsets of patients with pulmonary renal syndromes, particularly SLE, WG, and immune complex-mediated GN. However, more than two-thirds of patients with pulmonary renal syndromes are not mediated by *either* anti-GBM antibody or immune complexes. The term *pauci-immune glomerulonephritis* has been applied to this group of patients. Some patients with pauci-immune GN and DAH have clinicopathological features of WG. Others exhibit a multisystemic small-vessel vasculitis but lack

granulomatous inflammation of the respiratory tract. Historically, these patients were considered to have microscopic PAN. Currently, the term *microscopic polyangiitis* (MPA) is preferred. Some patients have acute DAH and pauci-immune RPGN but lack evidence for vasculitis elsewhere. The term *idiopathic RPGN* has been used to refer to these patients. The availability of serum assays for ANCAs has profoundly influenced the classification of immune DAH and GN. Most patients with pauci-immune DAH and GN have circulating ANCA. ANCA-positive patients formerly given a diagnosis of idiopathic RPGN and DAH are now considered to have MPA. The spectrum of ANCA-associated diseases is not limited to patients with pulmonary renal syndromes but includes individuals with MPA limited to the lung (i.e., manifesting as DAH) or kidney (i.e., necrotizing GN). To avoid further confusion, brief definitions of the major ANCA-associated vasculitides are outlined below.

Wegener's Granulomatosis

Wegener's granulomatosis (WG), the most common of the pulmonary vasculitides, typically involves the upper respiratory tract (e.g., sinuses, ears, nasopharynx, oropharynx, trachea), lower respiratory tract (bronchi and lung), and kidney, with varying degrees of disseminated vasculitis (see Chapter 83). Alveolar hemorrhage is a rare complication of WG, reflecting diffuse injury to the lung microvasculature (i.e., capillaritis) (Fig. 77-8). In this context, RPGN is present in more than 90 percent of patients. The salient histopathological features of WG include small-vessel vasculitis (involving capillaries, arterioles, venules), geographic necrosis, hemorrhagic infarcts, a mixed inflammatory cellular infiltrate, and a granulomatous component. Circulating antibodies directed against cytoplasmic components of neutrophils (c-ANCA) have been detected in more than 90 percent of patients with active generalized WG and in 40 to 70 percent with active regional WG. Oral cyclophosphamide (2 mg/kg per day) and prednisone is the initial treatment of choice for WG. With this regimen, remissions are achieved in 70 to 93 percent of patients, with early mortality rates of less than 15 percent. By 3 to 6 months, assuming complete remissions are achieved, azathioprine or methotrexate can be substituted for cyclophosphamide. Treatment should be continued for a minimum of 12 to 18 months (total duration). Relapses can be treated with cyclophosphamide and prednisone. Methotrexate may be used in patients with limited disease or those experiencing significant toxicity from cyclophosphamide. Trimethoprim/sulfamethoxazole may have an adjunctive role (together with cyclophosphamide and prednisone) to reduce relapse rates, but should not be considered as primary therapy.

Churg-Strauss Syndrome (Allergic Angiitis and Granulomatosis)

Churg-Strauss syndrome (CSS), also termed *allergic angiitis* and *granulomatosis,* is a rare, small-vessel vasculitis associated with a prominent allergic component, asthma, and eosinophils in blood or involved tissues (see Chapter 83). The annual incidence has been estimated at two to three cases per million. Pulmonary involvement, primarily asthma, is present in virtually all cases. Focal infiltrates are present on chest radiographs in 30 to 70 percent of cases. DAH is a rare complication. Circulating ANCAs (either p-ANCA

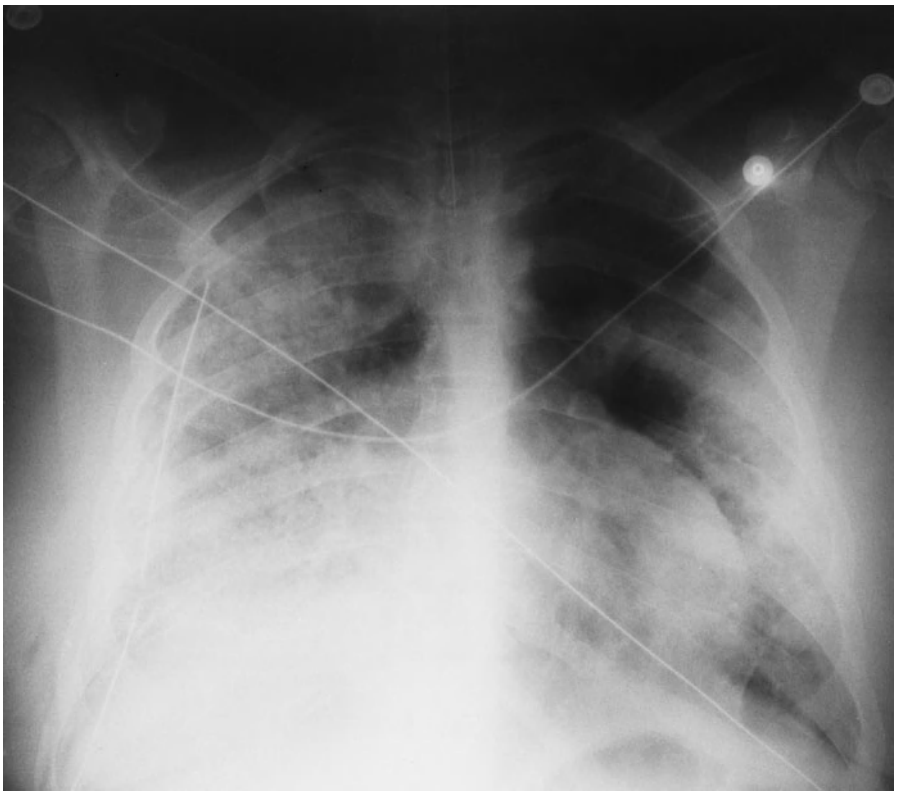

Figure 77-8 Wegener's granulomatosis (WG). Posterior-anterior (PA) chest radiograph demonstrated bilateral alveolar infiltrates in a 13-year-old girl with hemoptysis and respiratory failure. A right chest tube is in place from an open lung biopsy performed 2 days earlier. Open lung biopsy demonstrated capillaritis and massive alveolar hemorrhage. Pulse methylprednisolone, followed by oral cyclophosphamide and prednisone, was associated with a complete remission.

or c-ANCA) have been detected in 30 to 70 percent of patients with CSS. As with other ANCA-associated vasculitides, small vessels (capillaries, venules, and arterioles) are involved. Granulomas, eosinophils, and palisading histiocytes in extravascular tissues are hallmarks of the disorder. Pronounced granulomatous and eosinophilic components distinguish CSS from other vasculitides. In the classic form of CSS, vasculitis develops after a several-year history of atopy or asthma. The erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), and blood eosinophil count are elevated in more than 80 percent of patients during the acute phase of vasculitis or exacerbations. The diagnosis of CSS can be made, even when histological features are less than definitive, provided the clinical and laboratory features are characteristic.

Because of the rarity of CSS, data on therapy are limited. A variety of treatment regimens employing corticosteroids, immunosuppressive or cytotoxic agents, and plasmapheresis (alone or in combination) have been tried and generally were equally efficacious. Corticosteroids achieve remissions in more than 80 percent of patients with CSS and are first-line therapy for mild to moderate cases of CSS. Oral or pulse cyclophosphamide (or other immunosuppressive agents such as azathioprine or mycophenolate mofetil) should be added for severe or multisystemic disease or corticosteroid-recalcitrant cases or when unfavorable prognostic factors are present (such as central nervous system or gastrointestinal involvement, cardiomyopathy, severe renal insufficiency, or proteinuria greater than 1 g per day). Plasmapheresis should be considered only as adjunctive therapy in patients who are failing or those experiencing adverse effects from combined therapy.

Microscopic Polyangiitis

Microscopic polyangiitis (MPA, formerly termed *microscopic polyarteritis* or *polyangiitis overlap syndrome*) typically presents with GN and pulmonary capillaritis manifesting as DAH. Clinical and serological features of MPA overlap with WG and CSS. MPA is rare, with an estimated prevalence of two to five cases per million. As its name implies, MPA involves small vessels (arterioles, venules, or capillaries); extension to larger vessels occurs in a minority of cases. Small vessels are always spared in classic PAN. In contrast to WG or CSS, neither granulomas nor eosinophils are prominent in MPA. Circulating ANCA are present in 50 to 90 percent of patients with MPA, suggesting a relationship with other ANCA-associated vasculitides. By contrast, circulating ANCA are present in fewer than 20 percent of patients with classic (macroscopic) PAN. A necrotizing, crescentic pauci-immune GN is nearly invariably present in MPA but is rare in classic PAN. Alveolar hemorrhage, which is rarely observed in classic PAN, occurs in 30 to 50 percent of patients with MPA and is often the dominant and most life-threatening manifestation.

Prednisone, cyclophosphamide, and plasmapheresis, alone or in combination, have been used to treat MPA. Response rates and long-term survival have generally been similar with the various regimens. Most investigators use oral cyclophosphamide (2 mg/kg per day) plus prednisone (1 mg/kg per day, with gradual taper), similar to the regimen used for WG. With this approach, favorable responses are achieved in more than 80 percent of patients; 10-year survival exceeds 70 percent. By 3 to 6 months, once complete remissions have been achieved, azathioprine, methotrexate, or mycophenolate mofetil may be substituted for the cyclophosphamide.

ANCA-Associated Pulmonary Renal Syndromes: Clinical Features

The clinical and radiologic manifestations of ANCA-associated DAH are similar to other immune causes. Acute necrotizing GN is nearly always present, but the renal lesion is nonspecific. Distinguishing the specific underlying disorder may be difficult. The pathological lesions in ANCA-associated diseases share characteristic features, regardless of the organ affected. The three key histopathological findings are a segmental (focal) distribution of vascular injury, infiltration with neutrophils, and fibrinoid necrosis. The latter results from lysis of the vascular wall, allowing plasma coagulation factors to enter the interstitium and come into contact with thrombogenic substances, generating fibrin. Neutrophils that infiltrate vessel walls undergo disruption and karyorrhexis, leading to the typical leukocytoclastic pattern of injury in capillaries and venules. ANCA-associated vascular injury is accompanied by few, if any, immune deposits (pauci-immune). The salient lesion of renal vasculitis is a segmental necrotizing GN, usually accompanied by extracapillary proliferation of Bowman's capsule (crescents) (Fig. 77-5). Depending on the duration and extent of renal injury, varying degrees of glomerular fibrosis and sclerosis may be seen. Vasculitis affecting the kidney often involves only the glomerular capillaries; macroscopic arteritis is seldom apparent. When the lung is involved, the histopathology is nonspecific, demonstrating only capillaritis and intra-alveolar hemorrhage. Immune deposits are absent.

Clinical features of ANCA-associated DAH syndromes overlap. Striking elevations in the ESR and CRP may be observed in all the syndromes, particularly when disseminated vasculitis is present. Anemia and leukocytosis are common. Marked eosinophilia is characteristic of CSS but is not a feature of MPA or WG. Extrapulmonary and extrarenal manifestations suggesting small-vessel vasculitis (e.g., palpable purpura, leukocytoclastic vasculitis, mononeuritis multiplex, arthralgias or arthritis, ocular disease, sinusitis) may direct biopsies at these sites. Histological features of granulomatous vasculitis are consistent with WG or CSS whereas granulomas are lacking in MPA. Radiographic features may discriminate granulomatous vasculitides from MPA. In WG (and less commonly in CSS), focal nodular or cavitary mass lesions may be seen. These are not found in MPA. The diagnosis of CSS can usually be readily established by a pronounced eosinophilic component in the blood or in extravascular sites. However, discriminating WG from MPA may be difficult or impossible as small-vessel vasculitis is common to both disorders. By definition, WG is associated with concomitant granulomatous inflammation, typically, but not invariably involving

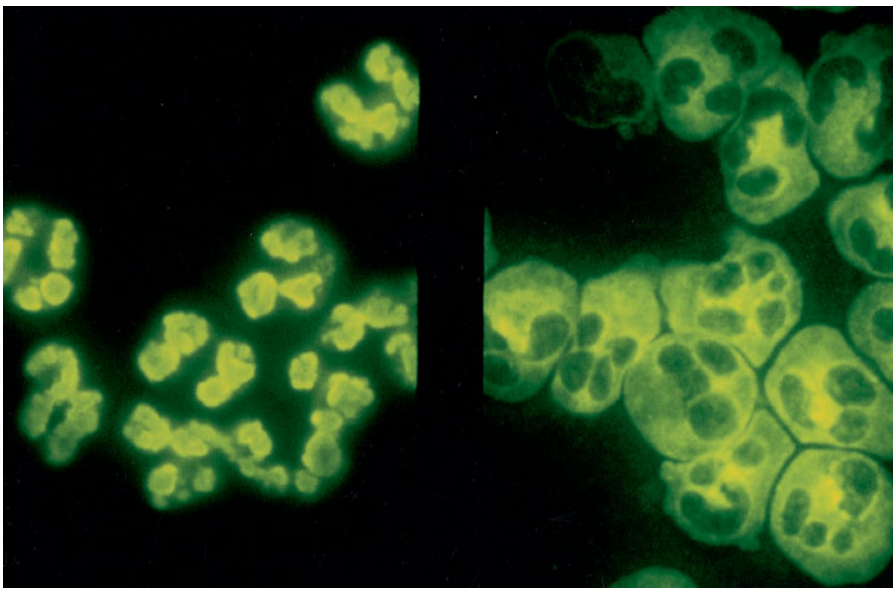

Figure 77-9 Indirect immunofluorescent stains demonstrating two distinct types of antineutrophil antibodies. On the left panel, note the perinuclear pattern of immunofluorescence characteristic of p-ANCA (myeloperoxidase epitope). On the right panel, a coarse granular pattern of immunofluorescence within the cytoplasm is evident, characteristic of c-ANCA (proteinase-3 epitope).

the upper and lower respiratory tracts. The latter may lead to the highly distinctive features attributed to WG including sinusitis, otitis media, nasal or laryngotracheal ulcerations, subglottic stenosis, and cavitary pulmonary nodules.

Characteristics of ANCA

The identification of circulating antibodies directed against cytoplasmic components of neutrophils and monocytes (i.e., ANCA) represented a major advance in the classification and understanding of vasculitis. Using ethanol-fixed granulocytes incubated with patient serum, two distinct patterns of ANCA are identified by IF techniques: cytoplasmic (c-ANCA) and perinuclear (p-ANCA) (Fig. 77-9). The p-ANCA pattern is an artifact of fixation causing movement of the target antigens to a perinuclear location. These differing IF patterns reflect distinct antigenic specificities.

In both radioimmunoassays and ELISA, the antibody responsible for c-ANCA is directed against proteinase 3 (PR-3). The p-ANCA pattern is usually due to an antibody to myeloperoxidase (MPO). MPO-ANCA is usually associated with small-vessel vasculitis, but multiple p-ANCA antibodies directed against a variety of antigens (e.g., cathepsin G, lactoferrin, and elastin) may be seen in nonvasculitic inflammatory disorders including collagen vascular diseases and inflammatory bowel or liver disease. Therefore, while c-ANCA is more than 90 percent specific for small-vessel vasculitis, p-ANCA is nonspecific. In untreated WG, circulating c-ANCA (PR3-ANCA) is detected in more than 70 percent of patients; the incidence is lower (40 to 65 percent) in patients with limited disease (e.g., involvement confined to the upper respiratory tract). By contrast, p-ANCA (MPO-ANCA) is rarely found in WG. Circulating ANCAs are present in more than 70 percent of patients with MPA and 30 to 70 percent of patients with CSS. In MPA either c-ANCA or MPO-ANCA may be present, but MPO is slightly more common. Serum ANCA, typically p-ANCA, has been detected in more than 50 percent of patients with pauci-immune GN. Circulating ANCAs have been found in fewer than 20 percent of patients with classic PAN. When present, antibodies have shown MPO antigenic specificity. Individual patients almost never have both c-ANCA and p-ANCA. Most ANCAs are of the IgG class. However, IgM ANCAs associated with severe DAH have been described, either concomitant with IgG-ANCA or in the absence of IgG-ANCA. It is unknown how often patients with ANCA-negative vasculitis would be ANCA-positive if reagents that detected IgM antibodies were used.

The antigenic specificities of ANCA (i.e., PR3 or MPO) may provide clues to the nature of the underlying disorder and may assist in categorizing the type of disease, but overlap exists. Biopsies are important to differentiate the nature of the underlying vasculitic disorder. For example, patients with c-ANCA and small-vessel vasculitis may be misclassified as MPA if clinically inapparent areas of granulomatous inflammation are overlooked. For clinical purposes, distinguishing WG from MPA is not critical, because therapy and management are similar. Circulating p-ANCA (MPO) or c-ANCA (PR3) are present in more than 70 percent of patients with pauci-immune necrotizing GN (renal vasculitis). ANCA-negative patients usually have disease limited to the kidney. Nearly all patients with concomitant DAH have circulating ANCA. Indeed, a negative ANCA provides very strong evidence against vasculitis as the cause of DAH and GN. When applied to patients with RPGN, a positive ANCA almost invariably predicts pauci-immune necrotizing GN. In the setting of clinical, laboratory and radiologic features that are highly suggestive of DAH and RPGN, a positive c-ANCA or MPO-ANCA, together with a negative anti-GBM and ANA assay, is virtually diagnostic of systemic vasculitis (e.g., WG or MPA). Similarly, a positive ANCA (usually MPO-ANCA) is sufficient to diagnose lung-limited MPA, provided the clinical presentation is typical of DAH and nonimmune causes of DAH have been excluded. Most patients previously diagnosed as having

idiopathic pulmonary hemosiderosis likely had lung-limited MPA or ANCA-associated pulmonary capillaritis.

Problems with using serum ANCA to diagnose vasculitis arise when the clinical presentation is ambiguous. The low incidence of vasculitis in the general population dictates that the positive predictive value of ANCA will be low when applied indiscriminately. Routine assay of serum ANCA in patients with nonspecific respiratory complaints yields a high rate of false-positive results. Given the risks of immunosuppressive therapy, misinterpretation of ANCA may lead to devastating consequences. Accordingly, results of serum ANCA assays must be interpreted in light of the entire clinical picture.

Anti-GBM disease and vasculitis have traditionally been viewed as distinct clinicopathological entities. However, recent studies have found that up to 30 percent of patients with anti-GBM disease (as evidenced by anti-GBM antibody in serum and linear deposits of IgG in kidney biopsy) also have serum MPO-ANCA. The coexistence of ANCA and anti-GBM antibodies is almost certainly not a chance occurrence, given the rarity of both antibodies in the general population. It is possible that ANCA initiates vascular injury, and anti-GBM antibody then forms in response to the damaged basement membrane. The prognosis for recovery of renal function is better among patients with both anti-GBM antibody and ANCA compared to patients with anti-GBM alone.

The role of ANCA in the pathogenesis of vasculitis is uncertain, but these antibodies probably mediate vascular damage. Sera from patients with either c-ANCA or MPO-ANCA induce neutrophils to undergo a respiratory burst with release of reactive oxygen species and proteolytic enzymes. Cytokine-primed neutrophils are stimulated by ANCA to damage human endothelial cells in vitro. These observations, together with correlations of ANCA titer with clinical disease in humans (although imperfect), suggest that ANCAs are not innocent markers of vasculitis but play a crucial role in mediating vessel injury.

Therapy

Therapy of DAH due to ANCA-associated syndromes depends on the underlying disorder and the extent and severity of symptoms. However, irrespective of etiology, the most immediate concern in patients with severe immune DAH is to control intrapulmonary bleeding, which may be fatal. Besides general supportive measures, high-dose "pulse" methylprednisolone (followed by a tapering regimen of corticosteroids) should be given. The presence of renal involvement or progression of DAH on corticosteroids is an indication for adding cyclophosphamide (with or without empiric plasma exchange). Plasma exchange has been used, with anecdotal successes, as therapy for ANCA-associated systemic vasculitis. Because ANCA may play a pivotal role in mediating tissue injury, plasmapheresis may be beneficial in selected patients (particularly those with severe renal failure, i.e., serum creatinine greater than 4 mg%).

One controlled trial randomized 52 patients with focal necrotizing GN (without anti-GBM antibodies) to either immunosuppression alone (prednisolone, cyclophosphamide, or azathioprine) or immunosuppression *plus* plasma exchange. Patients were stratified according to severity of renal function at the time of entry into the study. Patients not already on dialysis responded equally well to both regimens (more than 90 percent improvement). However, among patients with severe renal failure requiring dialysis at the time of entry into the study, plasmapheresis conferred significant benefit. Short-term improvement in renal function was noted in 10 of 11 patients in the plasmapheresis group, compared to only 3 of 8 responses in the control group (immunosuppressive therapy only). This study and subsequent studies suggest that *combining* plasmapheresis and immunosuppression may have a role in patients with acute DAH and severe GN requiring dialysis. When plasma exchange is used to treat ANCA-associated DAH, it may be preferable to use an apparatus that efficiently removes both IgM and IgG, because of the reported association of IgM-ANCA and DAH. Protein A immunoadsorption has also been used to treat patients with DAH and GN, in the hope of removing pathogenic antibodies without producing the side effects of plasma exchange. Additional strategies for patients resistant to conventional therapies include high-dose, intermittent intravenous immunoglobulin G (IVIG). The mechanism of action is uncertain but may involve binding of ANCA idiotype by anti-idiotype antibodies in the intravenous IgG preparation.

The role of serial ANCA determinations in following patients with vasculitis is controversial. We do not base therapeutic decisions on the ANCA titer alone. However, a rising titer should alert the clinician to the possibility of disease exacerbation and clinical follow-up should be intensified. Serial ANCA titers may help differentiate disease relapse from nonimmune causes of pulmonary infiltrates. However, ANCA titers do not obviate the need to aggressively evaluate patients with vasculitis presenting with a new pulmonary process while receiving immunosuppressive therapy.

Systemic Lupus Erythematosus

Alveolar hemorrhage is a potentially catastrophic complication of systemic lupus erythematosus (SLE), with mortality rates as high as 50 percent. Approximately 10 percent of cases of immune-mediated DAH have been attributed to SLE. Alveolar hemorrhage complicating SLE is usually accompanied by other manifestations of active SLE. Circulating antinuclear antibody (ANA) is present in more than 99 percent of patients. Alveolar hemorrhage is rarely the sole or presenting feature of SLE. Clinical and radiographic features of DAH complicating SLE are similar to other DAH syndromes. However, in SLE-associated DAH, GN is usually lacking. Diffuse, bilateral alveolar infiltrates, dyspnea, hypoxemia, and hemoptysis are characteristic (Fig. 77-10). With minor episodes, hemoptysis or hypoxemia may be lacking, obscuring the diagnosis. The diffuse pulmonary infiltrates must be differentiated from other pulmonary complications of SLE including lupus pneumonitis, opportunistic infections, congestive heart failure, uremia, or pulmonary embolism.

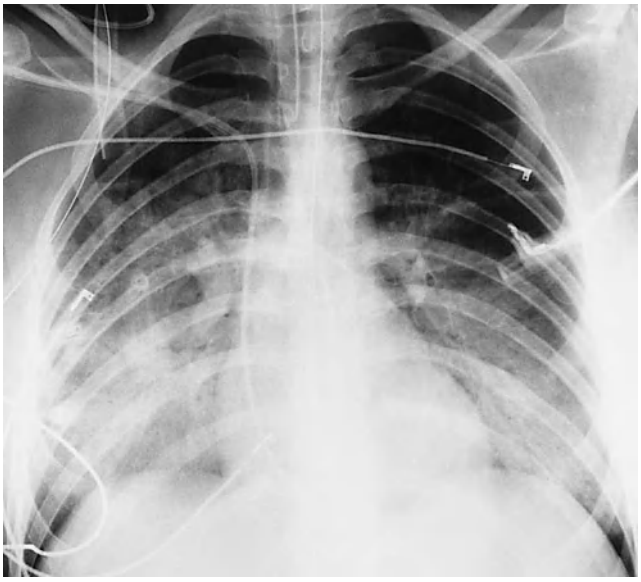

Figure 77-10 Systemic lupus erythematosus (SLE). Posterior-anterior (PA) chest radiograph reveals extensive bilateral alveolar infiltrates in a 22-year-old woman with SLE, hemoptysis, and anemia.

Lung biopsy may be needed to exclude alternative diagnoses and corroborate the diagnosis of DAH. However, the risk of lung biopsy may be substantial in critically ill patients with fulminant DAH and respiratory failure. In addition, as with other immune DAH syndromes, histopathological features of DAH complicating SLE are nonspecific. The dominant feature is intra-alveolar hemorrhage and capillaritis, without macroscopic necrosis. The small-vessel necrotizing vasculitis rarely extends to arterioles and small muscular arteries in addition to capillaries. Granular deposits of IgG or C3 (consistent with immune complexes) have been found in up to 50 percent of cases of DAH complicating SLE. As noted earlier, because of its potential morbidity, we rarely advise open or thoracoscopic lung biopsy to diagnose DAH. Provided clinical features are consistent, the diagnosis of DAH can often be established by fiberoptic bronchoscopy with BAL and transbronchial lung biopsies. Transbronchial biopsies may demonstrate foci of capillaritis with intra-alveolar hemorrhage, but due to sampling error, these features may be missed. However, the presence of gross blood in the airways or serosanguineous BAL fluid, large numbers of hemosiderin-laden macrophages, absence of purulent sputum, and lack of infectious organisms by appropriate stains strongly supports the diagnosis of autoimmune DAH and justifies institution of therapy. Transbronchial lung biopsies may be deferred in acutely ill patients with severe DAH and respiratory failure. In this context, BAL alone is adequate, primarily to exclude local or infectious causes of bleeding.

Due to the rarity of this syndrome, prospective, controlled trials evaluating therapy have not been performed. As with other causes of immune DAH, we recommend high-dose IV pulse methylprednisolone (1 g daily for 3 days) for severe DAH. The dose may be tapered to 60 to 120 mg of methylprednisolone or equivalent by the fourth day, with a gradual taper thereafter. For mild cases, high-dose prednisone (1 mg/kg per day) may be adequate as initial therapy. Symptoms, serial chest radiographs, complete blood counts, and anti-DNA titers reflect efficacy of therapy and guide the rate of taper of corticosteroid. Immunosuppressive or cytotoxic agents may be considered for DAH refractory to corticosteroids, but data are limited. Plasmapheresis (usually combined with corticosteroids or immunosuppressive agents) has been associated with anecdotal successes for acute flares of SLE or DAH. However, randomized, controlled trials found that plasmapheresis plus prednisone and cyclophosphamide was no more effective than prednisone and cyclophosphamide alone for severe lupus nephritis. Plasmapheresis is expensive, logistically cumbersome, and should be reserved for patients with severe DAH refractory to corticosteroids and/or cytotoxic agents.

Other Collagen Vascular Disorders

Anecdotal reports of DAH, with or without capillaritis, have been described in association with rheumatoid arthritis, scleroderma, mixed-connective tissue disease, polymyositis, antiphospholipid antibody syndrome, Henoch-Schönlein syndrome, and Behçet's disease. The clinical spectrum ranges from minimal hemoptysis to life-threatening respiratory failure. In addition to capillaritis and DAH, additional histopathological features on lung biopsies include vasculitis of small and medium muscular pulmonary arteries, diffuse alveolar damage (DAD), and cryptogenic organizing pneumonia. In view of the rarity of DAH complicating these diverse collagen vascular disorders, data regarding therapy are limited. High-dose (pulse) intravenous methylprednisolone is advised as initial treatment. In patients with fulminant or corticosteroid-recalcitrant disease, cyclophosphamide, alone or combined with plasmapheresis, should be added.

Alveolar Hemorrhage in Immunocompromised Hosts

Alveolar hemorrhage may occur in immunocompromised patients. Alveolar hemorrhage may reflect injury to pulmonary endothelial or epithelial cells (secondary to chemotherapy or radiation toxicity), thrombocytopenia (secondary to bone marrow toxicity), pulmonary edema, pulmonary malignancies, and diverse infectious and nonspecific interstitial pneumonias. The incidence of DAH in severely immunocompromised hosts with hematologic malignancies or bone marrow transplants has varied from 11 to 64 percent. The variable frequency in large part is due to differing diagnostic criteria for the diagnosis of DAH. Subclinical alveolar hemorrhage (as evidenced by increased numbers of hemosiderin-laden macrophages in BAL) occurs in up to one-third of immunocompromised hosts with pulmonary infiltrates and may reflect pulmonary endothelial or epithelial injury from diverse causes. Nonimmune causes of DAH in this patient population include coagulopathy, thrombocytopenia or platelet dysfunction, renal failure, congestive heart failure, bronchopulmonary Kaposi's sarcoma, and diverse

infections (e.g., invasive fungi—particularly *Aspergillus spp,* viruses, *Mycobacteria, Legionellae,* and bacteria).

Alveolar Hemorrhage Complicating Bone Marrow Transplantation

DAH occurs in approximately 15 percent (range 2 to 31 percent) of hematopoietic stem cell transplantation (HSCT) or bone marrow transplant (BMT) recipients receiving pre-BMT conditioning with high-dose chemotherapy or radiation therapy. Opportunistic infections or thrombocytopenia account for some cases of DAH, but a distinct syndrome of DAH in this population unrelated to infection is well accepted. The incidence of DAH is similar among autologous and allogeneic HSCT recipients. Risk factors for DAH which have been cited include age over 40 years, underlying solid tumors, severe oral mucositis, renal failure, airway injury prior to institution of chemotherapy, increased proportions of airway (bronchial) neutrophils and eosinophils, and leukocyte recovery. DAH usually develops within 10 to 40 days after BMT, but case reports of DAH developing immediately following autologous bone marrow transfusion suggest that components within the transfusion (e.g., dimethylsulfoxide [DMSO] for cryopreservation of blood stem cells) may mediate acute lung injury in some cases. Progressive dyspnea, hypoxemia, and respiratory failure is typical. Despite extensive DAH, hemoptysis is uncommon. Chest radiographs *initially* demonstrate predominantly interstitial opacities, which evolve to diffuse alveolar opacities, with a confluent alveolar pattern involving all lobes. Serosanguineous or frankly bloody BAL fluid, with negative stains for infectious organisms, support the diagnosis of DAH. However, BAL fluid may be normal even in the face of severe DAH. Lung biopsies or necropsies typically reveal histological features of both DAD and DAH. The clinical course is variable, but acute, fatal respiratory failure may develop. Mortality rates in patients requiring mechanical ventilatory support typically exceed 50 percent. Secondary infections are serious and potentially lethal. Coexisting pulmonary processes, most commonly DAD or infections, were noted in 10 of 11 BMT recipients with DAH in one necropsy series.

Multiple mechanisms may mediate alveolar hemorrhage in this patient population. Diffuse injury to the pulmonary microvasculature, secondary to chemotherapy or radiation therapy, coupled with a heightened inflammatory response in the airways, appear to be operative. Bleeding may be amplified by a precipitating factor such as coagulopathy, pulmonary edema, graft-vs-host disease (GVHD), or infections. DAD, a pathological hallmark seen in toxic lung injury from chemotherapy, radiation therapy, or viral infections, is frequently observed in lung biopsies or necropsies in bone marrow recipients with DAH. An association between microangiopathy and DAH in patients receiving BMT for hematologic malignancies has also been cited. Neutrophils and other inflammatory cells likely play important roles in the pathogenesis of DAH. The onset of DAH frequently coincides with marrow recovery and reappearance of neutrophils within the circulation or BAL fluid. Influx of neutrophils may promote the lung injury by release of oxygen radicals, proteases, and other phlogistic mediators. Hematopoietic growth factors (e.g., granulocyte colony-stimulating factor) may exacerbate alveolar damage and capillary leakage by increasing neutrophil influx into the lungs.

Although randomized controlled studies have not been done, high-dose corticosteroids (generally 125 to 250 mg of methylprednisolone every 6 h for 3 to 5 days, followed by oral corticosteroids) are considered standard of care. Unfortunately, DAH or bloody BAL fluid may be seen in infectious causes of pneumonia (particularly due to cytomegalovirus or *Aspergillus* spp), and high-dose corticosteroids could be disastrous under these circumstances. Infectious etiologies must be rigorously excluded. Among patients who respond favorably to corticosteroids, the dose can be gradually tapered over 2 to 6 weeks. A more prolonged course is appropriate for patients with GVHD or other complications requiring long-term corticosteroid therapy.

Alveolar Hemorrhage Complicating HIV Infection

DAH can complicate human immunodeficiency virus (HIV) infection. The incidence and clinical significance of DAH is not clear, as additional pulmonary processes (e.g., opportunistic infections, Kaposi's sarcoma) are usually present. Subclinical episodes of alveolar hemorrhage are common, as studies in HIV-infected patients with pulmonary infiltrates detected more than 20 percent hemosiderin-laden macrophages in BAL fluid in 15 to 44 percent of patients. Pulmonary capillaritis has been cited in occasional patients, most of whom had concomitant opportunistic infections. Cytomegalovirus (CMV) pneumonitis has been implicated as a cause of DAH in HIV-infected patients. CMV exhibits tropism for endothelial cells, and CMV may induce vascular injury or thrombotic microangiopathy. Antiviral therapy (e.g., ganciclovir) may be curative for CMV-associated DAH. Undoubtedly, opportunistic pathogens or endobronchial Kaposi's sarcoma account for the majority of cases of DAH in HIV-infected individuals. The incidence and appropriate therapy of DAH of unknown etiology in the setting of acquired immunodeficiency syndrome (AIDS) needs to be defined in prospective studies.

Alveolar Hemorrhage Due to Exogenous Agents

Certain exogenous agents or drugs (e.g., trimellitic anhydride, isocyanates, D-penicillamine, cocaine, diphenylhydantoin, propylthiouracil, all-*trans*-retinoic acid) are rare causes of DAH. Pulmonary capillaritis is the most frequent underlying histology. GN has occurred in DAH associated with D-penicillamine, hydralazine, and carbimazole but not with the other agents. Few lung biopsies have been performed in these cases of DAH. When biopsies were done, histological findings were nonspecific. Alveolar hemorrhage dominates without immune deposits.

All-*trans*-retinoic acid (ATRA), a therapeutic agent for acute promyelocytic leukemia, may be associated with "retinoic acid syndrome," which is characterized by fever, thrombosis, pulmonary infiltrates, and DAH. The onset is 2 to 21 days after initiation of treatment. In this circumstance, ATRA is continued but high-dose IV corticosteroids should be administered.

Propylthiouracil can cause a systemic small vessel vasculitis with necrotizing GN, leukocytoclastic vasculitis, and DAH secondary to pulmonary capillaritis. Withdrawal of the drug may be associated with resolution of the disease, but corticosteroids or immunosuppressive agents are indicated in patients with severe DAH or renal failure.

A variety of chemotherapeutic agents (e.g., bischloroethyl nitrosourea [BCNU], carmustine, cyclophosphamide, methotrexate, bleomycin, or busulfan) may cause lung injury and fibrosis. In some cases, DAH may result from epithelial injury and injury to the alveolar capillary basement membranes. In this context, fatality rates are high (more than 50 percent). High-dose corticosteroids are recommended, but efficacy is uncertain.

Trimellitic anhydride (TMA), a chemical used in manufacturing plastics and epoxy resins, may elicit pulmonary hemorrhage and anemia. Most patients with DAH secondary to TMA exposure recover within a few days following removal from the offending environment. An immune mechanism is likely, as circulating IgG antibodies against trimellitic protein were found in some patients with DAH, suggesting TMA acts as a hapten. TMA may cause asthma, rhinitis, and hemolytic anemia mediated by IgE antibodies directed against trimellitic protein. Animal models of TMA-induced lung disease have also been developed. Induction of serum antibodies against epitopes of TMA produced acute lung injury in guinea pigs, mediated by at least two types of humoral antibodies. It is also possible that TMA may exert a direct toxic effect on alveolar endothelium. This syndrome is exceptionally rare, since only sporadic cases have been described. Exposure to isocyanates in spray paint has been linked to severe DAH in a few cases. The mechanism is likely mediated by high levels of IgE and IgG antibodies against diisocyanates. Thus, exposure to TMA or isocyanates, and possibly other chemicals, can elicit hemorrhagic pneumonitis, likely mediated by circulating antibodies (IgG or IgE) and immune complexes.

Mild alveolar hemorrhage occurs in approximately 1 in 3000 patients receiving lymphangiogram dye. The mechanism is not clear. A latency period of 2 to 10 days precedes the onset of dyspnea, pulmonary infiltrates, or hemoptysis. This syndrome is usually mild and self-limited, but at least one fatality has been cited. Extrapulmonary involvement does not occur.

Smoking, snorting, or intravenous "crack" cocaine has been associated with hemoptysis and varying degrees of DAH, including rare fatalities. Histopathological features of cocaine-induced DAH are nonspecific, but include DAD, acute or chronic DAH, interstitial pneumonitis/fibrosis, and intra-alveolar edema. The mechanism of DAH is not clear but may relate to direct toxic injury from cocaine or its contaminants, vasospasm, or a combination of both mechanisms. This syndrome typically reverses with cessation of exposure. The frequency of clinically significant DAH associated with inhaled or intravenous use of cocaine has not been established.

When drug or hapten-induced DAH is suspected, immediate avoidance of the implicated agent or drug is essential. For acute or severe cases, a brief course of high-dose corticosteroids is warranted. Plasmapheresis or cytotoxic agents may be considered for fulminant cases refractory to corticosteroids, but data supporting their use are lacking.

Finally, coagulopathies, severe thrombocytopenia, or the use of anticoagulants, thrombolytic agents, or platelet inhibitors may rarely cause DAH. In this context, the histology is "bland" without evidence for capillaritis or acute inflammation.

Alveolar Hemorrhage Due to Exogenous Environmental Molds

Acute, life-threatening DAH in infants identified fungal contamination as the etiology. Exposure to *Stachybotrys chartarum* and other toxigenic fungi elicits the syndrome. *Stachybotrys chartarum* produces several classes of toxins including hemolysins, proteinases, macrocyclic trichothecenes, phenylspirodrimanes, and others. Acute respiratory distress, progressing to respiratory failure requiring mechanical ventilatory support, may occur. High-dose IV corticosteroids are warranted for acute DAH. Long-term management mandates removal of infants from the residential environment to avoid relapse. This syndrome has rarely been reported in adults, but must be considered in water-damaged homes or environs where mold/fungal contamination exists.

Idiopathic Pulmonary Hemosiderosis

Idiopathic pulmonary hemosiderosis (IPH) is an exceptionally rare cause of DAH that occurs primarily in infants and children. The estimated incidence is 0.2 to 1.2 cases per million. Many children with IPH have a history of milk or gluten sensitivity. A subset of adults with celiac sprue manifest IPH, which may respond to elimination of gluten from the diet. Clinical features of IPH are similar to immune causes of DAH, but extrapulmonary or renal involvement is lacking. Serum or tissue antibodies (including ANCA, immune complexes, anti-GBM antibody) are also absent. A diagnosis of IPH can be made *only* when other specific causes of DAH have been *reliably* excluded. The largest series of IPH, published in 1962, included 112 patients but antedated the availability of anti-GBM antibody or ANCA. Antibodies to lung or kidney were assayed in only six patients. In recent years, with the advent of immunological and serological assays, the diagnosis of IPH has rarely been substantiated. It now seems likely that most cases formerly diagnosed as IPH in adults had ANCA-associated vasculitis, MPA, or underlying collagen vascular disorders.

The clinical course of IPH is variable, but recurrent episodes of DAH over several years are characteristic.

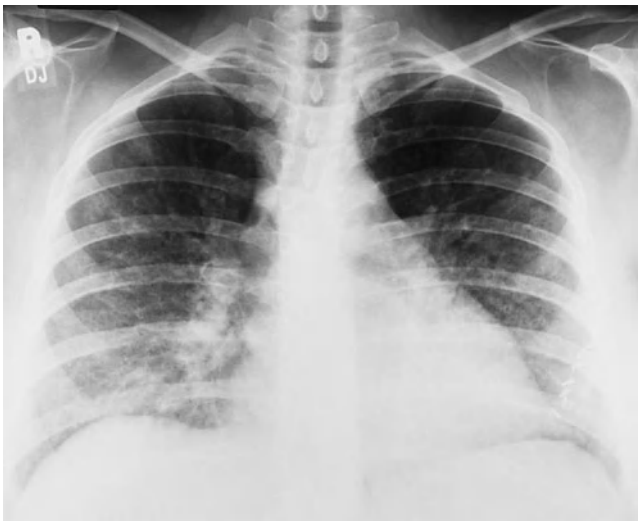

Figure 77-11 Idiopathic pulmonary hemosiderosis (IPH). Posterior-anterior (PA) chest radiograph demonstrates bilateral reticulonodular infiltrates in a 28-year-old woman with IPH confirmed 10 years earlier by open lung biopsy. (Note the surgical staples in the left lower lobe from a prior open lung biopsy.)

Spontaneous remissions without long-term sequelae have been cited in up to 25 percent of cases. One-third to one-half of patients die within 3 years of onset, usually from severe DAH. Sequelae of recurrent episodes of DAH include pulmonary fibrosis, progressive respiratory failure, and cor pulmonale. During acute episodes, chest radiographs demonstrate bilateral alveolar infiltrates. Following cessation of bleeding, chest radiographs may normalize within 1 to 2 weeks. Reticulonodular infiltrates may be observed as the process is resolving or with recurrent episodes (Fig. 77-11). CT reveals areas of ground-glass opacification, representing foci of alveolar hemorrhage. Thickening of interlobular septae and honeycombing may be observed in a subset of patients who progress to pulmonary fibrosis. Hemoptysis may be absent, particularly in young children who may be unable to expectorate blood. Iron-deficiency anemia is characteristic and can be profound. Iron deficiency may persist despite normal total body iron stores, because hemosiderin within alveolar macrophages is not available to developing erythrocytes. Siderophages may be found in sputum, BAL fluid, or tracheal or gastric aspirates in patients with recent episodes of DAH. Lung biopsies may reveal fresh areas of alveolar hemorrhage or patchy interstitial fibrosis and aggregates of hemosiderin-laden macrophages from prior episodes of alveolar hemorrhage (Fig. 77-12). Capillaritis has been described in some cases, but macroscopic vasculitis is not found.

The pathogenesis of IPH is not known. In children, associations between IPH and cow's milk hypersensitivity, celiac disease, IgA monoclonal gammopathy, autoimmune hemolytic anemia, and autoimmune thyrotoxicosis have been suggested, but a pathogenetic link has not been substantiated. Resolution of pulmonary symptoms following elimination of mild products or gluten from diet supports a role for exogenous factors in the pathogenesis in at least some cases. No genetic basis has been found, but clusters within families have been described.

In view of the rarity of IPH, optimal therapy is not clear. Controlled studies evaluating therapeutic regimens have not been done. Corticosteroids are considered the mainstay of therapy, but an epidemiological survey of 30 children with IPH concluded that corticosteroids did not alter the long-term course or prognosis. Because IPH is life-threatening, most physicians treat acute episodes with daily corticosteroids and taper to the lowest dose which appears to control the disease. Long-term (and possibly indefinite) therapy may be required to prevent recurrences. To minimize side effects, alternate dose corticosteroids should be considered after the acute hemorrhage has resolved. Favorable responses have been cited with azathioprine, cyclophosphamide, and plasmapheresis in patients failing corticosteroids. Chronic immunosuppressive agents may improve prognosis for patients with

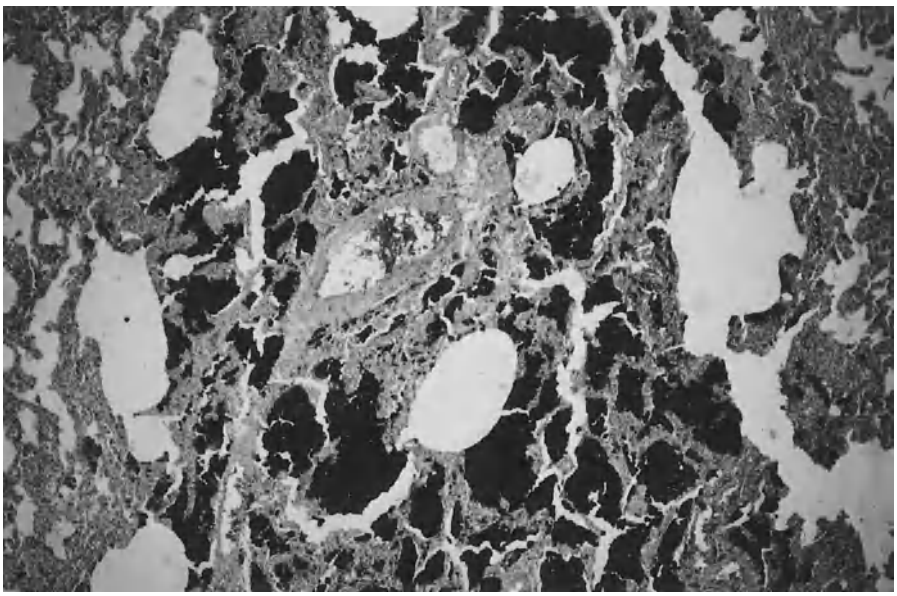

Figure 77-12 Idiopathic pulmonary hemosiderosis (IPH). Photomicrograph demonstrating extensive deposits of hemosiderin within alveolar interstitium (Prussian blue stain).

corticosteroid-recalcitrant disease or patients experiencing repetitive relapses of DAH. In this context, we prefer azathioprine over cyclophosphamide given the heightened risk of neoplasia and gonadal toxicities associated with the long-term use of cyclophosphamide.

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78

Mechanisms of Aspiration Disorders

Richard D. Zorowitz

Aspiration involves a spectrum of clinical situations, from laryngeal penetration to frank pulmonary aspiration. Aspiration presumes that the airways and lungs become soiled with nongaseous materials including consistencies that are solid or liquid, caustic or bland, infected or sterile. Pulmonary aspiration can involve segmental or lobar areas of the lung, can be associated with either focal or diffuse inflammatory reactions, and can evolve to include systemic effects such as bacteremia, sepsis, end-organ consequences of hypoxia, and death. *Aspiration pneumonitis* implies the presence of an inflammatory response to aspirated material not associated with infection, whereas *aspiration pneumonia* implies the presence of infection with pneumonitis.

Aspiration may be categorized by several different schemas. For instance, aspiration may be described in terms of the degree of the event. *Microaspiration* reflects the entry of subclinical amounts of bacterial and nonbacterial matter into the tracheobronchial tree but may predispose a patient to a more serious event. *Macroaspiration* involving the entry of nonendogenous materials into the lung from oropharyngeal or gastrointestinal sources represents the more serious clinical situation.

Aspiration also may be described as a function of oropharyngeal, esophageal, and gastrointestinal disorders with neuromuscular or mechanical (obstructive) etiologies. Further, medical or surgical interventions meant to treat conditions related or unrelated to swallowing or ventilation unintentionally may cause aspiration and should be considered separately from organic conditions. With an understanding of the normal anatomy and physiology of the larynx, pharynx, esophagus, stomach, and intestine, the clinician may better identify the mechanisms of aspiration and the preventable strategies which minimize aspiration and its complications.

NORMAL ANATOMY AND PHYSIOLOGY OF THE AERODIGESTIVE PASSAGE

Aspiration occurs when the integrity of the neuromuscular system used for swallowing becomes altered or impaired anatomically or physiologically (Figs. 78-1 and 78-2). Deglutition is a neurogenically controlled phenomenon requiring intricate cognitive and motor control, integration of sensory information, and multiple levels of central and peripheral reflex control. Normal deglutition consists of four phases: (1) *oral preparatory;* (2) *oral;* (3) *pharyngeal;* and (4) *esophageal.* A list of the muscles, their innervations and functions, and the phases in which they are associated is found in Table 78-1.

During the *oral preparatory* phase (Fig. 78-3*A*), food is manipulated in the mouth and masticated if necessary. Mastication involves a repeated cyclical pattern of rotary lateral movement of the labial and mandibular musculature. Some food normally falls into the pharynx during this phase but does not enter the respiratory tree. Once broken down into particles, food is collected into a bolus and held anterolaterally by the tongue against the palate. Liquids usually do not

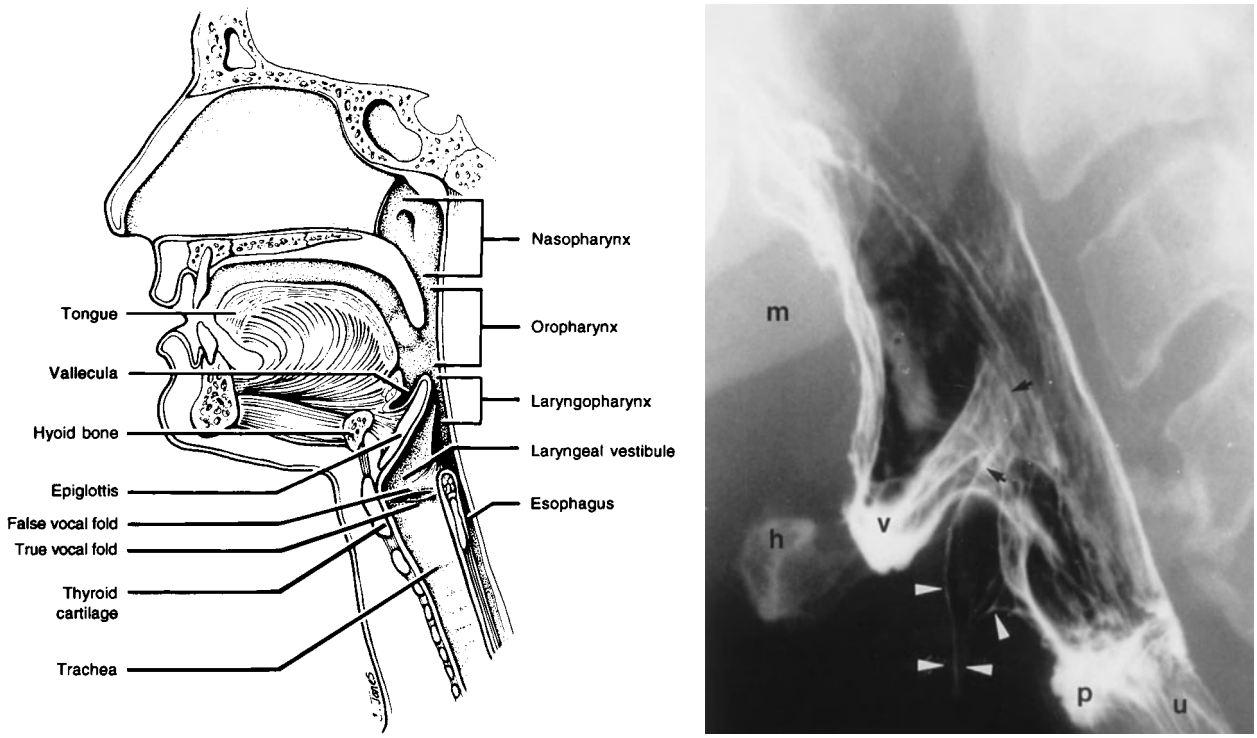


Figure 78-1 Lateral view of pharynx. *A*. Schematic view. *B*. Radiographic view. This view focuses on structures below the level of the mandible (m). The epiglottis (black arrows) tilts downward during a normal swallow but is not necessary for protection of the airway. It separates the valleculae (v) from the laryngeal vestibule (white arrows) and is tilted upward during the resting state. The valleculae and piriform sinuses (p) are sites for residue which may be aspirated when pharyngeal weakness is present. The upper esophageal sphincter (u) is actively contracted, and the hyoid bone (h) is in its resting position.

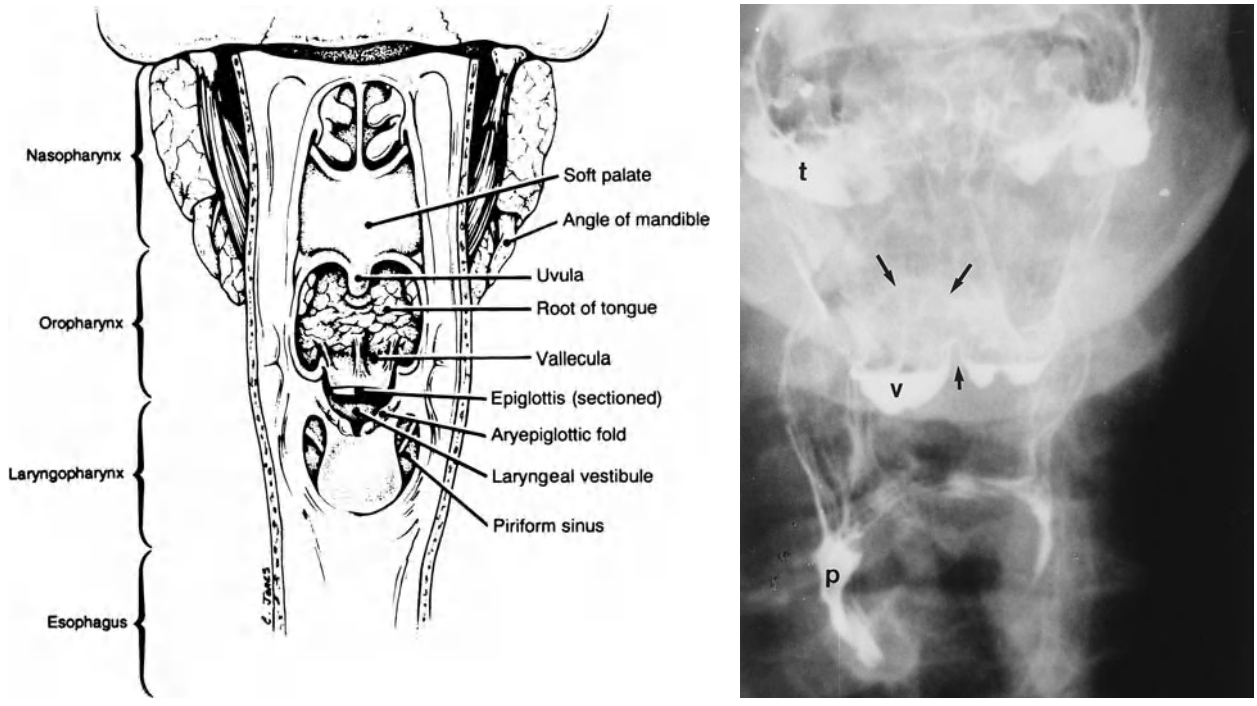


Figure 78-2 Anteroposterior view of pharynx. *A*. Schematic view. *B*. Radiographic view. The tonsillar pillars (t) are visualized in this view. The median glossoepiglottic fold (small arrow) delineates the two cup–shaped valleculae (v). The epiglottis (large arrows) appears as an inverted U. The piriform sinuses (p) lay along the anterior wall of the mid-hypopharynx.

Table 78-1

Muscles Involved in Swallowing

Muscle	Nerve	Stage	Action
Temporalis	V	OP	Elevates, retracts mandible
Masseter	V	OP	Elevates mandible
Pterygoideus medialis	V	OP	Elevates, protracts mandible
Pterygoideus lateralis	V	OP	Depresses, protracts mandible; moves mandible laterally
Obicularis oris	VII	OP,O	Opens, closes, protracts lips
Zygomaticus major	VII	OP,O	Elevates mouth angle upward, backward
Levator labii superioris	VII	OP,O	Elevates upper lip, mouth angle
Depressor labii inferioris	VII	OP,O	Depresses lower lip
Levator anguli oris	VII	OP,O	Elevates mouth angle
Depressor anguli oris	VII	OP,O	Depresses mouth angle
Mentalis	VII	OP,O	Elevates, protracts lower lip
Risorius	VII	OP,O	Retracts mouth angle
Buccinator	VII	OP,O	Flattens, retracts cheek, mouth angle
Hyoglossus	XII	OP,P	Depresses tongue
Genioglossus	XII	OP,P	Depresses, protrudes tongue
Musculus uvulae	IX,X,XI	O	Elevates uvula
Palatoglossus	IX,X,XI	O	Elevates posterior tongue; narrows fauces
Levator veli palatini	IX,X,XI	P	Elevates soft palate
Tensor veli palatini	V	P	Stretches soft palate
Mylohyoideus	V	P	Elevates tongue base, mouth floor, hyoid bone; depresses mandible
Digastricus	V	P	Elevates hyoid bone, tongue base
Geniohyoideus	XII,C1	P	Elevates hyoid bone, tongue
Stylohyoideus	VII	P	Elevates hyoid, tongue base
Thyrohyoideus	XII,C1	P	Depresses larynx, hyoid bone; elevates thyroid cartilage
Styloglossus	XII	P	Elevates, retracts tongue
Palatopharyngeus	IX,X,XI	P	Narrows oropharynx; elevates pharynx

Table 78-1

Muscles Involved in Swallowing (*Continued*)

Muscle	Nerve	Stage	Action
Stylopharyngeus	IX	P	Elevates, dilates pharynx
Salpingopharyngeus	IX,X,XI	P	Elevates nasopharynx
Aryepiglotticus	IX,X	P	Tilts epiglottis downward
Cricoarytenoideus lateralis	IX,X	P	Closes glottis, approximates vocal folds
Thyreoarytenoideus	IX,X	P	Closes glottis, shortens vocal folds
Constrictor pharyngeus superioris	IX,X,XI	P	Compresses pharynx
Constrictor pharyngeus intermedius	IX,X,XI	P	Compresses pharynx
Constrictor pharyngeus inferioris	X,XI	P	Compresses pharynx
Cricopharyngeus	X	P	Closes upper esophageal sphincter

OP = oral preparatory stage; O = oral stage; P = pharyngeal stage.

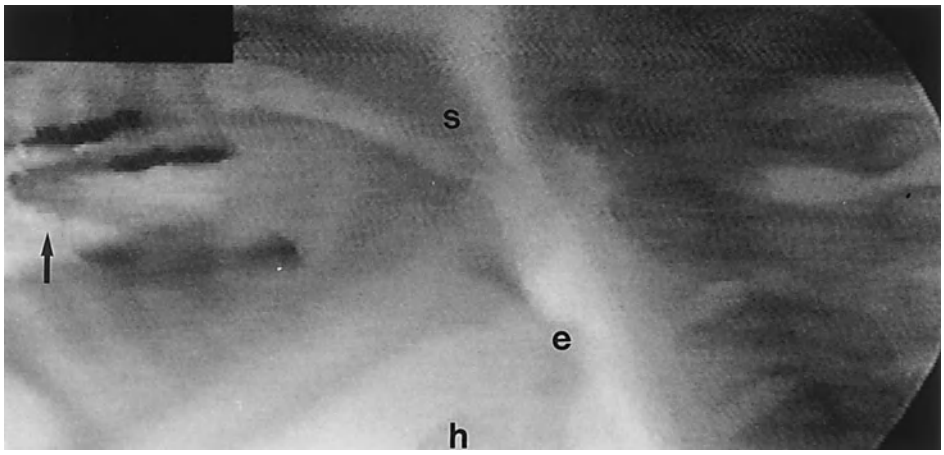
require mastication and may be transported into the oropharynx in one smooth, continuous motion.

During the *oral* phase (Fig. 78-3*B*), the tongue pushes upward and forward, contacting the hard palate anteriorly. As the tongue surface moves upward, the area of contact between the tongue and palate expands from the front of the palate posteriorly, resulting in propulsion of the bolus through the faucial arches into the oropharynx. The bolus may remain in the oropharynx for many additional chewing cycles, and the oral phase may repeat several times before the pharyngeal phase is initiated. A labial seal is maintained to prevent food or liquid from leaking from the mouth. Tension of the buccal musculature prevents food from falling into the lateral sulci between the mandible and the cheek. The oral phase is mediated through cranial nerves VII and XII.

During the *pharyngeal* phase (Fig. 78-3*C*), ventilation ceases temporarily. The nasopharynx closes when the soft palate makes contact with the lateral and posterior pharyngeal walls. The true vocal folds close tightly to prevent aspiration. The larynx pulls forward under the base of the tongue. The bolus deflects away from the laryngeal opening when the epiglottis tilts back. The tongue pushes the bolus posteriorly and inferiorly into the hypopharynx. The upper esophageal sphincter (UES), which usually is held closed between swallows by tonic contraction of the cricopharyngeus muscle, relaxes and opens. The hyoid bone and larynx are pulled forward and upward by contraction of the suprahyoid and thyrohyoid muscles. This pulls the cricoid cartilage and the attached anterior pharyngeal wall away from the posterior pharyngeal wall and underlying vertebral column, opening the pharyngoesophageal sphincter. The pressure of the descending bolus also contributes to the opening of the UES. The pharyngeal constrictor muscles clear the residual bolus from the pharynx by contracting sequentially from top to bottom. After the bolus enters the esophagus, ventilation resumes, and the pharyngeal and laryngeal structures return to their original anatomic position. Sensory receptors of the faucial arches, tonsils, soft palate, tongue base, and posterior pharyngeal wall transmits messages centrally through cranial nerve VII and through the superior laryngeal nerve via the tractus solitarius. Motor impulses are mediated through cranial nerves IX and X.

The tracheobronchial tree normally provides protection against foreign matter by a medullary reflex arc, mediated through the vagus nerve, which produces a cough. The larynx and carina are especially sensitive to irritation, and the terminal bronchioles and alveoli are very sensitive to corrosive chemical stimuli, such as chlorine. Activation of the reflex results in a deep breath; closure of the epiglottis and vocal folds; forceful contraction of the abdominal and internal intercostal muscles; opening of the epiglottis and vocal folds; and a strong compression of the lungs resulting in air velocities as high as 75 to 100 miles per hour. The generated cough usually extracts any foreign matter present in the respiratory tree.

During the *esophageal* phase, the bolus moves from the pharynx to the stomach. When the bolus reaches the gastroesophageal junction, the lower esophageal sphincter (LES) relaxes, allowing the bolus to enter the stomach. The esophagus consists of striated muscle in the upper third and smooth muscle in the lower two-thirds. The esophagus is



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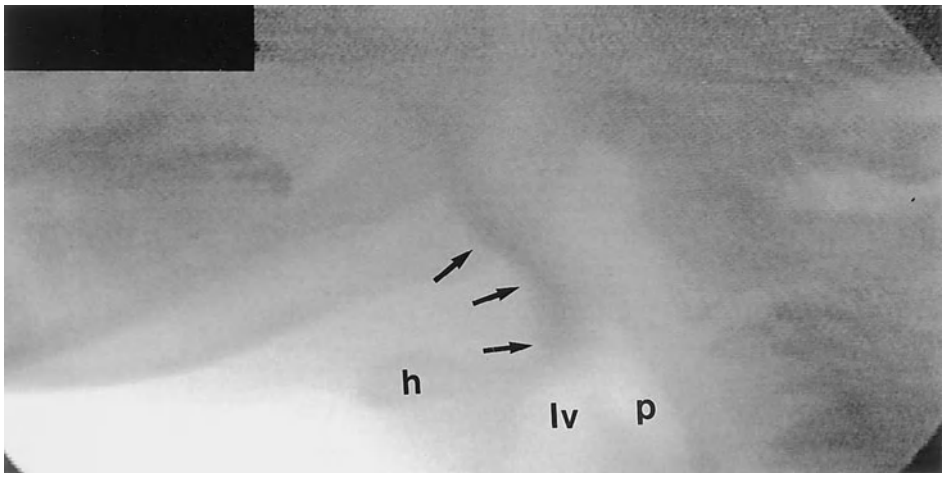

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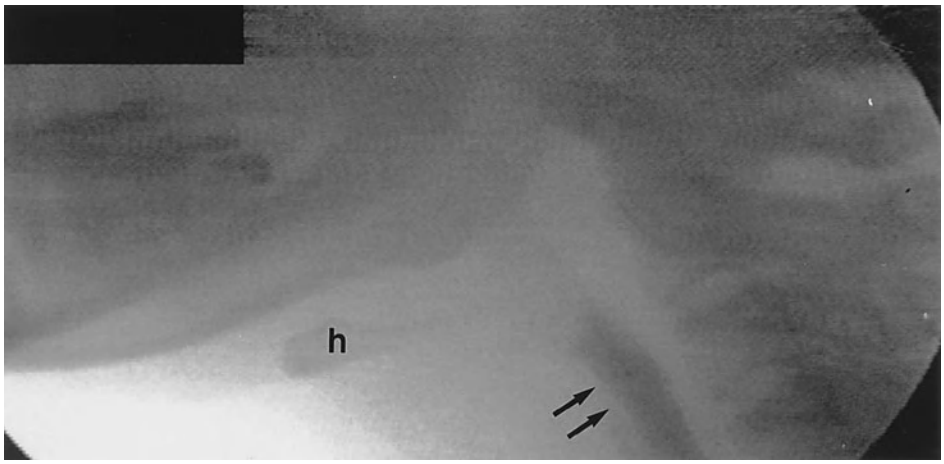


C

Figure 78-3 Phases of deglutition. *A*. Oral preparatory phase. The barium bolus (solid arrow) is masticated using a repeated cyclical pattern of rotary lateral movement of the labial and mandibular musculature. The soft palate (s) is not elevated to allow breathing. The hyoid bone (h) is positioned well below the mandible, and the epiglottis (e) is tilted upward. *B*. Oral phase. The bolus (arrows) has been pushed into the pharynx by elevation and posterior propulsion of the tongue. The soft palate contacts with the posterior pharyngeal wall to obliterate the velopharyngeal port and prevent nasal regurgitation. The hyoid bone (h) is still in its resting position, and the laryngeal vestibule (lv) and hypopharynx (p) are still visible. *C* . Pharyngeal phase. The pharyngeal constrictor muscles shorten and elevate the pharynx while the base of the tongue pushes the bolus toward the esophagus. The nasal passages are still sealed. The hyoid bone (h) is in its most superior and anterior position, correlating with closure of the larynx and the true vocal, false vocal, and aryepiglottic folds. The laryngeal vestibule is closed and cannot be visualized. The upper esophageal sphincter has relaxed, thus allowing the bolus (arrows) to pass into the esophagus.

innervated throughout its length by two nerve networks: *myenteric* (Auerbach's) and *submucosal* (Meissner's). The myenteric plexus serves as a relay between smooth muscle and the vagus nerve, but its function with respect to striated muscle is unclear. The submucosal plexus primarily controls gastrointestinal secretion and local blood flow.

Active movement within the esophagus occurs by peristalsis. For peristalsis to be effective, contractions must be orderly and sequential from the superior end of the esophagus caudally to the gastroesophageal sphincter. Adequate saliva must be present to propel the bolus toward the stomach. Different types of contractions assist with bolus propulsion. *Primary peristalsis,* which is initiated by a pharyngeal swallow, is the chief mechanism to carry a bolus through the esophagus. Primary peristalsis also produces a stripping wave to empty refluxed gastric contents back into the stomach. If the subject swallows again during esophageal peristalsis, primary peristalsis is interrupted and starts again at the top of the esophagus.

If the bolus does not empty into the stomach by primary peristalsis, esophageal distention activates *secondary peristalsis,* which is mediated intrinsically by the myenteric plexus and does not require vagal input. Secondary peristalsis also assists in transport of bicarbonate-containing saliva produced in the mouth to the distal esophagus, where it neutralizes any remaining gastric acid refluxed into the esophagus. In pathological conditions, nonperistaltic contractions known as *tertiary contractions* may occur and are nonfunctional in the transport process. High-amplitude tertiary contractions causing esophageal spasm usually are perceived as one form of noncardiac chest pain.

The esophagus contains a number of protective mechanisms against reflux and aspiration. First, the tonic contractions of the UES and LES act as physical barriers against gastric contents during the resting state. Pressures in the UES range up to 250 to 350 mmHg in the anteroposterior direction and 80 to 120 mmHg in the lateral direction. In the LES, pressures up to 10 to 30 mmHg relative to intragastric pressure have been recorded and prevent movement between the positive pressure of the abdomen and the negative pressure of the chest. Second, a small portion of the distal esophagus adjacent to the LES is located in the abdomen. Positive intra-abdominal pressure tends to keep the stomach and lower esophagus collapsed thereby preventing the transit of boluses into the intrathoracic esophagus. Third, the esophagus enters into the stomach at an acute angle (angle of His), which acts as a one-way valve. The angle decreases when deep inspiration causes descent of the diaphragm and gastric fundus. Even so, the right crus of the diaphragm usually contracts at the same time, preventing reflux by occluding the esophageal lumen.

In addition to afferent and efferent paths, the neural organization of swallowing consists of two centers. One is thought to be located in two regions of the pontine reticular formation—i.e., (1) dorsal, including the nucleus of the solitary tract and adjacent reticular formation, and (2) ventral, corresponding to the lateral reticular formation above the nucleus ambiguus. The dorsal portion appears to initiate and organize the swallowing motor sequence. The ventral portion distributes the motor impulses to the various motor neurons involved with swallowing. In animals, stimulation of the solitary tract or its nucleus in the cat, rat, or sheep can elicit a swallow.

A second swallowing center has been described just anterior to the orbital gyrus in the occipital lobe. In animals, single-pulse stimulation of this cortical center causes rhythmic activation of the ipsilateral nucleus of the solitary tract, resulting in a rapid decrease of the frequency of deglutition. Each cortical center is thought to receive information from its contralateral cortical center and oropharyngeal and laryngeal receptors. The center's purpose is not well understood but may be important for repeated swallowing or initiation of the motor sequence of deglutition.

Studies with transcranial magnetic stimulation demonstrate that swallowing musculature is discretely, somatotopically, and asymmetrically represented on the motor and premotor cortex of both hemispheres independent of handedness. Following stroke, dysphagia appears to be associated with smaller pharyngeal representation on the intact hemisphere, which increases in size with recovery of swallowing.

Swallowing is integrated with ventilation so that a bolus inadvertently does not enter the lower respiratory tract. Swallowing usually interrupts the expiratory phase of ventilation, and the completion of expiration occurs at the conclusion of the swallow. If a swallow is initiated during the inspiratory phase of ventilation, inspiration is interrupted, and a short expiration usually follows the completion of the swallow. Tidal volume may increase in the breaths following the swallow. Apnea occurs earlier in older adults and with larger boluses, but later with increased bolus viscosity.

Vomiting, which is diametrically opposed to swallowing, normally should not result in aspiration because of protective mechanisms observed during this reflex. Vomiting can be stimulated from several sources (Table 78-2). Stimuli reach

Table 78-2

Afferent Input Involved in Vomiting

Symptom	Source
Gastrointestinal tract irritation and overdistention	Vagal, sympathetic afferents
Drugs (e.g., narcotics, digoxin)	Chemoreceptor trigger zone
Vestibular stimuli	Labyrinth, vestibular nuclei, cerebellum, chemoreceptor trigger zone
Psychic stimuli (visual, auditory)	Cerebral, unknown origin

the vomiting center, located bilaterally in the medulla near the tractus solitarius at the level of the dorsal motor nucleus of the vagus nerve. Activation of the vomiting reflex results in a deep breath; elevation of the hyoid bone and larynx with UES opening; glottic and velopharyngeal port closure; simultaneous contraction of the diaphragm and abdominal wall musculature to increase intragastric pressure; and LES relaxation resulting in expulsion of gastric contents through the esophagus.

NEUROMUSCULAR MECHANISMS

Dysfunction of the central nervous system, lower sensorimotor neurons, neuromuscular junction, or muscle cells may result in aspiration. Neuromuscular disorders may cause sensory impairment or motor weakness or incoordination which hinders or circumvents the normal protective mechanisms of the gastroesophageal and tracheobronchial systems. Conditions affecting cognitive function may significantly impair intellectual controls which allow swallowing mechanisms to guide boluses safely toward the stomach. Etiologies of aspiration by neuromuscular mechanisms may be divided into two types: (1) dysphagia and (2) gastroesophageal reflux.

Dysphagia

Dysphagia, or swallowing difficulty, refers to symptoms manifested by a disease state but is not itself a disease. However, dysphagia is a convenient way to categorize certain neuromuscular disorders causing aspiration, since aspiration is a serious and prominent manifestation of swallowing problems. Swallowing difficulties resulting in aspiration occur in a variety of neuromuscular disorders (Table 78-3). Many of these conditions result in abnormalities affecting more than one phase of swallowing.

One framework for understanding swallowing and dysphagia involves *adaptation, compensation,* and *decompensation* of deglutition. Normal swallowing involves continuous adaptation of motor function in response to the ongoing conditions during each swallow, such as bolus size and consistency, head and neck position, and changes in pharyngeal diameter at different phases of respiration and phonation. When swallowing is impaired, compensation can be observed as a supranormal protective or reserve ability to prevent aspiration. Compensation involves a variety of voluntary strategies such as chewing food more thoroughly or limiting bolus size, as well as involuntary processes such as contraction of the superior constrictor muscles to close the velopharyngeal opening in the setting of palatal deficiency or kinking of the soft palate in apposition to weak or atrophied tongue to prevent premature leakage and laryngeal penetration. When compensatory strategies fail, decompensation or failure of the swallowing apparatus results. Decompensation occurs both from singular or multiple compromises in adaptational and compensatory mechanisms, including global suppression of the swallowing mechanism by fatigue or impairment of consciousness. Symptoms consistent with dysphagia and possible clinical indicators of aspiration are summarized in Table 78-4.

Mechanisms of aspiration due to dysphagia usually are classified temporally with respect to the onset of the pharyngeal swallow. Aspiration *before* the swallow is related to abnormalities in the oral or pharyngeal phases (Fig 78-4). Weak or abnormal tongue movements may cause premature spillage of the bolus into the pharynx. A lesion of the nucleus ambiguus or the brain stem or cortical swallowing centers may result in delay or absence of the onset of the pharyngeal swallow. In either case, the pharynx is unprepared to transport the bolus safely into the esophagus. The bolus may enter

Table 78-3

Examples of Neuromuscular Conditions Causing Aspiration

Upper motor neuron
Stroke
Traumatic brain injury
Parkinsonism
Multiple sclerosis
Huntington's disease
Alzheimer's disease
Neurosyphilis
Encephalitis
Meningitis
Spinocerebellar degeneration
Olivopontocerebellar atrophy
Progressive supranuclear palsy
Lower motor neuron
Poliomyelitis
Amyotrophic lateral sclerosis (ALS)
Guillian-Barré syndrome
Polyneuritis
Neuromuscular junction
Myaesthenia gravis
Botulism
Eaton-Lambert syndrome
Muscle
Polymyositis
Dermatomyositis
Muscular dystrophies—Duchenne (DMD), limb-girdle (LGMD), myotonic (MD), facioscapulohumeral (FSHMD)
Spinal muscular atrophy (SMA)
Scleroderma and collagen vascular diseases
Achalasia
Metabolic myopathy

Table 78-4

Symptoms of Dysphagia
Dry mouth
Drooling
Nasal regurgitation
Vomiting
Difficulty clearing phlegm
Postnasal drip
Globus (obstruction)
Odynophagia (pain in throat, chest, or stomach)
Exhaustion after eating or drinking
Dysphonia with or without "wet" voice
Dyspnea
Coughing or choking while eating or drinking
Mouth odor
Heartburn
Chest pain
Weight loss

the unprotected trachea, progressing into the bronchial tree if no protective cough is elicited.

Aspiration *during* the swallow usually reflects dysfunction of the laryngeal and pharyngeal musculature (Fig 78-5). Reduced elevation of the larynx and pharynx results from impaired hyoid bone elevation or thyrohyoid or palatopharyngeal dysfunction and may cause defective closure of the laryngeal vestibule. Vocal cord paresis or paralysis may produce an incompetent laryngotracheal port through which food or liquid boluses may pass.

Aspiration *after* the swallow can represent problems in the pharyngeal and esophageal phases of deglutition (Fig. 78-6). Weakness of the pharyngeal constrictor muscles may produce residue of the bolus in the valleculae or piriform sinuses, which subsequently spills into the laryngeal vestibule and trachea. The UES may fail to open due to impaired relaxation or distensibility, hypertrophy or hyperplasia, or fibrosis (Fig. 78-7). The obstruction may cause filling of the hypopharynx and overflow into the airway.

Similarly, the LES may remain contracted due to defective innervation of the smooth muscle of the esophagus and LES resulting in achalasia (Fig. 78-8). The primary etiology of achalasia usually is idiopathic, but secondary causes may include gastric carcinoma extending to the esophagus, lymphoma, Chagas' disease, irradiation, and certain medications and toxins. Patients with achalasia may experience dysphagia, chest pain, and regurgitation, but pulmonary aspiration may occur due to overflow of saliva and ingested food lodged in the esophagus.

Cerebral lesions can interrupt voluntary control of the preparatory and oral phases. Cortical lesions involving the precentral gyrus may produce contralateral impairment

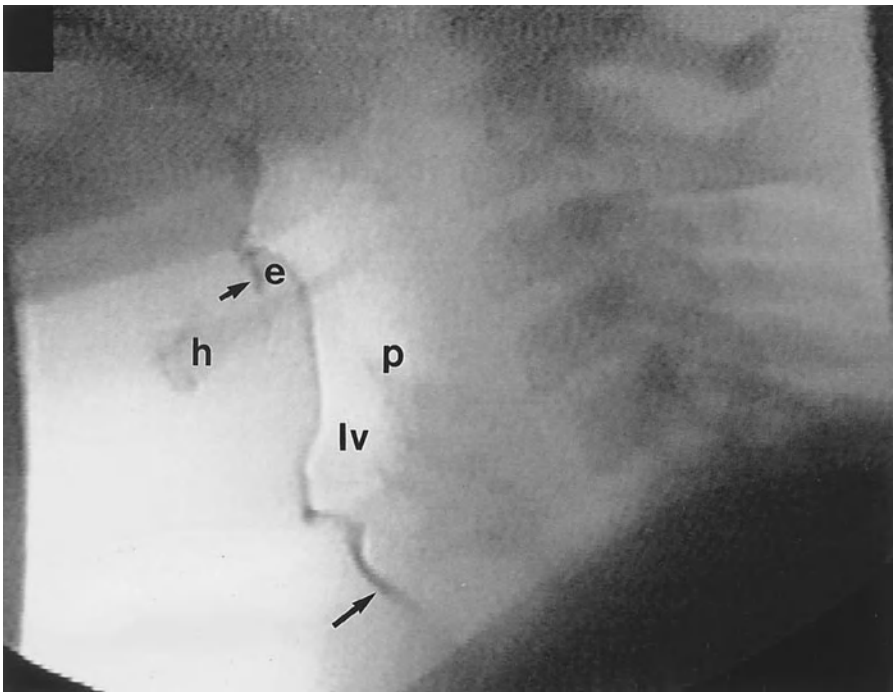


Figure 78-4 Aspiration before the swallow. Because of poor lingual control, a liquid bolus has spilled into the vallecula (small arrow), through the laryngeal vestibule (lv), and into the trachea (large arrow). The hyoid bone (h) and epiglottis (e) remain in their resting positions, and the laryngeal vestibule (lv) remains open. The hypopharynx (p) ends at the contracted upper esophageal sphincter.

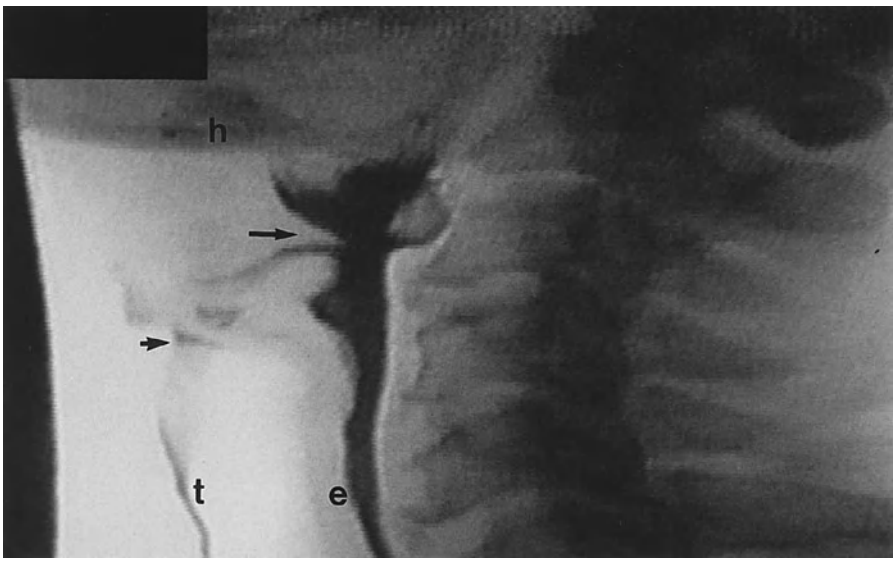


Figure 78-5 Aspiration during the swallow. Because of pharyngeal weakness represented in part by partial deflection of the epiglottis (long arrow), a portion of a liquid bolus enters the laryngeal vestibule and passes through the true vocal folds (short arrow) into the trachea (t), while the remainder successfully passes into the esophagus (e). Note that the hyoid bone (h) is in its most elevated position.

in facial, lip, and tongue motor control and contralateral compromise in pharyngeal peristalsis. A patient with impairments in cognitive function such as concentration or selective attention may not fully masticate food boluses. Oral apraxia seen in stroke or Alzheimer's dementia may result in nonpurposeful sequencing of food by the tongue, lips, and teeth. The bradyphrenia and bradykinesis of Parkinson's disease may challenge attentional vigilance during eating and slow pharyngeal transit. In all these cases, boluses may spill prematurely into an open airway due to abnormal or absent lingual control.

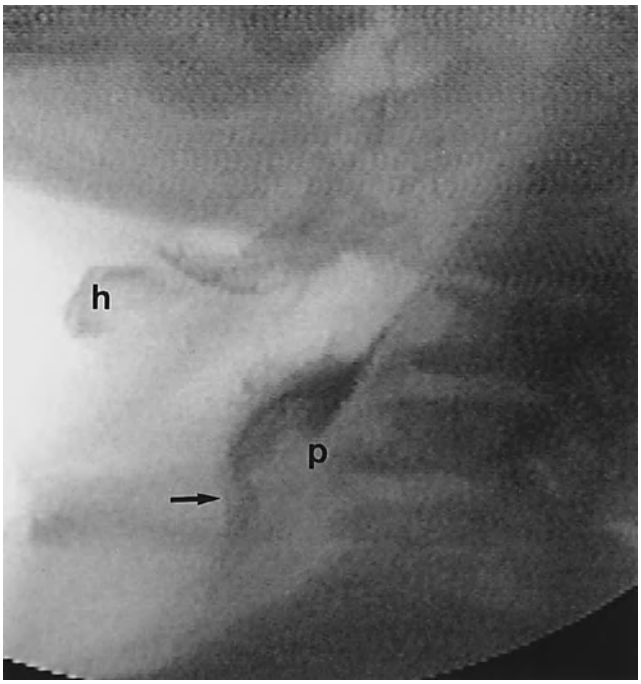


Figure 78-6 Aspiration after the swallow. A portion of a liquid bolus pools in the piriform sinuses (p) as a result of pharyngeal weakness. Eventually it spills over the aryepiglottic fold into the trachea (arrow). Note that the hyoid bone (h) is in its resting position.

Brain-stem lesions may result in compromised sensation of the mouth, tongue, and cheek, delay or absence of the pharyngeal reflex, reduced laryngeal elevation and vocal cord adduction with incomplete glottic closure, and poor cricopharyngeal relaxation. In stroke, for example, a delay or absence of the pharyngeal swallow may cause a bolus to enter

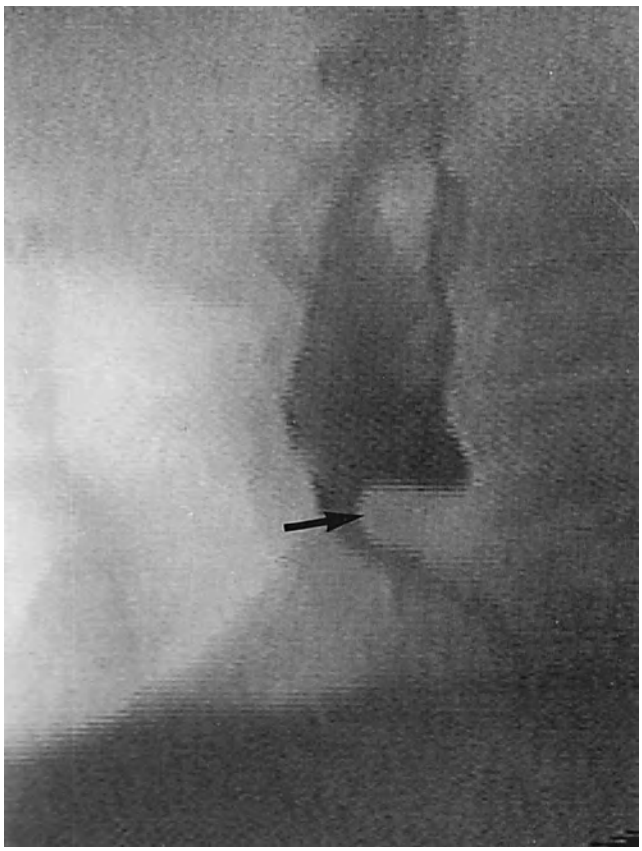


Figure 78-7 Cricopharyngeal dysfunction. The upper esophageal sphincter does not completely relax resulting in a "bar" (arrow) that may divert much of this liquid bolus from the esophagus into the airway.

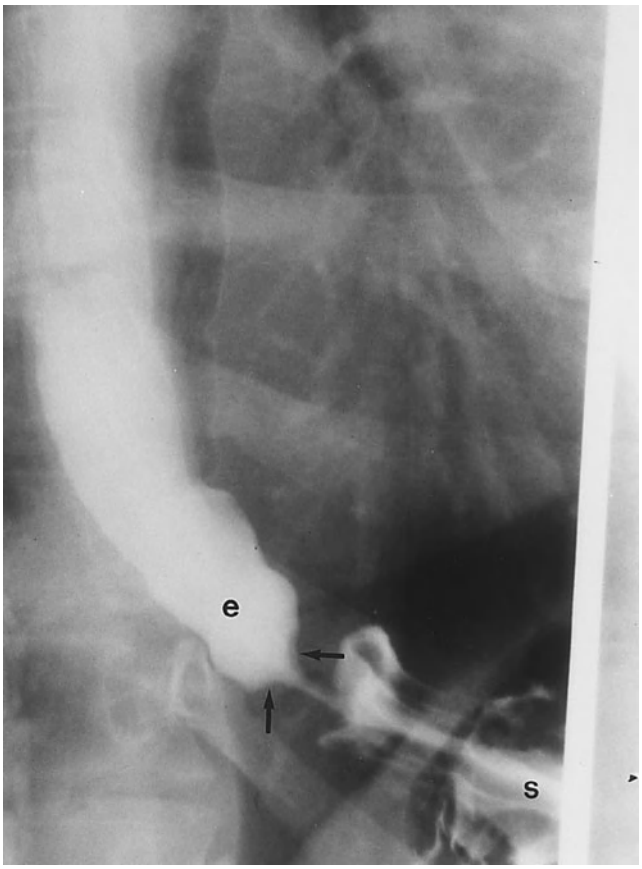


Figure 78-8 Achalasia. The esophagus has a characteristic "bird beak" appearance (arrows) where the gastroesophageal junction does not relax and allow passage of boluses. Residue may fill the esophagus and overflow into the airway (e = esophagus; s = stomach).

an unprotected airway even when the oral stage is normal. Pharyngeal weakness allows accumulation of residue in the valleculae and piriform sinuses which may spill into the larynx after the swallow. In Parkinson's disease, failure of contraction of the pharyngeal constrictor muscles against an unrelaxed cricopharyngeus results in trapping a food bolus in a high-pressure segment of the lower pharynx, ultimately hurling the bolus back toward the pharyngeal and nasopharyngeal opening. During vomiting, weakness or incoordination of the pharyngeal musculature may decrease protection of the larynx allowing vomitus to enter the tracheobronchial tree.

Much investigation of the predictors of aspiration has been directed toward cerebrovascular diseases or stroke. Dysphagia is reported to occur in at least 50 percent of stroke survivors. Of those, aspiration is reported to occur in up to 75 percent. "Silent" aspiration, or aspiration without reflexive cough, is demonstrable in about one-third to one-half of patients. Lesion site or bilaterality is not predictive of dysphagia, aspiration, or their related symptoms. The absence of the gag reflex is neither predictive nor protective of dysphagia and aspiration. The presence of "wet," dysphonic vocalizations may indicate aspiration risk, but its absence does not rule out this possibility. Thinner liquids, such as water, have a higher risk of being aspirated because they are more difficult to manipulate during the oral phase and present less afferent sensory stimulation to trigger the pharyngeal and esophageal reflexes. The single best predictor of aspiration is the presence of an involuntary cough during or for 1 minute after being challenged to drink and swallow 3 ounces of water without interruption.

A voluntary cough, however, does not necessarily indicate an effectively protective cough reflex. The absence of voluntary cough, however, should preclude further oral intake until further investigation. Bedside examination by clinicians may miss up to 40 percent of aspirations seen radiographically. During videofluorographic examination of dysphagic stroke survivors, slow or delayed initiation of the pharyngeal swallow and pharyngeal constrictor weakness were the best predictors of aspiration. Penetration of more than 10 percent of a bolus beyond the true vocal folds during videofluorographic evaluation is associated with increased risk of aspiration pneumonia, but findings of residue in the valleculae and piriform sinuses are not associated with aspiration pneumonia.

Stroke survivors with bilateral cranial nerve dysfunction are at the greatest risk of aspiration. Of the 40 percent of dysphagic stroke survivors who aspirate silently, these patients may express fewer subjective complaints and have a weaker cough. Dysphonia is the most common symptom associated with aspiration.

The relative risk of pneumonia in stroke survivors who aspirate radiographically is almost seven times greater than stroke survivors who do not aspirate. The risk of aspiration pneumonia is about five-and-one-half times greater in patients with silent aspiration when compared to nonaspirating stroke survivors. Aspiration pneumonia in stroke survivors occurs about three-and-one-half times more commonly from aspirating liquids than from aspirating solids.

Data have been collected on the incidence of aspiration in other diagnoses. In nonambulatory patients with Parkinsonism, aspiration occurs in up to 46 percent and is seen more commonly with liquid swallows than with solids or semisolids. Over 30 percent of persons with multiple sclerosis experience dysphagia, including 15 percent of those with mild disability. After resection of basal skull tumors, 75 percent of patients aspirated during videofluorographic swallowing studies.

Gastroesophageal Reflux Disease

Gastroesophageal reflux disease (GERD) typically presents with symptoms of heartburn and regurgitation and less typically with anginalike chest pain. Tracheopulmonary manifestations of reflux include chronic hoarseness *(reflux laryngitis)* associated with inflammation of the posterior larynx and vocal cords, nocturnal episodes of nonallergic asthma, chronic cough, or sustained hiccups.

For GERD to cause aspiration, gastric secretions and/or bacteria must traverse the LES, esophagus, and UES (Fig. 78-9). Gastric secretions normally have a pH of approximately

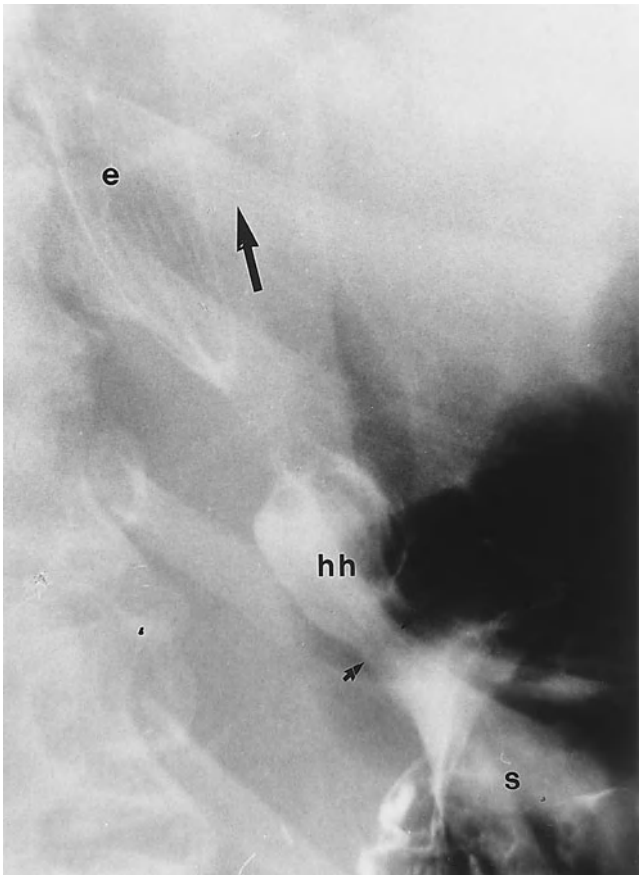


Figure 78-9 Gastroesophageal reflux. Incompetence in the LES (small arrows) permits liquid barium to reflux from the stomach (s) to the esophagus (e). A hiatal hernia (hh) may commonly be associated with gastroesophageal reflux.

0.8 when produced by parietal cells of the stomach. Chemical burns of the airways and lung parenchyma may result when gastric juices have a pH of less than 3.0. Mild desquamation of the parenchyma with delayed regeneration may occur when food particles have a pH greater than 3.0. Conditions such as Zollinger-Ellison syndrome worsen the risk of GERD due to the propensity for hyperacidity.

Increases in gastric pH create an environment more conducive to supporting bacterial colonization in the stomach. With administration of histamine-2 (H_2) antagonists, antacids, or continuous enteral feedings, bacteria typically found in the duodenum (e.g., *Escherichia coli, Streptococcus faecalis, Proteus mirabilis, Pseudomonas maltophilia)* may reflux into and colonize within the stomach independent of oropharyngeal flora. Tracheobronchial contamination then may ensue when GERD occurs. Also, duodenal contents combined with reduced or absent acid secretion may reflux after gastrectomy or in the presence of pyloric dysfunction, resulting in alkaline reflux esophagitis and chronic aspiration.

LES incompetence is most commonly due to transient or chronic reductions in LES tone. The intra-abdominal length of the esophagus correlates negatively with the degree of gastroesophageal reflux. Conditions and agents that decrease LES pressure are found in Table 78-5.

The association between hiatal hernia and GERD remains controversial. Hiatal hernias may be found in a large percentage of people, many of whom may be asymptomatic. However, current information suggests that gastric acid may become trapped in the hernial sac, making it more available to reflux into the esophagus when the LES relaxes. A recent study demonstrates that patients with large hiatal hernias tend to have lower LES pressures susceptible to reflux by abrupt increases in intra-abdominal pressure.

Esophageal motility must be dysfunctional for gastric secretions to ascend to the UES. However, the primary mechanism that links primary peristaltic dysfunction with reflux is unknown. In patients who aspirate due to GERD, peristalsis usually is not organized but is characterized by tertiary contractions. The amplitude of peristalsis is significantly decreased throughout the esophagus in GERD, while the amplitude of peristalsis is reduced only in the lower esophagus in patients with esophagitis. Absent or incomplete peristaltic contractions result in little or no volume clearance from the involved segments. The degree of peristaltic dysfunction is correlated with the amount of reflux.

The UES represents the final obstacle to aspiration of gastric contents. In patients with aspiration associated with GERD, the resting pressure of the UES is lower than that of normal patients or those with gastroesophageal reflux alone. The primary mechanism for the onset of UES hypotonia is unknown. In addition, UES tone is virtually absent during sleep, during which time reflux does not cause any reflex increase in UES pressure. Without preventive measures such as raising the head of the bed to increase the influence of gravitational forces, gastric secretions have easy access into the respiratory tree.

MECHANICAL MECHANISMS

There are numerous mechanical etiologies of dysphagia, including inflammatory (e.g., Ludwig's angina, retropharyngeal infections), anatomic (e.g., Zenker's diverticulum), traumatic, and cancer-related, but few actually lead to aspiration. Mechanical problems may divert the path of a bolus from the esophagus into the trachea; they may compress nerves resulting in abnormal sensory input or motor function which can cause aspiration. Treatment of these conditions may alleviate or exacerbate symptoms of aspiration.

Ludwig's angina is a submandibular space infection caused by abscesses, caries, or postextraction dental infection. The floor of the mouth becomes erythematous, edematous, and indurated, and the tongue is displaced. The suprahyoid region of the neck becomes swollen and stiff. Asphyxia, aspiration pneumonia, and lung abscess may be potential complications and require intravenous antibiotics. The submandibular abscess may require surgical incision and drainage.

Table 78-5

Examples of Agents and Conditions Causing Decreased LES Pressure

Medications	Hormones and Peptides	Foods	Medical Conditions	Surgical Conditions
Anticholinergics	Calcitonin gene-related peptide	Carminatives (spearmint, peppermint)	Amyloidosis	Lower esophageal sphincter myotomy (Heller)
Barbiturates	Cholecystokinin	Chocolate	Diabetes mellitus	Lower esophageal sphincter resection
Calcium channel blockers	Estrogen	Ethanol	Hypothyroid	
Caffeine	Glucagon	Fat	Pregnancy	
Diazepam	Neuropeptide Y		Scleroderma	
Dopamine	Progesterone		Transient lower esophageal sphincter relaxation	
Meperidine	Somatostatin			
Prostaglandins E_1 and E_2	Secretin			
Theophylline	Vasoactive intestinal polypeptide			

Retropharyngeal infections occur in the space between the posterior pharyngeal wall and the spine. They may be caused acutely by abscesses from the lateral pharyngeal wall or complications from neck trauma, or chronically by complications of osteomyelitis of the cervical spine. Epiglottitis, mediastinitis, meningitis, spontaneous rupture of the larynx with aspiration and asphyxiation, bronchial erosion, pyopneumothorax, and purulent pericarditis may complicate the course of the infection. Antibiotic therapy and surgical drainage may be required to alleviate the condition.

Zenker's diverticulum is an abnormal muscular outpouching that occurs in the cervical esophagus (Fig. 78-10). This outpouching may be located in the midline or laterally and inferior to the cricopharyngeus muscle insertion on the cricoid cartilage (Killian-Jamieson type). The etiology of Zenker's diverticulum is unknown but may be associated with esophageal diseases such as varices, carcinoma, hiatal hernia, and achalasia. These diseases occur more commonly in men in their sixth or seventh decade. Symptoms include coughing, choking, or wheezing. Aspiration occurs most often at night, but aspiration pneumonitis occurs in fewer than 10 percent of patients.

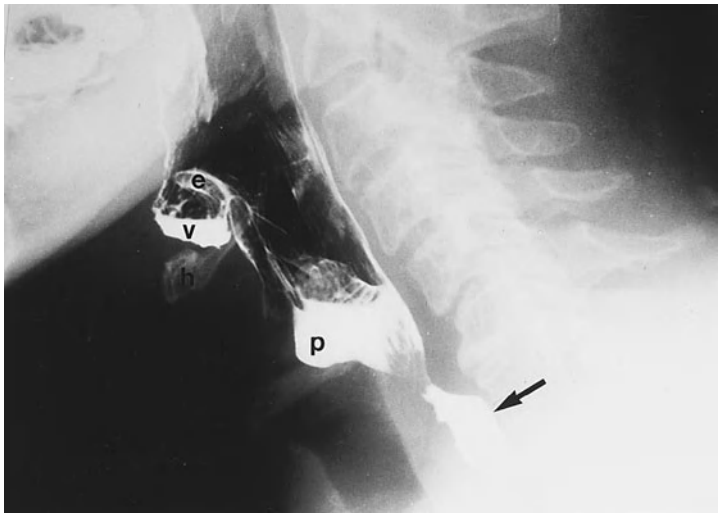
Traumatic alteration of the pharyngeal mucosa may lead to aspiration. Blunt trauma due to motor vehicle accidents, gunshot or knife wounds, or falls from significant heights can transform oropharyngeal anatomy or cause nerve damage which results in aspiration. Fistulae allow food to travel directly between the esophagus and the trachea.

Finally, primary tumors and their sequelae may cause aspiration. Tumors of the tongue or floor of the mouth may limit movements of the mandible and tongue resulting in premature spillage of a bolus into an open airway. Pharyngeal or esophageal tumors may obstruct the alimentary canal, cause backflow into the hypopharynx, and result in spillage of a bolus into the airway (Fig. 78-11).

IATROGENIC MECHANISMS

Nonoral Enteral Feeding

Aspiration not only is an indication for but also is a complication of enteral nutritional support. Nasoenteric, gastrostomy,



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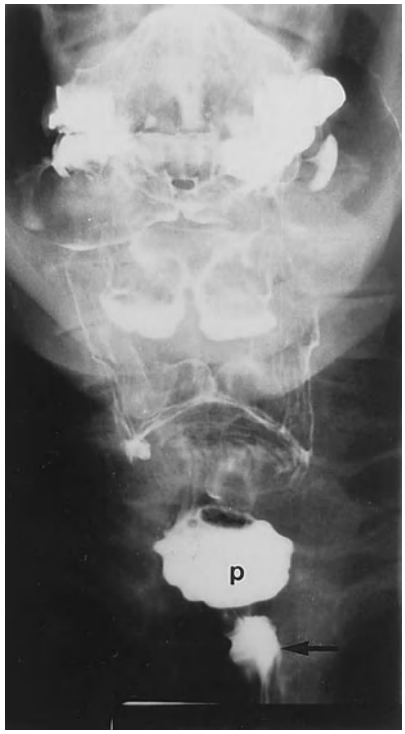

B

Figure 78-10 Zenker's diverticulum. This abnormality is located in the midline just inferior to the upper esophageal sphincter in the cervical esophagus (arrows). Residue may reflux into the pharynx and may be aspirated. *A*. Lateral view. *B*. Anteroposterior view (v = vallecula; e = epiglottis; p = piriform sinus).

and jejunostomy tubes all have been implicated as a cause of aspiration. The mechanical interruption of the pharynx, gastroesophageal junction, and pylorus of the stomach is presumed to augment any underlying predisposing factors.

Patients with neurogenic dysphagia receiving enteral nutrition by nonoral feeding methods have a higher incidence of aspiration pneumonia than those with dysphagia of mechanical origin. Further, the use of the nasoenteric route for enteral feeding is associated with higher rates of aspiration pneumonia and higher mortality from aspiration pneumonia than gastrostomy or jejunostomy. However, tube size, distal tube location, and feeding schedules (continuous or intermittent) have not been shown to influence the recurrence of aspiration.

The use of gastrostomy versus jejunostomy with respect to aspiration risk remains controversial. One review of complications associated with gastrostomy and jejunostomy feedings in patients with neurogenic dysphagia reported no significant difference in aspiration risk. However, another study suggested that patients with clinical or videofluorographic evidence of gastroesophageal reflux, aspiration, gastric atony, and/or gastric outlet obstruction may have a reduced risk of aspiration when jejunostomy tube feedings are used. When these contraindications for the use of a gastrostomy tube are present, the feeding tube should be placed distal to the gastroesophageal and pyloric sphincters, increasing protection against aspiration.

Nosocomial pneumonia may be related to enteral nutrition. Gastrostomy feedings may alkalinize the gastric environment, facilitating bacterial overgrowth (see "Gastroesophageal Reflux Disease" above). The use of jejunostomy feedings may result in less alkalinization of the gastric environment but may still result in lowering bacterial colony counts even when reflux and aspiration are present. Models simulating the effects of environmental influences on the upper gastrointestinal flora of patients receiving enteral feedings suggest that a gastric pH of less than 4 is not sufficient to prevent microbial overgrowth. Monitoring of tracheal secretions in critically ill hospitalized patients requiring tube feeding, especially when mechanically ventilated, using techniques such as methylene blue dye detection and glucose monitoring (glucose-positive indicating reflux and aspiration), may be useful. However, commonsense interventions, such as keeping these patients in at least a 30-degree semirecumbent position during and up to 1 to 2 hours after enteral feeding, may be more important in preventing aspiration.

Tracheal Intubation and Tracheostomy

Mechanical interruption of the larynx with a tracheostomy or endotracheal tube is associated with increased risk of aspiration in patients receiving both oral and enteral feedings. For example, in one study, 71.4 percent of the aspirations observed in patients receiving enteral feedings occurred in patients who had artificial airways. A tracheostomy or endotracheal tube will interfere with both laryngeal elevation and laryngeal closure during the pharyngeal phase of swallowing. Further, the cough reflex may be compromised such that there is insufficient subglottic pressure generated by a reflexive cough when laryngeal penetration occurs. Inflation of the tracheostomy cuff is thought to limit, however incompletely, laryngeal and upper-airway entry of nongaseous materials.

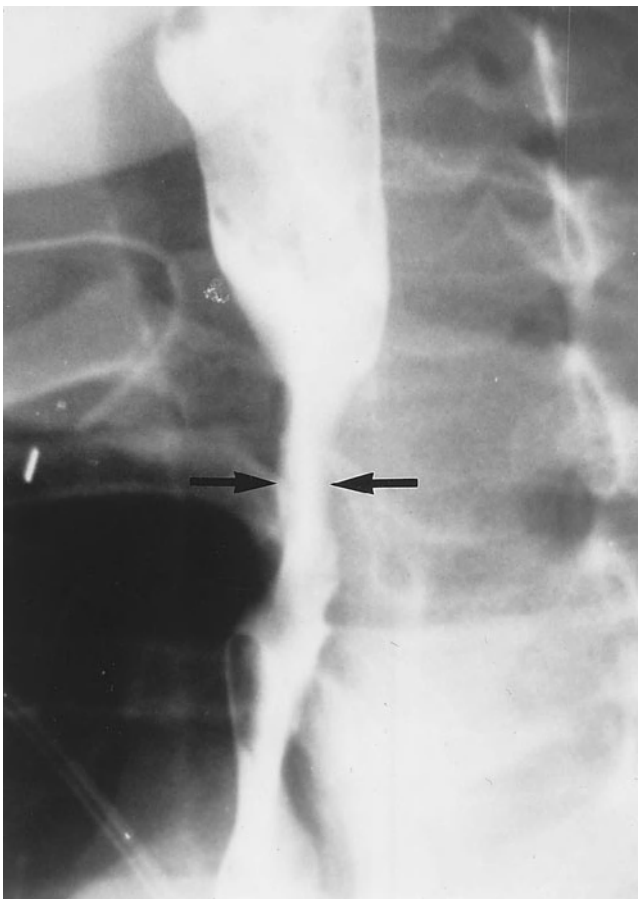

Figure 78-11 Esophageal carcinoma. This adenocarcinoma of the esophagus has a characteristic "apple core" appearance. Boluses may lodge in the esophagus or reflux into the pharynx with subsequent aspiration.

General Anesthesia

The use of general anesthesia for surgical procedures globally depresses consciousness as well as adaptational and compensatory mechanisms that are thought to protect from aspiration. The risk of aspiration is even higher when emergent surgical intervention allows inadequate time for gastric emptying of recently ingested food. Further, when the surgical procedure involves manipulation of the stomach or bowels, the possibility of regurgitation of gastric contents is high. Some investigators have explored the use of artificial airways that aim to prevent the aspiration of regurgitated gastric materials during surgical procedures. These artificial airways provide an esophageal seal that prevents passage of more solid gastric materials yet allows drainage of distal esophageal fluid. The efficacy of these types of airways is not yet established.

Head and Neck Cancer Treatments

Treatments for head and neck cancer may exacerbate swallowing problems which increase the incidence of aspiration. Resections of the retromolar trigone, base of the tongue, and floor of the mouth cause aspiration due to loss of bolus control and premature spillage of the bolus into the pharynx. Resections of the tonsils and superior or lateral pharynx may interfere with bolus transport because of altered sensation or decreased propulsion usually supplied by the pharyngeal constrictor muscles. Resection of the submental muscles impairs the laryngeal elevation and forward movement required to protect the larynx from foreign bodies. Hemilaryngectomy decreases the contact between the base of the tongue and the excised larynx, thus raising the risk of aspiration. Supraglottic laryngectomy, which includes resection of the aryepiglottic folds and one or both of the superior laryngeal nerves, can cause persistent aspiration when the arytenoid cartilage, piriform sinuses, and tongue base are removed. Tracheoesophageal puncture for placement of a prosthetic valve to facilitate voice after laryngectomy can be a site for liquid or secretions to leak into the trachea through the fistula and through the prosthesis. Even irradiation of resected tissues may result in tissue necrosis and fibrosis which can limit a significant amount of protective laryngeal movement.

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79

Pulmonary Alveolar Proteinosis

Bruce C. Trapnell • Jonathan Puchalski

Pulmonary alveolar proteinosis (PAP) is a syndrome characterized by progressive accumulation of surfactant phospholipids and proteins within alveoli and terminal airways. Our understanding of this rare and fascinating syndrome has improved greatly over the past decade due to important contributions from clinical, basic, and translational research. While improving our understanding of disease pathogenesis, these studies have also identified a critical role for granulocyte-macrophage colony-stimulating factor (GM-CSF) in surfactant homeostasis and host defense. Based on clinical, histopathological, and pathogenic differences, PAP is now recognized to occur as one of three distinct forms: primary, secondary, and congenital. Primary PAP (also referred to as acquired or idiopathic PAP) is a disorder of unknown etiology believed to result from decreased surfactant clearance by alveolar macrophages. Primary PAP is also complicated by secondary infections that contribute to increased mortality and suggest the presence of a defect in systemic immunity. Secondary PAP is a clinically heterogeneous syndrome occurring as a consequence of a co-morbid condition that impairs surfactant clearance. Congenital PAP is a pathogenically heterogeneous group of genetic disorders resulting in production of abnormal surfactant.

PATHOGENESIS

In their initial description of PAP in 1958, Rosen et al established that the alveolar material in PAP was composed of lipids, proteins, and a small amount of carbohydrate. Although the etiology of primary PAP remains unknown, strong evidence now supports a mechanism in which interruption of GM-CSF signaling impairs the terminal differentiation of alveolar macrophages and their ability to catabolize surfactant lipids and proteins. GM-CSF is a 23-kDa glycoprotein cytokine produced by various cell types including the respiratory epithelium. It was initially identified by its ability to stimulate the formation of macrophage and granulocyte colonies from hematologic progenitors and subsequently shown to stimulate functions in mature myeloid and other cells. The gene encoding GM-CSF is expressed similarly in humans and mice, and its biologic effects are mediated by binding

to heterodimeric cell surface receptors composed of a GM-CSF-binding α-chain (CD116) and an affinity-enhancing β-chain.

Surfactant Homeostasis

Surfactant is vital to the mechanical function of the lungs where it acts to reduce the surface tension at the air-liquid-tissue interface, thus preventing alveolar wall collapse. Surfactant is composed of approximately 90 percent lipids (largely phospholipids), 10 percent proteins (surfactant protein [SP] -A, -B, -C and -D]), and less than 1 percent carbohydrate. SP-B and SP-C are hydrophobic phosphoproteins and contribute significantly to the surface active properties of surfactant. SP-A and SP-D are hydrophilic protein members of the collectin family of proteins that contribute to lung host defense. Surfactant lipids and proteins are synthesized, stored, and secreted into the alveoli by type II alveolar epithelial cells. In the extracellular space, large aggregates of surfactant develop and contribute to the formation of a film that stabilizes the alveolus by lowering surface-tension. Surfactant is expelled from the film as small aggregates that are taken up by both type II cells and alveolar macrophages (Fig. 79-1). While type II cells are capable of recycling surfactant, alveolar macrophages catabolize both surfactant lipids and surfactant proteins, a process believed to be regulated by GM-CSF.

Animal Models of PAP

An important clue to the pathogenesis of PAP was provided by the serendipitous discovery that GM-CSF knockout mice develop a pulmonary phenotype biochemically, histologically and ultrastructurally indistinguishable from that of primary PAP (Fig. 79-2). Detailed studies of these mice revealed that production of surfactant lipids and proteins by type II cells is not increased and that surfactant uptake by alveolar macrophages is not decreased. In contrast, catabolism of both surfactant lipids and proteins by alveolar macrophages is markedly impaired. PAP could be corrected in GM-CSF knockout mice by replacement of GM-CSF in the lungs, adenoviral transfer of the GM-CSF gene into the pulmonary epithelium, or genetic reconstitution of GM-CSF expression specifically in the lungs. Ablation of the GM-CSF receptor β gene also caused PAP, confirming that GM-CSF signaling is critical for surfactant homeostasis in mice. PAP in this latter model was corrected by bone marrow transplantation, confirming that the defect was in macrophages, not lung epithelial cells. Surfactant catabolism in alveolar macrophages

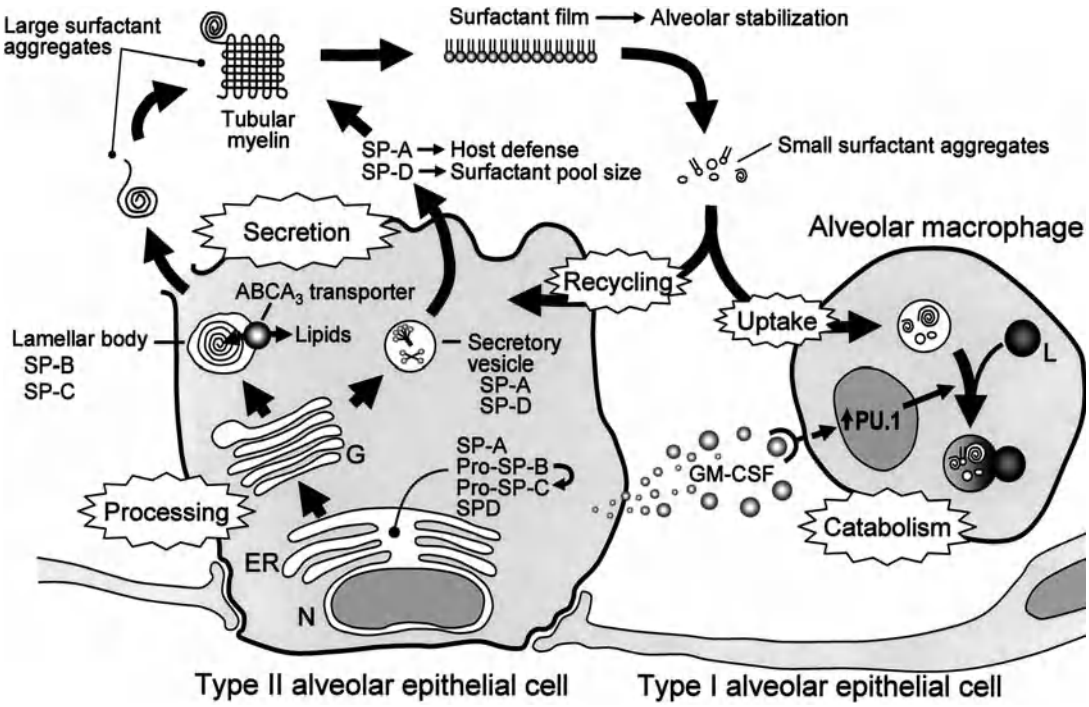


Figure 79-1 Schematic illustration depicting mechanisms of surfactant production, recycling and catabolism. Surfactant phospholipids and proteins are synthesized in type II alveolar epithelial cells that line pulmonary alveoli. Surfactant B and C precursor proteins are processed, transported to lamellar bodies, and then secreted into the alveolar space where they interact with surfactant protein A to form tubular myelin. Surfactant monolayers and multilayers are formed from tubular myelin and function to reduce surface-tension at the air-liquid-tissue interface, thus stabilizing the alveoli. Surfactant remnants are taken up and either catabolized or re-utilized by type II alveolar epithelial cells. Alveolar macrophages play a critical role in surfactant homeostasis by taking up and catabolizing surfactant remnants. GM-CSF is required to maintain surfactant homeostasis and acts by stimulating catabolism of surfactant lipids and proteins in alveolar macrophages. *(From Whitsett JA, Wert SE, Trapnell BC: Genetic disorders influencing lung formation and function at birth*. Hum Mol Genet *13[Spec No 2]:R207–R215, Fig. 2, 2004, with permission.)*

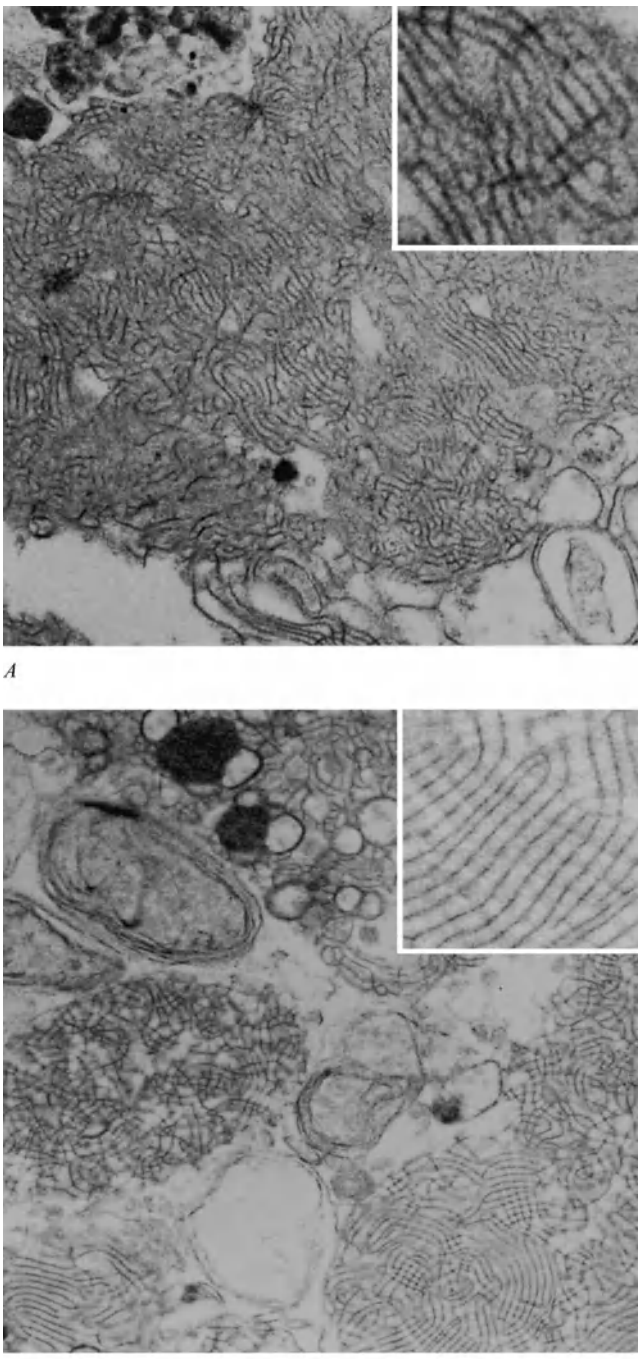


Figure 79-2 Ultrastructural appearance of the sediment from the lungs of a human patient with primary PAP (*A*) and a GM-CSF–deficient mouse (*B*). Note the presence of lamellated, fused membrane structures and amorphous debris (uranyl acetate, ×30,000).

from GM-CSF knockout mice can be rescued by retroviral expression of PU.1, a transcription factor normally expressed in murine alveolar macrophages in vivo under tight regulatory control of pulmonary GM-CSF. Together, these studies established that GM-CSF has a critical role in surfactant homeostasis in mice and acts by stimulating surfactant catabolism in alveolar macrophages via PU.1 (Fig. 79-3).

Other animal models of PAP exist. For example, over-expression of either interleukin (IL)-4 or IL-13 in the lungs of transgenic mice is associated with increased production of surfactant proteins and lipids and development of PAP. Genetically modified mice deficient in SP-B, SP-C, or ABCA3 have been created as animal models of congenital PAP. Naturally occurring mice with severe combined immunodeficiency (SCID) also develop PAP, presumably as a secondary consequence of the effects on alveolar macrophages.

GM-CSF and Innate Immunity

GM-CSF knockout mice have increased susceptibility to bacterial, fungal, parasitic, and mycobacterial infection and increased mortality from spontaneous infections. Alveolar macrophages from these mice have impaired cellular adhesion, cell-surface pathogen recognition receptors, phagocytosis, lipopolysaccharide-stimulated proinflammatory cytokine secretion, and antimicrobial killing activity. Importantly, as for the defect in surfactant catabolism, retroviral expression of PU.1 in alveolar macrophages corrects all of these macrophage immune defects (Fig. 79-3). The diversity and number of functions regulated by PU.1 in alveolar macrophages strongly suggest that GM-CSF, via PU.1, regulates alveolar macrophage terminal differentiation in mice. Translational studies show that GM-CSF also regulates expression of PU.1 and a number of PU.1-dependent genes in human alveolar macrophages, suggesting that it may also regulate terminal differentiation of human alveolar macrophages. While these observations suggest that defects in alveolar macrophage-mediated immunity likely contribute to impaired host defense in GM-CSF knockout mice, GM-CSF deficiency may also be important to the functions of other components of immunity.

Antibodies against GM-CSF in Primary PAP

A second clue regarding pathogenesis was the observation that high levels of anti–GM-CSF autoantibodies were present in blood and lungs of individuals with primary PAP, but not in those with secondary or congenital PAP or other lung diseases or in normal individuals (Fig. 79-4). Anti–GM-CSF antibodies in primary PAP are polyclonal, comprise all four immunoglobulin G (IgG) subclasses, have a very high affinity for GM-CSF, and are capable of neutralizing up to 50,000-fold more GM-CSF than is normally present, thus eliminating GM-CSF bioactivity in vivo. Primary PAP appears to comprise a human functional deficiency of GM-CSF. Notwithstanding their high specificity for primary PAP, levels of serum anti–GM-CSF antibodies do not correlate well with disease severity. This is not unexpected in the context of a mechanism in which anti–GM-CSF antibodies are not directly toxic but contribute to molecular and cellular pathology by neutralizing GM-CSF bioactivity and thereby impairing GM-CSF–dependent macrophage functions.

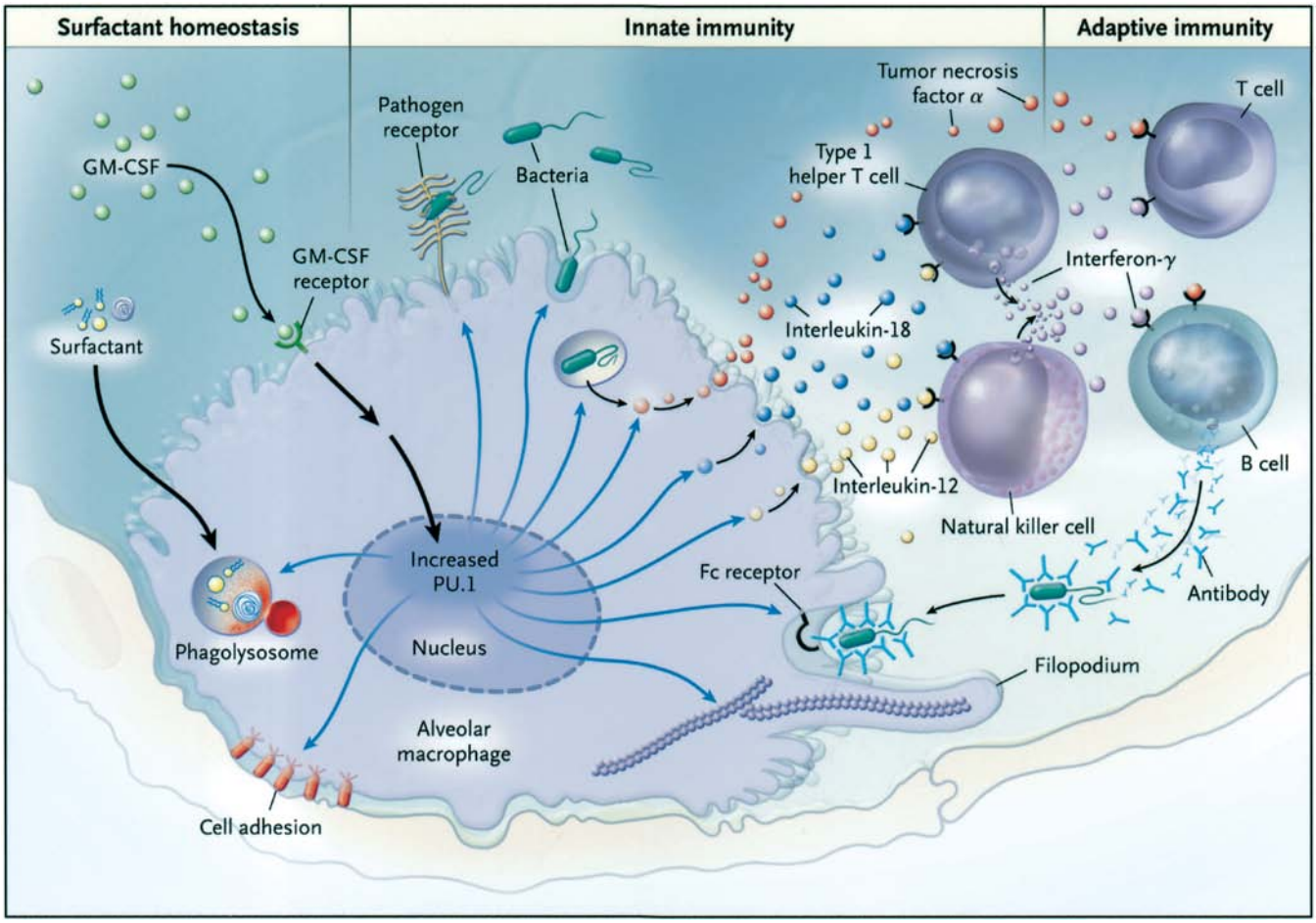


Figure 79-3 Role of GM-CSF in modulating the function of alveolar macrophages in mice. Pulmonary GM-CSF stimulates increased levels of the transcription factor PU.1 in alveolar macrophages in the lungs in vivo. Alveolar macrophages from mice deficient in GM-CSF have a number of functional defects including defects in cellular adhesion, catabolism of surfactant proteins and surfactant lipids, expression of pathogen-associated molecular pattern receptors (e.g., toll-like receptors and the mannose receptor), toll-like-receptor signaling, phagocytosis of pathogens, intracellular killing of bacteria (independent of uptake), pathogen-stimulated secretion of cytokines (tumor necrosis factor-α, interleukin [IL]-12, and IL-18), and Fc- receptor–mediated phagocytosis. Cytoskeletal organization is abnormal and may in part account for defects in phagocytosis. The ability of alveolar macrophages to release IL-12 and IL-18 severely impairs the interferon-γ response to pulmonary infection, thus impairing an important molecular connection between innate and adaptive immunity in the lung. Retroviral-mediated expression of PU.1 in alveolar macrophages from GM-CSF knockout mice corrects all these defects, suggesting that GM-CSF stimulates terminal differentiation of the macrophages primarily through the master transcription factor PU.1. The blue arrows represent the functions regulated by PU.1 that are affected by the absence of GM-CSF. *(From Trapnell BC, Whitsett JA, Nakata K: Pulmonary alveolar proteinosis. N Engl J Med 349:2527–2539, Fig. 4, 2003, with permission.)*

Secondary PAP

PAP can occur after exposure to an etiologic agent or clinical condition that results in either a functional impairment or reduced numbers of alveolar macrophages. Conditions associated with development of secondary PAP include heavy inhalation exposure to inorganic dusts (e.g., silica, titanium, aluminum) or fibrous insulation and various hematologic or oncologic disorders (e.g., chronic myeloid leukemia, myelomonocytic leukemia, acute myeloid leukemia, acute lymphoid leukemia, hairy cell leukemia, lymphoma, myelofibrosis, aplastic anemia, myelodysplasia, thrombocythemia, polycythemia vera, idiopathic thrombocytopenic purpura, myeloma, macroglobulinemia, Fanconi's anemia, and glioblastoma). Secondary PAP can also occur as a consequence of systemic infections, for example, during human immunodeficiency virus (HIV) infection. *Pneumocystis carinii* produces PAP-like lung histology, which can be identified by specific histological staining. Secondary PAP can be distinguished from primary PAP on the basis of the clinical context and histological or immunohistochemical evaluation of lung biopsy specimens. Although not well-studied, secondary PAP presumably occurs when the capacity for surfactant catabolism in the lungs is markedly impaired by a reduction in either the numbers or function of alveolar macrophages.

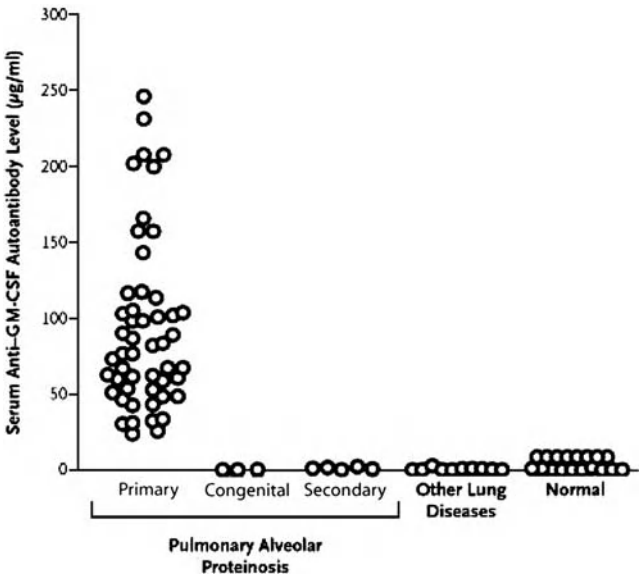


Figure 79-4 High levels of antibodies against GM-CSF in the serum of patients with primary PAP but not in congenital or secondary PAP, other lung diseases, or in normal individuals. *(From Trapnell BC, Whitsett JA, Nakata K: Pulmonary alveolar proteinosis.* N Engl J Med *349:2527–2539, Fig. 5, 2003, with permission.)*

Congenital PAP

PAP rarely occurs in neonates, infants, and children due to a specific homozygous defect in the genes encoding SP-B, SP-C, or ABCA3—a lipid transporter expressed in type II alveolar epithelial cells. In contrast to primary and secondary PAP, which occur due to defective surfactant clearance, these disorders result from abnormal surfactant production. Although convincing evidence of genetic mutations in the genes encoding GM-CSF or its receptor has not been found in human PAP, deficiency of the GM-CSF receptor itself has been reported.

EPIDEMIOLOGY

The annual incidence and prevalence of PAP have been estimated to be 0.36 and 3.7 cases per million individuals, respectively. A recent meta-analysis of published reports of PAP by Seymour in 2002 identified 410 separate cases, representing most, if not all, of the cases reported at that time. More than 90 percent of cases were idiopathic and no familial predispositions or genetic mutations were identified. The average age at onset was 39 years; 72 percent of individuals had a history of smoking; and the male to female ratio was 2.65 to 1.0. The gender difference is not present in nonsmokers. Primary PAP occurs in various ethnic backgrounds including Hispanic, Asian, black, and white. Secondary PAP occurs in about 5.3 percent of hematologic malignancies overall, and is slightly higher (8.8 percent) in neutropenic patients and in individuals with acute myeloid leukemia (10 percent). The incidence of congenital PAP is not well established.

CLINICAL FEATURES

Presentation

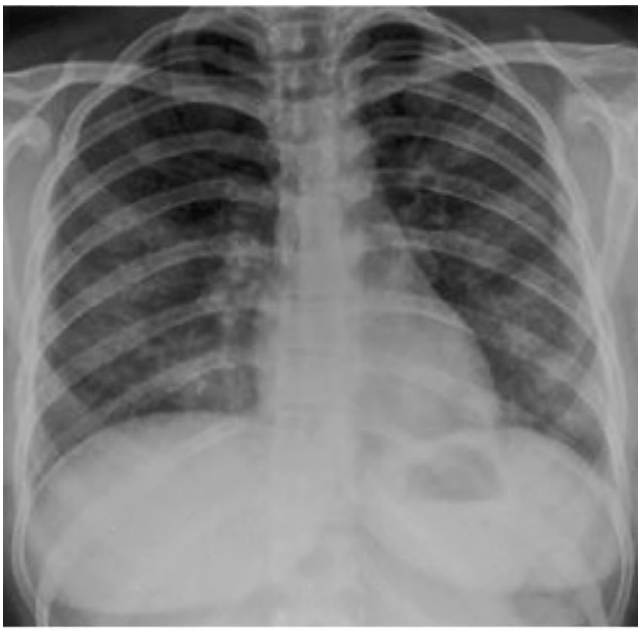
Primary PAP typically presents in previously healthy adults as progressive exertional dyspnea of insidious onset. Most individuals present between the ages of 20 and 50 years, although primary PAP has been diagnosed in children as young as 8 years old. About one-third of individuals complain of cough and less commonly, fever, chest pain, or hemoptysis, especially if secondary infection is present. Occasionally, the diagnosis is made in an asymptomatic individual when radiographic imaging is obtained for other reasons. A history of pneumonia poorly responsive or unresponsive to antibiotic therapy is sometimes present and should raise the suspicion of PAP. The physical examination is often normal, although there are crackles in up to 50 percent of patients, cyanosis in 25 percent, and digital clubbing in a small percentage.

Radiographic Appearance

The plain chest radiograph in uncomplicated primary PAP usually reveals bilateral symmetrical alveolar opacities located centrally in mid- and lower-lung zones, often with a perihilar predominance resembling the "bat wing" appearance of pulmonary edema but without other signs of left-sided heart failure (Fig. 79–5*A*). The peripheral lung is commonly spared, resulting in lucency along the diaphragmatic and mediastinal borders. High-resolution computed tomography scanning reveals a characteristic, geographical pattern of ground-glass opacifications with superimposed interlobular septal and intralobular thickening, commonly referred to as "crazy paving" (Fig. 79–5*B*). While characteristic of PAP, this pattern is not diagnostic and is observed in patients with various other pulmonary disorders. The extent of radiographic abnormalities is often disproportionately increased relative to the severity of the symptoms and physical findings but correlates with the degree of impairment in pulmonary function as measured by arterial blood gas analysis.

Laboratory Findings

Routine blood counts and chemistries are usually normal in primary PAP except for a mild elevation of the serum lactate dehydrogenase (LDH) in the range of about one to two times the upper limit of normal. The specific association of anti–GM-CSF autoantibodies with primary PAP has prompted the widespread use of antibody testing for identification of this disease. Results from ongoing clinical research studies indicate that the sensitivity and specificity of anti–GM-CSF autoantibody testing for primary PAP approaches 100 percent. Serum LDH correlates well with the degree of functional impairment as determined by physiological testing and arterial blood gas analysis and is useful in following the disease course. Serum levels of SP-A, SP-D, mucin KL-6, cytokeratin 19, and carcinoembryonic antigen are elevated in primary PAP; their potential use as biomarkers of disease is currently under study.



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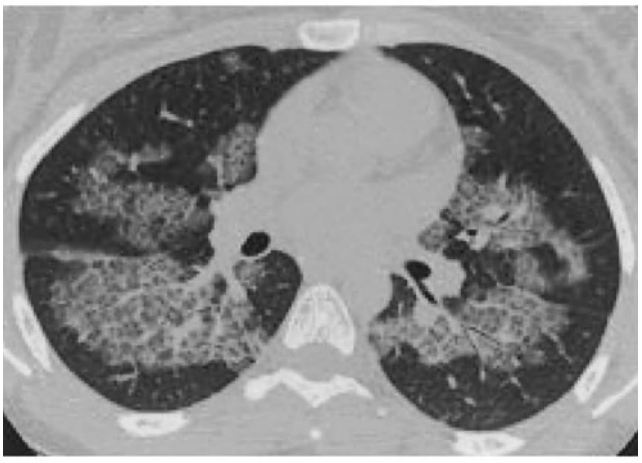

B

Figure 79-5 Radiographic appearance of primary PAP. *A*. Posteroanterior chest radiograph of a 25-year-old woman showing the typical features of PAP including bilateral, diffuse airspace disease. This individual had a disease severity of class 2 at the time of these studies (see Table 79-1). *B*. Corresponding high-resolution computed tomographic scan of the chest showing patchy areas of ground-glass opacification in a geographical distribution with superimposed interlobular thickening.

Lung Function

The results of lung function tests can be normal but most commonly show a restrictive pattern with modest impairment of the vital capacity and total lung capacity (TLC) and a disproportionate reduction of the carbon monoxide diffusing capacity (D_{LCO}). Arterial blood gas analysis in symptomatic patients reveals hypoxia caused by ventilation-perfusion inequality and intrapulmonary shunting, resulting in a widened alveolar-arterial diffusion gradient ($A\text{-}a_{DO_2}$).

Figure 79-6 Lavage fluid obtained during the whole lung lavage procedure has a characteristic turbid appearance and a sediment that forms upon standing. The marked opacity and sediment of the fluid observed at the beginning (left bottle) shows progressive clearing by the end of the procedure (right bottle).

Bronchoscopic Findings

The bronchoscopic appearance of the airways in uncomplicated PAP is normal but white, frothy proteinosis material is occasionally seen. The bronchoalveolar lavage (BAL) fluid is opaque and has a milky or waxy appearance and develops a thick layer of sediment upon standing overnight (Fig. 79-6). The sediment consists of large, acellular, eosinophilic bodies in a diffuse background of granular material that stains with periodic acid–Schiff (Fig. 79-7*A*). It also contains large, foamy macrophages (Fig. 79-7*B*) or monocyte-like macrophages and lymphocytes with relatively few neutrophils. Surfactant protein levels are markedly elevated and electron microscopy reveals the presence of lamellar bodies and tubular myelin that are characteristic of surfactant. GM-CSF, monocyte chemotactic protein-1 (MCP-1), and IL-8 levels are elevated in the lungs of individuals with primary PAP (and GM-CSF knockout mice) and may be of prognostic value as a biomarker of disease severity.

Lung Pathology

Macroscopically, the cut surface of the lung in primary PAP reveals a patchwork of 2 to 3 cm, grayish-yellow regions of firm consolidation that exudes fatty material. Microscopically, alveoli and terminal airspaces are filled with a fine eosinophilic material (Fig. 79-7*C*) that stains strongly for surfactant proteins (Fig. 79-7*D*). The alveolar wall and interstitial architecture are relatively well preserved but lymphocyte accumulation and, occasionally, fibrosis can be seen. The vasculature appears normal. Electron microscopy, which is seldom necessary, reveals characteristic, concentrically laminated surfactant structures within the granular material and in alveolar macrophages.

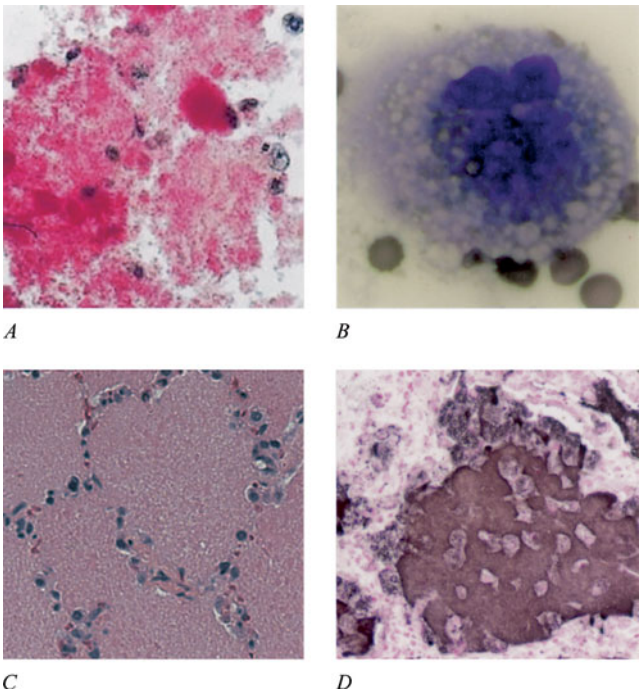

Figure 79-7 Cytological, pathological, and immunohistochemical appearance of the lipoproteinaceous material from patients with primary alveolar proteinosis. *A*. Positive periodic acid–Schiff staining of the sediment from bronchoalveolar lavage (×100). *B*. Cytological appearance of a typical "foamy" alveolar macrophage. *C*. Histopathological appearance of the lung-biopsy specimen from a 10-year-old child with primary PAP. Note the homogenous staining pattern, normal alveolar wall architecture, and the absence of inflammatory cells (H&E, ×200). *D*. Immunohistochemical staining reveals the presence of abundant accumulation of surfactant protein A in a lung biopsy specimen (human anti-surfactant protein A immunostain, ×200).

Secondary Infections

Individuals with primary PAP have an increased risk of infections, which contribute significantly to increased morbidity and mortality. Although pathogens commonly seen in community- and hospital-acquired lung infections are sometimes identified, more commonly, *Nocardia, Mycobacterium, Aspergillus, Cryptococcus*, and other opportunistic organisms are found. Infections occur at both pulmonary and extrapulmonary sites and suggest the possibility of a systemic host-defense defect, which may be explained by defects in the antimicrobial functions of macrophages and neutrophils.

DIAGNOSIS

A diagnosis of primary PAP is suspected on the basis of history, physical examination, radiographic studies, and pulmonary function testing but requires further investigation to exclude other conditions in the differential diagnosis such as cardiogenic pulmonary edema, atypical pneumonia, interstitial lung diseases, and lysinuric protein intolerance. In clinically suspected cases, bronchoscopic findings including transbronchial biopsy can usually establish the diagnosis. However, open lung biopsy remains the gold standard. The highly sensitive and specific anti–GM-CSF autoantibody assay provides a simple blood-based assay for diagnosis of primary PAP, and its potential predictive value and diagnostic accuracy is currently under evaluation. It is likely that a combination of routine clinical and radiographic information together with antibody testing may simplify the diagnosis of primary PAP in the near future.

NATURAL HISTORY

Individual cases of primary PAP fall into one of three categories: spontaneous improvement, stable but with persistent symptoms, or progressive deterioration. A retrospective analysis of cases for which sufficient information was available found spontaneous improvement in 8 percent of 303 cases and an overall 5-year survival rate of 85 percent in 343 cases. Of the deaths attributable to PAP, 47 were due to respiratory failure from alveolar proteinosis, 12 were due to uncontrolled infections, and one was due to cardiac arrest during lavage. A classification scheme for the disease severity in PAP (Table 79-1) has recently been proposed (Y. Inoue, personal communication) and its potential clinical use is currently under evaluation in several longitudinal studies of PAP.

THERAPY

The treatment of PAP depends on the underlying cause. Therapy for congenital PAP is supportive, although SP-B deficiency has been treated successfully by lung transplantation. Treatment for secondary PAP is aimed at the underlying clinical condition, the successful treatment of which generally corrects the associated PAP. In primary PAP, some patients

Table 79-1

Classification of Disease Severity in PAP

Class	Descriptor	Symptoms*	Pa_{O_2} (mmHg)
1	Mild	No	≥70
2		Yes	≥70
3	Moderate	Yes	≥60 and ≤70
4		Yes	≥50 and ≤60
5	Severe	Yes	≤50

** Symptoms can include dyspnea, cough, and, less frequently, fever.*

are asymptomatic despite significant radiographic abnormalities; others undergo spontaneous remission and do not require treatment. Consequently, treatment should be initiated when symptoms become limiting. Although a number of treatment approaches have been used in isolated cases, whole lung lavage emerged early as a successful approach for primary PAP and has remained the most widely accepted and effective form of treatment for more than four decades. While specific indications for whole lung lavage have not been clearly established, recommendations have included a definitive histological diagnosis and (1) Pa_{O_2} less than 60 to 65 mm Hg; (2) A-a_{DO_2} gradient greater than 40 mmHg; (3) shunt fraction greater than 10 to 12 percent; or (4) severe dyspnea at rest or with exercise.

Whole Lung Lavage

First described by Ramirez-Rivera in the 1960s, the technique of whole lung lavage has evolved considerably since its inception. The procedure is performed under general anesthesia using a double-lumen endotracheal tube so that one lung can be ventilated while the other is lavaged with warmed saline. The volume of saline infused as well as the method of instillation and drainage varies among centers performing the procedure. Additionally, some lavateurs use either manual or mechanical chest percussion in an attempt to improve surfactant clearance. Other variations have included extracorporeal oxygenation and hyperbaric oxygen. While a careful methodologic inventory has not been undertaken, in most centers, each lung is lavaged with 15 to 40 L of saline during separate procedures separated by one to two days. Although no established response criteria exist for therapeutic whole lung lavage, most patients experience clinical, physiological, and radiographic improvement following whole lung lavage. Physiological parameters demonstrated to improve with lavage include increases in forced vital capacity (FVC), TLC, D_{LCO}, P_{O_2} at rest and with exercise, and a decrease in A-a_{DO_2} and shunt fraction. In one study, whole lung lavage increased the 5-year survival rate (94 $\pm$ 2 percent with lavage as compared to 85 $\pm$ 5 percent without). While some individuals resolve without treatment and some require only one or several treatments, more than half of individuals require repeated therapeutic lavage. The median duration of response to therapeutic lavage has been reported to be 15 months. Successful treatment of PAP by repeated, sequential lobar lavage is used in some centers, although the practical clinical use of this approach is unclear.

Experimental Approaches

Specific knowledge of disease pathogenesis has prompted development of alternative treatment approaches for primary PAP. One strategy targeting the GM-CSF signaling deficiency involves administration of exogenous GM-CSF. The therapeutic potential of GM-CSF administered subcutaneously in daily doses ranging from 5 to 20 μg/kg has been evaluated in several small, limited-dose escalation studies. Altogether, 11 of 20 individuals in these studies showed symptomatic, physiological, or radiographic improvement. In another report that described administration of GM-CSF directly to the lungs via aerosol in three individuals, clinical improvement was observed in all three in parallel with a reduction in the GM-CSF–neutralizing capacity in lung lavage fluid, improved alveolar macrophage function, and improved respiratory function. Other strategies targeting the anti–GM-CSF autoantibody include plasmapheresis and anti–B-lymphocyte immunotherapy. Limited data are available regarding the potential use of these approaches, and further studies are warranted.

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A

Normal Values: Typical Values for a 20-Year-Old Seated Man

Ventilation (BTPS)	
Tidal volume (V_T), L	0.6
Frequency (f), breaths/min	12
Minute volume (V_E), L/min	7.2
Respiratory dead space (V_D), ml	150
Alveolar ventilation, V_A, L/min	5.4
Lung Volumes and Capacities (BTPS)	
Inspiratory capacity (IC), L	3.0
Expiratory reserve volume (ERV), L	1.9
Vital capacity (VC), L	4.9
Residual volume (RV), L	1.4
Functional residual capacity (FRC), L	3.2
Total lung capacity (TLC), L	6.3
Residual volume/total lung capacity × 100 (RV/TLC), %	22
Mechanics of Breathing	
Forced vital capacity (FVC), L	4.9
Forced expiratory volume, first second (FEV_1), L	4.0
Maximum voluntary ventilation (MVV), L/min	170
Forced expiratory volume in 1 s/forced vital capacity × 100 (FEV_1/FVC), %	83
Forced expiratory volume in 3 s/forced vital capacity × 100 (FEV_3/FVC), %	97
Forced expiratory flow during middle half of FVC (FEF_{25-75}), L/s	4.7
Forced inspiratory flow at the middle of FIVC (FIF_{50}), L/s	5.0
Static compliance of the lungs (Cst, l), L/cm H_2O	0.2
Compliance of lungs and thoracic cage (CRS, respiratory system compliance) L/cm H_2O	0.1
Airway resistance at FRC (Raw), cm H_2O/L/s	1.5
Pulmonary resistance at FRC, cm H_2O/L/s	2.0
Airway conductance at FRC (G_{aw}), L/s/cm H_2O	0.66
Specific conductance (G_{aw}/V_1)	0.22
Maximum inspiratory pressure, mmHg	−75
Maximum expiratory pressure, mmHg	120
Distribution of Inspired Gas	
Single-breath N_2 test (ΔN_2 from 750 to 1250 ml in expired gas), % N_2	<1.5
Alveolar N_2 after 7 min of breathing O_2, % N_2	<2.5
Closing volume (CV), ml	400
CV/VC × 100, %	8
Closing capacity (CC), ml	1900
CC/TLC × 100, %	30
Slope of phase III in single-breath N_2 test, % N_2/L	<2
Gas Exchange	
O_2 consumption at rest (STPD), ml/min	240
CO_2 output at rest (STPD), ml/min	192
Respiratory exchange ratio (R), CO_2 output/O_2 uptake	0.8

ALVEOLAR GAS	
PA_{O_2}, mmHg	105
PA_{CO_2}, mmHg	40
ARTERIAL BLOOD	
Pa_{O_2}, mmHg	95
Sa_{O_2}, %	98
pH	7.41
Pa_{CO_2}, mmHg	40
Pa_{O_2}, while breathing 100% O_2, mmHg	640
Alveolar Ventilation	
Alveolar ventilation, L/min	4.2
Physiological dead space/tidal volume × 100 (V_D/V_T), %	<30
Alveolar-arterial oxygen-gradient, (A-a) P_{O_2}, mmHg	10
Diffusing Capacity	
Diffusing capacity at rest for CO, single-breath (D_{LCOsb}), ml CO/min/mmHg	29
Diffusing capacity per unit alveolar volume (D_L/V_A)	4.8
Control of Ventilation	
Ventilatory response to hypercapnia, L/min/per Δ Pa_{CO_2} mmHg	>0.5
Ventilatory response to hypoxia, L/min per ΔS_{O_2} (%)	>0.2
Arterial blood P_{O_2} during moderate exercise, mmHg	95
Pulmonary Hemodynamics	
Pulmonary blood flow (cardiac output), L/min	5.4
Pulmonary artery systolic/diastolic pressure, mmHg	25/8
Pulmonary capillary blood volume, ml	100
Pulmonary "capillary" (wedge) blood pressure, mmHg	<10

B

Terms and Symbols in Respiratory Physiology

GENERAL SYMBOLS

P	Partial pressure in blood or gas. P_{O_2} = partial pressure of O_2
$\bar{X}$	A bar over the symbol indicates a mean value. $\bar{P}$ = mean pressure, as distinct from instantaneous pressure
$\dot{X}$	A time derivative (rate) is indicated by a dot above the symbol $\dot{V}_{O_2}$ = oxygen consumption per minute, ml $\dot{V}_{CO_2}$ = CO_2 production per minute, ml
% X	Percent sign preceding a symbol indicates percentage of the predicted normal value
X/Y%	Percent sign following a symbol indicates a ratio function with the ratio expressed as a percentage. Both components of the ratio must be designated. $FEV_1/FVC, \% = 100 \times FEV_1/FVC$
XA, Xa	A small capital letter or a lower-case letter on the same line following a primary symbol is a qualifier to further define the primary symbol. Alternatively, subscript letters may be used. XA = X_A, Xa = X_a Additional qualifiers of the primary symbol may be identified as shown. $P_{E_{CO_2}}$ = Pressure of CO_2 in the expired air, mmHg

GAS PHASE SYMBOLS

Primary Symbols

V	Volume of gas
$\dot{V}$	Flow of gas
F	Fractional concentration of a gas

QUALIFYING SYMBOLS

I	Inspired V_I = inspired volume
E	Expired V_E = expired volume $\dot{V}_E$ = expired volume per minute
A	Alveolar V_A = alveolar volume $\dot{V}$ = alveolar ventilation per minute
T	Tidal V_T = tidal volume
D	Dead space V_D = volume of dead space $\dot{V}_D$ = dead-space ventilation per minute
B	Barometric P_B = barometric pressure
STPD	Standard conditions: temperature 0°C, pressure 760 mmHg, and dry (0 mmHg water vapor)
BTPS	Body conditions: body temperature and ambient pressure, saturated with water vapor at these conditions
ATPD	Ambient temperature and pressure, dry
ATPS	Ambient temperature and pressure, saturated with water vapor at these conditions
an	Anatomic
p	Physiological
f	Respiratory frequency, per minute
max	Maximum
t	Time

BLOOD PHASE SYMBOLS

Primary Symbols

Q	Volume of blood
$\dot{Q}$	Blood flow $\dot{Q}$ = cardiac output, L/min

C	Concentration in the blood phase C_{O_2} = concentration of oxygen in blood, ml of O_2 per 100 ml of blood
S	Saturation in the blood phase S_{O_2} = Saturation of hemoglobin with O_2, percent

Qualifying Symbols

a	Arterial Ca_{O_2} = concentration of O_2 in arterial blood, ml of O_2 per 100 ml of blood
c	Capillary Cc_{O_2} = concentration of O_2 in capillary blood, ml of O_2 per 100 ml of blood
c′	Pulmonary end-capillary Pc'_{O_2} = partial pressure of O_2 in end-capillary blood, mmHg
v	Venous Cv_{O_2} = concentration of O_2 in venous blood, ml of O_2 per 100 ml of blood
$\bar{v}$	Mixed venous $C\bar{v}_{O_2}$ = concentration of O_2 in mixed venous blood, ml of O_2 per 100 ml of blood

VENTILATION AND LUNG MECHANICS TESTS AND SYMBOLS

Static Lung Volumes*

Primary Compartments

RV	Residual volume. Volume of air remaining in the lungs after maximum expiration.
CV	Closing volume. Volume of air expired from the onset of airways closure to residual volume. May be expressed as a fraction of VC: CV/VC, %.
ERV	Expiratory reserve volume. Maximum volume of air expired from the resting end-expiratory level.
V_T	Tidal volume. Volume of air inspired or expired with each breath during quiet breathing. When tidal volume is used in gas-exchange formulations, this symbol is used.
IRV	Inspiratory reserve volume. Maximum volume of air inspired from the end-tidal inspiratory level.

* Expressed as BTPS.

Lung Capacities*

IC	Inspiratory capacity. The sum of IRV and TV.
IVC	Inspiratory vital capacity. Maximum volume of air inspired from the point of maximum expiration, i.e., from RV
VC	Vital capacity. Maximum volume of air expired from the point of maximum inspiration, i.e., from TLC
FRC	Functional residual capacity. Sum of RV and ERV. FRC is the volume of air remaining in the lungs at the resting end-expiratory position.
TLC	Total lung capacity. Volume of air in the lungs after maximum inspiration. Also, the sum of all volume compartments of the lungs.
RV/TLC,%	Residual volume to total lung capacity ratio, expressed as a percentage.
CC	Closing capacity. Closing volume plus residual volume, may be expressed as a percentage of TLC: CC/TLC, %.

Forced Respiratory Maneuvers During Spirometry†

FVC	Forced vital capacity. The maximum volume of air forcibly expired from total lung capacity.
FIVC	Forced inspiratory vital capacity. Maximum volume of air forcibly inspired starting from residual volume.
FEV*t*	Timed forced expiratory volume. Volume of air expired in a specified time in the course of the forced vital capacity maneuver. FEV_1 = volume of air expired during the first second of the FVC.
FEV*t*/FVC, %	Ratio of time forced expiratory volume to forced vital capacity, expressed as a percentage.
FEF*x*	Forced expiratory flow, related to some portion of the FVC curve. Modifiers refer to the amount of the FVC that has been expired at the time of measurement.
$FEF_{200-1200}$	Forced expiratory flow between 200 and 1200 ml of the FVC (formerly called the maximum expiratory flow rate).
FEF_{25-75}	Forced expiratory flow during middle half of the FVC (formerly called the maximum midexpiratory flow rate or MMEF).

* Combinations of volumes for practical purposes.
† All values at BTPS.

PEF	Peak expiratory flow. Highest value for expiratory flow.
$\dot{V}_{max_x}$	Maximum flow when x percent of the FVC has been expired. $\dot{V}_{max_{75}}$ = flow (instantaneous) when 75 percent of the FVC has been expired.
FIFx	Forced inspiratory flow. As in the case of the FEF, appropriate modifiers designate the volume at which flow is being measured. Unless otherwise specified, the volume qualifiers indicate the volume inspired from RV at the point of measurement. FIF_{25-75} = forced inspiratory flow during the middle half of the FIVC.
MVV	Maximum voluntary ventilation. Volume of air exhaled during maximum breathing efforts within a specified time period. If breathing frequency is set by the examiner, it is indicated by the qualifier. MVV_{60} = MVV at a breathing frequency of 60 per minute.
PImax	Maximum inspiratory pressure. The maximum pressure generated during an inspiratory effort.
PEmax	Maximum expiratory pressure. The maximum pressure generated during an expiratory effort.

Measurements Related to Ventilation

$\dot{V}_E$	Expired volume per minute (BTPS)
$\dot{V}_I$	Inspired volume per minute (BTPS)
$\dot{V}_{CO_2}$	Carbon dioxide production per minute (STPD)
$\dot{V}_{O_2}$	Oxygen consumption per minute (STPD)
R	Respiratory exchange ratio, the ratio of CO_2 output to O_2 intake in the lungs
$\dot{V}_A$	Alveolar ventilation per minute (BTPS)
$\dot{V}_D$	Ventilation per minute of the physiological dead space (BTPS) defined by the equation $\dot{V}_D = \dot{V}_E \frac{Pa_{CO_2} - P_{E_{CO_2}}}{Pa_{CO_2} - P_{I_{CO_2}}}$
V_D	Volume of the physiological dead space, calculated as $\dot{V}_D/f$.
V_D/V_T	Ratio of dead space to tidal volume. The fraction, usually expressed as a percentage, of each breath that does not contribute to CO_2 elimination.

Mechanics of Breathing*

Pressure Terms

Paw	Pressure at any point along the airways
Pao	Pressure at the airway opening
Ppl	Pleural pressure
P_A	Alveolar pressure
Pbs	Pressure at the body surface
Pes	Esophageal pressure: used to estimate Ppl
P_A–Pbs	Transthoracic pressure
P_A–Ppl	Transpulmonary pressure
Ppl–Pbs	Pressure difference across the chest wall
Paw–Ppl	Transbronchial pressure, estimated as difference between airway and pleural pressures.

Flow-Pressure Relationships†

R	General symbol for frictional resistance, defined as the ratio of pressure difference to flow.
Raw	Airway resistance, calculated from pressure difference between airway opening (Pa_o) and alveoli (P_A) divided by the airflow, $cmH_2O/L/s$.
R_L	Total pulmonary resistance, measured by relating flow-dependent transpulmonary pressure to airflow at the mouth.
Rti	Tissue resistance (viscous resistance of lung tissue), calculated as difference between R_L and Raw.
Rus	Resistance of the airways on the upstream (alveolar) side of the point in the airways where intraluminal pressure equals Ppl, i.e., equal pressure point. Measured during a forced expiration.
Rds	Resistance of the airways on the downstream (mouth) side of the point in the airways where intraluminal pressure equals Ppl, i.e., equal pressure point. Measured during a forced expiration.
Gaw	Airway conductance, reciprocal of Raw.
Gaw/V_L	Specific conductance, airway conductance, expressed per liter of lung volume at which Gaw is measured.

*All pressures expressed relative to ambient pressure unless otherwise specified.

†Unless otherwise specified, resistance measurements are assumed to be made at FRC.

Volume-Pressure Relationships

C — General symbol for compliance of the lungs, chest wall, or total respiratory system. Volume change per unit change in applied pressure. For the lungs, the applied pressure is the pressure difference across the lungs, or transpulmonary pressure, Pao–Ppl; for the chest wall, the applied pressure is the transthoracic pressure, Ppl–Pbs; for the entire respiratory system, the applied pressure is Pao–Pbs.

C_L — Lung compliance. Value for the volume change divided by the transpulmonary pressure.

Cw — Chest wall compliance. Value for the volume change divided by the transthoracic pressure.

Cdyn — Dynamic compliance. Value for compliance determined at time of zero gas flow at the mouth during uninterrupted breathing. The respiratory frequency appears as a qualifier. $Cdyn_{40}$ = dynamic compliance at a respiratory frequency of 40 per minute.

Cst — Static compliance, value for compliance determined on the basis of measurements made during a period of zero airflow.

C/V_L — Specific compliance. Compliance divided by the lung volume at which it is determined, usually FRC.

Pst — Static pulmonary pressure at a specified lung volume.
Pst_{TLC} = static recoil pressure of the lung measured at TLC (maximum recoil pressure)

DIFFUSING CAPACITY TESTS AND SYMBOLS

D_Lx — Diffusing capacity of the lung expressed as volume (STPD) of gas (x) uptake per minute per unit alveolar-capillary pressure difference for the gas used. A modifier can be used to designate the technique:

D_{LCO}/sB = Single-breath CO diffusing capacity

D_{LCO}/ss = Steady-state CO diffusing capacity

D_M — Diffusing capacity of the alveolar-capillary membrane (STPD).

θ — Reaction rate coefficient for red blood cells. Determined as the volume of gas (stpd) that will combine per minute with 1 unit volume of blood per unit of gas tension. If the specific gas is not stated, θ is assumed to refer to CO and is a function of existing O_2 tension.

V_C — Capillary blood volume. This should be Qc for consistency with other symbols, but Vc is entrenched in the literature. In the equation that follows for $1/D_L$, Vc represents the effective pulmonary capillary blood volume, i.e., capillary blood volume in intimate association with alveolar gas.

$1/D_L$ — Total resistance to diffusion, including resistance to diffusion of test gas across the alveolar-capillary membrane, through plasma in the capillary, and across the red blood cell membrane (1/Dm), the resistance to diffusion with the red cell arising from the chemical reaction of the test gas and hemoglobin ($1/\theta Vc$), according to the formulation

$$\frac{1}{D_L} = \frac{1}{D_M} + \frac{1}{\theta Vc}$$

D_L/V_A — Diffusing capacity per unit of alveolar volume. D_L is expressed STPD, and V_A is expressed in liters, BTPS.

BLOOD GAS SYMBOLS

Symbols for these values are readily composed by combining general symbols. Some examples include the following:

Pa_{CO_2} — Arterial CO_2 tension, mmHg

Sa_{O_2} — Arterial O_2 saturation, percent

CcO_2 — Oxygen content of pulmonary end-capillary blood, ml of O_2 per 100 ml of blood

$(A\text{-}a)Po_2$ — Alveolar-arterial difference in the partial pressure of O_2, mm Hg

$Ca_{O_2}–C\bar{v}_{O_2}$ — O_2 content difference between arterial and mixed venous blood (arteriovenous O_2 difference), ml of O_2 per 100 ml of blood

PULMONARY SHUNT SYMBOLS

$\dot{Q}_s$ — Flow of blood via shunts. This is usually determined as percent of cardiac output ($\dot{Q}$) while breathing 100% O_2, according to the equation

$$\frac{\dot{Q}_s}{\dot{Q}} = \frac{CcO_2 - CaO_2}{CcO_2 - C\bar{v}O_2} \times 100$$

where
CcO_2 = O_2 content of end-capillary blood
CaO_2 = O_2 content of arterial blood
$C\bar{v}o_2$ = O_2 content of mixed venous blood

PART

IX

Disorders of the Pulmonary Circulation

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80

The Pulmonary Circulation

Alfred P. Fishman

The normal pulmonary circulation is a low-resistance, highly compliant vascular bed interposed between the two ventricles, lodged within the lungs and thorax. Its initial tone is low. Because of the way in which it is incorporated into the substance of the lung (Fig. 80-1), it can be greatly influenced by changes in airway and pleural pressures, on the one hand, and by the performance of the two ventricles, on the other.

Because pulmonary vascular pressures are low, and because the thin-walled pulmonary vessels are closely apposed to the air-containing elements of the lungs, modest changes in external forces can exert rather large hemodynamic effects. Moreover, the pulmonary circulation is poorly equipped for self-regulation. Consequently, it is important to monitor and control perivascular pressures when observations are intended to distinguish between active and passive changes in vascular calibers.

Passive influences can be quite subtle. For example, during each heartbeat, part of the ejectate from the right ventricle is retained with the pulmonary arterial tree, distending its walls, while the remainder flows through the pulmonary microvasculation toward the left side of the heart. How this stroke output is partitioned between the quantity retained and the quantity passing through to the pulmonary capillaries depends on a variety of influences: the intrinsic properties of the pulmonary arterial tree, the pressure drop along the length of the pulmonary arterial tree, the transmural pressures, and the resistance to outflow at the distal end of the arterial tree. A change in breathing pattern or cardiac performance—as may occur during a shift from rest to exercise—can passively affect the partition between the stored and pass-through components of the stroke volume as well as modify the peripheral transmission of the pressure and flow pulses.

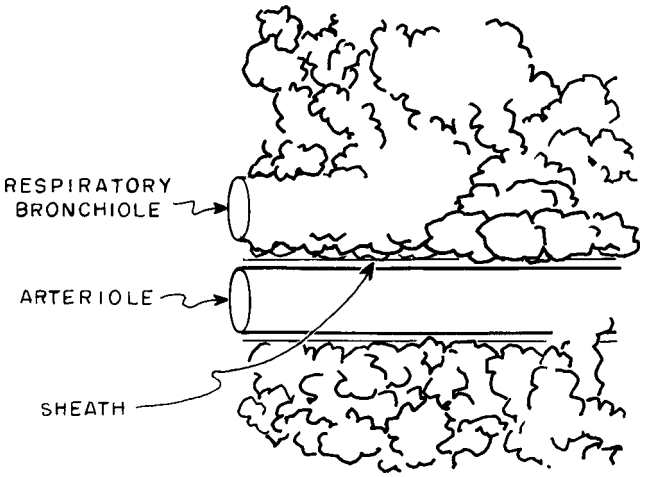

Figure 80-1 Incorporation of pulmonary arteriole into pulmonary parenchyma. The fascial sheath enables the vessel to slide in different directions within the lung tissue.

Until about 30 years ago, the predominant interest in the pulmonary circulation was on hemodynamics and gas exchange. Since then the focus has widened to include the nonrespiratory and water-exchanging functions of the lungs. Some of the nonrespiratory functions of the pulmonary circulation (e.g., the sieving of particulate matter) are simply mechanical; others are metabolic and endocrine, essential not only for the integrity of pulmonary structure and function (e.g., the generation of surfactant) but also as components of the neurohumoral and metabolic machinery of the body (e.g., the renin-angiotensin system) (Fig. 80-2).

The pulmonary circulation is not the sole blood supply to the lungs: systemic arterial branches (the "bronchial circulation") ensure the vitality of the conducting airways of the lungs and of the structures that support the gas-exchanging apparatus. Ordinarily this blood supply is exceedingly small; however, it is capable of remarkable proliferation when the pulmonary blood is compromised or when the lungs are the seat of certain chronic inflammatory processes.

Finally, both the structure and function of the pulmonary vessels can vary greatly, not only between species (Fig. 80-3) but sometimes also within species. For example, the pulmonary resistance vessels (small arteries and veins) of humans native to a high-altitude environment are more muscular than those native to a sea-level environment, apparently an adaptation to chronic hypoxia. Also, the pulmonary arterial pressor response to acute hypoxia can vary greatly from species to species. The fetus has thicker-walled media in its arteries and arterioles than does the adult, and these vessels respond more vigorously to vasomotor stimuli in the fetus than in the adult.

In this chapter, unless otherwise stipulated, the designation *normal pulmonary circulation* signifies the pulmonary circulation in the normal adult who lives at sea level (Table 80-1).

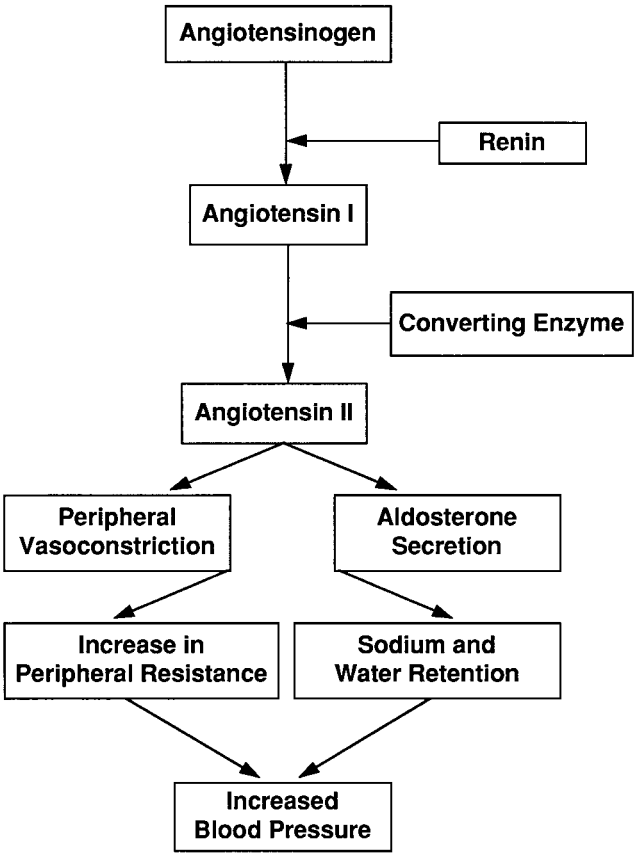

Figure 80-2 Renin-angiotensin system. The lungs play a central role in control of systemic blood pressure because of the converting enzyme on the luminal aspect of pulmonary capillary endothelium. Strategic disposition of the enzyme and huge expanse of pulmonary capillary endothelium enable rapid and efficient conversion of angiotensin I to angiotensin II as blood courses through the lungs.

PULMONARY HEMODYNAMICS

In clinical practice, thinking about the regulation of the pulmonary circulation centers around the concept of pulmonary vascular resistance (the hindrance offered by a vascular bed to the flow of blood through it). The hindrance changes during vasoconstriction or vasodilation. In the pulmonary circulation, the small pulmonary muscular arteries and arterioles are the only vessels that seem capable of appreciable vasomotor activity. Consequently, these precapillary vessels are generally referred to as *resistance vessels* and pictured as the principal sites of pulmonary vasomotor activity. Other contractile elements, such as perivascular contractile cells, are sometimes invoked to explain active changes in pulmonary vascular resistance, but as a rule, their effects are meager compared to the vasomotor activity of the small muscular arteries and arterioles.

Pulmonary Vascular Resistance

Different approaches have been used to detect changes in pulmonary vascular resistance (PVR). However, clinicians rely

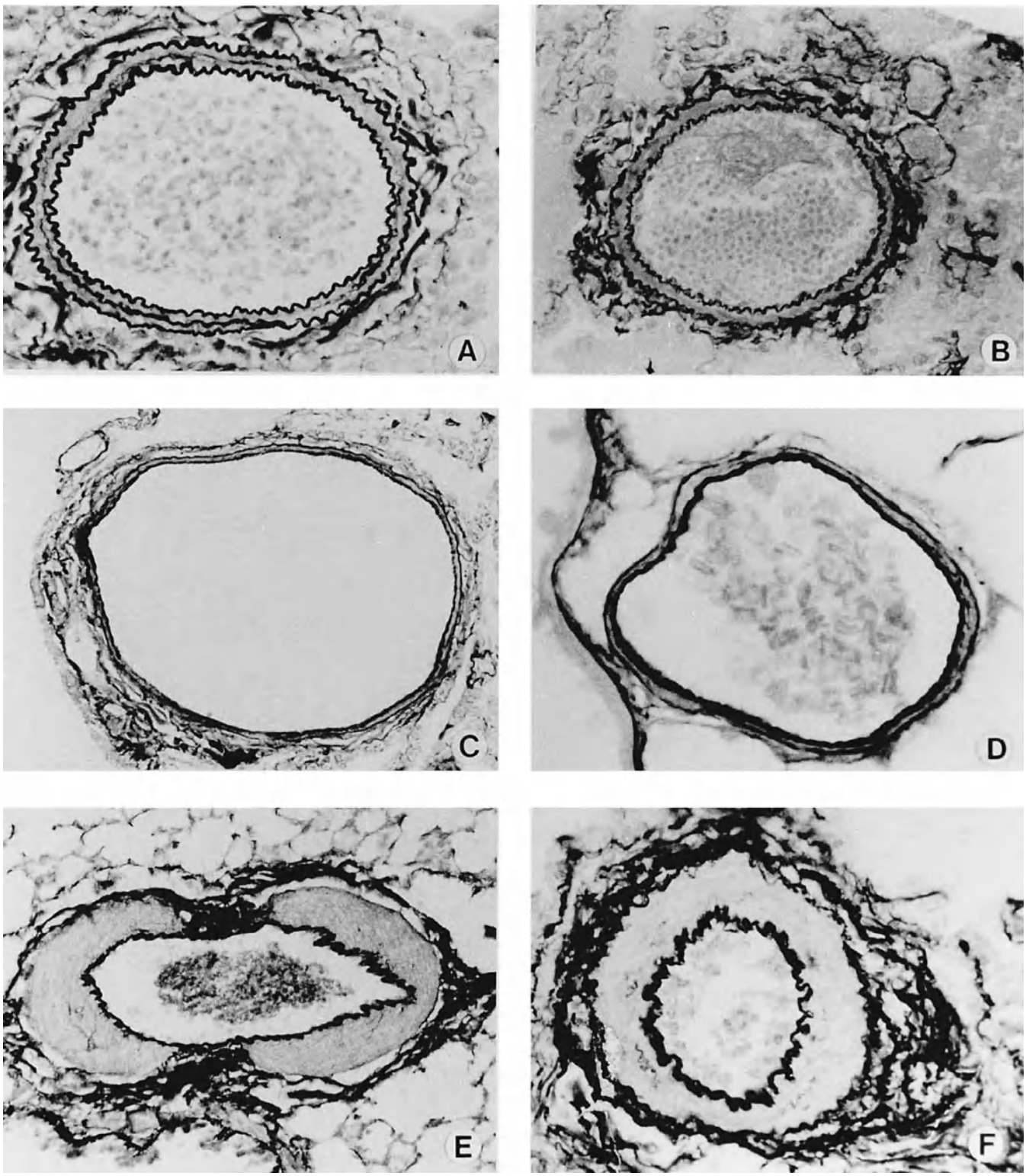

Figure 80-3 Muscular pulmonary arteries (resistance vessels) in pulmonary circulation of various animal species. *A*. Dog (×500). *B*. Cat (×500). *C*. Human (×200). *D*. Rat (×800). *A–D*. Tunica media is relatively thin. *E*. Guinea pig (×200). *F*. Cow (×500). *E and F*. Elastic–van Gieson stain. *(Micrographs courtesy of J. M. Kay.)*

Table 80-1

Representative Hemodynamic Values for Normal Adult Males at Rest and During Moderate Exercise

	Rest	Exercise
Cardiac output (L/min)	6	16
Heart rate (beats/min)	80	130
Right atrial pressure (mmHg)	4–6	6–8
Pulmonary artery pressures (mmHg)		
Systolic	20–25	30–35
Diastolic	10–12	11–14
Mean	14–18	20–25
Pulmonary wedge pressure (mmHg)	6–9	10–12
Systemic arterial pressure (mmHg)	120/180	150/95
Mean	90–100	110–120
Pulmonary vascular resistance (units)	0.70–0.95	0.60–0.90

heavily on calculations of PVR based on the following formula:

$$R = \frac{\bar{P}_{PA} - \bar{P}_{LA}}{\dot{\bar{Q}}_T}$$

where

R = PVR, either in R units or dynes·sec^{-1}cm^5

$\bar{P}_{PA} - \bar{P}_{PV}$ = drop in mean pressure between the pulmonary artery and left atrium, mmHg (pulmonary-wedge pressure, $\bar{P}_{PW}$, is generally substituted for $\bar{P}_{LA}$)

$\dot{\bar{Q}}_T$ = mean pulmonary blood flow, ml/s

The formula and units above express PVR in R (resistance) units. For the normal pulmonary circulation, the value for R is about 0.1 mmHg · L^{-1} min^{-1}. Some prefer to express PVR in dynes sec^{-1}· cm^5. To do so, the numerator of the equation is multiplied by 1332. The normal value is then around 100.

All too often, for the sake of expediency in clinical studies, the pulmonary arterial pressure, per se, is substituted for the pressure difference in the numerator. This omission of the outflow pressure $\bar{P}_{LA}$ is then indicated by referring to the value calculated for resistance as the "total PVR." Although this usage may be a practical expedient, the value calculated in this way is bereft of either physiological or physical meaning.

A change in calculated PVR is generally used to infer that a change has occurred in the calibers of resistance vessels (i.e., in the muscular pulmonary arteries and arterioles). The next step is to judge whether the change is active or passive. This distinction can be difficult if both pulmonary vascular pressures and flows undergo large changes between control and test periods (e.g., in the transition from rest to exercise). In normal persons, in whom pulmonary arterial pressures undergo relatively small changes during exercise despite a doubling of cardiac output (Fig. 80-4), it seems reasonable to interpret a drop in resistance as reflecting pulmonary vasodilation as long as both rest and exercise studies are conducted while the patient is supine. If a shift is made during exercise to an upright position, however, the drop in resistance may reflect recruitment of new vessels in the uppermost parts of the lungs rather than dilation of vessels already open.

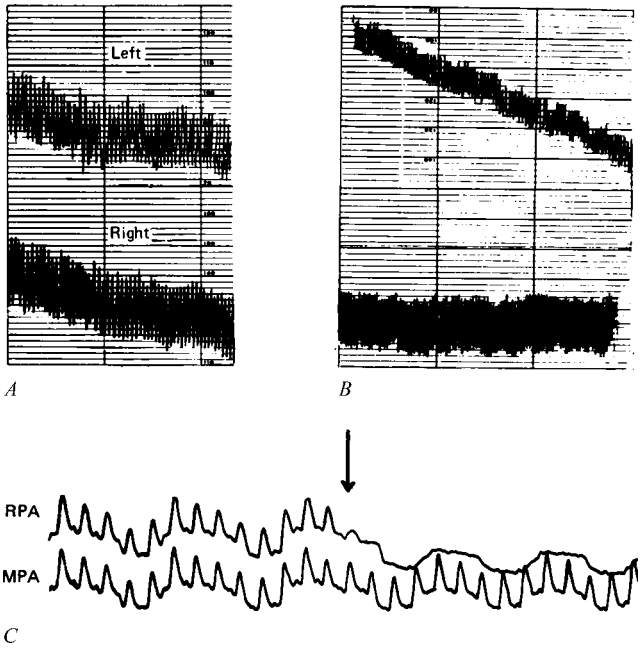

Figure 80-4 Effect of doubling blood flow through one lung on pulmonary arterial pressure in the main pulmonary artery (MPA). Bronchospirometric tracings of oxygen uptake before (*A*) and after (*B*) occlusion of the right pulmonary artery in a human subject. Oxygen uptake by the right lung ceases. *C*. Pulmonary arterial pressure. Inflation of the balloon (arrow) causes little change in pressure in the main pulmonary artery even though pulmonary blood flow has doubled.

In the pulmonary circulation of native residents at high altitude, the muscular media of the small pulmonary arteries and arterioles are thicker and precapillary smooth muscle extends further distally. Because of these anatomic features, PVR is ordinarily higher in native residents at altitude than in native residents at sea level.

Alternative Approaches to PVR

Physiologists advocate comparisons of the slopes and intercepts of pressure-flow curves, before and after a test stimulus, as a reliable approach (Fig. 80-5). Unfortunately, these curves are usually difficult to obtain in humans because of passive changes that accompany interventions (e.g., before and during assisted ventilation).

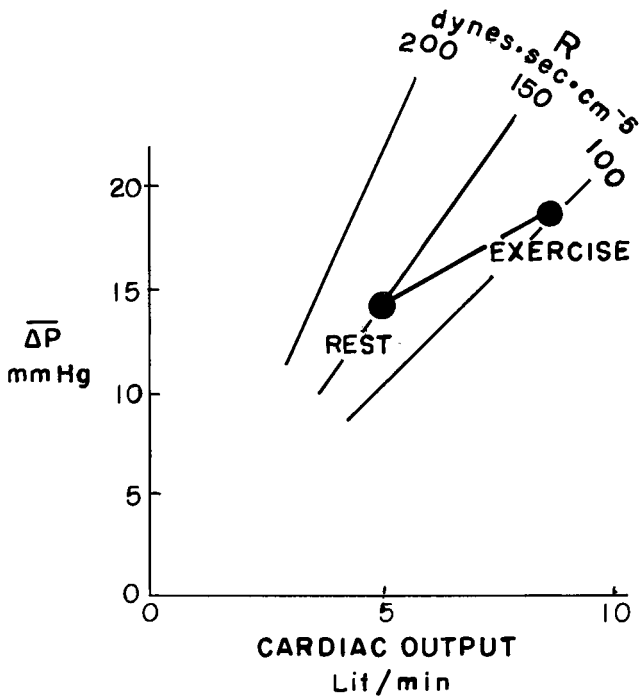

Figure 80-5 Pulmonary vascular resistance (PVR) at rest and during exercise. Background is family of PVR curves as isopleths. During exercise, resistance decreases as cardiac output and the difference between pulmonary arterial and left atrial pressures (ΔP) increases.

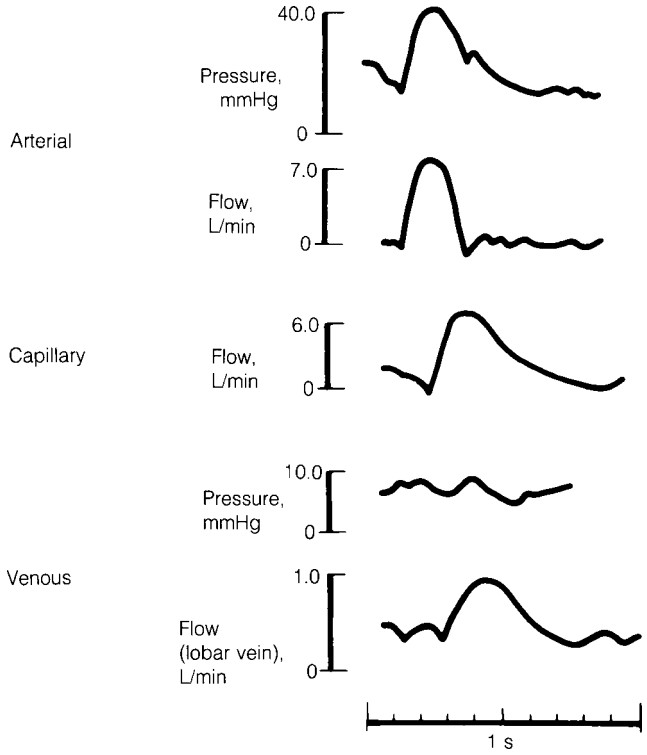

Figure 80-6 Transformation of pulsatile pressures and flows in consecutive segments of the pulmonary circulation. Pressure contours between the pulmonary artery and vein undergo considerable transformation, so the pulmonary venous pressure closely resembles the left atrial pressure. In contrast, flow surges ahead under the impulse of the right ventricle, retaining its pulsatile contour in the pulmonary veins. *(Based on data from Fishman AP: Pulmonary circulation, in Fishman AP, Fisher AB (eds), Handbook of Physiology, sec 3: The Respiratory System, Vol 1: Circulation and Nonrespiratory Functions. Bethesda, MD, American Physiological Society, 1985, pp 93–166, with permission.)*

A more sophisticated approach to the hindrance of blood flow through a vascular bed is the determination of vascular impedance. Instead of using mean pressures and flows, as in the traditional calculation of PVR, vascular impedance takes pulsability into account (Fig. 80-6). This use of pulsatile pressure and flows provides opportunity to gain information about the geometry and viscoelastic properties of the vessels, their dimensions, the sites of wave reflections, the occurrence of pulmonary vasomotor activity, and the relationship between the mechanical performance and energy expenditure of the right ventricle, on the one hand, and the pulmonary circulation, on the other.

Passive Modifiers of PVR

Testing for *active* changes in pulmonary vascular caliber is always haunted by the prospect of overlooking passive changes. Among these, three warrant special mention:

1. An increase in pulmonary arterial or pulmonary venous pressure automatically causes resistance to fall, either by opening segments of the pulmonary microcirculation that were previously closed (recruitment) or by distending resistance vessels that are already open.
2. Lung volumes passively affect PVR: calculated PVR due to passive influences is lowest at end-expiration and increases as lung volumes move in either direction. This topic is considered in detail later in the chapter under "The Pulmonary Arterial Microcirculation in Gas Exchange."
3. If alveolar pressure in the portion of the pulmonary vascular bed under consideration exceeds left atrial pressure, conventional calculation of PVR as

$$R = \frac{\bar{P}_{PA} - \bar{P}_{LA}}{\bar{Q}_T}$$

is meaningless, since alveolar, rather than left atrial, pressure becomes the outflow pressure. This topic is considered later in terms of the zones of the lungs. Here it will suffice to indicate that in the upright lung, resistance to blood flow decreases automatically from top to bottom as, under the influence of gravity, dependent vessels open wider the distention of open *vessels*, and vessels previously closed are forced open ("recruited").

Pulmonary Vascular Pressures

During each respiratory cycle, all intrathoracic vessels are affected to some extent by the swings in pleural pressure.

Whether blood pressure in the pulmonary circulation is referred to atmospheric or to pleural pressure depends on the use to which the results are to be put. For the calculation of PVR, mean blood pressures referred to atmosphere are used. In using left atrial pressure as the outflow pressure, care must be taken to ensure that left atrial pressure exceeds alveolar pressure—i.e., that zone 3 conditions prevail (see below).

In contrast to referring pressures to atmosphere, as in the calculation of vascular resistance, the pressures that determine the caliber of vessels (i.e., the transmural pressures) are referred to the intrathoracic pressures that surround them: for the alveolar capillaries, this pressure is calculated as the difference between the luminal pressure in the pulmonary capillaries and the alveolar pressure; for the other pulmonary vessels, the transmural pressure is determined as the difference between luminal and pleural pressure. In practice, esophageal pressure is generally substituted for pleural pressure, and pleural pressure is taken to be equivalent to perivascular pressure.

In Fig. 80-7, the pressure drop along the length of the pulmonary vascular tree is compared with that of the systemic circulation. Since pulmonary capillary pressures cannot be measured directly, they are generally estimated to be intermediate between the mean pulmonary arterial and pulmonary-wedge pressures. Pulmonary capillary flow can be recorded with a body plethysmograph and the nitrous oxide method.

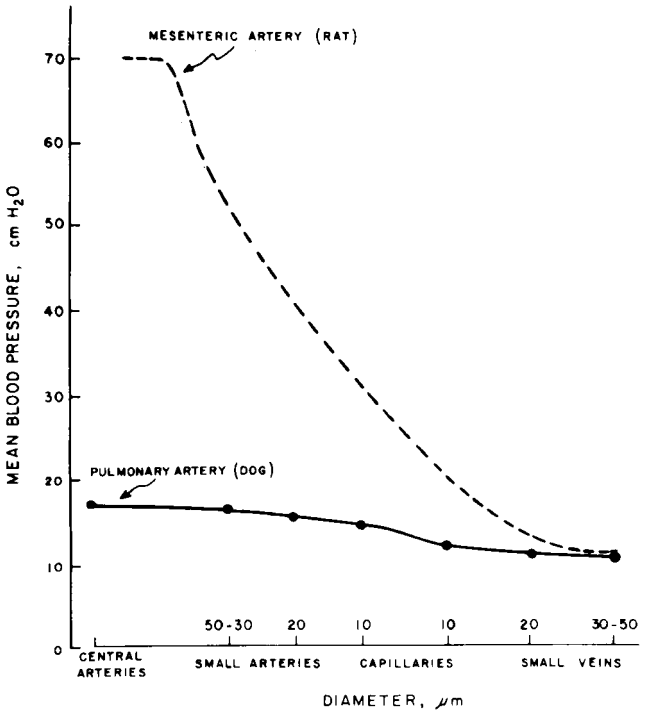

Figure 80-7 Pressure drop across the systemic (mesenteric) and pulmonary circulations. The decrements in pressures in the two vascular beds are strikingly different. Measurements were made by direct puncture of arterial and venous segments of the subpleural microcirculation. *(Based on* from *Bhattacharya J, Nanjo S, Staub NC: Micropuncture measurement of lung microvascular pressure during 5-HT infusion.* J Appl Physiol *52:634–637, 1982, with permission.)*

Pulmonary Arterial Pressures

Ordinarily, the mean pulmonary arterial pressure averages about 10 to 12 mmHg (on the order of one-eighth of that in the systemic circulation). During systole, pulmonary arterial pressure increases abruptly from diastolic values of 5 to 10 mmHg to 20 to 30 mmHg. Aging is associated with a slight increase in pulmonary arterial pressures.

The contour of the pulmonary arterial pressure resembles that recorded at the root of the aorta. Full-bodied pulmonary arterial curves are more apt to be recorded in pulmonary hypertensive states than when pressures are normotensive. Moreover, extrinsic mechanical influences deform contours when pulmonary arterial pressures are low.

Left Atrial and Pulmonary-Wedge Pressures

The drop in mean pressure between the pulmonary artery and left atrium is small—about 10 mmHg (about one-eighth of the pressure drop across the systemic circulation) (Fig. 80-7). Micropuncture of subpleural vessels suggests that most of the drop occurs in the pulmonary capillaries.

In intact, unanesthetized humans, the mean left atrial pressure is about 5 to 10 mmHg. During a single respiratory cycle, swings in pressure occur on the order of 3 to 12 mmHg. Because the left atrium is relatively inaccessible in the intact human, pulmonary-wedge pressures are generally used as a substitute.

The pulmonary-arterial-wedge pressure (P_w) is recorded by advancing a cardiac catheter through the right side of the heart and pulmonary arterial tree until it is impacted in a small precapillary vessel. By this procedure, a stagnant column of blood is created to measure pressure at its junction with flowing blood (i.e., in large pulmonary veins in the vicinity of the left atrium) (Fig. 80-8). An alternative practical approach to estimating left atrial pressure is the inflation of a balloon in a segmental pulmonary artery for the recording of pressures distal to an occlusive balloon. The tracing obtained in this way resembles that of the P_w.

Various criteria have been advanced to guarantee that a value obtained for P_w is a reliable measure of mean left atrial pressure: P_w less than mean pulmonary arterial and diastolic pressures, fully oxygenated blood withdrawn from the impacted catheter, the characteristic snap of the catheter as it is withdrawn from the wedge position, and the distinctive configuration of the wedge tracing. Unfortunately, even when all criteria are met, the P_w may fail to provide a measure of mean left atrial pressure if the catheter fails to be wedged properly or if the tip is wedged in an area where alveolar pressure exceeds pulmonary venous pressure (see "Zones of the Lungs", later in the chapter), if pulmonary arterial vessels between the catheter tip and the left atrium are occluded, or if the airways or the parenchyma of the intervening lung is sufficiently abnormal to generate abnormal perivascular pressures (e.g., by fibrosis or obstructive airways disease).

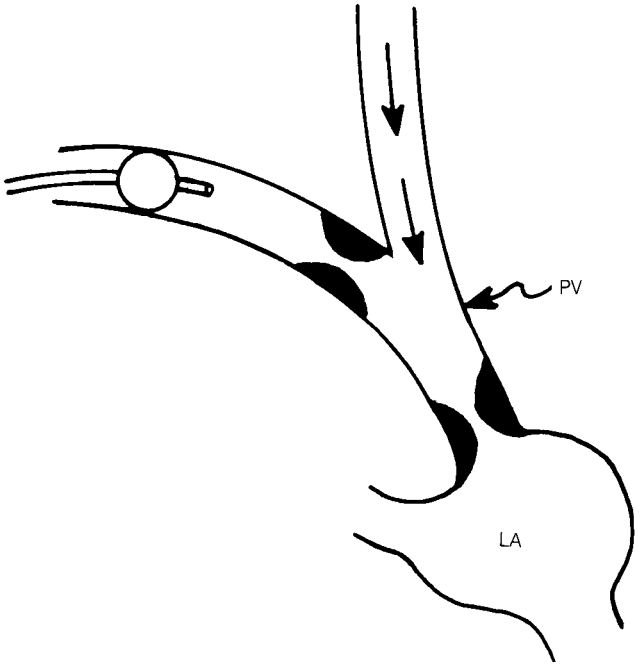

Figure 80-8 Meaning of pressure determined distal to an occlusive balloon. After the balloon is inflated, the pressure recorded is that which exists at the conjunction of flowing streams *(two arrows)* and the static pool beyond the occlusive balloon. Narrowing of pulmonary venule (PV) distal to the occlusive balloon, as by venoconstriction, does not affect the use of the postballoon pressure (or pulmonary-wedge pressure) as a measure of left atrial pressure until obstruction ensues that closes the channel to the left atrium. *(From Marini JJ:* Respiratory Medicine and Intensive Care. *Baltimore, Williams & Wilkins, 1981.)*

In brief, when used critically, the P_w, or the balloon-occlusion pressure, usually provides a reliable measure of the mean left atrial pressure. However, because of the possibility that pulmonary venous constriction in various disease states may cause pulmonary capillary pressure to exceed left atrial pressure, it is not used as a measure of pulmonary capillary pressure.

Cardiac Output (Pulmonary Blood Flow) and Oxygen Delivery

Averaged over several respiratory cycles, the outputs of the two ventricles are approximately the same; although the output of the left ventricle is slightly greater than that of the right ventricle because of the admixture of bronchial venous to pulmonary venous blood, this "anatomic venous admixture" is about 1 to 2 percent of the total left ventricular output. As noted above (Fig. 80-4), doubling of the cardiac output can be accommodated in the capacious pulmonary vascular bed with virtually no increase in mean pulmonary arterial pressure.

In humans, the cardiac output is generally determined by some application of the indicator dilution or Fick principle. For either, reliable determinations require a steady state; the time required to achieve a steady state is generally shorter for the indicator dilution techniques. Also, in practice, indicator dilution techniques are easier to apply. As a result, indicator dilution techniques are quite popular. However, the indicator dilution technique is not as reliable as the Fick technique unless carefully done, and it is apt to be misleading when cardiac output is low (as in heart failure). Other techniques for determining the cardiac output, such as those designed to determine pulmonary capillary blood flow, are neither easy to perform nor reliable.

In order to compare values obtained from subjects of different dimensions, cardiac output is generally expressed in terms of body surface area (i.e., as cardiac index). In normal adults lying quietly at rest, supine and in the postprandial state, the cardiac index averages about 3.12 L/min/m^2 (SD ± 14).

The primary mission of the coordinated interplay of the respiration, circulation, and blood is to deliver oxygen to tissues and organs in accord with their metabolic needs (Fig. 80-9) and to carry off the carbon dioxide that they generate in the course of metabolism. In the steady state, cardiac output is matched to metabolic rate: cardiac output (blood flow) increases by 600 to 800 ml per min per 10-ml increase in oxygen uptake ($\Delta \dot{V}O_2$). During heart failure, when blood flow fails to increase normally, the oxygen uptake is sustained by circulatory and ventilatory adjustments in the parameters shown in Fig. 80-9.

Oxygen delivery is defined as the product of cardiac output and the arterial O_2 content ($\dot{Q}T \times Ca_{O_2}$). An increase in O_2 requirement by the tissues (as during exercise) is ordinarily met by increasing the cardiac output, widening the arteriovenous O_2 difference, or both. In contrast to the roughly linear relation between oxygen uptake and cardiac output during exercise, the relation between oxygen uptake and the arteriovenous oxygen difference is hyperbolic. The relative contribution of an increase in cardiac output and a widening of the arteriovenous oxygen difference to satisfying the tissue requirements for oxygen depends on how the increase in metabolism is induced (by exercise, increase in body temperature, hormones, or drugs).

As noted above, the "oxygen delivery" to the tissues is equal to the product of the cardiac output and the arterial O_2 content ($\dot{Q}_T \times Ca_{O_2}$). Polycythemia enhances O_2 delivery by increasing the O_2-carrying capacity of the blood; but if the increase becomes excessive, complications such as thromboembolism, induced by an increase in red cell mass, tend to nullify the advantages of polycythemia for gas exchange. In states of low cardiac output or arterial hypoxemia, O_2 delivery can be enhanced by increasing the oxygen content of arterial blood (e.g., by breathing O_2-enriched inspired air or by mechanical ventilation).

In unanesthetized human subjects, the treadmill and bicycle ergometer are the conventional devices for achieving calibrated and reproducible levels of exercise. The hemodynamic effects of anxiety, caused by lack of familiarity with the procedure, may dominate the response, not only at rest but also during moderate exercise. For this reason, values of cot V O_2 at rest are often lower after exercise than *before* (i.e.,

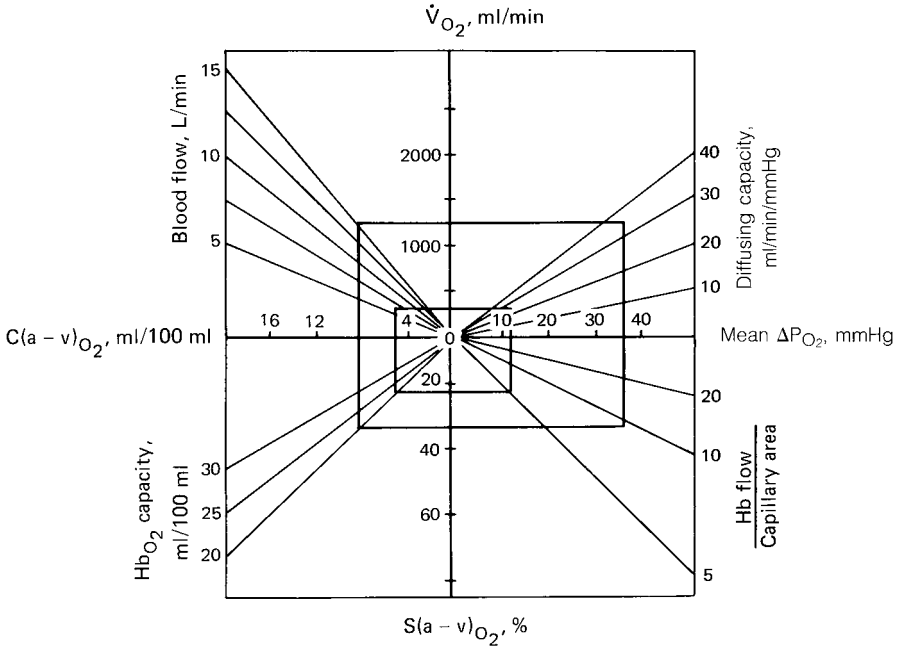

Figure 80-9 The Morgan-Murray diagram showing the interplay of the respiration and circulation in satisfying the O_2 requirement at rest and during exercise. At rest (inner rectangle), the oxygen uptake $\dot{V}_{O_2}$ is provided by a cardiac output of about 5 L/min and corresponding values for O_2 transport by the blood and diffusing capacity. The increase in O_2 uptake ($\dot{V}_{O_2}$) during exercise (outer rectangle) is met by an increase in blood flow, O_2 transport in the blood, and the diffusing capacity of the lungs (EX). A similar diagram can be drawn for O_2 delivery to the tissues.

after the threat of the unknown is gone). Quantification of the level of exercise is accomplished either by determining oxygen uptake or by assessing the workload. Tachycardia and the respiratory exchange ratio are often more reliable indices of anxiety than are clinical signs and symptoms.

Intrapulmonary Distribution of the Cardiac Output

Matching the blood flow ($\dot{Q}$) to alveolar ventilation ($\dot{V}A$) is a prime prerequisite for efficiency in gas exchange. A powerful stimulus for rearrangement of local pulmonary blood flow is acute alveolar hypoxia (as might be caused by a local inflammatory process). The classic demonstration of the vasoconstrictor property of acute hypoxia is considered in detail in a subsequent section ("Pulmonary Vasomotor Control").

Pulmonary Blood Volume

In normal humans, the pulmonary blood volume is about 10 percent of the total circulating blood volume. As a rule, it is measured by a variant of the indicator-dilution principle. In the hypothetical adult male weighing 70 kg, this value is approximately 400 to 500 ml. This volume is of interest on several pathophysiological accounts: (1) as a determinant of the mechanical behavior of the lungs, (2) as a reservoir that provides the preload for the left ventricle, (3) as a supply of hemoglobin for alveolar-capillary gas exchange, (4) as a source of water and macromolecules that engage in alveolar-capillary exchange, (5) as a potential mechanism for increasing pulmonary capillary pressures and promoting pulmonary edema, and (6) as a potential mechanism for evoking dyspnea.

Changes in pulmonary blood volume are at the expense of the air volumes. Thus, the vital capacity decreases in acute pulmonary congestion. The pulmonary blood volume varies with body position: it increases when the subject lies down and decreases when he or she stands; it is readily enlarged by intravenous infusions, by immersing the body in water, by inflation of an antigravity suit, by negative-pressure breathing, and by displacement of blood from the systemic circulation (as during systemic vasoconstriction). Conversely, the pulmonary blood volume decreases when the subject stands on his or her head, after a large venesection (one that decreases cardiac output), during positive-pressure breathing or the Valsalva maneuver, and during systemic vasodilatation.

In normal subjects, the pulmonary blood volume appears to be subdivided equally among the pulmonary arteries, capillaries, and veins. In the hypothetical 70-kg man, the pulmonary capillary blood volume can only be estimated: values range from 100 to 200 ml, depending on the method. Upon sitting up, the pulmonary capillary blood volume shares in the overall decrease in pulmonary blood volume; during exercise, as cardiac output goes up, pulmonary capillary blood volume also increases. More of the increase in volume is accomplished by recruiting new capillaries from the reserve than by dilating open vessels. As capillary blood volume enlarges as a result of recruitment and dilation, the endothelial surface area gas and fluid exchanges enlarge correspondingly.

Induced Changes in Pulmonary Hemodynamics

Mechanical Ventilation

From the hemodynamic point of view, the best-analyzed types of mechanical ventilation are *positive-pressure ventilation* and *positive end-expiratory* ventilation. In the former, airway pressures increase during inflation, returning promptly to atmospheric during expiration; in the latter, raised airway pressure is sustained throughout the breathing cycle. Terminology used in clinical practice generally focuses on the positive end-expiratory pressure (PEEP), and the designation generally

refers to *continuous* positive pressure ventilation rather than solely to positive *end-expiratory* pressure.

In normal humans, the imposition of PEEP at a level of 5 cm H_2O has several hemodynamic consequences: stroke volume, cardiac output, and central blood volume decrease while heart rate is unaffected. Pulmonary arterial pressures (referred to as *atmospheric pressures*) increase, and the increase in alveolar pressure causes pulmonary-wedge pressures to exceed left atrial pressures. At higher levels of PEEP, these hemodynamic effects are exaggerated. Stiffening of the lungs by pulmonary edema requires higher levels of PEEP to produce the same effects (e.g., 15 to 40 cm H_2O instead of 5 cm H_2O). At these levels, however, the risk of barotrauma to the lungs also increases markedly.

The cardiac output falls when normal lungs are subjected to PEEP, but how this decrease is effected remains enigmatic. At least three mechanisms have been proposed: the traditional one implicates a decrease in venous return (preload) to the *right* ventricle. The second entails a decrease in *left* ventricular preload and impairment of both right and left ventricular performance. The third attributes a negative inotropic effect to PEEP mediated by way of cardiovascular inhibitory mechanisms in the brain and the local release of prostaglandins. Clearly, the use of PEEP triggers an intricate resetting of regulatory mechanisms that seems to involve mechanical, reflex, and local humoral mechanisms. Which mechanism dominates at any given time may well depend on the experimental and clinical setting.

Exercise

The changes in pulmonary vascular pressures, flows, and resistances brought about by light exercise are indicated in Table 80-1. Despite the respiratory swings and the shifts in midposition of the lung during exercise that complicate accurate measurement of pressures, the hemodynamics are quite consistent: at the start of the exercise, the pulmonary arterial mean pressure (referred to atmosphere) increases abruptly by 3 to 5 mmHg. As exercise continues, a plateau is reached, generally at 1 to 2 mmHg less than peak values; the increase in systolic pressure is greater than the increase in diastolic pressure. Because of the increase in pulsatility and in mean pulmonary arterial pressure, perfusion of the apices improves.

Direct determinations of left atrial pressure during exercise in intact humans or dogs have not been reported. The pulmonary-wedge pressure is generally little affected by mild exercise, but intensification of the exercise tends to increase it. The concept of pulmonary capillary "stress failure" has been advanced as a limiting factor for maximal exercise.

PULMONARY VASOMOTOR CONTROL

In the normal pulmonary circulation at sea level, vascular tone is low (i.e., the pulmonary vascular bed is virtually fully dilated) (Fig. 80-10). It is considerably higher in the native resident at high altitude, in whom comparable increments in pulmonary blood flow elicit larger increments in pulmonary arterial pressures.

Initial Tone

The low initial tone in the pulmonary circulation at sea level is attributed to a balance in favor of vasodilation due to substances released by pulmonary vascular endothelium (Fig. 80-11). The predominant mediators in this balance are the vasodilator substances prostacyclin and nitric oxide, on the one hand, and endothelin-1, on the other. The vasodilators are released promptly in response to shear stresses, whereas endothelin-1 is released slowly and is active in more prolonged control of vascular tone.

Ion channels feature prominently in setting pulmonary vascular tone. Paramount among these are several different K^+ channels that are present on vascular smooth muscle:

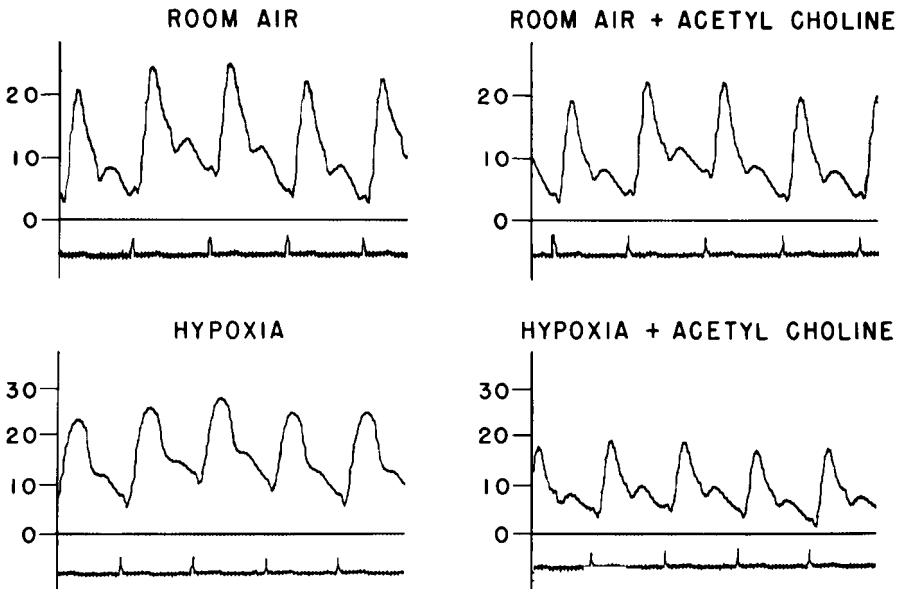

Figure 80-10 Effect of initial tone on vasodilator responsiveness. Administration of acetylcholine while the subject is breathing room air (upper panels) elicits no vasodilator response because of the low initial tone. During hypoxia, when tone is increased by vasoconstriction, administration of acetylcholine causes a considerable drop in pulmonary arterial pressures. *(From Fritts HW, Harris P, Clauss RH, et al: The Effect of Acetylcholine on the Human Pulmonary Circulation Under Normal and Hypoxic Conditions.* J Clin Invest *37:99–110, 1958.)*

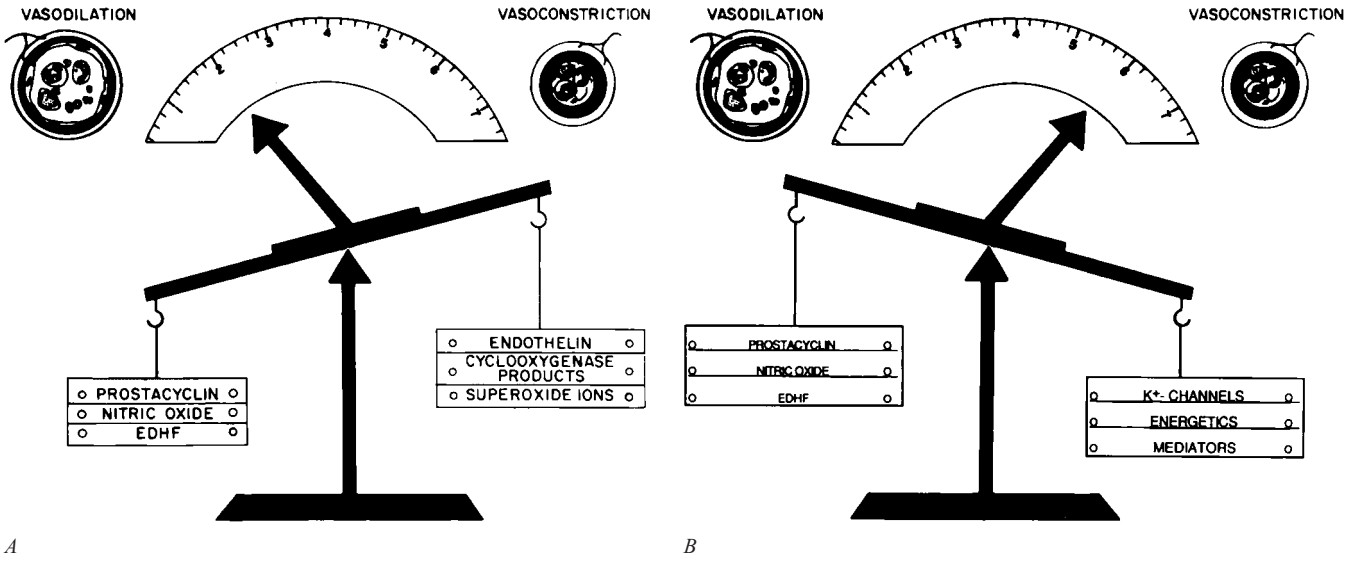

Figure 80-11 The balance between vasodilator and vasoconstrictor mediators. *A*. Under normal conditions, breathing ambient air at sea level, the balance favors vasodilation. *B*. During hypoxia, the balance is tilted to vasoconstriction.

adenosine triphosphate (ATP)-sensitive, Ca^{2+}-activated, and nonspecific, voltage-gated K^+ channels. Activation of these channels causes an increase in K^+ efflux and membrane hyperpolarization, followed by relaxation of smooth muscle.

Role of Nerves

Vasomotor responses can be elicited from the isolated lung devoid of all nervous connections and perfused by artificial fluids. This capability underscores the primary role played by vasomotor mechanisms intrinsic to the lungs in effecting vasomotor control. However, the predominance of intrinsic control in normal subjects or in patients studied in clinical settings does not exclude the possibility that extrinsic influences, such as sympathetic nerves, can contribute important elements of control should the occasion arise (e.g., the "fight or flight reaction" associated with a terrifying experience).

The sympathetic innervation to the pulmonary circulation includes α- and β-adrenergic receptors on pulmonary vascular smooth muscle. α-Adrenergic receptors appear to predominate. The α-adrenergic receptors (e.g., norepinephrine) are constrictor, whereas the β-adrenergic receptors (e.g., isoproterenol) are dilator. In the normal resting adult at sea level, adrenergic activity is modest and α-adrenergic influences predominate. Cholinergic activity does not appear to be implicated at any time in the control of the pulmonary circulation.

Nervous connections from without the lungs can mediate certain reflex effects on the pulmonary circulation. A systemic *depressor reflex* is evoked by an abrupt, large increase in pulmonary arterial or venous pressure and elicits modest bradycardia and *systemic* hypotension; sectioning the vagi abolishes this reflex. The outputs of the two ventricles are automatically adjusted by reflex mechanisms that avoid flooding of the lungs. Stimulation of systemic baro- and chemoreceptors elicits reflex changes in pulmonary vascular tone.

Reflex pathways also exist within the lungs. For example, the juxtacapillary reflex ("J" reflex) is elicited by deformation of the terminal airways (as by edema) to evoke tachypnea, bronchoconstriction, and reluctance to exercise. The Bainbridge reflex is triggered by distention of the pulmonary venoatrial junction and elicits reflex tachycardia. Occasionally, persons with pulmonary hypertension (as do deteriorating experimental preparations) show swings in pulmonary arterial pressure "vasomotor waves" reminiscent of Traube-Hering and Mayer waves. Imbalance in central vasomotor control has been held responsible for their genesis. Finally, it has been proposed that CO_2-sensitive receptors within the lungs can augment ventilation. These reflex patterns demonstrate that even though predominant control of the pulmonary circulation resides within the lungs per se, potential exists for activating a complicated system of extrinsic controls, by either disease or experimental conditions.

Prostacyclin and Other Arachidonic Acid Metabolites

Prostacyclin, a metabolic product of arachidonic acid metabolism (Fig. 80-12), has been identified as a major determinant of initial tone in the pulmonary circulation. Arachidonic acid is metabolized via two major enzymatic pathways: cyclooxygenase and lipoxygenase. The cyclooxygenase pathway gives rise to the prostaglandins and thromboxane A_2. The lipoxygenase pathway produces the leukotrienes and the 5-, 12-, and 15-hydroxy-eicosatetraenoic acids. A separate series of reactions involves a cytochrome P450 pathway, which produces oxygenated metabolites of arachidonic acid.

Arachidonic acid (eicosanoic acid), a 20-carbon polyunsaturated fatty acid, is the precursor of the

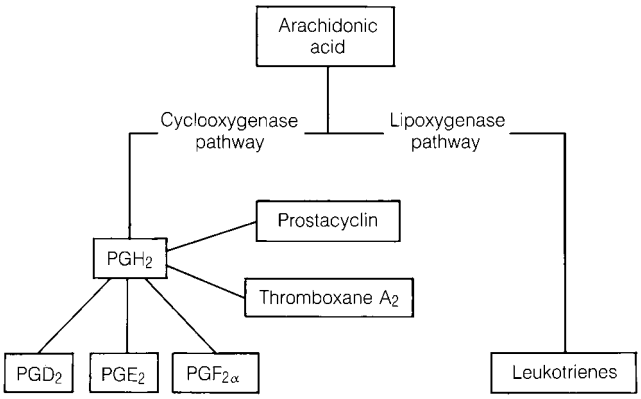

Figure 80-12 The arachidonic acid cascade illustrating the two pathways and a few metabolic products capable of pulmonary vasomotor activity. *(Based on data from Fishman AP: Pulmonary circulation, in Fishman AP, Fisher AB (eds), Handbook of Physiology, sec 3: The Respiratory System, Vol 1:* Circulation and Nonrespiratory Functions. *Bethesda, MD, American Physiological Society, 1985, pp 93–166, with permission.)*

prostaglandins (Fig. 80-12). It is released from tissue by deacylation of cellular phospholipids. Upon release, it is metabolized by either the cyclooxygenase or lipoxygenase enzyme systems. Because the arachidonic acid metabolites released from membrane lipids are both organ-specific and cell-specific, and because experimental conditions strongly influence the metabolism of arachidonic acid, either the cyclooxygenase or lipoxygenase pathway may predominate. Administered arachidonic acid need not have the same metabolic consequences as that generated endogenously. Nor are physiological and pharmacologic doses and patterns of release apt to be identical. Therefore, it is difficult to predict which pathway will dominate or how experimental circumstances are influencing the biologic effects. As a rule, arachidonic acid injected intravenously elicits pulmonary vasoconstriction largely because of the predominant effect of thromboxane A_2, even though prostacyclin, a potent vasodilator, is also released; leukotrienes do not appear to be operative in this circumstance.

Pharmacologic interruption of one pathway has been used to uncover the effect of metabolites produced by the other. For example, indomethacin, which inhibits prostaglandin synthetase, is a popular agent for blocking the cyclooxygenase pathway in order to disclose the actions exerted by metabolites of the lipoxygenase pathway. Diethylcarbamazine, which interferes with the lipoxygenase pathway, serves the same purpose for the cyclooxygenase pathway. However, specificity of these and other inhibitors for particular sites in the arachidonic acid cascade is rarely complete. Moreover, alternative pathways in the metabolism of arachidonate provide opportunity for subtle experimental quirks to channel the cascade into one pathway or another, thereby covertly shaping the vasomotor response of the pulmonary circulation, not only to prostaglandins (exogenous as well as endogenous) but also to inapparent neurohumoral influences and to biologically active molecules. Finally, considerable species variation exists in the intensity of the vasomotor response to particular products of arachidonic acid metabolism.

Considerable diversity of biologic effects exists among the prostaglandins: (1) certain metabolic products of the cyclooxygenase pathway are pulmonary vasoconstrictors (e.g., $PGF_{2\alpha}$, PGE_2, thromboxane A_2), whereas others are pulmonary vasodilators (e.g., PGE_1, PGI_2); PGE_2, which constricts the adult pulmonary vascular bed, dilates the neonatal pulmonary vascular bed; (2) leukotrienes, generated by the lipoxygenase pathway, include potent pulmonary vasoconstrictors; and (3) suspicion is high that the prostaglandins act as intermediaries in pulmonary vasomotor responses to other agents, such as the kallidins, histamine, and isoproterenol.

Prostacyclin (PGI_2) is both a potent pulmonary (and systemic) vasodilator and an antithrombogenic agent. It is formed in pulmonary vascular endothelium (Fig. 80-13) by the action of prostacyclin synthetase on the prostaglandin endoperoxide PGH_2. Shear stress of the endothelium and bradykinin seem to be powerful stimuli for the release of prostacyclin from endothelium.

Thromboxane A_2 is a potent pulmonary vasoconstrictor and a powerful stimulus for platelet aggregation. Prostacyclin antagonizes the effects of thromboxane A_2. An imbalance has been found between the excretion of thromboxane and of prostacyclin metabolites in pulmonary hypertension.

Nitric Oxide

Although the original view of endothelium as a passive lining of blood vessels had long been appreciated to be an oversimplification, particularly with respect to the exchange of water and biologic molecules, full understanding of its biologic role began with the demonstration in isolated aortic preparations that the vasodilation elicited by acetylcholine required the presence of an intact endothelial layer (Fig. 80-14). Subsequently, endothelium-derived relaxing factor (EDRF) was pinpointed as the mediator, followed by the identification of nitric oxide as EDRF.

In 1995, largely in recognition of its ubiquitous biologic role as an intercellular messenger in signal transduction in a wide variety of mammalian cells, nitric oxide (NO) was elevated from its lowly status as a gaseous air pollutant to the vaunted position of "molecule of the year"—an endogenous, ubiquitous regulator of a wide range of physiological processes. Although NO is a highly reactive molecule, in minute (physiological) quantities it is safe, transmitting signals and serving diverse biologic functions, such as the regulation of blood pressure. It is short-lived because of its interactions with oxygen. NO also reacts with superoxide radical (O^{2-}) and with ferrous hemoproteins, such as guanylate cyclase and hemoglobin. Because of its chemical properties, NO is less specific and less controllable than almost any other transmitter or hormone. Cigarette smoke contains up to 1000 ppm of NO. Silo-filler's disease, an interstitial pneumonitis, is caused by exposure to high levels of NO and NO_2.

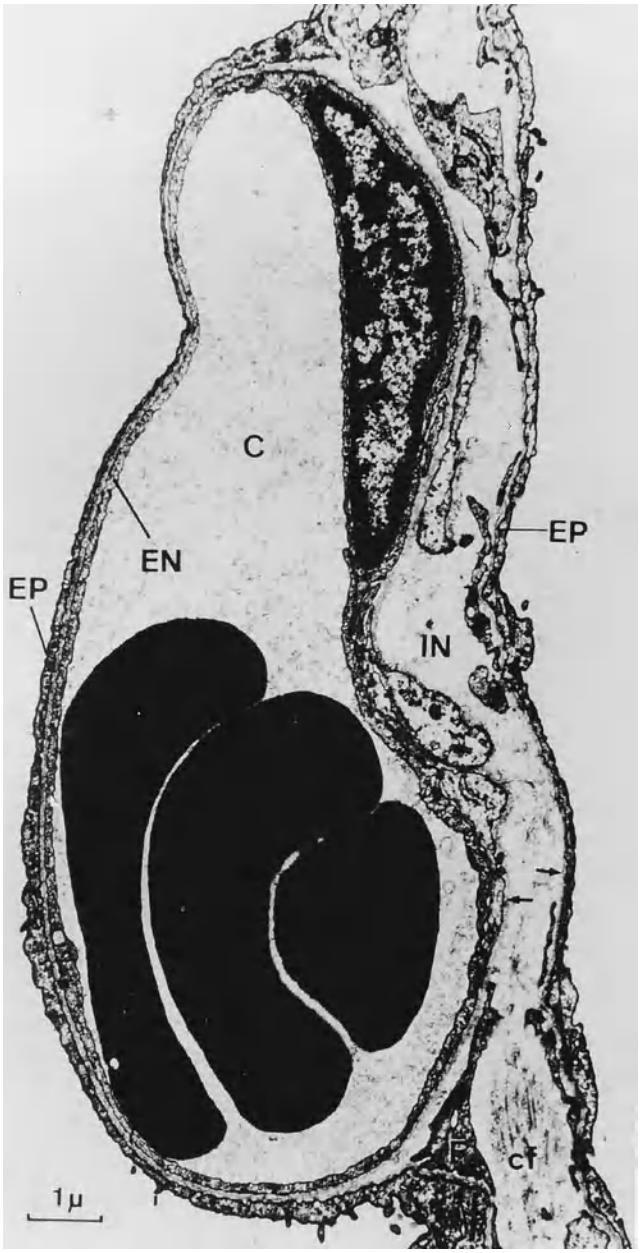

Figure 80-13 Cross-section of alveolar capillary from human lung lined by endothelium (EN). Endothelial nucleus is striking. Alveolar-capillary barrier is organized into thick (right) and thin (left) portions. Thick side includes considerable interstitial space (IN), containing connective-tissue elements (e.g., fibers [cf]). In contrast, interstitial space on thin side is obliterated by fusion of basement membranes, which forms a minimal air-blood barrier. C = capillary containing three red corpuscles in its lumen; EP = alveolar epithelium; F = fibroblast. *(Courtesy of E. Weibel.)*

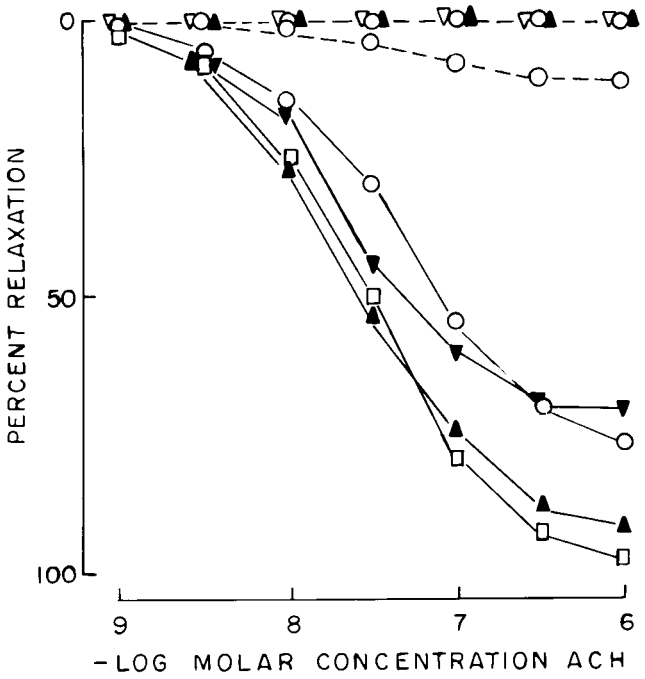

Figure 80-14 Influence of endothelium on responses of different vessels to acetylcholine (ACH). Increasing concentrations of acetylcholine were applied to rings of femoral, saphenous, splenic, and pulmonary arteries (circles) that had previously been contracted with norepinephrine. Vessels in which endothelium was intact (solid curves) responded with increasing vasodilation. In vessels without endothelium (dashed curves), virtually no vasodilation occurred. *(From* De Mey JG, Vanhouette PM: Heterogeneous behavior of the canine arterial and venous wall. Importance of the endothelium. *Circ Res 51:439–447, 1982, with permission.)*

NO is synthesized in endothelial cells from one of the guanidium nitrogens (L-arginine) by the enzyme nitric oxide synthase (NOS) (Fig. 80-15). Two major forms of NOS enzymes produce NO: constitutive isoforms, in endothelium and neurons, release small quantities of NO, in bursts, to signal adjacent cells; and inducible isoforms, in macrophages, release large amounts of NO continuously and serve to eliminate bacteria and parasites. NOS are a family of complex cytochrome P450-like hemoproteins. NO synthase can be inhibited by methylene blue and by L-*N*-monomethylarginine, an L-arginine analog.

Among its biologic functions is the regulation of pulmonary vascular tone. Its release is triggered by both physical factors, such as endothelial shear stress, and biochemical influences, such as bradykinin, histamine, and catecholamines. The NO produced by pulmonary endothelial cells is transported by the hemoglobin in the red blood cells to systemic arterioles, where it causes muscle relaxation. The cysteine residue of hemoglobin is active in the transport of NO to the peripheral blood vessels. The NO conveyed to the periphery enters the vascular smooth-muscle cell by diffusion to activate adenylate cyclase, leading to an increase in cyclic guanosine monophosphate (cGMP), which, in turn, causes muscle relaxation (vascular dilation) (Fig. 80-16).

Inhaled NO is currently being investigated as a therapeutic pulmonary vasodilator. It is administered by airway and is rapidly removed by hemoglobin in blood. The apparatus for delivering NO by inhalation is cumbersome. Because it is administered by inhalation, it has opportunity en route to interact with the wide variety of cells that comprise the epithelial lining, autonomic neurons, smooth muscle, and interstitium.

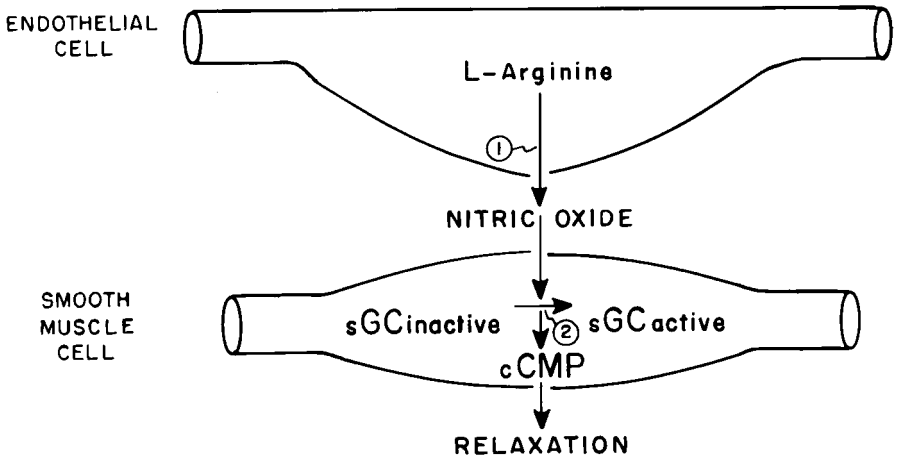

Figure 80-15 Synthesis of nitric oxide (NO) by vascular endothelium. 1. The enzyme nitric oxide synthase (NOS) synthesizes NO from L-arginine. 2. NO diffuses to the smooth muscle cell, where it activates the enzyme guanylate cyclase via cyclic GMP to smooth-muscle relation.

Endothelins

Endothelins (ET-1, ET-2, and ET-3) are a family of short (21 amino acids) peptides. Of the three, ET-1 is the only one produced by endothelial cells. It is a powerful vasoconstrictor and stimulant of cell growth. ET-1 is produced, on physiological demand, from a larger precursor molecule (ECE), which is being intensively investigated for its potential as an avenue for inhibiting endothelin formation in various disease states. Three endothelin receptors (ETA, ETB, and ETC) have been cloned. ETA receptors on vascular smooth muscle are responsible for vasoconstriction and growth promotion; ETB receptors on endothelium are related to release of prostacyclin or NO. Binding of ET-1 to ETA receptors initiates a cascade leading to vasoconstriction by way of phospholipase C and resulting in an increase in intracellular calcium ion concentration. Binding of endothelins to ETB receptors stimulates vasodilation.

In addition to its direct effects on vascular tone, ET-1 has a wide range of biologic actions, including constriction of extravascular smooth muscle, mitogenesis, and release of other mediators, such as prostacyclin, NO, and atrial natriuretic peptide. The lungs remove large amounts of endothelin from circulating blood. Within the lungs, endothelins are present in the parenchyma and pulmonary vessels. They are powerful bronchoconstrictors. Release of endothelins is stimulated by such receptor-mediated stimuli as epinephrine, angiotensin II, arginine vasopressin, thrombin, transforming growth factor-β and interleukin-1, and also by hypoxia. The endothelin-receptor antagonist bosentan prevents and reverses pulmonary hypertension in rats. Because of the diversity of their effects and widespread distribution in the body, the role of the endothelins is being explored in a wide variety of diseases, such as hypertension, arteriosclerosis, Raynaud's disease, ulcerative colitis, and renal failure.

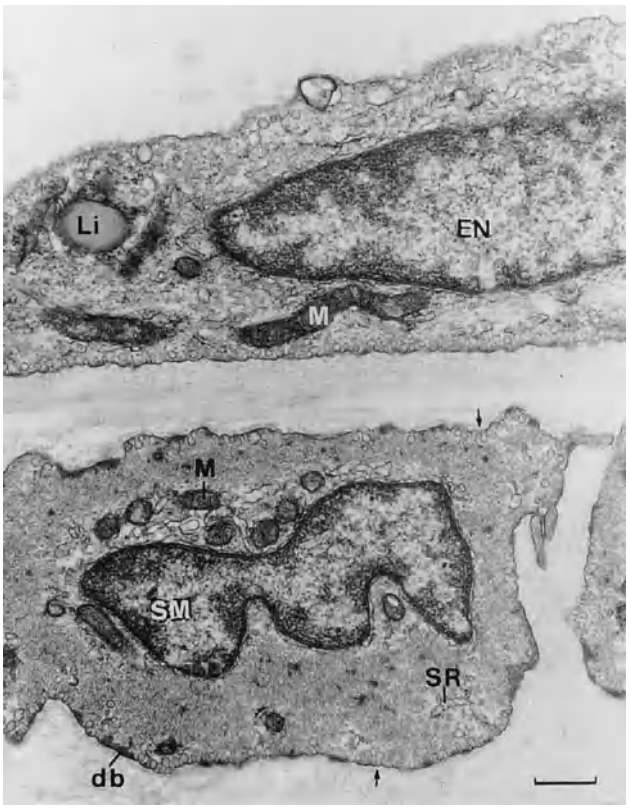

Figure 80-16 Electron micrograph of small muscular pulmonary artery from human lung showing endothelium (EN) and single layer of smooth muscle (SM). Thick endothelial cytoplasm and wealth of organelles (inset) comprising mitochondria (M), endoplasmic reticulum (ER), lipid droplet (Li), specific granules (asterisks), microtubules (mt), and many vesicles (arrows). Cross-sectioned smooth-muscle cells show central nucleus, mitochondria, sarcoplasmic reticulum (SR), membrane-bounded caveolae (arrows), filamentous matter with dense bodies (db), and cell-to-cell contacts (circle). cf = collagen fibrils; el = elastic fibers; bars = 0.5 μm. *(Courtesy of E. Weibel.)*

Respiratory Gases and pH

Acute Hypoxia

The classic demonstration of the pressor effect of acute hypoxia on the pulmonary circulation was made by Euler and Liljestrand on the open-chest cat (Fig. 80-17). In the ensuing half-century, acute hypoxia has proved to be a pulmonary vasoconstrictor in virtually all species indigenous to sea level. The authors not only documented the role of alveolar hypoxia in eliciting the pulmonary pressor response but also

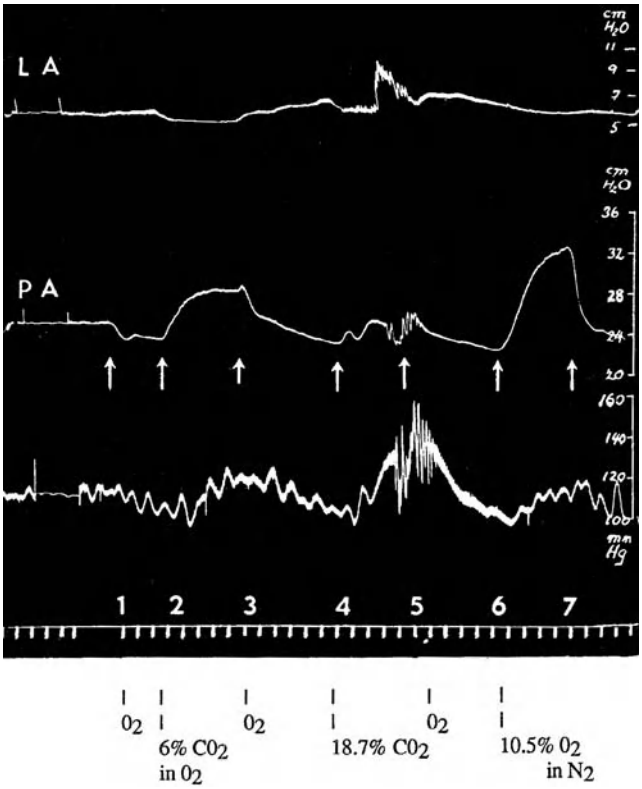

Figure 80-17 The classic recordings by Euler and Liljestrand showing the effects of acute hypoxia on the pulmonary arterial (PA) and left atrial (LA) pressures in the open chest cast (labels added). At the far right, breathing 10.5 percent O_2 caused a considerable rise in pulmonary arterial pressure without a corresponding increase in left atrial pressure. (Labels added at bottom of figure.) *(Based on data from Euler US, Liljestrand G: Observations on the pulmonary arterial blood pressure in the cat.* Acta Physiol Scand *12:301–320, 1946, with permission.)*

appreciated that local hypoxia (as by disease) might automatically redirect blood flow to better-ventilated parts of the lung by eliciting local vasoconstriction. Finally, they anticipated recent studies on the effect of shear on release of endothelial mediators by identifying as a subject for research the response of pulmonary vessels to large increases in pulmonary blood flow.

In human subjects, acute hypoxia causes an increase in pulmonary arterial pressure, does not affect left atrial pressure, and usually produces little increase in cardiac output. The pressor response starts within seconds, generally reaching its peak by 3 min, and attenuates gradually as hypoxia continues. Severe acidosis augments the hypoxic pressor response. The site of pulmonary vasoconstriction in response to acute hypoxia is predominantly at the precapillary level, involving the small muscular arteries and arterioles (Fig. 80-18).

Acute hypoxic vasoconstriction can be relieved by a variety of bronchodilators and vasodilators, such as inhalation anesthetics. Endothelial-derived vasodilators appear to be particularly effective. For example, prostacyclin administered intravenously can blunt or abolish the hypoxic pressor response. Similarly, inhalation of NO inhibits hypoxic vasoconstriction, whereas inhibitors of NOS augment the hypoxic pressor response by blocking the endogenous synthesis of NO.

The mechanisms of the hypoxic-pressor response have been investigated for years along two dominant lines: the first postulates a direct effect of hypoxia on the smooth-muscle cells of vascular media; the second proposes the release of a chemical mediator within the lungs during acute hypoxia (e.g., ET-1 by pulmonary vascular endothelium). Although both continue to have their proponents, the cumulative evidence favors the view that the hypoxic pressor effect is exerted directly on pulmonary vascular smooth muscle. Moreover, the many vasoactive substances that have been investigated as possible mediators of this effect (i.e., the postulated "indirect" effect) are actually modulators rather than mediators.

The direct effect has been explored along three lines: the sensing mechanism, the transduction mechanism, and the effector mechanism. Of these three components of the hypoxic pressor response, the most settled is the effector mechanism (i.e., an increase in cytosolic calcium concentration). For insights into the sensing and transducing mechanisms, investigators have turned to the type I cell of the carotid body that, like the pulmonary myocyte, is stimulated by hypoxia. In both types of cells, hypoxia has been found to inhibit an outward potassium current, thereby causing membrane depolarization and entry of calcium into the cells by way of voltage-dependent calcium channels. Also in both types of cells, changes in the redox status of the oxygen-sensitive potassium channel or channels may control current flow, so that the channel is open when oxidized and closed when reduced. Still unsettled is the type(s) of potassium channel that responds to hypoxia and how the ionic exchanges through these channels are gated. One attractive hypothesis being tested is that hypoxia is sensed by a hemoprotein in the membrane of the smooth-muscle cell—which, in turn, activates the responsive potassium channel(s).

Chronic Hypoxia

With few exceptions, such as the yak (a native resident at high altitude), chronic hypoxic pulmonary hypertension is a feature of life at high altitude. The exceptions are due to genetic influences that are manifested by variability in the hypoxic pressor response among species and even among strains. Chronic hypoxia elicits anatomic changes in the small pulmonary arteries and arterioles. These changes have been designated "pulmonary vascular remodeling." These structural changes are characterized by proliferation of the smooth muscle in the vessel walls, causing thickening and peripheral extension of smooth muscle in the media of small muscular arteries and arterioles. Concomitantly, elastin and collagen are synthesized and deposited in the extracellular matrix and adventitia. The end result is an increase in resistance to blood flow and a decrease in distensibility of the pulmonary resistance vessels. The stimuli for remodeling include not only hypoxia but also mechanical forces, such as increase in blood flow, which expose endothelial cells to increased shear stress and activate platelets to release promotors of smooth-muscle

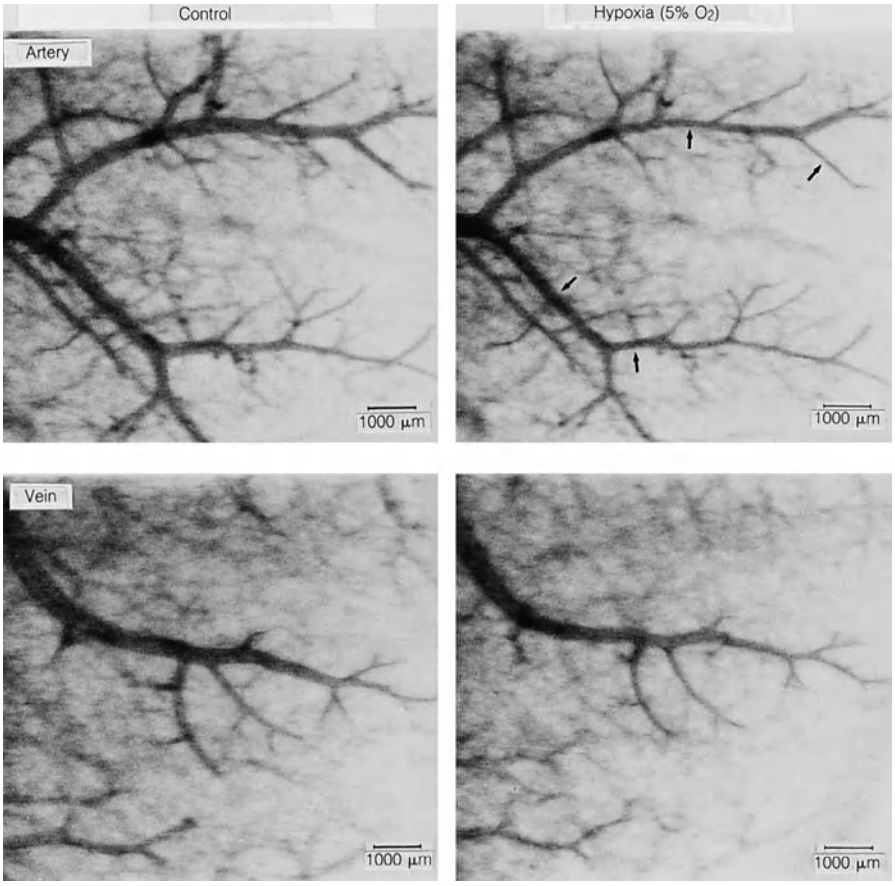

Figure 80-18 Direct visualization of the vasoconstrictor effect of acute hypoxia. During breathing of 5 percent O_2 in N_2, the pulmonary precapillary vessels, is attenuated by vasoconstriction, whereas the pulmonary veins undergo no appreciable change. *(Courtesy of Dr. I. Ninomiya, National Cardiovascular Research Institute, Osaka, Japan.)*

cell proliferation. Various genes are expressed in the process of hypoxic-induced vascular remodeling, some attributable to the hypoxia per se and others evoked by the vasoconstrictor response. Agents that block hypoxic pulmonary vasoconstriction also block the development of chronic hypoxic pulmonary hypertension and the remodeling response. In essence, a variety of influences, including mechanical factors, growth factors, and mediators, appear to be active in pulmonary vascular remodeling. With respect to both acute and chronic hypoxia, one tantalizing enigma is the reason why hypoxia causes pulmonary vessels to constrict and systemic vessels to dilate.

Considerable data about the pulmonary circulation at altitude have been gathered at Morococha, Peru (an altitude of 4540 m), where an ambient PO_2 of about 80 mmHg is associated in adults with a mean pulmonary arterial pressure of about 28 mmHg (about twice the average value of 12 mmHg in sea-level residents [Lima], even though cardiac output and pulmonary-wedge pressures are the same) (Fig. 80-19). During moderate exercise, mean pulmonary arterial pressure increases considerably: quadrupling the oxygen uptake intensifies arterial hypoxemia and doubles both the cardiac output (from 3.65 to 7.49 L/min/m^2) and the pulmonary arterial pressure (from 41/15, 29 mmHg, to 77/40, 60 mmHg). In persons suffering from chronic mountain sickness, in which severe arterial hypoxemia and hypercapnia are secondary to alveolar hypoventilation, pulmonary arterial pressures are much higher. Genetic factors seem to influence human susceptibility to pulmonary hypertension at altitude.

When native residents of high altitudes take up residence at sea level, pulmonary arterial pressure and PVR decrease somewhat, although not to normal (Fig. 80-20). PVR remains high because of anatomic changes in the pulmonary arterial tree elicited by the chronic hypoxia (i.e., by hypertrophy and hyperplasia of the small muscular arteries and arterioles, accompanied by extension of muscle peripherally into precapillary vessels that are ordinarily nonmuscular). In the face of this restructuring of precapillary vessels, the pulmonary capillaries and veins remain unchanged. Polycythemia, because it increases blood viscosity, contributes to the pulmonary hypertension associated with chronic hypoxia.

At sea level, the anatomic lesions of hypoxic pulmonary hypertension gradually revert toward normal. Nonetheless, 2 years after moving to sea level, the native high-altitude dweller still shows an inordinate increase in pulmonary arterial pressure, in response to a modest increase in pulmonary blood flow, presumably a consequence of persistent muscularization of the small pulmonary arteries.

Children born and raised at altitude undergo more gradual involution of pulmonary arterial pressures than do those born at sea level. Therefore, up to the age of 5 years, children raised at altitude have uniformly higher pulmonary arterial pressures (around 58/32, 44 mmHg) than do older children at altitude (41/18, 28 mmHg).

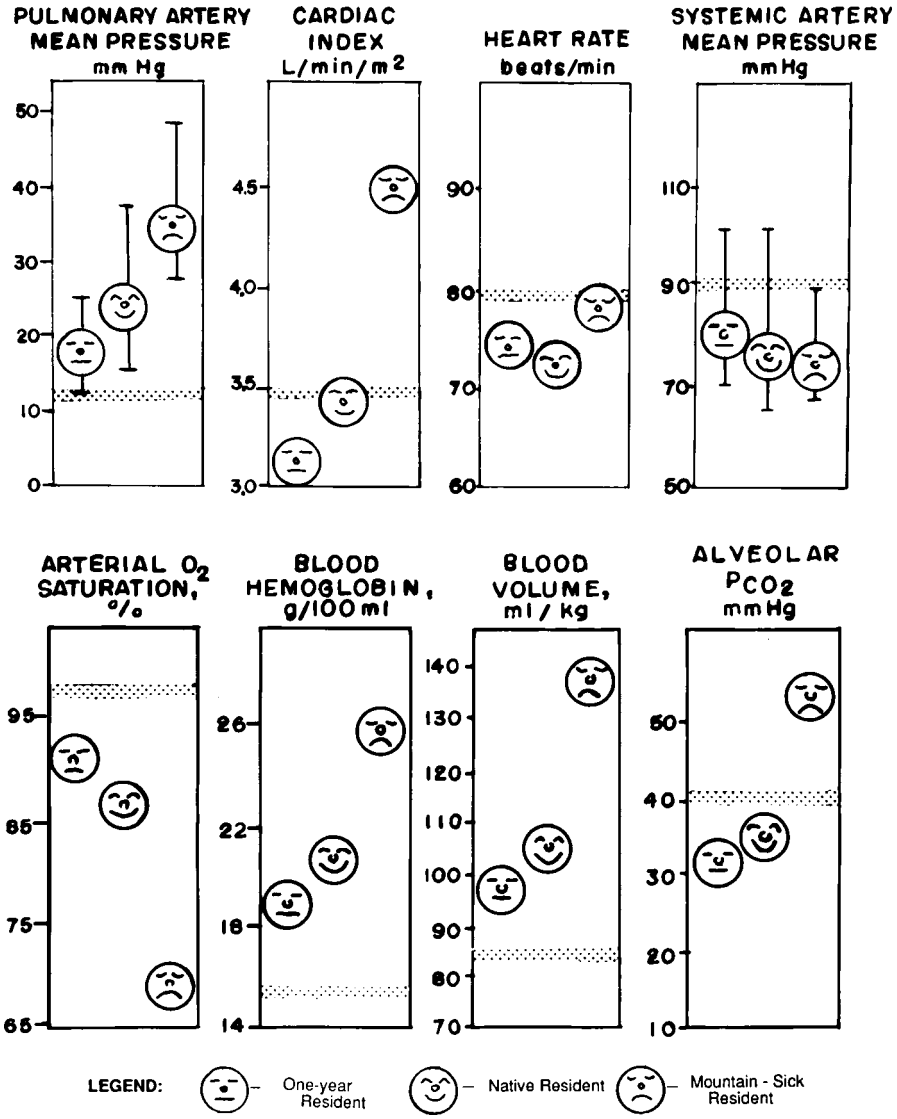

Figure 80-19 Schematic representations of respiratory and circulatory measurements in humans at altitude (14,900 feet). The three circles within each rectangle illustrate normal values for the 1-year resident (left circles), the native resident (middle circles), and the native mountain-sick resident (right circles). The facial expressions are intended to indicate the degree of acclimatization.

Acute Hypercapnia

Although Euler and Liljestrand found an increase in pulmonary arterial pressure during CO_2 breathing, it has since been shown that there is little response to inspired CO_2 if pH is maintained at near-normal levels (they did not measure pH). For example, enrichment of inspired air with tolerable concentrations of CO_2 (5 to 7 percent) has little effect on the human pulmonary circulation, presumably because the increase in ventilation minimizes change in blood pH. However, if the ventilatory response is limited (e.g., during anesthesia), a distinct pressor response is evoked as arterial blood becomes acidotic (i.e., as pH falls to 7.2 or less). The combination of moderate to severe acidosis—no matter how induced—and acute hypoxia elicits a greater response than either alone (i.e., the pressor response to acute hypoxia and acute hypercapnia combined is synergistic).

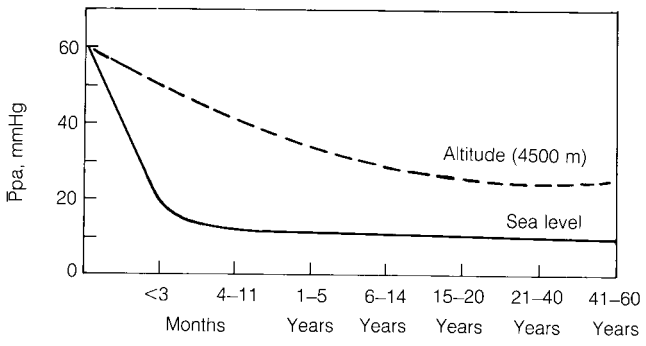

Figure 80-20 Return of pulmonary artery pressures to normal after prolonged residence at sea level.

Blood pH

Just as severe acidosis elicits pulmonary vasoconstriction, so does severe alkalosis cause pulmonary vasodilatation. The interplay between hypoxia and acidosis is believed to be of considerable importance in areas of alveolar hypoventilation in which the combination of local acidosis and hypoxia promotes the diversion of blood flow to better ventilated parts of the lungs.

Other Vasoactive Substances

A variety of endogenous and exogenous substances have been used to alter the tone of the pulmonary resistance vessels, predominantly the small pulmonary arteries and arterioles.

Vasodilators

Acetylcholine

As noted above, acetylcholine is a powerful pulmonary vasodilator when pulmonary vascular tone is high (Fig. 80-10). Observations on the role of endothelium in determining the responses of different vessels to acetylcholine marked the beginning of current interest in EDRF and led to the identification of NO as an agent that mimicked the EDRF effects.

Bradykinin

This pulmonary vasodilator is a member of a family of vasoactive polypeptides. It is inactivated by the same converting enzyme(s) in the lungs that convert(s) angiotensin I to II. Although it is consistently a powerful systemic vasodilator, it is not as predictable as a pulmonary vasodilator, usually evoking pulmonary vasodilatation. The biologic role of bradykinin in regulating the pulmonary circulation is unclear. The possibility has been raised that the origin of bradykinin in the pulmonary vascular endothelium constitutes a source of vasodilator agent for the systemic circulation. Although angiotensin II and bradykinin share a dependency on converting enzyme for their genesis, they act differently on vascular smooth muscle: angiotensin acts without intermediaries, whereas vasoactive prostaglandins are involved in the effects of the kallidins. Indeed, at least in some of the species, the variability in the vasoactive effects of bradykinin and the kallidins has been attributed to variations in the extent to which different prostaglandins are engaged as mediators of the vasodilator response.

Isoproterenol

In the normal pulmonary circulation, isoproterenol usually evokes a barely detectable drop in pressure; the modest response has been attributed to low initial tone due either to the paucity of β-adrenergic receptors or to the low level of their activity in the normal state. The vasodilator response is much more impressive in animal preparations in which initial tone is high and in some patients with pulmonary hypertension. It has been suggested that the pulmonary vasodilator effect of isoproterenol when pulmonary vascular tone is high depends not only on pulmonary vascular adrenergic receptors but also on vasodilator prostaglandins. One complicating feature in the use of isoproterenol as a pulmonary vasodilator is its powerful inotropic effect on the heart.

Vasoconstrictors

Catecholamines

Norepinephrine and phenylephrine, potent stimulators of the α-adrenergic system in the pulmonary circulation, consistently elicit pulmonary vasoconstriction. Epinephrine, which possesses α- and β-adrenergic effects, not only evokes less vasoconstriction on a weight-for-weight basis but can also, depending on the preparation, cause vasodilatation.

Angiotensin II

Angiotensin II, an octapeptide formed in the lungs by the action of converting enzyme from angiotensin I and decapeptide (Fig. 80-2), generally but not invariably elicits pulmonary vasoconstriction. Small doses (0.03 μg/kg/min, administered intravenously) suffice to increase pulmonary arterial pressure without discernible effect on the systemic circulation.

Histamine

Histamine (in doses of 10^{-5} g, given intravenously over a 2-min period) elicits more variable responses. Although species difference and the type of experimental preparation seem to influence the outcome, as a rule, histamine (like hypoxia) appears to be a powerful pulmonary vasoconstrictor and systemic vasodilator. At one time, it was suspected that histamine was an important local mediator in the regulation of the pulmonary circulation. However, this belief appears to have been discounted.

Discrepant effects of histamine on the pulmonary circulation can be rationalized in terms of H_1 and H_2 receptors and their blocking agents: chlorpheniramine to block H_1 receptors selectively, metiamide to block H_2 receptors. The use of these agents suggests that pulmonary vasoconstriction is mediated by H_1 receptors and vasodilatation by H_2 receptors.

Serotonin

Interest in the effects of serotonin (5-hydroxytryptamine, 5-HT) on the pulmonary circulation was stimulated by reports that individuals who ingested appetite suppressants that interact with 5-HT are at increased risk of developing idiopathic pulmonary arterial hypertension (IPAH). The first reports, in the 1960s, related the appetite suppressant aminorex to an outbreak of IPAH; a subsequent report, in the 1980s, implicated fenfluramine in a similar role. These clinical observations were supported by the occurrence of pulmonary hypertension in fawn-hooded rats, which have an inherited defect in platelet storage. Fenfluramine, difenfluramine, and aminorex act by inhibiting serotonin reuptake, triggering 5-HT release and interacting with 5-HHT and 5-HT receptors. In addition to its vasomotor effects, 5-HT exerts mitogenic effects on smooth-muscle cells.

Serotonin occurs in the mast cells of some species but not others. It is synthesized in the enterochromaffin cells of the gut from dietary tryptophan. The serotonin released by these cells is largely removed by the liver, the excess being almost completely removed by the endothelial cells of the pulmonary circulation (Fig. 80-21). Any serotonin that escapes the metabolic machinery of the liver and lungs is stored as dense granules in circulating platelets. In addition to direct effects on vessels, airways, and platelets, serotonin enhances

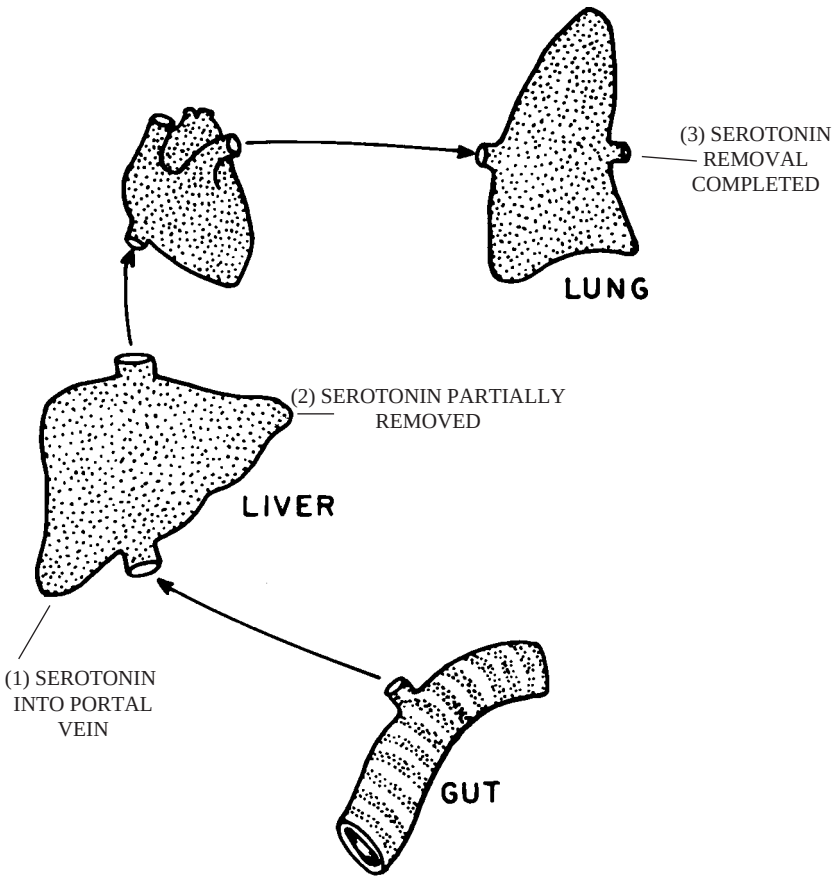

Figure 80-21 Handling of serotonin by the gut-liver-lung axis. During a single passage, serotonin is partly removed by the liver. Removal is completed by the lungs.

vasoconstriction and platelet aggregation produced by other vasoactive agents, such as norepinephrine and angiotensin II.

Two separate binding sites have been identified for serotonin: S_1 receptor binding sites that are labeled by serotonin and S_2 receptor binding sites that are labeled by serotonin antagonists (e.g., spiperone and ketanserin). The physiological and pharmacologic effects of serotonin (vasomotor activity, bronchoconstriction, platelet aggregation) appear to be related to the binding of serotonin to the S_2 receptor; no such effects have been attributed to binding to the S_1 receptor.

The distinction between S_1 receptors and S_2 receptors holds great promise for reexamining the role of serotonin in the bronchoconstriction and pulmonary vasoconstriction evoked by pulmonary embolism. In contrast to histamine, which seems to affect both pulmonary arterial and venous components, serotonin seems to constrict predominantly the precapillary vessels.

THE PULMONARY ARTERIAL MICROCIRCULATION IN GAS EXCHANGE

The pulmonary circulation is designed to operate in concert with alveolar ventilation for the sake of gas exchange. Certain aspects of this interplay warrant special mention: (1) the lungs receive the entire cardiac output; (2) the pulmonary blood flow is about the same as the alveolar ventilation; and (3) although the respiratory and circulatory processes are phasic, the rates are entirely different (i.e., about 15 breaths and 80 heartbeats per minute at rest). Therefore, matching of air and blood for optimal arterialization of mixed venous blood requires delicate tuning of operations that are not in phase, either at rest or during exercise; no vasomotor nerves or neurohumoral substances are at hand to make the speedy and fine adjustments of alveolar blood flow to alveolar ventilation.

Matching of air and blood for optimal gas exchange involves about 300 million alveoli that bear myriad capillary segments in their walls. The interposition of pulmonary capillaries between contiguous alveoli provides an enormous surface area for gas exchange, about 100 m^2 at rest, which increases further during exercise. The volume of blood in the capillaries at any one instance is approximately 100 to 200 ml, and red blood cells pass from one end of the gas-exchanging network to the other in about 0.75 s.

Four aspects of the distribution of the pulmonary circulation have attracted special attention with respect to gas exchange: (1) gas-exchanging vessels, (2) effects of gravity, (3) interplay among pressures influencing vascular calibers, and (4) effects of inflation.

Structure and Function of Intrapulmonary Vessels

Depending on the perivascular pressures to which they are exposed, three types of intrapulmonary vessels have been distinguished: alveolar, corner, and extra-alveolar (Fig. 80-22).

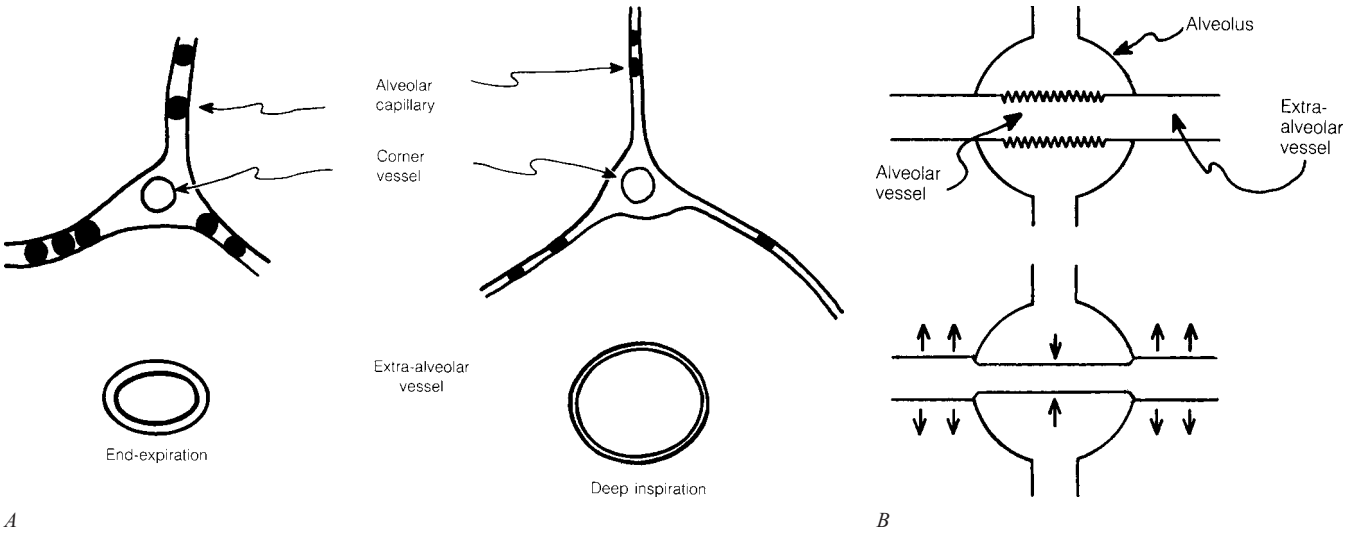

Figure 80-22 Schematic representation of the effects of a deep breath on the relative calibers of alveolar capillaries, "corner vessels," and extra-alveolar vessels. *Top:* At end-expiration, the alveolar capillaries (containing red cells) are wide-bored. The relative sizes of corner vessels and of extra-alveolar vessels are also shown. Deep inspiration narrows the alveolar vessels and widens extra-alveolar vessels, leaving inner vessels virtually unchanged in caliber. *Bottom:* The same phenomenon is shown for alveolar and extra-alveolar vessels. A = end-expiration; B = end-inspiration.

Alveolar Vessels

Alveolar vessels are capillaries that are contained within the walls that separate adjacent alveoli. They are surrounded by interstitium that varies in thickness and in the nature and content of cells, collagen, and elastic fibers. The appearance of the alveolar capillaries depends heavily on the route of fixation. Thus, fixation via the airways—which removes the surfactant lining—causes the capillaries to bulge into the alveoli, whereas fixation by perfusion—so that the lung remains air-filled—eliminates these deformations, widens capillaries unnaturally, and does away with alveolar pleats and folds. As the lung expands, alveolar walls unfold, and the connective-tissue elements surrounding them are rearranged. The calibers of the alveolar capillaries depend on the level of lung inflation, and they undergo compression (without change in wall thickness) when alveolar pressures increase. It is clear from the above that impressions of alveolar morphology are meaningful only when full account is taken not only of the route of fixation but also of the way in which the lung was handled during fixation.

As the lungs expand, largely because of the surfactant lining of the alveoli, the alveolar pericapillary pressure is less than the alveolar pressure but higher than the pressure surrounding extra-alveolar vessels. This difference between the interstitial pressures to which alveolar and extra-alveolar vessels are exposed is exaggerated at high levels of lung inflation.

Corner Vessels

Corner vessels (Fig. 80-22) are located at sites where three alveoli abut; there they are contained within pleats in the alveolar walls beneath sharp curvatures in the overlying alveolar film of surfactant. They are neither extra-alveolar vessels (see above)—in that they lack a surrounding sleeve of connective tissue—nor conventional components of the pulmonary microcirculation. Their location and anatomic arrangement within pleats seem to offer considerable protection against fluctuations in alveolar pressure. Indeed, blood flow persists in these vessels when alveolar pressure exceeds pulmonary arterial pressure by 10 cm H_2O. Originally pictured as arteriovenous anastomoses, they are now viewed as preferential channels through which blood flow continues in the face of wide swings in alveolar pressure.

Extra-Alveolar Vessels

Extra-alveolar vessels are, by definition, small vessels that are not affected by changes in alveolar pressure but do enlarge during lung inflation (Fig. 80-22). The definition is far more precise for physiologists than for anatomists, since the designation *extra-alveolar vessel* appears to include diverse components of the pulmonary microcirculation—notably veins, venules, arteries, and precapillaries.

Despite the morphologic diversity, the key to the physiological behavior of the extra-alveolar vessels appears to be the connective-tissue sheath that they share. Surrounding the extra-alveolar vessels is an interstitial space that is bounded by extensions of the fascial sheaths that envelop the trachea and esophagus. Within the perivascular interstitial space lies loose areolar tissue, collagenous fibers, and lymph vessels that drain lymph from the lung parenchyma; in pulmonary edema, excess fluid (and protein) accumulates within this space. The sheaths extend farther peripherally along the pulmonary arteries than the bronchi; for pulmonary arteries, and probably for pulmonary veins, the perivascular sheaths continue peripherally to vessels on the order of 100 μm in diameter. Dilatation of extra-alveolar vessels during inflation is a consequence of a drop in the surrounding interstitial pressure.

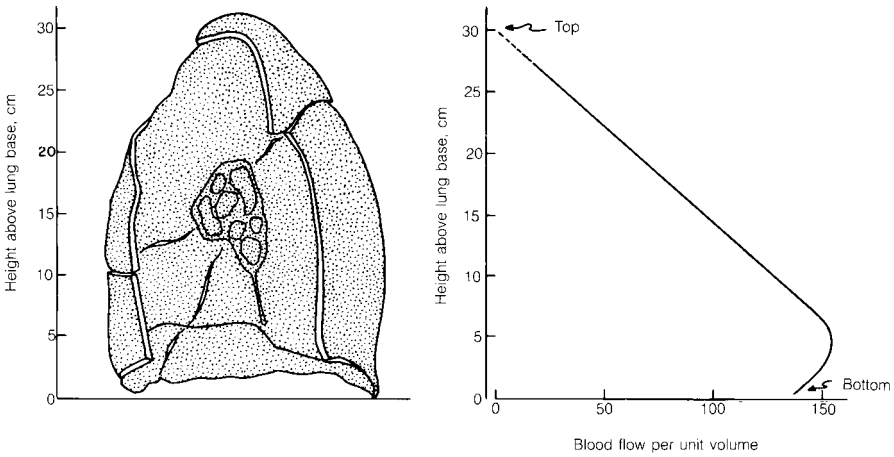

Figure 80-23 Blood flow in the upright lung as a function of vertical height. *(Based on data from Glazier JB, Hughes JMB, Maloney JE, et al: Measurements of capillary dimensions and blood volume in rapidly frozen lungs.* J Appl Physiol *26:65–76, 1969, with permission.)*

The degree to which extra-alveolar vessels widen during inflation depends on their initial calibers which, in turn, vary with lung volume. During deflation to levels below functional residual capacity (FRC), small arteries and veins tend to close, possibly because of inherent vascular tone abetted by alveolar hypoxia in the poorly expanded regions. At this time, the site of maximum resistance to blood flow shifts proximally in the arterial tree.

Effects of Gravity

A variety of techniques have been used to test the influence of gravity on the topographic distribution of blood delivered to the lungs. Among these have been the intravenous injection of a polysoluble gas (e.g., xenon), the inhalation of a very soluble gas (e.g., carbon dioxide), and the intravenous injection of microaggregated albumin, followed by radiographic determination of the distribution of radioactivity. Although interpretation of the results of these different methods is often complicated by individual peculiarities of the techniques, coupled with the different types of information that they provide, the results do suggest that in the upright lungs, blood flow decreases steadily from the bottom to the top (Fig. 80-23), that gravity is the compelling force, and that there is an interplay among pulmonary arterial, alveolar, and pulmonary venous pressures. As a consequence of these influences, in a relaxed, seated subject—particularly one with an elongated thorax—the apices are apt to be poorly perfused, especially in states of pulmonary hypotension or increased alveolar pressure.

Interplay among Pressures Influencing Vascular Calibers

In 1960, Banister and Torrance, in West, demonstrated that the level of alveolar pressure could influence pressure-flow relationships in the pulmonary circulation and drew an analogy between the behavior of the pulmonary arterial, pulmonary venous, and alveolar pressures and that of a Starling resistor (Fig. 80-24). The crucial point of their demonstration was that when alveolar pressure (chamber pressure) exceeded venous (downstream) pressure, the driving pressure bee arterial minus alveolar pressure and not arterial minus venous pressure. Permutt and colleagues compared this behavior to that of a waterfall, where height does not influence the flow of water over its brink.

Zones of the Lungs

Recognition of the effects of alveolar pressure on pressure-flow relationships in the pulmonary circulation, coupled with the formulation of the behavior of pulmonary microvessels in terms of the Starling resistor, paved the way for a model of the topographic distribution of blood flow in the lungs under the influence of gravity. As a result, it is now common to use "zones" of blood flow in the lungs as operative shorthand for specifying the interplay of pulmonary arterial, alveolar, and pulmonary venous pressures (Fig. 80-25).

In the normal, upright lung (estimated height of 25 cm at FRC), about 15 cm is above the left atrium and about 10 cm is below. Assuming that the mean pulmonary arterial pressure

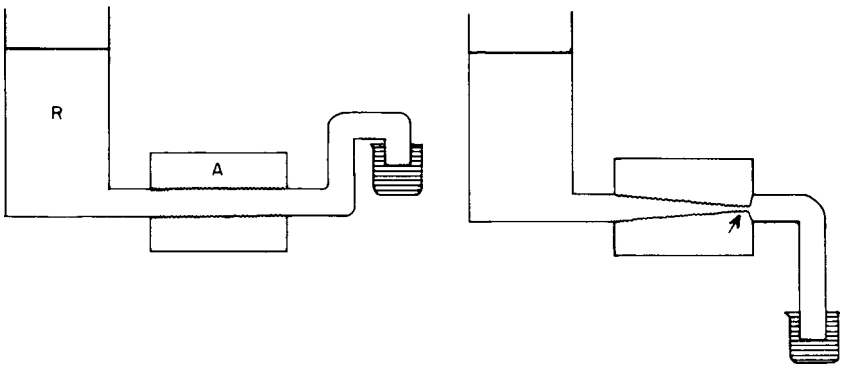

Figure 80-24 Principle of a Starling resistor. Thin-walled collapsible tube traverses a closed chamber (*A*) in which pressure can be varied at will. Fluid flows from reservoir (*R*) into collecting vessel (striped area), traversing collapsible tube en route. When outflow pressure exceeds chamber pressure (left), flow is determined by difference between inflow and outflow pressure. However, when chamber pressure exceeds outflow pressure, so that collapsible tube closes (arrow), flow is determined by difference between inflow and chamber pressure. *(From West JB, Dollery CT: Distribution of blood flow and the pressure-flow relations of the whole lung:* J Appl Physiol *20:175, 1965, with permission.)*

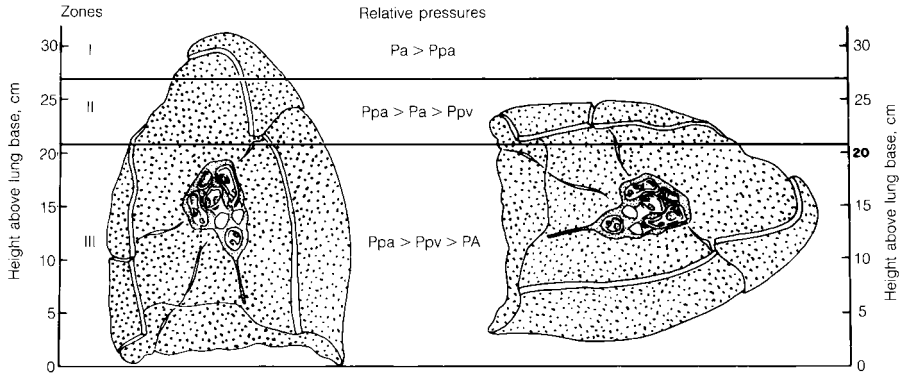

Figure 80-25 Zones of the lung. Topographic distribution of pulmonary blood flow according to relationship among pulmonary arterial pressure (Ppa), pulmonary venous pressure (Ppv), and alveolar pressure (P_A). Because of effect of surface tension, P_A is more accurately pericapillary pressure. Zone 1 (apex): P_A > Ppa > Ppv. There is no flow (except through corner vessels) because collapsible vessels close when pericapillary pressure exceeds the pressure inside the vessels. Vessels that close are capillaries and other alveolar vessels up to ~30 μm in diameter. Zone 2: Ppa > P_A > Ppv. Driving pressure is Ppa – P_A. This difference increases down lung, and so does flow. Zone 3: Ppa > Ppv > P_A. Driving pressure is Ppa – Ppv. Although Ppa – Ppv does not change down lung, Ppa and Ppv continue to increase from top to bottom. Flow down zone 3 is less than in zone 2. Zone 4 (appears at residual volume): This region of decreased flow appears during forced exhalation and has been attributed to either an increase in interstitial pressure at lung bases or closure of small airways at low lung volumes as the increase in P_A creates either zone 1 or zone 2 conditions. *(From West JB, Dollery CT: Distribution of blood flow and the pressure-flow relations of the whole lung:* J Appl Physiol *20:175, 1965, with permission.)*

measured at the level of the left atrium is around 15 cm H_2O and that left atrial pressure is about 7 cm H_2O, the top few centimeters of the lung will be hypoperfused during most of the cardiac cycle, except for flushes of blood during the peak ejection phase of systole. This zone has been designated as zone 1. In the next-lower zone (zone 2), blood flow increases regularly with distance down the lung. Below zone 2 is another zone of increasing blood flow, zone 3. Finally, a zone 4 may exist near the base; in this zone, blood flow decreases instead of increases. In this zone, although most alveolar capillaries appear to be attenuated or collapsed, extra-alveolar vessels in the alveolar corners often remain open, once again emphasizing that the extra-alveolar vessels are exposed to different forces than are the alveolar vessels. As noted previously, persistence of blood flow through parts of zone 1 presumably occurs via (corner) vessels.

Zone 1

In the vertical lung, blood flow in zone 1, where alveolar pressure exceeds arterial pressure (P_A > Ppa), is minimal (Fig. 80-25).

The apices of upright lungs would be deprived of pulmonary blood flow were it not for the pulsatility of pulmonary arterial blood flow; a flush of blood during systole perfuses the apices even though mean pulmonary arterial pressure is too low to sustain blood flow to the apices.

Zone 2

In zone 2, pulmonary arterial pressure exceeds alveolar pressure which, in turn, exceeds pulmonary venous pressure (Ppa > P_A > Ppv) (Fig. 80-25). In this constellation of pressures, blood flow is no longer determined by the usual pressure drop across the pulmonary circulation. Instead, the outflow pressure is alveolar pressure and the driving force is the pulmonary arterial-alveolar pressure difference. This hemodynamic situation, in which flow is independent of downstream pressure, has been likened to a "vascular waterfall."

Under the influence of gravity, the pulmonary arterial pressure increases by about 1 cm H_2O per centimeter of distance down the lung, whereas alveolar pressure remains unchanged; the driving pressure and, therefore, the blood flow increase down the zone. Changing relationships between alveolar and luminal pressures then shift outflow pressures from alveolar to pulmonary venous and then back. Flow through the capillaries of zone 2 is pictured as intermittent, as through "sluice gates" that open when pulmonary venous pressures exceed alveolar pressures and close when alveolar pressures exceed pulmonary venous pressures.

Zone 3

It is only in this zone that conventional calculations of PVR are valid: since pulmonary venous pressure is greater than alveolar pressure (Ppa > Ppv > P_A), blood flow is determined by the arteriovenous difference in pressure (since both exceed alveolar pressure) (Fig. 80-25). Resistance to blood flow in zone 3 is less than in zone 2. The driving pressure here remains fixed down to the bottom of the lung because the effect of gravity causes arterial and venous pressures to decrease equally per centimeter of distance as the lung base is approached. Despite the constant driving pressure, flow increases toward the bottom of the lung as resistance decreases. In contrast to zone 2, where the increase in blood flow from top to bottom of the zone is predominantly due to recruitment of vessels that were previously closed in zone 3, a comparable increase in blood flow is effected largely by distention of patient microvessels (i.e., capillaries).

Zone 4

The upright lung includes in its most dependent part, where vascular pressures are highest, an area of decreased blood flow (Fig. 80-23). The zone of reduced flow (zone 4) disappears on deep inflation. This paradox of high vascular pressures and low blood flow is not explicable in terms of the three-zone model, in which pulmonary arterial and pulmonary venous pressures are related to alveolar pressures in predicting distribution of blood flow. The mechanism is believed to reside in the extra-alveolar rather than in the alveolar vessels. Indeed, at residual volume, owing to the increase in perivascular pressure and mechanical distortion of extra-alveolar vessels, the distribution of blood flow throughout the lung is attributable to extra-alveolar vessels.

It is worth emphasizing that zones are a functional rather than an anatomic concept; instead of being fixed topographically, they vary in vertical height according to shifts in the relationships between pulmonary arterial, pulmonary venous, and alveolar pressures. For example, positive-pressure breathing enlarges zone 2 at the expense of zone 3, and zone 1 at the expense of zone 2. Awareness of the functional nature of these relationships affects the interpretation of changes in calculated PVR; for vessels in zone 2, because alveolar pressure rather than pulmonary venous pressure is the outlet pressure, the conventional calculation of PVR is meaningless; oppositely, for vessels in zone 3, the calculation is meaningful because pulmonary venous pressure rather than alveolar pressure determines the quantity of blood flow.

A change in body position reorients the zones of the lungs. For example, the supine position places more of the lung in zone 3 and virtually eliminates zone 1 (Fig. 80-25).

Effects of Inflation

It was pointed out above ("Pulmonary Vascular Resistance") that at either very high or low levels of lung inflation—no matter how accomplished—PVR increases. Inflation of the collapsed, isolated lung with *negative pressure* first *decreases* resistance and then *increases* resistance as high levels of inflation are reached. These observations can be reconciled by attributing the *high resistance* at high levels of inflation (alveolar pressure held constant) to narrowing of alveolar capillaries and the *high resistance* during lung collapse to closure, narrowing, and kinking of alveolar capillaries and extra-alveolar vessels.

Distention and Recruitment

The extent of the alveolar capillary network is quite variable, and the number, size, and shape of the open capillaries depend on the method of fixation for histological examination as well as on the experimental circumstances. But some uncertainty still persists about the relative roles played by recruitment (opening of new capillaries) or distention (increase in the caliber of patient capillaries) in enlarging the capillary network.

Not very long ago, pulmonary capillary distention was discounted, largely on the basis of extrapolation from the behavior of systemic capillaries. However, attempts to draw analogy between the distensibility of systemic and pulmonary capillaries appear predestined to fail because pulmonary capillaries are suspended in a sea of air and not embedded in tissue. Indeed, it has now been amply shown that pulmonary vascular calibers do increase appreciably as transmural pressures are raised. But it has also become evident that the relationship between vascular calibers and transmural pressure is far from simple. Moreover, there is no consensus about the extent to which the alveolar capillary bed is distensible.

How recruitment is affected remains unsettled. When blood flow is minimal (as in zone 1), only a few capillaries are open; these are predominantly "corner vessels" lodged within septal pleats. As transmural pressures increase, the extent of the open capillary bed enlarges, primarily by recruitment in zone 2 and by dilatation in zone 3. Some believe that as pulmonary arterial pressure increases, critical opening pressures of different arterioles are successively overcome to open new arteriolar domains to blood flow. Others favor the view that capillaries control their own destinies—i.e., that capillaries per se, rather than arterioles, are responsible for opening new portions of the capillary bed, and that both distensibility and recruitment occur at the capillary level.

Despite lingering doubts about the mechanisms at work in the operation of recruitment and distensibility under different conditions, a few generalizations can be made: (1) pulmonary capillaries are more distensible than systemic capillaries, presumably owing to the lack of supporting connective tissue in the lung; (2) both recruitment and distensibility are more affected by changes in pulmonary arterial than in pulmonary venous pressure; and (3) recruitment is the predominant mechanism for enlarging the capillary bed in the apices of the lungs in response to pulsatile flow, whereas recruitment and distensibility probably both contribute—although to different degrees, depending on the circumstances—in the more dependent parts of the lungs.

THE BRONCHIAL CIRCULATION

Although popular usage has firmly entrenched the designation *bronchial,* the term is inadequate on two accounts: (1) the systemic blood supply to the lungs originates not only from bronchial arteries but also from the aorta and other intrathoracic arteries, and (2) the systemic arterial blood is delivered not only to the walls of the bronchi but also to the adventitia or large vessels and structures of the lungs.

In the normal lung, the bronchial circulation has the features of a nutrient circulation: it is modest in size (1 to 2 percent of the cardiac output), carries arterialized blood, and is distributed primarily to the airways, blood vessels, and supporting structures of the lungs up to the respiratory bronchioles. Beyond this point, the pulmonary circulation takes over as the nutrient circulation. One likely function of the bronchial circulation is to air-condition the inspired air. For example, the disposition and architecture of the submucosal bronchial venous plexus seem to constitute an anatomic arrangement that could properly adjust the temperature and

water content of air passing to and fro in the airways. The nutrient function also comes into play in lung transplantation, where survival of the graft depends critically on an adequate blood supply.

Venous return from the bronchial circulation is via either bronchial or pulmonary veins. From the hilar structures and large bronchi, bronchial venous blood is returned to the right atrium via systemic veins; from more peripheral airways and the substance of the lung, bronchial venous blood is returned to the left atrium by two routes: via bronchopulmonary capillary anastomoses and by "bronchopulmonary veins" that connect bronchial capillaries to small pulmonary veins. The direction taken by bronchial venous outflow is determined by the relative pressures at the outlet of the two systems. For example, an increase in left atrial pressure detours bronchial venous drainage toward the right, rather than the left, atrium. In some animals, functioning communications exist not only between the bronchial and pulmonary capillary circulations but also between the bronchial arteries and other systemic arteries.

Certain features of the bronchial circulation merit special attention: (1) although difficult to demonstrate and of doubtful functional significance, microscopic anastomoses between bronchial and pulmonary arteries do appear to exist at the precapillary level in the normal lung; (2) the bronchial arteries proliferate remarkably in certain types of lung disease, liver disease, and congenital heart disease, often in association with clubbing of the digits; (3) the mechanisms responsible for the proliferation of the bronchial circulation are unclear, but certain influences, such as cortisone, retard its expansion, whereas growth hormone stimulates it; (4) the bronchial veins in the submucosa of the airways form a large plexus that runs the entire length of the tracheobronchial tree, sending off communicating branches to a corresponding venous plexus on the other side of the tracheal muscle; (5) the bronchial venules respond to certain vasoactive agents, notably histamine and bradykinin, as do other systemic venules; and (6) the bronchial venous circulation is involved in the pathogenesis of experimental pulmonary edema produced in the dog and sheep by histamine, endotoxin, and bradykinin.

The Bronchial Circulation in Disease

In the normal lung, the minute bronchial circulation operates covertly. But if the pulmonary circulation to an area is compromised or lost—as by ligation or an embolus—the bronchial circulation proliferates far beyond local metabolic need for viability and function (Fig. 80-26). The stimulus for proliferation is unclear. Expansion of the bronchial arterial circulation is clinically marked in two major categories of disease: (1) those producing severe curtailment of pulmonary atresia and (2) a chronic inflammatory bronchopulmonary process, such as bronchiectasis, old inflammatory cavities, chronic lung abscess, and lung cancer. Because clubbing of the digits, occasionally accompanied by hypertrophic osteoarthropathy, is also common in these disorders, question is often raised about the relationship between clubbing of the digits and expansion of the collateral circulation to the

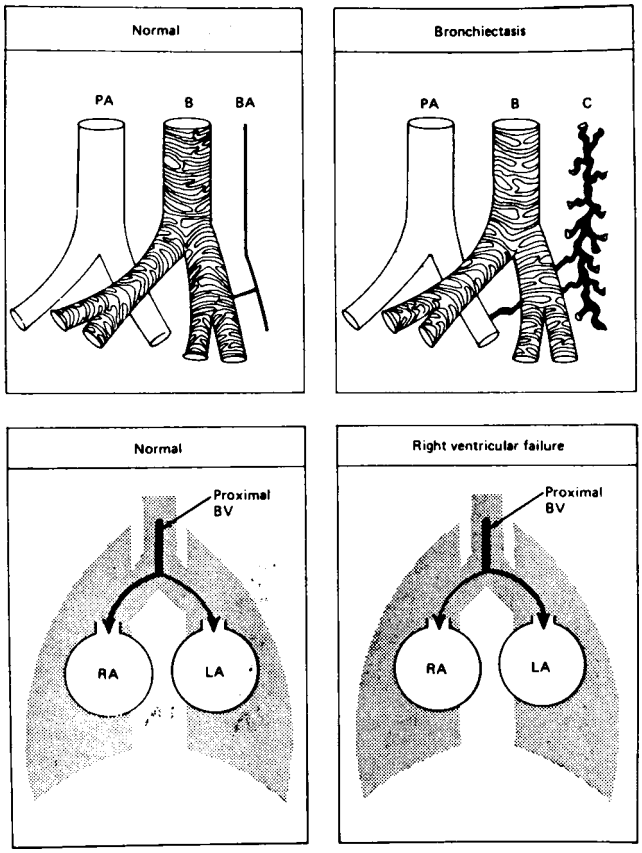

Figure 80-26 Schematic representations of bronchial circulation in bronchiectasis and right ventricular failure. *Top:* Bronchial arteries (BA). In chronic suppurative diseases of the lungs, bronchial arteries undergo considerable proliferation. *Bottom:* Bronchial veins (BV). Proximal bronchial veins drain into either the right atrium (RA) or left atrium (LA), depending on pressure levels in these two cardiac chambers. Normally most bronchial venous outflow from the lungs enters the right atrium (thicker curved arrow). However, in right ventricular failure, bronchial venous drainage to the left atrium increases.

lungs. In contrast to the disorders of the lungs associated with bronchial arterial blood is chronic mitral stenosis, in which hemoptysis usually originates from bronchial veins underlying the tracheobronchial mucosa.

An expanded bronchial arterial circulation can also constitute a hemodynamic burden (a left-to-right shunt). But rarely, as in widespread bronchiectasis, do the connections between the bronchial and pulmonary arteries enlarge sufficiently to cause cardiac embarrassment. If a wedged pulmonary arterial catheter lodges in the vicinity of bronchopulmonary arterial anastomoses, the pulmonary-wedge pressure is apt to be misleading.

As noted above, bronchial venous blood that drains into the left atrium contributes to anatomic venous admixture. Another source of anatomic venous admixture occurs in some patients with cirrhosis of the liver, in whom abnormal anatomic connections allow the passage of portal venous blood into the pulmonary venous system. Occasionally, in a patient with hepatic cirrhosis, the portal-pulmonary blood flow becomes quite extensive (about 5

to 15 percent of the cardiac output). These anastomotic channels occasionally enlarge sufficiently to be demonstrable during life with use of indicators or angiography. More often, the quantity of blood shunted from the portal to pulmonary venous system is too small to be measured reliably.

Since primary carcinoma of the lungs often receives much of its blood supply from systemic arteries, particularly if the neoplasm obstructs blood flow to the pulmonary artery, attempts have been made to deliver chemotherapeutic agents to the cancerous site via a bronchial artery. This approach has proved ineffective. Also, in patients in whom life-threatening hemoptysis complicates a carcinoma of the lungs, particulate matter has been injected as bronchial arterial emboli in the hope of occluding the feeder bronchial artery. Unfortunately, selective embolization is, at best, only transiently effective.

THE FETAL AND NEONATAL PULMONARY CIRCULATIONS

Before birth, the lungs play no role in gas exchange; this function is served by the placenta. For the sake of their nutrition and role as a metabolic organ, the lungs are provided with a modest blood flow, and most of the blood returning to the right side of the heart is directed toward the systemic circulation via the foramen ovale and ductus arteriosus. As a result of this diversion, the lungs before birth receive about 10 to 15 percent of the right ventricular output. After birth, as the lungs assume gas-exchanging functions and fetal connections close, the entire output of the right ventricle perfuses the lungs.

In the fetus approaching term, pulmonary arterial and aortic pressure levels are virtually identical; during gestation, blood pressures in both circuits increase in parallel, while pulmonary blood flow increases dramatically. At the same time, PVR decreases progressively as the number of minute vessels increases.

Near term, the small muscular arteries, which constitute the "resistance" vessels, are well endowed with smooth muscle. After birth, the media of the small muscular arteries regress rapidly. However, prolonging hypoxia, as by exposing the newborn to a continued decrease in inspired Po_2 for 2 weeks, not only retards the normal involution of pulmonary vascular smooth muscle but also leads to the development of new muscle in peripheral precapillary vessels that would otherwise be expected to be devoid of muscle.

Regulation of the Fetal Pulmonary Circulation

Compared to the adult pulmonary circulation, the fetal circulation affords much more vascular resistance, a higher initial tone, and, as has been noted above, a greater vascular reactivity; reactivity increases with gestational age. Also, in contrast to the adult pulmonary circulation, the fetal pulmonary circulation manifests a considerable reactive hyperemia.

The three categories of endothelial-derived substances (prostaglandins, endothelins, and NO) play an important role in regulating fetal and transitional pulmonary vascular tone. Disturbances in their interplay may culminate in persistent pulmonary hypertension of the newborn. It seems likely, however, that other mediators as well as abnormal developmental changes, entailing growth of vascular smooth muscle and the extracellular matrix, are involved in failure after birth of normal involution of the fetal circulation.

Postnatal Pulmonary Vasodilation

Ventilation of the lungs with air causes a marked drop in PVR. Two factors are concerned: predominant is the increase in Po_2; a much lesser role is played by physical expansion of the lungs. The mechanism by which relief of hypoxia exerts its vasodilator effect in the fetus is not settled. However, the prostaglandins seem to play a key role. This prospect stems from two types of observations: (1) distention of the lungs of adult animals results in the release of prostaglandins, particularly those of the E series; and (2) indomethacin blunts the continued drop in PVR that would be expected to continue for 10 to 20 min after the initial fall. Moreover, in the fetus, prostaglandin synthetase inhibitors enhance the pulmonary pressor response to acute hypoxia. The role of other vasodilators (e.g., NO) remains to be defined.

Attention has been called repeatedly in this section to the marked reactivity of the fetal pulmonary circulation. The purposes served by the marked pulmonary vasoreactivity are not certain. But since the increase in fetal PVR does direct the bulk of the pulmonary arterial inflow to the placenta, brain, and myocardium, the capability for marked pulmonary vasodilatation may be importantly involved in the circulatory rearrangements after birth.

Fetal hypoxia, no matter how induced, elicits intense pulmonary vasoconstriction. The magnitude of the response increases as gestation advances, consistent with the idea that pulmonary vascular smooth muscle grows increasingly responsive to hypoxia as gestation advances. In contrast to that in the adult, the sympathetic nervous system contributes significantly to initial tone and to the pressor response to acute hypoxia. As in the adult, acidosis elicits pulmonary vasoconstriction and greatly enhances the pulmonary pressor response to acute hypoxia; the more severe the acidosis, the greater the pressor and enhancing effects.

The Ductus Arteriosus

Despite its embryologic origin (as the distal segment of the left sixth aortic arch) and its location as a bridge between the pulmonary artery and the descending aorta, the ductus arteriosus leads a vasomotor life of its own, independent of the two circulations that it bridges (Fig. 80-27). For example, immediately after birth (i.e., at the switch from the hypoxic

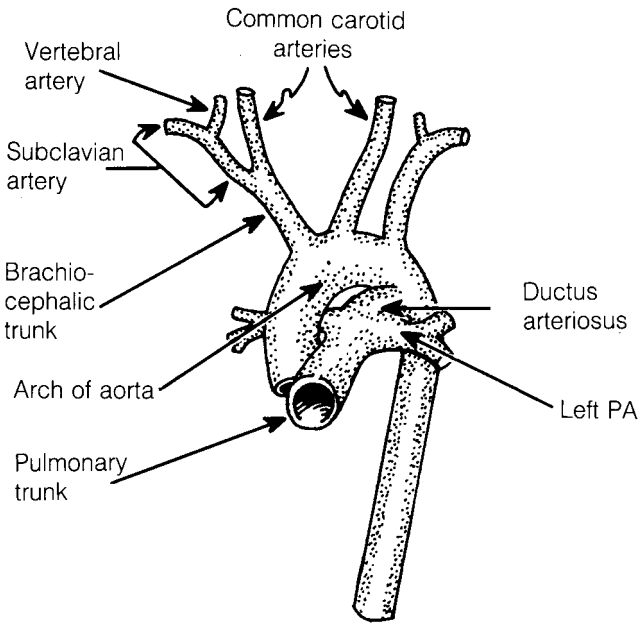

Figure 80-27 Relationship between ductus arteriosus and systemic vessels and the aorta. Acute hypoxia constricts pulmonary arteries but dilates the ductus arteriosus and systemic arteries.

environment in utero to the air-filled, oxygen-rich environment of independent neonatal life), the ductus arteriosus contracts vigorously to the point of self-obliteration of its lumen; at the same time, the pulmonary circulation vasodilates.

Closure of the ductus arteriosus immediately after birth depends heavily on prostaglandins in its walls. Conversely, premature closure of the ductus arteriosus (i.e., before birth), as may be caused by transplacental passage of indomethacin taken by the mother, may either cause fetal pulmonary arterial hypertension or interfere with the morphologic development of the pulmonary vascular bed. The vasomotor responses of the ductus arteriosus to prostaglandins and to inhibitors of the cyclooxygenase pathway have been turned to clinical advantage: on the one hand, PGE_2 or PGE_1 has been used to maintain patency of the ductus arteriosus in newborns and in patients with congenital heart disease, who need continued communication between the pulmonary and systemic circulations; on the other hand, indomethacin, an inhibitor of the prostaglandin synthetase element of the cyclooxygenase pathway, has been used to promote closure of a persistent ductus arteriosus in premature infants.

ABNORMAL PULMONARY VASCULAR COMMUNICATIONS

Systemic Artery-Pulmonary Vascular Communications

Communications between a systemic artery and the pulmonary circulation may be acquired or congenital.

Acquired Communications

Acquired systemic artery-pulmonary communications are much more common than congenital communications. Most are traumatic or iatrogenic and hemodynamically constitute a left-to-right shunt between an intrathoracic systemic artery (coronary, intercostal, or internal mammary) and the pulmonary circulation. Because of the large pressure gradient, flow through such connections can be large, but rarely sufficient to cause left ventricular failure. The characteristic physical finding is a continuous murmur over the site of communication and radiographic evidence either of the vessels operative in the communication (e.g., enlarged pulmonary vessels) or of adjacent local effects (e.g., pleural thickening). Selective angiography reveals the nature of these communications. Rarely does cardiac overload due to left ventricular failure become manifest. Instead, most patients remain asymptomatic.

Other acquired systemic artery-pulmonary vascular communications may complicate intrathoracic neoplasms or chronic inflammatory disorders. Their predominant clinical importance lies in the risk of brisk bleeding. Bronchiectasis is the most common cause of bleeding from such communications. If extensive, bronchial artery-pulmonary arterial inflow may replace pulmonary arterial blood in perfusing an affected lobe or an entire lung.

Bronchopulmonary Sequestration

Bronchopulmonary sequestration refers to a part of the parenchyma of the lung that has either incomplete or no connection with the airways and is supplied by an aberrant artery from the aorta or one of its branches. Sequestrations are further categorized as either intra- or extralobar: *intralobar* sequestrations have the same pleural covering with the adjacent lung, whereas *extralobar* sequestrations have their own pleural lining (i.e., separate from that of adjacent lung tissue).

Embryology

Bronchopulmonary sequestrations are held to be developmental abnormalities of the embryonic foregut. In this respect, they resemble bronchogenic cysts. Sequestration is believed to begin in an accessory lung bud that originates distal to the normal lung bud. Whether the sequestration will be intralobar or extralobar appears to depend on the stage of embryologic development at which this anomaly occurs: if the accessory bud forms before the pleura is formed, the bud remains within the pleura and results in an intralobar sequestration; if it forms after the pleura has formed, it causes an extralobar sequestration that is covered by its own pleura. Both types of sequestrations, but particularly extralobar sequestrations, are often associated with other congenital anomalies of the foregut.

Clinical Manifestations

Bronchopulmonary sequestration is suspected in a patient with recurrent infiltrates about a single chronically affected

area containing cystic spaces in a basilar segment of a lower lobe. A clue to the diagnosis may be provided by the presence of a continuous bruit over the chest or axilla on the afflicted side due to shunting of blood from systemic artery to pulmonary vein in the intralobar sequestration.

CONGENITAL PULMONARY ARTERIOVENOUS COMMUNICATIONS

Congenital pulmonary arteriovenous communications between the pulmonary arteries and veins can occur as lesions confined to the lungs or as part of the entity *hereditary hemorrhagic telangiectasia* (Rendu-Osler-Weber disease). In hereditary hemorrhagic telangiectasia, about 15 percent of affected family members have pulmonary arteriovenous fistulas, although about 50 percent of patients with pulmonary arteriovenous fistulas have evidence of other mucocutaneous telangiectases or a family history of hereditary hemorrhagic telangiectasis.

Pulmonary arteriovenous fistulas are local lesions that do not disturb the adjacent pulmonary tissue (i.e., there is no associated atelectasis, bronchiectasis, or pneumonia). Generally, the pulmonary artery supplies all the afferent blood, although occasionally, when it occurs in association with hereditary hemorrhagic telangiectasia, some of the afferent supply may be from a bronchial artery or from other systemic arteries. The lesions are multiple in one-third of the cases and are most frequently found in the lower lobes adjacent to the visceral pleura, although they can also be deep in the parenchyma.

Grossly, the lesions appear as thin-walled aneurysmal sacs connecting the artery and the vein. Thrombotic masses may be present within the aneurysmal sac. Microscopically, the sac walls contain various amounts of muscle, fibrous tissues, and occasionally small amounts of calcium.

The pulmonary arteriovenous fistulas act as bypass routes, allowing mixed venous blood to escape arterialization in the lungs. Despite the hypoxic stimulus, pulmonary hypertension has not occurred; however, the chronic arterial hypoxemia does evoke erythrocytosis and polycythemia.

Clinical Manifestations

Most patients with pulmonary arteriovenous fistulas are asymptomatic and come to medical attention because of an abnormal shadow found on routine radiography; some complain of dyspnea. Epistaxis is present in 50 percent of patients, usually in association with hereditary hemorrhagic telangiectasia. These patients may also have gastrointestinal bleeding, strokes, brain abscesses, or seizures. Most cases are diagnosed in the third or fourth decade of life.

On physical examination, the relatively few patients with dyspnea usually are cyanotic and clubbed. One-third of all patients with pulmonary arteriovenous fistulas also have mucocutaneous telangiectases. A characteristic feature of pulmonary arteriovenous fistula is an extracardiac murmur or bruit. Because pulmonary blood flow increases during inspiration, the intensity of the murmur increases during inspiration and decreases during expiration. Similarly, the Valsalva maneuver, by transiently decreasing pulmonary blood flow, decreases flow through the fistula and decreases or eliminates the murmur. As expected, the Müller maneuver (forced inspiration with a closed glottis after full expiration) does the opposite (i.e., increases the murmur). Occasionally, for unexplained reasons, the murmur may be atypical and either increase with expiration or be heard only during diastole.

The most important laboratory examination is chest radiography. A solitary fistula takes the form of a coin lesion or a bunch of grapes in the peripheral lung fields (Fig. 80-28). Fewer than 5 percent of pulmonary arteriovenous fistulas contain calcium demonstrable by radiography. Usually, feeding and draining vessels connect the lesion to the hilus. Tomography is useful in demonstrating the continuity of the hilar vessels and the fistula. Fluoroscopy usually demonstrates the pulsating nature of the mass. Angiography is not usually needed to make the diagnosis, but it can be used to demonstrate the vascular nature of the lesion and to determine the exact number of fistulas present. Patients with a significant shunt will have a secondary polycythemia, although if there has been significant bleeding, some patients may actually be anemic. The arterial P_{O2} is invariably decreased and does not increase appreciably with 100 percent O_2.

Local complications of pulmonary arteriovenous fistulas are due to rupture of the aneurysmal sacs, with bleeding either into the bronchi, causing hemoptysis, or into the pleura, where it produces a hemothorax. Thrombosis within the pulmonary arteriovenous fistula is common and is occasionally the cause of bland and septic emboli to the central nervous system. Strokes and seizures may result from telangiectases in the central nervous system.

Differential Diagnosis

The radiographic shadows may simulate bronchiectasis, tuberculosis, or other granulomatous disease, solitary pulmonary nodules, or metastatic carcinoma. The murmur or bruit must be differentiated from valvular or congenital heart disease. The cause of the cyanosis may erroneously be attributed to congenital heart disease. The normal white blood count, platelets, and spleen help to identify the polycythemia as secondary to hypoxia and not to polycythemia vera.

Treatment

The only available treatment for pulmonary arteriovenous fistulas is excision. Because of the vascular nature of the lesion, wedge resection and lobectomy have been the procedures of choice. Since adjacent lung parenchyma is normal, an attempt is made to preserve as much lung as possible. However, because as many as one-third of the patients have

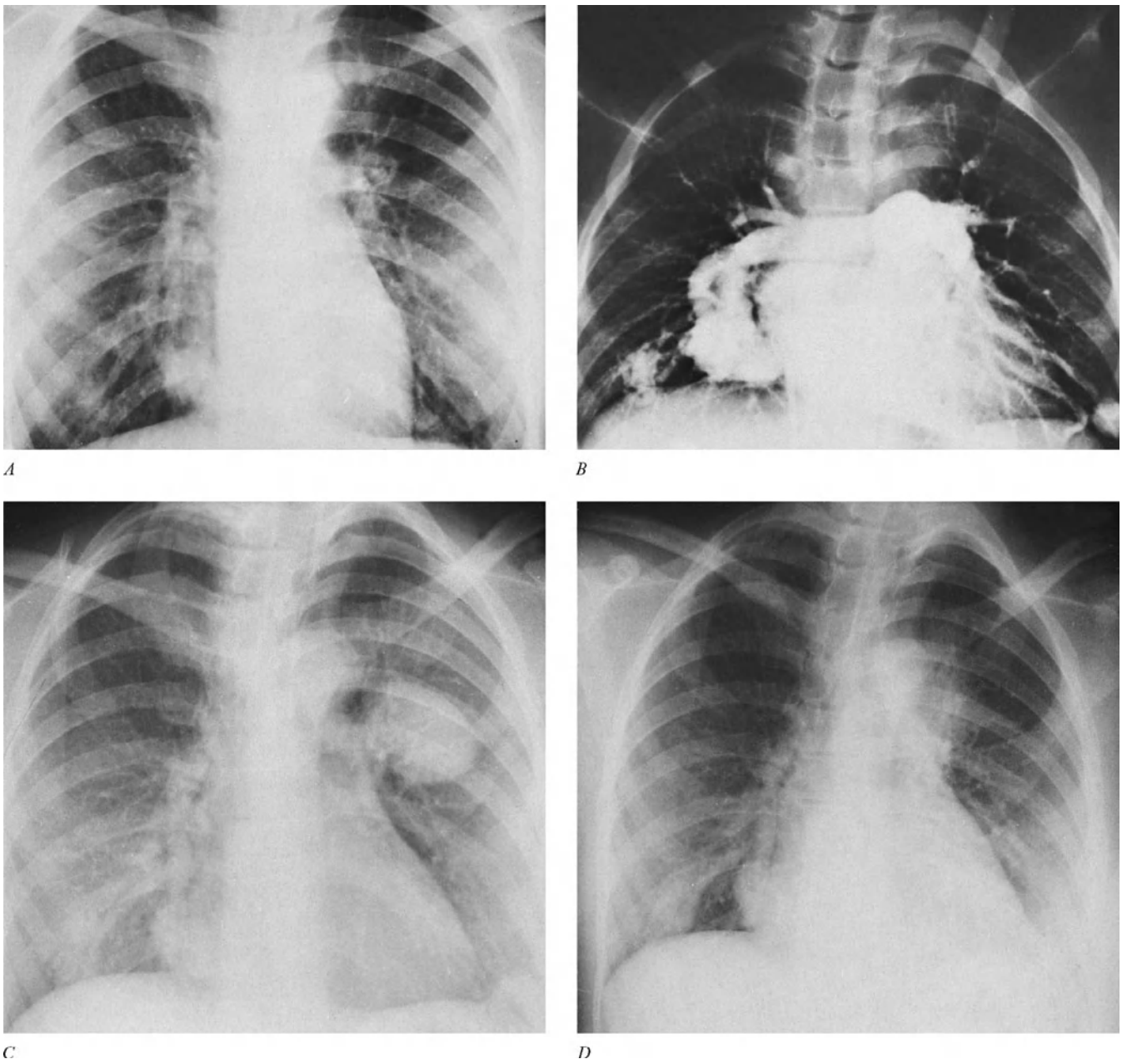

Figure 80-28 Pulmonary arteriovenous fistulas in a pregnant 24-year-old woman with hereditary hemorrhagic telangiectasia. *A*. Before pregnancy. Small, nodular densities are seen at both bases and in the left hilus. The shunt was estimated to be 49 percent of the cardiac output. *B*. Arteriogram before pregnancy, demonstrating arteriovenous fistulas of both lower lobes. *C*. Seven months pregnant, the patient was admitted to the hospital with hemoptysis and left hemothorax. The enlargement of the arteriovenous fistulas is striking. The pregnancy was terminated. *D*. Two weeks after termination of pregnancy. The nodular densities have decreased in size. *(Courtesy of M. Rossman.)*

multiple fistulas, recurrence is possible after surgery. Therefore, in all patients with cyanosis and polycythemia, hemoptysis, or rapidly increasing lesions for whom surgery is considered, preoperative pulmonary arteriogram is necessary so that all the fistulas can be identified. Generally, all symptoms due to the pulmonary arteriovenous fistulas are reversed if surgery is successful.

Prognosis

Because the anomaly is uncommon, the natural history is not well understood. Whereas some pulmonary lesions enlarge rapidly, others remain stable or enlarge slightly over a period of years. Serious complications are just as likely to be pulmonary (hemoptysis or hemothorax in about 10 percent) as neurologic (about 10 percent).

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81

Pulmonary Hypertension and Cor Pulmonale

Darren B. Taichman • Alfred P. Fishman

GENERAL ASPECTS

Pulmonary Hypertension

Pulmonary hypertension is defined as a mean pulmonary artery pressure greater than 25 mmHg at rest, or greater than 30 mmHg with exercise. Pulmonary hypertension can be due to diseases predominantly confined to the pulmonary vasculature, as in pulmonary *arterial* hypertension, or can occur in association with diseases in which the primary disturbance is in respiratory function or in the left heart. Disturbances of respiratory function that cause pulmonary hypertension include parenchymal lung diseases that impair gas exchange and elicit chronic hypoxia (e.g., chronic obstructive pulmonary disease or idiopathic pulmonary fibrosis) and impaired movement of air due to processes outside of the lungs (e.g., impairment of the respiratory muscles or the drive to breathe). Examples of cardiac dysfunction that result in pulmonary hypertension include left ventricular failure due to ischemic cardiomyopathy or mitral valvular stenosis. The generally accepted definition of *pulmonary arterial hypertension* calls for a mean pulmonary arterial pressure greater than 25 mmHg at rest or 30 mmHg with exercise, a pulmonary capillary occlusion pressure or left ventricular end diastolic pressure that is less than

15 mmHg, and an increase in pulmonary vascular resistance greater than 3 Wood units (240 dynes/sec/cm^{-5}) without significant respiratory or cardiac dysfunction. When the primary pathophysiological derangement appears to originate within the pulmonary circulation without an identifiable risk factor, *idiopathic pulmonary arterial hypertension* (IPAH) is considered to be present.

Cor Pulmonale

Cor pulmonale is an enlargement of the right ventricle due to derangements in the structure or function of the respiratory system (Fig. 81-1). The enlargement may represent hypertrophy or dilation or both. It results from an increase in afterload imposed by pulmonary hypertension. The frequency of cor pulmonale is linked to the diseases that cause pulmonary hypertension (e.g., chronic obstructive pulmonary disease, interstitial lung diseases, sleep-disordered breathing). Cor pulmonale accounts for as many as 20 percent of hospital admissions for heart failure and for a significant proportion of all cardiac disease.[1] It may occur acutely, following a pulmonary embolus or an acute exacerbation of chronic obstructive pulmonary disease. Cor pulmonale may reverse readily after treatment of the precipitating problem.

Cor pulmonale is a complication of pulmonary hypertension. Treatment is directed at the process that caused the pulmonary hypertension.

CLASSIFICATION OF THE PULMONARY HYPERTENSIVE DISEASES

Table 81-1 presents a current clinical classification of the pulmonary hypertensive diseases. This classification has evolved over the years. In the current classification, the group of patients formerly designated as "primary pulmonary hypertension" is demarcated from the group with known causes (e.g., due to chronic disease of the left heart or to hypoxic pulmonary disease).

Sclerosis of the pulmonary arteries *(Uber sklerose der lungen arterie)* without identifiable cause was first described by Ernst von Romberg in 1891.[2] Thereafter, until the 1950s, when cardiac catheterization was widely adopted for hemodynamic studies, Dresdale, Schultz, and Michtom described a hypertensive vasculopathy of the pulmonary circulation that involved pulmonary vasoconstriction, high pulmonary arterial pressures, and a pulmonary vasodilator response to injection of an agent that had been used as a systemic vasodilator (tolazoline).[3] No cause for the pulmonary hypertension could be identified and the term primary pulmonary hypertension (PPH) was coined.

Subsequent classifications schemes for diseases causing pulmonary hypertension have been adopted by international consensus panels. Current classifications have evolved from systems based primarily on histopathological findings to a model that relies on hemodynamic and clinical characteristics (Table 81-1).

In this classification, the group of patients with pulmonary arterial hypertension (PAH) is separate from the group with known causes of pulmonary hypertension (e.g., due to chronic left heart or respiratory disease and hypoxia). This grouping recognizes similarities in the histological and many clinical features of patients with identifiable genetic causes of PAH (i.e., those with familial PAH), collagen vascular or other diseases known to be associated with PAH (associated PAH), and patients in whom no known associated entity or genetic cause has been found. This last group is referred to as having idiopathic PAH (IPAH), in place of the previously (and often loosely) used term primary pulmonary hypertension (PPH).

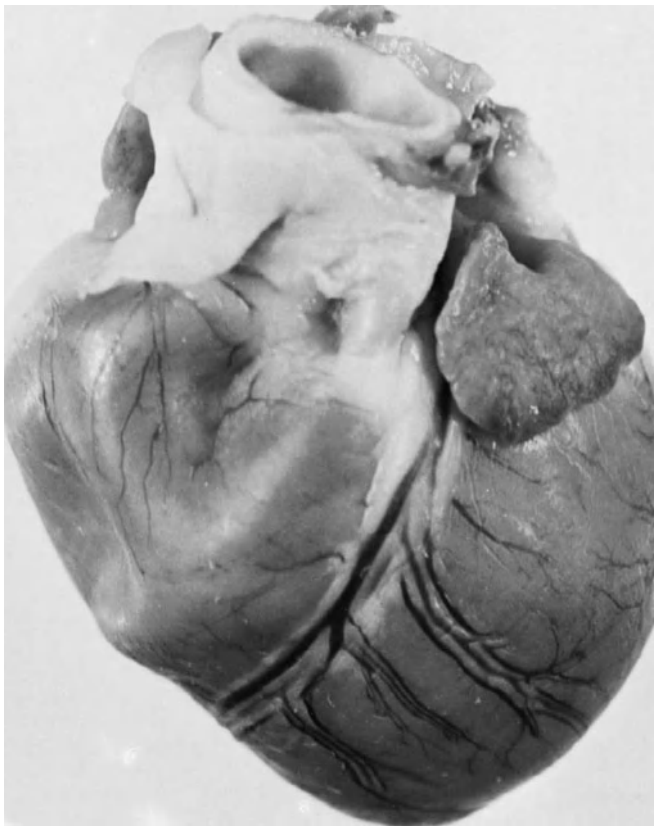
Abandonment of the term primary is important as a means of discouraging use of the confusing and clinically inappropriate term secondary pulmonary hypertension. Use of such "primary" and "secondary" groupings may inappropriately suggest clinical similarities among the many very different diseases previously referred to as secondary PH (e.g., between patients with COPD and those with congenital heart disease). It may also promote a failure to recognize important similarities in clinical features (including appropriate treatment) between what was previously called primary PH and entities inappropriately labeled secondary (e.g., patients with congenital heart disease or HIV infection).

PATHOLOGICAL CHANGES IN PULMONARY HYPERTENSION

Anatomic Alterations

The pulmonary vasculature reacts to chronic elevations in pressure in only a limited number of histologically recognizable patterns, regardless of the cause.[4,5] Accordingly, the histopathological changes seen are *qualitatively* similar regardless of the clinical classification of the disease. While *quantitative* differences occur in the distribution of histological changes between portions of the vasculature, neither the qualitative nor quantitative patterns in individual patients reliably indicates the etiology of the pulmonary hypertension. Indeed, both qualitative and quantitative differences in pathological findings have been noted even between members of the same kindred of patients with familial PAH.[6]

In the normal lung the muscle in the precapillary arteries thins progressively as the capillary bed is approached. A variety of lesions of these small muscular pulmonary arteries and arterioles can lead to pulmonary hypertension. Some lesions, such as those induced by chronic hypoxia, entail thickening of small muscular arteries and promote peripheral extensions of vascular smooth muscle. Others, such as thrombotic disease, encroach on pulmonary vascular lumens by intimal thickening and clotting. A third category consists of intimal fibrosis at the mouths of small pulmonary arteries, commonly in association with plexiform lesions.



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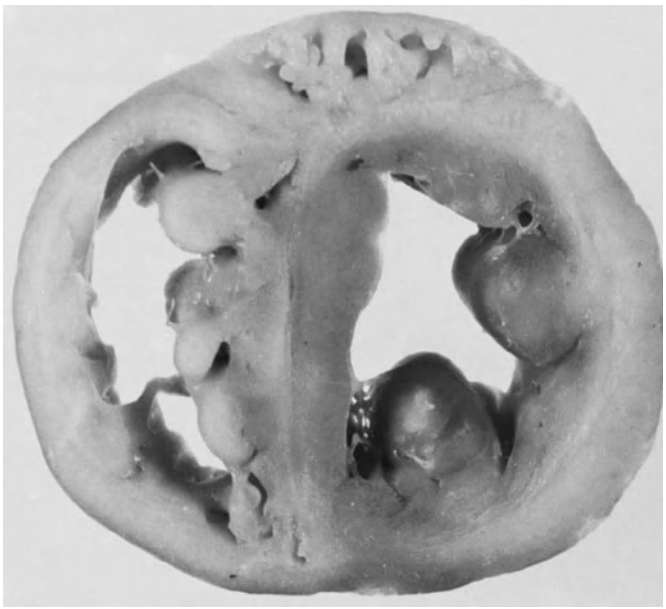


D

Figure 81-1 Cor pulmonale in experimental pulmonary arterial hypertension in the dog. *A*. Normal heart. *B*. Chronic cor pulmonale secondary to severe pulmonary arterial hypertension. *C*. Cross section of normal heart to show thin wall of the right ventricular cavity. *D*. Cross section of heart with chronic cor pulmonale to show hypertrophy of the right ventricular myocardium and enlargement of the right ventricular cavity. *(Courtesy of Dr. B. Atkinson.)*

Table 81-1

Clinical Classification of Pulmonary Hypertension*

Group 1. Pulmonary arterial hypertension (PAH)
- Idiopathic PAH
- Familial PAH
- Associated with (APAH):
  - Collagen vascular disease
  - Congenital systemic to pulmonary shunts (large, small, repaired, or nonrepaired)
  - Portal hypertension
  - HIV infection
  - Drugs and toxins
  - Other (glycogen storage disease, Gaucher disease, hereditary hemorrhagic telangiectasia, hemoglobinopathies, myeloproliferative disorders, splenectomy)
- Associated with significant venous or capillary involvement
  - Pulmonary veno-occlusive disease
  - Pulmonary capillary hemangiomatosis

Group 2. Pulmonary venous hypertension
- Left-sided atrial or ventricular heart disease
- Left-sided valvular heart disease

Group 3. Pulmonary hypertension associated with hypoxemia
- COPD
- Interstitial lung disease
- Sleep-disordered breathing
- Alveolar hypoventilation disorders
- Chronic exposure to high altitude

Group 4. Pulmonary hypertension due to chronic thrombotic and/or embolic disease
- Thromboembolic obstruction of proximal pulmonary arteries
- Thromboembolic obstruction of distal pulmonary arteries
- Pulmonary embolism (tumor, parasites, foreign material)

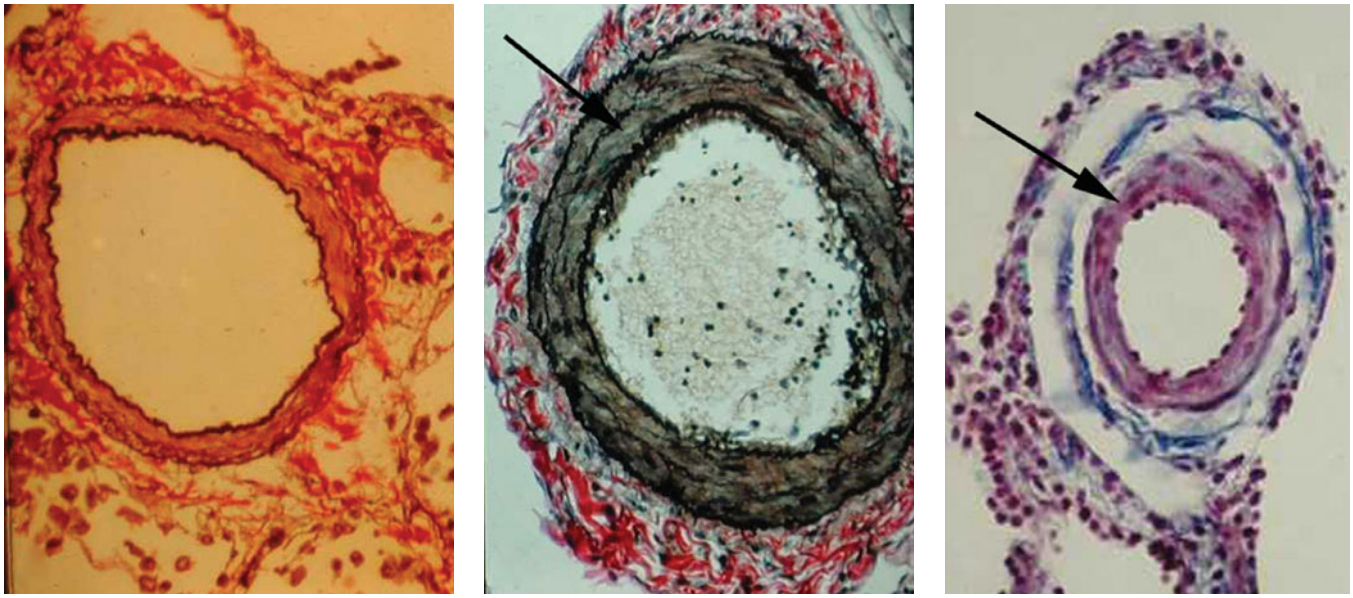
Group 5. Miscellaneous
- Sarcoidosis, histiocytosis X, lymphangiomatosis, compression of pulmonary vessels (adenopathy, tumor, fibrosing mediastinitis)

** Clinical classification of the pulmonary hypertensive states as adapted at the 2003 World Symposium on Pulmonary Arterial Hypertension in Venice, Italy. Note that the diseases are segregated into "groups" (e.g., group 1 being diseases considered forms of pulmonary arterial hypertension as distinct from group 3 diseases being disorders in which pulmonary hypertension is associated with hypoxic respiratory states.*
Source: Adapted from Simonneau G, et al: J Am Coll Cardiol *43:5S–12S, 2004; Rubin LJ:* Chest *126:7S–10S, 2004.*

Anatomic Changes Seen in All Forms of Pulmonary Hypertension

All causes of pulmonary hypertension can result in similar derangements of elastic and muscular pulmonary vessels: intimal atheromas, medial hypertrophy, and remodeling of muscular arteries. Intimal atheromas are confined to the elastic pulmonary arteries. Compared with the atherosclerotic changes found in the hypertensive *systemic circulation*, atheromas in the pulmonary circulation tend to be shallow and nonobstructing.[7,8] Similar changes occur in the nonhypertensive pulmonary circulation as part of normal aging, particularly at the branching points of large elastic arteries. Medial hypertrophy occurs in the muscular and elastic arteries and involves an abnormal increase in smooth muscle cell mass and reduplication of the elastic laminae. Pulmonary hypertension can also cause arterial dilation, which can obscure the changes of medial hypertrophy and, when severe, may compress adjacent airways (causing recurrent pneumonia) or the laryngeal nerve (resulting in hoarseness, the Ortner sign).

Persistent pulmonary hypertension, regardless of cause, can lead to the development of cor pulmonale with hypertrophy of the right ventricle, right ventricular dilation, and right ventricular failure (see Fig. 81-1).



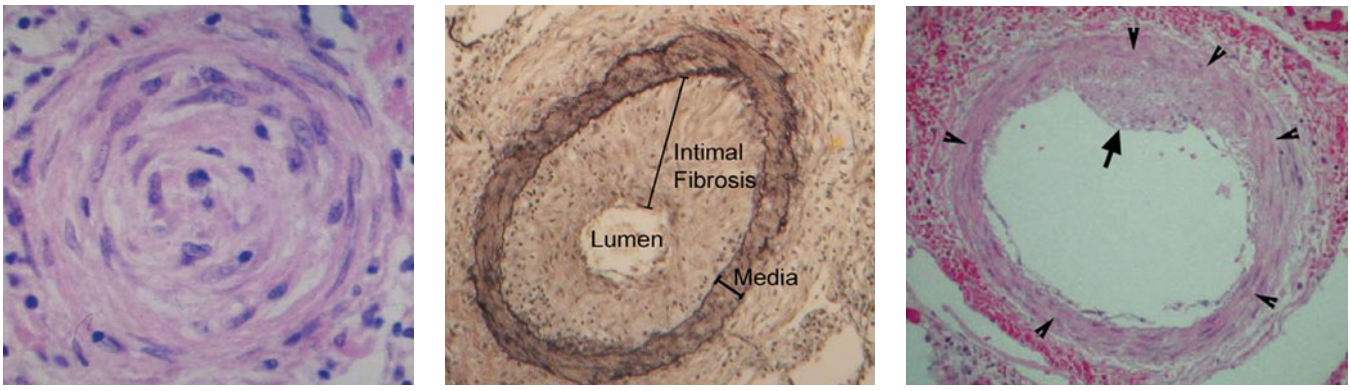
A *B* *C*

Figure 81-2 Medial hypertrophy. As compared with a normal vessel (*A*), hypertrophy of smooth muscle cells (arrow) is seen in the pulmonary artery of a patient with pulmonary arterial hypertension (*B*). Extension of muscle (arrow) into normally nonmuscularized small intra-acinar pulmonary vessels is another prominent feature of pulmonary arterial hypertension (*C*). *(Courtesy of Dr. GG Pietra and reproduced from Taichman DB, et al: Histopathology of pulmonary arterial hypertension, in Mandel J, Taichman DB (eds)*, Pulmonary Vascular Disease. *Philadelphia, Elsevier, 2006.)*

Histopathological Changes

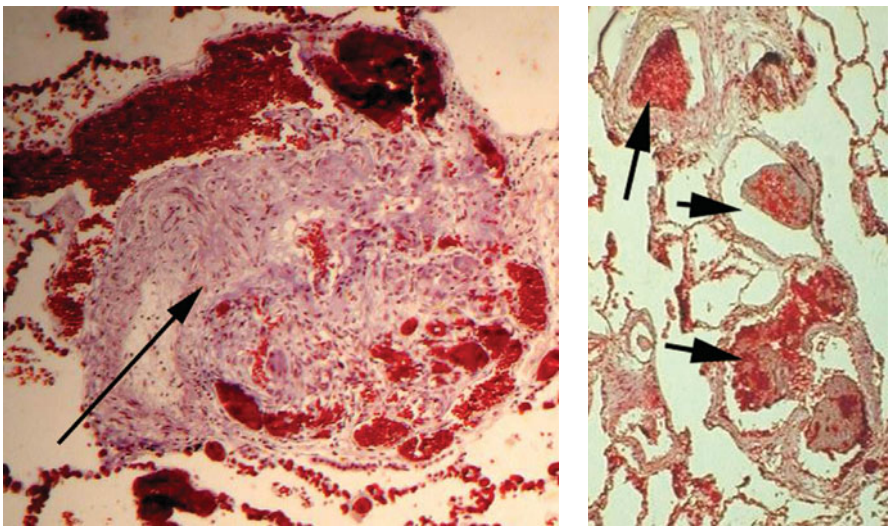
In addition to the changes described above seen in all types of pulmonary hypertension, distinctive histopathological patterns are found in pulmonary arterial hypertension. These patterns include constrictive lesions of the intima, remodeling of the media and adventitia, as well as complex lesions affecting the histological appearance of the entire vessel wall.[4,9,10]

Constrictive lesions include medial hypertrophy involving an increase in the number and size of smooth muscle cells. Extension of smooth muscle cells into vessels normally only partially muscularized or nonmuscularized is a common and often prominent feature of precapillary vessels[11] (Fig. 81-2). Marked smooth muscle hypertrophy can eventually cause medial atrophy, fibrosis, and the subsequent thinning of the media and dilation of the vessel lumen. Intimal thickening occurs with or without associated medial hypertrophy and in three patterns: concentric laminar, eccentric, and concentric nonlaminar (Fig. 81-3). Concentric laminar intimal thickening is a distinctive lesion composed of onionskin-like



A *B* *C*

Figure 81-3 Intimal thickening in pulmonary arterial hypertension. *A*. Concentric laminal intimal thickening (''onion skinning") with marked narrowing of the vessel lumen in a patient with focal fibrosis associated with systemic sclerosis. Nonlaminar intimal thickening can be concentric (*B*) or eccentric (*C*). *(Courtesy of Dr. GG Pietra and reproduced from Taichman DB, et al: Histopathology of pulmonary arterial hypertension, in Mandel J, Taichman DB (eds)*, Pulmonary Vascular Disease. *Philadelphia, Elsevier, 2006.)*



A *B*

Figure 81-4 Plexiform and dilation lesions. *A.* A plexiform lesion (arrow) characterized by small channels of blood and granulation tissue. *B.* Dilation lesions (arrows) consist of thin-walled sinusoidal channels. Such lesions are found distal to plexiform lesions. *(Courtesy of Dr. GG Pietra and reproduced from Pietra GG, et al:* J Am Coll Cardiol *43912:25S–32S, 2004.)*

layers of fibroblasts, myofibroblasts, and smooth muscle cells. Although such onion skinning is characteristic of the plexogenic arteriopathy previously thought to be a unique feature of idiopathic (primary) pulmonary arterial hypertension, this finding can be seen in other forms of PAH as well. Intimal thickening may be cellular and may involve fibrosis, and has been referred to as concentric laminar intimal fibrosis (CLIF). Eccentric and concentric nonlaminar intimal thickenings are collections of fibroblasts and connective tissue matrix. They have been described as resulting from the organization of thromboembolic material, although this has not been proved. Eccentric lesions are confined to one segment of the intima, while concentric thickenings obliterate the entire vessel lumen.

Complex lesions involve the entire vessel wall and include plexiform and dilation lesions. Although uncommon, the plexiform lesion is so distinctive a finding of the small muscular arteries that pathologists once favored the designation *plexogenic pulmonary hypertension* as the anatomic hallmark of IPAH[12] (Fig. 81-4). However, these lesions are not unique to IPAH since they also occur in the lungs of patients with severe PAH associated with left-to-right cardiac shunts, HIV infection, liver cirrhosis, and scleroderma. Although not pathognomonic, the plexiform lesion has been the focus of many studies of the cellular and molecular pathogenesis of PAH.[13–16] They contain collections of proliferating endothelial and smooth muscle cells, together with myofibroblasts and matrix proteins that can partially or completely occlude the vessel lumen. Narrowing or complete obliteration of the parent vessel by intimal thickening is a frequent associated finding, as is destruction of its media. Plexiform lesions often coexist with other obliterative vascular changes such as concentric laminar intimal thickening.[5] *Dilation lesions* are thin-walled vessels frequently occurring distal to plexiform lesions (Fig. 81-4*B*) and are possibly the site of rupture when pulmonary hemorrhage occurs in patients with PAH. Arteritis marked by the infiltration of acute and chronic inflammatory cells within the intima and media can also be found associated with complex lesions and may lead to vessel necrosis.

The pulmonary veins can also be affected in pulmonary arterial hypertension (Fig. 81-5). Fibrous tissue occludes veins of various sizes in pulmonary occlusive venopathy (POV), and can appear as loosely organized and edematous or dense and sclerotic fibrous tissue.[17,18] The lumen may have multiple channels, and the interstitium populated by large numbers of hemosiderin-laden macrophages. Dilation and fibrosis of the pulmonary lymphatics is another prominent feature of POV. Pulmonary microvasculopathy (PM) is a rare histological pattern marked by angioproliferative lesions. Numerous layers of small vessels containing many erythrocytes occlude capillaries and occasionally invade the surrounding interstitium and airways.[19–22]

In situ thrombosis of small vessels (both arterial and venous) is frequently noted in all forms of PAH (Fig. 81-6). These occur in the absence of findings to suggest an embolic source of the thrombotic material.[23–35]

No single histological feature distinguishes between the clinical PAH diagnoses. Each of the arterial and venous changes described can be seen in varying proportions in all clinical forms of PAH. For example, while the pathological designation pulmonary occlusive vasculopathy is the predominant histological finding in the clinical diagnosis of pulmonary veno-occlusive disease, arterial changes are seen in approximately one-half of the patients.[26] Similarly, pulmonary microvasculopathy is a pathological term describing the predominant histological findings in patients with the clinical manifestations of pulmonary capillary hemangiomatosis.

Widespread pulmonary interstitial disease commonly encroaches on the small pulmonary vessels, compressing and entrapping them in the fibrotic process (Fig. 81-7). In some

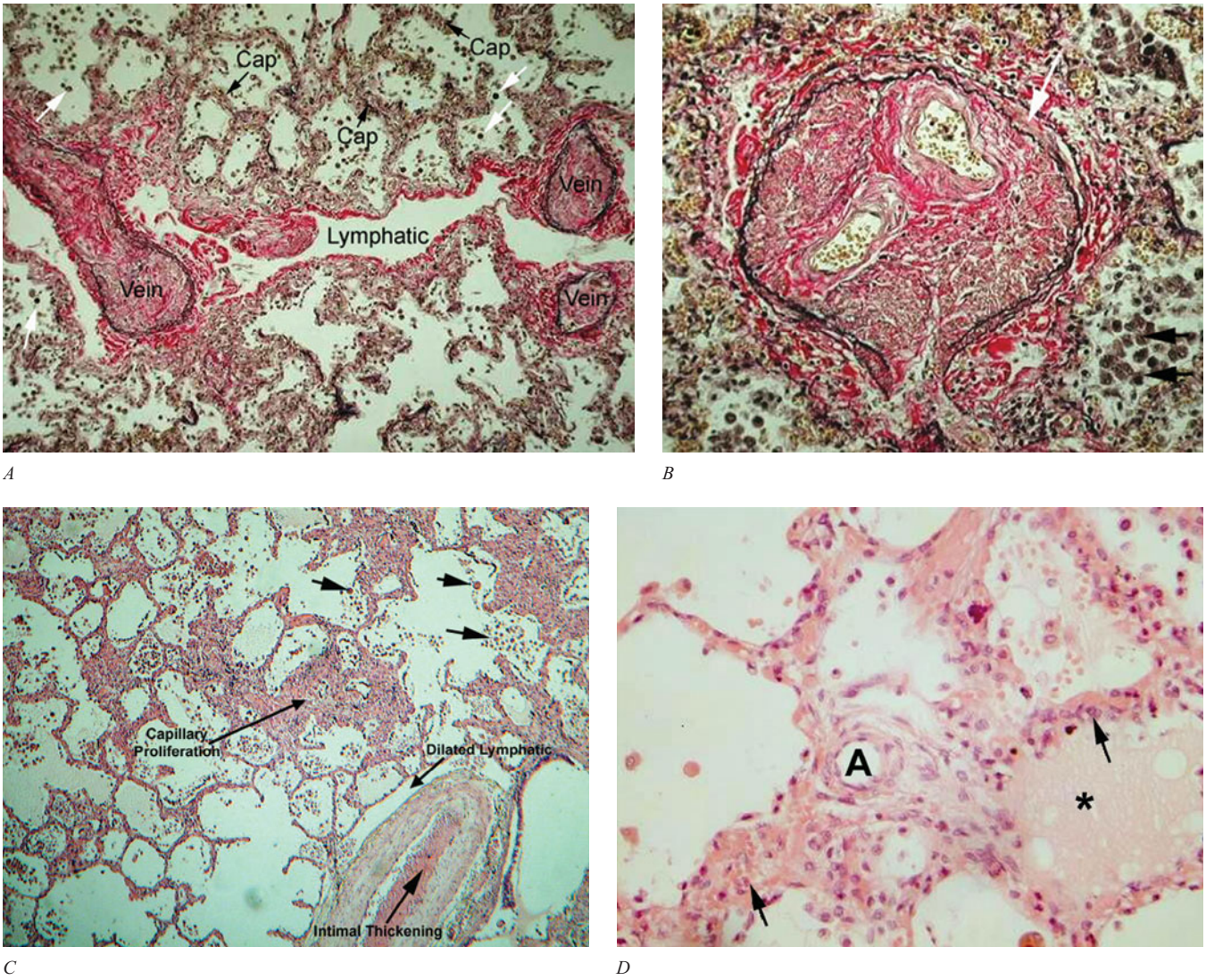
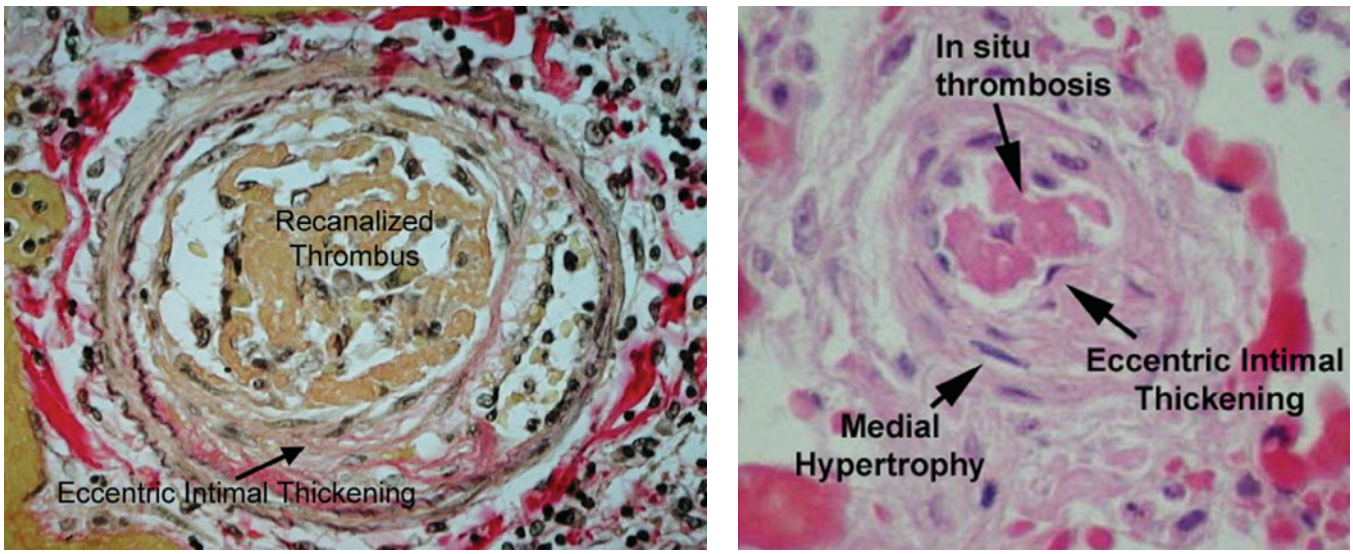


Figure 81-5 Pulmonary obstructive venopathy (POV) and pulmonary microvasculopathy (PM). *A*. Biopsy from a patient with pulmonary veno-occlusive disease with changes of POV, including the near total obstruction of pulmonary veins lymphatic dilation capillary congestion (black arrows) and the accumulation of hemosiderin-laden macrophages (white arrows). *B*. Higher power shows obstruction recanalization of a vein together with medial hypertrophy and thickened elastic laminae (white arrow). *C*. Biopsy from a patient with pulmonary capillary hemangiomatosis revealing capillary proliferation and the accumulation of hemosiderin-laden macrophages (arrows) within the alveoli and interstitium. *D*. Widened alveolar septa with more than one capillary (arrows) are seen as in an intra-acinar artery with medial hypertrophy (*A*). *(Courtesy of Dr. GG Pietra and reproduced from Taichman DB, et al: Histopathology of pulmonary arterial hypertension, in Mandel J, Taichman DB (eds)*, Pulmonary Vascular Disease. *Philadelphia, Elsevier, 2006. Panel A originally from Pietra GG, et al:* J Am Coll Cardiol *43912:25S–32S, 2004.)*

interstitial diseases, such as progressive systemic sclerosis, the parenchymal disease and the pulmonary vascular disease, can evolve independently. For example, in the CREST syndrome (calcinosis, Raynaud's phenomenon, esophageal dysfunction, sclerodactyly, and telangiectasia), a variant of scleroderma, pulmonary hypertension sometimes stems solely from obstructive vascular disease of the small muscular arteries, unaccompanied by pulmonary fibrosis. In other connective-tissue disorders, such as lupus erythematosus, combinations of interstitial disease and intrinsic vascular abnormalities contribute to pulmonary hypertension.

Pathobiologic Mechanisms

The pathogenetic mechanisms leading to pulmonary hypertension have been sorted into six categories (Table 81-2): (a) *passive,* due to obstruction to pulmonary venous outflow (e.g., fibrosing mediastinitis, mitral stenosis, or left heart failure); (b) *hyperkinetic,* due to abnormally high pulmonary blood flow (e.g., left-to-right shunts); (c) *obstructive,* due to pulmonary thromboembolic disease; (d) *obliterative,* due to curtailment of the pulmonary vascular bed by parenchymal proliferative disease; (e) *vasoconstrictive,* due to hypoxic



A *B*

Figure 81-6 In situ thrombosis within preacinar muscular arteries with organization and recanalization; also seen is eccentric intimal thickening. *(Courtesy of Dr. GG Pietra and reproduced from Taichman DB, et al: Histopathology of pulmonary arterial hypertension, in Mandel J, Taichman DB (eds)*, Pulmonary Vascular Disease. *Philadelphia, Elsevier, 2006.)*

vasoconstriction; and (f) *idiopathic* (i.e., without discernible cause). Over time, distinctions between categories tend to become blurred (e.g., thrombosis may complicate obliterative vascular disease). Also, by the time pulmonary hypertension becomes manifest clinically, the pulmonary arterial tree has undergone considerable remodeling that limits its extent and distensibility.

The anatomic curtailment of the pulmonary vascular tree involves thickening of the vascular walls of the small muscular pulmonary arteries and arterioles, partial or complete obliteration of their vascular lumens, and peripheral extensions of vascular smooth muscle toward the capillary bed as described above.[27] As a result, there is little capacity for distention and modest increments in pulmonary blood flow can elicit inordinate increments in pulmonary arterial pressures (Fig. 81-8). This situation is in marked contrast to that of the normal pulmonary circulation, in which an amputation of considerable lung volumes rarely suffices, per se, to raise pulmonary arterial pressures to pulmonary hypertensive levels.

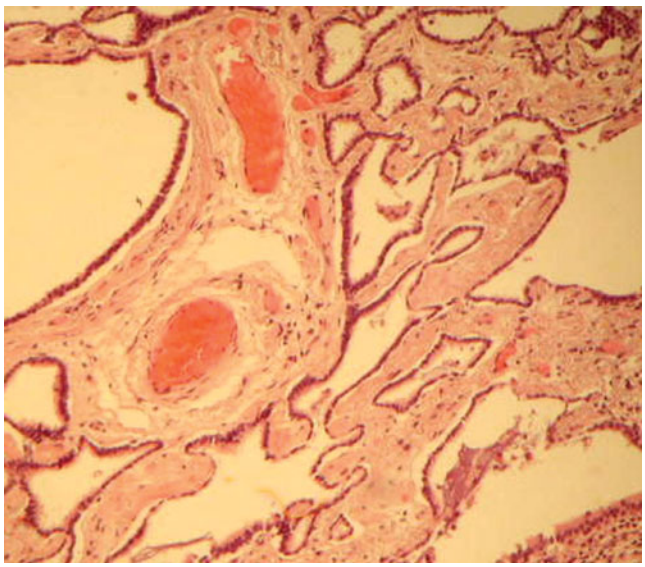


Figure 81-7 Interstitial pulmonary fibrosis in a patient with systemic sclerosis (scleroderma). In addition to the thickening and fibrosis of the interstitial spaces is the entrapment of vessels by fibrotic material. *(Courtesy of Dr. G.G. Pietra.)*

In the dog, more than two-thirds of the lungs must be ablated before pulmonary arterial pressures increase to hypertensive levels; in humans, occlusion of one major pulmonary artery, as by unilateral pneumonectomy, has little effect on pulmonary arterial pressures. Even in the individual with extensive pulmonary emphysema, as in α_1-antitrypsin deficiency, the striking decrease in the number of minute vessels in the emphysematous areas rarely suffices to elicit pulmonary hypertension. In contrast, widespread occlusion of the pulmonary vascular bed by multiple pulmonary emboli often causes pulmonary hypertension by obliterating large segments of the pulmonary arterial tree and increasing resistance to blood flow. Pulmonary vasoconstriction, as by acute or chronic hypoxia, may add to the increase in pulmonary vascular resistance.[28]

Vasoconstrictive Mechanisms: Hypoxia, Hypercapnia, and Acidosis

In some instances, pulmonary vasoconstriction can play an essential role in the pathogenesis of pulmonary hypertension. Hypoxia is by far the most powerful vasoconstrictor encountered clinically; acidosis is next, but is much less powerful.[29,30] Both exert their vasomotor effects directly on the pulmonary vessels. Although these "powerful" vasoconstrictors

Table 81-2

Pathogenetic Mechanisms of Pulmonary Hypertension*

	Mechanism	Examples
Passive	Pulmonary venous hypertension	Mitral stenosis, left atrial myxoma fibrosing mediastinitis pulmonary veno-occlusive disease
Hyperkinetic	Increased pulmonary blood flow*	Left-to-right intracardiac shunts
Obstructive	Thromboembolic pulmonary vascular disease	Widespread pulmonary thrombosis of minute vessels, multiple pulmonary emboli
Obliterative	Inflammatory and/or proliferative pulmonary vascular disease	Interstitial lung disease, pulmonary arterial hypertension, schistosomiasis
Venoconstrictive	Hypoxia	Chronic bronchitis and emphysema (COPD)
Idiopathic	Unknown	Dietary pulmonary hypertension, porto-pulmonary hypertension, HIV infection

** Most categories overlap to some extent. For example, increased pulmonary blood flow is usually coupled with anatomic changes in the resistance vessels to produce pulmonary hypertension.*

generally elicit only modest increments in pulmonary arterial pressure in the normal adult, acute hypoxia can elicit striking pulmonary pressor effects in the fetus and newborn and in some individuals with pulmonary hypertension. In chronic hypoxia, sustained pulmonary vasoconstriction elicits structural changes within a matter of weeks. This remodeling is characterized by thickening of the media of the small pulmonary arteries and arterioles (Fig. 81-9) and peripheral extension of muscle into minute pulmonary vessels that are normally devoid of muscle.[31] Acute hypercapnia has no direct pressor effect on the pulmonary circulation. However, it can contribute to pulmonary hypertension via the acidosis that hypercapnia elicits.

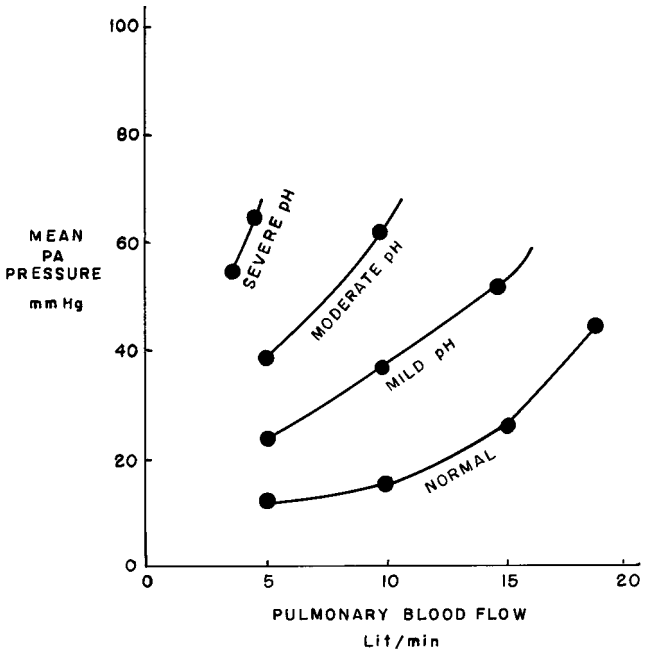
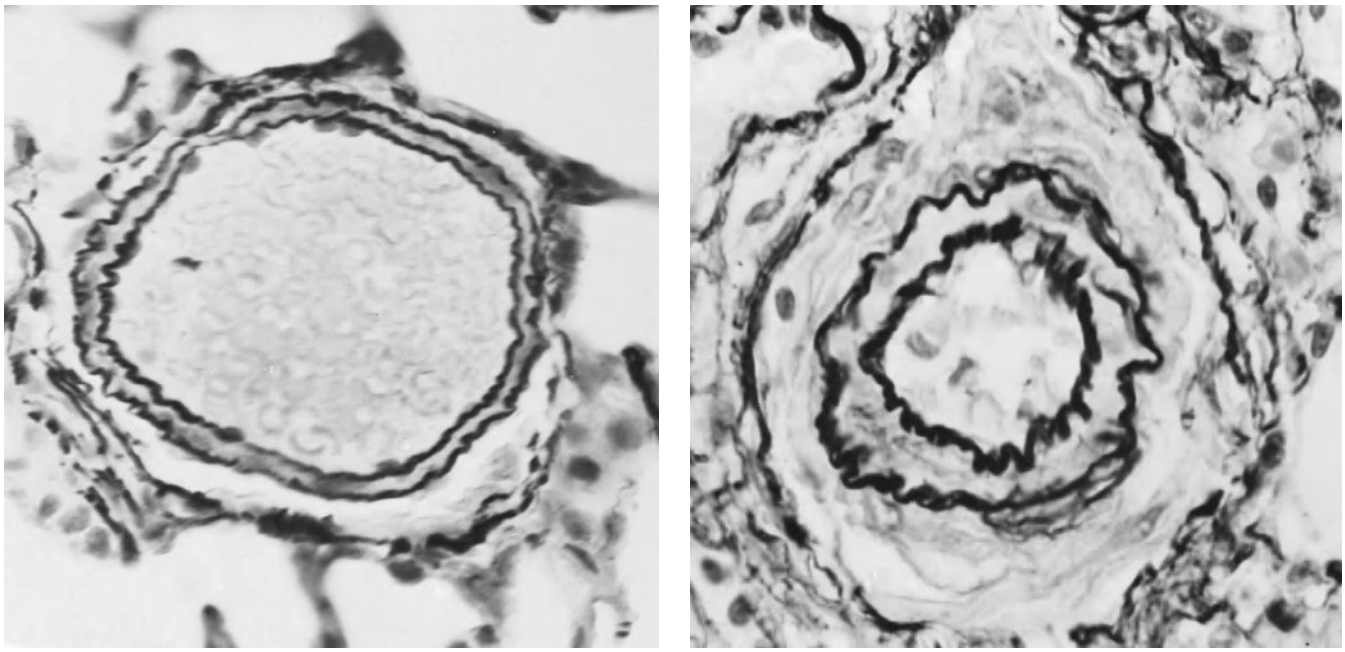


Figure 81-8 Schematic pulmonary arterial blood pressure-flow curves for the normal and pulmonary hypertensive circulations. At high levels of pulmonary hypertension small increments in pulmonary blood flow elicit inordinate increments in pressure.

Mechanisms of Idiopathic Pulmonary Arterial Hypertension

The initiating mechanisms of idiopathic and other forms of pulmonary arterial hypertension are obscured by the fact that the pulmonary hypertension itself may represent an end stage of the disease process. Abnormalities that initiate this process are difficult to trace once the anatomic changes are in place and by the time a sufficient amount of the normal vasculature has been curtailed to cause symptoms prompting clinical evaluation. This often long and quite variable interval between the original insults thought to initiate the pulmonary vascular disease and the onset of clinical signs and symptoms has been a major obstacle. In some patients, the insult appears to be present life-long (as in the case of congenital heart disease). In others, the inciting event is traceable to a few months or years of ingesting anorectic agents.[32,33]

Investigations using cells or tissues from patients with pulmonary hypertension have identified many cellular and molecular abnormalities. However, neither the experiments with cells or tissues nor animal models reproduced the changes of human PAH. Although alterations in ion channels,



A *B*

Figure 81-9 Normal and thickened pulmonary resistance vessels. *A*. Pulmonary arteriole showing thin muscular media double elastic lamina and widely patent lumen (40 μm). Aldehyde-fuchsin-elastic (×560). *B*. Pulmonary arteriole from pulmonary hypertensive dog showing marked thickening of the media decrease in lumen size and perivascular fibrosis (40 μm). Aldehyde-fuchsin-elastic (×560). *(Courtesy of Dr. B. Atkinson.)*

growth factors, and vasoactive proteins, together with gene mutations, have been identified as contributing to the abnormal endothelial, platelet, hemostatic, and smooth muscle function involved in the pathogenesis of PAH, distinguishing between initiating and secondary events remains problematic. It seems likely that instead of a single etiological factor, PAH can result from a number of abnormalities of pulmonary vascular cell function, initiated by one or more possible insults. The propensity of such abnormalities to produce disease appears to be determined by both the intensity and duration of these derangements, as well as an individual's genetic predisposition to abnormal vascular responses.

The development of pulmonary arterial hypertension involves disruptions in the normal balance of vasoconstriction and vasodilation, in the control of cellular proliferation, and thrombosis. Abnormalities in the expression of numerous vasoactive mediators cause, or result from, changes in endothelial, smooth muscle and platelet function, and result in a thickened vessel wall and markedly narrowed or even completely obliterated lumen (Fig. 81-10). Some mechanisms for this combination of uncontrolled vasoconstriction, cell proliferation, and thrombosis are highlighted here.

Imbalance of Vasoactive Mediators

Relative deficiencies of factors with vasodilatory properties and a simultaneous excess in those promoting vasoconstriction have been noted in both animal models and patients with PAH (Fig. 81-11). In addition to vasoconstriction/dilation, these same factors influence cell proliferation and thrombosis. Deficiencies in the production of the potent vasodilators nitric oxide (NO) and prostacyclin have been identified and both substances have been used in treating PAH. NO and prostacyclin are normally produced by vascular endothelial

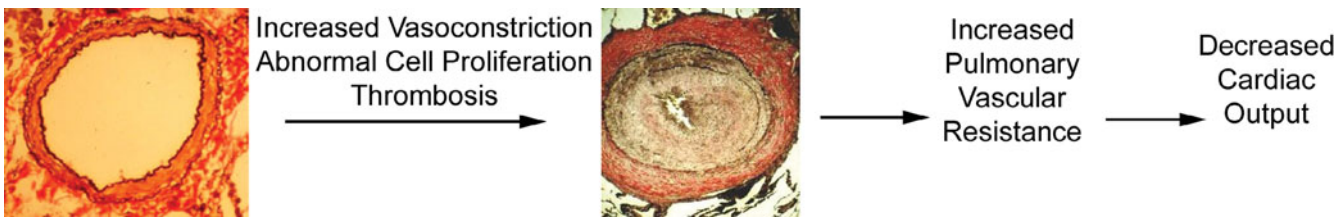


Figure 81-10 Schematic representation of the pathogenesis of pulmonary arterial hypertension in which multiple factors contribute to vascular changes that produce an increase in resistance and an impaired cardiac output. *(Histological images courtesy of Dr. GG Pietra and reproduced from Snow JL, et al: Histopathology of pulmonary arterial hypertension, in Mandel J, Taichman DB (eds)*, Pulmonary Vascular Disease. *Philadelphia, Elsevier, 2006.)*

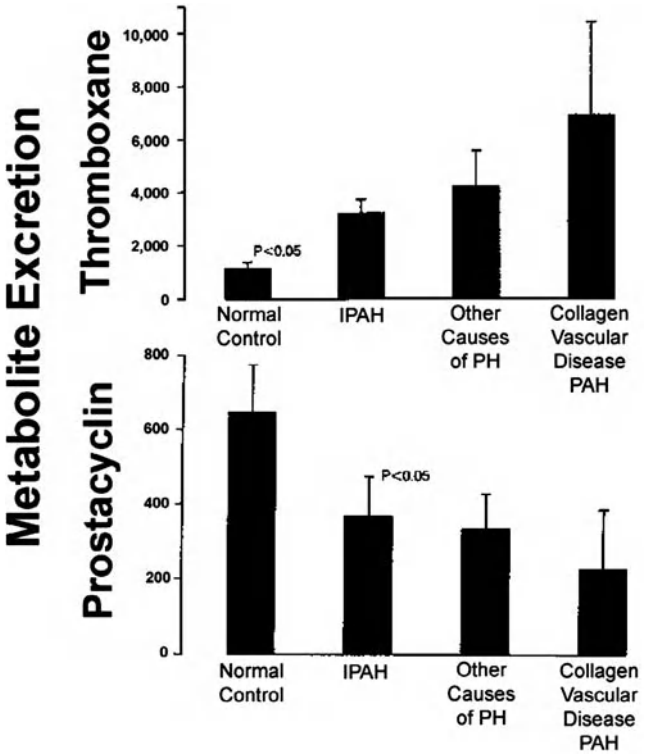


Figure 81-11 Imbalance in vasoconstrictor and vasodilator mediators found in patients with pulmonary hypertension. Urinary expression of vasoconstrictor (thromboxane) metabolites are increased, whereas vasodilator (prostacyclin) metabolites are decreased as compared with normal. *(Originally adapted from Christman BW, et al:* N Engl J Med *327:70–75, 1992; Snow JL, et al: Histopathology of pulmonary arterial hypertension, in Mandel J, Taichman DB (eds),* Pulmonary Vascular Disease. *Philadelphia, Elsevier, 2006.)*

cells, and each promotes the formation of cyclic nucleotides (cGMP and cAMP) by smooth muscle cells, thereby eliciting vascular relaxation and vasodilation. In addition, both prostacyclin and NO inhibit smooth muscle cell proliferation and platelet aggregation. The overexpression of NO synthase by transgenic animals protects against the development of hypoxia-induced pulmonary hypertension, whereas mice that lack the gene for this enzyme develop severe pulmonary hypertension upon exposure to mild hypoxia.[34–36] In rats, monocrotaline-induced pulmonary hypertension can be prevented, and even reversed, with the administration of endothelial progenitor cells that overexpress human eNOS.[37] In patients with PAH, the chronic administration of prostacyclin analogues improves hemodynamics, exercise capacity and survival.

Vasoactive intestinal protein (VIP) also promotes vasodilation, inhibits smooth muscle proliferation and platelet aggregation. Its levels are reduced in patients with PAH. In a preliminary study of eight patients with IPAH, treatment with inhalations of VIP improved hemodynamics and exercise capacity.[38]

In addition to deficiencies in vasodilators in patients with PAH, excesses occur of other mediators that are capable of promoting vasoconstriction, smooth muscle proliferation, or platelet aggregation. Among these is thromboxane, an arachidonic acid metabolite produced by endothelial cells and platelets. Thromboxane causes vasoconstriction, platelet aggregation, and is a smooth muscle mitogen. Increased thromboxane metabolites have been demonstrated in the urine of patients with PAH.[39]

Attention was called to the effects of serotonin (5-HT) on the pulmonary circulation by the epidemic of pulmonary arterial hypertension in patients who ingested the appetite suppressants aminorex and fenfluramine.[30] These agents increase plasma 5-HT levels by inducing the release of serotonin from platelets and interfering with its reuptake.[40] The hypothesis that serotonin may play a role in the pathogenesis of pulmonary hypertension was supported by the occurrence of pulmonary hypertension in fawn-hooded rats that have an inherited defect in the storage of serotonin by platelet and the observed increase in circulating serotonin in a patient with platelet storage disease and PAH.[41] Serotonin causes vasoconstriction and is a smooth muscle mitogen. A key regulator of 5-HT action is the serotonin transporter (5-HTT), the expression of which is above normal in the platelets and the pulmonary arteries of patients with IPAH. Overexpression of the 5-HTT gene in recombinant mice worsens hypoxia-induced pulmonary hypertension,[42] whereas loss of the gene's function is protective against hypoxia or monocrotaline-induced disease.[43,44] A polymorphism in the 5-HTT gene that increases its activity may confer increased susceptibility for the development of pulmonary hypertension in patients with COPD. Although some studies have suggested a similar role in IPAH,[45] larger data sets have not found such an association.[46]

Endothelin-1 (ET-1) is one of the most potent endogenous vasoconstrictors known. Levels of ET-1 are increased in the blood and tissues of patients with idiopathic and other forms of PAH and correlate with the severity of the disease.[47–49] In addition to its vasoconstricting properties, ET-1 is mitogenic for both smooth muscle cells and fibroblasts.[50,51] Its administration or overexpression in animal models has been shown to result in fibrosis, inflammation, and platelet aggregation.[52,53] ET-1 binds to receptors for endothelin A (ET_A) and B (ET_B) on the surface of smooth muscle cells resulting in potent vasoconstriction. ET_B receptors on vascular endothelial cells increase the production of NO, resulting in vasodilatation. ET_B receptors are also active in the clearance of endothelin. The net effect of endothelin's vasoconstricting or dilating actions may be both site and context dependent. Both the distribution and relative expression of the ET_A or ET_B receptors differ according to vessel location in normal lung tissue, and are altered in patients with IPAH.[54,55] Indeed, both selective ET_A and dual ET_A/ET_B inhibition ameliorates the hemodynamic derangements and clinical outcome of patients with PAH.[56–58]

Vascular tone may also be altered in PAH by changes in the expression of voltage-gated K^+ (Kv) channels. Their activation normally allows an efflux of K^+ and resultant changes in intracellular Ca^{2+} that promote vasodilation. Gene expression of Kv family members is downregulated by

hypoxia-induced pulmonary hypertension in rats,[59,60] whereas induction of their expression can reverse the hemodynamic effects.[59,61] The expression of specific Kv channels is decreased in the lungs of patients with IPAH[62–64] possibly contributing to heightened vasoconstriction. Kv channels may also be involved in the effects of certain drugs. The anorexigens dexfenfluramine and aminorex inhibit smooth muscle Kv1.5 activity, thereby causing pulmonary vasoconstriction.[65] In contrast, the enhanced activity of Kv channels may be a mechanism by which sildenafil promotes vasodilation in addition to its activity as an inhibitor of phosphodiesterase.[59] One final way by which decreased activity of Kv1.5 channels might promote the development of PAH is by inhibiting apoptosis, thus enabling unchecked smooth muscle cell proliferation. Apoptosis requires a loss in cell volume as well as the function of specific caspases, both of which require appropriate K^+ movement via Kv channels.[66,67] Increased expression of another ion channel (transient receptor potential channels) that permits the influx of Ca^{2+} for smooth muscle proliferation has been found in the lungs of patients with IPAH. As for the changes in Kv channels, it is not clear whether altered expression of these transient receptor potential channels in IPAH represents a primary event or a secondary effect of other mechanisms in the evolution of disease.[68]

Genetic Changes and Altered Cell Growth

Recent advances in molecular genetics have identified two genes involved in the pathogenesis of both idiopathic and familial pulmonary arterial hypertension. Bone morphogenetic protein receptor II (BMP-RII) and activin receptor kinase-like 1 (ALK1) are receptors of the transforming growth factor-beta (TGFβ) superfamily. This family of receptors is involved in diverse cell growth and differentiation processes in multiple systems. Engagement of a BMP receptor with its ligand normally results in the activation of intracellular mediators (Smads) and their translocation to the cell nucleus and regulation of the transcription of target genes. The resulting activation of some genes and the inhibition of others varies according to the BMP pathway and tissue involved. BMP signaling is essential to both normal vascular development and the maintenance of the normal adult pulmonary vasculature, presumably by regulating the growth and apoptosis of endothelial and smooth muscle cells. Loss of such regulation gives rise to pulmonary hypertension.[69] Germline mutations in *BMP-RII* have been identified in up to 60 percent of patients with familial PAH, and in some patients with idiopathic PAH,[70–74] as well as in PAH associated with anorexigens,[75] congenital heart disease,[76] and pulmonary veno-occlusive disease.[77] Mutations in *ALK-1* confer susceptibility to the development of PAH in patients with hereditary hemorrhagic telangiectasia.[78,79]

BMP-RII is normally found primarily on endothelium and to a lesser extent smooth muscle cells. The expression of BMP-RII is reduced and its function is abnormal in patients with various types of PAH, particularly in patients with mutations of the *BMP-RII* gene.[80] The ability of BMP to inhibit smooth muscle proliferation and induce apoptosis is suppressed in cells isolated from smaller pulmonary vessels in patients with IPAH (e.g., 1 to 2 mm, where occlusive vascular pathological changes predominate).[81–83]

Growth factors known to promote the maturation and stabilization of the developing vasculature have also been implicated in the pathogenesis of PAH. Increases in angiopoietin 1 and its ligand TIE2 correlate with disease severity in patients with multiple forms of PAH.[84] These patients had no known mutations in either *BMP-RII* or *ALK1*, but the increased levels of angiopoietin inhibited the expression of another member of the TGFβ family (BMP-R1A) that is required for normal signaling through BMP-RII. How angiopoietin becomes increased in these patients is not clear. Interestingly, in an animal model of PAH induced by monocrotaline, the overexpression of angiopoietin is actually protective.[85] Whether this discrepancy represents differences in studying human versus animal tissues or the differing insults to the vasculature involved is not yet clear. Another modulator of development, vascular endothelial growth factor (VEGF) and its receptor tyrosine kinase receptors are increased in the pulmonary vasculature of patients with PAH. Increased VEGF expression has been reported within plexiform lesions[14,86] in which its proangiogenic properties are hypothesized to mediate disordered endothelial cell proliferation.[87] Whether such changes are primary, secondary, or indeed detrimental is not entirely clear. Like elevations in angiopoietin, increments in the expression of VEGF, which are believed to be deleterious in some situations, might be beneficial in others that promote the development of pulmonary hypertension. In animal models of hypoxia, the inhibition of VEGF signaling results in proliferative vascular abnormalities[88] and promotion of VEGF signaling is protective against the development of monocrotaline-induced PH.[89]

In Situ Thrombosis

Thrombosis is common in the small vessels of patients with PAH. The thrombosis occurs without evidence of a remote (embolic) source of the thrombus,[23–25,90] suggesting a local imbalance of pro- and anticoagulant forces. In addition are pro-coagulant factors, including abnormal von Willebrand factor activity, increase in plasma fibrinopeptide-A and increases in the half-life of fibrinogen[91,92] and plasminogen activator inhibitor type-1.[93] Endothelial cell-dependent fibrinolytic activity is also decreased in most patients with IPAH. Activation and altered function of the endothelium leading to a shift from anti- to procoagulant activities may be due to the effects of shear stress associated with elevated pressure and/or flow. In addition to altered endothelial cell activity, platelets also promote thrombus formation by releasing vasoactive and mitogenic factors such as thromboxane metabolites and serotonin. These, as well as other platelet-derived products (e.g., platelet-derived growth factor, TGFβ and VEGF) probably also contribute to the remodeling of vessel walls seen in PAH.

Changes in the Extracellular Matrix

The normal turnover of extracellular matrix (ECM) proteins is accelerated with remodeling of the vasculature in pulmonary arterial hypertension.[94,95] The expression of tenascin-C (TN-C), for example, is increased in both experimental pulmonary hypertension induced by either monocrotaline in rats or increased blood flow in swine.[96–98] Indeed, inhibition of TN-C expression by antisense RNA ameliorates monocrotaline-induced pulmonary vascular lesions.[99] Increased levels of this ECM protein are also seen in the pulmonary arteries of patients with PAH.[100–101] TN-C might contribute to the pathogenesis of PAH by modulating the effects of receptor tyrosine kinases, such as epidermal growth factor and fibroblast growth factor-2, on the proliferation and survival of pulmonary artery smooth muscle.[102]

CLINICAL EVALUATION OF PULMONARY HYPERTENSION

Patient History in Pulmonary Hypertension and Cor Pulmonale

The symptoms of pulmonary hypertension are nonspecific (Table 81-3). Except for mild breathlessness—often attributed to being out of shape—pulmonary hypertension is generally asymptomatic until severe. Because of the nonspecific nature of the symptoms, under-recognition of the disease by healthcare providers, and confusion with other conditions are common. As a result, there is often a significant delay between the onset of symptoms and the diagnosis of PAH. By one estimate, an average of 2.5 years elapse between the development of symptoms and the diagnosis of IPAH. Most patients present with progressive dyspnea and significantly advanced disease.

Table 81-3

Clinical Manifestations of Pulmonary Hypertension

Symptom	Frequency*
Dyspnea	60–90
Fatigue	19
Chest pain	7
Near syncope	5
Syncope	8
Leg edema	3
Palpitations	5

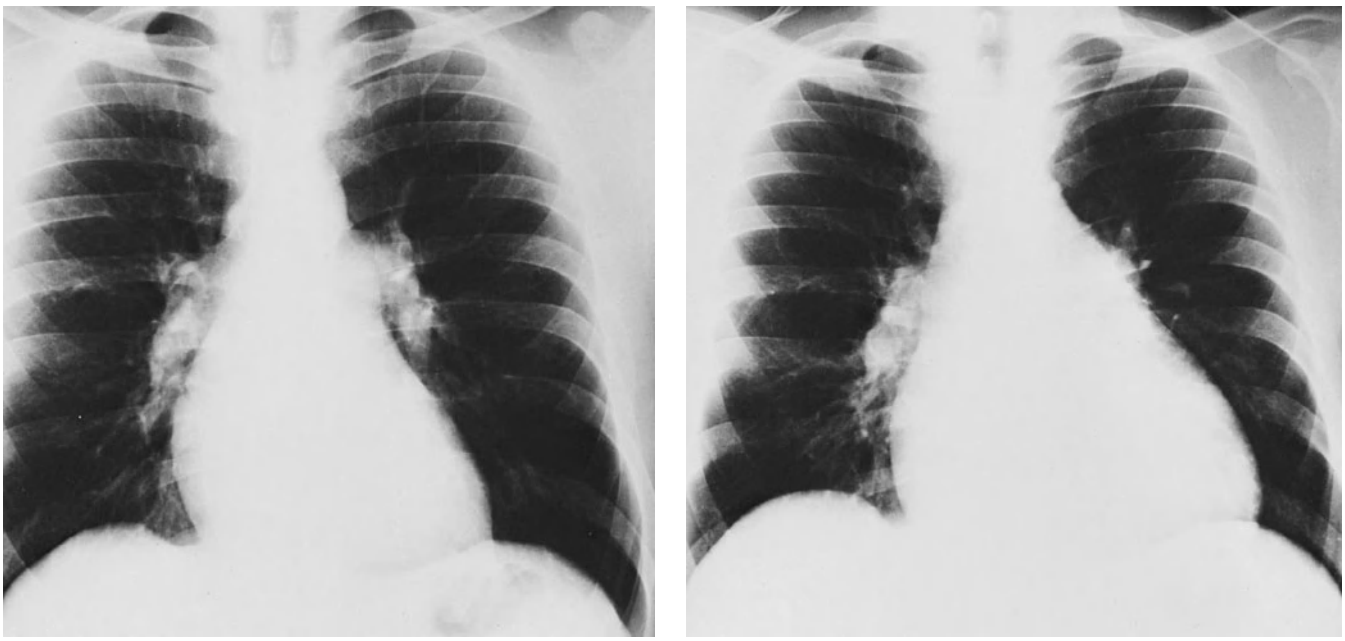
** In percent of patients.*

Symptoms due to pulmonary hypertension are generally difficult to dissociate from the symptoms of underlying pulmonary or cardiac disease. In idiopathic pulmonary arterial hypertension, the first symptoms generally occur during exertion, usually as dyspnea and, less often, chest pain, dizziness, or syncope.[103] Dyspnea on exertion is by far the most common presenting complaint. Often, because of the lack of other signs or symptoms, it is attributed to physical deconditioning or anxiety. The mechanism responsible for the dyspnea of pulmonary hypertension is unclear. Other initial complaints, particularly easy fatigability and chest discomfort, are often dismissed as neurotic. Angina-like or nondescript chest pain is common in patients with severe pulmonary hypertension and generally attributed to right ventricular overload and myocardial ischemia. Chest pain might also occur if the left main coronary artery is compressed by an enlarged pulmonary artery.[104]

In time, right-sided heart failure evolves. Syncope, or light-headedness on exertion, are less common but more ominous complications of pulmonary hypertension. These symptoms occur in patients with severe pulmonary hypertension and a fixed low cardiac output. The cause is inadequate cerebral blood flow due to the combined failure to increase cardiac output and the diversion of systemic blood flow to the exercising muscles. Syncope may also occur at rest in association with the onset of bradycardia, presumably vagal in origin. Hoarseness, due to paralysis of the left recurrent laryngeal nerve, may result from trapping of the nerve between the aorta and the dilated left pulmonary artery (a form of Ortner syndrome). If the right ventricle should fail, the typical manifestations appear. Lower extremity swelling is common as are abdominal complaints of fullness, often described as a sensation of bloating, early satiety, tender hepatomegaly, ascites, and even abdominal pain. Symptoms of right ventricular failure and the presence of syncopal events herald a worse prognosis.

Hemoptysis in pulmonary hypertension is usually due to pulmonary venous congestion. In contrast, in mitral stenosis is usually attributed to bleeding from bronchial veins. Occasionally, hemoptysis occurs in other forms of pulmonary hypertension and may originate in alveolar capillaries, precapillaries, and elsewhere in the pulmonary arterial tree.

Not infrequently, suspicion of pulmonary hypertension is raised by the presence of a known etiology for pulmonary hypertension (e.g., systemic sclerosis or mitral stenosis) or serendipitous discovery of right ventricular enlargement by an electrocardiogram or chest radiograph taken for other reasons (Fig. 81-12). Initial recognition of the presence of pulmonary hypertension also frequently occurs in the patient without symptoms when an echocardiogram is performed in the evaluation of a murmur heard upon auscultation of the heart. Alternatively, echocardiographic evidence of pulmonary hypertension may be found when the study is obtained as routine evaluation of a patient complaining of any of a number of chest symptoms, including dyspnea.



A *B*

Figure 81-12 Radiographic changes in idiopathic pulmonary hypertension. As compared to a chest radiograph 14 months earlier (*A*) enlargement of the cardiac silhouette has occurred in a 30-year-old man in association with increasing dyspnea (*B*). Decrease in the cardiac silhouette occurred in response to chronic pulmonary vasodilator therapy.

Patients with severe pulmonary hypertension are prone to sudden death and its occurrence may be the first (and last) indication of disease. Death has occurred unexpectedly during normal activities, cardiac catheterization, and surgical procedures, and after the administration of barbiturates or anesthetic agents. In a few instances, bradycardia leading to cardiac arrest has preceded sudden death.

Patients should be asked about important symptoms that might suggest the cause of pulmonary hypertension (Table 81-4). These include symptoms of collagen vascular disease (e.g., dysphagia, skin or joint changes, Raynaud's phenomenon), sleep apnea (e.g., witnessed apneic events, daytime hypersomnolence), risks for thromboembolism or HIV infection, liver disease, or anorectic agent use. A history of tobacco abuse and chronic sputum production, or a known history of asthma with poor control may afford important clues to the presence of obstructive airways disease and hypoxia as the cause of pulmonary hypertension. A prior history of recognized interstitial lung disease or any other cause of chronic hypoxia should be noted. A careful family history should be taken including asking about relatives who suffer(ed) poorly understood cardiopulmonary conditions.

Physical Examination

Until the right ventricle fails, preoccupation with the underlying pulmonary disease may divert attention from the presence of pulmonary hypertension and the development of right ventricular enlargement (cor pulmonale). Each pathogenetic sequence that culminates in cor pulmonale leaves its own imprint on the clinical manifestations. For example, COPD is usually associated with hyperinflation of the lungs, which shifts the position of the heart and makes heart sounds less audible. Another example is interstitial lung disease, which is accompanied by rapid shallow breathing. In mild to moderate pulmonary hypertension physical examination is apt to be unrevealing unless suspicion has been aroused that pulmonary hypertension may be present. Right ventricular enlargement is an important clue but notoriously difficult to detect on physical examination in its early stages. Evidence of pulmonary hypertension such as prominent closure of the pulmonary valve is apt to be overlooked or discounted, especially in younger people; recognition of tricuspid insufficiency or a right ventricular gallop is often delayed until pulmonary hypertension has become severe and has led to heart failure.

Once pulmonary hypertension is suspected, the physical examination can offer important signs. When symptoms first become manifest, a large *a* wave generally can be detected in the jugular venous pulse. Auscultation usually discloses splitting of the second heart sound with accentuation of the pulmonic component. A sharp systolic ejection click over the region of the pulmonary artery is usually heard. As pulmonary hypertension persists, enlargement of the right ventricle becomes evident as a palpable cardiac impulse near the left sternal border and in the hypogastrium. An important sign of cor pulmonale is a right-sided (ventricular), diastolic (S_3) gallop. In timing, it coincides with the third heart sound; it is accentuated by inspiration. Less helpful is the right atrial gallop (S_4), which occurs immediately before the first heart sound and represents an accentuation of the normal atrial

Table 81-4

Evaluation of Patients with Pulmonary Hypertension

Detection of pulmonary hypertension	Detailed history and physical examination	Suspicion of pulmonary hypertension and possible causes/associations
	Electrocardiogram	Exclude other causes of cardiopulmonary symptoms
	Chest radiograph	
	Echocardiogram (at rest, to consider repeat with exertion)	Evaluate for presence of pulmonary hypertension, assess chamber sizes and function, valvular abnormalities, contrast ("bubble") study to evaluate possible shunt
Essential testing	Pulmonary function testing	Exclude instrinsic lung disease
	Overnight oximetry	Screen for sleep disordered breathing
	Lung (V/Q) scan	Exclude thromboembolism
	Blood serologies (e.g., CBC, liver function, renal function, HIV, ANA, antiphospholipid antibodies)	Exclude collagen vascular disease, liver disease, infection and other possible causes of pulmonary hypertension
	Oxygen desaturation study	Assess need for supplemental oxygen (rest and exertion)
	6-Minute walk test	Establish baseline
	Right cardiac catheterization	Confirm diagnosis, assess other cardiac causes (shunt); consider left heart catheterization)
Contingent testing	Transesophageal echocardiogram	Assess patent foramen ovale (PFO)
		Characterize valvular function
	Computed tomogram of chest	Assess interstitial lung disease, adenopathy
	Polysomnogram	Diagnosis and treatment of sleep-disordered breathing
	Pulmonary angiogram	Assess presence and location of clot and suitability for pulmonary thromboendarterectomy
	Blood studies (BNP, clotting studies, genetic testing)	
	Lung biopsy	Exclude subtle interstitial lung disease vasculitis and other uncommon diseases (PVOD, PCH) to assist planning

Source: Adapted from: Barst RJ, et al: J Am Coll Cardiol *43:40S–47S, 2004.*

sound; it suggests an increase in the filling pressure of the right side of the heart.

In time, tricuspid insufficiency develops. It is manifested by a holosystolic murmur, best heard in the fourth interspace to the left of the sternum; the murmur characteristically increases in intensity during inspiration (as do the third and fourth heart sounds). A prominent *v* wave appears in the jugular pulse, and distended neck veins pulsate with each heartbeat. The onset of right ventricular failure is often marked by discomfort in the right upper quadrant due to hepatic engorgement as well as edema at the lower extremities. The liver often also shows expansive pulsations that are synchronous with the heartbeat. Hydrothorax and ascites are uncommon, even after right ventricular failure has progressed to the stage of hepatomegaly and pedal edema.

Systemic arterial hypoxemia is often present. Assessment of possible oxyhemoglobin desaturation during activity is an important component of the patient evaluation; if desaturation is noted, formal exercise testing to titrate oxygen therapy should be pursued promptly. Late in the disease, many patients develop peripheral cyanosis secondary to a reduced cardiac output and peripheral vasoconstriction; central cyanosis also occurs in some patients because of right-to-left shunting through a patent foramen ovale.

The physical examination should focus on the presence of additional signs to indicate a possible cause of pulmonary hypertension. Abnormal lung sounds might include wheezing suggesting airways obstruction, or crackles suggesting either pulmonary edema or interstitial disease. Additional findings suggestive of lung disease include hyper-resonance to percussion or hyperinflation of the thorax (barrel chest) suggestive of COPD; kyphoscoliosis may cause a restrictive pattern. Skin changes such as rash or telangiectasias are clues to the presence of collagen vascular disease; so are digital

ulcers in patients with the CREST variant of systemic sclerosis. The presence of digital clubbing may indicate congenital heart disease, certain forms of chronic hypoxic lung disease (e.g., cystic fibrosis or certain interstitial lung diseases) or pulmonary veno-occlusive disease.[105] A narrow posterior oropharynx, macroglossia, and a large neck size may suggest obstructive sleep apnea (OSA).

Diagnostic Studies

Diagnostic testing is used to confirm the presence of pulmonary hypertension, identify the etiology, assess severity and prognosis, and help to identify appropriate therapy (see Table 81-4).

When pulmonary hypertension is suspected, the echocardiogram is the appropriate first test.[103,106] Indeed, as noted, evidence of pulmonary hypertension on an echocardiogram is often what first brings the issue to attention. A carefully performed Doppler examination is able to quantify the tricuspid regurgitant jet in the majority of cases.[107] A modified Bernoulli equation is used to estimate the right ventricular systolic pressure (RVSP = $4v^2$ + right atrial pressure; where v = tricuspid jet velocity in meters per second) and is assumed to equal the pulmonary artery systolic pressure when the pulmonic valve is normal. Normal RVSP has been reported as 28 ± 5 mmHg. Echocardiographic evaluations during exercise are an additional consideration when estimates of RVSP at rest are normal and suspicion of pulmonary hypertension is high (e.g., dyspnea in a patient with systemic sclerosis and no other obvious cause). Echocardiographic measurements taken at peak exercise may reveal inordinate increases in pulmonary arterial pressures, perhaps signaling the presence of earlier disease. Normative echocardiographic values of RVSP during exercise have not been well established.

The echocardiogram can also reveal important information about cardiac structure and function. It enables evaluation for a patent foramen ovale and intracardiac or intrapulmonary shunting of blood (e.g., using a bubble contrast). Echocardiography can also help to rule out related anatomic abnormalities, such as acquired or congenital mitral valve disease or a left atrial myxoma. Left ventricular hypertrophy, diastolic noncompliance, decreased systolic function, or focal hypokinesis as well as mitral or aortic valvular defects are essential observations when evaluating the likely cause of pulmonary hypertension. Dilation and decreased function of the right ventricle are indications of the functional importance and severity of pulmonary hypertension. Taken together, an evaluation of right ventricular contraction, relaxation, and ejection can yield functional information with prognostic value in patients with PH.[108] The presence and size of a pericardial effusion are poor prognostic signs.[109–112] Flattening of the interventricular septum occurs with advanced dilation and failure of the right heart, and the leftward movement of the septum may denote impairment of left ventricular filling.

While the correlation between echocardiographic estimates of PASP and measurements taken at right heart catheterization are generally good, it must be remembered that there is significant variability. Confirmation by cardiac catheterization is required when the presence of pulmonary hypertension will influence the approach to treatment. For example, in the setting of some patients with severe COPD in whom an echocardiogram reveals evidence of pulmonary hypertension, confirmation by right heart catheterization might not influence medical therapy. If, on the other hand, surgical intervention for the COPD is a consideration (e.g., for lung transplantation or lung volume reduction), confirmation of the presence of pulmonary hypertension by cardiac catheterization is important. When the diagnosis is thought to be pulmonary arterial hypertension, diagnostic catheterization confirms the diagnosis and is useful in guiding therapy. Cardiac catheterization in evaluation of pulmonary hypertension is described in the following sections.

Once evidence of pulmonary hypertension has been established by echocardiography, testing for possible causes is in order. Pulmonary function tests, a ventilation-perfusion scan and overnight oximetry are essential to screen for possible underlying obstructive or restrictive lung disease, occult thromboembolism, and sleep-disordered breathing, respectively. Blood tests including HIV antibody, rheumatologic serologies (e.g., ANA), liver function tests, and a complete blood count are essential. A plain chest radiograph (together with the pulmonary function tests) may suggest the presence of parenchymal lung disease; in such patients further evaluation with CT is usually warranted. Early in the evolution of pulmonary hypertension, the chest radiograph appears normal. In time, the central pulmonary arteries become increasingly prominent as the peripheral vessels become attenuated, and the cardiac silhouette enlarges (Fig. 81-13). An electrocardiogram should be obtained and may indicate signs

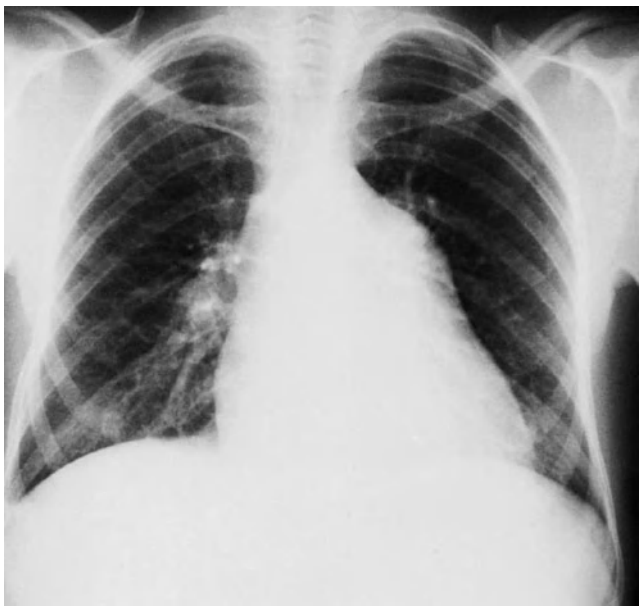


Figure 81-13 Prominent central pulmonary arteries in conjunction with the marked pruning of the peripheral tree reflect marked pulmonary hypertension in a patient with a history of multiple pulmonary thromboemboli.

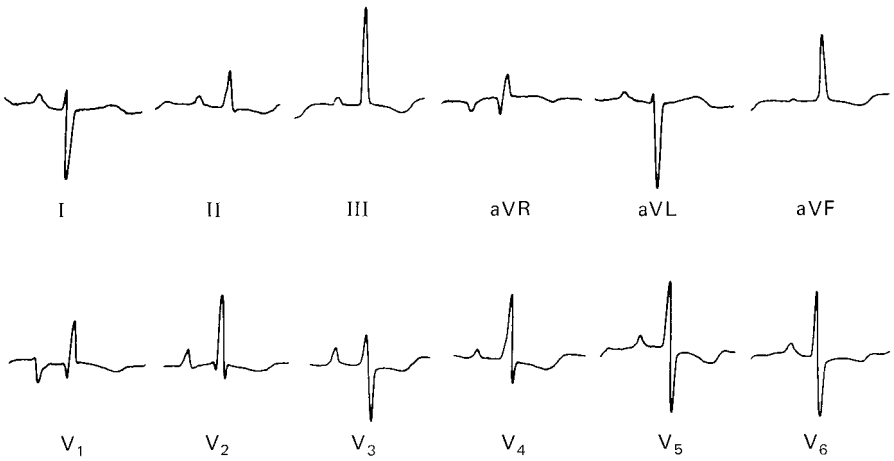


Figure 81-14 Twenty-six-year-old woman in whom the first evidence of idiopathic pulmonary arterial hypertension was by electrocardiography. The record shows marked right axis deviation and dominant R waves over the right precordium consistent with right ventricular hypertrophy.

of ischemic heart disease or conduction abnormalities. The electrocardiogram almost invariably shows some evidence of right ventricular overload, usually in conjunction with right atrial impairment (Fig. 81-14). Arrhythmias are uncommon until late in the course of the disease, when they may contribute to syncopal episodes.

Baseline testing should also include assessments of exercise tolerance and whether supplemental oxygen is required. A 6-minute walk test is a useful means of assessing exercise capacity and prognosis, and serial testing can be useful in evaluating the response to therapy. Measurements of arterial oxyhemoglobin saturation both at rest and during exercise are important to be sure that adequate oxygenation is maintained and, if not, to titrate with supplemental oxygen accordingly.

Cardiac catheterization is required in most cases to confirm the diagnosis of pulmonary hypertension, test for important cardiac causes and, in appropriate patients, perform vasodilator trials to determine therapy. Except in those considered to be at very low risk of coronary artery disease, many centers first perform left heart catheterization in all patients. In addition to coronary angiography, measurement of the LVEDP is important to exclude left atrial hypertension (e.g., as seen in diastolic dysfunction) as an important cause of pulmonary hypertension. Direct measurement may be required in the presence of severe pulmonary hypertension when an adequate estimate of LVEDP cannot be obtained using a wedged pulmonary artery catheter. Right heart catheterization, using a balloon-tipped flow-directed pulmonary artery catheter, is performed to confirm the presence of pulmonary hypertension. While advancing the catheter, serial measurements of blood oxygen saturation should be performed for evidence of a "step up" in oxyhemoglobin saturation that suggests the presence of left-to-right shunting of blood as an etiology for the pulmonary arterial hypertension. Attention also should be paid to the level of right atrial pressure since significant increase worsens the prognosis. As noted, pulmonary hypertension is defined as a mean pulmonary resting artery pressure greater than 25 mmHg. When pulmonary arterial pressure is normal at rest, measurement during exercise may be performed using serial leg lifts, arm raising with weights, or a stationary bicycle. A mean pulmonary artery pressure greater than 30 mmHg with exercise is also diagnostic of pulmonary hypertension (Fig. 81-15). Pulmonary arterial hypertension is present when there is pulmonary hypertension and an adequately measured pulmonary capillary wedge pressure or, if necessary, a directly recorded LVEDP, is less than 15 mmHg. The cardiac output is obtained either by thermodilution or measuring arterial and venous hemoglobin oxygen contents and applying the Fick principle. The latter is apt to be more accurate if either significant tricuspid or pulmonary regurgitation is present or the cardiac output is very low.

In patients with pulmonary arterial hypertension, vasodilator testing is performed at the time of right heart

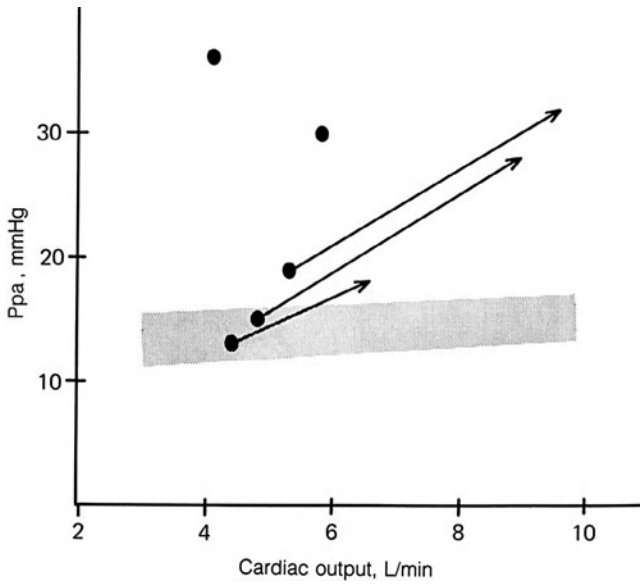


Figure 81-15 Hemodynamic observations in five patients with interstitial lung disease. Two of the five had pulmonary hypertension at rest; the other three became pulmonary hypertensive during exercise, although only in one did the mean pulmonary artery pressure rise above 30 mmHg = at rest; →= exercise. The shaded background indicates the normal pulmonary arterial pressure-flow relationship.

catheterization to identify those in whom treatment with oral calcium channel antagonists is appropriate. This testing is described in the section below in which therapy of PAH is addressed.

GENERAL ASPECTS OF DISEASE MANAGEMENT

This section describes general measures to be considered in the care of all patients with pulmonary hypertension and cor pulmonale. Treatment is also directed by the underlying disorder and the identification of any reversible causes.

Exercise and the Avoidance of Deconditioning

Regardless of the cause, patients with pulmonary hypertension and cor pulmonale should be encouraged to maintain as active a lifestyle as possible. Recommendations that the patient minimize exertion for fear of further raising pulmonary pressures generally result only in deconditioning of the muscles and an increase in fatigue and breathlessness when activity is attempted. Regular, steady aerobic exercise should be encouraged, and is often best initiated under guidance of a pulmonary or cardiac rehabilitation program. The benefits include a decrease in the fear many patients with dyspnea experience when initiating exercise programs. Many rehabilitation programs teach techniques to cope with dyspnea when it occurs, thereby enabling exercise to continue. The result is an increase in compliance with regular fitness regimens, overall improvement in exercise tolerance and in the sense of well-being and in reducing or avoiding obesity. Activities that tend to cause lightheadedness or syncope are to be avoided. Among these are hot showers or baths and bending over to lift heavy objects.

Oxygen Therapy

Of cardinal importance in the management of patients with pulmonary hypertension is the avoidance of acute hypoxia, as hypoxic pulmonary vasoconstriction adds to the burden on the right ventricle. Measurements of arterial oxyhemoglobin saturation should be performed at rest, during exertion, as well as during sleep. Levels of arterial oxygen saturation below 90 percent require supplemental oxygen. Maintenance of adequate oxygen saturation may be difficult in those patients with severe pulmonary hypertension in whom a patent foramen ovale allows right-to-left shunting.

Supplemental oxygen has been demonstrated to benefit patients with COPD.[113] Two separate trials, that of the Medical Research Council and of the National Heart, Lung, and Blood Institute (Nocturnal Oxygen Therapy Trial), have shown that intellectual function and survival of patients with COPD are improved in chronically hypoxemic patients (arterial P_{O_2} under 55 mmHg) who are polycythemic (hematocrit greater than 55 percent), edematous, and show P pulmonale on the electrocardiogram. However, in order to be effective, oxygen must be administered for at least 18 h per day—including at night, when arterial hypoxemia and respiratory acidosis intensify. Oxygen relieves hypoxic pulmonary vasoconstriction, thereby decreasing vascular resistance and improving the cardiac output, lessens renal vasoconstriction improving the urinary excretion of sodium, and alleviates tissue hypoxia by improving oxygen delivery.

Air travel is of particular concern because of the threat of hypoxic pulmonary vasoconstriction. As a rule, commercial airlines maintain cabin pressures equivalent to an altitude of about 8000 feet above sea level. Supplemental oxygen should be administered as necessary to avoid arterial oxygen saturation below 90 percent. Supplemental oxygen is usually required for those with borderline levels of arterial oxygen saturation at sea level; increased oxygen flow rates are apt to be needed for those who use oxygen therapy for the activities of daily life. Many pulmonary function laboratories can simulate conditions of high altitude by using an inspired oxygen concentration of 15 percent to determine whether the patient requires supplemental oxygen in order to maintain adequate oxyhemoglobin saturation. Patients must contact airlines in advance of travel to arrange for supplemental oxygen therapy while in flight.

Infection

Acute respiratory infection may precipitate right heart failure in patients with cor pulmonale. Acute exacerbations are a particular and often recurrent problem for patients with pulmonary hypertension due to COPD. Worsened hypoxia and/or respiratory acidosis may worsen pulmonary hypertension, increase the work of an already strained right heart, and precipitate cardiac arrhythmias. Treatment for pulmonary infection must be instituted promptly and include oxygen and antibiotic therapies. Airways obstruction may increase intrathoracic pressures and interfere with venous return causing hepatic congestion and peripheral edema. Bronchodilators should be given as needed to relieve airways obstruction and relieve hypoxia.

In patients receiving vasodilators (e.g., calcium channel antagonists or intravenous prostanoid therapies for pulmonary arterial hypertension) hypoxic vasoconstriction normally occurring at pneumonic infiltrates may be inhibited due to the drug's nonspecific action resulting in the shunting of blood and worsened hypoxemia.

Immunizations against influenza and pneumococcal pneumonia are important preventive measures in all patients with pulmonary hypertension and cor pulmonale.

Fluid Management and Diuretics

Careful attention to avoid fluid overload is central to the management of cor pulmonale of any cause. Patients must be educated regarding appropriate dietary habits and must restrict sodium intake in order to minimize fluid retention and the development of right heart failure. Patients should weigh

themselves daily so any trend toward fluid retention can be reversed. In addition to the harmful effects of excessive intravascular volume on cardiac function, the lungs share in the accumulation of excess water in the body; the excess fluid in the lungs further compromises pulmonary gas exchange and may heighten pulmonary vascular resistance. It has now been amply demonstrated that diuretics can improve alveolar ventilation and arterial oxygenation in cor pulmonale.

Management of right heart failure relies heavily on diuretic therapy. Spironolactone is often used to manage mild fluid retention. It may also have beneficial effects in heart failure by modulating neurohormones. Loop diuretics are often required to prevent more significant fluid retention and right heart failure. Indeed, high doses and combinations of diuretics may be required to maintain appropriate fluid balance, but must be used cautiously to avoid electrolyte imbalances and volume depletion. Diuretic-induced hypokalemic metabolic alkalosis is of particular concern as it may diminish the effectiveness of the CO_2 stimulus on the respiratory centers, thereby decreasing the ventilatory drive. Also, renal excretion of bicarbonate is compromised when diuretics decrease blood levels of potassium and chloride. For these reasons, careful monitoring of serum electrolytes—particularly bicarbonate, chloride, and potassium ions—is mandatory once a program of salt depletion, including salt restriction and diuretics, is begun. Carbonic anhydrase inhibitors (e.g., acetazolamide) were once first-line therapy for treating patients with cor pulmonale with chronic hypercapnia secondary to COPD. The rationale was to promote diuresis and loss of bicarbonate by the kidney. However, untoward effects, presumably the result of adding metabolic acidosis to the preexisting respiratory acidosis, have led many physicians to abandon the use of acetazolamide as a primary diuretic agent. At present, it is used only circumspectly to correct the alkalemia induced by excessive diuresis, contraction of the plasma volume and hypochloremia.

Digitalis and Theophylline

Whether cardiac glycosides should play a role in treating right heart failure is unsettled. Nonetheless, digoxin is commonly used empirically, particularly when pulmonary hypertension is accompanied by atrial fibrillation. It is used by some clinicians to support the failing right ventricle; others shy away from this agent even when right-sided heart failure is evident. They do so on two accounts: (a) the inotropic effect of digitalis on right ventricular performance is modest; and (b) patients with cor pulmonale and right ventricular failure are often hypoxemic and somewhat acidotic, thereby predisposed to dysrhythmia. Even small doses of digitalis may trigger a dysrhythmia. Digitalis seems most apt to benefit patients with demonstrable left ventricular failure. Heart rate is a poor guide to digitalis dosage because hypoxemia, as well as heart failure, evokes tachycardia. In essence, the safest use of digitalis for its cardiotonic effect is when right ventricular failure is unaccompanied by arterial hypoxemia, acid-base upsets, or the need for administration of bronchodilators (i.e., in disorders other than obstructive airway disease). Also predisposing to dysrhythmias are hypokalemia induced by diuretics and medications including theophylline, which are administered to relieve bronchospasm.

The effect of theophylline in patients with COPD has been inconsistent, although some patients may experience a reduction in symptoms without demonstrable relief of airflow obstruction. Such benefit may be due to the drug's ability to increase myocardial contractility and diaphragmatic strength as well as to promote mild pulmonary vasodilation. Theophylline's use in patients with pulmonary hypertension is not of established benefit and must be used cautiously. Careful attention to the level of the drug in blood is required to avoid the development of toxicity that might provoke cardiac dysrhythmias. This requirement may limit theophylline use.

Dysrhythmias

Dysrhythmias occur occasionally with cor pulmonale. Common precipitating mechanisms are anxiety and excessive use of bronchodilators. Occasionally, a bout of respiratory failure triggers an episode of atrial tachycardia, nodal rhythm, a wandering pacemaker, atrial flutter, or fibrillation. Stimuli that provoke intense adrenergic discharge increase the possibility of adverse effects from therapeutic agents, such as digitalis. As a rule, arrhythmias in cor pulmonale are transient and resolve with discontinuation of the precipitant (e.g., an acute respiratory infection.). However, arrhythmias may be life threatening if they occur in the presence of disturbances in acid-base balance, arterial hypoxemia, and heightened sympathetic activity. The occurrence of such a life-threatening arrhythmia, usually ventricular fibrillation, is most likely during a bout of acute respiratory failure, with its accompanying disturbances in gas exchange and electrolyte imbalances. Respiratory alkalosis, induced by mechanical hyperventilation and accompanied by hypokalemia, can also be a precipitating mechanism.

Pulmonary Vasodilators in non-PAH Forms of Pulmonary Hypertension

Many vasodilator drugs have been used in the attempt to reduce pulmonary vascular resistance and improve right heart function in cor pulmonale. However, except for an occasional patient with pulmonary arterial hypertension, the use of vasodilators has not been of benefit in cor pulmonale. Although overall success rates have been modest, occasional instances of dramatic improvement have been reported. Results in patients with cor pulmonale due to COPD, for example, have been mixed and, at best, successful only in the short term (see subsequent section on Pulmonary Hypertension Associated with Hypoxemic Lung Disease). For example, the use of calcium channel antagonists in patients with COPD may worsen ventilation-perfusion mismatch and hypoxemia. In addition, the depressant effects of these agents on cardiac inotropy may significantly worsen right heart function.

The use of pulmonary vasodilators is discussed in detail below in treatment specifically for pulmonary arterial hypertension.

Phlebotomy

When the hematocrit increased to more than 50 to 60 percent, phlebotomy was once standard treatment for the polycythemia of chronic hypoxia. However, even though repeated small phlebotomies often did result in symptomatic improvement and increase exercise tolerance, it proved difficult to show objective improvement in gas exchange, pulmonary mechanics, or pulmonary arterial pressure after "safe" phlebotomies (i.e., of 250 mL or so); larger phlebotomies were avoided because they occasionally resulted in minor strokes and episodes of hypotension. However, gradual restoration of hematocrits toward normal (i.e., by repeated 250-mL phlebotomies at intervals of several days or weekly) did decrease pulmonary arterial pressure as hematocrits approached normal levels (i.e., about 50 percent); lower hematocrits offer no further advantage. Therefore, small phlebotomies still have a role when secondary polycythemia becomes severe.

Supplemental oxygen therapy in hypoxemic patients with COPD should reduce the severity of secondary polycythemia and in most cases obviate the need for phlebotomy.

EPIDEMIOLOGY AND TREATMENT OF INDIVIDUAL PULMONARY HYPERTENSIVE DISEASES

Pulmonary Arterial Hypertension

Table 81-5 presents the known and suspected risk factors for the development of PAH, as assessed at the 1998 World Symposium on Pulmonary Hypertension.[26] Risks are ranked as "definite" if established by controlled studies or clear-cut epidemics (anorexigenic-associated PAH caused by fenfluramine)[114,115] and "possible" when based on fewer definitive data (e.g., case series). Intermediate levels of evidence are ranked accordingly.

Idiopathic Pulmonary Arterial Hypertension

Idiopathic pulmonary arterial hypertension (IPAH) is a rare disease with an estimated incidence in industrialized countries of one to two cases per million.[114,116,117] The paucity in the number of patients with IPAH and the likelihood that diverse causes and pathogenetic mechanisms can produce the same clinical syndrome have complicated descriptions of the natural history of the disease. For a while, certain stereotypes were regarded as prototypical, e.g., young women with Raynaud's syndrome, with the acute onset of dyspnea and fatigue and progression to death within 2 years. It is appreciated that even though there is such a subset, longevity in response to medical therapy is no longer unusual and that the disease may affect all ages, both sexes, and different ethnic groups.[118]

Table 81-5

Risk Factors for the Development of Pulmonary Arterial Hypertension

Drugs and toxins
Definite
Aminorex
Fenfluramine
Dexfenfluramine
Toxic rapeseed oil
Very likely
Amphetamines
L-Tryptophan
Possible
Meta-amphetamines
Cocaine
Chemotherapeutic agents
Unlikely
Antidepressants
Oral contraceptives
Estrogen therapy
Cigarette smoking
Demographic and medical conditions
Definite
Gender
Possible
Pregnancy
Systemic hypertension
Unlikely
Obesity
Diseases
Definite
HIV infection
Very likely
Portal hypertension/liver disease
Collagen vascular diseases
Congenital systemic-pulmonary-cardiac shunts
Possible
Thyroid disorders

Risk factors and conditions associated with the development of pulmonary arterial hypertension, as were assessed at the 1998 World Symposium on Pulmonary Hypertension in Evian, France.
Source: Adapted From: Simonneau G, et al: J Am Coll Cardiol *43:5S–12S, 2004.*

In order to overcome the limitations of sporadic reports, the National Institutes of Health (NIH) established a nationwide registry in 1981 to collect and analyze data on IPAH (then called PPH). Criteria for entry of a patient into the national registry included normal pulmonary function tests (except for a moderate reduction in diffusing capacity), a right heart catheterization to exclude congenital or left heart disease, perfusion scans, and angiography if the scans were

inconclusive for pulmonary emboli, and serologic testing to rule out collagen vascular disease. Included in the registry were certain associated diseases, such as hepatic cirrhosis, because the reason for the association between pulmonary hypertension and the liver disease was unclear and because of the suspicion that the association might provide a clue to etiology.

By the close of the registry in 1987, data were available on 187 patients.[119] The mean age was 36.4 years and similar for women and men, although the female-to-male ratio was 1.7:1. Few patients were older than 60 years, although race and ethnicity of the cohort were similar to that of the general population. Similar demographic trends have been reported in series from France, Israel, Japan, and Mexico.[117,120,121] Dyspnea was the most common initial symptom and the mean time to diagnosis among patients in the NIH Registry was 2 years.

Prognosis of IPAH

Without effective therapy the prognosis of IPAH is very poor. The median survival of patients in the NIH Registry was 2.8 years; estimated survival at 1, 3, and 5 years was 68, 48 and 34 percent, respectively.[119] Similar or even worse data have been reported in other series from various countries.[25,122] Most patients in these series died of right heart failure.

The outlook was worse with more advanced symptoms. NIH registry patients who had symptoms corresponding to those of World Health Organization (WHO) functional classes III and IV symptoms had a median survival of only 31.5 months as compared with a median survival of 58.6 months in patients with milder impairment (class I or II) (Table 81-6). Although the data have improved, functional status remains a significant indicator of prognosis even with effective therapy.[117,123–126] For example, functional assessment using the 6-minute walk test is a useful means of following the response to therapy and independently predicts prognosis.[125,127–129] Maximal oxygen consumption has also been used to assess response to therapy and also correlates with survival.[128]

On the echocardiogram, either enlargement of the right atrium and/or the presence of a large pericardial effusion is associated with an increased risk of death.[109–112] A relative increase in the isovolumetric contraction and relaxation times of the RV as compared to its ejection time indicates RV dysfunction and a poorer prognosis.[108]

Levels of endothelin, catecholamines, and atrial natriuretic peptide in serum have been correlated with disease severity, and increases in serum uric acid, von Willebrand factor, D-dimer, troponin-T, and brain natriuretic peptide have been individually associated with poorer survival in patients with IPAH.[130–137] Recently, a low serum albumin has been associated with an increased risk of death, independent of other measurements that reflect passive hepatic congestion or right heart dysfunction.[112] None of these putative prognostic markers is currently incorporated into clinical decision making.

Table 81-6

World Health Organization Functional Classification of Patients with Pulmonary Hypertension

Class I: Patients with PH but without resulting limitation of physical activity. Ordinary physical activity does not cause undue dyspnea or fatigue, chest pain, or near syncope.
Class II: Patients with PH resulting in slight limitation of physical activity. They are comfortable at rest. Ordinary physical activity causes undue dyspnea or fatigue, chest pain, or near syncope.
Class III: Patients with PH resulting in marked limitation of physical activity. They are comfortable at rest. Less than ordinary activity causes undue dyspnea or fatigue, chest pain, or near syncope.
Class IV: Patients with PH with inability to carry out any physical activity without symptoms. These patients manifest signs of right heart failure. Dyspnea and/or fatigue may even be present at rest. Discomfort is increased by any physical activity.

Source: Adapted from: Rich S. Primary Pulmonary hypertension: Excutive summary. Evian, France. World Health Organization, 1998.

Hemodynamic variables that reflect the development of right heart failure (e.g., an increased right atrial pressure and a decreased cardiac index) worsen the prognosis.[117,121,138,139] Decreased survival has been seen in association with both increasing and decreasing mean pulmonary artery pressures (mPAP). These observations are not necessarily contradictory. Instead, they reflect the natural history of right heart failure in PAH: mPAP increases initially as the vascular derangements grow worse only to fall later as the right heart fails and is no longer able to generate an increased pressure (Figs. 81-16 and 81-17).

A regression equation based on hemodynamic data from the NIH Registry has been used to predict survival.[121,140] Because of the dismal prognosis of the disease, the use of long term "control" groups without treatment in clinical trials is unethical and assessments of survival with new therapies has been compared with the outcomes predicted by the NIH equation. Such comparisons have demonstrated improved survival with the use of epoprostenol, calcium channel blockers, or endothelin receptor antagonists. These improvements are addressed in the discussion of individual therapies below. As the number of effective drugs grows and is routinely employed, the relevance of survival estimates based on data from an era that lacked effective treatment is questionable. In essence, the NIH Registry equation may no longer be sufficient at predicting survival as standards of care and therapies have since improved dramatically. Indeed, when applied to a

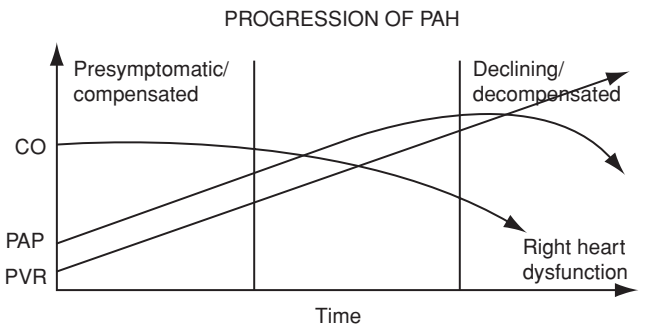


Figure 81-16 Hemodynamic changes during the progression of pulmonary arterial hypertension. With progressive increase in the pulmonary vascular resistance (PVR), the pulmonary artery pressure (PAP) initially increases until a failing right heart can no longer generate the required pressures to maintain cardiac output (CO). At this late stage both the cardiac output and pulmonary pressures may fall. (*Reproduced from Friedman EB, et al: Classification and prognosis of pulmonary arterial hypertension, in Mandel J, Taichman DB (eds),* Pulmonary Vascular Disease. *Philadelphia, Elsevier, 2006.)*

more recent cohort of patients treated with current agents, the NIH equation underestimated survival.[112]

It is not surprising that the prognosis of patients with IPAH who have suffered cardiac arrest is dismal even when resuscitative efforts are initiated promptly. In a retrospective review of the records of over 3000 patients, 132 episodes of attempted cardiopulmonary resuscitation (CPR) following cardiac arrest were identified. Survival at 90 days following CPR was only 6 percent.[141]

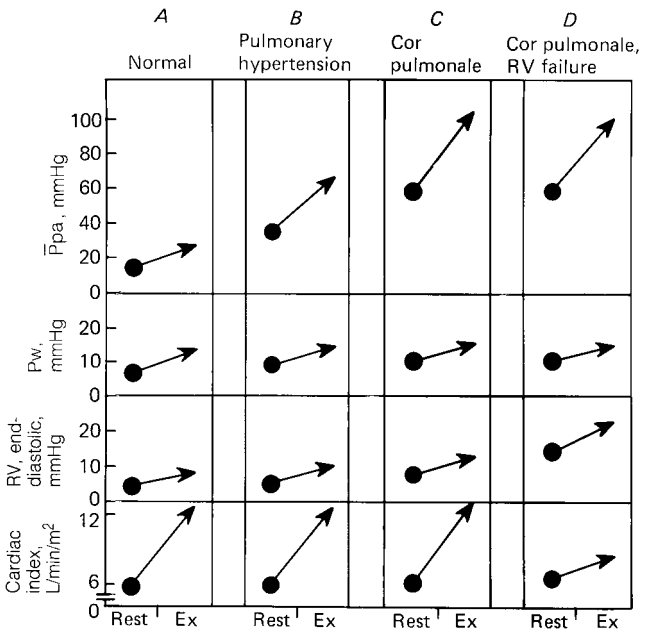


Figure 81-17 Schematic representation of evolution of chronic cor pulmonale. Hemodynamic studies at rest and during exercise in a normal subject (*A*). The stage of pulmonary arterial hypertension (*B*) is succeeded by cor pulmonale (*C*) in which the right ventricle performs normally despite pulmonary arterial hypertension but is known to be enlarged because of radiographic and echocardiographic findings. Once right ventricular failure supervenes (*D*) cardiac output fails to increase normally during exercise despite an increase of right ventricular filling pressure (end-diastolic) to abnormally high levels.

Familial Pulmonary Arterial Hypertension

A family of patients with IPAH, then termed primary pulmonary hypertension was first described by Dresdale in 1951.[3] Thereafter, additional families were reported. Subsequently, Loyd and Newman identified an autosomal dominant pattern of inheritance, an increased tendency for female carriers to manifest clinical disease, and an earlier onset in successive generations (genetic anticipation).[142,143] Linkage analysis led to a marker at chromosome 2q31-32, and mutations in the gene for a member of the TGF-β family of receptors, the bone morphogenetic protein receptor II (BMP-RII), was identified as the cause of familial PAH.[70,71,144,145] Moreover, mutations in another member of the TGFβ family, activin receptor-like kinase-1 (ALK 1) predispose patients with hereditary hemorrhagic telangiectasia to develop PAH.[78,79,146,147]

TGFβ receptors control an array of cell growth and differentiation systems. BMP signaling is involved in the control of normal vascular development as well as in the homeostasis of the adult pulmonary vasculature, probably by regulating the growth and apoptosis of endothelial and smooth muscle cells.[69] In an assessment of mutations from the coding sequence of *BMP-RII* in 210 patients, more than 140 distinct mutations were identified, the majority predicting premature truncation of the gene transcript. Disease is believed to be due to haploinsufficiency, which results in inadequate quantities of BMP-RII protein being produced for normal function.[148] In addition, the low penetrance observed in familial PAH suggests that environmental factors probably contribute to disease development in genetically susceptible individuals.[149]

Up to 60 percent of patients with familial PAH have germline mutations in a *BMP-RII*. So do some patients with idiopathic and other associated forms of PAH.[70–77] Clinically asymptomatic carriers may have evidence of mild pulmonary hypertension on the echocardiogram.[150] Common ancestries, identified in some individuals with IPAH, have linked some patients with PAH previously assumed to be sporadic. Failure to recognize familial cases of PAH may sometimes be due to incomplete family history taking or reporting and low disease penetrance, particularly in smaller families.[73,151]

There are no established differences between the approach to treating patients with familial PAH and those with IPAH. At present, the clinical evaluation of patients remains the same. Genetic testing of family members is to be considered in order to assess the risk that relatives will develop PAH. As a rough guide, there is a one-in-five chance of PAH developing in a first order relative who carries a disease-causing *BMP-RII* mutation. If genetic testing has not been performed, the risk of disease developing in the first-order relative of a patient with known familial PAH is approximately one in ten. In the absence of a disease causing *BMP-RII* mutation, the risk of disease is the same as in the general population (estimated at one in a million).[149] Because of the potential interpersonal, psychological, and economic implications of identifying an

at-risk genotype, genetic testing should only be performed in conjunction with professional genetic counseling.

Pulmonary Arterial Hypertension Associated with Specific Conditions

Collagen Vascular Diseases

The lungs, as well the pleura, are commonly affected in patients with collagen vascular disease. Although the frequency of pulmonary hypertension differs among the various collagen vascular diseases, fibrotic, interstitial changes are more common etiologies for pulmonary hypertension than is isolated involvement of the pulmonary vasculature. When present, however, pulmonary arterial hypertension is frequently a deadly development. It is important in this population to differentiate between pulmonary hypertension that is associated with hypoxia that stems from interstitial lung disease and hypoxia that occurs without significant interstitial changes. Pulmonary hypertension may also be due to left heart ischemic or diastolic dysfunction, or to thromboembolic complications of collagen vascular disease. Unfortunately, both interstitial disease and pulmonary arterial hypertension appear to coexist in many patients with collagen vascular diseases. Most clinical studies of therapy for pulmonary arterial hypertension have excluded patients with collagen vascular disease who have evidence of significant restrictive lung disease (usually defined as an FVC of less than 70 percent predicted) or evidence of interstitial changes in the lungs on chest radiographs. Extrapolation of efficacy data from such trials to justify the use of particular medications in patients with significant ILD may be problematic.

PAH occurs most often in systemic sclerosis among patients with limited disease or the CREST syndrome. Estimates have ranged significantly, but when confirmed by right heart catheterization, PAH has been found in between 7 and 29 percent of patients.[152] The prognosis of patients with scleroderma is worse when the disease is complicated by PAH than by severe pulmonary fibrosis. Nearly half of patients with PAH die within 1 year as compared with 3 years when the lung is affected by fibrosis alone.[153,154] Even with the use of equivalent therapies, the outcome of patients with PAH associated with systemic sclerosis is less favorable than for IPAH[56,124,153] (Fig. 81-18).

When estimated by echocardiogram, pulmonary hypertension has been identified in approximately 10 percent of patients with systemic lupus erythematosus, and as many as 43 percent when patients are followed prospectively.[155–159] In patients with mixed connective tissue disease, estimates are broad and without confirmation by catheterization. However, regardless of frequency, when pulmonary hypertension is present it appears to be a significant cause of death is these patients. PAH occurs in numerous other rheumatologic disorders, including Sjögren's disease and rheumatoid arthritis although firm data on incidence or survival are lacking.

Human Immunodeficiency Virus

Individuals infected with the human immunodeficiency virus (HIV) are at increased risk of developing pulmonary arterial hypertension. The mechanism by which HIV predisposes to the development of PAH is not known, but does not appear to be due to direct viral infection of pulmonary vascular endothelial cells.[160] Infection may elicit increases in the growth factors of mediators, such as endothelin and thereby result indirectly in the development of PAH.[161–163]

The estimated incidence of PAH among HIV-infected patients is 0.5 percent, significantly higher than the estimated annual incidence of 1.7 per million in the general population.[114,164] Symptoms, hemodynamic findings, and survival of PAH associated with HIV appear to be similar to those of IPAH.[165] As in the case of IPAH, prognosis is worse with more advanced symptoms (e.g., WHO functional class III or IV as compared with either I or II). A CD4 lymphocyte count below 212 cells/mm^3 is also associated with a poorer prognosis.[166] Mortality is more often directly attributable to PAH and right heart failure than to infectious complications.[165,166] The annual incidence of pulmonary hypertension at a large Swiss cohort of HIV-positive patients appears to be declining, having peaked at 0.24 percent in 1993 as compared with 0.02 percent in 2001; this decline may relate to the introduction of highly effective antiretroviral therapies.[167] It is possible, therefore, that better control of HIV infection decreases the risk of developing PAH. Whether this is true, or if therapy for HIV infection in individual patients with established PAH will alter the course of the pulmonary vascular disease remains unknown.

Portal Hypertension

The lungs may be affected by chronic liver disease in several ways, including vascular dilatations with resultant hypoxemia (the hepatopulmonary syndrome), the development of pleural effusions (hepatothorax), and pulmonary hypertension. Liver disease is frequently associated with a low systemic vascular resistance and a high cardiac output; the accompanying increase in blood flow and blood volume can cause pulmonary hypertension. Vascular changes that increase pulmonary vascular resistance occur when pulmonary arterial hypertension is associated with portal hypertension, i.e., the

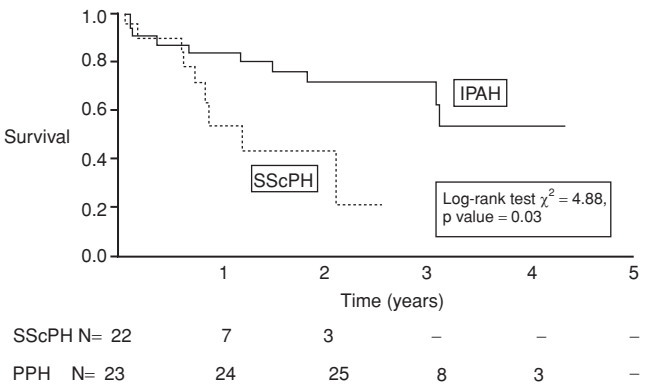


Figure 81-18 Survival of patients with systemic sclerosis associated pulmonary arterial hypertension is worse than that of patients with idiopathic pulmonary arterial hypertension despite equivalent therapies. *(Reproduced from Kawut et al: Chest 123:344–350 2003.)*

so-called portopulmonary hypertension (POPH). The pathogenesis of pulmonary hypertension in these patients may be difficult to unravel since the high cardiac output state that accompanies the liver disease may precede or accompany the development of POPH. Thus, as compared with patients with IPAH, patients with similar degrees of clinical impairment and POPH may manifest numerically smaller increments in pulmonary vascular resistance (PVR) or decrements in cardiac output.

The histopathological changes seen in POPH are the same as described in other forms of PAH: vasoconstrictive, proliferative, and obliterative changes that include both plexiform and thrombotic lesions.[168,169] The pathogenesis is not well understood. Although it has been suggested to involve abnormal proliferative (or other) vascular responses, the inducing trigger(s) have not been identified. As in other forms of PAH, altered levels of vasodilators and constrictors have been seen in patients with POPH.[170,171] In addition, portal hypertension might alter the vasoactive mediators to which the pulmonary circulation is exposed.[172] The severity of the portal hypertension does not appear to influence the risk of POPH.[173] Predisposing, probably genetic, factors are also believed to determine why only some patients with liver disease develop POPH. For example, whether mutations in *BMPRII* are involved in the development of POPH remains unknown.

The frequency of PAH in patients with liver disease has not been established. Estimates of up to 16 percent have been reported. But, these estimates are based on patients with more advanced liver disease.[170,174] In one series of patients evaluated for liver transplantation the prevalence of POPH was 8.5 percent.[168] Without effective treatment the prognosis of POPH is poor, a mean survival of only 15 months has been reported in one retrospective series of 78 patients.[175] Survival with current therapies is worse for patients with POPH than with IPAH. In a retrospective cohort of 13 patients with POPH, survival at 1 and 3 years was 85 and 38 percent as compared to 82 and 72 percent in 33 patients with IPAH.[176]

The symptoms and findings on physical examination of POPH are those of both PAH and of chronic liver disease. While shortness of breath may be overshadowed by abdominal complaints and fatigue, dyspnea becomes prominent as POPH advances. Differentiating between the contributions of PAH-related cor pulmonale and liver cirrhosis to the fatigue, edema, and abdominal complaints, including satiety, bloating, and ascites, can be difficult.

Compared with IPAH, relatively little is known regarding effective treatments for POPH. The small number of patients with POPH and the exclusion of these patients from clinical trials of therapy for PAH has resulted in less being known regarding the safety and efficacy of many agents. Mild disease usually does not require specific treatment; whether early therapy will prevent progression is unknown. Treatment for more severe disease differs from that of other patients with PAH in that some experts have advised against the use of calcium channel antagonists even if acute vasoreactivity to these agents has been demonstrated during cardiac catheterization. This concern is based upon the potential worsening of intrahepatic venous gradients by calcium channel antagonists.[177–180] Diuretics are particularly important in POPH due to the concomitant presence of cor pulmonale and cirrhosis, both of which cause fluid retention, edema, and ascites. Anticoagulation is less frequently used because of either underlying hepatic synthetic deficiencies and abnormal coagulation, or the presence of splenomegaly and the resulting significant thrombocytopenia. Individual patients have been treated with either intravenous or inhaled prostanoids.[181–188] The significant incidence of liver function abnormalities associated with endothelin antagonists has raised concern about their use in patients with POPH. Bosentan (Tracleer) was successfully used in a nonrandomized study of 11 patients with POPH and child class A resulting in improvements in hemodynamic values, exercise capacity, and no significant liver toxicity.[189] Randomized trials have not been done. The possibility exists of using relatively specific endothelin-A receptor antagonists with lower toxic profiles. Such agents might allow the treatment of additional patients with POPH. However, such studies have not been reported. Although individual instances of improved hemodynamics following the use of sildenafil in patients with POPH have been reported, no data are available from a randomized study.[190,191]

Many patients with advanced hepatic dysfunction require liver transplantation. However, the perioperative mortality is significantly increased by the presence of PAH and a mean PA pressure above 50 mmHg is a contraindication to transplantation.[192,193] Effective treatment has lowered pressure in some patients who subsequently underwent successful orthotopic liver transplantation.[181–184,190,194] Therefore, it is essential that POPH be recognized in patients being considered for liver transplantation prior to surgery. All potential liver transplant patients should be assessed by echocardiography followed by cardiac catheterization if the estimated right ventricular systolic pressure exceeds 50 mmHg. Serial monitoring should be performed to detect the development of pulmonary hypertension in patients listed for liver transplantation.[195] Unlike the hepatopulmonary syndrome in which liver transplantation results in resolution of the pulmonary vascular abnormality, liver transplantation is not consistently curative of POPH. While some instances of reversal have been reported, in other patients POPH has progressed after transplantation.[177]

Drugs and Toxins

The term dietary pulmonary hypertension refers to the fact that substances taken by mouth can damage the pulmonary circulation. In animals, ingestion of crotalaria spectabilis, an annual shrub, causes multiorgan injury, including damage to the lungs. In humans, certain appetite suppressant drugs exert similar effects.

ANORECTIC AGENTS: AMINOREX AND FENFLURAMINE DERIVATIVES Between 1966 and 1968, an epidemic of PAH erupted in Switzerland, Austria, and Germany in which the incidence of PAH

increased 20-fold.[196] The epidemic followed the introduction in these countries of an appetite-depressant agent, aminorex (2-amino-5-phenyl-2-oxazoline), in November 1965. Although only 2 percent of those exposed to the drug developed PAH, the relative risk compared to unexposed individuals was 52:1.[197] Aminorex resembles epinephrine and amphetamine in chemical structure; both of these agents release endogenous stores of catecholamines. Aminorex was banned in 1968, and the epidemic subsided. In some patients, the level of pulmonary hypertension decreased or stabilized at a tolerable level; in others, it seemed to reverse completely. Nonetheless, in many patients, after the drug was no longer obtainable, the disease continued inexorably from pulmonary hypertension to cor pulmonale and death. The pathology produced by aminorex in humans was identical with that of IPAH, including plexiform lesions and intimal fibrosis. Attempts to produce pulmonary hypertension by administering aminorex to experimental animals were consistently unsuccessful.

This outbreak had several important epidemiological implications: (a) a medication taken by mouth could damage pulmonary arteries and arterioles; (b) since only few of the many individuals who used the agent developed pulmonary hypertension, the possibility was raised of genetic susceptibility to injury by aminorex; (c) another possibility was that other anorectic medications that resemble the catecholamines and amphetamines in structure might have similar effects in predisposed individuals (this possibility was reinforced by subsequent experience with phenformin, an anorectic agent that resembles the amphetamines in structure); and (d) pulmonary hypertension can be reversible, particularly when detected early in its course and before pressures reach systemic levels.

After the aminorex epidemic, a variety of appetite-suppressant medications were used with little heed to the possibility that these agents might cause PAH. Then, in the early 1990s, Brenot et al. called attention to the coincidence in Europe of pulmonary arterial hypertension and the use of fenfluramine derivatives for weight reduction,[32] prompting the establishment of an international registry in Europe to assess the incidence and risks of IPAH. Among the 95 patients enrolled in the registry, the use of anorectic agents was clearly associated with an increased risk of PAH, especially when taken longer than 3 months (odds ratio 23.8). In 1996, Abenheim et al. sounded the alarm that an epidemic might be in the making: The Food and Drug Administration in the United States had approved the use of dexfenfluramine, a major fenfluramine derivative, for the long-term treatment of obesity, even though experience with its long-term use was extremely sparse.[114]

Approval of dexfenfluramine by the FDA was followed by a tremendous increase in sales of dexfenfluramines and other anorectic agents. A registry of idiopathic and anorectic agent-associated PAH in the United States revealed that use of fenfluramine was strongly associated with the development of PAH (odds ratio 7.5 with more than 6 months of use). A high frequency of the use of anorectic agents in patients with other forms of PAH was also seen, suggesting these agents might precipitate disease in the presence of other risks such as a collagen vascular disease.[115]

A few lessons were learned: (a) although aminorex and the fenfluramines differ in their pharmacologic characteristics, the pulmonary vascular lesions in the patients who die of pulmonary hypertension after taking either drug are identical; (b) the longer the anorectic agent is used, the more likely is pulmonary hypertension to occur; (c) early pulmonary hypertension is difficult to diagnose and mortality is high after the disease is established; and (d) the occurrence of pulmonary hypertension in users of anorectic agents is apt to be related to other determinants of susceptibility, perhaps genetic factors.

Aminorex and fenfluramine derivatives may cause PAH by altering blood levels of serotonin (5-HT). These agents cause the release of serotonin from storage in platelets and inhibit its reuptake.[40] Since 5-HT is a potent vasoconstrictor and induces aggregation of platelets, this may be a mechanism by which anorectic agents induce PAH (see Pathobiologic Mechanisms). Additional mechanisms by which aminorex and fenfluramine derivatives might contribute to pulmonary vasoconstriction is via the inhibition of potassium channels that mediate vasodilation.[65] As indicated, it has also been proposed that anorexigens play an inductive role in promoting the development of PAH in genetically susceptible individuals. Genotyping for the presence of mutations in *BMPRII* (with familial PAH) has not revealed a significant number of abnormalities among patients with anorexigen-associated PAH.[75,198]

In a series of 62 patients with fenfluramine-associated PAH evaluated over a 10-year period at a single center in France, the interval between drug exposure and the development of dyspnea was approximately 4 years. Hemodynamic values at the time of diagnosis were similar to those of a control group of patients with IPAH, although patients exposed to anorectic-agents were less likely to demonstrate acute vasoreactivity and, therefore, less likely to be treated with calcium channel antagonists.[199] The approach to therapy for PAH associated with the use of anorectic agenesis is the same as for IPAH.

Relatively little is known regarding the prognosis of anorectic agent-associated PAH. Compared with IPAH, the data concerning prognosis are conflicting. In a retrospective study of 104 patients with aminorex-associated PAH and 69 with IPAH, survival was better in both groups when treated with warfarin and better overall for the patients with anorectic-agent associated disease.[200] However, in one study, with the use of additional therapies, such as oral vasodilators and epoprostenol, survival in fenfluramine-exposed patients with PAH appears to be similar to that of IPAH patients. Another study of IPAH and fenfluramine-exposed patients, in which treatments and severity of the disease were matched, found poorer survival in the anorexigen group.[201]

TOXIC OIL SYNDROME Another episode in the story of dietary pulmonary hypertension unfolded with the occurrence of the toxic oil syndrome. In May and June 1981, adulterated

rapeseed oil, a bootleg pseudo-olive oil sold door-to-door in Spain, caused an outbreak of noncardiogenic pulmonary edema.[202] Twenty thousand persons were affected, and about 375 died. About 2000 experienced sequelae. As a consequence of close surveillance, the features of three stages of the disease were categorized: *early* (first 6 months), *intermediate* (6 months to 2 years), and *chronic* (persisting 5 years). From the outset, it was clear that the damage was widespread (affecting lungs, liver, skin, nervous system, immune system, muscle, and fat) and endothelial injury everywhere featured prominently in the pathogenesis of the clinical syndromes.

The early stage of the toxic oil syndrome was characterized by noncardiogenic pulmonary edema, eosinophilia, and in some individuals, pulmonary hypertension; these resolved within 6 months. The intermediate stage was marked by thromboembolic events, weight loss, and neuromuscular dystrophies; PAH developed in some but often resolved. The chronic stage (particularly 4 and 5 years after the oil was ingested) involved progressive PAH and cor pulmonale. Increasingly evident were the vascular lesions of intimal fibrosis and proliferation in association with organized pulmonary thromboemboli. Plexiform lesions were also seen.

Unfortunately, the chemical ingredients in the toxic oil responsible for the syndrome remain enigmatic and are unlikely to be identified, since the bootleggers provided no recipe for the adulterated cooking oil as they went out of business. Nonetheless, the outbreak did show that material taken by mouth—often in small quantities—could cause widespread endothelial injury in the lungs. It also underscored the spontaneous reversibility of the pulmonary hypertension (as well as the ineffectiveness of vasodilators tried at different stages in the disease).

Hemoglobinopathies

Patients with sickle cell anemia and β–thalassemia are at increased risk for the development of pulmonary arterial hypertension. Multiple factors might contribute to the pathogenesis of PAH in patients with hemolytic states, including recurrent thromboembolism, recurrent infectious or hemolytic crises causing lung damage and hypoxia, asplenia, and the hematologic effects of the intravascular hemolysis. Hemolysis contributes to the development of PAH by decreasing the bioavailability of NO. Hemoglobin is released into the plasma from destroyed red blood, where it can destroy NO. The substrate for NO production, L-arginine, is also destroyed by increased levels the enzyme arginase, which is released into the plasma by hemolysis. Further effects of hemolysis include an increase in the expression of vascular adhesion molecules, platelet activation, the production of free radicals, and increased levels of endothelin; all of which might contribute to the vasculopathy.[203–205]

The reported prevalence of pulmonary hypertension in patients with sickle cell anemia has ranged from zero to 40 percent depending upon whether the population was symptomatic, whether testing involved echocardiograms or catheterization, and the age of the patients. In a prospective study of 195 adult patients with sickle cell anemia, 32 percent of patients had echocardiographic evidence of pulmonary hypertension; more than 90 percent of the patients had the SS phenotype.[206] In thalassemia, the prevalence of pulmonary hypertension may vary.[207–210] Pulmonary hypertension has also been noted in patients with other chronic hemolytic disorders, including hereditary spherocytosis and paroxysmal nocturnal hemoglobinuria.[211,212] Pulmonary hypertension worsens the prognosis in patients with sickle cell anemia.[203,206]

The hemodynamic findings of PAH associated with sickle cell anemia differ from those seen in patients with idiopathic or other forms of associated PAH. In particular, the mean PAP tends to be lower and cardiac output higher in patients with sickle cell anemia and PAH than in patients with IPAH. In addition, many of the pulmonary hypertensive patients with hemoglobinopathy demonstrate a combination of intrinsic pulmonary vascular disease suggested by an increase in pulmonary vascular resistance in association with left heart diastolic dysfunction and an increase in pulmonary wedge pressure. For example, in 20 patients with PAH associated with sickle cell anemia the mean PAP was 36 mmHg, the cardiac output 8.6 L/min and the PCWP 16 mmHg; half of the patients had PCWP values greater than 15.[213]

The optimal treatment of patients with PAH associated with a hemoglobinopathy has not been established. Since markers of ongoing hemolysis correlate with the severity of the pulmonary hypertension as well as survival in patients with sickle cell disease, optimizing treatment of the hemolytic anemia is likely an important component in the control of PAH itself.[203,206] Treatment includes the use of hydroxyurea or transfusions in order to minimize anemia and ongoing hemolysis. Prostacyclin administered intravenously can acutely decrease the mean PAP and pulmonary vascular resistance in patients with PAH associated with sickle cell anemia, but its long-term benefits have not been established.[213] In an uncontrolled series of adult patients with PAH associated with sickle cell anemia, oral sildenafil acutely improved the mPAP, PVR, and cardiac index; when given chronically to 12 patients the 6-minute walk distance was improved.[214] Improvements with sildenafil have also been reported in a small, uncontrolled series that included patients with thalassemia, but further evaluations of efficacy and safety issues, such as the occurrence of headache and priapism are required.[215] Supplemental oxygen should be used as in other forms of PAH to prevent hypoxia. Anticoagulation to prevent thromboembolic complications of sickle cell anemia also warrants consideration.

Pulmonary Veno-occlusive Disease

Pulmonary veno-occlusive disease (PVOD) is a rare form of PAH in which the understanding of mechanisms and experience with treatment are even less than in other forms of PAH.[18,216] Pathological changes at both the arterial and venous sides of the pulmonary circulation are found in all forms of PAH, but arterial changes tend to be the preponderate in most. In contrast, alterations at the veins described

by the pathological term pulmonary occlusive vasculopathy are the predominant histological finding seen in PVOD[17,26] (described above under Anatomic Changes in Pulmonary Arterial Hypertension). In PVOD,[5] the pulmonary veins are occluded by fibrous tissue, intimal thickening, and large numbers of hemosiderin-laden macrophages. Lymphatic dilation in the lung and pleura are additional features.

The incidence and prevalence of PVOD are unknown, owing at least in part to its misdiagnosis as IPAH. Thirteen percent of cases in the National Institutes of Health Registry had histological changes of PVOD. In a series of IPAH patients in which patients who met the criteria for the diagnosis of PVOD, Mandel estimated the incidence to be 0.1 to 0.2 patients per million persons in the general population.[18] Prospective studies have not been performed, and the true incidence of PVOD may be higher, since patients are apt to be misclassified because of similarities in the radiographic appearance, as either interstitial lung disease or heart failure.[216] There is no apparent predilection for women (as occurs in IPAH) and the diagnosis has been made in patients ranging in age from infancy to the seventh decade of life.

The risk factors for PVOD are not well known. Since sibling cases of this apparently rare disease have been reported, a genetic predisposition has been postulated. Indeed, a mutation in *BMPRII* has been identified in a patient with PVOD whose mother had died of pulmonary hypertension (although the possible occurrence of PVOD in the parent could not be confirmed).[77] Case reports of PVOD complicating treatment of cancer with various chemotherapeutic agents (notably mitomycin, bleomycin, carmustine, and gemcitabine) or following bone marrow transplantation suggest that toxic exposures might elicit pathological vascular responses.[217–230] Other case reports have noted the development of PVOD in association with various thrombophilic states, autoimmune disorders, or following bacterial or viral infection, including HIV.[231–238]

Patients with PVOD usually present with dyspnea and fatigue; symptoms that are less typical in other forms of PAH such as cough, orthopnea, and hemoptysis have also been observed.[105,239–243] The presence of basilar inspiratory crackles on physical examination, although nonspecific, might favor a diagnosis of PVOD over other forms of PAH. Decreased breath sounds might suggest the presence of a pleural effusion, which tends to occur more commonly in PVOD.[244,245]

The diagnosis of PVOD is suggested by the triad of pulmonary hypertension, radiographic evidence of pulmonary edema and a normal pulmonary artery occlusion (wedge) pressure. Unfortunately, all three are not universally present in cases of PVOD and the diagnosis is often delayed by confusion with other findings. For example, "high probability" findings on ventilation-perfusion scanning may lead to an erroneous diagnosis of chronic thromboembolic pulmonary hypertension.[246] Findings on plain radiographs and CTs in PVOD might suggest left heart failure under other circumstances. These findings include enlargement of the central pulmonary arteries, peribronchial cuffing, Kerley B lines, interstitial infiltrates, and pleural effusions[105,247] (Fig. 81-19).

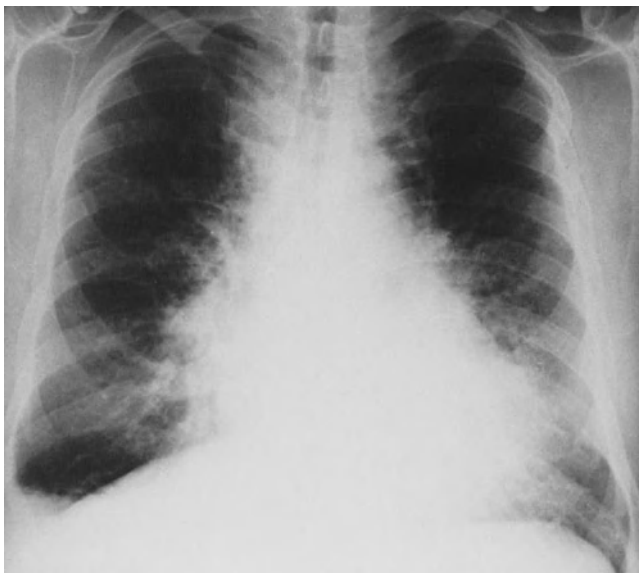


Figure 81-19 Pulmonary veno-occlusive disease. Posteroanterior chest radiograph demonstrates pulmonary venous engorgement and edema. Diagnosis established by cardiac catheterization angiography and lung biopsy.

However, unlike left heart failure, the pulmonary artery wedge pressure is normal in patients with PVOD.[248,249] Obtaining an adequate tracing, however, can be difficult. Of note has been the observation of a marked increase in pressure followed by a slow decrease to normal when saline is flushed through the wedged catheter; this sequence is presumably due to impaired run-off of fluid through the restricted pulmonary venous vessels. The diagnosis of PVOD often requires surgical biopsy, which may be too risky in the setting of severe pulmonary hypertension and not likely to lead to therapy that will alter outcome. However, the information may be helpful in avoiding needless and possibly harmful therapies and in providing the patient with information about the prognosis.

Features that are atypical for other forms of PAH (e.g., radiographic abnormalities that are consistent with left heart failure) should heighten caution when considering acute vasodilator testing.[105,247] Acute pulmonary edema has been precipitated by the administration of vasodilators to patients with PVOD, and deaths have been reported.

There are no established therapies for PVOD. Controlled studies have not been performed and only anecdotal reports are available; these indicate both positive and negative responses to various agents. Some patients have experienced benefit, while others have died following the use of either calcium channel antagonists or intravenous epoprostenol administered intravenously.[105,250–254] A single patient is reported to have experienced an improvement in exercise tolerance with the use of inhaled iloprost.[255] Glucocorticoids and other immunosuppressive agents have been attempted but here too the experience has been anecdotal, with mixed results, and their use not generally recommended except in patients in whom a concomitant inflammatory condition exists.[216,256,257] As in other forms of PAH, diuretics,

supplemental oxygen, and digoxin should be employed as indicated. Newer agents for the treatment of PAH have not yet been assessed (e.g., endothelin receptor antagonists and phosphodiesterase inhibitors); for some patients, lung transplantation may be the only therapeutic option.

The prognosis of patients with PVOD is poor, with most dying within 2 years of diagnosis.

Pulmonary Capillary Hemangiomatosis

Pulmonary capillary hemangiomatosis is another rare form of PAH with predominant involvement of the pulmonary veins. Pathologically, the findings are those of pulmonary microvasculopathy marked by angioproliferative capillary lesions that appear to invade the pulmonary vessels, interstitium, and in some instances, the airways.[19,258] The etiology is unknown. The presence of vascular growth factors as well as markers of altered endothelial cell proliferation has been reported; altered expression of NO synthase has also been noted.[259–261] A familial form has been identified in three siblings, but specific genetic linkage has not been reported.[262]

Since only scattered case reports are available for evaluation, the epidemiologic features of the disease are unknown. Pulmonary capillary hemangiomatosis may present with dyspnea and/or hemoptysis, and instances with and without associated pulmonary hypertension have been reported. The radiographic findings consist of diffuse bilateral reticulonodular infiltrates, often associated with enlargement of the central pulmonary arteries.[263,264] The prognosis is terrible with most cases reported as fatal, often rapidly. Attempts at treatment with epoprostenol administered intravenously have evoked pulmonary edema.[265–267] Successful treatment of a few patients with α-interferon has been reported; one patient with superimposed endotheliomatosis was stabilized with doxycycline.[22,268] Lung transplantation remains an option.

Therapy for Pulmonary Arterial Hypertension

Treatment for pulmonary arterial hypertension aims to reduce pulmonary vascular resistance, thereby improving cardiac output. Acute improvements occur in some patients with certain vasodilators. Used chronically, some agents also appear to have cellular effects that may ameliorate some of the vascular derangements seen in untreated disease. Whereas a diagnosis of IPAH was only recently associated with a dismal prognosis, recent remarkable progress has resulted in the availability of multiple therapies and a significantly improved outlook with many long-term survivors. No currently available medical treatment, however, is curative. Lung transplantation remains an option for some who fail medical therapy.

Most patients in controlled clinical trials of treatment with calcium channel antagonists, prostanoids, endothelin receptor antagonists, or phosphodiesterase inhibitors have had IPAH. Fewer patients have been studied with familial PAH or various forms of associated PAH. It is important to bear in mind the paucity of data available on the efficacy of certain agents when used in some forms of PAH. It is also important to recognize the limits of our knowledge regarding the relative efficacy of available agents. Data from head-to-head comparisons are lacking. Most often, patients treated with epoprostenol have been sicker than those treated with oral therapies.

In general, the choice of initial therapy depends upon the functional class and hemodynamic status of the patient. Most clinical trials have enrolled patients and assessed response, at least in part, on the basis of a WHO modification of the New York Heart Association functional assessment of patients with heart failure (Table 81-6). Such a scheme is often used as a rough gauge when deciding upon therapy. WHO functional class, however, should also be considered in the context of the patient's hemodynamic status. For example, a WHO functional class III patient who has not recently experienced acute clinical change and who has a cardiac index of 2.5 L/min/m^2 might be appropriately treated initially with oral therapy. In contrast, a WHO class III patient who is either experiencing a rapid clinical decline or has a severely depressed cardiac index (e.g., below 2 L/min/m^2), might be more appropriately managed initially with intravenous prostanoid therapy. Social factors often influence the type of treatment acceptable to the patient. In addition, psychosocial issues, cognitive abilities, and other determinants of patient compliance may make certain therapies unsafe even if otherwise medically indicated.[269]

Acute Vasodilator Testing and Calcium Channel Antagonist Therapy

The calcium channel antagonists diminish vascular tone by preventing an increase in cytosolic calcium concentration by inhibiting both the influx of extracellular calcium and the release of calcium from intracellular stores. The long-term prognosis is good for some IPAH patients who respond acutely to the administration of short-acting pulmonary vasodilators and are treated subsequently with calcium channel antagonists. However, since other patients may be harmed by such treatment, acute vasodilator testing is performed at the time of right heart catheterization to determine suitability for such treatment. Agents commonly used include inhaled NO, infused adenosine, or epoprostenol administered by either route.[270–276] Although the definition of a positive acute vasodilator response has varied, a decrease in the mPAP of at least 10 mmHg to less than 40 mmHg, and a cardiac output increased or unchanged is generally considered to be a positive response[103,277] (Fig. 81-20).

Acute vasodilator testing carries significant risk and deaths have been reported.[278] It should not be performed when pulmonary veno-occlusive disease is suspected, as the inability of the venous system to accommodate an acute increase in flow may precipitate pulmonary edema.[18] Acute vasodilator testing should be performed only at experienced centers and when the results will influence therapy.

Some patients who manifest acute vasoreactivity respond to treatment with oral calcium channel antagonists

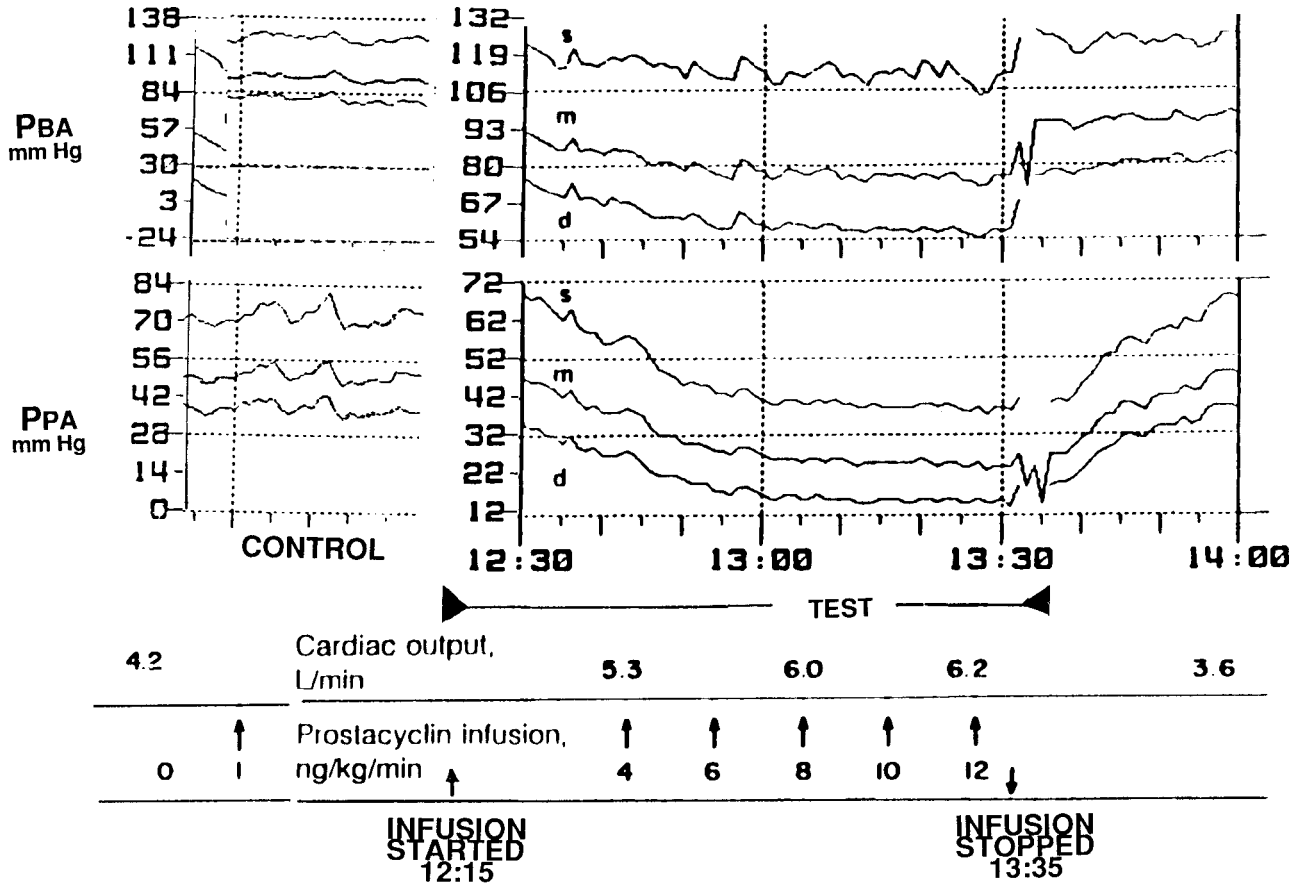


Figure 81-20 Acute vasodilator testing. An intravenous infusion of epoprostenol (prostacyclin) was used in a patient with idiopathic pulmonary arterial hypertension illustrating vasodilation in a ''responder." The infusion was started at 12:15. Within 15 min (12:30) the pulmonary arterial pressure (Ppa) had begun a dramatic decline despite an increase in cardiac output. The decrease in pulmonary vascular resistance lasted as long as the infusion was continued (until 13:35). After the infusion was stopped (13:35) the Ppa increased rapidly to preinfusion levels and the cardiac output dropped. The changes in systemic arterial pressure (Psa) were much less striking. *(Courtesy of Dr. H Palevsky.)*

and have a better prognosis. In one study, the survival rate of acutely responsive patients treated chronically with oral calcium antagonists was maintained at 94 percent when measured at 1, 3, and 5 years.[279] Unfortunately, relatively few patients demonstrate acute vasoreactivity (little more than 10 percent by recent estimates) and of these only about half experience a sustained clinical response.[280] Oral calcium antagonists should not be used as vasodilator therapy in the absence of acute vasoreactivity. Nonresponders not only fail to benefit but are also prone to adverse side effects, including systemic hypotension, a decrease in cardiac output because of a negative inotropic effect on the heart, arrhythmias, and retention of salt and water.

Patients who do manifest a significant acute pulmonary vasodilator response to short-acting agents should undergo monitored trials of oral calcium channel antagonists. Increasing doses of nifedipine or diltiazem are usually administered until pulmonary hemodynamics are improved (i.e., there is a significant decrease in pulmonary vascular resistance, pulmonary arterial pressure, and a possible increase in cardiac output). Agents such as verapamil, which exert negative inotropic effects, should be avoided. Testing is stopped if systemic hypotension develops or hemodynamic values tend to worsen. Relatively high doses of calcium channel antagonists are required to promote sufficient pulmonary vasodilation. In some instances, the required daily doses of nifedipine and diltiazem have exceeded 200 and 700 mg, respectively.[281] The total daily dose should be divided and administered in two or three doses of long-acting formulations to minimize peak and trough effects during the day. Patients treated with oral calcium antagonists must be monitored for the development of side effects including systemic hypotension or peripheral edema.

Endothelin Receptor Antagonists

Recognition of the role played by endothelin in the pathogenesis of pulmonary arterial hypertension has led to the rapid development of agents which inhibit interaction with its receptors (ET_A and ET_B). Both dual ET_A/ET_B and relatively ET_A-selective antagonists have been developed for oral use.

Bosentan is a dual ET_A/ET_B antagonist that improves hemodynamics, exercise capacity, WHO functional class and

the time to clinical worsening (defined as death, PAH-related hospitalization, need for altered therapy or lung transplantation).[56,282] At 16 weeks, in a double-blind, randomized, placebo-controlled trial of patients with IPAH and PAH associated with collagen vascular disease (predominantly systemic sclerosis), bosentan improved the 6-minute walk distance by 44 meters as compared with placebo. Exercise capacity was improved in IPAH patients, while stabilized or the rate of deterioration slowed in patients with systemic sclerosis.[56] Bosentan's beneficial effects on exercise capacity and functional class persist at 1 year with open-label use.[283] Survival of IPAH patients treated with bosentan in these trials and their open-label extensions was 96 percent at 1 year and 89 percent at 2 years as compared with expected survival of 69 and 57 percent, respectively, as predicted by the NIH registry equation.[58] In nonrandomized studies or case series, bosentan appears to be effective in patients with PAH associated with HIV infection,[284] adults with congenital heart disease[285] and those with chronic thromboembolic pulmonary hypertension.[286,287] Although data are limited, its use also appears to be effective in pediatric patients.[288–290]

Bosentan therapy is initiated at a dose of 62.5 mg twice daily by mouth. If liver function remains normal, the dose is increased after 1 month to 125 mg twice daily. Liver function must be monitored monthly as significant disturbances may occur; severe increases in transaminase levels (greater than eight times normal) require discontinuation of therapy. Notable side effects include peripheral edema (usually readily responsive to diuretics), anemia, and nasal congestion. Bosentan is contraindicated for use with either cyclosporine or glyburide.

Ambrisentan and sitaxsentan are relatively specific ET_A-receptor antagonists that, like bosentan, improve hemodynamics, exercise capacity and WHO functional class. In randomized controlled trials, each has demonstrated improvement in 6 minute walk distance (corrected for placebo effect).[291–293] Patients in these studies had IPAH, or associated PAH (e.g., in patients with scleroderma). One small study showed that most patients maintain this improvement after one year of open label sitaxsentan therapy. Both drugs appear to have a lower incidence of increase in liver enzymes than bosentan, but as of the time of this writing definitive evaluation and approval for use are pending.

Phosphodiesterase Inhibition

The relative deficiency of NO-mediated vasodilation and modulation of cell growth in patients with PAH has led to attempts to enhance its therapeutic effects. NO acts through the second messenger cGMP, which is metabolized in the lung predominantly by phosphodiesterase-5. Specific inhibitors of phosphodiesterase 5 (e.g., sildenafil, vardenafil, and tadalafil) can promote acute pulmonary vasodilation.[294] At present, published clinical experience is predominantly with the use of sildenafil citrate (Revatio).

In a double-blind, randomized placebo controlled trial of 267 patients predominantly with IPAH and fewer with either congenital heart or collagen vascular disease, sildenafil administered orally at 20, 40, or 80 mg three times daily improved hemodynamics, exercise capacity, and functional class.[295] Although the time to clinical worsening was not affected in this single trial, the improvement in exercise capacity (51 meters as compared with baseline) was maintained over 1 year with continued open-label use of sildenafil at 80 mg three times daily. No statistically significant dose-response was seen in this trial; the FDA-approved dosage for treatment of PAH is 20 mg by mouth three times daily. In a small noninferiority study of 26 patients with either IPAH or connective tissue–associated disease, no difference in the improvement of echocardiographic measurements or 6-minute walk distance was found after 16 weeks of treatment with either sildenafil, 50 mg three times daily, or bosentan (used as described above).[296] The most common side effects of sildenafil when used for treatment of PAH are headache, flushing, diarrhea, and epistaxis; systemic hypotension also has occurred, particularly when sildenafil is used in combination with nitrates.

Prostanoid Therapies

Prostacyclin analogs have played a key role in the management of idiopathic and other forms of PAH. Prostacyclin is a powerful vasodilator (both pulmonary and systemic) as well as an inhibitor of smooth muscle proliferation and platelet aggregation. It is a product of arachidonic acid metabolism and acts, at least in part, by stimulating the intracellular production of cAMP. Its major source is the vascular endothelial cell and deficiencies are noted in patients with PAH.

Several synthetic prostacyclin analogs are currently available for the long-term treatment of PAH, including formulations that are administered by continuous intravenous infusion (epoprostenol, treprostinil, and iloprost), or subcutaneous infusion (treprostinil) or via inhalation (iloprost). An oral prostanoid formulation (beraprost) is rarely used, except where more effective treatments are unavailable. Additional formulations are in development (e.g., treprostinil for inhalation or for oral use).

Epoprostenol (Prostacyclin) (Flolan)

Epoprostenol (Prostacyclin) was the first prostanoid therapy shown in randomized clinical trials to be beneficial in the treatment of PAH. Because of its short half-life (on the order of only minutes) it requires continuous intravenous infusion. Eighty-one patients with IPAH were randomized to receive epoprostenol infusion or treatment that was standard at the time (i.e., oral vasodilators, diuretics, cardiac glycosides, and anticoagulants).[297] After 12 weeks of treatment, hemodynamic values were improved in the epoprostenol group (e.g., a 21 percent decrease in pulmonary vascular resistance compared with an increase in the control patients) as was the 6-minute walk distance (increased by 31 meters compared with a decrease of 29 meters in the control patients). None of the patients treated with epoprostenol died during the

study, in contrast to a 20 percent mortality by 12 weeks with conventional therapy. Intravenous epoprostenol therapy for IPAH was approved by the FDA in 1995.

Additional reports have confirmed and extended these observations. Indeed, originally conceived as a bridge to lung transplantation in patients with severe PAH, the long-term use of epoprostenol and other treatments has resulted in a decrease in the demand for lung transplantation for this indication.[298] In 1998, Robbins et al. reported that more than two-thirds of their patients treated with epoprostenol were so much improved that their names could be removed from the waiting list for lung transplantation.[299] In a cohort of 162 IPAH patients, McLaughlin et al. observed 1- and 3-year survival rates of 88 and 62 percent, compared to rates of 59 and 35 percent predicted by the NIH Registry equation.[126] Remarkably similar results were observed by Sitbon et al. in a cohort of 178 epoprostenol-treated patients with IPAH at 1 and 3 years; somewhat lower results were obtained by Kuhn et al. In each report, survival was improved over that predicted by the NIH Registry equation.[124,125] Unfortunately, however, one-third of patients with idiopathic PAH died within 3 years and nearly half by 5 years (Fig. 81-21).

Epoprostenol infusion therapy has also been used in other forms of PAH. A randomized multicenter trial in patients with systemic sclerosis associated PAH (without significant interstitial lung disease) showed improvements in both hemodynamics and exercise capacity.[300] Favorable results of epoprostenol treatment have also been reported for patients with PAH due to systemic lupus erythematosus,[301] congenital left-to-right shunts,[302] the use of anorectic agents,[199] patients with HIV, portopulmonary hypertension,[181] and inoperable chronic thromboembolic pulmonary hypertension.[303] Epoprostenol has been used successfully in isolated instances of patients with pulmonary veno-occlusive disease. However, the use of epoprostenol in patients with PVOD must be approached with extreme caution, since its use in patients with impeded pulmonary venous blood flow might precipitate pulmonary edema.[18] Isolated attempts at epoprostenol infusion therapy in patients with pulmonary capillary hemangiomatosis (also characterized by predominant involvement of the pulmonary veins) have resulted in death.[22] In a single randomized trial of patients with left ventricular dysfunction, the use of epoprostenol was associated with a trend toward increased mortality.

Epoprostenol therapy is initiated at 1 to 4 ng/kg/min and progressively increased in 0.5 to 1 ng/kg/min increments, at intervals dictated by patient response and side effects. Continuous increases in dosage are required in order to maintain relief of symptoms. Often, daily or alternate-day increases in dosage are needed to relieve severe symptoms (e.g., dyspnea, lightheadedness). Such titration must be closely monitored for prostanoid side effects (e.g., nausea, tachycardia, diarrhea, masticatory jaw pain).[304] Patients typically reach a steady dosage between 20 and 40 ng/kg/min after several months. Thereafter, the dosage may be held stable or increased every few weeks. Even patients who do not manifest an acute vasodilator response (e.g., to infused epoprostenol) have shown improved hemodynamics and exercise capacity after sustained treatment, suggesting that epoprostenol's beneficial effects are not mediated merely through acute vasodilation, but also by effects on cell growth, platelet function and cardiac output.

Treatment with epoprostenol requires a tunneled intravenous catheter. Therefore, treatment is associated with a significant risk of bacterial infection. Infusion requires the use of a battery-powered portable infusion pump that must be carried at all times; the drug's short half-life demands the constant availability of a back-up medication cassette and pump since an interruption in the infusion of only a few minutes can result in hemodynamic compromise. In addition, the drug is unstable at room temperature and must be mixed daily and kept cool with ice packs. For these reasons, the patient must be relatively highly functional and compliant for the safe administration of epoprostenol intravenously, preferably in conjunction with a strong social support system at home. Intensive patient and family education is required for safe initiation of therapy and is often performed in the hospital until appropriate understanding has been demonstrated.[304]

Despite the significant risks and inconveniences, as well as the development of longer-acting formulations, experience and duration of benefit are greatest with epoprostenol infusion, which remains an important treatment for severe PAH. It is also a benchmark against which other therapies are often compared.

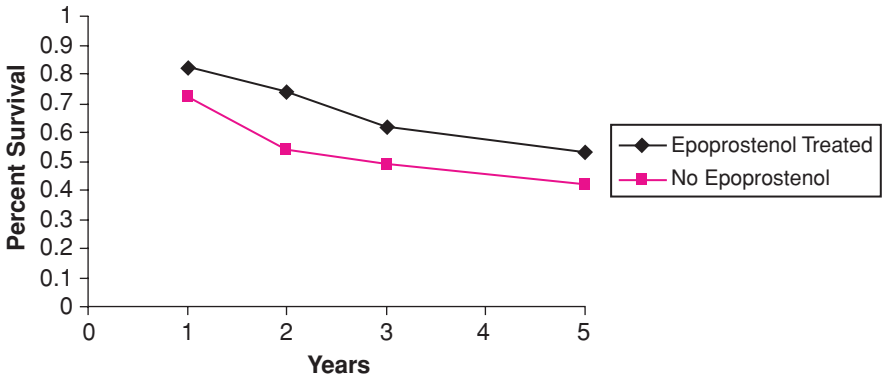


Figure 81-21 The effect of chronically infused epoprostenol therapy on survival in patients ($n = 431$) from multiple series with idiopathic pulmonary hypertension. Survival in the absence of epoprostenol was estimated using a predication equation derived from observations in the NIH registry of primary pulmonary hypertension at which time effective therapy was not available. *(Reproduced from McLaughlin VV, et al:* Chest *126:78S–92S, 2004.)*

Treprostinil

A longer half-life (3 hours) and stability at room temperature has prompted the development of treprostinil (Remodulin) as an alternative prostanoid analog for intravenous therapy. While fewer data are available regarding efficacy and duration of benefit as compared with intravenous epoprostenol, treprostinil appears to have acute hemodynamic effects similar to those of epoprostenol,[305] and was approved by the FDA in 2004 for the intravenous therapy of PAH. Its advantages over epoprostenol include the availability of prefilled syringes, thus obviating the need for daily mixing. Also, its stability at room temperature eliminates the need to carry ice packs to cool the infusion. Finally, the longer half-life lessens the risk of hemodynamic collapse should interruption of the infusion occur. Currently, treprostinil may be administered with the same infusion pump as that used for epoprostenol therapy, although the availability of smaller equipment may make for less inconvenient therapy. A higher dosage of treprostinil is required than epoprostenol in order to maintain improvement in symptoms. Further observation is required to establish whether survival with treprostinil is similar to that observed with epoprostenol.

Treprostinil is also available for subcutaneous administration. In a large randomized double-blind placebo-controlled trial of 470 patients with idiopathic or PAH associated with congenital heart or collagen vascular disease, subcutaneous treprostinil improved hemodynamic parameters and the distance walked in 6 minutes; the distance walked improved by 16 meters at 12 weeks.[306] The major advantage of subcutaneous treprostinil is the avoidance of an intravenous catheter and the associated risk of life-threatening bacteremia. While infections can occur at the subcutaneous infusion site, these are usually mild and manageable with oral antibiotics. Side effects are the same as for other prostanoid therapy (nausea, diarrhea, flushing, and jaw discomfort). The major drawback with subcutaneous treprostinil has been a considerable incidence of troublesome infusion site pain (occurring in 85 percent of patients in clinical trial).[306] There is no consistently effective treatment for discomfort at the infusion site. A significant number of patients require narcotic analgesics and/or discontinue the subcutaneous use. Another relative disadvantage is a slower possible rate of dosage titration as compared with intravenous therapy, making it less attractive for use in severely ill patients at the initiation of prostanoid therapy. In select patients, however, subcutaneous treprostinil has proved to be effective therapy with minimal side effects and has allowed for avoidance of the risks and inconveniences of intravenous therapy.

Reports of the development of treprostinil for either inhaled or oral administration remain preliminary at this time and require further study and review.

Iloprost

Iloprost (Ilomedin, Ventavis) is an inhaled prostacyclin analog that has been available in Europe for several years and was approved in the United States in 2004. Its major advantage over other currently available prostacyclins is the lack of need for any invasive administration equipment and a relative ease in the initiation of therapy. Inhaled iloprost requires multiple repeated administrations daily (six to nine treatments lasting approximately 10 minutes each while awake), and despite such frequency the hemodynamic effects wane prior to each administration.[307] Conflicting results of efficacy were seen in uncontrolled studies,[308–310] but a 12-week randomized, placebo-controlled trial of 203 patients demonstrated a placebo-corrected improvement of 36 meters in a 6-minute walk distance.[311] Most of the patients studied had IPAH; the remainder had either disease associated with an anorectic or collagen vascular agent, or had chronic thromboembolic pulmonary hypertension. The hemodynamic effects are not sustained between treatments; whether this affects the long-term benefits of inhaled iloprost therapy remains to be seen.

Iloprost inhalational therapy is initiated with a dosage of 2.5 μg and, if tolerated, increased to 5 μg with the subsequent dose. It is administered with any of several available delivery devices including a recently available battery-powered portable device. The major side effects are coughing, flushing, and jaw discomfort. Systemic hypotension and syncope which also occur have not been associated with clinical deterioration in clinical trials.[311]

Iloprost for intravenous administration is available in some European countries, but not the United States. In uncontrolled trials it has been used in patients with idiopathic collagen vascular disease associated and chronic thromboembolic pulmonary hypertension.[312–314] A major use has been in patients with systemic sclerosis for the treatment of digital ulcers. The acute hemodynamic effects are similar to those of epoprostenol, but no controlled trials of its efficacy are available.

Beraprost

An orally active prostacyclin analog, beraprost, has been studied in two randomized placebo-controlled trials of patients with various forms of PAH. The drug appears to result in a nonsustained improvement in exercise capacity. An initial trial of 130 patients demonstrated an improvement in 6-minute walk distance after 12 weeks of therapy, but in a subsequent study of 116 patients the effect was not sustained beyond 6 months.[315,316] Neither trial with beraprost demonstrated significant hemodynamic improvement as compared with placebo. Beraprost is rarely used currently except when other agents remain unavailable.

Combination Therapy

Despite the significant improvements in function and survival that have accompanied the advent of several classes of clinically effective drugs, PAH remains a life-threatening disease and many patients suffer progressive decline. As clinical deterioration progresses, it is tempting to replace one agent with another. Alternatively, additional agents are added and used in combination. Few data are available regarding the best approach.

In 33 patients with IPAH, bosentan was administered in a randomized, placebo-controlled trial 2 days after starting

epoprostenol. Both control and test groups demonstrated improved exercise capacity and hemodynamics, but no statistically significant difference resulted from the combination therapy. However, the small sample size may have precluded identification of differences in efficacy or safety.[317] Moreover, such evaluation does not inform whether there is benefit to the patient from adding either agent to the other in a patient who deteriorates despite treatment with the single agent. In an observational study of 20 patients who had already received an average of 16 months prostanoid therapy with either inhaled iloprost or oral beraprost, the addition of bosentan significantly increased the 6-minute walk distance and maximal oxygen consumption.[318] The majority of patients received beraprost, and an analysis of patients treated only with iloprost is not available. Although combination therapy appeared to be safe in each of these trials as long as liver function was monitored as for bosentan alone, adverse events did occur and firm conclusions about safety cannot be drawn.

The addition of inhaled iloprost to already established bosentan therapy has been evaluated in a randomized, double-blind, placebo controlled trial. Patients in this study had received at least 4 months of bosentan therapy prior to the initiation of iloprost. Sixty-seven patients with either idiopathic or associated PAH and WHO functional class 3 symptoms were enrolled. Following 12 weeks of inhaled iloprost there was a placebo-adjusted improvement in 6 minute walk distance of 26 meters. Hemodynamic values were also improved, as was the time to clinical worsening. It is not known whether the patient's initial response to bosentan monotherapy influences subsequent change with the addition of iloprost.[318a]

Experience with prostanoids used in combination with phosphodiesterase inhibitors is also limited. In a series of 14 patients who were deteriorating despite ongoing therapy with inhaled iloprost, the addition of sildenafil resulted in an improvement in exercise capacity that was sustained during 1 year of follow-up.[319] Patients had either idiopathic PAH or PAH related to collagen vascular disease, and the dosage of sildenafil was either 25 or 50 mg three times daily. Sildenafil may potentiate and prolong the vasodilatory effects of iloprost alone.[320–321] Further evaluation of the combination has not yet been performed.

There is little published experience with the combination of oral therapies. In a series of nine IPAH patients whose exercise capacity had initially improved but subsequently declined during an average of 11 months of bosentan monotherapy, the addition of sildenafil at up to 50 mg three times daily resulted in a recovery of the prior gain in 6-minute walk distance.[322] Although the improvement was sustained during a median of 9 months of combination therapy, randomized trials have not been reported. The combination of an endothelin receptor antagonist and a phosphodiesterase inhibitor may have beneficial pharmacologic effects, the clinical importance of which has not been fully studied.

Anticoagulation

In the absence of contraindications, most practitioners recommend anticoagulation with warfarin for patients with significant PAH. This is reasoned to be of benefit on the basis of autopsy studies, which have revealed in situ thrombosis of both venous and arterial vessels without evidence of an embolic source in a significant proportion of patients with PAH.[23–25] Anticoagulation is also justified on the basis of the increased risk of venous thromboembolic disease in patients with severe heart failure and immobility, and the anticipated poor tolerance of such patients for embolic events. However, the efficacy of anticoagulant therapy in patients with PAH has not been studied in randomized controlled trials. Nonetheless, uncontrolled observational reports have demonstrated an association between warfarin use and increased survival. In a study of 64 IPAH patients treated with or without calcium channel antagonists, survival after 5 years was greater among those patients in either group who at their provider's discretion had received warfarin.[279] In a retrospective evaluation of 173 patients with either idiopathic or anorexigen-associated PAH, anticoagulation was associated with a statistically greater survival in the anorexigenic-agent patients and a trend toward improvement after 5 years of therapy in patients with idiopathic PAH.[200] Extrapolating from such studies, warfarin is often prescribed to patients with other forms of PAH despite the absence of disease-specific data.

The generally recommended target international normalized ratio (INR) for warfarin therapy in patients with PAH is 1.5 to 2.5.[323] The severity of disease (e.g., threshold mean PAP or PVR) at which anticoagulation should be initiated has not been determined.

Surgical Treatments

Lung transplantation is addressed in detail elsewhere in this volume. Here, it suffices to note that lung transplantation remains an important option for some patients with IPAH whose disease fails to respond adequately to medical therapy. Single-lung, double-lung, and heart-lung transplants have been performed, but the outcomes favor a double-lung procedure.[324] The reported outcome of patients undergoing lung transplant for IPAH have been poorer than for other indications, with 1-year survival of approximately 65 percent in patients with IPAH as compared with 74 percent overall.[325] Fortunately, however, advances in medical therapies have markedly reduced the need for lung transplantation.[326] Whereas 10 percent of all lung transplant recipients in 1990 had IPAH, more recently these patients account for only 4 percent of procedures.[327] Recently, a new organ allocation system has been adopted for lung transplantation that aims to assign a priority score by assessing both acute need (expected survival in the absence of transplant) and likely benefit (survival with transplant) for individual patients. It remains unclear how this system will influence the availability and outcomes of transplantation for patients with IPAH. There is concern that the system may assign a lower priority to patients with IPAH by failing to account for factors indicating a poorer prognosis (and thus an increased acute need) in these patients. In addition, since likely benefit is assessed by survival rates 1 year following transplantation, this criterion may also lower the assigned priority of IPAH

patients to receive available organs. Although survival at 5 years is similar to that of other populations, rates for IPAH at 1 year after transplantation have been inferior.

Atrial septostomy has been performed as a palliative measure, as well as a "bridge" to lung transplantation in some patients with severe PAH and symptoms refractory to other therapies. The creation of a right-to-left shunt is aimed at decreasing the pressure overload of the right ventricle, and simultaneously increasing preload of the left ventricle, thereby improving systemic perfusion. Controlled studies have not been performed, and appropriate selection criteria are not known. Significant palliation of patients has been reported, but deaths have occurred as well. The procedure remains an option at institutions that are experienced in its use.

Other Considerations

Pregnancy in women with IPAH is associated with a high mortality, i.e. of the order of 30 to 50 percent.[328–330] Mechanical barriers to conception are recommended in females of child-bearing age. Most experts recommend early termination of pregnancy in this group.[331] Should pregnancy be continued, early hospitalization is advisable for monitoring and supportive therapy.[332] Case reports have appeared of the successful management of pregnant IPAH patients using intravenous epoprostenol and inhaled NO.[333–335] Postmenopausal hormonal replacement therapy using estrogens should be undertaken with caution because of the associated risk of thromboembolism; concomitant anticoagulation should be considered.

Patients should be queried about the concomitant use of medications and herbs. Warfarin is particularly apt to be associated with drug-drug interactions. The use of vasoconstrictor or serotoninergic medications for unrelated illnesses, such as migraine, should also be undertaken cautiously. Patients taking bosentan are at risk of interaction with such medications as cyclosporine and azole-type antimicrobial agents, and care must be taken to avoid glyburide-containing diabetic therapies. Surgical procedures may entail considerable operative and postoperative risk in patients with hemodynamic compromise from PAH.

Vulnerability of patients with severe PAH to vasovagal events has to be kept in mind. A vasovagal attack can be precipitated by pain, nausea, vomiting, or straining at the stool (Fig. 81-22). The induction of anesthesia and intubation is a particularly troublesome time. The combination of bradycardia and systemic vasodilation can lead to a precipitous drop in systemic blood pressure. Atropine or a similar agent should be kept at hand during invasive procedures.

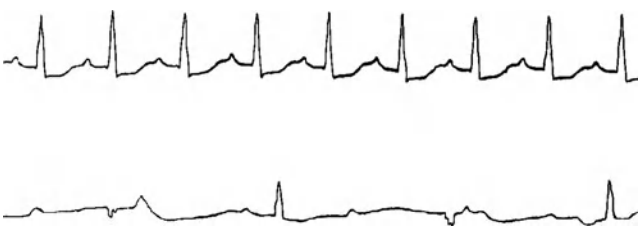


Figure 81-22 Idiopathic pulmonary arterial hypertension. Bradycardia and prolongation of atrioventricular conduction progressed to atrioventricular dissociation while patient was on bedpan. Associated with syncope.

Pulmonary Hypertension Associated with Left Heart Disease or with Extrinsic Restriction of Pulmonary Venous Blood Flow

Left heart disease, such as mitral stenosis and ventricular dysfunction, generally elicits pulmonary hypertension by increasing pulmonary venous pressure. Precapillary vasoconstriction, presumably a reflex phenomenon, contributes to the pulmonary hypertension. Elevated end-diastolic pressures in the left ventricle are additional contributing factors. This mechanism is operative in left ventricular systolic or diastolic dysfunction. The pulmonary hypertension is a consequence of parenchymal fibrosis secondary to interstitial edema, trapping of the resistance vessels in the perivascular fibrosis, and reflex arterial vasoconstriction elicited by pulmonary venous hypertension.

In chronic pulmonary hypertension due to heart disease, the muscular pulmonary arteries undergo changes that depend on the severity and chronicity of the pulmonary hypertension. These changes may determine the response to medical treatment, the benefit and risk of surgery, and the ultimate outcome. Early in the evolution of the pulmonary hypertension, the changes reflect, in large measure, the initiating mechanism—e.g., predominantly intimal changes in a large left-to-right shunt in contrast to predominantly medial changes in lesions that expose the vessels to systemic arterial pressures (e.g., Eisenmenger's disease). However, in unremitting chronic pulmonary hypertension such distinctions tend to blur and are often complicated by secondary effects, such as in situ thrombosis, perivascular fibrosis, and decrease in parenchymal elasticity.

In general, chronic pulmonary hypertension may be sustained by two mechanisms: vasoconstrictive, attributable to intrapulmonary reflexes, and/or heightened sympathetic activity; and structural changes in the vessels or in their immediate vicinity, which may reverse if pulmonary arterial pressures can be lowered. The possibility of vasoconstriction has been the basis for trials of pulmonary vasodilators. A role for remodeling of the small muscular arteries and arterioles is indicated by instances of striking relief of pulmonary hypertension 1 to 2 years after surgical treatment of mitral stenosis. Unfortunately, such remodeling is not universal, and pulmonary vascular derangements with progressive pulmonary hypertension can occur well after correction of the mitral valvular or other left heart abnormality.

In the management of pulmonary hypertension secondary to congestive heart failure, a cardiotonic regimen that features the use of diuretics and an inhibitor of the angiotensin-converting enzyme (ACE) plays a pivotal role. The role of digitalis is debatable. In general, pulmonary vasodilators (other than ACE inhibitors) have not been shown to be effective in maintenance therapy.[336] Indeed, the beneficial effect of ACE inhibition is more apt to be due to the reduction in systemic vascular resistance and the resultant

improvement in left ventricular function than to the modest direct effects of ACE inhibition on pulmonary vessels. Prostacyclin has increased morbidity and mortality, and in some patients, acetylcholine infusion has elicited pulmonary vasoconstriction instead of vasodilatation.

Increased pulmonary venous pressures can also result from obstruction of the large pulmonary veins en route to the left atrium. The underlying cause may be fibrosing mediastinitis (e.g., due to histoplasmosis), neoplastic invasion of lymph nodes (e.g., metastatic carcinoma of the breast), lymphoma (e.g., Hodgkin's disease), or lymphadenitis (e.g., due to sarcoidosis). Pulmonary vein stenosis can also occur as a complication of catheter ablation for treatment of atrial fibrillation. Isolated reports have described amelioration of patients with stenting of the affected pulmonary veins.[337,338]

Pulmonary Hypertension Associated with Hypoxemic Lung Disease

Various disorders and diseases of the breathing apparatus, including derangements of the respiratory muscles, chest wall, airways, and alveoli, and the drive to breathe can be accompanied by pulmonary hypertension. These include prevalent problems, such as COPD and OSA. As a result, these abnormalities comprise relatively common causes of pulmonary hypertension. In turn, pulmonary hypertension and associated cor pulmonale can contribute significantly to the morbidity and mortality of these diseases. Hypoxia is commonly present when these disorders result in pulmonary hypertension and can contribute to the increase in pulmonary arterial pressures. Management of pulmonary hypertension in each is generally aimed at optimal treatment of the underlying disorder. Little is known about therapy directed at the pulmonary hypertension itself in these settings and such efforts have not been shown to be helpful.

Chronic Obstructive Pulmonary Disease

Chronic hypoxic vasoconstriction is thought to contribute to remodeling of the vasculature in COPD. The remodeling involves hypertrophy of the pulmonary vascular smooth muscle with extension into normally nonmuscularized branches of the pulmonary arteries, intimal thickening, and an accumulation of extracellular matrix components (intimal fibroelastosis).[339] Such changes have also been reported in patients with milder COPD and in the absence of hypoxia.[340] Furthermore, treatment of hypoxia with oxygen, although beneficial, does not always result in complete resolution of the pulmonary hypertension. These data suggest the involvement of additional mechanisms in the vascular remodeling. Possibilities include endothelial cell dysfunction with abnormal levels of vasoactive mediators, including increased endothelin and decreased NO synthase.[341,342] Vascular injury might also be caused by smoking-induced oxidative stress or inflammatory infiltrates.[340,343] Increased blood viscosity (due to polycythemia) and flow have also been suggested. Finally, destruction of the pulmonary vasculature by emphysema itself will contribute to a decrease in vascular compliance (Fig. 81-23).

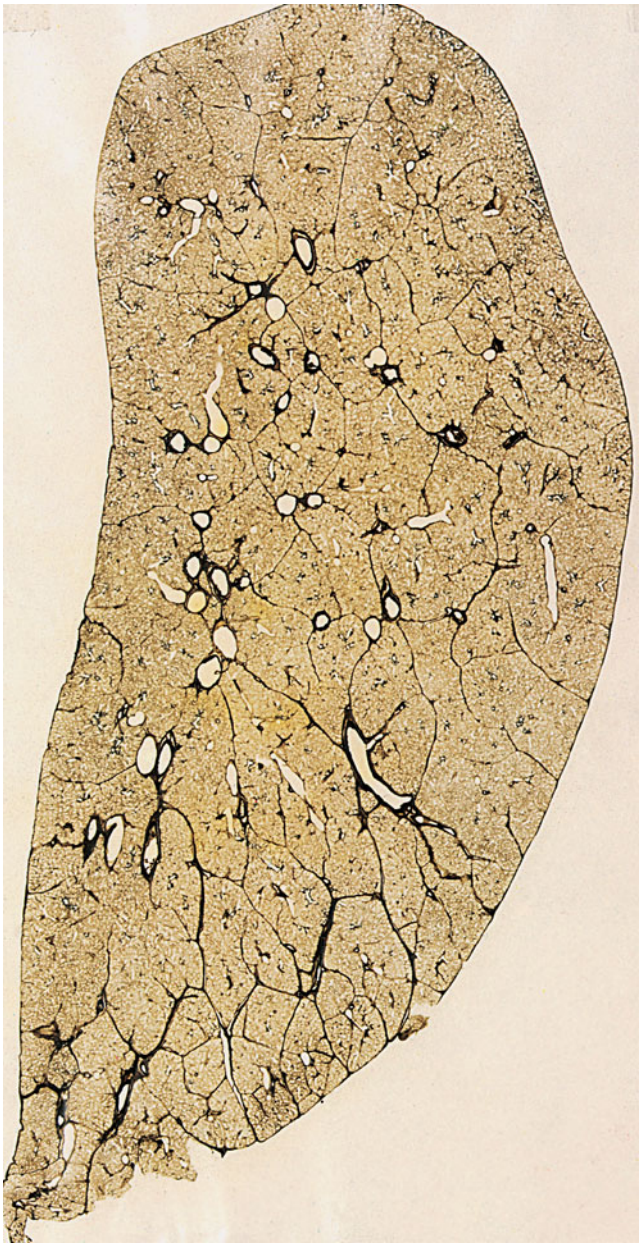
The prevalence of pulmonary hypertension in patients with COPD has not been firmly established. Right ventricular hypertrophy has been seen at autopsy in up to 40 percent of patients with COPD. When measured by right catheterization, pulmonary hypertension has been found in 20 to 90 percent of patients.[344–349]

Although the severity of the pulmonary hypertension tends to correlate with the degree of airflow obstruction and the severity of hypoxemia,[350,351] the degree of pulmonary hypertension tends to be mild to moderate. Mean PA pressure tend to be no higher than 35 to 40 mmHg even when the airways obstruction is severe[346,349,350] and progression over time is slow.[345,352] However, there does appear to be a small subset of patients with COPD who, despite only moderate degrees of airflow obstruction, develop severe hypoxemia (Pa_{O_2} of the order of 40 mmHg) and more severe pulmonary hypertension, with mean PAP greater than 45 mmHg.[349,353] Why some patients with COPD develop more severe pulmonary hypertension than others is not known. Hypotheses include an increased vasoconstrictor response to hypoxia or the possible presence of intrinsic pulmonary vascular disease in a patient who (independently) also has COPD.[354] Such patients must undergo a complete evaluation for additional causes of pulmonary hypertension (e.g., coexisting obesity hypoventilation, sleep apnea, or coronary artery disease). Other causes are common and may significantly influence therapy.[353]

In patients with COPD, whether mild or more severe, the presence of pulmonary hypertension is associated with an increase in hospitalization and a poorer prognosis.[344,346,355–357] Indeed in some studies the degree of pulmonary hypertension is a more powerful indicator of prognosis than are measures of airflow obstruction.[351] Abnormal right ventricular function is also associated with a poorer prognosis in patients with COPD.[358]

Hyperinflation of the lungs may obscure the physical examination, radiographic and electrocardiographic evaluation of pulmonary hypertension and cor pulmonale. Heart sounds are frequently less audible than normal in patients with severe COPD. Nonetheless, an accentuated second heart sound, ventricular gallops and a tricuspid regurgitant murmur can often be heard upon deep inspiration. Physical examination of the patient may also reveal tender hepatomegaly, as well as peripheral edema and cyanosis. On plain chest radiographs, prominence of the pulmonary arteries may be seen, together with peripheral vascular "pruning." The presence of cardiac enlargement may become evident in serial studies obtained in the course of treating cor pulmonale that is due to an acute exacerbation of COPD (discussed below). Electrocardiographic evidence of right ventricular or atrial enlargement can also be obscured by cardiac rotation and interposition of an increase in air between the heart and the chest wall.

As in other forms of pulmonary hypertension, the echocardiogram is often the first test performed when the presence of pulmonary hypertension is suspected. Frequently, these studies are limited technically due to hyperinflation of the chest that accompanies severe airways obstruction. As a result, a reliable estimate of pulmonary arterial pressure is frequently not possible.[359] Right heart catheterization is



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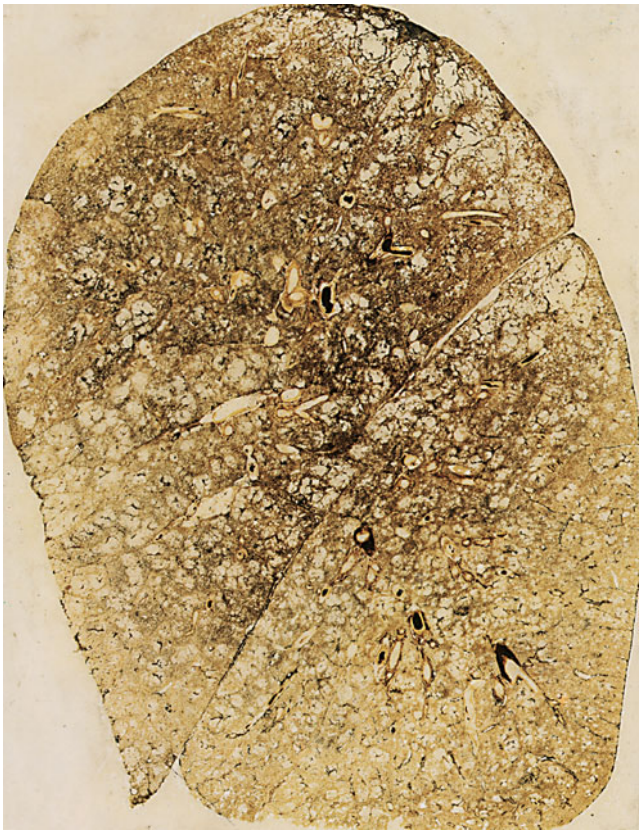


B

C

Figure 81-23 Gough (sagittal) sections. Lung architecture in normal lung and in obstructive airway diseases. *A*. Normal lung. Between large airways and vessels the parenchyma is intact. *B*. Centrilobular emphysema. *C*. Cystic fibrosis. The large airways are dilated and bronchiectatic, whereas the gas-exchanging surface is well preserved. *(Courtesy of Dr. S Moolten.)*

frequently needed to confirm the diagnosis when the presence of pulmonary hypertension will influence therapeutic decisions (e.g., in evaluation for lung transplantation or volume reduction surgery).

The treatment of pulmonary hypertension in patients with COPD applies, in general, to the management of patients with cor pulmonale. Most important for the treatment of pulmonary hypertension in patients with COPD is the prevention of arterial hypoxemia. Supplemental oxygen therapy is used to prevent hypoxic pulmonary vasoconstriction and can increase survival and quality of life in patients with COPD.[113] Oxygen therapy can also result in modest improvements in pulmonary hemodynamics, although pressures do not tend to normalize. Although long-term oxygen therapy has been shown to improve survival, this benefit may not be attributable to improvement in pulmonary hemodynamics.[360–363] Oxygen should be prescribed and titrated to maintain oxyhemoglobin saturation above 90 percent, not only at rest but also during exertion.

Treatment of airways obstruction with bronchodilators and antibiotics to clear acute respiratory infection is also important. Diuretics are often needed for management of cor pulmonale but must be used cautiously. Chloride-losing agents run the risk of promoting hypercapnia, which predisposes to respiratory depression and the aggravation of ventilatory insufficiency. The use of digitalis must also be undertaken with caution because of the threat of digitalis-associated cardiac dysrhythmias during hypoxia.

Vasodilators (other than oxygen) have no proven use in the management of pulmonary hypertension due to COPD. No pulmonary vasodilator has proved to be as effective as oxygen in chronic obstructive (hypoxemic) pulmonary disease with respect to either survival or exercise tolerance. Overall, the sporadic trials of vasodilators in COPD have shown little benefit: As a rule, pulmonary hemodynamics have shown little improvement, while gas exchange has been further compromised. Also, undesirable systemic side effects have been common. While some studies have demonstrated acute improvements in hemodynamic parameters following the administration of calcium channel antagonists, long-term benefit has not been proved. Moreover, these agents may worsen oxygenation by interfering with ventilation-perfusion matching and may precipitate ventricular dysfunction, systemic hypotension and dysrhythmias.[364–370] Prostacyclin has had only limited trials in COPD and has not become popular for both practical and theoretical reasons. Although it increases the cardiac output by dilating pulmonary vessels that are vasoconstricted due to hypoxia, prostacyclin runs the countervailing risk of aggravating ventilation-perfusion abnormalities. In the few studies to date, the increase in cardiac output resulting from pulmonary vasodilation has left pulmonary arterial pressure virtually unchanged without decrease in the work of the right ventricle.[371,372] Similarly, there is no proven benefit to the endothelin receptor antagonists or phosphodiesterase inhibitors in patients with COPD. In contrast, NO can improve pulmonary vascular resistance in patients with COPD and pulmonary hypertension, and long-term use with a "pulsed" inhalational delivery system may improve hemodynamics. Confirmation of a benefit from NO awaits further study.[373–375]

Alveolar Hypoventilation

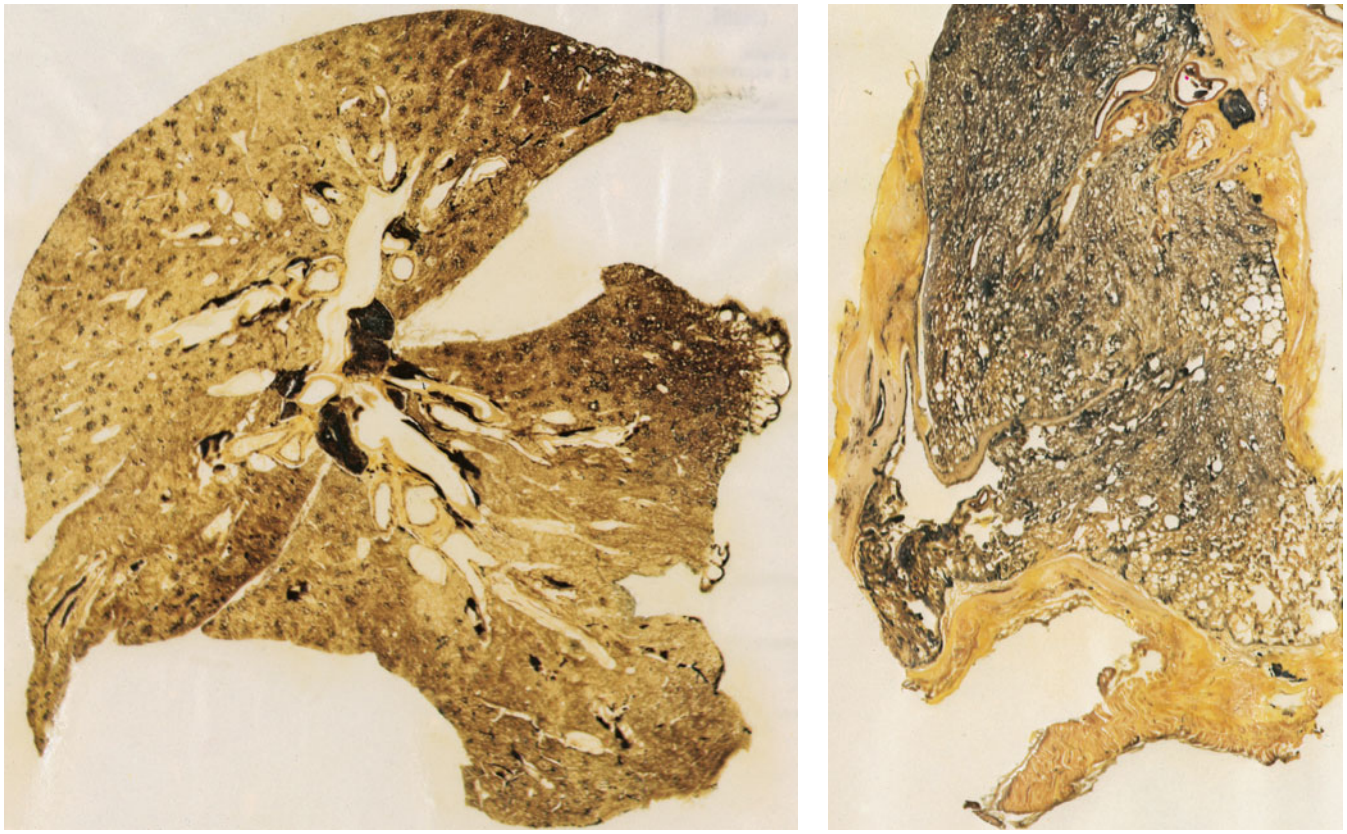
In patients with normal lungs who develop alveolar hypoventilation, the common pathogenetic denominators are alveolar hypoxia and arterial hypoxemia, often reinforced by respiratory acidosis. In contrast to the alveolar hypoventilation of obstructive airway disease, which is a consequence of ventilation-perfusion imbalances, alveolar hypoventilation in patients with normal lungs is global, affecting the lung everywhere, although not necessarily to the same extent. Global alveolar hypoventilation generally stems from an inadequate ventilatory drive or an ineffective chest bellows (Fig. 81-24). In particular, a variety of disorders, ranging from the sleep apnea syndromes, a "dead" respiratory center, paralysis of respiratory muscles in the Guillain-Barré syndrome, kyphoscoliosis, and morbid obesity, can each be responsible.[376]

The diverse causes share hypoxia and often respiratory acidosis as the common pathogenetic mechanism for pulmonary hypertension. In the chronic hypoventilation that follows damage to the respiratory center (as by encephalitis), the normal lungs and chest wall do not receive adequate ventilatory drive. Postpoliomyelitis damage to the respiratory center is often associated not only with paralyzed respiratory muscles but also with damaged nerves to the intercostal muscles. Extreme obesity imposes a mechanical burden on the respiratory apparatus, chiefly by way of the abdomen, but often the mechanical load is accompanied by another derangement (e.g., an inherently inadequate ventilatory drive) that contributes to the alveolar hypoventilation. In kyphoscoliosis, not only is the lung compressed and distorted but the mechanical operation of the chest bellows is compromised and the elastic properties of the lungs and chest wall are abnormal, albeit to different degrees.

Although the routes to hypoxia are different, once the arterial P_{O_2} falls below 40 to 50 mmHg, the pulmonary arterial walls of the patients undergo the same changes as those that occur spontaneously in native dwellers at high altitude: pulmonary arteries and arterioles undergo muscular hypertrophy, and a self-perpetuating mechanism appears to have been established (Fig. 81-32).

Obstructive Sleep Apnea

OSA is a common disorder characterized by repetitive episodes of hypoventilation and associated oxyhemoglobin desaturation. It is associated with alterations in sympathetic nervous system activity that results in systemic hypertension and an increase in the risk of stroke, myocardial infarction, and left heart dysfunction. In some patients, OSA is associated with the development of pulmonary hypertension. Participating in the pathogenesis of the pulmonary hypertension are believed to be hypoxic pulmonary vasoconstriction that accompanies repetitive episodes of hypoventilation, endothelial cell dysfunction, and progressive vascular remodeling.



A *B*

Figure 81-24 Gough (sagittal) sections. *A.* Alveolar hypoventilation secondary to abnormalities in chest wall and pleura. Kyphoscoliosis. *(Courtesy of Dr. J Gough Cardiff.) B.* Asbestosis. Encasement of lung by thickened pleura. *(Courtesy of Dr. S Moolten.)*

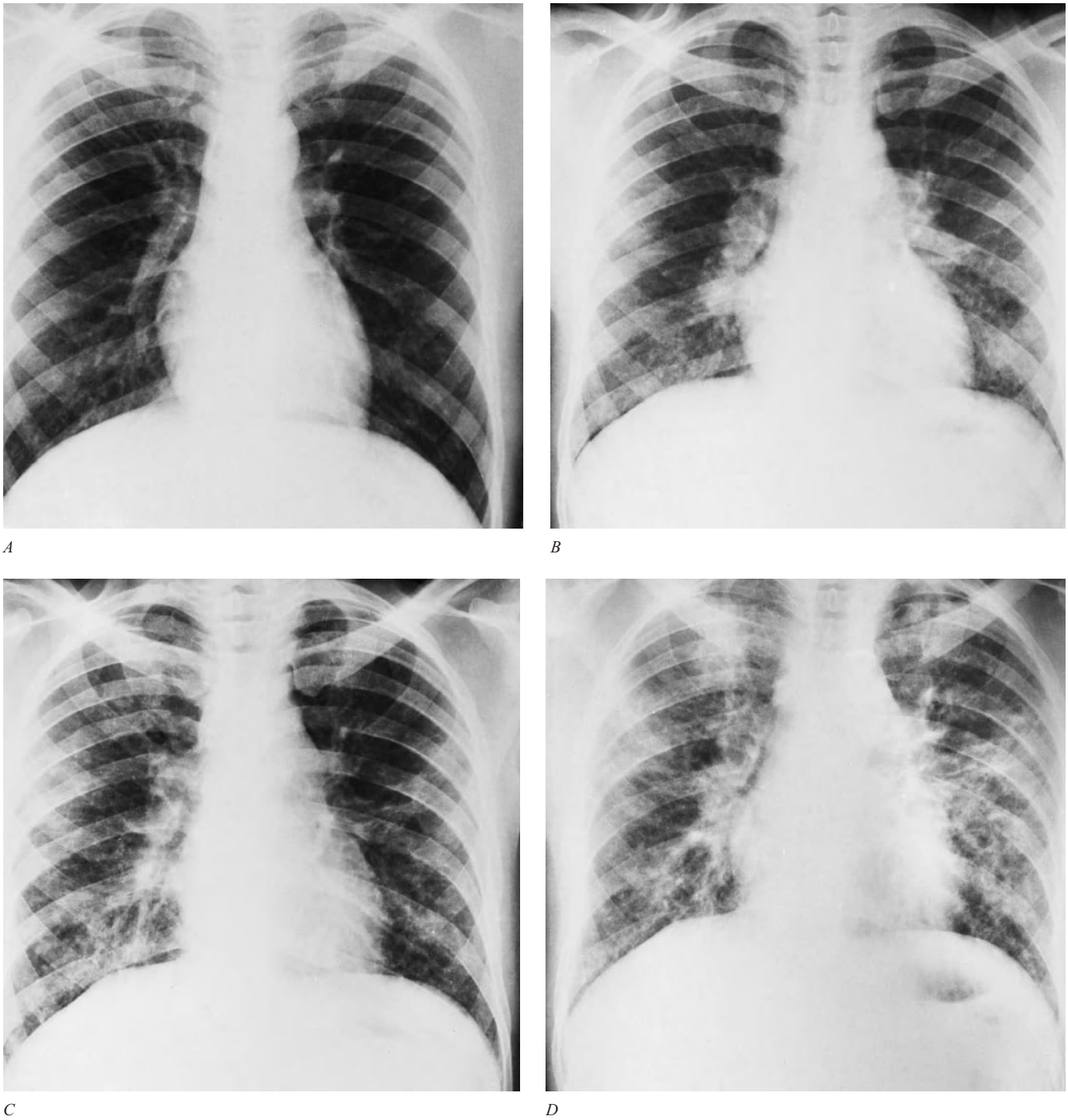
Estimates of the prevalence of pulmonary hypertension in patients with OSA have ranged from 17 to approximately 50 percent.[377] It must be noted that many studies have defined pulmonary hypertension at a value lower than that generally used (e.g., a pulmonary artery pressure greater than 20 mmHg) and that not all studies have excluded concomitant left heart or pulmonary disease. Consistent across several studies, however, has been a tendency for patients with OSA and pulmonary hypertension to be older and have more severe nocturnal hypoxemia and worse lung function (spirometric values) than the OSA patients without pulmonary hypertension. The apnea-hypopnea index, on the other hand, has not been consistently associated with the presence of pulmonary hypertension. Patients with OSA and chronic lung diseases have an increased propensity for developing pulmonary hypertension.[378–381] In one study, which defined pulmonary hypertension as a mean PAP greater than 20 mmHg, pulmonary hypertension was found in 17 of 27 patients (58 percent) with obesity hypoventilation as compared to 19 of 181 (9 percent) with only OSA; 11 or 26 (36 percent) of patients with OSA and COPD (the overlap syndrome) had pulmonary hypertension. The severity of OSA was similar in the three groups.[382]

Pulmonary hypertension in most patients with OSA is usually mild. Typically, mean PA pressures range between 20 to 35 mmHg.[381,383] Usually, patients with more severe pulmonary hypertension and right heart failure also have COPD, obesity hypoventilation, or other causes of daytime hypoxemia.[380,384] However, patients with OSA may have obesity that is severe enough not only to evoke more severe nocturnal hypoxemia, but also to result in restrictive ventilatory defects and daytime hypoxia.[381,383,385]

Treatment of the OSA itself using continuous, or bilevel, positive airway pressure usually suffices for the management of pulmonary hypertension. Oxygen should also be administered as required to prevent oxyhemoglobin desaturation during sleep and while awake. No specific therapy (e.g., pulmonary vasodilators) is usually required or indicated for treatment of mild pulmonary hypertension. Treatment of OSA for at least 3 months with continuous positive airway pressure in patients without concomitant lung or heart disease can decrease pulmonary artery pressures in patients with mild baseline increases in pulmonary arterial pressures.[386,387] The role of other therapies for more severe pulmonary hypertension in patients with OSA has not been specifically evaluated, nor when OSA is accompanied by significant left heart or lung disease.

Interstitial Lung Disease

A wide variety of pathological processes can evoke pulmonary interstitial fibrosis (see Figs. 81-25 and 81-26). These include sarcoidosis, asbestosis, idiopathic pulmonary fibrosis (IPF),

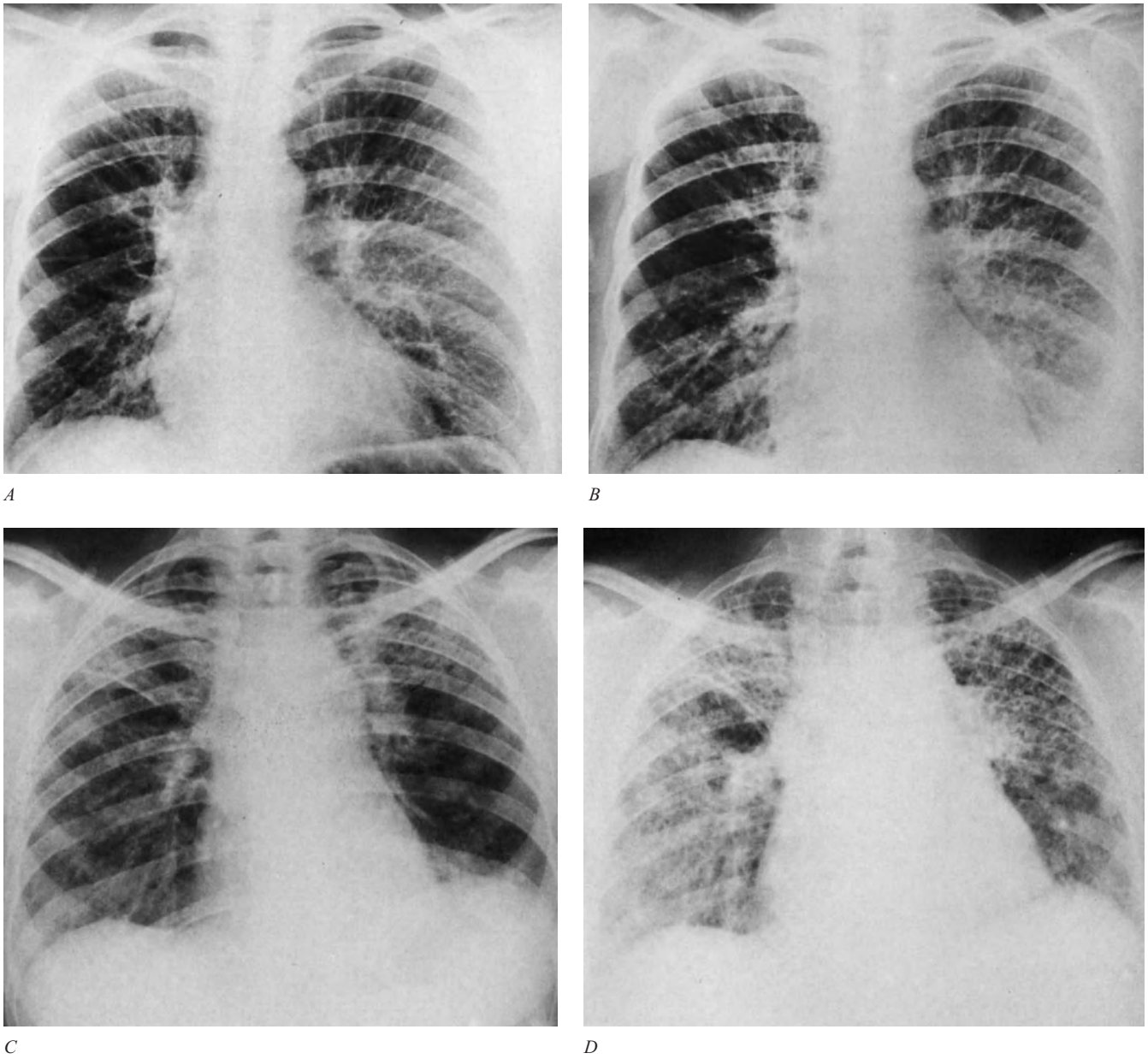


A *B*

C *D*

Figure 81-25 Sarcoidosis. Consecutive stages in evolution of diffuse pulmonary fibrosis that in time became associated with ventilation-perfusion abnormalities and cor pulmonale. (Courtesy of Dr. GG Pietra)

and radiation pneumonitis. Connective tissue diseases such as scleroderma, systemic lupus erythematosus (SLE), rheumatoid arthritis, Sjögren's syndrome, and mixed connective tissue disease, also are commonly complicated by interstitial lung disease (ILD). Lymphangitic spread of carcinoma within the lungs can produce the same effect (see Fig. 81-26). In these disorders, progressive fibrosis and infiltration not only thicken and distort the pulmonary interstitium, replacing the normal extracellular matrix with cells and scar tissue, but also entrap the pulmonary blood vessels and obliterate segments of the pulmonary vascular bed (see Fig. 81-7). As a result, some segments of the pulmonary vascular bed are amputated, others are encased in scar, and the overall distensibility of the pulmonary parenchyma is diminished. In some disorders, such as silicosis, distortion of the lung due to the pulling of scar tissue on normal and less-affected lung intensifies the derangements in the pulmonary parenchyma. Disorders such as sarcoidosis affect not only the parenchyma of the lung but



A *B*

C *D*

Figure 81-26 Diffuse interstitial disease. *A* and *B*. Lymphangitic spread of carcinoma of the breast in a 50-year-old woman. In the 2 years between the chest radiographs, dyspnea and tachypnea had progressed. The pulmonary function tests showed severe impairment of diffusion; the electrocardiogram indicated right ventricular enlargement (cor pulmonale). *C* and *D*. Sarcoidosis in a 50-year-old man. In the 2 years between the chest radiographs, pulmonary fibrosis had progressed strikingly. At autopsy pulmonary fibrosis was marked; bronchi were widely dilated and emphysematous areas were juxtaposed to areas of dense fibrosis. Cor pulmonale was confirmed.

also the walls of the airways. In each, hypoxic pulmonary vasoconstriction may contribute to the development of pulmonary hypertension. The resulting loss of vascular surface area and vasoconstriction increase pulmonary vascular resistance.

The common denominator in pulmonary interstitial disease is a pattern of restrictive lung disease. The original descriptions of this disease focused disproportionately on impairment of the diffusing capacity of the lungs by thickened alveolar-capillary membranes; hence, the designation "alveolar-capillary block." But since then, disturbances in ventilation-perfusion relationships have been appreciated as dominant features, particularly in the later stages of the disease.

The lungs are stiff (poorly compliant) because of the diffuse interstitial disease, which limits distensibility and increases pulmonary vascular resistance by obliterating small pulmonary arteries and arterioles. Elastic recoil is correspondingly elevated. In some diseases, such as asbestosis, thickening of the pleura can be another factor in reducing

pulmonary compliance. Oxygen consumption becomes abnormally high, largely because of an increase in the work of breathing.

As the disease progresses, lung volumes undergo gradual, concentric reduction. As an adaptation that minimizes the elastic work of breathing, the minute and alveolar ventilation are high and breathing is rapid and shallow. These adaptations help to maintain the arterial P_{O_2} at near-normal levels. However, exercise often elicits a precipitous drop in arterial P_{O_2}. When the interstitial process has advanced sufficiently to be seen on the chest radiograph, the arterial P_{CO_2} either remains slightly low or begins to return toward normal levels, largely as the result of ventilation-perfusion abnormalities (see below). The diffusing capacity decreases progressively as the interstitial fibrosis progresses; even though the value for the diffusion capacity may fall within normal limits at rest, it generally fails to increase normally during graded exercise.

Derangements in alveolar ventilation and blood flow are present early in interstitial disease but arterial blood oxygenation may remain at near-normal levels. But, in time, progressive disease exaggerates the imbalances sufficiently to cause arterial hypoxemia at rest. As long as the arterial hypoxemia remains mild, pulmonary hypertension is generally modest at rest, increasing during exercise. But as the disease progresses and arterial hypoxemia intensifies, the level of pulmonary hypertension also increases, and cor pulmonale begins to evolve. Arterial eucapnia or hypocapnia is gradually succeeded by hypercapnia. Right ventricular failure occurs late in the course of the disease, often in association with severe hypoxemia and respiratory acidosis.

The pulmonary hypertension associated with interstitial lung disease progresses over time, often with an accelerated course later in the disease. At this point further worsening of the interstitial process often cannot be detected by changes in lung function or in the appearance of chest radiographs. At this point, attention usually turns to the pulmonary hypertension as the "cause" of worsening dyspnea. However, distinction between the pulmonary vascular and interstitial contributions to the dyspnea is rarely clinically possible. Even though the pulmonary vascular derangements are doubtlessly contributing symptoms, therapy at this point frequently fails to bring about substantial relief. Dyspnea may become manifest at rest, and is often exacerbated by coexistent musculoskeletal complaints or anemia.[388]

Unlike that usually seen in most patients with COPD or OSA, the pulmonary hypertension associated with ILD can be severe. Estimation of pulmonary artery pressure by Doppler echocardiography in patients with advanced ILD can be difficult and at times inaccurate.[389] Cardiac catheterization is often required to confirm the diagnosis of pulmonary hypertension and exclude left heart disease as a contributing factor.

In addition to ILD, other causes of pulmonary hypertension must be considered in patients with collagen vascular disease. Categorizing the disease is frequently problematic. In particular, SLE, systemic sclerosis (scleroderma), and its variant forms, can each cause pulmonary hypertension in the absence of apparently significant interstitial lung disease. Characterization of these patients as having either pulmonary *arterial* hypertension associated with collagen vascular disease or alternatively pulmonary hypertension associated with interstitial lung disease may be difficult, as the two may frequently coexist. In the scleroderma spectrum of diseases, isolated pulmonary arterial hypertension is more likely to be seen in patients with the CREST variant (calcinosis, Raynaud's, esophageal dysmotility, sclerodactyly, and telangiectasias), while patients with systemic sclerosis more often have prominent pulmonary fibrosis and restrictive lung disease. In addition to ILD, sarcoidosis can cause pulmonary hypertension by direct granulomatous involvement of the pulmonary vasculature, by hypoxia from direct involvement of the airways or by extrinsic compression of the pulmonary veins by enlarged hilar lymph nodes.[390]

However, these distinctions are clinically important since, as a rule, no therapies have been established as useful for the specific treatment of pulmonary hypertension that complicates interstitial lung disease. On the other hand, drugs used for treatment of pulmonary arterial hypertension are known to be efficacious in the treatment of disease associated with collagen vascular disease (discussed above under Pulmonary Arterial Hypertension Associated with Specific Conditions).[300,391] As a rule, clinical trials that have demonstrated benefit have excluded patients with either significant restrictive ventilatory defects (typically a total lung capacity less than 70 percent predicted) or the subjective assessment of "significant" interstitial disease on chest radiographs.

Only isolated instances have been reported of hemodynamic improvement following with the administration of various vasodilators in patients with IPF and sarcoidosis. Convincing larger studies that demonstrate benefit are lacking.[392,394] In patients with ILD, the possibility of worsening ventilation-perfusion relationships and aggravating hypoxia by the administration of vasodilators has been a concern as in the use of vasodilators in patients with COPD. Inhalational therapy with vasodilators (e.g., iloprost or other prostacyclin analogs) has the theoretical advantage of avoiding ventilation-perfusion mismatch. A small series has demonstrated acute hemodynamic improvements with either inhaled prostacyclin or NO in patients with pulmonary hypertension and ILD, and long-term administration of inhaled iloprost was beneficial in a single patient.[395] It has been hypothesized that the antifibrotic activities of endothelin receptor antagonists will be of benefit in patients with ILD (with or without pulmonary hypertension), but this has not been proved.

Since the presence of pulmonary hypertension is a poor prognostic sign in patients with ILD, early referral for evaluation of lung transplantation should be considered.

Patients with hypoxemia at rest or with exertion should be treated with supplemental oxygen, titrated to prevent oxyhemoglobin desaturation. When cor pulmonale is present, diuretics may be beneficial, but must be used cautiously so as to prevent dehydration, systemic hypotension, or electrolyte derangements (as discussed above under General Aspects of Disease Management).

Chronic Thromboembolic Pulmonary Hypertension

Chronic thromboembolic pulmonary hypertension (CTEPH) is a more common complication of pulmonary embolism (PE) than has been previously appreciated.[396,397] At a large referral center that followed 223 patients for up to 5 years after an initial pulmonary embolus (PE), symptomatic CTEPH developed in 3.1 percent. CTEPH was found in 13.3 percent of 82 patients with a prior history of either deep venous thrombosis or PE. Symptoms and the diagnosis of CTEPH occurred in all cases within 2 years of pulmonary embolus. Risks identified in this population for developing CTEPH were idiopathic PE, younger age at presentation, multiple embolic events, and larger perfusion defects.[398] Prior cohorts have identified a significant risk of CTEPH following anatomically massive PE (defined as obstructing at least 50 percent of the pulmonary vasculature). In one study, 20 percent of 227 patients with massive PE developed CTEPH following initial thrombolytic treatment.[399] Perfusion defects do not consistently resolve following acute PE, and residual defects despite anticoagulation have been assumed to confer a greater risk of CTEPH, although this has not been definitively established.[400–403] The genetic, hematologic, or other determinants of clot resolution are also not completely understood. Various causes of thrombophilia have been studied with mixed results and none firmly established as increasing the risk of CTEPH.

It is not clear to what degree the eventual development of CTEPH is determined by each recurrent thromboembolic event, in situ thrombosis or by other changes in the vasculature distal to the vessels initially obstructed by clot (Fig. 81-27). In addition to recanalized clot, histological changes similar to those seen in other forms of pulmonary hypertension have been identified in patients with CTEPH[404] (Fig. 81-28).

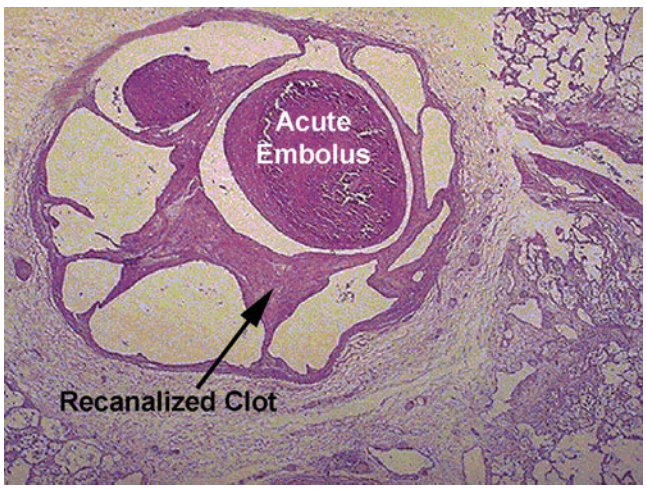
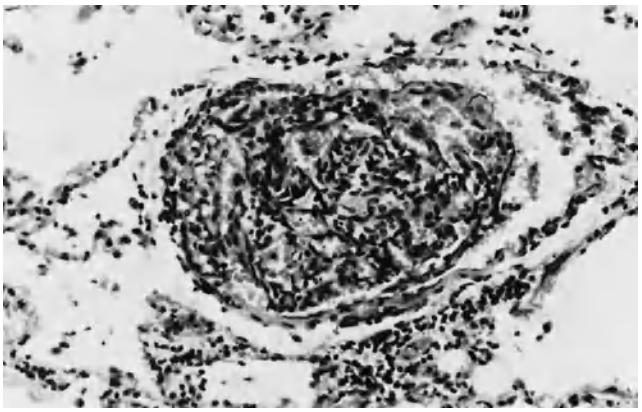


Figure 81-27 Acute and chronic clot within the pulmonary vasculature of a patient with chronic thromboembolic pulmonary hypertension. Recanalization of chronic clot has occurred. *(Courtesy of Dr. GG Pietra.)*



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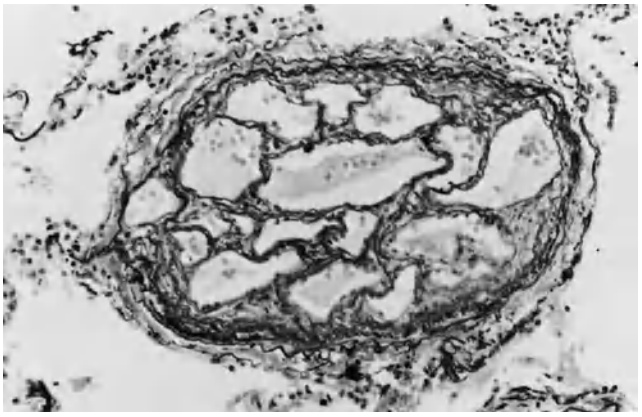
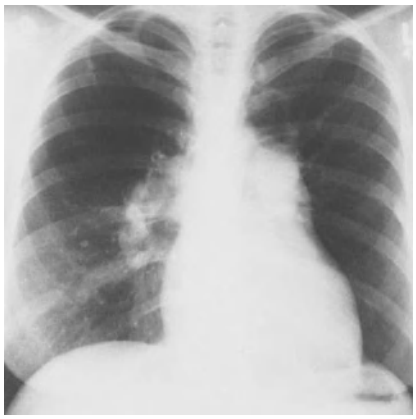


B

Figure 81-28 Contrast between plexiform and thromboembolic occlusions. *A*. Plexiform lesions in a muscular pulmonary artery in a 56-year-old woman with idiopathic pulmonary arterial hypertension. There is an active proliferation of intimal cells with capillary-like channels in between. The branch is dilated. To the left is focal destruction of the arterial wall, which contains some lymphocytes and polymorphs (H&E ×140). *B*. Muscular pulmonary artery in a 63-year-old man with chronic thromboembolic pulmonary hypertension. Many vessels were obstructed by intravascular fibrous septa as remnants of recanalized emboli. (Elastic-van Gieson stain ×140.) *(Courtesy of Dr. CA Wagenvoort.)*

Patients with CTEPH have symptoms of progressive dyspnea, fatigue, and presyncope or loss of consciousness similar to the symptoms of patients with other forms of pulmonary hypertension. Many are unaware of prior venous thromboembolic events and the diagnosis is appreciably delayed while other causes of dyspnea are pursued and possibly treated. Physical examination findings of cor pulmonale may predominate and are similar to those seen in other causes. Findings that might narrow consideration to CTEPH are chronic postphlebitic changes of the lower extremity and the presence of pulmonary flow murmurs, described as high pitched and best heard over the lung fields during an inspiratory breath-hold.[405] Recognition of the diagnosis usually follows identification of pulmonary hypertension on the echocardiogram and evidence of chronic thromboembolic disease by ventilation-perfusion scanning or pulmonary angiography (Fig. 81-29).



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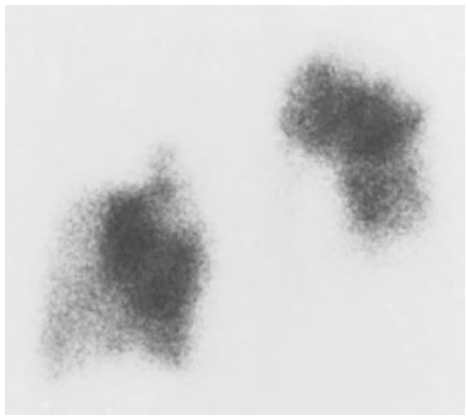

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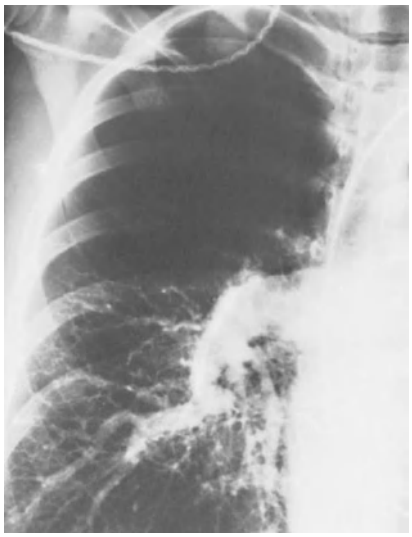

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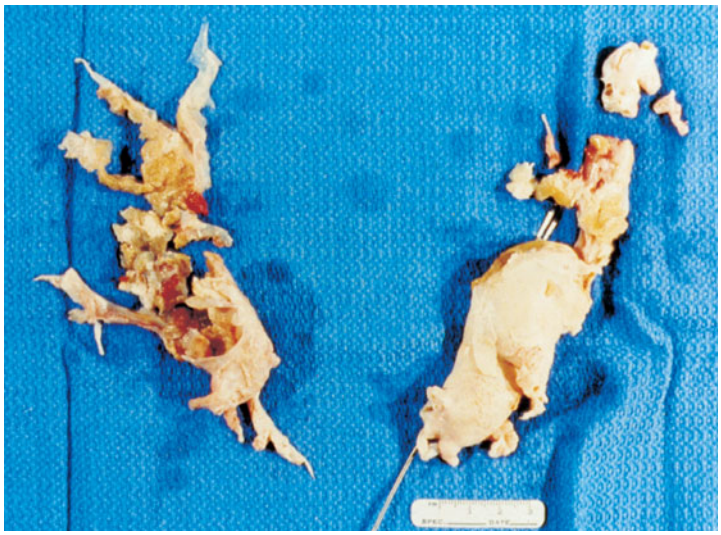

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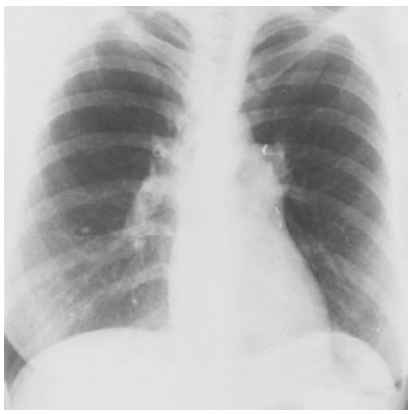

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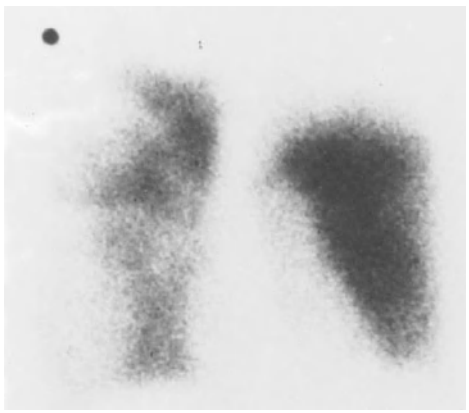

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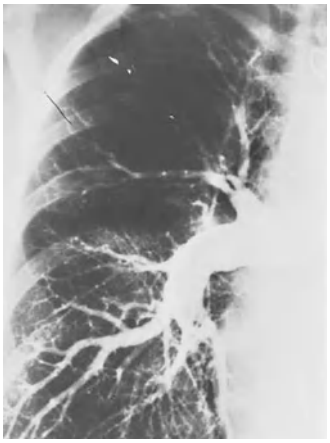


G

Figure 81-29 Chronic thromboembolic pulmonary hypertension before and after surgery in a 35-year-old woman suspected of having had episodes of pulmonary emboli between 1977 and 1979. Progressive pulmonary hypertension cor pulmonale and right ventricular failure. *A*. Preoperative chest radiograph. (Pulmonary arterial pressure = 96/78 mmHg; pulmonary wedge pressure = 4 mmHg; cardiac output = 31 L/min.) The chest radiograph reveals hyperlucency and diminished vasculature in the right upper and left lower lobes. Also cardiomegaly with prominent central pulmonary arteries. *B*. Preoperative perfusion scan. Confirms chest radiograph above. *C*. Preoperative angiogram of right upper lobe showing absence of blood flow. *D*. Organized clot removed by Dr. LH Edmunds from the right upper and left lower pulmonary arteries at surgery. *E*. Postoperative (1 year later) chest radiograph. The chest radiograph is virtually normal. (Pulmonary arterial pressure = 42/20 mmHg; cardiac output = 50 L/min.) *F*. Postoperative perfusion scan. Blood is now perfusing the right upper and left lower lobes *G*. Postoperative angiogram of right upper lobe. Larger vessels that were previously unfilled (see *C*) now extend to right upper lobe. *(Courtesy of Dr. H Palevsky.)*

Ventilation-perfusion radionuclide scanning is the best screening test for CTEPH. Multiple segmental or even larger perfusion defects are usually identified. These contrast with the "mottled" appearance and subsegmental defects often seen in cases of IPAH. In one study, 24 of 25 patients with CTEPH had a high probability scan.[406] A notable but significantly less common cause of mismatched perfusion defects of particular importance in evaluation of patients with pulmonary hypertension is pulmonary veno-occlusive disease.[246] It should also be noted that ventilation-perfusion scans may underestimate the severity of disease and do not predict the hemodynamic status. CT has also been reported to be sensitive and specific in the evaluation of CTEPH. However, CT is less sensitive at detecting chronic thrombus than acute intraluminal clot and instances of CTEPH have been missed.[324,397,408,409]

As in other forms of pulmonary hypertension, right heart catheterization is performed to establish the diagnosis. In addition, pulmonary arteriography is important to determining the location of the clot and its amenability to pulmonary thromboendarterectomy (Fig. 81-29*C*). Such angiography is best performed at a center where experienced operators can appropriately monitor the patient and assess the suitability of surgical intervention. In cases in which the results are not definitive, pulmonary angioscopy may be performed by those experienced with the procedure in order to better define the amenability of clot to surgical removal and predict the hemodynamic effect of removal.

Pulmonary thromboendarterectomy is distinct from embolectomy. In an embolectomy fresh clot is removed from the intraluminal space. A thromboendarterectomy, by contrast, involves meticulous dissection of chronic, fibrotic clot that has become incorporated within the vessel intima[410,411] (Fig. 81-29*D*). The procedure is performed through a sternotomy with cardiopulmonary bypass and complete hypothermic circulatory arrest to provide adequate visualization of the dissection plane within the vessel. Selection of patients involves not only careful assessment of the clot burden and its location, but also the prediction of the expected hemodynamic consequences of surgery and the patient's comorbid conditions.[324,412] The procedure should only be performed at experienced centers. At a single center where the majority of pulmonary thromboendarterectomies have been performed (UCSD Medical Center), mortality has declined progressively from 17 percent in the program's initial series to under 5 percent as experience has grown.[413,414]

Pulmonary thromboendarterectomy can markedly reduce and even normalize pulmonary hemodynamics. The majority of patients experience improvements in exercise capacity, gas exchange, WHO functional class and quality of life.[411,415–420] In a retrospective follow up of more than 500 patients who underwent pulmonary thromboendarterectomy at UCSD between 1970 and 1994, the probability of survival beyond 6 years was 75 percent.[420] Although direct comparison between populations and centers has not been performed, survival of patients at 5 years who were treated with anticoagulation alone in separate series was less than 30 percent.[421,422]

All patients, regardless of surgery, should be treated with lifelong anticoagulation provided contraindications do not arise. Experience with medical therapies beyond anticoagulation for CTEPH is limited. Small case series have reported improved hemodynamics or exercise capacity in patients treated with intravenous epoprostenol, or with oral bosentan, sildenafil, or beraprost.[286,287,303,313,423–425] A randomized, placebo-controlled study of inhaled iloprost in 203 patients with various forms of pulmonary hypertension, included 57 patients with inoperable CTEPH. Although subset analysis of the CTEPH patients alone was not shown, iloprost therapy was reported to improve hemodynamics, quality of life and WHO functional class in these patients.[311] Medical therapies have also been used in patients with residual pulmonary hypertension and symptoms following thromboendartectomy and in attempts to stabilize high-risk patients prior to surgery.[426,427] Once again, controlled studies are lacking.

Cor Pulmonale

The term *cor pulmonale* denotes hypertrophy and/or dilatation of the right ventricle secondary to a disturbance in the breathing apparatus, i.e. abnormal lungs, chest bellows, or the control of breathing (see Fig. 81-1). Cor pulmonale may be acute or chronic. The most common cause of *acute* cor pulmonale is a massive embolus to the lungs. Acute cor pulmonale may also occur during a bout of acute respiratory failure in the course of chronic obstructive lung disease. *Chronic* cor pulmonale is a consequence of the increased work of the right ventricle, almost invariably due to pulmonary hypertension. In chronic cor pulmonale, hypertrophy of the right ventricle generally predominates over dilation; in acute cor pulmonale, dilatation is the preponderant. The major physiological consequence of high pulmonary arterial pressure is that it increases the work of the right ventricle. Abrupt modest increments in mean pulmonary arterial pressure of up to 50 mmHg (e.g., after a large pulmonary embolus), can usually be accommodated by a normal right ventricle without a clinically significant decrease in cardiac output. However, larger acute surges in pressure usually cause either the right ventricle to fail or evoke a life-threatening dysrhythmia. If the higher afterloads are applied gradually, the right ventricle can sustain its output by a combination of dilation and hypertrophy.

The common denominator for cor pulmonale shared by diverse causes is pulmonary hypertension that stems from a primary disorder of the lungs or respiratory apparatus. Although the anatomic lesions underlying pulmonary hypertension may not be reversible, the functional component due to hypoxia can generally be alleviated or relieved, thereby decreasing a major vasoconstrictive component responsible for the pulmonary hypertension. Observations in the 1950s suggested that once the right ventricle fails and systemic venous congestion ensues, life expectancy is less than 4 years. But the ability to tide these patients over episodes of acute respiratory failure associated with infections and heart failure has improved enormously. In our own experience, 5- to 10-year

survival after the first appearance of peripheral edema is not unusual.

Incidence and Prevalence

The incidence of cor pulmonale varies from country to country, between urban and rural areas, and with exposure to air pollutants. In the United States, cor pulmonale averages about 6 to 7 percent of all types of adult heart disease, and COPD is the most common cause. In Delhi, India, where a large segment of the population lives under conditions of severe air pollution, the incidence has been estimated to be about 16 percent. In Sheffield, England, where air pollution is rife, cor pulmonale affects 30 to 40 percent of patients with clinical heart failure. In general, in areas in which smoking is widespread, air pollution severe, and chronic bronchitis and emphysema prevalent, the incidence of cor pulmonale is high. Historically, men have been more often affected than women because of their greater exposure to air pollutants.

Not all patients with COPD develop cor pulmonale. Many manage (e.g., by pursed-lip breathing, the "pink puffers") to maintain arterial oxygenation at near-normal levels, and thereby avoiding pulmonary hypertension. In general, the more deranged the ventilation-perfusion balance, the more likely abnormal blood gases, pulmonary hypertension, and cor pulmonale are to develop. Diffuse interstitial lung disease is a less common cause of cor pulmonale and right ventricular failure.

Most pulmonary disorders affect too little of the lungs, or are too circumscribed in their effects on alveolar-capillary gas exchange, to elicit pulmonary hypertension and cor pulmonale. Tuberculosis, although extensive, is rarely the cause of cor pulmonale, unless both lungs are extensively affected by destruction and conglomerate fibrosis or if surgical intervention has deranged the functioning of the chest bellows. Not uncommonly, alveolar hypoventilation, secondary to sleep apnea syndromes, is accompanied by pulmonary hypertension and chronic cor pulmonale (as discussed above). Cor pulmonale is uncommon in uncomplicated silicosis, anthrasilicosis, or tuberculosis. On the other hand, it is not uncommon when silicosis, anthrasilicosis, or long-standing fibrotic tuberculosis is complicated by extensive, conglomerate, massive fibrosis, distorted adjacent parenchyma, shrunken lobes, and bronchitis (Fig. 81-30). The likelihood of cor pulmonale is increased further by chronic pleurisy, fibrothorax, or excisional surgery. In such patients, a combination of anatomic restriction of the vascular bed and disturbances in gas exchange are implicated in the pathogenesis of the pulmonary hypertension. Disturbances in gas exchange brought about by an acute respiratory infection are usually the most reversible element of this disorder. Cystic fibrosis is another common cause of obstructive airways disease that results in pulmonary hypertension (see Fig. 81-23*C*). Here, too, the root cause is persistent alveolar and arterial hypoxia resulting from ventilation-perfusion abnormalities.

Hemodynamic Features of Cor Pulmonale

The normal right ventricle is a thin-walled, distensible muscular pump that accommodates considerable variations in systemic venous return without large changes in filling pressures. In response to chronic pressure overload imposed by pulmonary hypertension, the right ventricle enlarges, primarily by hypertrophy, which predominantly affects the free wall of the right ventricle. In time, if the pressure load continues, the right ventricle fails. The advent of heart failure is indicated hemodynamically by failure of the cardiac output to increase normally during exercise despite increases in the filling pressures of the right ventricle to abnormally high levels (see Fig. 81-17). Salt and water retention, expansion of the plasma volume, and systemic venous congestion are hallmarks of right ventricular failure; the interstitial water content of the lungs also increases. The mechanisms responsible for the salt and water retention in right ventricular failure are still indefinite.

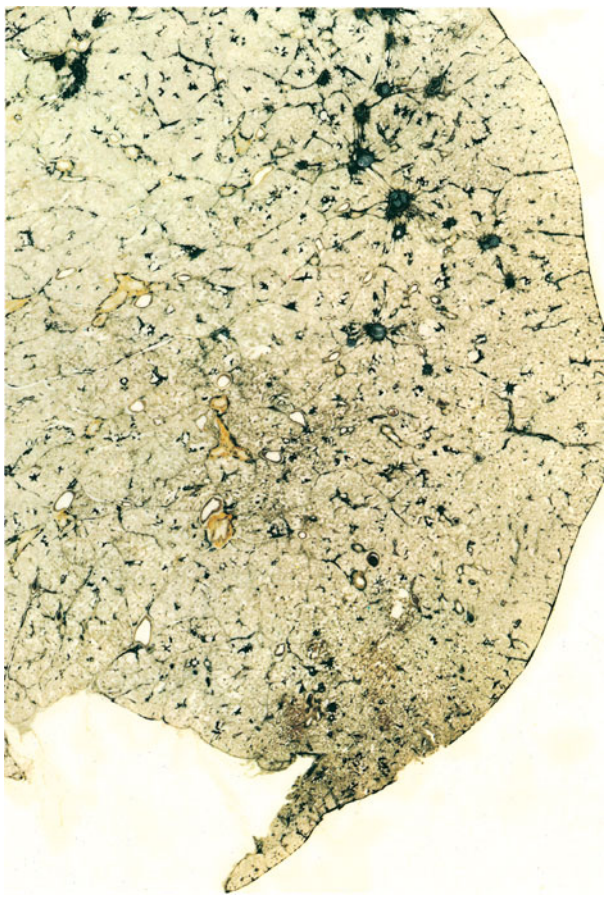
Recovery from right heart failure reverses the water and electrolyte disturbances. As relief of pulmonary hypertension diminishes the load on the right ventricle, its filling pressures return to normal, and the cardiac output once again responds appropriately to the level of exercise. Support of the heart by cardiotonic agents is much less effective than relief of the afterload (i.e., pulmonary hypertension) in restoring adequate cardiac performance.

The left atrial pressure remains normal in cor pulmonale except when circulating blood volume is increased or if right ventricular enlargement becomes severe enough to affect left ventricular filling. Proper function of one ventricle is dependent upon the performance of the other (so-called interventricular dependence). Severe enlargement of the right heart can displace the interventricular septum and impede the left ventricular performance. Further, both ventricles are bound by their common pericardial sac. As intrapericardial pressures increase with progressive enlargement of the right heart, further right ventricular dilatation becomes limited along with limited left ventricular distensibility.[428]

Perhaps the more usual cause of left ventricular failure in cor pulmonale is independent disease of the left ventricle (Fig. 81-31). In elderly people, it is usually reasonable to implicate the coincidence of independent arteriosclerotic disease of the coronary arteries. In the young patient with cor pulmonale and myocardial impairment, the inclination is to attribute the left ventricular dysfunction to underlying disease, such as granulomatous involvement of the myocardium in sarcoidosis. On the other hand, a damaged or overloaded left ventricle from any cause is not apt to perform well in a patient with persistent hypoxemia and acidosis, particularly if these derangements are severe.

Cor Pulmonale in COPD

The designation chronic obstructive *airway* disease includes not only COPD but also other obstructive diseases of the airways, such as cystic fibrosis (Fig. 81-23). Although chronic bronchitis and emphysema usually coexist, it is the chronic bronchitis, because of the ventilation-perfusion abnormalities that it produces, that is primarily responsible for the abnormal blood gases that lead to pulmonary hypertension. In dealing with COPD, one time-honored clinical approach has been the distinction between the "pink puffer"

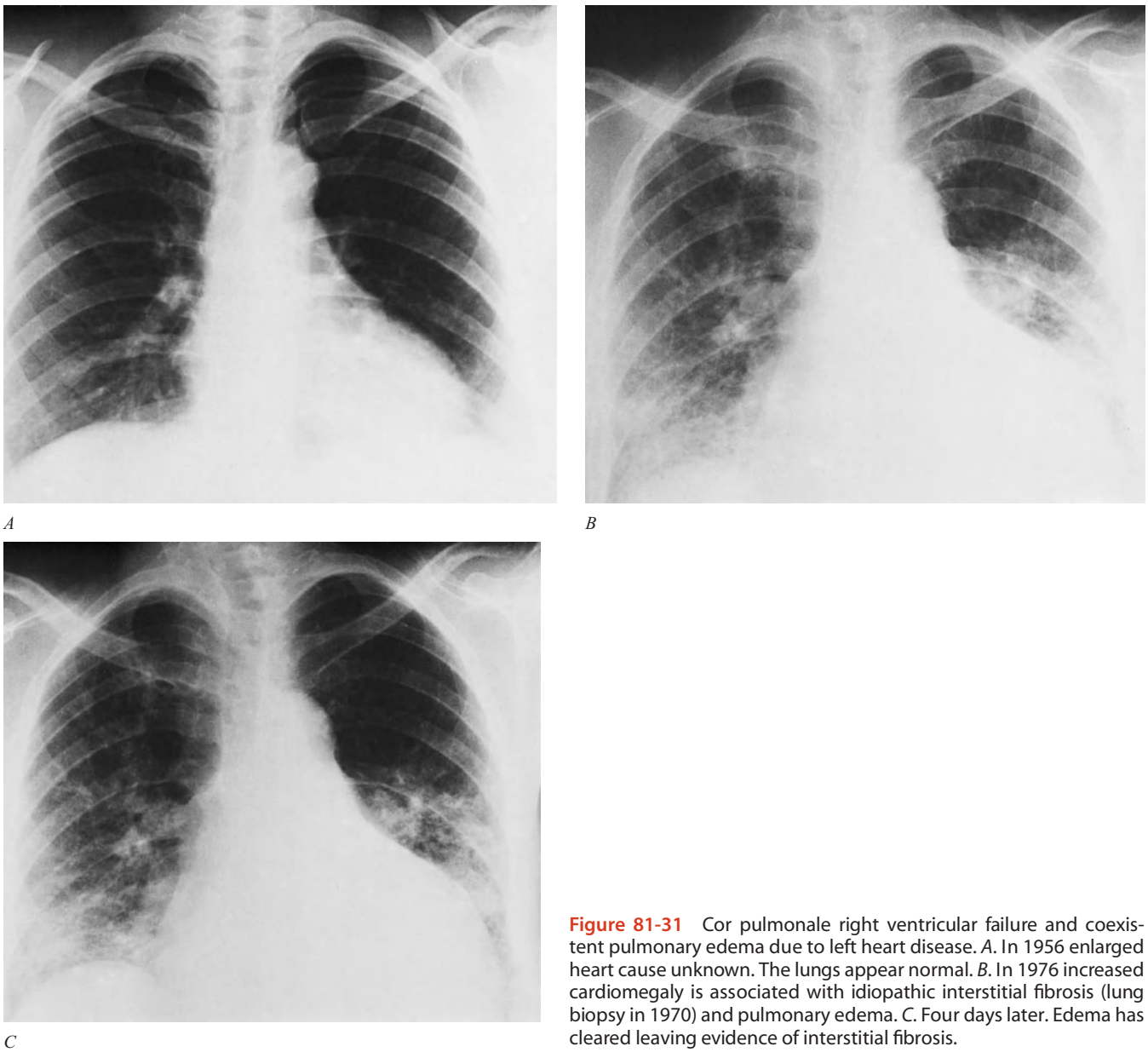


A

B

C

Figure 81-30 Gough (sagittal) sections. *A*. Coal miners' pneumoconiosis. Except for the coal macules (black starts *upper right*), the architecture is virtually normal. *B*. Anthracosilicotic nodules predominantly in vicinity of fissure. Background lung shows centrilobular emphysema. *C*. Progressive massive fibrosis. Cor pulmonale is uncommon in (*A*) unless parenchymal changes are associated with chronic bronchitis (which cannot be seen on these sections). However, cor pulmonale is not uncommon in (*B* and *C*), which often derange blood-gas composition severely. *(Courtesy of JC Wagner, Cardiff.)*



A

B

C

Figure 81-31 Cor pulmonale right ventricular failure and coexistent pulmonary edema due to left heart disease. *A*. In 1956 enlarged heart cause unknown. The lungs appear normal. *B*. In 1976 increased cardiomegaly is associated with idiopathic interstitial fibrosis (lung biopsy in 1970) and pulmonary edema. *C*. Four days later. Edema has cleared leaving evidence of interstitial fibrosis.

(predominantly emphysema) and the "blue bloater" (predominantly chronic bronchitis) (Fig. 81-33). The pink puffer spends a lifetime breathing through pursed lips—an automatic mechanism for achieving positive-pressure ventilation, which in turn maintains arterial P_{CO_2} at near-normal levels. In this group, pulmonary arterial pressures remain at near-normal levels unless some complication, such as a spontaneous pneumothorax or pneumonia, precipitates a bout of severe arterial hypoxemia. In contrast, the blue bloater is continuously on a downhill course of progressive arterial hypoxemia and hypercapnia, which lead to increasing pulmonary hypertension.

It is difficult to explain the onset of cor pulmonale in the blue bloater because work of the right ventricle is not greatly increased even when arterial hypoxemia is quite marked (e.g., PaO_2 of about 35 mmHg) and accompanied by respiratory acidosis (e.g., $PaCO_2$ of about 50 mmHg). At these levels, mean pulmonary arterial pressure is generally only about 30 mmHg, and the cardiac output is only moderately increased. Undoubtedly, the blood gas abnormalities increase during sleep and the activities of daily life. Nonetheless, the levels of pulmonary arterial pressure that have been recorded are generally tolerated without difficulty in native residents at high altitude, raising the question of what factors other than pulmonary hemodynamic abnormalities are at work on the road to right ventricular failure and peripheral edema.[429]

Clinical Evaluation

In chronic bronchitis and emphysema, cor pulmonale and right ventricular failure are encountered in three different settings: in the pink puffer during an acute respiratory infection, in the blue bloater who is chronically refractory to all

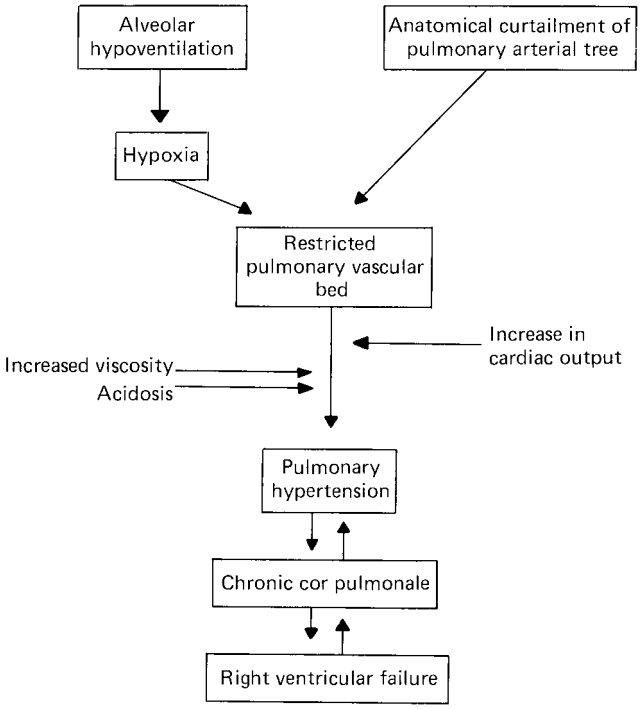


Figure 81-32 Evolution of pulmonary hypertension and cor pulmonale in chronic hypoventilation such as with kyphoscoliosis.

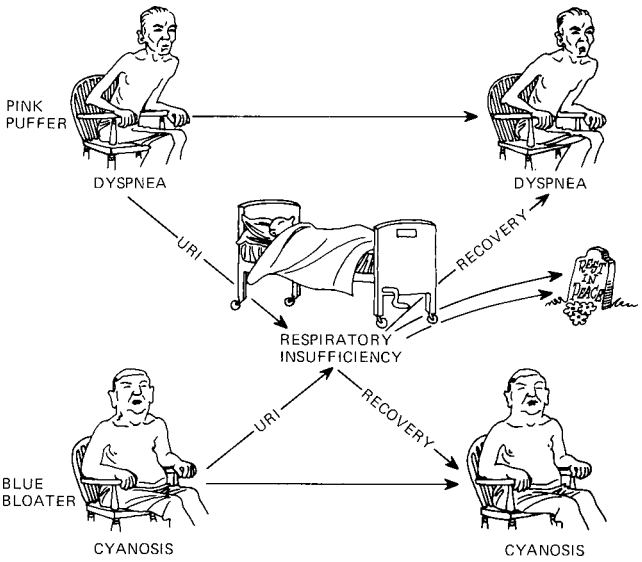


Figure 81-33 The pink puffer and the blue bloater. Natural histories. The pink puffer leads a breathless existence that is interrupted by bouts of acute respiratory insufficiency (*center*) from which he or she may recover completely (*upper right*) or go on to a stage of persistent cyanosis and respiratory acidosis (*lower right*). In contrast the blue bloater generally leads a briefer existence with more frequent bouts of acute respiratory insufficiency from which he or she is less apt to recover completely. During the stage of acute respiratory insufficiency the pink puffer and blue bloater are usually indistinguishable.

cardiotonic and pulmonary measures, and in the blue bloater during an acute respiratory infection.

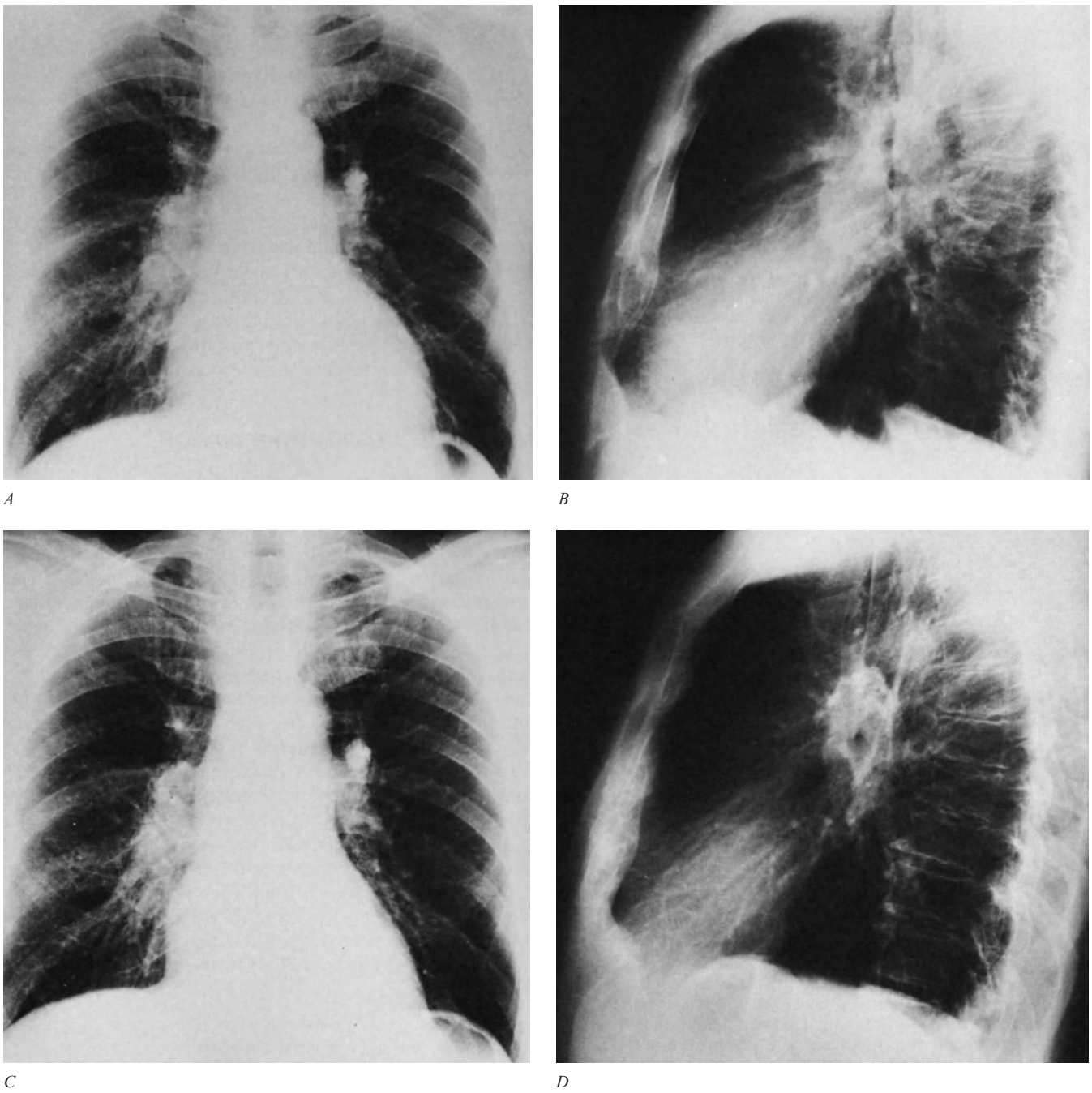
During a bout of respiratory failure, the clinical pictures of the pink puffer and the blue bloater are often indistinguishable. As the infection subsides, however, it usually becomes clear whether a patient is predominantly emphysematous or bronchitic (Fig. 81-33).

Hyperinflation of the lungs in patients with cor pulmonale secondary to COPD often obscures enlargement of the right ventricle. Although heart sounds at auscultation are often reduced with chest hyperinflation, S_3 and S_4 gallops of right ventricular failure are generally present, and the murmur of tricuspid insufficiency can often be elicited upon a deep inspiration. Additional characteristic features of right ventricular enlargement can be uncovered if looked for carefully: a rhythmic lift of the sternum with each heartbeat, a remote but accentuated pulmonary component of the second heart sound, cardiac pulsations in the epigastrium. Right ventricular failure is often accompanied by striking cyanosis, unexplained drowsiness or inappropriate behavior, distended neck veins, warm hands, suffused conjunctivae, hepatomegaly, and edema of the extremities. Not only is the liver generally displaced downward by the low diaphragm, it is also enlarged and tender to gentle pressure over the right upper part of the abdomen.

Once suspicion is raised that ventilation-perfusion abnormalities are the cause of the clinical picture, an arterial blood sample may confirm that the PaO_2 is low (less than 40 to 50 mmHg), the $PaCO_2$ is high (more than 50 mmHg), and respiratory acidosis is present. These blood gas values are rare in left ventricular disorders unless the patient is in frank pulmonary edema.

Plain chest radiographs may suggest enlargement of the right ventricle in a patient with COPD. The chest radiograph depends on the state of the underlying pulmonary disorder and the degree of pulmonary hypertension and right ventricular failure. Most characteristic is the combination of "dirty lungs," prominent pulmonary arterial trunks at the hili, and a pruned peripheral arterial tree. Serial radiographs are generally more useful in detecting changes in the cardiac silhouette as a result of acute exacerbations of cor pulmonale than is a single examination (Fig. 81-34). An initially enlarged cardiac silhouette is often more obvious in retrospect when compared with a repeat study performed after treatment and clinical improvement.

Electrocardiographic evidence of right ventricular enlargement is often blurred in patients with COPD by rotation and displacement of the heart, increased distance between the electrodes on the skin and cardiac surface, and the predominance of dilatation over hypertrophy in the cardiac enlargement. If a distinctive pattern of right ventricular enlargement does occur, the degree of cardiomegaly is invariably severe. Because of these limitations, it is not surprising that the standard criteria for right ventricular enlargement have been satisfied in only one-third of patients with chronic obstructive lung disease who have been shown to have right ventricular hypertrophy at autopsy.



A *B*

C *D*

Figure 81-34 Chronic bronchitis and emphysema. *A* and *B*. Posteroanterior and lateral views during episode of right ventricular failure. Enlargement of the cardiac silhouette is evident. *C* and *D*. Posteroanterior and lateral views 3 weeks later after recovery.

Treatment of Acute Cor Pulmonale in COPD

In the patient with COPD, as in the patient with *general alveolar hypoventilation* (despite normal lungs), the center of attention is the blood gases: Relief of arterial hypoxemia and hypercapnia (acidosis) may alleviate the pulmonary hypertension. The pulmonary hypertension itself usually requires no special treatment: Pulmonary arterial pressures generally decrease as a result of management of the obstructive airway disease: antibiotics to clear an acute upper respiratory infection, bronchodilators, and supplemental oxygen as needed.

The first episodes of right ventricular failure generally respond to a cardiotonic regimen that includes long-term oxygen therapy, diuretics, and digitalis. Each component of this regimen entails some uncertainty. Thus, although long-term oxygen therapy has been shown to improve survival, this benefit may not be attributable to improvement in pulmonary hemodynamics.[113,360] As far as diuretics are

concerned, chloride-losing agents run the risk of promoting hypercapnia, predisposing to respiratory depression, and aggravating ventilatory insufficiency. The use of digitalis must also be undertaken with caution because of the threat of digitalis-associated cardiac arrhythmias during hypoxia.

Right ventricular failure generally responds to clearance of the precipitating mechanism (e.g., an upper respiratory infection). As ventilatory failure increases, however, the margin for recovery from heart failure narrows. Nonetheless, many patients who experience one or more bouts of heart failure per year have survived for 5 to 10 years after the first episode.

Acute Cor Pulmonale or Respiratory Failure in Pulmonary Arterial Hypertension

Patients with PAH may become acutely unstable in a number of settings, including infection, volume overload with dietary indiscretion, or complications of medicines (Table 81-7). In many, an acute stress will convert a chronic state of clinically stable cor pulmonale into rapidly progressive hemodynamic failure. Acutely worsened hypoxemia, if not the precipitating cause of the hemodynamic instability will usually develop quickly as well.[428] Although the precipitating events may differ, each tends to lead to a vicious cycle that will result in worsening right ventricular function and hypotension (Fig. 81-35). Increased work of the right heart, whether due to acute hypoxia and pulmonary vasoconstriction, or fever and infection, will increase ventricular wall stress, further impeding ventricular performance. A decreased cardiac output will impede myocardial perfusion, as will the increase in intraventricular pressure. Worsening the situation may be resultant hypoxemia and left ventricular ischemia, acidemia from either respiratory insufficiency or poor systemic perfusion.

Table 81-7

Clinical Presentations of Patients with Pulmonary Arterial Hypertension with Acute Hemodynamic Instability

Acute recognition/late presentation Syncope, shock, renal failure, ascites, hypoxemia
Acute medication failure Medical noncompliance, interrupted infusions Intolerance (calcium channel antagonist)
Dietary indiscretion/fluid retention
Infection (sepsis with infused therapy)
Fever (environmental causes, infection)
Venous thromboembolism
Medical/surgical procedures/anesthesia
Pregnancy

Source: Reproduced from: Jeffery ME, Taichman DB: Management of the acutely ill patient with pulmonary arterial hypertension in Mandel J, Taichman DB (eds), Pulmonary Vascular Disease. *Philadelphia, Elsevier, 2006.*

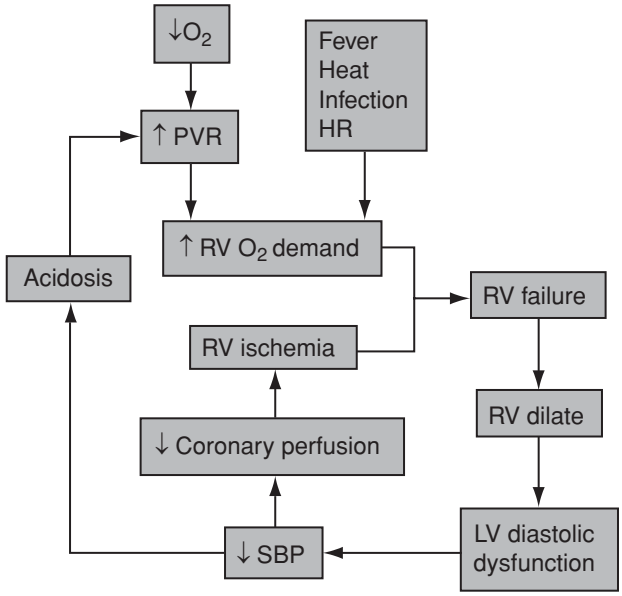


Figure 81-35 Interacting mechanisms in the acute development of worsened right heart function in patients with pulmonary arterial hypertension. A vicious cycle frequently results in both respiratory failure and hemodynamic instability. *(Reproduced from Jeffery ME, Taichman DB: Management of the acutely ill patient with pulmonary arterial hypertension in Mandel J, Taichman DB (eds),* Pulmonary Vascular Disease. *Philadelphia, Elsevier, 2006.)*

The goals of management are the same as for any patient who is hemodynamically unstable or in respiratory distress: to decrease the demand for oxygen while improving its delivery. Supportive care therefore aims to reverse the hypotension and hypoxemia.

Few data are available to guide the management of acute hemodynamic instability in patients with PAH. Studies of various agents have frequently been reported on in patients with acute right heart dysfunction following cardiac surgery, who generally do not suffer from severe underlying disease of the pulmonary vasculature. It is similarly important to recognize the limitations in extrapolating data from acute vasodilator trials performed on an elective basis in patients with PAH to the care of a hemodynamically unstable PAH patient. Although useful, data from published acute vasodilator studies have been performed in hemodynamically stable patients and may not necessarily reflect response in the setting of acute instability.

As in any patient, administration of fluids intravenously is an appropriate initial measure for hypotension, especially when infection or other factors exist that might predispose to hypovolemia. However, in many patients with PAH and chronic cor pulmonale acute hypotension is caused by, or complicated by, worsened right heart dilation that further impairs function. In such patients, fluid removal is required to restore right ventricular function. Vasopressors may be

needed for hemodynamic support while fluid removal is accomplished with diuretics. There are few data to firmly guide the choice of vasopressors. Norepinephrine or dopamine are often employed for their inotropic properties, while agents which may constrict pulmonary vessels such as neosynephrine are usually avoided if possible.[430–432] Attempts to promote pulmonary vasodilatation by intravenous or oral agents are frequently complicated by hypotension from the drugs' systemic effects; the use of inhaled agents (iloprost, NO, or aerosolized epoprostenol) is preferable.[395,433]

Oxygen is a potent pulmonary vasodilator and should be administered at concentrations adequate to prevent hypoxemia. When mechanical ventilation is required, the same principles apply as in other patients with respiratory failure, although certain points are worth noting in the management specifically of patients with PAH. While intra-alveolar vessels are stretched and their resistance increased by overdistention of alveoli, compression of extra-alveolar vessels by atelectasis at low lung volumes might increase their vascular resistance. Thus, at either extreme, pulmonary vascular resistance might increase. The application of positive end-expiratory pressure must also be done with attention to possible overdistention of alveolar vessels and a resultant increase in their resistance. Since hypercarbia tends to promote pulmonary vasoconstriction, lung-protective strategies that permit hypoventilation (and hypercapnia) must be carefully monitored to be certain of overall benefit.[434] Hyperventilation to induce mild alkalemia and pulmonary vasodilation has been used empirically, but with attention to avoid dynamic hyperinflation. Finally, care must be taken to avoid agitation by noxious procedures (e.g., endotracheal suctioning), which may promote further surges in vascular resistance; sedation and analgesia during such procedures should be employed judiciously.[435]

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82

Pulmonary Thromboembolic Disease

Gordon L. Yung • Peter F. Fedullo

Pulmonary thromboembolic disease refers to the condition in which blood clot(s) (thrombus or multiple thrombi) migrate from the systemic circulation to the pulmonary vasculature. Most of these blood clots arise from the "deep veins" of the lower and upper extremities (deep venous thrombosis, DVT). From the clinical standpoint, DVT and pulmonary embolism can be considered a continuum of the same disease, and the two terms are often collectively referred to as venous thromboembolism (VTE). This is distinct from cases of in situ thrombus formation in the pulmonary vascular tree, which is often part of a more complex condition such as idiopathic pulmonary arterial hypertension (primary pulmonary hypertension). Whereas in situ thrombus formation is a slow process, with typically subtle onset and progressive symptoms over a period of weeks to months, thrombus migration often results in dramatic and acute clinical changes. In some cases, unresolved pulmonary emboli can lead to a condition called chronic thromboembolism, with associated secondary pulmonary hypertension (chronic thromboembolic pulmonary hypertension).

In a retrospective analysis of data involving 2218 Olmsted County residents over a ten year period, community residents who were not hospitalized within a 90 days period had the incidence of pulmonary embolism of 3.6 (95 percent CI, 3.2–4.0) per 10,000 person-years. A slightly lower incidence of 2.3 per 10,000 person-years was also reported in an earlier study in Massachusetts. This translates to an annual incidence of approximately 100,000 cases in the United States. However, the true incidence of pulmonary embolism is likely to be much higher, since many cases remain undiagnosed. While 30 percent of patients with venous thrombosis (VTE) may develop symptomatic pulmonary embolism, an additional 40 percent may have asymptomatic disease noted on imaging studies. An earlier report estimated that as many as 630,000 patients develop pulmonary embolism every year in the United States with 200,000 related deaths, the majority in patients in whom the diagnosis was never made (Fig. 82-1). Although considerable effort is directed toward the development of new diagnostic techniques and therapeutic agents, a considerable impact on mortality related to the disease would arise from the routine use of prophylactic strategies, an understanding of the often subtle clinical presentation of the disease, and the appropriate application of existing diagnostic techniques.

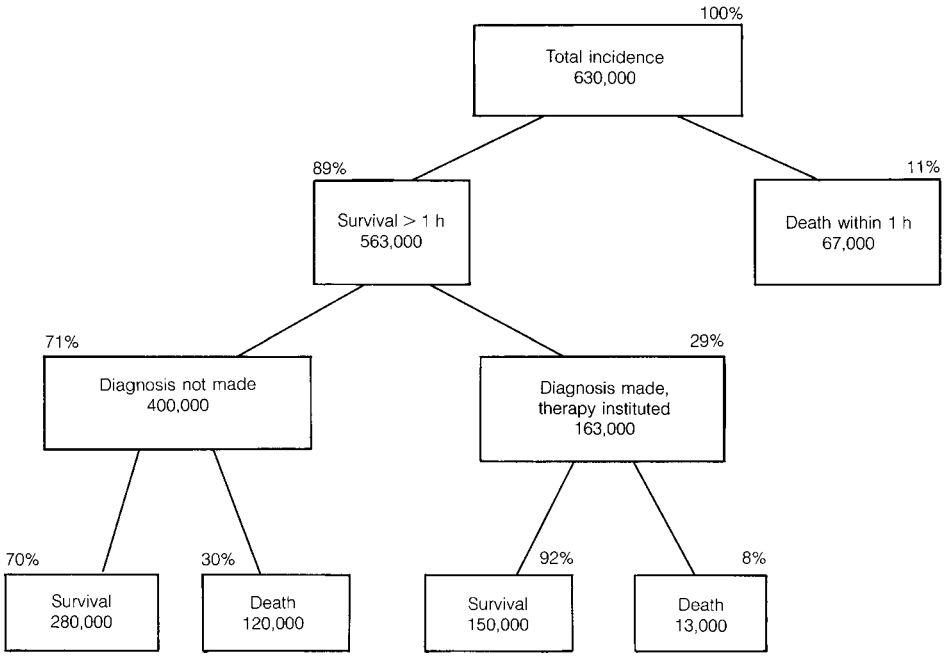

Figure 82-1 Estimated incidence and survival statistics for pulmonary embolism in the United States. *(From Dalen JE, Alpert JS: Natural history of pulmonary embolism. Prog Cardiovasc Dis 17:259–270, 1975.)*

SOURCES OF EMBOLI

Most cases (80–95 percent) of pulmonary embolism occur as a result of thrombus originating in the lower extremity. Thrombus often begins at a site where blood flow is turbulent, such as at a venous bifurcation, or behind a venous valve (Fig. 82-2). When thrombus propagation exceeds the rate of thrombus organization and adherence to the endothelium, part or all of thrombus may break away and migrate via the venous system to the lungs. Most thrombi originate in the deep veins of the calf and propagate proximally to the popliteal and femoral veins. Calf-limited thrombi pose a minimal embolic risk while those that extend into and above the popliteal vein represent the most common source of acute symptomatic pulmonary embolism. Emboli may originate from other sources, most often from the pelvic veins in which case a predisposing factor such as pregnancy, pelvic thrombophlebitis or pelvic infection, prostate disease, or recent pelvic surgery can often be identified. Emboli may also originate from upper-extremity thrombosis associated with central venous catheters or intravascular cardiac devices, or may be associated with thoracic outlet obstruction or effort thrombosis (Paget von Schroetter syndrome). A small number of patients with pulmonary embolism may have evidence of right ventricular thrombus at presentation and this has been associated with more hemodynamic instability and an increase in mortality.

Although the majority of cases of pulmonary embolism are the result of thrombus migration (hence *thrombo* embolism), other materials may occasionally obstruct the pulmonary vascular bed. These include blood born parasites (such as schistosomiasis), sickle cell disease, and various "contaminants" of illicit injected drugs (talc, cloth fibers, etc). Air embolism is usually iatrogenic and typically enters the blood stream accidentally through a central venous catheter. Less commonly, a patient's own tissues or cells may enter the blood stream and lodge in the pulmonary vasculature. Examples include amniotic fluid embolism, which can occur during or immediately after labor or late term abortion, fat embolism which is usually associated with long bone

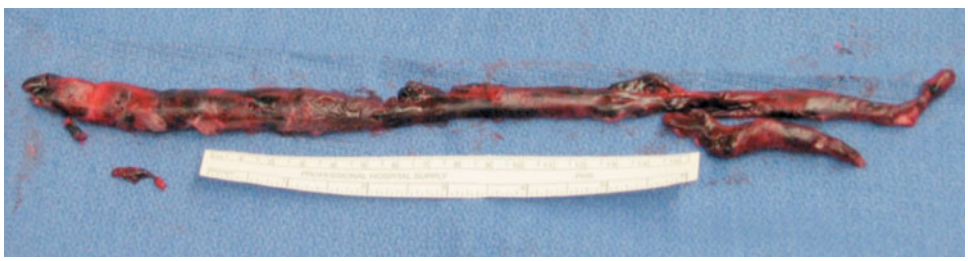

Figure 82-2 Large, well-organized embolus representing "cast" of a lower extremity vein removed from pulmonary artery at pulmonary embolectomy.

fractures, and tumor embolism. Pulmonary embolism due to sickle cell disease is caused by "clumping" of abnormal red blood cells in the setting of hypoxia and stress, and can cause both acute respiratory distress as well as a more progressive disease with secondary pulmonary hypertension.

PREDISPOSING FACTORS

Ruldoph Virchow first described the phenomena of "embolism" and "thrombosis" in the mid-nineteenth century, and identified three main factors contributing to the formation of venous thrombosis (Virchow's triad): venous stasis, hypercoagulability, and injury to the venous wall (endothelium). One hundred fifty years later, this basic classification remains useful in helping clinicians stratify individual patient's risk of developing venous thromboembolism (Table 82-1). It is important to recognize that many of these clinical predisposing factors involve multiple mechanisms leading to deep venous thrombosis and/or pulmonary embolism and that multiple factors can often be found in individual patients.

Acquired Risk Factors

General surgery represents a major risk factor for thrombosis. A high level of risk (30–50 percent) has been described in orthopedic, neurosurgical, gynecological, and urologic surgery. Major traumatic injuries, most notably those of the head, spine, and pelvis, are also associated with high risk. The basis for this risk is multifactorial, involving all three components of Virchow's triad. Normally endothelium acts as a barrier between subendothelial connective tissue and various components of blood and plays an active role in preventing blood from clotting while circulating in the body. Thrombosis is an important part of normal wound healing after injury. As a result of direct endothelial disruption, subendothelial basement membrane and collagen are exposed to platelets and contact–phase coagulation proteins, thereby impairing normal antithrombotic mechanisms by stimulating prothrombotic ones. The endothelium is a very active tissue and endothelial injury can occur through a wide variety of mechanisms, from direct trauma to local inflammation.

Table 82-1

Virchow's Triad: Clinical States Predisposing to Venous Thrombosis

Stasis	Immobility Bed rest Anesthesia Congestive heart failure/cor pulmonale Prior venous thrombosis
Hypercoagulability	Malignancy Anticardiolipin antibody Nephrotic syndrome Essential thrombocytosis Estrogen therapy Heparin-induced thrombocytopenia Inflammatory bowel disease Paroxysmal nocturnal hemoglobinuria Disseminated intravascular coagulation Protein C and S deficiencies Antithrombin III deficiency
Vessel wall injury	Trauma Surgery

Although initially recognized and studied in surgical patients, it is now appreciated that hospitalized medical patients may be equally prone to develop deep venous thrombosis. In about 80 percent of the cases, one or more risk factors may be present when extensive investigative testing is performed. Major risk factors include New York Heart Association class III and IV congestive heart failure, chronic obstructive pulmonary disease, sepsis and other inflammatory disorders, advanced age, stroke, critical illness, and prolonged bed rest.

Any prolonged period of immobilization may increase thromboembolic risk and explains the occurrence of thrombosis under such circumstances as paralysis, bed rest, and prolonged air travel. Long distance traveling (economy class syndrome) is associated with a 1.5- to threefold increase in thromboembolic risk, depending on the traveling distance. A flight time of more than 8 hours and a flight distance of more than 5000 miles have been associated with higher chance of venous thrombosis (1.6 and 5 percent for low and high-risk patients, respectively), even though the actual incidence of pulmonary embolism was still very low (2.57 and 1.5 cases of embolism per million passengers, respectively).

Pregnancy is the most common cause of VTE in women less than 40 years old, and if untreated may account for 20 to 50 percent of all pregnancy-related deaths. It occurs three to six times more often than in age-matched women not on oral contraceptives. The increase may be a result of decreased mobility, pregnancy-related hypercoagulable state (increase in factor I, II, VII, VIII, IX, X, XII, fibrinogen, and activated protein C resistance), and venous obstruction from uterine compression. The incidence is between 1 in 500 to 2000 pregnancies and occurs in roughly equal distribution over all trimesters as well as during the postpartum period. Cesarean section, premature birth, multiple births, preeclampsia, advance maternal age, and maternal history of cardiac disease have all been identified as contributing factors. Interestingly, 90 percent of all deep venous thrombosis cases are noted in the left leg, presumably because of the anatomic relationship between the uterus and inferior vena cava.

The use of oral contraceptive agents and hormonal replacement therapy has also been associated with an increased

risk of venous thromboembolism. In terms of oral contraceptive agents, the relative risk of developing venous thrombosis is a four- to sixfold increased risk. It should be noted that the absolute risk of thrombosis among young women is low and the overall influence of oral contraceptive agents on the overall occurrence of thrombosis is relatively low.

Hormone replacement therapy appears to be associated with a two- to fourfold increased risk. Given that the baseline risk of thrombosis increases with age, the use of hormonal replacement therapy in a postmenopausal population has a considerably higher impact on absolute rates of thrombosis.

Obesity has been associated with VTE, particularly in women. The Nurses' Health Study found that a body mass index greater than or equal to 29 kg/m^2 was an independent risk factor, and the Framingham Study confirmed that obesity is a risk factor for pulmonary embolism. The metabolic syndrome, defined by abdominal obesity, elevation of blood pressure, elevated fasting blood sugar and triglycerides, and low levels of high-density lipoprotein cholesterol, appears to be associated not only with an increased risk of atherosclerotic disease but also of venous thromboembolism.

The risk of venous thromboembolism increases with age. A recent study, using hospital discharge surveys over a 21-year period, found that patients 70 years or older have an approximately 25-fold increased risk, compared with those 20 to 29 years of age. Presumably the difference may be due to decrease in mobility and increase in co-morbidities in this population. Elderly patients also appear to have a higher mortality due to PE, and PE is suspected less commonly prior to death in the elderly patient.

Cancer patients, particularly those with primary malignancies from lung, pancreas, breast (mucin-secreting adenocarcinoma), prostate, stomach/colorectal and genitourinary tracts are at a high risk for VTE. Cancer is estimated to increase the risk of VTE by four- to sixfold. Patients with cancer also have a higher risk of thromboembolic recurrence and have a higher overall mortality rate than cancer patients without thrombosis. Multiple factors are probably involved and include the development of abnormalities in the hemostatic system related to the malignancy itself, hemostatic alterations induced by chemotherapeutic agents, immobility, infectious complications, and the presence of chronic indwelling central venous catheters. Although most instances of cancer-associated VTE occur after the diagnosis of the malignancy, approximately 5 to 10 percent of patients with "idiopathic" venous thrombosis have a malignancy diagnosed within the next 2 to 3 years. There is no evidence at this time to recommend an aggressive search for cancer in these patients, although recent data suggest that a limited approach (abdominal/pelvic CT, mammography, sputum cytology) may be cost effective.

Various hematologic conditions such as polycythemia vera, essential thrombocytosis, and acute leukemia may result in significant overproduction of different cell lines, which in turn may increase the risk of VTE by increasing blood viscosity (hyperviscosity syndromes). This type of thrombosis seems to occur more frequently in the hepatic or portal veins and may be the presenting symptoms of the underlying disorder.

Paroxysmal nocturnal hemoglobinuria is a rare condition associated with an incidence of VTE of approximately 40 percent. Many cases involve non–lower extremity sites, particularly in the intra-abdominal vessels. The reason for thrombosis is not clear but may be related to a decrease in blood complement levels in these patients.

The presence of antiphospholipid antibodies, including the lupus anticoagulant, appears to be an independent risk factor for VTE. Among patients with venous thrombosis, a lupus anticoagulant has been reported in 5 to 15 percent and this abnormality has been estimated to lead to a ninefold increased risk of thrombosis.

The frequency of VTE in patients with nephrotic syndrome may be as high as 40 percent, but the occurrence of pulmonary embolism is probably quite rare. There is a higher tendency for the thrombosis to present in unusual locations such as the cerebral sinus or as arterial thrombosis. Rarely, thrombosis may also be the presenting symptom of the nephrotic syndrome. The mechanism for VTE in these patients is not clear but various factors such as functional or quantitative changes in coagulation factors, diminished fibrinolytic activity, platelet hyperreactivity, and increase blood viscosity have been proposed.

Patients with inflammatory bowel disease are at substantially increased risk of both venous and arterial thrombosis. The exact pathogenetic mechanism remains unclear. The majority of thrombotic complications occur during an active phase of the disease and inflammatory mechanisms have been proposed.

Inherited Conditions

Many patients who develop VTE are found to have an inherited risk factor due to either abnormal levels of or functional abnormalities in coagulation factors (inherited thrombophilia). The relative risk of thrombosis varies widely depending on the hemostatic defect. In general, this group of patients tends to be younger (less than 50 years) and has a tendency to develop recurrent VTE.

The first known inherited thrombophilic trait was antithrombin III deficiency, originally described in 1965. Subsequently, a number of other genetic mutations associated with VTE have been reported. The most common of these inherited predispositions was first described in 1993 by Dahlbeck and designated as a Factor V Leiden mutation, is the consequence of a single point mutation on the factor V gene (adenine for guanine) resulting in factor V_a with diminished sensitivity to the natural anticoagulant effect of activated protein C . Approximately five percent of Caucasians in Europe and North America are heterozygous for this genetic defect; lower rates of carrier frequency have been reported among Native-American, African, and Asian populations. The heterozygous state carries a five- to 10-fold increase in lifetime risk for venous thromboembolism, whereas the risk among patients homozygous for this mutation may be increased

80-fold. Factor V Leiden mutation appears to be an important risk factor for venous thromboembolism during pregnancy, in the postpartum period, and during oral contraceptive use. Compared with women who do not use oral contraceptives and are not carriers of the Factor V mutation, the risk of thrombosis among those with both risk factors is increased approximately 30-fold.

Another common mutation has been identified in the 3′ untranslated region of the prothrombin gene (substitution of A for G at position 20210) and is present in 2 to 4 percent of the general population. This mutation results in an overproduction of prothrombin, which is otherwise normal. It is associated with a three- to fourfold increased risk of lower extremity venous thrombosis and appears to act in a synergistic manner with other forms of thrombophilia in increasing both the initial and recurrent thrombosis risk.

In clinical practice, factor V Leiden mutation and prothrombin gene mutation are the most common inherited conditions and account for more than half of the cases of inherited thrombophilia-related VTE; three other conditions (deficiencies in antithrombin III, protein C, or protein S) account for most of the remainder. Occasionally one may also encounter VTE patients who may have other conditions, particularly related to dysfibrinogenemias. It is important to recognize that, when multiple inherited risk factors coexist (such as factor V Leiden and prothrombin gene mutation), the risk of recurrent VTE may increase substantially, and lifelong anticoagulation may be necessary in these patients. Similarly, isolated hyperhomocysteinemia may not be independently associated with thrombosis, even though the risk for thrombosis may be further increased in patients with coexisting factor V Leiden.

PATHOPHYSIOLOGY

Once detached from their point of origin, emboli travel via the systemic venous system, through the right chambers of the heart, and eventually reach the pulmonary arterial system. The physiologic effects and clinical consequences of pulmonary thromboembolism vary widely, ranging from asymptomatic disease to hemodynamic collapse and death. Major factors that determine the outcome include: (1) size and location of emboli; (2) coexisting cardiopulmonary diseases; (3) secondary humoral mediator release and vascular hypoxic responses; and (4) the rate of resolution of emboli.

Hemodynamic Consequences

Obstruction of the pulmonary vascular bed by embolism acutely increases right ventricular afterload. The normal pulmonary arterial system is a low-pressure system capable of accommodating substantial increases in blood flow with only modest increases in pressure. The thin-walled right ventricle is poorly equipped to generate the pressure necessary to overcome any significant increase in pulmonary vascular resistance. Compensatory mechanisms exist that allow up to 70 percent obstruction of the pulmonary vascular bed before right ventricular failure develops.

In the absence of preexisting cardiopulmonary disease, obstruction of less than 20 percent of the pulmonary vascular bed results in minimal hemodynamic consequences as a result of recruitment and distention of pulmonary vessels. When the degree of pulmonary vascular obstruction exceeds 30 to 40 percent, modest increases in right ventricular pressure occur, but cardiac output is maintained through an increase in heart rate and myocardial contractility. Compensatory mechanisms begin to fail when the degree of pulmonary artery obstruction exceeds 50 to 60 percent. Cardiac output begins to fall and right atrial pressure increases dramatically. Mixed venous oxygen saturation falls and a lactic acidosis may develop. With further acute obstruction, the right heart dilates, right ventricular wall tension increases, right ventricular ischemia may develop, the cardiac output falls, and systemic hypotension develops. In patients without prior cardiopulmonary disease, the maximal mean pulmonary artery pressure capable of being generated by the right ventricle appears to be 40 mmHg (pulmonary artery systolic pressure of approximately 70 mmHg).

Other factors may affect the hemodynamic consequences of pulmonary embolism. Patients with preexisting cardiopulmonary disease often have diminished pulmonary vascular reserve and even a relatively minor embolus may result in significant hemodynamic instability (Fig. 82-3). Alternatively, if the right ventricle has had time (months to years) to hypertrophy in response to a gradual increase in demand (left ventricular disease, idiopathic pulmonary arterial

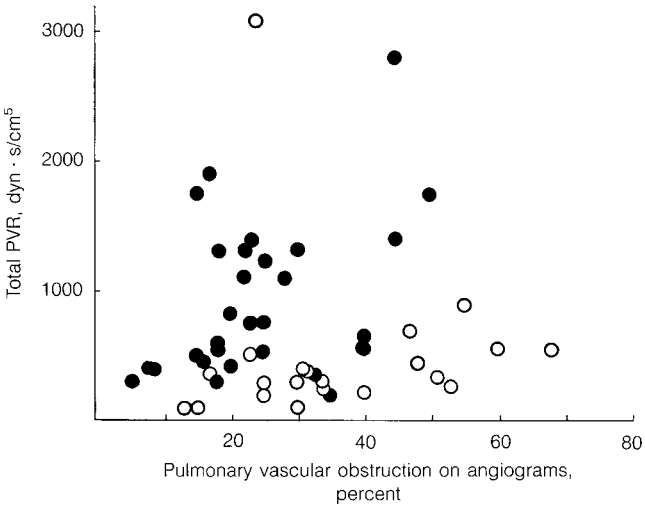

Figure 82-3 Hemodynamic consequences of pulmonary embolism and the underlying state of the pulmonary vasculature. Patients in whom the pulmonary vasculature was previously normal (open circles) develop little increase in pulmonary vascular resistance (PVR) until the clot burden exceeds 50 percent. In those with antecedent cardiopulmonary disease (solid circles), the pulmonary vascular resistance increases appreciably with only modest clot burden. *(From Sharma, McIntyre, Sharma, Sasahara: Clin Chest Med 5:421–437, 1984.)*

hypertension, chromic thromboembolism, etc.) a significantly higher pulmonary artery pressure may been seen.

Several observations suggest that other mechanisms are involved in hemodynamic consequences of acute pulmonary embolism. For example, patients develop only minimal hemodynamic instability during elective lobectomy, pneumonectomy, or even single lung transplantation despite complete and acute interruption of blood supple during cross clamping. In the experimental setting, cyproheptadine (a nonselective serotonin antagonist) and ketanserin (a selective serotonin antagonist) have been shown to diminish some of the hemodynamic and airway responses that occur after pulmonary embolization. Certain patients develop disproportionately large and fluctuating pulmonary hemodynamic changes in response to relatively small emboli, suggesting that other mechanisms such as reflex vasoconstriction and release of vasoactive compounds may also be involved.

As expected, large or multiple emboli tend to cause more severe symptoms and changes in oxygenation and hemodynamics. Given the large surface area of the peripheral pulmonary vascular bed compared to the central, symptomatic improvement may occur when a large central embolus is fragmented by forces generated by cardiac contractions or even with chest compressions during cardiopulmonary resuscitation. Eventually, the emboli may either resolve by fibrinolysis, or organize and become scar-like tissue that adheres to the vascular endothelium (Fig. 82-4). Recent data suggest that complete resolution is uncommon and that as many as 50 percent of patients have some residual obstruction 6 months after the embolic event.

Gas-Exchange Abnormalities

Hypoxemia is the most common immediate physiologic consequence of pulmonary embolism. Obstruction of the pulmonary vasculature prevents systemic venous blood from reaching the pulmonary capillaries of the involved vessels and re-directs the blood flow to other parts of the pulmonary vascular bed. This results in an increase in intra-pulmonary shunting, ventilation-perfusion (V/Q) inequality, and decreases in the mixed venous O_2 level, thereby magnifying the effect of the normal venous admixture. Further shunting and increase in alveolar dead space can also occur as a result of alveolar hemorrhage or to atelectasis related to loss of surfactant. Constriction of terminal bronchioles may further increase alveolar dead space as a result of regional hypocapnia and the release of vasoconstrictive substances from platelet aggregates and mast cells. Despite an increase in alveolar dead space, patients with pulmonary embolism often develop hypocapnia. This is thought to be due to hypoxia-induced intrapulmonary reflex vagal stimulation, with resulting hyperventilation. Finally, hypoxemia may lead to an increase in sympathetic tone, which in turn causes systemic vasoconstriction. Patients with no significant cardiopulmonary disease may then respond by a temporary compensatory increase in venous return and stroke volume. Finally, embolic events large enough to increase right atrial pressure may result in intracardiac right-to-left shunting through a patent foramen ovale.

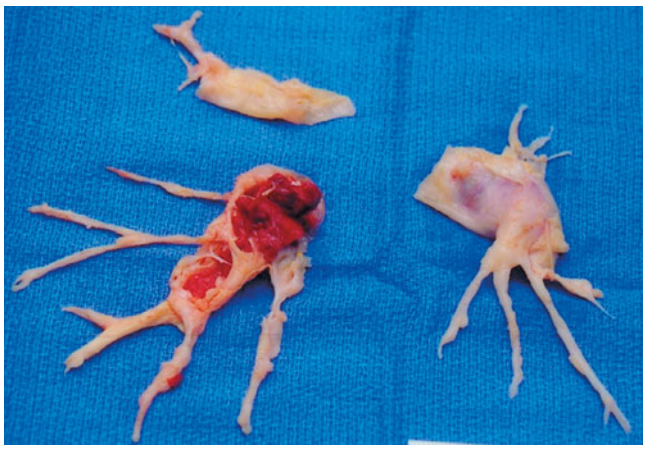

Figure 82-4 Chronic thromboembolic material dissected from pulmonary arteries at pulmonary thromboendarterectomy. Resolution of emboli is occasionally complete but certain patients may be left with significant emboli residua.

One uncommon consequence of pulmonary embolism is pulmonary infarction. Infarction is uncommon because the pulmonary parenchyma has three potential sources of oxygen: the pulmonary arteries, bronchial arteries, and airways. Two of these three sources apparently must be compromised before infarction develops (Fig. 82-5). Therefore, in a patient with no coexisting cardiopulmonary disease, infarction is rare. Infarction occurs in approximately 20 percent of patients with significant cardiac or pulmonary disease that compromise either bronchial arterial flow or airway patency. In patients with left ventricular failure, increased pulmonary venous pressure may decrease bronchial flow and infarction may occur.

Diagnosis of Pulmonary Embolism

The diagnostic approach to pulmonary embolism has undergone a fundamental transition over the past decade. Ventilation-perfusion scanning, the mainstay of diagnosis for almost three decades, has been relegated to a secondary role. The Prospective Investigation of Pulmonary Embolism Diagnosis (PIOPED) trial demonstrated the shortcomings of this technique while providing valuable insight into the diagnostic utility of clinical assessment. Computed tomography, highly sensitive D-dimer assays, stratification according to clinical assessment, and the application of Bayesian analysis to the diagnostic pathway have become the cornerstones of the current diagnostic approach. What has not changed is the understanding that clinical evidence per se, although capable of raising suspicion of the disease, is incapable of reliably confirming or excluding the diagnosis in the absence of objective testing. Recognition of the clinical signs and symptoms associated with embolism is valuable because clinical findings and clinical suspicion represent an essential first step in the diagnostic pathway.

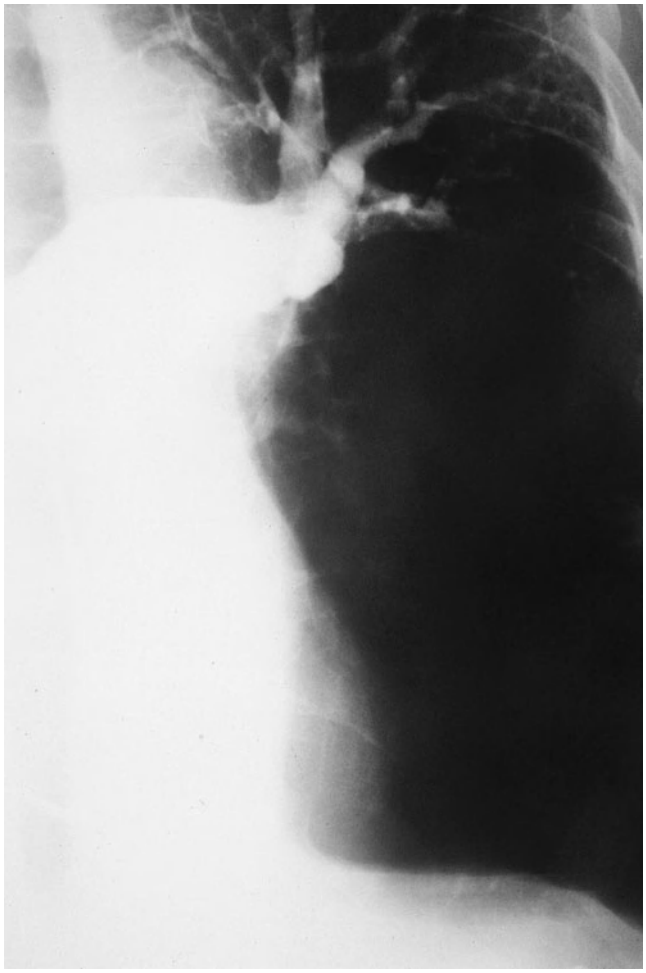

Figure 82-5 Pulmonary angiogram demonstrating thromboembolic obstruction of left pulmonary artery with absent blood flow to lingula and lower lobe. Despite extension obstruction, infarction did not occur as a result of lung's dual blood supply.

Clinical Presentation

The mainstay for the diagnosis of pulmonary embolism is a high index of suspicion tempered by the reality that most patients with embolism have one or more factors predisposing them to the condition. These predisposing factors need not be major or readily apparent. Advancing age, a period of bed rest, a prolonged air flight, or a minor traumatic injury can result in the development of venous thromboembolism. The absence of a known clinical or thrombophilic predisposition, however, should not dissuade an objective evaluation if the clinical presentation is consistent with embolism.

Although a somewhat arbitrary classification (as presenting symptoms and signs of embolism frequently overlap), the presentation of acute pulmonary embolism can be categorized into one of three clinical syndromes: (1) isolated dyspnea; (2) pleuritic pain or hemoptysis; and (3) circulatory collapse. Among patients without prior cardiopulmonary disease in the PIOPED study, the syndrome of pleuritic pain or hemoptysis was found to be the most common mode of presentation, occurring in approximately 60 percent of patients; isolated dyspnea occurred in approximately 25 percent, whereas circulatory collapse occurred in 10 percent.

Two additional modes of presentation are also possible. With the increasing use of computed tomographic studies, incidental emboli are occasionally found. Typically, these emboli are found in the peripheral segments of the pulmonary arterial vasculature and do not correlate with any clinical symptoms. At this time, the short- and long-term significance of these incidental findings is not clear. In patients who are known to be at high risk of recurrent disease, such as those with inherited thrombophilia and hormonal use, it is reasonable to consider treatment with anticoagulation or at least the use of more aggressive prophylactic therapies during at-risk situations, such as prolonged hospitalization or air travel.

Complete anatomic resolution of pulmonary embolism appears to be uncommon. Given sufficient residual pulmonary vascular obstruction, some patients may develop chronic thromboembolic pulmonary hypertension (CTEPH). Although exact values for frequencies vary, it is estimated that approximately 1 percent of patients may develop this condition following a symptomatic episode of pulmonary embolism. Approximately 30 percent of patients who present with CTEPH do not have a history of precedent acute embolism and are diagnosed during the evaluative process for pulmonary hypertension.

The most common presenting symptom of acute embolism is the sudden onset of dyspnea. However, dyspnea does not recur in approximately 25 percent of patients ultimately proven to have embolism. Other symptoms include pleuritic chest pain, cough, leg swelling or pain, and hemoptysis. The most common physical finding is unexplained tachypnea (respiratory rate greater than 20/minute) present in approximately 70 percent of patients with embolism. Less frequent physical findings include rales, tachycardia, and an increased pulmonic component of the second heart sound. Fever may develop some hours after the event and often reaches, but rarely exceeds, 38.3°C.

Obviously, these symptoms and signs are nonspecific (Table 82-2). In the PIOPED study, none of the presenting symptoms or signs with the exception of the presence of rales, a fourth heart sound, and an increased pulmonic component of the second heart sound could differentiate between those with positive and negative angiograms.

Clinical Assessment

A major advance in the diagnostic approach to pulmonary embolism has been a transition from a purely technique-oriented approach to one that uses Bayesian analysis. In doing so, the pretest probability of the disease, calculated independently of a particular test result using either empiric means or a standardized prediction rule, is calculated. This pre-test probability aids in the selection and interpretation of further diagnostic tests to create a post-test probability of the disease. This post-test probability can then be used as a basis for clinical decision making. For pulmonary embolism,

Table 82-2

Incidence of Signs and Symptoms of Pulmonary Embolism

	Massive PE (%)*	Submassive PE (%)*	PE Without Preexisting Cardiopulmonary Disease (%)†
Dyspnea	85	82	73
Pleuritic chest pain	64	85	66
Cough	53	52	37
Hemoptysis	23	40	13
Tachypnea	95 (>16/min)	87 (>16/min)	70 (>20/min)
Tachycardia (>100/min)	48	38	30
Increased P2	58	45	23
Rales	57	60	51
Phlebitis	36	26	11

* *Source: Data from NIH-Sponsored urokinase and streptokinase clinical trials.* Am J Med *62:355–360, 1977.*
† *Source: Data from NIH-sponsored PIOPED trial.* Chest *100:598–603, 1991.*

three such scores have been developed and validated (Tables 82-3 to 82-5). Wells and co-workers have prospectively tested a rapid seven-item bedside assessment to estimate the clinical pretest probability for PE. An alternative scoring system, the Geneva score, involved seven variables and required gas exchange and radiographic information. Recently, a revised Geneva score requiring eight clinical variables without gas exchange or radiographic information was validated and published. Although such scoring systems have not proved to be more accurate than clinical assessment, they do provide a method of standardization that compensates for variability in physician experience and judgment.

Laboratory Data

Routine laboratory testing is not useful in confirming or excluding the diagnosis of pulmonary embolism but may be helpful in suggesting other diagnoses. A modest leukocytosis may accompany embolism but rarely exceeds 20,000/mm^3.

Hypoxemia is common in acute PE although the diagnosis of acute PE cannot be excluded based upon a normal Pa_{O_2}. The more massive the obstruction, the more severe the hypoxemia is likely to be. However, many other conditions also cause hypoxemia, and embolism often does not cause hypoxemia or even a widening of the (A-a) O_2 gradient. Hypocapnia usually accompanies embolism. Hypercapnia, on the other hand, is rare and appears with embolism only in patients with marked antecedent ventilatory limitation or when such limitation has been imposed because the patient is on controlled mechanical ventilation when embolism occurs.

Electrocardiogram

The electrocardiogram is nonspecific in the diagnosis of pulmonary embolism, and its major value may be in identifying other clinical disorders (e.g., acute myocardial infarction and pericarditis) that may be confused with pulmonary embolism. Findings in acute PE are generally nonspecific and include T-wave changes, ST-segment abnormalities, and left- or right-axis deviation (Fig. 82-6). Atrial arrhythmias may occur but appear to be more common in patients with underlying cardiopulmonary disease. The S1Q3T3 pattern, commonly considered to be specific for PE, is seen in only a minority of patients. Electrocardiographic findings can offer insight into the extent and hemodynamic consequence of the embolism. The electrocardiogram is rarely normal in the setting of embolism associated with right ventricular dysfunction. The presence of an S1Q3T3 pattern, right bundle branch block, or T-wave inversion in leads V1-V3 in a patient with embolism should suggest the presence of right ventricular dysfunction.

Chest Radiography

Most patients with pulmonary embolism have abnormal but nonspecific chest radiographic findings. Common radiographic findings include atelectasis, pleural effusion,

Table 82-3

The Wells Clinical Prediction Score

Variable	Points
DVT symptoms/signs	3.0
PE al likely or more likely than alternative diagnosis	3.0
Heart rate >100	1.5
Immobilization/Surgery previous 4 weeks	1.5
Previous DVT or PE	1.5
Hemoptysis	1.0
Malignancy	1.0
Total Score	**Pretest Probability**
<2.0	Low
2.0–6.0	Moderate
>6.0	High
Dichotomized Score	
#4	PE unlikely
>4	PE likely

Source: Wells PS, Anderson DR, Rodger M, et al.: Derivation of a simple clinical model to categorize patients' probability of pulmonary embolism: Increasing the models utility with the SimpliRED D-dimer. Thromb Haemost *83:416–420, 2000.*

Table 82-4

The Original Geneva Clinical Prediction Score

Variable	Points Score
Age	
60–79 years	1
>80 years	2
Previous DVT or PE	2
Recent surgery	3
Pulse rate >100	1
Pa_{CO_2}, kPa (mmHg)	
<4.8 (36)	2
4.8–5.19 (36–38)	1
Pa_{CO_2}, kPa (mmHg)	
<6.5 (<48)	4
6.5–7.99 (48–60)	3
8.0–9.49 (61–71)	2
9.5–10.99 (72–82)	1
Chest radiograph appearance	
Platelike atelectasis	1
Elevated hemidiaphragm	1
Total Score	**Pretest Probability**
0–4	Low
5–8	Moderate
9–16	High

Source: Wicki J, Perneger TV, Junod AF, et al.: Assessing clinical probability of pulmonary embolism in the emergency ward. Arch Intern Med *161:92–97, 2001.*

pulmonary infiltrates, and mild elevation of a hemidiaphragm. Classic findings of pulmonary infarction—such as Hampton's hump or decreased vascularity (Westermark's sign)—are suggestive but infrequent. There is some confusion about the diagnostic configuration of infiltrates due to embolism. These infiltrates, although usually abutting a pleural surface, can be of any shape, not necessarily wedge-shaped. Although pleural effusions occur in almost half of the patients, the majority of effusions are small and involve only blunting of the costophrenic angle. The main use of the chest radiograph in suspected embolism is to exclude diagnostic possibilities such as pneumothorax, which may simulate the disease. A normal chest radiograph in a patient with otherwise unexplained acute dyspnea or hypoxemia is strongly suggestive of embolism.

D-Dimer

The development of a rapid and accurate blood test capable of diagnosing venous thromboembolism has been the subject of considerable investigative interest. A number of different hemostasiologic markers have been investigated. Of these, D-dimer, alone and in combination with other noninvasive studies has been subjected to the most rigorous clinical evaluation. D-dimer testing has proven to be highly sensitive but not specific. Increased levels are present in nearly all patients with thromboembolism, but also occur in a wide range of other circumstances, including advancing age, pregnancy, trauma, infections, the postoperative period, inflammatory states, and malignancy. Therefore, the

Table 82-5

The Revised Geneva Clinical Prediction Score

Variable	Points
Age >65 years	1
Previous DVT or PE	3
Surgery (under general anesthesis) or lower limb fracture within 1 month	2
Active malignancy (currently active or considered cured <1 year)	2
Symptoms	
Unilateral lower limb pain	3
Hemoptysis	2
Clinical signs	
Heart rate: 75–94 beats/minute	3
∃ 95 beats/minute	5
Pain on lower-limb deep venous palpation or unilateral edema	4
Total Score	**Pretest Probability**
0–3	Low
4–10	Moderate
∃ 11	High

Source: Le Gal G, Righini M, Roy P-M, et al.: Prediction of pulmonary embolism in the emergency department: The revised Geneva Score. Ann Intern Med *144:165–171, 2006.*

role of D-dimer testing is limited to one of thromboembolic exclusion.

Multiple assays for D-dimer have been developed with sensitivities that range from 80 to almost 100 percent. Highly sensitive assays such as the enzyme-linked immunosorbent assay (ELISA) are capable of excluding thromboembolism but are associated with such a high frequency of false-positive results, especially when applied to an inpatient population, as to limit their clinical utility. Less sensitive assays (e.g., latex agglutination, red cell agglutination) lack the ability to exclude thromboembolism in isolation but have been used successfully in combination with either a clinical probability estimate or noninvasive diagnostic study. D-dimer testing has been used successfully as part of a number of different diagnostic strategies. Negative results of standardized, highly sensitive assays (ELISA), using a cutoff value of 500 ng/ml, have proved capable of safely excluding pulmonary embolism in outpatients presenting with a low or intermediate clinical likelihood of the disease. Certain non-ELISA assays are capable of excluding embolism as a stand-alone study in outpatients with a low probability of disease but are more appropriately used in a multi-branch diagnostic pathway.

Computed Tomography

Computed tomography (CT) has become the first-line imaging test for pulmonary embolism (Fig. 82-7). CT technology has evolved from single detector scanners to multi-row detectors and from 4- to 64-MDCT. Using the latest generation scanners, visualization of the entire chest with submillimeter resolution extending to the sixth generation arteries can now be performed within a single breath hold. Unfortunately, these technological advances have considerably outstripped substantiating research data. For example, the recently published PIOPED II trial, which used predominantly 4-MDCT technology and a composite reference standard, demonstrated sensitivity for the diagnosis of embolism of 83 percent, specificity of 96 percent, positive predictive value of 86 percent, and negative predictive value of 97 percent. The predictive value of CT varied substantially when clinical assessment was taken into account, with the major variance occurring when there was discordance between the clinical assessment and CT finding (Table 82-6). Both the positive predictive value in patients with a low clinical probability and the negative predictive value in those with a high clinical probability were in the range of 60 percent.

At the present time, CT can be considered confirmatory in excluding embolism in patients with a low or intermediate likelihood of disease and confirming embolism in patients with intermediate or high probability of disease. When discordance exists between the clinical assessment and CT findings, additional studies should be performed. It is possible this recommendation will change as studies with 64-MDCT scanners are published.

Ventilation-Perfusion Scanning

Despite limitations, ventilation and perfusion lung scanning can provide valuable information if used and interpreted appropriately. A negative study rules out the diagnosis of pulmonary embolism with the same degree of certainty as a negative pulmonary angiogram and with a higher degree of certainty than can be achieved by a negative CT scan (Fig. 82-8). The positive predictive value of a "high probability" study (one characterized by multiple, segmental-sized, mismatched defects) approximates 88 percent (Fig. 82-9). Unfortunately, only 28 percent of patients in PIOPED had scans characterized as high probability or normal, the only categories that can be considered definitive. The majority of patients with embolism do not have a high probability scan, while the majority of those without embolism do not have a normal scan.

The PIOPED study also undertook to correlate the clinical impression of the likelihood of pulmonary embolism with

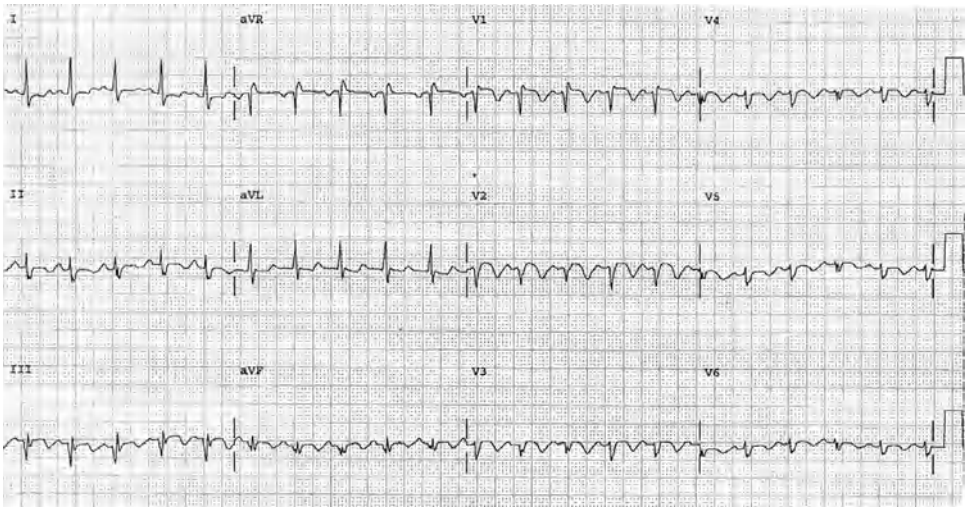

Figure 82-6 Electrocardiogram demonstrating findings consistent with embolism including sinus tachycardia, incomplete right bundle branch block, S1Q3T3 pattern, and inverted precordial T waves.

the interpretation of the lung scan (Table 82-7). When interpretation of the lung scan and clinical assessment were concordant (both high and low probability), diagnostic accuracy was greater than that of the lung scan alone. In contrast, when interpretation of the lung scan and clinical assessment were discordant, the predictive value of the lung scan was decreased. In as many as two-thirds of patients suspected of pulmonary embolism, the combination of the lung scan and clinical assessment were either discordant or indeterminate and failed to diagnose or exclude pulmonary embolism.

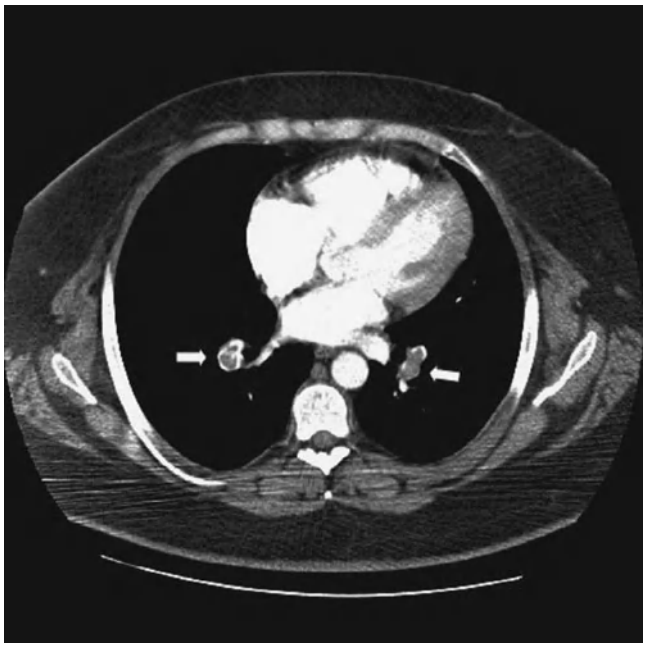

Figure 82-7 Computed tomographic angiogram demonstrating nearly occlusive thrombus in both lower lobe pulmonary arteries (arrows).

Echocardiogram

Echocardiography may serve a valuable role in the diagnostic approach to pulmonary embolism. Under appropriate clinical circumstances, the detection of unexplained right ventricular volume or pressure overload should suggest the possibility of embolism and lead to confirmatory testing. Properly performed *transesophageal* echocardiography has demonstrated sensitivity and specificity exceeding 90 percent in the detection of proximal emboli involving the pulmonary trunk and the right and left main pulmonary arteries. Echocardiography also may prove valuable in the evaluation of competing diagnostic possibilities such as right ventricular infarction, endocarditis, pericardial tamponade, and aortic dissection in patients with unexplained shock and evidence of elevated central venous pressure. The overall sensitivity of *transthoracic* echocardiography in pulmonary embolism approximates 50 percent. Therefore, it cannot be considered a primary diagnostic technique. Consideration can be given to its use in that subset of patients with suspected massive pulmonary embolism who are too ill for transportation or have an absolute contraindication to the administration of a contrast agent.

Lower Extremity Evaluation

Duplex ultrasonography, which refers to the combination of Doppler venous flow detection and real-time B-mode imaging, has assumed a central role in the noninvasive diagnosis of symptomatic lower extremity deep venous thrombosis. A number of criteria are used to diagnose venous thrombosis, the most reliable of which is non-compressibility of a venous segment. Secondary, less reliable criteria include the presence of echogenic material within the venous lumen, venous distention, and loss of phasicity, response to Valsalva, and augmentation of spontaneous flow. The absence of an echogenic luminal mass cannot be considered useful in excluding the diagnosis of venous thrombosis because acute thrombus may

Table 82-6

Prevalence of Pulmonary Embolism in PIOPED II: Value of Correlating CT Interpretation with Clinical Assessment

		Clinical Assessment		
		High No./Total/%	**Intermediate No./Total/%**	**Low No./Total/%**
CT scan interpretation	PPV of CTA	22/23 (96%)	93/101 (92%)	23/38 (58%)
	PPV of CTA-CTV	27/28 (96%)	100/111 (90%)	24/42 (57%)
	NPV of CTA	9/15 (60%)	121/136 (89%)	158/164 (96%)
	NPV of CTA-CTV	9/11 (82%)	114/124 (92%)	146/151 (97%)

Source: Stein PD, Fowler SE, Goodman LR, et al.: Multidetector computed tomography for acute pulmonary embolism. N Engl J Med *354:2317–2327, 2006.*

not demonstrate echogenicity. Multiple studies over the past decade have demonstrated sensitivities and specificities exceeding 95 percent in *symptomatic* patients with proximal venous thrombosis. Although simplified compression examinations limited to the symptomatic leg or to the common femoral and popliteal veins (rather than the entire lower extremity venous system) have been suggested, the time saved with such approaches is limited and a number of isolated superficial femoral vein or calf-limited thrombi may be overlooked. Asymptomatic thrombi in the contralateral leg can be detected in approximately 5 to 10 percent of patients presenting with symptomatic acute venous thrombosis. Although the detection of asymptomatic, contralateral thrombi has little impact on the immediate management of the patient, it may have long-term consequences when recurrence is suspected. A more prudent approach appears to be a complete examination extending from the inguinal ligament to the popliteal vein and examination of the contralateral extremity if thrombus is detected in the symptomatic leg.

Impedance plethysmography (IPG), an indirect technique which measures the rate of venous outflow, has been well standardized and carefully validated against contrast venography.

False-positive studies may result from conditions that diminish arterial inflow (congestive heart failure, shock, peripheral arterial disease) or that impede venous return (right ventricular failure, obstructive lung disease), thereby lowering the specificity of the technique. Early studies reported sensitivities of approximately 90 percent in symptomatic patients with proximal venous thrombosis. Calf thrombi are detected in approximately 25 percent, a figure that reflects the lesser degree of venous obstruction in most (though not all)

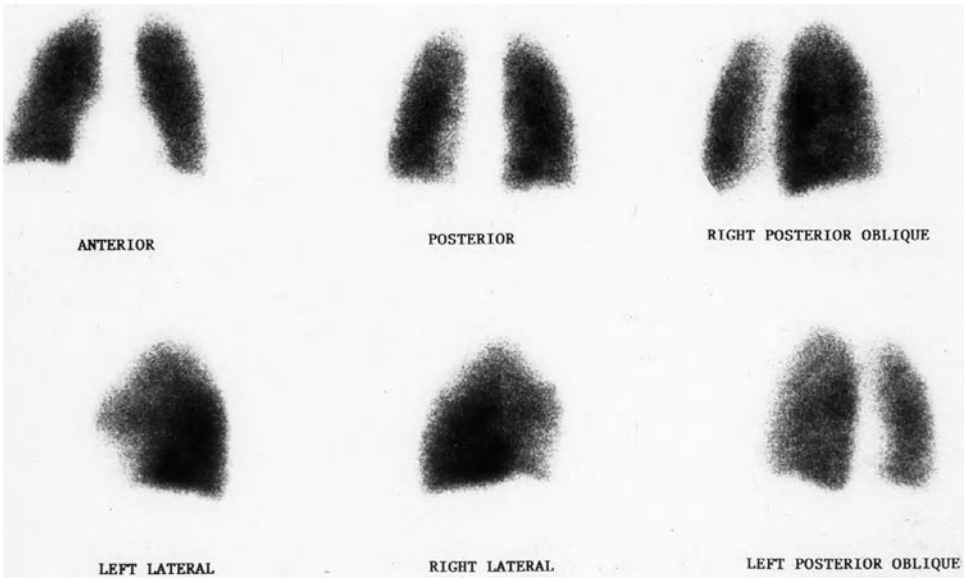

Figure 82-8 Normal 6-view perfusion scan. Such a scan finding has a negative predictive value equivalent to a negative pulmonary angiogram and higher than that of a negative computed tomographic study.

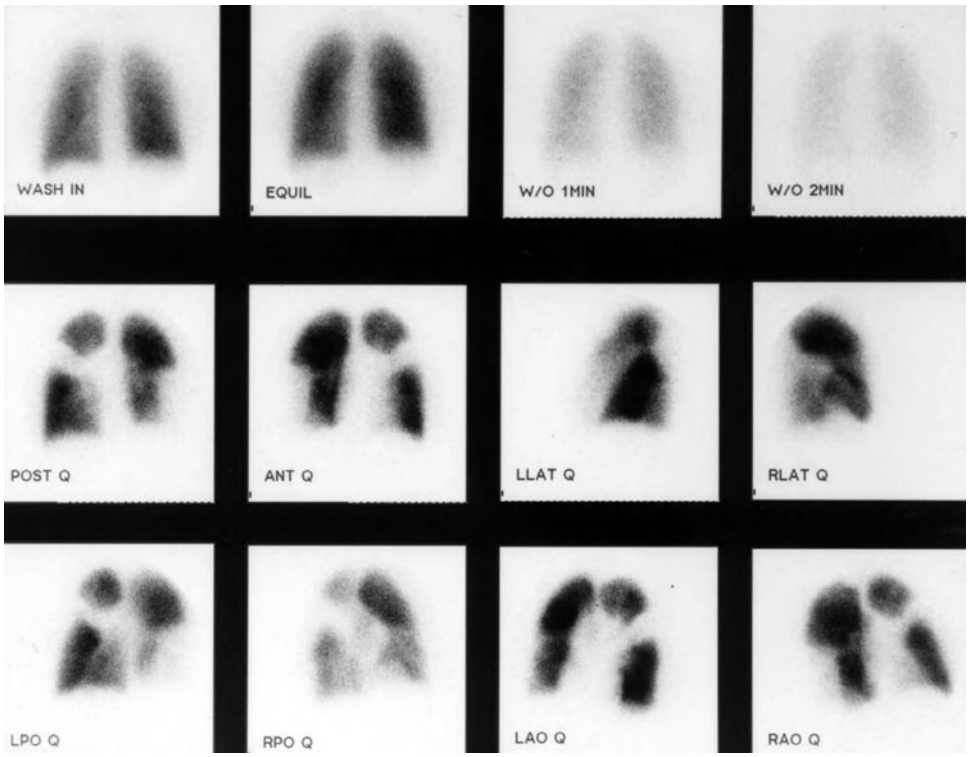

Figure 82-9 "High probability" ventilation/perfusion scan demonstrating normal ventilation and multiple mismatched segmental and larger defects.

calf thrombi. Subsequent studies of IPG accuracy have raised questions regarding the ability of IPG to detect even symptomatic, proximal vein thrombosis. Reported sensitivities in these studies have been in the range of 65 to 75 percent. The low sensitivity of IPG in these studies may result from its use in patients with less severe symptoms because these patients are more likely to have small, nonocclusive, or distal thrombi that IPG cannot readily detect.

The role of computed CT venography as a stand alone test for venous thrombosis is limited. The sensitive and specificity of CT venography appear to be comparable to ultrasonography, but mandates contrast injection with its associated risks and radiation exposure. Potential advantages of CT venography include the ability to visualize the pelvic veins and vena cava. The concept of combined CT pulmonary angiography and venography is attractive. Such an approach would provide visualization of the embolus and its source in a single study as well as potentially increase diagnostic yield in comparison with the use of CT angiography alone. However, the absolute increase in diagnostic yield appears to be modest and comes at the cost of increased expense, substantial pelvic radiation exposure, and the risk of hemorrhagic

Table 82-7

Prevealence of Pulmonary Embolism in PIOPED: Value of Correlating Lung Scan Interpretation with Clinical Assessment

		Clinical Assessment		
		High No./Total/%	**Intermediate No./Total/%**	**Low No./Total/%**
Lung scan interpretation	High probability	96% (28/29)	88% (70/80)	56% (5/9)
	Intermediate probability	66% (27/41)	28% (66/236)	16% (11/68)
	Low probability	40% (6/15)	16% (30/191)	4% (4/90)

Source: The PIOPED Investigators: Value of the ventilation/perfusion scan in acute pulmonary embolism. Results of the prospective investigation of pulmonary embolism diagnosis. JAMA *263:2753–2759, 1990.*

complications from providing anticoagulation to patients with false-positive studies.

Magnetic Resonance Imaging

Magnetic resonance imaging (MRI) techniques for detecting venous thrombosis and pulmonary embolism have been investigated. Preliminary reports suggest that MRI is at least as sensitive and specific as duplex ultrasonography in detecting venous thrombosis. A potential advantage of MRI is that the entire length of the venous system, including the pelvic veins, can be evaluated. MR angiography appears to be as sensitive as 16-MDCT in detecting emboli. Disadvantages associated with MRI include cost, limited access, motion artifacts related to the time necessary to perform the study, and a high degree of expertise required to properly perform and interpret the studies.

Pulmonary Angiogram

Pulmonary angiography remains the accepted "gold standard" for PE diagnosis although it has a number of limitations as a gold standard (Fig. 82-10). It requires expertise in study performance and interpretation; it is invasive and has associated risks, although published studies suggest that the use of modern techniques and contrast materials has reduced the reality of that risk well below its lingering perception. Only two angiographic findings are diagnostic of acute embolism: the filling defect and abrupt cutoff of a vessel. Technical adequacy of the angiogram is critical to accurate identification of both. Flow artifacts can falsely suggest a filling defect. It is essential that good vessel opacification be obtained and that the filling defects be identified as real on a sequence of films.

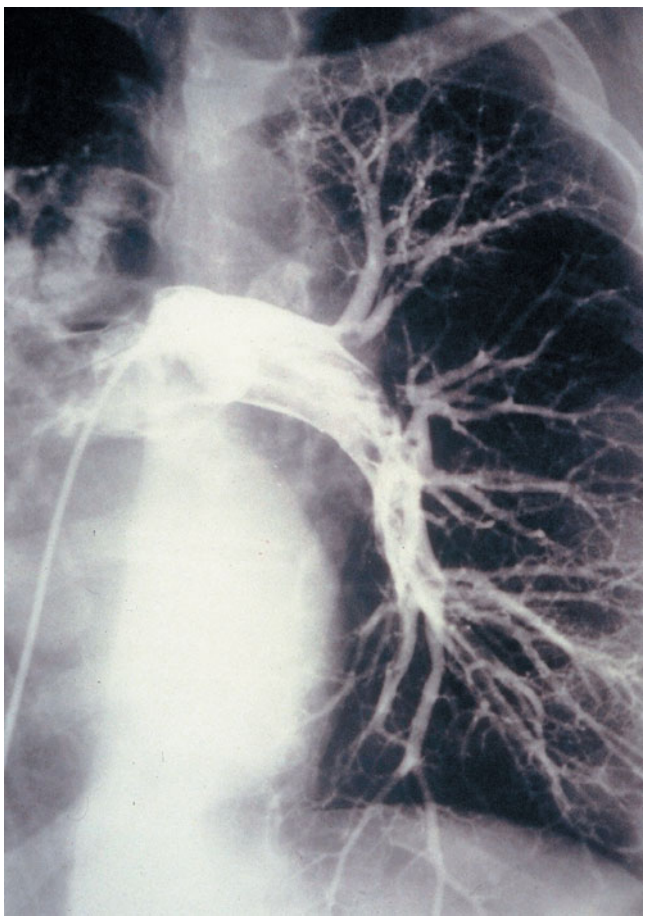

Figure 82-10 Conventional contrast pulmonary angiogram demonstrating extensive embolus within the left main pulmonary artery and extending into lobar branches.

Angiography is reserved for the small subset of patients in whom the diagnosis of embolism cannot be established or excluded by less invasive means. Even under this defined circumstance, angiography appears to be underused.

Diagnostic Approach

The diagnostic approach to pulmonary embolism should be targeted toward the patient population being studied (Figs. 82-11 and 82-12). For outpatients, the use of a clinical prediction rule coupled with D-dimer testing can substantially reduce the number of imaging studies performed. The specificity of D-dimer testing in inpatients is so low as to render the utility of the study nearly meaningless. Furthermore, the presence of co-morbid conditions substantially limits the utility of clinical prediction rules.

In an outpatient setting, D-dimer testing should be the initial diagnostic study, except in patients with a high clinical probability of disease. In the latter group, D-dimer results would not alter the need for an objective imaging study. In patients with a low or intermediate clinical likelihood of embolism, a negative D-dimer study is sufficient to exclude the possibility of embolism, assuming a highly sensitive assay is used. CT angiography should be performed in all patients with a high probability of disease as well as those with a low or intermediate probability whose D-dimer tests are positive. In patients with a high or intermediate clinical probability, a positive CT angiogram confirms the diagnosis. In patients with a low or intermediate clinical probability, a negative CT angiogram excludes the diagnosis. The only patients who require additional testing (duplex ultrasonography and/or conventional angiography) are those in whom the clinical assessment and CT findings are discordant (low clinical probability and positive CT scan or high clinical probability and negative CT scan), unless the CT scan is of adequate quality and demonstrates evidence of embolic disease in the main or lobar arteries in a patient with a low clinical probability assessment. If readily available, duplex ultrasonography should be considered prior to chest imaging. Although not confirming the diagnosis of embolism, a positive study has the same therapeutic implication and avoids the need for contrast administration and radiation exposure. A negative study, however, is incapable of excluding the disease.

A ventilation/perfusion (V/Q) scan approach can be used in settings such as pregnancy, contrast allergy, or renal insufficiency. Lower extremity evaluation should be considered prior to chest imaging given the likelihood that the V/Q scan will not be diagnostic. A negative V/Q scan is

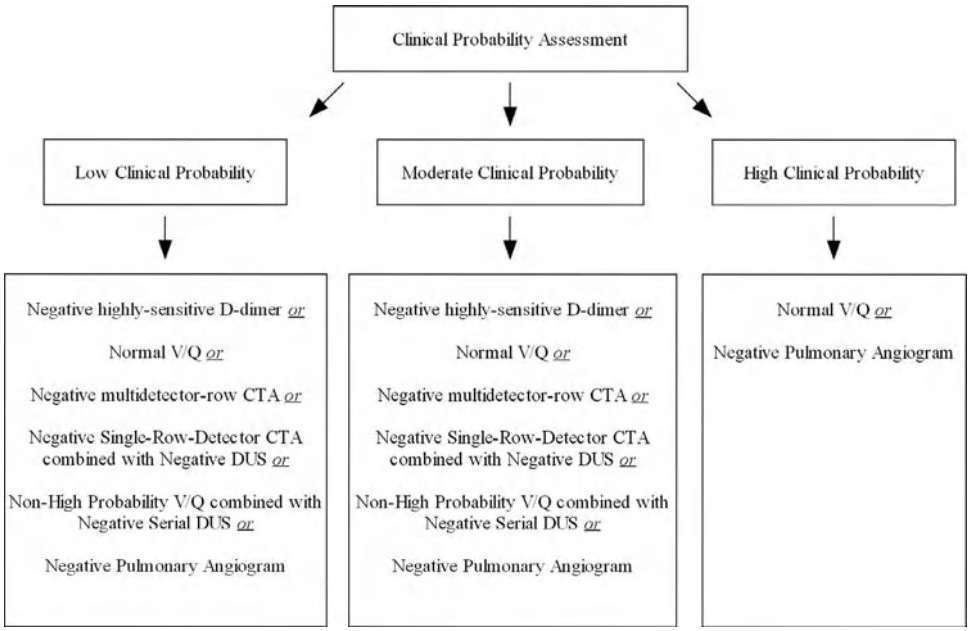

Figure 82-11 Current diagnostic strategies capable of excluding diagnosis of pulmonary embolism.

capable of excluding the diagnosis regardless of the clinical assessment. A high probability scan is capable of confirming the diagnosis in patients with a high clinical suspicion. All other circumstances (high clinical probability with low or intermediate V/Q result, intermediate clinical probability regardless of V/Q result, and low clinical probability with a high or intermediate V/Q scan result) require additional testing.

Whatever approach is undertaken, the treating physician should be aware of the type of D-dimer assay, discriminant value of that particular assay, and generation of CT scanner used. "Negative" findings on a low-sensitivity D-dimer assay or a single-row CT scanner have very different implications than similar findings using a highly sensitive D-dimer assay or 64-MCTD CT scanner.

As noted, the role of D-dimer testing and clinical assessment in hospitalized patients is limited. Approximately 90 percent of hospitalized patients have a positive highly sensitive D-dimer result, and co-morbid conditions affect the clinical likelihood assessment. Therefore, a far higher proportion of embolic suspects require an imaging study to confirm or exclude the diagnosis. In patients with limited cardiopulmonary reserve, high clinical probability assessment, and negative CT scan, pulmonary angiography should be strongly considered given the potentially fatal consequences of a recurrent embolic event. In patients with adequate cardiopulmonary reserve, a

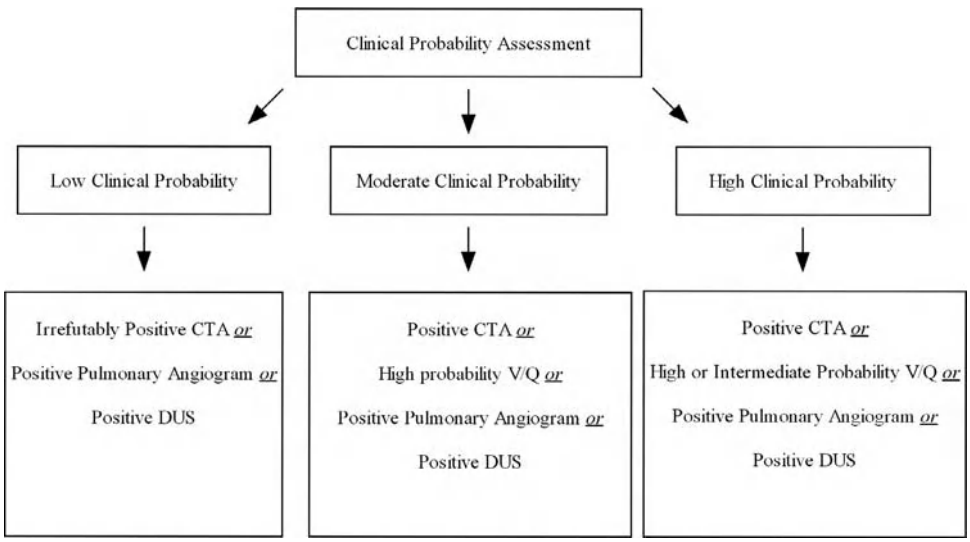

Figure 82-12 Current diagnostic strategies capable of confirming diagnosis of pulmonary embolism.

strategy incorporating sequential lower extremity evaluation can be undertaken.

TREATMENT

Management of acute pulmonary embolism consists of a systematic approach that involves early intervention, patient risk stratification, selection of therapy, and determination of treatment duration. The goals of therapy in PE are severalfold—to assure adequate oxygenation, provide hemodynamic support, and prevent thrombus propagation and embolic recurrence.

When a diagnosis of VTE is suspected, empiric treatment should be considered until the diagnosis is either objectively excluded or confirmed. Given the ready availability of rapid D-dimer assays and computed tomography, diagnostic confirmation should require a relatively short period of time. Early empiric treatment should be initiated if diagnostic tests are not readily available. An exception can be made in those patients with a low clinical likelihood of disease, adequate cardiopulmonary reserve, and a high risk of bleeding complications.

The availability of low-molecular-weight heparin potentially allows selected patients to be managed in the outpatient setting. Although there are good data to support treating uncomplicated cases of venous thrombosis entirely in the outpatient setting, most physicians still advocate a short period of hospitalization in patients with newly diagnosed acute pulmonary embolism. Hospitalization should be mandatory for older patients who may have less cardiopulmonary reserve, or significant co-existing illnesses, or those who may not be able to follow instructions or have adequate follow-up. Other indications for hospitalization include hypoxemia, hypotension, or hemodynamic instability.

Heparin

Anticoagulation with heparin remains the standard initial therapy. The major anticoagulant effect of heparin is to reduce thrombus propagation and prevent embolic recurrence. Choices include either intravenous unfractionated heparin (UFH) or subcutaneous low-molecular-weight heparin (LMWH) preparations. Given that failure to achieve rapid therapeutic levels of anticoagulation appears to be associated with an increased recurrence rate, it seems reasonable to attempt to ensure adequate anticoagulation as soon as possible.

Physician practices in the administration of intravenous unfractionated heparin have often resulted in substantial delays before adequate prolongation of the aPTT was achieved. To overcome these problems, standardized protocols for heparin administration and monitoring have been recommended. One commonly employed dosing regimen using an initial intravenous bolus of 80 units of heparin per kilogram followed by a continuous infusion initiated at 18 units per kilogram per hour has been demonstrated to reach therapeutic thresholds more quickly than regimens using fixed dosing. The heparin drip is adjusted based on monitoring of the activated partial thromboplastin time (aPTT), drawn 6 hours after the initial bolus dose, then 6 hours after each dose adjustment, with a target aPTT ratio of 2.0 to 3.5.

More recently, an approach using a fixed dose of subcutaneous unfractionated heparin, administered as an initial dose of 333 U/kg followed by a dose of 250 U/kg every 12 hours, has been demonstrated to be as safe and effective as low-molecular-weight heparin in patients presenting with venous thrombosis and pulmonary embolism.

With the exception of special circumstances, low-molecular-weight heparin preparations have displaced unfractionated heparin as the anticoagulant of choice in uncomplicated venous thromboembolism. Situations in which the use of UFH is appropriate include renal insufficiency, extremes of body weight, hypertensive crisis, and circumstances in which a rapid adjustment of anticoagulation is needed, such as women in the late stage of pregnancy who may need Caesarian sections, patients with recent surgery or recent history of bleeding, and hemodynamically unstable patients with VTE who may need surgical procedures such as emergency embolectomy.

Available evidence suggests that LMWH is at least as effective as UFH in treating acute pulmonary embolism. Advantages of LMWH compared with UFH include: (1) longer half-life and ease of use; (2) ability to consistently achieve early therapeutic anticoagulation; (3) no need to monitor anticoagulant effects; and (4) reduced incidence of major bleeding complications. There are few data comparing different LMWH preparations. Even though there are differences in their FDA-approved indications in the United States, it is not clear if their actions differ significantly. At this time, enoxaparin and tinzaparin are indicated for treatment of established DVT in the outpatient setting or for DVT (with or without PE) in the inpatient setting, and dalteparin is approved for prevention of venous thrombosis and acute pulmonary embolism.

In general, therapeutic monitoring is not needed with LMWH, but there are situations where the therapeutic effects may be less predictable and monitoring with anti-Xa levels is indicated. Typical examples include: (1) patients with antiphospholipid antibodies or other circulating anticoagulants who have elevated baseline aPTT; (2) extremes of body weight (less than 40 kg and greater than 150 kg); (3) significant renal disease (creatinine clearance less than 30 ml/min); (4) pregnancy; and (5) unexplained bleeding or recurrent thrombosis during therapy. A therapeutic target range for anti-Xa levels ranges from 0.6 to 1 U/mL, four hours after administration. Prophylactic anti-Xa levels are lower, ranging from 0.1 to 0.3 U/mL.

Novel Agents

Fondaparinux, a synthetic pentasaccharide, represents the first in a new class of antithrombotic agents. Unlike heparin and low-molecular-weight heparins, the antithrombotic

properties of fondaparinux are selective for factor Xa. By binding rapidly and strongly to antithrombin, fondaparinux catalyzes specifically the inhibition of factor Xa, which results in inhibition of thrombin generation. It does not bind to other plasma components or platelets, has a half-life of approximately 17 hours, and is excreted almost completely by the kidneys. It has been approved for prophylaxis in patients undergoing hip, knee, and abdominal surgery as well as for treatment of venous thrombosis and pulmonary embolism in conjunction with warfarin.

Direct thrombin inhibitors (bivalirudin, lepirudin, argatroban) represent another new class of anticoagulant agents. Their mechanism of action differs from that of heparin and the synthetic pentasaccharides in that they directly inhibit the active site of thrombin and do not require interaction with antithrombin to produce an anticoagulant effect. Argatroban is a synthetic agent derived from arginine. It has a half-life of approximately 45 minutes and is cleared by the liver. Lepirudin is a recombinant polypeptide similar to hirudin. It has a half-life of 40 to 60 minutes and is cleared by the kidneys. Both agents are administered by continuous intravenous infusion and dose adjustments made with monitoring of the aPTT. Both agents affect the international normalized ration (INR), thereby complicating the transition to oral warfarin therapy. Both drugs have been approved for the management of patients with heparin induced thrombocytopenia.

Thrombolytic Therapy

Unlike anticoagulants, thrombolytic drugs cause direct lysis of thrombi by increasing plasmin production through plasminogen activation. The potential benefits, however, are often offset by the relatively high incidence of hemorrhagic complications.

Multiple thrombolytic agents are available, and the most studied include streptokinase, recombinant tissue plasminogen activator (rt-PA), and urokinase, all of which are FDA approved for use in the United States. Streptokinase, a polypeptide derived from beta-hemolytic streptococci, was the least expensive agent but was occasionally associated with severe side effects such as anaphylaxis and hypotension. Urokinase is obtained from cultures of neonatal kidney cells while rt-PA is produced by recombinant DNA technology. Through different mechanisms, these agents convert circulating plasminogen to plasmin. Streptokinase must first bind to circulating plasminogen before becoming an enzyme capable of cleaving additional plasminogen; urokinase is itself a plasminogen activator. Doses of streptokinase and urokinase sufficient to cause fibrinolysis of thrombi also generate circulating free plasmin that overwhelms and depletes α_2-antiplasmin and other plasma inhibitors. As a result, systemic hemostasis is impaired because of degradation of circulating fibrinogen and other coagulation proteins and because of an increase in fibrin degradation products. In *physiological* amounts, t-PA does not bind to circulating plasminogen. Therefore, it does not produce circulating plasmin, which would induce systemic fibrinolysis or fibrinogenolysis; nor are circulating inhibitors of plasmin, particularly á$_2$-antiplasmin, depleted by the clot-selective action of t-PA. In principle, t-PA, because of its intense affinity for fibrin, should have its lytic effects restricted to fibrin in thrombi. At pharmacologic doses, however, some degree of systemic fibrinolysis is the rule.

The exact role of thrombolytic agents in acute pulmonary embolism remains controversial. While thrombolytic therapy does appear to accelerate the rate of thrombolysis, there is no convincing evidence to suggest that it decreases mortality, increases the ultimate extent of embolic resolution when measured at 7 days, reduces thromboembolic recurrence rates, improves symptomatic outcome, or decreases the incidence of thromboembolic pulmonary hypertension. The one issue about which there can be little controversy is that the use of thrombolytic agents is associated with a substantially increased risk of bleeding, including intracranial hemorrhage. Intracranial hemorrhage has occurred in 0.5 to 2.0 percent of patients treated with thrombolytic agents in trials evaluating the use of these agents in both pulmonary embolism and myocardial infarction.

Based on these data, and assuming there is no contraindication to its use, the use of thrombolytic therapy in pulmonary embolism is appropriate when an accelerated rate of thrombolysis may be considered lifesaving; that is, in patients with pulmonary embolism who present with hemodynamic compromise, patients who develop hemodynamic compromise during conventional therapy with heparin, and patients with embolism associated with intracavitary right heart thrombi.

The role of thrombolytic therapy in patients with anatomically massive embolism or echocardiographic evidence of right ventricular dysfunction in the absence of systemic hypotension is less well defined. Risk stratification approaches using echocardiography, troponin or BNP levels are currently under investigation and may help resolve this area of controversy. At the present time, the finding of right ventricular dysfunction on echocardiography in the absence of hemodynamic instability would not appear to serve as a justification for the routine use of thrombolytic therapy. Approximately 40 to 50 percent of patients with symptomatic pulmonary embolism have echocardiographic evidence of right ventricular dysfunction. Patients with evidence of right ventricular dysfunction, as determined by echocardiography or elevated BNP or troponin levels in the absence of systemic hypotension, appear to be at risk for an adverse outcome when compared with patients without right ventricular dysfunction. However, until criteria have been established that more clearly define that subset of patients who will benefit from thrombolytic therapy, there is little basis for exposing all such patients to the considerable risk of hemorrhagic complications associated with this intervention.

Because of the side effects and the prolonged period of infusion required, many physicians are reluctant to use thrombolytics in cases of venous thrombosis, whether delivered systemically or by local catheter-directed infusion. In selected patients with symptomatic ileo-femoral thrombosis,

catheter directed thrombolysis either alone or combined with angioplasty or stent placement may result in increased venous patency and may improve quality of life. Catheter-directed techniques have been successfully employed in the setting of acute ileo-femoral DVT using doses of urokinase ranging from 1.4 to 16 million units delivered over an average of 30 hours. Results from a national registry of patients with ileo-femoral thrombosis treated with local, catheter-directed therapy indicates that this approach is frequently successful and may improve health-related quality of life.

Interventional Radiologic Techniques

Interventional thrombus fragmentation represents a potential alternative to systemic thrombolysis or surgical embolectomy. If the bleeding risk it not exceedingly high, catheter fragmentation may be combined with local or systemic thrombolysis. A wide variety of fragmentation and embolectomy devices designed to either fragment and/or remove fresh embolic material have been tested in patients with pulmonary embolism. In general, the devices use either pressured saline or a rotating impeller to fragment central thrombi. The fragments are either aspirated through a separate port on the catheter or allowed to migrate distally. Most of the devices appear to be effective, safe, and potentially life-saving in the presence of central, acute clots. However, none of the devices has been investigated in a large controlled trial, and all commercially available devices have important limitation. There limitations, including a risk of paradoxical embolism from the clot fragments. Therefore, the intervention is contraindicated in patients who have an intracardiac communication, such as a patent foreman ovale.

Pulmonary Embolectomy

Embolectomy has been used for the emergency removal of pulmonary emboli. Small observational studies comparing surgical embolectomy and thrombolytics did not show significant advantage using embolectomy, although there was a trend toward better survival and lower bleeding rates in the surgical group. Based on current data, it is therefore reasonable to consider surgical embolectomy in patients with persistent hypotension, shock, or cardiac arrest who either failed thrombolysis or have contraindications to thrombolytics. Its use has also been advocated in patients who are at high risk of paradoxical embolism and who are not candidates for thrombolytics, although further validation for this indication is needed.

Long-Term Management

Anticoagulation

Oral Anticoagulant

Recurrence is common following an acute thromboembolic event. Therefore, treatment should be continued until the benefits of ongoing therapy no longer outweigh the potential risks.

Oral anticoagulation using warfarin, a vitamin K antagonist, is generally used for long term treatment of VTE because of its proven efficacy. Warfarin inhibits gamma carboxylation activation of coagulation factors II, VII, IX, and X as well as proteins C and S. With proper monitoring, less than three percent of patients using warfarin develop significant bleeding. The drug is usually started soon after the initiation of heparin therapy. Use of warfarin without heparin is strongly discouraged as it generally takes 3 to 5 days of warfarin to achieve full therapeutic efficacy. In patients with protein C deficiency, skin necrosis or paradoxical thrombosis may occur in the absence of concurrent heparin therapy.

Warfarin has a narrow therapeutic index and patients are generally monitored closely by measuring the prothrombin time corrected to the reagent being used (the International Normalized Ratio or INR). To maximize efficacy while minimizing side effects, an INR range between 2 and 3 is recommended for most patients. Recent data suggested that, even in patients with a high risk of thrombosis, an INR over 3 may not confer significant additional protection, whereas a higher incidence of bleeding was observed. Besides bleeding complications, warfarin has been associated with fetal abnormalities particularly when given during the sixth to 12th weeks of gestation. Another rare complication of warfarin use is cholesterol microembolism ("purple toes" syndrome), which is thought to be due to cholesterol crystal release from ulcerated intravascular plaques.

Individuals metabolize warfarin differently and age, genetic variations in CYP2C9 alleles, nutritional factors, and concomitant medications can affect anticoagulant levels significantly. Multiple mechanisms of drug interaction are possible including alterations of absorption (cholestyramine), induction of hepatic CYP450 (barbiturates, carbamazepine), inhibition of CYP3A4 (amiodarone), inhibition of CYP2C9 (metronidazole, clotrimazole), and displacement of protein bound warfarin (phenytoin).

Suggested dosing regimens involve an initial daily dose of 5 or 10 mg with use of a standardized nomogram to dose adjust based on INR values obtained on days 3 and 5. Once the therapeutic range of INR is reached, monitoring is then done at 1- to 2-week interval, depending on the stability of INR results. Elderly malnourished and debilitated patients tend to require less warfarin and the initial dose should be lowered accordingly. Some medical conditions, such as concomitant liver or kidney failure, alcoholism, malignancy, and recent history of gastrointestinal bleeding or trauma, are additional factors that may predict dose titration difficulties and higher risk of bleeding

To minimize potential subtherapeutic anticoagulation, it is generally recommended that patients should receive at least 5 days of combined heparin and warfarin therapy, including at least 2 days in which the INR is in a therapeutic range prior to stopping heparin. Specialized anticoagulation clinics have been shown to provide a safe and effective means

to adjust warfarin dose for patients requiring anticoagulant therapy. In carefully selected patients, self-management of warfarin therapy using INR measurement with "point of care" devices may also be done.

There are occasional instances in which heparin should be considered for long-term anticoagulation, despite the cost and inconvenience associated with subcutaneous or intravenous administration. Because of the teratogenic potential of warfarin, UFH or LMWH should be used in pregnant women who developed VTE in the first and possibly early second trimesters. Since the risk of venous thromboembolism may be highest in the postpartum period, anticoagulation should be continued for at least 3 to 6 months, including a minimum of 4 to 6 weeks after delivery. Patients with cancer complicated by thromboembolism appeared to have fewer recurrent thromboembolic events when treated with LMWH compared with warfarin. Whether this affect is intrinsic to the drugs or simply a reflection of fluctuating INR levels in patients with cancer treated with warfarin is uncertain.

Duration of Therapy

Over the past decade, data have emerged that have significantly changed our recommendation regarding duration of anticoagulation after VTE. Central to this change has been awareness that venous thromboembolism often represents a recurrent disease and that the risk for recurrence is based on the initiating factors, persistence or resolution of those factors, and anatomic consequences of the initial event.

Patients with venous thromboembolism associated with a temporary risk factor appear to be at the lowest risk of recurrence. However, the risk of recurrent disease after 3 months of anticoagulation is still in the region of 10 percent; therefore, patients should be treated with warfarin for 3 to 6 months. Patients with idiopathic thromboembolism have a substantially higher rate of recurrence, one that approaches 30 percent following 3 months of anticoagulation. In these patients, anticoagulation may simply delay subsequent recurrent thromboembolic events and ongoing risk factors may be present that have yet to be identified. Therefore, it is recommended that this group of patients be treated with at least 6 to 12 months of anticoagulation and consideration given to lifelong therapy in those with a low risk of bleeding complications. In certain patients it is reasonable to consider a 6- to 12-month course of therapy and to counsel about short-course prophylaxis when additional risk may be encountered in the future (such as pregnancy and prolonged air travel). In patients with VTE associated with an irreversible risk factor, the absolute recurrence risk depends on the underlying disease or condition. Patients with heterozygous Factor V Leiden mutation do not appear to benefit from prolonged anticoagulation, while those with homozygous disease or a combined thrombophilia (e.g., heterozygous Factor V Leiden combined with heterozygous prothrombin mutation) do benefit. Patients with antiphospholipid antibody syndrome are at considerable risk for thromboembolic recurrence, and a minimum of 12 months of therapy is recommended with consideration given to lifelong therapy. In patients with two or more episodes of recurrent VTE, the current recommendation is to consider life-long anticoagulation with interval re-assessment of the risk-benefit ratio. Determining which patients remain at increased risk of thromboembolic recurrence is the target of ongoing investigative efforts. A number of clinical and serologic factors have been identified that predict a higher likelihood of recurrent venous thromboembolism following an initial course of therapy. These include pulmonary embolism as the initial presenting manifestation, evidence of residual lower extremity venous thrombosis by ultrasonography, elevated D-dimer levels, elevated Factor VIII levels, and an abnormally short activated partial thromboplastin time. How such findings apply to an anticoagulation withdrawal decision-making strategy in an individual patient remains to be determined.

Vena Cava Interruption and Vena Cava Filter

The concept of vena cava interruption came from the historical practice of surgical ligation (by complete vascular ligation or partial interruption using surgical suture) of the inferior vena cava in an attempt to prevent thrombus migration. A variety of vena cava filters are now available, both permanent and temporary, and surgical ligation is rarely performed in the modern era

The reason for inferior vena cava (IVC) filter placement is to prevent pulmonary embolism in patients who either have a contraindication to anticoagulation or develop recurrent VTE while on adequate anticoagulation. Filters are sometimes placed in patients who have documented massive pulmonary embolism, and those in whom embolism occurs in the setting of residual lower extremity venous thrombosis and poor cardiopulmonary reserve. Based on these principles, the prophylactic use of IVC filters may also be appropriate in trauma or high-risk orthopedic patients, patients with cancer and a history of VTE, and prior to anticipated pulmonary embolectomy or pulmonary thromboendarterectomy.

Many case reports have documented the potentially life-saving benefits of IVC filters. However, long-term studies suggest that IVC filters, although capable of preventing short-term embolic recurrence, are associated with a long-term increase in the incidence of venous thromboembolism. Similarly, although IVC filters have been associated with short-term (90 days) reduction in mortality, this benefit may be lost in the long run. This observation, together with the many long-term side effects of IVC filters led to the recent development of retrievable filters. Four different retrievable vena caval filters have received approval by the FDA (Gunther tulip filter, ALN filter, Recovery filter, OptEase filter). Because of endothelialization of the filters at the point of vascular contacts, the rate of successful retrieval may decrease significantly over time.

Chronic Thromboembolism

Anatomic resolution of pulmonary embolism is rarely complete. However, resolution in most patients suffices not to

impair pulmonary hemodynamics or exercise tolerance. In a few the residual thromboembolic burden is sufficiently extensive to cause thromboembolic pulmonary hypertension (CTEPH). Estimates of the incidence of CTEPH range from 0.5 to 3.8 percent following an initial episode of embolism, to 13.4 percent following recurrent episodes of venous thromboembolism. Approximately 30 percent of patients who develop chronic thromboembolic pulmonary hypertension have no documented history of acute DVT or PE, and this feature greatly impedes the diagnosis. Anticardiolipin antibodies or a lupus anticoagulant have been detected in approximately 10 percent of patients and elevated Factor VIII levels detected in 40 percent. No other defined thrombophilic or fibrinolytic abnormality has been encountered in this population.

The mortality of untreated CTEPH is high, with a 5-year survival of only about 10 percent in those who have a mean pulmonary artery pressure of over 50 mmHg. The treatment of choice for CTEPH is surgery (pulmonary thromboendarterectomy or PTE), which involves the dissection of endothelialized thrombi under cardiopulmonary bypass and deep hypothermia. For the majority of patients, successful PTE is considered curative. However, the hemodynamic outcome is incomplete in approximately 20 percent of patients. These patients have been treated with medical therapies that are used in patients with idiopathic pulmonary arterial hypertension. Indications for medical therapy in chronic thromboembolic pulmonary hypertension include: (1) "inoperable" cases of CTEPH in patients who have either distal disease or significant secondary vasculopathy; (2) as a "bridge" to thromboendarterectomy in patients with severe right ventricular dysfunction; and (3) persistent or recurrent pulmonary hypertension after PTE. Patients with inoperable CTEPH or persistent pulmonary hypertension despite PTE may be considered for lung transplantation. Because thromboendarterectomy is performed by way of a sternotomy, single lung transplantation is usually performed to minimize scar dissection. In selected patients, the survival of these patients after transplantation may be comparable to those with other diseases.

Prophylaxis

Although the efficacy of mechanical and pharmacological prophylaxis is well documented, the incidence of VTE does not appear to have changed during the past few decades, suggesting a failure in effective use of prophylaxis in at-risk patients.

Initial assessment should focus on the following questions: (1) What is the risk of VTE in this patient? (2) What type(s) and intensity of prophylaxis should be used? (3) When is the best time to use prophylaxis? Because a patient's thrombotic risk may change over time, periodic assessment of the best prophylactic strategy should also be done (Table 82-8).

Several risk scores have been proposed in an attempt to objectively and quantitatively describe the relative risk of VTE in hospitalized patients. It is important to stress that none of these methods has been validated prospectively. Most hospitalized patients are at risk of VTE and should receive some form of VTE prophylaxis unless its use is contraindicated. Prophylaxis may not be necessary in rare instances, as in the case of a young (less than 40 years) ambulatory patient who is admitted for a short (less than 48 to 72 hours) hospital stay without prior VTE history or recent surgery.

Three categories of drugs have been used successfully, all administered subcutaneously: UFH (5000 units two or

Table 82-8

Example of a Risk Stratification Approach to Assist in Determining the Intensity of Thrombosis Prophylaxis

Degree of Risk	Age	Surgery	Risk Factors	Prophylactic Options
Low	<40	Minor	No	Early ambulation
Moderate	<40 40–60 Any age	Major Minor Minor	No No Yes	UFH (q12h) LMWH IPC or GCS
High	>40 >60	Major Major	Yes No	UFH (q8hr) ± IPC or GCS LMWH + IPC or GCS
Very High	Any age	Major	Multiple	LMWH + IPC or GCS Warfarin Fondaparinux (orthopedic) IVC filter

UFH = unfractionated heparin; LMWH = low molecular weight heparin; IPC = intermittent pneumatic compression devices; GCS = graduated compression stockings.

three times daily), LMWH (Enoxaparin, either 40 mg once daily or 30 mg twice daily; Dalteparin, 2500 or 5000 units once daily), and Fondaparinux (2.5 mg once daily). When administered correctly in appropriate patients, prophylactic anticoagulation is safe and effective with an absolute reduction in the incidence of VTE in the range of 40 to 50 percent. Major bleeding complications occur in less than 1 percent of patients.

Prevention of venous thromboembolism may also be achieved by the use of mechanical devices. These devices fall into two categories, graduated compression stockings and intermittent pneumatic compression stockings. Although studied less rigorously than pharmacologic methods of prophylaxis, the use of pneumatic compression has been shown in selected patients to be as effective as subcutaneous unfractionated heparin in preventing thrombosis. Mechanical methods of prophylaxis are especially useful in patients at bleeding risk and as an adjunct to pharmacologic methods in patients at high risk of thrombosis.

Whatever form of prophylaxis is used, its intensity should be based on a patient's thrombotic risk determined by both personal and clinical circumstances. Prophylaxis adequate for a 41-year-old patient undergoing an elective appendectomy would be inadequate for a 70-year-old patient with cancer undergoing hip replacement surgery. Recommended prophylactic strategies for a variety of different clinical circumstances have been published by the American College of Chest Physicians. It should also be recognized that thromboembolic risk does not necessarily end at the time of hospital discharge. The trend toward early hospital discharge has only served to transfer risk to the outpatient setting. Whether on an inpatient or outpatient basis, prophylaxis should continue until the thrombotic risk has resolved.

The potential for bleeding complications associated with prophylaxis is a common dilemma in surgical or trauma patients where bleeding may occur from the surgical site, especially in the immediate postoperative period. On the other hand, effective prophylaxis depends on timely administration of therapy before a thrombus develops. Recommendations can be drawn from multiple studies with regard to the appropriate timing for anticoagulation in different surgical settings. In cases in which anticoagulation may be delayed, it is customary to use either graduated compression stockings or pneumatic compression devices either before surgery begins or as soon a surgery is completed. In high-risk patients in whom pharmacologic prophylaxis is contraindicated, it is reasonable to obtain serial lower extremity ultrasonography, and consideration should be given to the placement of a retrievable IVC filters.

Other Varieties of Embolic Disease

Because the lung receives all of the blood flow returned from the venous system, the pulmonary vascular bed serves as a "sieve" for all particulate substances entering the venous blood and is the first vascular bed to be exposed to any toxic substance injected intravenously. As a result of its strategic position, the pulmonary vascular bed is, therefore, exposed to a wide variety of potentially obstructing and injurious agents.

Venous Air Embolism

An increasingly common form of non-thrombotic embolism in the United States is venous air embolism. The increasing frequency of the problem reflects the wide variety of invasive surgical and medical procedures now available, the broad use of indwelling central venous catheters, the use of positive pressure ventilation with high levels of positive end-expiratory pressure, and the frequency of thoracic and other forms of trauma. The simple inadvertent transection or loss of closure of a large-bore intravenous catheter, particularly in the jugular or subclavian vein, can result in ingress of substantial quantities of air. Air bubbles enter the pulmonary vascular bed and, from there, can enter the arterial system and be diffusely distributed throughout the body by way of either an intracardiac shunt (atrial septal defect, patent foramen ovale) or, more likely, through microvascular pulmonary shunts.

Physiologic consequences include an abrupt rise in pulmonary artery pressure. Non-cardiogenic pulmonary edema may develop, lung compliance falls, and hypoxemia ensues. The symptoms of venous air embolism are variable and nonspecific, and may include alterations in sensorium, chest pain, dyspnea, or a sense of impending doom. These and other consequences appear to be due to two phenomena: actual lodgement of the bubbles in capillary beds that interfere with nutrient supply to the affected organs, and the formation of platelet-fibrin aggregates, creating diffuse microthrombi. Thrombocytopenia may be seen as a consequence of this latter event. The most serious consequences result from cerebral or coronary artery air embolism, the severity of the consequences depending upon the rate and volume of air gaining access to the circulation.

The best approaches to air embolism are prevention and early detection. Treatment consists of measures designed to restore flow and promote reabsorption of the intravascular air. Measures designed to restore flow include patient positioning (Trendelenburg position with the left side down), removal of air through central venous catheters or direct needle aspiration, and closed chest cardiac massage. Measures designed to increase absorption include the use of 100 percent oxygen and hyperbaric oxygen therapy. Using such aggressive measures, mortality from venous air embolism has been dramatically reduced.

Fat Embolism

Another reasonably frequent and dramatic form of non-thrombotic embolism is fat embolism. A rather characteristic syndrome follows entry of neutral fat into the vascular system, consisting of the onset of dyspnea, hypoxemia, petechiae, and mental confusion. Seizures and focal neurologic deficits have been described. There is a variable lag time of 24 to 72 hours in the onset of the syndrome following the inciting event;

rarely, cases occur within 12 hours or as late as 2 weeks after the event.

By far, the most common inciting event is traumatic fracture of long bones, with incidence rising with the number of fractures. However, orthopedic procedures and trauma to other fat-laden tissues (e.g., fatty liver) occasionally can be followed by the same syndrome. Although considerably less common, fat embolism syndrome has been reported following both liposuction and lipoinjection procedures.

The basis for the variability in the incidence and severity of the syndrome after apparently comparable injuries has not been well defined; neither has the reason for the delay in clinical presentation been explained. The pathophysiologic consequences appear to derive from two events: (1) actual vascular obstruction by neutral particles of fat; and (2) the injurious effects of free fatty acids released by the action of lipases on the neutral fat. The latter effect is probably the more important, causing diffuse vasculitis with leakage from cerebral, pulmonary, and other vascular beds. The time necessary to produce toxic intermediaries may explain the delay from the inciting event to clinical presentation.

The diagnosis of fat embolism syndrome is a clinical one suggested by the onset of dyspnea, neurologic abnormalities, petechiae, and fever in the proper clinical context. Petechiae, typically distributed over the head, neck, anterior chest, and axillae, are present in only 20 to 50 percent of cases. Therefore, their absence should not preclude consideration of the disease. No laboratory test is diagnostic of the syndrome. Fat can be demonstrated in the serum of a majority of fracture patients with evidence of fat embolism syndrome. The finding of lipid-laden cells in bronchoalveolar lavage fluid appears to occur commonly in patients with traumatic injuries irrespective of the presence of fat embolism syndrome.

Although a variety of treatments have been suggested (e.g., intravenous ethanol, albumin, dextran, heparin), none has proved effective. The role of corticosteroid therapy to prevent the onset of fat embolism syndrome after an inciting event remains controversial. Supportive treatment, including mechanical ventilatory support when necessary, is the primary approach, and survival is now the rule with meticulous support.

Amniotic Fluid Embolism

Another special form of embolism is amniotic fluid embolism, a rare but unpredictable and catastrophic complication of pregnancy that represents the third leading cause of maternal mortality. This disorder occurs during or after delivery when amniotic fluid gains access to uterine venous channels and, therefore, to the pulmonary and general circulations. The delivery may be either spontaneous or by Cesarean section and usually has been uneventful. Most cases occur during labor, but delayed onset of symptoms up to 48 hours after delivery can occur. Advanced maternal age, multiparity, premature placental separation, fetal death, and meconium staining of amniotic fluid have been associated with increased risk of amniotic fluid embolism.

Amniotic fluid embolism syndrome is primarily a clinical diagnosis. There is unexpected sudden onset of severe respiratory distress, cyanosis, hypotension, cardiovascular collapse and, often, disseminated intravascular coagulation. Occasionally, seizure activity occurs. It has been postulated that there is a biphasic pattern of hemodynamic disturbance: an initial period of pulmonary hypertension, commonly seen in animal models, followed by left ventricular dysfunction and cardiogenic shock. Patients who survive the first several hours develop noncardiogenic pulmonary edema coincident with improvement in left ventricular dysfunction.

Amniotic fluid contains particulate materials that can cause pulmonary vascular obstruction, but the major pathogenetic mechanism of the syndrome remains uncertain. Amniotic fluid has thromboplastic activity that leads to extensive fibrin deposition in the lung vasculature and, occasionally, other organs. As a consequence of fibrin deposition, severe consumptive coagulopathy develops, including marked hypofibrinogenemia and thrombocytopenia. Following the acute event, an enhanced fibrinolytic state often occurs.

The diagnosis of amniotic fluid embolism is based on a compatible clinical picture, often enhanced by finding amniotic fluid components in the pulmonary circulation. The presence of squamous cells in pulmonary arterial blood, once considered pathognomonic, has proved to be a nonspecific finding. Serological assays and immunohistochemical staining techniques have been described as having high sensitivity for amniotic fluid embolism.

Although various forms of therapy have been suggested (e.g., antifibrinolytic agents such as aminocaproic acid, cryoprecipitate), the best approach is supportive. Pulmonary artery catheterization is useful to monitor left ventricular function and volume status and to guide the appropriate use of inotropic and vasoactive agents. Even in the setting of aggressive supportive measures, however, maternal mortality has approached 80 percent.

Septic Embolism

Septic embolism is another special disorder that, unfortunately, is also increasing in frequency owing to widespread intravenous drug abuse and the expanding use of indwelling intravenous catheters. Previously, septic embolism was almost exclusively a complication of septic pelvic thrombophlebitis due to either septic abortion or post-puerperal uterine infection. However, almost any venous structure can be involved, either as a focus of primary infection or from intravascular or contiguous spread; septic cavernous sinus thrombosis resulting from meningitis, sinusitis, or facial cellulitis; septic portal venous thrombosis resulting from diverticulitis or liver abscess; septic tonsillar or internal jugular venous thrombosis (Lemierre's syndrome) resulting from oropharyngeal infection. Increasingly common causes are those related to intravenous drug use and those that are iatrogenic; namely, infections secondary to indwelling catheters inserted for a variety of diagnostic or therapeutic purposes.

Microscopically, septic phlebitis consists of purulent material admixed with fibrin thrombus. Embolization from

such material does occur and can result in obstruction of small pulmonary vessels, but the major consequence is pulmonary infection. Characteristically, the chest roentgenogram displays scattered pulmonary infiltrates that undergo cavitation. An increasing number of such infiltrates develops over periods of hours to a few days. Symptoms and signs include a septic temperature course, dyspnea, cough, pleuritic chest pain, and hemoptysis. Initial treatment consists of appropriate antimicrobial drugs. If an indwelling catheter is the source of the infection, it should be removed. If there is not a prompt response to this regimen, surgical isolation of the septic vein, if present, should be considered. The role of systemic anticoagulation remains uncertain. Endocarditis may complicate septic phlebitis, or mimic it, particularly in drug addicts.

Tumor Embolism

Involvement of the pulmonary vascular bed by tumor cells is not unusual given the frequency with which circulating tumor cells can be identified in patients with a wide range of malignancies and the frequency with which tumor emboli are discovered as an incidental finding at autopsy. Tumor embolism becomes clinically apparent, however, in only a minority of patients with malignancy.

Microvascular tumor embolism is associated with a wide range of malignancies, the most common sites of origin being the breast, lung, prostate, stomach, and liver. Tumor embolism of large fragments occurs rarely and may mimic acute thromboembolic disease. In this setting, survival following tumor embolectomy has been reported.

The clinical presentation of microvascular tumor embolism is typically subacute and involves progressive dyspnea, tachycardia, and tachypnea. Jugular venous distention, a prominent P2, tricuspid regurgitation or a right-sided S3 may be present on physical examination if the extent of pulmonary vascular obstruction is sufficient to cause pulmonary hypertension.

The development of pulmonary hypertension is a common accompaniment of symptomatic, microvascular tumor embolism and remains a major cause of mortality. Pulmonary hypertension appears to result from both an obliteration of the pulmonary vascular bed by an admixture of tumor cells and thrombus as well as the development of medial hypertrophy, intimal fibrosis, and fibrinoid necrosis encountered in other etiologies of pulmonary hypertension.

Hypoxemia and a compensated respiratory alkalosis are commonly present. The chest radiograph is most often normal but focal or diffuse infiltrates, which may be fleeting, have been described. Ventilation-perfusion scanning most commonly demonstrates a mottled appearance or peripheral, subsegmental defects; segmental or larger defects, indistinguishable from those associated with thromboembolic embolism, may occur in those rare instances of large-vessel involvement. CT may demonstrate peripheral, wedge-shaped defects consistent with infarcts; a pattern of multifocal dilatation and beading of the peripheral pulmonary arteries has been described.

Pulmonary angiographic findings may include delayed vascular filling, pruning and tortuosity, similar to that seen in other forms of small-vessel pulmonary hypertension. The angiographic findings in large fragment tumor embolism may be indistinguishable from those seen in acute thromboembolic disease.

Pulmonary microvascular cytology on specimens aspirated through a wedged pulmonary artery catheter may demonstrate malignant cells. Positive cytologies, however, can also be obtained in the setting of lymphangitic carcinomatosis. The misidentification of megakaryocytes obtained in this manner has been reported to lead to false-positive results.

Although diagnosis by transbronchial biopsy has been reported, diagnostic confirmation may require open-lung biopsy. Before proceeding to that step, however, it must be stressed that the impact of early diagnosis on outcome is uncertain. This intervention should only be considered in the setting of a primary malignancy for which effective chemotherapeutic options are available.

The differential diagnosis of tumor embolism includes thrombotic embolism, parenchymal metastasis, lymphangitic carcinomatosis, malignant pericardial effusion, and chemotherapy-related lung toxicity. The premortem diagnosis is often one of exclusion. Parenchymal metastasis, lymphangitic carcinomatosis and chemotherapy-related lung toxicity can be differentiated from tumor embolism by findings on high-resolution CT. Differentiation of tumor embolism from thrombotic embolism may be somewhat more problematic, especially if there is large vessel involvement.

Sickle Cell Disease

Sickle cell disease affects the lungs by causing local thrombosis and occasionally by embolization of bone marrow elements. Small pulmonary arteries, arterioles, and capillaries are generally affected. Thrombosis in the pulmonary circulation is part of the general proclivity of red blood cells containing S hemoglobin to sickle under appropriate circumstances, particularly hypoxia; stagnation and clotting follow sickling. In some instances, the thrombus organizes, vascular lumen is obliterated, and perivascular fibrosis ensues in the adjacent lung; in others, the thrombus recanalizes. Occasionally, infarction occurs.

Of the factors that predispose in thrombosis in the lungs in sickle cell disease, the most important is the low Po_2 of mixed venous blood. Not only is the mixed venous Po_2 inordinately low but also the O_2 dissociation curve is shifted to the right, thereby handicapping O_2 uptake in the lungs.

Any pulmonary disease that causes alveolar hypoventilation or hypoxemia of blood in the lungs of persons with sickle cell disease favors sickling and thrombosis. Since patients with sickle cell disease are prone to intercurrent pulmonary infections, particularly pneumonia and tuberculosis, they are predisposed to local areas of alveolar hypoventilation and hypoxia. Patients with severe sickle cell anemia and large fractions of hemoglobin S in their red blood cells are particularly susceptible to intense sickling and thrombosis anywhere, including the lungs. However, vulnerability is not restricted

to states of hemoglobin S. In some heterozygous sickle states—e.g., hemoglobin SC, S-thalassemia, and hemoglobin SA—enough hemoglobin S is present to cause extensive thrombosis and infarction during an episode of severe hypoxemia, acidosis, or septicemia associated with fever and leukocytosis.

The clinical picture of pulmonary infarction in patients with sickle cell disease can mimic or coexist with bronchopneumonia. The latter may promote local hypoxia, which leads to in situ pulmonary thrombosis. An episode often begins with poorly defined or pleuritic chest pain, fever, and sputum that is blood streaked but fails to disclose any specific bacterial cause. A fleeting episode of breathlessness is usually overlooked. Cyanosis is rare because of the severe anemia. The subsequent course is characterized by an unconvincing response to antibiotics and slow clearing; often a linear scar in the lungs remains as a residue of the infarction. Suspicion of infarction should be high in any black person with hemoglobin S and in white people of Greek or Italian descent with S-thalassemia.

Sometimes, occlusive disease is sufficiently extensive to cause pulmonary hypertension and cor pulmonale. For this sequence to evolve, many severe episodes of sickling are required. The cor pulmonale that results is unusual because of its association with a high cardiac output (due to the anemia) and with the intrinsic myocardial damage that generally complicates sickle cell disease.

Management of the patient with pulmonary thrombosis and infarction in sickle cell disease relies heavily on experience with the disease. Few specific measures can be advocated other than conventional supportive treatment. Distinguishing between in situ thrombosis and thromboembolism can be difficult clinically and even with invasive procedures such as angiography, although in situ thrombosis tends to be in small, distal vessels. Moreover, because radiographic contrast materials may promote sickling, they have to be used cautiously. To complicate matters, some patients with sickle cell disease are also at increased risk of thromboembolus because of predisposing factors, such as bed rest, congestive heart failure, and dehydration.

Anticoagulants are generally not used in sickle cell disease, since there are no data to substantiate their effectiveness in treating in situ thrombosis.

Other Emboli

Because of its sieve function, the lung may also be embolized on occasion by a wide variety of other materials. Trophoblastic tissue can escape the uterus and lodge in the pulmonary circulation during pregnancy. After head trauma, brain tissue has been found in the lungs; the same is true of liver cells following abdominal trauma and bone marrow after cardiopulmonary resuscitation.

Finally, in this era of intravenous drug abuse, noninfectious vasculitic-thrombotic complications are being seen with increasing frequency in association with the intravenous use of drugs intended for oral use. Medications associated with pulmonary complications include methylphenidate hydrochloride, oral opiates (pentazocine, meperidine), and antihistamines. Particulate and irritant drug carriers (e.g., talc, cellulose) and occasionally the drugs themselves may cause vascular inflammation and secondary thrombosis. The clinical presentation may be diverse and includes lower lobe emphysema, diffuse interstitial fibrosis, and progressive massive fibrosis. Repetitive insults may lead to severe and irreversible pulmonary hypertension. In many intravenous drug users, perfusion scans demonstrate segmental or smaller defects. Distinguishing these defects from those due to venous thromboembolism may be difficult.

The diagnosis is often suggested by the clinical history. Radiographic findings include small, diffuse well-defined nodular densities. These nodules can progress and massive fibrosis may ensue. Lower lobe emphysematous changes may also be present. Diagnostic confirmation often requires lung biopsy, either open or transbronchial. The prognosis is poor with progressive pulmonary disease being the rule.

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83

Pulmonary Vasculitis

Ulrich Specks

NOMENCLATURE AND DEFINITIONS

Pulmonary vasculitis is usually a manifestation of a systemic disorder leading to inflammation of vessels of different sizes by a variety of immunologic mechanisms. Vasculitis can be separated into primary and secondary vasculitis. The primary systemic vasculitides are a heterogeneous group of syndromes of unknown etiology, which share a clinical response to immunosuppressive therapy (Table 83-1). Their wide spectrum of frequently overlapping clinical manifestations is defined by the size and location of the affected vessels as well as the nature of the inflammatory infiltrate. Secondary vasculitis may represent significant management problems in the context of a well-defined underlying disorder, such as diffuse alveolar hemorrhage caused by systemic lupus erythematosus. Alternatively, secondary vasculitis may be an incidental histopathological finding, for instance, in the context of an infection or necrotizing sarcoid granulomatosis.

Classification schemes and definitions of the various forms of vasculitis have evolved over the past decades. Historically, the classification of the vasculitides has been based on the size of the most prominently affected vessels. The primary purpose of classification and nomenclature is to standardize communication between clinicians and investigators and to facilitate more uniform treatment approaches. Ideally, they reflect the current understanding of pathogenesis. Two schemes of classification and definitions are currently in use. In 1990, the American College of Rheumatology (ACR) developed criteria for the classification of the vasculitides. The ACR effort identified clinical features that allow separation of one form of vasculitis from another. The 1990 ACR criteria have several major drawbacks for clinical practice. First, the underlying data were collected before testing for antineutrophil cytoplasmic antibodies (ANCA) became available. Second, these criteria precede the acknowledgment of the concept of microscopic polyangiitis, which has been widely accepted in Europe for many decades. In the U.S. literature preceding the

Table 83-1

Chapel Hill Consensus Nomenclature of the Primary Systemic Vasculitides

Name	Respiratory Manifestations	Presence of ANCA
Large vessel vasculitis		
Giant cell arteritis	Rare	No
Takayasu's arteritis	Frequent	No
Medium-sized vessel vasculitis		
Classic polyarteritis nodosa	Rare	No
Kawasaki's disease	No	No
Small vessel vasculitis		
Wegener's granulomatosis	Frequent	>80%
Microscopic polyangiitis	Frequent	>80%
Churg-Strauss syndrome	Frequent	>50%
Henoch-Schönlein purpura	Rare	IgA-ANCA reported
Essential cryoglobuinemic vasculitis	No	No

1990s, cases with microscopic polyangiitis were either referred to as "hypersensitivity vasculitis" or lumped with classic polyarteritis nodosa.

An international consensus conference on the nomenclature of systemic vasculitides held in 1992 in Chapel Hill aimed to reconcile definitions and classification schemes used by European and American investigators. The resulting nomenclature and definitions are based mainly on histopathological criteria, particularly the size of the vessels involved. However, radiographic and clinical surrogates may be used to fulfill the definitions. Although the Chapel Hill consensus nomenclature takes the presence or absence of ANCA into account, the presence of ANCA is not required for the diagnosis of an "ANCA-associated vasculitis," such as Wegener's granulomatosis or microscopic polyangiitis. Finally, the conference acknowledged the occasional need to change the diagnosis in certain patients as their clinical presentations change over time. For instance, a patient originally diagnosed as having microscopic polyangiitis may have to be diagnosed as having Wegener's granulomatosis when characteristic necrotizing granulomas develop. In this chapter, the specific definition of each form of vasculitis is discussed in detail as part of the description of the clinical manifestations and differential diagnosis of each entity.

The Chapel Hill nomenclature has been criticized for a variety of reasons. However, from a pulmonologist's perspective, it represents the clinically most useful attempt to

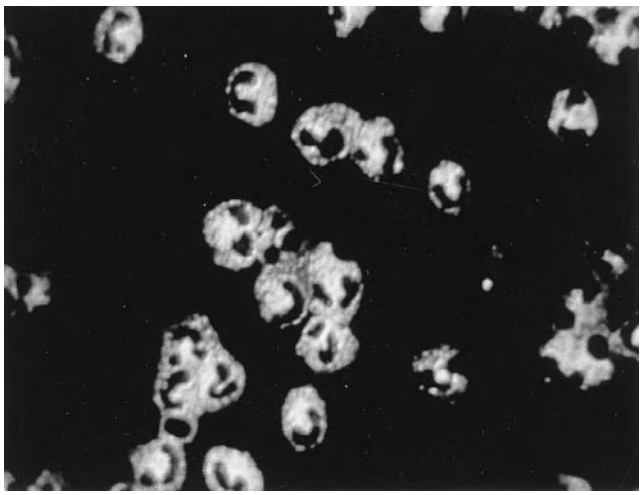


Figure 83-1 Cytoplasmic indirect immunofluorescence (C-ANCA) pattern in ethanol-fixed neutrophils caused by ANCA reacting with PR3.

categorize the primary systemic vasculitides. The categories reflect the clinical and histopathological pulmonary features, are in accordance with the ANCA data, and facilitate the therapeutic approach to individual patients. The three small vessel vasculitides that present most often with respiratory symptoms are Wegener's granulomatosis, MPA, and the Churg-Strauss syndrome. Most patients with these syndromes have ANCA detectable in the serum at the time of initial presentation. Consequently, this group of small vessel vasculitides is frequently referred to *in cumulo* as "ANCA-associated vasculitis." Clinicians convinced of the pathogenic significance of these antibodies even prefer the term "ANCA vasculitis."

In patients with vasculitis, two types of ANCA are of clinical significance. In more than 80 percent of patients with Wegener's granulomatosis (Fig. 83-1), ANCA occurs and is associated with a cytoplasmic immunofluorescence pattern (C-ANCA) on ethanol-fixed neutrophils that react with the neutrophil granule enzyme, proteinase 3 (PR3-ANCA). In contrast, ANCA that causes a perinuclear immunofluorescence pattern (P-ANCA) on ethanol-fixed neutrophils and reacts with myeloperoxidase (MPO-ANCA) occurs in fewer than 10 percent of patients with Wegener's granulomatosis but in the majority of patients with microscopic polyangiitis (Fig. 83-2). MPO-ANCA are also the predominant type of ANCA encountered in patients with Churg-Strauss syndrome, in which PR3-ANCA is the exception. Despite these circulating autoantibodies, hardly any immunoglobulin deposits can be detected in the tissue lesions of ANCA-associated vasculitis, and they are consequently called "pauci-immune" lesions.

EPIDEMIOLOGY

The primary systemic vasculitides are rare and few epidemiologic studies have been conducted, mostly in ethnically homogenous populations. Giant-cell arteritis is the most

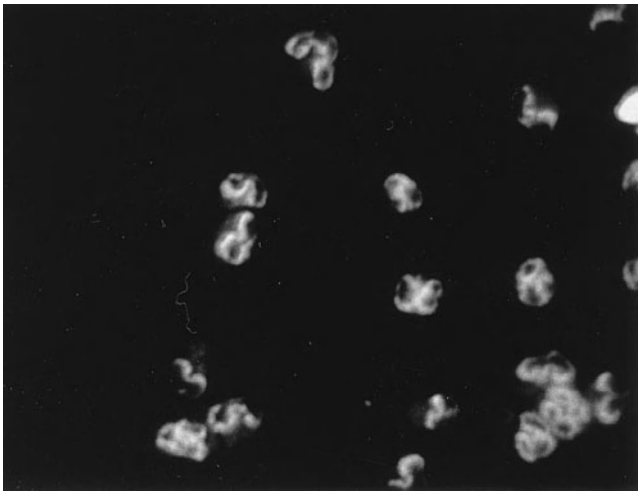


Figure 83-2 Perinuclear indirect immunofluorescence (P-ANCA) pattern in ethanol-fixed neutrophils caused by ANCA reacting with MPO.

frequent form of systemic vasculitis with an annual incidence of 13 per million adults (40 per million over the age of 60). It appears to be increasing in frequency and becoming cyclical over time. The latter observation has been interpreted as possibly suggesting a relationship with infections. Respiratory manifestations rarely represent significant management problems in these patients. Various studies from different regions of the world report a fairly uniform incidence of one to two cases per million for Takayasu's arteritis. Pulmonary vascular complications occur in about half of the afflicted patients. The estimated annual incidence of Wegener's granulomatosis has been rising over the decades from 0.5 to 0.7 per million during the 1970s and early 1980s to current estimates of about 10 to 12 per million. Similar increases in annual incidence have been observed for microscopic polyangiitis and Churg-Strauss syndrome. The average frequency of microscopic polyangiitis is similar to that of Wegener's granulomatosis; for the Churg-Strauss syndrome it is estimated to be of the order of one to three per million. The ANCA-associated vasculitides have different ethnic predilections: Wegener's granulomatosis affects predominantly whites, and northern Europeans appear more prone to develop Wegener's granulomatosis. In contrast, individuals of southern European and Mediterranean descent appear to be relatively more apt to develop microscopic polyangiitis. Wegener's granulomatosis and microscopic polyangiitis can affect individuals of any age. However, the incidence of Wegener's granulomatosis plateaus after age 50, whereas the likelihood of developing microscopic polyangiitis continues to increase with age.

The annual incidence of the secondary vasculitides varies widely. The reported frequencies for rheumatoid vasculitis and vasculitis in systemic lupus erythematosus are 12.5 per million and 3.6 per million, respectively. Behçet's disease has a peculiar geographic distribution along the old Silk Road, with the highest prevalence being reported from Turkey, central and far-eastern Asia, where the frequencies range from 100 to 380 per 100,000, compared with only one per 100,000 in western Europe.

The available population-based studies need to be interpreted with some caution because they do not distinguish between whether the observed increased incidence of systemic vasculitis is true, or the result of more frequent recognition of the disease. Moreover, whether individual diagnoses are accurate is challenged by the changing definitions of the syndromes. For instance, if the ACR 1990 criteria for polyarteritis nodosa (PAN) are applied, the incidence of PAN would be 2.4 per million annually. In contrast, application of the definitions of the Chapel Hill Consensus Conference has resulted in the almost complete disappearance of PAN, whereas the incidence of microscopic polyangiitis would seem to be 3.6 per million annually. Finally, the advent of ANCA testing may have affected the apparent incidences of Wegener's granulomatosis and microscopic polyangiitis.

ANCA-ASSOCIATED VASCULITIS

Wegener's Granulomatosis: Clinical Presentation and Diagnosis

Wegener's granulomatosis is the most common form of vasculitis to involve the lung. The Chapel Hill Consensus Conference defined Wegener's granulomatosis as "granulomatous inflammation involving the respiratory tract, and necrotizing vasculitis affecting small to medium-sized vessels." However, it is important to recognize that Wegener's granulomatosis is a systemic disease that can affect almost any organ (Table 83-2). The most frequently involved sites are the upper airways, lungs, and kidneys. Symptoms and clinical disease manifestations are the result of necrotizing granulomatous inflammation and small vessel vasculitis that occur in variable degrees of combination.

In the 1960s the term "limited Wegener's granulomatosis" was introduced to indicate those patients who lacked renal disease. The use of this term and its implications have evolved over the last two decades. Even in the absence of renal involvement, patients may have life-threatening pulmonary or neurological disease requiring aggressive immunosuppressive treatment. For instance, a patient who "only" has alveolar hemorrhage in the absence of glomerulonephritis should never be classified as having "limited Wegener's granulomatosis." Consequently, today, the use of the term "limited Wegener's granulomatosis" implies that: (a) the pathology is predominantly a necrotizing granulomatous and the vasculitis seen on biopsy is of lesser clinical significance; and (b) there is no immediate threat either to the patient's life or that the affected organ is at risk for irreversible damage. In this sense, limited Wegener's granulomatosis is distinguished from severe Wegener's granulomatosis, which by definition either threatens the patient's life (alveolar hemorrhage) or a vital organ with the risk of irreversible damage (rapidly progressive glomerulonephritis, scleritis, or mononeuritis

Table 83-2

Organ Systems Affected by ANCA-Associated Vasculitis

Feature	Wegener's Granulomatosis	Microscopic Polyangiitis	Churg-Strauss Syndrome
Upper airway disease	90–95%	No	50–60%
Pulmonary parenchymal disease	54–85%	20%	30%
Alveolar hemorrhage	5–15%	10–50%	<3%
Glomerulonephritis	51–80%	60–90%	10%–25%
Gastrointestinal tract	<5%	30%	30–50%
Eyes	35–52%	<5%	<5%
Nervous system	20–50%	60–70%	70%–80%
Heart	8–16%	10–15%	10–15%
Skin	33–46%	62%	50–60%
Eosinophilia	Rare	Rare	Yes
Asthma	No*	No*	Yes
Granulomatous inflammation	Yes	No	Yes

**Not more than general population.*

multiplex). These definitions and distinctions form the basis for stratification of current standard therapy.

Over 90 percent of patients with Wegener's granulomatosis first seek medical attention for symptoms arising from either the upper and/or lower airway. Nasal and sinus disease is characterized by congestion and epistaxis due to mucosal friability, ulceration, and thickening. Patients may also have features of chronic sinusitis and recurrent or chronic serous otitis. Perforation of the nasal septum and/or saddle nose deformity may result from ischemia of the nasal cartilage (Fig. 83-3). Oral manifestations include gingival hyperplasia (Fig. 83-4) and oropharyngeal ulcerations. Subglottic stenosis occurs in approximately 20 percent of patients and can cause life-threatening compromise of the airway. Subglottic stenosis may occur in the absence of other features of active Wegener's granulomatosis, and its symptoms may be nonspecific, e.g., dyspnea, hoarseness, cough or stridor; the latter is occasionally mistaken for wheezing.

Wegener's granulomatosis involving the lower airways can affect the pulmonary parenchyma, the bronchi, and rarely the pleura. Presenting features of parenchymal involvement may include cough, dyspnea, chest pain, or hemoptysis. However, some patients may be completely asymptomatic. Patients with diffuse alveolar hemorrhage usually present with progressive dyspnea and anemia (Fig. 83-5). Hemoptysis is absent in about one-third of patients. Patients with diffuse alveolar hemorrhage may deteriorate rapidly and experience respiratory failure, which has a mortality rate of 50 percent.

The clinical presentation of alveolar hemorrhage is caused by pulmonary capillaritis (Fig. 83-6). The predominant inflammatory cells are neutrophils. However, eosinophils or monocytes may also be present. Capillaritis usually causes fibrinoid necrosis of alveolar and vessel walls and may culminate in the destruction of the underlying architecture of the lung. An important hallmark of capillaritis is the presence of pyknotic cells and nuclear fragments from neutrophils undergoing apoptosis, a feature called leukocytoclasis. This hallmark enables distinction between true capillaritis and margination of neutrophils related to surgical trauma. Depending on the acuteness and duration of alveolar hemorrhage, hemosiderin-laden macrophages and interstitial hemosiderin deposits may be present.

The most common form of pulmonary involvement in Wegener's granulomatosis is that of nodules or mass lesions, which may cavitate (Figs. 83-7, 83-8, and 83-9). Frequently, these lesions are incidental findings on thoracic imaging studies as they cause little symptoms and do not result in significant abnormalities of pulmonary function. These lesions are

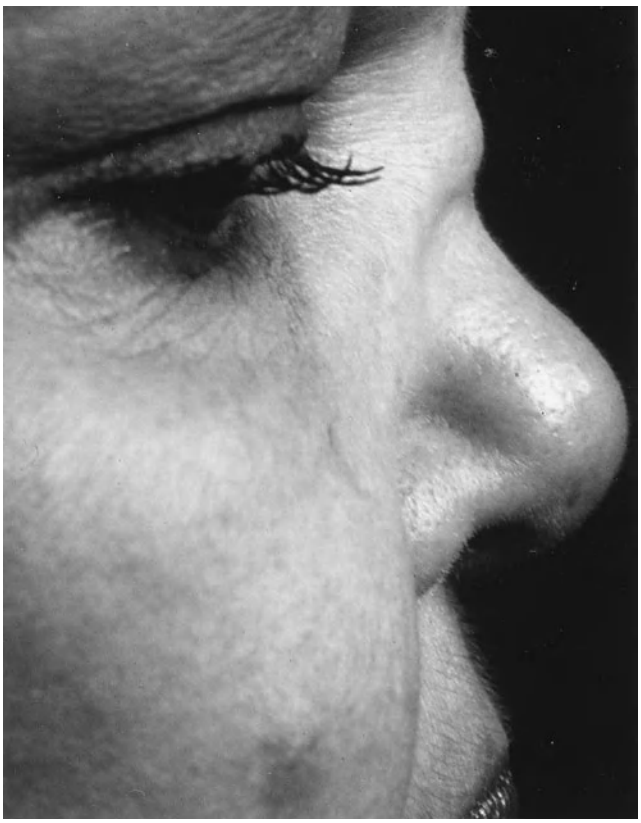


Figure 83-3 Saddle nose deformity of Wegener's granulomatosis.

caused by necrotizing granulomatous inflammation. Prominent air-fluid levels can be seen when the necrotic center of the inflammatory lesion gets superinfected (Fig. 83-8). These necrotizing granulomatous lesions are a disease-defining feature of Wegener's granulomatosis. Their presence easily separates Wegener's granulomatosis from microscopic polyangiitis. In the absence of other features of small vessel vasculitis in other organs, the differential diagnosis of these lesions consists primarily of infections, particularly caused by fungal or mycobacterial organisms, and less likely of malignancies or necrotizing sarcoid granulomatosis.

The lung nodules of Wegener's granulomatosis have very characteristic histopathological features. Small necrotizing microabscesses appear to be the earliest lesion. They enlarge and coalesce until the typical geographic and basophilic appearance of the necrosis has developed (Fig. 83-10). The necrotic center is surrounded by palisading histiocytes and scattered giant cells. Occasionally the necrosis may be bronchocentric. When this type of necrotizing granulomatous inflammation extends into the walls of small vessels it is referred to as granulomatous vasculitis (Fig. 83-11). In contrast to capillaritis, this type of vasculitis seems to be a secondary phenomenon of the necrotizing granulomatous inflammation affecting the lung parenchyma. The inflammatory background of the granulomatous necrosis and vasculitis consists of a mixed cellular infiltrate containing lymphocytes, plasma cells, scattered giant cells, and eosinophils. It may cause extensive parenchymal consolidation mimicking organizing pneumonia. Well defined sarcoidlike non-necrotizing granulomas are not found in Wegener's granulomatosis.

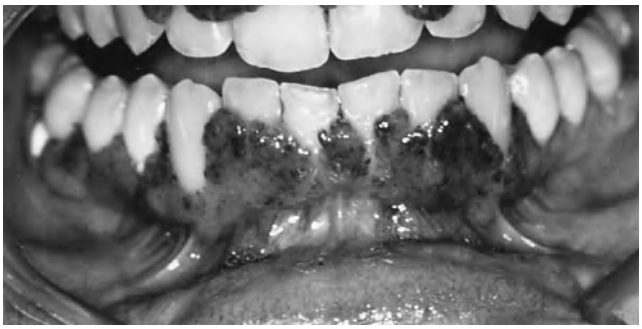


Figure 83-4 Strawberry or mulberry gums in a patient with Wegener's granulomatosis.

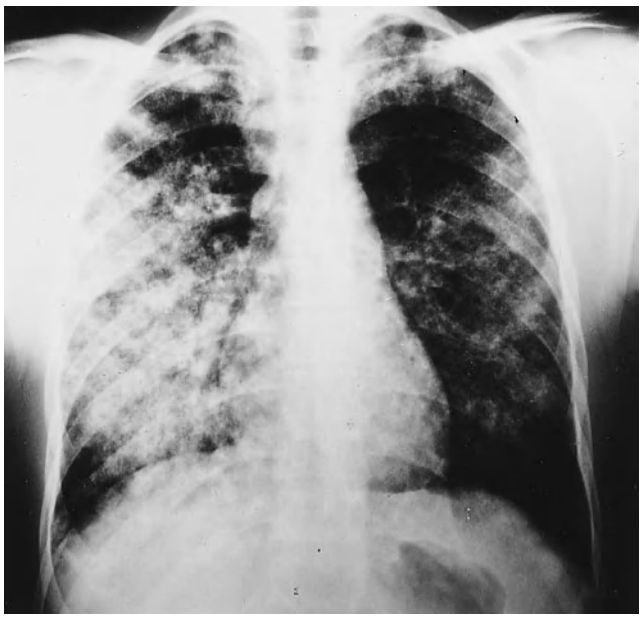


Figure 83-5 Chest radiograph of a patient with Wegener's granulomatosis displaying an alveolar filling pattern indicative of diffuse alveolar hemorrhage.

Inflammation and stenosis of the tracheobronchial tree occurs in at least 15 percent of patients with lung involvement. Endobronchial disease may be an incidental finding on bronchoscopy or present with cough, hemoptysis, wheezing, dyspnea, or symptoms related to parenchymal collapse or postobstructive infection. Spirometry including inspiratory and expiratory flow-volume loops may show characteristic abnormalities indicative of degree and location of airway narrowing. Subglottic stenosis represents a fixed airway obstruction resulting in flattening of both the inspiratory and expiratory loops. If the intrathoracic trachea, or more commonly, one or both mainstem bronchi are affected, flattening of the expiratory curve can be found. Pleural effusions may occur, but are usually small, asymptomatic, and incidental findings (Fig. 83-9). Other thoracic manifestations of Wegener's granulomatosis include inflammatory pleural pseudotumors or hilar

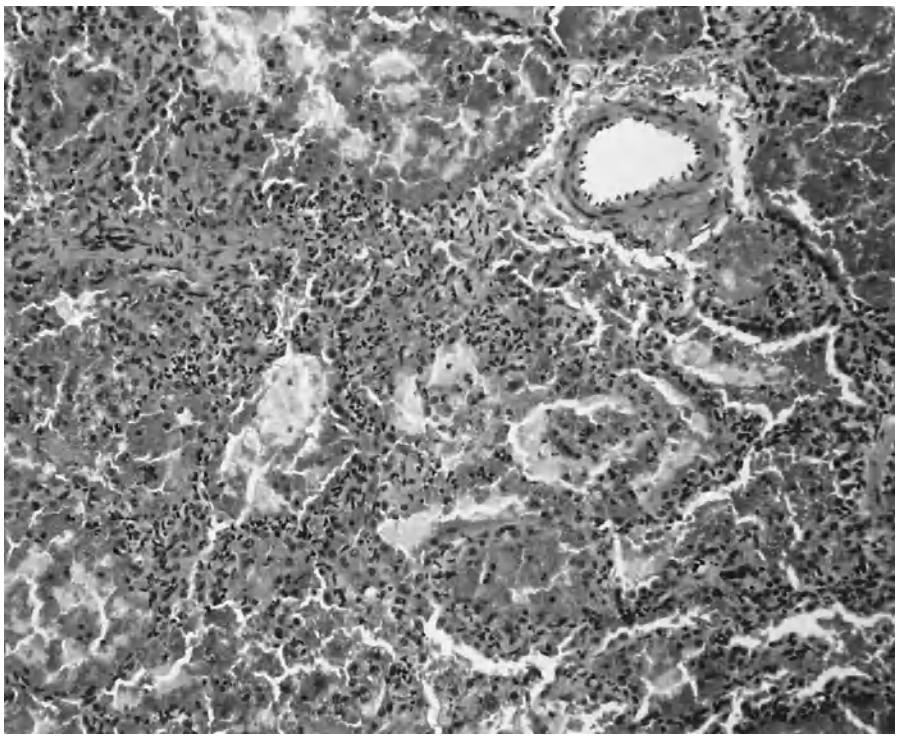


Figure 83-6 Alveolar capillaritis causing pulmonary hemorrhage in Wegener's granulomatosis.

adenopathy. The latter should raise the suspicion of infection, sarcoidosis, or lymphoma.

Glomerulonephritis is among the most concerning disease manifestations of Wegener's granulomatosis as it can progress to complete renal failure in the absence of symptoms. It is usually detected by the presence of abnormal laboratory results such as active urine sediment with microscopic hematuria and red cell casts, proteinuria, and declining renal function. Continued vigilance for glomerulonephritis is essential as it is present at diagnosis in less than half of all patients. However, over the course of their disease, the kidneys are affected in 80 percent of patients.

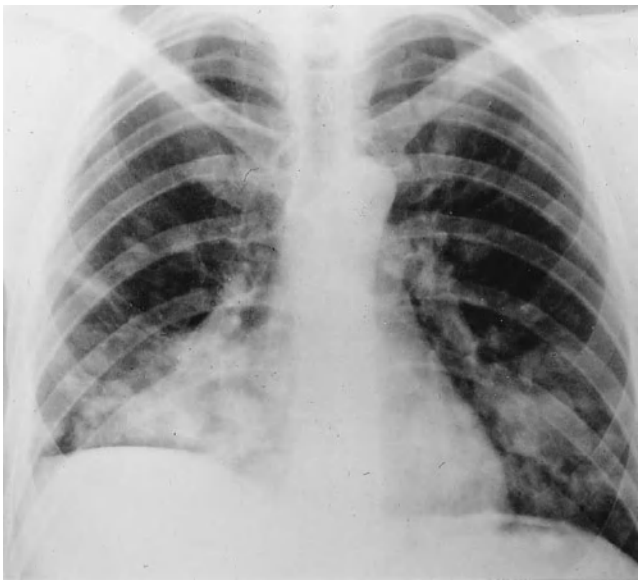


Figure 83-7 Chest radiograph of a patient with Wegener's granulomatosis displaying multiple nodules with and without cavitation.

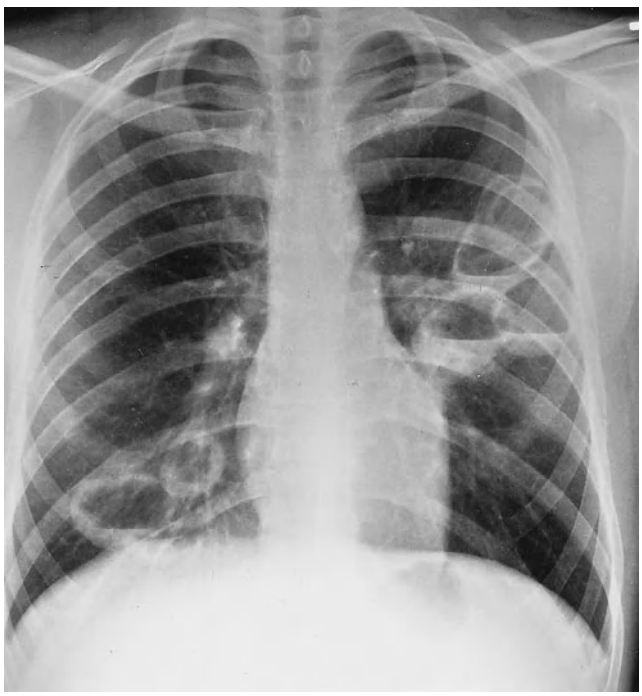


Figure 83-8 Chest radiograph of a patient with Wegener's granulomatosis showing multiple large cavities, some with air-fluid levels.

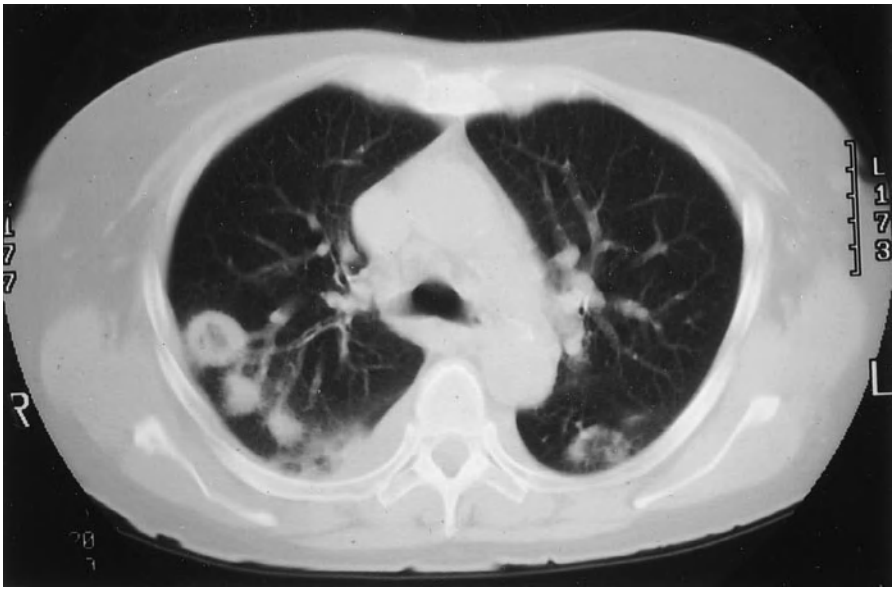


Figure 83-9 Computed tomography scan of a patient with Wegener's granulomatosis showing multiple nodules, some with cavitation. There are also small bilateral pleural effusions.

A renal biopsy is useful to establish a diagnosis of ANCA-associated vasculitis and to determine the renal prognosis. The glomeruli are not affected uniformly (focal) by segmental, necrotizing inflammation (Fig. 83-12), and cellular crescents (Fig. 83-13) are frequently found. The number of glomeruli affected, degree of crescent formation, and destruction of individual glomeruli as well as the amount of sclerosis found determine the chance of recovery of renal function. Direct immunofluorescence reveals no or only scant immune deposits (pauci-immune glomerulonephritis). Granulomatous inflammation affecting the renal parenchyma and tubulointerstitial nephritis can also be found rarely.

A wide spectrum of ocular manifestations has been observed in Wegener's granulomatosis, which may threaten vision by affecting the eye directly or involving its contiguous structures. Manifestations may include conjunctivitis, episcleritis, scleritis, keratitis, corneal ulceration, uveitis, and retinal vasculitis. Involvement of the lacrimal system may result in epiphora, dacryocystitis, and fistula. Retro-orbital inflammatory pseudotumors may affect one or both eyes, threaten the vision, and represent the most difficult challenge in the management of Wegener's granulomatosis (Figs. 83-14 and 83-15). Any patient with Wegener's granulomatosis who presents with eye pain or redness, proptosis, change in visual acuity, diplopia, or loss of visual field should be referred for emergent ophthalmologic consultation.

Nervous system involvement may occur in up to one-third of patients. Mononeuritis multiplex of the peripheral nervous system caused by inflammation of the vasa nervorum as well central nervous system vasculitis and pachymeningitis represent severe disease manifestations with substantial risk of irreversible damage, persisting even after the acute inflammation is adequately controlled.

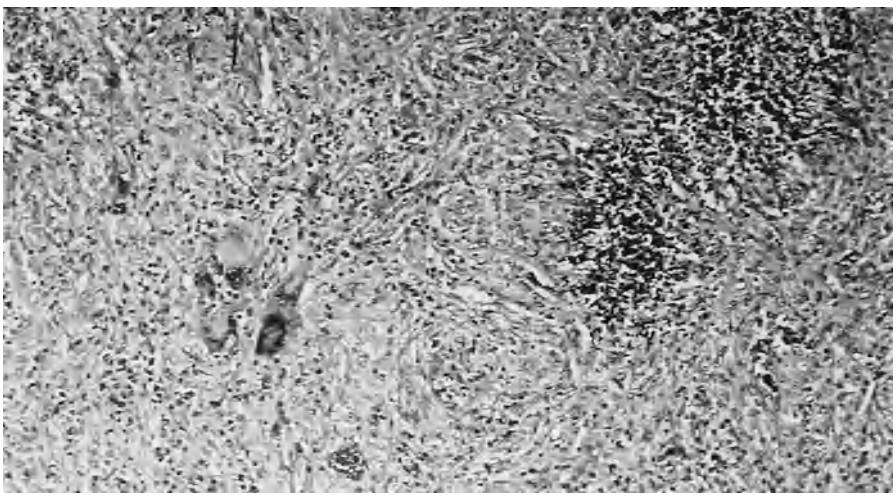


Figure 83-10 Geographic basophilic necrosis with palisading histiocytes and giant cells from a lung nodule in a patient with Wegener's granulomatosis.

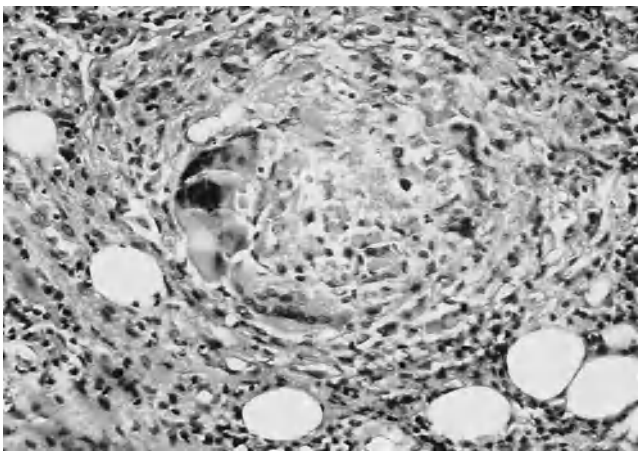


Figure 83-11 Granulomatous vasculitis with giant cells in a lung biopsy of a patient with Wegener's granulomatosis.

Cardiac involvement may be occult. Regional wall motion abnormalities with a noncoronary distribution pattern are frequent echocardiographic findings. It is unclear whether this type of cardiomyopathy is the result of small vessel disease or inflammatory infiltration of the cardiac muscle. Pericarditis, valvulitis, and inflammatory pseudotumor have also been described.

A wide spectrum of cutaneous manifestations may be observed in Wegener's granulomatosis. Leukocytoclastic vasculitis presenting as palpable purpura is most common, followed by pyoderma gangrenosum-like lesions (Fig. 83-16) and so-called Churg-Strauss granulomas.

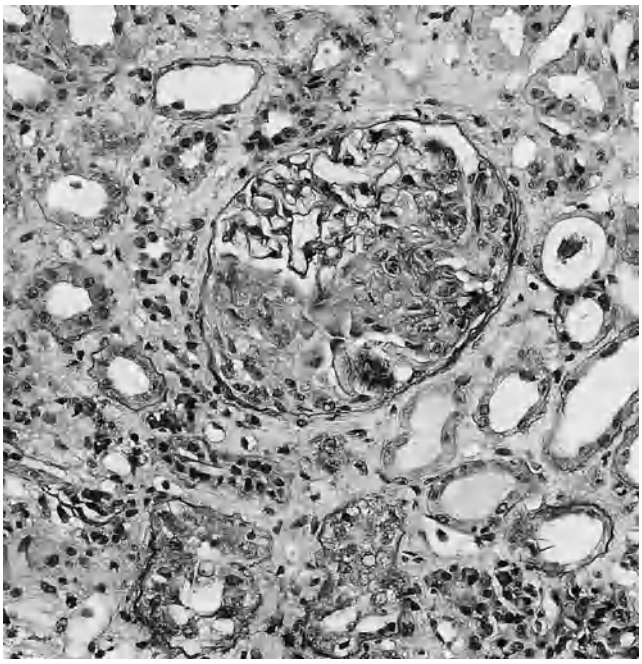


Figure 83-12 Focal necrotizing glomerulitis of Wegener's granulomatosis.

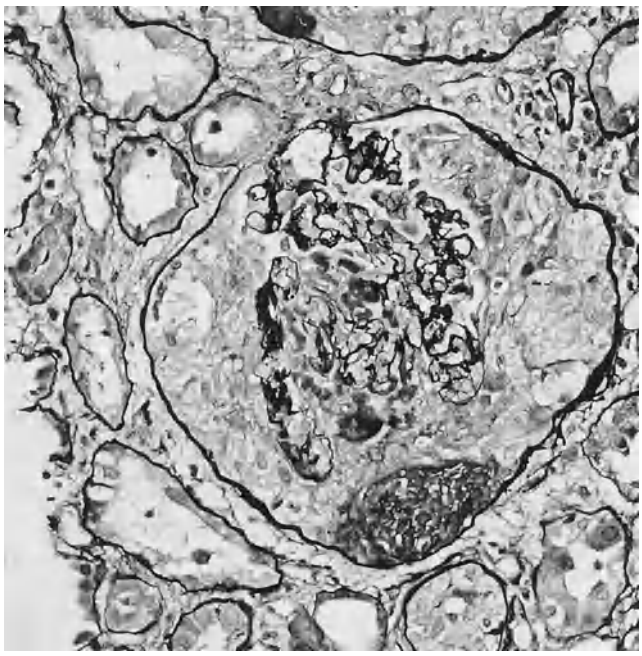


Figure 83-13 Rapidly progressive crescentic glomerulonephritis in Wegener's granulomatosis.

Microscopic Polyangiitis: Clinical Presentation and Diagnosis

Histopathologically, the necrotizing small vessel vasculitis of microscopic polyangiitis including necrotizing crescentic glomerulonephritis and pulmonary capillaritis are indistinguishable from that encountered in Wegener's granulomatosis. Consequently, there is substantial overlap in organ manifestations and symptoms between microscopic polyangiitis and Wegener's granulomatosis (Table 83-2). A timely diagnosis of microscopic polyangiitis may be delayed by a gradual onset or the nonspecific nature of symptoms such as fever, malaise, and weight loss. All organ systems may be involved. The kidneys are most commonly affected in up to 80 percent

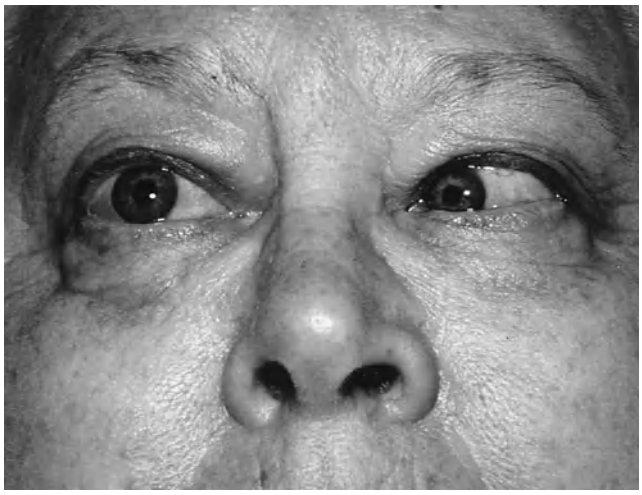


Figure 83-14 External ophthalmoplegia of the left eye due to orbital involvement with Wegener's granulomatosis.

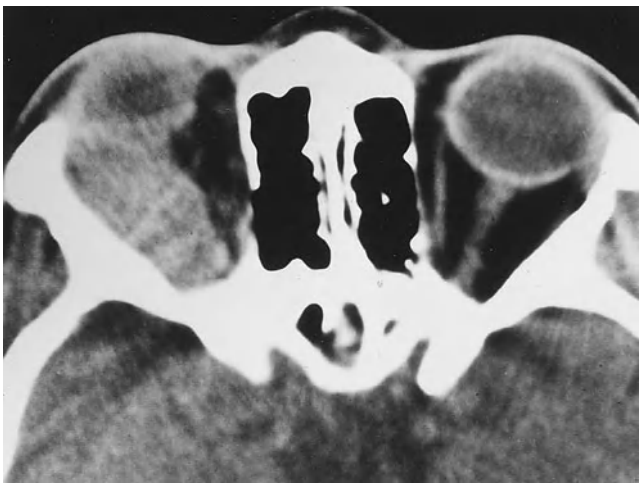


Figure 83-15 Computed tomography scan of the orbits in a patient with Wegener's granulomatosis showing a mass in the right orbit causing external ophthalmoplegia.

of patients. Other commonly encountered disease manifestations include diffuse alveolar hemorrhage due to pulmonary capillaritis affecting 10 to 30 percent of patients. Microscopic polyangiitis is the most frequent cause of pulmonary-renal syndrome. Several cases of microscopic polyangiitis in association with a variety of nonvasculitic pulmonary disorders including pulmonary fibrosis, severe obstructive airways disease, and bronchiectasis, have also been described. Palpable purpura caused by leukocytoclastic vasculitis of the skin, and musculoskeletal complaints, such as arthralgias and myalgias, are also common. Gastrointestinal involvement occurs in about one-third of patients. This is in contrast to Wegener's granulomatosis, in which gastrointestinal involvement is very rare. Visceral angiography is generally not helpful for the evaluation of abdominal symptoms as the vessels involved are too small to be visualized. CT with or without contrast injection may be more helpful if gastrointestinal involvement is suspected. However, the use of contrast is relatively contraindicated in patients with active renal involvement. Sinusitis and asthma are rarely found in microscopic polyangiitis, and should lead to the consideration of an alternative diagnosis.

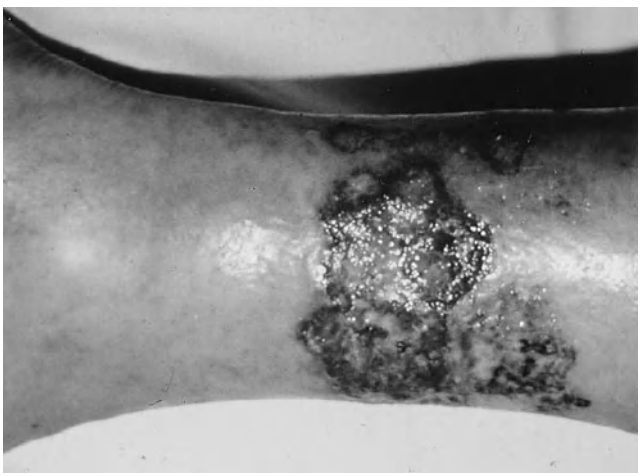


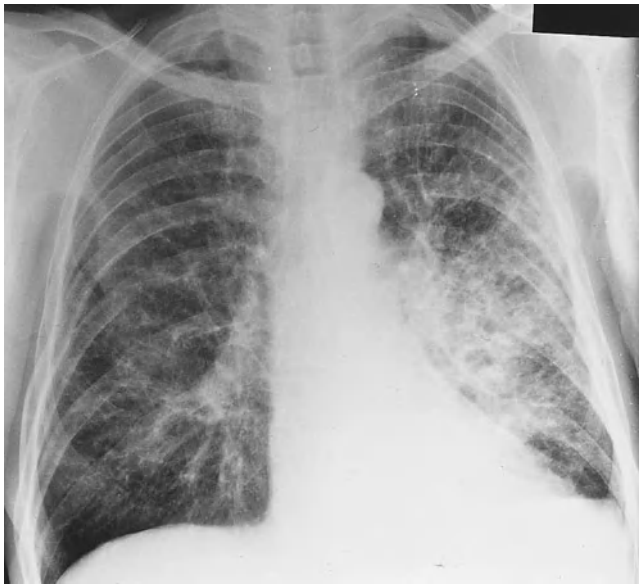
Figure 83-16 Pyoderma gangrenosum of the leg in a patient with Wegener's granulomatosis.

Most patients with microscopic polyangiitis have ANCA, and in 40 to 80 percent they are of the P-ANCA variety, reacting with MPO. C-ANCA reacting with PR3 is seen less frequently. Occasionally patients with microscopic polyangiitis later develop granulomatous inflammation and are reclassified as having Wegener's granulomatosis; this is more likely to occur in patients with C-ANCA.

As in Wegener's granulomatosis, a histopathological diagnosis should be obtained before the patient is committed to prolonged immunosuppressive therapy. The biopsy specimen should be sought from the most accessible site. Renal biopsy shows pauci-immune focal segmental necrotizing glomerulonephritis, with extracapillary proliferation forming crescents. In contrast to Wegener's granulomatosis, granulomatous inflammation is not a feature of microscopic polyangiitis. All other histopathological features are indistinguishable from those of Wegener's granulomatosis. Treatment of microscopic polyangiitis should follow the principles applied to the management of Wegener's granulomatosis. Consequently, most cases of microscopic polyangiitis require immunosuppressive therapy used for patients with severe Wegener's granulomatosis.

Churg-Strauss Syndrome: Clinical Presentation and Diagnosis

Churg-Strauss syndrome is the third type of vasculitis that commonly affects the lung. The Chapel Hill Consensus definition for the disease is "eosinophil-rich and granulomatous inflammation involving the respiratory, and necrotizing vasculitis affecting small to medium-sized vessels, and associated with asthma and eosinophilia." The inclusion of Churg-Strauss syndrome among the ANCA-associated vasculitides remains controversial, as only 40 to 70 percent of patients with active Churg-Strauss vasculitis are ANCA positive. Churg-Strauss syndrome is primarily distinguished from Wegener's granulomatosis and microscopic polyangiitis by a high prevalence of asthma and peripheral blood and tissue eosinophilia. Three distinct disease phases of the disease have been described. The first is a prodromal allergic phase with asthma. This phase may last for a number of years. The second is an eosinophilic phase with prominent peripheral and tissue eosinophilia. This phase may also last a number of years and the manifestations may remit and recur over this time period. The differential diagnosis for patients in this phase of the disease includes parasitic infection and chronic eosinophilic pneumonia. The third vasculitic phase consists of systemic vasculitis and may be life threatening. The three phases are not seen in all patients and do not necessarily occur in this order; they may even concur. However, asthma usually predates vasculitic symptoms by a mean of 7 years (range 0 to 61). Formes frustes of Churg-Strauss syndrome have also been described with eosinophilic vasculitis and/or



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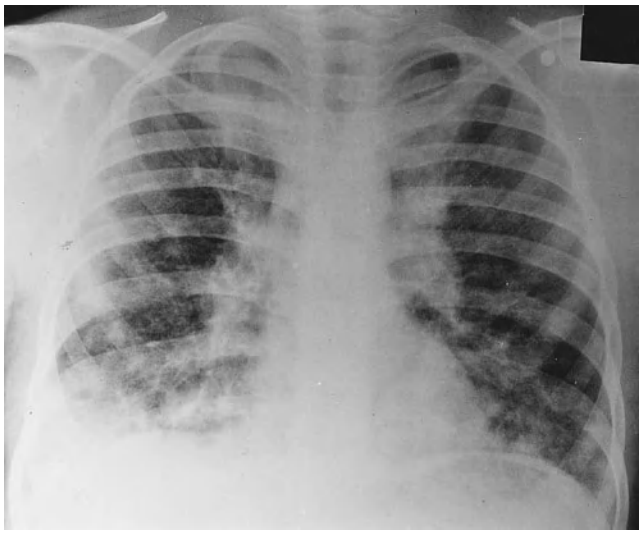

B

Figure 83-17 Chest radiographs of patients with Churg-Strauss syndrome: *A*. Nonspecific gnomonic infiltrates. *B*. Multiple vague, patchy infiltrates. *(Reproduced by permission from Mayo Clin Proc 52:482, 1977.)* Chumbley LC, Harrison EG, DeRemee RA: Allergic Granulomatosis and angiitis (Churg-Strauss syndrome): Report and analysis of 30 cases. *Mayo Clin Proc* 52: 477–484, 1977.

eosinophilic granulomas in isolated organs without evidence of systemic disease.

Pulmonary parenchymal involvement occurs in 38 percent of patients. Transient alveolar-type infiltrates are most common (Fig. 83-17). These have a predominantly peripheral distribution and are indistinguishable from infiltrates seen in chronic eosinophilic pneumonia. Occasionally, nodular lesions may be seen in Churg-Strauss syndrome. In contrast to Wegener's granulomatosis and microscopic polyangiitis, alveolar hemorrhage is exceedingly rare. Renal involvement in Churg-Strauss syndrome is less prominent than in Wegener's granulomatosis and microscopic polyangiitis and does not generally lead to renal failure. In contrast, peripheral nerve involvement, typically in the form of mononeuritis multiplex, is more frequent. Skin, heart, central nervous system, and abdominal viscera may also be involved.

The classic histopathological picture consists of necrotizing vasculitis, eosinophilic tissue infiltration, and extravascular granulomas. However, not all features are found in every case, and they are not pathognomonic of the condition. Particularly the finding of a "Churg-Strauss granuloma" on skin biopsy should not be confused with the diagnosis of Churg-Strauss syndrome. While this type of necrotizing extravascular granuloma may be seen in Churg-Strauss syndrome, it may occur in other systemic autoimmune diseases, including Wegener's granulomatosis and rheumatoid arthritis.

If ANCA are present, they are usually P-ANCA reacting with MPO. The ANCA status appears to correlate with disease activity. Recent studies suggest a more vasculitic disease phenotype in the presence of ANCA, but not all studies have found this, and there remains substantial overlap of organ manifestations between patients with Churg-Strauss syndrome who are ANCA positive and those who are ANCA negative.

In recent years significant attention has been devoted to Churg-Strauss syndrome detected in patients using leukotriene receptor antagonists. Available case studies and limited population-based incidence estimates suggest that these agents may lead to unmasking of vasculitic symptoms in asthmatics, by allowing dose reductions or discontinuation of oral glucocorticoid therapy. There is no evidence suggesting that these agents cause Churg-Strauss syndrome.

The prognosis of Churg-Strauss syndrome is better than that of Wegener's granulomatosis or microscopic polyangiitis, as the overall mortality is lower and not significantly different from the normal population. Most deaths are secondary to cardiac involvement.

Pathophysiology of ANCA-Associated Vasculitis

The etiology of ANCA-associated vasculitis remains unknown. A genetic predisposition for autoimmunity is suspected. An association with the major histocompatibility complex documented for several autoimmune disorders has not been identified in AAV. Nevertheless, skewing in polymorphisms of immune response genes and genes encoding for ANCA target antigens and α_1-proteinase inhibitor with potential effects on disease outcome have been reported.

Many clinical observations suggest that the presence or absence of ANCA as well as the specific type of ANCA (PR3-ANCA versus MPO-ANCA) define the disease phenotype. Patients with limited Wegener's granulomatosis who remain ANCA negative rarely develop systemic vasculitic disease manifestations. Patients with glomerulonephritis and PR3-ANCA loose their renal function much more rapidly than patients with MPO-ANCA. Patients with PR3-ANCA also have a higher relapse rate than patients with MPO-ANCA. Experimental data and animal models support a pathogenic role of ANCA in the development of vasculitis. A couple of recent

studies have also suggested a different clinical phenotype of ANCA-positive patients with Churg-Strauss syndrome compared with ANCA-negative patients.

In Wegener's granulomatosis, the presence of PR3-ANCA appears most closely related to the development of vasculitic complications. Furthermore, systemic vasculitic relapses without recurrence of ANCA are extremely rare. Yet, remission may be maintained for extended periods of time in up to one-half of the patients despite the presence of ANCA. These clinical observations suggest that ANCA alone are not sufficient to cause disease activity, but ANCA seem to be required for the development of vasculitic complications of Wegener's granulomatosis and systemic relapses.

Many in vitro studies have demonstrated proinflammatory effects of PR3-ANCA and MPO-ANCA on neutrophils, monocytes, and endothelial cells, which enhance and perpetuate endothelial cell and tissue damage. ANCA may increase the adhesion of neutrophils to endothelial cells by enhancing the expression of cell adhesion molecules on endothelial cells. ANCA can activate primed neutrophils, resulting in the release of oxygen radicals and proteolytic enzymes. The latter may in turn induce endothelial cell apoptosis. ANCA-mediated neutrophil activation involves both Fc-γ-receptor engagement and recognition of expressed target antigen on the surface of primed neutrophils. ANCA may also cause endothelial cell damage by direct cytotoxicity or localized immune complex formation with target antigens bound to the endothelial cell surface. The latter may initiate localized complement activation. Finally, ANCA are thought to contribute to the recruitment of more inflammatory cells to the area of tissue injury by stimulating the release of chemotactic chemokines and agents from neutrophils, monocytes, and endothelial cells. For a detailed description of pathways and mechanisms by which ANCA may directly and indirectly contribute to damage of the vascular endothelium, the reader is referred to other recent reviews.

Many patients with ANCA-associated vasculitis relate the onset or recurrence of their disease to preceding infectious episodes. The following link to infection has been hypothesized. Most ANCA-mediated effects on neutrophils and monocytes require priming of the cells. This cytokine-dependent process is not unique to vasculitis. Cytokine stimulation of neutrophils and monocytes, typically by tumor necrosis factor (TNF), with resulting increased surface expression of ANCA target antigens, occurs normally in the context of infections. Patients with active vasculitis have indeed been shown to have both increased expression of ANCA target antigens on the surface of their neutrophils and elevated levels of TNF. In combination, these observations allow the hypothesis that neutrophil priming, which occurs in response to cytokine stimulation during infection, enables ANCA to interact with their target antigen on the neutrophil surface. This in turn sets the documented proinflammatory effects of ANCA in motion, which aggravate and perpetuate the inflammatory reaction at the endothelial cell interphase.

Rodent models of MPO-ANCA associated vasculitis support this hypothesis of a pathogenic role of ANCA. They clearly indicate that ANCA contribute directly to the development of vasculitis and glomerulonephritis, and that the interaction of ANCA with its target antigen is required for the development of lesions. Furthermore, the localization of lesions is determined by the site of this interaction. At the same time, animal models support the significance of genetic determinants for the development of autoimmunity, vasculitis, and a specific phenotype with characteristic organ involvement and histopathological features. Finally, animal model studies indicate that infections may be significant disease modifiers. Even though proinflammatory effects of murine PR3-ANCA could also be documented in vivo, the animals did not develop organ pathology typical for Wegener's granulomatosis or microscopic polyangiitis, and good animal model for PR3-ANCA associated vasculitis remains elusive. This may be due to substantial differences between human and murine PR3, as the latter behaves more like human elastase than human PR3.

To date, the causes of the production and persistence of ANCA remain poorly understood. Yet infections may be instrumental for the development of this specific type of autoimmunity. ANCA directed against a broad variety of target antigens have been documented in association with viral, fungal, bacterial, and protozoal infections. In the rare instances of C-ANCA/PR3-ANCA observed in infections, the ANCA disappeared with appropriate antimicrobial therapy. These observations may suggest that ANCA can occur transiently in the setting of infection, and that the persistent ANCA response in patients with vasculitis may be the result of molecular mimicry in susceptible hosts. Subsequent diversification of T- and B-cell responses ("epitope spreading") may lead to responses against different epitopes on the same target molecule (intramolecular spreading) or extend to other molecules (intermolecular spreading).

Bacterial superantigens have also been implicated in the pathogenesis of ANCA-associated vasculitis. Wegener's granulomatosis patients colonized with superantigen-producing *S. aureus* are at high risk for relapse. Wegener's granulomatosis patients had expansion of T cell clones expressing Vβ genes specific for *S. aureus* superantigens more frequently than controls. This supports the theory that *S. aureus* contributes to the pathogenesis of vasculitis. By inducing potent T- and B-cell activity, superantigens produced during an *S. aureus* infection could initiate and maintain both ANCA production and cytokine release, thought to be required for the cascade that results in necrotizing granulomatous inflammation and vasculitis.

Treatment of ANCA-Associated Vasculitis

Treatment of Wegener's Granulomatosis and Microscopic Polyangiitis

The first goal of therapy for patients with ANCA-associated vasculitis is to induce a remission as quickly as possible, so that irreversible organ damage is minimized. To this end, early diagnosis and prompt application of an appropriate immunosuppressive regimen are crucial. At the same time the treatment plan needs to include the prevention of

treatment-related toxicity. Once remission has been induced, the second goal of therapy is to maintain remission with as few side effects as possible. Finally, once the patient has enjoyed a stable remission, surgical interventions aiming to repair damage may proceed as necessary.

Remission Induction Therapy

Remission induction therapy is best tailored to the patient's degree of disease severity, extent, and acuity. Patients who present with indolent Wegener's granulomatosis localized to the upper and/or lower airways and who are ANCA negative can be treated with trimethoprim/sulfamethoxazole (T/S) at a dose of 160/800 mg twice daily. The mechanism of action of T/S is unclear, but possibly related to antimicrobial effects on *Staphylococcus aureus,* the organism most frequently cultured from the nostrils of patients with Wegener's granulomatosis. It is also possible that this agent has some immunemodulatory effects not shared with other antibiotics. T/S monotherapy should never be used alone in the setting of glomerulonephritis or any other severe disease manifestation, and patients treated with T/S need continued long-term observation, as some will later develop more severe disease manifestations requiring immunosuppressive therapy.

Standard remission induction therapy for most patients with limited Wegener's granulomatosis consists of oral prednisone at doses of 0.5 to 1 mg/kg per day (generally not to exceed 80 mg/day) in combination with methotrexate with a target dose of 20 to 25 mg once a week. This dose can be applied orally or subcutaneously. To minimize toxicity and the risk of *Pneumocystis* pneumonia (PCP), this immunosuppressive regimen should be supplemented by folic acid, 1 mg/day and standard PCP prophylaxis.

Standard remission induction therapy for patients with severe disease consists of oral prednisone and oral cyclophosphamide at a dose of 2 mg/kg daily. With this regimen, remission can be achieved in up to 90 percent of patients. To minimize the risk of bone marrow toxicity the dose of cyclophosphamide should be adjusted in patients with impaired renal function, and the patient's complete blood counts need to be monitored at least biweekly for the duration of therapy. Optimal dosing with cyclophosphamide is achieved when the lymphocyte count is reduced, but the total white blood count is maintained above 3500. To avoid bladder toxicity of cyclophosphamide, the entire dose is applied in the morning and patients are instructed to drink at least three liters of fluid per day.

In patients with rapidly progressive fulminant disease, such as those presenting with alveolar hemorrhage or rapidly deteriorating renal function, intravenous methylprednisolone, 1000 mg per day for 3 to 5 days may be necessary for effective control of inflammation. If this therapy does not generate the desired effects, plasma exchange should be implemented.

Remission Maintenance Therapy

Once remission has been induced the prednisone dose is tapered gradually over the course of 5 to 6 months with the goal of complete discontinuation. Patients with limited disease should be maintained on methotrexate for remission maintenance. Patients treated with cyclophosphamide for remission induction should be switched to either methotrexate or azathioprine for remission maintenance. Azathioprine is preferred in patients with any degree of renal insufficiency. Mycophenolate mofetil is an alternative for patients who can not tolerate either methotrexate or azathioprine for remission maintenance. Remission maintenance therapy is continued for at least 12 months beyond achievement of remission, and longer in patients who have suffered relapses. Early discontinuation of immunosuppressive therapy is associated with an unduly high relapse rate. Long-term remission maintenance therapy with T/S beyond immunosuppression may also be beneficial. In one study, patients who received T/S at a dose of 160/800 mg twice daily had a lower rate of disease relapse than those who received placebo.

Treatment of Patients Refractory to Standard Therapy

About 10 percent of patients do not respond adequately to standard therapy and fail to achieve remission. These patients are particularly challenging. Initial enthusiasm about the adjunct use of anti-TNF-α agents in such patients has vanished over the course of the last few years. The Wegener's granulomatosis Etanercept Trial, the first multicenter, double-blind, placebo-controlled, randomized trial conducted in this disease, has shown no efficacy of etanercept when added to standard therapy. Moreover, a higher frequency of malignancies was observed in the treatment arm compared with the control arm of that trial. All patients with malignancies had also received cyclophosphamide. For this reason, the use of etanercept in patients who have received cyclophosphamide is now strongly discouraged. Smaller, uncontrolled open-label studies with infliximab conducted in Europe have suggested some efficacy of that agent, but many complicated infections were observed in these patients. Based on very encouraging preliminary results in patients with refractory Wegener's granulomatosis who were treated with rituximab, which depletes B lymphocytes selectively, a large multicenter trial is currently being conducted that evaluates this agent as a potential alternative to cyclophosphamide for remission induction in ANCA-associated vasculitis.

Supportive Therapy

PCP still carries a mortality of up to 35 percent. Therefore, PCP with T/S is recommended for all non–sulfa allergic Wegener's granulomatosis patients receiving immunosuppressive therapy. Patients who have a sulfa allergy manifesting itself with a skin rash can be desensitized against the drug. Those who fail this approach or have other contraindications for the use of this drug should be given other agents for PCP prophylaxis. Patients receiving methotrexate for remission induction or maintenance should also receive PCP. This can be safely accomplished with T/S at recommended doses for this purpose, provided that folic acid, 1 mg daily, is also given. Patients undergoing intense immunosuppression

during the remission induction phase may also benefit from prophylactic antifungal therapy. Finally, every patient treated with glucocorticoids for ANCA-associated vasculitis should receive osteoporosis prophylaxis with calcium and vitamin D supplements and possibly bisphosphonates.

Treatment of Churg-Strauss Syndrome

Even though mortality of Churg-Strauss syndrome is lower than that of Wegener's granulomatosis or microscopic polyangiitis, the management of Churg-Strauss syndrome remains a challenge. Systemic glucocorticoids remain the mainstay of therapy. There are no clinical trials that provide clear guidance. The reports from the French Vasculitis Study Group are difficult to interpret with respect to this disease, because patients with Churg-Strauss syndrome were not separated from those with polyarteritis nodosa and microscopic polyangiitis, two diseases with distinct clinical manifestations, pathophysiology, and prognosis. Yet, these studies suggest that it is appropriate to treat Churg-Strauss syndrome according to the principles applied to the management of ANCA-associated vasculitis. Accordingly, cyclophosphamide should be added to glucocorticoids for remission induction in all patients with disease manifestations that threaten the patient's life or the function of a vital organ, i.e., particularly those with central or peripheral nerve involvement, glomerulonephritis, heart involvement, or alveolar hemorrhage. Methotrexate, azathioprine, and mycophenolate-mofetil have been used as glucocorticoid-sparing agents in less severe disease and for remission maintenance. Refractory disease and disease dominated by difficult-to-control eosinophilic inflammation may respond to interferon-α therapy. However, continued long-term interferon-α therapy may be necessary, and this treatment carries the risk of substantial toxicity.

OTHER DISORDERS PRESENTING WITH PULMONARY VASCULITIS

Giant-Cell Arteritis

Giant-cell arteritis is a generalized inflammatory disorder involving large and medium-sized arteries. It is the most common form of vasculitis in the white population, and appears to affect predominantly elderly patients. Respiratory symptoms have been reported in up to 25 percent of patients. However, pulmonologists rarely see patients with giant-cell arteritis for the management of its respiratory complications. Cough, hoarseness, and throat pain usually resolve promptly with prednisone therapy. Chest roentgenograms and pulmonary function tests rarely show abnormalities attributable to the disease. Occasionally respiratory symptoms are the initial manifestations of giant-cell arteritis. Therefore, this possibility should be considered in any elderly patient with new onset of cough, hoarseness, or throat pain without other identifiable cause, and it is reasonable to measure the erythrocyte sedimentation rate in such patients. Isolated cases with pleural effusion or multinodular pulmonary lesions have also been reported in giant cell arteritis. Such cases are difficult to interpret. Particularly in the latter situation, Wegener's granulomatosis should be considered in the differential diagnosis, because it may also present with temporal arteritis.

Takayasu's Arteritis

Takayasu's arteritis is a large vessel vasculitis affecting predominantly the aorta and its major branches in young patients. Pulmonary complications are the result of a unique arteriopathy predominantly of the large- and medium-size pulmonary vessels. Progressive defects in the outer media of the arteries and ingrowth of granulation tissue-like capillaries associated with thickened intima and subendothelial smooth muscle proliferation lead to pulmonary artery stenoses and occlusion as well as pulmonary hypertension in up to one-half of all patients. The involvement of pulmonary arteries is common but often asymptomatic. It is detectable by conventional angiography, perfusion scan, or magnetic resonance angiography. CT may show areas of low attenuation as a result of regional hypoperfusion, subpleural reticulolinear changes, and pleural thickening. Fistula formation between pulmonary artery branches and bronchial arteries, as well as nonspecific inflammatory interstitial lung disease, has also been reported.

Therapy for Takayasu's arteritis consists primarily of immunosuppression with glucocorticoids. Other immunosuppressive agents, including methotrexate are used as in conjunction with glucocorticoids for remission induction and as glucocorticoid-sparing agents for remission maintenance. Unfortunately, many patients relapse when the glucocorticoid dose is reduced below 15 mg daily. Most recently, the use of antitumor necrosis factor-α agents has been reported as beneficial in patients who are refractory to standard therapy. Vascular bypass procedures may be beneficial in severe disease.

Classic Polyarteritis Nodosa

Since its formal separation from microscopic polyangiitis, this form of vasculitis affecting predominantly medium-sized vessels is diagnosed rarely. Because it does not affect capillaries, it does not cause either glomerulonephritis or alveolar hemorrhage. However, classic polyarteritis nodosa can affect the bronchial or bronchiolar arteries on rare occasions. Most cases of classic polyarteritis nodosa diagnosed today are associated with viral infections, specifically hepatitis B and C. Consequently, antiviral therapy plays a prominent role in the management of such cases in addition to immunosuppression. Classic polyarteritis nodosa is far less likely to relapse than microscopic polyangiitis, and therefore can generally be treated with a shorter course of immunosuppression.

Behçet's Disease

Behçet's disease is a rare chronically relapsing systemic inflammatory disorder characterized by aphthous oral ulcers and at least two or more of the following: aphthous genital ulcers, uveitis, cutaneous nodules or pustules, or meningoencephalitis. Respiratory manifestations are common in Behçet's disease and include cough, hemoptysis, chest pain, and dyspnea. Hemoptysis is often massive and fatal. The vasculitis of Behçet's disease is immune complex–mediated, and may affect vessels of all sizes. If the veins are affected secondary thrombosis with major venous occlusion can occur. This type of thrombosis may not be preventable by anticoagulation, but the use of aspirin 80 mg/day has been advocated. Massive hemoptysis is the result of destruction of the elastic lamina of pulmonary arteries leading to the characteristic aneurysm formation, secondary erosion of bronchi, and arterial-bronchial fistulae. Pulmonary artery aneurysms are detectable by CT or MR angiography, and pulmonary angiography is no longer necessary. Recurrent pneumonia as well as bronchial obstruction as a consequence of mucosal inflammation has also been described.

Therapy of the underlying disease consists of immunosuppression. Prednisone alone may not be sufficient to control the vasculitis. The addition of other drugs, such as colchicine, chlorambucil, methotrexate, cyclosporin, or azathioprine is recommended. The addition of azathioprine or cyclophosphamide to glucocorticoids has resulted in resolution of pulmonary aneurysms. Once pulmonary arteritis has been identified in these patients, anticoagulation should be avoided. The prognosis of pulmonary involvement is poor. About one-third of patients die within 2 years of developing pulmonary involvement, most from fatal pulmonary hemorrhage. Embolization therapy may be used as treatment and prevention of hemorrhage from pulmonary artery aneurysms.

Idiopathic Pauci-immune Pulmonary Capillaritis

Diffuse alveolar hemorrhage as a result of capillaritis in the absence of symptoms or serologic evidence of any detectable underlying systemic disorder may occur rarely. Direct immunofluorescence studies of the lung tissue did not reveal any immune deposits. This isolated pauci-immune pulmonary capillaritis is histopathologically indistinguishable from that of ANCA-associated vasculitis. It is a diagnosis of exclusion, and such patients are best treated with an immunosuppressive regimen according to the guidelines for severe Wegener's granulomatosis or microscopic polyangiitis.

Systemic Lupus Erythematosus and Other Collagen Vascular Disorders

The disease manifestations of systemic lupus erythematosus (SLE) are highly variable. Pulmonary capillaritis leading to diffuse alveolar hemorrhage is rare in patients with SLE. However, it represents one of the most serious complications

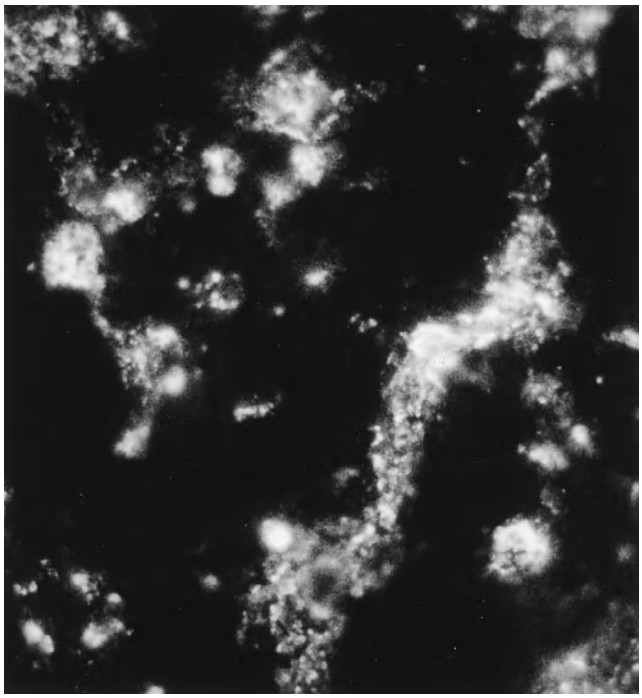

Figure 83-18 Lung biopsy of a patient with lupus erythematosus and alveolar hemorrhage showing so-called lumpy, bumpy deposition of immune complexes as demonstrated by direct immunofluorescence.

of the disease. In contrast to the pauci-immune pathology of ANCA-associated vasculitis, prominent immune complex deposits can be detected by direct immunofluorescence in the affected tissue of patients with SLE (Fig. 83-18). Hence, the development of pulmonary capillaritis in systemic lupus erythematosus is thought to be immune complex mediated. The onset of diffuse alveolar hemorrhage in patients with SLE is usually abrupt, and it is seldom the first sign of SLE. In the overwhelming majority of patients the rapid development of pulmonary infiltrates is associated with fever. Hemoptysis may be absent in up to one-half of the patients. Consequently, the differentiation of diffuse alveolar hemorrhage from infection may be difficult in patients with SLE, and may require a diagnostic bronchoalveolar lavage. Mechanical ventilation, infection, and cyclophosphamide therapy were identified as negative prognostic factors in one cohort. However, no multivariate analysis was performed, and these factors may simply identify patients with more severe disease. The reported mortality from diffuse alveolar hemorrhage in SLE varies widely, between 0 and 90 percent. Treatment consists of glucocorticoids and cyclophosphamide. The use of plasma exchange has been suggested, but its benefit remains unproved.

Respiratory complications are very common in all other types of collagen vascular or connective tissue disorders. However, pulmonary capillaritis presenting as diffuse alveolar hemorrhage is rare. Isolated cases have been reported with polymyositis, rheumatoid arthritis, and mixed connective tissue disease. Consequently, serologic testing performed as part of an evaluation of diffuse alveolar hemorrhage should

include studies aimed at the identification of these potential underlying disease entities.

Antiphospholipid Syndrome

Antiphospholipid syndrome is defined by arterial and venous thromboses, or recurrent miscarriages occurring in patients with antiphospholipid antibodies (anticardiolipin antibodies, lupus anticoagulant, or both). If antiphospholipid syndrome in the context of another autoimmune disease, malignancy, or drug exposure, it is labeled secondary antiphospholipid syndrome. In the absence of other coexisting disorders, it is considered primary. Hypercoagulability can cause pulmonary embolism and infarction, pulmonary microthrombosis, and pulmonary arterial thrombosis with secondary pulmonary hypertension as consequence. However, primary pulmonary hypertension has also been reported in antiphospholipid syndrome. Acute respiratory distress syndrome (ARDS) is another possible complication of antiphospholipid syndrome. Antiphospholipid syndrome can also be complicated by diffuse alveolar hemorrhage, presenting with cough, dyspnea, fever, and bilateral pulmonary infiltrates. Because of this nonspecific clinical presentation, the possible occurrence of diffuse alveolar hemorrhage in the context of ARDS, and the lack of hemoptysis in over one-half of the reported antiphospholipid syndrome patients with alveolar hemorrhage, and early bronchoalveolar lavage may help in the differential diagnosis. Tissue necrosis from microthrombosis as well as pulmonary capillaritis has been implicated as the cause of alveolar hemorrhage in antiphospholipid syndrome. As in SLE, the capillaritis of antiphospholipid syndrome appears to be immune complex–mediated. Most patients respond to glucocorticoids. Yet, the coexistence of thrombosis and capillaritis with alveolar hemorrhage represents a therapeutic dilemma, as anticoagulation may need to be interrupted to control the hemorrhage. Early plasma-exchange in addition to immunosuppressive therapy should be considered in patients with antiphospholipid syndrome and alveolar hemorrhage.

Antiglomerular Basement Membrane Disease

Historically the syndrome of alveolar hemorrhage and glomerulonephritis has been called Goodpasture's syndrome. Today's terminology restricts the use of the term Goodpasture's disease to alveolar hemorrhage or necrotizing glomerulonephritis caused by autoantibodies directed against the NC1-domain of the α3 chain of basement membrane collagen type IV. This epitope is only accessible for autoantibodies in the basement membranes of kidneys and lungs. Diffuse alveolar hemorrhage is common in anti-GBM disease, but is thought to require an additional inhalational injury, particularly smoking for the development of the pulmonary manifestation of this disease. Isolated alveolar hemorrhage in the absence of renal disease is rare in anti-GBM disease. The finding of circulating anti-GBM autoantibodies in the serum may facilitate the early implementation of appropriate therapy. However, methods used for their detection are of highly variable sensitivity and specificity, and a definitive diagnosis depends on the documentation of linear anti-GBM deposits in the kidney or lung (Fig. 83-19). In most patients, tissue from the kidney is more easily accessible for histopathological evaluation than lung tissue. Anti-GBM is arguably not a vasculitis. Bland pulmonary hemorrhage is the most frequently described histopathological pattern in diffuse alveolar hemorrhage associated with anti-GBM disease. However, capillaritis as a secondary histopathological feature has been encountered in some patients. Early implementation of immunosuppressive therapy in conjunction with plasma exchange is the key to a favorable outcome in patients with anti-GBM disease.

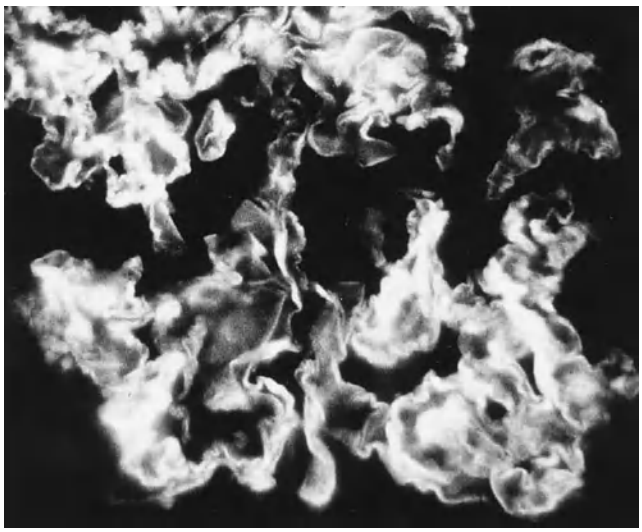

Figure 83-19 Kidney biopsy of a patient with Goodpasture's syndrome showing linear immunofluorescence of the glomerular basement membrane due to fixation of IgG anti-GBM antibodies.

Henoch-Schönlein Purpura

Pulmonary manifestations of Henoch-Schönlein purpura are rare. Only 26 cases have been reported to date, and capillaritis has been documented histopathologically only in a minority of them. IgA deposits along the pulmonary capillary walls, analogous to those found in vessels of the skin and glomeruli of affected kidneys are pathognomonic features of Henoch-Schönlein purpura, detectable by direct immunofluorescence.

Drug-Induced Vasculitis

The list of drugs described in association with vasculitis includes a long list of therapeutic agents as well as drugs of abuse. The clinical spectrum of drug-induced vasculitis ranges from isolated and mild vasculitis of the skin to severe multiorgan system disease. Small to medium-sized vessels are usually affected. Based on clinical manifestations, drug-induced vasculitis cannot be distinguished from the primary vasculitis syndromes.

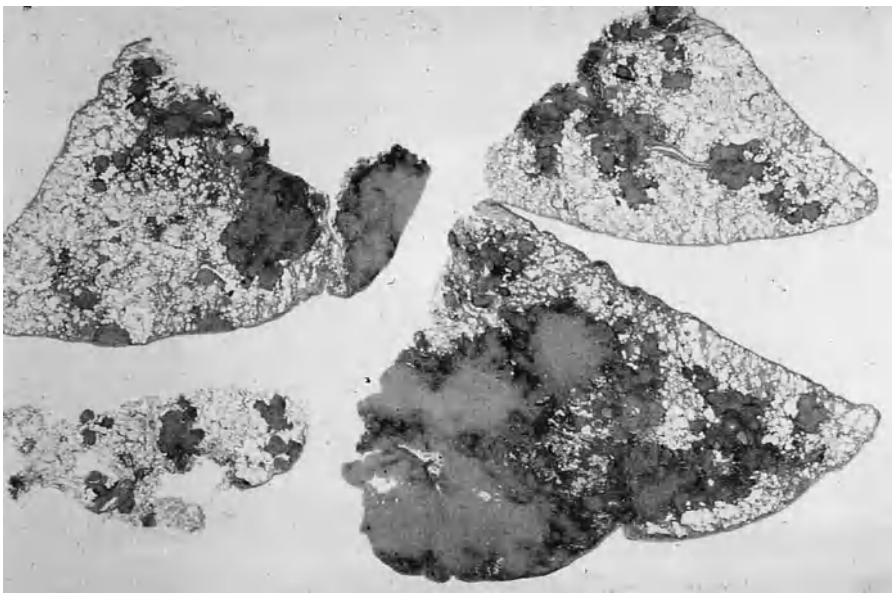

Figure 83-20 Low-power photomicrograph of lung revealing coalescing necrotizing granulomas in a patient with necrotizing sarcoid granulomatosis.

The following drug-induced syndromes merit special attention. First, a variety of drugs including propyl-thiouracil, D-penicillamine, hydralazine, sulfasalazine, minocycline, allopurinol, and others can induce an ANCA-associated vasculitis. Pulmonary capillaritis as a manifestation of an ANCA-associated vasculitis induced by these agents is well documented. Drug-induced ANCA-associated vasculitis should be treated with immunosuppression according to the principles for primary ANCA-associated vasculitis. However, once the offending drug has been eliminated, the likelihood of a relapse seems low.

The use of all-trans-retinoic acid in acute promyelocytic leukemia can cause a syndrome of fever, leukocytosis, fluid retention, hemorrhage, thrombosis, and organ failure. Pulmonary complications of this syndrome are frequent, and pulmonary capillaritis has been reported in this context.

Some chronic nasal cocaine abusers develop severe midline destructive lesions. In its early stage, such a lesion is clinically and histopathologically difficult to differentiate from limited Wegener's granulomatosis, particularly in patients who do not volunteer the history of abuse. The presence of ANCA reacting with human neutrophil elastase appears to be an immunologic marker separating patients with cocaine-induced midline destructive lesions from those with Wegener's granulomatosis.

Pulmonary Capillaritis after Lung Transplantation

Five cases of acute rejection after lung transplantation with prominent pulmonary capillaritis, histopathologically distinct from typical rejection, have been reported. In these cases, the capillaritis was thought to represent a form of severe, acute vascular rejection. Early histologic diagnosis and aggressive immunosuppression, possibly in conjunction with plasma exchange, was suggested to control the inflammatory activity and prevent relapses.

Necrotizing Sarcoid Granulomatosis

Vasculitis is a prominent histopathological feature of necrotizing sarcoid granulomatosis. The disease is usually limited to the lungs. The characteristic pulmonary nodules are bilateral, and may be an incidental finding in asymptomatic patients. Alternatively, patients may complain of cough, dyspnea, or phlegm production. Generalized constitutional symptoms occur rarely. The differential diagnosis of necrotizing sarcoid granulomatosis includes primarily infectious processes. Special sputum and tissue stains and cultures should always be obtained to exclude mycobacterial or fungal disease. Clinically, these patients are difficult to differentiate from limited Wegener's granulomatosis. Histopathologically, there are characteristic necrotizing epithelioid granulomas that may form aggregates (Fig. 83-20). In contrast to Wegener's granulomatosis, these granulomas are well circumscribed. Vasculitis is a central histopathological feature of necrotizing sarcoid granulomatosis. Liebow originally described three types of vasculitis: an epithelioid-granulomatous form, a form reminiscent of giant-cell arteritis with prominent histiocytes and multinucleated giant cells in the inflammatory infiltrate of the vessel wall, and a lymphocytic form lacking granuloma formation and giant cells. The separation from sarcoidosis remains controversial. Yet, the extensive vasculitis and necrosis seen in necrotizing sarcoid granulomatosis are unusual for sarcoidosis. The chest roentgenographic appearance of pulmonary nodules, or masses and pleural involvement are also atypical for sarcoidosis. Finally, extrapulmonary involvement has only rarely been documented in necrotizing sarcoid granulomatosis.

It is debatable whether necrotizing sarcoid granulomatosis should be included with the systemic vasculitides.

Most authors would argue against this inclusion because of its limitation to the lungs and good prognosis (spontaneous remission may occur). Therapeutically, necrotizing sarcoid granulomatosis can be approached as cases with chronic pulmonary sarcoidosis. Decisions about the use of oral glucocorticoid therapy should be individualized based on symptoms, pulmonary function data, and their evolution over time.

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84

Pulmonary Arteriovenous Malformations

Daniel M. Goodenberger

HISTORY

Pulmonary arteriovenous malformations (PAVMs) were first described relatively recently in medical history; Churton reported the autopsy findings in a young boy with cyanosis in 1897. PAVMs were first diagnosed during life in 1939. As in many later cases, clubbing and polycythemia were present in a 40-year-old man. Based on the correlation of physical with postmortem findings, the triad of cyanosis, clubbing, and polycythemia was identified with PAVM in 1932. Hereditary hemorrhagic telangiectasia (HHT) was first connected to pulmonary arteriovenous malformation in 1938.

As described in the following, HHT is often intimately related to PAVMs—a fact that prompts the subsequent discussion of the history of HHT.

Hereditary epistaxis was first described in 1864, although neither that nor Babbington's description a year later reports an association with telangiectasia. These reports were not generally recognized; nor were subsequent descriptions of telangiectasia, hereditary transmission, and epistaxis by Legg in 1876, or a similar kindred reported by Chiari in 1887. The first widely recognized connection of epistaxis to telangiectasia was made by Rendu in 1896. Osler added three cases, and recognized familial occurrence in 1901. Weber elucidated the familial nature and lack of coagulation abnormality, and thus earned his eponymic association. By precedence of description, this eponym should be Rendu-Osler-Weber, even though Osler-Weber-Rendu is the most common usage. Hanes was responsible for naming the syndrome hereditary hemorrhagic telangiectasia, the designation now most often preferred, in 1909.

PATHOPHYSIOLOGY

Structure

By far the most common form of PAVM has a pulmonary arterial supply and pulmonary venous drainage. In one series, 60 of 63 PAVMs had a pulmonary arterial blood supply. This is similar to our experience, although we have been consulted on two patients with PAVMs in whom the arterial supply originated from the internal mammary artery. Approximately 80 percent of PAVMs have a single feeding and a single draining vessel; the remaining 20 percent are complex, with two or more of each. PAVMs appear to develop between precapillary arterioles and venules, with intervening epithelial dysplasia. After development, they are clusters of dilated,

tortuous vessels with both arterial and venous elements with no intervening capillary beds.

Number

In one series, more than one-third of the patients had two or more PAVMs. In general, multiple PAVMs correlate with HHT; in the experience of our clinic, most patients with HHT have more than one PAVM. A small percentage have diffuse, multilobar PAVMs.

Size

PAVMs may vary from malformations too small to be seen by radiography or angiography to those greater than 5 cm in diameter.

Location

Up to 65 percent of PAVMs are located in the lower lobes—a phenomenon that may be due to the increased pulmonary blood flow and pressure, and subsequent "stretch" due to hydrodynamic forces. This location is probably the cause of the often associated orthodeoxia (desaturation in an upright position) and platypnea (dyspnea in an upright position). These symptoms may also occur with cirrhosis, which evidences the pulmonary vascular abnormalities described in the following. Location may also account for an increase in right-to-left shunt which occurs at total lung capacity. PAVMs have been observed to increase in size during pregnancy (Fig. 84-1). This supports the blood flow hypothesis, due to the increased blood volume and hyperdynamic state of pregnancy, although endocrine factors may also have an influence.

Causes and Disease Associations

Early observers thought that all PAVMs were due to HHT. The estimates of frequency of PAVMs due to HHT have varied substantially, from 36 to 95 percent.

Estimates of the percentage of patients with HHT who have associated PAVMs have varied widely. Various series have reported frequencies of 15, 20, 24, 33, 49, and 57 percent.

As noted, the proportion of PAVMs that are multiple has been reported to be approximately one-third; multiple PAVMs are highly associated with HHT. Of note is that the homozygous form of HHT appears to be lethal, resulting either in miscarriage or neonatal death, associated with explosive growth of mucocutaneous telangiectasias and diffuse PAVMs.

Other Associations

Cirrhosis may result in diffuse small arteriovenous connections. Nearly all such patients have cutaneous spider angiomas. The right-to-left shunt is probably due not to true PAVMs but, rather, to vasodilation of pleural vessels, which resemble the cutaneous spiders, and increased numbers of peripheral small arteriolar branches with precapillary arteriole-to-venous connections in the peripheral respiratory lobule. As many as 44 to 60 percent may have positive contrast echocardiography indicative of intrapulmonary shunt; many of these patients have shunt eliminated by liver transplantation. A PAVM of significant size, known as a Rasmussen aneurysm, may also develop as a result of tuberculosis. Metastatic thyroid carcinoma, a highly vascular tumor, may mimic pulmonary arteriovenous fistula.

GENETICS

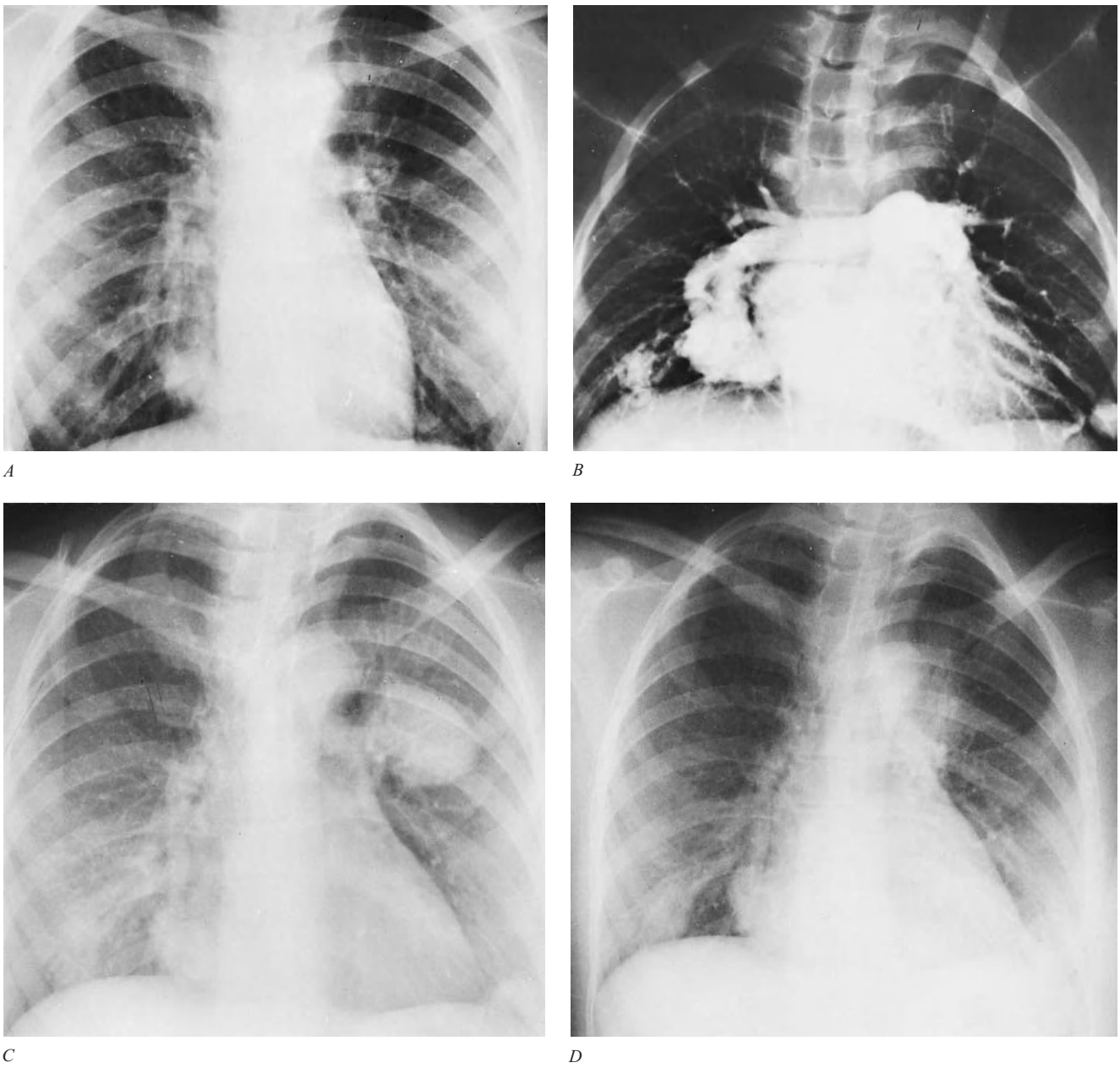
The genetic basis, if any, of isolated PAVMs remains unknown. HHT is an autosomal dominant disease. Its frequency was believed until relatively recently to be less than 3 per 100,000 people. Newer studies suggest a much higher prevalence. The highest frequency reported, 1:1331, occurs in the Afro-Caribbean population of the Netherlands Antilles, presumably due to a founder effect. Other estimates vary geographically; 1:6410 in Denmark, 1:8,000 in Japan, and 1:16,500 in Vermont. Phenotypic variation is extreme, ranging from asymptomatic to severely symptomatic, and from cases with no or few mucocutaneous lesions to those with diffuse cutaneous telangiectasias. For many patients, the disease remains undiagnosed by their primary care physicians, suggesting that disease frequency may be greater than reported, and that some patients with "isolated" PAVMs may actually have HHT.

A gene for HHT was first localized to chromosome 9, region q^{33-34} (9 q^{33-34}). Investigation revealed the protein product to be endoglin, which associates with different signaling receptors and can modify TGF-β-1 signaling. The same work showed the disease to be genetically heterogeneous, with multiple mutations in the responsible gene. It rapidly became clear that there were other chromosomal mutations resulting in the same syndrome, and the endoglin mutation disease was designated HHT-I. It was noted to be associated more often with PAVMs than were those with non-$9q^3$ mutations. A haploinsufficient mouse model also demonstrated phenotypic heterogeneity that was very dependent on the genetic background.

The activin receptor-like kinase 1 gene (ALK-1 or ACVRL1) on chromosome 12 is the second locus for hereditary hemorrhagic telangiectasia. It produces a transforming growth factor (TGF)-β superfamily type I receptor. Mice heterozygous for a loss-of-function mutation in ALK-1 develop age-dependent vascular lesions in the skin, extremities, oral cavity and in the lung, liver, intestine, spleen and brain, similar to those seen in HHT patients. Disease resulting from mutations in this gene has been designated HHT-2.

A small number of patients with juvenile polyposis also have hereditary hemorrhagic telangiectasia.This appears to be due to mutations in MADH4 (encoding SMAD4); SMAD proteins influence the cellular response to TGF-β.

A fourth gene abnormality producing clinical HHT in a family on has been described on chromosome 5. The gene product is as yet unidentified.



A *B*

C *D*

Figure 84-1 Pulmonary arteriovenous fistulas in a pregnant 24-year-old woman with hereditary hemorrhagic telangiectasia. *A*. Before pregnancy. Small nodular densities are seen at both bases and in the left hilus. The shunt was estimated to be 49 percent of the cardiac output. *B*. Arteriogram before pregnancy demonstrates arteriovenous fistulas of both lower lobes. *C*. Seven months pregnant, the patient was admitted to the hospital with hemoptysis and left hemothorax. The enlargement of the arteriovenous fistulas is striking. The pregnancy was terminated. *D*. Two weeks after termination of pregnancy, the nodular densities have decreased in size. *(Courtesy of Dr. M. Rossman.)*

A fifth genetic abnormality in a family with HHT has been described on the short arm of chromosome 7. The gene product of this mutation is also unknown at present.

Most HHT appears to be caused by mutations in endoglin and ALK-1. Mutations can be identified in up to 88 percent affected individuals; in one series, 61 percent were in endoglin, 37 percent in ALK-1, and 2 percent in MADH4. ALK-1 mutations appear to be more common in France and Italy, with endoglin mutations more frequent in northern Europe and North America. Pulmonary arteriovenous malformations are more frequent and on the average of larger size in HHT1.

CLINICAL PRESENTATION

The occurrence and frequency of symptoms related to PAVMs depend on how the patients are found; that is, whether they

present with manifestations of disease or they are discovered as a result of screening. The asymptomatic state is most common when screening is the method of detection, with an incidence typically between 25 and 59 percent.

The age at onset is usually in the third or fourth decade. The mean age at detection in various series is remarkably constant at 38 to 40 years. In one series, the patients ranged in age from 5 to 76 years, with a mean of 36; 26 percent presented at an age less than 21 years.

However, PAVMs are uncommon in childhood; only 4 percent of affected persons are under 10. Twenty-five to fifty-eight percent of patients are asymptomatic. Pulmonary symptoms include dyspnea on exertion, with a frequency ranging from 27 to 71 percent. Platypnea and orthodeoxia also may occur. Hemoptysis ranges in frequency from 4 to 18 percent. Extrapulmonary symptoms include chest pain in 6 percent and epistaxis (largely seen in HHT), ranging from 32 to 85 percent. The mean age at onset of epistaxis in HHT is 12 years, with 54 percent of patients presenting by age 10. Severity of epistaxis ranges from mild to severe, with up to 45 episodes per month. Headache is also remarkably common in HHT patients, occurring in 43 percent. Transient ischemic attack occurs in up to 57 percent of patients with PAVM, and symptomatic cerebrovascular accident in 18 percent.

Physical signs caused by the PAVM itself are relatively uncommon. As many as 25 percent of patients may exhibit no findings at all. Hypoxemia, when present, is secondary to the right-to-left shunt, and may result in cyanosis and secondary polycythemia. This tends to occur in advanced disease, and has been reported in 9 to 73 percent (mean, 30 percent). The frequency of clubbing has been reported in an average of 32 percent; it is much less common in our experience. Clubbing is nearly always associated with cyanosis. Clubbing may resolve after the PAVM is removed or occluded. A pulmonary bruit, which is often described, is also variable; its frequency, probably influenced by selection bias, ranges from less than 10 percent to 58 percent.

Telangiectasia have been reported in up to 66 percent of patients with PAVM, depending on the frequency of HHT. These small red vascular blemishes occur most frequently on the face, followed in descending order by the lips, nares, tongue, ears, hands, chest, and feet. They often increase in size and number with age, and cutaneous telangiectasias are seldom identifiable until the second or third decade. We have been struck by the frequency with which classic tongue and lip telangiectasias have been passed off as nonspecific blemishes by primary care physicians.

Laboratory results are nonspecific. A complete blood count may show polycythemia, although this tendency may be overshadowed by iron deficiency anemia in patients with HHT. Anemia was present in 94 of 292 (34 percent) in our series. This was more often due to GI bleeding when severe. GI blood loss of variable severity was present in 65 of 292 (22 percent).

The severely affected person may have arterial hypoxemia at rest; those less severely affected may have orthodeoxia documented by supine and upright arterial blood gases. Arterial blood gases, determined on blood samples drawn while the patient is breathing room air, followed by 100 percent oxygen, may reveal a significant right-to-left shunt.

CLINICAL DIAGNOSIS

Early in the history of this disorder, the diagnosis was made only when it was advanced, when polycythemia and clubbing were present, or after death. Currently, making the diagnosis requires clinical suspicion in the appropriate clinical setting. Diagnosis is approached differently in the two most common situations.

Evaluation of a Radiographic Abnormality

Earlier techniques for determining that a pulmonary nodule detected as an incidental finding was a pulmonary arteriovenous malformation were principally radiographic. Fluoroscopy might reveal the nodule to be pulsatile; a Müller maneuver might cause the lesion to decrease in size, and a Valsalva maneuver might cause it to increase in size. Laminography typically revealed the lesion to be a grapelike cluster, with visible feeding and draining vessels.

Computed tomography (CT) scan of the chest with contrast enhancement may show the typical lesion with feeding and draining veins (Fig. 84-2), but vascular tumors may cause false-positive results. A perfusion lung scan may detect a right-to-left shunt. Ordinarily, 95 percent of the technetium-labeled macroaggregated albumin, with an average diameter of approximately 35 μ, is trapped in the pulmonary capillaries. When there is an intracardiac or intrapulmonary shunt, unusually large amounts may pass through the lung and travel to the brain and kidneys, resulting in excess radioactivity in those areas. However, this method cannot differentiate intracardiac from intrapulmonary shunt.

Echocardiography, using indocyanine green as a contrast material, was found to be effective in the diagnosis of intrapulmonary shunt, with delayed appearance of the contrast material in the left side of the heart. This was rapidly improved by the use of agitated saline as contrast (Fig. 84-3). The intrapulmonary nature of the shunt can be determined by the delay, averaging four to five cardiac cycles, of left heart contrast appearance; when the echo is performed transesophageally, the region of a radiographically undetectable PAVM may be inferred by the appearance of contrast in one or another pulmonary vein. If contrast echocardiography is negative, a PAVM is very unlikely, and an alternative cause of the pulmonary nodule should be sought. On rare occasions, if the PAVM is fed by a systemic artery, the contrast echocardiogram is negative, and pulmonary angiography should be undertaken if suspicion is high. If the contrast echocardiogram is positive, the definitive test is pulmonary angiography. Angiography is 100 percent sensitive in our experience, with correct application of the appropriate views, for vessels of 2 mm or more. However, experience elsewhere has not always been concordant with ours (vide infra).

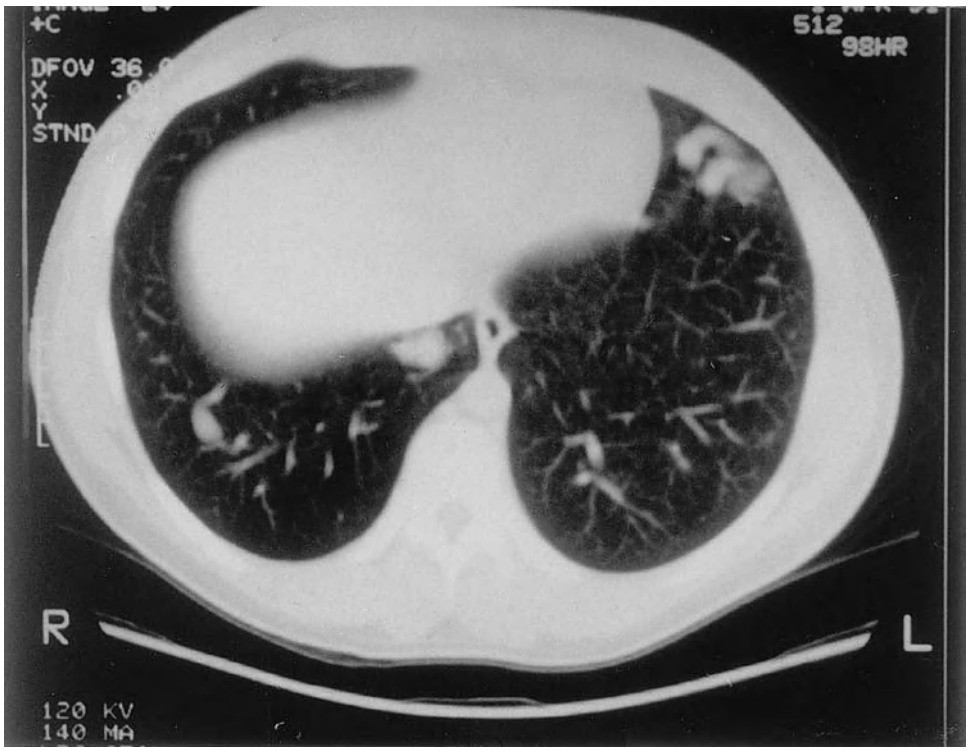


Figure 84-2 Characteristic CT image appearance of PAVM in left hemithorax. Portions of two PAVMs are seen in right hemithorax.

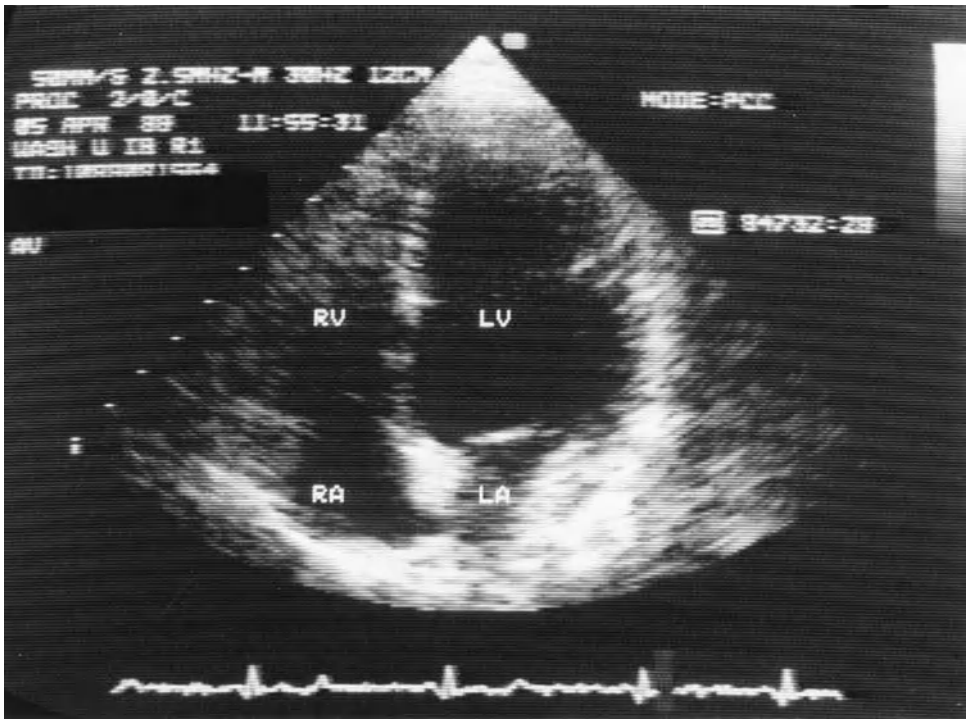
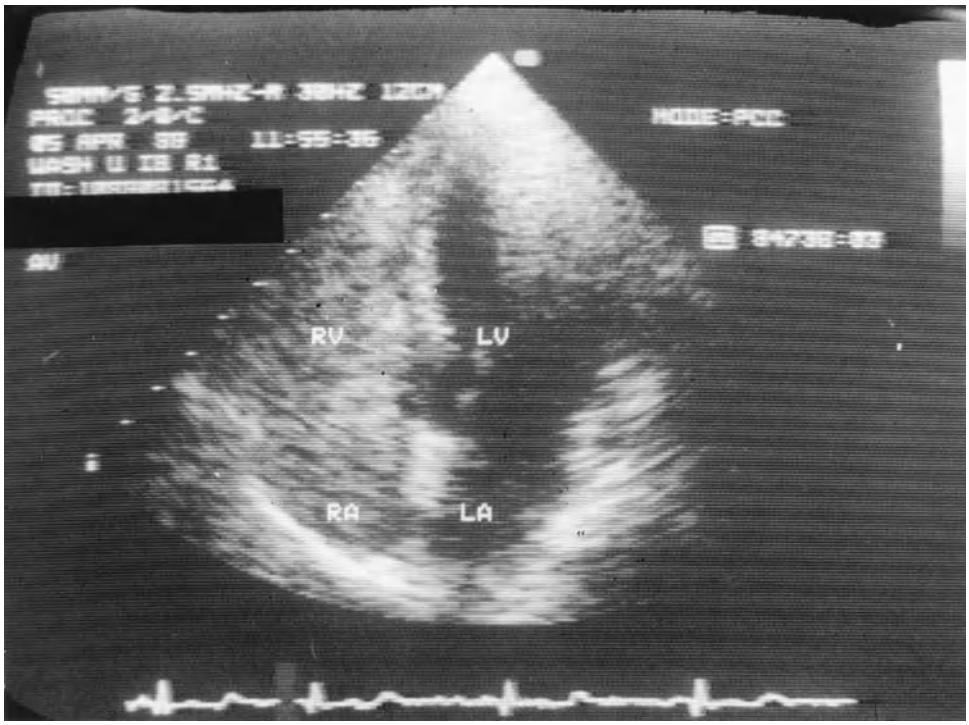


Figure 84-3 Echocardiographic images using saline contrast: *A*. Before contrast. *B*. Right-sided chamber opacification. *C*. Delayed high-degree left-sided chamber opacification indicative of large intrapulmonary shunt.



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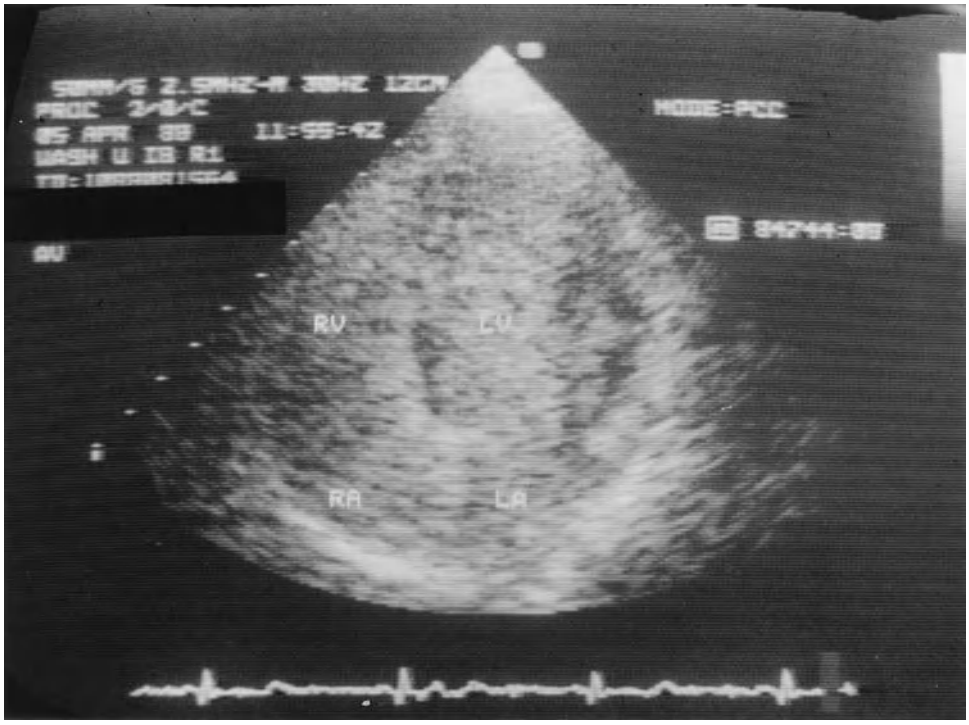


C

Figure 84-3 (*Continued*)

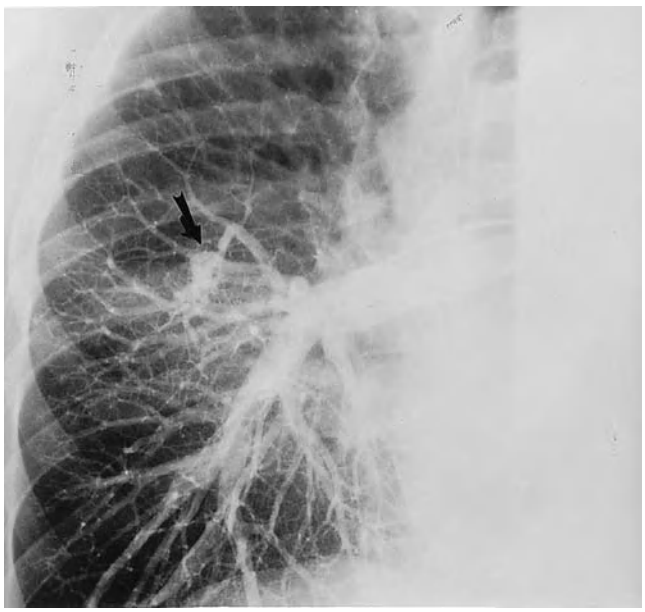


Figure 84-4 Example of PAVM not seen on standard chest radiography. Right pulmonary angiogram showing small PAVM (arrow).

Screening of Probands or Relatives

Because the majority of PAVMs occur in HHT, it is important to evaluate individuals with PAVMs for HHT, and to screen individuals with HHT for PAVMs. Criteria for diagnosis of HHT include: (1) spontaneous and recurrent epistaxis; (2) multiple characteristic telangiectasia (typically found on lips, tongue, malar eminence, pinnae, and digits); (3) visceral lesions (gastrointestinal telangiectasia with or without gastrointestinal bleeding, pulmonary arteriovenous malformations, hepatic arteriovenous malformations, and cerebral arteriovenous malformations); (4) family history with a first-degree relative with HHT. In addition, relatives of patients with HHT should be evaluated for that diagnosis and screened for PAVMs.

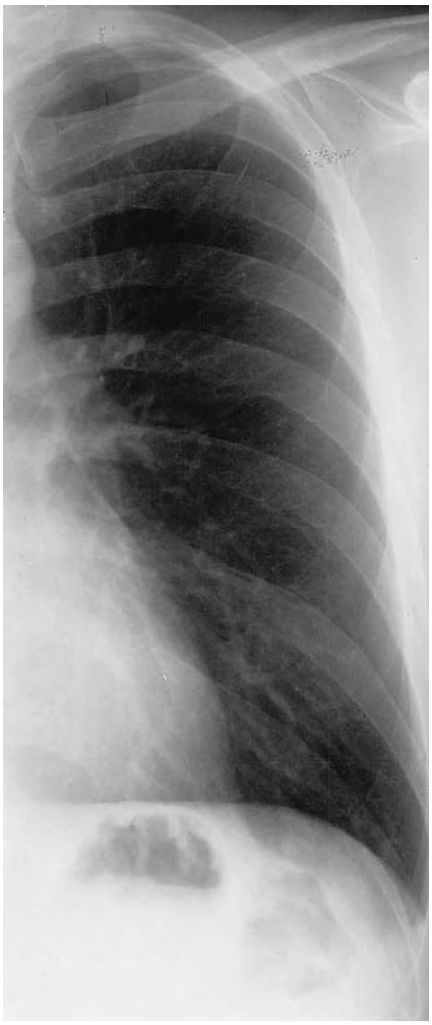
The best approach to screening is a subject of considerable discussion in the literature, and the approach at HHT centers of excellence varies somewhat. The discussion that follows summarizes the evidence for various screening tests, and is followed by a description of the approach at the Washington University HHT Center.

The reported sensitivity of chest radiographs varies widely, depending on whether they are used for screening or in patients with symptomatic disease. Rates of abnormality on the chest radiograph range from 41 to 100 percent. In our experience, chest radiography does not reliably detect PAVMs less than 20 mm in size (Fig. 84-4), and it may miss larger PAVMs when they are located in radiographically inopportune places, such as the costophrenic sulci, the retrocardiac region, or the proximal hila (Fig. 84-5).

The sensitivity and specificity of chest CT are unknown, although this modality appears to be more sensitive than are chest radiographs. One early study suggested that CT enabled identification of more than 98 percent of PAVMs and was superior to pulmonary angiography. CT has also been advocated for pre-therapy planning. Our experience has been somewhat less favorable; among 15 patients with CTs showing PAVMs, 20 percent had PAVMs missed, representing 42 percent of PAVMs in those patients. CTs interpreted as negative were falsely negative in 6 of 9 patients, representing 10 PAVMs.

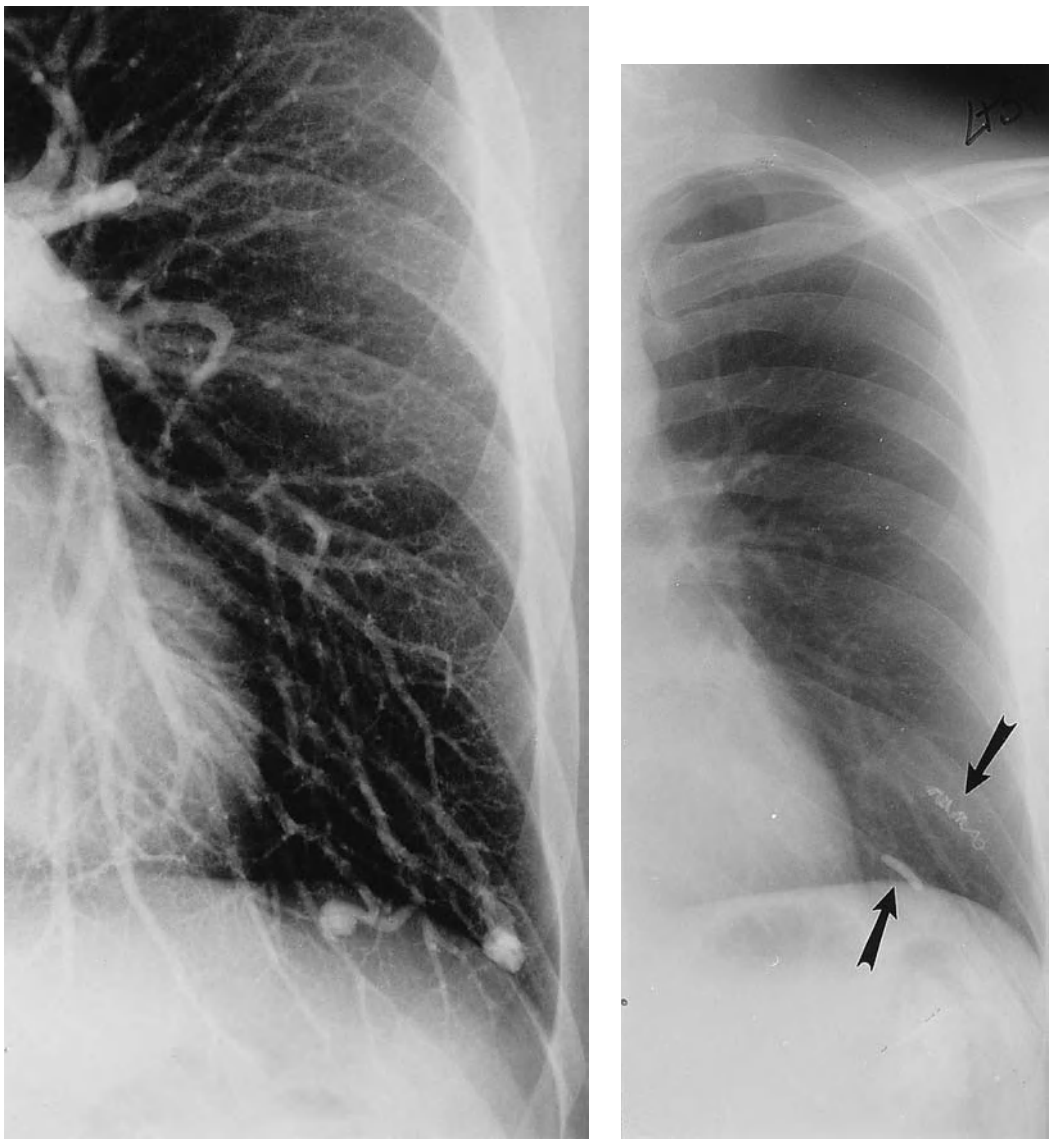
Gradient-echo magnetic resonance imaging (MRI) shows promise, but it can mistake tumors for PAVMs. Gadolinium contrast-enhanced pulmonary magnetic resonance angiography (CEMRA) detected 79 percent of PAVMs found by helical CT, and all of those with a feeding artery diameter of at least 3 mm (i.e., PAVMs with clinical consequences).

Arterial blood gases, determined on samples drawn while the patient is supine and upright, have been advocated for screening. However, this technique has not proved



A

Figure 84-5 Example of patient with PAVMs that were not seen on standard radiography but were detected by echocardiographic screening: *A*. Before embolization. *B*. Angiogram. *C*. After embolization, showing both coil and balloon emboli.



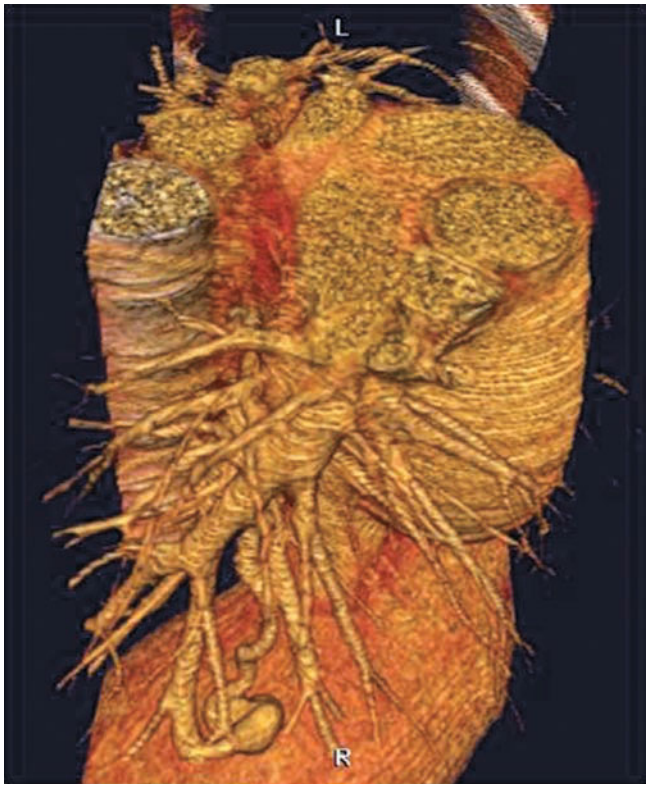
B *C*

Figure 84-5 (*Continued*)

useful. Various combinations of shunt measurement using albumin microspheres labeled with ^{99m}Tc, Pa_{O_2} on room air, shunt measurement in subjects breathing 100 percent oxygen, and erect oxygen saturation measurement have been used, but all have insufficient sensitivity, specificity, or both.

Contrast echocardiography is more sensitive than symptoms, plain radiography, measurements of Sa_{O_2}, Pa_{O_2} on room air, and Pa_{O2} breathing 100 percent oxygen. It is positive in 55 to 73 percent of patients. and may be the only positive screening study in 31 percent of patients. Up to 80 percent have persistently positive contrast echo findings after undergoing embolotherapy. In patients with diffuse small PAVMs or telangiectasia, transephogeal contrast echocardiographymay provides the definitive evidence. Based on this information, a screening algorithm based on contrast echocardiography and anteroposterior chest radiograph, followed by chest CT if either test is positive, is used in many centers. This algorithm is based on studies in which CT without contrast was used as the gold standard, with confirmatory pulmonary angiogram only if positive.

However, for many years our center has followed a scheme in which patients with HHT are screened with saline contrast echocardiography. Those with positive findings undergo pulmonary angiography. This approach identified PAVMs in 57 percent of patients screened. In combination with our observations regarding false-negative chest CT, we believe the frequency of PAVMs identified greater than in any other series justifies this approach. In approximately 15 percent of patients with angiographically detectable PAVMs using this approach, no therapeutic embolization results. These PAVMs represent an opportunity to more fully understand the natural history and complication rates of PAVMs.



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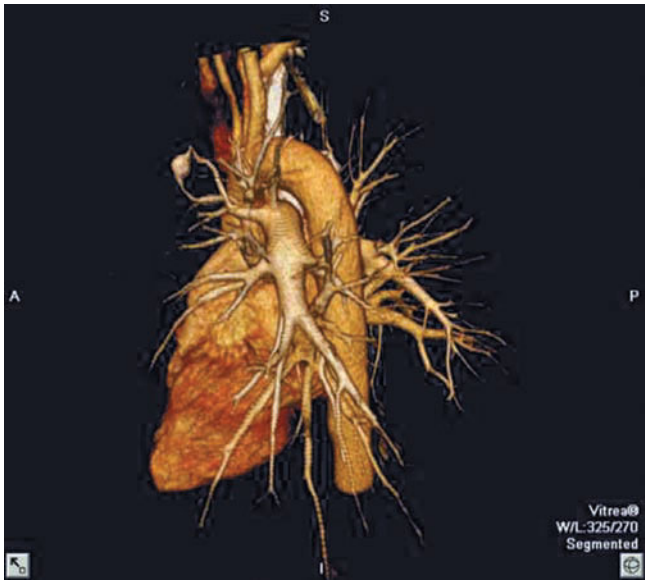

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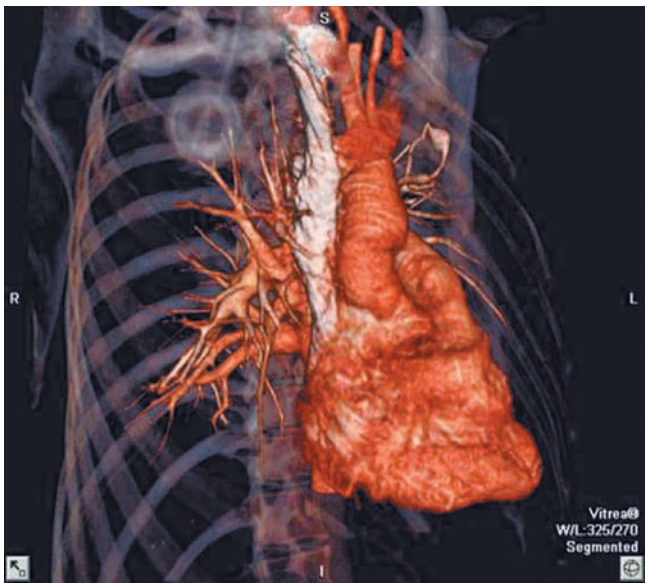


C

Figure 84-6 *A–C* Three-dimensional reconstruction of PAVMs on 64-row multidetector array CT.

Technology is having an impact on this approach. 64-row multi-detector array chest CT with reconstruction is under evaluation in our center as an alternative to angiography. Preliminary results in more than 60 patients suggests that this technique is at least equivalent to pulmonary angiography (Fig. 84-6).

COMPLICATIONS

Pulmonary Complications

Significant hemoptysis occurs in fewer than 10 percent of patients; in our most recent series, it occurred in 5 of 142 (less than 4 percent). Two of five occurred during pregnancy. It may be massive and life threatening. Bronchial telangiectasias may be the cause, but all cases in untreated patients in our experience have been due to PAVMs. An increasingly frequent problem in recent years is hemoptysis following extensive embolotherapy after a delay of months to years. This has generally been due to post-embolization bronchial collateral formation.

Hemothorax has been reported in up to 9 percent of patients, but is usually less than 2 percent. Pregnancy may cause PAVMs to enlarge, and has been associated with hemothorax on several occasions. Hemothorax may also occur without any other predisposing factors, presumably caused by rupture of large subpleural PAVMs into the pleural space.

Pulmonary hypertension is uncommon. Patients with PPH in HHT have ALK-1 mutations rather than mutations in the bone morphogenetic protein receptor type II (BMPR2) gene.

Central Nervous System Complications

The pulmonary capillary vascular bed appears to be an important filter for otherwise asymptomatic small emboli, and may also have a significant role in cleansing the bloodstream during transient bacteremias. Most neurologic complications, which occur in 8 to 12 percent of patients with HHT, are complications of PAVMs. In one series, 60 percent were due to PAVM, including brain abscess, paradoxical embolus, and hypoxemia.

Transient ischemic attacks occur in approximately 37 percent of patients with PAVMs. PAVMs can cause symptomatic cerebrovascular accidents (Fig. 84-7); the frequency of this complication ranges from 6 to 27 percent. In our clinic, 28 of 132 patients screened by MRI had evidence of prior paradoxical embolic stroke. Unfortunately, paradoxical embolization to the brain may be the first manifestation of an occult pulmonary venous malformation. This has been a particularly regrettable repetitive problem in young women taking oral contraceptives while smoking.

Brain abscess occurs in 3 to 10 percent of patients with PAVMs. In a series in our clinic, 5/132 (4 percent) had prior brain abscess. Up to 1 percent of HHT patients may have brain abscesses (1000 times the incidence in the general population). In one series, 5 of 31 patients had recurrent abscess; in another, 6 of 128. Up to 8 percent of brain abscesses in the general population may be due to PAVMs. Unfortunately, brain abscess may also be the first symptom of an occult PAVM (Fig. 84-8), and many years may elapse before diagnosis of PAVM (Fig. 84-9). Most occur following dental work. For that reason, antibiotic prophylaxis following the standard American Heart Association protocol for prevention of endocarditis is recommended.

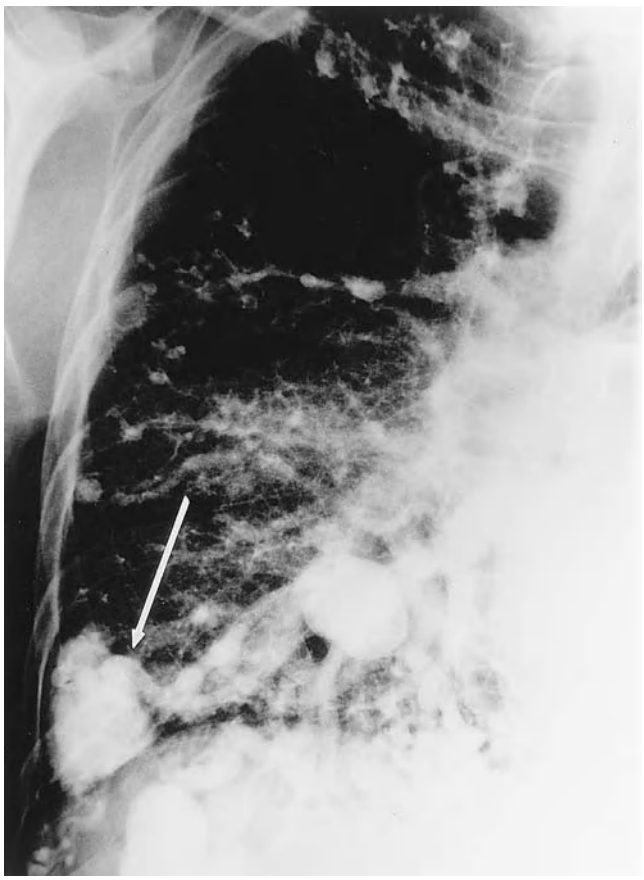


Figure 84-7 Right-sided pulmonary angiogram showing multiple PAVMs in a middle-aged man with clubbing, polycythemia, and CT evidence of several prior strokes.

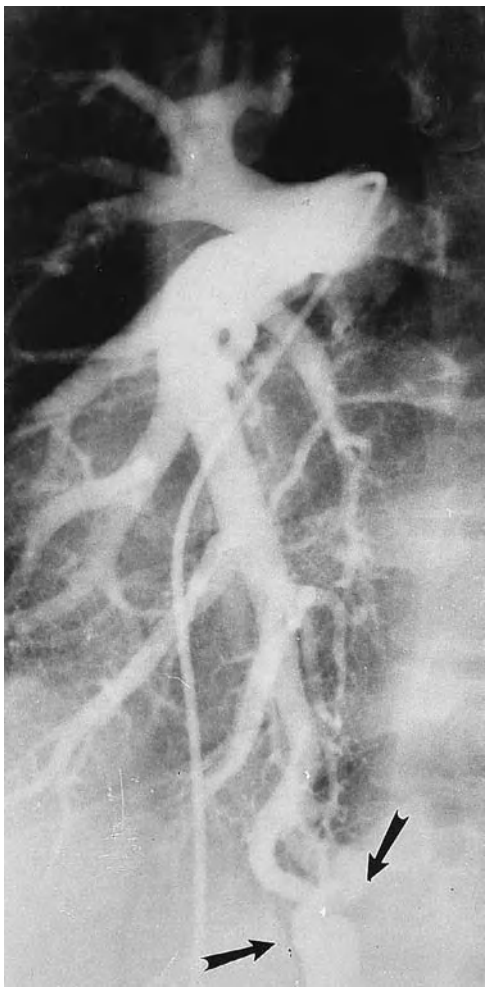


Figure 84-8 PAVM detected in patient with HHT after initial presentation with brain abscess: The pulmonary angiogram and lateral chest radiographs were read as normal on several examinations. Right pulmonary angiogram with inferomedial PAVM (arrows).

Migraine is more common in HHT than in the general population, and appears to be more common in those with PAVM. In one series, migraine occurred in 88 patients with HHT, a prevalence of 16.4 percent. The prevalence of migraine in patients with PAVM was 21.2 percent, which was significantly higher than in patients without PAVM (13.3 percent). In our experience, migraines occurred in 74/292 (25 percent) with HHT.

Cerebral AVMs occur in up to 5 percent of patients. Cerebral arteriovenous malformations (CAVMs) occur in 4 to 8 percent of patients with HHT and tend to run in families.

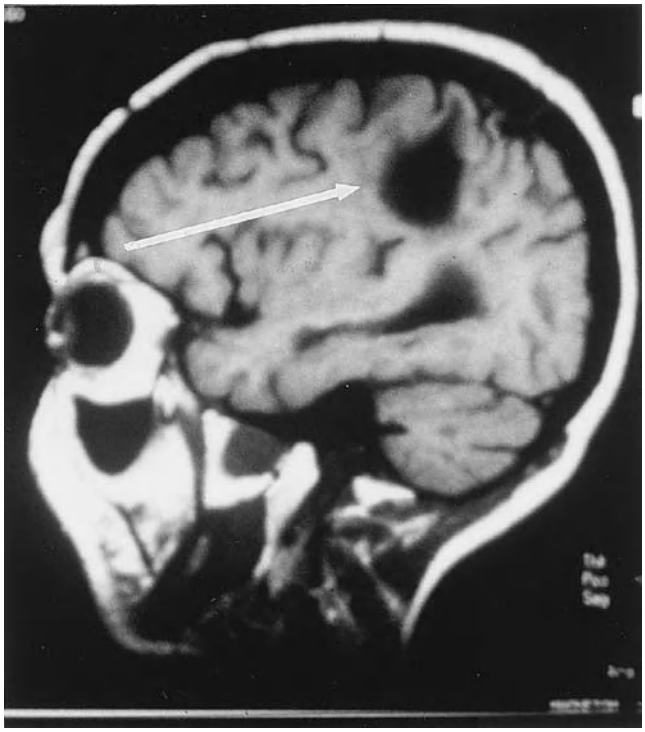


Figure 84-9 MRI showing brain abscess residua in patient whose brain abscess preceded diagnosis of pulmonary arteriovenous fistula by 17 years.

Although CAVMs are not complications of PAVMs, they occur more frequently in patients with endoglin mutations, as do PAVMs. In our series of 149 patients screened by MRI, 11 had CAVM (7 percent). An additional 16 (11 percent) had telangiectasia or venous angioma (11 percent). Although some have argued that the complication rate does not warrant routine screening, the hemorrhage rate in individuals with cerebral AV malformations appears to be 1.4 to 2.0 percent annually, comparable to figures in the non-HHT population with cerebral AV malformations. Cerebral MRI is currently the most sensitive non-invasive test, although it will fail to detect a significant proportion of AVMs. Some authors believe MRI should not be performed in patients with pulmonary AVMs embolized with non-MRI compatible coils; however, we have performed many cerebral MRI examinations in such individuals without complications, with the caveat that the MRI is not done for a minimum of 6 weeks after embolotherapy.

Miscellaneous Complications

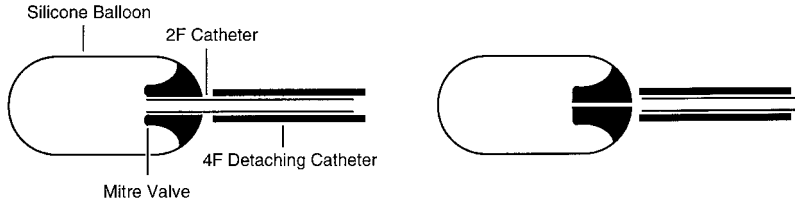
The other complications that may be associated with PAVMs are those connected with HHT. Epistaxis is the most common bleeding manifestation. It occurs in up to 85 percent of patients, with 10 percent having little or no bleeding and approximately 30 percent each suffering from mild, moderate, or heavy bleeding. GI bleeding, which tends to occur later in life, occurs in approximately 20 to 25 percent of patients. Genitourinary and intracerebral bleeding occurs in less than 10 percent each.

AVMs may also occur in the liver. The most common manifestation is high-output heart failure. This may result in pulmonary hypertension associated with elevated left-ventricular end-diastolic pressure; this must be differentiated from primary pulmonary hypertension. During a 9-year period between 1997 and 2006, 346 patients with HHT were evaluated at the Washington University HHT center. Of these patients, 17 (4.9 percent) were found to have high output cardiac state: 13 due to hepatic AVMs. Other presentations include manifestations of portal hypertension, such as ascites or variceal bleeding, and manifestations of biliary disease, such as an elevated alkaline phosphatase level and abnormalities on bile duct imaging. Ischemia related to shunting may result in noncirrhotic fibrous nodules (telangiectasia-associated hepatic fibrosis or pseudocirrhosis). On rare occasions, this may result in liver failure. In one series, hepatic AVM occurred in 17 percent of patients with ALK-1 mutations. Liver transplantation may be lifesaving.

TREATMENT

Early treatment of PAVMs consisted of thoracotomy and resection. The first successful surgical approach was pneumonectomy, reported in 1942. As thoracic surgery improved, the extent of surgery diminished; by 1959, local excision was the procedure of choice. Surgical removal of a PAVM inevitably results in loss of viable lung tissue, a problem for patients with multiple PAVMs; the record is probably held by a patient who underwent staged bilateral thoracotomies with removal of 23 PAVMs, with substantial symptomatic improvement. Thorascopic resection has recently been described. Although surgical mortality can be as low as 0 percent, the general anesthesia, morbidity of thoracotomy, and loss of viable lung tissue made a new approach desirable.

Embolization of PAVMs has proved to be an excellent alternative. This procedure was first performed using homemade coils. The procedure was refined and perfected at Johns Hopkins by Terry, White, and colleagues. The original procedure used silicone balloons unless the feeding vessel was larger than 9 mm in diameter, in which case embolization coils with thrombogenic Dacron tails were used (Fig. 84-10*A,B,C*). Currently, the choice of coil vs. balloon generally reflects PAVM size, operator preference and center experience. Generally, all PAVMs with feeding vessel diameter of 3 mm or larger are embolized. Results have been very good, with success rates greater than 93 percent, and embolization therapy is now the procedure of choice, with an apparent mortality of 0 percent, few serious complications, no loss of pulmonary parenchyma, and no exposure to anesthesia or thoracotomy. Pregnant women requiring urgent embolotherapy because of hemoptysis or hemothorax may safely undergo embolization, with radiation exposure to the fetus acceptable after 16 weeks of gestational age, with successful pregnancy outcome. Embolotherapy may also be performed safely and effectively in children.



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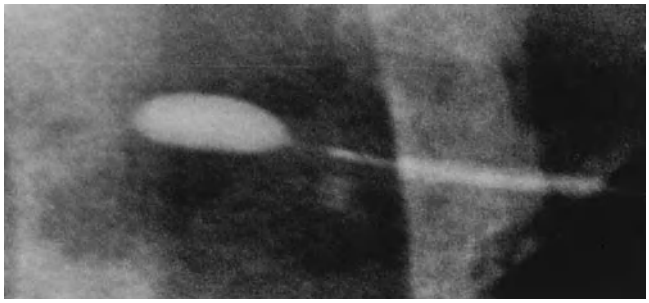

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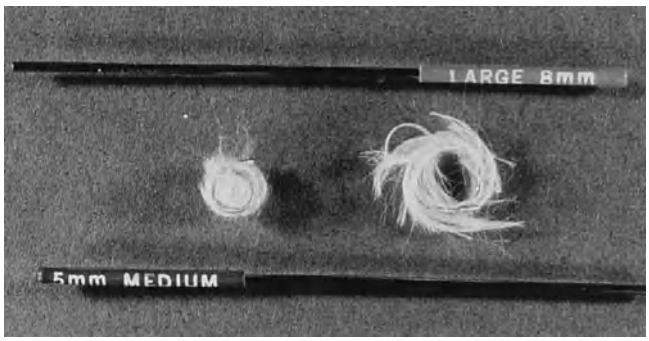

C

Figure 84-10 Embolotherapy devices: *A*. Detachable balloon mechanism from catheter. *B*. Fluoroscopic image of balloon in vivo. *C*. Embolization coils of two sizes.

There are some limitations. The feeding vessel must be 2 to 3 mm in diameter or larger. It is technically feasible to embolize most PAVMs, but occasionally this is not possible. All but three patients in our 18-year experience have been able to be treated with embolotherapy (2/132 in the most recent series). A majority have persistent intrapulmonary shunt and should receive pre-dental antibiotic prophylaxis.

Recanalization of the embolized vessel may occur. Rates of 2 to 8 percent have been reported. This may require repeated embolotherapy, and it has been suggested that follow-up by CT occur at 1 month and 1 year.

Although observations documenting serial growth of small PAVMs are somewhat limited, there is published evidence to support their growth with time. Progression of PAVMs appears more likely in those with multiple PAVMs. It has been suggested that patients with treated PAVM need follow-up every 5 years to detect growth of small PAVMs that could become large enough to cause paradoxical embolization and stroke.

In general, successful embolization of most or all visible PAVMs results in abatement of hypoxemia and its complications, but a small number of patients have diffuse small PAVMs not amenable to embolization.

Occlusion of all PAVMs with feeding vessels 3 mm or larger greatly reduces the risk of embolic stroke. Complex PAVMs must have all feeding vessels embolized for success. Embolotherapy may reduce the risk of brain abscess, but abscess may recur even after successful therapy. Although no data regarding efficacy exist, standard American Heart Association endocarditis guidelines for antibiotic prophylaxis before embolotherapy seem recommended. Because of the frequent observation of small persistent left-to-right shunt demonstrated by echocardiography even after successful embolotherapy, antibiotic prophylaxis is recommended for dental and other surgical procedures.

Serious complications of embolotherapy are rare. Because of the potential for systemic air and particulate embolism, all intravenous tubing is equipped with micropore filters and embolization precautions are taken. Air embolism during the procedure is rare, occurring in less than 5 percent in one series. It is generally manifested by perioral paresthesias or angina without permanent effect. The most common postembolization symptom is pleurisy, and has been reported at rates ranging from 10 to 31 percent. The onset may be delayed for up to 17 days in our experience, and severity may range from mild pain to a level of discomfort requiring hospitalization. These episodes are sometimes accompanied by large pleural effusions. The effusions and resulting hypoxemia always resolve within several weeks. Other complications have included migration of an embolic device, PAVM perforation,

transient ischemic attack (TIA), early cerebral infarction after embolization. and paradoxical embolization of a device during deployment (4 percent).

Diffuse PAVMs resulting in hypoxemia whch are not amenable to embolotherapy represent a difficult problem. A few such cases have been successfully treated with lung transplantation.

PROGNOSIS

Early reports suggested a high mortality for patients who did not undergo treatment of PAVMs. Examination of family trees in older reports impresses one with the frequency of death from meningitis, brain abscess, and stroke. Some of this apparently high mortality may have been due to selection bias. More recent studies suggest that the prognosis may be more benign, and complications may be non-existent when PAVMs are discovered by screening. In one series, mortality was approximately 10 percent. Two-thirds of deaths were due to cerebrovascular accident, and all of these patients were cyanotic and polycythemic.

In summary, patients with PAVM can be successfully treated, with resolution of essentially all symptoms and substantial reduction in risk of complications. Embolotherapy is the treatment of choice for most patients. The relatives of patients with PAVMs or HHT should be screened with contrast echocardiography to prevent central nervous system complications as the first manifestation of disease. Patients with PAVMs should be fully educated about their diagnosis, potential clinical complications, and the often hereditary nature of the problem. Educational materials for patients with HHT, and the location of specialized centers for managing HHT and PAVM, are available from the HHT Foundation International at www.hht.org. Caregivers are also urged to consult the website for updated recommendations.

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PART

X

Disorders of the Pleural Space

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85

Non-Malignant Pleural Effusions

Martin L. Mayse

Pleural effusion is the abnormal accumulation of fluid in the pleural space. A pleural effusion is always abnormal and indicates the presence of an underlying disease. Approximately 1.4 million people in the United States develop a pleural effusion each year. Despite the fact that there are many causes of pleural effusion (Table 85-1), it is estimated that 90 percent of all pleural effusions are the result of only 5 disease processes; congestive heart failure, pneumonia, malignancy, pulmonary embolism, and viral infection. The diagnostic approach to patients with a pleural effusion is detailed elsewhere in this volume. This chapter outlines the importance of descriminating transudative effusions from exudative effusions and details the major causes of exudative pleural effusions; including signs and symptoms, characteristics of pleural fluid analysis, treatment options, and prognosis.

The first step in the evaluation of a pleural effusion is a detailed history and physical examination; the importance of the history and physical arises from the fact that a significant percentage of pleural effusions have no definitive diagnostic features on pleural fluid analysis or pleural biopsy. Diagnosis of the cause of many pleural effusions is based on the clinical setting and exclusion of other alternative causes.

The next step is sampling of the pleural fluid and categorization as a transudate or exudate. Transudative pleural effusions result from systemic diseases that do not directly involve the pleura but instead produce an imbalance of Starling's forces, resulting in movement of fluid into the pleural space. The diagnostic focus for transudates call for recognition of the systemic disease. Such systemic diseses include congestive heart failure, cirrhosis with ascites, and the nephrotic syndrome. Treatment of transudative effusions

Table 85-1

Differential Diagnosis of Non-Malignant Pleural Effusions

Transudative Pleural Effusions	Exudative Pleural Effusions
Congestive heart failure	Infectious diseases
Cirrhosis	Bacterial infections
Peritoneal dialysis	Tuberculosis
Nephrotic syndrome	Fungal infections
Superior vena cava obstruction	Viral infections
Myxedema	Parasitic infections
Pulmonary thromboembolization	Pulmonary thromboemboli
Gastrointestinal disease	
Pancreatitis	
Esophageal perforation	
Intra-abdominal abscesses	
Collagen vascular diseases	
Rheumatoid arthritis	
Lupus erythematosus	
Churg-Strauss syndrome	
Drug-induced pleural disease	
Nitrofurantoin	
Dantrolene	
Methysergide	
Bromocriptine	
Interleukin-2	
Procarbazine	
Amiodarone	
Asbestos exposure	
Chylothorax	
Hemothorax	
Postsurgical	
Abdominal surgery	
Coronary artery bypass	
Sarcoidosis	
Post-cardiac-injury (Dressler's) syndrome	
Uremic pleuritis	
Yellow nail syndrome	

Source: Modified from Light RW: Pleural Diseases. DISEASE-A-MONTH *28:263–331, 1992.*

should focus on treatment of the underlying disease. Exudative pleural effusions result from local or systemic diseases that directly injure the pleural surface. The diagnostic focus for exudative effusions is to recognize the responsible intrapleural disease.

Exudative pleural effusions have any one or more of the following characteristics: (1) the pleural total fluid protein divided by the serum total protein is greater than 0.5; (2) the pleural fluid lactic dehydrogenase (LDH) divided by the serum LDH is greater than 0.6; and (3) the absolute level of LDH in the pleural fluid is greater than two-thirds of the upper normal limit for serum. Transudative pleural effusions meet none of the above three criteria.

In addition to the measurement of pleural fluid protein and LDH to differentiate transudate from exudate, other tests that can be helpful include: white blood cell count and differential; glucose; amylase; cytologic examination; and cultures for aerobic and anaerobic bacteria, mycobacteria, and fungi. For example, a pleural fluid cell population with a high percentage of small lymphocytes suggests that the patient has pleural tuberculosis or pleural malignancy and serves as an indication for a needle or thoracoscopic biopsy of the pleura. Most patients who have more than 10 percent of eosinophils in their pleural fluid have had either blood or air in their pleural spaces. If this is not the case, one should consider a drug reaction, paragonimiasis, or the Churg-Strauss syndrome. A pleural fluid glucose below 60 mg/dl narrows the diagnostic possibilities to seven: parapneumonic effusion, malignant effusion, tuberculous effusion, rheumatoid effusion, hemothorax, paragonimiasis, or the Churg-Strauss syndrome. An elevated pleural amylase limits the diagnostic possibilities to three: esophageal rupture, pancreatic disease, or malignant pleural effusion. With esophageal rupture and malignant pleural effusion, the amylase present in the pleural fluid is a salivary type. Depending on the patient, other tests are sometimes useful in determining the cause of a pleural effusion. For example, if a chylothorax is suspected, one should measure the level of triglycerides in the pleural fluid, and measurement of the adenosine deaminase (ADA) is useful in establishing the diagnosis of tuberculous pleuritis.

PARAPNEUMONIC EFFUSIONS AND/OR EMPYEMA

Parapneumonic Effusions

A parapneumonic effusion is any pleural effusion associated with bacterial pneumonia or lung abscess. Parapneumonic effusions occur in approximately 40 percent of the more than 1 million patients in the United States who have bacterial pneumonia each year, making pneumonia the most common cause of exudative pleural effusions. The possibility of a parapneumonic effusion should be considered each time a patient with acute pneumonia is evaluated. Parapneumonic effusions are often small, but if the depth of the effusion is greater than 10 mm on the decubitus chest radiograph, a diagnostic thoracentesis should be strongly considered.

Pleural effusions secondary to pneumonia arise from an inflammatory process contiguous to the visceral pleura. The effusion derives from fluid entering the lung interstices, transversing the visceral pleura, and accumulating in the pleural space when the rate of accrual exceeds the capacity of the parietal pleural lymphatics to remove fluid. The fluid initially has a low white blood cell count, low concentration of lactic

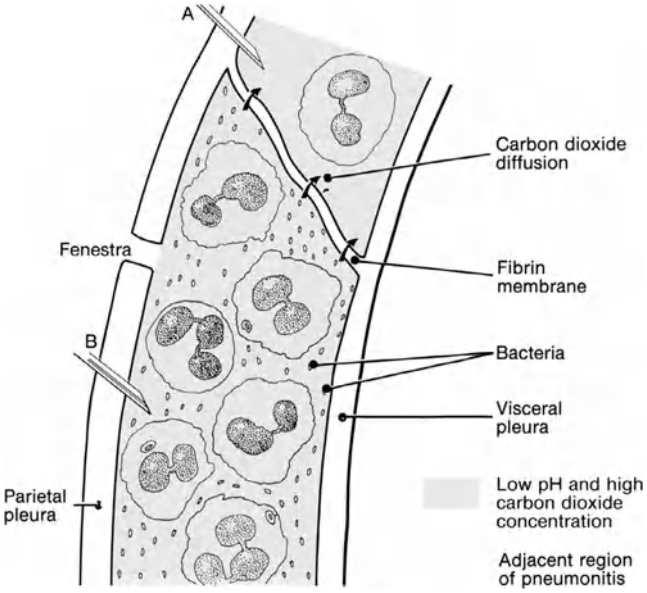


Figure 85-1 Compartmentalization of pleural fluid in empyema resulting from inflammation and the formation of semipermeable fibrin membranes. In compartment B of the schematic, bacteria and polymorphonuclear leukocytes abound; pleural fluid sampled from this area will be culture-positive and have an elevated white cell count, low pH, and decreased glucose level. The fibrin membrane prevents migration of bacteria and polymorphonuclear leukocytes to the adjacent compartment A. However, the semipermeable membrane permits diffusion of carbon dioxide from compartment B to compartment A, and glucose diffusion from A to B. Thus, fluid taken from compartment A, although sterile and with a low polymorphonuclear leukocyte count, will have a low pH and glucose, indicating the presence of neighboring infection.

dehydrogenase (LDH), normal concentration of glucose, pH greater than 7.3, and no demonstrable bacteria. This is an "uncomplicated parapneumonic effusion." If appropriate antibiotic therapy for the pulmonary infection is initiated at this stage, the effusion usually does not progress, pleural drainage is frequently unnecessary, and the pleural process resolves with antibiotic therapy alone. However, if the infection in the pulmonary parenchyma is unchecked, the infectious agent invades the pleural space to create an empyema. Once bacterial infection has involved the pleural space, the effusion increases in size with a concomitant increase in the number of polymorphonuclear leukocytes and fall in pleural fluid pH and glucose. At this point, fibrin frequently is deposited in the pleural space forming semipermeable barriers that envelop or loculate the infected area and lead to regional variation in the composition of pleural fluid (Fig. 85-1). In the region of bacterial proliferation, white blood cells are actively phagocytosing bacteria, and the resultant oxidative burst results in an increased consumption of glucose with increased production of CO_2 and lowering of the pH. Neighboring compartments equilibrate glucose and CO_2 across the semipermeable loculations producing a low pH and glucose; the loculations, however, are impervious to white cells and bacteria (Fig. 85-1). Sampling the infected loculation demonstrates pus and/or bacteria and establishes a diagnosis of empyema thoracis. Fluid from neighboring loculations demonstrates a low pH and low glucose but no bacteria. The latter identifies a "complicated parapneumonic effusion" and strongly suggests infection in nearby loculations and the need for pleural space drainage.

The incidence of parapneumonic effusions depends, in part, on the infecting organism. For example, a parapneumonic effusion occurs in 50 percent of *Streptococcus pneumoniae* infections of the lung, but the organism can be demonstrated in pleural fluid in fewer than 5 percent of patients. In contrast, culture of the pleural fluid is positive in 20 percent of adults and 80 percent of children with pleural effusions secondary to *Staphylococcus aureus* infections. Pleural effusions also develop in 40 to 50 percent of gram-negative aerobic pneumonias, and the majority of these are culture-positive. *Pseudomonas* species and *Escherichia coli* account for more than two-thirds of all infections of the pleural space caused by aerobic gram-negative organisms. Pleural effusions occur in 30 to 50 percent of patients with pneumonia due to *Legionella* species.

Although the morbidity and mortality rates in patients with pneumonia and effusion are higher than those with pneumonia alone, most uncomplicated parapneumonic effusions resolve with antibiotics alone. Less than ten percent ultimately require pleural drainage for resolution. Decortication and/or open drainage are rarely needed in the management of an uncomplicated parapneumonic effusion.

Uncomplicated parapneumonic effusion that enlarges in the face of antibiotic therapy should undergo repeat thoracentesis to assess if the effusion has become complicated. Complicated parapneumonic effusions require tube thoracostomy for drainage and adequate treatment (Table 85-2). The tube should be positioned in the dependent portion of the effusion and connected to an underwater seal drainage system. If the patient fails to improve clinically and radiographically within 48 hours, ultrasonic examination of the pleural space is performed to detect undrained loculated fluid; if a pocket is identified, additional chest tubes should be inserted. Decortication and/or open drainage are sometimes needed in the management of complicated parapneumonic effusions.

Empyema

Empyema is defined by the presence of pus in the pleural space. Direct extension of a pulmonary parenchymal infection into the pleural space causes more than half the cases of empyema; postsurgical infection accounts for an additional 20 percent. Empyema also occurs after penetrating or blunt trauma to the thorax. Sometimes bacteria from abdominal infection, such as a subdiaphragmatic abscess, cross the diaphragm and enter the pleural space. Rarely does empyema complicate thoracentesis or pleural biopsy. Sixty to seventy percent of patients with empyema have an underlying serious disease. Chronic obstructive pulmonary disease and pulmonary neoplasm are each found in approximately one-third

Table 85-2

Criteria for Tube Thoracostomy in Parapneumonic Effusions and Empyema

Radiographic criteria
Pleural fluid loculations
Effusion filling more than half the hemithorax
Air-fluid level
Microbiologic criteria
Pus in the pleural space
Positive stain for microorganisms
Positive pleural fluid cultures
Chemical criteria
Pleural fluid pH < 7.2
Pleural fluid glucose < 60 mg/dl

Source: Modified from Colice GL, Curtis A, Deslauriers J, et al: Medical and surgical treatment of parapneumonic effusions. An evidence-based Guideline. Chest *118:1158–71, 2001.*

of patients with empyema. Other associated illnesses include alcoholism, diabetes, esophageal disease, and disorders of the central nervous system that lead to aspiration of oropharyngeal contents.

The symptoms of empyema are usually non-specific. Eighty percent of patients have dyspnea and fever, and 70 percent complain of cough or chest pain. However, some patients with empyema present with only constitutional complaints, such as weight loss, fatigue, and malaise. Evidence of fluid in the pleural space is the principal radiographic finding; most empyema patients also have a recognizable parenchymal infiltrate.

The bacteriology of empyema has changed considerably in the past 50 years. Prior to the availability of antibiotics, *S. pneumoniae* and *S. pyogenes* accounted for most pleural infections. After the use of penicillin became widespread in the 1940s, *S. aureus* succeeded *S. pneumoniae* and *S. pyogenes* as the major cause of empyema. Since the advent of β-lactamase-resistant semisynthetic penicillins in the early 1960s, the incidence of staphylococcal empyema has decreased, and infections caused by anaerobic bacteria and aerobic gram-negative rods have increased markedly.

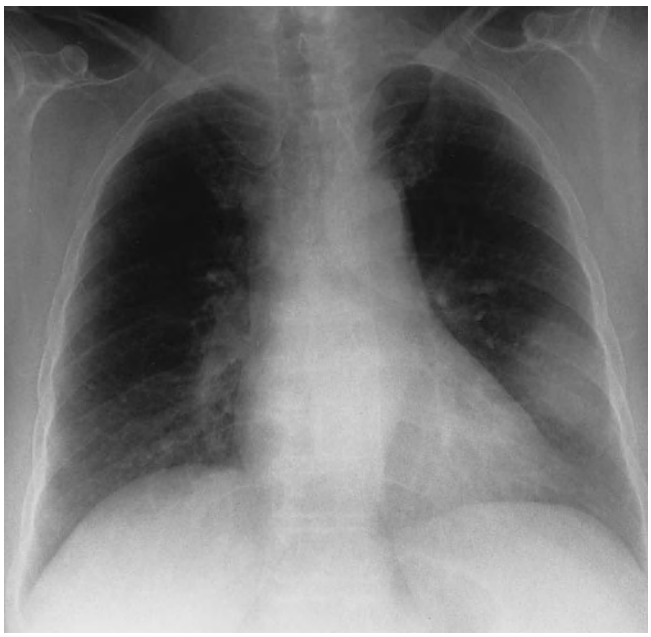
Anaerobic organisms are now isolated from up to 75 percent of patients with empyema; about half of the isolates consist of only anaerobic organisms and the other half of mixed anaerobic and aerobic organisms. Approximately 75 percent of patients with empyema have multiple infecting organisms, averaging three bacterial species per patient. Anaerobic bacteria in the pleural space may originate in the mouth or from a subphrenic source via transdiaphragmatic spread or, less commonly, reach the pleura via the bloodstream. Carious teeth or advanced periodontal disease should alert the clinician to the possibility of anaerobic infection. Despite careful sampling and meticulous culturing, pleural fluids are culture-negative in up to 20 percent of patients with empyema.

The mortality from empyema is ranges from 11 to 50 percent, depending on the patient population. Contributing to a poor prognosis in patients with empyema are underlying pulmonary disease, underlying malignancy, persistent systemic symptoms, gram-negative bacterial infection, and advanced age.

A good outcome demands prompt recognition, appropriate antibiotic therapy, and adequate pleural drainage. Apart from reducing the risk of sepsis, early antibiotic therapy also decreases the degree of residual pleural fibrosis. The initial choice of antibiotics depends on the clinical setting and should be guided by the results of the gram stain of pleural fluid and sputum. Antibiotics should be modified when culture results become available and the in vitro sensitivity patterns of the infecting bacteria are determined. In patients in whom empyema is suspected, empiric antibiotic therapy is started immediately. Until proved otherwise, anaerobic involvement is presumed, and an antibiotic that is effective against this group of organisms is started. For patients with empyema thoracis from community-acquired infection, the second-generation cephalosporins provide coverage against most aerobic gram-positive cocci, anaerobic bacteria including bacteroides species, and some gram-negative rods (*Haemophilus* spp., *Klebsiella* spp., *E. coli* and *Enterobacter* spp.). In the absence of a positive gram stain, coverage for *Legionella* species and *Chlamydia pneumoniae* should be added. For nosocomial infections, broader antibiotic coverage for gram-negative organisms is recommended. Initially, the antibiotics are administered parenterally. However, should the infection prove to be caused by highly susceptible organisms, oral antibiotics are often substituted after the empyema is adequately drained and signs of sepsis have resolved. The duration of antibiotic therapy depends on the individual response. As a rule, antibiotics are continued until: (1) the patient is afebrile and the white blood cell count is normal; (2) the tube thoracostomy drainage yields less than 50 ml of fluid daily; and (3) the radiograph shows considerable clearing. Typically, 3 to 6 weeks of antibiotic therapy is required to achieve these results.

Prompt external drainage of infected pleural fluid collections is a mainstay of treatment (Fig. 85-2) and indicated for all patients with empyema thoracis. Several therapeutic options are available and include: (1) thoracentesis; (2) non–image-guided chest tube placement; (3) image-guided catheter drainage; (4) thoracoscopy with lysis of adhesions and directed chest tube placement; (5) thoracotomy with debridement and directed chest tube placement; and (6) thoracotomy with pleural decortication.

Percutaneous drainage is most effective in patients with a short duration of symptoms, free-flowing or unilocular parapneumonic effusions, absence of a thick pleural peel on sonography or computed tomography (CT) scans, and fluid that can be aspirated easily by needle. Chest tube placement with or without image guidance is usually the initial procedure. Sonography or CT can accurately guide drainage



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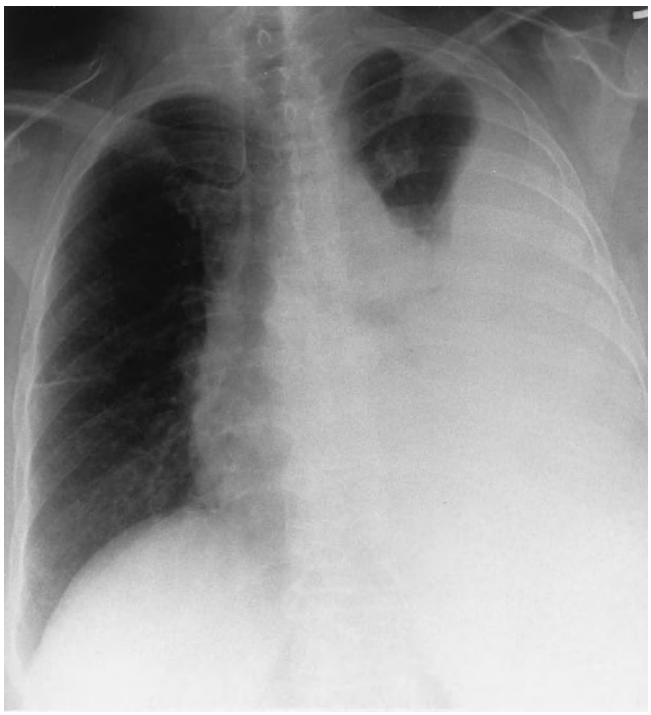

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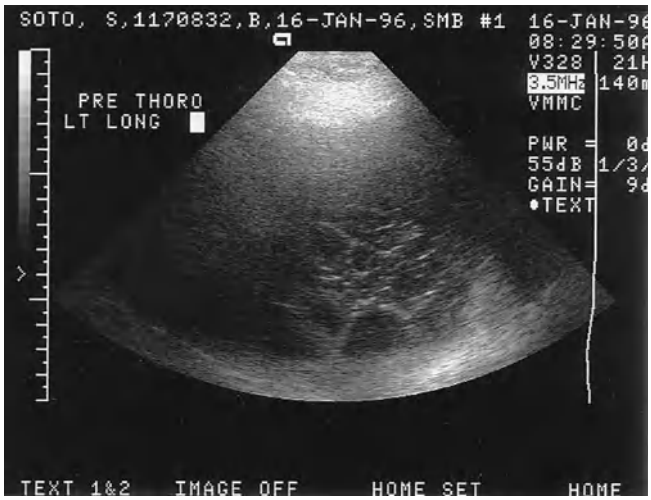

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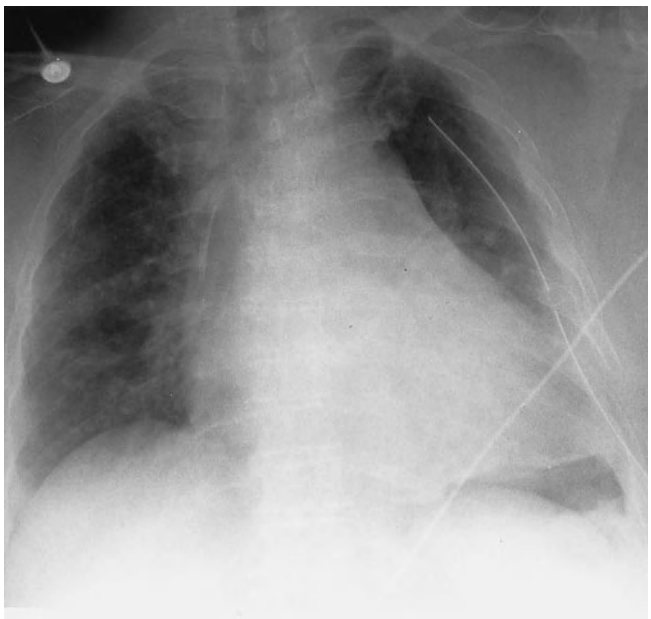

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Figure 85-2 *A*. Chest radiograph of a 63-year-old woman with left lower lobe pneumonitis. *B*. The patient developed a large left-sided pleural effusion despite 5 days of oral antibiotic therapy. *C*. Sonographic study of the pleural space showed marked septation throughout the fluid collection. *D*. Adequate drainage was established with thoracotomy, digital lysis of adhesions, and operative placement of a chest tube.

catheter placement, with sonography the procedure of choice. Radiologically guided pleural drainage procedures have success rates that are slightly increased over that of non–image-guided chest tube drainage.

Close radiographic or sonographic follow-up is indicated to ensure adequate drainage. Successful percutaneous tube drainage of an empyema or complicated parapneumonic effusion should see clinical and radiologic improvement in 48 hours. If the patient fails to improve, the drainage is either inadequate or antibiotic selection is incorrect. In patients with inadequate drainage, the choices are: (1) percutaneous insertion of additional chest tubes; (2) intrapleural injection of a fibrinolytic agent; (3) thoracoscopy with lysis of adhesions; or (4) thoracotomy with digital lysis of adhesions, operative placement of chest tubes with or without decortication.

Intraplerual fibrinolytics can dissolve fibrin membranes and potentially facilitate drainage of the pleural space, although long-term outcomes with this therapy have been mixed. Streptokinase, urokinase, and more recently tissue

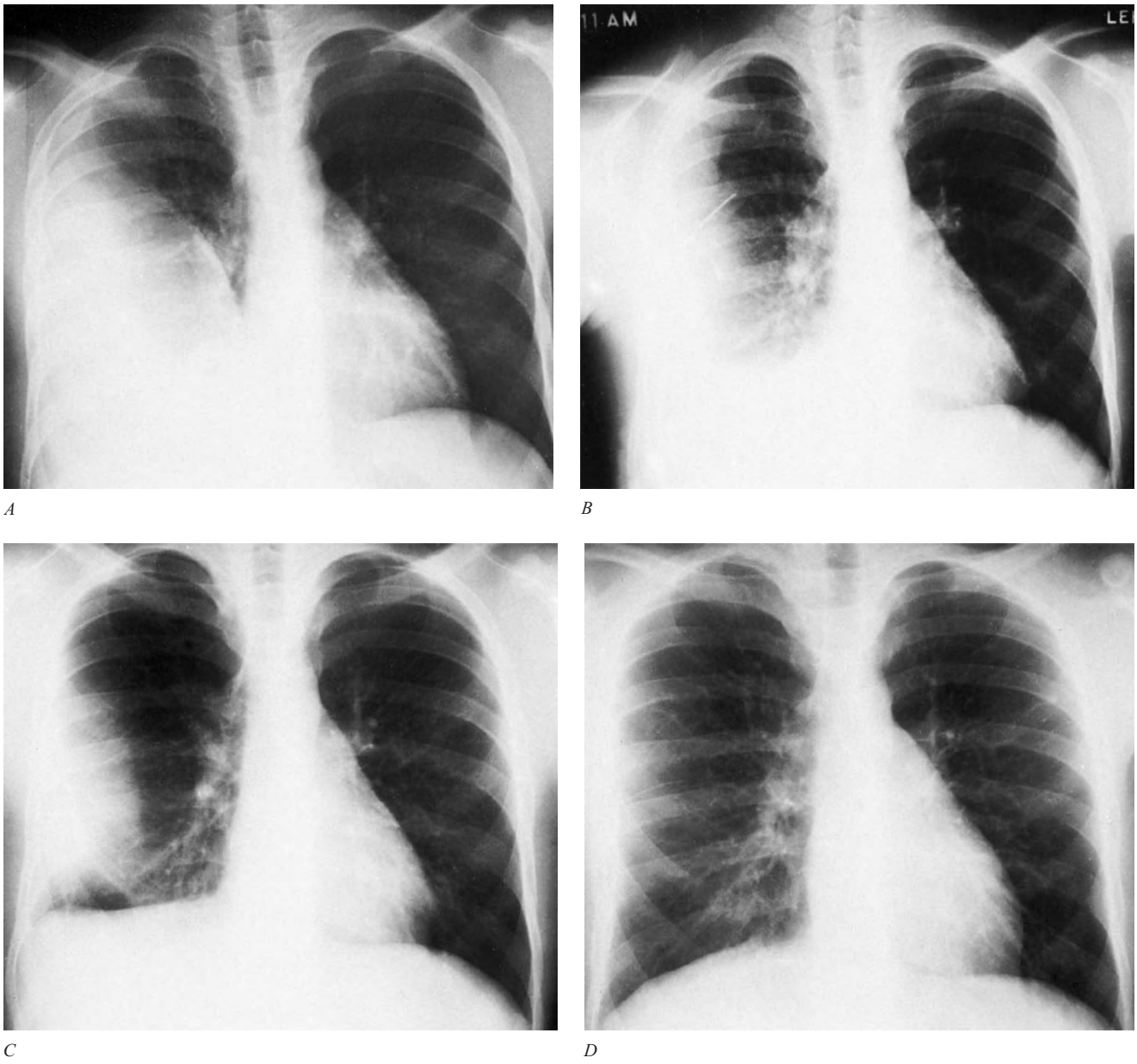


Figure 85-3 The course of pneumococcal empyema in a 16-year-old immunocompetent patient. *A*. When first seen, the patient has a large volume of loculated pleural fluid with distinct anterior and posterior margins and a meniscus high up on the lateral chest wall forming an obtuse angle between the pleural density and the adjacent parenchyma. *B*. Five days after tube thoracostomy the volume of pleural fluid is reduced by over 50 percent. *C*. One month after chest tube removal the patient remains free of symptoms of infection, but significant loculated pleural density remains. *D*. Three months later the pleural abnormality has totally resolved, and the chest radiograph is normal.

plasminogen activator have been used in this setting. Diluted in 50 to 100 ml of normal saline solution, these fibrinolytics can be injected directly through a chest tube into the pleural space. The chest tube is then clamped for 4 hours and returned to low level suction when the tube is unclamped. This form of therapy can be repeated daily up to 14 days, depending on the rapidity of improvement. Successful response is indicated by an increase in the amount of chest tube drainage, radiographic improvement, and decrease in the systemic signs of infection.

Once the patient's condition has improved, a decision has to be made about when to remove the chest tube. Criteria for tube removal are: (1) system signs of infection are controlled—usually after 7 to 10 days of therapy; (2) less than 50 ml of fluid is being drained per day; (3) the lung has expanded as fully as possible; and (4) if a bronchopleural fistula was present, it has sealed. Should the lung not completely reexpand and the volume of unfilled pleural space exceed 100 ml, reexpansion of the lung should be attempted before removing the chest tube. To do so sometimes requires the

placement of an additional chest tube or surgical decortication of the lung.

In 20 to 30 percent of patients with thoracic empyema, antibiotics and drainage with percutaneous chest tubes fail to control the infection. In these patients, thoracotomy with digital lysis of adhesions and operative placement of chest tubes should be strongly considered. Procrastination in moving to thoracotomy is a common error. Thoracotomy frequently returns the patient to good health most quickly. Decortication is used only for control of pleural infection. It is not used in patients in whom the infection is controlled, but the pleura remains persistently thickened; this type of thickening usually resolves spontaneously over several months (Fig. 85-3).

Adequate pleural drainage is particularly crucial in an empyema that is accompanied by a bronchopleural fistula. Undrained pleural fluid can spill through the fistula into the lung and cause a diffuse pneumonitis. A bronchopleural fistula is suspected when the chest radiographs show pleural air-fluid levels and when a patient raises more sputum than anticipated, especially when the production of sputum is position dependent.

TUBERCULOUS PLEURAL EFFUSIONS

In the United States, tuberculosis is responsible for approximately 2 percent of all pleural effusions. Although usually considered a chronic illness, one-third of patients with tuberculous pleuritis have an acute illness of less than 1 week's duration, and two-thirds seek medical attention within 1 month of the time of onset of symptoms. Nonproductive cough, pleuritic chest pain, and fever occur in most patients; however, as many as 15 percent of patients may be afebrile. Patients with chronic infection frequently present with weight loss, malaise, and dyspnea.

Tuberculous effusions are usually unilateral and moderate in size. In approximately one-third of patients with tuberculous pleural effusions, coexisting parenchymal disease is evident radiographically. If there is no radiographic evidence of parenchymal disease, the infection usually signifies primary tuberculosis. In 65 percent of patients with tuberculous pleuritis in whom the effusion resolves spontaneously, symptomatic parenchymal disease will occur within 12 months. In 30 percent of patients with tuberculous pleural effusion, the *initial* tuberculin skin test is negative. However, a repeat test, within 8 weeks of the development of symptoms, is likely to be positive.

A tuberculous effusion is usually serous, may be serosanguineous, but is almost never frankly bloody. Examination of pleural fluid is diagnostic of tuberculosis only if mycobacteria are demonstrated by smear or culture. Unfortunately this is an uncommon occurrence as mycobacteria are demonstrable on smear in less than 10 percent of patients and on culture in only 25 percent of patients. Decisions regarding treatment are usually made without confirmatory stains and well before the culture results are available. Certain features of tuberculous pleural fluid are helpful in either supporting or discounting the diagnosis of tuberculosis. Typically, more than 50 percent of all white blood cells in a tuberculous pleural effusion are mature lymphocytes, and a differential count that reveals more than 80 percent mature lymphocytes strongly suggests either tuberculosis or malignancy. The eosinophil count rarely exceeds 10 percent in tuberculous pleural fluid. Mesothelial cells are rare; indeed, more than 5 percent mesothelial cells in the differential count argues strongly against a tuberculous etiology. A pleural effusion ADA greater than 70 IU/l has been shown to be highly sensitive and specific for the diagnosis of pleural tuberculosis in patients suspected of having tuberculosis. Increased ADA levels have also been found in patients with malignancy or empyema, and histologic or bacteriologic confirmation of tuberculosis remains a necessity. The total protein content of the tuberculous effusion tends to be quite high; values above 5 g/dl suggest a tuberculous effusion. The concentration of glucose in pleural fluid is usually greater than 60 mg/dl; the pH varies widely and is of little diagnostic help.

Biopsy of the pleura demonstrates granuloma in approximately 80 percent of patients. Pleural tuberculosis is the only non-neoplastic pleural exudate *readily* diagnosed by a pleural biopsy. Culture of the pleural biopsy is helpful as well since *Mycobacterium tuberculosis* can be isolated from over 85 percent of biopsies. Although other diseases, including fungal infection, sarcoidosis, and rheumatoid arthritis, may produce granulomatous pleuritis, more than 95 percent of patients with demonstrable pleural granuloma have tuberculosis.

Even though pleural biopsy and pleural fluid examination fail to substantiate the diagnosis of tuberculosis, empiric antituberculous therapy is appropriate in certain patients. A positive tuberculin skin test in a patient less than 40 years old, in combination with a pleural fluid analysis that is compatible with tuberculosis, is an indication for empiric antituberculous therapy. In contrast, the patient with a suspected tuberculous pleural effusion who is more than 40 years old and who has risk factors for bronchogenic carcinoma should be subjected to thoracoscopy or open pleural biopsy rather than to empiric therapy. The absence of granulomatous inflammation in the open pleural biopsy of a tuberculin-positive patient virtually excludes the diagnosis of tuberculosis and obviates the need for antituberculous therapy.

With antituberculous therapy, the average patient becomes afebrile within 2 weeks and radiographic clearing usually occurs in 6 to 12 weeks. The addition of corticosteroids may lead to more rapid resolution of symptoms and pleural fluid on chest radiograph. Tuberculous effusions may be accompanied by pleural thickening, but the thickening usually undergoes striking resolution in response to antituberculous therapy. Fibrothorax is rare. Therefore, consideration of decortication for pleural thickening should be delayed until the patient has had at least 6 months of antituberculous therapy.

Tuberculosis in the form of pleural disease sometimes becomes manifest in a patient in whom long-dormant tuberculous disease reactivates and forms a bronchopleural fistula. The patient then usually produces sputum and develops fever, sometimes in conjunction with chest pain; most have bacterial superinfections of the pleural space. Empyema thoracis in a patient with previous tuberculosis, particularly one who has never received chemotherapy, should rouse the strong suspicion of reactivation of tuberculous infection. The diagnosis is suggested by the development of an air-fluid level in the pleural cavity. A tuberculous bronchopleural fistula requires antituberculous chemotherapy and chest tube drainage of the infected pleural cavity. In some individuals in whom antituberculous therapy has succeeded in eliminating mycobacteria from the sputum, a persistent bronchopleural fistula requires decortication for relief.

FUNGAL PLEURAL EFFUSIONS

Fungal diseases account for only 1 percent of all pleural effusions. The most common cause is *Aspergillus* infection (usually *A. fumigatus*), which invades the pleural cavity via a bronchopleural fistula complicating lung resection or reactivation tuberculosis. The signs and symptoms mimic chronic bacterial infection of the pleura. In pleural fluid, clumps of hyphae appear as brown suspended particles, and their gross appearance raises a suspicion of aspergillosis. In patients with pleural aspergillosis, precipitating antibodies in the serum and the wheal and flare cutaneous reaction are almost always positive. Optimal therapy consists of surgical evacuation of the pleural cavity, closure or excision of the bronchopleural fistula, and administration of amphotericin B systemically.

An entirely different expression of *Aspergillus* infection is localized pleural thickening developing in the vicinity of an *Aspergillus* mycetoma. This is considered in detail elsewhere in this volume. However, it is worth emphasizing that occasionally in patients with chronic cavitary or cystic parenchymal disease the *initial* radiographic feature of *Aspergillus* infection is focal pleural fibrosis followed, months later, by a mycetoma in the abnormal adjacent parenchyma.

Approximately 20 percent of patients with acute *Coccidioides immitis* infection show evidence of pleural disease on the chest radiograph, and 70 percent complain of pleuritic chest pain. Free fluid in the pleural cavity is demonstrable in approximately 7 percent of patients. The patients are almost always febrile, and about one-half have either erythema nodosum or erythema multiforme. In about 50 percent of patients, parenchymal infiltrates accompany the pleural effusion. The effusions are usually unilateral. Examination of the pleural fluid reveals a predominance of lymphocytes on the white cell count, a glucose concentration greater than 60 mg/dl, and, rarely, eosinophilia. Pleural fluid cultures are positive for *C. immitis* in 20 percent of patients; culture of the pleural biopsy specimen has a much higher yield. Complement fixation titers higher than 1:16 are common even when the disease is not disseminated. Most patients with primary coccidioidomycosis and pleural effusion do not require systemic antifungal therapy.

Cryptococcosis is another rare cause of pleural effusion. Pleural cryptococcosis appears to result from extension of a primary subpleural cryptococcal infection into the pleural space. More than half of the patients have serious underlying disease, most often leukemia, lymphoma, or the acquired immunodeficiency syndrome (AIDS). The pleural effusion is usually unilateral; cultures are positive for the organism in approximately 50 percent of patients. Cryptococcal pleural effusions have high titers of cryptococcal antigen. Patients with serious coexisting disease should receive amphotericin B and 5-fluorocytosine. However, immunocompetent patients may recover without specific therapy.

Histoplasmosis rarely produces pleural effusions, i.e., less than 1 percent of patients with histoplasmosis manifest pleural fluid radiographically. Treatment is unnecessary, since the effusion usually resolves spontaneously in several weeks.

VIRAL PLEURAL EFFUSIONS

The true incidence of viral pleural effusions is unknown. It is also believed that many self-limited effusions represent undiagnosed viral infections; these would account for approximately 10 to 15 percent of the total of all effusions. Rarely is a particular viral agent identified, so the diagnosis of viral pleural effusion is almost invariably one of exclusion. Pleural effusions occur in approximately 10 percent of patients with adenovirus infections. In addition to adenovirus infections, pleural effusions also occur with influenza virus, cytomegalovirus, herpes simplex virus, Epstein-Barr virus, and infectious hepatitis. A pleural fluid cell count usually reveals a predominance of mononuclear cells.

PARASITIC INFECTIONS OF THE PLEURAL SPACE

Amebic liver abscess is the most common extraintestinal site of infection by *E. histolytica.* In turn, pleural pulmonary amebiasis is the most common complication of amebic liver abscess and is usually due to the erosion of the abscess through the diaphragm to involve the pleural space or lung parenchyma. Sympathetic pleural effusions and atelectasis are common accompaniments of liver abscesses and do not indicate extension of infection into the pleural space. Patients with pleural pulmonary complications present with cough, pleuritic pain, and dyspnea. Empyema due to rupture of the abscess into the pleural cavity presents with sudden respiratory distress and pain and has a substantial mortality. In some instances, a hepatobronchial fistula forms and has been associated with spontaneous drainage of the hepatic abscess. The diagnosis of amebic abscess is suggested by the discovery of

"anchovy paste" or "chocolate sauce" pleural fluid. *E. histolytica* is usually demonstrable in the pleural collection. Treatment consists of metronidazole 750 mg PO tid for 5 to 10 days plus diloxanide furoate 500 mg 3 times a day for 10 days.

Human infection by the lung fluke *Paragonimus westermani* is widely distributed in Africa, Asia, and South America. The cercariae are ingested orally, transit the intestinal wall, and migrate through the peritoneal cavity across the diaphragm into the pleural cavities and then into the lungs, where they ultimately lodge. The clinical manifestations of paragonimiasis are eosinophilia and chest complaints, including a cough productive of brown sputum with intermittent hemoptysis. Up to half of patients will have pleural effusions, and in some they may be quite large. The characteristics of the pleural fluid with paragonimiasis are glucose less than 10 mg/dl, LDH level above 1000 IU/l, the pH below 7.1, and differential count with a high percentage of eosinophils. The diagnosis is established by demonstrating the presence of operculated eggs in sputum or feces. A serum complement fixation test is also available and helpful.

The hydatid cysts of *E. granulosus* form in the liver in 50 to 70 percent of patients and in the lung of 20 to 30 percent of patients. Pleural disease develops when either a hepatic or parenchymal lung cyst ruptures into the pleural space. The patient develops an acute illness with severe chest pain, dyspnea, and sometimes shock, secondary to severe allergic reactions to parasitic antigens suddenly released. The diagnosis is established by recognition of daughter cysts in the pleural fluid. Optimal treatment is surgical resection to drain the pleural space and removal of the original cyst.

PULMONARY EMBOLI

Pulmonary emboli likely represent a very common and underappreciated cause of pleural effusion. In fact, pleural effusions occur in 30 to 50 percent of patients with pulmonary emboli. Different mechanisms have been postulated to account for the pathogenesis of pleural effusion in these patients and to account for the fact that about 25 percent of the effusions are transudates and about 75 percent are exudates. In patients with pleural effuions and any level of suspicion for pulmonary embolism exists, it is prudent to evaluate this patient. Computed tomography with contrast enhancement per pulmonary embolism protocol is the modality of choice in this situation because it can provide additional diagnositic information about the pulmonary parenchyma and pleural space. This topic is covered in detail elsewhere in this volume.

PANCREATITIS

Approximately 20 percent of patients with acute pancreatitis develop pleural effusions. Although most of the effusions are unilateral and left-sided, the effusion is sometimes bilateral and occasionally only right-sided. The effusion results from contact of the pleura with enzyme-rich peripancreatic fluid that gains access to the pleural space, most commonly via transdiaphragmatic lymphatics, and less often, through a sinus tract between a pancreatic pseudocyst and the pleural space. Rarely, pancreatic fluid can transverse the aortic and esophageal hiatuses into the mediastinum, where an inflammatory response may evoke a mediastinal pseudocyst.

Usually the symptoms of pancreatitis (abdominal pain, nausea, and vomiting) dominate the clinical picture. At times, however, pleuritic chest pain and dyspnea may be the presenting complaint. The diagnosis is established by demonstrating abnormally high levels of amylase in the pleural fluid. The pleural fluid amylase is invariably higher than the serum amylase in pancreatitis-induced pleural effusions, often with a ratio of 6:1 or more. High levels of amylase in pleural fluid are not necessarily diagnostic of pancreatic disease; similar increments also occur after esophageal rupture into the pleura and occasionally with a malignant pleural effusion. About 10 percent of patients with malignant pleural effusions have high levels of amylase in their pleural fluids. However, the degree of increase is only slight to moderate in malignant effusions, and isoenzyme analysis will show the amylase to be salivary in type. The pleural fluid associated with pancreatitis is frequently serosanguineous and sometimes bloody. The concentration of glucose in the pleural fluid is normal, and the white blood cell count may vary from 1000 to 50,000 cells per cubic millimeter; as a rule, polymorphonuclear leukocytes predominate.

Pleural effusions secondary to pancreatitis usually resolve promptly as the pancreatic inflammation subsides. If resolution has not occurred within 2 weeks, the possibility of a pancreatic pseudocyst or abscess is likely. Should a sizable effusion remain after 2 to 3 weeks of nasogastric suction, no oral intake, and repeated thoracenteses, the abdomen should be reimaged or even surgically explored, looking for abscess, pseudocyst, and pancreaticopleural sinus. At the time of operation, a pancreatogram is performed to search for the sinus tract that can be ligated or excised. If no sinus is identified, careful dissection of the retroperitoneum in the region of the aortic and esophageal hiatus is undertaken in search of the tract.

ESOPHAGEAL PERFORATION

Approximately two-thirds of esophageal perforations occur as a complication of esophagoscopy. This is particularly true when the procedure is performed in an attempt to remove a foreign body or dilate an esophageal stricture. Other potential causes include esophageal carcinoma, gastric intubation, chest trauma, and finally, spontaneous rupture as a complication of vomiting (Boerhaave syndrome).

Perforation of the esophagus introduces oropharyngeal contents into the mediastinum, thereby evoking an acute

mediastinitis. The inflammatory reaction, in turn, often ruptures through the mediastinal pleura to produce a pleural effusion that is frequently complicated by a pneumothorax. Pleural effusions occur in approximately 60 percent of patients with esophageal perforation; 25 percent have a pneumothorax. The pleural effusion is usually left-sided but is sometimes right-sided or bilateral. Radiographic findings include widening of the mediastinum and pneumomediastinum. Most of the morbidity from esophageal perforation is due to the infection of the mediastinum and the pleural space by oropharyngeal bacterial flora. Clinical symptoms are dominated by chest pain that is usually quite severe. Hematemesis occurs in about half of the patients. Subcutaneous emphysema as a late manifestation occurs in about 10 percent of patients with esophageal rupture.

Examination of the pleural fluid reveals an exudative reaction: the amylase level is high, the pH is very low (frequently less than 6.0), squamous epithelial cells are present, and rarely, there may be ingested food particles. The amylase that has entered the pleural space through the esophageal defect is salivary rather than pancreatic. The treatment of choice for esophageal rupture is exploration of the mediastinum, primary repair of the esophageal tear, and drainage of the pleural space and mediastinum.

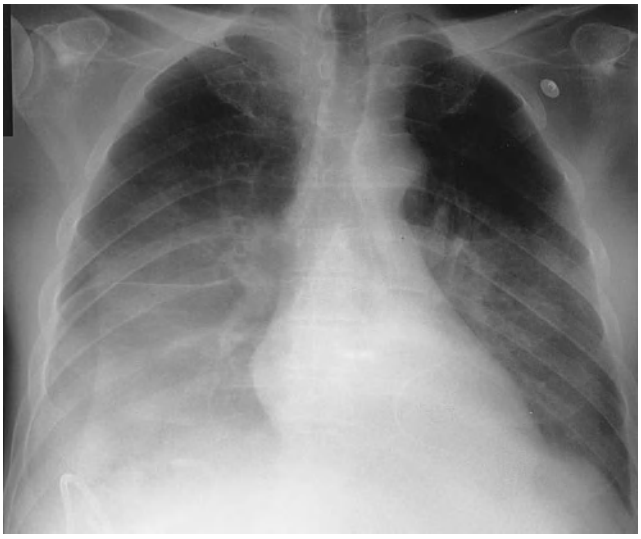
INTRA-ABDOMINAL ABSCESS

Pleural effusion occurs in about 80 percent of patients with a subphrenic abscess. The infection usually follows an intra-abdominal surgical procedure; splenectomy and exploratory laparotomy for trauma are the more common antecedents. A surgically related subphrenic abscess usually becomes clinically evident 1 to 3 weeks postoperatively. Other predisposing illnesses include gastric, duodenal, or appendiceal perforation, diverticulitis, cholecystitis, pancreatitis, or trauma.

The pleural fluid is an exudate in which polymorphonuclear leukocytes predominate. The pleural fluid white blood count may be as high as 50,000 per cubic millimeter, but the pH is higher than 7.2, and the glucose concentration exceeds 60 mg/dl. It is uncommon for the pleural fluid to become infected.

The diagnosis of a subphrenic abscess is often first made on the basis of a routine chest or abdominal radiograph. An air-fluid level, below the diaphragm and outside the gastrointestinal tract, is demonstrable in about 70 percent of these patients. Abdominal CT scans and ultrasound studies are very effective in diagnosing subphrenic abscesses. A CT-guided percutaneous aspiration of the subphrenic abscess is frequently helpful in finalizing the diagnosis and in identifying the responsible organisms. Treatment should be directed at the abdominal abscess with appropriate antibiotics and percutaneous or surgical drainage.

About 20 percent of patients with a hepatic abscess develop a pleural effusion; the effusion is usually, though not invariably, right-sided (Fig. 85-4). Most of the patients manifest fever, abdominal pain, and abnormal liver function tests, especially an increase in the concentration of alkaline phosphatase in the blood. CT scanning of the abdomen is currently the most sensitive means of detection; definitive diagnosis can be made using CT scanning as a guide to percutaneous aspiration.



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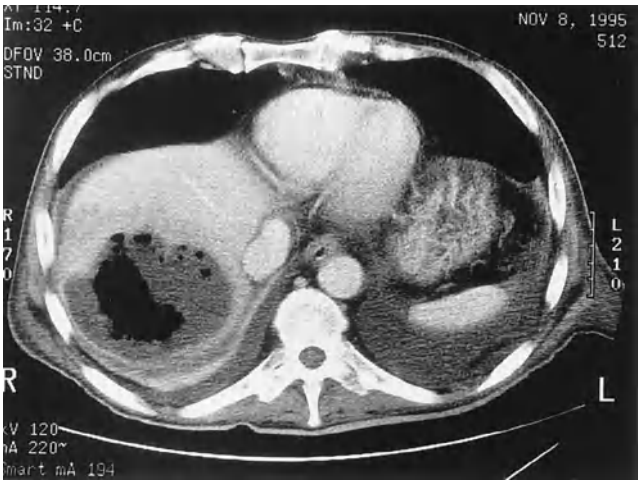

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Figure 85-4 *A*. Chest radiograph of a 62-year-old man with insulin dependent diabetes mellitus and bilateral pleural effusions. *B*. The CT scan revealed a large abscess in the right lobe of the liver complicating chronic pancreatitis. The pleural fluid was an exudate and sterile. Aspirate of the hepatic abscess yielded *Enterococcal* spp. and *Clostridium* spp.

COLLAGEN VASCULAR DISEASES

Rheumatoid Arthritis

Pleural thickening and effusions are the most common pulmonary manifestations of rheumatoid arthritis. They are frequently symptomatic and occur in 8 percent of men and

2 percent of women with rheumatoid arthritis in whom chest radiographs are made serially. Autopsy studies have revealed that 40 to 50 percent of patients with rheumatoid arthritis have histologic evidence of pleural disease.

Although in most patients pleural disease develops a few weeks to months after the onset of joint symptoms, in about 5 percent the pleural disease precedes the arthritis; in another 15 percent, the onset of the pleural disease is simultaneous with the initial episode of synovitis. The severity of arthritis, in terms of the number of joints involved or destruction on joint radiographs, does not correlate with the presence of pleural disease. However, the incidence of pleural effusions increases in those patients who have high titers of rheumatoid factor and subcutaneous nodules. In some patients, pericardial effusion occurs concurrently. About one-third of patients with rheumatoid pleural effusions have no respiratory symptoms. However, most notice some combination of pleuritic chest pain, cough, dyspnea, or fever. Sometimes the joint symptoms flare coincident with the onset of the pleural syndrome.

The pleural effusions are usually small in volume but occasionally become large enough to produce respiratory compromise. Eighty percent of patients have a unilateral pleural effusion; in 20 percent, the effusions are bilateral. Both intrapulmonary nodules and diffuse fibrosis sometimes accompany rheumatoid pleural disease. The nodules are often subpleural; at times, they undergo necrosis to produce a pyopneumothorax.

The pleural fluid in rheumatoid arthritis is usually an exudate; the concentration of total protein ranges from 3.5 to 6.0 g/dl and the LDH concentration is greater than 700 units. In 80 percent of the patients, the concentration of glucose in the pleural fluid is less than 30 mg. The pH is usually less than 7.2. The predominant cell is either the polymorphonuclear leukocyte or, less often, the lymphocyte; a mixture of both cell types is not uncommon. In many patients, the ratio of pleural fluid complement to serum complement is less than 0.4. Pleural biopsy is usually nonspecific but can rarely demonstrate pleural rheumatoid nodules that are diagnostic. For the most part, the etiologic diagnosis of the pleural effusion is one of exclusion.

Most patients can be treated with a nonsteroidal anti-inflammatory/analgesic medication such as aspirin, indomethacin, or ibuprofen. Only one-third of patients require systemic corticosteroids for pleural disease. The response to steroids is good, with symptomatic relief and control of pleural fluid volume occurring in more than 75 percent of those treated. The duration of active pleural inflammation is limited in most patients. Fifty percent of patients (both treated and untreated) undergo resolution of the pleural disease within 4 months of onset. Many are left with an asymptomatic, pleural density on chest radiograph. If the patient is asymptomatic and the pleural fluid has not recurred while off therapy for 6 months, the chance of recurrence of the pleural syndrome is small; fewer than 10 percent of patients develop a late recurrence. The postinflammatory pleural residuum is rarely clinically significant, but a few patients show a modest reduction in vital capacity. An overt fibrothorax that produces symptomatic restrictive ventilatory disease and requires decortication is rare.

However, about 20 percent of the patients develop a chronic, persistent pleural syndrome that tends to flare when therapy is stopped. The therapeutic goal for these patients should be symptomatic relief. The frequency of residual pleural fibrosis and restrictive ventilatory defects is higher in this group than in patients who undergo rapid spontaneous remission. There is little evidence to suggest that either nonsteroidal or corticosteroid therapy reduces the degree of long-term respiratory dysfunction. The majority of patients who experience chronic rheumatoid activity undergo remission of the pleural syndrome in 1 to 5 years.

Systemic Lupus Erythematosus

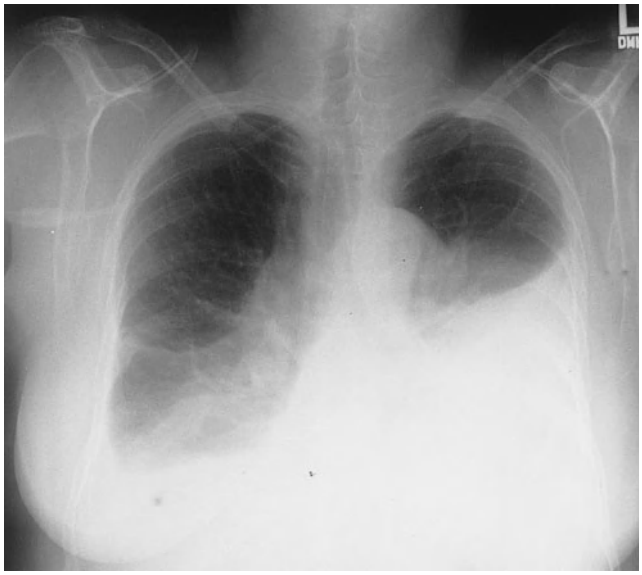
Pleural effusions occur in up to 40 percent of patients with SLE (Fig. 85-5). Even more have pleuritic chest pain without effusion at some time during the course of their illness. A comparable incidence of pleural effusions has been reported in drug-induced SLE.

In most patients with lupus pleuritis, arthritis or other symptoms precede the pleuritis; however, the pleural disease occasionally presents first. The pleural effusions are small in volume and bilateral in about 50 percent of the patients; in the remainder, the incidence is about equally divided between the right and left sides. In 20 percent of the patients, the effusions flit from side to side. Chest radiographs often show lesions other than the pleural effusions—parenchymal infiltrates, platelike atelectasis, and cardiomegaly due to myocardiopathy, pericardial effusion, or both.

The pleural fluid is usually clear and yellow; the white cell count reveals a preponderance of polymorphonuclear leukocytes or lymphocytes. The concentration of complement in the pleural fluid of most patients with lupus pleuritis is subnormal, and the ratio of pleural fluid to serum complement is less than 0.4. In contrast to rheumatoid arthritis, the pH of the SLE effusion is usually higher than 7.20, the concentration of glucose is greater than 60 mg/dl, and the LDH is less than 500 units. A pleural fluid ANA titer greater than or equal to 1:160 and a pleural fluid to serum ANA ratio greater than or equal to 1 is strongly suggestive of lupus pleuritis. The demonstration of LE cells in pleural fluid is diagnostic of lupus pleuritis. The pleural effusion associated with lupus usually responds well to corticosteroids.

Churg-Strauss Syndrome

This syndrome is a disorder characterized by hypereosinophilia and systemic vasculitis occurring in individuals with asthma and allergic rhinitis. Approximately 30 percent of patients with this syndrome have a pleural effusion. The pleural fluid is characterized by a very high LDH, low glucose and pH levels, and a high percentage of eosinophils. The only other disease with comparable findings is paragonimiasis. This syndrome responds well to treatment with corticosteroids.



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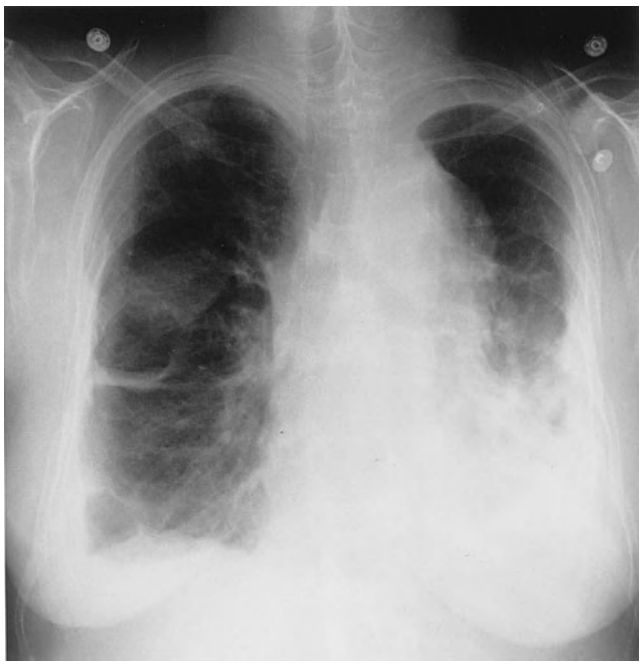


B

Figure 85-5 *A*. Chest radiograph of a 60-year-old woman with bilateral pleural effusions from systemic lupus erythematosus. The pleural fluid was an exudate with a pleural fluid to serum C4 ratio of 0:11, pleural fluid ANA titer 1:320, and pleural fluid/serum ANA ratio of 2:1. *B*. The pleural effusions ultimately required pleurodesis for control; talc slurry on the left and surgical parietal pleurectomy on the right.

PLEURAL EFFUSION FROM DRUG REACTIONS

Few pleural effusions are induced by drugs. It is very difficult to make an accurate diagnosis of a drug reaction on clinical grounds. Rechallenge is seldom feasible in clinical practice, and there are no readily available laboratory tests which accurately link the medication to the adverse event. The diagnosis is important, as discontinuation of the drug is frequently followed by a spontaneous reversal of the pleural disease.

Most drug-induced pleural reactions are associated with a parenchymal abnormality. The symptoms sometimes are acute, i.e., chills, fever, cough, and dyspnea develop within hours to days after taking the offending drug. An acute reaction of this type usually develops when prior use has sensitized the patient to the medication. Nitrofurantoin and procarbazine are identified with this pattern of acute illness. Acute pleuropulmonary reactions are often accompanied by eosinophilia in both blood and pleural fluid.

If the offending medication is continued, a chronic syndrome developing over weeks to months can occur. Methysergide, dantrolene, and practolol tend to produce a chronic pleural syndrome with effusion and/or fibrosis. Pleural disease is occasionally not evident clinically until 2 to 3 years after the initial administration of the drug. The pleural changes are either unilateral or bilateral. After stopping the medication, the pleural reaction improves in most patients over a period of 6 months; however, some are left with a fibrothorax.

PLEURAL EFFUSION SECONDARY TO ASBESTOS EXPOSURE

Three percent of asbestos workers develop pleural effusions related to their asbestos exposure. There is a direct relationship between the level of asbestos exposure and the development of the pleural effusion. In patients with heavy, moderate, and mild asbestos exposure, the incidence of pleural effusion was 9.2, 3.9, and 0.7 effusions per 10,000 person-years of observation, respectively. The pleural effusion frequently develops within 10 years of the initial exposure, in contrast to the occurrence of pleural plaques and calcification, which usually do not occur until more than 10 years have passed since the initial exposure. It is hypothesized that an asbestos fiber is inhaled, passes to the periphery of the lung, ultimately pierces the visceral pleura, and there rubs against and irritates the parietal pleura creating an inflammatory reaction that will lead to effusion and/or plaque. Microscopic examination of the parietal pleura reveals chronic fibrosing pleuritis with varying degrees of inflammation, but asbestos bodies and fibers are conspicuous for their absence in both the pleural plaque and effusion. There is, however, a heavy burden of asbestos fibers and ferruginous bodies in the lymphatic plexus beneath the visceral pleura, and a lung biopsy can demonstrate the causative agent.

Almost two-thirds of patients with asbestos-related pleural effusions are asymptomatic. Pleuritic chest pain and dyspnea are seen in the other third. Pleural friction rubs are rare. The chest radiograph usually reveals a small or moderate unilateral pleural effusion. In 10 percent of patients, the effusions are bilateral. Approximately 20 percent have associated pleural plaques, fewer than 5 percent have pleural

calcification, and fewer than 10 percent develop pulmonary fibrosis. The pleural fluid is either serous or serosanguineous. The total white blood count in the pleural fluid may be as high as 20,000 per cubic millimeter, and either polymorphonuclear leukocytes or mononuclear cells predominate. Pleural fluid eosinophilia is common.

The diagnosis of asbestos pleural effusion is one of exclusion. Patients should be carefully evaluated for mesothelioma or bronchogenic carcinoma. An extensive evaluation, including direct visualization of the pleural space by thoracoscopy, or an open pleural biopsy is necessary to feel confident that all other possibilities have been excluded.

In most patients, asbestos pleural effusion resolves in 1 to 2 years. Approximately 20 percent will progress to massive pleural fibrosis; another 5 percent develop mesotheliomas. In 30 percent of patients, the volume of the effusion waxes and wanes over a long period.

Rounded atelectasis, or folded lung, is an unusual form of asbestos-associated pleural disease that results in a subpleural focus of airless lung. Radiographically such patients present with a subpleural, rounded mass usually at the lung base. Specific for the syndrome is a curvilinear shadow extending from the lower border of the mass toward the hilus, the "comet tail" sign. In most instances, the pleura immediately adjacent to the mass is thickened, often in conjunction with thickening of the lobar fissures. The initial event in the pathogenesis of rounded atelectasis is believed to be thickening of the parietal and visceral pleurae incident to the asbestos exposure; the adjacent pulmonary parenchyma then undergoes atelectasis. Fusion of the parietal and visceral pleurae immobilizes the lung at its periphery, and further atelectasis causes the airless lung to curl, thereby drawing blood vessels and bronchi to the inferior pole of the mass and creating the comet tail. Once radiographically visible, the rounded atelectasis usually does not progress either in size or contour over many years.

CHYLOTHORAX

Most absorbed fat is conveyed to the blood by the thoracic duct in the form of chylomicrons. Fat enters the intestinal lacteal vessels and then travels to the cisterna chyli, a lymphatic structure located on the body of the second lumbar vertebra. From the cisterna chyli, the thoracic duct traverses the esophageal hiatus of the diaphragm to enter the thoracic cavity. The thoracic duct then ascends extrapleurally in the posterior mediastinum along the right side of the anterior surface of the vertebral column in proximity to the esophagus and the pericardium. At the level of the fourth to sixth thoracic vertebra, the duct crosses to the left of the vertebral column and continues cephalad to terminate in the left subclavian vein.

A chylothorax is formed when the thoracic duct is disrupted and chyle enters the pleural space. Chyle is a milky, opalescent fluid that contains chylomicrons, triglycerides, and lymphocytes; it is bacteriostatic and non-irritating and has little propensity to form fibrothorax. Fifteen hundred to twenty-five hundred milliliters of chyle normally empty into the venous system daily. As a result, pleural effusions resulting from disruption of the thoracic duct can be quite large and tend to reaccumulate rapidly following drainage. The flow of lymph through the thoracic duct can be increased 2 to 10 times the resting level by ingesting fat, whereas ingestion of protein or carbohydrates has little effect on lymph flow. The protein content of chyle is usually above 3 g/dl, and the electrolyte composition is similar to that of serum.

More than 50 percent of chylothoraxes are related to tumor invading the thoracic lymph duct; lymphoma being responsible for 75 percent of the malignancy-associated chylothoraxes. Therefore, nontraumatic chylothorax is an indication for a diligent search for malignancy. Trauma is the second leading cause of chylothorax, responsible for 25 percent of cases. Surgery is the most common cause of traumatic chylothorax, especially in operations that mobilize the left subclavian artery. Chylothorax also may be a result of left subclavian lines complicated by clot that obstructs the thoracic duct ostium. Penetrating trauma to the chest, such as gunshot or knife wounds, occasionally sever the thoracic duct, but nonpenetrating trauma can also produce the syndrome. A chylothorax secondary to closed trauma is usually on the right side, and the site of rupture is in the region of the ninth and tenth thoracic vertebra. Falls, motor vehicle accidents, and compressive injuries to the trunk and abdomen are common causes. However, everyday stresses such as coughing, sneezing, vomiting, and lifting heavy objects may produce a chylothorax. Approximately 25 percent of chylothoraxes have no identifiable cause; they are presumed to be secondary to minor trauma. Pulmonary lymphangiomyomatosis, which is a rare interstitial parenchymal disease, has been associated with chylothorax.

The symptoms of chylothorax are almost exclusively related to the volume of fluid in the thoracic cavity. Fever and chest pain are virtually absent. After trauma, the chylothorax usually develops in 2 to 10 days. Lymph collects extrapleurally in the mediastinum after the thoracic duct is disrupted to form a chyloma, a posterior mediastinal mass. In time, the mediastinal pleura ruptures, and chyle enters the pleural space.

A pleural fluid that is white, odorless, and milky in appearance suggests the diagnosis of chylothorax. Effusions of this appearance are chylothorax, a pseudochylothorax caused by high lipid levels (cholesterol or lecithin-globulin complexes) in chronic pleural effusions, or an empyema. The first step in differentiation is to centrifuge the fluid. If the supernatant clears, the white color is due to large numbers of white blood cells, and the patient probably has an empyema; the supernatant of a chylous or pseudochylous effusion remains opalescent after centrifugation. Cholesterol crystals are usually easily recognized as rhomboid structures on smears of the sediment. A second way to identify cholesterol is to add 1 to 2 ml of ethyl ether to the pleural fluid, which clears if a high concentration of cholesterol is responsible for the

opalescence. Pseudochylothorax accounts for approximately 10 percent of effusions rich in lipids; rheumatoid pleuritis and tuberculosis are the most common underlying diseases for pseudochylothorax.

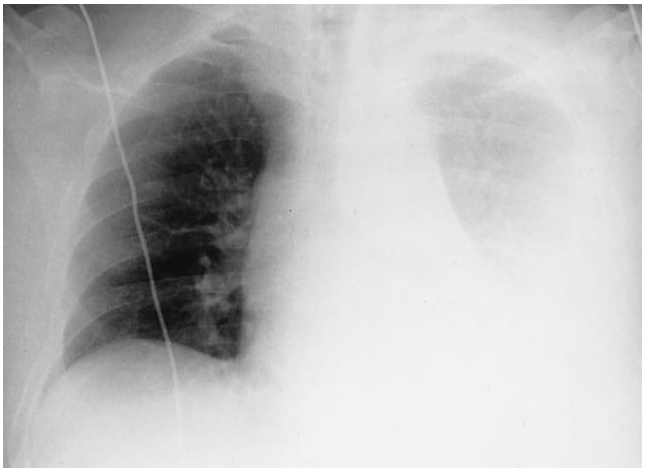
The best way to establish the diagnosis of chylothorax is to determine the concentrations of the triglyceride in the pleural fluid. Triglyceride concentrations greater than 110 mg/dl usually indicate a chylothorax. Levels below 50 mg/dl virtually exclude a chylothorax. In patients with the intermediate values (50–110 mg/dl), a lipoprotein analysis of the pleural fluid is performed. The demonstration of chylomicrons by lipoprotein analysis establishes the diagnosis of chylothorax. Remember that not all chylous fluids have a classic milky appearance. Indeed, almost half are either bloody or turbid in appearance. Therefore, determination of the triglyceride content of an exudative fluid of unknown etiology, particulary in patients with mediastinal malignancy, thoracic trauma, or recent thoracic surgery, is a must.

For patients with chylothorax resulting from traumatic or surgical disruption of the thoracic duct, therapeutic efforts should be directed toward correction of the leak rather than simply removing the fluid. The defect in the thoracic duct often closes spontaneously if caused by trauma. In the dyspneic patient, management begins with placement of either a pleuroperitoneal shunt or chest tube. Efforts are then made to reduce chyle formation; these include placing the patient on constant gastric suction and keeping the patient at bed rest; fluid and nutrition are best supplied by parenteral hyperalimentation. Medium-chain triglycerides have been proposed as a means of providing an oral source of calories to these patients. The rationale is that the medium-chain triglycerides are absorbed into the portal vein directly and thus enter the circulatory system rather than travel through the thoracic duct. In most instances, the drainage of chyle will slow or stop within the first 7 days following chest tube insertion. Malnutrition and lymphopenia are likely to occur in a patient with chylothorax if large amounts of lymph are drained. If lymph drainage has not stopped spontaneously within 7 days, surgical ligation of the thoracic duct is in order. At the time of surgery, an attempt is made to find the leak in the duct and ligate on both sides of the leak. In many instances, the leak will not be found, and the thoracic duct is ligated both high and low in the thorax. Pleurodesis is a therapeutic alternative that is reserved for poor-risk patients who are not surgical candidates.

The management of a nontraumatic chylothorax poses a challenge to the clinician to identify the cause of the leak and treat it successfully. Lymphoma is a key candidate. Often the patient with lymphoma and chylothorax has no evidence of lymphoma outside the thorax. A CT study of the mediastinum should be done on all such patients. The initial management of the patient with chylothorax suspected of occult intrathoracic lymphoma is as described above: inserting a chest tube, placing the gastrointestinal tract at rest, and preserving the patient's nutritional status by using parenteral hyperalimentation. If the CT scan and/or chest radiograph show evidence of intrathoracic tumor, the patient should undergo biopsy of this tumor to establish diagnosis. In a patient known to have lymphoma or metastatic carcinoma, chylothorax may be treated by chemotherapy and mediastinal irradiation in anticipation that the leak will stop. Surgical ligation of the thoracic duct is less successful in chylothorax resulting from malignancy. Pleurodesis may still be effective and for chylothorax secondary to lymphoma has been shown to be highly effective.

HEMOTHORAX

Hemothorax is the presence of significant amounts of blood in the pleural space (Fig. 85-6). The most common causes



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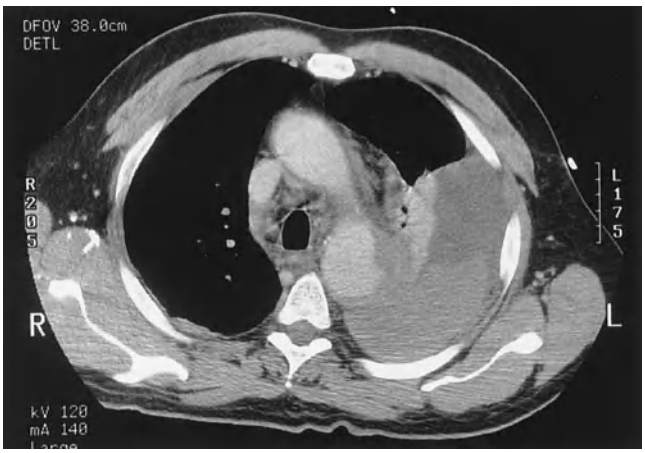

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Figure 85-6 *A.* Admission chest radiograph of a 56-year-old man with a 1-week history of left-sided chest pain showed total opacification of the left hemithorax. Thoracentesis demonstrated a hemothorax. *B.* A CT scan of the thorax showed a dissecting aneurysm of the ascending thoracic aorta with hemorrhage into the left pleural space.

are penetrating and non-penetrating chest trauma. Occasionally iatrogenic procedures, such as percutaneous placement of central venous catheters in the subclavian or internal jugular veins, or translumbar aortography, produce a hemothorax.

Hemothorax should be considered to be present when the hematocrit of the pleural fluid is more than half that of the peripheral blood. The diagnosis should be entertained in any individual with thoracic trauma and a pleural effusion on the chest radiograph. A number of bleeding sites may be responsible for the hemothorax, complicating either blunt or penetrating trauma. These sites include pulmonary parenchymal laceration, intercostal vessel laceration, and rupture of pleural adhesions. Much less common is mediastinal injury that causes damage of a major blood vessel or decompression of abdominal hemorrhage through a traumatic diaphragmatic injury. The vast majority of hemothoraxes are due to bleeding from the low-pressure, pulmonary parenchymal vessels; they stop bleeding spontaneously when the hemothorax is evacuated and the pleural surfaces are reapposed.

In 60 to 80 percent of these patients, an associated pneumothorax is found, after both nonpenetrating and penetrating trauma. The treatment of choice is the immediate insertion of a chest tube. The chest tube is useful to: (1) evacuate blood from the pleural space, thereby decreasing the incidence of empyema and/or fibrothorax; (2) stop bleeding from pulmonary parenchyma or pleural lacerations by apposing the pleural surfaces to create a tamponade; and (3) provide a quantitative measure of continued bleeding. Immediate thoracotomy is rarely indicated, since tube thoracostomy controls bleeding in about 85 percent of cases. But cardiac tamponade, continued bleeding, evidence of a major bronchial rupture, or sucking chest wounds require immediate thoracotomy. If bleeding is more than 200 ml/hour and shows no signs of slowing over 4 to 6 hour, thoracotomy should be seriously considered to control bleeding. Thoracotomy is not indicated for removal of retained blood in patients without active bleeding. The incidence of empyema thoracis is the same in patients undergoing surgical evacuation as in those who are allowed to undergo spontaneous lysis of the pleural clot. Approximately 85 percent of patients with hemothorax and retained blood are left with no pleural abnormalities on follow-up examination.

Empyema occurs in approximately 5 percent of patients with hemothorax. Those with gross contamination of the pleural space at the time of their original injury are most susceptible. Empyema is also more common in patients who are in shock on admission, in those with associated abdominal injuries, and in patients who require prolonged pleural drainage.

An exudative pleural effusion occasionally follows a hemothorax after removal of the chest tubes. This occurs in 15 to 30 percent of patients and is more common in those with residual hemothorax when the tube is removed. When such an effusion does occur, a diagnostic thoracentesis is performed to rule out the possibility of pleural infection. If a pleural infection is not present, the pleural effusion usually clears spontaneously without residual disease. Fewer than 1 percent of patients with hemothorax develop a fibrothorax.

Nontraumatic hemothorax is uncommon. But when it does occur, it usually indicates pleural malignancy. It can also occur during anticoagulant therapy for pulmonary embolus. Other causes include bleeding disorders such as hemophilia or thrombocytopenia, complication of spontaneous pneumothorax, ruptured thoracic aorta, and pancreatic pseudocyst.

POSTSURGICAL PLEURAL EFFUSIONS

Two to three days after an upper abdominal surgical procedure, pleural effusions can be identified on the decubitus chest radiograph in up to 70 percent of patients. The effusions are usually small with only 20 percent measuring more than 10 mm in thickness on the decubitus films. Postoperative pleural effusions are more common in patients undergoing upper abdominal surgical procedures, in patients with postoperative atelectasis, and in those with free abdominal fluid at the time of operation. Large effusions are particularly apt to occur after splenectomy. The effusions resolve spontaneously.

The incidence of pleural effusion following coronary artery bypass surgery is as high as 40 percent. The mechanism is unknown but probably involves trauma to the pleura and pericardium during surgery. Effusions are frequently bilateral or unilateral on the left but rarely unilateral on the right. Proper management is usually observation, and a diagnostic tap is not warranted.

SARCOIDOSIS

Pleural sarcoidosis has typically been identified at thoracotomy or autopsy. Small pleural effusions and pleural thickening from sarcoidosis are rarely extensive enough to produce clinical or physiological consequences and often are not readily apparent on chest radiographs. CT scanning, however, has demonstrated a high incidence of minor pleural abnormalities. Pleural thickening is often seen in association with extensive parenchymal disease. Pleural abnormalities are often located in the lower lung fields.

A pleural effusion can occur in up to 7 percent of patients with sarcoidosis. One-third of cases are bilateral. Pleural biopsy often reveals multiple non-caseating granuloma. Effusions are free-flowing, rarely loculate, and generally small to moderate in size. The fluid is usually an exudate and invariably shows a predominance of lymphocytes. The pleural effusion is rarely associated with acute symptoms such as pleuritic pain, fever, or dyspnea. In some, the effusion may clear spontaneously or with corticosteroid therapy in 1 to 2 months; in others, the effusion can progress to chronic pleural

thickening. Because of its relatively rare occurrence, the presence of a pleural effusion in association with pulmonary sarcoidosis should raise a possibility of other causes, including tuberculosis, pneumonia, or heart failure.

POST-CARDIAC INJURY (DRESSLER'S) SYNDROME

The post-cardiac injury syndrome consists of fever and pleuropericarditis developing after injury to the pericardium or myocardium. The syndrome has been described following myocardial infarction, cardiac surgery, and blunt chest trauma and occurs in approximately 1 percent of patients with acute myocardial infarction and up to 30 percent of patients undergoing surgical procedures involving the pericardium. Dressler's syndrome is thought to be an immunologic response to damage of the pericardium, and antibodies to cardiac antigens can be demonstrated in many patients.

Affected individuals develop fever, chest pain, pericarditis, pleuritis, and sometimes air space disease after the cardiac injury. Symptoms usually occur in the second or third week following myocardial injury. Almost all patients have a pericardial friction rub, and many have a pericardial effusion. Most patients have a peripheral leukocytosis and an elevated erythrocyte sedimentation rate. The pleural effusion may be either unilateral or bilateral and is usually small. Pericarditis is the dominant clinical feature. The pleural fluid is an exudate with a normal pH and a normal glucose level. Almost a third of patients will have bloody pleural fluid. The pleural fluid cell population will vary from polymorphonuclear predominance to lymphocyte predominance in the more chronic syndromes. The diagnosis is one of exclusion.

Non-steroidal anti-inflammatory treatment is typically quite effective at relieving symptoms and hastening resolution of the effusion. For those who fail non-steroidal anti-inflammatory treatment, oral corticosteroids are typically effective.

UREMIC PLEURITIS

Fibrinous pleuritis is found at autopsy in approximately 20 percent of patients dying of uremia. The pleuritis frequently is asymptomatic but sometimes produces pleuritic chest pain, pleural friction rubs, and pleural effusions. The incidence of pleural effusions with uremia is approximately 3 percent; half of the patients are symptomatic. Sometimes, the effusions are quite large and may occupy more than 50 percent of the hemithorax. The fluid is an exudate that is frequently serosanguineous or hemorrhagic. The glucose level is normal, and the differential white blood count reveals a predominance of lymphocytes in most patients. Pleural biopsy results are nonspecific and reveal chronic fibrinous pleuritis. The diagnosis of uremic pleuritis is again one of exclusion in the patient with chronic renal failure. Dialysis is the treatment of choice. With dialysis, the effusion gradually disappears within 4 to 6 weeks in the majority of patients.

YELLOW NAIL SYNDROME

The *yellow nail syndrome* refers to thickening, yellowing, and curvature of all the nails in association with lymph edema. It may be associated with pleural effusions, chronic pulmonary infections, and bronchiectasis. The basic abnormality is hypoplasia of the lymphatic vessels. It is conjectured that pleural effusions may develop when a lower respiratory tract infection or pleural inflammation further damages already compromised lymphatic vessels. Pleural effusion occurs in approximately one-third of patients with the yellow nail syndrome. The pleural effusions are bilateral half the time and vary in size from small to massive. The pleural fluid is a clear yellow exudate with normal glucose and predominant lymphocytes in the pleural fluid differential. No specific treatment is available. Spontaneous remission is very unlikely. If the effusion is large, and produces dyspnea, pleurodesis should be considered.

PLEURAL EFFUSIONS IN PATIENTS WITH AIDS

Pleural effusions occur in up to 27 percent of hospitalized patients with AIDS. A series of 59 AIDS patients with pleural effusions revealed the cause to be infectious in 39 (66 percent), noninfectious in 18 (31 percent), and unknown in 2 (3 percent). Pleural effusions were caused by bacterial pneumonia in 18 (31 percent) patients, *Pneumocystis carinii* pneumonia in 9 (15 percent), *Mycobacterium tuberculosis* in 5 (8 percent), septic embolization in 2 (3 percent), *Nocardia asteroides* in 2 (3 percent), *Cryptococcus neoformans* in 2 (3 percent), and *Mycobacterium avium intracellulare* in 1 (2 percent). Among noninfectious causes (18 patients), hyperalbuminemia was the cause in 11 patients (19 percent), cardiac failure in 3 (5 percent), and atelectasis, Kaposi's sarcoma (KS), uremic pleurisy, and adult respiratory syndrome in 1 (2 percent) each. Patients with AIDS who had pleural effusions have significantly lower serum albumin levels and lower CD4 counts than those without pleural effusions.

In some patients with *Pneumocystis carinii*–associated pleural effusion, the diagnosis can be established by demonstrating the organism in pleural fluid stained with Gomori's methenamine-silver. The pleural fluid is an exudate with normal pleural fluid glucose and pH.

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86

Malignant Pleural Effusions

Steven A. Sahn

A malignant pleural effusion is diagnosed by detecting exfoliated malignant cells in pleural fluid or demonstrating these cells in pleural tissue obtained by percutaneous pleural biopsy, thoracoscopy, or thoracotomy, or at autopsy. In a number of patients, even though the pleural effusion is caused by the malignancy, neoplastic cells cannot be demonstrated in pleural fluid or pleural tissue and, in fact, probably are not present in these tissues. It makes sense to categorize these pleural effusions associated with malignancy, in which there is no direct pleural involvement with tumor and no other cause for the effusion is found, as paramalignant effusions (Table 86-1). Lymphatic obstruction appears to be the most common mechanism for the development of a paramalignant effusion, for the accumulation of large volumes of fluid. Other local effects of the tumor causing a paramalignant effusion are bronchial obstruction resulting in pneumonia or atelectasis. Furthermore, it is important for the clinician to recognize that effusions can result from systemic effects of the tumor and adverse effects of therapy.

Establishing the diagnosis of a malignant pleural effusion secondary to lung cancer signals incurability. A malignant effusion secondary to a non-lung primary is a manifestation of far advanced disease and is associated with limited survival.

MALIGNANCIES ASSOCIATED WITH PLEURAL EFFUSIONS

Carcinoma of any organ can metastasize to the pleura. However, carcinoma of the lung is the most common malignancy to invade the pleura and produce malignant and paramalignant effusions (Table 86-2). Carcinoma of the breast is second in incidence and, in some populations, exceeds lung cancer as a cause of malignant effusions. After lung and breast cancer, the frequency declines markedly, with ovarian and gastric cancer representing up to 5 percent of malignant pleural effusions. Lymphoma accounts for approximately 10 percent of all malignant pleural effusions and is a common cause of chylothorax. Carcinomas of the lung, breast, ovary, and stomach and lymphomas account for about 80 percent of all malignant pleural effusions. In approximately 7 percent of patients with malignant pleural effusions, the primary site is unknown when the diagnosis of a malignant pleural effusion is first established.

A less common cause of a malignant pleural effusion, other than metastatic carcinoma and lymphoma, is a primary tumor of the pleura, malignant mesothelioma. The association of asbestos exposure and malignant mesothelioma was

Table 86-1

Causes of Paramalignant Pleural Effusions

Cause	Comment
Local effects of tumor	
Lymphatic obstruction	Predominant mechanism for pleural fluid accumulation
Bronchial obstruction with pneumonia	Parapneumonic effusion; does not exclude operability in lung cancer
Bronchial obstruction with atelectasis	Transudate; does not exclude operability in lung cancer
Chylothorax	Disruption of thoracic duct or its major tributaries; lymphoma a common cause
Systemic effects of tumor	
Pulmonary embolism	Hypercoagulable state; adenocarcinomas
Hypoalbuminemia	Serum albumin <1.5 g/dl; anasarca typically present
Complications of therapy	
Radiation therapy	
Early	Pleuritis 6 weeks to 6 months following completion of radiation
Late	Mediastinal fibrosis Constrictive pericarditis Vena caval obstruction
Chemotherapy	
Methotrexate	Pleuritis or effusion ± blood eosinophilia
Procarbazine	Blood eosinophilia; fever and chills
Cyclophosphamide	Pleuropericarditis
Mitomycin	In association with interstitial disease
Bleomycin	In association with interstitial disease

Table 86-2

Causes of Malignant Pleural Effusion*

Tumor	n	Percent
Lung	641	36
Breast	449	25
Lymphoma	187	10
Ovary	88	5
Stomach	42	2
Unknown primary	129	7
All other malignancies	257	14

* $n = 1793$. *Combined data from nine series.*

documented in the 1960s following an initial report from the North Western Cape Province of South Africa and a subsequent study of insulation workers in this country. Owing to the long latency period of 20 to 40 years between exposure and onset of disease, death due to mesothelioma is expected to reach 9000 in 2020 in Europe and 2200 annually in the United States.

PATHOGENESIS

Lymphatics are situated beneath the parietal pleura over the intercostal spaces. An important feature of the parietal pleura is lymphatic stomata, 2- to 12-μm openings between parietal pleural mesothelial cells. The stomata and their associated lymphatic channels form lymphatic lacunae immediately beneath the mesothelial layer. These lacunae coalesce into collecting lymphatics, which join the intercostal trunk vessels with flow directed mainly toward the mediastinal lymph nodes. The lymphatic system of the parietal pleura plays a major role in the resorption of pleural liquid and protein. Interference with the integrity of the lymphatic system between the parietal pleura and mediastinal lymph nodes can result in a pleural effusion. Autopsy series have indicated that impaired lymphatic drainage from the pleural space is the predominant mechanism for the accumulation of fluid associated with malignancy: A strong relationship was found between carcinomatous infiltration of the mediastinal lymph nodes and the occurrence of pleural effusion; in contrast, no relationship was found between the extent of direct pleural involvement by metastasis and the occurrence of pleural effusion. Further support for this mechanism is provided by the observation that pleural effusions generally do not develop when the pleura is involved by sarcoma because of the characteristic absence of lymphatic metastases.

When pleural metastases occur, tumor cells either "seed" the mesothelial surface or invade the subserous layer: When the mesothelial surface is involved, abundant tumor cells can be found in pleural fluid; with subserous involvement, a paucity of malignant cells are exfoliated into the pleural space. Tumor involvement of the pleura causes reactive changes in the mesothelium that may lead to mesothelial shedding, mesothelial thickening, and, on occasion, marked pleural fibrosis. Pleural fibrosis, usually observed in the more advanced stage of tumor involvement of the pleura, is at least partially responsible for the low concentrations of glucose and

the low pH seen in some malignant pleural effusions and for the failure to achieve pleurodesis after instillation of chemical agents.

A bloody, malignant pleural effusion usually results from direct invasion of blood vessels, occlusion of venules, tumor-induced angiogenesis, or possibly increased capillary permeability due to vasoactive cytokines and chemokines. Malignant pleural effusions usually contain a large number of morphologically normal lymphocytes, usually in the 50 to 70 percent range, but typically less than occurs with tuberculous pleurisy (usually greater than or equal to 80 percent). Although the reason for the lymphocytosis is not clear, these lymphocytes are predominantly T lymphocytes that appear to play a role in the local defense against tumor invasion of the pleural cavity. The percentage of mesothelial cells in malignant effusions is variable, ranging from few to a large percentage of the total cells. An abundance of mesothelial cells occurs early in the course of pleural infiltration, before pleural fibrosis and marked infiltration with tumor; in more advanced stages of pleural metastasis, fewer mesothelial cells are generally seen because of pleural fibrosis.

Autopsy data in patients with malignant effusions have provided valuable information about the pathogenesis of pleural metastases. When carcinoma of the lung metastasizes to the pleura, both the visceral and parietal pleural surfaces tend to be involved. The visceral pleural surface is rarely, and the parietal pleural surface almost never, the sole site of involvement. Parietal pleural involvement in lung cancer probably results from neoplastic spread across the pleural cavity from visceral pleural sites along pleural adhesions that are either preformed or secondary to the malignant process. The pathogenesis of visceral pleural metastasis in lung cancer appears to be through pulmonary artery invasion and embolization. The histological type of lung cancer does not seem to determine the propensity for pulmonary arterial invasion. Adenocarcinoma of the lung is the most common cell type to involve the pleura because of its peripheral location and spread by contiguity. Bilateral pleural metastases in lung cancer are almost always associated with evidence of hepatic involvement and parenchymal invasion of the contralateral lung.

Pleural metastases from primary sites below the diaphragm generally are a manifestation of a tertiary spread from established liver metastases. The data with breast cancer are conflicting; some studies show a high incidence of ipsilateral pleural effusion, while others show no such predilection. Probably two mechanisms are operative, chest wall lymphatic invasion resulting in an ipsilateral effusion and hepatic spread with bilateral or contralateral disease.

At diagnosis, pleural effusions are rare in Hodgkin's disease but not infrequent in non-Hodgkin's lymphoma. Pleural effusions can be found in previously untreated patients with non-Hodgkin's lymphoma, even in the absence of detectable intrathoracic lymphadenopathy; however, the pleural effusion is usually not an isolated manifestation of the disease. At autopsy in Hodgkin's disease, lymphomatous infiltration of the lung rather than direct pleural invasion or mediastinal adenopathy has been found in association with the pleural effusion. Lymphomatous invasion of the pleura appears to be an uncommon and late finding in Hodgkin's disease but is seen with increased frequency in non-Hodgkin's lymphoma. As Hodgkin's disease progresses, the incidence of pleural effusion increases and approaches 30 percent. At autopsy, a 30 to 60 percent incidence of pleural effusions and a 7 to 30 percent incidence of pleural nodular infiltrative lesions have been noted.

While pleural effusion in lymphoma can be due to impaired lymphatic drainage secondary to mediastinal adenopathy, pleural or pulmonary infiltration, or thoracic duct obstruction, impaired lymphatic drainage appears to be the primary mechanism in Hodgkin's disease and direct pleural infiltration the predominant cause in non-Hodgkin's lymphoma.

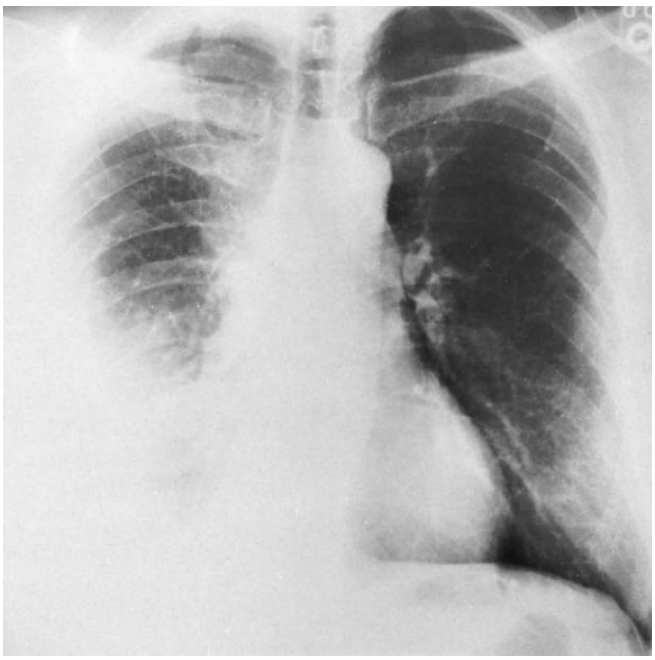
Malignant mesothelioma (see Chapter 88) is usually a unilateral disease (Fig. 86-1); bilateral tumors are present in less than 10 percent of patients. An early manifestation of the tumor is pleural effusion that is reabsorbed or organized and then largely replaced by tumor and fibrosis. At autopsy, the lung is often encased in tumor that involves both visceral and parietal pleural surfaces. The pleural space is often obliterated, and the amount of pleural fluid is variable. The tumor seldom penetrates deeply into the lung parenchyma; instead, it extends into interlobar fissures. Hilar lymph nodes are involved by tumor in less than 50 percent of patients. Distant hematogenous metastases are unusual but have been described in liver, bone, adrenals, thyroid, and kidneys.

The two distinct histological types of malignant mesothelioma (epithelial and sarcomatous) generally behave differently. Some patients have mixed tumors with both epithelioid and sarcomatous features. The clinical features of epithelial mesothelioma are similar to those of metastatic carcinoma of the pleura associated with tumor spread by direct extension, i.e., a large pleural effusion and metastases to regional lymph nodes. In contrast, patients with sarcomatous mesotheliomas tend to have features characteristic of sarcomas, i.e., distant metastases are common, whereas there is little or no pleural effusion. These data are consistent with the pathogenesis of pleural effusions in carcinoma of the pleura, i.e., the pleural effusion is due primarily to invasion of the lymphatic system. Moreover, the large bulk of tumor on the pleural surface would be expected to interfere with the removal of pleural fluid by the parietal pleural lymphatics even if the lymphatics were not directly involved with tumor.

Benign asbestos pleural effusions (BAPE) probably develop as a result of the pleural inflammation that occurs during the passage of asbestos fibers across the pleural space to the parietal pleural lymphatics.

CLINICAL PRESENTATION

Patients with carcinoma involving the pleura most often present with symptoms attributable to a large pleural



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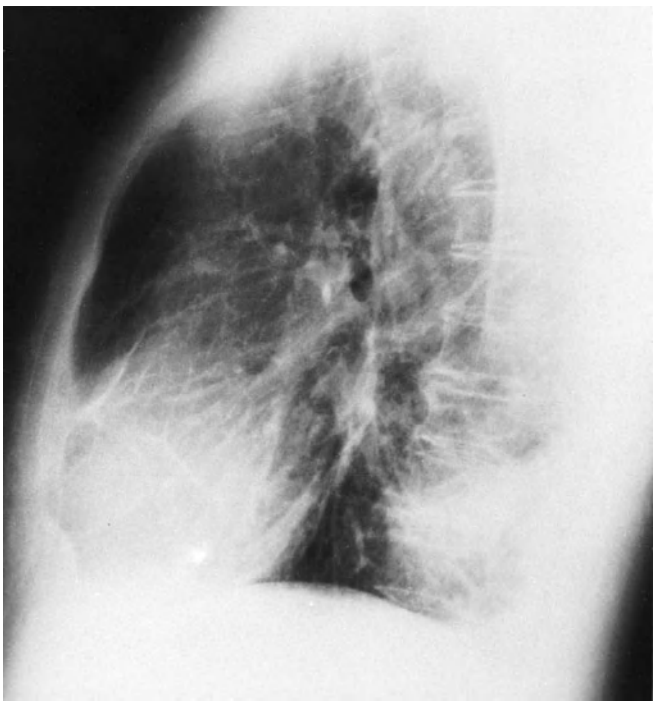

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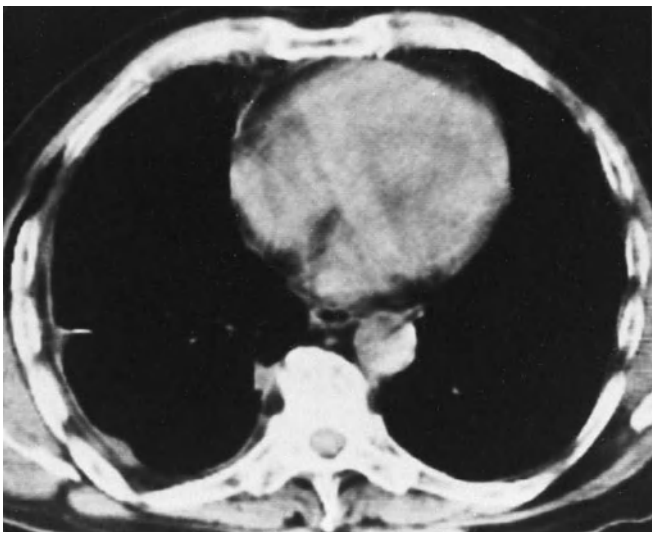

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Figure 86-1 Malignant mesothelioma in a 64-year-old man. *A,B.* Diffuse, right-sided involvement. *C.* Computed tomography scan shows peripheral disposition of mesothelioma along right pleura. The radiodensity in the right hemithorax is a consequence primarily of pleural tumor with little pleural effusion, subsequently treated by right extrapleural pneumonectomy. *(Courtesy of Dr. David Murphy.)*

effusion, dyspnea on exertion and cough. The presence and degree of dyspnea depends on the size of the effusion and the patient's underlying pulmonary function. A therapeutic thoracentesis results in relief of dyspnea in most patients. However, the volume of pleural fluid removed at thoracentesis does not correlate with the change in lung volume. The increase in total lung capacity (TLC) approximates one-third of the volume of fluid removed, while the forced vital capacity (FVC) increases to about one-half of the TLC. Indeed, the mechanism of dyspnea caused by a large pleural effusion appears to be multifactorial in origin, probably entailing a decrease in the compliance of the chest wall, a contralateral shift of the mediastinum, inversion of the ipsilateral diaphragm, and a decrease in ipsilateral lung volume modulated by neurogenic reflexes from the lungs and chest wall. An obstructive pneumonitis, endobronchial lesion that causes atelectasis, or infiltrative malignant disease of the pulmonary parenchyma may also contribute to dyspnea and cough.

Since malignant involvement of the pleura signifies far advanced disease, these patients commonly have substantial weight loss and appear chronically ill. Chest pain may be present because of involvement of the parietal pleura, ribs, or chest wall. However, in a large series of patients with metastatic carcinoma of the pleura, almost 25 percent were "asymptomatic" at the time of presentation. In these patients, the malignant pleural effusion was first suspected on physical examination or diagnosed on routine chest radiograph; in almost 50 percent of patients, the pleural effusion was the first indication of cancer.

The respiratory symptoms of patients with pleural effusion due to lymphoma are indistinguishable in nature and frequency from those due to carcinoma. About 20 percent of patients with lymphoma have no respiratory symptoms when the malignant pleural effusion is diagnosed.

Most patients with carcinoma of the pleura have evidence of a pleural effusion on physical examination when first seen by the physician; physical signs of pleural effusion are to be expected, since the volume of pleural fluid in most malignant effusions is greater than 500 mL. Cachexia and lymphadenopathy are present in about one-third of patients on initial presentation; ipsilateral chest wall tenderness and pleural friction rub are rare.

In contrast to patients with carcinomatous involvement of the pleura, virtually all patients with malignant mesotheliomas are symptomatic when first seen by the physician: In six series of patients encompassing 160 cases of malignant mesothelioma, only one patient was asymptomatic at presentation. Chest pain is the most common presenting symptom and occurs in 60 to 70 percent of patients. Dyspnea and cough are next in frequency and are present in about 25 and 20 percent of patients, respectively.

Pleural effusion due to asbestos exposure is a diagnosis of exclusion. Its frequency of occurrence in exposed workers is estimated to be up to 7 percent. BAPE is the most common manifestation of asbestos-related pleuropulmonary disease in the first 20 years after initial asbestos exposure. Two-thirds of patients with BAPE are asymptomatic at presentation, with the effusion diagnosed on a routine chest radiograph. Approximately 20 percent of patients present with pleuritic pain and 10 percent with dyspnea. The effusion generally persists for several months and resolves within a year. Recurrent effusions, either on the ipsilateral or contralateral side, occur in approximately 25 percent of patients. The differential diagnosis centers around distinguishing BAPE from mesothelioma. Since BAPE occurs sooner after initial exposure than does mesothelioma, i.e., 20 years being the rough dividing line, the pleural effusion in a young asbestos-exposed individual is more likely to represent BAPE than is an effusion that occurs 20 to 40 years after initial exposure. Also, an asymptomatic pleural effusion is more apt to be benign. The absence of other radiographic manifestations of asbestos exposure is not helpful in distinguishing between benign effusion and mesothelioma. Preoccupation with asbestos-related disease occasionally leads to overlooking treatable disorders, such as tuberculosis.

CHEST RADIOGRAPHY

A pleural effusion ipsilateral to the primary lesion is the rule in carcinoma of the lung. When the primary site of the cancer is elsewhere than the lung, with the possible exception of breast cancer, there seems to be no ipsilateral predilection and bilateral effusions are common.

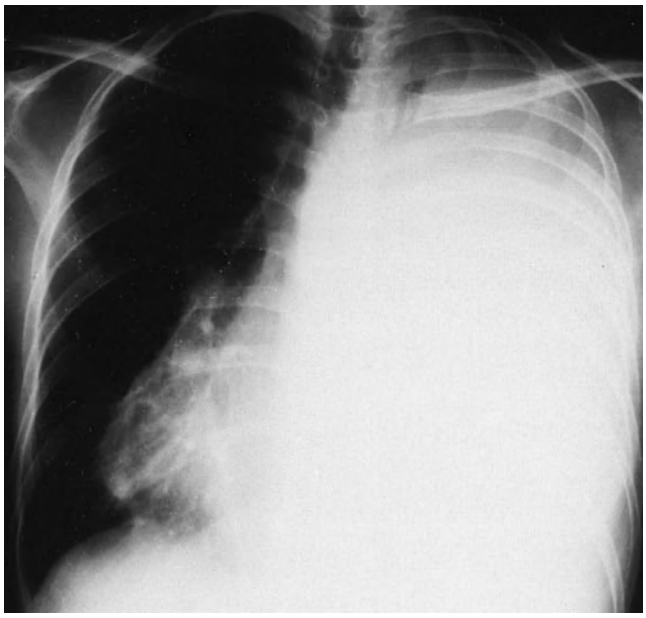

Figure 86-2 Carcinoma of the cervix metastatic to the left pleura and mediastinum. The massive pleural effusion is associated with a contralateral shift of the mediastinum.

In three of four patients who present with carcinomatous involvement of the pleura, the pleural effusion is moderate to large, i.e., with volumes ranging from 500 to 2000 ml of fluid. Approximately 10 percent present with effusions of less than 500 ml; another 10 percent present with massive pleural effusions (complete opacification of the hemithorax) (Fig. 86-2). Some 70 percent of patients with a massive pleural effusion have a malignancy.

The finding of bilateral effusions and a normal heart size also suggests a malignant etiology (Fig. 86-3). Approximately 50 percent of patients who present with this radiographic

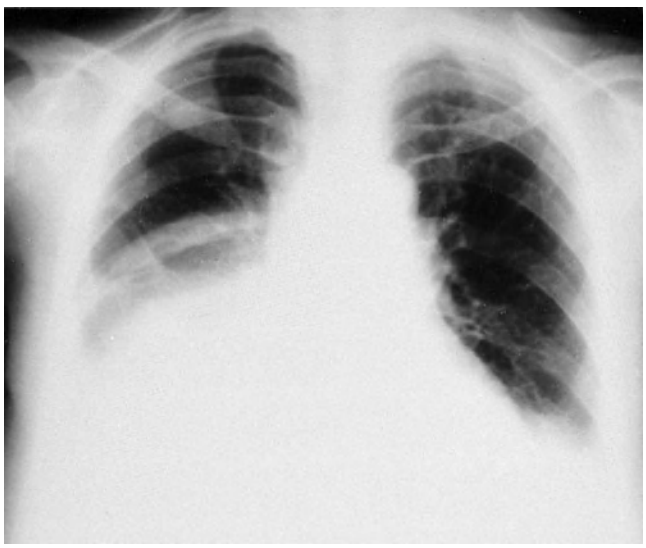

Figure 86-3 Carcinoma of the lung involving right lower lobe, with metastasis to right pleura and mediastinal lymph nodes. The pleural effusions are bilateral and the heart size is normal.

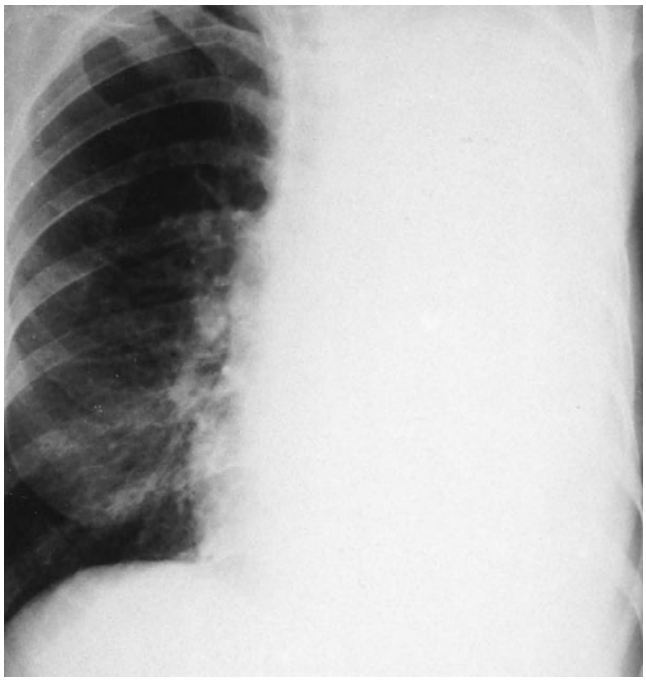

Figure 86-4 Carcinoma of the left mainstem bronchus resulting in complete atelectasis of the left lung. The left hemithorax is completely opacified, and the mediastinum has shifted to the side of the bronchial occlusion. The radiographic opacity represents a combination of collapsed lung and pleural fluid.

finding have a malignant effusion; however, lupus pleuritis, hypoalbuminemia, constrictive pericarditis, rheumatoid pleurisy, BAPE, and cirrhosis must also be considered in the differential diagnosis.

If the mediastinum does not shift contralaterally in the face of a large pleural effusion (greater than 1500 ml), malignancy is highly likely. The following diagnoses are then considered: (1) carcinoma of the ipsilateral mainstem bronchus resulting in atelectasis (Fig. 86-4); (2) a fixed mediastinum due to malignant lymph nodes; (3) malignant mesothelioma (the radiodensity represents predominantly tumor with only a small effusion); and (4) extensive tumor infiltration of the ipsilateral lung radiographically mimicking a large effusion. Interstitial infiltrates with effusions (lymphangitic carcinomatosis) and multiple nodules with effusions also suggest malignant disease.

Depending on the stage of the mesothelioma at the time of presentation, the chest radiograph may show a moderate to large pleural effusion (early) or a nodular, thickened pleura with extension to the apex of the hemithorax (late). Contralateral mediastinal shift often occurs early, i.e., when the pleural effusion is large; but, as fluid resorbs and is replaced by tumor, the ipsilateral hemithorax shrinks in size and the mediastinal structures either remain in the midline or shift ipsilaterally (Fig. 86-1). Contralateral manifestations of asbestos-induced pleuropulmonary disease, such as pleural plaques with or without calcification and interstitial lung disease, often reinforce the diagnosis. In the more advanced stages of malignant mesothelioma, other radiographic findings are mediastinal widening due to lymph node involvement, an enlarged cardiac silhouette due to pericardial involvement with effusion, and extrapleural lesions such as soft tissue masses or rib destruction.

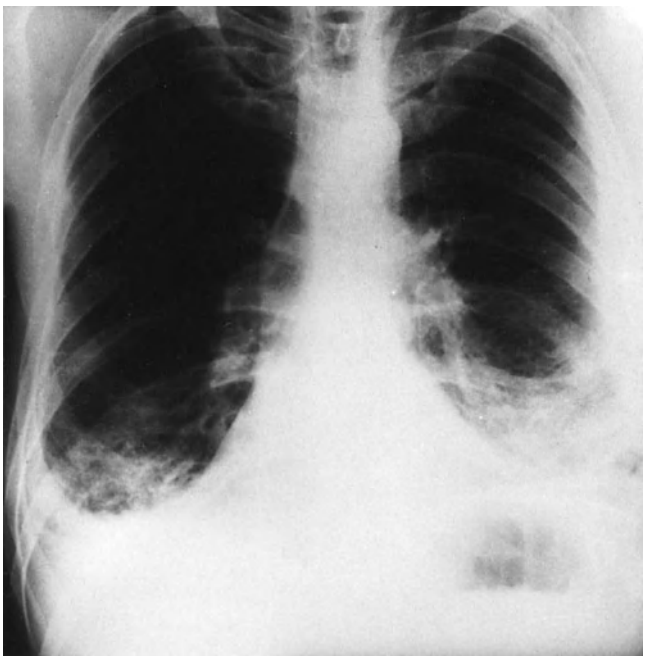

Figure 86-5 Bilateral pleural thickening in a 44-year-old man exposed to asbestos for 18 months 20 years ago. Bilateral pleural effusions were succeeded by progressive pleural thickening.

Benign asbestos pleural effusions are small to moderate (less than 1000 ml) unilateral effusions with evidence of pleural plaques or asbestosis identifiable in less than 20 percent of patients. Calcified pleural plaques are rare, since calcifications require 25 to 40 years from the time of initial asbestos exposure, whereas BAPE tends to be the earliest manifestation of asbestos pleuropulmonary disease. Some patients are left with normal chest radiographs, but most have residual abnormalities. These include a blunted costophrenic angle (most common), crow's feet (converging fibrous strands creating a likeness of a bird's foot), rounded atelectasis (in which a portion of the lung periphery has become atelectatic due to pleural adhesions that collapse small bronchi), and diffuse pleural thickening that is sometimes progressive (Fig. 86-5).

PLEURAL FLUID CHARACTERISTICS

Malignant pleural fluid may be serous, serosanguinous, or grossly bloody. The number of nucleated cells in the pleural fluid is modest (1500 to 4000/μl) and consists of lymphocytes, macrophages, and mesothelial cells. In about one-half of malignant pleural effusions, lymphocytes predominate (50 to 70 percent of nucleated cells). Malignant cells in pleural fluid are rare in some patients; in others they constitute virtually the complete population. Polymorphonuclear

leukocytes usually represent less than 25 percent of the cell population; but, rarely, when pleural inflammation is active, they predominate. The reported prevalence of pleural eosinophilia in malignant effusions ranges from 8 to 12 percent. However, malignancy was as frequent in eosinophilic as noneosinophilic pleural effusions. Therefore, the finding of pleural fluid eosinophilia should not be considered a predictor of benign disease.

The pleural fluid in patients with carcinoma of the pleura is usually an exudate with a protein concentration of about 4 g/dl. However, protein concentrations have been reported in the range of 1.5 to 8.0 g/dl. Often unappreciated is the fact that less than 5 percent of malignant pleural effusions can be transudates. These transudates are due either to concomitant congestive heart failure, atelectasis from tumor obstructing a major bronchus, or the early stages of lymphatic obstruction. Since protein can exit from the pleural space only by parietal pleural lymphatics, a few weeks are necessary for protein to accumulate (from the 1.5 g/dl of normal pleural liquid) to a level of greater than 50 percent of the serum concentration. Chronic pleural effusions and those with a low pleural fluid pH and glucose tend to have a higher total protein concentration and are virtually never transudates. Sometimes, the total protein pleural fluid to serum ratio may be low (less than 0.50), but the fluid would qualify as an exudate by lactic dehydrogenase (LDH) criterion alone.

In about one-third of patients with malignant pleural effusions at the time of diagnosis, the pleural fluid pH is low (less than 7.30), ranging from 6.95 to 7.29. In these low-pH effusions, the glucose concentration is also low (less than 60 mg/dL, or the ratio of pleural fluid to serum glucose is below 0.5), the lactate concentration is high, the Pc_{O_2} is high, and the P_{O_2} is low. On rare occasions, the glucose is as low as 5 mg/dl; but as a rule the concentrations are in the range of 30 to 55 mg/dl.

These low-pH, low-glucose effusions have usually been present for several months and are associated with a large tumor burden and fibrosis of the pleura. The markedly abnormal pleura interferes with glucose transport from blood to pleural fluid; the glucose that does enter is metabolized by normal and malignant pleural cells to form CO_2 and lactate. The abnormal pleura impairs the efflux of these end products of glucose metabolism from the pleural space, resulting in pleural fluid acidosis. About 10 percent of malignant pleural effusions have high amylase concentrations. The finding of a high level of salivary-like isoamylase in a patient without esophageal rupture essentially establishes the diagnosis of malignancy, most likely adenocarcinoma of the lung.

Early in the course of malignant mesothelioma, the pleural fluid may be serous; later, it tends to be hemorrhagic. The effusion associated with malignant mesothelioma is an exudate with a protein concentration in the range of 4 to 5 g/dl and a modest number of nucleated cells (less than 5000/μl), predominantly mononuclear. The LDH concentration tends to be higher than in the patient with carcinoma of the pleura; frequently the concentration exceeds 600 IU/L. In 60 percent of patients with malignant mesothelioma, at the time that the diagnosis is established, the pleural fluid pH is low (below 7.30) and the glucose concentration is also low (pleural fluid/serum ratio below 0.5); in contrast, the incidence of low pH and low glucose concentration in carcinoma of the pleura is about 30 percent. The natural progression of malignant mesothelioma resulting in large tumor masses and concomitant fibrosis that obliterate the pleural membrane provides a reasonable explanation for these biochemical findings. In some instances of malignant mesothelioma, the viscosity of pleural fluid is greatly increased because of a high concentration of hyaluronic acid. Although a high concentration of hyaluronic acid in pleural fluid does raise the question of malignant mesothelioma as the cause, this test is not specific and only moderately sensitive; thus, it is of no diagnostic value.

The pleural fluid in BAPE is a sanguineous, lymphocyte-predominant exudate with pleural fluid eosinophilia in 30 percent of cases. During the acute stage, there may be a moderate number of polymorphonuclear leukocytes. The pH and glucose are in the normal range (above 7.30 and 60 mg/dl, respectively).

DIAGNOSIS

Malignant pleural effusion can be diagnosed only by demonstrating malignant cells in pleural fluid or pleural tissue. Cytology is a more sensitive test for the diagnosis than percutaneous pleural biopsy, because pleural metastases tend to be focal and the latter is a blind sampling procedure. The yield on either procedure increases as the disease becomes more advanced. However, the yield from pleural biopsy with a proven malignant effusion averages 50 to 60 percent. It appears, based on thoracoscopy, that initial pleural metastases originate near the mediastinum and diaphragm; as the disease progresses, tumor spreads cephalad and costally. With improved techniques, the yield from exfoliative cytology now approaches 90 to 95 percent. If the clinician suspects a malignant effusion, several hundred milliliters of fluid should be removed at the initial diagnostic thoracentesis. This maneuver will not improve the yield on the initial study but, if it is negative, a repeat procedure several days later may provide fluid with fewer degenerative mesothelial cells and freshly exfoliated malignant cells. Percutaneous pleural biopsy should be reserved for the second thoracentesis if the initial pleural fluid cytological examination is negative. If the second cytological examination and initial pleural biopsy are negative, a third cytological examination and second pleural biopsy soon after usually is not diagnostic.

There are several options for the patient with suspected malignancy and negative pleural fluid and pleural tissue examination. These include observation for a few weeks with repeat studies, thoracoscopy, or open pleural biopsy. Before proceeding to more invasive procedures, other causes of an exudative pleural effusion must be excluded. Tuberculous pleurisy should always be considered in the patient

with a lymphocyte-predominant exudate with or without a positive tuberculin skin test. The yield from pleural biopsy culture and histology, in conjunction with pleural fluid culture, should provide a bacteriological diagnosis of tuberculous pleurisy in 90 to 95 percent of cases. Even if diagnostic studies are negative, patients with a positive purified protein derivative skin test and a lymphocyte-predominant exudate should be treated for tuberculous pleurisy because of the high risk (43 to 65 percent) of developing active pulmonary or extrapulmonary tuberculosis within 5 years if untreated. Bronchoscopy has a low diagnostic yield for an idiopathic pleural effusion without parenchymal lesions on chest radiograph, ipsilateral mediastinal shift, or hemoptysis. The value of computed tomographic examination of the chest in an undiagnosed exudative effusion is unknown and probably not cost effective. If observation is the course undertaken, the clinician would expect a malignant pleural effusion to be stable or progress and an effusion not due to malignancy to be stable or regress over time. Failure to identify a malignant pleural effusion for several weeks is rarely a disservice to the patient, who has incurable disease. Exceptions are those malignancies that tend to be responsive to therapy, such as breast cancer, prostate cancer, thyroid cancer, small-cell lung carcinoma, germ-cell neoplasms, and lymphomas.

The diagnostic utility of immunohistochemistry in the diagnosis of malignant pleural effusions secondary to adenocarcinoma, mesothelioma, and lymphoma has been established. Carcinoembryonic antigen (CEA), Leu-M1, B 72.3, Ber-EP4, and BG-8 are the best markers for the diagnosis of adenocarcinoma. Calretinin and cytokeratin 5/6 are the best markers for mesothelioma.

Flow cytometry, a technique used to quantitate nuclear DNA levels, is useful in the evaluation of lymphocytic pleural effusions in which lymphoma is a possible diagnosis. The ability of tumor markers to discriminate between benign and malignant pleural effusions is poor. Markers such as CEA, vascular endothelial growth factor (VEGF), carbohydrate antigens (e.g., CA 15-3, 19-9, and 72.4), cytokeratin 19, and enolase have significant overlap between benign and malignant pleural effusions. Hyaluronan does not appear to discriminate between pleural effusions from adenocarcinoma and mesothelioma.

Inflammatory processes involving the pleura may mimic mesothelioma, and patients are often subjected to a battery of tests and consultations before the diagnosis is established. An accurate diagnosis is imperative for proper epidemiological records, appropriate therapeutic intervention, and litigation. Early in the course of the mesothelioma, establishing a definitive diagnosis may be problematic. Pleural fluid cytology and pleural biopsy may allow the diagnosis of malignancy but usually cannot distinguish between mesothelioma and adenocarcinoma. Sarcomatous type mesothelioma can be confused with rare tumors such as fibrosarcomas or hemangiopericytomas. Thoracoscopic biopsy or open thoracotomy is usually necessary to obtain adequate tissue to confirm the diagnosis. Thoracoscopic biopsy has a high diagnostic yield for mesothelioma, approaching 100 percent in some series, while the yield for pleural fluid cytology alone is 25 percent and that for combined pleural fluid cytology and closed pleural biopsy is 40 percent. Histochemical and immunochemical studies in conjunction with electron microscopy have improved the accuracy of the diagnosis of malignant mesothelioma.

PROGNOSIS

The diagnosis of a malignant pleural effusion signals a poor prognosis. Patients with carcinoma of the lung, stomach, and ovary tend to have a survival time of only a few months from the time that the malignant effusion is diagnosed; patients with breast cancer may survive longer, several months to years, depending on the response to chemotherapy. Patients with lymphomatous pleural effusions tend to have survival times intermediate between those of breast cancer and other carcinomas.

When pH and glucose concentrations in the malignant pleural effusion are low (below 7.30 and 60 mg/dl, respectively), the survival time is less (average 2 months) than in those with a normal pH and glucose (average 10 months). Thus, the pH and glucose in the pleural fluid may provide helpful information with respect to a rational plan of palliative treatment.

A pleural effusion in the setting of lung cancer usually excludes operability; however, approximately 5 percent of these patients have a paramalignant effusion or effusion from another cause and may be operable and curable. Thus, it is essential to establish the cause of the pleural effusion before deciding that the patient is no longer a candidate for curative surgery.

Survival following the diagnosis of malignant mesothelioma is related to the stage of the disease at the time of presentation. Those patients with only ipsilateral involvement of the pleura and lung survive the longest, whereas those with distant hematogenous metastases have the shortest survival. Chest pain portends a worse prognosis than dyspnea, reflecting a more advanced stage of disease. Overall, the median survival in malignant mesothelioma is about 9 months. The epithelial type has a median survival approximately twice that of the sarcomatous type; long-term survivors of more than 3 years are seen almost exclusively with the epithelial type. As in metastatic carcinoma of the pleura, a low pH effusion in malignant mesothelioma is also predictive of a short survival.

Benign asbestos pleural effusions tend to resolve within 3 to 4 months, leaving some residual on the chest radiograph. Although malignant mesothelioma occasionally develops in patients with BAPE, it does not appear to be a harbinger of mesothelioma. Obviously, the risk of developing mesothelioma is greater in these asbestos-exposed individuals than in the general population.

Table 86-3

Management of Malignant and Paramalignant Pleural Effusions

Option	Comment
Observation	Small asymptomatic effusion; most will progress and require therapy
Therapeutic thoracentesis	Prompt relief of dyspnea; recurrence rate variable
Chemotherapy	May be effective in lymphoma, small-cell lung cancer, breast cancer
Radiotherapy	Mediastinal radiation may be effective in lymphoma and lymphomatous chylothorax
Indwelling catheter	Patient controlled symptom relief; spontaneous pleurodesis in 50% by 2 months. Effective for symptomatic relief with lung entrapment.
Chest tube drainage with talc slurry	Control of effusion in >90 percent of cases if lung entrapment not present
Thoracoscopy with talc poudrage	Control of effusion in >90 percent of cases if lung entrapment not present
Pleuroperitoneal shunt	When other options have failed or not indicated; may be useful for chylothorax
Pleural abrasion and partial pleurectomy	Virtually 100 percent effective; requires VATS or thoracotomy

TREATMENT

When the pleural effusion has been proved to be malignant or paramalignant and the patient is not a surgical candidate, the type of palliative therapy is weighed, taking into account the patient's general condition, symptoms, and expected survival. Several management options are available (Table 86-3). Asymptomatic patients need not be treated; however, most will develop progressive pleural effusions that will evoke symptoms and require therapy, but some will reach a steady state of pleural fluid formation and removal and not progress to a symptomatic stage. In the debilitated patient in whom a short survival is expected based upon the general health, extent of disease, and biochemical characteristics of the pleural fluid, periodic therapeutic thoracentesis as an outpatient is often preferable to hospitalization for tube thoracostomy and intrapleural instillation of a chemical agent. However, outpatient pleurodesis using small-bore catheters can be accomplished successfully with decreased cost and morbidity.

The use of indwelling catheters (PleurX, Denver Biomaterials, Golden, Colorado) has gained popularity; because it is an outpatient procedure, and the patient and family can manage the pleural effusion in a timely fashion at home. Approximately 50 percent of patients develop spontaneous pleurodesis by 2 months. The infection rate appears to be low. However, the expense of the drainage bottles can be prohibitive for some patients. An option with the indwelling catheter is to perform chemical pleurodesis through the catheter 1 or 2 weeks following insertion depending upon the clinical situation. Because the patient with a malignant pleural effusion frequently has lung entrapment signifying that there are two mechanisms responsible for the volume of fluid, the patient is instructed to remove fluid when dyspnea occurs and stop drainage immediately when chest pain develops. The onset of substernal chest pain signals the point when the "malignant fluid" has been evacuated, leaving the unexpandable lung from tumor involvement of the visceral pleural surface. The remaining fluid simply represents hydrostatic equilibrium.

Pleural abrasion with or without pleurectomy is almost always effective in obliterating the pleural space and controlling a malignant pleural effusion. However, pleurectomy is a major surgical procedure associated with considerable morbidity and some mortality. Accordingly, this procedure is reserved for patients who are in good general condition and have a reasonably long expected survival or who have failed a sclerosing agent procedure.

In general, systemic chemotherapy is disappointing for the control of malignant pleural effusions. However, some patients with lymphoma, breast cancer, or small-cell carcinoma of the lung manifest a good response to chemotherapy. In patients with carcinoma of the breast, procurement of quantitative data about steroid receptors from the malignant pleural fluid can provide valuable information relating to the potential response to hormonal manipulation.

As a rule, radiation of the hemithorax is contraindicated in malignant pleural effusions from lung cancer, since the adverse effects from radiation pneumonitis outweigh possible benefits of therapy. However, when involvement of mediastinal nodes predominates, radiotherapy may be helpful in patients with lymphoma and lymphomatous chylothorax.

Until recently, the most common method of controlling a malignant pleural effusion was chest tube drainage and intrapleural instillation of a chemical agent. A number of antineoplastic and nonantineoplastic chemical agents have been used for pleurodesis with variable success. Currently, the most widely used agents are talc, doxycycline, and bleomycin. Talc pleurodesis by either poudrage or slurry has been shown by numerous investigators to have a success rate of about 90 percent. In head-to-head comparisons with tetracycline and bleomycin, talc has been shown to be more effective. Talc is available to administer as a slurry or an aerosol. When used as a slurry through a chest tube, talc is less expensive than doxycycline and substantially less expensive than bleomycin. The use of VATS to administer talc significantly increases the cost and usually requires a few days of hospitalization.

The degree of pain associated with talc has been variously reported from nonexistent to severe. Fever following talc poudrage and slurry is common, occurring 16 to 69 percent of the time. Fever, occasionally as high as 102°F, characteristically occurs 4 to 12 hours after talc instillation and may last for 72 hours.

Other complications that have been reported with talc include empyema, arrhythmia, and respiratory failure, including adult respiratory distress syndrome (ARDS) and pneumonitis. The method of administration (poudrage or slurry) does not appear to be associated with the development of respiratory failure, and both high (10 g) and low (2 g) doses have been implicated. The size of the talc particles may be the major risk factor for respiratory failure, with fewer episodes reported with large particle size. Patients with severe pulmonary impairment appear to be at greatest risk of developing acute respiratory failure.

Before instituting chest tube drainage for intrapleural instillation of a chemical agent, it is necessary to demonstrate that fluid removal improves dyspnea. Determination of the FVC and P_{O_2} during the first 12 hours after therapeutic thoracentesis can be misleading. Some patients experience a transient decrease in P_{O_2} and minimal improvement in pulmonary function despite relief of dyspnea, as dyspnea is largely related to decreased chest wall compliance and stimulation of the neurogenic receptors of the chest wall and lung.

Following the initial therapeutic thoracentesis, the recurrence rate and the interval for return of symptoms should be noted. If recurrence is rapid, with return of dyspnea, pleurodesis should be considered. If the expected survival is at least several weeks, the patient is not debilitated, and the pleural fluid pH is above 7.30, the patient is a suitable candidate for pleurodesis. However, it is fruitless to attempt pleurodesis if the lung cannot be expanded fully, as with bronchial occlusion or lung entrapment. Furthermore, demonstrating a low pleural fluid pH not only suggests a shorter survival but also predicts a poorer response to chemical pleurodesis. A large tumor bulk involving the pleural surfaces, seen with low-pH, low-glucose pleural effusions is associated with diminished effectiveness of the chemical agent.

Ideally, when contemplating chemical pleurodesis the patient should undergo pleural manometry with therapeutic thoracentesis. A simple water manometer connected to a digital analog system can determine whether the patient has lung entrapment. If lung entrapment is present, the pleurodesis procedure will not be completely successful. Pleural manometry measures elastance of the pleural space by evaluating the pressure change in relationship to the volume of fluid removed. Individuals with lung entrapment have a significant drop in pleural pressure with removal of fluid. When the patient's pleural elastance is normal (less than 14.5 cm H_2O/L of fluid removed) there is a high likelihood of successful pleurodesis with proper technique. The pleural space should be drained as completely as possible so that the pleural surfaces remain in close contact during the time of the initial inflammatory insult. This is best accomplished by tube thoracostomy. A small-bore chest tube, 14 to 16°F, is as effective as a standard large-bore chest tube and causes less morbidity for the patient. When the follow-up chest radiograph demonstrates that the effusion has been drained and the lung is fully expanded, 5 g of talc slurry should be instilled into the pleural space. Following instillation, the tube should be clamped for 1 to 2 hours. It has been demonstrated that the instillation of radiolabeled tetracycline through a chest tube disperses rapidly and completely in the pleural space without patient repositioning. However, with talc slurry it is currently recommended that the patient be rotated frequently during the period when the chest tube is clamped, including Trendelenburg and sitting upright. The chest tube should be removed when drainage is less than 150 ml in 24 hours. If a large volume of drainage persists, a repeat dose of talc should be instilled. With the properly selected candidate and rigorously applied technique, the malignant effusion is controlled with talc slurry in about 90 percent of cases.

A further option available for the patient with an intractable, symptomatic, malignant effusion who cannot undergo pleurodesis is a pleuroperitoneal shunt. These shunts have been found to be safe and effective. The shunt may be particularly beneficial in refractory chylothorax, as it allows recirculation of chyle. Few complications have been associated with shunt placement, and it can be inserted in patients who are poor surgical candidates. With experienced operators, palliation is obtained in 80 to 90 percent of properly selected patients. The major problem has been shunt failure, which is most commonly due to clotting of the catheter. It is unknown whether patients who have experienced shunt occlusion are at greater risk for occlusion after a new shunt is placed.

In general, there is a nihilistic attitude regarding the management of patients with malignant mesothelioma because of the tumor's poor response to chemotherapy and radiation therapy. Early in the course of some patients with

a mesothelioma, a large unilateral pleural effusion can cause substantial dyspnea. Pleurodesis may be successful in some patients; however, in others, the procedure is unhelpful because of lung entrapment from the tumor burden in the pleural space.

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87

Pneumothorax

Deborah J. Levine • Edward Y. Sako • Jay Peters

A pneumothorax is defined as the accumulation of air in the pleural space with secondary collapse of the surrounding lung. Pneumothoraces can be divided into *spontaneous pneumothorax* and *traumatic pneumothorax.* Spontaneous pneumothorax is subclassified as either *primary spontaneous pneumothorax* or *secondary spontaneous pneumothorax.* Primary spontaneous pneumothorax occurs without a precipitating event in a person with no clinical evidence of lung disease. Many of these individuals have occult lung disease with subpleural blebs on computed tomography (CT) scans. In contrast, secondary spontaneous pneumothorax occurs as a complication of underlying lung disease, most often chronic obstructive lung disease (COPD).

Traumatic (or nonspontaneous) pneumothorax occurs as the result of blunt (nonpenetrating) or penetrating trauma disrupting the lung, bronchus, or esophagus. A subcategory of traumatic pneumothorax is *iatrogenic pneumothorax,* which occurs as a consequence of diagnostic or therapeutic maneuvers (i.e., thoracentesis, insertion of a central venous catheter, surgery, or mechanical ventilation).

PATHOPHYSIOLOGY

The pressure within the pleural space is negative with respect to the alveolar pressure during the entire respiratory cycle. This negative pressure results from the inherent tendency for the lung to collapse (elastic recoil) and the chest wall to expand. The negative intrapleural pressure is not uniform throughout the pleural space; a gradient of 0.25 cm of water per centimeter of vertical distance can be measured between the apex and base of the lung. At the apex, the pressure is more negative than at the base, and this pressure difference tends to favor a greater distention of the alveoli located in this region.

When a communication develops between an alveolus and the pleural space, air will move from the alveolus into the pleural space until there is equalization of pressure or the communication is sealed. The same happens with a communication between the chest wall and pleural cavity. Although the mechanism responsible for spontaneous pneumothorax

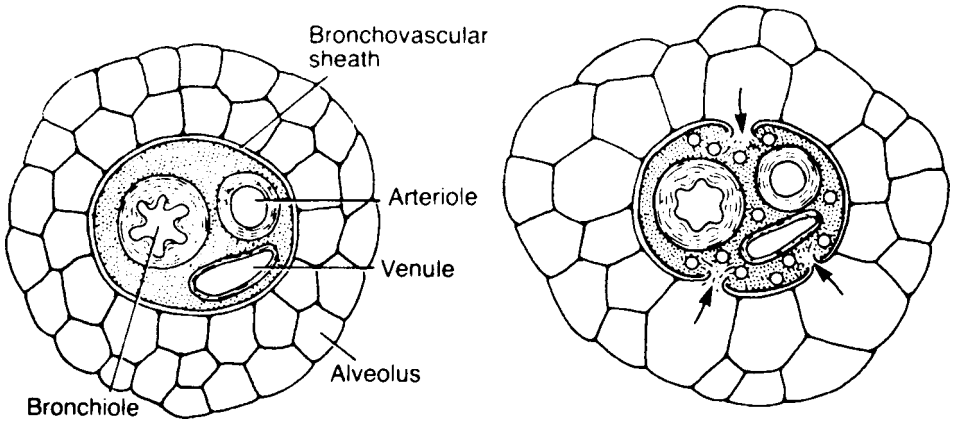

Figure 87-1 Proposed mechanism of alveolar rupture in spontaneous pneumothorax. *A.* Normal structures. *B.* Overdistention of marginal alveoli. Pressure in the adjacent bronchovascular sheath remains lower than in the overdistended alveoli. This pressure gradient may lead to rupture of the alveoli with dissection of air toward the pleura or mediastinum. (*From Maunder: Arch Intern Med 144:1449, 1984.*)

is not completely understood, experimental overdistention of normal lungs results in rupture of subpleural alveoli. Air can dissect along the bronchovascular sheath medially to produce pneumomediastinum, which may be accompanied by subcutaneous emphysema or pneumothorax (Fig. 87-1), or it can dissect to the peripheral portion of the lung. Peripheral dissection of air may result in an air-containing space within or immediately below the visceral pleura. Pathological studies of a resected lung from patients with spontaneous pneumothorax usually show one or both of these types of airspaces, a bleb or a bulla. A bulla is lined partly by thickened fibrotic pleura and partly by fibrous tissue within the lung itself, whereas a bleb is situated entirely within the pleura. A pneumothorax may occur when these peripheral bullae or blebs become distended and rupture into the pleural space.

The main physiological consequences of a pneumothorax are a decrease in the vital capacity of the lung and a decrease in Pa_{O_2}. Total lung capacity, functional residual capacity, and diffusing capacity are also reduced, although less than vital capacity. Air in the pleural space eliminates the gravitational gradients of pleural pressure and regional lung volume so that regional ventilation is uniform. The reduction in arterial Pa_{O_2} appears to be caused by low ventilation-perfusion ($\dot{V}_A/\dot{Q}$) ratios, anatomic shunts, and, occasionally, alveolar hypoventilation. Anthonisen reported that lungs demonstrate airway closure at low lung volumes and suggested that airway closure is the main cause of ($\dot{V}_A/\dot{Q}$) imbalance in patients with pneumothorax. If perfusion to the collapsed lung is preserved, there is an increase in pulmonary shunt and substantial hypoxemia. If perfusion to the collapsed lung is reduced by hypoxic vasoconstriction, hypoxemia may be minimal. In general, pneumothoraces occupying less than 25 percent of the hemithorax are not usually associated with significant shunts. Under normal circumstances, despite the degree of pneumothorax; hypoxemia tends to abate within 24 hours, presumably because of redistribution of pulmonary blood flow.

In the healthy person, the decrease in vital capacity and Pa_{O_2} is well tolerated. In patients with compromised pulmonary function before the pneumothorax, the decrease in vital capacity may result in significant hypoxemia, alveolar hypoventilation, and respiratory acidosis. When air is evacuated from the pleural space, the Pa_{O_2} usually improves. In animal studies, the Pa_{O_2} returns to baseline immediately after re-expansion of the lung. In humans, normalization of the Pa_{O_2} takes longer and may occur over hours to several days. The delay in improvement may be related to the duration of the pneumothorax.

REABSORPTION OF PLEURAL GASES

Gas reabsorption from the pleural space is achieved by simple diffusion from the pleural space into the venous blood. The rate of gas reabsorption depends on four variables: (1) the pressure gradient for the gases between the pleural space in relation to the venous blood; (2) the diffusion properties for the gases present in the pleural space; (3) the area of contact between the pleural gas and pleura; and (4) the permeability of the pleural surface (i.e., a thickened, fibrotic pleura will absorb less than normal pleura).

The solubility and diffusion properties of different gases vary considerably, and the speed of reabsorption depends on the type of gas. Oxygen is absorbed 62 times faster than nitrogen, the slowest gas to be reabsorbed. Carbon dioxide is absorbed 23 times faster than oxygen, and carbon dioxide and water vapor equilibrate almost instantaneously. If a patient develops a pneumothorax while receiving 100 percent oxygen, the pleural gas will be composed mostly of

oxygen and contain no nitrogen. The pneumothorax reabsorbs much faster for two reasons: the pneumothorax is filled with the more soluble oxygen, and the pressure gradient between the pneumothorax and venous blood is larger, because 100 percent oxygen washes out nitrogen from the alveoli and, eventually, the venous blood.

Under normal circumstances, the total gas pressure in the pneumothorax is within a few millimeters of mercury of that of the atmosphere, or 760 mmHg. Tissue gas tensions are close to those of systemic venous blood: typically $Pc_{O_2} = 46$ mmHg, $P_{O_2} = 40$ mmHg, $PH_2O = 47$ mmHg, and $pN_2 = 569$ mmHg, giving a total pressure of 702 mmHg. This positive-pressure gradient between the pneumothorax and venous blood constitutes the driving force responsible for gas reabsorption from a pneumothorax.

If the gas in the pneumothorax equilibrates with tissue in terms of P_{O_2} and Pc_{O_2}, the P_{N_2} must be about 627 mmHg (atmospheric pressure less the sum of P_{O_2}, Pc_{O_2}, and PH_2O), and N_2 is reabsorbed. This reabsorption decreases the volume of the pneumothorax, but decreases its total pressure only slightly, so that P_{O_2} and Pc_{O_2} increase. As they equilibrate with tissue, PN_2 again rises and is reabsorbed in a continuing cycle (Fig. 87-2). The time required to absorb all gases in a pneumothorax is quite variable. It has been estimated that between 1 and 6 percent of a pneumothorax is absorbed in 24 hours.

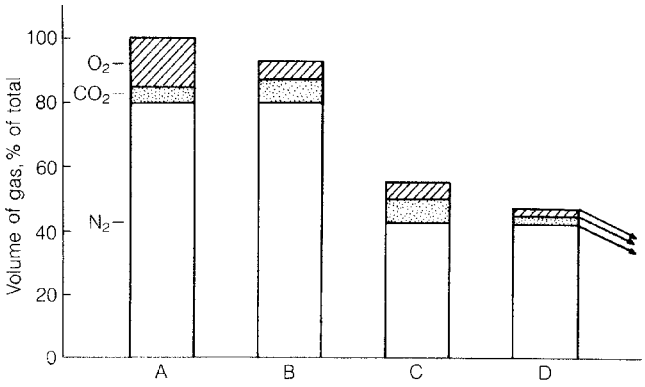

Figure 87-2 Hypothetical representation of the resorption of a spontaneous pneumothorax. *A*. Closed pleural space after leak has stopped. The alveolar gas in the space contains 15 percent O_2, 5 percent CO_2, and 80 percent N_2. *B*. CO_2 and O_2 have quickly equilibrated with the surrounding tissues; the amount of N_2 in the pneumothorax is unchanged. The pneumothorax is already decreased by about 10 percent. *C* . The number of N_2 molecules is unchanged, but the total volume of the pneumothorax has decreased (see *B*). Therefore, the outward diffusion of N_2 increases because pN_2 in the pleural space is greater than PN_2 in the tissues. As N_2 diffuses out, the total volume of gas in the pleural space decreases and concentrations of O_2 and CO_2 increase. As a result, O_2 and CO_2 diffuse out of the pleural space. *D*. The high N_2 concentration promotes the exit of N_2 from the pleural space and continues the cycle by which the pneumothorax grows smaller. (*From Farhi:* JAMA *188:986, 1964.)*

SYNDROMES

Primary Spontaneous Pneumothorax

Incidence and Patient Demographics

Primary spontaneous pneumothorax (PSP) is an entity that occurs most commonly in young men between the ages of 20 and 40 years of age. Although women have a much lower incidence of PSP, they tend to develop PSP 2 to 5 years earlier than men. A patient rarely presents with a primary episode after the age of 40 years.

Patients with primary spontaneous pneumothoraces tend to be taller and thinner than control populations. A study on military recruits who developed spontaneous pneumothorax found that they were, on average, 2 inches taller and 25 pounds lighter than the typical military recruit. In another study by Melton and colleges, primary spontaneous pneumothorax was found to be increased with increased height and reached an incidence of 200 per 100,000 person-years for subjects at least 76 in tall.

A population-based study of residents of Olmsted County, Minnesota, between 1950 and 1974, there was 141 cases of spontaneous pneumothorax (77 primary, 64 secondary) reported among the county's population. The age-adjusted incidence of primary spontaneous pneumothorax was 7.4/100,000/year for males and 1.2/100,000/year for females. The male-to-female predominance for primary spontaneous pneumothorax ranges from 6-to-1 to 3-to-1.

Tobacco smoking significantly increases the risk of spontaneous pneumothorax. In one study it was found that it was associated with a ninefold or greater risk of developing a first PSP. The relative risk of PSP has been shown to be dependent on the quantity of cigarettes per day and the length of exposure, with the relative risk increasing more than 20 times in men who smoke one-half pack per day and 100 times higher in men who smoke one pack per day compared to nonsmokers. The lifetime risk in healthy smoking men may be as much as 12 percent, as opposed to 0.1 percent in nonsmokers. One review of 402 patients with spontaneous primary pneumothorax reported that 92 percent of the patients were smokers or exsmokers. Another study showed that patients who had stopped smoking more than 1 year before their first spontaneous pneumothorax had no recurrence during a follow-up of 5.2 years.

ETIOLOGY

Although the definition of PSP is a pneumothorax that occurs in patients without primary lung disease; it may be that these patients do have some underlying pathology. A more accurate definition may be that PSPs occur in patients with no obvious lung disease. This is because PSP is most often associated with the rupture of subpleural blebs or bullae on the apical portion of the upper lobes. Although these blebs

are demonstrated on chest radiographs in only 20 percent of cases, their visualization may be facilitated radiographically in expiration or at the time of maximal pulmonary collapse. Computed tomography (CT) more often reveals blebs (often bilateral) that may not be visualized on plain radiographs.

On CT exams, blebs and bullae are designated as emphysema-like changes (ELC). In two studies, ELCs were found in 89 percent on the ipsilateral side and up to 80 percent bilaterally, while only 20 percent of those without PSP had these changes. Another study showed that 81 percent of nonsmokers with healed PSP had ELCs, while those nonsmokers without PSP had none. Although there are multiple other studies showing an association between ELC and the risk of PSP, *this* theory remains controversial as there are also at least two large studies using CT scan changes that do not reveal this potential association between ELC and PSP.

These changes are not only seen radiographically, but also at the time of thoracotomy. One series identified these blebs in 85 to 100 percent of surgical cases.

There are multiple studies showing an association between ELC and the risk of PSP. A study by Bense found that on CT scan of the chest of patients with PSP, 81 percent of patients had ELC mainly in the upper lobes, while those without PSP had none. This theory remains controversial as there are also two large studies using CT scan changes that do not reveal this potential association between ELC and PSP.

The pathogenesis of these subpleural blebs or bullae is unknown; however, it is thought to be related to airway inflammation. Airway inflammation secondary to cigarette smoking may be associated with or contribute to the development of these blebs. Respiratory bronchiolitis in smokers may either contribute to or be a leading factor in PSP. Pathologic evidence of respiratory bronchiolitis was found on more than 88 percent of smokers undergoing surgery for PSP. Other etiologies include abnormalities of connective tissue (e.g., Marfan's syndrome), inflammation of the bronchioles, bronchial abnormalities, and overdistention of alveoli with poor collateral ventilation.

Pleural pressure is most negative at the apices, and the degree of negativity relates to the height of the lungs. The alveoli of taller persons are subjected to greater mean distending pressures. Over a long period, this phenomenon could lead to the formation of subpleural blebs in a taller population genetically predisposed to bleb formation.

There are multiple reports throughout the literature of genetic associations or patterns of PSP. Some reports suggest that PSP is inherited through an autosomal-dominant gene with variable penetrance, while others report an associated autosomal recessive or X-linked recessive inheritance pattern. Genetic risk factors that have been associated to PSP include the HLA haplotype A_2B_{40}, the α_1-antitrypsin phenotypes M_1M_2, and the FBN1 gene mutations.

The rate of recurrence after a primary spontaneous pneumothorax is approximately 25 percent (range, 23 to 52 percent). Recurrence usually occurs within 1 to 2 years after the first episode.

The rate of recurrence may increase with each successive pneumothorax. Gobbel and coworkers found the risk of recurrence increased to more than 60 percent after the second pneumothorax and to 83 percent after the third. Although there is no predilection for the right or left hemithorax with the initial episode, more than 75 percent of recurrences occur on the same side as the first pneumothorax. Despite the documentation that pleural blebs occur bilaterally in many patients with primary spontaneous pneumothorax, the risk of contralateral pneumothorax is only 5 to 10 percent.

The recurrence rates reported for both primary and secondary pneumothoraces vary widely in the literature. This difference may be secondary to treatment choices and duration of follow up. Recently, Guo and his group described risk factors for recurrence in a retrospective study in 182 patients. They found that greater height, lower weight, and the existence of pre-existing lung disease (secondary spontaneous pneumothorax) *were associated with higher risk of recurrence.*

Death rarely occurs after primary spontaneous pneumothorax. In a study of spontaneous pneumothorax, in which patients ages ranged from 15 to 34 years (most likely representing patients with PSP) the mortality rate was reported to be 0.09 percent for men and 0.06 percent for women.

Secondary Spontaneous Pneumothorax

Incidence and Demographics

Secondary spontaneous pneumothorax (SSP) is more serious than primary spontaneous pneumothorax because, by definition, the patient already has underlying lung disease. A pneumothorax in these patients with already diminished pulmonary reserve, can be life threatening.

The incidence of secondary spontaneous pneumothorax is similar to that of primary spontaneous pneumothorax. In Olmsted County, Minnesota, the incidence of secondary spontaneous pneumothorax was 6.3/100,000/year for males and 2.0/100,000/year for females. On average, patients with secondary spontaneous pneumothorax are 15 to 20 years older than patients with primary spontaneous pneumothorax.

The risks of recurrence for SSP are somewhat higher than those for PSP and vary from 40 to 80 percent in the literature.

Etiology

Multiple pulmonary diseases have been associated with spontaneous pneumothorax, but chronic obstructive pulmonary disease (COPD) is the most common. The Veterans Administration Cooperative Study on Pneumothorax noted that pneumothorax tended to occur in patients with moderately severe COPD, with a quarter of the participants having an FEV_1 below 1 L and a mean FEV_1/FVC ratio of 57 percent. Persistent bronchopleural fistula was also noted to be common in patients with obstructive lung disease, and 35 percent of patients had an air leak for more than 5 days.

Table 87-1

Etiology of Secondary Spontaneous Pneumothorax

Obstructive lung disease
Chronic obstructive lung disease (COPD)
Asthma
Interstitial lung disease
Idiopathic pulmonary fibrosis (usual interstitial pneumonitis [UIP])
Non-specific interstitial pneumonitis
Eosinophillic granuloma
Lymphangioleiomyomatosis
Sarcoidosis
Langerhans cell granulomatosis
Radiation pneumonitis or fibrosis
Histocytosis X
Infection
P. jerovici pneumonia
Tuberculosis
Coccidioidomycosis
Acute bacterial pneumonia (i.e.: staphylococcus)
Malignancy
Primary lung carcinoma
Pulmonary metastasis (especially sarcomas)
Complications of chemotherapy
Connective tissue disease
Rheumatoid arthritis
Ankylosing spondylitis
Marfan's syndrome
Ehlers-Danlos syndrome
Polymyositis/dermatomyositis
Scleroderma
Other
Catamenial pneumothorax
Pulmonary infarction
Pulmonary hemorrhage
Pulmonary alveolar proteinosis
Tuberous sclerosis
von Recklinghausen's disease
Wegener's granulomatosis

Although airway diseases (COPD, CF, and severe asthma) are the most common, virtually every other pulmonary disease process has been associated with secondary spontaneous pneumothorax. The spectrum of diseases associated with secondary spontaneous pneumothorax is extensive (Table 87-1).

In contrast to the low mortality rate in PSP, in patients with SSP, there is a much higher risk of mortality. Although the mortality for recurrent pneumothorax was only 1.5 percent in the VA Cooperative Study, previous studies with secondary pneumothorax in patients with COPD have a combined mortality of 16 percent. In the VA cooperative study, the mortality was up to 36 percent, but most of these deaths were secondary to the patient's underlying COPD or cancer. Videm et al. showed that SSP increased the mortality of age-matched COPD patients by 3.5 times.

Cystic Fibrosis

Pneumothorax is a serious complication in patients with cystic fibrosis (CF) and is far more common than in the general population. It occurs in patients with more advanced disease and results in a significant increase in both morbidity and mortality.

The etiology of spontaneous pneumothorax in CF patients has not been clearly established, but likely is associated with the rupture of subpleural blebs or cysts, which are usually located in the apices of the lungs. Another etiology may be that there is significantly increased pressure and volume in the alveoli because of mucus plugging and inflammation of the proximal airways leading to rupture in the pleural space.

Multiple studies have shown the high incidence in this population. One study found that spontaneous pneumothorax occurred in 12.5 percent of 144 patients with cystic fibrosis over 10 years of age. A multicenter study by Flume using data from the national CF Foundation Patient Registry showed that approximately 6 percent of all patients with cystic fibrosis and 16 to 20 percent of those who reach age 18 will have an episode of pneumothorax.

Prior reports of pneumothorax in CF patients from single centers have suggested that the mean age of occurrence was between 15 and 17 years of age. These reports were between the years 1968 and 1990. A recent analysis of patients in the 1990s reveals that pneumothoraces generally occur later in life with the mean age of occurrence in the early twenties. This may be because the median survival of CF patients has increased over time because of advanced therapies.

The risk of developing a pneumothorax increases as age increases and pulmonary function (FEV_1) decreases. In one study, greater than 50 percent of patients with an $FEV_1 > 20$ percent predicted had at least one pneumothorax. Additional risk factors include the presence of *P. aeruginosa, B. cepacia*, and *Aspergillus* in the airways. The presence of these pathogens may cause increased inflammation as well as significant airway secretions leading to obstruction of the distal airways with air trapping.

Recurrence of pneumothorax is more frequent in this population as well. An older study revealed a recurrence rate of spontaneous pneumothorax treated with tube thoracostomy alone to be 50 percent. A more recent study confirmed that more than one in five of the patients experienced at least two events in separate years. Because the recurrence rate is so

high, consideration should be given to preventative measures after pneumothorax even after the first episode occurs. In the past, pleurodesis was not easily offered, as it was thought that it would preclude patients from lung transplantation. However, recent studies have shown that pleurodesis did not add appreciably to complications during lung transplantation. Although center-dependent, pleurodesis is no longer considered a contraindication to transplantation.

Pneumothorax in CF patients is associated with a high rate of mortality and is an indicator of a poor prognosis in patients with CF. In one study, the median survival after the first spontaneous pneumothorax was only 29.9 months.

Traumatic Pneumothorax

Trauma is the most common cause of pneumothorax. Patients who have either multitrauma or trauma to the thorax are at risk for pneumothorax. Between 1950 and 1974, there were 318 cases of pneumothorax in Olmsted County, Minnesota. Trauma was responsible for 177 of these cases (56 percent), of which 102 were iatrogenic. Noniatrogenic traumatic pneumothorax can result from either penetrating or nonpenetrating chest injury. The diagnosis needs to be considered in any patient who is evaluated for significant trauma.

Penetrating chest trauma produces a pneumothorax by allowing air to enter the pleural cavity directly through the chest wall. In addition, if the visceral pleural is penetrated; air may leak from the tracheobronchial tree. If the continuity of the chest wall is disrupted, an open pneumothorax is produced. If the opening in the chest wall is larger than the diameter of the trachea (1.2 to 1.5 cm in an adult), air movement occurs through the pathway of least resistance, and air is preferentially inspired into the thoracic cavity through the open chest wound. Any open chest wound must be occluded to assure adequate ventilation of the patient.

Pneumothorax is also a frequent finding in patients with blunt trauma to the chest. The visceral pleura may be lacerated secondary to a rib fracture or dislocation; however, in almost one-half of patients with pneumothorax secondary to blunt trauma, there are no associated rib fractures. This is especially common with blunt trauma to the chest secondary to blast injuries and high-altitude falls into water. In such incidents, the abrupt increase in the pressure gradient between the alveolus and the adjacent bronchovesicular sheath causes disruption of the alveolar membrane. Dissection of air through the interstitial space results in either pneumothorax or pneumomediastinum.

Occasionally, patients with traumatic pneumothorax have coexisting injuries of the tracheobronchial tree or of the esophagus. In a patient with a traumatic pneumothorax, fiberoptic bronchoscopy should be performed in the presence of hemoptysis or a persistent air leak. Eighty percent of injuries to the tracheobronchial tree are within 2.5 cm of the carina, most commonly on the right side at the membranous-cartilaginous interface. The main lobar bronchi and cervical trachea are the next most common sites of injury.

Traumatic rupture of the esophagus usually produces a hydropneumothorax. Therefore, if a patient with a traumatic pneumothorax also has a pleural effusion, the possibility of esophageal rupture should be entertained. Almost all patients with perforation of the thoracic esophagus also have dysphagia and pneumomediastinum. An elevated pleural fluid amylase concentration is a reliable screening procedure for esophageal rupture. Once the diagnosis is suspected, contrast radiographic studies of the esophagus should be performed as soon as possible. Untreated, esophageal rupture results in mediastinitis and septic shock; therefore, a high index of suspicion is essential in making an early diagnosis.

Increasing utilization of invasive diagnostic as well as therapeutic interventions has significantly increased the rate of iatrogenic cases of pneumothoraces. These cases may have considerable increased morbidity and mortality and account for prolonged hospitalization for the affected patient.

Iatrogenic pneumothorax can occur as a complication of multiple procedures, but the leading cause of iatrogenic pneumothorax is transthoracic needle aspiration. The incidence ranged between 20 and 40 percent in three large trials. Two to eight percent of these patients required tube thoracoscopy post procedure. Cox noted that CT evidence of COPD and a smaller lesion (less than 2 cm) correlated with the occurrence of pneumothorax. Other factors associated with pneumothorax in transthoracic needle aspiration were increased depth of the lesion into the lung, diagnosis of COPD, and the severity of the underlying lung disease. This incidence of pneumothorax has remained relatively unchanged as no reported techniques to decrease the risk have been successful (i.e., positioning patients, use of a blood patch, use of fibrin glue).

Central venous catheterization carries the second highest risk of iatrogenic pneumothoraces. The risk that has been reported throughout the literature ranges from 2 to 12 percent. Subclavian catheterization carries a higher risk than internal jugular catheterization.

Thoracentesis also carries a moderate risk of pneumothorax. The incidence has been reported to be 5 percent. Twenty to 50 percent of these will require chest tube placement. The incidence is increased in patients with COPD. Pneumothorax may also occur with transbronchial biopsy, Wang needle aspiration, liver biopsy, intercostal nerve block, mediastinoscopy, and tracheostomy. Iatrogenic pneumothoraces may have a delayed presentation, but most are apparent within 24 hours after the procedure.

Another cause of pneumothorax that is frequently overlooked is chest tube malfunction. Common causes of chest tube malfunction include inadequate securing of the chest tube to the drainage system, failing to fill the U-manometer in the water seal chamber, failing to refill the water in the suction control chamber, and permitting intermittent disconnection of the system during diagnostic or therapeutic studies.

Mechanical ventilation is a frequent, potentially lethal cause of iatrogenic pneumothorax. The overall incidence of pneumothorax during mechanical ventilation ranges from 4 to 15 percent, but may be significantly higher in patients

with underlying inflammatory diseases such as aspiration pneumonia. The incidence of pneumothorax is also increased during mechanical ventilation if patients have chronic pulmonary disease, are on increased amounts of positive end-expiratory pressure, or have right main stem intubation.

The incidence of pneumothorax has been reported to occur in 6.9 to 14 percent of patients with ARDS. Another study reported a 48.8 percent incidence of pneumothorax in patients with severe ARDS requiring extracorporeal support.

A pneumothorax should be suspected in any patient whose clinical status acutely decompensates on the ventilator. Any patient who demonstrates a sudden increase in tachypnea or becomes dyschronous with the ventilator should be evaluated for a pneumothorax. An increase in the peak and plateau pressure on the ventilator can be a sensitive indicator if the patient is on volume control ventilation. The peak inspiratory pressure often rises suddenly as the lung compliance falls. If the patient is on pressure control ventilation, decreased tidal volumes will be a sign of a pneumothorax.

Radiographs of critically ill/mechanically ventilated patients are frequently obtained only in the supine or semisupine position. In a study by Tocino and colleagues, supine and semierect radiographs were obtained in 88 critically ill patients with 112 cases of pneumothorax. The radiologist initially failed to detect the pneumothorax in 30 percent of the cases. The patient with extensive infiltrates, as in those patients with ARDS, may have no suggestion of lung collapse on chest radiograph. In these patients, the only radiological sign which may be evident is that of a deep sulcus on the side of the pneumothorax. Any increased lucency in a supine film should be evaluated by erect or decubitus views to detect the presence of a pneumothorax If erect or decubitus films cannot be obtained, CT scans of the chest may be necessary.

Recipients of heart-lung transplants do not have an intact mediastinum. Physicians performing procedures on these patients need to be aware that the patient can develop bilateral pneumothoraces because of this anomaly.

Catamenial Pneumothorax

Catamenial pneumothorax (CP) is a rare condition in which women recurrently develop pneumothoraces during their reproductive years, usually in their third or fourth decade of life. Catamenial pneumothorax represents 3 to 6 percent of spontaneous pneumothorax in women. However; more recent studies suggest the incidence of this disorder may actually be much higher.

There is no single definitive etiology for CP. One theory suggests pleural and/or diaphragmatic endometrial implants as being responsible for this disorder; however, only one-third of women have implants at the time of thoracotomy. Theories also include peritoneal air entering the thoracic cavity through diaphragmatic defects during menstruation, intrapulmonary implants causing bronchiolar obstruction, and the production of prostaglandin $F_{2\alpha}$ by endometrial tissue resulting in bronchiolar and vascular constriction.

The diagnosis of this syndrome is based on recurrent pneumothorax occurring within 48 to 72 hours of the onset of menses. The patient classically develops chest pain and dyspnea within this time. It has been reported more likely to occur if the patient's menstrual period is preceded by mental or physical stress. The majority (90 to 95 percent) of catamenial pneumothoraces affect the right hemithorax, but isolated left side or bilateral pneumothoraces have been reported.

Medical treatment is aimed at suppressing the ectopic endometrium using oral contraceptives to suppress ovulation. Danazol, a weak androgen, has also been used to suppress ovulation. Gonadotropin-releasing hormone (GnRH) and the GnRH agonist Lupron have also been used to effectively suppress CP. If menses is not suppressed, there is a 50 percent recurrence rate within 1 year. Surgical treatment for CP including thoracoscopy with closure of any diaphragmatic defects, stapling of any blebs, and pleural abrasion have all been used to prevent recurrent pneumothorax. Hysterectomy with bilateral oophorectomy will induce surgical menopause and thus prevent pneumothorax.

Pneumothorax in Acquired Immunodeficiency Syndrome

Patients with acquired immunodeficiency syndrome (AIDS) have a significantly increased risk of developing a pneumothorax. About 2 to 5 percent of patients with AIDS experience pneumothorax unrelated to trauma or a pulmonary procedure. In one study, pneumothorax complicated 1.2 percent of all 599 HIV patient admissions over 3 years. Mortality was increased (31 percent) in those who had a pneumothorax vs. 6 percent in those who did not.

Pneumothorax in patients with AIDS is associated with multiple infectious etiologies. *Pneumocystis jiroveci,* pyogenic infections, Kaposi's sarcoma, cytomegalovirus, pulmonary *Cryptococcus, Coccidiomycosis,* and mycobacterial disease have all been associated with spontaneous pneumothoraces. Most patients have a CD4+ count less than 100 cells/mm^4.

The risk of spontaneous pneumothorax in HIV patients is higher if the patient is receiving inhaled pentamidine, smokes cigarettes, or presents with a pneumatocele on chest radiograph. The majority of HIV patients presenting with a pneumothorax have active PCP infection, therefore, evaluation and treatment for PCP is recommended in any patient with AIDS who presents with a spontaneous pneumothorax.

The large numbers of pneumothoraces seen in patients with *Pneumocystis jiroveci* are thought to be secondary to the high incidence of subpleural cystic cavities and subpleural necrosis associated with this entity. Extensive tissue invasion within the alveolar interstitium is common in severe PCP and may result in subpleural necrosis. These cystic changes are thought to be due to repeated episodes of inflammation and cytotoxic effects of HIV on pulmonary macrophages. These lesions occur most frequently at the apices of the lungs and consist of necrotic alveoli filled with *Pneumocystis jiroveci* organisms, macrophages, eosinophilic exudate, and fibrous

material. Histological examination of patients who have recovered from *Pneumocystis jiroveci* demonstrates both subpleural blebs and bullae as well as pneumatoceles.

Because of the necrotizing nature of the pneumonia, spontaneous pneumothorax is notoriously difficult to treat. Persistent air leaks often require tube thoracostomy for 3 to 4 weeks, and up to one-fourth of patients require surgical intervention.

The incidence of bilateral cystic disease in these patients is extremely high, and the incidence of contralateral pneumothorax was about 50 percent in one study. Therefore, if surgical intervention is planned, some authors recommend preoperative CT scans of the chest and median sternotomy in patients with significant bilateral disease. Others recommend early thoracoscopic therapy in good surgical candidates to avoid prolonged hospitalization.

Tuberculosis

With the rise of AIDS, the frequency of pulmonary tuberculosis has increased within the general population. Tumbarello et al. found 6.8 percent of HIV patients with pulmonary tuberculosis developed a pneumothorax. All pneumothoraces associated with tuberculosis should be treated and often require prolonged periods of chest tube drainage. In cases of tuberculosis, surgery should not be considered until the patient has received antituberculous therapy for at least 6 weeks.

CLINICAL FEATURES

The main symptoms with the development of a pneumothorax are chest pain and dyspnea, which occur in 95 percent of patients. The pain is usually acute, localized to the side of the pneumothorax, and typically pleuritic. Cough, hemoptysis, orthopnea, and Horner's syndrome are uncommon manifestations of a pneumothorax. A small percentage of patients are asymptomatic or complain only of generalized malaise.

Spontaneous pneumothorax usually occurs at rest, and fewer than 10 percent of them occur during strenuous exercise. In primary spontaneous pneumothorax, both the dyspnea and chest pain may subsequently abate over the first 24 hours. This may explain why nearly half of patients have symptoms for 2 days before seeking medical attention and why 18 percent wait for more than a week. Most patients with secondary spontaneous pneumothorax have more severe symptoms than patients with PSP, and dyspnea frequently seems out of proportion to the size of the pneumothorax.

Small pneumothoraces (less than 20 percent) are usually not detectable on physical exam. In patients with obstructive lung disease, even larger pneumothoraces may be difficult to detect since decreased breath sounds and hyperresonance may already be present in patients with obstructive lung disease. On physical exam, vital signs are usually normal, with the exception of moderate tachycardia. Examination of the chest may reveal the affected side to be larger and move less during respiration. Tactile fremitus is absent, the percussion note is hyperresonant, and breath sounds are absent or reduced on the side with the pneumothorax. Hamman's sign may be detected. This sign, also heard with pneumomediastinum, has been described as crunching or clicking noises synchronous with the heartbeat but influenced by respiration and body position. Severe tachycardia, with a heart rate above 140 beats a minute, hypotension, cyanosis, or tracheal deviation, suggests the possibility of a tension pneumothorax.

Arterial blood gases often show hypoxemia and perhaps hypocarbia from hyperventilation. Hypoxemia is usually mild in primary spontaneous pneumothorax when less than 25 percent of the lung is affected. When more than 25 percent of the lung is involved, pulmonary shunts occur more frequently and hypoxemia may be severe. In patients with secondary spontaneous pneumothorax, pulmonary reserve is already diminished and life-threatening hypoxemia and hypercarbia may be present. In a study by Dines et al., the mean Pa_{O_2} was 48 mmHg and the mean Pc_{O_2} was 58 mmHg when patients with emphysema presented with a spontaneous pneumothorax.

Patients with a left pneumothorax may show changes suggesting an anterolateral myocardial infarction. A rightward shift of the frontal QRS axis and clockwise rotation of the heart result in a diminution of precordial R-wave voltage, a decrease in the QRS amplitude, and precordial T-wave inversion. These electrocardiographic features differ from a transmural myocardial infarction because of the absence of ST-segment elevation or significant Q waves. An anterior subendocardial infarction may present with T-wave inversion but without the rightward shift in the frontal axis. The electrocardiographic changes with a left pneumothorax may normalize when the patient is in the upright or right lateral decubitus position.

RADIOGRAPHIC APPEARANCE

The diagnosis of a pneumothorax is established by demonstrating the outer margin of the visceral pleura (and lung) separated from the parietal pleura (and chest wall) by a lucent gas space devoid of pulmonary vessels (Fig. 87-3). The pleural line may be difficult to detect with a small pneumothorax unless high-quality upright films are obtained. In erect patients, pleural gas collects over the apex, and the space between the lung and chest wall is most notable there. In the supine position, gas migrates along the broad ventral surface of the lung, making detection on a frontal radiograph difficult. In the supine position, the juxtacardiac area, lateral chest wall, and subpulmonic region are the best areas to search for evidence of pneumothorax. When a suspected pneumothorax is not definitely seen on an inspiratory film, an expiratory film may be helpful. At end-expiration, the constant volume of the pneumothorax gas is accentuated by the reduction in the

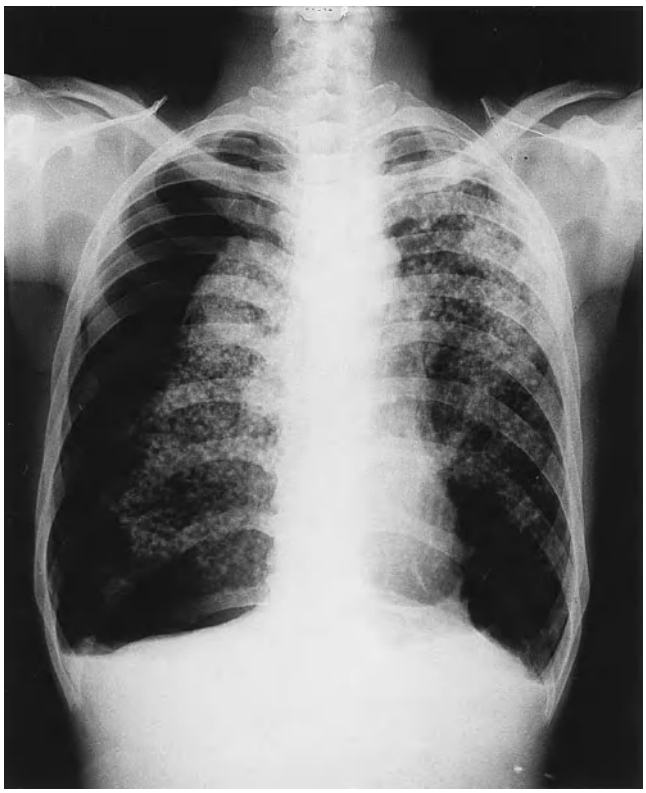

Figure 87-3 Patient with nodular silicosis and a spontaneous secondary pneumothorax. The visceral pleural line is clearly seen with the absence of vascular workings beyond the pleural line. There are cicatricial bullae in both bases.

size of the hemithorax. Therefore, the pneumothorax may be more easily recognized. Similar accentuation can be obtained with lateral decubitus studies of the appropriate side. However, several recent studies have showed that the expiratory films have little or no advantage over upright inspiratory films in the diagnosis of pneumothorax. The recent BTS guidelines do not recommend the routine use of expiratory chest films in the evaluation of suspected pneumothorax.

It is very important to differentiate the pleural line of a pneumothorax from that of a skinfold, clothing, tubing, or chest wall artifact. Careful inspection of the film may show that the artifact extends beyond the thorax, or that lung markings are visible beyond the apparent pleural line. In the absence of underlying lung disease, the pleural line of a pneumothorax usually parallels the shape of the chest wall. Artifactual densities generally do not parallel the course of the chest wall over their entire length. Avascular bullae or thin-walled cysts can be mistaken for a pneumothorax. The pleural line caused by a pneumothorax is usually bowed at its center toward the lateral chest wall. As opposed to a pneumothorax, the inner margins of bullae or cysts are, in general, concave rather than convex and do not exactly conform to the contour of the costophrenic sulcus. A pneumothorax with a pleural adhesion may also simulate bullae or lung cysts. A synechia tends to form a straight line connecting the lung to the parietal pleura; bullae or cysts have rounded edges. Such features are not 100 percent specific, and if there is any doubt as to whether the patient has a bulla or cyst or a pneumothorax, a CT scan should be obtained as CT can usually differentiate the two. Pleural effusions may occur coincident with pneumothorax in up to 20 to 25 percent of cases. Hemopneumothorax occurs in 2 to 3 percent of cases of spontaneous pneumothorax. Bleeding is believed to represent rupture or tearing of vascular adhesions between the visceral and parietal pleura as the lung collapses.

Quantification of the size of a pneumothorax is helpful; unfortunately, however, the methods for quantifying lack uniformity and are by no means precise. Light suggested the measurement of the average diameters of the collapsed lung and of the affected hemithorax, with the cubing of these diameters to estimate the percentage of collapsed lung. For example, if the diameter of the collapsed lung is 6 cm and the diameter of the hemithorax is 10 cm, the collapsed lung is estimated by the formula $100 - 6^3/10^3$. Thus, the estimated size of the pneumothorax is 78 percent. Rhea and coworkers proposed the use of a nomogram to calculate the size of the pneumothorax. With this method, the average intrapleural distance is calculated by measuring the interpleural distance at the apex and at the midpoints of both the upper and lower lungs. These three values are then averaged, and the number is reported on a nomogram, which gives an estimated size of the pneumothorax. An example of these calculations is shown in Fig. 87-4.

The most common radiographic manifestations of tension pneumothorax are mediastinal shift, diaphragmatic depression, and rib cage expansion (Fig. 87-5). Any significant degree of displacement of the mediastinum from the midline position on maximum inspiration, or any depression of the diaphragm, should be taken as evidence of tension. The degree of lung collapse is an unreliable sign for or against the presence of a tension pneumothorax, since underlying lung disease may prevent collapse even in the presence of tension.

Ultrasound can be used to both detect pneumothoraces as well as direct the site of drainage. CT scans of the chest are being used with increasing frequency in patients with pneumothorax. CT scans may be necessary to diagnose pneumothorax in critically ill patients when upright or decubitus films are not possible. CT scans may prove helpful in predicting the rate of recurrence in patients with spontaneous pneumothorax. One study demonstrated that patients who have larger or more numerous blebs on thoracic CT scans are more likely to have recurrence.

Traumatic pneumothoraces, if large, can be detected both clinically and with chest radiography. However, a small post-traumatic pneumothorax may be easily missed by both physical exam and chest radiograph. One prospective series revealed that 51 percent of trauma patients presented with an occult pneumothorax that was not seen on initial chest radiograph, but identified on CT imaging. In another large series looking at multiple trauma patients, 4.4 percent had a pneumothorax and 38.8 percent of these were detected only by CT scan. Early incorporation of a routine CT scan in all

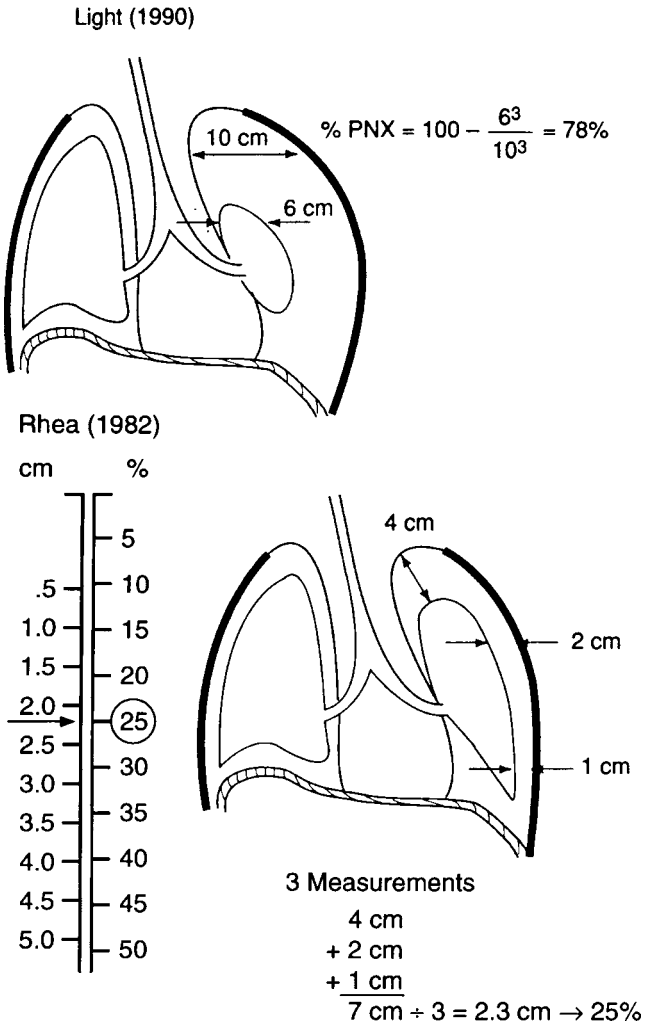

Figure 87-4 Estimation of the size of the pneumothorax according to the method described by Light et al. (*From Beauchchamp, in Pearson (ed),* Textbook of Thoracic Surgery, *1995, 1043.*)

patients with chest trauma or multiple traumatic injuries may be required to successfully diagnose traumatic pneumothoraces.

THERAPY

The basic tenets of therapy for pneumothoraces are to evacuate the space, achieve closure of the leak, and either prevent or reduce this risk. A variety of treatment methods and adjuncts exist. The choice of therapy depends on many factors, including the clinical status of the patient, the cause of the pneumothorax, evidence for concomitant lung disease, prior history of pneumothorax, risk of recurrence, and, finally, the experience and preferred techniques of the physicians caring for the patient as well as the availability of specific therapeutic options. Major categories of treatment methods are listed below, followed by suggested guidelines for their application.

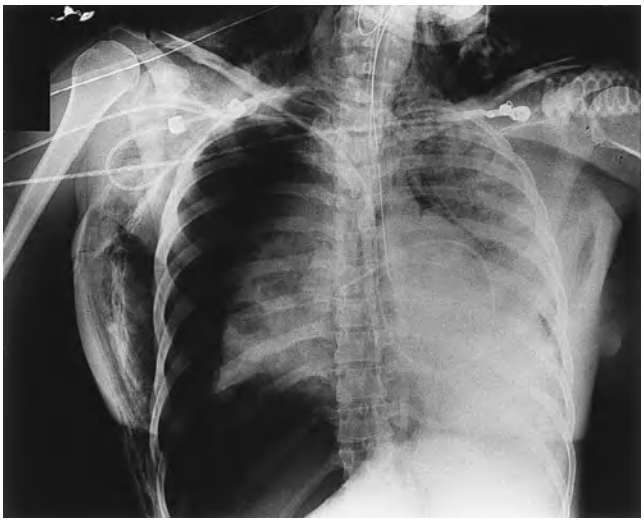

Figure 87-5 Right tension pneumothorax in a young patient with staphylococcal endocarditis and septic emboli. There is marked depression of the right hemidiaphragm, shift of the mediastinum, and subcutaneous emphysema. *Note:* The pulmonary artery catheter, endotracheal tube, and nasogastric tube (midchest) are all displaced to the left.

Observation

Simple observation of the patient with a pneumothorax requires evidence that the air leak is sealed (i.e., that there is no further progression of the pneumothorax). This form of management is generally reserved for asymptomatic patients with a small (greater than 20 percent) unilateral pneumothorax.

A suggested protocol is the performance of serial chest radiographs over the initial 24 hour to assess for further progression of the pneumothorax. Some have suggested that this approach could be performed safely on an outpatient basis with close observation and limited patient activity. This form of management is risky because complications may occur rapidly, with potential morbidity. In one study of observation, 5 percent mortality was reported owing to the development of tension pneumothorax from an unrecognized pleural leak. Inpatient monitoring during the initial phase of therapy also allows the use of adjunct measures such as supplemental oxygen, which increases the rate of absorption of pleural gas. Depending on the circumstances and level of patient compliance, continued follow-up may be done on an outpatient basis.

Aspiration

Aspiration of a pneumothorax has been advocated by some; with varied levels of success. These reports have prompted the British Thoracic Society to recommend simple aspiration as first line therapy for all patients with first time spontaneous pneumothorax. This is in contrast to the American College of Chest Physicians Delphi Consensus Statement on this issue illustrating the controversial nature of this form of therapy. A meta-analysis of a randomized controlled trial

of simple aspiration versus chest tube insertion concluded that simple aspiration was advantageous because of shorter hospitalization times and no significant difference in recurrence rates at 1 year. In these studies, approximately 66 percent of patients had resolution of their pneumothorax. Patients with secondary or a recurrence of spontaneous pneumothorax generally do not have good results with simple aspiration.

The procedure consists of insertion of a 16- or 18-gauge plastic catheters under local anesthesia using sterile technique. The recommended point of insertion is the second anterior intercostal space in the midclavicular line. The catheter is connected to a three-way stopcock and a large-volume syringe. Aspiration is performed until no further gas can be withdrawn. Follow-up chest radiographs are performed. Again controversy exists regarding a second attempt at aspiration only if the first attempt is unsuccessful. If large volumes are aspirated without resolution or the second attempt is unsuccessful, a tube thoracostomy should be performed.

Long-Term Aspiration

This entails the placement of an indwelling catheter into the pleural space for continual removal of the interpleural gas. The classic method is the use of standard tube thoracostomy. For uncomplicated pneumothorax without evidence of significant amounts of fluid or blood, one may use tubes ranging in size from No. 16- to 24-French to minimize the discomfort of a larger tube in the intercostal space.

The tube is then connected to a pleural drainage system. Commercial systems commonly employ variations on the three-chamber system (Fig. 87-6). The three-chamber system consists of a fluid collection chamber attached to a waterseal chamber to allow egress of gas from the pleural space, but in a one-way fashion. The final connection is to a manometer bottle, which regulates the degree of suction being applied to the system. After placement of tube thoracostomy, care should be taken with regard to immediate placement to suction because of the potential for postexpansion pulmonary edema (see below). In many cases it may be prudent to leave the tube to water seal and allow the lung to expand gradually. Once the majority of the pneumothorax is evacuated, suction is applied for the next 24 hours. If an air leak exists, as evidenced by continual or intermittent egress of gas through the water seal chamber, suction is maintained. Once there is no evidence of an active air leak, the tube may be placed to underwater seal. After an additional period of observation of 12 to 24 hours, the chest tube may be removed if the pneumothorax does not recur. Tube thoracostomy alone will result in closure of an air leak in most cases by complete evacuation of the pleural space and apposition of the visceral and parietal pleura. Persistence of an air leak for more than 72 hours generally presages a leak that will not close by this regimen and should prompt consideration of more aggressive therapy, usually surgical with or without some form of pleurodesis.

In order to have a less traumatic method of placement of an indwelling tube, as well as to minimize the discomfort from a large-bore tube in the intercostal space, a variety of smaller catheters have been suggested for use as an interpleural drain. The method of placement is similar to needle aspiration in terms of preparation and location of entry. Once the pleural space is entered with the needle, the Seldinger technique is used to pass a soft tip wire. The 8-French pigtail catheter is then placed over the wire into the pleural space and the wire withdrawn. The catheter is left in place and attached to the pleural drainage system as described in the preceding. Potential problems with smaller catheters relate to a greater propensity for blockage of the tube. Also, the smaller size makes them more prone to kinking, clotting from blood or fluid, and sealing around the tube by the lung, resulting in a loculated pneumothorax. In cases in which the pneumothorax is associated with significant amounts of blood or fluid, tube thoracostomy using a larger-bore chest tube (26- to 32-French) is recommended.

Use of these types of catheters has created the possibility of a form of hybrid therapy in which these catheters are placed and simple aspiration performed as noted. If the lung fails to re-expand or the volume of air obtained is excessively large, suggesting a continued air leak, the catheter may be left in and connected to longer-term drainage.

A variation on the use of pleural drainage systems has been the substitution of a one-way valve to permit greater mobility by the patient. The most common is the Heimlich flutter valve, which may have some application in cases in which long-term indwelling catheterization is required but surgical therapy is declined or not possible. This valve is not widely recommended, however, owing to a potential for problems with blockage, which may not be immediately recognized on an outpatient basis.

Pleurodesis

Pleurodesis is an adjunct to the other forms of therapy. The goal is to achieve pleural symphysis, or adhesion of the visceral and parietal pleura to obliterate the pleural space. Sealing the visceral and parietal pleura together will prevent future air leaks and prohibit the lung from "falling away" from the chest wall. The basic mechanism entails chemical or physical irritation of the pleural surface to promote an inflammatory response and subsequent adhesion formation.

The goal of pleurodesis is to prevent recurrence in both PSP and SSP. There is good consensus for the use of pleurodesis in both; however, when and how to achieve pleurodesis depends on both the kind of pneumothorax as well as if there has been a recurrence.

Chemical pleurodesis may be used in combination with tube thoracostomy or surgical therapy. In patients who are unable to undergo a surgical procedure (e.g., severe comorbidity), pleurodesis can be achieved with administering the sclerosing agent through a chest tube. The success of the antibiotics (tetracycline, doxycycline, minocycline) and talc by slurry have been shown to have results that are better than

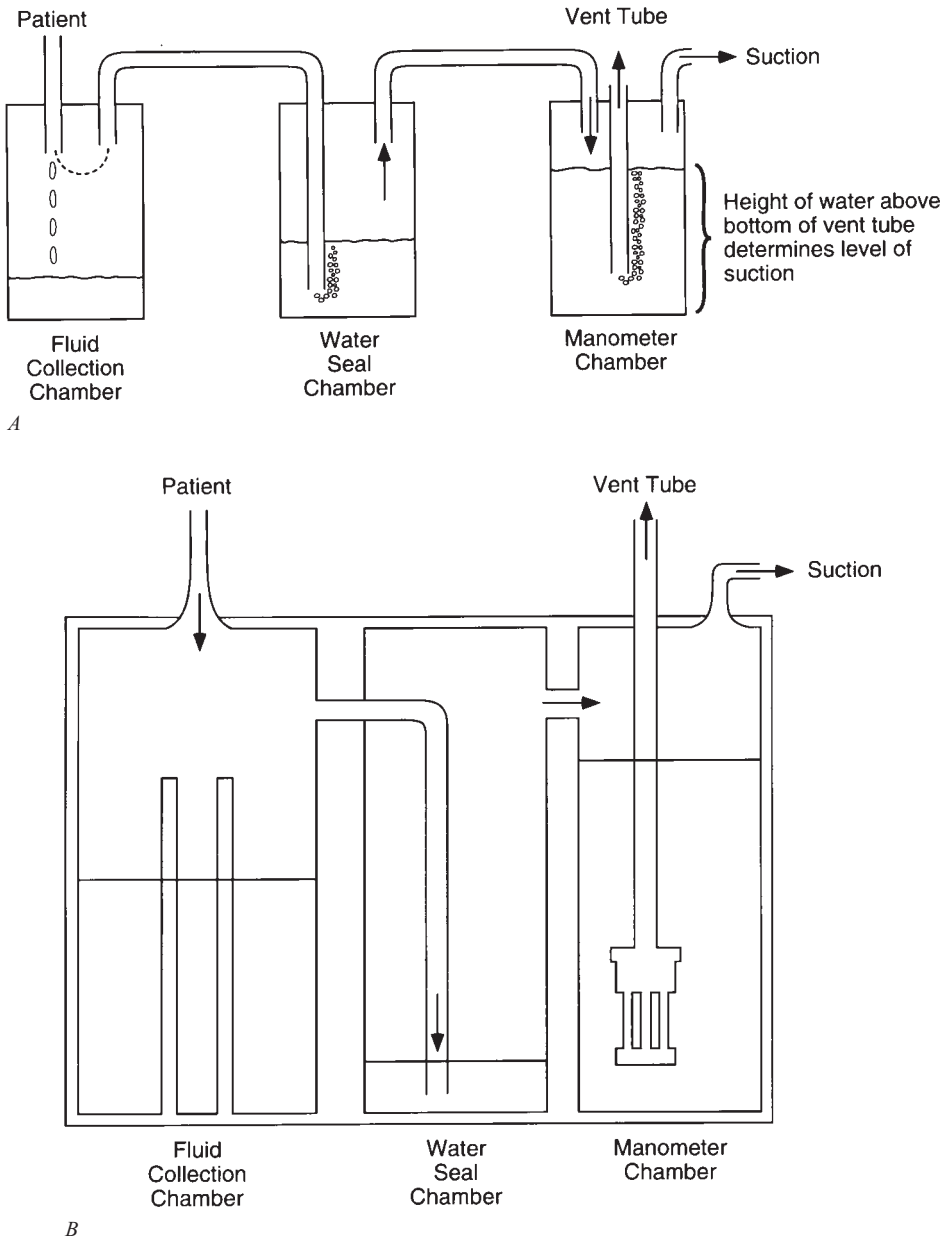

Figure 87-6 *A*. Three-bottle chest tube drainage system. The system consists of a collection bottle, a water-seal bottle, and a suction-control bottle. The collection bottle allows sterile drainage from the pleural spaces. The water-seal bottle acts as a one-way valve in the absence of suction, and the suction bottle allows for the regulation of negative pressure applied to the pleural space. *B*. Commercially available, compartmentalized plastic drainage system.

chest tube drainage alone, but not as good as thoracoscopic treatment.

As an adjunct to tube thoracostomy, the chemical of choice is suspended in fluid and instilled through the tube. The tube is clamped for 6 to 8 hours, then placed back to either suction or water seal. Periodically changing patient position during this period is believed to effect more even distribution of the irritant. General requirements for the performance of chemical pleurodesis via the tube are that pleural fluid output be less than 150 to 200 ml/day and that there be no air leak. Success is largely dependent on apposition of the visceral and parietal pleura during the period of inflammation while the tube is clamped. Excessive pleural fluid will dilute the sclerosing agent, and an air leak will allow the lung to separate from the chest wall. Pleurodesis in the face of an air leak has been tried, but in our experience it has rarely been successful.

The ideal agent should be effective, safe, easy to administer, and widely available and affordable. A number of pleural irritants have been suggested, including quinacrine, silver nitrate, bleomycin, autologous blood, antibiotics (tetracyclines), and talc. Minor side effects of pleurodesis with a sclerosing agent include chest pain and low-grade fevers.

Tetracycline was shown to be very effective in creating sufficient pleural fibrosis formation when compared to

hydrochloric acid, quinacrine, nitrogen mustard, bleomycin, or sodium hydroxide. A randomized study comparing the recurrence rates in PSP after drainage alone with that of drainage plus tetracycline or talc found recurrence rates of 36, 13, and 8 percent, respectively. Tetracycline, however, is no longer commercially available. Minocycline and doxycycline have been suggested as replacements for tetracycline with experimental data that suggest equal efficacy. Typical doses of these antibiotics are 0.5 to 1.0 g of doxycycline in 50 to 100 ml normal saline and 600 mg of minocycline in 50 to 100 ml of normal saline.

Talc has also been shown to be a very effective sclerosing agent when applied as a slurry via a chest tube or by talc poudrage during thoracoscopy. In an experimental study, talc was noted to be as efficacious as mechanical abrasion. In a meta-analysis, talc achieved a "success rate" of 91 percent. Doses between 2 to 10 g of talc in 100 to 200 ml of normal saline have been reported. There is no standardized practice when using talc administered by chest tube. The drawbacks of talc slurry are prolonged pleural drainage and inhomogeneity of deposition. The distribution of talc may lead to loculation and incomplete symphysis. The advantages are it can be performed easily at the bedside. There are data, however, that suggested an increased incidence of adult respiratory distress syndrome associated with the use of talc as a sclerosant. The size of the talc particles (less than 15 μm) and the dose (greater than 5 g) may be associated with a higher incidence of ARDS. In a comprehensive literature review, Sahn et al. found acute respiratory failure in 0.15 percent of patients treated with talc poudrage.

As an adjunct to surgical therapy, the most commonly described material is talc. Sterile, asbestos-free talc is insufflated during thoracoscopy or thoracotomy to coat the visceral pleural surface. Typically, 2 to 10 g are used.

Mechanical pleurodesis is performed as part of a surgical procedure. It may consist of simple abrasion of the parietal pleural surface or may entail stripping of the parietal pleura (pleurectomy). The second method has a greater potential for complications, including injury to an intercostal neurovascular bundle or excessive bleeding from the large raw surface area. Also considered in this category is the use of an Nd:YAG laser or an argon beam coagulator, which essentially cauterizes the pleural surface. Experimental studies have not borne out their effectiveness.

The performance of pleurodesis is somewhat controversial owing to the degree of pleural symphysis that can be obtained and with these methods. Either talc or mechanical pleurodesis, especially pleurectomy, may result in rather significant adhesion formation. Clearly there is a considerable reduction in the incidence of recurrence. However, in some cases, there are concerns that future surgical procedures, such as pulmonary resection, open lung biopsy, and lung transplantation, may be hampered by this degree of pleural symphysis. The application of pleurodesis thus depends on an assessment of the risk of recurrent pneumothorax and the potential morbidity to the patient should a recurrence occur versus the potential for later operative procedures in the thorax. One suggested compromise is limitation of the pleurodesis to the apical area, as this is the most common location for air leaks to occur. Later thoracic procedures may be done, albeit with more difficulty, by entrance inferior to the area of pleurodesis and subsequent adhesion lysis apically. Localized pleurodesis is not possible when it is performed as an adjunct to tube thoracostomy. A second potential compromise is the use of tetracycline analogs such as minocycline or doxycycline. Experimental studies and anecdotal reports indicate that with the use of tetracycline, the degree of pleural symphysis and density of adhesions are not as great as with talc or mechanical pleurodesis.

Operative Therapy

Operative treatment is generally thought to be the most effective in assuring expansion of the lung, with complete evacuation of the pleural space, and providing for the best means of reducing the risk of recurrence. In addition, it provides a means of potentially identifying an air leak and closing it. However, increased patient discomfort, risks of general anesthesia, and greater costs of the procedures, combined with moderate success of the less invasive methods, result in restricted application of surgery for pneumothorax.

Operative therapy is indicated in cases in which the above-mentioned, less invasive techniques have failed, with a persistence or recurrence of the pneumothorax, or in cases of initial presentation of patients with factors suggesting increased risk of later recurrence. This risk of recurrence also includes an assessment of the potential morbidity to the patient should another pneumothorax occur.

Longitudinal studies have indicated that after tube thoracostomy treatment of a spontaneous pneumothorax, the recurrence rate is approximately 30 percent. Among patients in whom the disease recurs once, the subsequent recurrence rate continues to increase. Evidence suggests that a more definitive procedure—namely, surgery—is indicated with the first recurrence. In patients with underlying lung disease, such a large bulla is also believed to have an increased risk of recurrence, and in most cases, surgery is indicated for the initial episode. Patients who have high-risk lifestyles, such as pilots or scuba divers, or patients who may not have ready access to medical care may possess a relative indication for surgical treatment of a first occurrence of spontaneous pneumothorax because of the risk to the patient should a pneumothorax occur. Patients who present with bilateral or tension pneumothorax may also fall in this category of morbidity assessment.

Patients with a pneumothorax from any cause who have a persistent air leak despite chronic aspiration therapy should also be considered for operative therapy. An air leak that fails to close after 72 hours of suction has a very low chance of closing spontaneously. This is the recommended time for surgical referral. Finally, patients in whom the previous forms of therapy result in incomplete re-expansion of the lung should be considered for surgery. This situation may reflect loculation of the pneumothorax or trapping of the

lung by a fibrotic "peel," which will require surgery to be released.

Thoracoscopy

In recent years, a greater emphasis on "minimally invasive surgery," and the advent of improving technology and video assistance, video-assisted thoracoscopic surgery (VATS) has become a popular surgical modality. Less postoperative discomfort and decreased length of hospital stay have made this a more accepted procedure. The decreased morbidity is the result of the ability to examine the pleural space and manipulate the lung without significant muscle division or rib spreading.

In most cases, the technique requires general anesthesia with double-lumen endotracheal ventilation (single lung ventilation). Those patients who are high risk (elderly or significant underlying lung disease) can undergo this procedure under local and epidural anesthesia.

Up to three separate ports are placed in the intercostal spaces to effect installation of the camera as well as manipulating devices. The entire lung can be inspected and a search for the air leak carried out. Generally speaking, the apical area is the location, and this area can then be closed with the use of a stapler. In patients with concomitant lung disease, particularly COPD, the staple line can be reinforced with the aid of bovine pericardium to minimize persistence of air leaks. The pleural surface can then be abraded or talc insufflated, as mentioned, to achieve some degree of pleural adhesion following re-expansion of the lung. Long-term follow-up of recurrence rates has shown results similar to those for open thoracotomy. Stapled resection of bullae and talc poudrage can be performed safely.

The less invasive nature of VATS compared to open thoracotomy has prompted earlier and more frequent surgical referral. While the risks associated with general anesthesia remain, overall costs are generally less than thoracotomy owing to a decreased postoperative period. The cost of VATS as an initial procedure for spontaneous pneumothoraces may be less in the course of the treatment of the disease as compared with more conservative therapies for both PSP and SSP. These conclusions; however, are not based on prospective randomized trials and should be verified in larger prospective studies.

Open Thoracotomy

Classically, thoracotomy was believed to be the ultimate and most effective form of therapy for pneumothorax. Recurrence rates are generally less than 2 percent. Thoracotomy allows examination of the lung for the site of an air leak, enables lysis of previous adhesions that may lead to a loculated pneumothorax, and enables the release of a fibrotic peel that occasionally forms, leading to incomplete re-expansion of the lung. Drawbacks include the potential risks associated with general anesthesia, increased costs, and the significant amount of patient discomfort. Discomfort is generally most severe with a standard lateral or posterolateral thoracotomy with muscle division and rib spreading.

In an effort to minimize the level of discomfort, variations have been developed, including the use of smaller incisions, so-called muscle-sparing thoracotomies, and the axillary thoracotomy. Lung examination and air leak closure and possible pleurodesis or pleurectomy then can still be performed.

While thoracoscopy has supplanted thoracotomy as the surgical treatment of pneumothorax in many institutions, open thoracotomy remains a valuable option in the treatment of complicated cases.

Suggested Guidelines for Therapy

Based on the relative efficacy of the various forms of therapy (Table 87-1), combined with relative risks for the major categories of pneumothorax, the following guidelines are suggested.

Primary Pneumothorax

Patients with a first-time primary spontaneous pneumothorax who are asymptomatic and whose pneumothorax is thought to be less than 20 percent may be treated with observation and sometimes adjunct measures, including the use of supplemental oxygen. Patients with primary spontaneous pneumothorax who are symptomatic or whose pneumothorax is greater than 20 percent should undergo an attempt at catheter aspiration. Subsequent small- or large-tube thoracostomy is indicated for failure of simple aspiration.

Patients who undergo successful tube thoracostomy with complete lung re-expansion and absence of an air leak may be considered for further chemical pleurodesis, with doxycycline or talc as the suggested agent. This will reduce the risk of recurrence, but it should not completely obviate the ability to perform later surgical procedures. Patients with tube thoracostomies that have persistent air leaks for more than 72 hours should be referred for surgical therapy.

Because of the progressive increase in risk of recurrence, patients with their first recurrence of a primary pneumothorax should undergo chemical pleurodesis or be referred for surgical therapy, preferably thoracoscopy with stapling of any air leak and pleural abrasion or chemical pleurodesis. Indications for surgery in primary pneumothorax are listed in Table 87-2.

Secondary Pneumothorax

In general, therapy for secondary pneumothorax should be more aggressive because of the higher rate of recurrence due to the underlying lung pathology. Specific conditions with pneumothorax as a common occurrence are as listed below.

COPD

Most cases of pneumothorax in patients with COPD should be treated with some form of long-term aspiration, typically tube thoracostomy. In patients who are not good surgical candidate chemical pleurodesis with doxycycline or talc should be performed once there is complete reexpansion and absence

Table 87-2

Indications for Surgery in Primary Spontaneous Pneumothorax

First episode
Prolonged air leak
Incomplete re-expansion of lung
Associated single large bulla
Occupational hazard (flight personnel, divers)
Absence of medical facility in isolated areas
Tension pneumothorax*
Hemopneumothorax*
Bilateral pneumothorax*
Second episode
Ipsilateral recurrence
Contralateral recurrence after first pneumothorax*

** Relative indication.*

of an air leak. In COPD patients who are good surgical candidates or in patients with a persistent air leak longer than 72 hours, more aggressive therapy should be considered. Recommended therapy would include thoracoscopy, VATS, or thoracotomy with talc insufflation, mechanical pleurodesis, stapling resection, and/or pleurectomy. This approach provides a better means of achieving a lower risk of recurrent pneumothorax.

Cystic Fibrosis

In a retrospective review of patients with cystic fibrosis and pneumothorax, the entire spectrum of therapeutic options were utilized as clinically indicated. Patients undergoing surgical therapy did better and had fewer episodes of recurrence and complications. Therefore, this is the primary recommendation for this subgroup of patients. Because of the growing application of lung transplantation to patients with cystic fibrosis, localized pleurodesis is recommended as an adjunct to surgical closure of the air leak.

AIDS

For most AIDS patients presenting with a pneumothorax, tube thoracostomy is the primary mode of initial treatment. Because of the high primary and secondary treatment failure rates, patients who have no air leak with complete lung reexpansion should undergo talc slurry pleurodesis. For patients with a persistent air leak who are felt to be poor surgical risks because of severe debilitation, a Heimlich valve may be utilized. For patients who are deemed good risks for surgery, thoracoscopy with talc insufflation is recommended.

Other Conditions

While there are insufficient data to make firm recommendations for the following situations, some suggestions are offered. Patients having pneumothorax secondary to iatrogenic causes may be treated with observation or aspiration according to the guidelines previously listed. Patients who have a pneumothorax secondary to trauma should have large-bore tube thoracostomy, because there is a high association with hemothorax and the margin of safety may be decreased owing to other injury. Patients who experience a pneumothorax while on positive-pressure ventilation should have tube thoracostomy placement to avoid progression to a tension pneumothorax. Patients who present with bilateral pneumothoraces or a tension pneumothorax, but who are not on positive-pressure ventilation, should have placement of tube thoracostomy. Further therapy with regard to chemical pleurodesis versus surgery is dependent on underlying lung pathology.

COMPLICATIONS

Tension Pneumothorax

A tension pneumothorax is present when the intrapleural pressure is greater than atmospheric throughout expiration and often during inspiration as well. The term *expiratory tension pneumothorax* has been proposed to highlight the fact that in a spontaneously breathing person, pleural pressure must be negative in relation to atmospheric pressure during part of the respiratory cycle for air to enter the pleural space. The mechanism responsible for tension pneumothorax is the disruption of the visceral or parietal pleura in such a manner that a one-way valve develops. During inspiration, the respiratory muscles contract and create negative intrapleural pressure, allowing for air movement into the pleural space. Then, during expiration, when the expiratory muscles relax, the pleural pressure becomes positive and the one-way valve prevents the egress of air from the pleural space. As a tension pneumothorax progresses, the pleural pressure remains positive during a greater portion of the inspiratory cycle. If the patient is on mechanical ventilation, the alveolar pressure remains positive throughout inspiration and expiration.

A tension pneumothorax can occur after any type of pneumothorax; it is independent of the etiology. It can sometimes occur after a spontaneous pneumothorax but is more common after a traumatic pneumothorax, with mechanical ventilation, or during cardiopulmonary resuscitation.

The clinical picture associated with the development of a tension pneumothorax is striking. The patient will appear acutely ill, develop severe dyspnea, marked tachycardia, profuse diaphoresis, and cyanosis. On physical examination, the patient may develop profound hypotension and hypoxemia, exhibit distended neck veins, tracheal deviations to the side opposite the pneumothorax, subcutaneous emphysema, and may show unilateral chest hyperinflation. The involved hemothorax will enlarge and there will be widened interspaces. Arterial blood gases reveal severe hypoxemia and can show a severe respiratory acidosis. Chest radiographs

may show mediastinal shift to the contralateral side of the pneumothorax. Patients receiving mechanical ventilation often develop a sudden increase in their peak and plateau pressures, with an associated decrease in the oxygen saturation. If the patient is on pressure control ventilation and is paralyzed, arterial blood gases will show a respiratory acidosis as the patient is unable to increase his respiratory rate.

The development of a tension pneumothorax is a medical emergency requiring immediate chest drainage to relieve the intrapleural pressure. It should be suspected in any patient with a pneumothorax whose condition deteriorates acutely or in any patient with cardiopulmonary collapse after a procedure known to cause a pneumothorax, or with mechanical ventilation. One should also suspect a tension pneumothorax in any patient undergoing cardiopulmonary resuscitation that is difficult to ventilate or develops electromechanical dissociation. A tension pneumothorax may develop because of improper connection of a one-way flutter valve to the chest tube. It can occur even if there is a chest tube in place, due to either malpositioning of the tube or disconnection at the site of tube or the site of the pleural-vac container.

When the diagnosis of a tension pneumothorax is considered, the patient should be given a high concentration of oxygen to alleviate the extreme hypoxemia seen with this syndrome. Radiographic documentation may not be possible in an emergency situation. Tension pneumothorax is a clinical diagnosis and therapy should not be held up by confirmation of the chest radiograph. A large-bore needle should be inserted into the second anterior intercostal space. Optimally, the needle should be connected to a syringe partly filled with sterile saline. Air bubbling outward through the fluid confirms the diagnosis. The needle or its plastic outer sheath should be left in place, and the patient should be prepared for immediate tube thoracostomy.

The decompensation of the cardiopulmonary status in patients with tension pneumothorax is usually attributed to diminished venous return and marked decrease in the cardiac output, which is the most life-threatening. However, there is also a significant decrease in the Pa_{O2}, which also needs to be addressed immediately as well.

Animal studies demonstrate that cardiac output is maintained by the tachycardia and the increase in negative intrathoracic pressure during inspiration. Deterioration has been shown to be related to severe hypoxemia, probably because of increased shunting and ($\dot{V}_A/\dot{Q}$) mismatch in the compressed lung. Preterminally, animals develop CO_2 retention and respiratory acidosis. The importance of negative intrathoracic pressure swings in maintaining cardiac output was demonstrated by the precipitous fall in cardiac output when mechanical ventilation was initiated.

Bronchopleural Fistula

A bronchopleural fistula is a communication between the pleural space and the bronchial tree. It is a rare, but serious complication associated with several pulmonary conditions. In the setting of a spontaneous or nonspontaneous pneumothorax, it is consistent with a prolonged air leak.

Most air leaks seal within 24 to 48 hours after tube thoracoscopy. Only 3 to 5 percent of patients with pneumothorax have a persisting air leak. If an air leak persists for more than 48 hours, continuous suction for 8 to 10 days results in only minimal increase in pulmonary healing. Current ACCP guidelines recommend if the leak persists over 4 days, the patient should be evaluated for surgery to close the air leak and perform a pleurodesis procedure to prevent recurrence. Thoracoscopy is the preferred procedure for managing bronchopleural fistulas. Use of an additional chest tube may occasionally help, but surgery should be considered after 3 to 4 days of tube drainage.

Patients with cystic fibrosis or COPD are at increased risk for the development of persistent bronchopleural fistula. For those who are not candidates for thoracotomy, the fistula may be localized by bronchoscopic balloon catheter occlusion and subsequently injected with a variety of substances to promote sealing of the air leak. Fibrin glue, liquid bioadhesive (isobutyl 2-cyanocrylate), sterile gelatin sponge, and even lead shot have been used for this purpose. Autologous "blood patch" pleurodesis has also been accomplished, using 50 to 100 ml of the patient's blood and injecting it into the chest tube. In our experience, however, these patients almost all come to thoracoscopic surgery because these procedures usually fail, and the air leak persists for more than 7 to 10 days.

Re-expansion Pulmonary Edema

Re-expansion pulmonary edema (REPE) is a rare but potentially lethal condition that can occur with the rapid re-expansion of a collapsed lung (after a varied period of time) after tube thoracostomy is used to drain air (pneumothorax) or fluid (pleural effusion) from the pleural space.

The pulmonary edema is most commonly unilateral (ipsilateral to the re-expanded lung), but on occasion, can become bilateral, sometimes requiring intubation and mechanical ventilation. Although rare, this syndrome is potentially fatal. Although the mortality is not well defined, in 1988, Mahfood and colleagues reviewed the literature of re-expansion pulmonary edema and found only 53 cases, but 11 (21 percent) were fatal. The incidence in the literature is unknown. There were no cases reported in the Veterans Administrative Cooperative study of more than 200 patients with spontaneous pneumothoraces. The single largest retrospective study ($n = 21$) reported an incidence of 14 percent. It is likely that both fatal and nonfatal cases are under reported in the literature.

The pathogenesis of REPE is not completely understood. A number of mechanisms have been suggested. It appears that at least to some degree, REPE is due to increased permeability of the pulmonary capillaries that are damaged

by mechanical stress during re-expansion of the lung. Reperfusion injury due to free radicals may also be responsible for increased capillary permeability. Other theories include ischemia reperfusion injury, free radical injury, decreased surfactant, airway obstruction, and decreased lymphatic flow.

There are several factors that have been evaluated and associated with an increase in the incidence of REPE. The duration of pneumothorax prior to drainage has been shown to be significant. Animal models demonstrate that reexpansion pulmonary edema occurs when a pneumothorax has been present for 3 days or more and the lung has been expanded with more than –20 cm H_2O pleural pressure. The severity of the pneumothorax may also be predictive of developing REPE. In Matsuura's series, no patient with a pneumothorax less than 30 percent of the lung field versus 17 percent of patients with total collapse and 44 percent of patients with tension pneumothorax developed this complication. Lastly, the method (with suction or without suction) and the rate of expansion (too rapid) have also been implicated as a potential risk factor. Probably there is no single factor that predicts the likelihood of developing REPE, and they are all important when trying to prevent REPE.

The clinical presentation of REPE can be relatively benign or present as a life-threatening event. When serious, its onset is sudden and dramatic. Onset can be immediate, with the majority of patients presenting with symptoms within 1 hour and all are symptomatic within 24 hours. Typically, patients will have a severe persistent cough and develop chest pain immediately or within an hour after chest tube thoracostomy. The patients develop hypoxemia, tachypnea, tachycardia, and often hypotension. It is characterized by decreased pulmonary compliance and patchy or diffuse alveolar infiltrates in the re-expanded lung. Symptoms usually progress for 24 to 48 hours. If the patient survives the first 48 hours, recovery is usually complete.

Treatment is supportive and sometimes, if severe enough, patients require mechanical ventilation. The best option is to try to prevent REPE. There are no randomized controlled trials to support a particular preferred method to prevent REPE. However, when thoracostomy is performed for a spontaneous pneumothorax of unknown duration, the tube initially should be connected to underwater-seal drainage rather than to negative pressure. If the lung fails to fully expand after 12 to 24 hours, negative pressure can be applied to the pleural space.

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Malignant Mesothelioma and Other Primary Pleural Tumors

Daniel H. Sterman • Leslie A. Litzky • Steven M. Albelda

The pleura is a membranous structure covering the entire surface of the lung and lining the inside of the chest cavity. It is composed of a thin mesothelial layer with underlying fibroblasts and varying amounts of collagenous fibrous tissue with interdigitating capillaries and venules. The most common tumors of the pleura are metastatic neoplasms, predominantly of lung, breast, or colonic origin. Tumors arising primarily from the pleura are rare, but still constitute a variety of benign and malignant lesions from several different cells of origin, some of which have yet to be identified.

MALIGNANT MESOTHELIOMA

The most common primary malignant tumor of the pleura is malignant mesothelioma, an insidious neoplasm with a dismal prognosis arising from the mesothelial surfaces of the

pleural and peritoneal cavities, as well as from the tunica vaginalis and pericardium. Eighty percent of all cases of mesothelioma are pleural in origin.

Epidemiology

The incidence of mesothelioma in the United States is estimated to be 2200 cases per year, with reported rates increasing by as much as 50 percent in the past decade. Incidence is also increasing in Europe, Japan, and Australia. In Great Britain mesothelioma death rates rose from 153 people in 1968 to 1848 people in 2001. Similar numbers of deaths are expected annually until the year 2015. After that time, mesothelioma rates are expected to drop in England and other developed countries because of legislation aimed at reducing asbestos exposure in the workplace and the general environment. In contrast, mesothelioma incidence rates are predicted to escalate for much longer times in the Third World because of poor regulation of asbestos mining and widespread industrial and household utilization of asbestos.

Etiology

Asbestos Exposure

Inhalational exposure to asbestos has been clearly established as the predominant cause of malignant mesothelioma in humans. Approximately 70 percent of cases of pleural mesothelioma are associated with documented asbestos exposure. In ancient Greece, the philosopher Pliny first established the association between asbestos exposure and lung disease by making the observation that slaves working in asbestos mines were less healthy than other slaves. It was not until 1960, with the publication by Wagner and colleagues of a series of 33 mesothelioma cases occurring in a crocidolite mining community in South Africa, that the etiologic connection between asbestos and mesothelioma was established. Wagner's study was soon followed by several other accounts of mesothelioma afflicting asbestos workers at locations around the world. In addition to asbestos miners and workers, other occupations at especially high risk include plumbers/pipefitters, mechanical engineers, ship and boat building and repairing.

Although the lifetime risk of developing mesothelioma among asbestos workers is thought to be as high as 8 to 13 percent, there is no direct correlation of pleural disease incidence to the amount or duration of asbestos exposure. The absence of a definite dose-response relationship between asbestos and pleural mesothelioma is of significant concern because as many as 8 million persons living in the United States have been occupationally exposed to asbestos over the past 50 years. Also, many well-documented cases of mesothelioma occur after very brief or low-level exposures to asbestos (i.e., spouses of asbestos workers exposed by washing clothes).

Asbestos is not a specific compound, but the commercial name for a group of hydrated magnesium silicate fibrous minerals divided into two major types: the serpentines and the amphiboles. Serpentine chrysotile fibers are spiral-shaped and pliable, whereas the amphiboles (crocidolite, amosite, tremolite, anthophyllite, actinolite) are long and needle-like. The carcinogenicity of certain types of asbestos is thought to be due, in part, to the physical properties of the fibers rather than their chemical composition. Fibers with a high length-to-width ratio, such as crocidolite, which are able to more readily penetrate through the lung to the pleural surface, are considered more carcinogenic. Among the remaining asbestos fibers, amosite has an intermediate carcinogenic risk, chrysotile the lowest. It is unclear whether the cases of mesothelioma attributed to chrysotile exposure are caused by the chrysotile itself or by contamination with tremolite fibers.

Molecular Pathogenesis

The latency period from asbestos exposure to the development of mesothelioma ranges from approximately 20 to 50 years, suggesting the necessity of multiple genetic alterations for eventual malignant transformation of the mesothelium. Despite extensive investigatory effort, the exact mechanisms of asbestos carcinogenesis have not yet been fully elucidated. In rodent model systems, asbestos fibers act like tumor promoters in combination with a carcinogen, eliciting proliferation of mesothelial cells. Asbestos fibers can also interact with the mitotic spindle to cause missegregation of chromosomes and aneuploidy. In rat pleural mesothelial cells, asbestos fibers and erionite have been shown to induce the protooncogenes c-fos and c-jun in a prolonged and dose-responsive manner. Several growth factors, secreted by mesothelial/mesothelioma cells in an autocrine fashion, have been implicated in various stages of mesothelioma tumorigenesis. Platelet-derived growth factors A and B (PDGF A and B), insulin-like growth factors 1 and 2 (IGF-1 and IGF-2), basic fibroblast growth factor (bFGF), and transforming growth factor-β1, 2, and 3 (TGF β1, 2, and 3) constitute a complex mixture of autocrine and paracrine stimuli for mesothelioma cell proliferation as well as initiation of tumor angiogenesis. There is also evidence implicating aberrant activation of the Wnt signaling pathway in mesothelioma.

It has been well established that chronic inflammation predisposes to cancer development. Asbestos fibers appear to stimulate the production of chronic oxidative stress in lung macrophages and other cells for many years. In animal models, crocidolite fibers clearly induce specific DNA adducts (8-hydroxydeoxyguanosine, 8-OHdG) associated with oxidative damage in the DNA from peritoneal cells and macrophages of asbestos-exposed animals. These same type of 8-OHd DNA adducts have been observed in the blood lymphocytes of asbestos-exposed individuals decades after exposure suggesting very chronic exposure to oxidant stress.

Analysis of explanted human mesotheliomas and cultured human mesothelioma cell lines has revealed a number of cytogenetic aberrations that may predispose to the development of the malignant phenotype. Partial or total loss of chromosomes 1, 3, and 4, deletions of 9p, and monosomy of chromosome 22 are the most common abnormalities seen. For mesotheliomas, 9p deletions have been associated with the loss of function of the $p16^{INK4}$ cdk inhibitor, a putative

tumor suppressor gene, engendering unchecked cdk4-mediated phosphorylation of the retinoblastoma 1 (Rb1) gene product and leading to loss of regulation of cell division. Monosomy 22, the most frequent numerical cytogenetic abnormality in mesothelioma, has recently been correlated with mutations in the neurofibromatosis 2 (NF2) tumor suppresser gene—mutations more commonly associated with acoustic neuromas, schwannomas, and meningiomas. The product of NF2, Merlin, appears to inhibit cell proliferation and cell cycle progression by repressing cyclin D1 expression as well as inhibiting invasiveness. The ubiquitous presence of the Wilms' tumor suppresser gene (WT1) in human mesotheliomas raises the possibility that alterations in this gene or binding of the WT1 gene product to the p53 tumor suppressor may predispose to mesothelial cell carcinogenesis.

Viral Oncogenes

Simian virus-40 (SV-40) is a polyoma virus with oncogenic potential in humans. Its actions are thought to result from inactivation of tumor suppressor genes such as the retinoblastoma gene (Rb) and wild-type p53 (wt p53) by a peptide known as the SV-40 large T-antigen (Tag). SV-40 is a potent oncogenic virus in human and rodent cells; importantly, SV-40 DNA sequences have been identified in brain tumors, osteosarcomas, and lymphomas. Cellular and animal studies have shown that crocidolite asbestos and SV40 can act as cocarcinogens. Several studies have documented the presence of SV-40 in a significant proportion of mesothelioma cases (some of which did not have obvious asbestos exposure), as well as in cases of atypical mesothelial proliferation. As an example, one report examined 35 archival mesothelioma specimens and found that SV-40-like sequences were present in 86 percent of cases. However, the possibility that technical factors can produce false-positive results suggestive of SV-40 infection also has been raised. Despite the fact that there was worldwide dissemination of SV-40 contaminated polio vaccines in the 1950s and 1960s, there is no convincing epidemiological evidence linking SV-40 exposure to the development of malignant mesothelioma.

Nonetheless, it is possible that Tag interference with Rb and wt p53 may play an accessory role in the carcinogenesis of malignant mesothelioma. If this hypothesis is validated, novel strategies of vaccination to prevent mesothelioma, or molecular techniques to improve early diagnosis may become possible.

Genetic Predisposition

Gene polymorphism studies are in their early stages in asbestos-exposed populations. Some suggestive associations in DNA repair genes with mesothelioma development have been reported, but need validation. Hirvonen et al. described an increased incidence of mesothelioma among asbestos-exposed individuals in Finland found to be lacking the glutathione-S-transferase M1 (GSTM1) gene and carrying the "slow-acetylator" type of the *N*-acetyltransferase 2 (NAT-2) gene. The GSTM1 gene is important in the detoxification of several carcinogens, including polycyclic aromatic hydrocarbons; NAT-2 is associated with the biotransformation of aromatic amines. Some genetically predisposed families have been identified, but without idenfication of a specific "mesothelioma" gene.

Other Etiologic Factors

The development of malignant pleural mesothelioma has also been associated in rare cases with other etiologic factors, including therapeutic irradiation, intrapleural thorium dioxide (Thorotrast), and inhalation of other fibrous silicates such as erionite. Epidemiologic studies of a region in central Anatolia (Turkey) with an abnormally high incidence of pleural mesothelioma (22 per 10,000 individuals over 25 years old) implicated routine household use of a locally ubiquitous silicate, erionite, as a potential etiologic agent. However, it appears that only specific families (who appear to have as yet to be defined genetic abnormality) are susceptible to eronite-induced mesothelioma.

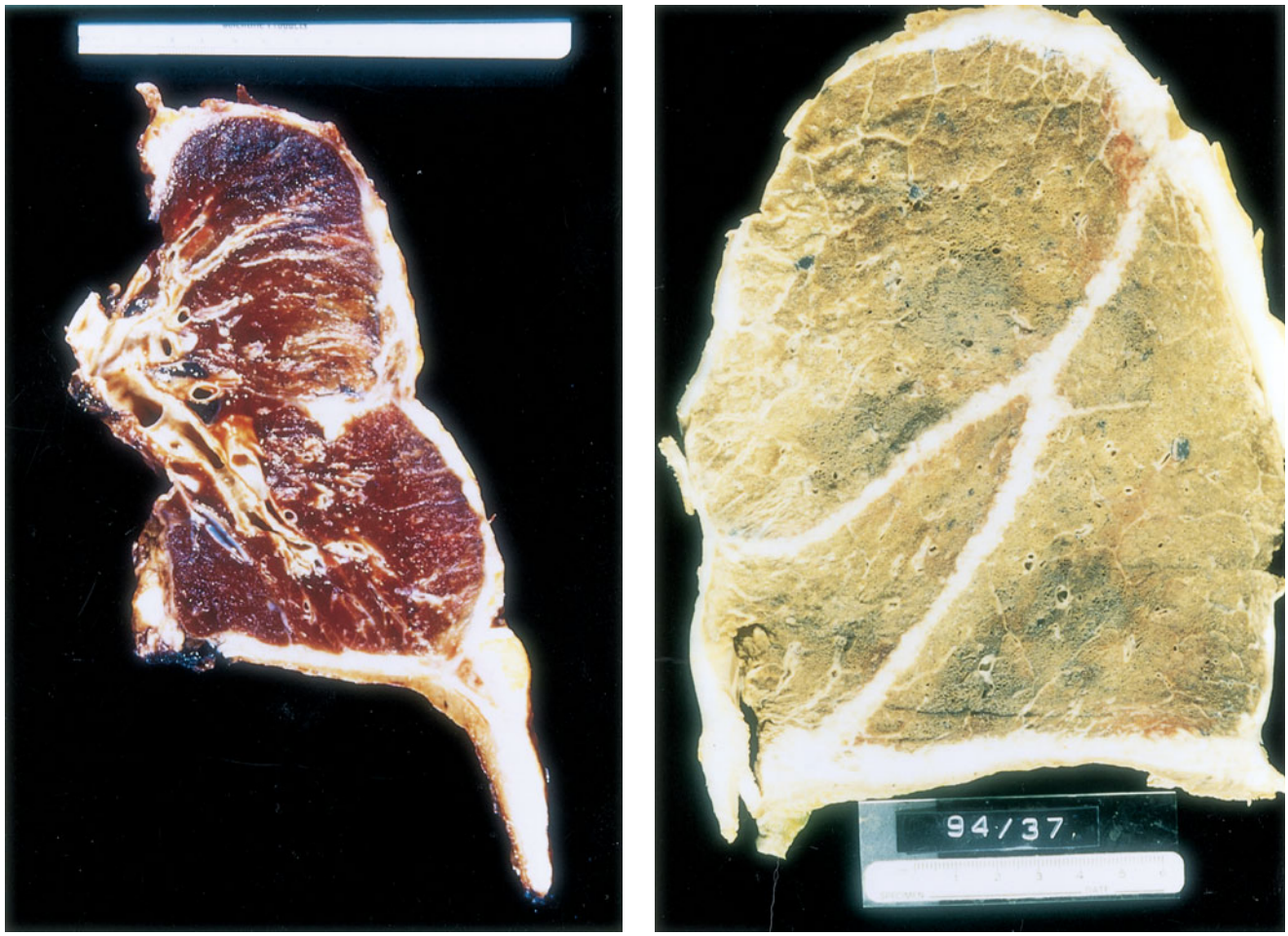
Pathology

Gross Pathology

The vast majority of malignant mesotheliomas involving the pleura are those tumors that diffusely involve the pleura and are properly termed "diffuse malignant mesothelioma." A rare localized gross variant of malignant mesothelioma that forms a single mass attached to the pleura but is otherwise microscopically identical to diffuse malignant mesothelioma has been described and termed "localized malignant mesothelioma." Diffuse malignant mesothelioma begins as multiple discrete nodules that, in earlier stages, tend to preferentially involve the parietal pleura over the visceral pleura. In time, these nodules tend to coalesce on the visceral and parietal pleural surfaces with subsequent fusion of the pleurae. Progressive tumor growth typically leads to partial or complete encasement of the lung with rinds of pleural tumor that can be several centimeters in thickness, but may show only minimal penetration of the underlying lung parenchyma (Fig. 88-1). Advanced cases show more extensive spread along interlobar fissures, deeper invasion into the underlying lung parenchyma and through the diaphragm, as well as contiguous involvement of the chest wall, pericardium, and mediastinum. Although it is rare for patients with mesothelioma to present clinically as metastatic disease, it is not at all true that peribronchial lymphovascular spread, regional lymph node metastases, and extrathoracic hematogenous metastases are uncommon. Seventy percent of patients have mediastinal lymph node involvement at autopsy. Hematogenous metastases follow the exact same pattern of spread as non–small cell lung carcinomas with involvement of the contralateral lung and pleura, liver, adrenals, bone, brain, and kidney.

Histology

The 2004 revision of the WHO classification of pleural tumors recognizes four major histological subtypes—epithelioid,



A *B*

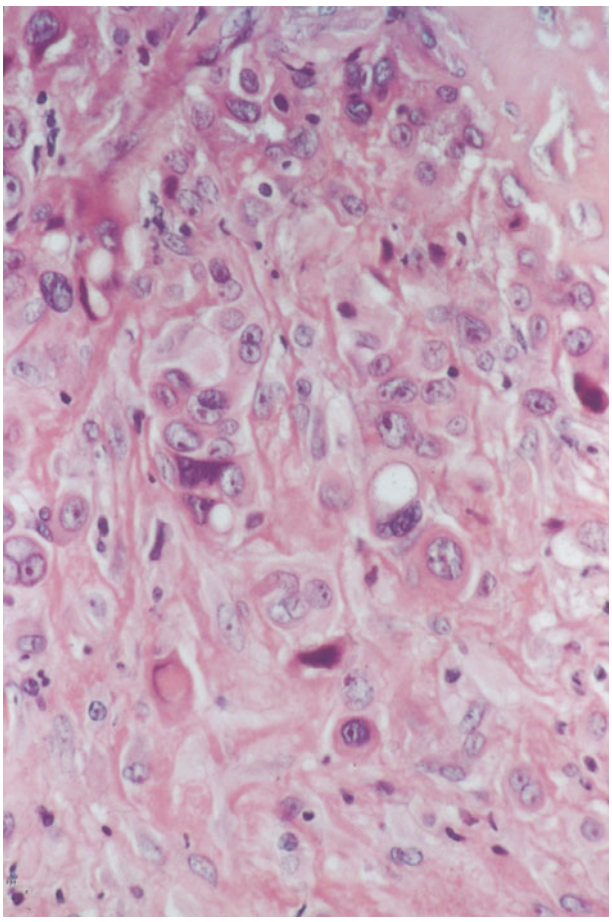
Figure 88-1 *A*. Transverse section of an extrapleural pneumonectomy surgical specimen with the entire right lung, parietal and visceral pleurae, portions of pericardium, and the majority of the right hemidiaphragm. Note the thick rind of tumor along the pleural surface encasing the lung and invading the diaphragm. *B*. Postmortem mesothelioma specimen with overnight formalin inflation and fixation. The right lung pictured is covered by a thick, whitish rind of tumor involving the entire pleural surface, which has also infiltrated and demarcated the interlobar fissures.

sarcomatoid, desmoplastic and biphasic. In the 2004 WHO classification, the use of the term "well-differentiated papillary mesothelioma" is restricted to an exceptionally rare and distinctive mesothelial tumor that has bland cytologic features, stout papillary architecture, and a tendency toward superficial spread without invasion. Part of the diagnostic utility of the WHO classification is that each subtype is associated with a particular differential diagnosis that guides the pathology work-up. This work-up requires additional time and expense. Multiple sections may be taken and ancillary studies are usually required for definitive diagnosis. From a prognostic perspective, most studies have shown that the purely epithelioid subtype has the longest survival but these differences in survival, on the basis of histological subtype, are within the range of only a few months. It should be recognized that the larger the tissue sample, the more frequent the histological variation and the higher the incidence of biphasic tumors.

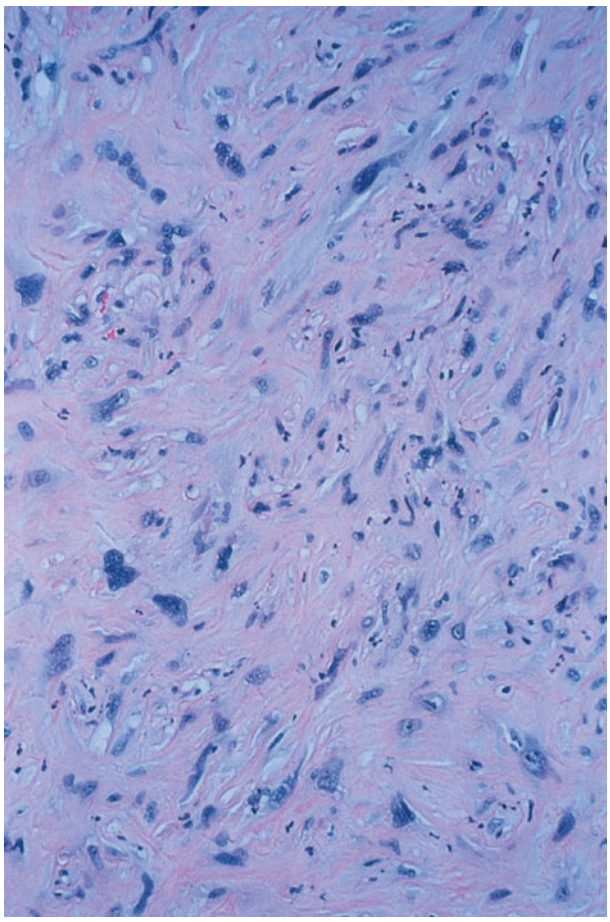
The epithelioid variant is the most common with a wide range and mix of histological patterns. Typical histological appearances of this subtype include tubulopapillary, glandular/microglandular, and solid sheet-like patterns (Fig. 88-2 *A*). A myxoid matrix may be prominent and may be mistaken for mucin, but this matrix is actually hyaluronate and shows hyaluronidase-sensitive staining with Alcian blue.

Sarcomatoid mesotheliomas can also have a wide variety of histological patterns. The most frequently encountered pattern is that of fibroblastic-like spindle cells arranged in storiform, fascicular, or haphazard patterns that mimic a fibrosarcoma (Fig 88-2 *B*). Other variants include a malignant fibrous histiocytoma-like tumor and malignant mesotheliomas with malignant smooth muscle, chrondroid, osseous, or rhabdomyoblastic differentiation.

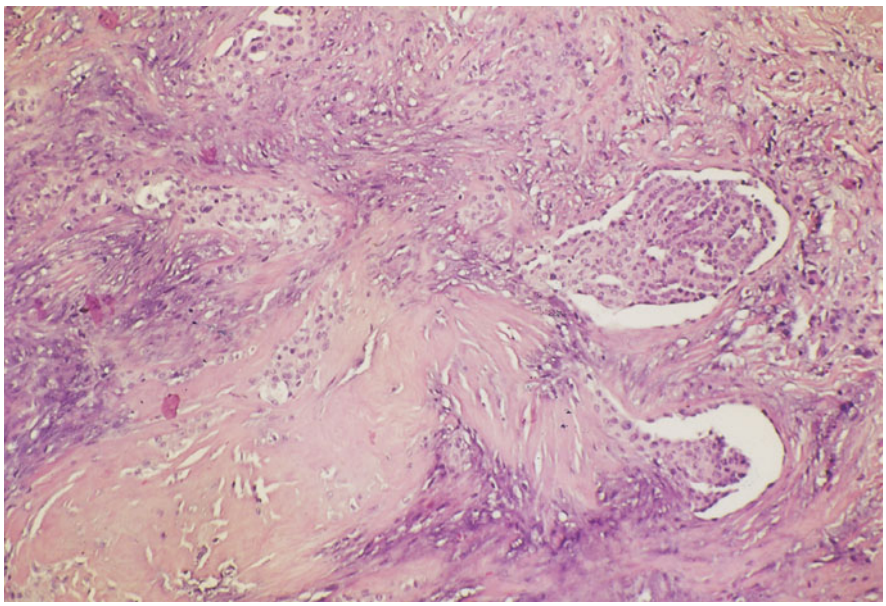
Desmoplastic mesotheliomas, by definition, have areas of densely collagenized tissue with atypical cells arranged in a storiform or "patternless" pattern. This pattern should comprise at least 50 percent of the tumor. The deceptively bland appearance of the tumor makes its separation from fibrous pleuritis exceedingly difficult, particularly with limited



A



B



C

Figure 88-2 *A*. Photomicrograph of an epithelial malignant mesothelioma. These sheets of pleomorphic cells are epithelial in appearance, with eosinophilic cytoplasm and fairly well defined cell borders. Note the cytoplasmic vacuoles, which can lead to confusion with a signet ring type of adenocarcinoma. By electron microscopy, these vacuoles can be shown to contain crystallized hyaluronic acid (H&E, ×400). *B*. Photomicrograph of a sarcomatoid malignant mesothelioma. This tumor has a malignant mesenchymal appearance with bizarre spindled cells and a growth pattern resembling that of a sarcoma. These cells demonstrated strong cytokeratin positivity on immunohistochemical staining, distinguishing this tumor from a sarcoma (H&E, ×400). *C*. Photomicrograph of a biphasic malignant mesothelioma. This tumor demonstrates several areas of epithelioid histology with a papillary growth pattern seen against a background of spindled and more poorly differentiated epithelioid cells (H&E, ×200).

sampling. Studies that have examined the criteria used for diagnosis have highlighted the importance of "interface biopsies" in which unequivocal evidence of invasion into the underlying adipose tissue, skeletal muscle, or lung may be demonstrated. Other criteria, which may require multiple tissue sections to detect, include obvious sarcomatoid areas, foci of necrosis, and distant metastases. Bone metastases similarly may be deceptively bland and confused with a primary benign fibrous tumor of bone.

Biphasic mesotheliomas have both epithelioid and sarcomatoid components (Fig. 88-2*C*). Each component should represent at least 10 percent of the tumor for the designation of biphasic. Biphasic mesotheliomas represent about 30 percent of cases. As previously noted, the percentage of biphasic tumors, which have a prognosis that is intermediate between the epithelioid and sarcomatoid subtypes, increase with larger tumor samples.

Immunohistochemistry

Immunohistochemistry (IHC) has largely replaced electron microscopy as the gold standard for diagnosis. This is because of the comparative low cost, ease, and greater availability of immunohistochemistry, as well as the expanded array of commercially available antibodies that are reliable markers of mesothelial differentiation. Because there is no single marker with sufficiently high enough sensitivity and specificity for malignant mesothelioma, it is standard practice for pathologists to employ a panel of markers (both positive and negative) to confirm the diagnosis of malignant mesothelioma. Institutions will vary somewhat in their selection of which markers to include and these panels are typically refined as publications appear with comparative utility studies. As in any instance in which immunohistochemistry is used as an adjunct in tumor diagnosis, careful consideration must be given to the tumor's histological appearance as well as the clinical-radiographic context and the differential diagnosis that is generated from this information.

Broad-spectrum cytokeratin (CK) antibody cocktails are extremely useful in the diagnosis of malignant mesothelioma. In epithelioid tumors, strong and diffuse cytokeratin positivity can be used to exclude the rare case of large-cell lymphoma, epithelioid vascular tumors, or melanoma involving the pleura. CK reactivity usually differentiates malignant mesotheliomas from many sarcomas, although there are occasional cytokeratin negative sarcomatoid mesotheliomas as well as focally CK-positive sarcomas. Although CK positivity does not distinguish malignant mesothelioma from reactive lesions, positive cytokeratin staining may help to highlight invasion into adjacent structures.

Common affirmative immunohistochemical markers, which, if positive, can be used to support a diagnosis of malignant mesothelioma include calretinin, CK5/6, the Wilms' tumor-I (WT1) antigen, and D2-40 (Fig. 88-3). These markers are most useful in the narrow differential diagnosis of malignant epithelioid mesothelioma vs. primary pulmonary adenocarcinoma. It should be noted that these markers do not invariably exclude other tumors, including metastases from non-pulmonary primary sites. A wide variety of markers can be used to support a diagnosis of adenocarcinoma, as opposed to malignant mesothelioma. Markers such as CEA, Leu-M1 (CD15), thyroid transcription factor-1 (TTF-1), Ber-EP4, B72.3, Bg8, and MOC 31 are commonly included in such panels. The sensitivity and specificity of

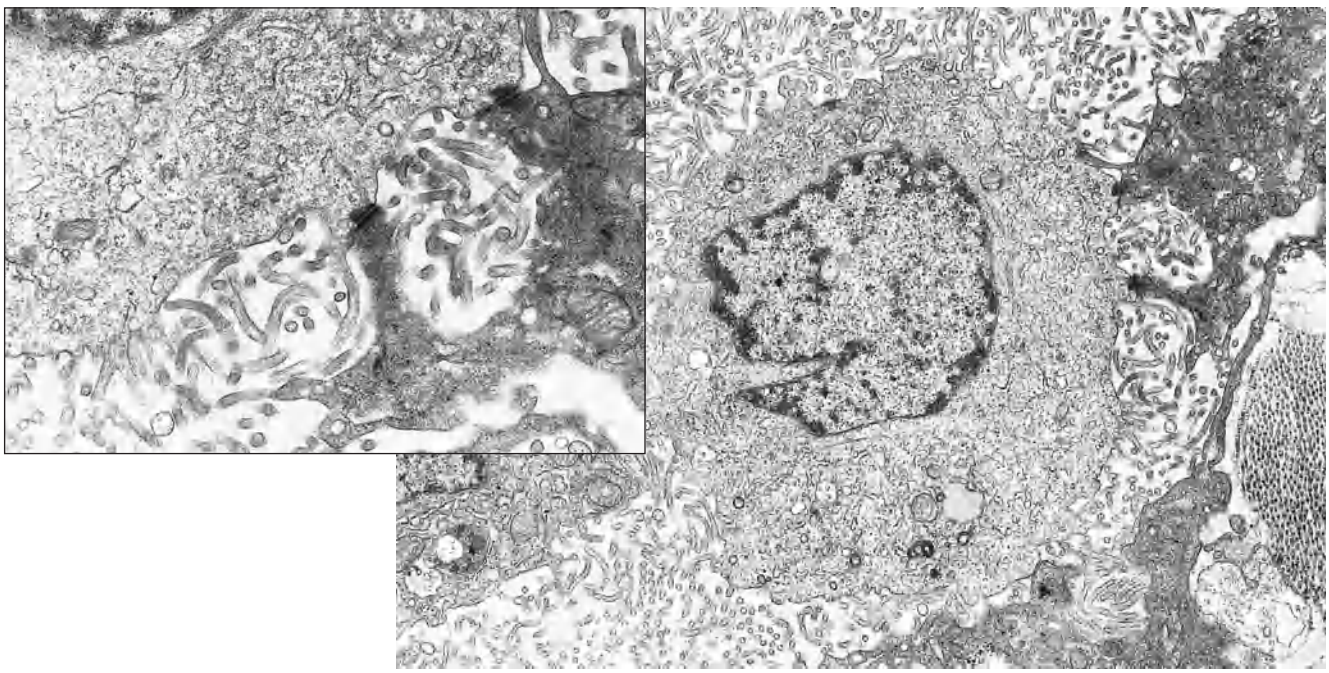


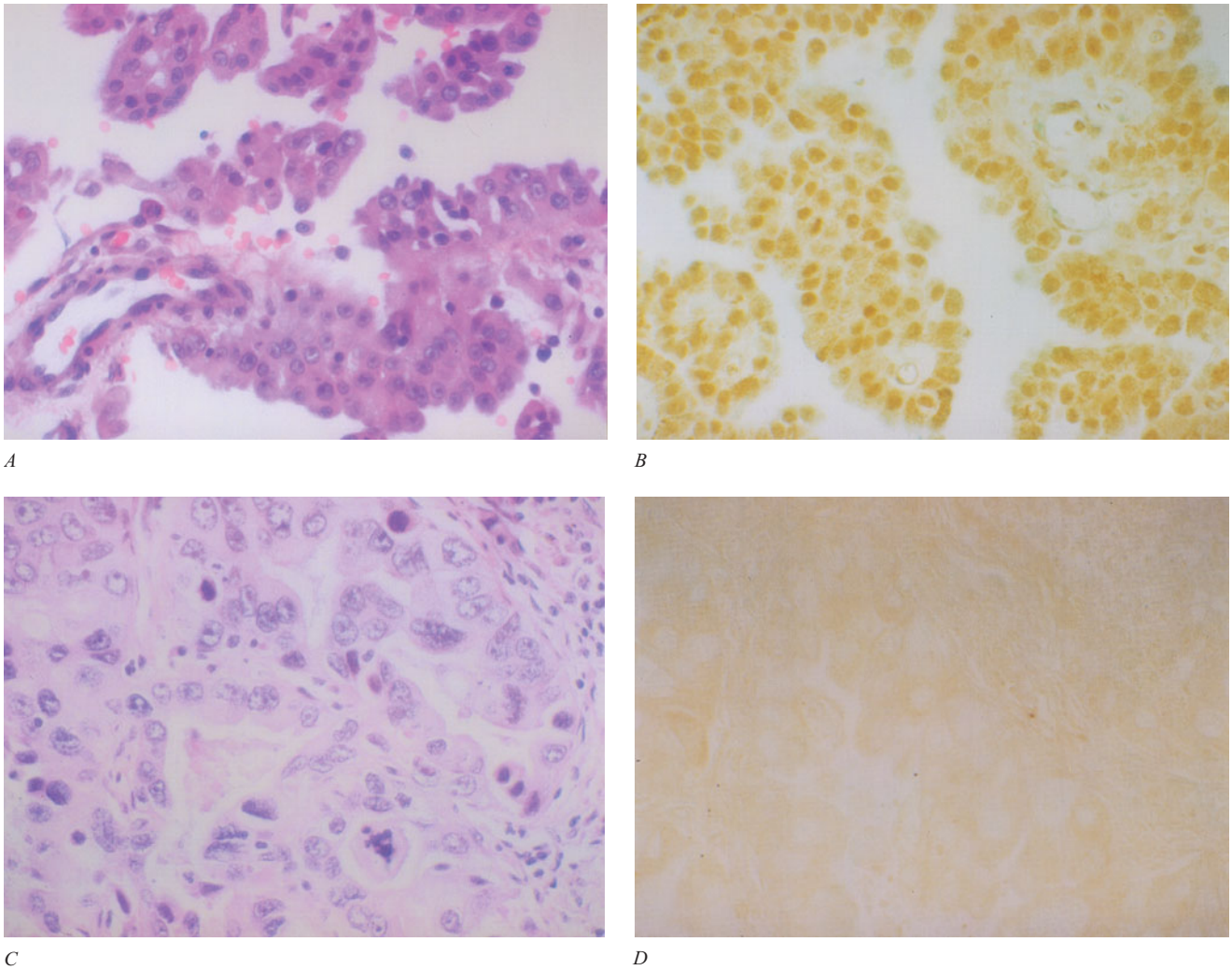
Figure 88-3 Electron micrograph of a human mesothelioma cell showing abundant microvilli arising from the cell surface and prominent desmosomes (×10,500; inset, ×30,000). *(Courtesy of Dr. Giuseppe G. Pietra, Department of Pathology and Laboratory Medicine, University of Pennsylvania Medical Center, Philadelphia.)*

both the affirmative mesothelioma markers as well as the adenocarcinoma markers vary greatly when the differential diagnosis is broadened to include other subtypes of primary pulmonary carcinoma such as squamous cell carcinoma or metastases from extrapulmonary sites such as the kidney and ovary. Both categories of markers are generally less reliable in the differential diagnosis of sarcomatoid lesions. The immunohistochemical panel that is recommended for the initial evaluation of a sarcomatoid tumor involving the pleura includes cytokeratins (including AE1/3, CAM5.2, CK18, and CK7), calretinin, and D2-40. If other types of sarcomas are being considered, then the marker panel should be expanded accordingly to include antibodies such as CD31, CD34, desmin, myoglobin, and S-100.

Other Ancillary Studies

Histochemical stains for the presence of intracytoplasmic mucin are still commonly used as a means of differentiating adenocarcinomas from epithelioid malignant mesotheliomas. Mucicarmine and periodic acid-Schiff (PAS) with diastase are the two most frequently used. These stains are technically easy to perform, inexpensive, and rapid. Care must be taken to exclude the possibility of false-positive staining that can be seen with hyaluronate. The use of histochemical staining (Alcian blue with hyaluronidase) to detect the high levels of hyaluronic acid in mesothelioma cells was used far more frequently before the widespread use of immunohistochemistry.

Electron microscopy had traditionally been considered the gold standard for the diagnosis of malignant mesothelioma and ultrastructural analysis can still be useful in occasional problematic cases. The predominant epithelioid form is composed of polygonal cells with numerous long surface microvilli, prominent desmosomes, and abundant tonofilaments (Fig. 88-4). Electron microscopy of the sarcomatoid variant reveals the presence of elongated nuclei, cytokeratin and vimetin filaments, as well as copious rough



A *B* *C* *D*

Figure 88-4 *A*. Photomicrograph of an epithelial mesothelioma (H&E, ×400). *B*. Photomicrograph of epithelial mesothelioma demonstrating positive nuclear staining with an antibody to the Wilms' tumor 1 (WT1) gene product (×400). *C*. Photomicrograph of an adenocarcinoma metastatic to the pleura (H&E, ×400). *D*. Photomicrograph of pleural adenocarcinoma stained with an anti-WT1 antibody (×400). Only minimal background staining is present.

endoplasmic reticulum, some intracellular attachments, and rare microvilli. Electron microscopic studies may be inconclusive in poorly differentiated tumors of either subtype and have no utility in the diagnosis of desmoplastic malignant mesothelioma. Molecular analysis can be performed on formalin-fixed, paraffin-embedded tissue to demonstrate the X:18 translocation characteristic of synovial sarcoma—a biphasic or monophasic sarcomatoid tumor that can involve the pleura. As discussed at the end of the chapter, synovial sarcoma should be considered in the differential diagnosis of a pleural tumor with a biphasic or monophasic spindle cell appearance.

Molecular Profiling

As compared with routine histological evaluation and classification, the examination of multiple expressed genes and/or proteins within individual tumors may be more informative for making diagnoses, estimating prognosis, and response to therapy. The development of microarray methodology, which permits the expression of thousands of genes to be assayed simultaneously, represents a powerful technique to read the "molecular signature" of an individual patient's tumor, a process termed gene expression profiling. Gene expression profiling studies have been used to identify genes with potential pathogenic significance, such as aurora kinases or key inhibitors of apoptosis proteins. Profiles have also been identified that help to reliably differentiate different subtypes of mesothelioma. By using gene expression ratios, it is possible to reliably distinguish between epithelioid mesothelioma and lung adenocarcinoma or ovarian carcinomas from peritoneal mesotheliomas. An area of active investigation (and some debate) is the use of expression profiles as a means of predicting outcome and clustering groups of patients with pleural mesothelioma into those with good risk (i.e., more likely to be cured using aggressive therapy) and poor risk disease (i.e., with a low cure rate despite aggressive therapy). Some groups have found this approach to be highly predictive, whereas others suggest the the accuracy has been overestimated.

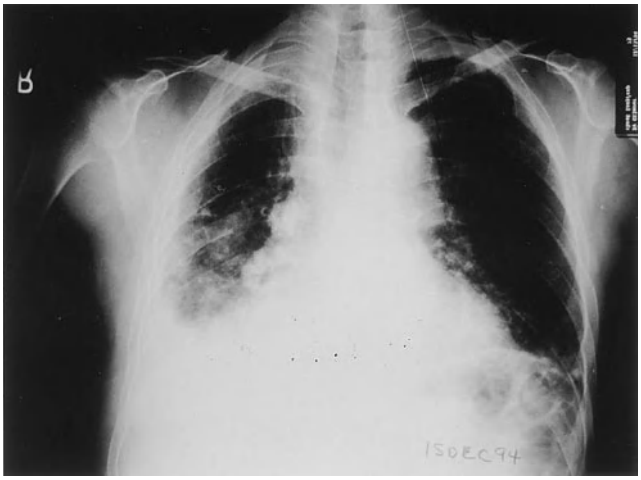
Given these provocative early findings, it is highly likely that these expression-based assays will be increasingly used for diagnostic and therapeutic decisions in mesothelioma.

Clinical Presentation

Malignant pleural mesothelioma most commonly presents in the fifth to seventh decades of life. Most patients diagnosed with mesothelioma earlier in life have a history of childhood asbestos exposure. The most frequent presenting symptoms of pleural mesothelioma are nonpleuritic chest pain (60 to 70 percent of patients), dyspnea (25 percent), and cough (20 percent). Some patients are asymptomatic at diagnosis, with unilateral pleural effusions found incidentally on routine chest radiographs. Mesothelioma is typically a unilateral disease—only 10 percent of patients with mesothelioma have bilateral involvement at presentation. In more advanced stages of disease, physical findings may include unilateral dullness to percussion throughout the hemithorax, palpable chest wall masses, and scoliosis toward the side of the malignancy.

Radiographic Presentation

The most common initial radiographic manifestation of pleural mesothelioma is a large unilateral pleural effusion, often with contralateral mediastinal shift (Fig. 88-5*A*). Sixty percent of patients have right-sided lesions; putatively related to the gravitational predilection for inhaled asbestos fibers and



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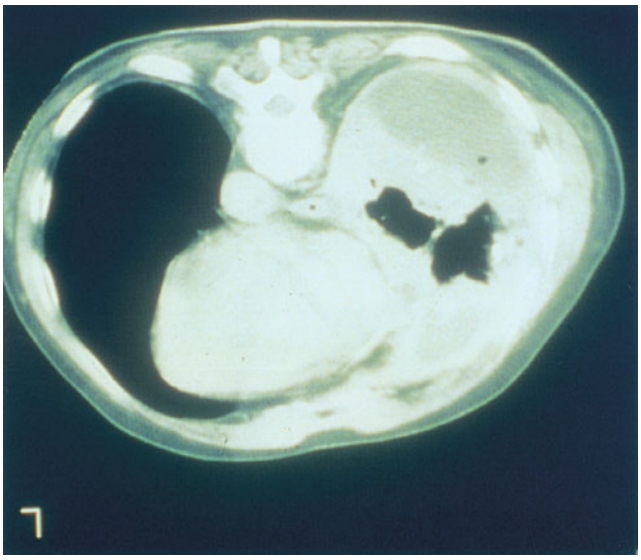


B

Figure 88-5 *A*. Posteroanterior chest radiograph in a patient with malignant pleural mesothelioma demonstrating significant right-sided pleural effusion and diffuse pleural thickening associated with marked volume loss of the right hemithorax. No definite calcified pleural plaques are seen. *B*. Computed axial tomographic image from a patient with pleural mesothelioma, illustrating complete encasement of the ipsilateral lung with a thick rind of tumor, neoplastic invasion of the interlobar fissures, small residual pleural effusion, and marked unilateral volume loss.

dusts to travel directly to the right lower lobe airways. Occasionally, mesothelioma can present as a pleural mass or with diffuse pleural thickening with involvement of the interlobar fissures in the absence of pleural effusion. Only 20 percent of patients with pleural mesothelioma have radiographic signs of asbestosis (i.e., bibasilar interstitial fibrosis), although many have evidence of pleural plaques and/or calcifications. In later stages of disease, ipsilateral mediastinal shift is seen secondary to encompassment of the lung by a thick rind of tumor and resultant significant unilateral loss of lung volume. Patients with advanced mesothelioma may also have radiographic findings of mediastinal widening owing to direct tumor invasion or lymph node involvement, enlargement of the cardiac margins secondary to pericardial invasion with effusion, and evidence of rib destruction or soft tissue masses extending from the chest wall. Chest computed tomography (CT) is important in detecting invasion of chest wall, ribs, and mediastinal structures (Fig. 88-5*B*). Coronal magnetic resonance imaging (MRI) is helpful in discerning the extent of disease, particularly extension of pleural mesothelioma through the diaphragm into the peritoneal cavity. In one study of 65 patients with pleural mesothelioma, MRI was directly compared with CT scanning. The overall diagnostic accuracy for mediastinal nodal disease was approximately 50 percent for both modalities, but MRI outperformed CT for detection of diaphragmatic invasion (82 percent versus 55 percent accuracy, respectively, $p = 0.01$), and for detecting invasion of endothoracic fascia or chest wall (69 percent versus 46 percent percent, $p = 0.05$).

Positron Emission Tomography

The role of positron emission tomography (PET) imaging, particularly PET/CT, in the care of patients with mesothelioma is multifold. It can be used in diagnosis and staging by evaluating the extent of pleural disease, establishing mediastinal lymph node involvement, evaluating tumor invasion into the lung and thoracic wall, and aid in diagnosing extrathoracic metastases. It is becoming particularly useful to assess the treatment response to chemotherapy, and radiotherapy and also plays an important role in the planning of radiation treatment.

The role of PET scanning with 18-fluorodeoxyglucose (FDG) in staging and preoperative evaluation is evolving. In a small study of 28 patients with suspected pleural mesothelioma who underwent 18-FDG PET scanning followed by thoracoscopic or open surgical biopsy, PET was shown to be better than CT for differentiating malignant from benign pleural processes. Uptake of FDG was significantly higher in malignant lesions, and an overall sensitivity and specificity of 91 and 100 percent could be achieved with PET scanning for the detection of malignant as compared with benign disease. However, hypermetabolic lymph nodes were detected in 12 patients (of whom nine had a normal CT scan), and only five had histologically proven malignant nodal disease.

In a small pilot study done by Carretta et al., PET assessment demonstrated pleural lesions in 12/13 patients with malignant pleural disease (malignant pleural mesothelioma in ten patients, adenocarcinoma in two and liposarcoma in one), also revealing distant metastases in two patients. A patient with an epithelial mesothelioma had a false-negative result. Buchmann et al. demonstrated the accuracy of FDG-PET in 16 patients with pleural changes, and showed that PET correctly classified all malignant changes (12/12), and all patients (4/4) who had no FDG uptake had benign pleural disease (fibroma, tuberculous pleurisy, empyema, and pleural fibrosis).

PET scan appears more sensitive than CT for finding extrathoracic disease, but has limited sensitivity for locoregional staging (i.e., determining potential resectability). In one retrospective study, 60 patients with malignant pleural mesothelioma were identified who had undergone PET scanning pre-operatively and the results of clinical staging were compared with surgical and pathologic results. FDG uptake was detected in 59, and the one false-negative case had disease limited to the parietal pleura (stage IA). The sensitivity of PET scanning for determining the presence of T4 (unresectable) disease was only 19 percent (7 of 21 patients). Among the 31 patients whose nodal status was assessed pathologically, only one of nine patients with N2 disease was correctly identified by PET scan, and the overall sensitivity for nodal disease was only 11 percent.

One of the potential future uses of PET that needs to be further evaluated is its utilization in the screening of patients with a history of significant asbestos exposure. These patients may potentially harbor microscopic disease, not apparent on CT or MRI, which may be amenable to early aggressive therapy. Because of the limits of detection of current 18-FDG PET technology, the use of PET for screening for pleural mesothelioma may await the development of novel radiopharmaceuticals.

Another exciting area is the use of PET scans to predict survival and response to therapy. One study has found that patients with high standardized uptake value tumors had decreased survival. Another study showed that decreased radiopharmaceutical uptake on follow-up PET scans performed early after treatment may be an excellent predictor of overall clinical response.

Laboratory Studies

Although there are no specific pleural fluid biomarkers for malignant mesothelioma, evaluation of pleural fluid chemistries may still be beneficial. Effusions associated with mesothelioma are strongly exudative, with elevated protein concentrations in the range of 4 to 5 g/dL and a lymphocytic predominance. Pleural fluid lactate dehydrogenase (LDH) concentrations often exceed those of patients with carcinomatous pleural effusions, with levels greater than 600 IU/L. In patients with advanced disease and extensive involvement of visceral and parietal pleura, pleural fluid pH, and glucose are commonly low. In patients with mesothelioma, the presence of a low pleural fluid pH denotes both a poor overall prognosis, as well as refractoriness to attempts at achieving palliative

pleurodesis. In addition, the pleural effusion associated with mesothelioma is characteristically highly viscous, presumably because of elevated concentrations of hyaluronic acid. An increased pleural fluid hyaluronidase level is suggestive but not diagnostic of mesothelioma. The cytokine profile of pleural effusions related to mesothelioma is somewhat unique in that the tumor constituitively produces high concentrations of interleukin-6 (IL-6) and transforming growth factor-β (TGF-β), but relatively low levels of IL-1β and tumor necrosis factor-α. These elevated intrapleural levels of IL-6 in patients with malignant mesothelioma are postulated to induce systemic manifestations such as fever, cachexia, and thrombocytosis. Pulmonary function testing typically demonstrates a restrictive pattern resulting from pleural effusions, tumor encasement of the lung, or chest wall involvement.

Mesothelin and Other Novel Serum Markers

There is increasing evidence for clinical utility for a monoclonal antibody-based serum assay for a soluble form of the protein mesothelin, SMRP. Mesothelin is a 40-kDa glycoprotein that is found on the cell surface of normal mesothelial cells, mesothelioma, and ovarian cancer cells. Increased levels of soluble mesothelin (SMRP) were found in serum samples from 37 of 44 patients with mesothelioma (87 percent), compared with three of 160 patients with other cancers or inflammatory lung or pleural diseases (2 percent), and none of 28 controls without a past asbestos exposure. For the present time, SMRP levels will likely play an adjunctive role in the diagnosis of patients with mesothelioma. It is intriguing to posit that SMRP may also play a role in screening of high-risk patients for incipient mesothelioma, given the fact that 7 of 40 asbestos-exposed individuals in the original *Lancet* report had elevated levels; four of whom subsequently developed mesothelioma or lung cancer within 1 to 5 years. Other serum markers, such as osteopontin, are also being evaluated.

Diagnosis

The differential diagnosis of malignant pleural mesothelioma includes both benign and malignant processes. Inflammatory reactions such as chronic, organized empyema can mimic the dense pleural thickening and large, viscous pleural effusions characteristic of mesothelioma. As discussed, epithelial mesotheliomas can be extremely difficult to distinguish grossly and histologically from metastatic adenocarcinoma to the pleura from any number of primary sources, including lung, breast, stomach, kidney, ovary, and prostate. Sarcomas such as fibrosarcoma and malignant fibrous histiocytoma can present in similar fashion and infiltrate like sarcomatous mesotheliomas. The mixed-cellular type of mesothelioma can bear a significant histological resemblance to sarcomatoid carcinomas and synovial sarcoma.

Accurate diagnosis of malignant mesothelioma is important in the event of subsequent litigation, for proper epidemiologic records and appropriate therapeutic intervention. Thoracentesis or closed pleural biopsy can often establish the diagnosis of pleural malignancy but may not provide enough diagnostic material to confirm the presence of mesothelioma. Cytologic evaluation of pleural fluid is helpful for detecting the presence of malignancy but has difficulty in distinguishing epithelioid mesothelioma from adenocarcinoma and the sarcomatoid type from fibrosarcomas or hemangiopericytomas. Immunohistochemical markers and monoclonal antibodies may aid in differentiating mesothelioma from adenocarcinoma on cytology specimens. In addition, certain cytopathological features of cells obtained from pleural fluid have been found to correlate well with the presence of mesothelioma, including papillary aggregates, multinucleation with atypia, cell-to-cell apposition, nuclear pleomorphism, and macronucleoli. Gene expression ratios may also be increasingly helpful in this regard.

Surgical intervention, via video-assisted thoracoscopic biopsy or open thoracotomy, is often necessary to firmly establish the diagnosis. Boutin and colleagues from Marseille prospectively evaluated thoracoscopy for the diagnosis of malignant pleural mesothelioma in 188 consecutive patients from 1973 to 1990 and found that thoracoscopic biopsy was diagnostic in 98 percent of cases, compared with only 26 percent for thoracentesis alone, and 39 percent for fluid cytology and closed pleural biopsy. These procedures were performed under local anesthesia in an endoscopy suite with minimal morbidity or complications.

Concurrent bronchoscopy may be important in distinguishing between mesothelioma and metastatic adenocarcinoma of the lung, as endobronchial lesions are rarely seen in mesothelioma. In addition, mediastinoscopy plays an increasingly important role in the diagnosis and staging of mesothelioma, as recent studies have documented the significant negative prognostic implications of mediastinal nodal invasion in this disease. Approximately 10 percent of patients who undergo a diagnostic procedure for mesothelioma seed the biopsy site with tumor cells, later developing chest wall recurrences. This complication can potentially be prevented by prophylactic radiation therapy to the surgical incision or thoracentesis sites.

Staging

The staging of malignant mesothelioma has proved to be more controversial than that of many other tumors. The most commonly used schema was devised by Butchart in 1976 (Table 88-1). Although useful, its ability to predict survival is weakened by lack of inclusion of lymph node involvement and chest wall invasion.

For this reason, the Union Internationale Contre le Cancer (UICC) in 1990 first proposed a staging system based on the TNM (tumor/node/metastasis) standard used for many other tumors. More recently, Rusch and colleagues from the International Mesothelioma Interest Group (IMIG) proposed an updated staging system based upon tumor descriptors, providing precise anatomic definitions of the local extent of the primary tumor. This staging system (Table 88-2) was designed to provide the framework for proper analysis of prospective clinical trials of new treatment modalities.

Table 88-1

Butchart Staging System

Stage I	Tumor confined within the "capsule" of the parietal pleura
Stage II	Tumor invading chest wall or involving mediastinal structures
Stage III	Tumor penetrating diaphragm to involve peritoneum; involvement of opposite pleura; lymph node involvement outside the chest
Stage IV	Distant blood-borne metastases

Table 88-2

International Mesothelioma Interest Group (IMIG) Staging System

T1	T1a: Tumor limited to ipsilateral parietal pleura T1b: Tumor involving ipsilateral parietal pleura, with scattered foci of tumor on visceral pleural surface
T2	Tumor involving all ipsilateral pleural surfaces with diaphragmatic invasion or extension into underlying pulmonary parenchyma
T3	Involvement of the endothoracic fascia; mediastinal fat; solitary, resectable chest wall focus; or nontransmural pericardial invasion
T4	Diffuse extension into chest wall, peritoneum, spine, mediastinal organs, contralateral pleura, internal surface of pericardium or myocardium
NO	No regional lymph nodes metastases
N1	Metastases in the ipsilateral bronchopulmonary or hilar lymph nodes
N2	Metastases in the subcarinal or ipsilateral mediastinal lymph nodes
N3	Metastases in the contralateral mediastinal or internal mammary lymph nodes or any supraclavicular node metastasis
Staging	
Stage I	Ia: T1aN0M0 Ib: T1bN0M0
Stage II	T2N0M0
Stage III	Any T3M0, any N1M0, any N2M0
Stage IV	Any T4, any N3, any M1

Clinical Course and Complications

Mesothelioma exerts its morbidity and mortality via inexorable local invasion. Patients typically develop shortness of breath and chest pain as tumor and fibrosis gradually obliterate the pleural space and replace any pleural fluid. As the tumor spreads, it covers both visceral and parietal pleural surfaces, encasing the ipsilateral lung with a thick, fibrous peel that extends into interlobar fissures and occasionally into lung parenchyma. Deoxygenated blood is shunted through the trapped lung, leading to significant dyspnea and hypoxemia that is often refractory to supplemental oxygen. Dyspnea also results from abnormal chest wall mechanics secondary to tumor invasion into ribs as well as intercostal nerves and muscles. Local invasion of crucial thoracic structures can result in dysphagia, hoarseness, cord compression, brachial plexopathy, paralysis, Horner's syndrome, and superior vena cava syndrome. Hilar and mediastinal lymph node involvement occurs in less than 50 percent of patients but is a harbinger of poor prognosis. Transdiaphragmatic spread into the abdominal cavity rapidly leads to intraperitoneal dissemination, with encasement of the mesentery, and small and large bowel. Local invasion into the pericardial space can lead to pericardial effusion and tamponade. Distant metastatic disease, by hematogenous spread, is unusual in mesothelioma but may present in liver, bone, brain, adrenals, thyroid, and kidney. Metastatic disease is typically an end-stage manifestation of malignant mesothelioma.

Mortality

Median survival of patients with mesothelioma is between 9 and 12 months and varies depending on stage, histological subtype, and concomitant medical problems. Patients with pleural mesothelioma die from local extension and respiratory failure, primarily related to spread to the contralateral hemithorax. As mentioned, tumor extension below the diaphragm may result in death from small bowel obstruction. Patients may also die from arrhythmias, heart failure, or stroke caused by tumor invasion of the heart or pericardium.

Paraneoplastic Syndromes

Disseminated intravascular coagulation, migratory thrombophlebitis, thrombocytosis, Coombs-positive hemolytic anemia, hypoglycemia, and hypercalcemia associated with secretion of a parathyroid hormone–like peptide have all been described in the setting of mesothelioma.

PROGNOSTIC FACTORS

Poor prognosis at the time of presentation is indicated by the presence of thrombocytosis, leukocytosis, low hemoglobin, fever of unknown origin, sarcomatoid or mixed histology, age greater than 65 to 75 years, poor performance status, and male gender. Good prognosis at presentation is associated with epithelial histology; stage I disease; age under 65 years; Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 1; absence of chest pain; and the presence of symptoms for more than 6 months prior to diagnosis.

The prognostic scoring systems derived by the Cancer and Leukemia Group B (CALGB) and the European Organization for Research and Treatment of Cancer (EORTC) are the most useful clinical prognostic scoring schemes available.

CALGB Prognostic Index

The CALGB evaluated the impact of clinical characteristics on the survival of 337 patients treated with chemotherapy for advanced mesothelioma in sequential phase II treatment studies over a 10-year period. In multivariate analysis, serum lactate dehydrogenase (LDH) greater than 500 IU/L, poor performance status, chest pain, platelet count over 400,000/μL, non-epithelial histology, and age older than 75 years jointly predicted poor survival. Six distinct prognostic subgroups were generated with median survival times ranging from 1.4 to 13.9 months. The median survival overall was 7 months. This prognostic schema was subsequently validated in an American phase II trial evaluating the investigational agent Ranpirnase, and in an independent European data set.

EORTC Prognostic Scoring System

Similarly, the EORTC reviewed data from 204 adults who were entered into five consecutive phase II trials over 9 years. When five factors were taken into consideration (poor performance status, high WBC count, male gender, sarcomatoid cell type, and the certainty of the diagnosis), good and bad prognostic groups could be delineated, with 1-year survival rates of 40 and 12 percent, respectively. Median survival from the date of study entry was 8.4 months.

CURRENT APPROACHES TO TREATMENT OF MESOTHELIOMA

Over the past decade, advances have been made that have improved our ability to treat malignant pleural mesothelioma. We have evidence that some of these treatments are increasing the quality and quantity of life for patients with mesothelioma. Multimodality treatment programs that combine surgical cytoreduction with novel forms of radiation therapy and more effective chemotherapy combinations may offer significant increases in survival for certain subgroups of mesothelioma patients. Innovative palliative approaches have proved successful in alleviation of the symptoms experienced by many mesothelioma patients. Experimental treatments such as immunotherapy and gene therapy present a window of hope for all mesothelioma patients, and in the future, may be combined with "standard therapy" in multimodality protocols.

Chemotherapy

Over the past 20 years, several phase II single-agent and combination chemotherapy studies have been performed in mesothelioma. These studies have demonstrated some evidence of anti-tumor activity with anthracyclines, platinum derivatives, and anti-metabolites. Combination chemotherapy has been associated with higher overall response rates, but not, until recently, longer median survivals.

The current standard of care for first-line chemotherapy in mesothelioma patients with good performance status is combination treatment with cisplatin and pemetrexed. Pemetrexed (Alimta, Eli Lilly and Company, Indianapolis, IN) is an anti-folate compound which targets multiple enzymes in the folate metabolism pathway. Pemetrexed is a potent inhibitor of thymidilate synthase (TS), the rate-limiting step in the synthesis of thymidilate, which is required for DNA synthesis and is also the enzyme inhibited by the cytotoxic agents 5-fluorouracil and raltitrexed.

In 2003, Vogelzang and colleagues reported the results of a phase III randomized clinical trial in chemotherapy-naive mesothelioma patients comparing treatment with pemetrexed and cisplatin with cisplatin monotherapy. A total of 456 patients were randomized: 226 received pemetrexed and cisplatin, 222 received cisplatin alone, and eight never received therapy. Median survival time in the pemetrexed/cisplatin arm was 12.1 months versus 9.3 months in the cisplatin only arm ($p = 0.020$, two-sided log-rank test). The hazard ratio for death of patients in the combination arm versus those in the control arm was 0.77. Median time to progression was significantly longer in the pemetrexed/cisplatin arm: 5.7 months versus 3.9 months ($p = 0.001$). Response rates were 41.3 percent in the pemetrexed/cisplatin arm versus 16.7 percent in the control arm (p less than 0.0001). The addition of folic acid and vitamin B12 to chemotherapy resulted in reduction in the severity and frequency of hematologic and non-hematologic toxicities in the pemetrexed/cisplatin arm. Another randomized Phase III study of cisplatin with a newer-generation antifolate, raltitrexed (Tomudex), showed very similar, small but significant, increases in survival.

The combination of gemcitabine and carboplatin is also a valid first-line option in the treatment of mesothelioma owing to its acceptable toxicity profile, good response rate, and palliative effects. A Northern Italian Phase II study of gemcitabine and carboplatin in patients with pleural mesothelioma reported a 26 percent partial response rate, a median response duration of 55 weeks; and significant palliative benefit, 46 percent with less dyspnea, 40 percent with weight gain, and 26 percent with pain reduction. Median survival for patients in this study was 66 weeks.

There is, however, no current standard of care for second-line chemotherapy in mesothelioma following

treatment with cisplatin and pemetrexed. The most commonly used second-line regimens include gemcitabine, or other drugs with single-agent activity such as vinorelbine. There exists insufficient evidence to recommend second-line chemotherapy as a standard treatment. Patients with adequate performance status should be enrolled onto clinical trials of second-line treatment.

Radiation Therapy

Contrary to the prevailing wisdom that malignant pleural mesothelioma is a radioresistant neoplasm, it has been demonstrated that mesothelioma cell lines are actually more responsive to ionizing radiation in vitro than non–small cell lung cancer cell lines. External-beam radiation therapy for mesothelioma is, however, limited by the large treatment volumes required and the radiation sensitivity of the surrounding organs (heart, lung, esophagus, spinal cord). Although palliative radiotherapy with an attempt to treat the entire involved pleural surface is technically difficult, and associated with a high risk of radiation pneumonitis, myelitis, hepatitis, and myocarditis, it can provide effective local palliation in up to 50 percent of patients.

There are anecdotal reports of long-term survivors following high-dose external beam irradiation, and even intrapleural administration of radioactive isotopes. Most studies have shown no significant effect upon overall survival in patients with mesothelioma. However, radiation therapy may play a role by preventing chest wall recurrences after thoracoscopy/thoracotomy and in improving local control after pleurectomy or extrapleural pneumonectomy.

Mesothelioma frequently implants along the tracts of biopsies, chest tubes, thoracoscopy trocars, and surgical incisions, producing uncomfortable subcutaneous nodules. This can be prevented with prophylactic radiotherapy. In a small randomized trial, Boutin and colleagues demonstrated that 21 Gy administered in three daily fractions, 10 to 15 days after thoracoscopy, decreased local recurrence from 40 to 0 percent.

Multimodality approaches commonly include adjuvant radiation following surgery, although there are no randomized trials that demonstrate its efficacy. Because the lung remains in place after pleurectomy, radiotherapy doses must be lower than when EPP is performed.

The Radiation Oncology group at the University of Texas M.D. Anderson Cancer Center reported encouraging results using intensity-modulated radiotherapy (IMRT) following EPP. Using careful treatment planning and IMRT, radiation doses of up to 50 to 60 Gy were possible without severe toxicity. With the combination of EPP and IMRT, local recurrences after surgery were virtually eliminated; however, novel distant disease patterns have begun to emerge. These data suggest that the combination of EPP and IMRT requires an additional treatment modality (i.e., chemotherapy or immunotherapy) to limit distant tumor growth. Although intensity-modulated radiotherapy (IMRT) following EPP appeared to be more effective for local disease control in this initial series, a second series from the Dana-Farber Cancer Center suggested there was a significant increase in severe toxicity. In that report, six of 13 patients developed fatal pneumonitis.

Surgical Approaches to Treatment of Mesothelioma

Surgery for malignant pleural mesothelioma can be diagnostic, palliative, and even potentially curative in its intent. Although not infrequently associated with substantial morbidity, surgical management has made significant strides in palliating the major symptoms of the disease, as well as potentially offering some improvement in survival for highly selected patients.

The increased use of thoracoscopy, as well as novel biomarkers, has facilitated early diagnosis of mesothelioma in more patients, at which point they may be candidates for more aggressive attempts at definitive surgical treatment (along with neo-adjuvant/adjuvant therapies). However, definitive surgical intervention is only possible in a small percentage of patients; furthermore, fewer than 25 percent of those eligible for aggressive surgical intervention will be alive at 5 years, and even fewer will be disease-free at that time point. The vast majority of of pleural mesothelioma patients have locally advanced disease at the time of presentation, which, along with advanced age and/or other co-morbid medical illnesses, often precludes aggressive surgical intervention.

Pleurodesis

The most common and discomforting symptom in mesothelioma is debilitating dyspnea from large, unilateral pleural effusions. A reasonable palliative approach is complete drainage of the pleural effusion (by tube thoracostomy or video thoracoscopy) and introduction of a sclerosing agent into the pleural space (by instillation or insufflation) to induce pleurodesis.

At present, the most widely used compound for pleurodesis is sterile, asbestos-free talc, administered either as a powder or a slurry. Thoracoscopic application (poudrage) may be more successful than other methods of pleurodesis (e.g., by tube thoracostomy). The effect of talc may be enhanced by an ability to induce apoptosis in some mesothelioma cell lines in vitro.

The presence of bulky tumor in the pleural space, or "trapping" of the lung by a thick visceral pleural peel of tumor compromises the efficacy of pleurodesis in patients with pleural mesothelioma. In the setting of "trapped lung," the use of semi-permanent tunneled intrapleural catheters (Pleurx Catheter, Cardinal Health, Dublin, OH) for intermittent drainage of recurrent effusions provides excellent palliation of dyspnea. Pleuro-periotoneal shunting, an alternative approach for dealing with lung entrapment in pleura mesothelioma, carries the overt risk of malignant seeding of the peritoneal cavity. The primary concern regarding the use of tunneled pleural catheters in mesothelioma is the

development of tumor implants at the insertion site or along the subcutaneous tunnel.

Pleurectomy

Parietal pleurectomy, i.e., open surgical stripping of the pleura from the apex of the lung to the diaphragm, is more successful than talc pleurodesis in reducing the recurrence of pleural effusion in mesothelioma. More recently, thoracoscopic pleurectomy has been employed to achieve similar results as the open procedure, but with less morbidity. Complete parietal and visceral pleurectomy (pleurectomy/decortication), however, has not been shown to prolong survival in patients with mesothelioma.

Some investigators have evaluated the combination of pleurectomy/decortication with postoperative intrapleural therapy, external beam irradiation, and/or systemic chemotherapy. One single institution study reported a median survival of 22.5 months and a 2-year survival rate of 41 percent in a group of 27 patients, predominantly with the epithelial subtype. There is no evidence, however, for better survival for mesothelioma patients who underwent pleurectomy/decortication compared with those treated with extrapleural pneumonectomy.

Extrapleural Pneumonectomy

Extrapleural pneumonectomy (EPP) is a radical surgical procedure involving complete removal of the ipsilateral lung along with the parietal and visceral pleura, pericardium with portions of the phrenic nerve, and the majority of the hemidiaphragm. EPP achieves the greatest degree of cytoreduction, and, because the lung has been removed, allows higher radiation doses to be delivered to the ipsilateral hemithorax. It is the only debulking procedure possible when a thick tumor rind obliterates the pleural space. There are a small group of long-term survivors following EPP when it is a component of a multimodality treatment program, suggesting that this procedure may alter the natural history of the disease in appropriately selected patients with early stage disease. Unfortunately, the utility of EPP is limited by the availability of skilled surgeons who routinely perform this technically demanding procedure, and the few patients who are candidates for it.

EPP alone is an excellent means of palliating the profound dyspnea and orthopnea associated with the severe ventilation/perfusion mismatch resulting from lung encasement by mesothelioma. However, EPP alone has no influence on survival in the absence of adjuvant therapy. In most EPP series, median survival from surgical debulking alone is less than 2 years, and 10 to 20 percent of operated patients are 5-year survivors, with biphasic/sarcomatoid histology and/or involvement of mediastinal lymph nodes conferring a poorer prognosis and lack of demonstrable survival benefit from surgical intervention.

Several approaches for adjuvant therapy in conjunction with EPP have been studied: The investigators at Brigham and Women's Hospital in Boston have combined EPP with sequential postoperative chemotherapy and up to 55 Gy of adjuvant radiation therapy to the postoperative hemithorax. More recently, the Brigham Thoracic Program has been investigating the role of hyperthermic intracavitary chemotherapy as an adjuvant to maximal cytoreductive surgery, in combination with hemithoracic irradiation and systemic chemotherapy. In addition, several investigators have evaluated the utility of post-resectional photodynamic therapy (PDT) with or without adjuvant chemotherapy or immunotherapy. However, one randomized trial conducted by Pass and colleagues at the National Cancer Institute failed to confirm any benefit for adjuvant PDT compared with surgery alone.

Other novel multicenter clinical trials combine maximal surgical debulking with adjuvant IMRT or alternatively assess the role of neoadjuvant chemotherapy prior to cytoreductive surgery to improve long-term outcomes. EPP in these contexts is designed as a cytoreductive, not a curative procedure. It is associated with significant morbidity (major in up to 25 percent) and an operative mortality that exceeds 5 percent, depending upon the experience of the center and the preoperative condition of the patient. Therefore, patients must be carefully selected.

Treatment of Nonpleural Forms of Mesothelioma

Patients with peritoneal mesothelioma, the second most common form of mesothelioma after the pleural form, most often present with abdominal pain, distention, and ascites, but may have symptoms for several months prior to establishment of a definitive diagnosis. In addition, peritoneal mesothelioma can be associated with hypoalbuminemia, night sweats, inguinal and umbilical hernias, and hypercoagulability. Laboratory investigations show an increased platelet count in about 50 percent of patients and many patients also have elevation of the tumor marker CA-125. As with pleural mesothelioma, single-agent general chemotherapy for the peritoneal variant has a response rate of 10 to 15 percent, whereas combination chemotherapies, such as cisplatin plus pemetrexed, improve the response rate to about 25 percent. Immunotherapeutic agents such as interferons and various cytokines may have a role in treating this disease, especially when the amount of disease is minimal.

Patients diagnosed with peritoneal mesothelioma appear to have a better overall prognosis relative to the pleural form. This may reflect the technical ease of delivery of intraperitoneal chemotherapy as well as the capacity for multiple resections/debulking of peritoneal masses. One-third of 25 patients with peritoneal mesothelioma in a Dana-Farber phase II series remain disease-free at 2 to 3 years after treatment. Multimodality treatment protocol includes surgical debulking followed by intraperitoneal administration of cisplatin, doxorubicin, and gamma interferon, second laparotomy with attempted resection of any residual disease and intraoperative hyperthermic perfusion with cisplatin and mitomycin followed subsequently by whole abdominal

radiotherapy. The median overall survival of the 27 patients treated in this study was 68 months.

Pericardial mesothelioma is quite rare, but characteristically presents with pericardial effusion, and often tamponade physiology. Mesotheliomas of the tunica vaginalis are even less common than the pericardial variant, but typically present with a bloody hydrocele. There is no effective therapy for mesothelioma of the pericardium or tunica vaginalis other than palliation; these neoplasms share the dismal prognosis of the pleural form of the disease.

NEW THERAPEUTIC APPROACHES

Despite the small but significant improvement in survival achieved with intensive multimodality therapy for mesothelioma, it is obvious that less morbid, more effective interventions are needed. Many investigators over the past two decades have attempted to treat this disease primarily by direct instillation of chemotherapeutic and other compounds into the pleural space, but with minimal success. Based on reports that mesothelioma patients with greater amounts of intratumoral lymphocytic infiltration had improved median survival rates, several groups have looked at immunotherapy as an alternative means of achieving better tumor response rates.

Immunotherapy

The use of compounds to stimulate an antitumor immune response against pleural malignancy stemmed from the observation that patients who developed empyemas postthoracotomy for primary lung carcinoma had improved survival rates. Subsequently, intrapleural bacille Calmette-Guérin (BCG) was studied as a surgical adjuvant, but no significant benefit was seen. Several systemic immunotherapies have been administered to patients with mesothelioma, including interleukin-2 (IL-2) and interferon-gamma (IFN-γ), both of which demonstrated limited efficacy and significant side effects. Subcutaneous IFN-α-2a was found to have some efficacy, one complete response, and three partial responses out of 25 patients studied and was well tolerated clinically. One European phase I and II studies of intrapleural IL-2 administered by continuous infusion via an intrapleural catheter revealed a 19 percent partial response rate with marked dose-related toxicity, primarily the development of ipsilateral empyemas. Of note were the high ratios of intrapleural/systemic IL-2 levels approaching 1000:1, particularly in the highest doses.

Boutin and colleagues in Marseilles, France, pioneered the intrapleural administration of immunostimulants to treat mesothelioma, and demonstrated significant local tumor responses with both intrapleural IL-2 and IFN-γ. Most impressive were the results of intrapleural IFN-γ in patients with early-stage mesothelioma (Butchart stages I and II). A total of 89 patients were treated over 46 months with an overall response rate of 20 percent. Eight patients had histologically confirmed complete responses and nine had partial responses with greater than 50 percent reduction in tumor volume. Overall, patients with stage I disease had a response rate of 45 percent. The effectiveness of IFN-γ against mesothelioma was thought to be mediated in part by direct inhibitory effects on mesothelioma cell growth as well as by decreased intrapleural IL-6 production, with resultant activation of tumor-directed macrophages and cytotoxic T-lymphocytes.

Other groups have demonstrated only limited activity with the combination of intrapleurally administered autologous activated macrophages and interferon-gamma. The overall response rate was 11 percent (two of 19 enrolled patients), with one patient having a partial response that lasted for 30 months. Immunotherapy trials in Australia demonstrated some significant tumor regression with repeated intralesional injection of GM-CSF, but with substantial complications related to the catheters used for cytokine instillation.

"Targeted" Therapy

The identification of active platelet–derived growth factor and epidermal growth factor pathways in some mesothelioma cell lines suggested that novel agents which inhibited these pathways might prove useful clinically, either alone, or in combination with cytotoxic chemotherapy. Unfortunately, early-phase clinical trials of imatinib mesylate and gefitinib, inhibitors of the tyrosine kinase enzymes inherent to the PDGF and EGF pathways, respectively, have failed to demonstrate any significant clinical benefits. Clinical trials are ongoing with other novel "targeted" agents, such as the anti-angiogenic agents, bevacizumab and thalidomide, and the copper-chelating agent, tetrathiomolybdate, which removes copper, which is a key co-factor in tumor angiogenesis.

Gene Therapy

In the absence of other effective, nontoxic therapies for malignant mesothelioma, several groups of investigators have looked to the newly evolving technologies of gene therapy for new treatment modalities. Gene therapy is attractive because mesothelioma remains localized initially and pleural access is to the tumor easy and safe. A large number of approaches have been used in cell culture and in animal models. Gene therapy vectors have included liposomal/DNA complexes and modified herpes, vaccinia, and adenoviruses. Transgenes have included suicide genes, cytokines, tumor suppressor genes (i.e., p53), and pro-apoptotic genes. Studies have also been done using replication-competent, but tumor selective adenoviruses and herpes viruses as well as carrier cells.

Some Phase I clinical trials have also been performed. These include the instillation of recombinant adenovirus (rAd) genetically engineered to contain the herpes simplex virus thymidine kinase "suicide gene" (HSVtk). The rationale for the suicide gene approach for mesothelioma was that administration of Ad.HSVtk into the pleural cavity would sensitize the cells to the normally non-toxic antiviral agent

ganciclovir (GCV). The vector was well tolerated, gene transfer was seen at higher doses, and a number of patients had clinical responses, including patients with minimal radiographic evidence of disease 7 years after Ad.HSVtk/GCV with no other intervening anti-neoplastic therapy. The HSVtk gene was also introduced into patients using an irradiated allogeneic ovarian cancer cell line. No information on clinical responses has been reported. A second adenoviral trial was recently completed using immunogene therapy delivering the cytokine interferon-beta (IFN-β), which has a number of anti-tumor immune effects. The vector was well tolerated, resulted in detectable pleural IFNβ levels in most patients, and was accompanied by anti-tumor immune responses in 7 of 10 patients. A number of patients with low tumor burdens had disease stability or clinical responses. A modified vaccinia virus expressing interleukin-2 has been injected intratumorally into six patients. The vector was well tolerated, but no clinical responses were noted. Gene therapy approaches thus appear promising but still in the experimental stage.

OTHER PRIMARY PLEURAL NEOPLASMS

Solitary fibrous tumors of the pleura had been previously referred to in the literature as "benign mesothelioma." This is an inappropriate expression; both in terms of histogenesis and the potential for confusion with malignant mesothelioma. Solitary fibrous tumors (SFTs) have also been called localized fibrous tumor because of the occasional incidence of multiple masses. Solitary fibrous tumor is a mesenchymal tumor of probable fibroblastic origin and similar tumors have been described in other extrathoracic sites. It is important to note that there is no significant association of solitary fibrous tumors with asbestos exposure or other environmental agents. Although the peak age range of affected patients is similar (40 to 70 years), solitary fibrous tumors can affect patients of all ages, including children as young as 5 years old. In addition, there is no significant association of benign fibrous tumors of the pleura with asbestos exposure or other environmental agents.

Clinical Presentation

Patients with solitary fibrous tumors of the pleura are usually asymptomatic and are diagnosed incidentally at routine chest radiography, but they can present with nonpleuritic chest pain, dyspnea, cough, or pleural effusion. A significant proportion (up to 40 percent) of patients present with symptomatic hypoglycemia, thought to be secondary to elaboration of insulinlike growth factors. Clubbing of fingers and toes is common, as are diffuse arthralgias, but the incidence of pulmonary hypertrophic osteoarthropathy is controversial.

Radiography

Benign fibrous tumors typically present radiographically as large, rounded, well-circumscribed pleura-based masses, but occasionally they can appear to be intraparenchymal. Some of these masses can be very large (over 15 cm in diameter) and can cause clinically significant compression of the lung. About 17 percent present with an ipsilateral pleural effusion. Asbestos-related pleural plaques are rarely seen in association with SFTs.

Gross Pathology

The typical solitary fibrous tumors of the pleura arises from a pedicle off of the visceral pleura surface and rarely invade the visceral pleura itself (Fig. 88-6*A*). They are usually well circumscribed, firm, often pedunculated masses that vary in size from 1 cm to more than 30 cm in diameter. When sectioned, the cut surface has a whorled appearance. Attention should be paid to areas of hemorrhage or necrosis. Malignant solitary fibrous tumors have been described, although they are less frequent.

Microscopic Pathology

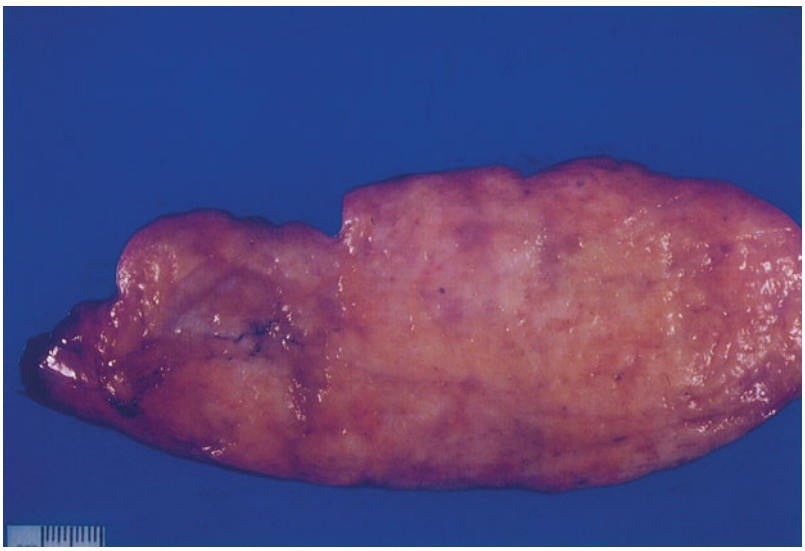
Histologically, solitary fibrous tumors have what has been described as a "patternless pattern" (Fig. 88-6*B*). Sections typically show alternating areas of hypocellularity and hypercellularity with short fascicles of interlacing spindle cells, creating a storiform pattern. These fascicles are interspersed between areas of variably collagenized tissue. A hemagiopericytoma-like branching vascular pattern is also quite typical. Histological criteria that may predict a malignant course include high cellularity, infiltrative growth, moderate to marked cytologic atypia, and high mitotic rate (greater than 4 mitoses per 10 high-power fields). Immunohistochemical stains confirm the diagnosis. These tumors are CD34 (Fig. 88-6*C*) and bcl-2 positive but cytokeratin negative. Malignant SFTs are not always positive for CD34 and bcl-2; therefore, the diagnosis requires the exclusion of other malignant tumors such as malignant mesothelioma, monophasic synovial sarcoma, and peripheral nerve sheath tumors.

Treatment

Surgical resection of solitary, benign fibrous tumors of the pleura is curative with little risk of recurrence. There is typically a discrete separation between the tumor and underlying compressed lung, so pulmonary resection is usually unnecessary. Some tumors may require a limited chest wall resection. A small percentage of patients develop recurrences several decades after surgical resection and may die from extensive local disease. Some of these recurrent, localized fibrous tumors of the pleura demonstrate more aggressive histological features but are often successfully cured by surgical excision, in particular the pedunculated lesions.

Other Primary Pleural Tumors

As discussed in the differential diagnosis of sarcomatoid mesotheliomas, there are other relatively rare malignant mesenchymal tumors that can be primary within the pleura. These tumors include vascular tumors (pleural epithelioid hemangioendothelioma/angiosarcoma) and synovial sarcoma.



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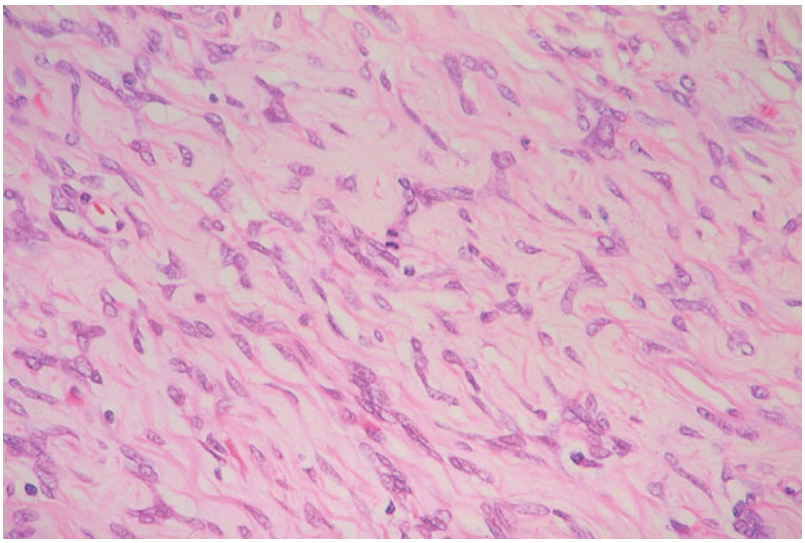

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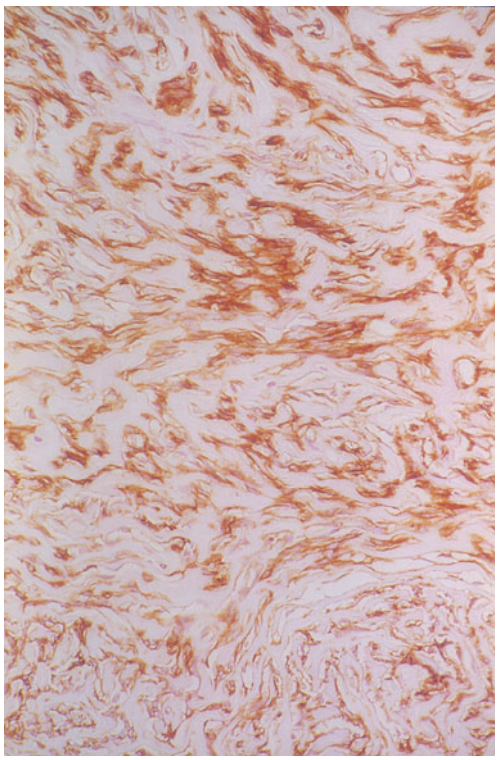

C

Figure 88-6 *A.* Gross photograph of a surgically resected, solitary, benign pleural fibrous tumor. Note the well-circumscribed nature of this firm, slightly lobulated mass with its smooth-cut surface and punctate areas of hemorrhage and necrosis. *(Courtesy of Dr. Matt van de Rijn, Department of Pathology and Laboratory Medicine, University of Pennsylvania Medical Center, Philadelphia.) B.* Photomicrograph of a typical solitary fibrous tumor demonstrating the "patternless-pattern" (H&E, ×400). *(Courtesy of Dr. Matt van de Rijn.) C.* Photomicrograph of a section of solitary fibrous tumor stained with an antibody directed against CD-34, a cell surface marker found commonly on endothelial cells and some smooth muscle and vascular tumors (×400). Positive staining for CD-34 helps distinguish these lesions from mesotheliomas and other pleural neoplasms. *(Courtesy of Dr. Matt van de Rijn.)*

Pleural epithelioid hemangioendothelioma is a low- to intermediate-grade vascular tumor. High-grade epithelioid vascular tumors are termed epithelioid angiosarcoma. The clinical presentation of patients with these tumors, as well as the radiographic features and gross appearance, are essentially identical to malignant mesothelioma. Patients present with diffuse pleural thickening, pleural effusion, and/or chest pain. Microscopic examination with the ancillary use of immunohistochemistry is required for diagnosis. These tumors usually have a biphasic pattern with nests of epithelioid cells embedded within a spindle cell stroma. The epithelioid cells characteristically have intracytoplasmic vacuoles and the associated stroma typically has a distinctive mxyo-hyaline or chondroid appearance. As with malignant mesotheliomas, a tubopapillary pattern may also be present. Vascular differentiation is demonstrated by strong positive staining with one or more endothelial markers (CD31, CD34, Fli1, or factor VIII). Cytokeratin positivity may also be present and can be misleading if the diagnosis of a vascular tumor is not considered. These tumors behave aggressively and there is, at the current time, no effective therapy.

The diagnosis of pleural synovial sarcoma has improved with increased awareness and the greater availability of molecular testing for its distinctive X:18 translocation that now can be demonstrated in formalin-fixed paraffin embedded tissue. Synovial sarcomas present as either a biphasic epithelioid and spindled cell tumor or as a monophasic spindle cell tumor. In either instance, synovial sarcoma can be mistaken for malignant mesothelioma or a pulmonary sarcomatoid carcinoma. On average, patients tend to be younger than those with malignant mesothelioma but there is a wide reported age range that encompasses older patients into their eighth decade. There is a similar overlap in clinical presentation with malignant mesothelioma that includes chest pain, pleural effusions, dyspnea, and pneumothorax. Although pleural synovial sarcoma is more commonly a localized, solid tumor, diffuse pleural thickening does occur. The tumors can be quite large (mean size of 13 cm) and can have areas of necrosis and cystic degeneration. There are some histological features that are suggestive of synovial sarcoma, in particular its long interweaving fascicles, but the immunohistochemical profile of these tumors is not distinctive. The epithelioid component may show focal positive staining for cytokeratin, EMA, CEA, or BER-EP4. The spindled cell component may express calretinin. Confirmation of the diagnosis requires molecular testing for the X:18 translocation. Pleural synovial sarcoma is an aggressive disease with a generally poor prognosis.

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PART

XI

Diseases of the Mediastinum

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89

Nonneoplastic Disorders of the Mediastinum

Cameron D. Wright

ANATOMY

Boundaries

The mediastinum is defined as the potential space between the two pleural cavities bounded by the sternum anteriorly, the vertebral column posteriorly, the thoracic inlet superiorly, and the diaphragm inferiorly (Fig. 89-1). The major mediastinal structures are the heart and great vessels, the trachea and main bronchi, and the esophagus, all closely related to one another and connected by loose connective tissue. Hence, air or infection can disseminate widely throughout the mediastinal space, contained laterally only by the mediastinal pleural reflections. The mediastinum communicates with both the neck and the retroperitoneum, and these portals can also serve as routes of egress from the mediastinum. Fascial planes connect the neck, mediastinum, and retroperitoneum and thus facilitate movement of air or infection from one location to another.

Compartments

Several subdivisions of the mediastinum have been emphasized in the surgical and radiologic literature but there is no consensus. Most often, three compartments are proposed: anterior, middle (visceral), and posterior (paravertebral sulcus) (Fig. 89-2). The boundaries of these divisions are not agreed upon, further emphasizing their nonanatomic origins. Shields proposed a simple three-compartment subdivision in 1972, which makes both anatomic and surgical sense. The anterior compartment is bounded by the sternum and the anterior surface of the pericardium and great vessels. The middle (visceral) compartment extends from the posterior limit of the anterior compartment to the anterior surface of the vertebral columns and then to the thoracic inlet. The posterior compartment (paravertebral sulcus) extends from the anterior surface of the vertebral column to the anterior surface of the paravertebral ribs. The structures in these compartments are listed in Table 89-1. The pericardial

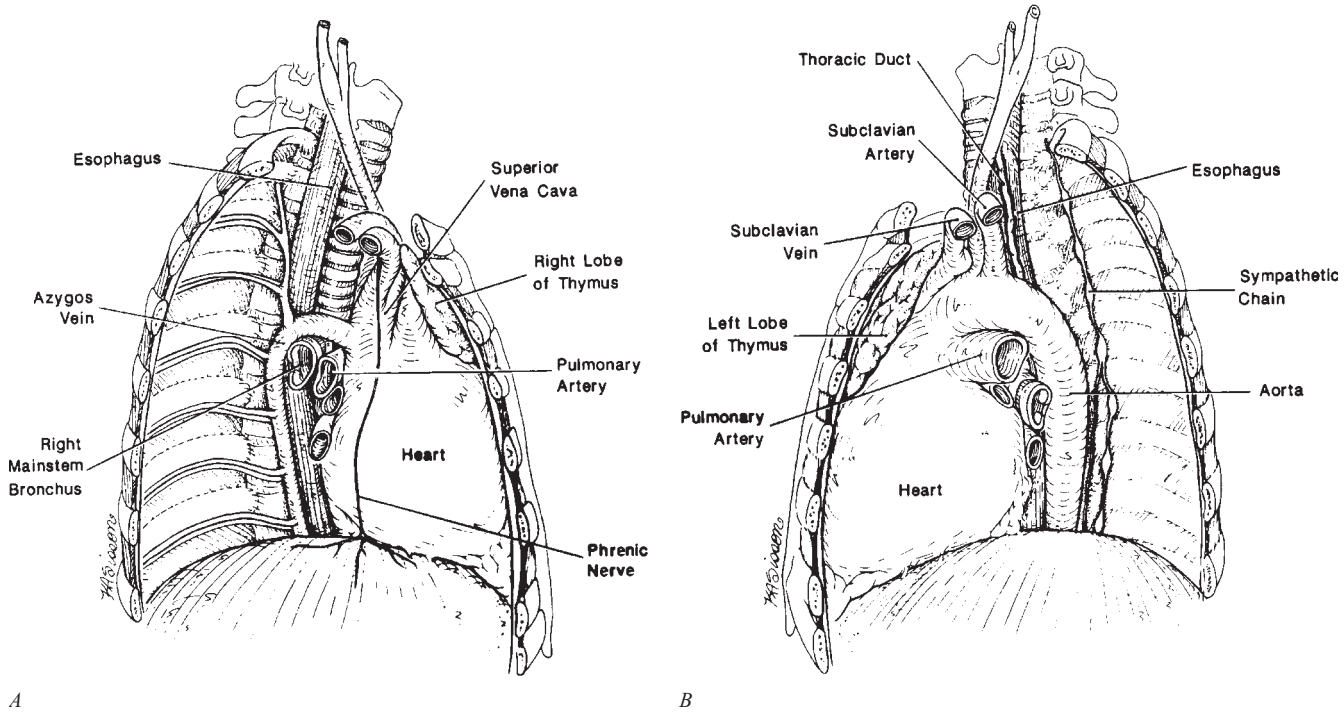


Figure 89-1 *A.* Lateral view of the mediastinum as seen through a right thoracotomy. *B.* Lateral view of the mediastinum as seen through a left thoracotomy. *(From LoCicero J: Median sternotomy and thoracotomy, in Shields TW (ed):* Mediastinal Surgery. *Philadelphia, Lea & Febiger, 1991, p 95, with permission.)*

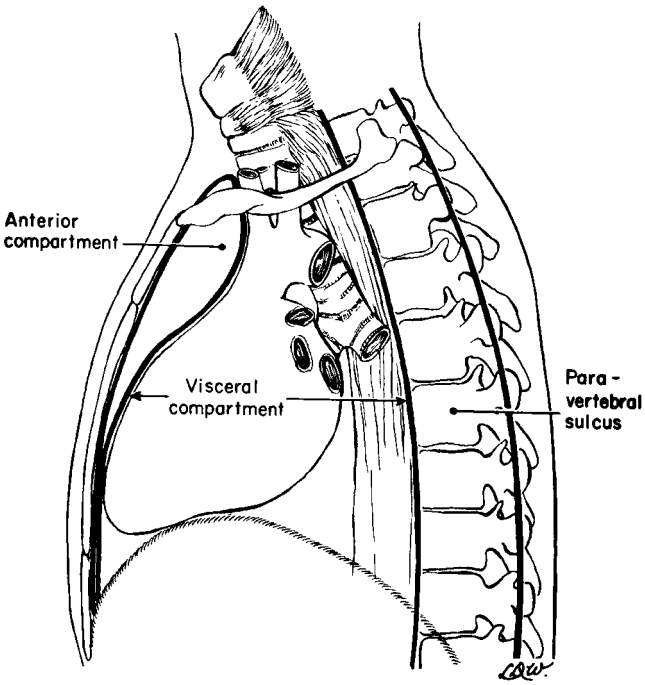


Figure 89-2 Compartments of the mediastinum. Note continuity of visceral (middle) compartment with the neck and retroperitoneum. *(From Shields TW: The mediastinum and its compartments, in Shields TW (ed):* Mediastinal Surgery. Philadelphia, Lea & Febiger, 1991, p 4, *with permission.)*

sac is the only true compartment of the mediastinum and it provides a strong barrier to infection. Subdividing the mediastinum into compartments proves most helpful when one is interpreting a plain radiograph that shows a

Table 89-1

Contents of Mediastinal Compartments

Anterior	Middle	Posterior
Thymus gland	Pericardium	Azygos and hemiazygos veins
Pericardial fat	Heart	
Lymph nodes	Trachea and main bronchus	Thoracic duct
	Esophagus	Symphathetic trunk
	Aorta	
	Phrenic and vagus nerves	Intercostal nerves
	Lymph nodes	

mediastinal mass. Knowledge of the contents of the involved compartment facilitates arriving at a proper diagnosis.

Lymphatics

The mediastinal lymphatic system is quite complex and variable. Mediastinal lymph nodes are interconnected; thus, involvement of one group of lymph nodes in a pathological process frequently leads to involvement of other groups. Just as subdividing the mediastinum into compartments, naming individual nodal stations is somewhat arbitrary and leads to the mistaken notion that these nodal stations are discrete. To the contrary, the mediastinum is covered in a dense network of lymphatic vessels and lymph nodes with no predictable boundaries. Nonetheless, there are commonly accepted nodal stations that have clinical importance, especially in the staging of lung cancer. The lymph node map proposed by Naruke in 1978 has been widely accepted and serves as a standard for communication of lymph node involvement (Fig. 89-3).

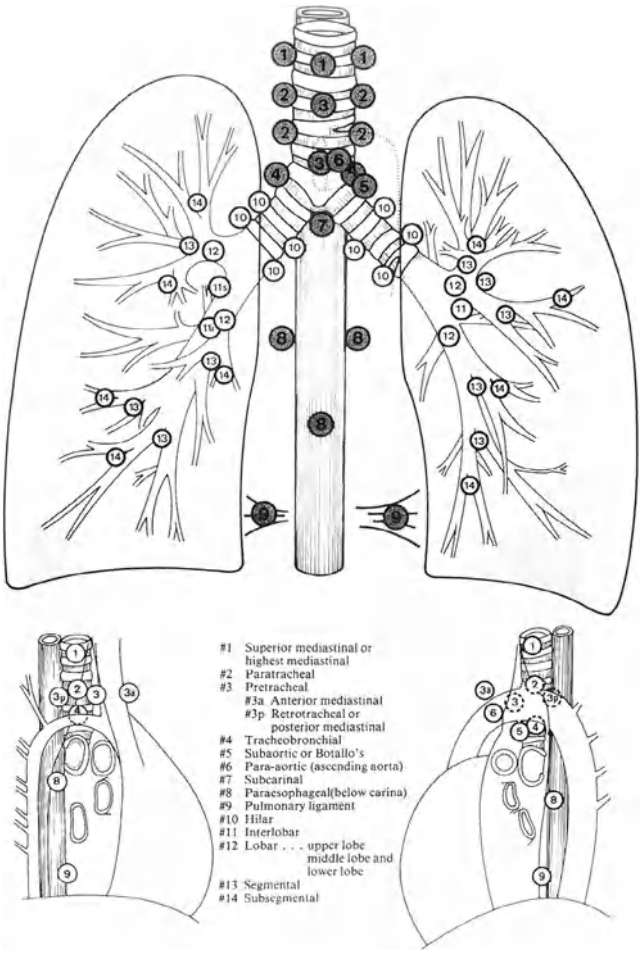


Figure 89-3 Lymph node groups of the lungs and mediastinum. *(From Naruke T, Suemasu K, Ishikawa S: Lymph node mapping and curability at various levels of metastasis in resected lung cancer.* J Thorac Cardiovasc Surg *76:832–839, 1978, with permission.)*

PNEUMOMEDIASTINUM

Pneumomediastinum (mediastinal emphysema) is an uncommon condition but now is being seen with increasing frequency due to the common use of mechanical ventilation—specifically, certain modes of mechanical ventilation. Air (or gas) outside the normal confines of the respiratory and gastrointestinal tracts is always abnormal and always requires explanation. Treatment is directed at the underlying abnormality if one can be identified.

Anatomic Considerations

Pneumomediastinum is frequently associated with other forms of extra-alveolar air, including pulmonary interstitial emphysema, pneumopericardium, pneumothorax, subcutaneous emphysema, pneumoretroperitoneum, and pneumoperitoneum. The key to understanding the distribution of extra-alveolar air lies in the recognition of the common fascial planes that unite these areas. In the neck, the deep layer of the deep cervical fascia ensheaths the trachea and esophagus as they descend into the mediastinum. The trachea and esophagus are thus enclosed in this visceral space; therefore, air or infection can readily travel from the mediastinum to the neck or retroperitoneum (Fig. 89-4). This fascial plane extends into the hilum of the lung and merges with the bronchovascular sheaths that surround the terminal bronchioles, arteries, and veins. The bronchovascular sheath also merges with and is continuous with the pericardium. After alveolar rupture, air enters the perivascular interstitium and dissects proximally within the bronchovascular sheath toward the mediastinum (Fig. 89-5). Air can then enter the pericardial space, resulting in pneumopericardium, or it may dissect along the adventitia of the great vessels (Fig. 89-6). Mediastinal air can also decompress by extension into the cervical, subcutaneous, and retroperitoneal spaces. A pneumomediastinum that ruptures into the free pleural space results in a pneumothorax. Pneumothorax may also result from air dissecting out toward the visceral pleural surface of the lung and rupturing. Macklin, in 1944, in an elegant experimental cat model, confirmed this theory of progression of extra-alveolar air following alveolar rupture. Pneumomediastinum usually results from a ruptured alveolus due to a Valsalva maneuver or mechanical ventilation. There are many other possible sources, however, which must be considered when the physician has to manage a patient with pneumomediastinum (Table 89-2). Dental procedures, especially those on the mandible with the addition of compressed air to maintain a clear field, are an occasional cause of mediastinal emphysema.

Spontaneous Pneumomediastinum

Idiopathic spontaneous pneumomediastinum is a rare self-limited condition that most commonly affects young adult men. Hamman, in 1939, described crepitation synchronous with the heartbeat in these patients. The majority of patients

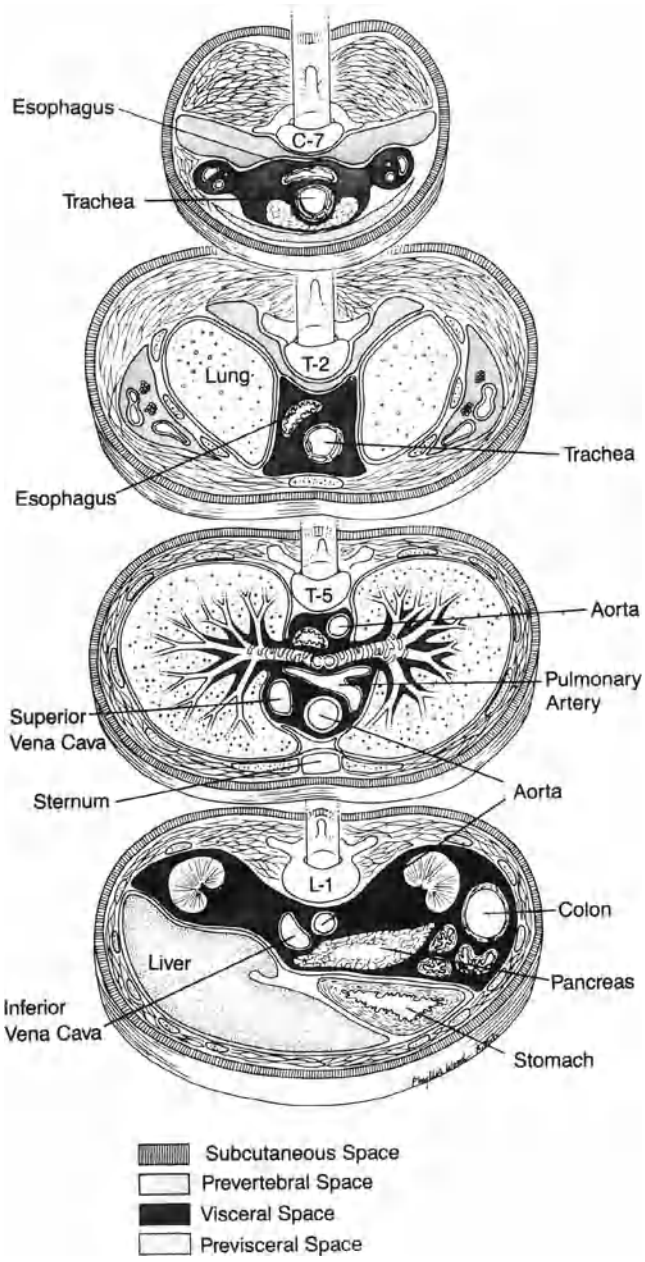


Figure 89-4 Soft tissue compartments of the neck, thorax, and abdomen demonstrating continuity of visceral space between regions. *(From Maunder RJ, Pierson DJ, Hudson LD: Subcutaneous and mediastinal emphysema.* Arch Intern Med *144:1447–1453, 1984, with permission.)*

with spontaneous pneumomediastinum have predisposing factors that cause increase in airway pressure, which leads to alveolar rupture. Most commonly, this results from straining against a closed glottis, as during vomiting, coughing, or exercising. Other mechanisms include sudden and/or severe increases in lung volume, as occur during marijuana smoking, inhaling of cocaine, and/or during a seizure. Localized airway obstruction from tumor, foreign bodies, asthma, or parenchymal lung disease can also cause alveolar rupture. An accurate history is most important in order to define the mechanism in a particular patient.

Spontaneous pneumomediastinum almost always presents with substernal pain, often pleuritic, which may radiate to the neck or back. Patients may experience, either separately or in combination, dyspnea, dysphagia, odynophagia, and dysphonia. Air in the subcutaneous tissues of the neck produces a characteristic change in voice quality, a higher-pitched nasal tone, that the experienced clinician easily recognizes. Examination often reveals palpable subcutaneous emphysema in the neck. Auscultation of the chest may reveal a crunching or clicking sound heard over the pericardium, synchronous with the heartbeat (Hamman's sign). Low-grade fever is present in about one-third of cases and mild leukocytosis in about one-half. Nonspecific electrocardiographic changes, such as ST-T wave changes and ST elevation, may also be present. A chest radiograph usually demonstrates a thin radiolucent strip along a mediastinal fascial plane, most commonly along the left heart border. The aortic knob may be highlighted as well (see Fig. 89-6). Computed tomography (CT) is more sensitive in detecting air than are plain radiographs (Fig. 89-7). Air may be evident deep in the neck as well as in the subcutaneous tissue.

The differential diagnosis is broad and includes musculoskeletal, pleural, pulmonary, cardiac, and esophageal causes. Although most patients who present are not acutely ill, an occasional patient may suffer an acute, catastrophic onset with hypotension and hemodynamic compromise. Esophageal perforation is the condition most likely to be confused with spontaneous mediastinal emphysema. Worrisome features suggestive of esophageal perforation include recent esophageal instrumentation, a history of esophageal problems, severe retching, the presence of a pleural effusion, or shock. A contrast esophagogram should be obtained immediately if there is any question of an esophageal perforation, since a delay in making this diagnosis often proves fatal. A high index of suspicion regarding esophageal perforation should always be present whenever a patient presents with mediastinal emphysema.

Treatment of spontaneous mediastinal emphysema is supportive and is primarily directed at pain relief and reassurance. Appropriate management of contributing causes such as foreign bodies, asthma, and parenchymal lung disorders should be instituted. The patient should be followed both clinically and radiographically to exclude another cause for mediastinal emphysema and detect a possible pneumothorax. Prompt resolution is the rule. Supplemental oxygen to hasten reabsorption (similar to that proposed for pneumothorax) has been reported but is probably not necessary. Needle aspiration or skin incision to relieve subcutaneous emphysema is almost never necessary. Prophylactic tube thoracostomy is unnecessary. For patients who present with minimal findings and a clear inciting factor (such as coughing), only a short period of observation in the emergency department is required.

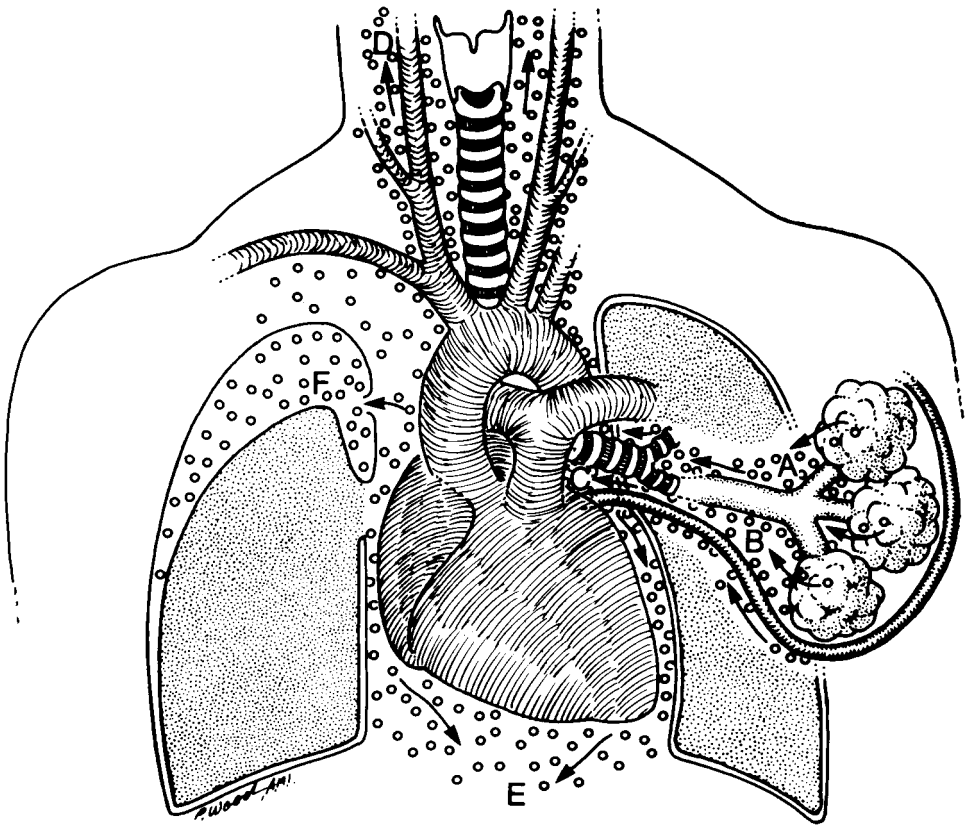


Figure 89-5 Possible routes of air following alveolar disruption. Air from the alveolus (*A*) enters perivascular interstitium (*B*), dissecting proximally within bronchovascular sheath toward mediastinum (*C*). As mediastinal pressure rises, decompression occurs in cervical (*D*), subcutaneous, and retroperitoneal (*E*) soft tissue spaces. A pneumothorax is possible if the pleura (*F*) is ruptured. *(From Maunder RJ, Pierson DJ, Hudson LD: Subcutaneous and mediastinal emphysema.* Arch Intern Med *144:1447–1453, 1984, with permission.)*

Pneumomediastinum Associated with Mechanical Ventilation

Mechanical ventilation is commonly associated with pneumomediastinum and may often lead to life-threatening tension pneumothorax. Alveolar rupture results from high peak inspiratory pressures, which increase alveolar pressures in patients with abnormal airways or parenchyma (decreased compliance). Classic predisposing factors include high tidal volumes, high levels of positive end-expiratory pressure (PEEP), and "fighting" the ventilator. Air trapping with occult positive end-expiratory pressure (auto-PEEP) is probably an underrecognized cause of barotrauma. It is not clear if one mode of ventilation (pressure-controlled versus volume-limited) is associated with a decreased incidence of barotrauma.

Unlike spontaneous mediastinal emphysema, pneumomediastinum occurring in a patient on mechanical ventilation is potentially catastrophic because of its frequent association with tension pneumothorax. The chest radiograph should be closely examined to detect even a small pneumothorax and, if such is present, tube thoracostomy should be promptly performed. Obviously, a sudden deterioration marked by hypotension and increased pulmonary pressures

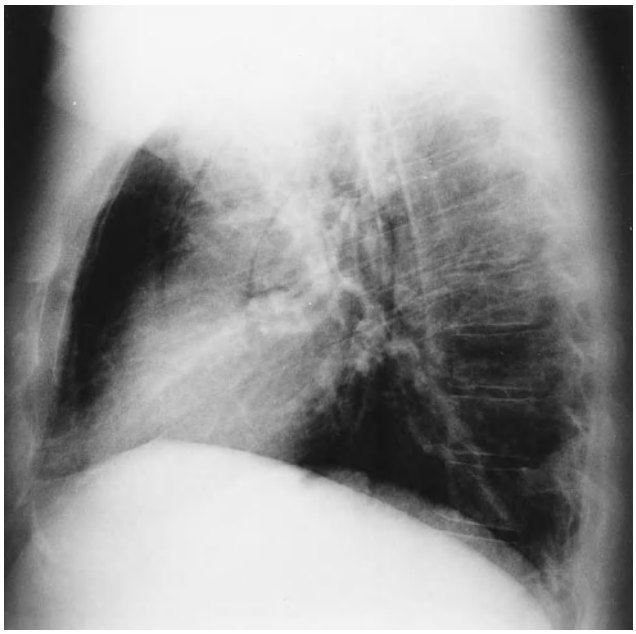


Figure 89-6 Lateral radiograph of a middle-aged patient with an acute asthma attack requiring hospital admission. Mediastinal air is seen outlining the aorta and esophagus. This resolved spontaneously.

Table 89-2

Etiology of Pneumomediastinum

Upper respiratory tract
Head and neck infection
Fracture of facial bones
Trauma to hypopharynx and larynx (especially intubation)
Dental procedures (especially mandibular)
Lower respiratory tract
Trauma
Bronchoscopy, especially therapeutic bronchoscopy (i.e., YAG laser, rigid core-out, and transbronchial biopsy)
Lung
Trauma
Surgery
Spontaneous alveolar rupture
Straining and Valsalva maneuver
Local airway obstruction
Scuba diving
Mechanical ventilation
Gastrointestinal tract
Esophageal perforation
Perforated viscus
Infection
Acute mediastinitis
Descending necrotizing mediastinitis
Air from outside the body
Trauma
Surgery (especially mediastinoscopy, tracheostomy, and sternotomy)
Pneumoperitoneum (especially with laparoscopic hiatus hernia repair)

Source: Adapted from Pierson with permission.

should prompt immediate attention with insertion of unilateral or bilateral chest tubes, depending on the clinical examination. The issue of inserting a tube prophylacticaly is controversial and unresolved. At a minimum, a thoracostomy tray should be kept at the patient's bedside and the nursing staff reminded of the signs of a pneumothorax in a mechanically ventilated patient. If a physician is not readily available around the clock, it may be advisable to perform bilateral prophylactic tube thoracostomy in certain patients. Removing the patient from mechanical ventilation as soon as possible is appropriate. Since this is seldom possible, efforts should be directed at minimizing alveolar distention. These efforts include relief of bronchospasm, minimizing "fighting" the ventilator, reducing tidal volume and PEEP, and manipulation of inspiratory flow and timing to reduce auto-PEEP.

Pneumopericardium

Pneumopericardium as a form of barotrauma is much more frequent in neonates, presumably due to immature fascial planes. Hemodynamically significant tamponade is also much more likely to occur in infants rather than adults and has resulted in collapse and death. Pericardial drainage with a subxyphoid tube should be performed promptly in the neonate. In the adult, drainage should be performed only if there is hemodynamic embarrassment.

ACUTE MEDIASTINITIS

Acute mediastinitis is a life-threatening disorder that causes severe morbidity in the afflicted patient. All three mediastinal compartments can be affected; the anterior compartment most commonly after sternotomy for cardiac surgery, the middle compartment usually from esophageal perforation, and the posterior compartment from direct extension from the lung or spine. Instrumental perforation of the esophagus is the most common cause of acute mediastinitis in the United States. A summary of the causes of acute mediastinitis is presented in Table 89-3.

Mediastinitis from Esophageal Perforation

Instrumental perforation of the esophagus now accounts for almost one-half of all esophageal perforations. Perforation is more common after rigid esophagoscopy, dilation of a stricture, and pneumatic dilation for achalasia, but it also occurs after variceal sclerosis, esophageal tube placement (nasogastric, Sengstaken-Blakemore, and salivary bypass tubes), and simple flexible esophagoscopy. Boerhaave's syndrome (postemetic rupture) was described in 1724 but still represents a diagnostic challenge and remains a major consideration in patients with otherwise unexplained mediastinitis (Fig. 89-8). Patients usually present with the abrupt onset of severe substernal chest pain, which is pleuritic after forceful vomiting or retching. Dyspnea is common even in the absence of pneumothorax. Shock develops quickly and the patient usually appears gravely ill. Examination reveals tachypnea, tachycardia, fever, hypotension, splinting of the chest and abdomen, and cervical emphysema. Radiographic findings may show cervical or mediastinal emphysema, pneumothorax, and (commonly) pleural effusion. Noncontrast radiographic studies are normal in 10 to 30 percent of cases of esophageal perforation. A contrast esophagogram (usually with water-soluble contrast) should be performed immediately when the diagnosis is suspected, but one should be aware that this study has a false-negative rate of 10 percent. A chest CT scan is the next best study in a patient in whom esophageal perforation is suspected but who has a negative esophagogram. Prompt

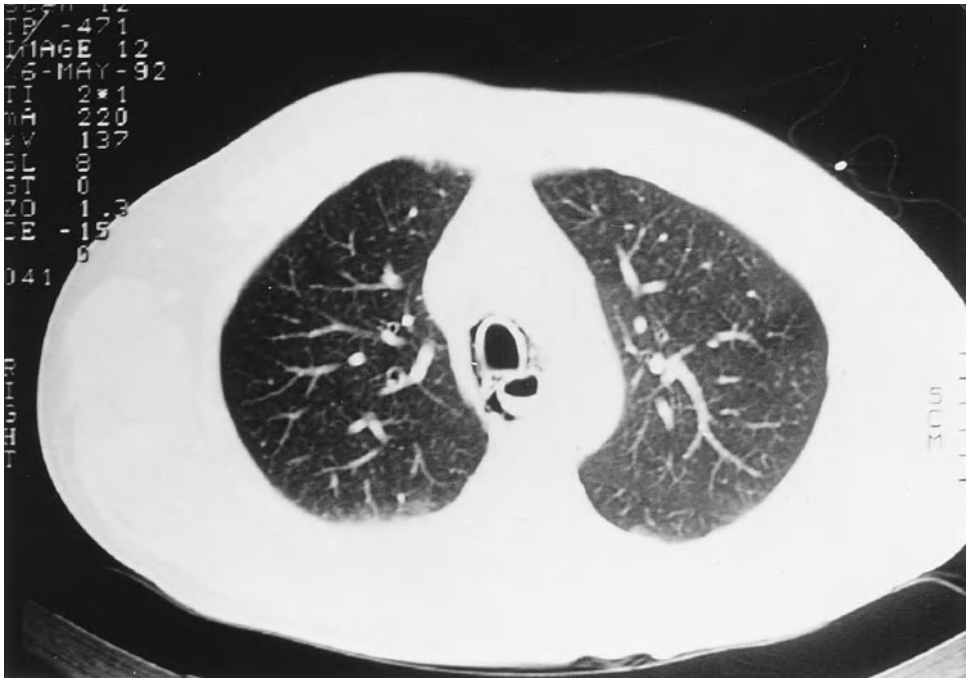


Figure 89-7 Computed tomography of a man with an 8-hour-old postemetic esophageal rupture. Posteroanterior radiograph was normal. Mediastinal air is seen outlining trachea and esophagus.

diagnosis and, therefore, a high index of suspicion are essential, as the frequency of complications and the mortality rate are directly dependent on the time elapsed between perforation and treatment. The differential diagnosis is broad and includes perforated ulcer, acute pancreatitis, myocardial infarction, pneumonia, aortic dissection, and pulmonary embolism.

Treatment should be instituted urgently and involves surgical debridement of necrotic tissue, secure closure of the perforation, correction of any distal obstruction, and wide drainage, usually performed through a left thoracotomy. Appropriate broad-spectrum antibiotics with anaerobic coverage and the maintenance of proper nutrition are also integral components of the management plan. Esophagectomy is occasionally required in the presence of a perforated, nondilatable stricture, a destroyed esophagus in which direct repair is not possible, or cancer. Nonoperative treatment is *rarely* appropriate but may be instituted in highly selected cases (i.e., contained, asymptomatic instrumental perforations) in which a significant interval has passed and the patient is clinically stable. Mortality is less than 10 percent if the perforation is recognized and repaired within 24 h, whereas mortality increases to 30 to 40 percent if more than 24 h have elapsed between perforation and repair. The mortality rises even higher with advanced age of the patient.

Tracheobronchial Perforation

Tracheobronchial perforation is rare and is most commonly seen following trauma or instrumentation. Severe mediastinitis is rare after tracheobronchial disruption, presumably due to the less noxious nature of its contents and better containment. Intubation is now the most frequent cause of tracheobronchial injury, but it should be avoidable with gentle and proper technique. Blood in the airway, airway obstruction (infrequent), subcutaneous and mediastinal emphysema, and pneumothorax are the common presenting signs. Prompt

Table 89-3

Etiology of Acute Mediastinitis

Esophageal perforation
Instrumental
Postemetic (Boerhaave's syndrome)
Trauma
Foreign body
Operative injury
Caustic ingestion
Cancer
Direct extension
Tracheobronchial perforation
Descending necrotizing mediastinitis
Direct extension (pulmonary and pancreatitis)
Poststernotomy mediastinitis
Anthrax mediastinitis

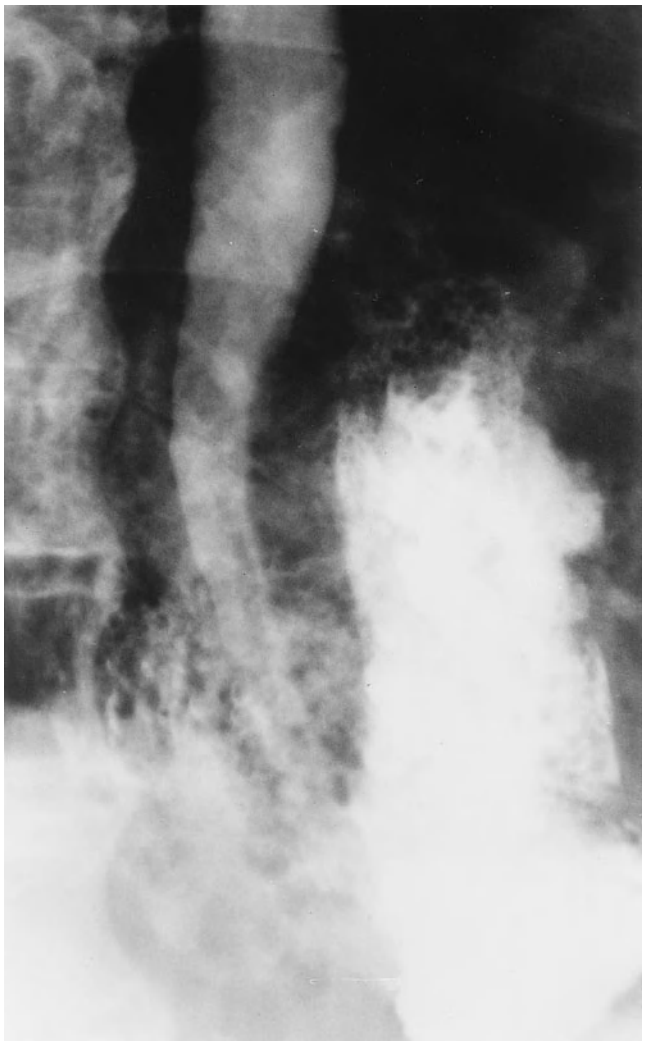


Figure 89-8 Water-contrast esophagogram of a patient with Boerhaave's syndrome. Note extensive extravasation of contrast and mediastinal emphysema.

recognition and operative repair are necessary and yield excellent results, although small tears in the cervical trachea may often be managed with antibiotics alone, without operation.

Descending Necrotizing Mediastinitis

Mediastinitis occasionally develops after severe deep cervical infections that originate from the oropharynx. Most patients present with a mixed aerobic and anaerobic infection. Previously these infections had a fulminant, often lethal course with mortality as high as 40 percent. Extension of the cervical infection down the prevertebral or visceral space into the mediastinum leads to this syndrome of descending necrotizing mediastinitis. Computed tomography should be performed on all severe neck infections to identify signs of mediastinitis that may not be clinically apparent. Aggressive surgical drainage (cervical, substernal, and transthoracic) and antibiotics have reduced mortality, though prompt management is essential.

Mediastinitis from Direct Extension

Necrotizing pneumonias may cause mediastinitis by direct extension, most often in immunocompromised patients. Aspergillosis of the posterior mediastinum has been reported with increasing frequency and is highly lethal. Treatment involves reversal of immunosuppression (if possible), appropriate antibiotic therapy, and surgical drainage and debridement.

Pancreatitis can extend from the retroperitoneum into the mediastinum and may present as a mediastinal process with evidence of mediastinitis. Pancreatic pseudocysts can also erode into the mediastinum and cause pleural effusions with increased levels of amylase. Treatment is directed at providing adequate drainage of the pseudocyst, usually by internal drainage into the stomach. The pleural effusion(s) may require tube thoracostomy drainage.

Poststernotomy Mediastinitis

Sternal wound infection with resulting mediastinitis is a relatively new entity, which emerged in the era of modern cardiac surgery. The incidence remains low at 0.5 to 1 percent of all sternotomies, but such infection is a source of major morbidity, prolonged hospital stay, and significant mortality (0 to 30 percent; average, 15 percent). Multivariate analysis has demonstrated that prolonged preoperative stay, reoperation, blood transfusions, and re-exploration for bleeding are significant risk factors. The presence of diabetes mellitus and use of internal thoracic artery grafts (which may devascularize the sternum) also are significant risk factors. Organisms commonly isolated include *Staphylococcus epidermidis* and *aureus,* various gram-negative organisms, as well as *Candida* species and atypical mycobacteria. The etiology appears to be a combination of intraoperative contamination and hematogenous seeding of mediastinal clot in the early postoperative period. Breaks in technique during the operation or inadequate sterilization of instruments before it probably cause the majority of these infections.

Most patients with poststernotomy mediastinitis have an insidious presentation with low-grade fever and leukocytosis, wound problems (erythema, drainage, sternal instability), and eventually bacteremia. Infections caused by gram-negative organisms tend to become manifest earlier than those caused by gram-positive organisms. Most infections occur within the first or second week following the operative procedure. A high index of suspicion must be maintained so that an early diagnosis can be made and appropriate treatment instituted. Wound aspiration, local wound exploration, and a CT scan aid in making the diagnosis. Exploration in the operating room remains the definitive diagnostic maneuver and material should be obtained for culture at that time if it has not been obtained before or has been unrevealing.

If the infection is relatively early and the bony sternum appears viable, debridement, drainage, and saline (or antibiotic) irrigation with reclosure are indicated. Although it may seemingly violate time-honored surgical principles (leaving

contaminated wounds open, to close by secondary intention), primary closure of the early infected sternum yields excellent results in many patients if adequate debridement is carried out. Of course, proper and prolonged antibiotic therapy is necessary. Reported mortality rates approach zero for these early infections if managed appropriately. Late sternal wound infections with mediastinitis present a more formidable challenge, in part due to the extensive sternal osteomyelitis and necrotic soft tissue which, when debrided, result in significant dead space, thereby creating a favorable environment for continued bacterial proliferation and persistent infection. Most surgeons favor extensive sternal debridement, usually with total sternal excision and rotation of pectoralis muscle flaps (bilateral) or transposition of gastrocolic omentum to fill the dead space with viable tissue. The presence of prosthetic material, such as sutures, Teflon pledgets, or prosthetic grafts further complicates the problem and may lead to catastrophic hemorrhage with a fatal outcome. Mediastinitis in the presence of a prosthetic aortic graft is a particularly disastrous complication.

Anthrax Mediastinitis

Anthrax, caused by *Bacillus anthracis,* was previously found primarily in the Middle East, with farm animals as the primary reservoir. Following the advent of substantial immigration and bioterrorism, anthrax has been diagnosed in the United States and has been prominent in the mainstream media. An index case of fatal inhalational anthrax complicated by hemorrhagic mediastinitis due to bioterrorism in the United States has been reported in detail. The inhalation of anthrax spores allows entry into the lungs with subsequent transport to the mediastinal lymph nodes by alveolar macrophages. A hemorrhagic mediastinitis typically quickly ensues and death is common. Gram-positive bacilli are present in tissue specimens, and the initial treatment involves the initial use of either ciprofloxacin or doxycycline plus one or two additional antimicrobial agents with activity against B. anthracis.

CHRONIC MEDIASTINITIS

Granulomatous mediastinitis is a disease of the mediastinal lymph nodes usually resulting from infection by *Histoplasma capsulatum* and occasionally from tuberculosis or other fungi. In certain areas of the country (Mississippi river valley) where *Histoplasma* is endemic, this disease is fairly common. Coalescence of caseous mediastinal lymph nodes can result in a single large mass that incites a considerable fibrotic response, which can result in encapsulation and produce a mediastinal granuloma. The right paratracheal area is the most common site for development of an encapsulated mass. When calcification is absent and the patient presents with what appears to be mediastinal adenopathy, a tissue diagnosis is required to exclude malignancy. With progressive increase in the size of this "benign" mass, compression of the trachea, superior vena cava, or esophagus can occur. In a report from the Mayo Clinic, 34 percent of patients with mediastinal granuloma went on to develop mediastinal fibrosis over a 2-year period. Based on such reports, most authors suggest that there exists a spectrum of disease ranging from mediastinal granuloma to fibrosing mediastinitis. Caseating lymph nodes can also erode into and rupture in the esophagus, be associated with esophageal diverticula (Fig. 89-9), and erode into the airway, causing obstruction or bleeding.

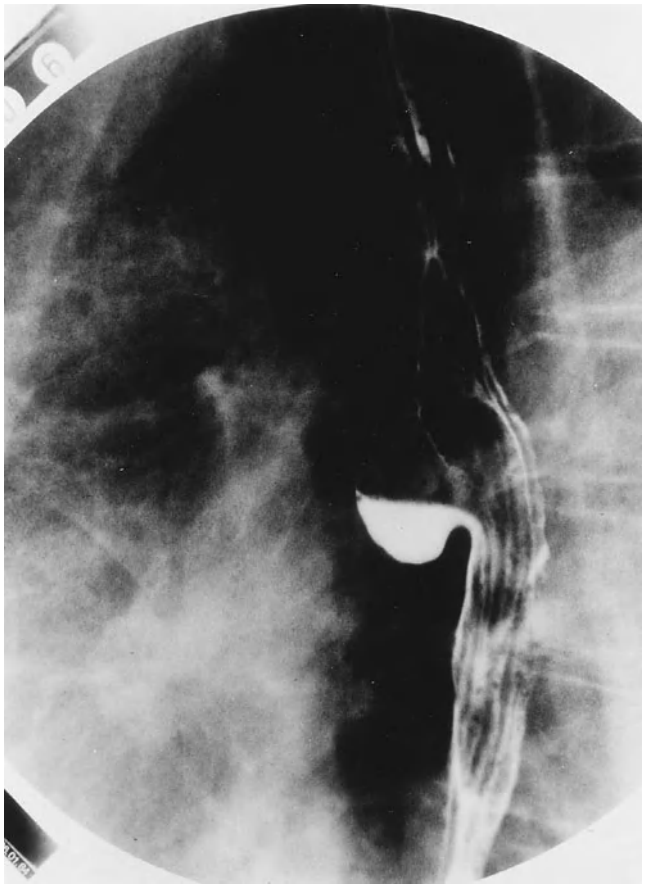


Figure 89-9 Barium swallow of an elderly woman with a history of treated tuberculosis with symptomatic diverticulum of midesophagus adjacent to the subcarinal lymph nodes.

Mediastinal granulomas should be excised if symptomatic. Although complete excision is possible, the intense surrounding fibrosis places important structures at risk for operative injury. Evacuation of the granulomatous mass is usually a safer option. Specimens for culture and special stains should be obtained at the time of operation, but organisms can rarely be identified or grown in culture.

Mediastinal lymph nodes involved by the granulomatous process may become calcified as individual masses and—because of the proximity of lymph nodes to the tracheobronchial tree—ultimately erode into the airway. Erosion into the airway, if it occurs, does so over a prolonged period of time and may remain asymptomatic, only to be noted if a bronchoscopy is performed for some other indication. The presence of calcified lymph node masses within the bronchi

is referred to as *broncholithiasis* and may also present with symptoms of obstruction or bleeding. Symptomatic broncholithiasis should prompt bronchoscopy for documentation of findings only. Rarely, if ever, should broncholiths be removed bronchoscopically, the exception being the occasional "stone" that is completely free within the bronchus. An effort to remove a broncholith that is not completely detached from the wall of the bronchus may be accompanied by catastrophic hemorrhage due to the close proximity of pulmonary artery branches to the bronchus. Most symptomatic broncholiths should be removed at thoracotomy, where the pulmonary artery may be managed. These can be extremely difficult and hazardous operations and should be carried out by thoracic surgeons experienced in the management of granulomatous disease. Usually lobectomy or segmentectomy is required, since removal of the calcified mass will almost certainly take a portion of the bronchial wall.

Fistulas occurring between the trachea and esophagus or esophagus and mediastinum should be closed and reinforced with viable tissue. There is no consensus regarding management of large asymptomatic mediastinal granulomas but some have recommended excision to forestall the development of fibrosing mediastinitis. This, however, remains controversial.

Fibrosing Mediastinitis

Fibrosing mediastinitis may cause a variety of clinical syndromes due to the compression and/or erosion of vital mediastinal structures by the dense fibrous tissue reaction that is present. Although the syndrome itself is rare, the common causative agents—*Histoplasma* and, rarely, *Mycoplasma tuberculosis*—are relatively ubiquitous. Other very rare causes include other fungi, silicosis, the drug methysergide, autoimmune disorders, and familial multifocal fibrosclerosis. Goodwin proposed the currently accepted (by most) hypothesis that fibrosing mediastinitis results from a delayed hypersensitivity reaction to fungal, mycobacterial, or other antigens. Pathological features include the presence of dense fibrotic tissue surrounding the trachea and hila of the lungs, often extending into contiguous structures. Compression of the airway, pulmonary arteries, or veins may occur because of this process. Histological features include dense hyalinized collagenous tissue, aggregates of plasma cells and lymphocytes, and occasionally granulomas. Cultures are almost always negative, as are special stains for organisms.

Symptoms are primarily caused by compression of vital mediastinal structures. Fibrosis around the right peritracheal area commonly causes superior vena cava syndrome. Subcarinal fibrosis can extend posteriorly to encase the esophagus or extend laterally to involve the pulmonary veins. Hilar fibrosis can obstruct either the tracheobronchial tree or pulmonary arteries (Fig. 89-10). Rarely, constrictive pericarditis or obstruction of the trachea or proximal main bronchi can also occur. The signs and symptoms may progress over a period of time.

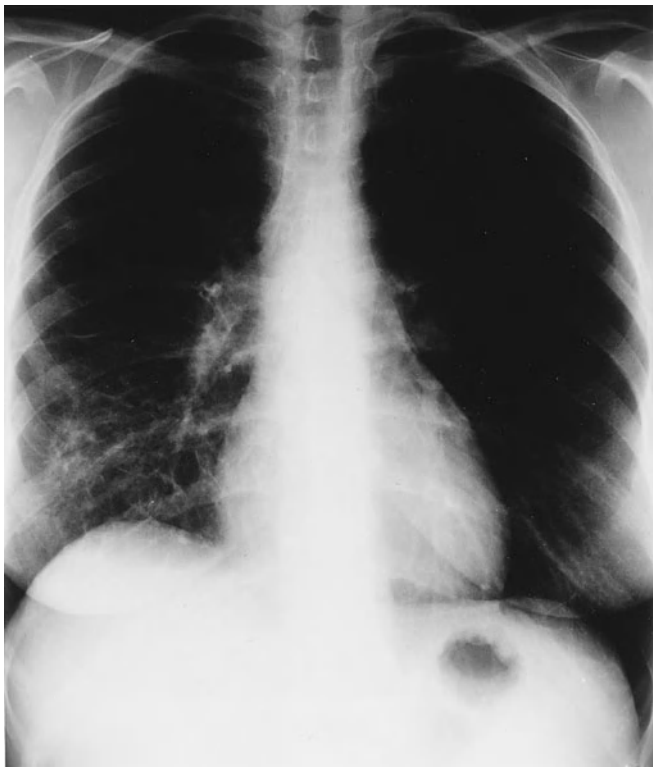
Superior Vena Cava Syndrome

The most common mediastinal compression syndrome seen in fibrosing mediastinitis is the superior vena cava (SVC) syndrome, which occurs in 20 to 50 percent of patients. In the vast majority of patients, the SVC syndrome is due to malignant disease; fibrosing mediastinitis is the most common benign cause. Patients present with distention of the veins in the neck; edema and plethora of the face, neck, and arms; and central nervous system complaints such as headache and visual disturbances. Men often note as a first sign an increase in collar size; and symptoms become worse upon bending over. Because this syndrome is usually of gradual onset, venous collaterals develop over the anterior chest wall and, in many patients, provide adequate decompression (Fig. 89-11). Confirmation of the diagnosis of SVC syndrome is easily made with contrast CT or venography, which demonstrate blockage of contrast at the thoracic inlet and the presence of collateral vessels. Bilateral upper extremity venograms demonstrate the precise anatomy of the involved veins and are helpful if surgical decompression is contemplated. Surgical bypass is reserved for patients with intractable symptoms and is performed by connecting an unobstructed large brachiocephalic vein to the right atrial appendage with a graft of either a saphenous vein or an externally supported polytetrafluoroethylene graft. Favorable long-term results have been reported. Percutaneous angioplasty and stenting of a stenotic superior vena cava has been reported, but long-term follow-up is limited.

Other Compression Syndromes

Tracheobronchial compression is also common and leads to dyspnea, obstructive pneumonias, wheezing, hemoptysis, cough, and the middle lobe syndrome (see Fig. 89-10). A localized stenotic area can be dilated sometimes, but often pulmonary resection is required, usually of the right middle and occasionally lower lobes. Resection is the procedure of choice if chronic infection has been present. Bronchoplastic procedures are appropriate sometimes if lung parenchyma remains normal. The placement of stents into the trachea and/or mainstem bronchi may allow for adequate management of a compressed airway. A Y-bifurcation stent and individual self-expanding stents placed in the trachea or bronchi are available. Airway management must be individualized based on findings at bronchoscopy.

Complete or partial unilateral or bilateral pulmonary artery obstruction can result from fibrosing mediastinitis (see Fig. 89-10). Dyspnea and signs of right heart failure can be present. The differential diagnosis should include chronic pulmonary thromboembolism. The fibrosis may also extend to involve the pulmonary veins, producing pulmonary venoocclusive disease. Some patients present with complaints similar to those of patients presenting with mitral stenosis: dyspnea, cough, and hemoptysis. Surgical correction of these disorders is rarely possible due to the extreme fibrosis present around the vessels. If the situation is unilateral, a pneumonectomy may be an alternative.



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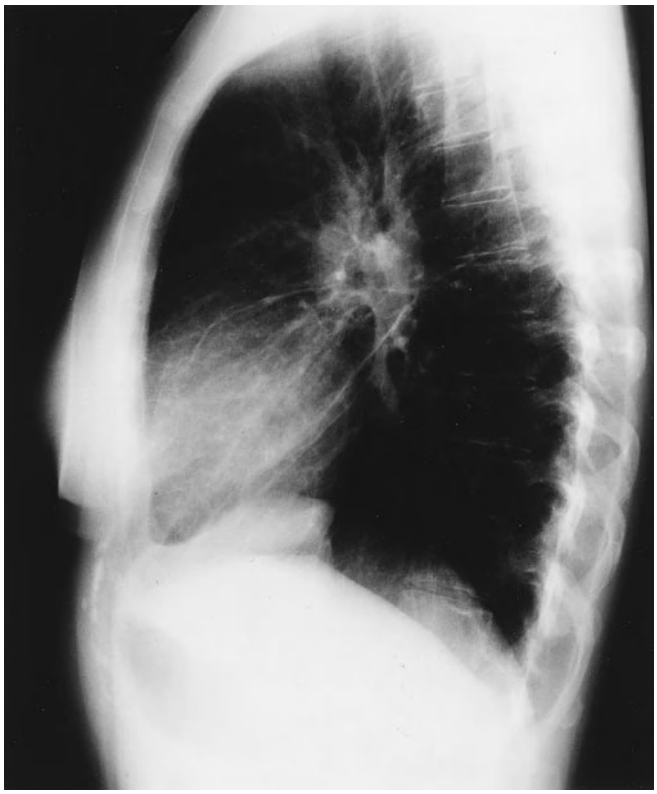

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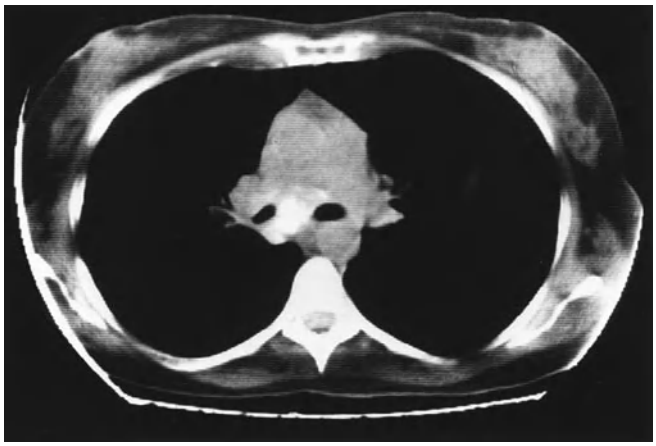

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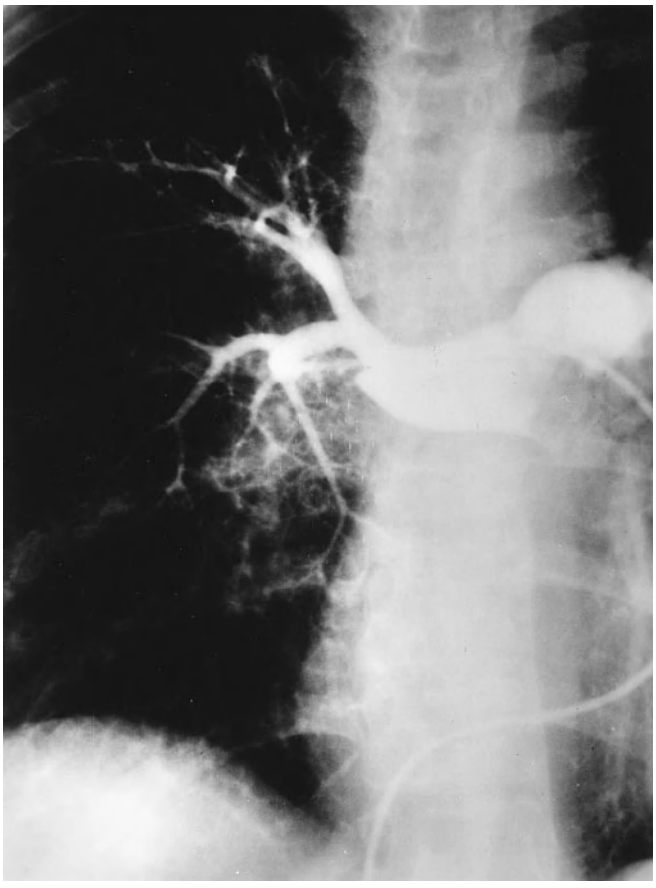

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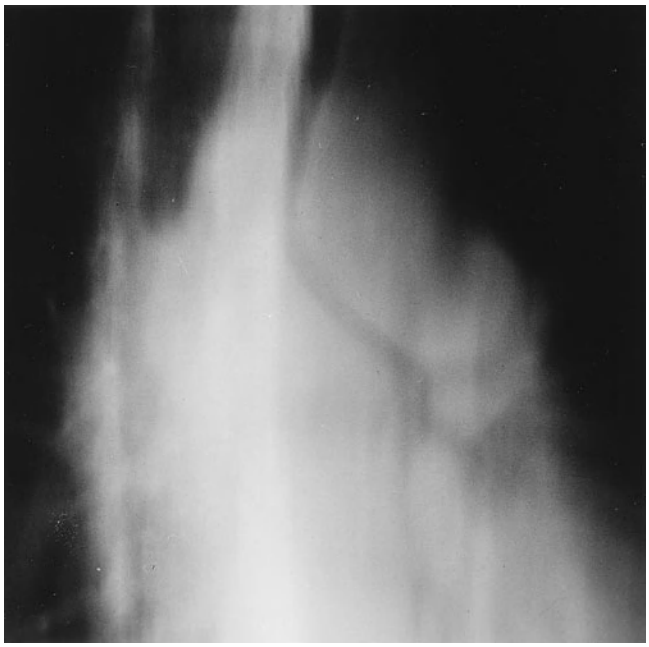
Figure 89-10 Mediastinal fibrosis due to histoplasmosis in a middle-aged nurse with narrowing of the trachea and main bronchi as well as occlusion of the right pulmonary artery. *A.* Posteroanterior radiograph demonstrating focal infiltrate in right lower zone with right hilar fullness. *B.* Lateral radiograph demonstrating a mass centered around the carina with mild narrowing of the distal trachea. *C.* Computed tomography shows calcified mass around bronchus intermedius with mild compression of bronchus. *D.* Pulmonary angiogram demonstrates complete occlusion of right pulmonary artery beyond the anterior trunk due to mediastinal fibrosis. The left pulmonary artery was moderately narrowed. *E.* Oblique tomogram demonstrating narrowing of distal trachea and left main bronchus. *F.* Oblique tomogram demonstrating narrowing of right bronchus intermedius with large mass of lymph nodes anterior and posterior to the airway.



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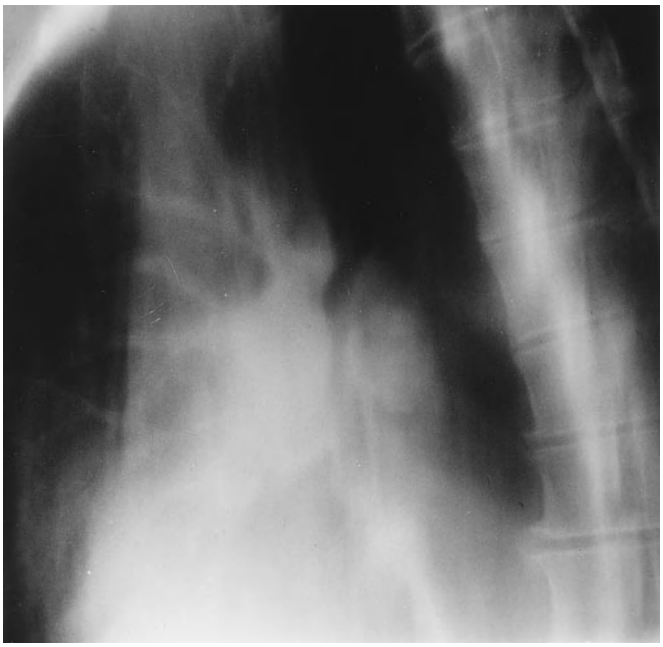

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Figure 89-10 (*Continued*)

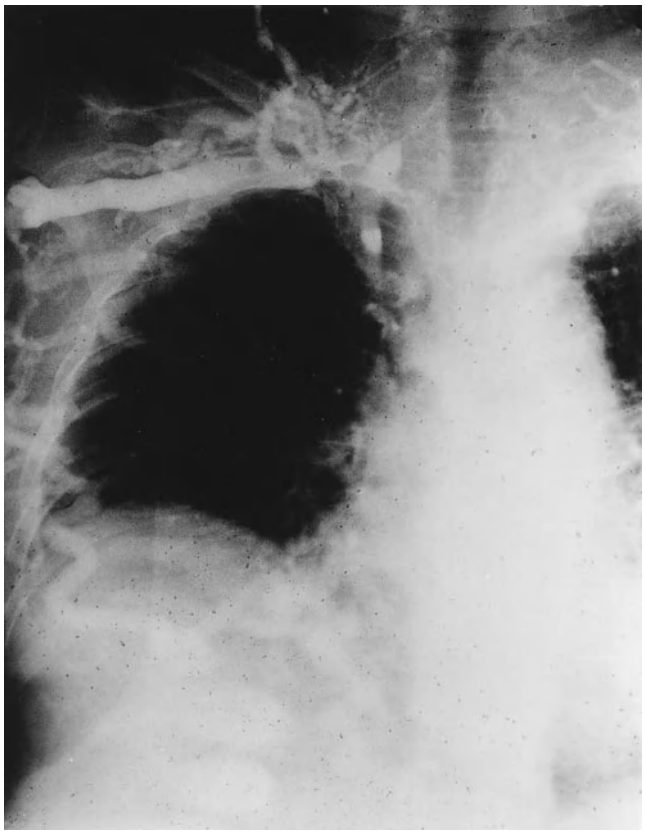


Figure 89-11 Patient with SVC syndrome secondary to mediastinal fibrosis due to histoplasmosis. Numerous dilated and tortuous collateral veins present on the chest wall are characteristic of chronic SVC obstruction.

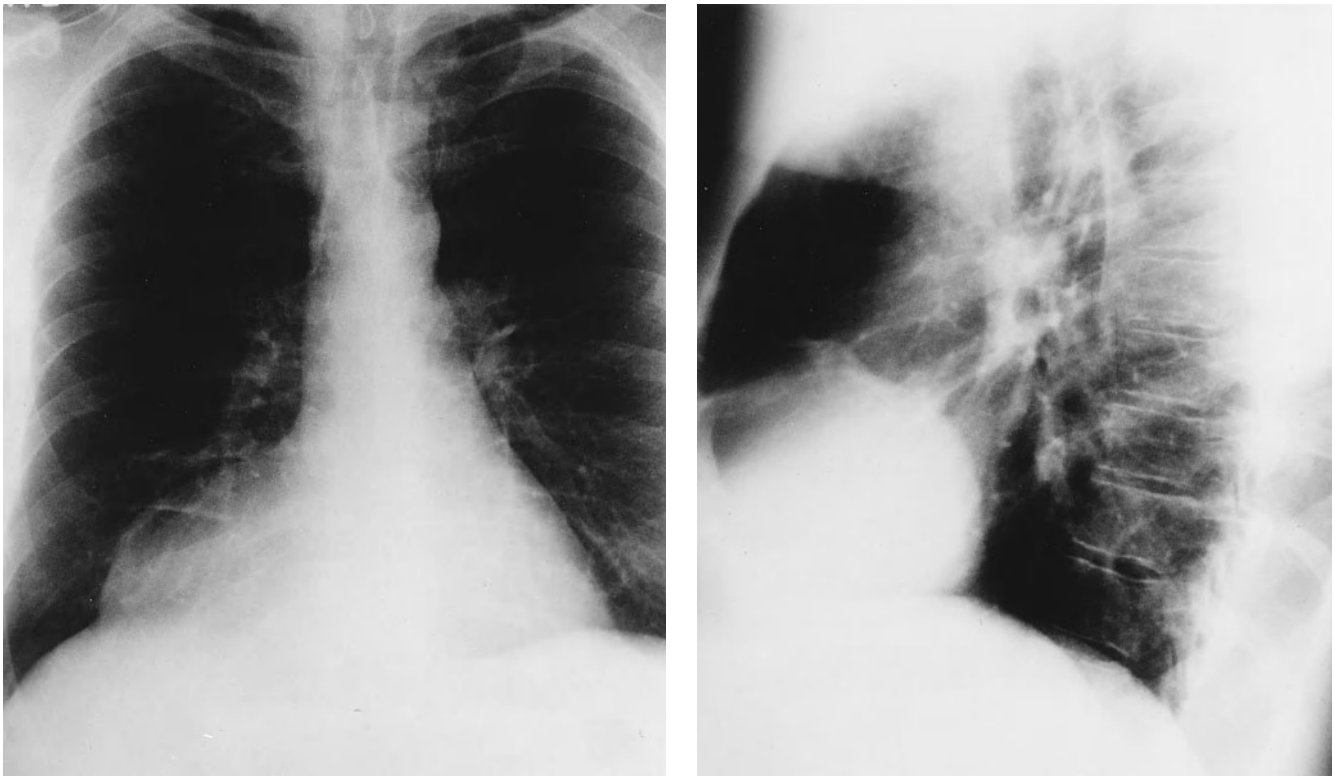
Esophageal obstruction is not uncommon in fibrosing mediastinitis, and the middle third of the esophagus is most frequently involved because of its relationship to the subcarinal space. Dilation, enucleation of scar, and resection are therapeutic options. Fistulas may also occur between the subcarinal lymph nodes and the esophagus or into the tracheobronchial tree. Operative treatment for fistula formation is directed at closing the fistula and separating structures using viable tissue such as muscle. An esophageal diverticulum may form from inflammatory adherence to the subcarinal lymph nodes but is usually asymptomatic (see Fig. 89-9).

Corticosteroids have not proved of benefit in fibrosing mediastinitis despite its obvious inflammatory nature. The majority of reports of treatment with chemotherapeutic agents directed against the suspected causative organism have been negative. Urschel reported success in six patients who were treated with prolonged ketoconazole therapy. Patients were selected based on an increased sedimentation rate and histoplasmosis complement fixation titer and were given ketoconazole following appropriate surgical decompression. These patients are probably not typical or representative of most patients with fibrosing mediastinitis but rather closer to those with granulomatous mediastinitis.

MISCELLANEOUS MEDIASTINAL PATHOLOGY

Foramen of Morgagni Hernias

Hernias occurring through the foramen of Morgagni are rare causes of cardiophrenic angle masses (Fig. 89-12). The hernia



A *B*

Figure 89-12 Foramen of Morgagni hernia. This man presented with substernal discomfort and heaviness. Incarcerated omentum was present in the hernia sac. *A.* Posteroanterior radiograph demonstrating large, smooth mass obscuring the right cardiophrenic angle. *B.* Lateral radiograph showing large, smooth substernal mass.

results from failure of the normal fusion of the diaphragmatic components during embryologic development. Small hernias are usually asymptomatic but large ones can contain the entire omentum, transverse colon, and even stomach and thus cause symptoms. Symptoms include substernal discomfort and dyspnea; rarely, they may point to intestinal obstruction. The diagnosis is now easily confirmed by CT and operative repair is always indicated.

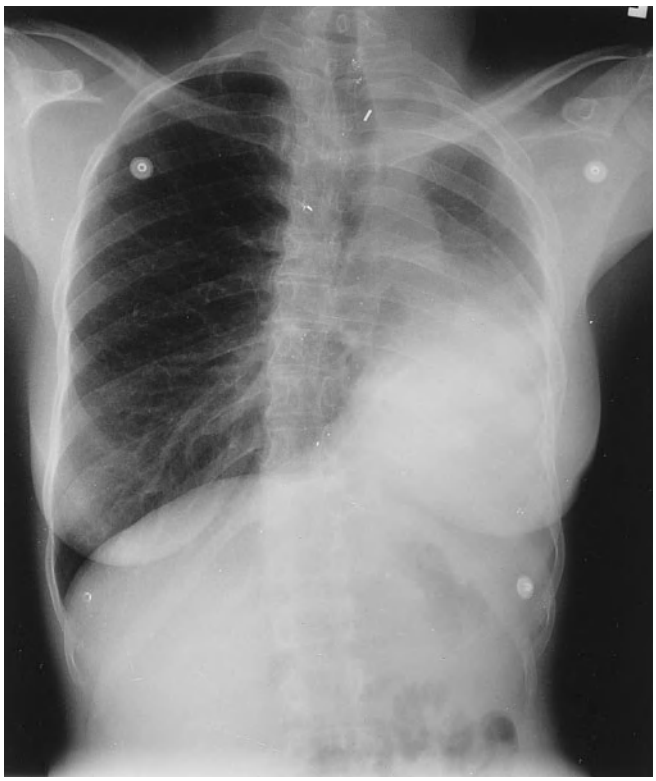
Mediastinal Repositioning in Postpneumonectomy Syndrome

Following pneumonectomy, airway compression may be caused by extreme mediatinal shift and rotation, manifested by herniation and overdistention of the remaining lung. This problem is rare but is more common after right pneumonectomy. It may also occur after left pneumonectomy, especially in the presence of a right aortic arch. The problem has been particularly noted in children but also occurs in younger adults. When extreme shift of the mediastinum occurs after pneumonectomy, compression of the main bronchus occurs against the aorta and/or vertebral column (Fig. 89-13). Patients may develop disabling dyspnea, stridor, and recurrent pulmonary infections.

Computed tomography confirms the diagnosis, and pulmonary function studies generally show severe obstruction, flattened flow-volume loops, and an increase in the ratio of residual volume to total lung capacity. Bronchoscopy delineates the extent of airway compression and is helpful in assessing any malacia that may be present. Operative repair is indicated and consists of mediastinal repositioning through the original thoracotomy incision by placing expandable saline breast prostheses (see Fig. 89-13). In the absence of severe malacia, airway compression is relieved and clinical results are excellent. Management of residual airway malacia is troublesome and is probably best handled by internal stenting.

Spontaneous Mediastinal Hemorrhage

Spontaneous mediastinal hemorrhage is quite rare. Mediastinal hemorrhage due to aortic dissection, contained rupture of a thoracic aortic aneurysm, or iatrogenic injury is much more common. Symptoms are usually of sudden onset and consist of substernal pain, dyspnea, and, rarely, hemodynamic compromise. The hemorrhage is usually brief and self-limited. Treatment is supportive, and secondary causes of mediastinal hemorrhage must be excluded. Mediastinal fibrosis has rarely been reported following mediastinal hemorrhage.



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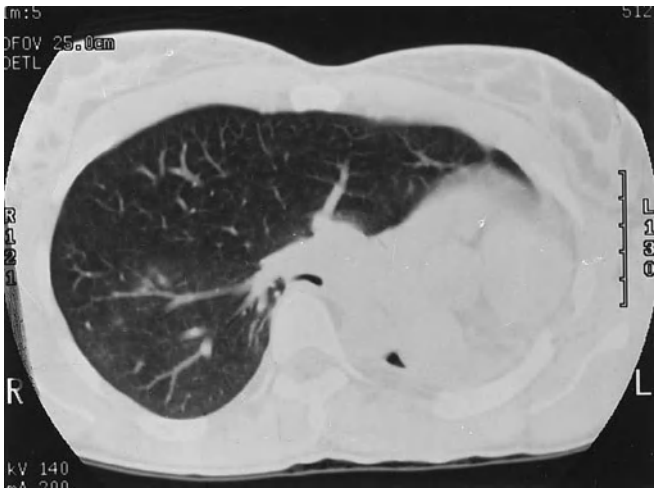

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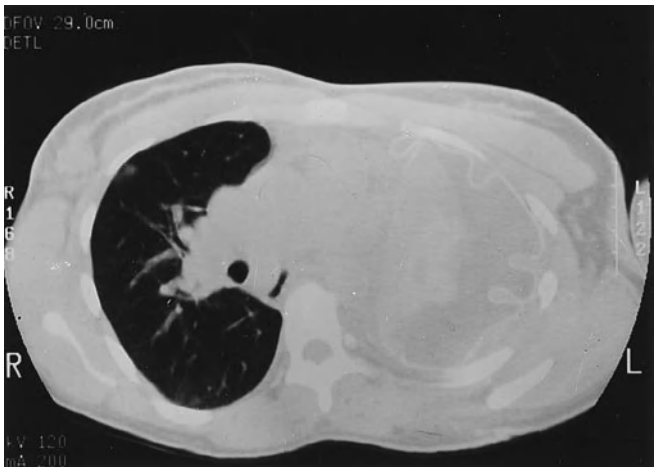

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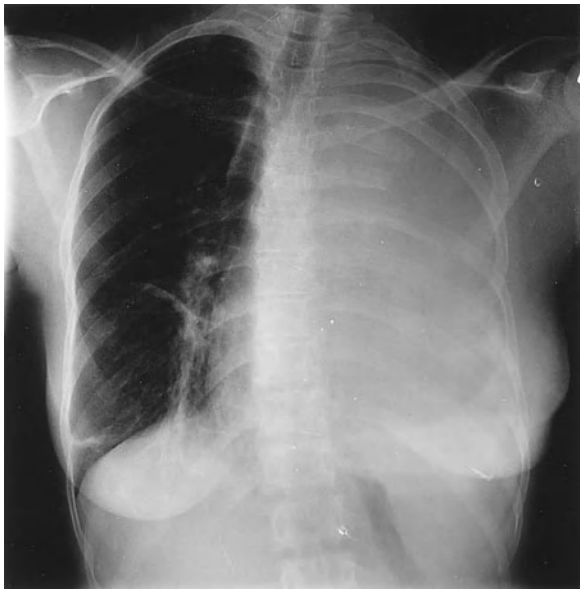

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Figure 89-13 Thirty-year-old woman with previous left carinal pneumonectomy for granular cell tumor with postpneumonectomy syndrome. She presented with worsening dyspnea, which worsened with recumbency. She became asymptomatic after mediastinal repositioning. *A.* Posteroanterior radiograph demonstrating marked overexpansion of right lung with mediastinal shift. Right tracheobronchial tree appears narrowed. *B.* Computed tomography scan confirming severe compression of right bronchus intermedius against the spine. *C.* Posteroanterior radiograph early after mediastinal repositioning with 1000 mL of saline implants. *D.* Computed tomography scan at level of bronchus intermedius after mediastinal repositioning demonstrating relief of bronchial compression.

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Congenital Cysts of the Mediastinum: Bronchopulmonary Foregut Anomalies

Neel R. Sodha • Malcolm M. DeCamp, Jr.

Mediastinal masses represent a diverse collection of tumors arising from, and associated with, each of the organs found within the thorax. Cystic lesions account for up to 25 percent of reported mediastinal masses. These cysts may be congenital or acquired or may represent cystic degeneration of a previously solid tumor. In this chapter, we focus on congenital cystic lesions within the mediastinum, specifically addressing bronchopulmonary anomalies arising from the foregut. We briefly consider simple cysts arising from or associated with the thymus, pericardium, and thoracic duct. Many other solid mediastinal neoplasms (dermoids, teratomas, thymomas, parathyroid adenomas, and thyroid goiters) may present with cystic components. These lesions are discussed in other chapters.

ANATOMY

Cysts arise in each of the three distinct anatomic regions of the mediastinum (see Chapter 30).

The *anterosuperior compartment* extends from the manubrium and the first rib inferiorly to the diaphragm. The anterior border of this region is the posterior sternal table, and the posterior margin includes the pericardium and innominate vein. Endocrine lesions, such as thyroid goiters and cystic adenomas of the parathyroid gland, as well as thymic cysts, are found in this compartment.

The *middle mediastinum* is the site of origin of most bronchopulmonary foregut cysts. The boundaries of the middle mediastinum include the pericardial reflections superiorly and anteriorly and the diaphragm inferiorly. The posterior margin of the middle mediastinum is the anterior border of the spine. Pericardial cysts, as well as bronchogenic cysts, are found in this region.

The *posterior mediastinum* extends from the superior aspect of the first thoracic vertebral body inferiorly to the diaphragm. Its anterior border is the ventral aspect of the vertebral bodies, and it extends posteriorly to the articulation of the vertebral transverse process with each rib. The posterior mediastinum includes both costovertebral sulci and segmental nerve roots as well as the sympathetic chain. The structures

found within the posterior compartment include the esophagus, both vagus nerves, the thoracic duct and azygous vein, as well as the descending aorta. Neurenteric cysts, thoracic duct cysts, as well as some esophageal duplication cysts are found in this area. Lesions that arise primarily within the mediastinum may extend above the chest into the neck or below the diaphragm into the retroperitoneum, where they present as extrathoracic mass lesions.

EPIDEMIOLOGY

In reported series of mediastinal masses, the prevalence of primary cysts ranges from 10 to 25 percent and has remained steady for the past 6 decades (Table 90-1) with relatively similar incidences in males and females. Some minor heterogeneity over this time span is accounted for by variations in the ages of patients reported in each series. For example, the relatively low 9 percent incidence of cysts in one series from the 1970s reflects a predominance of adults in this series.

Table 90-1

Prevalence of Primary Cysts in Reported Series of Mediastinal Tumors over the Past 60 years

Year	*n*	Mediastinal Cysts (%)	Reference
1952	101	20	Sabiston & Scott*
1963	92	24	Heimberger et al.†
1972	209	9	Benjamin et al.‡
1987	400	25	Davis et al.§
1993	257	18	Azarow et al.#
1999	124	4	Whooley et al.¶
2003	806	13	Takeda et al.¶¶

* *Sabiston DC Jr, Scott HW Jr: Primary neoplasms and cysts of the mediastinum.* Ann Surg *136:777–797, 1952.*
† *Heimberger I, Battersby JS, Vellios F: Primary neoplasms of the mediastinum: A fifteen-year experience.* Arch Surg *86:978–984, 1963.*
‡ *Benjamin SP, McCormack LJ, Effler DB, et al.: Primary lymphatic tumors of the mediastinum.* Cancer *30:708–712, 1972.*
§ *Davis RD Jr, Oldham HN Jr, Sabiston DC Jr: Primary cysts and neoplasms of the mediastinum: Recent changes in clinical presentaion, methods of diagnosis, management and results.* Ann Thorac Surg *44:229–237, 1987.*
# *Azarow KS, Pearl RH, Zurcher R, et al.: Primary mediastinal masses: A comparison of adult and pediatric populations.* J Thorac Cardiovasc Surg *106:67–72, 1993.*
¶ *Whooley BP, Urschel JD, Antkowiak JG, et al. Primary tumors of the mediastinum.* J Surg Oncol *70:95–99, 1999*
¶¶ *Takeda S, Miyoshi S, Minami M, et al. Clinical spectrum of mediastinal cysts.* Chest *124:125–132, 2003.*

Table 90-2

Origin of Mediastinal Cysts

Cyst Type	All Ages ($n = 419$)	Pediatric Only ($n = 70$)
Bronchogenic	36%	53%
Enteric	12%	35%
Pericardial	29%	1%
Other	23%	11%

Fontenelle LJ, Armstrong RG, Stanford W, et al.: The asymptomatic mediastinal mass. Arch Surg. *102:98–102, 1971.*
Haller JA Jr., Mazur DO, Morgan WW Jr.: Diagnosis and management of mediastinal masses in children. J Thorac Cardiovasc Surg. *58:385–393, 1969.*
Heimburger IL, Battersby JS: Primary mediastinal tumors of childhood. J Thorac Cardiovasc Surg. *50:92–103, 1965.*
Massie RJ, Van Asperen PP, Mellis CM. A review of open biopsy for mediastinal masses. J Paediatr Child Health. *33:230–233, 1997.*
Pokorny WJ, Sherman JO. Mediastinal masses in infants and children. J Thorac Cardiovasc Surg. *68:869–875, 1974.*
Takeda S, Miyoshi S, Minami M, et al.: Clinical spectrum of mediastinal cysts. Chest. *124:125–132, 2003.*
Whittaker LD Jr., Lynn HB: Mediastinal tumors and cysts in the pediatric patient. Surg Clin North Am. *53:893–904, 1973.*
Whooley BP, Urschel JD, Antkowiak JG, et al.: Primary tumors of the mediastinum. J Surg Oncol. *70:95–99, 1999.*
Zambudio AR, Lanzas JT, Calvo MJ, et al.: Non-neoplastic mediastinal cysts. Eur J Cardiothorac Surg. *22:712–716, 2002.*

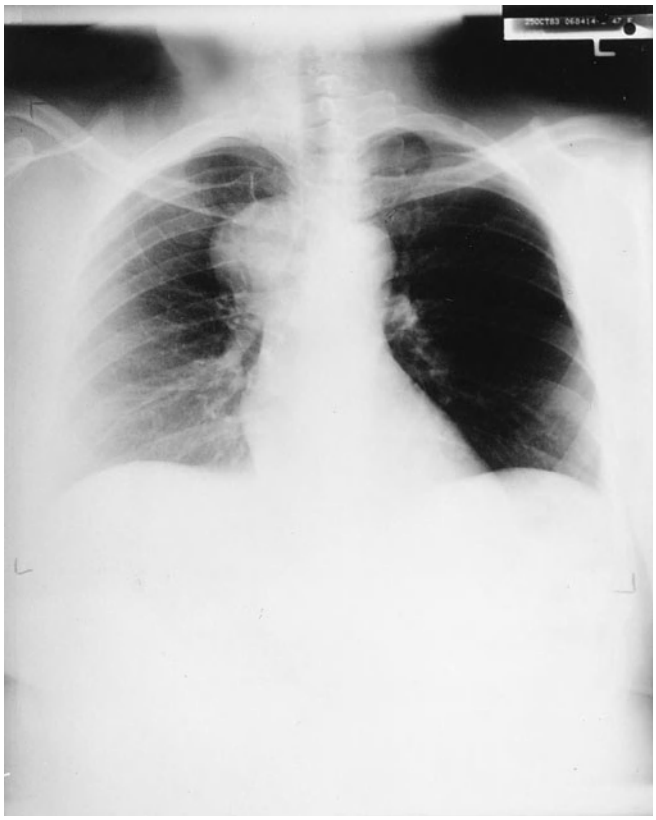
The etiology and distribution of cystic mediastinal masses are different in children and adults. Cysts of foregut origin account for only half of the lesions found in adults, whereas they constitute nearly 90 percent of cystic lesions reported in pediatric series (Table 90-2). Conversely, pericardial cysts account for up to one-third of all cystic lesions in adults, whereas true pericardial cysts are exceedingly rare in children. Among congenital lesions of the foregut and tracheobronchial tree seen in children—including pulmonary sequestrations, congenital lobar emphysema, cystic adenomatoid malformations, arteriovenous malformations, and bronchial atresias—simple foregut cysts (bronchogenic, enterogenous, and neurenteric) compose between 13 and 29 percent of reported cases.

Although the relative frequencies of cystic and solid mediastinal masses have remained fairly constant, the advent of cross-sectional imaging techniques, such as computed tomography (CT) and magnetic resonance imaging (MRI), has increased the detection of all mediastinal lesions.

BRONCHOGENIC CYSTS

Embryology and Terminology

The primitive foregut gives rise to a variety of aerodigestive organs and tissues, beginning with the pharynx and



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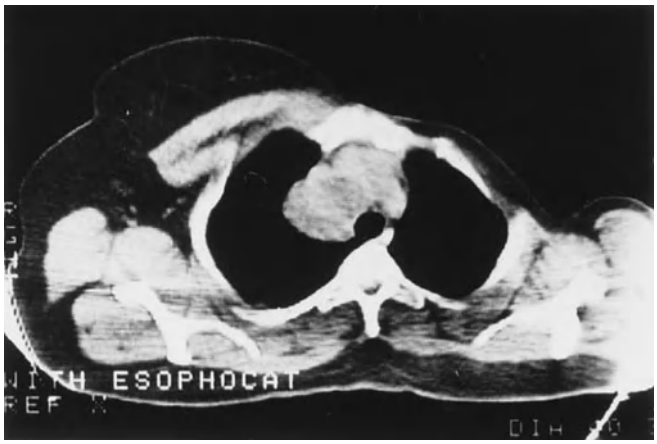

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Figure 90-1 *A.* Posteroanterior radiograph of a smooth-walled paratracheal bronchogenic cyst. *B.* Computed tomogram of the same paratracheal bronchogenic cyst. Note that the cyst contents are somewhat heterogeneous but generally of lower density than the surrounding mediastinal structures.

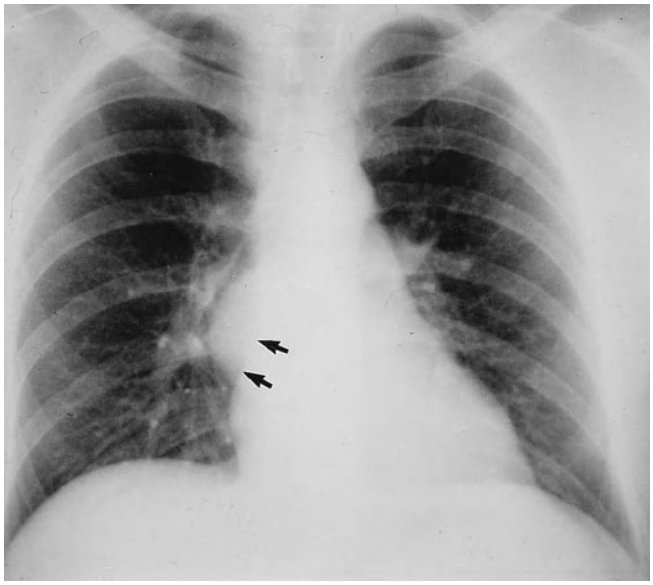
subsequently giving rise to the larynx, upper and lower respiratory tracts, esophagus, stomach, proximal duodenum, liver, pancreas, and associated ducts (see Chapter 5). Cystic malformations of foregut origin may have a variety of epithelial linings that reflect the embryological tissues from which they are derived. The lung bud develops caudally from the laryngotracheal tube, beginning in the fourth week of gestation. By the fifth week, the single bud has divided into right and left main bronchi, which grow into the surrounding splanchnic mesenchyme and are destined to become bronchial cartilage and smooth muscle as well as visceral pleura. Dichotomous branching of the primitive bronchi continues until about the 24th week, when the terminal bronchioles begin to give rise to primitive alveoli.

Throughout this period of embryogenesis, abnormal bronchi and bronchioles may form larger saccular structures, which are clinically recognized as bronchogenic cysts. Such saccular malformations may be invested by their own splanchnic mesenchyme (neopleura). Usually abutting on the trachea, carina, or hilum, they are termed *mediastinal bronchogenic cysts* (Figs. 90-1 and 90-2). Less frequently, these lesions are contained within the pulmonary parenchyma. Rarely do they maintain communication with the respiratory tract. Malformations within the lung are termed *intrapulmonary bronchogenic cysts* (Fig. 90-3). Some investigators believe that mediastinal bronchogenic cysts arise early in the cycle of bronchial branching, whereas intrapulmonary bronchogenic cysts represent derangements later in fetal development. Because they uniformly arise before alveoli form (at 28 weeks), bronchogenic cysts have no gas exchange potential even if their bronchial communications persist.

Presentation and Diagnosis

Most patients with bronchogenic cysts have symptoms at the time of diagnosis (Table 90-3). The pediatric population is predisposed to symptomatic cysts secondary to the smaller size of their thorax and more malleable airway. Eraklis and colleagues noted life-threatening respiratory compromise in 70 percent of infants with foregut cysts. Mass effects from the cysts, which caused compression, "ball valving," or differential ventilation, were the predominant causes of distress. These neonates were often cyanotic, with wheezing or stridor, and their radiographs demonstrated inhomogeneous aeration, lobar collapse, and/or mediastinal shift. In a series of nonneonatal children, up to 95 percent had symptoms. Especially in the older children, signs and symptoms of infection led the list of problems.

In adults, symptomatic bronchogenic cysts are less common. In the 1950s, a report of a large series indicated that symptoms were present in about one-third of patients. Most of the complaints were due to pain, cough, and dyspnea. More recent series have varied with 75 to 95 percent of patients without symptoms when the lesions were detected. Many patients who are followed without treatment develop subtle, local symptoms and/or signs of secondary infection. Symptoms of chronic infection such as fever and weight loss in the setting of a mediastinal mass on plain films can initially lead to the initial misdiagnosis of lymphoma.



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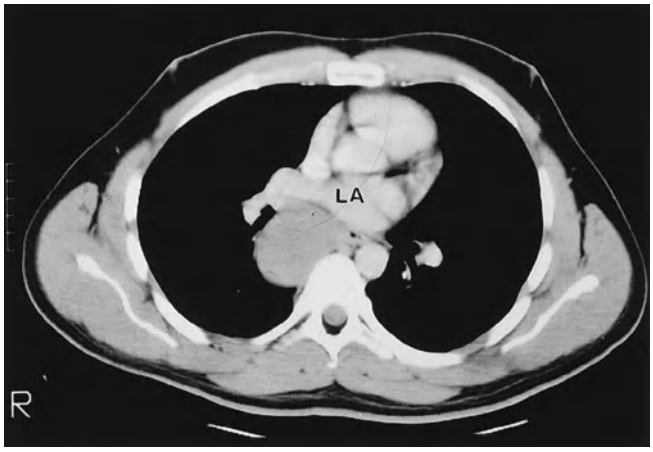

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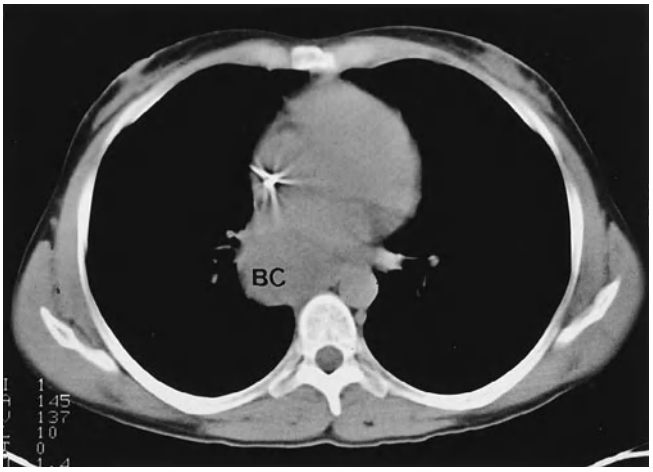
Figure 90-2 *A.* Posteroanterior radiograph of a smooth-walled subcarinal bronchogenic cyst. Note that the cyst is distinct from the right heart border (arrows). *B.* Contrast-enhanced axial CT image of the homogenous, subcarinal bronchogenic cyst. This patient presented with atrial dysrhythmia attributed to left atrial (LA) compression by the cyst. *(From DeCamp MM Jr, Swanson SJ, Sugarbaker DJ: The mediastinum, in Baue AE, Geha AS, Hammond GL, et al* (eds), Glenn's Thoracic and Cardiovascular Surgery, *6th ed. Stamford, CT, Appleton & Lange, 1996, pp 643–663.)*



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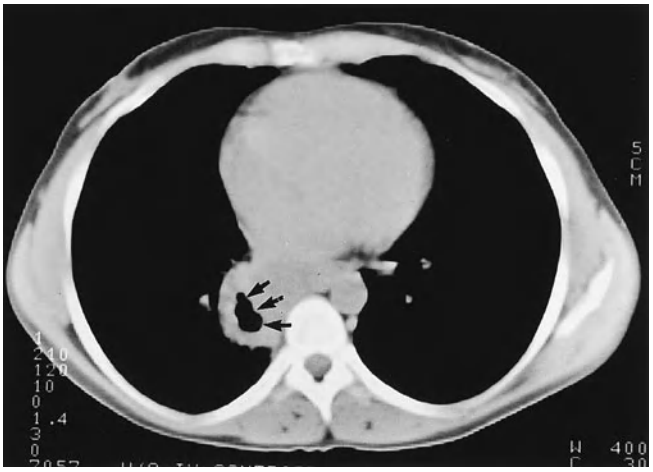

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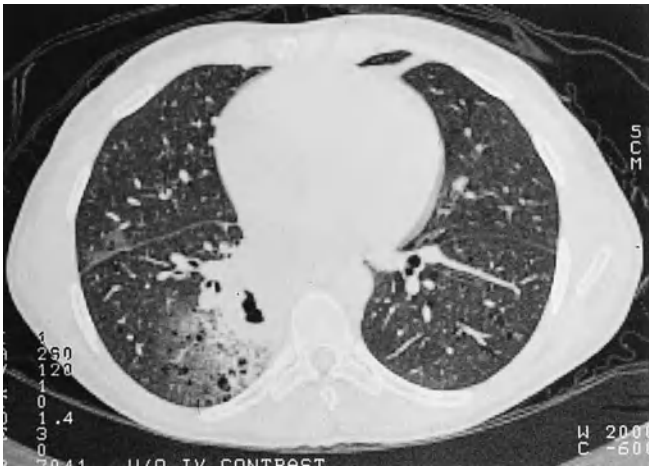

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Figure 90-3 *A.* Nonenhanced CT image of an asymptomatic bronchogenic cyst (BC). *B.* Nonenhanced CT image of the same cyst after 6 months of expectant management. The cyst has "cavitated" (arrows) indicative of secondary infection. *C.* Axial CT image with "lung windows" of the infected, intraparenchymal bronchogenic cyst. Note the associated right lower lobe pneumonitis surrounding the cyst, not appreciated by the "mediastinal" window in image *B.*

Table 90-3

Clinical Characteristics in Cysts in the Mediastinum (Symptoms and Signs)*

Characteristics	Bronchogenic, $n = 47$	Esophageal, $n = 4$	Thymic, $n = 30$	Pericardial, $n = 12$	Pleural, $n = 7$	Others, $n = 5$	Total, $n = 105$
Asymptomatic	28	3	18	10	6	2	67 (63.8)
Chest pain	6	0	6	2	0	1†	15 (14.3)
Dyspnea	3	1	3	0	1	0	8 (7.6)
Cough	5	0	2	0	0	0	7 (6.7)
Fever	5	0	1	0	0	0	6 (5.7)
Hoarseness	1	0	4	0	0	0	5 (4.8)
Sputum	3	0	0	0	0	0	3 (2.9)
Dysphagia	1	1	1	0	0	0	3 (2.9)
Cyanosis	0	0	0	0	1	0	1
Hemoptysis	1	0	0	0	0	0	1
Others	1	0	1	0	0	2‡	4

** Data are presented as No. or No. (%).*
† Chest pain associated with thoracic duct cyst.
‡ Neurofibromatosis associated with meningocele.
Reproduced with permission from Takeda S, Miyoshi S, Minami M, et al. Clinical spectrum of mediastinal cysts. Chest *124:125–132, 2003.*

The presence of a bronchogenic cyst is suggested by plain chest radiographs in up to two-thirds of cases in any age group. The usual appearance is that of a 2- to 10-cm ovoid, smooth, homogeneous mass that abuts on the mediastinum or hilum or splays the carina. An air-fluid level connotes either persistent bronchial communication or secondary infection of the cyst (Fig. 90-3). As mentioned, some cysts (especially in infants) may exert a mass effect, causing airway compression, parenchymal atelectasis, or cardiovascular compression (Fig. 90-2*B*). In 60 to 65 percent of patients, posteroanterior and lateral plain chest radiographs make it possible to diagnose these lesions and document their precise location.

Ultrasonography has been helpful in confirming the cystic nature of mediastinal lesions in infants and children. Prenatal diagnosis is also feasible. Such forewarning allows for the expeditious management of these infants antenataly or at the time of delivery, when most quickly develop symptoms after the lungs are inflated. In the adult, because air within the large lungs is a poor conductor of sound, surface ultrasonography has little to offer in the acoustic visualization of suspected bronchogenic cysts.

Cross-sectional imaging techniques, using either CT or MRI, have become the diagnostic procedures of choice for investigating mediastinal masses. These methods provide helpful details of cyst structure, including the density and type of cyst fluid, amount of calcium in the cyst wall, vascularity of the cyst, and the relationships of the cyst to adjacent mediastinal structures. MRI and CT are probably equally useful in the diagnosis of mediastinal-based cysts. CT is superior for the examination of intrapulmonary cysts because of its ability to delineate more sharply the cystic lesion from the surrounding air-filled parenchyma (Figs. 90-1 to 90-3). Characteristic findings on CT include the presence of a smooth, rounded mass with uniform attenuation and an indiscernible wall, while T2-weighted MR images will demonstrate high signal intensity.

Therapy

Bronchogenic cysts are the most commonly treated mediastinal foregut anomaly. They accounted for 60 percent of all mediastinal lesions reported by the Mayo Clinic over a 40-year period. The treatment options for bronchogenic cysts include observation, resection, and aspiration. One option for asymptomatic simple cystic lesions is continued observation (see below). All symptomatic lesions should be removed. Traditionally, a thoracotomy was necessary. Videothoracoscopy is being used with increasing frequency to resect mediastinal cysts with excellent results, low conversion rates to open procedure, and no significant increases in recurrence rates. Urschel and Horan have described piecemeal resection of a mediastinal bronchogenic cyst using a Carlens mediastinoscope introduced through a small suprasternal incision.

Treatment of asymptomatic cysts remains controversial. Some surgeons feel the benign nature and unknown natural history of asymptomatic simple cysts, combined with the availability of excellent imaging for observation obviates the need for mandatory surgical intervention. Conversely, two large clinics advocate resection for even asymptomatic lesions. They report a trend in time for asymptomatic patients to develop symptoms. Both reports document a higher incidence of perioperative complications when symptomatic lesions were resected, implying that waiting for symptoms to develop before resection places patients at increased operative risk.

Whatever the operative approach, the goal of surgery should be complete excision of all elements of the cyst. Occasional case reports of malignancy arising from the cyst mucosa

support the general concept of complete resection for any bronchogenic cyst. Partial resection of a bronchogenic cyst may occasionally be necessary if the cyst is found to be adherent to and inseparable from the membranous airway, main pulmonary vessels, or aorta. When subtotal excision is necessary, symptomatic recurrences requiring re-excision have been reported.

Aspiration of a cyst to confirm a benign diagnosis and instill a sclerosing agent (ethanol or bleomycin) has been used to manage some cysts. The advent of endobronchial ultrasonography with transbronchial intervention has resulted in an even less invasive management option. Reports of long-term follow-up for this approach to both the diagnosis and therapy of bronchogenic cysts are scant. However, it may represent a useful form of therapy for inoperable patients.

ENTEROGENOUS CYSTS

Embryology and Terminology

Enterogenous cysts are also termed *esophageal duplications*. They arise from the elongating esophagus, which separates from the respiratory tract in about the fifth week of gestation (see Chapter 5). As with most intestinal duplications, enterogenous cysts represent failure of normal recanalization during embryogenesis. Most esophageal duplications are of the closed and cystic type. Rarely are they tubular, and communication is preserved with the alimentary tract.

Presentation and Diagnosis

Nearly 75 percent of esophageal duplication cysts are recognized in childhood. For unclear reasons, there is a two-to-one predilection for cysts to be on the right side. Symptoms commonly include cough and dyspnea and occasionally stridor. These are clearly related to a mass effect by the cyst on the nearby respiratory tract. Dysphagia is surprisingly infrequent. In asymptomatic patients, the most common clue leading to this diagnosis is the coexistence of other gastrointestinal duplication(s). Unlike bronchogenic cysts, which are always lined with respiratory mucosa, enterogenous cysts may have a variety of epithelial linings, including the squamous epithelium native to the esophagus, or rarely aberrant pancreatic tissue. However, most esophageal duplications have a glandular epithelium with a subset that contains gastric mucosa containing parietal cells capable of acid secretion. The finding of an acid-secreting mucosa in 60 percent of patients with enterogenous cysts lends credence to other case reports of cyst hemorrhage and rupture.

Esophageal duplications usually present radiographically as smooth-walled, posterior mediastinal lesions at the base of the right hemithorax (Fig. 90-4*A*). A barium swallow demonstrates deviation of the lumen around the cyst, but rarely shows communication with it (Fig. 90-4*B*). Proximal esophageal dilatation is not common because the cysts usually are not obstructive. In patients with suspected duplication, a technetium pertechnetate nuclear scan may suggest the presence of ectopic gastric mucosa within the chest. Cross-sectional imaging (CT or MRI) is almost routinely employed to characterize the contents of a cyst and to define the relationship of the cyst to contiguous structures (Fig. 90-4*C*). The characteristic CT and MR findings are identical to those of bronchogenic cysts, except the wall may be thicker and in closer contact with the esophagus. Endoesophageal ultrasound has provided a useful, minimally invasive tool to investigate these lesions and allow sampling of cyst contents to confirm that the lesion, in an otherwise asymptomatic patient, is benign.

Therapy

As in the case of bronchogenic cysts, esophageal duplications are likely to become infected in time. The common occurrence of gastric mucosa within the enterogenous cyst predisposes to spontaneous hemorrhage and/or ulceration. Because of existing symptoms or the natural history of the cyst to become symptomatic, resection is recommended for all enterogenous cysts.

Such lesions can be approached through a standard thoracotomy or, at experienced centers, with the videothoracoscope. Despite the lack of communication with the esophageal lumen, cyst resection may leave defects in the esophageal wall that must be meticulously repaired. The esophagus should be closed primarily in layers, and the repair should be reinforced with a locally procured flap of vascularized tissue. Options for buttressing, such as esophageal repair, include the pericardial fat pad, pleura, intercostal muscle, the pericardium itself, or omentum. A case report documenting the occurrence of an adenocarcinoma in an esophageal duplication, which was carefully followed for a long time, underscores the need for resection of these lesions at the time of diagnosis.

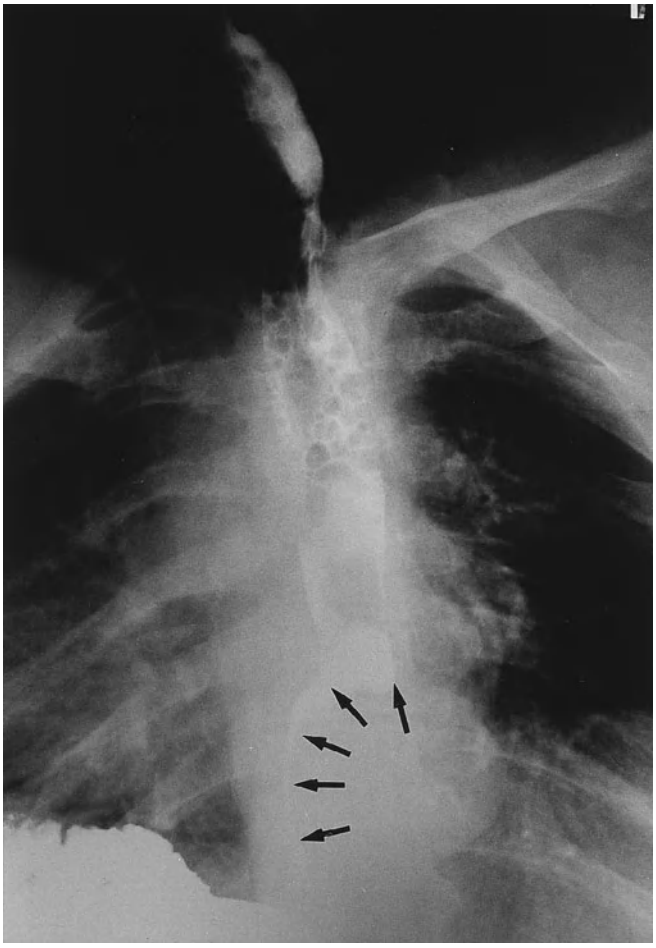
NEURENTERIC CYSTS

Embryology and Terminology

During the third week of normal embryogenesis, the notochord should separate from the primitive foregut (see Chapter 5). If this separation is incomplete, the mesodermal masses, which normally encircle the neural tube, cannot enclose it and vertebral anomalies arise. The attached foregut often spawns an associated mediastinal enteric cyst. The bony abnormalities may include butterfly vertebrae, hemivertebrae, and anterior spina bifida. When enterogenous cysts are found associated or contiguous with vertebral anomalies, the cyst is considered neurenteric.

Presentation and Diagnosis

Neurenteric cysts are exceedingly rare. Virtually all present in childhood. More than half of afflicted children have CNS complaints or findings. These include back pain, motor deficits of a lower extremity, and gait disturbance, especially



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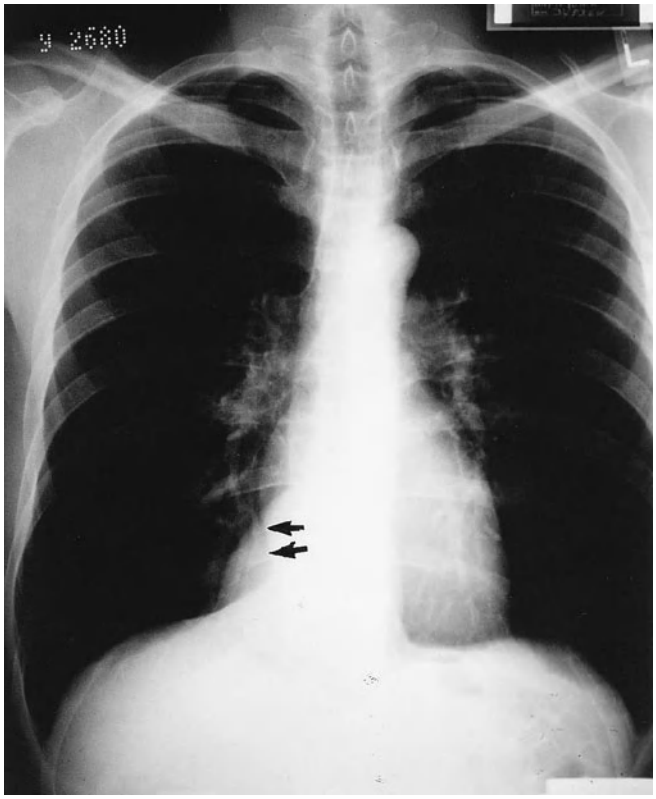

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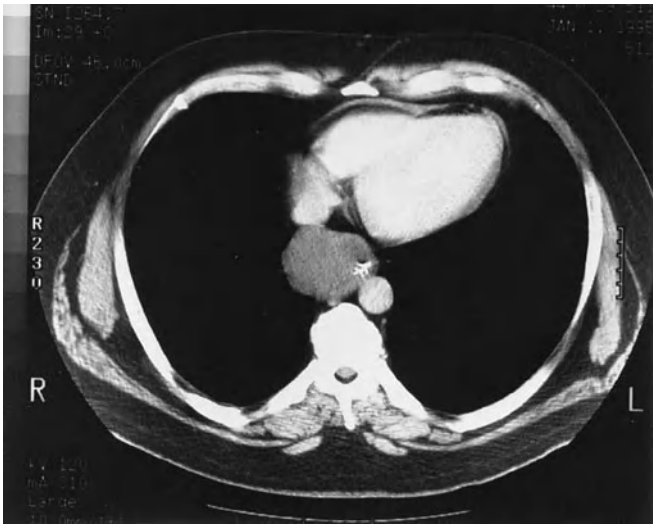


C

Figure 90-4 *A.* Frontal radiograph demonstrating smooth-walled posterior mediastinal mass consistent with an enterogenous cyst. The lesion is easily separable from the right heart border (arrows). *B.* Barium esophogram of the same patient demonstrating deviation of the true esophageal lumen around the smooth extramucosal lesion, found at resection to be an enterogenous cyst (esophageal duplication). *C.* Oral and intravenous contrast-enhanced CT image of the enterogenous cyst. The lesion is radiographically inseparable from the esophagus but free of all cardiac structures.

if there is communication with the spinal canal. Often the triad of a mediastinal mass, airway symptoms, and a vertebral anomaly is present. The diagnosis is usually made after detection of vertebral anomalies on the chest radiograph. CT can define the specifics of bony abnormalities and demonstrate extension of the cystic lesion into the spinal canal. This study must often be combined with the injection of intrathecal contrast in order to obtain a CT myelogram. MRI has recently supplanted CT myelography. Because of its ability to image in the axial, coronal, and sagittal planes and the availability of gadolinium as an enhancing agent, MRI provides a complete, noninvasive assessment of the bony abnormality,

the intraspinal extent of the cyst, and the degree of spinal cord or nerve root compression associated with a neurenteric cyst. Any suspected neurenteric cyst warrants an MRI evaluation of both the thoracic spine and posterior mediastinum.

Therapy

This form of congenital cyst accounts for only 5 to 10 percent of all foregut lesions. These cysts are consistently associated with some bony anomaly of the spine. The spectrum of vertebral anomalies extends from fused vertebrae to include butterfly or hemivertebrae. The vertebral abnormality is usually cephalad to the cystic lesion, since the esophagus descends (or the pharynx ascends) during fetal development. Careful imaging of suspected neurenteric cysts is paramount for successful extirpation. MRI is useful to exclude extension of the cystic component into a neural foramen or the spinal canal proper and to exclude an associated meningocele. Such findings would require a staged resection employing a posterior neurosurgical approach first, to decompress the cord or its nerve roots, followed by resection of the mediastinal component by standard thoracotomy or video-assisted technique.

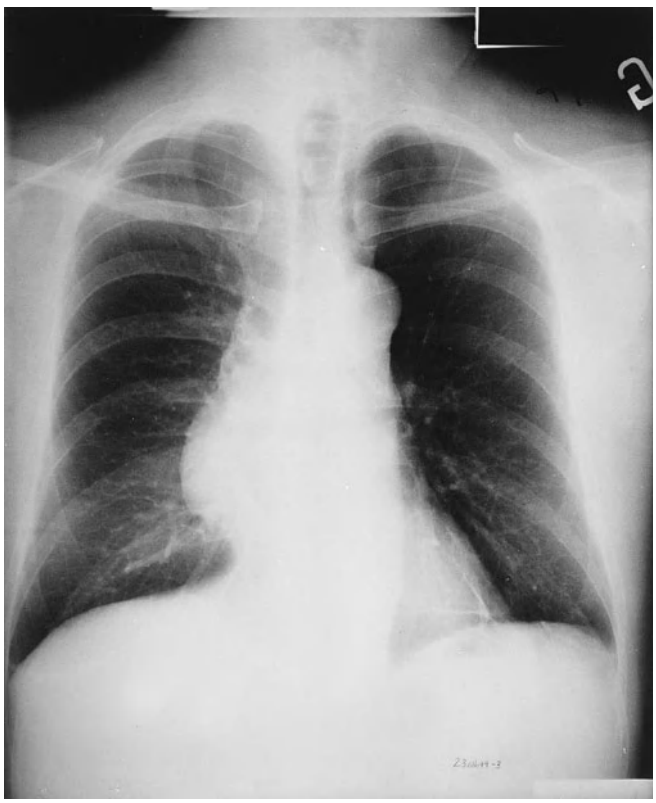
THYMIC CYSTS

The thymus is derived from the third pharyngeal pouch. Its development is incomplete at birth, and the gland continues to grow throughout childhood into adolescence. Cysts within the gland are thought to occur during adulthood, when gland architecture involutes and central cells degenerate and are replaced by fat.

Thymic cysts are rare congenital or acquired lesions embryologically derived from the pharyngeal pouches. Although thymic cysts are benign, they must be distinguished from thymomas, germ cell tumors, and lymphomas—all of which may have areas of cystic degeneration. These cysts arise in the anterior mediastinum (Fig. 90-5) and may extend to the middle mediastinal compartment, especially in the aortopulmonary window (Fig. 90-6). Plain radiographs do not differentiate thymic cysts from other nonlobulated thymic masses, therefore CT and MRI are employed for diagnosis. Both CT and MRI demonstrate clear tissue plains separating the cyst from other vital structures (Figs. 90-5 and 90-6). In older people, benign cysts may degenerate and present as a complex, thickened cystic mass with calcified walls that contain heterogeneous fluid (Fig. 90-5). Such lesions are easily confused with a mediastinal teratoma. Excision using an open or video-assisted technique excludes other, more worrisome histologies and is curative.

PERICARDIAL CYSTS

Pericardial cysts are exceedingly rare in children, suggesting that they may be acquired. However, their common position



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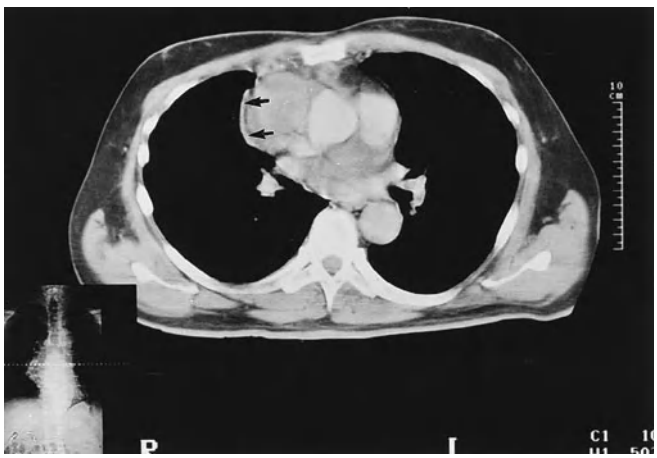

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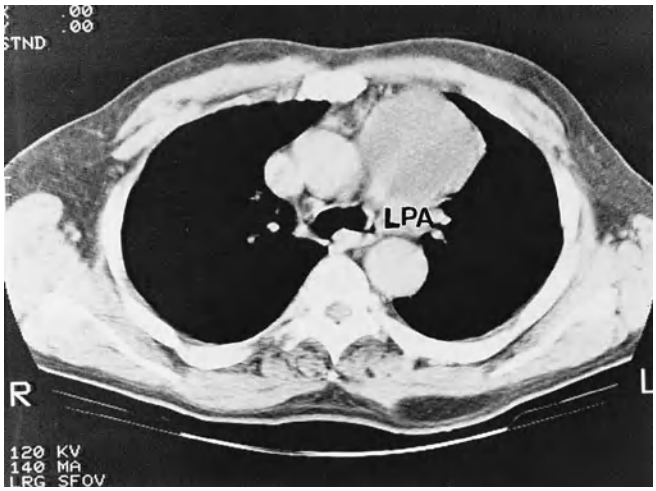
Figure 90-5 *A.* Frontal radiograph of an anterior mediastinal mass inseparable from the right heart border. *B.* Axial CT image of this mass demonstrates its thick, focally calcified (arrows) wall containing homogenous nonenhancing fluid. At resection what was feared to be a teratoma was found to be a thymic cyst. (*From DeCamp MM Jr, Swanson SJ, Sugarbaker DJ: The mediastinum,* in Baue AE, Geha AS, Hammond GL, et al. (eds), Glenn's Thoracic and Cardiovascular Surgery, *6th ed. Stamford, CT, Appleton & Lange, 1966, pp 643–663.*)



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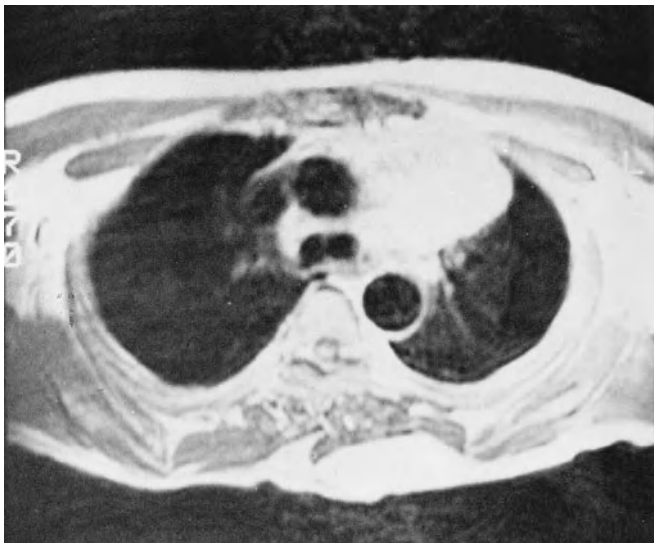

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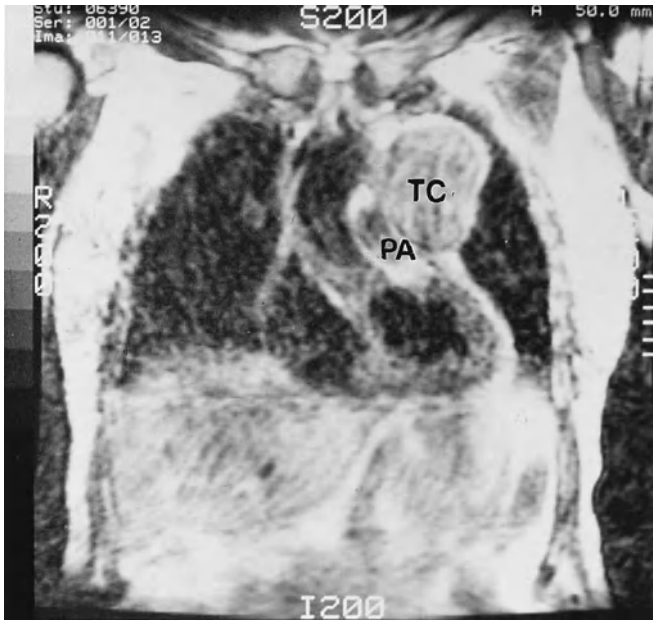

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Figure 90-6 Equivalent axial-enhanced CT (*A*) and axial MRI (*B*) images of an aortopulmonary window mass that appears to compress if not invade the left pulmonary artery (LPA). Coronal MR image (C) of the same lesion demonstrating an intact tissue plane separating the benign thymic cyst (TC) from the pulmonary artery (PA).

at or near the cardiophrenic angles suggests a possible embryological defect, whereby fusion of the pleuropericardial membranes and the septum transversum of the developing diaphragm is incomplete.

Pericardial cysts are simple, smooth-walled cystic lesions (Fig. 90-7) that are commonly located at the lateral basal edge of the pericardium, where it fuses with the diaphragm. They can be mistaken for foramen of Morgagni hernias or prominent pericardial fat pads. They can be differentiated from more solid mediastinal tumors by CT scanning with a computer analysis of the radiographic density of cyst fluid. Pericardial cysts characteristically contain clear, low-density serous fluid; hence their synonym, "spring water cysts." They have no malignant potential and, after aspiration has confirmed the diagnosis, can be followed clinically. Resection should be reserved for cysts that cause symptoms (hemodynamic compromise, arrhythmia, atelectasis) or for change in radiographic appearance over time. The operative approach, whether endoscopic or open is dependent upon the location, size, and proximity of the cyst to vital structures. Because a cyst often overlies a phrenic nerve, an unroofing procedure or subtotal resection is acceptable therapy if total excision would jeopardize diaphragmatic function. Rarely do pericardial cysts erode into vital structures. Such cases suggest secondary infection of the cyst and may require circulatory support for safe extirpation.

THORACIC DUCT CYSTS

Lymphatic channels develop from the lateral plate mesoderm, either as outgrowths of the venous system or by the fusion of mesenchymal clefts into vessels. The lymphatic sacs that

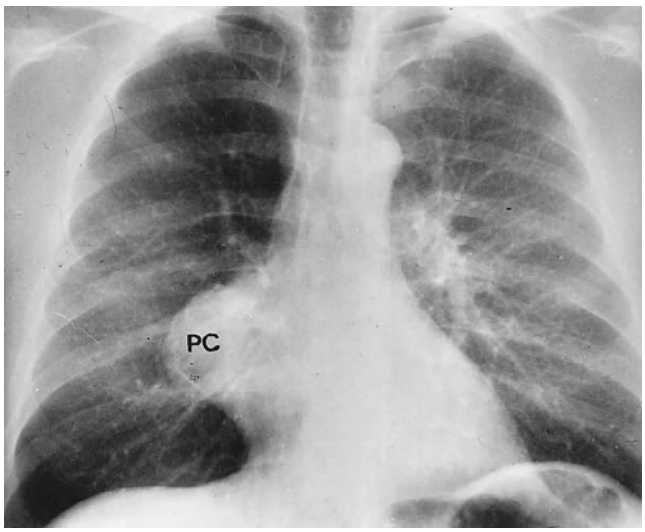

Figure 90-7 Frontal radiograph of a mediastinal mass, isodense with and inseparable from the right heart border. Thoracoscopy showed this to be a broadly based pericardial cyst (PC).

develop by the second month of gestation, are connected by these primitive lymphatic channels. It is these channels that unite the jugular lymph sacs to the cisterna chyli, which form the thoracic duct. A congenital weakening of the thoracic duct wall is postulated to be responsible for some thoracic duct cysts. Their incidence is exceedingly rare (fewer than 40 cases reported) and histologically they are similar to the thoracic duct with the presence of occasional endothelial cells lining the cyst, occurring anywhere along the course of the duct. Symptoms arise from compression of adjacent structures resulting in dyspnea, cough, or dysphagia. Plain films may demonstrate a posterior mediastinal mass, with CT demonstrating a smooth, homogenous cystic mass (Fig. 90-8). MRI is superior to CT for evaluation, allowing for superior delineation of the cyst boundaries (Fig. 90-9). Confirmatory

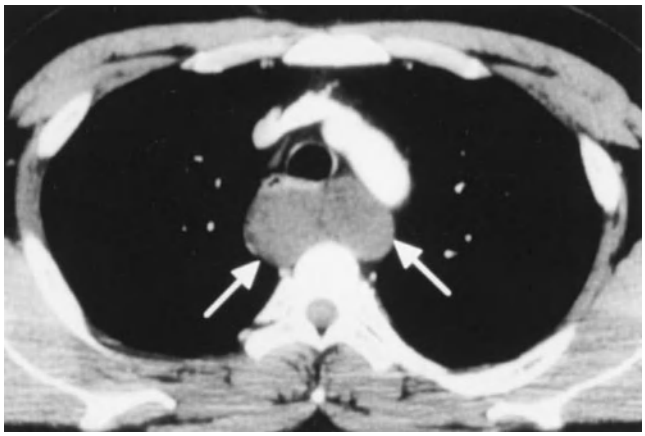

Figure 90-8 Axial contrast-enhanced CT scan of the chest revealed a large cystic mass measuring 3 × 5 × 15 cm (arrow) in the posterior mediastinum, displacing the esophagus and trachea anteriorly. *(From Chen F, Bando T, Hanaoka N, et al.: Mediastinal thoracic duct cyst.* Chest *115:584–584, 1999.)*

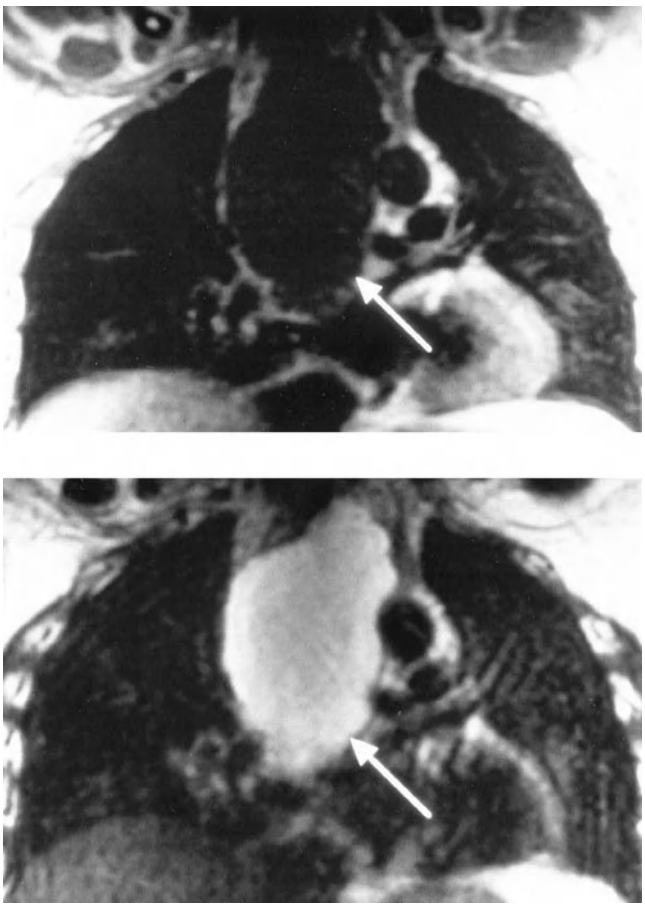

Figure 90-9 MRI scan. *Top:* coronal T1-weighted imaging showing a low-intensity mass with a well-circumscribed margin (arrow). *Bottom:* coronal T2-weighted imaging showed a high-intensity mass (arrow). (*From Chen F, Bando T, Hanaoka N, et al.: Mediastinal thoracic duct cyst.* Chest *115:584–584, 1999.)*

diagnosis may be made using lymphangiography or the presence of high triglyceride content in cyst aspiration fluid, but these techniques are not commonly employed. Small cysts are generally followed, whereas symptomatic and larger cysts are excised with care taken to ligate all communication with the thoracic duct to avoid postoperative chylothorax.

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91

Acquired Lesions of the Mediastinum: Benign and Malignant

John R. Roberts • Larry R. Kaiser

SUPERIOR VENA CAVA SYNDROME

Lesions that originate in the mediastinum are rare compared to the diverse lesions that can involve the mediastinum secondarily. Although neoplasms of the mediastinum are diverse, they have in common a single clinical manifestation: widening of the mediastinum on the chest radiograph taken in the upright position. This shared feature has not lent itself readily to differential diagnosis. In recent years, however, the advent of computed tomography (CT) and magnetic resonance imaging (MRI) has greatly enhanced the evaluation and subsequent treatment of these lesions.

The mediastinum extends from the thoracic inlet to the diaphragm superoinferiorly and from pleural space to pleural space (Fig. 91-1). Contained within it are heart, aorta, brachiocephalic vein, esophagus, tracheobronchial tree, and

This chapter has been slightly modified from the version that appeared in the third edition of *Fishman's Pulmonary Diseases and Disorders.*

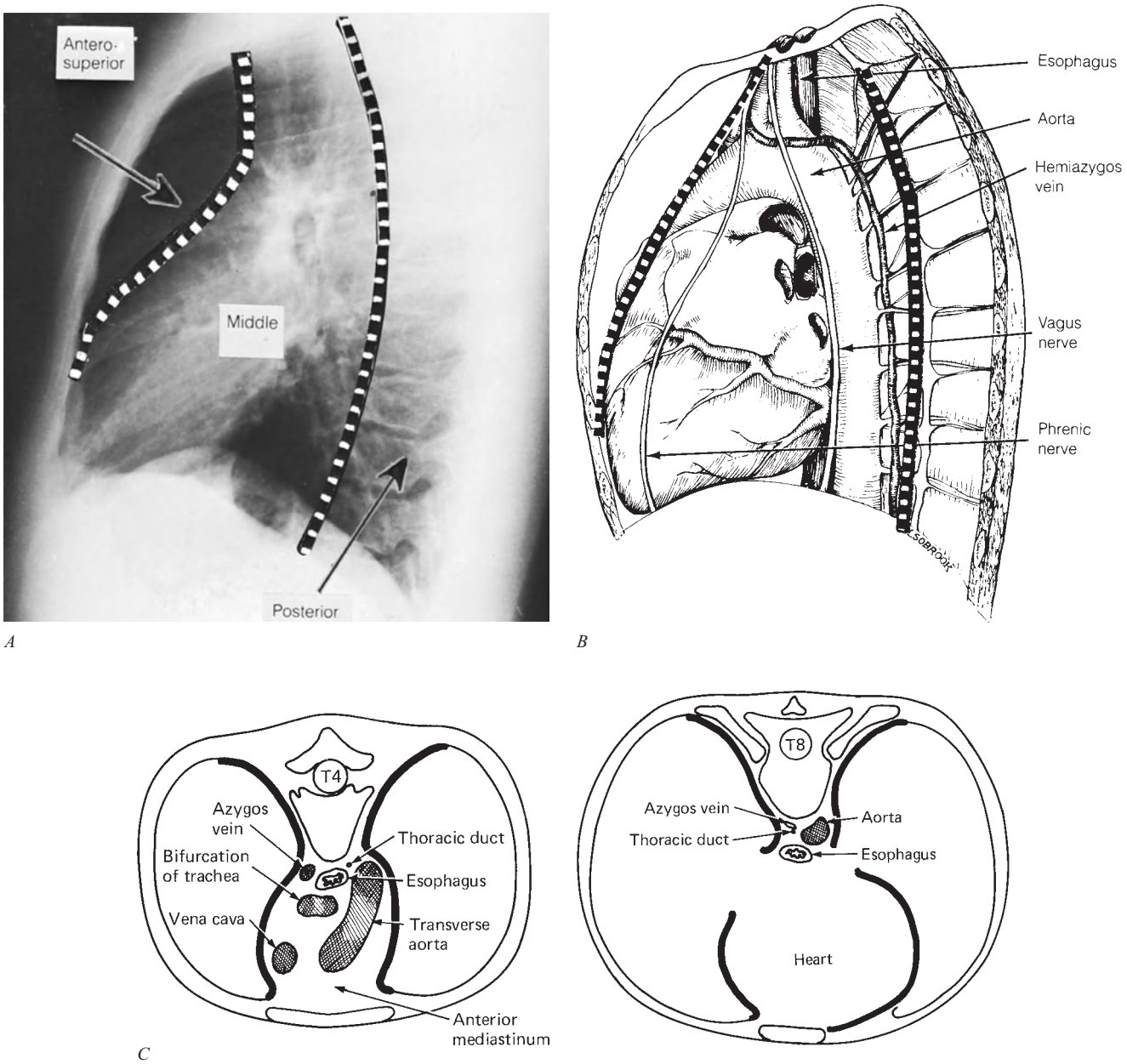


Figure 91-1 Compartments of the mediastinum. *A*. Lateral radiograph of chest. *B*. Schematic representation of the contents of the three mediastinal compartments. *C*. Cross sections of the thorax at T4 (left) and T8 (right) to show relative positions of mediastinal structures. *(Based on the data of Lyerly and Sabiston, Primary neoplasms and cysts of the mediastinum, in Fishman J (ed)* Pulmonary Diseases and Disorders, 2d ed. *New York, McGraw-Hill, 1988.)*

elements of the autonomic nervous and lymphatic systems. Further, various endocrine organs may project into it, distant malignancies may metastasize to it, and infectious processes can manifest themselves within it.

This chapter focuses on lesions that either originate in the mediastinum or represent disease processes of the mediastinum.

HISTORY

The history of the diseases of the mediastinum derives mostly from the impact of study of three specific entities—substernal goiters, ectopic parathyroid glands, and myasthenia gravis. Substernal extension of goiters into the mediastinum was first described in the middle of the eighteenth century. Billroth described resection of goiters in 1869. Kocher subsequently reported 1000 thyroidectomies and he described techniques for removing substernal goiters. Churchill first described recognition of ectopic mediastinal parathyroid glands, and Creswell and Wells subsequently reported a series of more than 6000 patients who underwent parathyroidectomy. Two percent of those patients required sternotomy for resection of a parathyroid gland in the mediastinum.

Early knowledge of myasthenia gravis also developed largely from the work of German clinicians, who described

the symptom triad of ptosis, dysarthria, and weakness in the late 1800s. Jolly unified these findings and coined the term *myasthenia gravis pseudoparalytica* in 1885. Laquer and Weigert connected the manifestations of myasthenia gravis to thymic disease in 1901. Not until 1974, however, were the autoimmune aspects of the disease clarified when Almon and colleagues described serum antibodies to the acetylcholine receptor.

Blalock performed the first thymic resection via median sternotomy at Johns Hopkins Hospital in 1936. In 1944, Blalock reported a series of 20 patients who had undergone thymic resection and advocated thymectomy for patients with myasthenia gravis. This approach has an appreciable mortality, however, so a transcervical approach for patients with nonthymomatous myasthenia gravis is now preferred in some clinics.

MEDIASTINAL COMPARTMENTS

The mediastinum has been variably described by different authors. As shown in Fig. 91-1, the simplest system divides the mediastinum into three compartments: anterosuperior, visceral (or middle), and paravertebral (or posterior).

Anterosuperior Compartment

This compartment extends from the manubrium and the first ribs to the diaphragm. Its posterior border is defined by the anterior aspect of the pericardium inferiorly and curves posteriorly to include the arch of the aorta and great vessels. Structures contained within it include the ascending aorta, superior vena cava, azygous vein, thymus gland, lymph nodes, fat, connective tissue, transverse aorta, and great vessels (Table 91-1). Common major lesions contained within the anterosuperior mediastinal compartment are thymomas, lymphomas, and germ cell tumors (Table 91-1; Fig. 91-2). Less common lesions are tumors of mesenchymal origin, vascular lesions, and displaced thyroid or parathyroid glands.

Middle Compartment

The middle compartment is also called the visceral compartment (Fig. 91-1). The superior pericardial reflection defines the superior border, whereas the diaphragm defines the inferior border. The posterior border extends to the spine. Contained within this compartment are the heart and pericardium, trachea and major bronchi, pulmonary vessels, lymph nodes, fat, and connective tissue (Table 91-1). Lesions contained within the visceral compartment include cysts of the foregut, primary and secondary tumors of the lymph nodes, and, less commonly, pleural, pericardial, neuroenteric, and gastroenteric cysts (Table 91-1, Fig. 91-2).

Posterior Compartment

The posterior compartment is also called the paravertebral compartment. It extends from the superior aspect of the first

Table 91-1

Structures and Lesions in the Three Compartments of the Mediastinum

Structures	Common Lesions	Rare Lesions
Anterosuperior compartment		
Ascending aorta	Thymomas	Vascular lesions
Superior vena cava	Lymphomas	Mesenchymal tumors
Azygous vein	Germ cell tumors	Endocrine tumors
Thymus gland		
Lymph nodes		
Transverse and great vessels		
Connective tissue		
Middle compartment		
Heart and pericardium	Foregut cysts	Pleural and pericardial cysts
Trachea and bronchi	Lymphatic tumors	Neuroenteric and gastroenteric cysts
Pulmonary vessels		
Connective tissue		
Posterior compartment		
Sympathetic chain	Tumars of neurogenic origin	Vascular tumors
Vagus nerves		Mesenchymal tumors
Esophagus		Lymphatic lesions
Thoracic duct		
Lymph nodes		
Descending aorta		

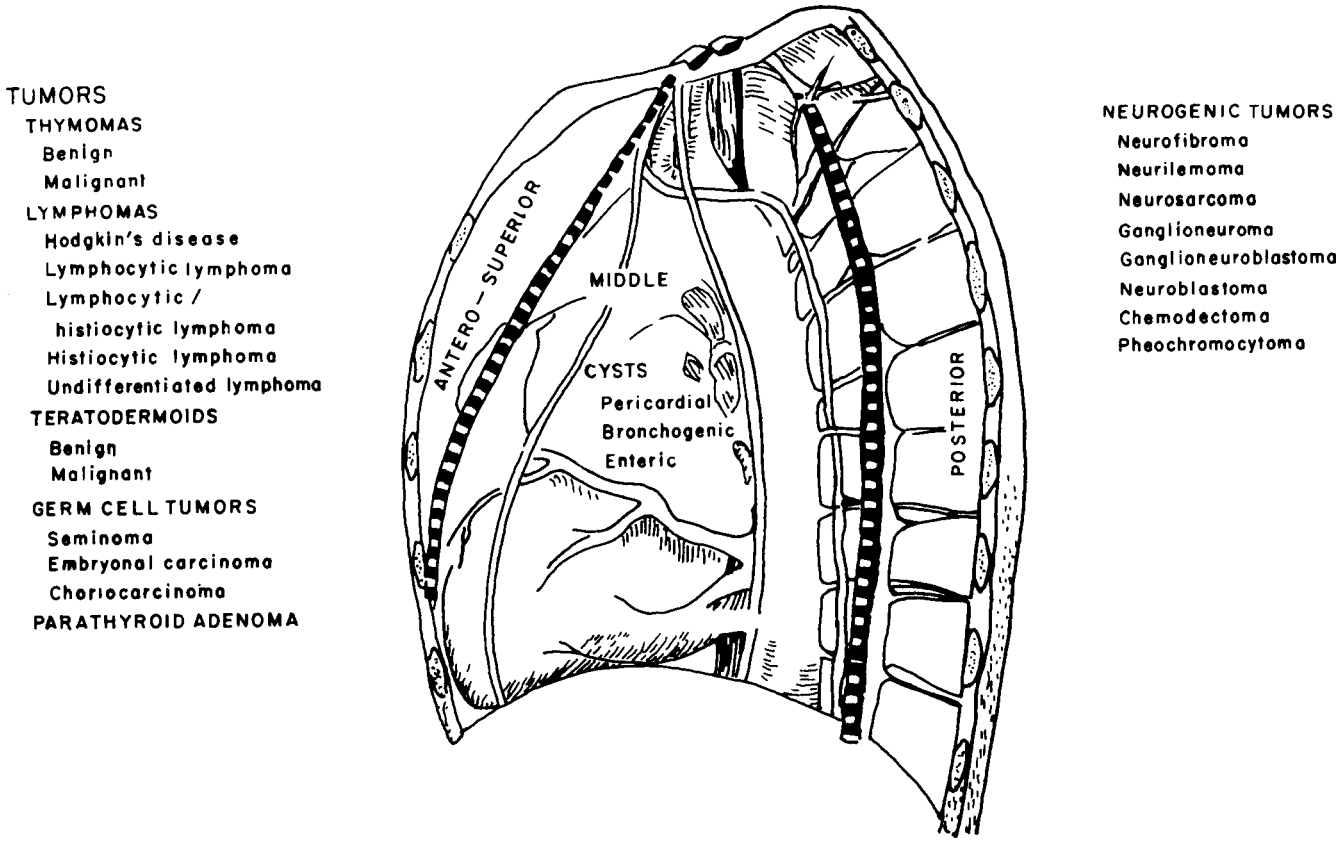


Figure 91-2 Most common location of specific neoplasms and cysts within the subdivisions of the mediastinum.

thoracic vertebral body to the diaphragm anteriorly and then posteriorly to the posterior-most curvature of the ribs (Fig. 91-1). Contained within it are the sympathetic chain, vagus nerves, esophagus, thoracic duct, various lymph nodes, and the descending aorta. Lesions contained within it are primarily tumors of neurogenic origin. Less common is a potpourri of lesions, including vascular tumors, mesenchymal tumors, and lymphatic lesions (Table 91-1; Fig. 91-2).

EPIDEMIOLOGY AND INCIDENCE

The mix of mediastinal lesions in adults has changed considerably during the past 5 decades: As may be seen in Table 91-2, significant changes have occurred in the proportions of thymoma and lymphoma, whereas the proportions of other lesions have remained relatively stable. Sabiston and Scott examined patients with 101 primary cysts and neoplasms of the mediastinum presenting at Johns Hopkins Hospital from July 1933 to July 1951. Heimberger and coworkers described 92 mediastinal lesions over a 15-year period. Benjamin and colleagues described a series of 209 patients in 1972, Davis and coworkers a series of 400 patients in 1986, Cohen and associates a series of 230 patients in 1991, and Azanow's team a series of 257 patients in 1993. Results of the six series presented in Table 91-2 show a relative increase in the proportion of lymphomas and relative stability in the proportion of neurogenic tumors, cysts, and thymomas. The reason for the increased incidence of lymphomas is unclear.

Great differences exist between children and adults with respect to the location of mediastinal lesions. In adults, 65 percent of the lesions arise in the anterosuperior, 10 percent in the middle, and 25 percent in the posterior compartments. This distribution is reversed in children, in whom 28 percent of lesions arise in the anterosuperior, 10 percent in the middle, and 62 percent in the posterior compartments. In general, the incidence of posterior lesions is higher in children, whereas anterior lesions predominate in adults.

SIGNS AND SYMPTOMS

Approximately half of all mediastinal lesions are asymptomatic and are detected on chest radiographs taken for unrelated reasons. The absence of symptoms suggests that a lesion is benign, whereas the presence of symptoms suggests malignancy. The percentage of patients with symptoms from mediastinal masses closely parallels, or equals, the percentage of malignant lesions (Table 91-2). In adults, 48 to 62 percent of lesions are symptomatic, whereas the percentage of symptomatic lesions is higher in children—58 to 78 percent. Since the incidence of symptoms parallels the incidence

Table 91-2

Histology of Mediastinal Masses as Reported over Five Decades

Histology *n*	Sabiston and Scott (1952) 101	Heimberger et al. (1963) 92	Benjamin et al. (1972) 209	Davis (1987) 400	Cohen et al. (1991) 230
	Frequency, % of Total				
Cysts	17	24	9	25	20
Neurogenic	20	21	23	14	17
Thymic	17	10	16	17	24
Lymphoma	11	9	15	15	16
Germ cell	9	10	13	10	10
Mesenchymal	1	4	11	6	7
Endocrine	2	8	11	3	2
Other	23	14	2	10	4

of malignancy, a child with a mediastinal mass is considerably more likely to have a malignancy than is an adult with a mediastinal mass.

The most common symptoms are cardiorespiratory—in particular, chest pain and cough. Other manifestations are heaviness in the chest, dysphagia, dyspnea, hemoptysis, signs of superior vena caval obstruction with facial swelling, and cyanosis (Table 91-3). Recurrent respiratory infections are a common complaint. As is discussed in the following in greater detail, several mediastinal lesions are associated with other clinical syndromes—thymoma with myasthenia gravis, red-cell aplasia, hypogammaglobulinemia, and nonthymic cancers; Hodgkin's disease with recurrent fevers; and von Recklinghausen's disease with neurofibromas.

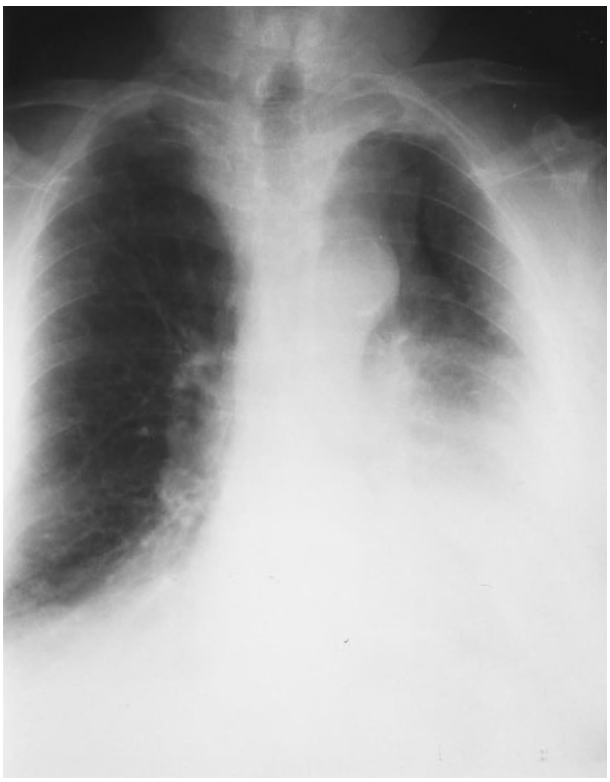
Table 91-3

Common Symptoms and Their Mechanisms in Patients with Mediastinal Lesions

Symptom	Mechanism
Cough	Airway narrowing, compression
Chest pain	Chest wall invasion, neural invasion
Dyspnea	Airway compromise, pericardial tamponade, pleural effusions, pulmonary stenosis, congestive heart failure
Hemoptysis	Bronchogenic carcinoma, airway invasion, pulmonary stenosis, congestive heart failure
Dysphagia	Esophageal narrowing/obstruction, esophageal motor dysfunction
Hoarseness	Vocal cord paralysis
Facial swelling	Superior vena cava syndrome

INVESTIGATION OF MEDIASTINAL MASSES

Mediastinal masses commonly present on routine chest radiographs obtained for other purposes. History and physical examination are occasionally useful in diagnosis, especially in patients with one of the rarer symptoms (e.g., hoarseness and Horner's syndrome). The age of the patient can also narrow diagnostic possibilities. However, the chest radiograph remains the most important lead to diagnosis, followed by CT of the chest. The latter has revolutionized the diagnosis and evaluation of mediastinal masses and should be part of the routine workup of a mediastinal mass. In contrast to



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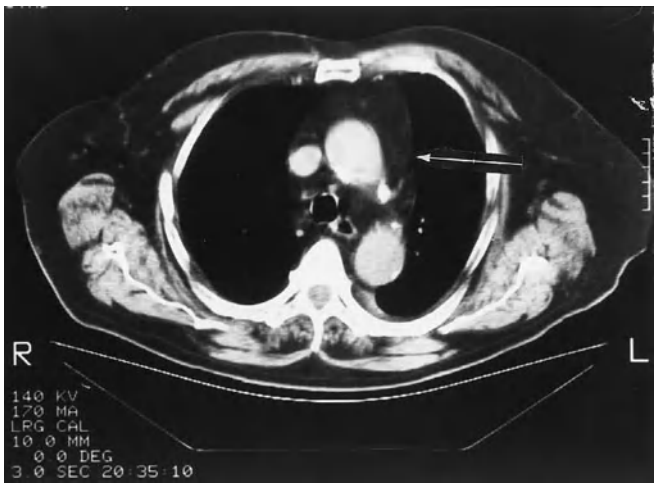

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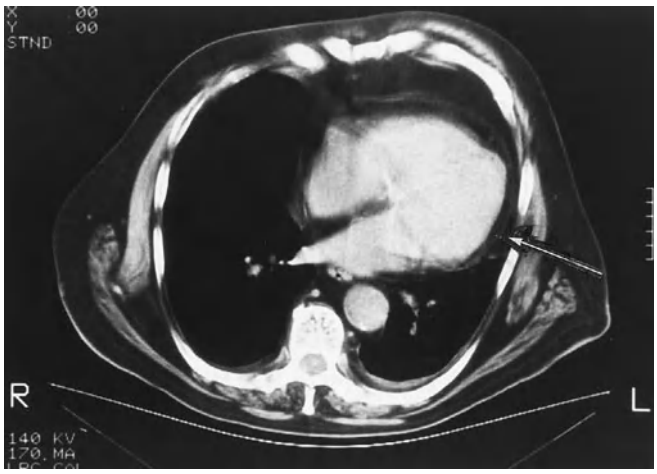

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Figure 91-3 Mediastinal lipomatosis. *A*. PA radiograph of an 82-year-old woman with urinary incontinence and bladder infection. Chest radiograph shows a widened mediastinum with apparent pleural collection. *B*. Chest CT at level of aortic arch showing normal mediastinum except for diffuse fatty infiltration (arrow). *C*. Chest CT at the level of the heart demonstrating cardiomegaly and mediastinal fatty infiltration (arrow).

CT, standard tomography offers little beyond that afforded by chest radiographs and is rarely indicated.

Noninvasive Diagnostic Procedures

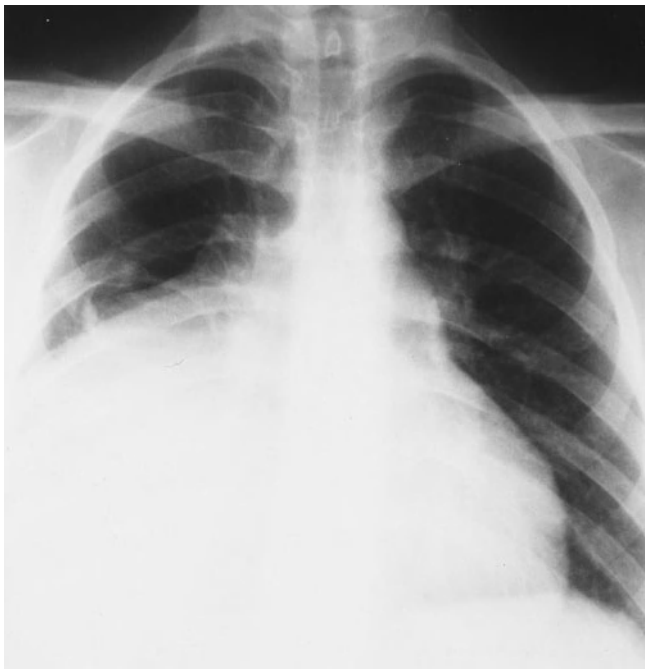
Computed Tomography

As noted, chest CT should be routine for all suspected or confirmed mediastinal masses. Although CT is poor with respect to distinguishing between cystic and solid structures, it provides excellent examination of the mediastinum. Indeed, the diagnosis of certain lesions—such as aortic aneurysms, mediastinal lipomatosis, and pericardial fat pads—is so straightforward with CT that further search or biopsy is not necessary (Fig. 91-3). CT scanning is the most common technique used to obtain fine-needle aspiration (FNA) biopsies and provide information about invasion. Additionally, if biopsy or resection is indicated, CT can assist in the selection of the surgical approach (left chest, right chest, mediastinoscopy, or median sternotomy). Finally, chest CT may aid in the use of anesthesia.

Magnetic Resonance Imaging

MRI is superior to CT imaging in three specific circumstances: when preoperative determination of a tumor's invasion of vascular or neural structures is crucial, when coronal or radial body sections are necessary, and when contrast material cannot be given intravenously because of renal disease or known allergy to contrast (Fig. 91-4). Gadolinium can be used to provide additional vascular contrast with MRI but is generally unnecessary because the high inherent contrast between mediastinal masses and cardiovascular structures generally suffices to define those masses. For lesions below the aortic arch, electrocardiographic gating can improve image quality. The ability to perform T_1- and T_2-weighted images allows discrimination of mediastinal masses from mediastinal fat on T_1-weighted images and from the heart and chest wall on T_2-weighted images. The use of the combination of these sequences can usually clearly delineate mediastinal masses from surrounding soft tissues. Finally, all neoplasms have higher T_1 and T_2 values than inflammatory lesions, with bronchogenic carcinoma generating the greatest T_1 and T_2 values. The difference between T_1 and T_2 values for bronchogenic carcinoma and chronic inflammatory processes has been shown to be highly significant ($p < 0.001$).

For lesions close to the thoracic inlet, MRI is probably better than CT at identifying invasion of the brachial plexus and vertebral foramina. Similarly, MRI can clarify lesions at



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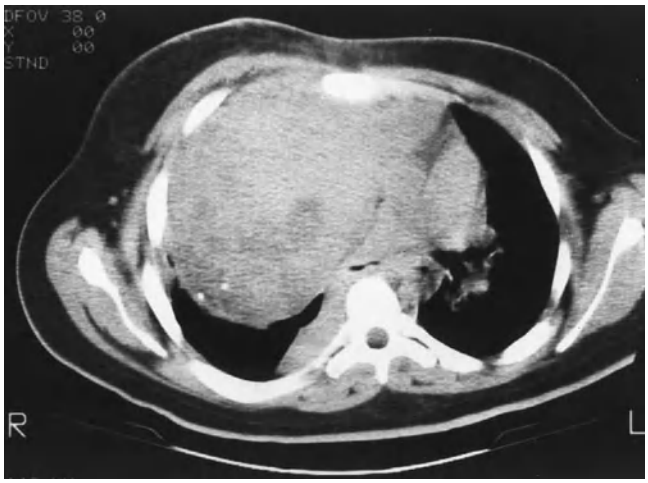

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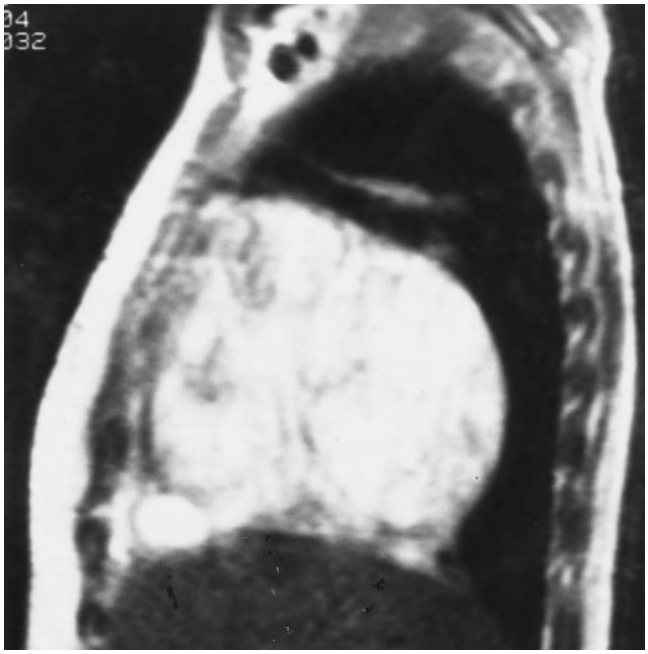


C

Figure 91-4 Comparison of CT and MRI in evaluation of mediastinal masses. Nineteen-year-old man with a 1-month history of fever, heaviness in the chest, and cough. Examination revealed a tall, very thin man with dystrophic testes (habitus consistent with Klinefelter's syndrome). Serum AFP was 32,000 and βHCG was 25,000. *A*. PA radiograph of the chest reveals large mediastinal mass projecting into right hemithorax. *B*. CT at the level of the diaphragm demonstrates an inhomogeneous mass. Diaphragmatic invasion could not be assessed. *C*. Sagittal MRI view demonstrates the mass apparently contained by the diaphragm (arrows). Biopsy demonstrated embryonal cell carcinoma. This patient received high-dose cisplatin, vinblastine, and bleomycin, with resultant regression of tumor and normalization of serum markers. Subsequent resection revealed a mature teratoma.

the inferior aspect of the mediastinum that invade the diaphragm (Fig. 91-4). It is the method of choice for evaluation of neurogenic lesions, vascular anomalies, and anomalies of the aortic arch. However, MRI also has some disadvantages: longer times for acquisition of data, greater expense, and unavailability at some institutions. Also, patients are less likely to comply with MRI because of claustrophobia and difficulties inherent in lying still for longer periods.

Ultrasonography

Ultrasonography is used in some clinics to determine the nature of the mediastinal mass, particularly whether it is cystic or solid; in other clinics, it is used to direct fine-needle biopsies. Although the value of ultrasound in differentiating cystic and solid masses is recognized, the use of ultrasound has probably been supplanted in most institutions by CT, MRI, and radionuclide scintigraphy. It is particularly useful in evaluating masses in children because lying still is not as critical. Additionally, endoscopic ultrasound is increasingly useful in evaluating lesions of the esophagus and various periesophageal structures.

Radionuclides

Several radionuclide agents are useful in evaluating mediastinal masses (Table 91-4). Thyroid scintigraphy with ^{131}I or ^{123}I may be helpful in patients with obscure substernal anterosuperior compartment lesions. Although reports in the surgical literature generally find thyroid scans to be nondiagnostic for substernal thyroids, Park and colleagues found a sensitivity of 93 percent, specificity of 100 percent, and overall accuracy of 94 percent for thyroid scintigraphy when performed using current techniques. Technetium use in the mediastinum is

Table 91-4

Radionuclides in the Evaluation of Mediastinal Masses

Radionuclide	Mediastinal Mass
^{131}I or ^{123}I	Substernal goiter
^{131}I-metaiodobenzylguanine	Pheochromocytoma
Gallium 67	Lymphoma
Selenomethionin	Parathyroids
Technetium	Ectopic gastric mucosa

complicated because the salivary glands secrete technetium, which is swallowed, so the entire esophagus is invariably positive. However, technetium can help to identify rests of gastric mucosa in the esophagus if scanning is performed immediately after several glasses of liquid are swallowed to clear the esophagus.

^{131}I-metaiodobenzylguanine can help to identify pheochromocytomas or functioning paragangliomas anywhere in the body, including the mediastinum. Subsequent CT or MRI scanning is necessary to delineate the anatomy of "hot spots" identified in this way. Selenomethionine scans can localize parathyroid adenomas and thymic cysts. Finally, gallium 67 scanning has been used to distinguish benign from malignant anterior mediastinal masses, especially to differentiate lymphomas from benign lesions. Institutional expertise in the use of these markers and interpretation of the data they yield are at least as important as the choice of diagnostic technique.

Biochemical Markers

All patients with anterior mediastinal masses, particularly young men, should have determinations of levels of alphafetoprotein (AFP), beta human chorionic gonadotropin (βHCG), and carcinoembryonic antigen (CEA). Serum levels of AFP, βHCG, or both increase in the presence of nonseminomatous malignant germ cell tumors or of some teratomas and carcinomas.

Pheochromocytomas are accompanied by increases in serum catecholamines and in several urinary products—e.g., catecholamines, vanillylmandelic acid, and homovanillic acid. These markers are more valuable in following patients after treatment—i.e., to detect recurrence—than in screening. The levels of these substances should be determined in patients who present with flushing, tachycardia, or headache for which there are no other explanations. Some paravertebral masses—such as paragangliomas, ganglioneromas, and some neuroblastomas—can also elaborate norepinephrine and epinephrine.

Invasive Biopsy Procedures

The decision to biopsy mediastinal masses is not straightforward. Biopsy before resection is not necessary in some cases and potentially harmful in others. The likelihood of a positive biopsy depends on several factors: (1) the presence or absence of local symptoms; (2) the location and extent of the lesion; (3) the presence or absence of various tumor markers; and (4) gallium uptake by the lesion. (Methods of biopsy are discussed in the following.)

Locally asymptomatic lesions should not undergo biopsy before removal if they do not extend beyond the anterior compartment, show no increase in levels of tumor markers, and do not take up gallium. In particular, biopsy of a clinically suspected well-encapsulated thymoma should be avoided because it may cause spillage of tumor cells and prevent resection of an early-stage neoplasm from being curative. For patients with symptoms of locally invasive disease—such as severe chest pain, dyspnea, cough, dysphagia, pleural effusion, and superior vena caval obstruction—incisional or fine-needle aspiration biopsy (FNAB) before surgery is mandatory. These lesions are usually malignant and require chemotherapy or radiotherapy as primary or definitive therapy, rather than resection.

Bulky adenopathy should always undergo biopsy, since surgical intervention is seldom the primary means for treating these lesions. Most lesions in the anterosuperior mediastinum can be easily accessed by mediastinoscopy or FNA, whereas lesions in the posterior mediastinum are amenable to FNA or thoracoscopic techniques. Lesions in the middle mediastinum (visceral), just deep to the sternum, can be sampled by way of subxyphoid mediastinoscopy, whereas other middle-mediastinal lesions require FNA or thoracoscopic techniques.

It is critical to perform biopsy on patients with mediastinal masses in whom levels of AFP, βHCG, or CEA are increased. The treatment of choice for patients with these clinical features—i.e., with the features of metastatic non–small cell bronchogenic carcinoma or nonseminomatous germ cell tumors—is chemotherapy followed by surgical resection. Occasionally, chemotherapeutic treatment for oncologic emergencies may be initiated on the basis of increased levels, per se, of tumor markers. In contrast, increased concentrations of catecholamines in serum or urine contraindicate biopsy, since disturbance of a pheochromocytoma or pharmacologically active paraganglioma before preparation with alpha and beta blockade is dangerous.

Gallium uptake is useful in differentiating lymphomas from thymoma. Gallium is avidly taken up by lymphomas and other inflammatory processes, whereas it is usually taken up by bronchogenic carcinomas, rarely taken up by thymomas, and unpredictably taken up by carcinoids and germ cell tumors.

Method of Biopsy

FNAB may fail to obtain diagnostic tissue, especially in patients with lymphoma. FNAB is diagnostic in approximately

75 percent of mediastinal masses, although it lacks the precision to stage mediastinal and pulmonary malignancies. Heilo obtained a diagnosis in 84 percent of 62 patients undergoing ultrasound-guided core needle biopsy. It is important to emphasize that the primary benefit of FNAB in this group of patients is to prevent needless surgical intervention. Accordingly, in a candidate for surgery, a diagnosis other than lymphoma, small cell carcinoma, or stage IIIB non–small cell bronchogenic carcinoma will not obviate surgery, since all other diagnoses of solid tumor require surgical staging or resection. In a group of 35 patients in whom diagnostic tissue was obtained, ultrasound-guided needle biopsy prevented subsequent surgery in only 17 patients.

Patients with potential early thymomas should not undergo FNAB, as the procedure may spread tumor cells along needle tracks, thereby preventing subsequent curative surgery. Although a core biopsy may suffice for the diagnosis of a specific lymphoma, most often more invasive and definitive approaches—such as cervical mediastinoscopy, anterior or parasternal mediastinoscopy, and videothoracoscopy—are necessary. In summary, FNAB is inconsistently useful for diagnosis of diseases of the mediastinum, and its use must be carefully assessed. However, complications of FNAB are rare.

Surgical approaches to obtain tissue from mediastinal lesions include cervical mediastinoscopy, extended cervical mediastinoscopy, anterior mediastinotomy (Chamberlain procedure), subxyphoid mediastinoscopy, and videothoracoscopy. Descriptions of these specific techniques are beyond the scope of this chapter, but some generalizations may be helpful. The diagnosis of lymphoma usually requires a large tissue sample to identify the subtype, especially for non-Hodgkin's lymphomas. Also, lesions at different sites vary with respect to accessibility. Thus, cervical mediastinoscopy, performed through a small incision in the suprasternal notch, can sample masses in the anterior mediastinum or lymph nodes in the subcarinal and paratracheal location (levels 1, 2, 3, 4, 7, and 10 in the American Thoracic Society staging system). Anterior mediastinotomy performed through a small incision over the second or third rib on either side can sample lymph nodes in the para-aortic position (levels 5 and 6) or anteriormediastinal masses. These procedures can be performed in the outpatient setting, have a very low complication rate, and do not delay chemotherapy or radiotherapy. A portion of the specimen should be kept fresh for formal evaluation of T- and B-cell subpopulations and a sample of any enlarged node sent for culture.

The use of mediastinoscopy to sample large masses that compromise the airway or elicit clinical signs of superior vena caval obstruction may be problematic. However, mediastinoscopy can still be useful with cautious anesthetic management (awake intubation and extubation). Mediastinoscopy poses no greater risk of bleeding for patients with superior vena caval syndrome than for normal persons undergoing mediastinoscopy.

Subxyphoid mediastinoscopy, performed through an incision below the xyphoid process, is an unusual procedure. It is used to obtain biopsies of tissues located inferiorly in the mediastinum. Videothoracoscopic approaches to either the left or right side of the mediastinum are straightforward and obtain adequate tissue samples with minimal morbidity. However, thoracoscopic biopsies are not currently being done as outpatient procedures.

MEDIASTINAL INFECTIONS

Mediastinal infections can present as mediastinal masses. The various infections that can present in this way fall into four groups: (1) mediastinitis, secondary to transsternal cardiac procedures; (2) acute perforation of the esophagus secondary to vomiting, tumor, or attempts at esophageal dilation; (3) acute descending necrotizing mediastinitis resulting from descent of oral infectious processes into the mediastinum; and (4) upward extension of a subdiaphragmatic infectious process into the mediastinum by way of the various tissue planes that connect the mediastinum with the retroperitoneum and the peritoneum. Of these categories, the first two are the most common. Diagnosis of mediastinitis after surgery on the mediastinum is uncomplicated.

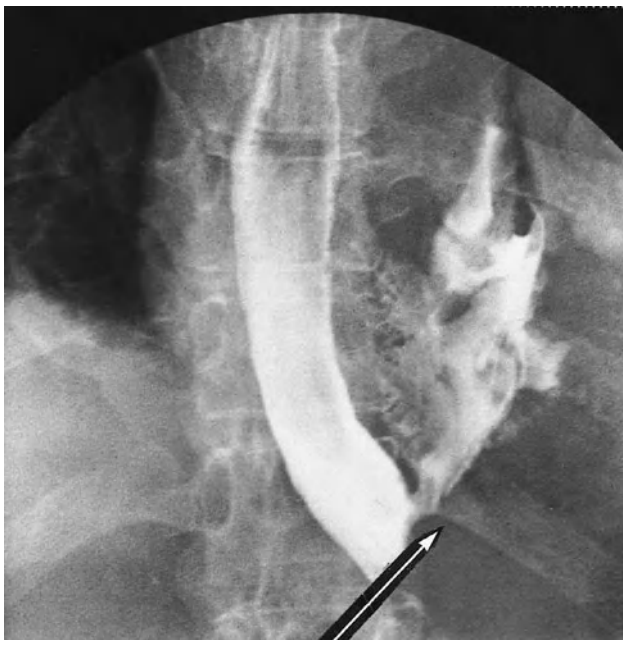
Transsternal Cardiac Procedures

The diagnosis of mediastinitis after surgery on the mediastinum is evident. The therapeutic approach is described in surgical texts.

Esophageal Perforations

Acute infections of the mediastinum caused by esophageal disease are usually due to esophageal perforation from retching or vomiting, malignancy, ingestion of a foreign body, or diagnostic or therapeutic instrumentation (Fig. 91-5). Along with clinical suspicion, two radiologic criteria are helpful in establishing the diagnosis: pneumomediastinum and pleural effusion. In distal esophageal perforations, the pleural effusion typically presents on the left side, whereas midesophageal and proximal esophageal lesions typically present with right-sided pleural effusions. Although pneumomediastinum is invariably present after an esophageal perforation, it does not localize well to the site of perforation because of dissection along tissue planes. A swallow of water-soluble contrast can confirm the diagnosis of esophageal perforation. If the swallow fails to reveal the perforation, it is repeated with a small amount of dilute barium. Although water-soluble contrast is safer from the standpoints of infection and surgery, barium affords a more detailed examination and can disclose a small perforation that is not identified by a water-soluble agent.

In general, the treatment of an esophageal perforation is surgical drainage and repair of the perforation. However, appropriate timing for repair has been debated: The older surgical literature holds that a perforation more than 24 h old should be repaired only after diversion of the cervical



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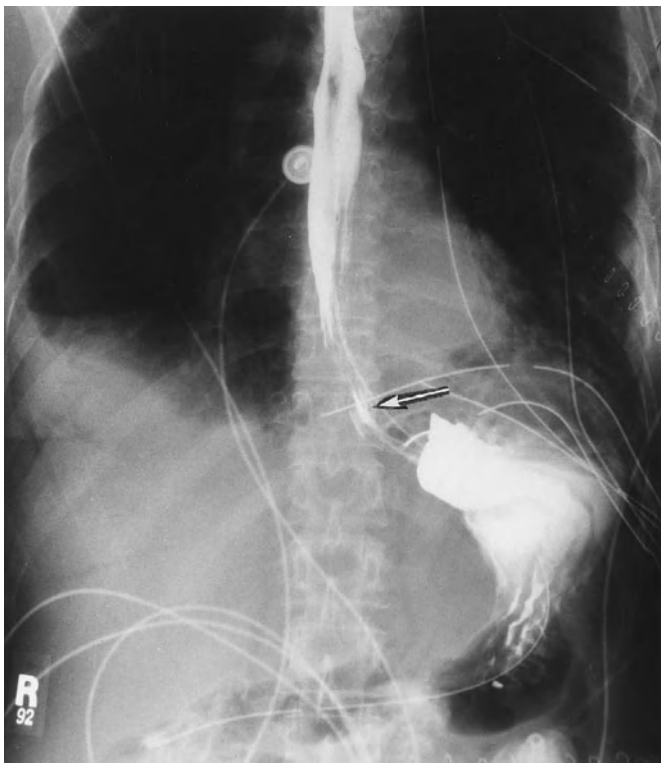


B

Figure 91-5 Esophageal tear with communication to pleura. Sixty-three-year-old woman with multiple myeloma receiving chemotherapy in inpatient setting. After an episode of vomiting, she developed a left pleural effusion and leukopenia (WBC of 500). *A*. Contrast study reveals leak into left chest (arrow). *B*. Postoperative film after primary repair reveals normal flow of contrast.

esophagus. The more recent literature indicates that many of the late-presenting perforations can be repaired without diversion. Finally, small perforations that drain back into the gastrointestinal tract without significant soilage of the mediastinum or larger injuries that can be well drained by tube thoracostomy can be treated with antibiotics as long as the patient shows no signs of sepsis. Such fistulas that are managed without surgery may either heal spontaneously or require surgical repair at a later date.

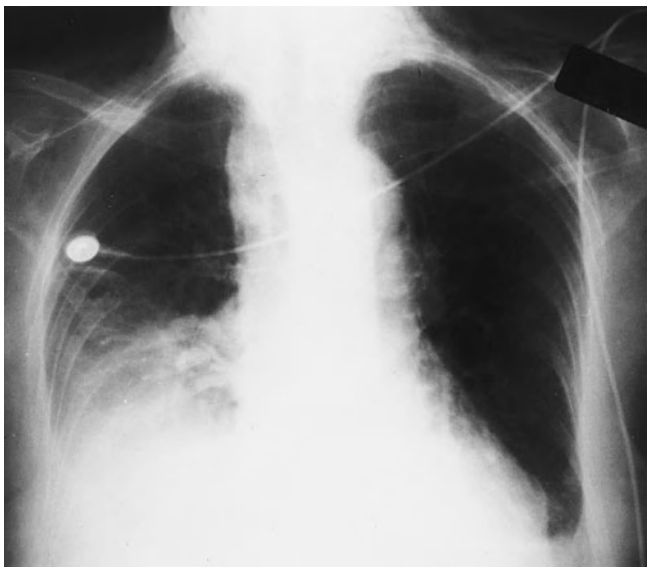
Acute Descending Necrotizing Mediastinitis

Acute descending necrotizing mediastinitis is a complication of cervical, pharyngeal, or oropharyngeal abscesses. Odontogenic diseases (molar abscesses, peritonsillar abscesses, retropharyngeal abscesses, Ludwig's angina, and adult epiglottitis) and iatrogenic injury are the most common causes (Fig. 91-6). The infections are mixed, and culture may grow aerobic beta-hemolytic streptococcus, *Bacteroides,* peptostreptococcus, or anaerobic streptococci. Initial treatment usually entails the use of antibiotics and cervical drainage. Should these measures fail, mediastinitis can develop within 48 h.

There are no pathognomonic radiographic manifestations. Mediastinal involvement is suggested by widening of the retrocervical space with an air-fluid level, anterior displacement of the tracheal air column on lateral neck or chest radiographs, mediastinal emphysema, or the loss of the normal lordosis of the cervical spine. A CT scan of the chest and neck can verify the presence of a descending mediastinitis.

The mainstays of treatment are broad-spectrum antibiotics, surgical drainage, and tracheostomy. Antibiotics should be chosen to cover gram-negative, gram-positive, and anaerobic organisms. Cervical drainage is often the definitive treatment: Careful review of the chest CT scan can indicate whether more invasive approaches are necessary. Bilateral anterior mediastinotomies may be sufficient if the infection has not progressed below the fourth thoracic vertebra. Soft, pliable drains prevent erosion into major neck vessels. Subxyphoid drainage may be necessary if the anterior space is affected. Extensive infections can be treated successfully by wide drainage of the mediastinum.

The role of tracheostomy in treatment is debatable. A tracheostomy can protect the airway, especially in patients with significant cervical inflammation and edema. Despite aggressive treatment, reported mortality ranges up to 40 percent. Death can result from pulmonary sepsis, blood vessel erosion and exsanguination, and intracranial infection. A high level of suspicion that mediastinitis may be present and early surgical management are critical for successful outcome.



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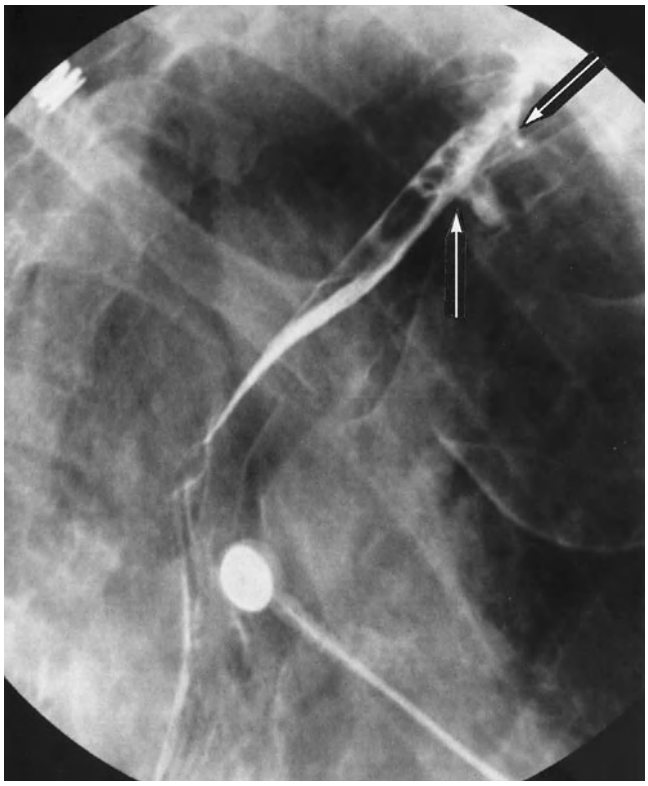

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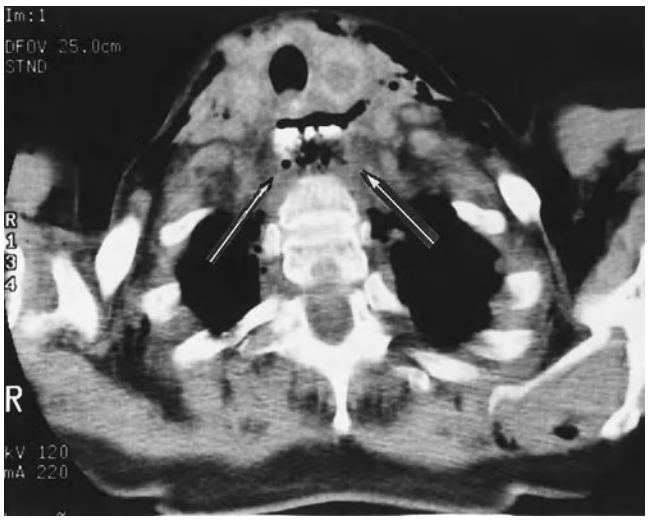

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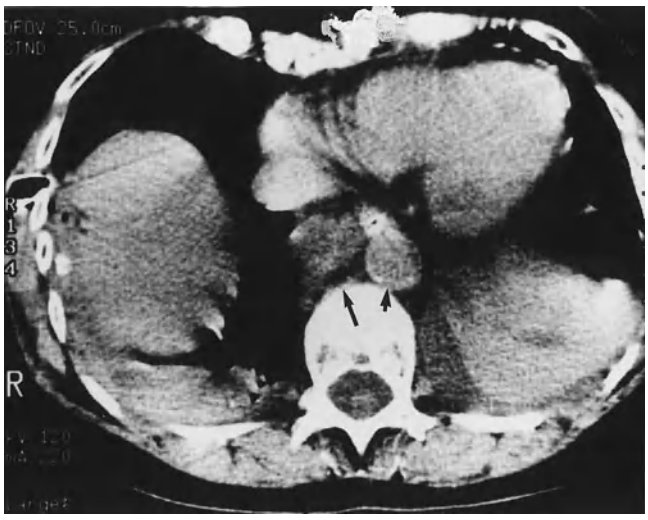

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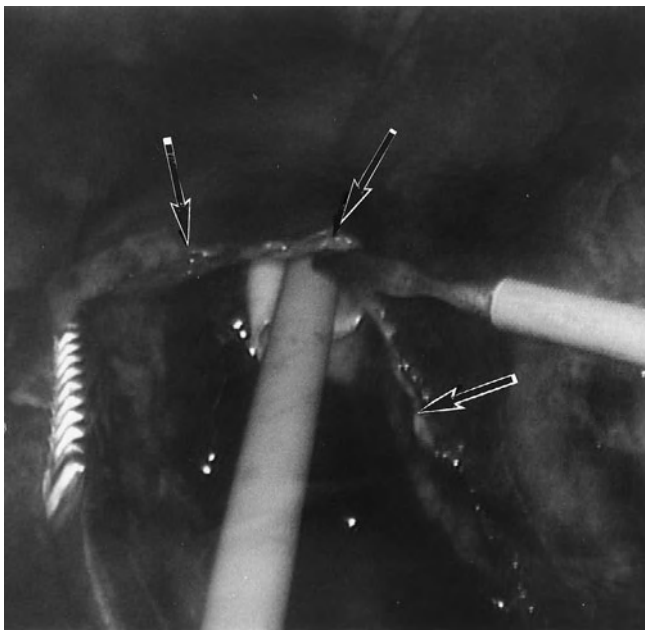
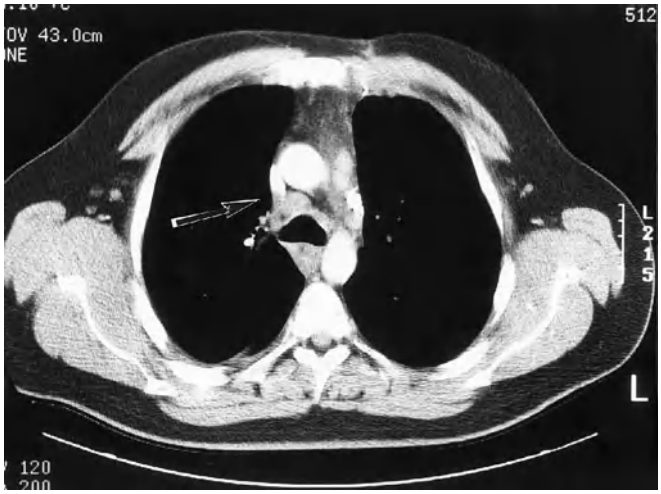


E

Figure 91-6 Acute descending necrotizing mediastinitis. Sixty-nine-year-old woman developed cervical neck mass and subcutaneous emphysema 96 h after attempted esophagoscopy. *A*. PA radiograph reveals a widened mediastinum with pneumomediastinum and pleural effusion. *B*. Contrast study demonstrates leak in the proximal esophagus (arrows). *C*. CT scan at the thoracic inlet reveals 5-cm irregular abscess (arrows). *D*. CT scan of chest close to the diaphragm reveals that the abscess extends the length of the chest (arrows). *E*. Combined thoracoscopic and cervical drainage resulted in clearing of the abscess (arrows).



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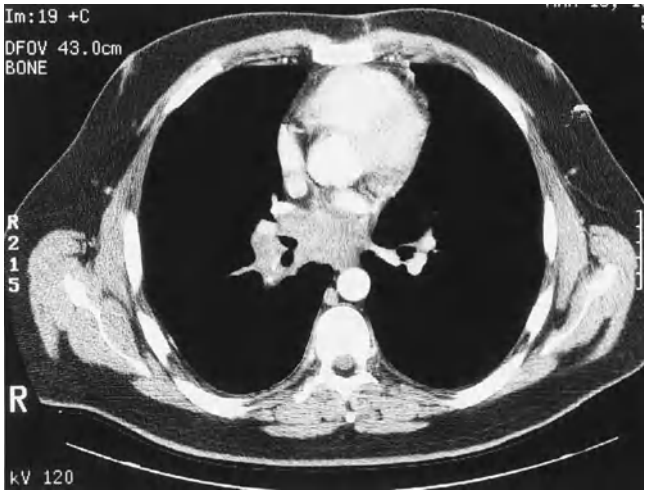

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Figure 91-7 Chronic fibrosing mediastinitis. Thirty-year-old man with malaise and one episode of hemoptysis. Chest radiograph is normal. *A*. Chest CT at the level of the carina reveals paratracheal mass (arrow) surrounding the airway. *B*. The same process extends along the airways into inferior mediastinum. Mediastinoscopy was done to perform biopsy. Patient was treated successfully with steroids.

Subacute Mediastinitis

The incidence of subacute mediastinitis is increasing in the growing population of immunocompromised patients. This diagnosis applies only to patients with mild and evanescent symptoms (e.g., substernal pain, fever, and night sweats) and with an identifiable anterior or visceral mediastinal mass. In immunocompetent patients, the most common causes are histoplasmosis and tuberculosis. Mycotic infections are rare. In immunocompromised patients, the most common causes are *Mycobacterium avium-intracellulare* and *Mycobacterium tuberculosis*. Gallium scintigraphy or indium-labeled leukocyte scintigraphy may be useful in identifying subacute infections early in their course but is less effective in more chronic infections.

Chronic Mediastinitis

Patients with chronic mediastinal infections often have cough, hemoptysis, fever, and dysphagia. Causes of chronic mediastinal infections are granulomatous lymphadenopathies, such as tuberculosis; fungal infections, such as histoplasmosis and coccidiomycosis; sarcoidosis; and Wegener's granulomatosis. Whereas tuberculosis was the most frequent cause in the early twentieth century, now fungal infections cause most chronic mediastinal infections. The diagnosis requires biopsy and culture.

Complications of chronic mediastinal infections are uncommon. Airway compromise may require surgical relief. Seventy-five percent of all benign obstructions of the superior vena cava result from mediastinal granulomatous disease. Calcified lymph nodes may erode into airway (bronchiolithiasis) and require removal. Most symptoms resulting from *benign* lesions that cause obstruction of the superior vena cava resolve with time. Medical treatment consists of diuretics, anticoagulation, and observation. In contrast, malignant obstruction of the superior vena cava requires urgent nonsurgical treatment.

Chronic Fibrosing Mediastinitis

This entity is also referred to as chronic sclerosing mediastinitis, chronic granulomatous mediastinitis, or chronic idiopathic mediastinitis. It differs from chronic mediastinitis in its compression and obliteration of vessels, bronchi, or esophagus (Fig. 91-7). In keeping with the supposition that chronic fibrosing mediastinitis (CFM) is the result of infection, cultures of mediastinal tissue sometimes grow *Histoplasma capsulatum* or *M. tuberculosis*. Most instances of CFM involve the vicinity of the thoracic duct and its main tributaries. Most patients have strongly positive gallium scans and serum reactions to *Histoplasma* antigens.

Patients with CFM present with a chronic smoldering inflammatory process that deposits woody, fibrous tissue throughout the visceral compartment of the mediastinum. This fibrous tissue extends beyond lymph node boundaries. A diagnosis of CFM is appropriate only if the process includes obstruction of one of the major airways, pulmonary arteries, pulmonary veins, or esophagus. Occasionally, patients have similar fibrotic processes elsewhere—e.g., in the retroperitoneal space, the orbit (orbital pseudotumor), or the thyroid (Riedel's struma). The diffuse fibrosis, which also occurs in patients with systemic lupus erythematosus or rheumatoid disease or those who have received methysergide, suggests an immune mechanism.

Clinical features are puzzling, and the disorder may be self-limiting. The highest incidence of CFM is in young adults, primarily in white women 19 to 25 years of age, who develop the disease three times more often than do men of the same age. Sixty percent of patients have symptoms that depend on the structures affected. The radiologic

findings are variable. The superior mediastinal shadow may be abnormally wide because of an asymmetric mass that projects into either hemithorax. In some instances in which the chest radiograph is normal, a CT scan may demonstrate compression of the trachea, arterial compression, or other abnormalities. Contrast venograms, anteriograms, or MRI can document vascular obstruction even when CT scans are unrevealing. Bronchoscopy and mediastinoscopy are usually sufficient to obtain tissue for diagnosis, although thoracotomy may be necessary. Esophagoscopy can be diagnostic in patients with dysphagia. Any tissue obtained should be cultured for mycobacteria and fungus. Serum sent for complement fixation studies for histoplasmosis and coccidiomycosis can contribute to the diagnosis. Culture and histologic evaluation of material for fungal and acid-fast organisms are essential but often unrewarding: They may be negative even in patients who later respond to antibacterial treatment.

Treatment

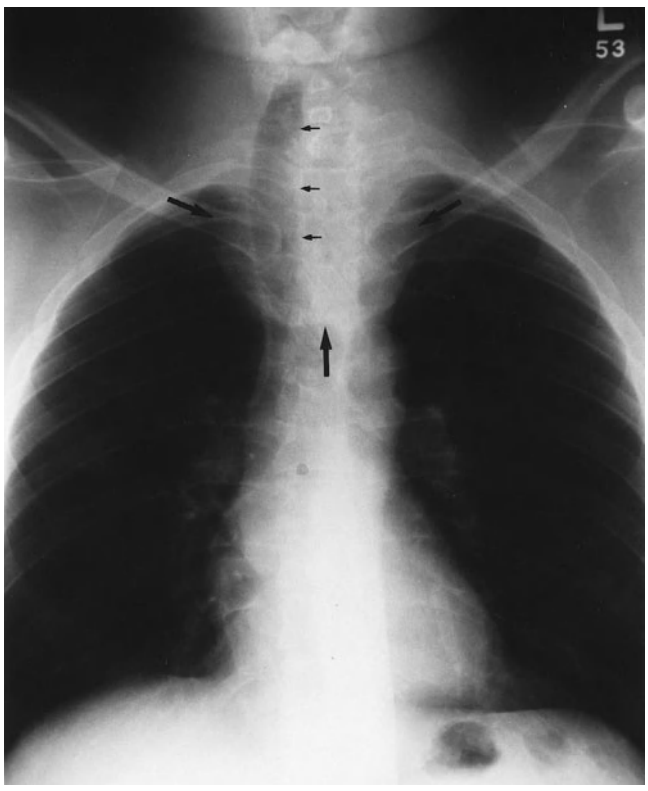
In a series of 22 patients with CFM, 13 had superior vena caval obstruction, three had dysphagia, three had stridor and dyspnea, two had pericardial involvement, and one had pulmonary artery obstruction. Ketoconazole improved outcomes in patients with high titers for histoplasmosis (greater than 1:32). It is recommended before resection because its use may obviate surgery in some patients and improve outcome in patients who require surgery. Amphotericin is of value only for acute infections. Medical treatment, using steroids, has not been effective in reversing the fibrotic process.

Because major surgical resections entail high morbidity and mortality, they are worthwhile only when other measures have failed. Superior vena caval replacement by spiral vein graft may be useful for patients with localized superior vena caval obstruction and unremitting symptoms. In a series of 18 patients who underwent major surgical resections for CFM, there were four deaths, most of them in patients who required carinal pneumonectomy.

LESIONS MASQUERADING AS MEDIASTINAL TUMORS

Substernal Goiter

Substernal goiters usually present as anterosuperior mediastinal masses (Fig. 91-8), even though ectopic thyroid tissue can also be found in retrotracheal and retroesophageal locations. Essentially all substernal thyroids descend into the mediastinum from the neck; primary mediastinal thyroids are vanishingly rare. Two-thirds of patients with a substernal



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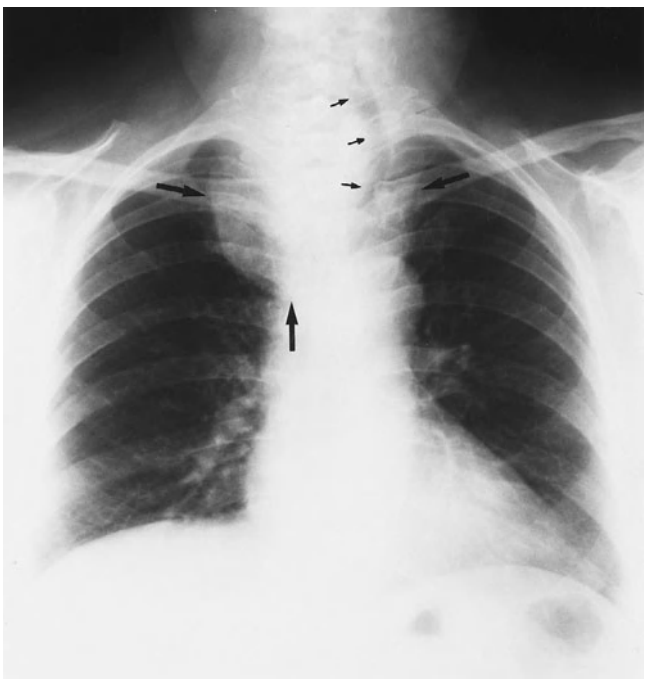


B

Figure 91-8 Substernal goiter. *A*. Substernal thyroid in 33-year-old man (arrow). He underwent subsequent uncomplicated thyroidectomy by way of collar incision. *B*. Substernal thyroid in 67-year-old woman with diabetes and congestive heart failure (arrows). Thyroid suppression was followed by a decrease in the size of the goiter.

goiter complain of a neck mass. Most are otherwise asymptomatic. Twenty-five percent complain of dyspnea or dysphagia. The occurrence of symptoms does not herald malignancy. CT and MRI scans are the most useful studies in the diagnosis and evaluation of these lesions. Modern radioactive ^{131}I scans can delineate the substernal goiter, although there is some debate about the incidence of false-negative scans. A combined analysis of available studies indicates that modern techniques of thyroid scintigraphy are diagnostic of most substernal goiters.

Three recent studies, with 50 to 80 patients included in each, dealt with the evaluation and resection of substernal goiters. These reports indicate that even the most bulky lesions can be resected through cervical incisions: The lesion usually does not extend beyond the uppermost portion of the anterosuperior compartment, and ligation of the vascular supply in the neck allows delivery of the mediastinal goiter to the neck. In these series, six patients (3.3 percent) required median sternotomy or thoracotomy along with cervical incision to achieve resection. There were no deaths due to surgery in any of the series. Three patients in one series had significant intraoperative bleeding. The overall major complication rate was 1.6 percent; the rate of minor complications was 15.4 percent.

The reported incidence of malignancy has ranged from 2.5 to 21 percent. These data are particularly pertinent to the decision to recommend surgery for asymptomatic substernal goiters. Everyone would support resection if 21 percent of all substernal goiters were malignant. Unfortunately, FNAB was seldom successful in identifying the lesions that ultimately proved to be malignant. Weighing in the balance the frequency of malignancy (about 2 to 20 percent), the potential danger of acute airway obstruction, and the relative safety of the surgical procedure, surgical excision seems reasonable even in asymptomatic patients. This balance in favor of surgery can obviously be tilted against it by the presence of medical complications.

Cystic Hygromas

Mediastinal lymphangiomas typically extend from cervical cystic hygromas along the phrenic nerve into the chest. Cystic hygromas may be evident at birth or may not be discovered until later in life. Symptoms are caused by infection, hemorrhage, or continued growth. Resection is accomplished by combined cervicomediastinal approaches. Some of these lesions gradually regress spontaneously without surgical intervention. Sclerosis (e.g., injection of tetracycline) is possible but is generally not effective.

Lesions Originating from the Thoracic Skeleton

Most skeletal lesions in the mediastinum are bony tumors that project from the thoracic spine. Chordomas of the spine are ectopic embryonic remnants of primitive notochords that may be manifest in the paravertebral sulcus. CT scanning usually shows destruction of vertebral bodies in association with soft tissue mass. These tumors are malignant and require extensive excision and reconstruction of the spinal cord. As a rule, 5-year survival is poor.

Other lesions associated with the thoracic skeleton are paravertebral abscesses caused by staphylococcal hematogenous infections of paraspinal muscles, similar to retroperitoneal abscesses. The treatment of these is the same as for all infectious lesions—i.e., drainage and appropriate antibiotic treatment.

An anterior meningocele may occur in the paravertebral sulcus. These are generally asymptomatic masses discovered incidentally on CT scan. They may be confused with primary neurogenic tumors. Patients with anterior meningoceles often have peripheral neurofibromatosis, skeletal abnormalities, or both. Myelography or MRI is crucial in the diagnosis of these lesions. If the diagnosis is made preoperatively, no treatment is needed unless symptoms become manifest.

Extramedullary Hematopoiesis

Hematopoietic tissue can present in the mediastinum, typically in the posterior mediastinum. This process of extramedullary hematopoiesis develops as a compensatory mechanism in patients with abnormal bone marrow function. It may be manifest in several organs, such as the adrenals, liver, lymph nodes, and lungs. Large masses of extramedullary hematopoiesis are designated as erythroblastoma and myelolipoma. Consideration of this diagnosis is appropriate in patients with blood dyscrasias, especially thalassemia, who present with mediastinal masses. The tissue is pathologically characteristic, so FNAB is often diagnostic. Resection is not indicated if the diagnosis is made preoperatively.

Vascular Lesions

Vascular lesions in the mediastinum may be either arterial or venous lesions and either pulmonary or systemic. Validation of lesions suspected of being vascular requires either angiography or MRI scanning to avoid dangerous biopsy. Appropriate therapy depends on the diagnosis.

Esophageal Lesions

Several benign esophageal lesions—such as diverticula, duplications, large leiomyomas, hiatal hernias, and achalasia—may present as mediastinal masses. Esophageal carcinoma with extramural spread, bulky adenopathy, or contained perforation can manifest as bulky visceral or posterior mediastinal masses. Chest CT scan with oral contrast can differentiate most of these lesions. Formal contrast studies and esophagoscopy are reserved for puzzling circumstances.

Pulmonary Lesions

Pulmonary lesions may manifest primarily as mediastinal masses, particularly as mediastinal adenopathy. Small cell

lung cancer often presents as bulky adenopathy with either a small or an involuted primary lesion. Extralobar sequestration may also present on the chest radiograph as a paramediastinal mass in a patient with recurrent pneumonia.

Subdiaphragmatic Lesions

Subdiaphragmatic lesions may present as mediastinal masses. The gastrointestinal tract (typically the stomach) may herniate through the esophageal hiatus posteriorly (to form a hiatal hernia) or through the foramen of Morgagni anteriorly. Pancreatic pseudocysts rarely present as mediastinal masses. They occur in patients with characteristic histories of previous pancreatitis or known abdominal pancreatic pseudocysts. These lesions should be drained by laparotomy rather than thoracotomy.

ANTERIOR MEDIASTINAL NEOPLASMS

Lesions of the Thymus

Thymoma

Thymomas appear benign histologically even when they are invasive. They derive from either cortical or medullary epithelial cells. They are the most common of the thymic malignancies (Table 91-5). Five histologic grades have been described, based on lymphocytic infiltration: lymphocytic, lymphoepithelial (mixed), epithelial, spindle cell, and unclassified. Thus, a *lymphocytic thymoma* consists of 67 to 80 percent lymphocytes. *Mixed thymomas* are tumors with 50 percent lymphocytes and 50 percent epithelial cells. In *epithelial thymomas,* 67 to 80 percent of the cells are epithelial cells. *Spindle cell tumors* have a characteristic appearance, and *unclassified tumors* are typically too undifferentiated to classify. The number of mitotic figures in these tumors is very low, so cytologic preparations always appear benign.

Table 91-5

Thymic Malignancies

Thymoma
Thymic carcinoma Low grade: squamous cell carcinoma, muco-epidermoid, basaloid High grade: small cell, undifferentiated, sarcomatoid, clear cell
Thymic carcinoid
Oat cell carcinoma of thymus
Thymic hyperplasia

Table 91-6

Staging of Thymic Malignancies

Stage	Description	10-yr Survival (%)
I	Encapsulated tumors without gross or microscopic invasion	85–100
II	Capsular or pleural invasion	60–84
III	Macroscopic invasion of surrounding tissuse (lung, pericardium, vena cava, or aorta)	21–77
IVA	Disseminated disease within the chest	26–47
IVB	Distant metastases	Unknown

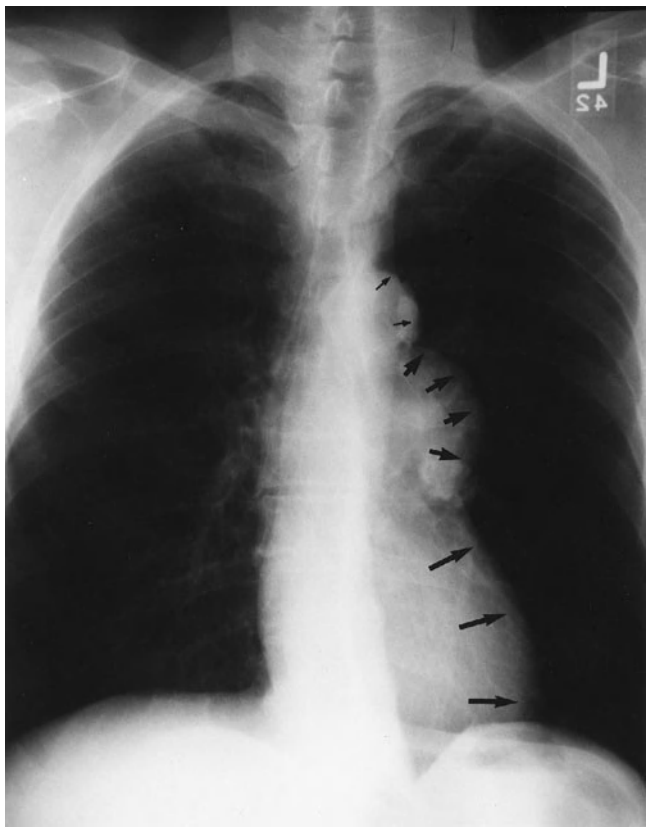
SOURCE: *Adapted from Masaoka A, Monden Y, Nakahara K, et al. Follow-up study of thymomas with special reference into their clinical stages.* Cancer *48:2485–2492, 1981.*

A second classification depends on the relative predominance of thymic medullary or thymic cortical cells. Medullary tumors are less aggressive, with rare recurrences, whereas cortical thymomas (and the most aggressive subtype, thymic carcinoma) tend to recur and metastasize. Differentiation between lymphomas and thymomas can be difficult without substantial tissue and often cannot be made with needle biopsy.

Tumor stage at the time of treatment indicates prognosis better than tumor grade. Table 91-6 lists the most common staging mechanism applied to thymic malignancies. Stage I lesions are generally considered benign. Tumor node metastasis (TNM) staging has not been widely adopted. A peculiar characteristic of the benign histologic appearance of many of these lesions is that invasion of adjacent structures, and thus the stage of the tumor, can usually be more easily determined by the surgeon at the time of operation than by the pathologist at the time of microscopy.

Thymoma is the most common primary neoplasm of the mediastinum, comprising approximately 15 percent of all thymic lesions. These tumors occur with equal frequency in men and women 40 to 60 years of age. Seventy-five percent present in the anterior mediastinum; more than 90 percent are visible on the chest radiograph.

The mainstay of therapy, even for extensive lesions, is surgical resection (Figs. 91-9 and 91-10). In a series of 141 patients who underwent resection followed by routine radiotherapy (30 Gy in 3 weeks to 50 Gy in 6 weeks), those who underwent complete resections, even up to stage III, had survival rates of 100 percent at 5 years and 94.7 percent at 10 and 15 years. There was no difference between stages as long as



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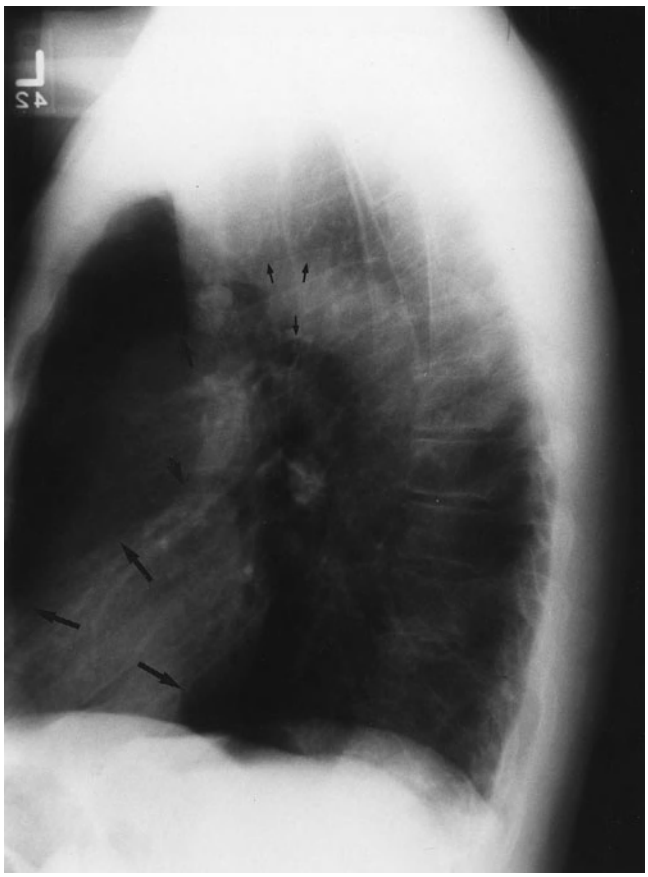

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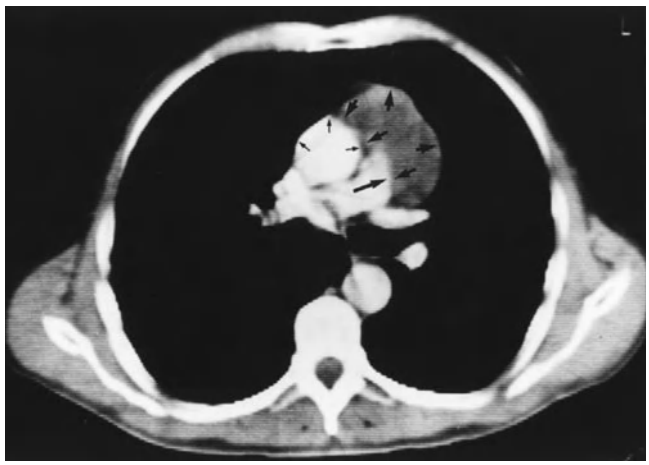


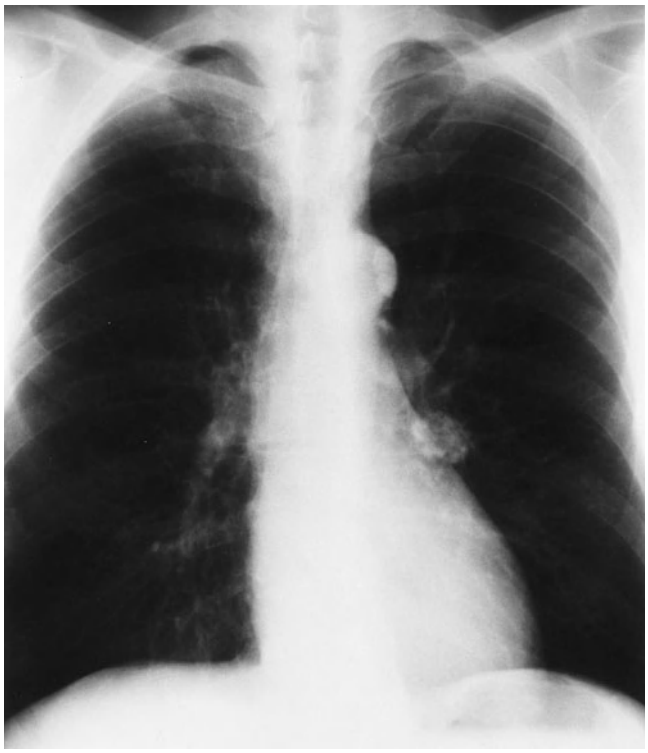
C

Figure 91-9 Thymoma. Sixty-two-year-old man after successful treatment of gastric cancer and aortic aneurysm. *A* and *B*. PA and lateral radiographs demonstrate an anterior mediastinal mass projecting into left hemithorax (arrows). *C*. CT scan demonstrates 4-cm mass abutting thoracic aorta (arrows). No obvious invasion. *D* and *E*. Postoperative films showing remaining calcified lymph nodes but no thymoma.

the resection was complete. Most surgeons, even those experienced in thoracoscopy, recommend median sternotomy for the procedure. Another study reported 5- and 10-year survivals of 74 percent and 57 percent, respectively, following a treatment regimen that included surgery and postoperative radiotherapy for all patients and postoperative chemotherapy for some patients with high-grade lesions. For patients who had total resection, the reported 5-year survival was 89 percent.

Most recurrences are local, either in the pleural space or mediastinum. Distant recurrences, when they do develop, are most often in bone. Recurrences are potentially curable, requiring several therapeutic methods, including repeated surgical exploration. Re-exploration and successful resection were reported for 23 patients who had recurrence of thymoma after previous complete resections.

All patients in whom an invasive thymoma has been resected should receive postoperative radiotherapy, which is strongly recommended for all but stage I patients. Surgery alone yields a recurrence rate of 28 percent, whereas radiation and surgery together yield a recurrence rate of 3 percent. Whether noninvasive and encapsulated thymomas respond



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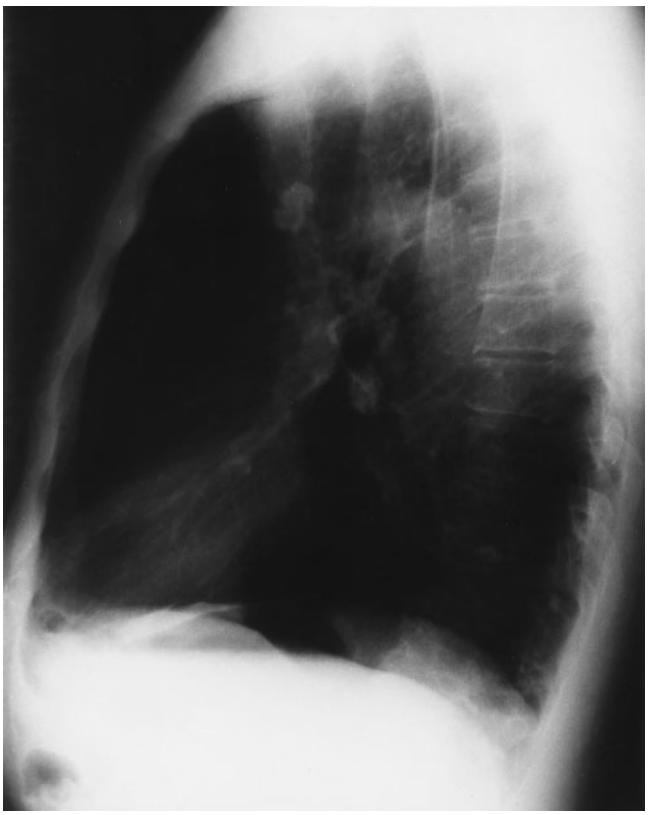


E

Figure 91-9 (*Continued*)

to irradiation is unsettled. Dosage is usually 3500 to 5000 rads over 3 to 6 weeks. A dosage of more than 5000 rads does not increase the response rate but does increase the frequency of complications.

Patients with thymomas, even when the disease is unresectable, recurrent, or metastatic, often respond to treatment with cisplatin, doxorubicin, and cyclophosphamide. In an intergroup study of 22 patients with locally unresectable or metastatic disease, there were three complete and 11 partial responses, for a total response rate of 70 percent. The median survival of all patients was 59 months; three patients remained disease-free after 3 years of follow-up.

Paraneoplastic Syndromes

Myasthenia gravis is the most common thymoma-associated systemic syndrome. Many other syndromes may also be related to thymoma. Table 91-7 lists the four well-established syndromes and some others that are less characteristically associated.

The most commonly used clinical staging classification is shown in Table 91-8. Patients with myasthenia gravis present with muscle weakness that intensifies with repetitive activity. The pathophysiology of myasthenia gravis entails the autoimmune-mediated binding of antibodies to the acetylcholine receptor, followed by their lysis by complement-mediated factors. Striking clinical improvement may occur after thymectomy without any change in measurable immune parameters, including the absence of change in the serum levels of autoantibodies. Unfortunately, the likelihood of improvement after thymectomy is significantly less for patients with thymomas.

No randomized studies have demonstrated a benefit of thymectomy for any group or subgroup of patients with myasthenia gravis, with or without thymomas. In a series of 149 patients with juvenile myasthenia gravis who were followed for a median of 17 years, half of the patients who underwent thymectomy sustained complete remission, whereas only one-third of the medically treated patients had the same response. The patients who underwent thymectomy also had slightly improved long-term survival. Because of such information, thymectomy has become standard for patients with myasthenia gravis, except for those who have only ocular symptoms.

Myasthenia gravis is present in approximately one-third of patients with thymomas. This disorder may either precede or follow the development of thymoma by many years. Any type of thymic tumor may occur in patients with myasthenia gravis. Patients with thymoma and myasthenia gravis derive less neurologic benefit from resection than do those with myasthenia gravis without a thymoma.

Among patients with myasthenia gravis without thymomas, remission can be expected in one-fourth to one-half:

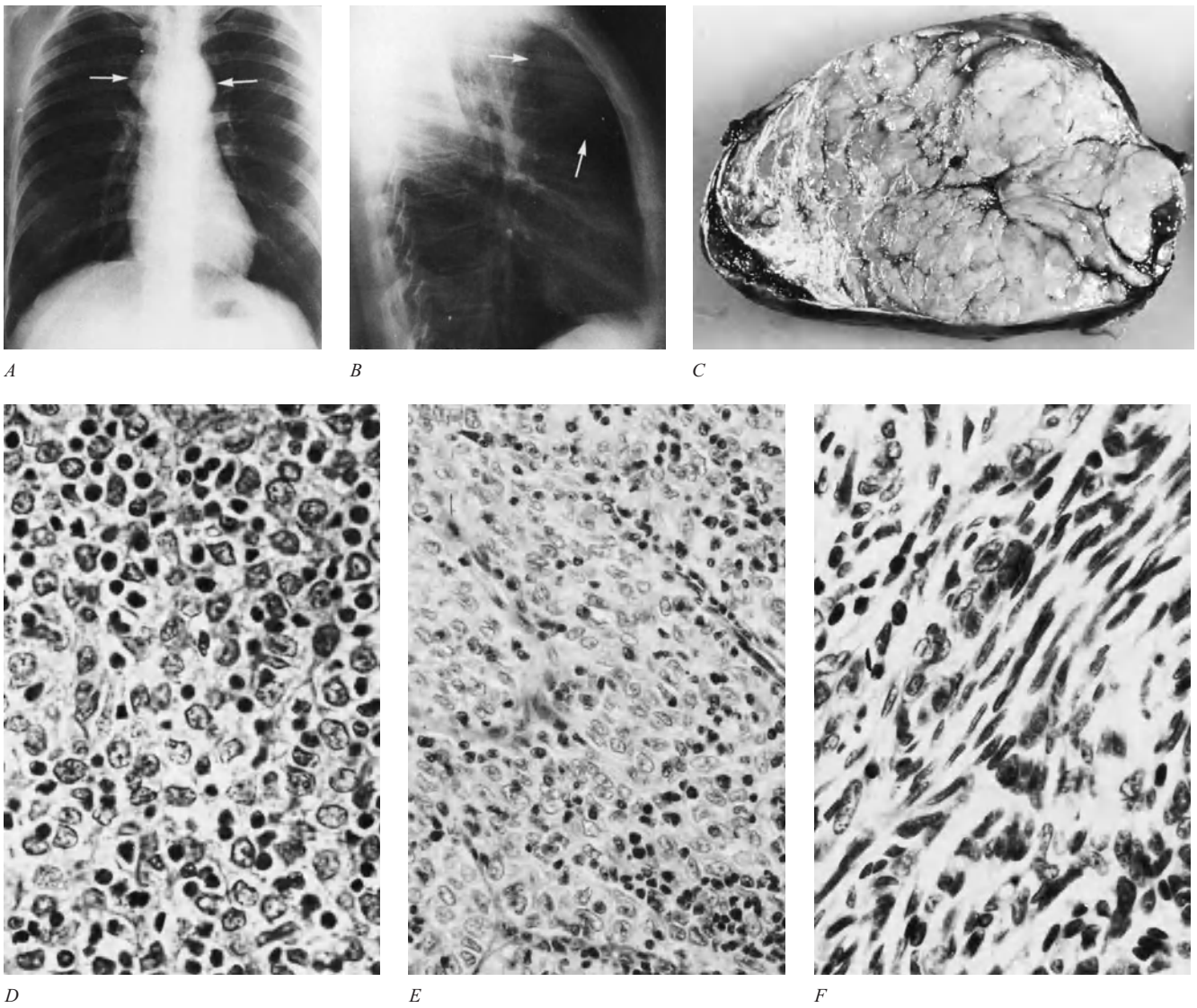


Figure 91-10 Benign thymoma of anterior mediastinum. *A* and *B*. Radiographic appearance of thymoma. *C*. Gross appearance of a benign thymoma. The tumor has a thick fibrous capsule. *D* to *F*. Varied histologic appearances of thymomas. In *D*, the cells are mixed epithelial (large cells with clear nuclei) and lymphocytic, ×250. In *E*, epithelial cells predominate, ×224. In *F*, the predominant cells are spindles, ×248. *(Based on data of Lyerly and Sabiston, Primary neoplasms and cysts of the mediastinum, in Fishman J (ed),* Pulmonary Diseases and Disorders, 2d ed. *New York, McGraw-Hill, 1988.)*

in about 20 percent, remissions are completely drug-free; in up to 30 percent, remission is maintained by drugs—i.e., a combined remission rate of 50 percent. Improvement can be expected in one-third to one-half of patients, no change is evident in 10 percent, and a rare patient gets worse after surgery. Patients with myasthenia gravis and thymoma fare more poorly after resection than do those without a thymoma. Their symptomatic improvement after surgery is poorer, with combined remission rates of only 30 percent, and there is considerable risk of recurrence of the thymoma. Combined cervical and mediastinal incisions have been recommended to accomplish a maximal thymectomy. Postoperative radiotherapy decreases the recurrence rate after resection. Radiation therapy without resection can worsen myasthenia gravis. The dose of radiotherapy should be 3500 to 5000 rads.

Red-cell aplasia occurs in 5 percent of patients with thymomas. It is a rare disorder that results in a severe normochromic normocytic anemia. Erythroid precursors in the bone marrow are decreased or absent, so reticulocytosis is markedly decreased. Thirty-three to fifty percent of patients with red-cell aplasia have thymomas. Thymectomy produces remissions in approximately 40 percent of patients. It is more likely to be effective in patients with thymoma or thymic enlargement (remissions in up to 50 percent of patients) than in patients without thymomas.

Hypogammaglobulinemia occurs in 5 to 10 percent of patients with thymomas. It is more common in patients with

Table 91-7

Paraneoplastic Syndromes Associated with Thymoma

Well established (proven)
Myasthenia gravis
Pure red-cell aplasia
Acquired hypogammaglobulinemia
Nonthymic cancers
Less well established (associated)
Pancytopenia
Lambert-Eaton
Peripheral neuropathies
CNS changes
Multiple endocrine defects
Multiple rheumatologic disorders
Nephrotic syndrome

both thymoma and rheumatoid arthritis, ulcerative colitis, many cytopenias, and some extrathymic cancers. Thymectomy has not proved beneficial.

Extrathymic cancers develop in up to 20 percent of patients who survive thymoma, most commonly as lymphomas, bronchogenic carcinomas, and thyroid cancers. The management of these patients should be determined by the extrathymic malignancy and not by the previous thymoma.

Table 91-8

Osserman Clinical Staging Classification for Myasthenia Gravis

Group 1	Ocular myasthenia gravis
A	Ocular symptoms, stable for 4 years
B	Ocular symptoms only, with history of generalized symptoms
Group 2	Generalized myasthenia gravis
A	Mild generalized
	Ocular weakness gradually spreading to skeletal involvement
	Respiratory and bulbar muscles not affected
B	Moderate generalized
	Progression to generalized involvement of skeletal and bulbar muscles
	Dysarthria, dysphagia, difficult mastication
C	Severe generalized
	Skeletal and bulbar muscle weakness
	Respiratory muscle involvement

SOURCE: *Adapted from Blossman GB, Ernstoff RM, Howells GA, et al: Thymectomy for myasthenia gravis.* Arch Surg *128:855–862, 1993.*

Thymic Carcinoma

These are epithelial neoplasms of thymic origin with considerably more cytologic and architectural features of malignancy than manifested by thymomas. Several subtypes exist, with significant differences in outcomes after surgical resection. In 60 patients who underwent surgery with or without adjuvant chemoradiotherapy, the 5-year survival rate was 33 percent. As may be seen in Table 91-5, patients with low-grade lesions (squamous cell carcinoma, mucoepidermal carcinoma, and basaloid carcinoma) sustained a 95 percent cure rate. However, treatment of high-grade lesions (lymphoepithelioid lesions, small cell or neuroendocrine lesions, clear cell and sarcomatoid carcinomas, and anaplastic tumors) yielded only a 15 percent long-term survival. All high-grade lesions should be considered for resection, followed by postoperative chemotherapy, since the more malignant group of tumors may respond to cisplatin-based regimens. These malignancies often are positive for Epstein-Barr virus (EBV) or demonstrate EBV-associated nuclear antigens in carcinoma cells. However, not all thymic carcinomas demonstrate a linkage to EBV.

Thymic Carcinoid

These are distinctly uncommon neuroendocrine cell neoplasms that may present with a paraneoplastic syndrome. Patients in whom the tumors have a small cell appearance on histology need postoperative chemotherapy; those in whom the histology is carcinoid require resection alone.

Thymolipomas

These are tumors of fatty tissue within the thymus gland. They are benign tumors that masquerade as cardiomegaly. If the diagnosis is made preoperatively, they are best followed with CT scans and do not require resection. However, concern about possible malignancy usually necessitates resection.

Thymic Hyperplasia

True hyperplasia is a large bulky benign tumor that most commonly presents in young boys with massive thymic enlargement. This true hyperplasia occurs in children after treatment of other malignancies and recovery from other systemic disease states. It is a common form of presentation in patients who develop bulky thymus glands after treatment for Hodgkin's lymphoma.

Tumors of Lymph Nodes

Together, lymphomas and metastatic cancer constitute the most common mediastinal masses. The anterior mediastinum not only is the most common site of primary mediastinal lymphomas but also can be invaded by cervical or visceral disease.

Lymphoma

Lymphomas constitute 10 to 14 percent of mediastinal masses in adults. They make up 20 percent of anterosuperior mediastinal masses and 20 percent of middle mediastinal masses, ranking second in frequency in both compartments. Lymphomas are rare in the posterior mediastinum. The numerous classifications proposed for lymphoma are generally no better for determining prognosis or managing patients than is simple classification into either Hodgkin's or non-Hodgkin's lymphoma.

Fully 20 to 30 percent of patients with lymphoma are asymptomatic, even with bulky malignant disease. Of the symptomatic patients, 60 to 70 percent have symptoms of local invasion and 30 to 35 percent have systemic symptoms, including fever, weight loss, and pruritus (so-called B type symptoms). Local symptoms include chest heaviness, discomfort, and cough. Tracheal or bronchial compression can cause associated wheezing or stridor. Dysphagia is an unusual complaint. Superior vena cava syndrome is a rare presentation.

Diagnosis requires significant tissue samples. FNA biopsies are not adequate in most circumstances, although the yield improves with radiologic (ultrasound or CT) techniques that target specific areas of the mediastinal mass. The yield is relatively low, but so is the complication rate. Therefore, an attempt is reasonable, especially in patients for whom general anesthesia is problematic. Biopsies under local anesthesia of more accessible cervical nodes or of mediastinal nodes by mediastinoscopy or anterior mediastinotomy (under general anesthesia) have the greatest yield.

Mediastinal Hodgkin's Disease

The age distribution of patients with mediastinal Hodgkin's disease is bimodal—20 to 30 years of age or greater than 50 years of age. Among young adults, men and women are affected equally, although mediastinal lymphoma is more common in older men than in older women. The nodular sclerosing subtype of Hodgkin's disease accounts for almost 90 percent of patients who present with mediastinal invasion. Of these, half have only mediastinal disease and the other half have mediastinal disease with associated neck disease. Systemic symptoms of night sweats, fever, malaise, and weight loss are common. Mild local symptoms such as pain and cough are not uncommon. Severe local symptoms, such as superior vena cava syndrome, are very uncommon.

Chest radiographs reveal superior mediastinal masses that typically arise in the anterior or visceral compartment. In 108 patients with newly diagnosed Hodgkin's disease, CT of the chest disclosed a predictable pattern of contiguous spread: The disease typically began in the anterior mediastinal/paratracheal area and spread to the other mediastinal lymph node groups and subsequently to the hila and into the lungs. So predictable was this pattern of spread that the demonstration of noncontiguous or skip disease should prompt consideration of diagnoses other than Hodgkin's disease. Furthermore, impairment of lungs or pericardium consistently occurred only when the diameter of the mediastinal mass was greater than 30 percent of the thoracic diameter.

This consistent progression of Hodgkin's disease of the mediastinum correlates with the staging of the disease. Table 91-9 depicts the Ann Arbor staging system for Hodgkin's disease. In stages IA and IIA, mediastinal irradiation alone is used. In the more advanced stages, chemotherapy is combined with radiotherapy (Fig. 91-11). Different clinics use somewhat different therapeutic approaches. Most patients (70 to 85 percent, depending on the stage of disease at presentation) respond to treatment with long-term disease-free survivals. Chemotherapy is so effective against Hodgkin's disease that relapses can be treated effectively.

Table 91-9

Ann Arbor Staging System for Hodgkin's Disease

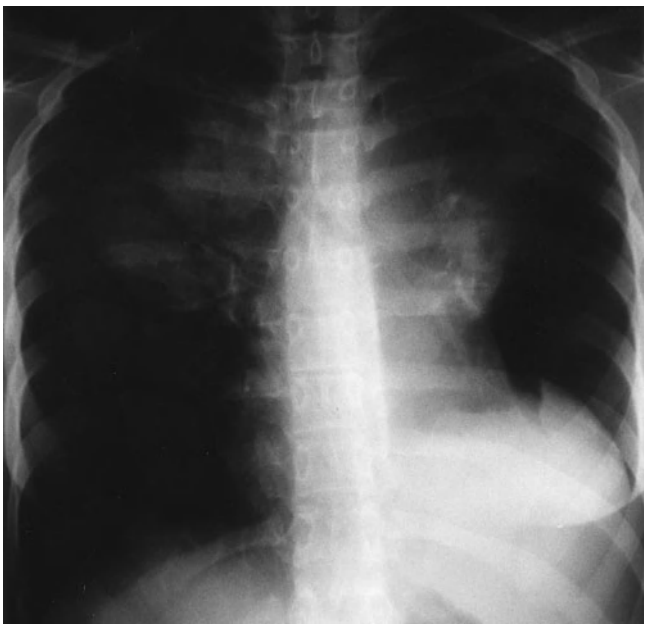
Stage	Characteristics
I	One lymph node region on either side of the diaphragm
II	Two or more lymph node regions on the same side of the diaphragm
III	Two or more lymph node regions on both sides of the diaphragm
IV	Diffuse or disseminated organ involvement

Non-Hodgkin's Lymphoma

Whereas about 75 percent of patients with Hodgkin's disease present with mediastinal disease, only 5 percent of patients with non-Hodgkin's lymphoma present with mediastinal involvement. Abdominal lymph nodes, cervical lymph nodes, and lymphoid tissue of Waldeyer's ring are more commonly affected than are mediastinal nodes. Large irregular anterior and superior mediastinal masses are common and are often associated with large pleural effusions, large pericardial effusions, and large pulmonary parenchymal changes. Because lymph nodes other than mediastinal nodes and body fluids are more accessible, mediastinoscopic biopsy is not usually necessary.

Radiation alone is poor treatment for non-Hodgkin's lymphoma because the disease spreads in a less predictable manner than does Hodgkin's disease (Fig. 91-12). These malignancies may consist of T cells, B cells, diffuse large cell lymphomas, or lymphoblastic lymphomas. Because of the aggressive nature of these lymphomas, a modified staging system (Table 91-10) has been proposed for non-Hodgkin's lymphomas *(lymphocytic lymphomas)*.

Radiation therapy is effective in treatment for patients with early-stage low-grade lymphoma. In some patients it



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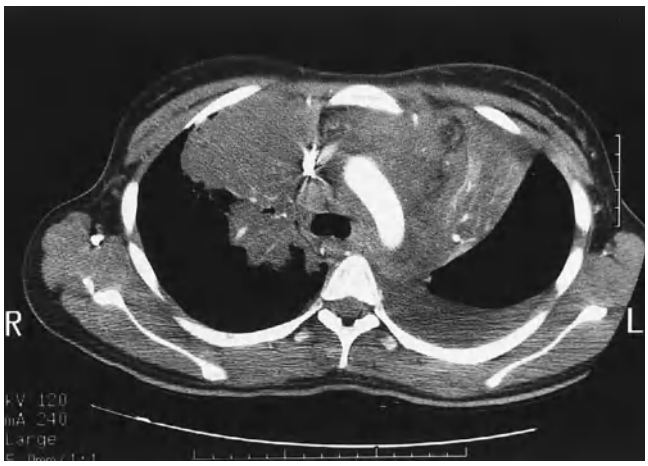

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Figure 91-11 Hodgkin's disease. *A*. Bulky mediastinal mass demonstrated to be Hodgkin's disease by mediastinoscopy. *B*. Chest CT demonstrates bulky mediastinal mass and pleural effusion. The mass disappeared in response to combination chemotherapy and radiotherapy. The patient is well at 18 months.

may be curative (10 years disease-free survival rates of 50 to 60 percent). Chemotherapy may improve results in this group of patients. Patients with advanced low-grade lymphoma may not benefit from treatment. Indeed, no treatment has demonstrated consistent ability to induce a long-term disease-free survival or to alter the natural history of the disease in these patients. Most oncologists would treat patients with Ann Arbor stage III disease with combinations of chemotherapy and radiotherapy, anticipating a 10-year survival of 40 percent.

The treatment of a localized lymphoma that appears histologically to be aggressive consists of combination chemotherapy, either with or without radiation therapy of the affected field. Stages I and II patients can expect 5-year disease-free survival rates of 80 to 100 percent. The benefit of radiotherapy is unclear, as comparisons between patients who receive radiotherapy and those who do not demonstrate no differences in survival. Patients with advanced aggressive disease clearly benefit from combination chemotherapy and can expect survival rates of 35 percent at 10 years.

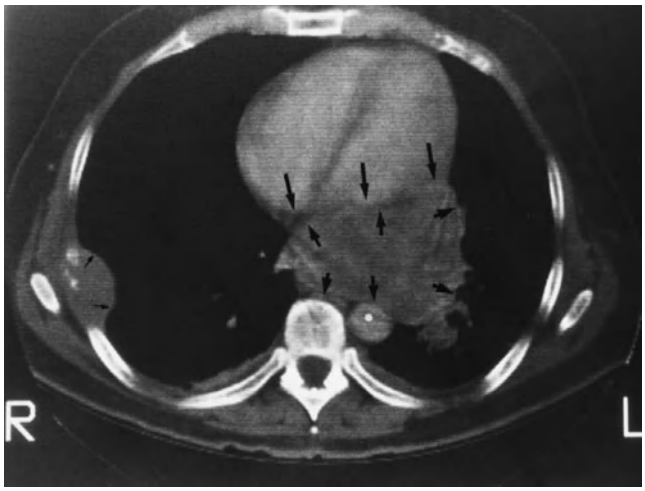


Figure 91-12 Non-Hodgkin's lymphoma. Chest CT shows large middle and posterior mediastinal mass with distant metastasis to a rib in the contralateral chest. This skip involvement is typical of non-Hodgkin's lymphoma.

Table 91-10

NCI Modified Staging for Intermediate and High-Grade Lymphomas

Stage	Characteristics
I	Localized nodal or extranodal disease (Ann Arbor stage I or IB)
II	Two or more sites of disease or a localized extranodal site plus draining nodes with *none* of the following: Performance status <70 B sysmptoms Any mass >10 cm in diameter Serum Ldh >500 Three or more extranodal sites of desease
III	Stage II plus any poor prognostic factors

SOURCE: *From DeVita VT Jr et al: Lymphatic lymphomas, in DeVita VT Jr, Hellman S, Rosenberg SA (eds),* Cancer: Principles of Oncology, *3d ed. Philadelphia, Lippincott, 1989.*

Castleman's Disease

Castleman's disease (giant lymph node hyperplasia) is characterized by mass lesions that occur most often in the anterosuperior mediastinum (52 percent) and less often (26 percent) in the neck, abdomen, and axilla. The mass is a vascular tumor often surrounded by lymphadenopathy. This arrangement makes CT useful diagnostically, since CT may reveal lymphadenopathy surrounding an encapsulated mass that enhances brightly and is distinct from the aorta.

The term is applied to three lesions that are histologically distinct: hyaline vascular, plasma cell, and generalized. The first two represent localized disease, whereas the third refers to multicentric (generalized) disease (Fig. 91-13).

Hyaline vascular Castleman's disease comprises 90 percent of cases. It is a localized lesion found incidentally in asymptomatic patients. Surgical excision is the treatment of choice; radiotherapy has not been effective. The plasma cell variant, also localized, is much less common. Patients are much more likely to have symptoms and present with fever, fatigue, weight loss, and hemolytic anemia. The sedimentation rate is often high and associated with hypergammaglobulinemia, which results from the production of interleukin 6 by the hyperplastic lymph nodes. Resection is the treatment of choice to prevent malignant degeneration.

Generalized, or multicentric, Castleman's disease has the histologic features of both localized forms. The disease occurs in older patients, who typically present with severe systemic symptoms, generalized lymphadenopathy, and hepatosplenomegaly. The mortality from this disease is 50 percent, and the median survival is 27 months. Progression to lymphoma is common. The diagnosis of lymphoma is made from biopsy, and treatment is directed at managing the lymphoma.

Sarcoidosis

Sarcoidosis often presents with mediastinal or hilar adenopathy that is characterized histologically by noncaseating granulomas. The typical patient is in the third or fourth decade of life, is asymptomatic, and has been found to have a mediastinal mass consistent with adenopathy. Some patients present with fatigue and malaise or with complaints referable to particular organ systems. Cough and dyspnea are common; the most common sites of extrapulmonary involvement are the eyes (uveitis, conjunctivitis, and retinitis) and the skin (nodules, plaques, and erythema nodosum). The clinical and laboratory features of sarcoidosis are described elsewhere in this volume. Chest radiograph typically (in 80 percent of patients with this disease) shows bilateral hilar and mediastinal adenopathy, often accompanied by parenchymal involvement of the lungs.

The diagnosis is one of exclusion but may require biopsy of skin lesions or the mediastinal nodes. Part of the tissue obtained by biopsy is smeared and cultured for acid-fast or other likely organisms. The condition of most patients improves, or remains stable, without treatment. About 20 percent suffer progressive pulmonary impairment, with an overall mortality at 5 years of 4 percent.

Germ Cell Tumors

Both benign and malignant teratomas are classified as germ cell tumors. They are the fourth most common lesion in the adult mediastinum. Most lesions in the adult (60 to 80 percent) are benign; in children, a smaller proportion (about 57 percent) are benign.

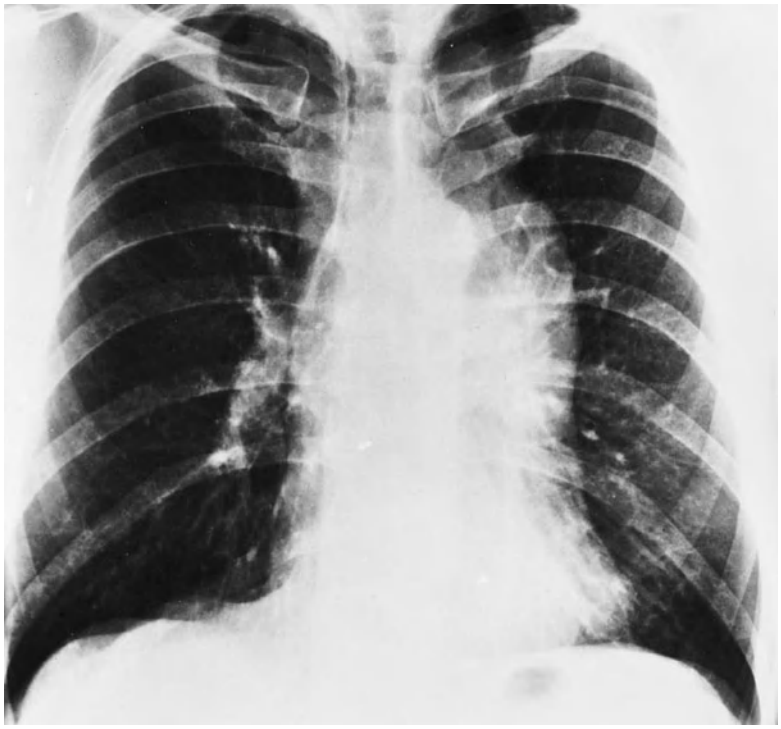
Mediastinal germ cell tumors are of several types. *Benign teratomas* constitute 70 percent of the lesions in children and 60 percent of the lesions in adults. The predominant malignant lesions are *seminomas,* which constitute 50 percent of all malignant lesions. Nonseminomatous malignant lesions include a mix of tumors: malignant teratomas, malignant teratocarcinomas, yolk sac tumors, endodermal sinus tumors, choriocarcinomas, and embryonal cell carcinomas (Table 91-11).

All types of germ cell tumors that have been found in the testes have been reported to occur in the mediastinum. Nonetheless, compared to testicular tumors, extragonadal germ cell tumors are uncommon. Three percent of all germ cell tumors in adults and 7 percent of germ cell tumors in children are extragonadal. An even smaller percentage (1 to 2 percent) of germ cell tumors originate in the mediastinum. Blood levels of alpha-fetoprotein (AFP) and human chorionic gonadotropin (HCG) should be determined for all patients in whom malignant germ cell tumors are suspected. Mediastinal metastasis is common in testicular neoplasms. In weighing the possibility of a germ cell tumor, a primary testicular tumor should always enter into the differential diagnosis because cells responsible for mediastinal germ cell tumors may derive from germ cell rests that migrated to the mediastinum from the urogenital ridge. Metastases from the testes, however, are unlikely. Germ cell tumors usually develop along the body midline in the cranium, mediastinum, retroperitoneum, and presacral areas.

Benign Germ Cell Tumors (Teratomas)

These tumors are of multiple tissues that are foreign to the part of the body in which they develop. They consist of a disorganized mixture of derivatives of the three germinal layers—ectoderm, mesoderm, and endoderm. Consequently, they may contain elements of skin and its appendages, bone, cartilage, intestinal and respiratory epithelium, and neurovascular tissue. About 80 percent of these lesions are benign. A dermoid cyst (benign cystic teratoma) is a variant that contains sebaceous material within a lining of squamous epithelium.

The lesions occur most often in adolescents or adults; the incidence is about equal in males and females. In one series of 86 patients in whom benign mediastinal teratomas had been resected, the mean age was 28 years. About one-third of the patients are asymptomatic, but symptoms are likely to develop if the cysts become infected and erode into the pericardial space, the pleural space, or a bronchus. Occasionally,



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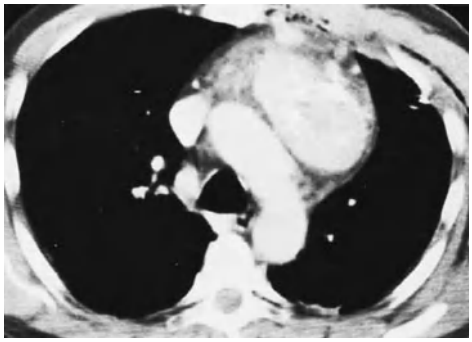

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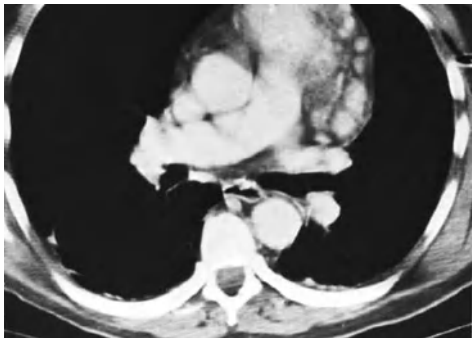

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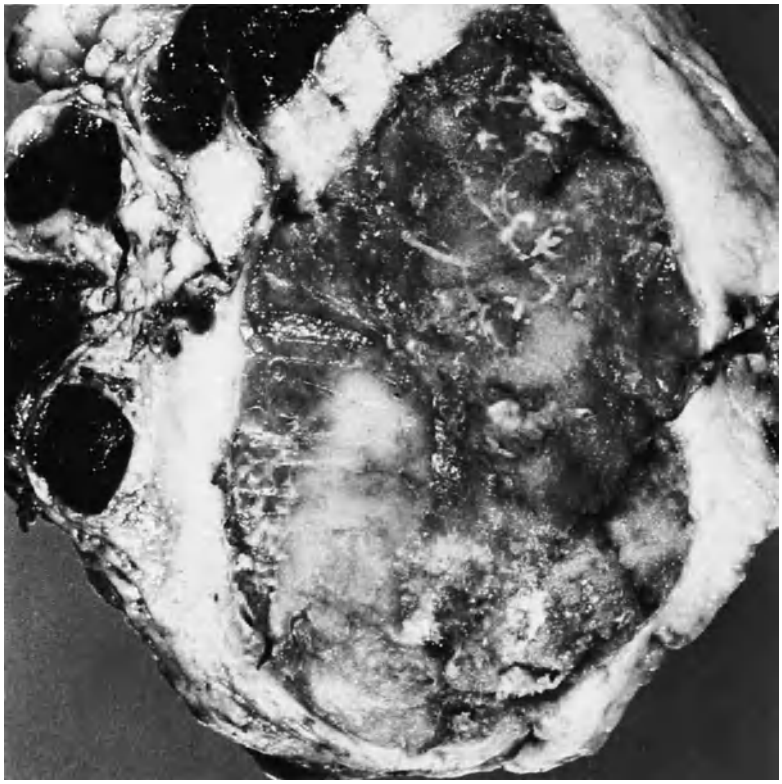

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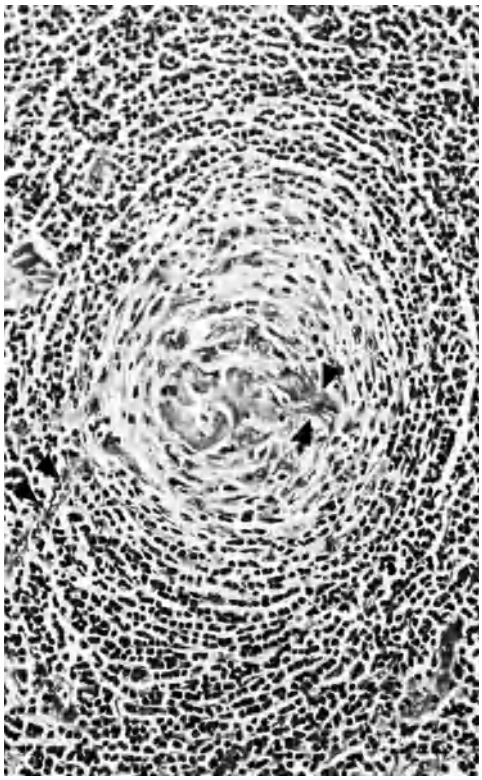


E

Figure 91-13 Giant lymph node hyperplasia (Castleman's disease). *A*. Posteroanterior radiograph. Lobulated superoanterior mediastinal mass extending into the left hemithorax and containing areas of dense calcification (that were quite striking on the lateral chest radiograph). *B* and *C*. CT scans reveal enhancing mass that extends throughout the anterior mediastinum as far as the orgin of the pulmonary artery. The mass contains calcifications and is surrounded inferiorly by multiple lymph nodes. *D*. Excised specimen. Maximum diameter of 13.5 cm. Thick, fibrous capsule that also envelopes adjacent, anthracotic lymph nodes. *E*. Histologic appearance. Many lymphoid follicles with prominent germinal centers. The germinal centers are permeated by radially oriented capillaries and surrounded by concentrically arranged lymphocytes.

Table 91-11

Mediastinal Germ Cell Tumors

Histology	Primary Treatment Method	Overall 5-year Survival (%)
Benign teratomas	Surgical resection	>90
Malignant teratomas	Chemotherapy + surgical resection	~50
Seminomas		
Metastatic	Cisplatin-based chemotherapy	60–85
Resectable	Surgery + radiation + cisplatin chemotherapy	>90
Nonseminomatous lesions	Cisplatin-based chemotherapy	30–50

SOURCE: *Table compiled from Parker D, Holford CP, Begent RHJ, et al: Effective treatment for malignant mediastinal teratoma.* Thorax *38:897–902, 1983; Dulmet EM, Macchiarini P, Suc B, et al: Germ cell tumors of the mediastinum: A 30-year experience.* Cancer *72:1894–1901, 1993; Logothetis CJ, Samuels ML, Selig DE, et al:* J Clin Oncol *3:316–325, 1985; Goss PE, Schwertfeger L, Blackstein ME, et al:* Cancer *73:1971–1979, 1994.*

episodes of hypoglycemia occur in patients with benign mediastinal teratomas and are relieved by resection of the tumor. Approximately a third of these lesions are calcified. In the series of 86 patients, all of the surgical deaths (5 of 86) occurred before 1945. If the benign lesions were completely resected, no postoperative radiation was given and the disease-free interval averaged 10 years. In general, complete resection results in cure.

Malignant Germ Cell Tumors

The origin of malignant germ cell tumors is unclear. The several different types behave differently and require different therapies.

Malignant Mediastinal Teratomas

Malignant teratomas typically include elements of mature (benign) teratoma, immature teratoma, choriocarcinoma, yolk sac carcinoma, embryonal carcinoma, and seminoma in various proportions. These tumors produce either AFP or HCG, the presence of either of which is diagnostic for malignant as opposed to benign tumor. In a series of eight patients, neoadjuvant chemotherapy resulted in a decrease in hormone levels. Two regimens—one with vincristine, methotrexate, bleomycin, and cisplatin and the other with etoposide, dactinomycin, and cyclophosphamide—were given. Six of the eight patients subsequently underwent resection; one patient, who had residual tumor, also received postoperative chemotherapy. One surgical patient died eight months after surgery; the others were alive and well 13 to 136 months after the start of treatment. The two patients who were treated medically died 1 and 15 months, respectively, after the operation.

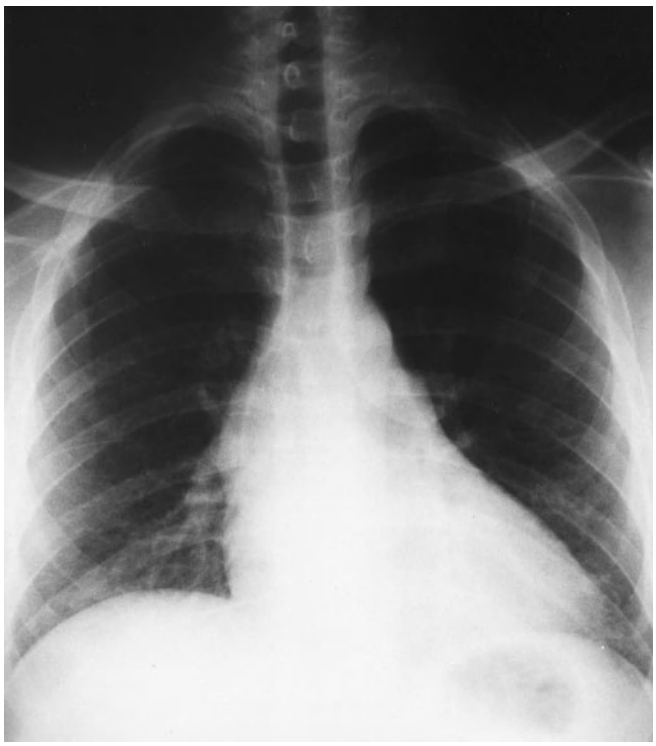
Mediastinal Seminomas

The embryologic origins of mediastinal seminomas are unclear. One theory holds that they derive from somatic cells of the bronchial cleft. The other holds that they derive from extragonadal or embryonic yolk sac germ cells arrested near the developing thymus in the course of their migration along the urogenital ridge to the gonad.

Pure seminomas constitute 50 percent of all germ cell tumors of the mediastinum. They occur principally in men 20 to 40 years of age (Fig. 91-14); fewer than 5 percent occur in women. Mediastinal seminomas are the most common of the malignant germ cell tumors of the mediastinum. They often present with intrathoracic metastases that preclude excision. A CT scan of the testicles is necessary to rule out a primary lesion that originates in the testicles. Serum levels of AFP and HCG rarely increase in patients with mediastinal seminomas; if their levels are increased, another diagnosis is likely.

Seminomas are very radiosensitive. Radiotherapy is appropriate primary therapy for early-stage lesions, as is surgical resection. Criteria for resectability are that the patient is asymptomatic, that the mass is confined to the anterior mediastinum, and that neither intrathoracic nor distant metastases are present. Only complete resections contribute to cure or palliation. Even after complete resection, radiation (4500–5000 rads) improves outcome.

Chemotherapy benefits patients whose lesions appear histologically to be particularly malignant and therefore suggest a high risk of failure. The regimens most commonly used are vinblastine, bleomycin, and cisplatin. Chemotherapy given to patients with disseminated disease can yield 5-year disease-free survivals of 60 to 90 percent. Extensive disease and prior radiotherapy presage poorer prognosis.



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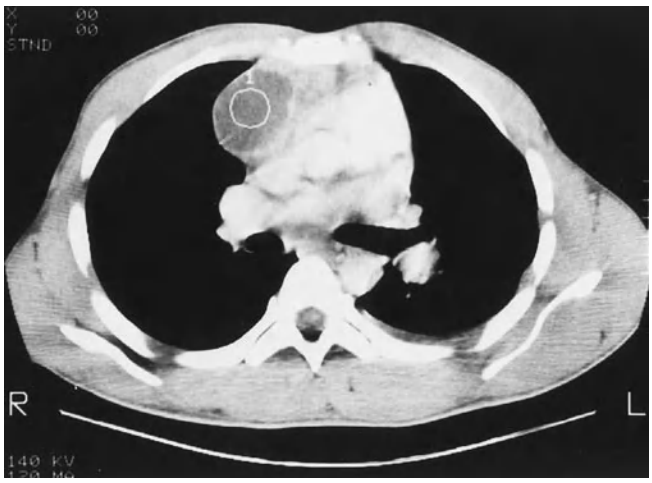

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Figure 91-14 Mediastinal seminoma. Twenty-nine-year-old man, HIV positive, with generalized malaise and 5- to 10-pound weight loss. *A*. Chest radiograph reveals inferior mediastinal enlargement. *B*. Chest CT shows homogeneous mass within thymic fat.

In a series of 41 patients with advanced abdominal seminoma who were re-evaluated after treatment with cisplatin-based chemotherapy, 23 were found to have a residual mass; in 14 of these patients, the mass was greater than 3 cm in diameter. Nineteen of the patients with residual lesions underwent subsequent excision or biopsy. In 6 of the 14 patients in whom the residual mass was greater than 3 cm, viable seminoma was found. These observations suggested that patients in whom the residual mass is greater than 3 cm in diameter should receive follow-up treatment with either radiotherapy or additional chemotherapy, depending on the clinical situation.

Nonseminomatous Tumors

These tumors are less common than seminomatous malignant germ cell tumors. They form in the anterior mediastinal compartment. Nonseminomatous tumors present with symptoms of compression or invasion of local thoracic structures. Patients also have systemic symptoms of weight loss, fatigue, and fever. In 85 to 95 percent, there is one site of distant metastasis. Serum HCG or AFP greater than 500 mg/ml is diagnostic of nonseminomatous malignant germ cell tumors (Fig. 91-4). Nonseminomatous malignant germ cell tumors include pure and mixed embryonal carcinomas, teratocarcinomas, chorio-carcinomas, and endodermal sinus (or yolk sac) tumors.

The typical patient is a young male (median age of 35 years). In all patients with these tumors, βHCG or AFP levels in serum are increased. Nonseminomatous tumors usually have a heterogeneous density on CT scan, whereas seminomas tend to have a homogeneous density. They can present with pleural effusions. These tumors are relatively more frequent in patients with Kleinfelter's syndrome.

Embryonal carcinomas occur in both adults and children and are clinically similar to seminomas.

Choriocarcinomas typically present in young adult men, half of whom have gynecomastia. This results from production of βHCG by the tumor. Therefore, βHCG is a tumor marker in these patients and helps in following the course and recurrence of the disease.

Endodermal sinus (yolk sac) tumors form in both adults and children. They occur infrequently in the mediastinum and more commonly in sacrococcygeal teratomas and in the gonads. They produce AFP no matter where they are located; the blood level of this protein helps in following therapy.

Teratocarcinomas are mixed-cell lesions. They are similar to embryonal and endodermal sinus tumors in that they occur in adults and children and may present with distant metastases.

Management of these tumors does not require surgery initially, since the lesions are generally unresectable at presentation. Treatment with chemotherapy and radiotherapy is the mainstay. More aggressive regimens, particularly the addition of cisplatin, improve the results of treatment of extragonadal nonseminomatous tumors. In such responders who are left with a residual mass, resection is appropriate. Testicular tumors are more chemosensitive than all extragonadal tumors, and retroperitoneal tumors are more sensitive than mediastinal tumors. The chemotherapy regimens include bleomycin, cisplatin, vinblastine, and etoposide. These regimens can yield

complete response rates of 40 to 60 percent and 30 to 50 percent long-term survivors (Table 91-11).

Patients with nonseminomatous germ cell tumors, especially those with yolk sac or embryonal cell carcinoma in combination with teratoma, are prone to develop hematologic neoplasms. The median time to development of the hematologic malignancy (usually megakaryoblastic leukemia or malignant histiocytosis) is 6 months. Thirteen of 16 reported patients developed the second hematologic malignancy within 1 year after the diagnosis of the mediastinal germ cell tumor. The course of the hematologic malignancy is particularly virulent. Although all these patients had received cisplatin, it could not be implicated as the etiologic agent because reviews of large numbers of patients who received cisplatin for other malignancies have revealed no similar hematologic malignancies. A marking isochromosome (12p) in the mediastinal germ cell tumor and in the associated leukemic blasts in one patient has suggested that these tumors may arise from a common progenitor cell.

Any mass that remains after chemotherapy should be resected if two conditions are met: the patient has had a good response to the chemotherapy, and levels of tumor markers in serum fall to normal. Any tumor left behind is usually a benign teratoma or necrotic tumor mass that can degenerate and redevelop malignancy. If the tumor markers do not fall but the tumor shrinks, surgery is of no benefit.

A few mediastinal germ cell tumors are composed of a single cell type. Testicular biopsy or testicular CT is necessary in patients with such mediastinal germ cell tumors to rule out a primary testicular neoplasm. Testicular biopsy is indicated if a mass is palpated, if high-resolution ultrasound is abnormal, and if CT demonstrates involvement of pelvic or retroperitoneal lymph nodes.

MIDDLE MEDIASTINAL MASSES

Bronchogenic Cysts

Mediastinal cysts constitute 20 percent of all mediastinal masses, and bronchogenic cysts make up 60 percent of all mediastinal cysts. Symptoms are present in two-thirds of patients, usually from compression of adjacent structures. If the diagnosis of a bronchogenic cyst is made preoperatively and patients are asymptomatic, observation is an appropriate course. If there is any question of malignancy—based on radiographic appearance, positive cytology, or evidence of enlargement or recurrence—the lesion should be resected. The presence of symptoms—especially pain, cough, or hemoptysis—suggests the advisability of resection. The presence of an air-fluid level indicates connection with the bronchopulmonary tree and the likelihood of recurrent infection and indicates that resection is in order. Symptoms tend to develop with time, and resection at an asymptomatic stage may be best in healthy subjects. Also, malignancy or infection can develop in these cysts if the decision is made to observe instead of operating. Video-assisted techniques offer the opportunity to resect less threatening lesions with low morbidity (Fig. 91-15).

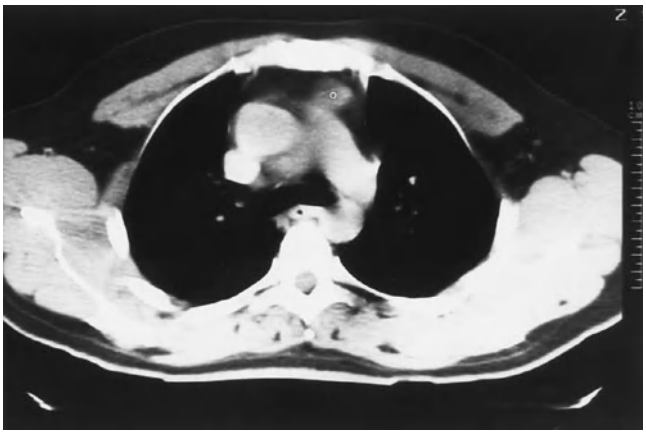


Figure 91-15 Bronchogenic cyst. CT scan obtained to evaluate dull chest ache. The lesion was thoracoscopically excised, and the patient was discharged home 2 days after the operation.

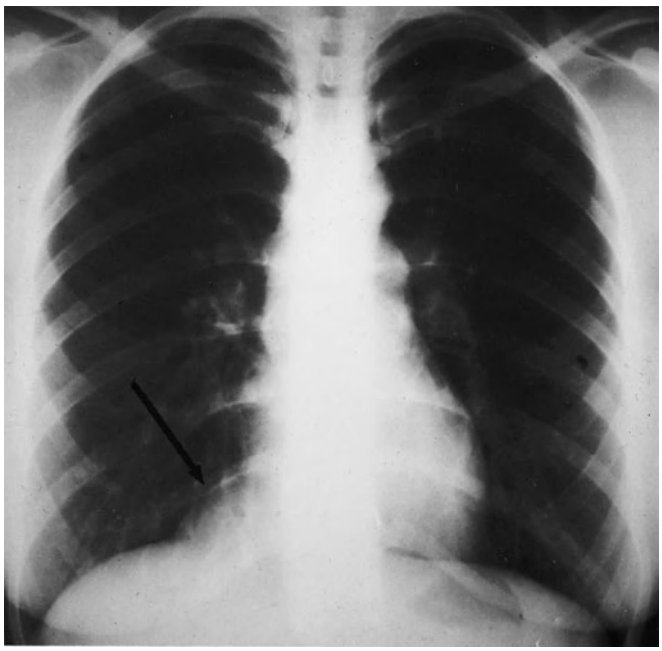
In 86 patients followed for 20 years at the same institution, 20 of whom had bronchogenic cysts of the lung and 66 of the mediastinum, 33 percent were asymptomatic at the time of operation. At operation in these 86 patients, fistulization, ulceration, hemorrhage, or infection was found in 33 percent of the resected lesions. Overall, the experience indicated that 82 percent of these patients had a bronchogenic cyst that was symptomatic, complicated, or both. There were no surgical deaths, and one major complication ensued (reintubation and ultimate tracheostomy for respiratory failure). In view of these results, the authors recommended resection of all bronchogenic cysts, asymptomatic or not.

Esophageal Cysts

Esophageal cysts are periesophageal lesions that are smooth and possess some form of gastroesophageal epithelial lining. Diagnosis is possible with esophageal ultrasound, chest CT scan, or contrast studies of the upper gastrointestinal tract. Resection is the therapy of choice, whether by thoracoscopic or open technique. The site of the resection should be buttressed with vascularized tissue.

Neuroenteric Cysts

Neuroenteric cysts make up 5 to 10 percent of foregut lesions and are associated with vertebral anomalies. They possess not only endodermal but also ectodermal or neurogenic elements. They are usually connected by a stalk to the meninges and spinal cord. They present in infants before 1 year of age and are uncommon in adults. A CT scan showing a cystic mediastinal lesion with an associated vertebral abnormality—such as congenital scoliosis, hemivertebrae, and spina bifida—should prompt consideration of neuroenteric cysts.



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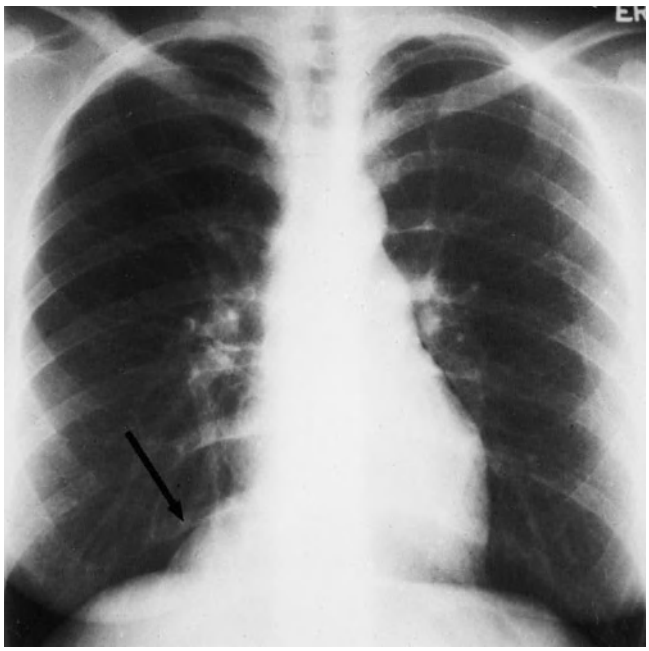

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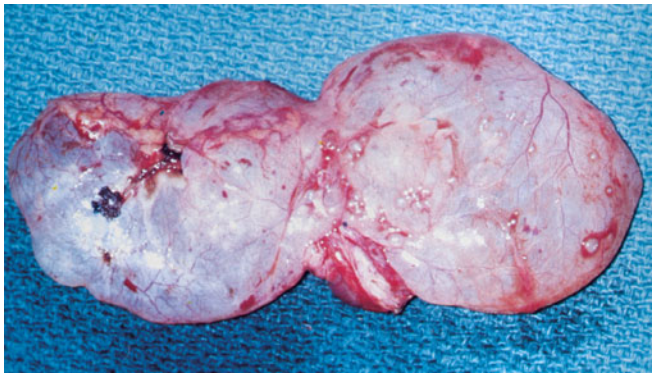

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Figure 91-16 Pericardial cyst. *A*. Posteroanterior radiograph when patient was first seen. Arrows outline cyst. *B*. Three years later. *C*. Specimen removed at surgery.

Mesothelial Cysts

Mesothelial cysts have been described as pericardial, pleuropericardial, spring water, cardiophrenic, and simple cysts.

Pericardial or Pleuropericardial Cysts

Pericardial cysts are commonly located in the cardiophrenic angles. They have fibrous walls and contain clear, watery fluid. Mesothelial cysts are benign, and if the diagnosis is secure, resection is not necessary. If symptoms develop or if the lesions cannot be differentiated from hernias, bronchogenic cysts, or sequestra, resection is necessary (Fig. 91-16).

Thoracic Duct Cysts

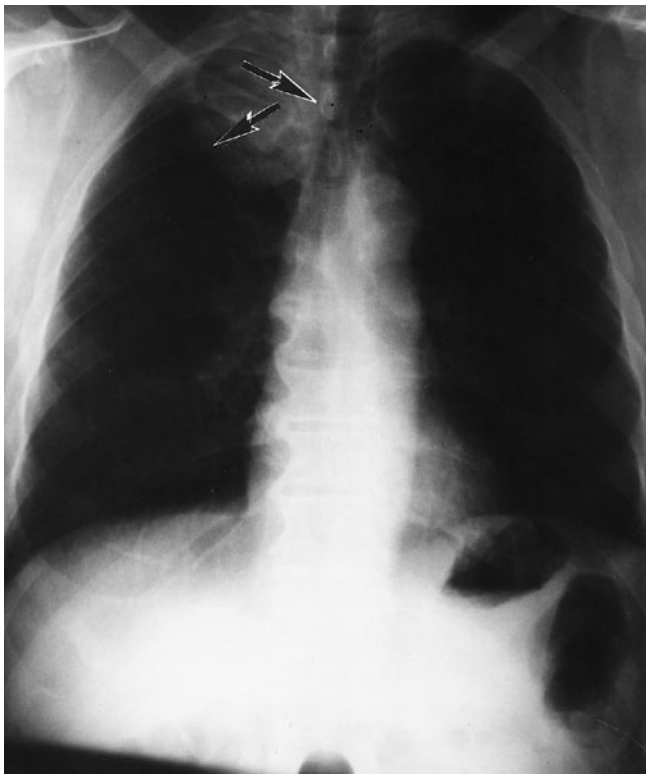
These cysts are rare. They may arise at any level of the thoracic duct but do not retain a communication with the thoracic duct. The lesion may distort the trachea or esophagus. Observation is appropriate if the diagnosis can be made preoperatively, since there is no malignant potential. Ligation of the thoracic duct may be necessary to resect a thoracic duct cyst.

POSTERIOR MEDIASTINAL MASSES

Neurogenic Tumors

The most common masses in both children and adults used to be neurogenic tumors. In recent decades, although these tumors continue to be the most common malignancy in children, in adults they have become less common than either thymomas or lymphomas. They now represent approximately 15 percent of all mediastinal masses in adults. Furthermore, in adults, the malignancy rate of neurogenic tumors is less than 10 percent (and probably only 1 to 2 percent). In children, fully 50 percent of these lesions are malignant.

Neurogenic tumors develop from the embryonic neural crest cells around the spinal ganglia and from either



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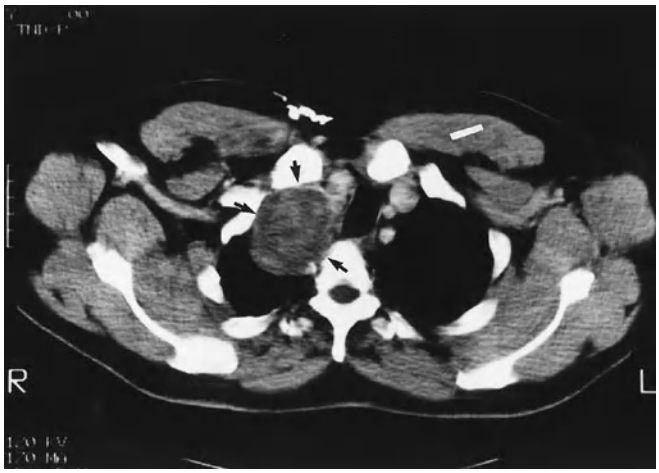

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Figure 91-17 Schwannoma. PA radiograph of 67-year-old man with chronic cough who had undergone a total thyroidectomy 20 years earlier. *A*. Chest radiograph demonstrates superior mediastinal mass projecting into the right hemithorax. *B*. Lesion high in thoracic inlet abutting anterior and posterior chest walls.

sympathetic or parasympathetic components. Almost all these lesions form in the paravertebral sulci in association with intercostal nerves. Lesions can also develop from vagus and phrenic nerves. Most of the lesions are asymptomatic, although some patients manifest symptoms of spinal cord compression or have cough, dyspnea, chest wall pain, and hoarseness. Horner's syndrome is an unusual presentation.

Most patients with neurogenic tumors are asymptomatic, so the initial diagnosis is usually made on chest radiographs obtained for other reasons. A rare patient may present with a pheochromocytoma or a chemically active neuroblastoma or neuroganglia. In all symptomatic patients, serum catecholamine levels and 24-h urine levels of homovanillic acid and vanillylmandelic acid should be determined.

CT scanning is necessary to rule out intraspinal extension along the vertebral nerve roots (so-called dumbbell tumors). These patients often present with symptoms of spinal cord compression. About 10 percent of patients with mediastinal neurogenic tumors have extension through a vertebral foramen. Although the vast majority of these lesions are benign, approximately 1 to 2 percent are malignant. The CT scan typically shows a smoothly rounded homogeneous density abutting the vertebral column. For patients with dumbbell extensions through the intravertebral foramina or lesions abutting on the thoracic vessels, MRI may be useful in demonstrating involvement of the vertebral column and extension into the spinal cord. Nerve sheath tumors account for 65 percent of all mediastinal neurogenic tumors. Widening of the intervertebral foramen calls for myelography to determine whether there is involvement of the spinal cord. Combined laminectomy and thoracic resection at the same site has been popularized by Grillo's team.

Tumors of Nerve Sheath Origin

Benign lesions are classified as either neurilemoma (schwannoma) or neurofibromas (Fig. 91-17). Neurilemomas are more common than neurofibromas. Twenty-five to 40 percent of patients with nerve sheath tumors have multiple neurofibromatosis (von Recklinghausen's disease).

Malignant tumors (neurogenic sarcomas or malignant schwannomas) are unusual. The incidence of malignancy is greater in tumors that are part of von Recklinghausen's disease (10–20 percent).

Neurilemomas are well encapsulated, firm, and grayish tan. Melanotic schwannomas are grossly pigmented, and most of them extend into the spinal cord.

In general, the prognosis with any malignant tumor of nerve sheath origin is poor. Neurogenic sarcomas occur at the extremes of age—in the first and second decades of life and in the sixth and seventh decades. They represent less than 10 percent of all thoracic neurogenic tumors. The primary method of treatment is resection, by either thoracotomy or video-assisted thoracic resection. CT scanning is necessary to identify any intraspinal extension. If intraspinal extension is present, it should be resected at the same time with neurosurgical assistance. Postoperative radiation is always given.

So-called dumbbell tumors are neurogenic tumors that extend through the intravertebral foramen into the spinal column. Akwari and associates found that 9.8 percent of patients with mediastinal neurogenic tumors had extension through an intervertebral foramen. These patients present with symptoms of spinal cord compression. MRI is useful to delineate vertebral column impairment and intraspinal extension.

Tumors of Autonomic Nervous System

Neuroblastomas and ganglioneuroblastomas typically occur in children and are rare in adults. They are malignant and should be resected if identified.

ENDOCRINE TUMORS

Mediastinal Pheochromocytoma

These tumors usually cause no symptoms. Occasionally, however, they do present with varying degrees of hypertension, diabetes, and hypermetabolism. The tumors produce epinephrine, norepinephrine, or both. Vanillylmandelic acid and homovanillic acid are the chief urinary excretion products, but epinephrine and norepinephrine may also be secreted in the urine. Normal levels of vanillylmandelic acid in the urine are 2 to 9 mg/24 h. Normal levels of epinephrine in the urine should be less than 50 μg/24 h; normal norepinephrine levels in urine should be less than 150 μg/24 h.

Large masses may be visible on the chest radiograph, but in most patients CT scans are necessary to visualize the tumors. On MRI, a nonhomogeneous mass with a flow void will be visualized. ^{131}I-metaiodobenzylguanidine scintigraphy is particularly useful for mediastinal lesions: It can be used to localize lesions not seen on other scans.

The tumors may produce functioning peptides that can cause Cushing's syndrome, secretory diarrheas, and polycythemia vera. In the thorax, they probably derive from neuroendocrine cells and typically develop in the paravertebral sulci. Treatment requires surgical excision. However, the patient should first undergo alpha blockade with phenoxybenzamine for 1 week and then beta blockade with metoprolol or propranolol. Typically, the fluid volume of these patients is contracted and will normalize during the period of alpha blockade. For emergency surgery, simultaneous alpha and beta blockade and fluid restoration are necessary.

Parathyroid Adenomas

Normal parathyroid glands occur in abnormal positions in 20 percent of the population—in the lower part of the neck, thymic capsule, or anterior mediastinum. Approximately 20 percent of parathyroid adenomas localize to the mediastinum: 80 percent in the anterior mediastinum and 20 percent in the visceral compartment. It is unusual to be able to identify these lesions either by chest radiography or CT scan. Usually, a search in the mediastinum begins only after a negative neck exploration for hyperparathyroidism. After a negative exploration of the neck, further search using MRI, technetium scanning, thallium scanning, single photon emission computed tomography (SPECT) scanning, and venous sampling for parathyroid hormone can help to localize the lesion.

OTHER MEDIASTINAL TUMORS

Mesenchymal Tumors

These tumors constitute approximately 2 percent of all tumors that occur in the mediastinum. More than half of these mesenchymal lesions are malignant, however, and they run the entire gamut of soft tissue tumors. Their management resembles that of soft tissue tumors in the rest of the body; resection is indicated if possible.

Fatty Tumors

Some fatty tumors, if they can be reliably identified before surgery, do not require resection. Lipomatosis is overgrowth of mature fat seen as a widening of the mediastinum (Fig. 91-3). It results from exogenous obesity, steroids, or Cushing's disease and should not be resected. Lipomas can form in the mediastinum and do not require resection unless they appear to be growing rapidly. Large lipomas can cause respiratory embarrassment and may require resection for symptomatic reasons.

Lipomoblastomatosis is an unusual benign lesion seen principally in children. It is associated with fatty overgrowth in the mediastinum and compression of structures. It should be resected. *Liposarcomas* of the mediastinum are rare. On CT scanning, the density of these masses is midway between that of fat and water. The lesions are large and ill defined. They cause local symptoms, including superior vena caval obstruction and tracheobronchial compression. They should be resected.

SUPERIOR VENA CAVA SYNDROME

In the first part of the twentieth century, the most common causes of superior vena cava (SVC) syndrome were benign mediastinal diseases, specifically syphilitic aneurysms. Currently, malignant tumors, such as lymphoma, bronchopulmonary cancers, thymic malignancies, and germ cell tumors of the mediastinum, account for more than 90 percent of all SVC obstructions. Lung cancer is most common, especially small cell cancer, although lymphoma is also common. Other malignancies are rare. Five to 10 percent of cases of SVC obstruction are due to benign causes. Most result from invasive monitoring techniques, such as the placement of central venous lines, Swan-Ganz catheters, and interventional techniques, such as the placement of pacemakers and central venous catheters for chemotherapy.

Congestion of venous outflow from the head, neck, and upper extremities results in swelling of the face, neck, arms, and upper chest. Patients may have headaches, dizziness, tinnitus, and a bursting sensation. In addition, the face may appear cyanotic even though capillary refill is normal. Venous hypertension in SVC syndrome may lead to serious consequences (e.g., jugular venous and cerebrovascular thrombosis). Therefore, this syndrome requires urgent treatment.

Chest radiography may show mediastinal widening but is nonspecific. CT scanning, using intravenous contrast, can document the SVC syndrome but must show opacification of the SVC above the mass and nonopacification below to establish the diagnosis. Thrombosis, compression, and invasion of the SVC are common causes. If the CT scan is nondiagnostic, bilateral phlebography using arm veins may demonstrate caval obstruction, especially for the SVC syndrome that is secondary to chronic fibrosing mediastinitis or indwelling intravenous catheters or pacemaker leads. Radioactive iodine scans may be useful for SVC obstruction secondary to goiter.

In order to obtain tissue for diagnosis, FNAB may be diagnostic. Experienced surgeons and anesthesiologists can perform mediastinoscopy safely in this group of patients. Intraoperative complications, including bleeding, are rare, but the airway management is complicated. Patients with the SVC syndrome, or any large anterior mediastinal mass, often must be intubated and extubated while awake so that airway obstruction can be prevented during the surgical procedure.

If the underlying disease is malignant, it is important to obtain tissue from the mediastinal neoplasm causing the SVC syndrome in order to direct therapy. Because the SVC syndrome may cause cerebral venous thrombosis, it is an oncologic emergency. In patients with respiratory or neurologic symptoms, treatment without tissue diagnosis may be necessary. The treatment of choice is very high-dose radiation therapy: 3000 to 4000 rads for 4 days.

Additional medical measures include salt restriction, diuretic treatment, steroid administration, and anticoagulation. Although radiotherapy is the mainstay of treatment, patients with small cell carcinoma, lymphoma, and undifferentiated carcinoma may benefit from the addition of chemotherapy. Intravascular stenting with expandable venous stents (Gianturco or Palmaz) has been successful in many patients and is appropriate therapy for poor-risk patients who do not respond to radiotherapy. Surgical resection is aggressive therapy but is appropriate in good-risk patients. In a series of 22 patients who underwent resection of lung cancers ($n = 6$) and malignant mediastinal tumors ($n = 16$), combined with resection of the SVC and subsequent reconstruction, the mortality was modest (4.5 percent) and the survival rates surprisingly good: the overall actuarial survival rate was 48 percent at 5 years. The survival rate of patients with mediastinal tumors was 60 percent at 5 years.

For benign causes of SVC syndrome, treatment must be tailored to the specific origin. Substernal goiters should be resected. Aneurysmal disease causing SVC syndrome requires cardiopulmonary bypass and repair. Anticoagulation and antibiotic administration are the best initial treatments of idiopathic thrombophlebitis or septic thrombophlebitis and iatrogenic thrombosis of the SVC. Failure of these approaches calls for the use of fibrinolytic agents such as urokinase and streptokinase.

The treatment of SVC syndrome in patients with chronic fibrosing mediastinitis is controversial. Replacement of the SVC with vein or ringed polytetrafluoroethylene (PTFE) grafts is possible, but the technique is reserved for severe symptoms recalcitrant to medical treatment. The best approach in this case is median sternotomy. Unless the benign process continues to progress, however, most symptoms will resolve without surgery as collaterals develop.

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PART

XII

Disorders of the Chest Wall, Diaphragm, and Spine

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92

Nonmuscular Diseases of the Chest Wall

George E. Tzelepis • F. Dennis McCool

The chest wall, an integral part of the respiratory pump, consists of the rib cage, rib cage muscles, diaphragm, and abdomen. Like the respiratory muscles, the nonmuscular structures of the chest wall (i.e., thoracic spine, ribs) are also essential for normal respiratory function. Disorders primarily affecting these structures, by themselves or in combination with other disease processes, may impose elastic and resistive loads on the inspiratory muscles, weaken them and ultimately lead to respiratory failure and death. In some disorders, such as kyphoscoliosis and obesity, the load on the respiratory muscles is chronic and progressive. In contrast, with flail chest, the load on the respiratory muscles is acute. The respiratory muscles have little time to adapt and respiratory failure may quickly ensue. Other disorders, such as ankylosing spondylitis and pectus excavatum, have minimal impact on respiratory function. Diseases directly affecting the respiratory muscles are discussed in Chapter 93.

KYPHOSCOLIOSIS

Diagnosis and Etiology

Kyphoscoliosis refers to a group of spinal disorders characterized by curvature of the spine in the lateral direction (scoliosis), sagittal plane (kyphosis) as well as rotation of the spine itself (Fig. 92-1). Kyphoscoliosis may be: (a) congenital; (b) secondary to other disorders; or (c) idiopathic (Table 92-1). Congenital kyphoscoliosis is usually present at birth. Not necessarily familial, congenital kyphoscoliosis may be related to isolated malformations of the vertebrae during prenatal development or may be a manifestation of a more generalized disorder such as muscular dystrophy, Ehlers-Danlos syndrome, or neurofibromatosis. Secondary kyphoscoliosis is usually associated with diseases that primarily affect the neuromuscular system. Kyphoscoliosis associated with

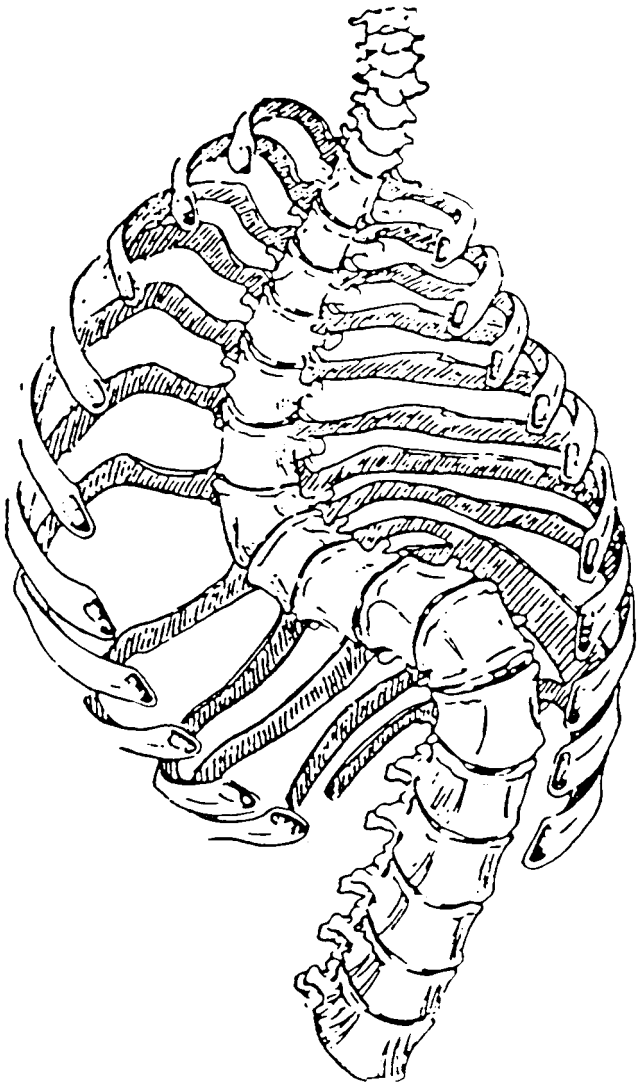

Figure 92-1 Schematic representation of the rotation of the spine and the rib cage seen with scoliosis. *(Based on data of Bergofsky EH, Torino GM, Fishman AP:* Cardiorespiratory Failure in Kyphoscoliosis. *Medicine (Baltimore) 38:263–317, 1959.)*

neuromuscular disease is sometimes referred to as "paralytic" kyphoscoliosis. The most common causes of paralytic kyphoscoliosis are polio, muscular dystrophy, cerebral palsy, and spina bifida. Idiopathic kyphoscoliosis, the most common cause of all forms of kyphoscoliosis, usually begins in late childhood or early adolescence and involves females more often than males with a ratio of 4:1.

In severe kyphoscoliosis, the deformity is readily apparent on physical examination. The dorsal hump seen on examination is due to the angulated ribs rather than to the spine. The shoulders and hips are also rotated and on different planes because of the spinal rotation. In children and adolescents with idiopathic kyphoscoliosis, the initial changes in spinal curvature may be very subtle and require careful inspection to detect them. However, as the degree of kyphosis progresses the spinal deformity becomes easily recognized.

The true degree of spinal rotation and flexion is not apparent on physical examination, especially in mild cases

Table 92-1

Causes of Kyphoscoliosis

Congenital
Paralytic or secondary
Neuromuscular
Poliomyelitis
Muscular dystrophy
Cerebral palsy
Friedreich's ataxia
Charcot-Marie-Tooth disease
Disorders of connective tissue
Marfan's syndrome
Ehlers-Danlos syndrome
Morquio's syndrome
Vertebral disease
Osteoporosis
Osteomalacia
Vitamin D-resistant rickets
Tuberculous spondylitis
Spina bifida
Post-thoracoplasty
Idiopathic

of kyphoscoliosis. The severity of the defect is more accurately assessed by radiographically measuring the Cobb angle, which is the angle formed by the intersection of two lines, each of which is parallel to the top and bottom vertebrae of the scoliotic or kyphotic curves (Fig. 92-2). The greater the Cobb angle, the more severe is the deformity. Cobb angles of greater than 100 degrees are more likely to be associated with respiratory symptomatology. Typically, symptoms consist of dyspnea on exertion that progress with age and the degree of spinal deformity.

Respiratory Mechanics and Pulmonary Function Tests

The combined effects of kyphosis, scoliosis, and rotation of the spine reduce the compliance of the chest wall and increase the recoil pressures of the chest wall and the respiratory system at any given lung volume, with the recoil pressures being greatest as one approaches total lung capacity (TLC) (Fig. 92-3). The most pronounced reductions in respiratory system and chest wall compliance are usually seen in individuals with severe kyphoscoliosis and Cobb angles greater than 100 degrees. These individuals may exhibit the most severe reductions in chest wall and respiratory system compliances when compared with other diseases of the chest wall (Table 92-2). Those with scoliotic angles of less than 50 degrees usually have minimal changes in respiratory system compliance. However, children with congenital kyphoscoliosis may have

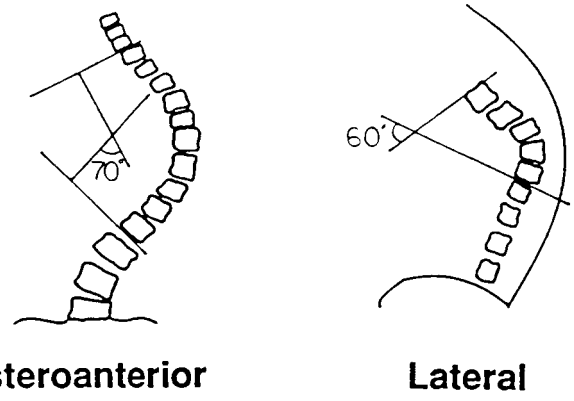

Figure 92-2 Schematic of the posteroanterior radiograph depicting the lines constructed to measure the Cobb angle of scoliosis and the lines drawn on the lateral radiograph to measure the Cobb angle of kyphosis. *(Based on data of Rochester DF, Findley LJ: The lungs and neuromuscular and chest wall disorder in Murray and Nadel (eds),* Textbook of Respiratory Medicine. *Philadelphia, WB Saunders, 1988, p 1942.)*

normal chest wall compliance despite pronounced chest wall deformity. This may reflect a very compliant rib cage in newborns and young children. The lung also becomes less distensible, but its compliance is not as severely affected as that of the chest wall. It is thought that the reduced lung compliance results from microatelectasis due to breathing with low tidal volumes rather than from intrinsic lung disease.

Respiratory muscle strength, assessed by measurements of maximal static inspiratory and expiratory pressures (PI_{max} and PE_{max}, respectively), may be normal or reduced in patients with kyphoscoliosis. Individuals with kyphoscoliosis secondary to neuromuscular diseases have the most pronounced inspiratory muscle weakness, whereas respiratory muscle strength is typically normal in young patients with idiopathic scoliosis and Cobb angles of less than 50 degrees. When the Cobb angle is greater than 50 degrees, there may be mild to moderate reductions in PI_{max} and PE_{max}. In the absence of neuromuscular disease, the reduced strength may be related to altered geometry of the chest wall, which in turn affects the mechanical advantage of the respiratory muscles. In patients with secondary kyphoscoliosis due to neuromuscular diseases, the reduced respiratory system compliance in conjunction with respiratory muscle weakness may result in a profound restrictive process. These individuals are at extreme risk for developing respiratory failure.

Kyphoscoliosis can lead to one of the most profound restrictive patterns of any of the chest wall diseases (Table 92-3). TLC and vital capacity (VC) may be reduced to 30 percent of predicted with severe deformities of the spine. Residual volume (RV) may be normal or slightly increased. Since the RV is not as severely affected as TLC, the RV/TLC ratio may be high. Individuals with mild and moderate degrees of

Table 92-2

Respiratory Mechanics in Diseases of the Chest Wall

	KS	Post-THOR	PE	AS
CRS (% predicted)	50	50	—	70
CCW (% predicted)	30	40	—	60
CL (% predicted)	60	50	80	80
Pimax (cm H_2O)	37	50	90	56
MVV (L/min)	37	37	107	80

Notes: Abbreviations: KS = kyphoscoliosis; Post-THOR = post-thoracoplasty; PE = pectus excavatum; AS = ankylosing spondylitis; CRS = compliance of respiratory system; CCW = compliance of chest wall; CL = compliance of lungs; PI_{max} = maximum inspiratory pressure; MVV = maximum voluntary ventilation.

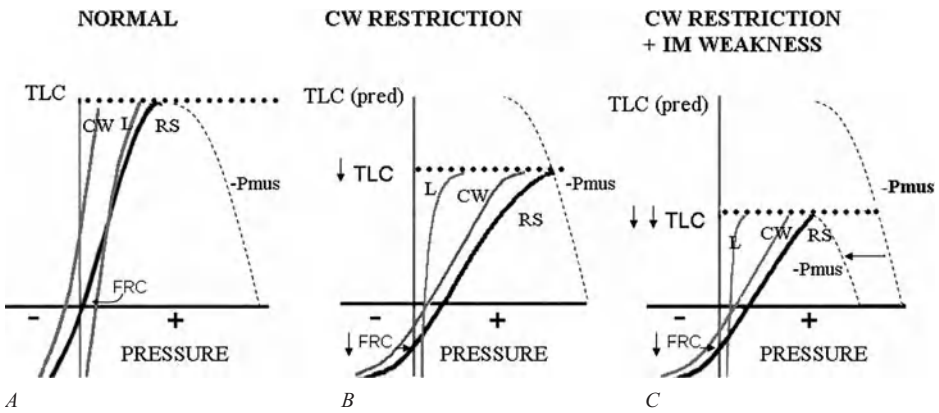

Figure 92-3 Schema showing the volume-pressure relationships of the chest wall (dashed line), lung (dot and dashed line), and respiratory system (solid line) for (*A*) healthy individuals, (*B*) individuals with chest wall restriction, and (*C*) individuals with chest wall restriction complicated by inspiratory muscle (IM) weakness. *C*. Maximal inspiratory muscle pressures (P_{mus}) are reduced by about half in this panel. *B*. The reduction of chest wall compliance lowers respiratory system compliance, FRC, and TLC. *C*. The restriction is amplified by the presence of IM weakness.

Table 92-3

Pulmonary Function in Diseases of the Chest Wall

	KS	Post-THOR	PE	AS
TLC (% predicted)	44	64	90	85
VC (% predicted)	30	49	90	79
RV (% predicted)	94	91	100	97
FEV_1 (% predicted)	40	41	93	81
FEV_1/FVC	80	57	81	74

Note: Abbreviations: KS = kyphoscoliosis; Post-THOR = post-thoracoplasty; PE = pectus excavatum; AS = ankylosing spondylitis; TLC = total lung capacity; VC = vital capacity; RV = residual volume; FEV_1 = forced expiratory volume in 1 s; FVC = forced vital capacity.

kyphosis and scoliosis (Cobb angles less than 60 degrees) may only have mild reductions in VC and TLC. Individuals with Cobb angles greater than 90 degrees, however, invariably have restricted lung volumes. Other factors contributing to the degree of restriction include: (a) the number of vertebrae involved; (b) the location of the curve; (c) the patient's age; (d) the presence of kyphosis; and (e) the degree of rotation of the spine. Although indices of forced expiratory flow are typically reduced, i.e. a low FEV_1, the ratio of FEV_1/FVC remains normal, thereby indicating no concomitant obstructive process.

Although the degree of spinal curvature is associated with the extent of pulmonary restriction, inspiratory muscle strength is another factor that importantly determines severity of the restrictive pattern. In patients with paralytic kyphoscoliosis (spinal deformity secondary to neuromuscular disease), the neuromuscular weakness itself seems to be the predominant factor promoting restriction and the association between the degree of spinal curvature and extent of restrictive dysfunction is not as strong. Individuals with paralytic kyphoscoliosis are thus likely to have greater pulmonary function impairment for a similar degree of spinal deformity than patients with idiopathic scoliosis. Similarly, individuals with congenital scoliosis have a greater loss in VC for a given degree of spinal deformity than patients with idiopathic scoliosis. Coexisting rib deformities or underlying lung abnormalities amplify the restrictive process in individuals with congenital scoliosis.

The combination of reduced chest wall and lung compliance increases the elastic work of breathing. Since the oxygen cost of breathing increases with increasing loads placed on the respiratory system, it is not surprising that the resting oxygen cost of breathing is three to five times that seen in healthy subjects. Inspiratory muscle weakness diminishes respiratory muscle reserve by reducing maximal forces and velocities of shortening that the muscles can develop. Since respiratory muscle fatigue is, in part, a function of the balance between the loads placed upon the respiratory muscles and their reserve to overcome these loads, it is clear that individuals with severe kyphoscoliosis are at high risk for developing respiratory failure.

Exercise Capacity

Individuals with combined restrictive defect and inspiratory muscle weakness have impaired exercise tolerance. Maximum oxygen consumption may be reduced to about 60 to 80 percent of predicted. Because these individuals exhibit a restrictive pattern on pulmonary function testing, the breathing pattern response to exercise in patients with severe kyphoscoliosis differs from that seen in normal subjects. Specifically, the ratio of tidal volume to vital capacity (VT/VC) is greater than 0.5 and the ratio of maximum exercise ventilation to maximum voluntary ventilation (VE_{max}/MVV) can reach 70 percent. Deconditioning and lack of regular aerobic exercise may be contributing to the poor exercise tolerance in individuals with moderate to severe scoliosis. Supplemental oxygen may improve oxygenation during exercise but usually does not affect walk distance.

Control of Breathing

When an elastic load is imposed on the respiratory muscles in a healthy individual, the neural drive to breathe is increased. Accordingly, one may predict that the added elastic load of the stiffened chest wall would provide a greater stimulus to breath in individuals with kyphoscoliosis. Thus, during quiet breathing or breathing stimulated by carbon dioxide or exercise, indirect measures of neural drive to the respiratory muscles, such as the mouth occlusion pressure at 100 ms (P0.1), may be elevated in these individuals. The mouth occlusion pressure (P0.1) has been shown to correlate positively with the degree of scoliotic deformity. Increased drive may not be seen as an increase in ventilatory response to CO_2 as the stiffened chest wall has reduced mobility and cannot increase ventilation in response to increased respiratory muscle drive or activity. Thus, the drive to breathe may be normal in these individuals, but compensatory increases in minute ventilation are limited by mechanical factors of the rib cage. The effects of aging and its influence on the control of breathing require further clarification in this population as any blunting of respiratory drive increase the risk of CO_2 retention.

Another means of compensating for heightened elastic loads is to alter breathing pattern (i.e., raise respiratory frequency and lower tidal volume). Patients with severe kyphoscoliosis may adopt a rapid shallow breathing pattern consisting of low tidal volumes and shortened inspiratory time. Both of these factors are found to correlate negatively with the angle of scoliosis. The advantages of adopting such a breathing pattern include: (a) a reduction in the work per breath, but not necessarily the cumulative work per minute; and (b) the reduction of the ratio of pressure needed to inhale

(P breath) to PI_{max}. In theory, reducing this ratio would lessen the likelihood of developing inspiratory muscle fatigue. However, the disadvantages of adopting this breathing pattern include worsening microatelectasis leading to further reduction of lung compliance.

Sleep Disordered Breathing

Patients with kyphoscoliosis may be predisposed to hypoventilation during sleep. The increased elastic load due to stiffened chest wall heightens respiratory drive so that diaphragm activation increases and there is greater recruitment of the inspiratory muscles of the rib cage. Since neural drive to the intercostal muscles is diminished during non-rapid eye movement (non-REM) sleep and may be absent during REM sleep, the burden of expanding the nondistensible chest wall falls more on the diaphragm. If there is any degree of diaphragm weakness, this can result in hypoventilation, especially during REM sleep. Consequently, the degree of oxyhemoglobin desaturation during sleep is more severe in individuals with severe kyphoscoliosis than that seen during sleep in patients with other respiratory diseases, such as chronic obstructive pulmonary disease or interstitial lung disease. The magnitude of hypoxia may not correlate with the degree of thoracic deformity. Persistent nocturnal desaturation during sleep may further exacerbate respiratory muscle dysfunction, lead to cor pulmonale, and predispose these individuals to cardiorespiratory failure. Obstructive sleep apnea, which has a prevalence similar to that seen in the general population, may further complicate nocturnal hypoventilation in these patients. Because sleep-related disorders represent a potentially treatable cause of respiratory failure, they should always be evaluated in kyphoscoliotic patients with carbon dioxide retention.

Gas Exchange

Persistent nocturnal desaturation may eventually be associated with daytime hypoxemia and hypercapnia. The cause of hypoxemia may be multifactorial; ventilation/perfusion (V/Q) mismatching is commonly present and is worse in patients with Cobb angles greater than 65 degrees. In addition to V/Q mismatch, intrapulmonary shunt related to underlying atelectasis as well as alveolar hypoventilation may also account for the hypoxemia in some individuals. Hypercapnia initially appears during sleep and with exercise; eventually, as the disease progresses, hypercapnia is seen during the day. Prolonged hypoxemia may result in pulmonary hypertension. The degree of hypoxemia is positively associated with the degree of kyphosis, but not with the etiology of kyphoscoliosis, or age of onset of scoliosis. Individuals with severe kyphoscoliosis may have oxyhemoglobin desaturation with minimal activity.

Clinical Course

Congenital kyphoscoliosis may exhibit a rapidly progressive course with spinal cord compression further compromising the respiratory system. Similarly, individuals with neuromuscular disease who develop secondary kyphoscoliosis may also have pronounced respiratory disability. Those at greater risk for developing respiratory complications are individuals who have an onset of the spinal deformity at an early age, rapid progression of the deformity during growth, and continued progression after skeletal maturity. By contrast, individuals with idiopathic kyphoscoliosis typically have a more benign course. If the thoracic deformity is mild, they have an excellent prognosis with little impairment in breathing or overall lifestyle. Individuals with mild idiopathic kyphoscoliosis are no more likely to develop ventilatory failure or have any greater loss of lung volume with aging than the general population. However, those with moderate or severe idiopathic kyphoscoliosis may be at higher risk for respiratory compromise. In general, individuals with thoracic deformities greater than 50 degrees at skeletal maturity are at risk for a progressive increase in the spinal angulation at a rate of about 1 degree annually.

Although individuals with severe idiopathic kyphoscoliosis younger than 35 years of age are usually asymptomatic, those who are older need to be closely monitored for respiratory compromise. These individuals may have an insidious onset of shortness of breath, initially with exertion and then at rest. As the spinal deformity progresses during aging, respiratory failure may ensue. Once cor pulmonale develops, the prognosis is generally poor and, without treatment, death may occur within 1 year. This risk depends on the degree of deformity. Factors such as inspiratory muscle weakness, underlying neuromuscular disease, sleep disordered breathing, and airway compression should be entertained. Concomitant obstructive dysfunction heightens the risk for respiratory failure. In contrast, pregnancy poses no added risk for respiratory complications; however, patients with severe degrees of kyphoscoliosis and reductions in VC to less than 1 L may have respiratory difficulties during pregnancy. The observation that patients with Cobb angles of greater than 100 degrees may survive into their seventh decade with minimal or mild cardio-respiratory impairment supports the notion that factors other than the spinal deformity also importantly influence outcome.

Treatment

General supportive care for adults with kyphoscoliosis includes immunization against influenza and pneumococci, prompt care of respiratory infections, use of supplemental oxygen, smoking cessation, and maintenance of body weight within a desirable level. Preventive measures include interventions such as chest physiotherapy, use of bronchodilators, diuretics, and physical activity to improve exercise capacity and minimize deconditioning. Supplemental oxygen may be needed with activity or exercise and can be beneficial in improving exercise tolerance.

Specific treatment of nocturnal hypoventilation can be accomplished with noninvasive positive pressure ventilation, which is typically delivered by a nasal or full-face mask.

Indications for initiating noninvasive nocturnal ventilation include symptoms suggestive of nocturnal hypoventilation (i.e., fatigue, morning headache, dyspnea) or signs of cor pulmonale with either an elevated daytime arterial P_{CO_2} or nocturnal oxygen saturation less than 88 percent for 5 consecutive minutes.

The advent of this method of ventilatory support has provided an alternative to the clinician for treating respiratory failure. Treatment of respiratory failure with these devices may avert or delay the need for tracheotomy. Both negative and positive pressure devices have been used to ventilate individuals with kyphoscoliosis noninvasively. Initially, negative pressure ventilators such as cuirass, body wrap ventilators, or tank ventilators were used. However, drawbacks of using such devices included induction of upper airway obstruction during sleep, the bulky nature of the equipment, and the need to custom fit devices such as a cuirass ventilator to the chest wall. In contrast, noninvasive positive pressure ventilation has become a more accepted therapy because the equipment is compact and more portable than negative pressure devices. Furthermore, if there is associated sleep apnea, positive pressure devices are well suited to minimize the apneic episodes. When prescribing a positive pressure device, either a pressure- or volume-preset ventilator can be recommended. Apart from a greater leakage with the pressure modality, these two modalities have equivalent effects on physiological and clinical parameters and overall health status. The rapid shallow breathing pattern that is usually adopted by these patients highlights the importance of having a ventilator that has a short response time and minimizes patient-ventilator asynchrony. Contraindications to noninvasive ventilation include the inability to protect the upper airway due to impaired cough or excessive airway secretions.

The benefits of noninvasive nocturnal ventilation in patients with kyphoscoliosis have been well documented and include improvements in quality of life, gas exchange, sleep architecture, and pulmonary hemodynamics (Table 92-4). It has much less of an impact on measurements of VC and respiratory muscle strength, including twitch trans-diaphragmatic pressure or endurance. The likely mechanism of improvement in respiratory failure is increased ventilatory response to carbon dioxide rather than improvement in respiratory muscle contractility. Long-term noninvasive ventilation significantly reduces the number of days spent in the hospital as well as number of hospitalizations for respiratory failure. It is also likely that there is a survival benefit in patients with kyphoscoliosis who have had an episode of respiratory failure (Fig. 92-4). In uncontrolled studies at 1 and 5 years, survival of patients with kyphoscoliosis and respiratory failure who were treated with noninvasive ventilation was 90 and 80 percent, respectively. The role of noninvasive ventilation in acute respiratory failure is not as well documented. In this instance, volume cycle ventilation via an endotracheal tube would be the treatment of choice.

Operative treatment traditionally consists of spinal fusion and/or insertion of Harrington rods. These approaches have been used for many years to correct the spinal deformity and stabilize the spine. However, these interventions are often accompanied by complications later in life, such as chronic back pain or further spinal deformation. Spinal fusion and Harrington rod placement may not significantly improve the VC or gas exchange in patients over the age of 20. Typically, immediately following surgery, there is a reduction in the compliance of the chest wall and respiratory system as well as in VC, although improvements in pulmonary function may occur in some individuals. In children and adolescents, the results are more promising. In the short term ($1^1/_2$ to 3 years following surgery) lung function may improve. The role of surgery may be most important in patients with

Table 92-4

Therapeutic Benefits of Noninvasive Mechanical Ventilation in Patients with Kyphoscoliosis

Gas exchange indices	
Pa_{O_2}	Increase
Pa_{CO_2}	Decrease
Bicarbonate	Decrease
Pulmonary Function Tests	
FVC	No change
FEV_1	No change
TLC	No change
FRC	No change
Respiratory mechanics	
MIP, MEP	No change or slight increase
Twitch Pdi	No change
Chest wall compliance	No change
Lung compliance	No change
Hemodynamic parameters	
PAP	Decrease
Ventilatory control	
Hypercapnic ventilatory response	Increase
Sleep	
Epworth sleepiness score	Decrease
Quality of life	Improvement
Survival	Increase

Efficacy data derived from mostly nonrandomized, noncontrolled studies. Notes: Abbreviations: MIP = maximal inspiratory pressure; MEP = maximal expiratory pressure; Pdi = transdiaphragmatic pressure; PAP = pulmonary artery pressure.

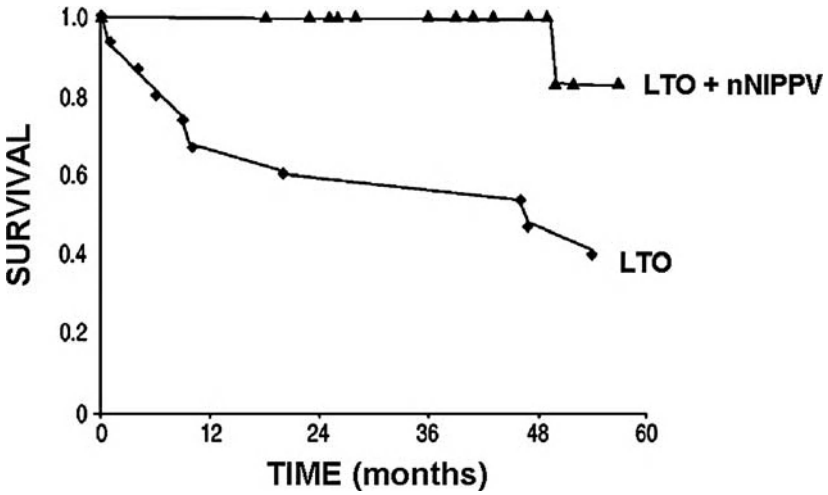

Figure 92-4 Survival curves of kyphoscoliotic patients treated with long-term oxygen therapy (LTO) or LTO and nocturnal nasal intermittent positive pressure ventilation (nNIPPV). *(From Buyse B, Meersseman W, Demedts M: Treatment of chronic respiratory failure in kyphoscoliosis: oxygen or ventilation?* Eur Respir J *22:525–528, 2003, with permission.)*

kyphoscoliosis secondary to neurological disorders. In these individuals, early stabilization of the spine may help prevent progressive myelopathy. Surgery has recently evolved to include less invasive procedures such as titanium rib implantation with rib cage expansion. Initial results are promising in individuals with congenital kyphoscoliosis.

In summary, severe kyphoscoliosis alters the mechanics of the chest wall, imposes an elastic load on the respiratory muscles, increases the work of breathing, and ultimately leads to hypercapnic respiratory failure and cor pulmonale. The degree and onset of respiratory impairment depend to a large extent on the underlying cause of kyphoscoliosis, rate of progression of deformity, onset in relation to skeletal maturity, coexisting respiratory muscle weakness, and sleep disordered breathing. Noninvasive positive pressure ventilation is highly effective in improving gas exchange, overall clinical status, and prognosis in patients with respiratory failure.

THORACOPLASTY

Prior to the advent of antituberculous chemotherapy, surgery involving the lung and/or rib cage was one approach to treat tuberculosis. The varied surgical procedures are referred to as thoracoplasty and were intended to compress the underlying lung (Fig. 92-5). Thoracoplasty consists of different combinations of rib removal, rib fractures, phrenic nerve resection, or compression of underlying lung by filling the pleural space with foreign material (i.e., ping pong balls). Since this procedure was performed in the 1940s and 1950s, very few people, who are alive today, have had these procedures. However, much can be learned from the natural history of patients who have undergone thoracoplasty. These individuals commonly developed dyspnea, severe restrictive dysfunction, and chronic respiratory failure as they aged. The severity of the restrictive pattern was related to a number of factors including the number of ribs removed, the presence of fibrothorax, progressive lung fibrosis due to underlying granulomatous disease, previous lung resection, or phrenic nerve damage. Often, surgery on the rib cage was followed by progressive scoliosis with aging and further deterioration of respiratory function. The severity of restriction and stiffening of the chest wall was similar to that seen with kyphoscoliosis leading to an increase in the oxygen cost of breathing, limited exercise tolerance, and impairment in gas exchange. In general, hypoxemia was common in these patients and cor pulmonale often developed as a harbinger of a poor prognosis. As with severe kyphoscoliosis, treatment consisted of domiciliary oxygen, antibiotics when appropriate, and noninvasive nocturnal ventilation. Although it is unlikely that one may encounter post-thoracoplasty patients, knowledge of the natural history and progressive impairment of respiratory function following aggressive surgery on the rib cage may be useful in understanding and anticipating complications due to similar chest wall surgery for other reasons, such as postinfectious empyema or aggressive treatment of lung cancer.

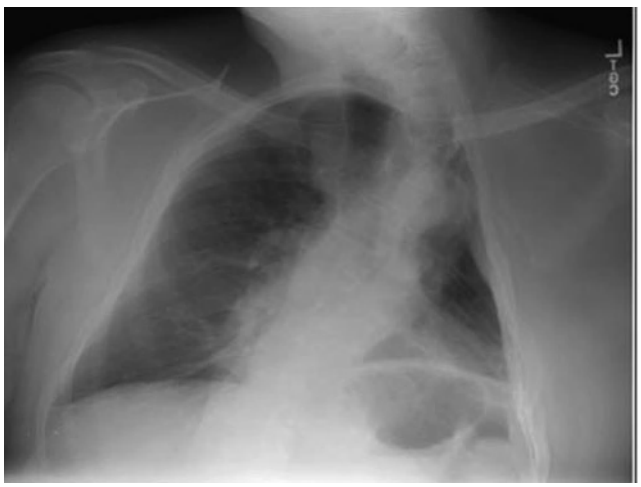

Figure 92-5 Chest radiograph of a patient with a history of *M. tuberculosis,* demonstrating marked deformity of the left hemithorax consistent with prior thoracoplasty.

PECTUS EXCAVATUM

Pectus excavatum is a chest wall deformity characterized by excessive depression of the sternum which affects between 0.5 and 2 percent of the population. It occurs once in every 1000 children and is the most common chest wall deformity seen by pediatricians. The deformity occurs more frequently in males than females (3:1 ratio). The sternal depression can be minimal or extreme. In extreme cases it is readily apparent at birth and progresses as the child grows, especially during the teenage years. The etiology of pectus excavatum is unknown. It is possible that a defect in the connective tissues surrounding the sternum may be present. Connective tissue disorders such as Marfan's syndrome have a higher incidence of pectus deformity. A family history may or may not be present and other factors such as scoliosis, congenital heart disease, and functional heart murmurs occur in patients with pectus excavatum.

The most frequent complaints of patients with pectus excavatum are cosmetic and usually become most troublesome between the ages of 15 and 20 years. Dyspnea with activity and exercise intolerance occurs in 30 to 70 percent of patients. These symptoms are usually out of proportion to what one would expect from the mild restrictive pattern or normal echocardiography. Although rare, respiratory failure can occur in adults with severe pectus deformity.

The degree of deformity is assessed radiographically, most often with chest computed tomography (CT), by measuring the ratio of the transverse to anterior-posterior (AP) diameters of the rib cage at the level of the deepest sternal depression (Fig. 92-6). If the ratio is greater than 3.25, the pectus deformity is considered significant.

Respiratory Mechanics and Exercise Capacity

Impairment in pulmonary function is usually minimal, with TLC and VC being normal or mildly reduced. In most cases, there is no underlying lung disease and lung compliance is normal. If restriction is apparent on pulmonary function testing, it may be related to the presence of concomitant scoliosis. In contrast to individuals with ankylosing spondylitis, the mobility of the rib cage is not impaired during quiet breathing or exercise.

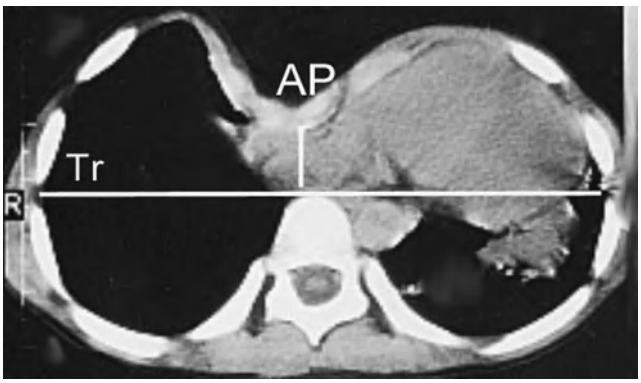

Figure 92-6 Chest computed tomography of a patient with pectus excavatum. The distance between the anterior aspect of the vertebral body and the posterior aspect of the sternum is decreased.

Cardiopulmonary exercise testing is often normal in these individuals. Indices such as maximal work rate, maximal oxygen consumption, and maximal heart rate, as well as the oxygen pulse, are similar among patients with pectus excavatum and controls. Only the most severe deformities may be associated with reductions in maximal work rate or a decrease in oxygen consumption at a given work rate. In these instances, the reduction in exercise capacity is out of proportion to what one would expect from the mild restrictive process. Therefore, other factors leading to decreased exercise tolerance may be operant. Among postulated mechanisms is a reduction in venous return to the heart associated with right ventricular compression due to sternal deformation. In keeping with this postulated mechanism, cardiac anomalies such as compression of the right ventricle, narrowing of the right ventricular outflow track and sacculations of the right ventricular wall have been observed using two-dimensional echocardiography.

Treatment

Medical therapy for pectus excavatum is generally supportive. However, certain individuals with severe deformities have undergone surgical repair of the rib cage. Some individuals selected for surgical repair have had a chest CT scan demonstrating a transverse to AP diameter ratio of greater than 3.25 at the level of the greatest sternal depression. Others with lesser degrees of deformity (transverse to AP diameter ratio less than 3.25) also have undergone repair. Although surgery is most often performed for cosmetic purposes, occasionally it is indicated to relieve pulmonary restriction.

The surgical approaches may be invasive or minimally invasive. Earlier operations, such as the Ravitch repair, include resection of costal cartilage and a sternal osteotomy with or without fixation of the sternum with external or internal supports. This procedure may be complicated by sternal necrosis, infection, or recurrence of the deformity especially in younger children in whom sternal supports are not used. Surgery at an age less than 4 may be further complicated by arrest in growth of the rib cage and worsening of the restrictive process.

A less invasive approach has been developed over the last decade. The Nuss procedure provides a minimally invasive alternative to the traditional approach to correcting pectus deformity. The Nuss procedure consists of placing a curved metal bar under the sternum at the point of its deepest depression through small incisions made on each side of the rib cage (Fig. 92-7). Coastal cartilage is not resected and the sternum is pushed forward and stabilized by the metal bar. The bar generally is in place for 2 to 4 years, resulting in permanent chest wall remodeling. The approach leads to immediate cosmetic improvement. Complications

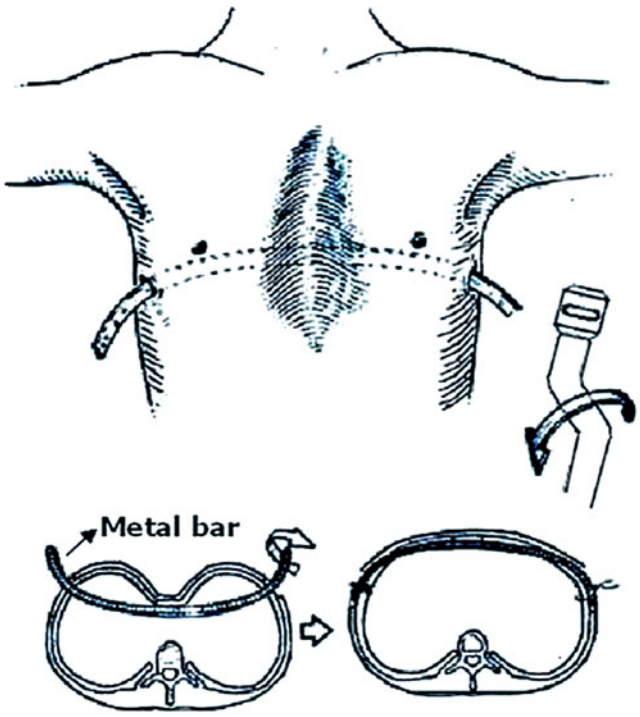

Figure 92-7 Schema depicting the Nuss procedure in a patient with pectus excavatum. A curved bar is inserted behind the sternum and then rotated to displace the depressed sternum ventrally.

of the minimally invasive approach include bar displacement or rotation that would require reoperation, as well as pneumothorax, pericarditis, and infection. Both procedures afford a positive effect on the psychosocial well-being of the patient.

Physiological benefits of either invasive or minimally invasive procedures remain controversial. Pulmonary function may actually deteriorate and exercise capacity and dyspnea may improve slightly. Because most studies of pulmonary function were performed in patients undergoing the more invasive Ravitch operation, the deterioration in pulmonary function seen early or several years after surgical repair has been attributed to disordered chest wall mechanics as a result of structural changes in the sternal and parasternal areas. In theory, the minimally invasive procedure should have fewer adverse effects on pulmonary function. The effects of surgery on exercise tolerance are controversial. Improvements in exercise tolerance, cardiac output and $\dot{V}O_{2max}$ after surgical correction have been reported in some but not in all studies. Discrepancies among studies may be due to differences in patient selection, surgical techniques, interval after the operation, or the effects of growth on pulmonary function.

In summary, pectus deformities apart from their aesthetic effects may also be accompanied by slight decreases in exercise capacity, TLC, and VC. Selection of patients for surgical correction is based on radiographic measurements of the transverse and AP diameter of the chest wall. The minimally invasive correction techniques may cosmetically restore chest appearance but are not always associated with improvements in pulmonary function or exercise capacity.

ANKYLOSING SPONDYLITIS

Etiology and Clinical Features

Ankylosing spondylitis (AS), a chronic inflammatory disease of unknown etiology, is the prototype of a group of related disorders known as the spondyloarthritides, the main characteristic of which is inflammation of the axial skeleton. The spinal involvement in AS can be more severe than that seen in other spondyloarthritides. In particular, the chronic inflammation of the spinal structures and sacroiliac joints may lead to fibrosis and ossification of these structures, thereby limiting spinal mobility. Bony ankylosis of the costovertebral and sternoclavicular joints causes considerable limitation in rib cage expansion.

The annual incidence of AS is 6.6 per 100,000 Caucasian Americans, afflicting men more commonly than women. There is a genetic predisposition for AS, as 95 percent of Caucasian with AS have the HLA-B27 antigen. Clinically, AS patients typically complain of low back pain and stiffness beginning in late adolescence or early adulthood; onset of the disease after the age of 45 is rare. Symptoms are worse in the morning or after rest. Chest pain due to inflammation of manubriosternal junction and/or the sternoclavicular joints and inability to fully expand the chest on inspiration are infrequent complaints. On physical examination, there may be tenderness of the anterior chest wall, or over the costochondral region or the manubriosternal junction. Exercise intolerance and dyspnea are uncommon, unless the patient has parenchymal lung disease, diaphragmatic dysfunction, or cardiac disease. Frequently, sleep interruption due to back pain and stiffness may lead to daytime somnolence and fatigue. Upper airway obstruction due to cricoarytenoid cartilage involvement is a rare complication. In late stages, the limited rib cage expansion may be obvious on inspection while the individual is in the seated position. The change in rib cage circumference at the level of the fourth intercostal space can be measured between a full inspiration and full expiration. If not explained by another condition, rib cage expansion less than 2.5 cm is abnormal and should raise the possibility of AS in young patients with chronic low back pain.

Respiratory Mechanics and Pulmonary Function Tests

Limited expansion of the rib cage is the hallmark of respiratory involvement in AS. This limitation results from fusion of the costovertebral and sternoclavicular joints and possibly intercostal muscle atrophy. The direction of rib cage motion is similar to that in healthy individuals, but the extent of movement is diminished (Fig. 92-8). As with kyphoscoliosis, chest wall and total respiratory system compliance is reduced

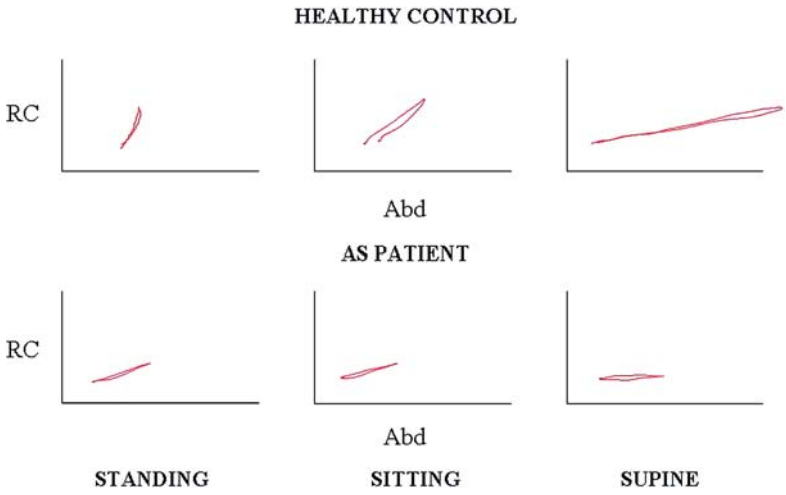

Figure 92-8 Changes in anteroposterior dimensions of the rib cage (RC) and abdomen (Abd) in a healthy individual and one with ankylosing spondylitis (AS). There is limited mobility of the rib cage in all positions resulting in greater motion of the abdomen relative to the rib cage.

in AS, while chest wall resistance is increased. In general, lung compliance is normal unless there is fibrobullous lung disease.

Since expansion of the rib cage is severely limited, displacement of the abdomen by diaphragm displacement is the primary pathway for inflating the chest wall, as rib cage expansion is severely limited. Accordingly, most of the volume change during quiet breathing or exercise can be attributed to caudal displacement of the diaphragm and abdominal wall expansion. For example, in healthy individuals, transdiaphragmatic pressure increases by 1.4-fold during stimulated CO_2 rebreathing. In contrast, transdiaphragmatic pressure in AS increases 2.2-fold for a given amount of minute ventilation during stimulated CO_2 rebreathing. The combination of increased diaphragm shortening and decreased chest wall compliance increases the work performed by the diaphragm and may potentially provide a training stimulus to the diaphragm.

Measurements of pulmonary function usually reveal only mild reductions in VC and TLC. VC is generally reduced to 70 percent of predicted; the reduction is positively correlated with lack of rib cage expansion, disease activity and duration, and spinal mobility. TLC is reduced on average to 80 percent of predicted, and its reduction is proportional to the radiographic severity of spinal ankylosis. Because the rib cage is often fixed in an inspiratory position, both FRC and RV may be increased above predicted normal levels; consequently, the RV/TLC ratio may also be higher. In this setting, the increased RV/TLC ratio should not be interpreted as related to obstructive airway disease.

Osteoporosis of the thoracic spine, which is frequently found in AS, especially in late stages, may lead to kyphosis, modest spinal deformity, and worsening of the restrictive defect. However, the kyphosis angle does not correlate with VC in AS because the effects of posterior fusion of the ribs play a greater role in limiting rib expansion and VC than the degree of kyphosis. Because the rigid osteoporotic spine is excessively fragile, spinal fractures can occur even with minimal trauma. These fractures may also lead to kyphosis and further compromise of respiratory function. Cervical spine fractures, usually at the C6 or C7 level, can result in tetraplegia and respiratory failure. They are associated with a high mortality.

Modest decrements in indices of respiratory muscle strength, especially PI_{max} and PE_{max}, have been described in patients with AS. Because these maximal pressures are limited by the rib cage and accessory muscles, the reduction in these pressures may be related to possible intercostal muscle atrophy secondary to decreased rib cage mobility rather than to diaphragmatic dysfunction. The ability of diaphragm to generate pressure appears to be intact in these patients.

Gas Exchange and Exercise Capacity

Gas exchange is usually normal, with Pa_{O_2} either within the normal range or slightly reduced. Modest hypoxemia may be due to concomitant apical fibrobullous lung disease. Exercise capacity may be mildly decreased in patients with AS, especially in those with marked chest wall restriction. The mechanism of exercise limitation does not appear to be due to ventilatory impairment, as patients usually attain adequate minute ventilation during exercise. Instead, peripheral deconditioning or cardiac limitation may be responsible for the decreased exercise capacity. In support of a cardiac etiology are recent studies showing a decreased stroke volume during exercise in normal individuals with chest wall restriction caused by strapping the rib cage.

Pleuropulmonary Abnormalities

A small percentage (1 to 4 percent) of AS patients develops upper lobe fibrobullous disease. Although the causes are not entirely known, they may include decreased upper lobe ventilation, mechanical stress due to rib cage rigidity, and recurrent lung infections due to impaired cough. Fibrobullous disease is more common in male patients with long-standing disease and may manifest as interstitial infiltrates, fibrosis with honeycombing, or cavitation that mimics tuberculosis. Patients with AS manifest an increased propensity for spontaneous

pneumothorax and infections with *Aspergillus* or atypical mycobacteria. The course of fibrobullous disease is usually progressive and not affected by steroid therapy. Because resection of the lung with fibrobullous disease is complicated by bronchopleural fistula in 50 to 60 percent of patients, surgery should be reserved for the treatment of major hemoptysis. Additional pleuropulmonary abnormalities may be detected only by high resolution CT in patients with AS. These abnormalities include interstitial lung disease, pleural thickening, parenchymal bands, or mild bronchial wall thickening. These changes are subtle and do not correlate with clinical or functional impairment.

Treatment

Medical treatment in patients with AS should focus on relief of symptoms and maintenance of posture and movements, including chest wall expansion. Physiotherapy is regarded as an essential element of the overall management in AS, and should incorporate chest wall expansion and breathing exercises. The exercises are preferably taught to patients by a respiratory physiotherapist. Smoking should be avoided and baseline chest radiographs and spirometry should be obtained. These interventions improve the likelihood of maintaining full employment.

The recent introduction of antagonists of tumor necrosis factor (TNF) in the treatment of AS has revolutionized the overall management of the disease. Recent studies have shown remarkable improvements in all aspects of the disease, including rib cage expansion and quality of life. The extent to which these drugs will affect the natural history of the disease and prevent or delay spinal ankylosis will require long-term studies. An adverse effect of the anti-TNF therapy may be reactivation of tuberculosis. Therefore, AS patients who are candidates for anti-TNF treatment should be screened with a tuberculin skin test and receive prophylactic treatment with isoniazid prior to starting treatment.

In summary, ankylosing spondylitis, through chronic inflammation that primarily affects the axial skeleton, limits spinal flexion, reduces rib cage compliance, and restricts chest wall expansion. These mechanical alterations are associated with only mild reductions in VC, TLC, and exercise capacity. The diaphragm/abdomen pathway compensates for the reduced rib cage distensibility by an increased contribution to ventilation during quiet breathing and exercise. Apical fibrobullous disease, which is occasionally found in advanced cases, may require special attention.

OBESITY

Obesity is a major health problem, with more than half of the adults in the United States being either overweight or obese. This epidemic is not confined to the United States. Indeed, the prevalence of obesity is increasing throughout the world. The most commonly used index to assess the severity of obesity is the body mass index (BMI). This is calculated as the body weight (BW) in kilograms divided by the square of the height (Ht) in meters (BW/Ht^2). The body mass index is positively associated with morbidity and mortality. An individual with a BMI between 18.5 and 24.9 kg/m^2 is normal; a BMI between 25 and 29.9 kg/m^2 is overweight, and a BMI greater than 30 kg/m^2 is considered obese. Those with a BMI greater than 40 kg/m^2 are especially predisposed to develop restrictive lung disease.

Obesity-associated respiratory morbidity can be considered in the context of its effects on: (a) chest wall mechanics and pulmonary function; and (b) the control of breathing. Obesity may or may not be associated with hypoventilation. Individuals in whom there is carbon dioxide retention during wakefulness are considered to have the obesity hypoventilation syndrome (OHS); whereas individuals who are eucapnic are considered to have simple obesity (SO). Individuals with OHS are more likely to have disordered chest wall mechanics and individuals with SO usually exhibit minimal or no pulmonary compromise. Obese, eucapnic individuals with compromised pulmonary function are considered to be morbidly obese.

Chest Wall Mechanics and Pulmonary Function

In individuals with SO, the most common abnormalities in pulmonary function tests are a decrease in expiratory reserve volume (ERV) and FRC with preservation or mild reduction in TLC (Table 92-5). The lower than predicted FRC is a consequence of decreased chest wall compliance by fat in the rib cage and abdomen. The stiffened chest wall changes the slope of the chest wall volume-pressure (V-P) relationship (Fig. 92-3). This shift in the V-P characteristics of the chest wall alters the balance between the recoil of the chest wall and lung so that the FRC occurs at a lower lung volume. In contrast, RV may be normal or even slightly increased in SO. As a result, the difference between the two volumes (ERV) is markedly reduced. In patients with OHS, the reductions in FRC, RV, and TLC are more pronounced. Since similar degrees of obesity in SO and OHS may result in different degrees of lung restriction, the adverse effects of obesity on pulmonary function cannot be entirely explained by the absolute load of adipose tissue on the chest wall. One factor that may account for this difference is the distribution of body fat. Upper body or central fat distribution has a greater effect on pulmonary function than lower body fat distribution, whereas lower fat distribution is more often associated with sleep disordered breathing. Diverse methods have been used to assess the distribution of body fat. These include measurement of waist/hip circumference ratio, abdominal girth/hip breadth ratio, and the thickness of skin folds at multiple sites. CT or MRI imaging has also been used to assess the cross-sectional area of the visceral fat/subcutaneous fat ratio.

Expiratory flow rates are generally normal in SO except for modest reductions in forced vital capacity (FVC) when the

Table 92-5

Respiratory Mechanics in Simple Obesity (SO) and Obesity Hypoventilation Syndrome (OHS)

	Normal	SO	OHS
BW (% ideal)	105	195	201
BW/Ht (kg/cm)	0.42	0.75	0.78
BMI (kg/m^2)	24	45	46
TLC (% predicted)	100	95	83
CRS (L/cm H_2O)	0.11	0.05	0.06
RRS (cm H_2O L^1 sec^1)	1.2	4.0	7.8
Work (J/L)	0.43	0.74	1.64
MVV (L/min)	159	129	89
PI_{max} (cm H_2O)	100	95	60

Note: Abbreviations: BW = body weight; BMI = body mass index; TLC = total lung capacity; CRS = compliance of the respiratory system; RRS = respiratory system resistance; PI_{max} = maximal inspiratory pressure; MVV = maximum voluntary ventilation.

BMI exceeds 45 kg/m^2. Although the FEV_1/FVC ratio may be normal, airways resistance is often increased. The increase in resistance may be due in part to the reduction in lung volume. However, even after correcting for lung volumes, specific airways conductance may be reduced to up to 50 to 70 percent of normal. This may be especially evident in the supine position. When supine, further increases in intra-abdominal pressure may reduce lung volume and increase respiratory resistance. The same mechanisms, especially in the supine position, can promote expiratory flow limitation during tidal breathing and in morbidly obese individuals may lead to the development of intrinsic positive end-expiratory pressure (PEEP) and/or orthopnea.

The reduction in the compliance of the entire respiratory system and increase in its resistance increase the elastic and resistive loads on the respiratory muscles. The work of breathing and oxygen cost of breathing may be 60 percent higher in SO and as much as 250 percent higher in OHS. A two- to threefold increase in intra-abdominal pressure at FRC further impedes breathing by constituting a threshold load that the inspiratory muscles need to overcome to initiate inspiration. This threshold load, in combination with the increased elastic and resistive loads imposed by the lung and chest wall, increases the oxygen cost of breathing at rest in SO by about fivefold and in OHS by nearly tenfold.

It is critical that the inspiratory muscles maintain their strength in order to overcome the heightened loads imposed by obesity. In patients with SO, inspiratory and expiratory muscle strength are generally well preserved. In contrast, individuals with OHS often have weakened respiratory muscles, with strength diminished to approximately 40 percent of predicted. In these individuals, respiratory muscle weakness may be related to deconditioning, fatty infiltration of muscle, or other factors related to chronic disease. Regardless of mechanism, inspiratory muscle weakness may be one of the mechanisms underlying CO_2 retention in individuals with OHS. Another factor may be related to disordered respiratory control (Fig. 92-9).

Control of Breathing

In nonobese individuals, added elastic or resistive loads alter the control of breathing so that neural drive to the respiratory muscles increases. Similarly, one may expect that the increased elastic load due to excess chest wall adipose tissue would increase neural drive to the respiratory muscles in obese individuals. Indeed, respiratory drive in SO is either normal or increased when compared with those of

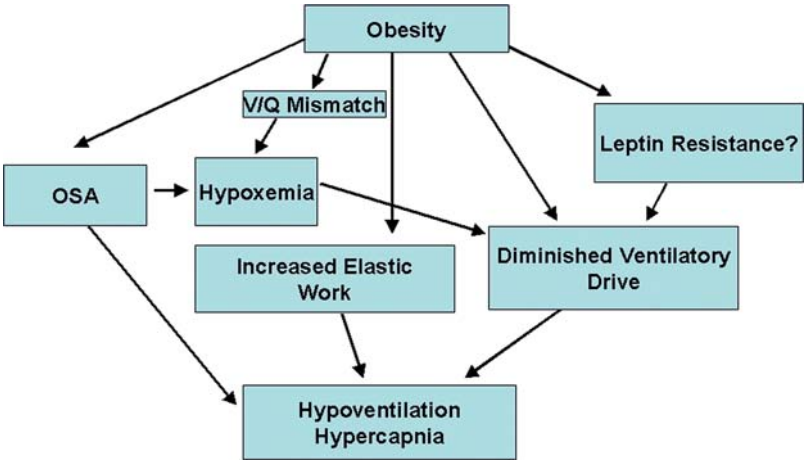

Figure 92-9 Factors involved in the pathophysiology of obesity hypoventilation syndrome.

nonobese subjects during resting ventilation as well as during ventilation stimulated by hypoxia or hypercapnia. The increased chemosensitivity in SO may correlate with BMI and can decrease following weight loss. In contrast, patients with OHS have blunted respiratory drive. In these individuals, there may be significant depression of the ventilatory responses to hypercapnia and hypoxemia, with the response to hypoxia blunted to a greater extent than the ventilatory response to hypercapnia. Peripheral or central factors may underlie the reduced ventilatory drive. Peripheral limits to ventilation due to the stiff chest wall could limit the level of ventilation that can be achieved despite a normal respiratory drive. However, other indices of central respiratory drive, such as the mouth occlusion pressure ($P_{0.1}$) and a reduced diaphragmatic EMG in OHS suggest that a central rather than a peripheral mechanism is responsible for the decreased ventilatory responses to hypercapnia and hypoxemia. Possible explanations for the diminished respiratory drive include either a genetic predetermination or an acquired cause, such as persistent hypoxemia or sleep apnea. Mediators such as leptin have also been implicated as a cause of the reduced ventilatory drive.

Obese individuals also may adapt to the added elastic and resistive loads by changing breathing pattern. Lowering tidal volume and raising the breathing frequency reduces the elastic and resistive work per breath. Individuals with SO have about a 40 percent higher respiratory frequency than nonobese individuals. The increase in breathing frequency is accomplished by shortening both inspiratory and expiratory times. Thus, the ratio of inspiration to total breath time (Ti/Ttot) remains normal. Since tidal volume during quiet breathing is generally not reduced in SO, resting ventilation may be higher. This may reflect an increase in basal metabolism. Those with OHS have a breathing frequency that is higher and a tidal volume that is about 25 percent lower than those with SO.

Exercise capacity is near normal in individuals with SO. Minute ventilation, respiratory rate, heart rate, and oxygen consumption during treadmill exercise are higher in obese subjects than in normal weight individuals; however, the anaerobic threshold is lower than in normal weight individuals. With weight loss, the metabolic demands are reduced and carbon dioxide production and alveolar ventilation during exercise fall by approximately 20 percent.

Gas Exchange

Hypoxemia may either be mild or absent in individuals with SO, whereas it is generally present in individuals with OHS. The mechanism is due in part to hypoventilation, which lowers the partial pressure of oxygen in the alveoli. In addition venous admixture due to ventilation-perfusion mismatch may widen the alveolar-arterial oxygen gradient, thereby worsening hypoxemia. The mismatch of ventilation and perfusion is likely to occur at the lung bases, which are generally well perfused in obesity but poorly ventilated because of airway closure or frank alveolar collapse. These alternations in gas exchange are amplified when obese individuals assume the supine position. Practical consequences of these changes relate to anesthesia and sleep. In both SO and OHS, hypoxemia becomes more pronounced in the supine position; this can be a major concern during induction of anesthesia. During sleep, the increase in metabolic rate with obesity, coupled with the worsening of ventilation perfusion mismatch, produces a more rapid decrease in arterial oxygen saturation during apnea than in nonobese subjects.

Treatment

Weight loss is the optimal treatment for obesity. However, it is not only difficult for individuals to lose weight but even more so to maintain weight loss. One difficulty is that weight loss decreases total energy expenditure in both normal and obese subjects, whereas the opposite is true with weight gain. In patients with OHS and acute or chronic respiratory failure, nasal intermittent noninvasive ventilation may improve gas exchange, daytime somnolence, and overall clinical status.

The effects of weight loss induced by diet or surgery on pulmonary function in SO have been well documented. A weight loss of 40 kg may have little effect on VC and TLC in SO, but a pronounced effect on increasing ERV and lesser effects on increasing FRC. There is generally better ventilation to the lung bases resulting in an increase in arterial P_{O_2} of about 4 to 8 mmHg. With OHS, the effects of weight loss on ERV and FRC are even more pronounced and vital capacity increases as well. These changes are positively associated with weight loss. The oxygen consumption required for a given level of exercise is also diminished. In contrast, respiratory control remains essentially unaltered after weight loss. The effects of laparoscopic gastroplasty on pulmonary function need further clarification; however, this has become a more accepted means of inducing and maintaining weight loss in subjects with SO and OHS.

In summary, respiratory impairment due to obesity may manifest as a sole mechanical impairment (simple obesity) or may be combined with disordered ventilatory control (obesity hypoventilation syndrome). In SO, the VC, TLC, and respiratory compliance are mildly decreased, whereas respiratory muscle strength, ventilatory drive, and eucapnia are well preserved. By contrast, in OHS, all measurements of respiratory mechanics are decreased to a greater extent than in simple obesity; in addition, hypoventilation with hypoxemia and hypercapnia, which results from complex interactions between impaired respiratory mechanics and abnormal ventilatory control, may lead to respiratory failure and cor pulmonale. Obstructive sleep apnea may coexist with either entity. Noninvasive positive-pressure ventilation can efficiently improve gas exchange and overall clinical status in OHS. Weight loss may reverse the impaired pulmonary function and gas exchange due to obesity.

FLAIL CHEST

Flail chest can occur in up to 25 percent of adults who have blunt chest wall trauma. It is a condition in which fractures of the ribs produce a segment of the rib cage that deforms markedly during breathing. Generally, double fractures of three or more contiguous ribs or the combination of sternal and rib fractures are required to create a flail segment of the rib cage. During inspiration, the flail segment is displaced inward rather than expanding outward in concert with the remainder of the rib cage. The most common cause of flail chest is trauma related to automobile accidents or falls. It may also be seen following aggressive cardiopulmonary resuscitation. Rarely, flail chest is due to pathological fractures of ribs, as may occur with multiple myeloma or congenital rib defects. In spontaneously breathing patients with a history of blunt trauma to the chest wall, the diagnosis of flail chest can be made at the bedside by observing the paradoxical motion of the flail segment of the chest wall. Chest radiographs demonstrating multiple rib fractures support the diagnosis. A CT scan yields more information than a chest radiograph with respect to the extent of the injuries of the pleura and pulmonary parenchyma, including pulmonary contusion.

Pulmonary complications such as pulmonary contusion, hemothorax, and pneumothorax can occur in up to 60 percent of patients with flail chest. Thus, the mortality from flail chest may be high. With chest wall trauma alone, mortality ranges between 7 and 14 percent; when chest wall trauma is complicated by flail chest, the mortality rate increases further. Trauma sufficient to cause flail chest is often accompanied by other injuries, such as fractures of the long bones and vertebrae, head trauma, rupture of the aortic arch or other arteries, or laceration of the liver or spleen. Patients with multiple trauma and lung contusion complicating flail chest have a mortality rate as great as 56 percent. This high mortality is not solely attributed to respiratory complications. If the patient survives the initial injury, long-term disability after flail chest is relatively common. Symptoms consist of chest tightness, chest pain, dyspnea, and limitation of ability to exercise.

Pulmonary Function and Respiratory Mechanics

The disordered movement of the flail segment is related to changes in pleural pressure during the breathing cycle (Fig. 92-10). During inspiration, pleural pressure becomes subatmospheric; this is inflationary to the lung but deflationary to the rib cage. Normally, rib cage expansion is due to several factors, including: (a) diaphragm insertional forces on the lower rib cage; (b) the actions of the intercostal muscles on the upper rib cage; (c) positive intra-abdominal pressure in the zone of apposition of the diaphragm to the rib cage; and (d) the passive outward recoil of the rib cage at high lung volumes. Once multiple rib fractures uncouple a segment of the rib cage from the remainder of the chest wall, the deflationary effect of intrapleural subatmospheric pressure is unchecked by the factors that promote rib cage expansion. Consequently, unopposed subatmospheric intrapleural pressure causes the flail segment to move inward during inspiration. During expiration, pleural pressure becomes more positive and the flail segment moves outward. This paradoxical motion of the flail segment is amplified by anything that further lowers pleural pressure, such as pulmonary contusion, which reduces lung compliance or an increase in airway secretions, which increases airways resistance.

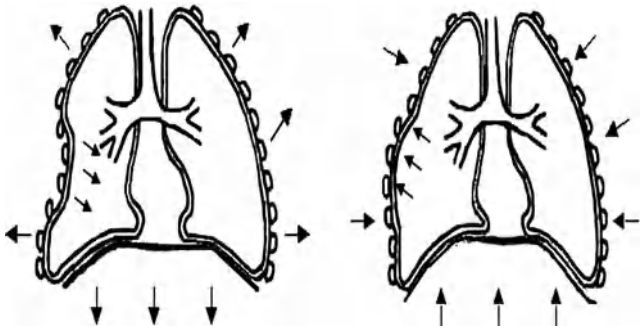

Figure 92-10 During inspiration, pleural pressure becomes more negative causing the flail segment to move paradoxically inward as the remainder of the chest wall is moving outward. During expiration, pleural pressure increases, causing the flail segment to move outward as the remainder of the chest wall becomes smaller.

Fractures involving the lateral rib cage provide the most common location for flail chest (Fig. 92-11). Anterior flail chest occurs when there is separation of the sternum from the ribs; and posterior flail chest is associated with less severe clinical derangement because of splinting provided by the back muscles. The pattern of paradoxical rib cage and abdomen motion is not unique to the location of the flail segment. Flail patterns may occur within the rib cage itself (i.e., between the upper and lower rib cage), or between the rib cage and abdomen (i.e., lower rib cage and anterior abdominal wall). These different patterns of motion of flail chest may reflect differences in the patterns of recruitment of the respiratory muscles. The observation that external intercostal

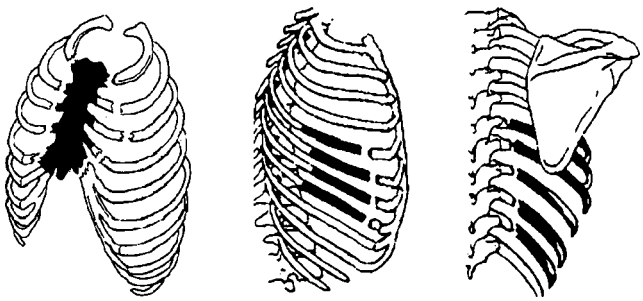

Figure 92-11 Schema of the rib cage depicting different locations of rib fractures producing flail segments in varied locations.

EMG activity increases more than threefold in the flail area supports this mechanism.

Flail chest may severely reduce VC and FRC to as much as 50 percent of predicted. The reductions in lung volume can be attributed to both paradoxical movements of the flail segment and, in certain patients, to underlying pulmonary contusion. In those individuals who have flail chest uncomplicated by pulmonary contusion and survive the initial injury, VC and FRC return to baseline values within 6 months or remain mildly reduced. In contrast, patients with pulmonary contusion complicating flail chest can have persistent reductions in lung volumes for up to 4 years. These changes have been attributed to fibrous changes in the contused area.

Although it is easy to ascribe respiratory failure to paradoxical motion of the rib cage in patients with flail chest, the pathogenesis of respiratory failure is complex; contributing factors include hypoventilation and flail-induced changes in lung and respiratory muscle function. Flail chest in itself is accompanied by considerable pain, which in turn impairs cough effectiveness, causes regional atelectasis, rib cage muscle spasm, and alters patterns of respiratory muscle activation and recruitment. Flail chest may increase elastic loads presented to the respiratory muscles by promoting regional atelectasis near the flail segment, generalized microatelectasis due to splinting and pain, or pulmonary contusion. Flail chest further increases the work of breathing by causing the inspiratory muscles to shorten more for a given tidal volume. The excessive muscle shortening represents extra work (force X distance) that is not measured using standard calculations of work per breath (pressure X volume). The added inspiratory muscle shortening due to the flail segment causes the inspiratory muscles to operate over shorter lengths. This reduces inspiratory muscle efficiency, thereby adding to the oxygen cost of breathing. Thus, the added work of breathing, respiratory muscle inefficiency, hypoxemia due to atelectasis, and contusion all combine to predispose these patients to respiratory muscle fatigue and respiratory failure (Fig. 92-12).

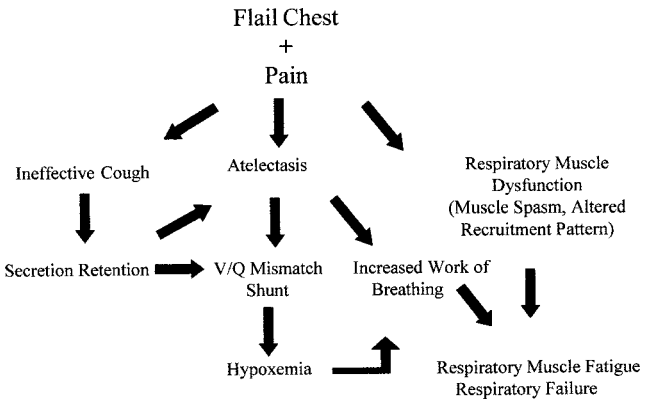

Figure 92-12 Factors involved in the pathophysiology of flail chest.

Treatment

The mainstay of treatment is to control pain because of its central role in the development of atelectasis and promoting ineffective cough. Pain control also reduces splinting, improves tidal volume, and minimizes areas of atelectasis. It can be accomplished by use of oral or intravenous narcotics, intercostal nerve blocks, or epidural anesthesia. Pain relief in combination with supplemental oxygen, improving tracheal bronchial toilet, and cautious fluid replacement often results in successful treatment of flail chest with avoidance of respiratory failure. Attempts to stabilize the flail segment by applying tape, strappings, or other external devices to the chest wall have met with limited success. However, stability of the flail segment may be accomplished with the use of positive pressure mechanical ventilation or surgical fixation in selected individuals.

Mechanical ventilation with positive pressure breathing has been shown to stabilize the flail segment by eliminating subatmospheric changes of pleural pressure during inspiration. This "internal pneumatic stabilization" was initially accomplished by tracheostomy combined with prolonged mechanical ventilation. However, complications of mechanical ventilation often supervened and increased morbidity and mortality. Consequently, mechanical ventilation is no longer recommended as a primary means of stabilizing the chest wall; instead, it is recommended when there is respiratory failure, concomitant central nervous system or intra-abdominal injuries, shock, or need to operate for other injuries. If mechanical ventilation delivered via an endotracheal tube is instituted, ventilator modes that minimize patient effort and the generation of subatmospheric pleural pressure should be employed. For example, low impedance modes of mechanical ventilation, such as high flow continuous positive airway pressure, are accompanied by less chest wall distortion during inspiration.

Positive pressure ventilation delivered by noninvasive techniques may provide an alternative means of stabilizing the flail segment by preventing subatmospheric changes in pleural pressure during inspiration. Noninvasive ventilation to selected patients who are breathing spontaneously in conjunction with regional anesthesia can improve gas exchange and enable physiotherapy and early patient mobilization. In selected patients with flail chest, noninvasive ventilation may significantly reduce morbidity and length of hospitalizations. A randomized control trial comparing patients with mask CPAP vs. assist control ventilation found that patients treated with mask CPAP had fewer complications, fewer days in hospital and intensive care unit, and less ventilator time than patients with similar degrees of blunt thoracic trauma treated with assist control ventilation. This technique has not been fully evaluated in patients with flail chest.

The chest wall can also be stabilized by a variety of surgical procedures. In selected individuals, external fixation of the chest wall with wires, steel plates, and staples to approximate the fractures improves respiratory mechanics and reduces the duration of mechanical ventilation as well

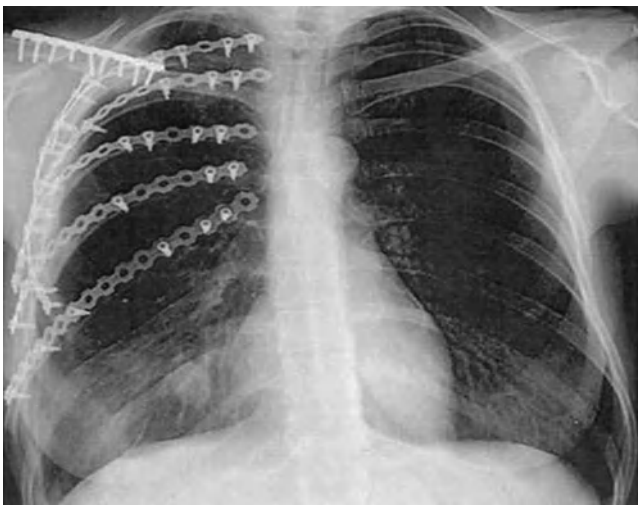

Figure 92-13 Chest radiograph depicting osteosynthesis plates in an individual who has undergone operative chest wall fixation. *(From Engel C, Krieg JC, Madey SM, et al: Operative chest wall fixation with osteosynthesis plates.* J Trauma *58:181–186, 2005, with permission.)*

as hospital stay (Fig. 92-13). The proper selection of candidates for operative stabilization is uncertain; however, it is likely to benefit individuals who are ventilator dependent and unable to protect their upper airways. Individuals with concurrent problems, such as those undergoing thoracotomy for intrathoracic injuries, young patients with severe chest wall deformation, or patients with large unstable segments and borderline pulmonary function may also be potential candidates.

To summarize, flail chest is associated with acute respiratory failure most often in the setting of trauma in which, in addition to a mechanically inefficient rib cage, there is concomitant lung contusion. Pain and respiratory muscle dysfunction also contribute to the pathogenesis of respiratory failure. The essential components of nonsurgical treatment include pain control and mechanical ventilation for respiratory failure. Surgical fixation of the flail segment may be needed in some patients and may reduce the duration of mechanical ventilation and decrease the incidence of pulmonary infections and barotrauma. However, the indications for external fixation are not fully defined.

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93

Effects of Neuromuscular Diseases on Ventilation

Gerard Joseph Criner • Nathaniel Marchetti

Neuromuscular diseases comprise a diverse group of disorders that vary markedly in etiology, rate of progression, pattern of respiratory involvement, prognosis, and therapy. Neuromuscular disorders impair the respiratory system as a vital pump; however, depending on the particular disease, the respiratory pump may be impaired at the level of the central nervous system (e.g., cerebral cortex or brain stem), spinal cord, peripheral nerve, neuromuscular junction, or respiratory muscle (Table 93-1).

The pattern of ventilatory impairment among these disorders is highly dependent on the specific neuromuscular disease. For example, some disorders may impair ventilation at only one level (e.g., isolated diaphragm paralysis) or simultaneously affect it at different levels (e.g., multiple sclerosis). Additionally, the severity of impairment may be minimal and totally resolve with time and proper treatment (e.g., Guillain-Barré syndrome) or is characterized by relentless progression to eventual respiratory death (e.g., amyotrophic lateral sclerosis). Moreover, some neuromuscular diseases concomitantly affect several structures (e.g., swallowing dysfunction in poliomyelitis, interstitial lung disease in polymyositis), increasing ventilatory workload in patients who already have diminished ventilatory reserve.

This chapter describes the etiology, pathophysiology, and treatment of ventilatory dysfunction in neuromuscular diseases.

RESPIRATORY PATHOPHYSIOLOGY

Substantial information exists concerning the ventilatory function of patients with neuromuscular disease at rest and during sleep, as well as the effects on maximum static inspiratory and expiratory efforts and responses associated with these disorders to hypoxic and hypercapnic challenges. In

Table 93-1

Levels of Respiratory System Dysfunction Induced by Neuromuscular Diseases and Conditions

Level	Disease or Condition
Upper motoneuron	
Cerebral	Vascular accidents
	Cerebellar atrophy
	Trauma
Spinal cord	Trauma
	Tumor
	Syringomyelia
	Multiple sclerosis
Lower motoneuron	
Anterior horn cells	Poliomyelitis
	Spinal muscle atrophy
	Amyotrophic lateral sclerosis
Motor nerves	Cardiac surgery
	Charcot-Marie-Tooth disease
	Diabetes
	Polyneuropathy
	Toxins
	Guillain-Barré syndrome
	Neuralgia amyotrophy
	Critical illness polyneuropathy
Neuromuscular junction	Myasthenia gravis
	Eaton-Lambert syndrome
	Botulism
	Organophosphate poisoning
	Drugs
Muscle	Dystrophy
	Acid maltase deficiency
	Malnutrition
	Corticosteroids
	Polymyositis

general, the response of the respiratory system to moderate or severe neuromuscular disease is relatively stereotyped. The typical features are a reduced forced vital capacity, reduced respiratory muscle strength, and in some cases, malfunction of the neurons that control breathing.

CONTROL OF BREATHING

The breathing pattern is often abnormal in patients with neuromuscular disease. In comparison with healthy subjects, patients with respiratory muscle weakness have a low tidal volume and a high respiratory rate that persists in response even to hypoxic or hypercapnic challenge. Moreover, this rapid, shallow breathing pattern is not due to abnormalities in gas exchange (i.e., hypoxemia or hypercapnia) but is more likely to be due to severe muscle weakness and/or disordered afferent and efferent output in motoneurons impaired by the underlying neuromuscular disease.

Changes in ventilation can be used to evaluate ventilatory drive in subjects with normal lung and respiratory muscle mechanics. However, ventilation is not a good index of respiratory motor activity in subjects with significant respiratory muscle weakness because the thoracic bellows cannot perform increased work of breathing. Decreased ventilatory response to hypoxic or hypercapnic challenge in these patients could indicate abnormalities in afferent information from diseased respiratory muscles, abnormal lung or chest wall mechanics, or upper motoneuron dysfunction rather than an abnormality in the central control of breathing. In some neuromuscular diseases, degenerative changes in the muscle spindle, impaired afferent stimulation from abnormal stretch reflexes in the muscle spindles, or decreased mechanoreceptor output from tendons may explain the altered breathing pattern.

Measurement of mouth occlusion pressure generated during the first 100 ms of inspiration ($P_{0.1}$) is relatively independent of inspiratory effort and therefore is a more reliable estimate of central ventilatory drive independent of respiratory muscle mechanics. $P_{0.1}$ is maintained or increased in patients with neuromuscular disease despite substantial muscle weakness. The relationship between respiratory mechanics, respiratory muscle strength, and control of ventilation has been examined in patients with neuromuscular diseases in comparison with healthy control subjects. Although patients had 37 and 52 percent reductions in maximum inspiratory and expiratory mouth pressures, respectively, their $P_{0.1}$ was 66 percent greater than that of controls.

Similar findings were encountered when normal subjects had acute muscle weakness induced by curarization. After severe muscle weakness was induced, significant increases in $P_{0.1}$ were observed during hypercapnic challenge. Partial curarization of spontaneously breathing cats also produced a marked increase in phrenic nerve discharge despite a substantial decrease in minute ventilation. These studies indicate that under conditions of substantial respiratory muscle weakness, ventilation is not a reliable measure of central respiratory drive, and that central respiratory drive, at least when measured by $P_{0.1}$, is usually well preserved.

Respiratory Muscle Function

Patients with neuromuscular disease who develop significant respiratory muscle weakness may demonstrate fatigue, dyspnea, and impaired control of secretions, recurrent lower respiratory tract infections, acute or chronic presentations of respiratory failure, pulmonary hypertension, and cor pulmonale.

The pattern, prognosis, and degree of respiratory muscle weakness attributable to a neuromuscular disorder are

varied. They depend on the level of neuromuscular system impairment, the prognosis of the underlying disorder, and whether therapy is available. Patients with neuropathy, such as Guillain-Barré syndrome, tend to have less severe respiratory muscle weakness than patients with lower motoneuron lesions or neuromuscular junction disorders, such as myasthenia gravis. Even when respiratory muscle dysfunction is observed, not all respiratory muscles are equally impaired, and the course of the underlying neuromuscular disease and degree of respiratory and nonrespiratory muscle impairment can be very different among patients with the same disease. In some neuromuscular disorders, respiratory muscle weakness is the only presentation of an underlying disease (i.e., neuralgia amyotrophy of the diaphragm); in the case of muscular dystrophy, significant respiratory muscle weakness may occur only late in the disease course. Severe, relentless, progressive dysfunction of the respiratory muscles may occur, as in amyotrophic lateral sclerosis, or be characterized by exacerbations and relapses (e.g., multiple sclerosis). Finally, respiratory muscle weakness may completely reverse with time (phrenic nerve injury after open-heart surgery) or therapy (plasmapheresis in myasthenia gravis).

A significant number of patients with severe respiratory muscle weakness were also found in 50 percent of 30 asymptomatic patients with stable chronic neuromuscular disease. Reductions in inspiratory and expiratory mouth pressures did not correlate with general muscle strength assessment; however, both the type of neuromuscular disease and distribution of general muscle weakness correlated with respiratory muscle impairment. Patients with myopathy, rather than polyneuropathy, whose involvement produced proximal rather than distal limb muscle weakness, were more likely to have significant respiratory muscle weakness. Pulmonary symptoms correlated poorly with evidence of respiratory muscle weakness.

Explanations for the lack of pulmonary complaints in these two studies despite significant muscle weakness are not clear. Patients with chronic and severe neuromuscular disease are usually sedentary and incapable of exertion and, therefore, seldom stress the respiratory system, which may explain their lack of symptoms.

The rapid, shallow breathing pattern found in patients with respiratory muscle weakness may be due to decreased respiratory muscle force generation, but it also may be due to changes in lung and chest wall elastic recoil. A decrease in inspiratory muscle tone may lead to unopposed lung elastic recoil, which reduces lung volume and produces chronic changes in chest wall tone and distensibility. Once inspiratory muscle strength decreases to approximately 30 percent of normal, abnormalities in gas exchange (manifested primarily by hypercapnia) commonly occur.

Expiratory muscle weakness is also commonly observed in patients with neuromuscular disease. It causes ineffectual cough and impaired secretion clearance, which in some patients leads to recurrent lower respiratory tract infections. In normal persons, dynamic compression of the central intrathoracic airways by large changes in pleural pressure generated by forceful contraction of the expiratory muscles acts to propel secretions proximally, where they can be expectorated. As expiratory muscle weakness progresses, pleural pressures generated during coughing efforts are reduced and airway clearance is impaired.

Lung and Chest Wall Mechanics

A characteristic hallmark of chronic neuromuscular disease is a decreased vital capacity (VC). The VC is reduced because of respiratory muscle weakness, and the decrease in VC parallels the progression of the underlying disease, but the magnitude of the reduction in VC is greater than expected solely based on the reduction in respiratory muscle force. The sigmoidal shape of the pressure-volume curve suggests that large reductions in pressure initially produce only small reductions in lung volume. In 25 patients with a variety of neuromuscular diseases, De Troyer found that reductions in VC were much greater than expected, solely based on the reductions in inspiratory muscle strength (Fig. 93-1).

Similar results were observed in studies on the effect of curare on maximum static pressure-volume relationships in normal volunteers. It appears that in addition to muscle weakness, alterations in the mechanical properties of the lung and chest wall contribute to the reduced VC. Using the mean deflationary pressure-volume curve of the lung in 25 patients with moderate to severe neuromuscular disease, De Troyer and colleagues found, on average, a 40 percent decrease in lung compliance (Fig. 93-2). Because of the hysteresis of the pressure-volume curve obtained by static expiratory

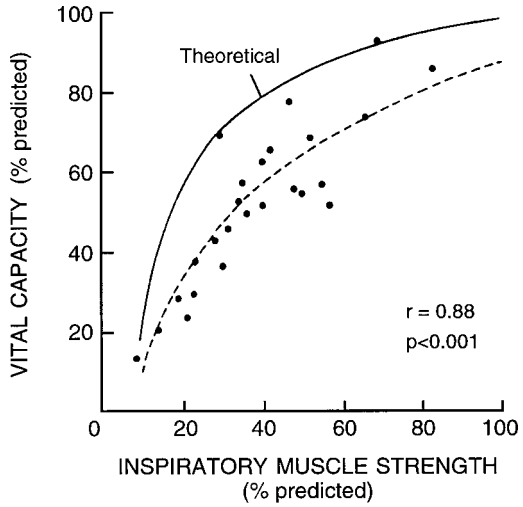


Figure 93-1 The solid curve represents the theoretic effect of respiratory muscle weakness on vital capacity (VC) on the assumption that the relaxation pressure-volume characteristic of the lung and chest wall are normal and that the inspiratory and expiratory muscles are uniformly involved. Dashed curve is the logarithmic regression calculated in 25 patients with neuromuscular disease (closed circles). Data suggest that loss of lung volume is out of proportion to the degree of inspiratory muscle weakness. (*Based on data of De Troyer A, Borenstein S, Cordier R. Analysis of lung volume restriction in patients with respiratory muscle weakness.* Thorax *35:603–610, 1980, with permission.*)

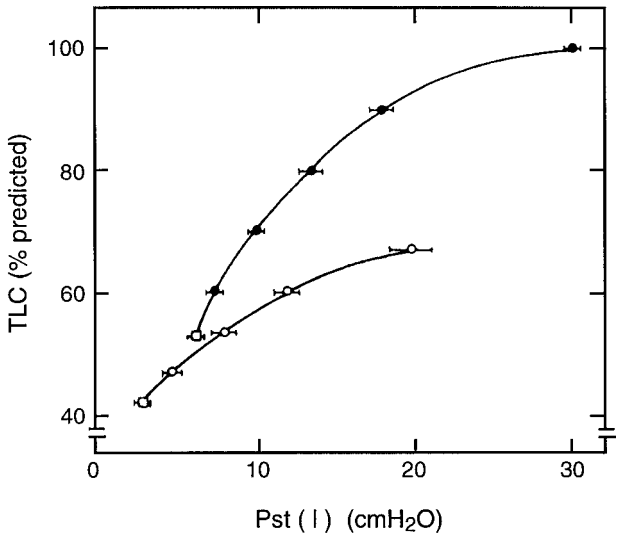


Figure 93-2 Static expiratory pressure-volume curve in patients with neuromuscular disease and respiratory muscle weakness. Open circles represent average data in 25 patients. Volume is displayed on the Y axis as a percentage of predicted total lung capacity (TLC). Closed circles represent mean predicted values. In patients, absolute lung volume was decreased for any given transpulmonary pressure. (*Based on data of De Troyer A, Borenstein S, Cordier R. Analysis of lung volume restriction in patients with respiratory muscle weakness.* Thorax *35:603–610, 1980, with permission.*)

maneuvers, a reduction in static compliance achieved on full inspiration alters the position of the expiratory curve and tends to underestimate measured static expiratory compliance. However, this effect is small, and does not account for the significant reductions in expiratory pulmonary compliance observed in their study. Furthermore, measurements of static lung compliance measured during inspiration in patients with neuromuscular diseases also show marked reductions, suggesting that chronic respiratory muscle weakness changes the elastic properties of the lung itself.

The cause of reduced lung distensibility in patients with neuromuscular disease is unknown. Several causes—such as failed maturation of normal lung tissue in the presence of childhood or congenital neuromuscular diseases, the presence of microatelectasis or macroatelectasis, increased alveolar surface tension caused by breathing chronically at low tidal volumes, and alteration in lung tissue elasticity—all have been proposed.

Impaired lung maturation is unlikely, since patients who develop neuromuscular disease in adulthood also have a reduction in VC that is disproportionate to the magnitude of respiratory muscle weakness. The presence of microatelectasis and macroatelectasis also appears untenable, because most patients who have significant reductions in VC do not have alveolar collapse on chest radiograph or chest computed tomography. In the minority of patients who have atelectasis on radiographic examination, the areas of atelectasis are usually insufficient to account for the reductions in lung compliance. Studies in rats and dogs demonstrate that breathing at small tidal volumes is associated with reductions in lung compliance and may promote increased alveolar surface tension. In experimental models of increased alveolar surface tension, a few deep inspirations rapidly restored lung distensibility. Although rapid and shallow breathing patterns are encountered in patients with chronic severe neuromuscular disease, mechanical hyperinflation of the lung does not restore lung distensibility. Therefore, increased alveolar surface tension is not considered the principal cause of reduced lung compliance in patients with chronic neuromuscular disease.

Theoretically, a reduction in lung tissue elasticity may also contribute to a reduction in lung compliance in patients with neuromuscular disease, but there is no evidence that lung collagen, elastin, and other matrix proteins change in these diseases. Currently, the reason for the reduction in lung compliance in patients with chronic neuromuscular disease is unknown and awaits further study.

Many studies indicate that chest wall compliance is decreased by approximately 30 percent in patients with chronic neuromuscular disorder. In 16 patients with chronic neuromuscular diseases (e.g., spinal cord injury, Duchenne muscular dystrophy, and myasthenia gravis), the weighted spirometer technique was used to examine chest wall compliance in comparison with that of 20 healthy control subjects. The weighted spirometer technique delivers an airway pressure that causes an increment in thoracic volumes so as to construct the pressure-volume relationship. In 12 of these patients, chest wall compliance was reduced (Fig. 93-3). Based on the contour of the pressure-volume curve of the normal relaxed chest wall at lower lung volumes, a reduction in functional residual capacity (FRC), as seen in patients with chronic neuromuscular diseases, may in itself reduce static chest wall

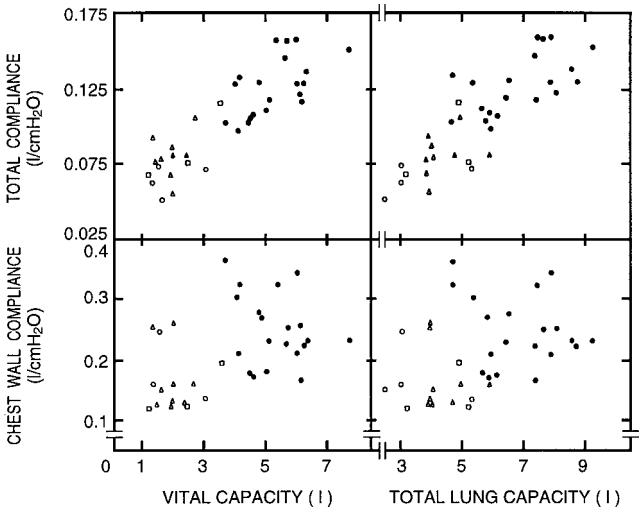


Figure 93-3 Relationships between total respiratory system compliance and VC and TLC (upper panels) and between chest wall compliance and VC and TLC (lower panels) in 16 patients with chronic neuromuscular diseases (open symbols) compared with 20 healthy controls (closed circles). Triangles symbolize patients who are quadriplegic, squares symbolize patients who are paraplegic, and circles symbolize four patients who had generalized neuromuscular diseases. In patients, total respiratory system and chest wall compliance were significantly reduced. *(Based on data from Estenne A, Heliporn A, Dellez L, et al. Chest wall stiffness in patients with chronic respiratory muscle weakness.* Am Rev Respir Dis *128:1002–1007, 1983.)*

compliance. However, in other disorders in which FRC is decreased owing to parenchymal lung disease (i.e., pulmonary fibrosis), a reduction in chest wall compliance has not been demonstrated. The mechanism for the reduction in chest wall compliance in patients with chronic neuromuscular disease has not been definitely established, but limitations in respiratory excursions have been proposed to lead to increased rib cage stiffness by decreasing the viscoelasticity of chest wall structures (i.e., tendons, ligaments, and costovertebral and costosternal articulations). Regardless of the mechanism, it appears that a reduction in chest wall compliance, along with a decrease in lung compliance, contributes to the marked decrease in VC observation in patients with neuromuscular disease.

Although reductions in VC appear to be clearly established in patients with chronic neuromuscular disease, data examination of the effect of chronic neuromuscular disease on FRC and residual volume (RV) are contradictory. FRC has been reported to be unchanged, decreased, or mildly increased. Similarly various results have been reported for RV. Discrepancies among these studies could be explained by differences in the type of, severity, and stages of neuromuscular diseases studied or body positions in which testing was performed. However, in two separate studies, patients with a wide variety of chronic neuromuscular diseases, all studied in a similar seated position, were found to have approximately 20 percent reductions in FRC but normally predicted values of RV. Furthermore, confirmation of these findings was demonstrated in eight patients with myasthenia gravis given pyridostigmine, which acutely decreased FRC by approximately 15 percent without any significant change of RV. Further corroboration of the maintenance of RV and reduction in FRC in states of respiratory muscle weakness was again demonstrated when normal subjects partially curarized were found to have a reduction in FRC and no change in RV.

On the basis of the preceding data, it appears that patients with chronic neuromuscular disease have moderate reductions in VC and total lung capacity (TLC) that are associated with a moderate decrease in FRC and a normal RV. The decrease in VC not only is due to respiratory muscle weakness but also appears to result from decreased lung and chest wall compliance. Table 93-2 summarizes the effect of neuromuscular diseases on both lung volumes and central respiratory drive.

Table 93-2

Characteristic Changes in Respiratory Mechanics in Patients with Neuromuscular Disease

Central drive	Rapid shallow breathing pattern Decreased ventilatory response to hypoxic or hypercapnic challenge Normal or increased $P_{0.1}$ to hypoxic or hypercapnic challenge
Lung volumes	Decreased vital capacity (VC) Decreased inspiratory capacity (1C) Decreased functional residual capacity (FRC) Decreased expiratory reserve volume (ERV) Maintained residual volume (RV)

Sleep-Related Breathing Disturbances

Breathing during sleep is often abnormal in patients with neuromuscular disease. Impaired sleep quality and hypopnea and hypercapnia related to rapid eye movement (REM) sleep are frequent. Patients with chronic neuromuscular disease of various causes have significant and numerous episodes of nocturnal desaturation, which are most prevalent during REM sleep and are characterized by hypoventilation rather than upper-airway obstruction (Fig. 93-4). Of six patients, 16 to 22 years of age, with advanced Duchenne muscular dystrophy, randomized to breathing either air or oxygen on two consecutive nights, five demonstrated significant oxygen desaturation during REM sleep and approximately 35 percent reductions in minute ventilation compared with their baseline awake values. Furthermore, the severity of diaphragmatic dysfunction was related to the degree of oxygen desaturation.

Several hypotheses have been proposed to explain nocturnal desaturation. Patients with chronic neuromuscular diseases develop an even more rapid and shallow breathing pattern during REM sleep. A rapid and shallow breathing pattern leads to increased dead-space ventilation, which promotes hypercapnia and worsened oxygenation. Reductions in ventilatory drive may be accentuated during sleep in patients with underlying neuromuscular disease, especially in those who have preexisting abnormalities of ventilatory control, which may further contribute to worsened nocturnal hypoventilation.

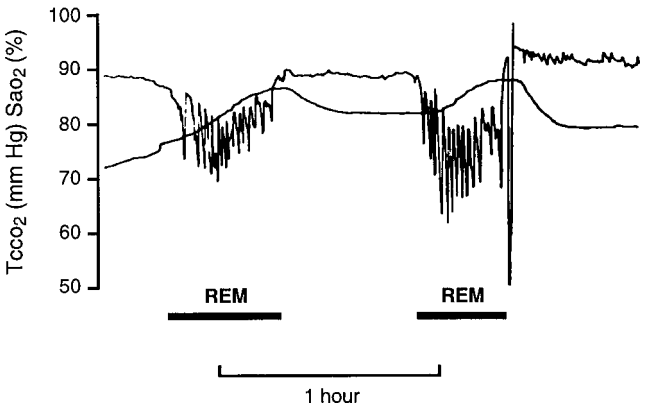


Figure 93-4 Oxygen desaturation and hypercapnia in rapid eye movement sleep shown from a recording of an all-night sleep study. Transcutaneous carbon dioxide (Tcc_{O_2}) is shown in the smooth solid line; arterial hemoglobin oxygen saturation (Sa_{O_2}) is shown in the line with sharp deflections. (*Taken from the data of Bye PT, Ellis ER, Issa FG, et al. Respiratory failure and sleep in neuromuscular disease.* Thorax *45:241–247, 1990.*)

It has been hypothesized that patients with neuromuscular disease, especially with diaphragmatic dysfunction, may be more prone to nocturnal desaturation during REM sleep. Intercostal muscle and accessory respiratory muscle activity during REM sleep are depressed, with a greater contribution of the diaphragm required for maintenance of eucapnia and oxygenation. Support for this hypothesis comes from studies that have found diaphragm dysfunction to be highly correlated with the presence and magnitude of REM-related oxygen desaturation. A direct relation has been found between the lowest Sa_{O_2} value measured during REM sleep and the percentage fall in VC measured between the erect and supine positions, using the latter measurements as an index of diaphragm weakness. Similarly, among patients who have paradoxical abdominal movement, signifying a decrease in diaphragmatic contribution to ventilation, a greater oxygen desaturation in both REM and non-REM sleep is observed. In contrast, patients with isolated diaphragmatic dysfunction with intact accessory muscle function are not predisposed to severe nocturnal hypoventilation. Accordingly, severe hypoventilation may become evident only when diaphragmatic weakness is found in the background of global accessory and intercostals muscle weakness, or when ventilatory reserve is severely reduced for other reasons, such as asthma or chronic obstructive pulmonary disease (COPD).

Abnormalities in nocturnal gas exchange are harbingers of problems in daytime gas exchange. Hypoventilation during sleep precedes the appearance of daytime hypercapnia, and patients with the most impaired gas exchange during REM sleep have the greatest degree of daytime hypercapnia. Moreover, patients with normal nocturnal gas exchange are unlikely to have abnormal daytime values. Noninvasive (e.g., nasal positive-pressure ventilation, external negative-pressure ventilation) or invasive (e.g., positive-pressure ventilation by tracheostomy) mechanical ventilation improves nocturnal gas exchange and sleep quality, with simultaneous improvement in daytime gas exchange.

Two theories have been proposed to explain the sustained improvements in gas exchange during daytime spontaneous breathing in patients with chronic neuromuscular disease who receive nocturnal ventilatory support. One theory states that nocturnal ventilation rests chronically fatigued respiratory muscles, thereby permitting improved spontaneous ventilation and gas exchange. In keeping with this theory, several studies have demonstrated that noninvasive ventilation relieves inspiratory muscle fatigue in patients with neuromuscular disease, or that mechanical ventilation consistently increases respiratory muscle strength. An alternative hypothesis suggests that nocturnal ventilatory support lowers the CO_2 set point of the central respiratory center, thereby setting the central controller to maintain a lower spontaneous daytime CO_2 level. This hypothesis is supported by studies showing that after several weeks of chronic nocturnal ventilation, hypoventilation was less severe in nocturnal studies without ventilation than it had been on baseline nights before chronic intermittent ventilation. Moreover, interruption of successful nocturnal noninvasive ventilation in patients with neuromuscular disease and chronic respiratory failure results in a return of nocturnal hypoventilation and symptoms of impaired gas exchange without evidence of respiratory muscle dysfunction. To date, neither of the preceding theories has been established conclusively, and further investigation is warranted, as one or the other, or both, may be valid in different patients.

ASSESSMENT OF RESPIRATORY FUNCTION

Patients with significant respiratory muscle impairment may range from being totally asymptomatic to having moderate dyspnea at rest or, in some cases, overt respiratory failure. Some patients with neuromuscular disease may have significant weakness of the respiratory muscles and be asymptomatic, whereas others may present with ventilatory failure without an established history of a neuromuscular disease. In the latter patients, the diagnosis of neuromuscular disease may initially be entertained only after difficulty is encountered in weaning the patient from mechanical ventilation. A detailed history and physical examination, coupled with appropriate diagnostic tests, enable the physician to diagnose the presence and type of neuromuscular disease and its effect on the respiratory system. The following section reviews features of the history and physical examination and the diagnostic studies considered useful in the assessment of respiratory function in patients with neuromuscular disease.

In order to provide an organized approach to direct the clinical history taking and physical examination of patients with neuromuscular disease, Table 93-1 characterizes the types of neuromuscular diseases that present at different levels of the neuromuscular system, and Table 93-3 describes the innervation of the different groups of respiratory muscles.

Clinical History

The signs and symptoms of respiratory muscle weakness due to a neuromuscular disease are usually nonspecific and of limited value. Moreover, the clinical manifestations of respiratory muscle dysfunction depend on the specific muscle or muscles affected and the extent of their impairment. In conditions of mild weakness, or in the early stages of neuromuscular disease, the patient may be totally asymptomatic. As respiratory muscle weakness progresses, however, dyspnea on exertion followed by dyspnea at rest occurs. Disturbances in sleep and daytime hypersomnolence resulting from nocturnal hypoventilation may occur, and if the expiratory muscles are affected, patients may have impaired cough and repeated lower respiratory tract infections. As respiratory muscle weakness becomes more severe, hypercapnia or hypoxemia becomes evident and respiratory failure may ensue, requiring ventilatory support.

The clinical history is invaluable in that it may be the first clue that a neuromuscular disease is the cause of the patient's pulmonary dysfunction. A history is also useful

Table 93-3

Innervation of the Respiratory Muscles

	Innervation	
Muscle Group	**Level**	**Nerve**
Upper airway		
Palate, pharynx	IX, X, XI	Glossopharyngeal, vagus, spinal accessory
Genioglossus	XII	Hypoglossal
Inspiratory		
Diaphragm	C_{3-5}	Phrenic
Scalenes	C_{4-8}	
Parasternal intercostals	T_{1-7}	Intercostal
Stenocleidomastoid	X_1. C_1.C_2	Spinal accessory
Lateral external intercostals	T_{1-12}	Intercostal
Expiratory		
Abdominal	T_7-L_1	Lumbar
Internal intercostals	T_{1-12}	Intercostal

in characterizing the type of neuromuscular disease that is present. Dyspnea and impaired cough with or without recurrent lower respiratory tract infections may be the first clinical clues that a neuromuscular disease is present. Impaired swallowing due to bulbar symptoms and the presence of peripheral limb muscle weakness are indications that one is dealing with disseminated neuromuscular disease.

Physical Examination

Although the physical examination may yield normal results in patients with early or mild impairment of the respiratory system, patients with more established disease often demonstrate tachypnea at rest. Further clinical information on the nature of the underlying disease and the extent of underlying muscle impairment can be gleaned from the pattern of respiratory muscle contraction in both seated and supine positions. Respiratory rate should be recorded along with any evidence of nasal flaring, intercostals muscle retraction, or palpable evidence of contraction of the sternocleidomastoid and scalene muscles. Furthermore, inward paradoxical motion of the rib cage or abdomen should be sought, as its presence may indicate a respiratory workload that is greater than the patient's respiratory muscle strength, or evidence of severe weakness of the diaphragm as a result of the underlying neuromuscular disease. Besides gross paradoxical movement of the rib cage or abdominal compartments, asynchronous compartmental movements (e.g., one compartment moving faster than the other) may be early evidence of impaired respiratory pump performance.

The hallmark of severe diaphragm weakness or paralysis is paradoxical inward movement of the abdomen with inspiration. In the presence of severe diaphragm weakness, the upper abdomen moves inward when the upper rib cage moves outward, in stark contrast to the normal pattern of synchronized outward movements of the rib cage and abdominal compartments. Besides paradoxical movement of the upper abdomen, a marked increase in respiratory rate, accompanied by progressive accessory muscle use and increased dyspnea occur when patients assume the recumbent position due to hypoxemia, hypercapnia, and placing the accessory inspiratory muscles at mechanical disadvantage. Upon reassuming the upright posture, patients may have palpable phasic contractions of the abdominal expiratory muscles. Physiologically, this inward movement of the abdomen on expiration enables passive outward movement of the upper abdomen and diaphragm descent during expiratory muscle relaxation in early inspiration.

Besides a detailed examination of the respiratory musculature and breathing pattern, the physical examination should include a complete neuromuscular examination to exclude systemic involvement. Inspection for atrophy or fasciculations of respiratory and nonrespiratory muscles may point to a lower motoneuron disease. The presence of scoliosis may contribute to the development of restrictive ventilatory pattern.

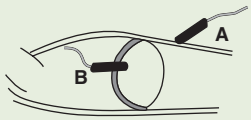
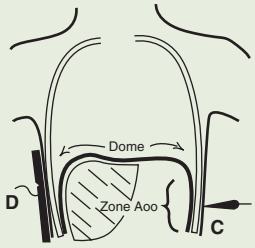
Radiographic Assessment

In patients with severe inspiratory muscle weakness or bilateral diaphragm paralysis, maximum inspiration is limited and lung volume appears reduced on the chest radiograph. Unilateral hemidiaphragm paralysis produces an elevated hemidiaphragm on the affected side.

Fluoroscopy is often used in the assessment of diaphragm paralysis while the patient makes a forceful sniff

Table 93-4

Respiratory Muscle Testing

Name of Test	Information Provided	Diagnostic Purposes	How to Perform
		Diaphragm	
Dome ultrasound 	Movement of right (or left) dome	Unilateral or bilateral diaphragm paralysis	Ultrasound probes with sufficient penetration (3 or 3.5 MHz) placed over abdomen (A) or over lateral rib cage (B). M-mode
Zone of apposition ultrasound 	Thickness at different lung volumes, relaxed or contracted	Detect contraction during tidal breathing or inspiratory efforts Effects of pulmonary or neuromuscular disease, training, and disuse Placement of intramuscular electrodes	High-resolution probe with less penetration (7.5 MHz) over intercostal space, usually in anterior axillary line. B- or M-mode (C) Linear probe in craniocaudal plane over lateral rib cage. B-mode (D)
	Length at different lung volumes	Estimates of diaphragm length and swept volume	Both measurements are usually made on the right side

Taken from the ATS/ERS statement on respiratory muscle testing. Am J Respir Crit Care Med *166:518–624, 2002.*

in the supine position. In unilateral diaphragm paralysis, a positive "sniff" test may demonstrate paradoxical upward movement of the affected hemidiaphragm. However, "sniff" tests have a false-positive rate as high as 6 percent in normal persons. The use of the "sniff" test to diagnose bilateral diaphragm paralysis is limited by compensatory abdominal muscle contraction. With abrupt cessation of abdominal muscle contraction during early inspiration, the abdominal contents descend caudally. The abdominal wall moves outward and the diaphragm will then appear to descend caudally, at least radiographically. Besides the fact that passive diaphragm descent due to active abdominal muscle contraction is a limitation during fluoroscopy, the fluoroscopic observational field used to examine the diaphragm is limited because of the small visual band that encompasses only the diaphragmatic dome and adjacent ribs. If rib cage rostral movement exceeds diaphragm ascent, the diaphragm will appear to descend lower than the thorax thereby falsely, suggesting shortening of the diaphragm.

Although the diaphragm itself is poorly echogenic, ultrasound can be used to assess its function because the parietal pleura and peritoneal membranes lining the diaphragm are brightly echogenic. The two approaches used are the visualization of the dome or measurement of the muscle thickness at the zone of apposition. Craniocaudal movement of the dome of the diaphragm can be measured by placing an ultrasound probe on the upper abdomen or on the lateral chest, as shown in Table 93-4. This technique has compared favorably to the traditional fluoroscopic procedures used to assess diaphragm movement. Because the costal portion of the diaphragm is close to the skin, the zone of apposition (Table 93-4) is an ideal area to use ultrasound for assessment of the diaphragm thickness and estimation of length. The thickness of the diaphragm increases with increasing lung volumes and is inversely proportional to its length. Measurement of the zone of apposition permits the detection of diaphragm contraction during inspiratory efforts when trying to diagnose diaphragm paralysis. As the subject with diaphragm paralysis makes an inspiratory effort there will not be thickening of the diaphragm at the zone of apposition. Measurement of the thickness also allows for the assessment of atrophy or the effect of neuromuscular diseases.

Arterial Blood Gas Analysis

Arterial blood gas abnormalities usually occur only in patients with severe respiratory muscle weakness. Hypoxemia is usually mild and may occur as a result of macroatelectasis and subsequent intrapulmonary shunting or ventilation-perfusion mismatch. In addition, patients with impaired muscle strength have impaired cough and may retain

secretions that further contribute to the development of hypoxemia. Measurement of arterial oxyhemoglobin saturation by pulse oximetry, which has become an extremely common laboratory test for oxygenation, is an insensitive indicator of hypoventilation. In patients with mild to moderate respiratory muscle weakness, the value of solely measuring the level of oxygenation is limited and may be misleading.

Hypercarbia is an insensitive measure of respiratory muscle strength. The Pa_{CO_2} does not increase until respiratory muscle strength (measured by maximum inspiratory and expiratory mouth pressures) is less than 50 percent of predicted. In patients with severe respiratory muscle weakness, however, an increase in Pa_{CO_2} may occur. Examination of the bicarbonate and pH values may help to determine whether an acute or chronic respiratory acidosis is present. Because daytime hypercapnia is usually followed by nocturnal hypoventilation, the presence of daytime hypercapnia should prompt investigation of the breathing pattern and gas exchange during sleep, so that appropriate therapy (e.g., nocturnal supplemental oxygen or noninvasive ventilation) can be implemented.

RESPIRATORY MUSCLE STRENGTH

Maximum Mouth Pressures

Maximum static inspiratory and expiratory mouth pressures, measured at the airway opening during a voluntary contraction against an occluded airway, are the simplest and most commonly performed tests of respiratory muscle strength. Although several methods exist, the technique of Black and Hyatt is still the most widely used. In this technique, mouth pressures are measured using a hand-held manometer with the patient seated upright and wearing a nose clip. During these maneuvers, the patient purses the lips inside a circular wide-bore rubber mouthpiece, which prevents perioral air leakage. This small orifice (2 mm in diameter, 15 mm in length) is placed in the circuit to minimize the contribution of the facial muscles to airway pressure and keep the glottis open. Maximum inspiratory pressures (PI_{max}) are measured near residual volume after maximal expiration, while maximal expiratory pressures (PE_{max}) are measured at or near total lung capacity. In each case, efforts are maintained for at least 1 second. Maximum inspiratory and expiratory mouth pressures in normal males and females are listed in Table 93-5. Reported values in normal subjects vary widely and may be due to differences in techniques between different studies or a learning effect in subjects who perform these maneuvers.

A major factor affecting PI_{max} is lung volume. PI_{max} is greatest at residual volume, so that the inspiratory muscles are at greatest mechanical advantage and the outward elastic recoil of the respiratory system is maximal. On the other hand, measurement of PE_{max} is greatest at total lung capacity because expiratory muscles are at greatest mechanical advantage and inward elastic recoil of the respiratory system is greatest (Fig. 93-5). Only at functional residual capacity, in which the respiratory system recoil pressures measured at the airway opening are zero, are maximum inspiratory and expiratory mouth pressures solely a function of the pressure generated by actively contracting respiratory muscles (P_{MOS}).

Changes in lung volume due to chest wall or lung pathology may have important effects on the generation of maximum respiratory pressures in patients. For example,

Table 93-5

Reported Values for Maximum Static Airway Pressures in Normal Adults

Study	Sex	No. of Subjects	Age Range (Years)	PI_{max} (cmH_2O)	PE_{max} (cmH_2O)
Black and Hyatt, 1969	Males	60	20–54	124±22	233±42
	Females	60	20–54	87±16	152±27
Rinqvist, 1966	Males	100	18–83	130±32	237±46
	Females	100	18–83	98±25	165±30
Leech et al., 1983	Males	325	17–35	114±36	154±82
	Females	480	15–35	71±27	94±33
Rochester and Arora, 1983	Males	80	19–49	127±28	216±41
	Females	121	19–49	91±25	138±39
Vincken et al., 1987	Males	46	16–79	105±25	140±38
	Females	60	16–79	71±23	89±24
Cook et al., 1964	Males	17	18–47	133±39	237±45
	Females	9	18–32	100±19	146±34
Wilson et al., 1984	Males	48	19–65	106±31	148±34
	Females	87	18–65	73±22	93±17

Values are mean ± standard deviation.

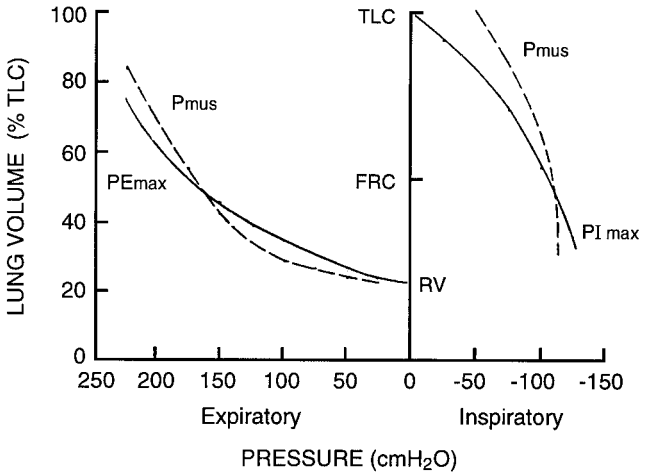


Figure 93-5 The effect of lung volume on maximum respiratory pressures (PI_{max} and PE_{max}) measured at the airway opening displayed by solid lines. Both PI_{max} and PE_{max} are made up of two components: The pressure generated by the respiratory muscles (P_{mus}, dashed lines) and the recoil pressure of the respiratory system. At functional residual capacity, both PE_{max} and PI_{max} are equal to P_{mus}.

patients with COPD and significant hyperinflation have a larger FRC and residual volume than normal subjects; therefore, PI_{max} performed at FRC or RV usually results in lower values than in age- and sex-matched normal subjects. Likewise, a reduction in total lung capacity due to restrictive ventilatory diseases may result in a reduction in measured values for PE_{max}. Therefore, it is important to realize that in patients with pathologically altered lung volumes, all or part of the reduction in mouth pressures may be due to inspiratory muscle mechanical disadvantage.

Maximum inspiratory and expiratory mouth pressures in patients with neuromuscular diseases range from normal to severely reduced. Patients may have significant respiratory muscle weakness without any pulmonary complaints, and no correlation exists between respiratory muscle strength and the presence of generalized nonrespiratory muscle weakness. When PI_{max} falls below 30 cm H_2O, ventilatory failure commonly ensues.

The assessment of a patient's ability to generate an effective cough is extremely important when managing the pulmonary effects of neuromuscular diseases. Nearly all of these disorders result in weak cough, which puts the individual at risk for aspiration and pneumonia. While a normal PE_{max} ensures that the patient has adequate cough, a low PE_{max} could result from poor effort, bulbar weakness not allowing a tight seal around the mouthpiece, or true expiratory muscle weakness. Therefore, there is interest in developing a test that will allow the assessment of cough strength in a nonvolitional manner. Measurement of positive pleural pressures during a forceful cough (P_{es} cough) has also been proposed as a measure of expiratory muscle strength. P_{es} cough has been shown to decrease in parallel with PE_{max} when expiratory muscle weakness is induced by progressive curarization. A study examined the use of measurement of gastric pressures during cough (P_{GA} cough) in a group of normal subjects and in those with suspected respiratory muscle weakness from pulmonary and neuromuscular disease. The measurement of P_{GA} cough is theoretically better because it takes into account the abdominal musculature, eliminates the problem of leak around the mouth piece, and a cough maneuver is easier to perform than the PE_{max} maneuver. In 122 patients with a normal PE_{max}, more than 95 percent also had a normal P_{GA} cough, but in 171 patients with a low PE_{max} 72 had a normal P_{GA} cough suggesting a high false-positive rate of a low PE_{max}. Conversely, in 105 patients with a low P_{GA} cough only six had a normal PE_{max}, suggesting a low false positive rate for a low P_{GA} cough.

Transdiaphragmatic Pressure Measurement

While maximum static airway pressures are useful measures of global respiratory muscle strength, they fail to assess individual respiratory muscle function. Since the diaphragm is the primary muscle of inspiration, and may be susceptible to isolated disease (e.g., phrenic nerve paralysis after open heart surgery or idiopathic diaphragm paralysis), specific testing of diaphragm strength is desirable in some patients. Assessment of diaphragm strength is made by measuring gastric (Pga) and endoesophageal (Pes) pressures with balloon-tipped catheters placed in the stomach and midesophagus, respectively. Transdiaphragmatic pressure (Pdi) is then calculated as the algebraic subtraction of Pes from Pga ($Pdi = Pga - Pes$).

Maneuvers to elicit maximum transdiaphragmatic pressures (Pdi_{max}) have been the subject of intensive study. Earlier studies measured Pdi during maximum static inspiratory efforts against a closed airway (e.g., Mueller's maneuver) at FRC or RV. However, this maneuver results in submaximal diaphragm activation, with the degree of activation varying widely from subject to subject. Several studies have demonstrated significant intraindividual variability, with a coefficient of variation as high as 40 percent in measurement of Pdi_{max} during Mueller's maneuver. When five maneuvers to measure Pdi_{max} in 35 subjects (10 normal, 13 with restrictive lung disease, and 12 with COPD) were compared, a combined maneuver of active expulsion with superimposed Mueller's maneuver yielded the most reproducible and maximal transdiaphragmatic pressure.

Phrenic Nerve Stimulation

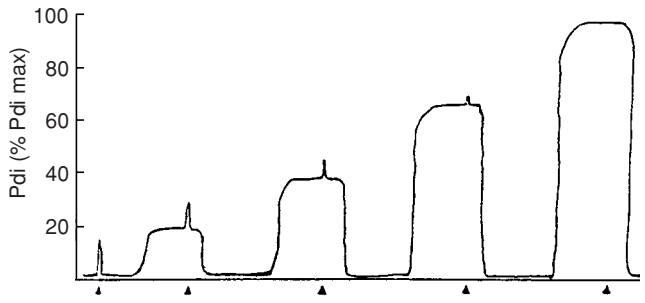
A crucial factor in the measurement of diaphragm strength is the ability to consistently obtain maximal activation of the diaphragm during volitional efforts. Electrophrenic stimulation is a method that has been recently utilized to consistently activate the diaphragm. Although phrenic nerve stimulation as a means of providing artificial respiration in patients has been known since the 1950s, its application in assessing diaphragm contractile function was not studied until the past decade. Besides assessing diaphragm strength, this technique has the added advantage of assessing phrenic nerve conduction and excluding the possibility of phrenic nerve injury in patients with diaphragm weakness of unknown origin.

The phrenic nerve is stimulated in the neck near the posterior border of the sternocleidomastoid muscle, at the level of the cricoid cartilage, where the phrenic nerves are most superficial. Stimulation may be performed either transcutaneously with surface electrodes (electrical stimulation electrodes), magnetic coil, or percutaneously with needle or wire electrodes. The percutaneous method is rarely used now. Stimulation of the phrenic nerves must be supramaximal with regard to voltage and current. Supramaximal conditions are ensured by increasing the stimulus intensity until maximum diaphragm muscle action potential (DMAP) or Pdi is achieved. The DMAP is measured by surface EMG electrodes, and the Pdi is measured by measuring the esophageal and gastric pressures via two pressure transducers as described above. The DMAP is then checked periodically throughout the study to ensure that consistent stimulation is maintained.

The most commonly used technique of electrophrenic stimulation now employs a frequency of one pulse per second to measure Pdi during a single unfused twitch contraction (e.g., Pdi_{twitch}). Pdi_{twitch} has also been used to assess maximal static Pdi indirectly by the twitch occlusion technique. In this method, single twitches are superimposed on progressively stronger voluntary Pdi contractions. As voluntary effort and Pdi increase, the increment in Pdi produced during the twitch (the twitch deflection superimposed on the Pdi) decreases (Fig. 93-6*A*). When there is no discernible Pdi_{twitch} deflection, it is assumed that the diaphragm is maximally activated. An inverse linear relationship exists between the amplitude of the superimposed twitch and Pdi measured during volitional effort. The extrapolation of the line of this relationship to the X-axis has been interpreted as representing maximum static Pdi (Fig. 93-6*B*).

An alternate way to perform phrenic nerve stimulation is via magnetic stimulation. In this technique, an electric current is run through a coil, thereby producing a magnetic field. The coil is placed over the spinous process of the seventh cervical vertebral body (cervical magnetic stimulation) stimulating the C_3-C_5 cervical roots of the phrenic nerve causing the diaphragm to contract. Magnetic stimulation of this area also stimulates contraction of neck and upper rib cage muscles as well. The advantages of this technique are that it is less painful than the electrical stimulation method, and it is easier to evoke diaphragm contractions. Also it is possible to perform magnetic stimulation of the phrenic nerve while the patient is in the supine position by placing the magnetic coil anterior to the sternum. This allows for hospitalized bed-bound patients to be evaluated for diaphragm weakness via phrenic nerve stimulation. One of the disadvantages of magnetic stimulation is that it lacks the specificity that electrophrenic stimulation has for the diaphragm and obtaining an EMG_{di} signal can be more difficult with magnetic stimulation. When comparing magnetic stimulation Pdi_{twitch} to electrophrenic Pdi_{twitch}, the Pdi_{twitch} tends to be 20 to 25 percent higher with magnetic stimulation.

In addition to assessing diaphragm strength, phrenic nerve stimulation can be used to assess phrenic nerve function. The EMG_{di} is measured via surface or esophageal electrodes during electric or magnetic phrenic nerve stimulation and the phrenic nerve conduction time can be measured. This measurement is useful when assessing possible injury to the phrenic nerve from thoracic surgery, trauma, or neuropathies (i.e., critical illness polyneuropathy or Guillain-Barré syndrome). The normal conduction time via electrical stimulation is 7.5 to 9 ms, but the normal conduction time via magnetic stimulation has not been well defined because activation of the brachial plexus affects the phrenic nerve conduction time. However, a recent paper has shown that if the magnetic coil was placed anteriorly to the cricoid cartilage, then the phrenic nerve conduction time was very similar to that obtained by electric stimulation. If the magnetic coil was lowered to just above the clavicle, the conduction time slowed significantly. The authors believe that this occurred because there was more brachial plexus activation in the lower position compared with the higher position.



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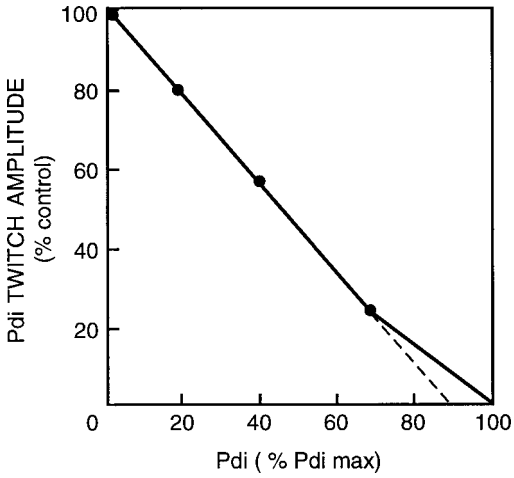

B

Figure 93-6 *A*. Illustration of a typical Pdi tracing during twitch occlusion study. As the Pdi increases during volitional efforts, the superimposed Pdi deflection during phrenic nerve 1-Hz stimulation (twitch) decreases. At 100 percent of Pdi_{max}, the diaphragm is maximally activated and no superimposed twitch is seen. Arrows on the horizontal axis mark indicate the phrenic nerve twitches. *B*. Data from A plotted as Pdi_{twitch} amplitude versus voluntary Pdi. Using linear regression, Pdi_{max} can be extrapolated from results obtained during submaximal efforts. It has been suggested that extrapolation performed from Pdi values below 70 percent of maximum may underestimate Pdi_{max} by approximately 10 percent (dashed line).

Because of the relative invasiveness of electrophrenic stimulation of the diaphragm, and the large coefficient of variation in some studies in which Pdi was measured during maximal volitional efforts, some investigators prefer measuring maximum inspiratory pressures during a sniff maneuver. In this technique, the subject performs a vigorous sniff against an unoccluded airway. During such an effort, the nose acts as a Starling resistor, thereby generating intrathoracic pressures against an occluded airway. Some investigators argue that this maneuver approaches a more natural respiratory effort than other types of maneuvers used to measure maximum inspiratory pressures and thus should be easily mastered by patients and more reproducibly performed by technicians.

Analysis of Rib Cage and Abdominal Motion

During normal tidal breathing, the chest and abdominal compartments move synchronously in an outward direction, owing to diaphragm contraction, decreasing pleural pressure, and increasing abdominal pressure. In situations in which the diaphragm is severely paretic or paralyzed, however, the flaccid diaphragm cannot counterbalance the negative changes in pleural pressure generated by contraction of the inspiratory muscles of the neck and rib cage. Instead of moving normally in a caudad direction the flaccid diaphragm moves paradoxically cephalad into the thorax. This change in diaphragm motion gives rise to a paradoxical inward motion of the upper abdomen indicative of severe diaphragm weakness or paralysis.

Changes in rib cage and abdominal pressure, or volume displacement during respiration, can provide important information about diaphragm strength. Partitioning of respiration can be examined from changes in abdominal and pleural pressures, as proposed by Macklem and colleagues. Changes in abdominal and pleural pressures during inspiration, expressed as the ratio of delta P_{ab}: Delta P_{PL} are normally negative as pleural pressure becomes more negative and abdominal pressure becomes more positive. This ratio has a maximum value of +1 when the diaphragm does not contribute to inspiration and is valid only if the expiratory muscles do not contribute significantly to the pressures being generated. Alternatively, the partitioning of ventilation can be noninvasively measured by compartmental changes in rib cage and abdominal volume by respiratory inductance plethysmography or magnetometry.

Spirometry

Respiratory muscle weakness induced by neuromuscular disease produces a restrictive pattern on spirometric testing with a reduction in VC. As mentioned, the reduced VC is commonly out of proportion to the reduction in maximal respiratory muscle force. Reductions in lung and chest wall compliance also probably contribute. Moreover, because of the contour of the pressure-volume curve, large reductions in the respiratory muscle forces have to occur before VC is significantly reduced. A decrease in VC greater than 25 percent on moving from the upright to supine postures has been used as a sign of diaphragmatic weakness and a greater likelihood of sleep-related hypoventilation.

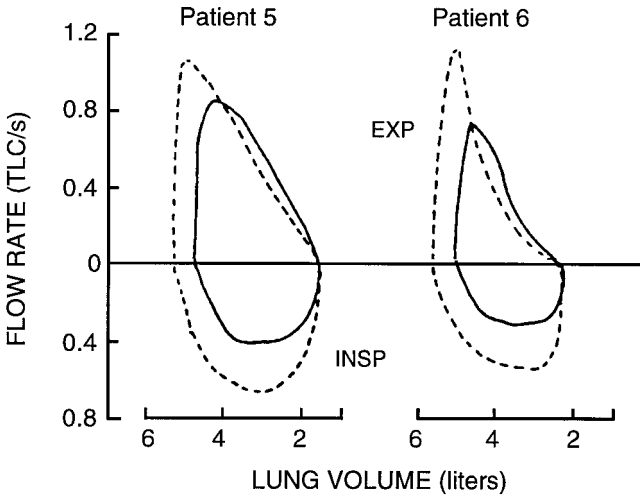

Figure 93-7 Two representative patients with myasthenia gravis and respiratory muscle weakness illustrating the effect of anticholinesterase therapy on maximum expiratory and inspiratory flow-volume curves. Solid curves represent pretreatment data; dashed curves were obtained following the injection of pyridostigmine. (*From DeTroyer A and Borenstien S. Acute changes in respiratory mechanics after pyridostigmine injection in patients with myasthenia gravis:* Am Rev Respir Dis *121:629–638, 1980, with permission.)*

Forced expiratory volume in 1 s (FEV_1) and measurements of midexpiratory flow rates ($FEF_{25–75}$ or FEF_{50}) are often greater than normal predicted values in patients with neuromuscular disease. The supranormal increases in midexpiratory flow rates appear to be due to the fact that maximum expiratory flow can be achieved over most of the vital capacity with low driving pressures. Further increases in expiratory flow may occur in patients with neuromuscular disease due to increased lung recoil. Two independent studies have shown that partial curarization in normal subjects produces a decrease in peak expiratory flow with an increase in midexpiratory flow rates compared with baseline. Moreover, in patients with myasthenia gravis who are in their baseline state of weakness before the administration of pyridostigmine, midexpiratory flow rates are increased over the range of vital capacity when referenced to absolute lung volume (Fig. 93-7).

Flow-Volume Loops

Changes in the configuration of the flow-volume loop occur in various neuromuscular diseases. These changes reflect respiratory muscle weakness or malfunction of upper-airway muscles. "Saw toothing" of the flow contour is seen in extrapyramidal disorders affecting upper-airway muscles. Similarly, plateauing of the inspiratory flow wave form, indicative of extrathoracic airway obstruction, has been described in vocal cord paralysis caused by extrapyramidal neuromuscular disorders. An abnormal flow-volume curve is significantly more common in patients with clinically apparent bulbar muscle involvement (90 versus 15 percent, respectively), and the presence of an abnormal, flow-volume loop

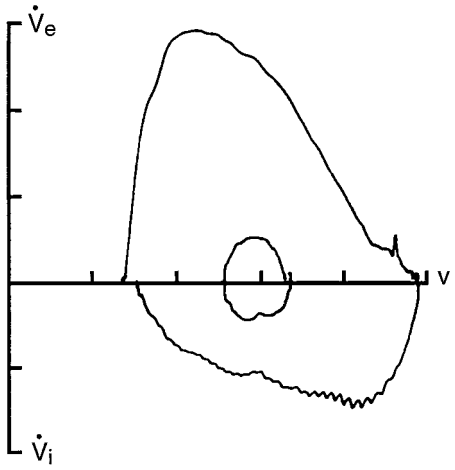

Figure 93-8 Flow-volume loop in a patient with motor neuron disease, showing inspiratory flow oscillation and inspiratory flow limitation. Subdivisions on volume and flow axis represents 1L, flow axis 1 L/s. (*Based on data of Vincken W, Elleker MG, Cosio MG: Determinants of respiratory muscle weakness in stable chronic neuromuscular disorders.* Am J Med *82:53–58, 1987, with permission.*)

predicted bulbar and upper muscle involvement by a neuromuscular disease with a high sensitivity and specificity. A characteristic flow-volume contour showing involvement of the upper-airway muscles by motor neuron disease is shown in Fig. 93-8.

Among patients with stable, chronic neuromuscular disease, the flow-volume loop is significantly more disturbed in those with respiratory muscle weakness, and these abnormalities correlate with reduced mouth pressures. Several features of flow-volume loop configuration correlate with reduced maximum static inspiratory and expiratory mouth pressures; a reduced peak expiratory flow, decreased slope of the ascending limb of the maximum expiratory curve, a drop-off of forced expiratory flow near residual volume, and a reduction in forced inspiratory flow at 50 percent of vital capacity (Fig. 93-9). A flow-volume loop score composed of the above parameters has a high degree of specificity and 90 percent sensitivity in predicting respiratory muscle weakness.

Lung Volumes

A restrictive ventilatory pattern is demonstrated in patients with neuromuscular disease. A reduced TLC and a normal or reduced FRC are common. The RV is usually elevated and is a sign of expiratory muscle weakness.

Maximum Voluntary Ventilation

Maximum voluntary ventilation (MVV) is an index of respiratory muscle endurance in the presence of normal expiratory flow rates. This appears to be appropriate in patients with neuromuscular disease, since airway resistance and FRC are usually within the normal range. Values for MVV correlate with respiratory muscle strength and may be even more sensitive than VC in detecting respiratory muscle weakness.

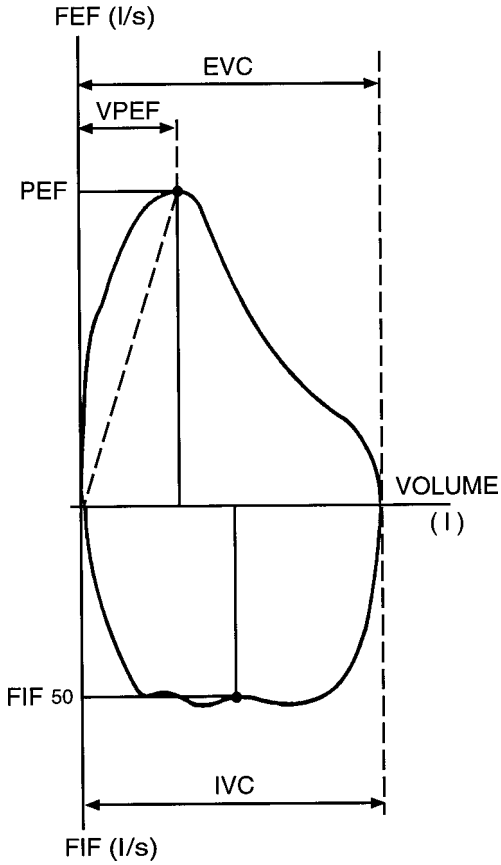

Figure 93-9 Representative flow-volume loop of a patient with chronic neuromuscular disease, showing different volume loop parameters indicative of respiratory muscle weakness. These parameters quantify the effects of respiratory muscle strength on the effort-dependent portions of the flow-volume loop. These four parameters are peak expiratory flow (PEF); ratio of PEF to the exhaled volume at which PEF was achieved, rapid vertical drop of forced expiratory flow at residual volume, and forced midinspiratory flow. (*Based on data of Vincken W, Elleker MG, Cosio MG: Determinants of respiratory muscle weakness in stable chronic neuromuscular disorders.* Am J Med *82:53–58, 1987, with permission.*)

SELECTED NEUROMUSCULAR DISEASES

A helpful approach toward understanding how specific neuromuscular diseases affect the respiratory system is to localize the anatomic involvement of the respiratory system. A detailed description of the neuroanatomy of respiration is outside the scope of this chapter (see Chapter 10). In general, however, neuromuscular disorders can be broken down into disorders that involve the upper motoneuron, lower motoneuron, or muscle itself.

Lesions that arise in the cerebral cortex, brain stem, or spinal cord are classified as upper motoneuron lesions and are characterized by an increase in muscle tone or spasticity, the presence of an extensor plantar response, and increased reflex activity. Lesions in the lower motoneuron system demonstrate flaccidity, depressed reflexes, muscular fasciculations, and atrophy. The location and character of the patient's weakness may enable one to identify the exact site of the lesion in the

lower motoneuron system (i.e., the anterior horn cell, peripheral nerve, neuromuscular junction, or muscle itself).

The following describes the effect of specific neuromuscular disease on the respiratory system and makes recommendations for treatment.

Upper Motoneuron Lesions

Stroke

Hemispheric ischemic strokes reduce chest wall and diaphragm movement on the side contralateral to the cerebral insult. Decreased diaphragm excursion with stroke correlates with diaphragmatic cortical representation identified by transcranial magnetic stimulation. Bilateral hemispheric strokes are also associated with Cheyne-Stokes respiration, which is progressive hyperventilation alternating with hypoventilation and ending in apnea (see Chapter 10). This breathing pattern may result from increased responsiveness to carbon dioxide as a result of interruption of normal cortical inhibition. The significance of Cheyne-Stokes respiration to stroke remains unclear but appears to be more common with bilateral than unilateral insults. Besides it effects on an alteration of breathing pattern, up to 50 percent of patients with strokes may have signs of pulmonary aspiration due to dysfunction of upper-airway muscles that protect the airway.

Spinal Cord Injury

The degree of respiratory impairment depends on the level and extent of the spinal cord injury. High cervical cord lesions (C_1 to C_3) cause paralysis of the diaphragmatic, intercostal, scalene, and abdominal muscles. Because all respiratory muscle activity is lost except for accessory and bulbar muscle function, high cervical cord injuries almost always require ventilatory assistance. In some patients, spontaneous breathing can be accomplished by glossopharyngeal breathing or diaphragmatic pacing because the phrenic nerve motoneurons (C_3 to C_5) remain intact.

Middle cervical cord (C_3 to C_5) lesions destroy the phrenic motoneurons and prohibit the use of phrenic nerve pacing. Patients with more caudal lesions (i.e., C_4 to C_5 level) have an improved chance to wean from ventilator support compared with those with more cranial lesions. (Forty percent of patients with C_3 lesions remain ventilator dependent.) Patients with lower cervical (C_6 to C_8) and upper thoracic (T1 to T6) cord lesions have intact diaphragm and neck accessory muscle action, but have denervated intercostal and abdominal muscles. These patients usually require ventilatory support only during the period immediately after the injury and rarely require long-term ventilation.

In a study of C_5 or lower spinal cord–injured patients, inspiratory muscle strength was reduced to approximately 60 percent of predicted but was dependent on the level of cord injury. In this study, PI_{max} values in low cervical, midthoracic, and lower thoracic-upper lumbar lesions were 61, 69, and 75 percent of predicted, respectively, whereas PE_{max}values were 30, 32, and 54 percent of predicted, respectively. The lower PE_{max} values were explained by a paralysis of abdominal and intercostal muscles, resulting in reduced cough and decreased clearance of bronchial secretions. Abdominal muscle paralysis probably accounts for an abnormally compliant abdomen in patients with lower spinal cord injury, which is in stark contrast to the 30 percent reduction in chest wall compliance believed to be due to abnormal rib cage stiffness.

Patients with spinal cord injuries also have alterations in thoracoabdominal motion during tidal breathing that is further accentuated by changing from the erect to supine position. In patients with quadriplegia with relatively intact diaphragm function, the distribution of respiratory muscle weakness results in paradoxical inward motion of the upper rib cage during inspiration owing to weakness of the parasternal and scalene muscles. This pattern of abnormal thoracoabdominal movement is more marked in the supine than the upright position. Patients with high quadriplegia (above C_3 to C_5) may be able to sustain short periods of spontaneous respiration because of inspiratory activity of the sternocleidomastoid and trapezius muscles. Phasic inspiratory electromyography (EMG) activity has been observed in the platysma, mylohyoid, and sternohyoid muscles. Analysis of rib cage motion in these patients shows increased upper rib cage diameter, due to the inspiratory action of the neck accessory muscles pulling the sternum cranially and expanding the upper rib cage.

The distribution of muscle paralysis in low cervical cord spinal patients also has a profound effect on the performance of forced expiratory maneuvers. In contrast to healthy normal subjects, in whom VC is moderately decreased on assuming the supine position, in patients with quadriplegia there is a paradoxical increase in VC in the supine compared with seated position without a significant increase in TLC. In 14 patients with quadriplegia (C_4 to C_7), there was a 16 percent increase in VC on changing from the upright to supine position and a reduction in RV (29 percent) and TLC (on average, 6 percent). The mechanism believed to be responsible for the increase in VC in supine patients with quadriplegia is the hydrostatic effect of abdominal contents, causing cephalad displacement and diaphragm lengthening and thereby placing the diaphragm on a more favorable portion of its length tension curve. The use of elastic binders when quadriplegics assume upright posture has been advocated to prevent the increase in abdominal compliance. Abdominal binding may have physiological benefit by maintaining diaphragm precontraction length in a more optimum position on its length-tension curve.

It was previously believed that all expiratory muscles were paralyzed in lower cervical cord injuries. However, studies of C_5 to C_8 quadriplegics indicate that phasic EMG activity of the clavicular portion of the pectoralis major is associated with a marked decrease in the anteroposterior diameter of the upper rib cage. This portion of the pectoralis muscle receives innervation from the C_5 to C_6 cord level. With the arms placed at the subject's side, contraction of the caudate head of the pectoralis major causes caudal displacement of the manubrium sterni and upper rib cage. This expiratory action

has been shown to decrease expiratory reserve volume (ERV) by 60 percent when the shoulders are held in abduction. After 6 weeks of pectoralis muscle isometric training, patients with low quadriplegia can have a marked increase in maximum pectoralis muscle isometric strength and a significant reduction in ERV. Conceivably, therefore, training of this muscle could improve the effectiveness of cough in patients with low spinal cord injury.

Pulmonary function typically improves in the months following spinal cord injury. In patients with spinal injuries below the C_5 level, VC is approximately 30 percent of predicted in the first week after injury, but by the fifth week increases to 45 percent of predicted, and by the fifth month to approximately 60 percent of predicted. Improvements in VC have been attributed to spasticity developing in previously flaccid intercostal and abdominal muscles, thereby increasing the rigidity of the thorax and abdomen and improving diaphragm force generation.

There is a role for corticosteroid use in the acute management of spinal cord injury. Methylprednisolone given as a 30 mg/kg bolus followed by a 24-h infusion at 5.4 mg/kg/h has been shown to improve motor function at 6 weeks, 6 months, and one year, but only in those who received the drug within 8 hours of injury. A subsequent study compared methylprednisolone infusion (5.4 mg/kg/h) for 48 to 24 hours after the administration of a bolus (30 mg/kg). There was no difference in functional outcome between the two infusion periods except in those in which the bolus dose was given 3 to 8 hours after the injury. If the methylprednisolone was started 3 to 8 hours after the injury, then those who received the infusion for 48 hours did have improved motor function at 6 weeks and 6 months. There were higher rates of pneumonia and sepsis in the 48-hour infusion group, but mortality was not different. No trial has shown a mortality benefit, and it should be recognized that the outcome measured was an improvement in the functional independence measure (FIM) score and not a return to normal motor function.

Parkinson's Disease

Parkinson's disease is due to degeneration of neurons in the substantia nigra and has a prevalence in the United States of approximately 200 cases per 100,000 people. Parkinson's disease can be primary (e.g., idiopathic); or secondary, as in postencephalitic parkinsonism associated with the influenza pandemic, or part of a more generalized disorder, such as multiple system atrophy or drug abuse with MPTP (1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine).

Respiratory abnormalities are common in Parkinson's disease, with pneumonia being the most common cause of death. A substantial problem with Parkinson's disease is glottic muscle dysfunction. An abnormal flow-volume loop contour showing regular or irregular flow oscillations commonly occurs. On direct fiberoptic visualization of the upper airway, these oscillations correspond to rhythmic involuntary movements of glottic and subglottic structures. Physiological evidence of upper-airway obstruction may be present. In addition to the presence of oscillations in flow, a rounding off of the peak of the midexpiratory flow-volume curve, a lowered peak expiratory flow rate, and a delayed appearance of peak expiratory flow have been observed in Parkinson's patients. These results have been interpreted as evidence for less coordinated or less "explosive" respiratory muscle contractions.

Patients with mild to moderate Parkinson's disease are able to perform simple single respiratory efforts (e.g., measurements of lung volume and maximum static inspiratory pressures), but have difficulty performing more complex, repetitive ventilatory efforts (i.e., sustaining inspiratory resistive loads to exhaustion and performing maximum unloaded breathing efforts). Performance of repetitive respiratory tasks is associated with an increased work of breathing when compared with that of an age-matched control group. These findings are similar to derangements in task performance exhibited by peripheral skeletal muscle groups in Parkinson's patients.

Treatment (e.g., with apomorphine) significantly improves neurological scores, maximum expiratory pressures, and peak inspiratory flow. Deep brain stimulation by stereotactically placing electrodes into the suprathalamic nucleus or globus pallidus nucleus recently has been shown to be effective when treating medically resistant patients. The electrodes produce a low-voltage high-frequency stimulation that results in inhibition of the neurons in the nucleus. Although the effect on respiratory function has not been directly studied, this procedure has been shown to improve motor function by about 60 percent.

In summary, Parkinson's disease results in problems in coordination and activation of upper airway and chest wall muscles that may result in functional glottic obstruction and/or failed coordination of repetitive respiratory tasks. These abnormalities are favorably treated with antiparkinsonian medications.

Multiple Sclerosis

Multiple sclerosis (MS) is a demyelinating disorder of the central nervous system, characterized clinically by remissions and relapses of clinical symptoms due to disseminating central nervous system lesions. MS is the most common neurological disease afflicting young adults, with an estimated prevalence of 250,000 to 300,000 cases in the United States in 1990. The cause of the disease is unknown, although epidemiological evidence points to genetic and environmental factors. Classic clinical symptoms include paresthesia, motor weakness, diplopia, blurred vision, dysarthria, bladder incontinence, and ataxia.

Symptoms are typically aggravated by an increase in temperature, which precipitates conduction block in partly demyelinated fibers. Although the disease course initially is remitting and relapsing and may persist for years, many patients will develop a progressive form of MS known as secondary progressive MS. The duration of the secondary progressive stage is variable with some progressing to severe debilitation rapidly whereas others have slow progression over a number

of years. Some patients will develop primary progressive MS and have a steady deterioration in function related to recurrent acute attacks. Pathologically, the lesions of MS have a predilection to invade the periventricular white matter of the cerebral hemispheres, optic nerves, brain stem, and cervical spinal cord.

Because MS can cause focal lesions anywhere in the central nervous system, different patterns of respiratory impairment can occur. Impairment of the respiratory centers and the medulla can cause failure of automatic breathing (Ondine's curse), apneustic or neurogenic pulmonary edema. The three most common respiratory manifestations of MS are respiratory muscle weakness, bulbar dysfunction, and abnormalities in respiratory control.

Acute respiratory failure rarely occurs in this disease, but it can occur because of severe demyelination of the cervical cord. Diaphragmatic paralysis resulting in respiratory insufficiency has also been reported. Even with severe disability and impaired respiratory muscle strength, patients with MS seldom complain of dyspnea. This paucity of respiratory complaints may be due to restricted motor activities and greater expiratory than inspiratory muscle dysfunction. Clinical signs that may be helpful in predicting respiratory muscle impairment are weak cough and inability to clear secretions, limited ability to count on a single exhalation, and upper extremity involvement. Advanced MS is frequently complicated by aspiration, atelectasis, and pneumonia.

In a group of 38 patients that were not bed ridden or wheelchair bound without bulbar involvement and a diagnosis of MS for 9.2 years, there was a significant decrease in the maximal inspiratory pressure (MIP) and the maximal expiratory pressure (MEP) to 77 and 60 percent predicted, respectively. However, in 60 patients who were bed ridden secondary to advanced MS, pulmonary function studies revealed severely decreased MIP (47 percent predicted), MEP (30 percent predicted), and vital capacity that was 80 percent of predicted. In those with a vital capacity below 80 percent predicted, the MIP and MEP were significantly lower than those with a normal vital capacity. In both of these studies the MEP was more affected than the MIP, and the respiratory muscle weakness directly correlated with the severity of the subject's overall neurological function. Smeltzer et al. developed a pulmonary dysfunction index for patients with MS and found that it correlated with MEP measurements. The score assesses the patient's assessment of cough and ability to handle secretions, the examiner's assessment of cough, and how high the patient can count on a single exhalation (Table 93-6). A subject with normal cough efficacy would have a score of 4, while an individual with the most impairment would have a score of 11. Gosselink et al. examined the effect of respiratory muscle training (e.g., three sets of 15 expiratory contractions at 60 percent of MEP twice daily) on respiratory muscle strength and the subject's pulmonary index score in a group of MS patients. At 3 months there was a statistically significant improvement in the MIP, but although the MEP improved, the p value was 0.07 compared with control patients. The pulmonary index was statistically better at 3 and 6 months. Patients who are quadriplegic with prominent bulbar involvement are at high risk for the development of acute respiratory failure.

Table 93-6

Pulmonary Dysfunction Index for Multiple Sclerosis Patients

Clinical Signs		Score
Patient rating		
History of difficulty handling secretions	No	1
	Yes	2
Cough	Normal	1
	Weak	2
Examiner rating		
Strength of cough when asked to cough voluntarily as hard as possible	Normal	1
	Weak	2
	Very weak/ inaudible	3
Value reached when patient counts aloud on a single exhalation after a maximal inspiratory effort	>30	1
	20–29	2
	10–19	3
	<9	4

Based on data from Smeltzer SC, Skurnick JH, Troiano R: "Respiratory function in multiple sclerosis. Utility of clinical assessment of respiratory muscle function." Chest *101:479–484, 1992.*

Treatment of MS has traditionally included the use of immunosuppressive agents such as high-dose corticosteroids, cyclophosphamide, and azathioprine. Other treatments included intravenous immunoglobulin (IVIG), plasmapheresis, and recently medications such as glatiramer, mitoxantrone, and interferon-β (INFβ-1b). The choice of therapy depends on the clinical situation and whether relapsing remitting or secondary progressive disease is being treated.

Most of the available data have focused on treating acute attacks of the relapsing remitting form of the disease. The use of ACTH or methylprednisolone during an acute attack has been shown to be protective against disease worsening, but the exact duration of therapy has not been determined. In one randomized placebo-controlled study, treatment with 10 days of high-dose oral methylprednisolone resulted in improved neurological function, but there was no difference in the reoccurrence of future acute exacerbations. There are no data available on the effect of long-term use of corticosteroids on MS progression. Cyclophosphamide, methotrexate, and cyclosporine are not recommended secondary to limited clinical benefit and the risk of severe adverse reactions. Interferon-β1a has been shown in a multicenter, double-blind placebo controlled study to decrease the relapse rate after 1 and 2 years of therapy. Additionally, therapy delayed progression of disability and lowered the number of active lesions on brain

MRI when compared with placebo. A follow-up multicentered study found that interferon-β1a at 44 μg given three times weekly was more effective at preventing relapses of the disease and decreased the number of brain lesions seen on MRI compared with 30 μg given once weekly. Both the American Academy of Neurology and the MS Council for Clinical Practice Guidelines recommend the use of interferon-β for the treatment of acute attacks in relapsing-remitting MS. Currently there is no evidence to support the use of interferon-β for the treatment of secondary progressive MS. The use of IVIG has been controversial due to a lack of randomized controlled trials, but it does appear that IVIG can both delay and prevent the occurrences of acute attacks in the relapsing and remitting form of the disease in some patients. Achiron et al. has shown that in patients given IVIG within the first 6 weeks of neurological symptoms there was a significant reduction in disease activity as measured by MRI imaging and neurological symptoms. However, there was no significant additional benefit to adding IVIG to methylprednisolone therapy, and a recent study looking at the effect of IVIG use for 27 months in secondary progressive multiple sclerosis failed to show any difference in progression of disability. Glatiramer acetate, a random polypeptide made up of four amino acids, is thought to act by modulating the activity of T cells. The early studies with this agent showed a significant but minimal benefit. However, a recently published study has shown a significant decrease in the relapse rate when compared with placebo. Additionally, subjects in the placebo arm were permitted to crossover at the end of the trial to the glatiramer arm, and all patients were followed for 8 years. After 8 years the relapse rate decreased to a rate of one every 5 years, and those that were in the glatiramer arm from the beginning had better disability scores throughout the study, suggesting an advantage to starting the medication earlier. Mitoxantrone, an anthracenedione antineoplastic agent, is approved for use in secondary progressive MS. It has been shown to have a beneficial effect on disease progression in those with progressive disease, but its use is limited because the drug can cause heart failure. Plasmapheresis has no role in the treatment of secondary progressive MS, but may have a role in the treatment of severe acute attacks in previously nondisabled patients.

Lower Motor Neuron Lesions

Poliomyelitis

In the early part of the twentieth century, poliomyelitis was the most common cause of lower motor neuron disease in the United States. Paralytic poliomyelitis is the most devastating respiratory presentation of poliomyelitis infection and is preceded by a period of fever and mild illness. After several days of mild fever and myalgia, symptoms disappear; then, 5 to 10 days later, fever reoccurs with signs of meningeal irritation and asymmetric flaccid paralysis. Respiratory motor nuclei may be directly involved, resulting in diaphragmatic or other respiratory muscle dysfunction. In 6 to 25 percent of paralytic cases, bulbar symptoms may arise, increasing the risk of upper-airway obstruction, pooling of pharyngeal secretions, and pulmonary aspiration. Moreover, the central respiratory centers can be directly affected, resulting in irregular respirations. In contrast to Guillain-Barré syndrome, sensation is intact. Tendon reflexes are significantly diminished or absent. Cerebrospinal fluid analysis shows a pleocytosis associated with mild protein elevation, and electroneuromyography shows widespread patchy denervation.

Fifteen to 30 percent of adults with paralyzing infection die and treatment overall is supportive. Many patients require aggressive ventilatory and hemodynamic support during the acute phases of their illness. As temporarily damaged nerve cells regain function, recovery begins and may continue for as long 6 months. Paralysis persisting beyond that point is permanent, however, and may be associated with complaints of severe pain, which sometimes recurs years after the illness.

Some patients develop progressive muscle weakness 20 to 30 years after the initial infection. This has been termed "postpolio syndrome." Symptoms vary from mild to moderate deterioration of function, with fatigue, joint pain, or weakness that may progress to muscle atrophy. The most common symptom is muscle pain (typically after exertion), which occurs in 36 to 86 percent of the patients. The weakness tends to progress slowly, with an average decline in muscle strength of approximately 1 percent per year. The pathogenesis appears to be due to dysfunction of surviving motor neurons, with slow disintegration of axonal terminals eventually leading to muscle denervation. Although respiratory complaints are common in this disorder, significant hypoventilation with elevated Pa_{CO_2} rarely occurs. Respiratory failure is more common in those that required mechanical ventilation during the acute poliomyelitis phase.

Amyotrophic Lateral Sclerosis

Amyotrophic lateral sclerosis (ALS) is a chronic, degenerative neurological disorder characterized by death of motoneurons in the cerebral cortex and spinal cord. The result is a combination of upper and lower motoneuron dysfunction, manifested by spasticity and hyperreflexia muscle wasting, weakness, and fasciculations. It has an incidence of approximately one to two cases per 100,000 people. Males are more commonly affected than females, by a 2:1 ratio. Most cases are sporadic, but approximately 5 to 10 percent of cases demonstrate an autosomal dominant inheritance pattern. Recent reports incriminate abnormal glutamate metabolism as a potential cause in the development of sporadic ALS. Glutamate has been shown to exert specific neurotoxic effects and induces neuronal degeneration, both in vivo and in vitro. Additional mechanisms are likely important as well with recent work focusing on oxidative stress, loss of neurotrophic factors such as vascular endothelial growth factor (VEGF), and chronic inflammation. A familial form of ALS has been localized to

chromosome 20, and a defect in gene coding for superoxide dismutase has been identified in some families.

The usual clinical presentation is progressive weakness of the distal extremities, although severe respiratory muscle weakness, particularly intercostal muscle and diaphragm weakness, has resulted in some ALS patients presenting with respiratory insufficiency as the initial symptom. Respiratory muscle impairment is more evident in the advanced stages of the disease. Abnormalities in pulmonary function are apparent, even in patients with mild extremity weakness. Progression of respiratory impairment is much faster in ALS than in other chronic neuromuscular disorders, and serial lung function studies in ALS patients show progressive reduction in FVC and MVV. In contrast to patients with other neurological disorders, however, patients with ALS usually have a normal or slightly elevated transpulmonary pressure at FRC, and RV is usually increased and continues to rise as the disease progresses with maintenance of a normal TLC. These changes are thought to be due to earlier involvement of the abdominal musculature, with preservation of intercostal and diaphragm function. Support for these physiological findings comes from pathologic studies that show a more pronounced loss of motoneurons in the lumbosacral and lower thoracic spinal segments than in the upper and midthoracic regions.

The use of respiratory muscle testing has been used to help determine the prognosis and help clinicians decide when to initiate ventilatory assistance. Recently, the sniff nasal inspiratory force (SNIF) was used to predict survival in ALS. The SNIF test is theoretically easier for the patient with ALS, particularly those with bulbar muscle involvement, because a tight seal around a mouthpiece is not required. A sniff is a short voluntary inspiratory maneuver, which has been shown to correlate with invasive nonvolitional tests of diaphragm strength. A SNIF less than 40 cm H_2O was found to predict nocturnal hypoxemia better than FVC. More importantly, a SNIF less than 40 cm H_2O was associated with a hazard risk for death of 9.1 with a median 6-month survival of 50 percent. Surprisingly, in those with SNIF less than 40 cm H_2O 66 percent had an FVC above 50 percent and the hazard risk for death was 13.6 in this group. When comparing the two techniques for the ability to predict 6-month mortality, the SNIF test had a sensitivity of 97 percent and specificity of 79 percent, while the FVC was 58 percent sensitive and 96 percent specific. A second study also has shown that in ALS patients without bulbar involvement the SNIF was superior to both vital capacity and maximal inspiratory pressure in predicting the development of respiratory failure as defined by hypercapnia (Pa_{CO_2} greater than 45 mm Hg). In patients with significant bulbar involvement, there was no single test of respiratory muscle function that reliably predicted the development of respiratory failure.

The shape of the flow-volume curve may also pinpoint the subgroup of ALS patients with greater weakness of the expiratory muscles. In patients with severe expiratory muscle weakness, the flow-volume curve near RV shows a sharp drop in flow such that the maximum expiratory curve has a concave appearance. This group of ALS patients usually has lower maximum expiratory pressures, smaller VC, reduced expiratory reserve volume, and a higher RV than do ALS patients with more-normal–appearing flow-volume curves.

ALS is a progressive and uniformly fatal neuromuscular disease and all patients eventually develop respiratory failure, which necessitates the discussion of mechanical ventilation. Currently, guidelines from the American Academy of Neurology recommend treatment with noninvasive mechanical ventilation once the FVC is below 50 percent of predicted. Ventilation with bilevel positive airway pressure has been shown to increase both survival and quality of life in patients with ALS, while those with orthopnea seemed to derive the most benefit. One study examined the role of bulbar symptoms in the use of noninvasive ventilation. In a group of 57 patients receiving noninvasive ventilation the survival in those without bulbar involvement was significantly longer (27 months vs. 15 months) compared with those with bulbar involvement. Although not prospectively done, this paper also suggested that starting noninvasive ventilation earlier in those without bulbar involvement based on a protocol (presence of orthopnea, FVC less than 50 percent predicted or decrease in FVC of 500 ml, nocturnal desaturations, or Pa_{CO_2} greater than 45 mm Hg) improved survival.

Treatment of the other respiratory complications of ALS includes a high index of suspicion for impaired swallowing due to bulbar involvement. Difficulty in swallowing food or even saliva predisposes ALS patients to a markedly high risk for pulmonary aspiration. Special swallowing precautions, earlier placement of enteral feeding tubes, or antisialogues may be required.

Currently, the antiglutamate drug riluzole is the only pharmacologic agent approved for use in ALS. This drug has been shown to induce a significant improvement in survival and decrease the rate of deterioration in muscle strength in comparison with a placebo. So far, no other agent has been shown to be beneficial, but because of the discovery of a genetic mutation in the superoxide dismutase gene, a transgenic mouse model has been developed permitting the investigation of novel agents. Ceftriaxone, minocycline, insulin-like growth factor I (IGF-I), COX-2 inhibitors, and *N*-acetyl-L-carnitine have all been shown to prolong survival in transgenic animal models of ALS. Randomized, placebo controlled clinical trials are being designed to look at the effectiveness of these agents in patients afflicted with ALS.

However, despite any pharmacologic interventions, ALS is a progressive and fatal neuromuscular disease and all patients eventually develop respiratory failure; therefore, ventilatory assistance needs to be considered. In those without bulbar involvement, noninvasive forms of ventilatory support are clearly indicated and will provide both a survival and quality of life benefit. Airway intubation may be required because of bulbar dysfunction further impairing cough and the inability to clear secretions. Long-term invasive ventilatory support is infrequently applied in ALS patients, but decisions must be made on an individual basis.

Disorders of Peripheral Nerves

Phrenic nerve dysfunction can be a significant cause of respiratory weakness in patients with neuromuscular diseases due to a variety of causes.

Diaphragm Paralysis

Unilateral or bilateral diaphragm paralysis following phrenic nerve injury can result from cardiac surgery, trauma, mediastinal tumors, infections of the pleural space, or forceful manipulation of the neck. Phrenic nerve injury during open heart surgery is one of the most common causes of unilateral and bilateral diaphragm paralysis and is due either to cold exposure during cardioplegia or to mechanical stretching of the phrenic nerve during surgery. Diaphragm paralysis may also be seen with a variety of motoneuron diseases, myelopathies, neuropathies, and myopathies.

Bilateral diaphragm paralysis is characterized by a severe restrictive ventilatory impairment, with VC being frequently less than 50 percent of predicted in the upright position and a further reduction of 25 percent or more in VC in the supine position. TLC is also markedly decreased, as well as FRC and static pulmonary compliance. In most patients with nontraumatic bilateral diaphragm paralysis, the most important clinical feature is orthopnea out of proportion to the severity of the underlying cardiopulmonary disease.

In patients with nontraumatic bilateral diaphragm paralysis, the diaphragm usually goes unrecognized until they present with cor pulmonale or cardiorespiratory failure. A chest radiograph showing elevation of both hemidiaphragms with volume loss and/or atelectasis at the lung bases is common. The diagnosis of bilateral diaphragm paralysis should be considered when any of the following four abnormalities is present: (a) a 40 percent or greater reduction in VC in the supine compared with upright position; (b) fluoroscopically observed paradoxical movements of both hemidiaphragms during a "sniff" test; (c) absence of phrenic latency or phrenic nerve conduction velocity tests or lack of EMG evidence of spontaneous diaphragm activity; and (d) transdiaphragmatic pressure two standard deviations below the expected mean for normal subjects with paradoxical inward abdominal motion during maximum inspiratory efforts.

Because in most patients, bilateral diaphragm paralysis occurs in the context of global respiratory muscle impairment, measurements of PI_{max} and PE_{max} may be sufficient to arouse suspicion of diaphragm paralysis as a cause of the patient's complaints. With diaphragm paralysis, a marked reduction in PI_{max} with preservation of PE_{max} should be found, and in general, there is a correlation between maximum inspiratory pressures and Pdi_{sniff}. Reductions in Pdi_{sniff} to less than 30 cmH_2O are accompanied by orthopnea, a supine decrease in VC, and the presence of abdominal paradox. In most cases, the presence of severe bilateral diaphragm weakness can be diagnosed from physical exam, measurements of VC in the upright and supine positions, and PI_{max} and PE_{max}. In cases in which the diagnosis is uncertain, or when definite documentation is desired, measurement of transdiaphragmatic pressures, phrenic nerve conduction times, EMG activity, transdiaphragmatic pressures during phrenic nerve stimulation, or ultrasound imaging of the diaphragm may be desired. An elevation in $PaCO_2$, particularly in the supine position in patients with diaphragm paralysis has been reported, but is not consistent.

Hemidiaphragm paralysis is more common than bilateral paralysis and is usually diagnosed from unilateral elevation of the hemidiaphragm on chest radiograph. Ultrasound of the diaphragm can be performed to confirm the diagnosis as well. Most disorders reported as causing bilateral diaphragm paralysis have also been reported as causes of unilateral paralysis (e.g., cervical spondylosis, spine cord injury, poliomyelitis, and muscular dystrophy). Other, more specific causes of unilateral diaphragm paralysis are pneumonia, trauma from central vein cannulation, and viral infections of the cervical nerve roots.

Patient complaints and physical examination abnormalities in unilateral diaphragm paralysis are usually the same as with bilateral diaphragm paralysis but are less striking. Orthopnea is a frequent complaint, but it is less dramatic than in patients with bilateral paralysis. Moreover, physical examination findings are nonspecific, but occasionally may show paradoxical inward motion of the paralyzed hemidiaphragm with a reduction in breath sounds at the affected lung base and an increase in percussible dullness. The alveolar arterial oxygen gradient may be increased with mild hypoxemia due to the reduction in ventilation and perfusion of the lower lobe on the affected side.

Tests of diaphragm function are intermediate between those in patients with bilateral diaphragm paralysis and normal predicted values. VC in the upright posture may be reduced to 74 to 81 percent of predicted, with a fall in VC also present in the supine compared with erect position, but of lesser magnitude than in patients with bilateral diaphragm paralysis. In patients with right hemidiaphragm paralysis, the fall in VC may be almost twice as great (19 versus 10 percent) in comparison with left-sided paralysis, owing to the weight of the liver further encroaching on lung volume. Maximum inspiratory mouth pressures are frequently reduced to approximately 50 to 62 percent of normal. Similar reductions are also found in maximum Pdi measured during maximum static voluntary efforts and during maximum sniff.

Treatment of patients with bilateral diaphragm paralysis is similar to that of other patients with chronic neuromuscular diseases. Eliminating nocturnal hypoventilation, especially during REM sleep is warranted, and the implementation of noninvasive ventilation, especially positive-pressure ventilation, may be indicated. In some cases of symptomatic unilateral hemidiaphragm elevation, surgical plication of the affected hemidiaphragm may relieve symptoms and improve FVC and transdiaphragmatic pressure.

Guillain-Barré Syndrome

Guillain-Barré syndrome (GBS) precipitates respiratory failure more often than any other peripheral neuropathy. It is

an acute idiopathic polyneuritis with an annual incidence of 0.6 to 1.9 cases per 100,000 people. It usually presents as paresthesia and ascending paralysis of the lower extremities with absent deep tendon reflexes in a symmetrical distribution. Objective findings of sensory loss are variable, and the degree of motor weakness can range from mild paresis to complete paralysis. Maximum weakness of the lower extremities occurs within 2 weeks in 50 percent of cases, and 90 percent of cases reach their nadir in weakness by 4 weeks. After the nadir is reached, patients remain at that level for an additional 1 to 4 weeks before recovery begins. Facial, ocular, and oropharyngeal muscles may be impaired as well as the respiratory muscles. Respiratory muscle weakness and, specifically, severe diaphragm weakness may be found in patients with GBS.

The distribution of muscle weakness between respiratory and nonrespiratory muscles is not uniform in GBS, and peripheral muscle strength does not correlate with the presence or absence of respiratory muscle weakness. However, ventilatory failure correlates with diaphragmatic weakness.

The impairment on respiratory tests in GBS is similar to that for other generalized neuromuscular diseases. A decline in FVC and maximum inspiratory and expiratory mouth pressures, impairment in nocturnal gas exchange during REM sleep, and the onset of hypercapnia detected by arterial blood gas analysis have all been reported in symptomatic GSB patients. An FVC of 15 cc/kg is a sign of imminent respiratory failure in GBS. Hypercapnia is a late sign of respiratory failure, with the average $PaCO_2$ at the time of intubation 43 mmHg when FVC is less than 12 cc/kg.

Respiratory treatment of GBS patients is mainly supportive. Since bulbar involvement, leading to swallowing dysfunction, increases the propensity for pulmonary aspiration, special precautions for feeding and control of upper-airway secretions may be required. Primarily because of bulbar dysfunction in those with respiratory failure, noninvasive ventilation has not been used outside of a few case reports. Individual cases without bulbar dysfunction merit special consideration and the use of noninvasive ventilation may be appropriate. Earlier intubation and assisted ventilation may be indicated to avoid complications that arise from progressive respiratory failure, overwhelming pulmonary infections, or both. When indicated, intubation and mechanical ventilation should be initiated early because emergent intubations have been associated with worse outcomes. It is well established that mechanical ventilation is indicated when the vital capacity falls below 15 cc/kg. However, it would be ideal to predict the need for mechanical ventilation at an earlier time. A recent study involving patients that were enrolled in plasma exchange trials showed by multivariate analysis that time from onset to admission (fewer than 7 days), inability to lift the elbows above the bed, inability to stand, inability to lift the head, ineffective cough, and increased liver enzymes all predicted the need for endotracheal intubation and mechanical ventilation. Patients that had at least four of these risk factors had an intubation rate of 85 percent. Aggressive pulmonary toilet, including repeated bronchoscopy, may be needed to decrease atelectasis and the incidence of nosocomial pneumonia.

In a multicenter trial, plasmapheresis (total of four treatments), using either albumin or fresh frozen plasma as replacement fluids, produced short-term benefits in earlier motor recovery, ambulation, reduction in number of patients who required assisted ventilation, and shortened the duration of mechanical ventilation. Plasmapheresis should be started within 2 weeks of the onset of symptoms or earlier, if possible. In patients with rapidly deteriorating neurological symptoms, however, plasmapheresis may still offer some benefit even if the duration of the disease is greater than 3 weeks. A subsequent study from the same group showed that two plasmapheresis treatments were better than none in mild disease, but four were better than two in moderate and severe disease. More than four treatments was not beneficial even in severe disease. Intravenous immunogammoglobulin (IVIG), given within 2 weeks after the onset of GBS, may also be effective therapy. Because plasmapheresis is an effective therapy, IVIG has never been compared with placebo. However, IVIG has been compared with plasmapheresis and recovery was as effective as plasmapheresis and may have been slightly better. In a study of 150 patients with GBS, 53 percent of the group treated with IVIG had an improvement of one grade (on a 7-point scale) in muscle strength compared with 34 percent of those treated with plasmapheresis after 4 weeks of therapy. A subsequent study comparing IVIG, plasmapheresis and IVIG with plasmapheresis showed that there was no difference between the groups. Currently, there is no evidence from randomized controlled trials to support the use of corticosteroids in the treatment of GBS.

Critical Illness Polyneuropathy

Critical illness polyneuropathy (CIP) was initially described in five patients that had survived sepsis and multisystem organ failure, and the entity is now recognized as a serious complication of critical illness that contributes significantly to morbidity and mortality. The disease is common with as many as 68 percent of patients with sepsis and multisystem organ failure requiring mechanical ventilation having evidence of CIP on electromyography/nerve conduction studies. Patients affected by this disorder typically exhibit varying degrees of musculoskeletal weakness, which ranges from mild weakness to near total paralysis with hyporeflexive deep tendon reflexes. Unfortunately, physical examination is unreliable as the sole means of diagnosis, and electromyography with nerve conduction studies (EMG/NCS) are required to confirm the diagnosis. EMG studies in these patients show a reduction in the amplitude of the compound muscle action potential without significant prolongation of stimulus latency, suggesting primarily axonal nerve damage rather than a demyelinating process.

Recognition of CIP is important because the disease affects patient management and prognosis of the recovery from critical illness. Patients who develop CIP tend to require

a longer period of mechanical ventilation and longer hospital stays compared with those without CIP. Garnacho-Montero et al. found that in a group of patients with sepsis and prolonged mechanical ventilation that those with CIP required 34 days of mechanical ventilation versus only 14 days for those without CIP. Additionally, the weakness associated with CIP results in an extended rehabilitation period, and there is evidence of persistent neuropathy on EMG/NCS as long as 5 years after discharge from the intensive care unit. Patients that develop CIP appear to have a higher mortality with one study showing a 3.5-fold increase in ICU mortality, and another with significantly higher in hospital mortality.

Although the exact mechanism for axonal damage in this syndrome is unknown, several risk factors for the development of CIP have been described. Two of the most important risk factors are the presence of the systemic inflammatory response syndrome (SIRS) and the APACHE III score. One study looked at 98 patients prospectively and found that 72 percent of patients with SIRS and an APACHE III score above 85 develop CIP. Multivariate analysis of associated risk factors from another study found that hyperosmolality, parenteral nutrition, the use of neuromuscular blocking agents, and neurological failure (GCS less than 10) were associated with an increased risk of developing CIP. Exactly how these risk factors lead to the development of CIP is not known, but possibilities include nerve toxins released during episodes of multiple system organ failure, antibiotics impairing neuromuscular transmission, protracted use of neuromuscular blocking agents, and hyperglycemia causing nerve ischemia by endovascular shunting.

Because no specific therapy for CIP exists, treatment is purely supportive and includes aggressive rehabilitation, nutrition support and treatment of any medical complications. It should be emphasized to both patient and family that recovery may be prolonged (as long as 5 years).

Disorders of the Neuromuscular Junction

Myasthenia Gravis

Myasthenia gravis is an autoimmune disorder characterized by impaired transmission of neural impulses across the neuromuscular junction due to the production of antibodies directed against the acetylcholine receptor. The prevalence of myasthenia gravis is estimated to be approximately 1 in 10,000 people with 2-to-1 female-to-male predominance. It occurs more often in younger than older adults. The typical myasthenic patient presents with fluctuating muscular weakness, with improvement after rest and the administration of anticholinesterase agents (e.g., edrophonium chloride). Ocular, facial, and neck muscles are commonly affected, but patients who have the most severe respiratory involvement have either acute fulminating or late severe classifications of myasthenia gravis.

In patients with moderate, generalized myasthenia gravis, pulmonary function studies before the administration of edrophonium chloride reveal a mild reduction in FVC and moderate reductions in both maximum inspiratory (approximately 46 percent of predicted) and expiratory (reduced to approximately 18 percent of predicted) mouth pressures. Because of increased lung recoil pressure, normal or supranormal values of maximal expiratory flow are seen in relation to lung recoil pressure or absolute lung volume. Although upper airway obstruction due to bulbar muscle involvement is theoretically possible, it has rarely been reported. However, Putman and Wise examined flow volume loops in myasthenia gravis patients that were adequate for interpretation. They found that in 12/61 patients with myasthenia gravis with reproducible flow volume loops 7 had either a variable extrathoracic or fixed upper airway obstruction suggesting that upper airway obstruction may be more common than previously thought.

Acute respiratory failure usually occurs in the setting of a myasthenic crisis or cholinergic crisis or as the initial presentation of the disease. A myasthenic crisis refers to worsening of the basic underlying disease, usually precipitated by decreased anticholinesterase medication, surgery, administration of neuromuscular blocking medication, and emotional upset. The most common complications of myasthenic crisis are respiratory failure and recurrent pneumonias due to aspiration from bulbar involvement and impaired cough. The mean duration of mechanical ventilation in myasthenia gravis in a series of 22 patients (12 postoperative myasthenic or cholinergic crises, four myasthenic crises, two cholinergic crises, and four other medical disorders) was 8 days, with six patients (32 percent) requiring tracheostomy for prolonged mechanical ventilation. Of the 22 patients 21 survived and were totally weaned from ventilatory support over 1 to 32 days. Noninvasive bilevel (BiPAP) positive pressure ventilation is a viable option to treat respiratory failure during a myasthenic crisis until effective therapy is delivered. BiPAP was used in a series of 11 myasthenic crisis events in nine patients. The mean pressures used were 13/5 cm H_2O, and endotracheal intubation was avoided in all but four instances. Bulbar weakness was clearly documented in seven of the episodes and all patients were treated with either IV immunoglobulin or plasmapheresis. The only predictor for failure of BiPAP was a $PaCO_2$ above 50 mmHg. Clinical parameters useful in predicting the development of postoperative respiratory failure include the severity of the disease (e.g., acute fulminating or late severe categories of myasthenia gravis), a low preoperative VC, and bulbar symptoms.

The treatment of myasthenia gravis includes anticholinesterase agents, high-dose corticosteroids, thymectomy, and plasmapheresis in patients refractory to steroid or immunosuppressive therapy. Anticholinesterase agents are the first line of treatment. Most patients improve significantly with anticholinesterase agents, but only a few regain normal function. Remissions can be induced in up to 80 percent of patients with the use of corticosteroids. However, corticosteroids may cause temporary worsening of muscle weakness, usually on the sixth to tenth day of therapy, and close observation for signs of respiratory insufficiency is advisable. Other

immunosuppressive agents (e.g., cyclosporine and azathioprine) may be useful with or without concomitant corticosteroids.

In retrospective studies, thymectomy improves survival and relieves clinical symptoms, even in the absence of thymoma. In patients with thymoma, thymectomy is also indicated because the risk for malignant transformation is high in patients less than 55 years of age. In up to 80 percent of myasthenia gravis patients without thymoma, clinical improvement after thymectomy occurs during prolonged follow-up.

Plasmapheresis and the use of intravenous immunoglobulin (IVIG) produce a temporary reduction in acetylcholine receptor antibody level and may be helpful in patients with respiratory failure not responding to anticholinesterase and immunosuppressive agents. Plasmapheresis and IVIG have been compared and both are equally efficacious. However, IVIG was associated with less severe adverse reactions and therefore is the preferred initial agent in the treatment of myasthenic crisis.

Eaton-Lambert Syndrome

Eaton-Lambert syndrome is a rare myasthenia disorder resulting from a reduction in neurotransmitter release from presynaptic terminals that develops in association with tumors (especially small-cell lung carcinoma). Although patients may respond weakly to administration of edrophonium chloride, the disease is differentiated from myasthenia gravis by the predominant involvement of limb and girdle muscles compared with the ocular and bulbar muscle involvement in myasthenia gravis. Respiratory muscle weakness is often detected on pulmonary function tests, but respiratory failure is infrequent.

Botulism

Botulism is a rare disorder caused by the *Clostridium botulinum* toxin. It occurs as a result of eating improperly cooked food, wound contamination by the organism, or, especially in infants, the absorption of toxin from the gastrointestinal (GI) tract. There are eight types of toxins, although human diseases are usually caused by type A, B, or E.

Botulinum toxin binds to the calcium channel in presynaptic terminals, impairing neuromuscular transmission of acetylcholine. GI symptoms predominate early in the disease, followed by neurological impairment, including descending paralysis of the neck, trunk, and limb muscles. Weakness of the respiratory muscles requiring mechanical ventilation is frequent, especially with botulinum type A toxins. Spirometry usually reveals a restrictive ventilatory defect, and recovery from respiratory muscle weakness may take months, often requiring prolonged mechanical ventilation. The average duration of ventilatory support for type A poisoning is 58 days, in contrast to 26 days for type B botulism. Exertional dyspnea and poor exercise tolerance may persist, even with normal lung function.

Table 93-7

Myopathies Likely to Produce Respiratory Abnormalities

Inherited Myopathies	Acquired Myopathies
Muscular dystrophies	Inflammatory
Duchenne	(dermatomyositis,
Myotonic	polymyositis)
Fascioscapulohumeral	Systemic lupus
Limb-girdle	erythematosus
Oculopharyngeal	Endocrine myopathies
Congenital myopathies	Thyroid dysfunction
Nemaline myopathy	Hyperadrenocorticism
Centronuclear myopathy	Acute steroid myopathy
Metabolic myopathies	Electrolyte disorders
Acid maltase deficiency	Rhabdomyolysis
Mitochondrial myopathies	

Muscular Dystrophies and Acquired Myopathies

Respiratory function may be significantly affected by a variety of inherited muscle disorders and acquired myopathies (Table 93-7). The inherited muscular dystrophies refer to a heterogeneous group of progressive, degenerative, hereditary skeletal muscle diseases that cause severe muscle weakness, eventually resulting in repeated pneumonias, respiratory failure, and, in some cases, death. Respiratory failure, often accompanied by pneumonia, contributes to death in more than 75 percent of patients with Duchenne's muscular dystrophy.

Inherited Myopathies

Duchenne's Muscular Dystrophy

Duchenne's muscular dystrophy (DMD) is the best characterized of these heredofamilial muscle diseases. This disease is transmitted by an X-linked recessive gene, although approximately one-third of cases arise from spontaneous mutation. The disease is due to the mutation of the gene for skeletal protein dystrophin, a subsarcolemma protein believed to play a major role in providing structural integrity in the muscle cell surface membrane. Lack of dystrophin leads to a weaker cell membrane that is damaged and further worsened with muscle contraction. Muscle inflammation, necrosis and fibrosis subsequently lead to severe atrophy and loss of function. Approximately 30 to 40 percent of the normal amount of dystrophin must be expressed in order to prevent major myopathic symptoms. The diagnosis is confirmed by demonstrating mutation of the dystrophin gene in DNA from peripheral leukocytes, or an absence or abnormality in dystrophin in muscle biopsy samples.

Symptoms usually present in early childhood. Gait disturbances and delayed motor development are common manifestations, with proximal weakness resulting in an

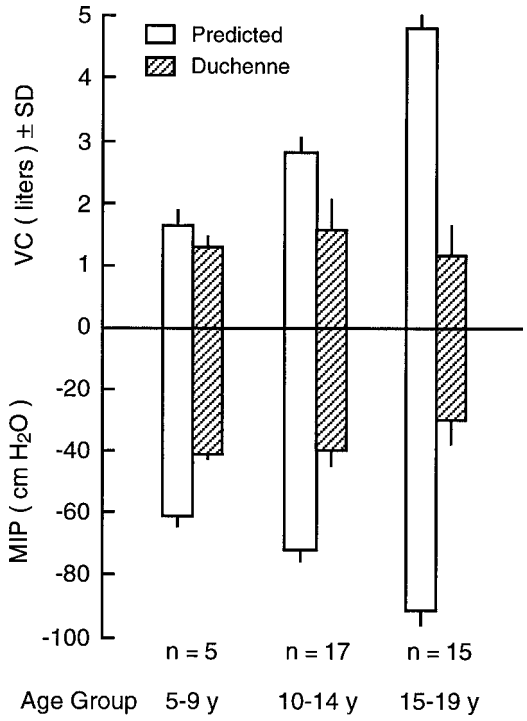

Figure 93-10 Mean vital capacity (VC) and maximum static inspiratory pressures (MIP) in 37 DMD patients in three age groups (shaded bars) in comparison to normal predicted values (unshaded bars). MIP decreases gradually as DMD progresses, despite body growth, whereas VC increases until patients reach their early teens. (*Based on data of Smith PEM, Edwards RHT, Evans GA, et al: Practical problems in the respiratory care of patients with muscular dystrophy.* New Engl J Med *316:1197–1205, 1987, used with permission.*)

exaggerated lumbar lordosis. Most patients are wheelchair bound by the age of 12 to 15 years, with death occurring around the age of 20 years as a result of progressive respiratory failure and pneumonia. Kyphoscoliosis commonly develops as a result of severe muscle weakness and further contributes to a restrictive ventilatory deficit. Pulmonary symptoms are often minimal early on, despite significant weakness of the respiratory muscles. Maximum inspiratory pressure is reduced at all lung volumes in patients with DMD and declines with time. FVC increases with growth during the first decade and may mask early respiratory muscle dysfunction before it plateaus and progressively decreases about 5 to 6 percent per year after 12 years of age (Fig. 93-10). Reductions in maximum inspiratory pressure, therefore, occur early in the clinical course of DMD and may precede the reduction observed in VC. Inspiratory muscle weakness does not necessarily parallel the development of expiratory muscle weakness. Maximum expiratory mouth pressures are substantially lower than maximum inspiratory mouth pressures, possibly leading to a marked decrease in the effectiveness of cough.

Despite severe and progressive muscle weakness, hypercapnia is uncommon in patients with DMD in the absence of pulmonary infections. The absence of hypercapnia despite severe muscle weakness is believed to be due to relative preservation of diaphragm function until very late in the illness. Once hypercapnia occurs, however, the course is rapidly progressive and mean survival is approximately 10 months.

Since ventilation is heavily dependent on diaphragmatic function in DMD patients, severe nocturnal hypoventilation may occur during REM sleep, when activity of chest wall and neck muscles is markedly attenuated. Indeed, REM hypoventilation may occur during REM sleep, when activity of chest wall and neck muscles is markedly attenuated. REM hypoventilation has been documented in DMD patients, even in those who have normal daytime gas exchange. Sleep-related hypoxemia may contribute to respiratory insufficiency and the development of cor pulmonale.

Management of patients with DMD is mainly supportive. Ambulation should be maintained and encouraged as long as possible to retard the development of scoliosis. Surgical correction may attenuate the scoliotic contribution to the fall in VC and improve patient morale and quality of life overall. However, the downward trend in VC continues despite spine surgical stabilization. General physiotherapy may be helpful in preventing contractures. Maintenance of proper nutrition, with an emphasis on weight control, is important. Patients with DMD have a propensity to become overweight through a combination of inactivity, reduced energy requirements, and a misguided desire to improve muscle bulk by overeating. Some authors have emphasized a high-protein (more than 80 g protein daily), low-calorie diet, aiming to achieve a body weight somewhat lower than the ideal weight in patients of a similar height and normal muscle mass.

Inspiratory muscle training (IMT) has been examined as a tool to prevent further decrease in respiratory muscle function in those with DMD, but its routine use remains controversial. Because there is loss of the protective mechanism of nitric oxide release in children with DMD, IMT could potentially be detrimental. Koessler et al. studied the effect of 2 years of IMT on a group of 27 patients with neuromuscular disease (18 with DMD and nine with spinal atrophy), and showed a clear increase in PI_{max} and MVV. There was a plateau reached after 10 months of training, but despite this there was no change in the vital capacity at 2 years compared with baseline. Because there is potential for harm and no long-term studies to support its use, American Thoracic Society (ATS) guidelines do not suggest the use of routine IMT in this group of patients.

Maintenance of cough and adequate airway clearance is extremely important in attempting to prevent atelectasis and pneumonia in this patient population. A PE_{max} of at least 60 cm H_2O has been shown to be adequate to generate an effective cough in patients with DMD, while a drop below 45 cm H_2O has been associated with ineffective cough. Once an ineffective cough is recognized there are multiple treatment modalities. The most studied technique is the use of a manual insufflator-exsufflator, which stimulates cough by providing a positive pressure breath immediately followed by a negative pressure exsufflation. The technique can be used on patients with or without a tracheotomy, and is generally well tolerated. It has been shown to be effective in generating cough and clearing airways in children with DMD, especially

once scoliosis has developed. Respiratory tract infections are a serious complication in DMD patients, and must be treated aggressively with physiotherapy, postural drainage, assisted cough techniques, and appropriate antibiotics. All patients, regardless of cough status, should receive vaccination against pneumococcal pneumonia and influenza.

In some patients, assisted ventilation is required once respiratory insufficiency or symptoms of sleep-related breathing disorders are present. Intermittent noninvasive positive-pressure ventilation (NPPV) prolongs survival, improves quality of life, and may attenuate the decline in FVC and MVV. Longer-term follow-up of DMD patients treated with noninvasive ventilation demonstrates that pulmonary function continues to deteriorate 3 to 4 years after the initiation of noninvasive ventilation, with patients requiring longer periods of ventilation and/or transition to tracheostomy with positive-pressure ventilation. Once patients require the use of NPPV, the pressure should be titrated in the sleep laboratory to eliminate nocturnal apneas and hypopneas. Generally, bilevel positive airway pressure (BiPAP) should be used in those with significant daytime or nocturnal hypoventilation, and continuous positive airway pressure (CPAP) should be used primarily in those with obstructive sleep apnea without evidence of hypoventilation.

DMD is a relentlessly progressive disease that eventually will lead to respiratory failure requiring invasive mechanical ventilation (see Chapter 94). End-of-life care and plans for the use of invasive mechanical ventilation should be discussed with the family and the patient well in advance if at all possible. While the institution of mechanical ventilation has been shown to prolong life in the appropriate setting, little is known of the effect on quality of life, and decisions must be made on an individual basis.

There is evidence to suggest that prednisone treatment is beneficial. In a randomized, double-blind, controlled 6-month trial of prednisone in 103 boys, age 5 to 15 years, with DMD, patients were assigned to one of three regimens: prednisone 0.5 mg/kg per day, prednisone 1.5 mg/kg per day, or placebo. Both prednisone groups showed significant improvements in muscle strength and functional scores. After 6 months of therapy, patients randomized to high-dose prednisone had an improvement in time needed to stand, climb stairs, or lift weights, and a significantly larger FVC (1.7 versus 1.5 L), compared with the placebo group. A recent study examined the effect of alternate day dosing of prednisolone (0.75 mg/kg) for an average of 2.75 years in 66 boys with DMD compared with a historical control group not treated with steroids. The investigators found greater muscle strength and less scoliosis in the steroid group. Although there were more ankle contractures, the loss of ambulation was delayed in the steroid group compared with historical controls. Although these results are preliminary and not placebo controlled, they are encouraging and suggest that corticosteroid therapy may have a potential future role in DMD. To date there has not been a randomized controlled trial examining the effect of corticosteroids in the long-term management of the disease.

Gene therapy will be applicable to DMD in the future. Preliminary animal studies examining adenovirus-mediated in vivo gene transfer to dystrophic mouse diaphragm suggest that the adenovirus vector delivery of functional dystrophin gene to impaired muscle may be feasible. The large size of the dysmorphin gene limits the ability of viral vectors to deliver the gene to skeletal muscle. There has been more interest lately in using naked DNA plasmids and DNA plasmid-liposome complexes to deliver the gene to skeletal muscles. In fact, phase I trials have begun examining the effectiveness of this approach and early results show that the gene can be delivered to the target tissue.

Myotonic Dystrophy

Myotonic dystrophy is the most common form of hereditary muscular dystrophy in adults, with an estimated incidence of 1 in 8000 people. The gene responsible for the disease is located on the long arm of chromosome 19 and demonstrates an autosomal dominant inheritance pattern. Symptoms usually present during adolescence and in early adulthood, although the syndrome may be recognized as early as infancy.

Respiratory muscle weakness is common and can be severe, despite mild limb muscle weakness. Myotonia of the respiratory muscles contributes to an increased work of breathing by increasing inspiratory impedance. Studies have suggested that the presence of a chaotic breathing pattern may explain the higher prevalence of chronic hypercapnia in patients with myotonic dystrophy than in patients with other forms of muscular dystrophy. Support for these findings came from studies that showed abnormal ventilatory responses to hypercapnic challenges in patients with myotonic dystrophy. However, studies that have used mouth occlusion pressures ($P_{0.1}$) have revealed normal or supranormal responses in $P_{0.1}$ in patients with myotonic dystrophy compared with controls. These data seem to suggest that prior studies showing hypercapnia in patients with myotonic dystrophy underestimated the severity of respiratory muscle weakness by itself as a limitation in the ability to mount a normal ventilatory response. The chaotic breathing pattern observed in some patients with myotonic dystrophy has been suggested to be related to disordered afferent information from diseased muscle spindles.

Patients with myotonic dystrophy are particularly susceptible to development of respiratory failure with general anesthesia and sedatives. Postoperative respiratory monitoring is essential if surgery or the use of these agents is required. Pharyngeal and laryngeal dysfunction increases the risk of aspiration. Sleep-related breathing disturbances are common and may include both central and obstructive forms of sleep apnea. Nocturnal positive-pressure ventilation should be tried when hypercapnia and hypoxemia are present.

Facioscapulohumeral Dystrophy

Other inherited adult muscular dystrophies are facioscapulohumeral dystrophy (FSH) and limb-girdle dystrophy. FSH is an autosomal dominant dystrophy that primarily affects muscles of the face and the proximal portion of the upper

extremities. FVC is significantly reduced in patients with FSH, although facial weakness complicates spirometric assessment. In 20 percent of patients with FSH, the disease affects pelvic girdle and trunk muscles, sometimes impairing respiratory function.

Limb-Girdle Dystrophy

Limb-girdle dystrophy is a heterogeneous group of autosomal dominant recessive disorders. The disease usually becomes evident in the second or third decade of life. Several case reports have documented the development of chronic hypercapnia in patients with limb-girdle dystrophy who have severe diaphragm weakness or bilateral diaphragm paralysis as the basis for hypercapnia. However, not all patients with limb-girdle dystrophy develop hypercapnia. Most patients have moderate respiratory muscle weakness with normal gas exchange.

Acid Maltase Deficiency

Two metabolic myopathies, acid maltase deficiency and mitochondrial myopathy, have received attention as potential causes of respiratory failure. Acid maltase deficiency is a type I glycogen storage disease due to the deficiency of the lysosomal enzyme responsible for hydrolysis of both the α 1 to 4 and α 1 to 6 linkages of glycogen. The disease presents in three clinical forms: infantile, childhood, and adult. In adult-onset disease, onset usually occurs after 20 years of age and presents with progressive proximal muscle weakness. The diagnosis may be difficult to establish in some patients, as respiratory failure or sleep-related complaints, secondary to respiratory deterioration during REM sleep, may be the initial presentation.

Diagnostic studies include elevated serum muscle enzymes; myopathic changes on electromyography, and vacuoles filled with lysosomal breakdown products on muscle biopsy. A report that a weight-reducing, high-protein diet improved respiratory function in a patient with an acid maltase deficiency has not been confirmed, and treatment remains supportive.

Mitochondrial Myopathy

Mitochondrial myopathy represents a heterogeneous group of disorders that affect mitochondrial function and may present as complex multisystem disorders with brain and striated skeletal muscle being the predominant organs affected: (a) Kearns-Sayre syndrome; (b) myoclonic epilepsy, "ragged red fibers," and mitochondrial myopathy; and (c) encephalopathy, lactic acidosis, and stroke-like episodes. The clinical manifestations may be broad and include myalgia and exercise intolerance, proximal muscle weakness, and external ophthalmoplegia with unexplained respiratory failure. All three disorders are characterized by hypoventilation and depressed responses to hypoxia and hypercapnia and, in some cases, unexplained respiratory failure. Skeletal muscle biopsy establishes the diagnosis of mitochondrial myopathy by showing "ragged red fibers," which are accumulations of mitochondria identified with modified trichrome staining. Treatment is supportive. Once identified, patients should be cautioned regarding the use of sedatives, and special attention is required when sedation or surgery is planned.

Acquired Myopathies

Acquired myopathies include inflammatory polymyopathies (polymyositis and dermatomyositis), systemic lupus erythematosus, endocrine myopathies (hyper- or hypothyroidism), hyperadrenocorticism, electrolyte disturbances, rhabdomyolysis, and the use of high-dose exogenous corticosteroids, with or without concomitant use of neuromuscular blocking agents.

Inflammatory Myopathies

Pulmonary complications are the major cause of morbidity and mortality in dermatomyositis and polymyositis. These include interstitial pneumonitis, pulmonary vasculitis, recurrent aspiration from oropharyngeal dysfunction, and, rarely, hypoventilatory failure from respiratory muscle weakness. Respiratory failure is uncommon in the inflammatory myopathies and is usually due to clinically significant interstitial lung disease. Ten to 30 percent of patients with inflammatory myopathies have interstitial lung disease, manifested by dyspnea, nonproductive cough, and hypoxemia, with radiographic evidence of diffuse interstitial lung disease and impaired gas exchange.

Corticosteroids may be successful in the treatment of interstitial pneumonitis and myositis. Successful treatment appears to be enhanced by early initiation of therapy, as patients in later stages of the disease become more refractory to corticosteroids and cytotoxic agents.

Systemic Lupus Erythematosus

Diaphragm dysfunction and respiratory muscle weakness with small lung volumes occur without apparent involvement of the peripheral skeletal muscles in patients with systemic lupus erythematosus (SLE). This syndrome has been called "the shrinking lung syndrome." Decreased lung volumes appear not to be due to parenchymal lung disease or phrenic neuropathy but, rather, to a myopathic process affecting diaphragm strength. It is estimated that approximately 25 percent of SLE patients have diaphragm weakness, even in the absence of a generalized myopathy.

Steroid Myopathy

Although a syndrome of acute myopathy secondary to high-dose steroid use was first described almost 30 years ago, the development of severe respiratory muscle weakness and prolonged respiratory failure following the use of high-dose steroids has received renewed interest. Most patients have received neuromuscular blocking agents, along with high-dose steroids before weakness becomes evident. Some patients require months of mechanical ventilation before eventual recovery. The serum CPKs are often normal, and EMG data show nonspecific changes. Overall, it is difficult to incriminate

specific neuromuscular blocking agents or steroids as the only factors responsible for myopathic changes because an underlying severe illness, under nutrition, multiple medications, and disuse atrophy are usually concurrent.

TREATMENT

Principles of Management

Principles in management of respiratory dysfunction in patients with neuromuscular disease include: (a) preventive therapies designed to minimize the impact of impaired secretion clearance and alveolar hypoventilation on gas exchange and lower respirator tract infections; and (b) stabilization of patients who develop acute or chronic respiratory failure (see Chapters 94, 148).

Because patients with neuromuscular disease usually have nonpulmonary symptoms and signs before the onset of respiratory problems, preventive actions can be taken to preserve their respiratory status. In neuromuscular disorders causing bulbar dysfunction, swallowing precautions and airway control measures are required. With advanced bulbar symptoms, upper-airway control with a cuffed tracheostomy tube may be needed to protect the airway and facilitate suction of lower respiratory track secretions, averting atelectasis and pneumonia. In patients with impaired cough, assisted coughing (e.g., ancillary hand thrust in the substernal location to increase intrathoracic pressure and expel secretions mouthward) may be helpful, along with posture drainage and the use of incentive spirometry.

Preventive Therapies

Intermittent Positive Pressure Breathing

There is no evidence for a beneficial effect of intermittent positive-pressure breathing on respiratory system compliance in patients with chronic neuromuscular disorders.

Respiratory Muscle Training

Inspiratory and expiratory muscle training may be helpful in some neuromuscular diseases. One could hypothesize that respiratory muscle weakness is key to the development of respiratory tract infections and ventilatory failure in patients with chronic neuromuscular disease. Besides weakened muscles, a reduction in lung and chest wall compliance and, in some cases, the presence of hypoxemia and hypercapnia all act to increase ventilatory workload in patients who already have markedly diminished ventilatory pump capacity. Strengthening weakened respiratory muscles relieves cough, improves secretion clearance, and increases ventilatory capacity.

Respiratory muscle training improves strength and ventilatory endurance in normal subjects and in patients with pulmonary diseases. Several uncontrolled studies, performed in patients with muscular dystrophy, showed that inspiratory muscle training may improve respiratory muscle endurance and strength.

Some authors have questioned the wisdom of training respiratory muscles of patients with significant neuromuscular dysfunction. Breathing through resistive loads may be harmful and perhaps further damage or tire already weakened respiratory muscles. Also, the training techniques do not apply to upper-airway and pharyngeal musculature.

The effects of inspiratory muscle training have also been examined in patients with quadriplegia, who may be a more appropriate group for respiratory muscle training because, although weakened, their respiratory muscles are normal. In small numbers of patients with quadriplegia, 6 to 16 weeks of inspiratory resistive training improved inspiratory muscle strength and endurance, and 6 weeks of pectoralis muscle isometric training significantly increased expiratory reserve volume in C_6 to C_8 patients with quadriplegia. Such increases in expiratory reserve volume suggest that these patients may have a more effective cough. Although these changes may be physiologically beneficial, no study has correlated such improvements with better clinical outcome; accordingly, the therapeutic value of inspiratory muscle training remains speculative.

Mechanical Ventilation

In patients with severe respiratory impairment, mechanical ventilation may be indicated to provide complete ventilatory support. Indications for mechanical ventilation are shown in Table 93-8. Comparisons of the situations in which invasive or noninvasive mechanical ventilation is applicable are

Table 93-8

Indications for Mechanical Ventilation in Patients with Neuromuscular Diseases

Acute respiratory failure
Severe dyspnea
Marked accessory muscle use
Copious secretions
Unstable hemodynamic state
Hypoxemia refractory to supplemental O_2
Acute severe gas exchange disturbances (increased $PaCO_2$ with pH $\leq$7.25)
Chronic respiratory failure
Symptoms of nocturnal hypoventilation (e.g., morning headaches, decreased energy, nightmares, enuresis)
Dyspnea at rest or increased work of breathing impairing sleep
Cor pulmonale due to hypoventilation, $PaCO_2$ >45, pH <7.32 after treating reversible conditions
Nocturnal desaturation (SaO_2 <88%) despite supplemental O_2 therapy

summarized in Table 93-9. The types of ventilation available and their advantages and disadvantages are provided in Table 93-10. Patients who present with the onset of severe dyspnea, CO_2 retention and moderate to severe hypoxemia require intubation and mechanical ventilation. In patients with acute respiratory failure who are awake, alert, and able to control their airway and do not have copious secretions, noninvasive ventilation (e.g., positive-pressure ventilation with a face mask rather than an endotracheal or tracheostomy tube) may obviate intubation (see Chapter 148).

In some patients, the onset of respiratory failure is insidious, manifested by the gradual onset of dyspnea, daytime hypersomnolence, morning headaches, nightmares, enuresis, and easy fatigability. In patients with these symptoms, arterial blood gas analysis is warranted, especially if vital capacity falls below 1.5 to 1 L. Daytime measurements may be misleading, however, because impaired gas exchange may occur only during REM sleep. Nocturnal oximetry or a full polysomnogram should be considered to exclude the presence of nocturnal hypoventilation. In patients who have chronic hypoventilation, uncompensated respiratory acidosis, hypoxemia refractory to supplemental oxygen, or worsening symptoms such as easy fatigability and morning headaches, the implementation of nocturnal mechanical ventilation should be anticipated (Table 93-8).

In most cases, noninvasive forms of ventilatory support should be considered first. Since the polio epidemic in the 1940s and 1950s, correction of nocturnal and daytime hypoventilation with a range of noninvasive

Table 93-9

Invasive Versus Noninvasive Mechanical Ventilation in Patients with Neuromuscular Disease

Invasive Ventilation (Endotracheal or Tracheostomy Tube and Positive-Pressure Ventilation)	**Noninvasive Ventilation (No Airway Cannulation)**
Copious secretions	Awake, cooperative patient
Inability to control upper airway	Good airway control
Inability to tolerate or failure of noninvasive ventilation	Minimal secretions
Impaired cognition	Hemodynamic stability
Unstable hemodynamics	Reversible cause of respiratory failure

Table 93-10

Types of Noninvasive and Alternative Forms of Ventilation Used in Patients with Neuromuscular Disease

Tank	**Advantages**	**Disadvantages**
Negative-pressure ventilators Tank Pulmowrap Cuirass	Familiar and dependable No airway cannulation Can significantly augment ventilation Rare hemodynamic concerns Simple devices	Cumbersome Induces obstructive apnea Constrains body posture Bulky (tank) Limits nursing care Controlled ventilation
Positive-pressure by mask or mouthpiece	Averts upper-airway obstruction, pressure preset, leak compensates Patient initiated machine breaths	Attachment bothersome Leaks Aerophagia Skin breakdown
Glossopharyngeal breathing	Decreases ventilator dependency	Learning curve Limited ventilation
Diaphragmatic pacing	Decreases ventilator dependency	Expensive Upper-airway obstruction Requires surgery Diaphragm fatigue

ventilators—including Drinker respirators, cuirasses, and poncho-wrap ventilators—has supported patients' nocturnal and daytime gas exchange for months to years. Although these types of ventilators are relatively inexpensive, durable, and successful, there are limitations to their use (Table 93-10).

Negative-pressure ventilators function by intermittently applying subatmospheric pressure to the thorax and abdomen that increases transpulmonary pressure and inflates the lung. The efficacy of negative-pressure ventilation is determined by thoracic and abdominal compliance, as well as the surface area over which negative pressure is applied. Tank ventilators are the most efficient form of negative-pressure ventilators and cuirass ventilators, less so, since tank ventilators surround a greater thoracic and abdominal surface area. Although tank ventilators are very reliable, they are large, cumbersome, and claustrophobia inducing for patients, and markedly interfere with nursing care. Chest cuirasses and poncho-wrap ventilators are more portable than tank ventilators, but both require that the patient remain recumbent, induce a rocking motion in the lower posterior thoracic spine, and may induce discomfort and pressure sores at areas of skin contact. Moreover, all forms of negative-pressure ventilation tend to induce obstructive sleep apnea due to upper-airway collapse during a mechanically delivered breath. This problem is overcome by noninvasive positive-pressure ventilation, whereby positive pressure applied to the upper airway acts as a pneumatic stent that maintains a patent upper airway during a machine-delivered breath.

Rocking beds and pneumobelts (abdominal displacement ventilatory) have been used as ventilatory assist devices in patients with mild to moderate ventilatory failure. Both devices augment diaphragmatic motion by displacing the abdominal viscera against gravity. The rocking bed consists of a mattress on a motorized platform that rocks in an arc of 40 degrees with the patient lying recumbent. As the bed rocks with the head dependent, gravity induces the abdominal contents and diaphragm to move cranially, thereby assisting exhalation. In the next cycle, as the bed tilts upward, gravity acts to move the diaphragm and abdominal contents in a caudad direction, thereby assisting inspiration. The bed rocks between 12 and 24 times per minute and may be adjusted to optimize patient comfort and achieve minute ventilation targets.

The pneumobelt is an inflatable bladder that is worn over the anterior abdomen and connected to a positive-pressure ventilator that intermittently inflates it. With a patient seated upright, bladder inflation increases intra-abdominal pressure, forcing the diaphragm cephalad and thereby inducing active exhalation. When the bladder deflates, gravity moves the abdominal contents and diaphragm caudally, thereby facilitating passive inspiration. Tidal volume can be augmented by increasing bladder inflation pressures to target goals.

Both devices should be considered methods to assist ventilation in impaired patients rather than to replace mechanical ventilation in more acutely ill subjects. Both devices are limited by their constraints on patient posture. The rocking bed is bulky, stationary, and limited by the degree of ventilatory assistance that it provides. Similarly, the pneumobelt requires that the patient use it in the upright position, the amount of ventilatory assistance provided is limited, and some patients complain of pain and discomfort when high bladder inflation pressures are required to sufficiently augment ventilation.

Several studies have examined the application of noninvasive positive-pressure ventilation given only at night or intermittently throughout the 24-hour period using nasal, oronasal, or mouthpiece attachment. Several authors have shown significant improvements in daytime gas exchange after 3 months of nocturnal ventilation, with the mean increase in PaO_2 approximately 15 mmHg and the decrease in $PaCO_2$ approximately 14 mmHg. Beneficial effects of chronic intermittent noninvasive ventilation, besides better gas exchange, include abatement in patients' symptoms and improvement in functional status. There is an inconsistent effect on increasing maximum inspiratory and expiratory mouth pressures and lung volumes.

The mechanisms for the improvement with chronic intermittent noninvasive ventilation in daytime gas exchange in patients with neuromuscular diseases are unknown, but several hypotheses have been proposed: (a) respiratory muscle resting treats patients who suffer from chronic intermittent fatigue; (b) preventing nocturnal hypoventilation resets the central respiratory center $PaCO_2$ threshold; (c) there is improved ventilation-perfusion matching; and (d) improved lung and chest wall compliance decreases the work of breathing.

Although none of the above mechanisms has been established as a conclusive mechanism for the improvement in gas exchange observed in these patients following noninvasive ventilation, resetting of the central controller $PaCO_2$ level appears to be the most tenable. The presence of chronic inspiratory muscle fatigue has never been proved in any patient group, and other studies have shown that intermittent positive-pressure breathing does not decrease the incidence of atelectasis or improve lung volume. Whatever the mechanism(s), however, all studies reported to date show that noninvasive positive-pressure ventilation improves gas exchange and alleviates symptoms of nocturnal hypoventilation in patients with chronic neuromuscular diseases.

Other Forms of Ventilatory Assistance

In certain patients with neuromuscular diseases, glossopharyngeal breathing and diaphragmatic pacing may be important aids to augment ventilation.

Glossopharyngeal Breathing

Intermittent glossopharyngeal breathing using oral, pharyngeal, and laryngeal muscles, may augment ventilation (see Chapter 94). Short periods of spontaneous ventilation are possible once patients have mastered this technique. With glossopharyngeal breathing, the patient gulps in air by lowering and raising the tongue against the palate in a piston-like fashion, thereby injecting air into the trachea. After practice,

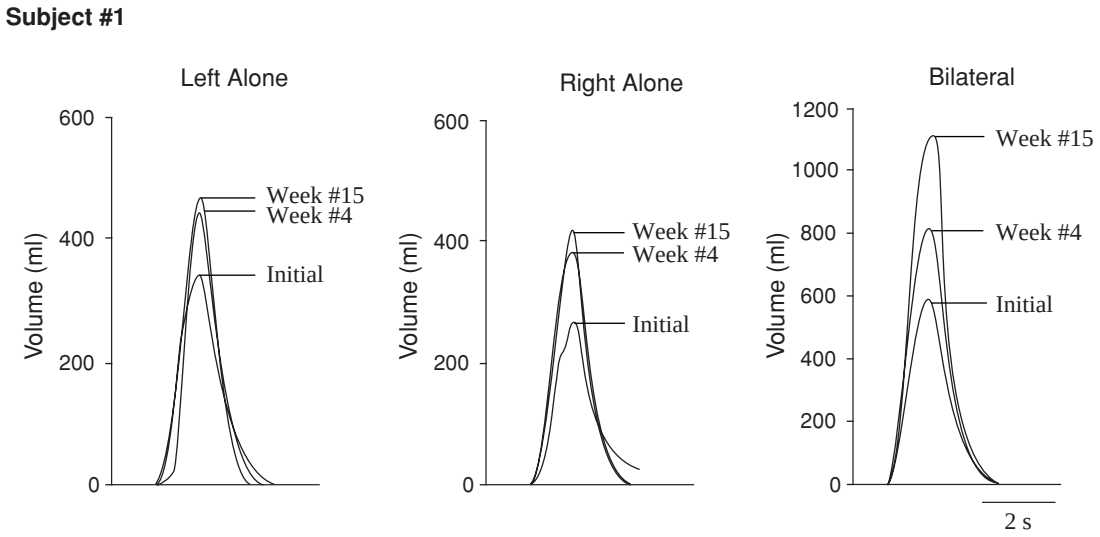

Figure 93-11 Reconditioning of the diaphragm as evidenced by increased inspired volumes initially, at 4 and 15 weeks postoperatively after left and right hemidiaphragm and bilateral diaphragm contraction via diaphragmatic electrode pacing. (*From data of DiMarco AF, Onder BP, Ignagni A, et al. Phrenic nerve pacing via intramuscular diaphragm electrodes in tetraplegic subjects.* Chest 127:671–678, *2005, used with permission.*)

patients may be able to gulp approximately 50 to 150 cc of air every half second. Patients may then repeat gulps in series without preventing air from escaping into the trachea so that, with repeated gulping, a tidal volume of approximately 500 to 600 cc may be achieved. With a repeating series of gulps, normal minute ventilation can be achieved for short periods. Although this technique is difficult for some patients, patients with high spinal cord injuries, postpolio syndrome, and other neuromuscular disease successfully utilize this technique.

Diaphragmatic Pacing

To increase independence from mechanical ventilation, diaphragmatic pacing may be a treatment option in selected patients. Although phrenic nerve pacing by external stimulation has been well documented since the late 1940s, long-term phrenic nerve stimulation did not become a reality until a small implantable electrode and receiver were developed in the late 1960s. Diaphragmatic pacing consists of a radiofrequency transmitter and an antenna that discharges stimulatory signals to a receiver that when activated by radiofrequency waves, transmits electrical impulses in an electrode placed over the phrenic nerve. Surgery is required to implant the electrodes and receiver. Electrode implantation around the phrenic nerves can be achieved by a cervical or thoracic approach; however, the thoracic approach is preferred, to ensure stimulation of all phrenic nerve roots while avoiding the brachial plexus. The subcutaneous receiver is usually placed in the lower anterolateral rib cage to allow it to be superficial, but in an area in which soft-tissue movement is limited. The subject must have intact phrenic nerves in order for the procedure to be successful, and the phrenic nerve is typically assessed by measuring conduction times along the nerve. Electric stimulation is applied transcutaneously in the neck region and surface diaphragm EMG is monitored. The nerve conduction time can then be calculated with normal being around 7.5 to 9 ms.

Diaphragmatic pacing has a number of potential limitations, including its high cost, the potential to fail abruptly, the development of upper-airway obstruction, and the induction of diaphragm fatigue. On the other hand, successful implantation allows patients to be independent from ventilatory support for prolonged periods, and to speak more freely.

While implantation of phrenic nerve electrodes has become an accepted procedure, there is ongoing research into placing diaphragmatic electrodes laparoscopically. This approach would be less invasive, more cost efficient and have less morbidity than the current approach. Two electrodes are placed on each hemidiaphragm near the motor points of the phrenic nerve. Initially, removable suction electrodes are placed until a location is found that induces maximal contraction of the diaphragm and a large intra-abdominal pressure change both by twitch and high-frequency stimulation. The wires are then brought through the skin and connected to the stimulator. Because patients on chronic mechanical ventilation develop diaphragm atrophy, a reconditioning period is required before the restoration of maximal diaphragm function. Figure 93-11 shows the tidal volume generated gradually increased with time as the muscle is reconditioned and the tidal volume is greatest with bilateral stimulation. In a recent case series using this technique, three of five subjects achieved independence from mechanical ventilation. One other was free of mechanical ventilation for 20 hours per day, and the other did not have activation of the diaphragm. This individual most likely did not have intact phrenic nerves. Intact phrenic nerves are required for successful intramuscular diaphragm pacing as evidenced by animal studies showing no diaphragm activation with intramuscular pacing after

transection of the phrenic nerves. This probably occurs because the mechanism of intramuscular pacing is by stimulation of phrenic nerve roots in the diaphragm.

Because the intercostal muscles are capable of contributing up to 35 to 40 percent of the vital capacity they should be able to liberate a subject from mechanical ventilation if stimulated through pacing. In animal models, stimulation of the ventral surface of T1-T3 resulted in maximal inspired volumes, and when combined with bilateral phrenic nerve pacing results in tidal volumes that approach the inspiratory capacity. However, when applied to a group of spinal cord injury patients with phrenic nerve damage; very little volumes were generated with stimulation of ventral aspect of T1-T3, and subject were unable to breath without mechanical ventilation for short time periods (20 min to 2.45 h). This discrepancy between animal and human studies may be secondary to the different shape of the human thoracic cage or the reduction in rib cage and lung compliance in those with tetraplegia. Additionally, stimulation of T1-T3 resulted in the movement of several nonrespiratory muscles, which led to hypertrophy of the upper trunk musculature. A follow-up trial that combined intercostal pacing with unilateral diaphragm pacing in a small group of patients that had unilateral phrenic nerve injuries in addition to spinal cord injury demonstrated that all patients were able to have significant periods of free time from mechanical ventilation. The main limitations to this approach remain contraction of nonrespiratory muscles, which makes the process metabolically inefficient and can lead to uncontrollable muscle activity.

The main group of patients who appear to benefit from diaphragmatic pacing are ventilator-dependent patients following high cervical cord injury. Approximately one-third of patients with high cervical spinal cord injuries may be suitable for this type of treatment. Although short-term improvements are noted in terms of ventilator independence and improvement in functional status, no long-term studies demonstrating efficacy have been published to date.

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94

Management of Neuromuscular Respiratory Muscle Dysfunction

John R. Bach

Patients with ventilatory impairment due to ventilatory muscle dysfunction are often evaluated and managed according to practices developed for patients with chronic lung diseases. However, pulmonary function laboratories, designed primarily for assessment of lung diseases, do not evaluate breath-stacking (insufflation) capacities or cough flows, which are important in the assessment of patients with ventilatory muscle dysfunction. In the setting of ventilatory muscle dysfunction, polysomnograms may be misinterpreted as central or obstructive apneas and hypopneas instead of hypoventilation due to inspiratory muscle dysfunction, and continuous positive airway pressure (CPAP) or nocturnal bilevel positive airway pressure (BiPAP) is prescribed. In the context of ventilatory muscle dysfunction CPAP does not increase tidal volumes, and may actually reduce them by causing them to approach maximum lung capacity in these patients with severe pulmonary restriction, while BiPAP is often used at pressures inadequate to support alveolar ventilation, provide inspiratory muscle rest, or assist in coughing. In addition, the patients are often treated with supplemental oxygen to correct hypoxemia when efforts to improve oxygenation should be directed at clearance of airway secretions. With advancing inspiratory and expiratory muscle weakness, the common scenario is that respiratory failure ensues that is treated by mechanical ventilation via endotracheal intubation. When ventilator weaning fails, a tracheostomy is performed and mechanical ventilation is continued indefinitely, often in an institution.

Therapeutic modalities commonly used for respiratory diseases can have adverse effects in patients with neuromuscular disorders. Bronchodilator therapy can augment anxiety and tachycardia that are common in myopathic patients, many of whom have cardiomyopathies. Oxygen therapy increases the risk of pulmonary morbidity, rate of hospitalizations, and mortality by comparison with the use of ventilatory assistance or no treatment at all. As noted, oxygen therapy may obscure recognition of mucus plugging because it alleviates oxyhemoglobin desaturation without attention to the expulsion of airway mucus. Oxygen therapy may also prolong hypopneas and apneas during rapid eye movement (REM) sleep, and it appears to suppress the reflex muscular activity needed for effective noninvasive intermittent positive pressure ventilation (IPPV) during sleep. Translaryngeal intubation, tracheostomy, and tracheal suctioning continue to be used for patients with neuromuscular diseases, even though noninvasive IPPV, noninvasive suctioning, and mechanical in-exsufflation can be more effective and comfortable.

Despite the proven effectiveness of measures to support ventilation noninvasively for long periods, even in situations of dire ventilatory muscle dysfunction, these therapeutic modalities have yet to be adopted by many physicians. In the United Kingdom, 82 percent of patients with ALS die receiving morphine and 64 percent receive benzodiazepines, while few are provided with respiratory muscle aids to prevent respiratory failure. This approach both smoothes and hastens passage to the grave by leading to CO_2 narcosis. Often, without consulting the patient, the physician judges the patient's quality of life to be unacceptable and the disease terminal, ignores options that prevent respiratory complications, renders the patient and family hopeless, and biases the family against ventilator use, which the physician associates with tracheostomy. Proclaimed as "palliation," the results of this professional point of view are anguish and hopelessness and frequently result in patients seeking assisted suicide. Over a recent 5-year period, 12 publications in the *New England Journal of Medicine* concerned clinical management and assisted suicide for patients with ALS. In none of these reports was prevention of respiratory complications or ventilatory assistance by invasive or noninvasive means considered.

Surveys of Jerry Lewis Muscular Dystrophy Association clinic directors in 1992 and 2000 demonstrated that the great majority of morbidity and mortality in neuromuscular disease continues to be due to respiratory muscle weakness and is preventable.

PATHOPHYSIOLOGY

Patients with neuromuscular disorders can develop respiratory failure because of some combination of respiratory muscle dysfunction (Table 94-1); that is, dysfunction of inspiratory, expiratory, and bulbar-innervated muscles. These muscle groups are considered here and the reader is referred to Chapters 92 and 93 for detailed discussions of the physiological disturbances associated with chest wall and neuromuscular disorders that affect ventilation.

Ventilatory muscle weakness, mechanical dysfunction of the chest wall and lungs associated with thoracic deformities, hypopharyngeal collapse or other upper airway narrowing, extreme obesity, abdominal distention, and the use of improperly fitting thoracolumbar orthoses can cause or exacerbate alveolar hypoventilation and lead to respiratory failure. In individuals with neuromuscular disorders, pulmonary infiltrations and respiratory failure are often precipitated by bronchial mucus plugging due to an ineffective cough and fatigue during acute respiratory infections.

Autonomously breathing patients with advanced ventilatory muscle dysfunction develop a rapid, shallow breathing pattern with inability to take deep breaths. If untreated, this can lead to chronic microatelectasis and decreased lung and chest wall compliance. Acute respiratory tract infections with

Table 94-1

Physical Medicine Respiratory Interventions Benefit Patients with the Following Conditions

- Myopathies
  - Muscular dystrophies
    - Dystrophinopathies—Duchenne and Becker dystrophies
    - Other muscular dystrophies—limb-girdle, Emery-Dreifuss, facioscapulohumeral, congenital, childhood autosomal recessive, and myotonic dystrophy
  - Non-Duchenne myopathies
    - Congenital and metabolic myopathies, such as acid maltase deficiency
    - Inflammatory myopathies, such as polymyositis
    - Diseases of the myoneural junction, such as myasthenia gravis, mixed connective tissue disease
    - Myopathies of systemic disease, such as carcinomatous myopathy, cachexia/anorexia nervosa, medication associated
- Neurological disorders
  - Spinal muscular atrophies
  - Motor neuron diseases
  - Spinal cord injuries
  - Poliomyelitis
  - Neuropathies
    - Hereditary sensory motor neuropathies
    - Phrenic neuropathies—associated with cardiac hypothermia, surgical or other trauma, radiation, phrenic electrostimulation, familial, paraneoplastic or infectious etiology, and lupus erythematosus
    - Guillain-Barré syndrome
  - Multiple sclerosis
  - Disorders of supraspinal tone such as Friedreich's ataxia
  - Myelopathies of rheumatoid, infectious, spondylitic, vascular, traumatic, or idiopathic etiology
  - Tetraplegia associated with pancuronium bromide, botulism
- Sleep-disordered breathing, including obesity hypoventilation, central and congenital hypoventilation syndromes, and hypoventilation associated with diabetic microangiopathy, or familial dysautonomia
- Skeletal pathology, such as kyphoscoliosis, osteogenesis imperfecta, and rigid spine syndrome

pulmonary scarring and the kyphosis and scoliosis that are common in these patients can cause further loss of lung compliance.

In the context of neuromuscular disorders, hypercapnia develops insidiously as a consequence of shallow breathing. It can decrease respiratory muscle strength. If not corrected by using inspiratory muscle aids, respiratory control centers reset to accommodate hypercapnia, and increasing central nervous system bicarbonate levels depress ventilatory drive. This permits worsening of hypoventilation and decreases the effectiveness of its treatment by the nocturnal use of noninvasive IPPV. The risk of pulmonary morbidity and mortality from acute respiratory failure correlates with increasing hypercapnia.

Patients with generalized muscle dysfunction usually also have concomitant expiratory and oropharyngeal muscle weakness that decrease cough peak flows (CPF). When CPFs do not exceed 2.7 L/s, cough may be completely ineffective. CPFs are reduced by airway obstruction caused by tracheal stenosis, laryngeal incompetence, postintubation vocal cord adhesions or paralysis, hypopharyngeal collapse due to bulbar-innervated muscle weakness or spasticity, or obstructive pulmonary disease. CPFs are reduced further when patients cannot take or receive a breath greater than 1.5 L. Thus, the airway secretions that develop during upper respiratory tract infections and after surgical anesthesia often result in pneumonia and acute respiratory failure. Smoking, the presence of an endotracheal cannula that causes bronchorrhea, or bronchorrhea for any other reason increases the tendency to develop mucus plugging that is all too frequently managed by intubation, repeated bronchoscopy, and tracheotomy. The latter results in a burden of pathogenic bacteria that exceeds the commonly accepted threshold for diagnosing ventilator-associated pneumonia.

For patients with ventilatory muscle dysfunction, arterial hypoxemia and hypercapnia occur initially during REM sleep and later extend throughout sleep and eventually throughout the awake hours (see Chapter 93). Cough reflex is also suppressed during sleep, which is when mucus plugs are most likely to cause sudden and severe hypoxemia. Normocapnic arterial hypoxemia is also common during sleep, most likely reflecting ventilation-perfusion mismatches associated with microatelectasis, scoliosis, and pulmonary scarring.

Narcotics and other sedatives, and supplemental oxygen can reduce ventilatory drive and exacerbate alveolar hypoventilation. Beta blockers may increase airway resistance. Malnutrition, acidosis, electrolyte disturbances, cachexia, infection, fatigue, and muscle disuse or overuse can all exacerbate ventilatory insufficiency.

Oxygen therapy often results in CO_2 narcosis; otherwise hypoventilation is usually first recognized during an intercurrent respiratory infection when bronchial mucus plugging triggers acute respiratory failure. Ventilatory failure can develop suddenly or over a period of hours or days in patients with acute cervical myelopathies, Guillain-Barré syndrome, myasthenia gravis, acute poliomyelitis, or exacerbations of multiple sclerosis.

The Respiratory Muscle Groups

The diaphragm is the principal muscle of inspiration. The abdominal muscles are the principal muscles of expiration or coughing. The bulbar-innervated muscles are the muscles of the upper airway. They include the muscles of the mouth, uvula and palate, tongue, larynx and hypopharynx. While these muscles do not have a direct action on the chest wall, they are essential for keeping the upper airway patent; they affect airway resistance and airflow; and they permit glossopharyngeal breathing.

Decreased inspiratory muscle function results in decreased vital capacity (VC), atelectasis, increased relative work of breathing, and eventually hypoventilation. Expiratory, inspiratory, and bulbar-innervated muscle dysfunction results in an ineffective cough. The latter can also result in loss of speech, swallowing, and aspiration of food and saliva.

Fortunately, the inspiratory and expiratory muscles can be substituted for by physical medicine interventions. Indeed, numerous patients with no muscle function below the neck and no measurable VC for over 50 years do not need tracheostomy tubes or develop hypercapnic respiratory failure. However, a tracheotomy needs to be performed if bulbar-innervated muscles deteriorate to the point that aspiration of saliva results in an irreversible decrease in Sp_{O_2} below 95 percent (Table 94-1).

INSPIRATORY AND EXPIRATORY MUSCLE AIDS

Inspiratory and expiratory muscle aids are devices and techniques that involve the manual or mechanical application of forces to the body or pressure changes to the airway to assist or substitute for inspiratory or expiratory muscle function. Negative pressure applied to the airway during expiration assists the expiratory muscles for coughing, just as positive pressure applied to the airway during inhalation (noninvasive IPPV) assists inspiratory function.

A manual thrust applied to the abdomen during expiration, especially when in combination with mild chest compression, assists expiratory muscle function and increases cough flows. The devices that act on the body to enhance inspiratory and expiratory muscle function include body ventilators. The intermittent abdominal pressure ventilator (IAPV) involves the intermittent inflation of an elastic air sac that is contained in a corset or belt worn beneath the patient's outer clothing (Fig. 94-1). The sac is inflated by a positive pressure ventilator. Bladder action against the abdominal wall moves the diaphragm upward, causing a forced exsufflation. During bladder deflation, the abdominal contents and diaphragm return to the resting position, and inspiration occurs passively. A trunk angle of 70 to 80 degrees from the

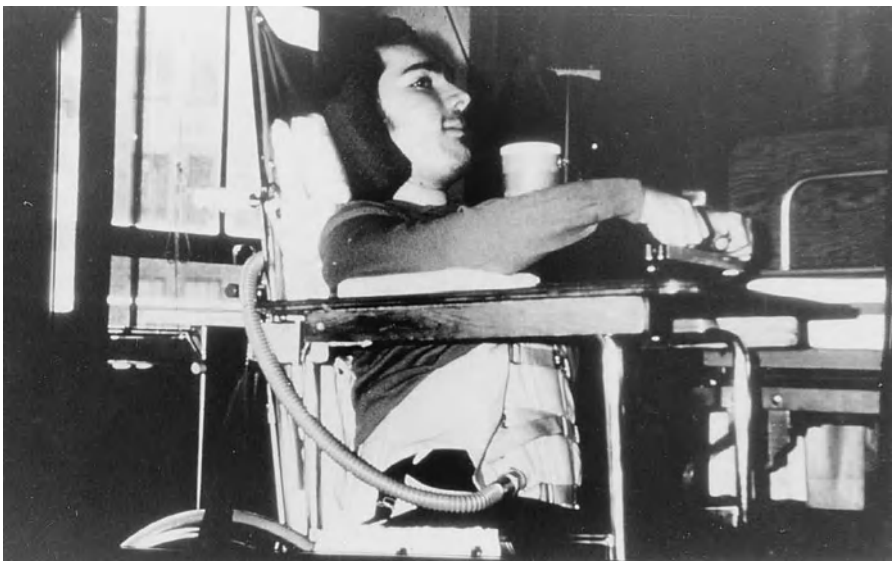

Figure 94-1 The girdle of the intermittent abdominal pressure ventilator with its air sac connected to the tubing of a volume-cycled ventilator. This Duchenne muscular dystrophy patient with no measurable vital capacity used the abdominal pressure ventilator for daytime ventilatory support for 15 years.

horizontal is ideal for use. The patient who has any inspiratory capacity or is capable of GPB can add autonomous volumes to the mechanical insufflations. The IAPV generally augments tidal volumes by about 300 ml, but volumes as high as 1200 ml have been reported when there is no scoliosis or obesity. Patients with less than 1 h of ventilator-free breathing ability tend to prefer to use the IAPV rather than use noninvasive IPPV during daytime hours.

Note, CPAP does not assist inspiratory or expiratory muscles and should rarely if ever be used for these patients whose symptoms of sleep-disordered breathing are associated with muscle weakness rather than central or obstructive sleep apneas.

CLINICAL GOALS

The goals of management are to optimally inflate the lungs and chest wall to maintain pulmonary compliance, maintain normal alveolar ventilation around-the-clock, and maximize CPF. Many patients who require continuous ventilatory support can be sustained for decades without being hospitalized.

Goal 1: Maintain Pulmonary Compliance and Chest Wall Mobility

Incentive spirometry or deep breathing can expand the lungs; however, no greater than the vital capacity. As the vital capacity decreases, the effectiveness of incentive spirometry as a tool for lung expansion vanishes. Like limb articulations, the lungs and chest wall require regular mobilization. This can be achieved by air stacking, providing deep insufflations, or nocturnal noninvasive ventilation for infants.

A patient's maximum insufflation capacity (MIC) is the largest volume of air that can be held with a closed glottis. The patient "air stacks" consecutively delivered volumes from a volume-cycled ventilator or a manual resuscitator, holding these volumes with a closed glottis. The air is delivered via a mouth piece, a lip seal (Fig. 94-2) if the lips are too weak to retain the air, or nasal interface. This is performed multiple times in three daily sessions. The patient stacks the volumes until the lungs are maximally expanded. Patients who learn glossopharyngeal breathing can often air stack consecutive gulps to or beyond the MIC. The difference between the MIC and the VC is a function of bulbar-innervated muscle integrity (force of glottic closure). If the bulbar muscles are too weak for deep air stacking, single deep insufflations are provided via a mechanical insufflator-exsufflator at 40 to 70 cm H_2O

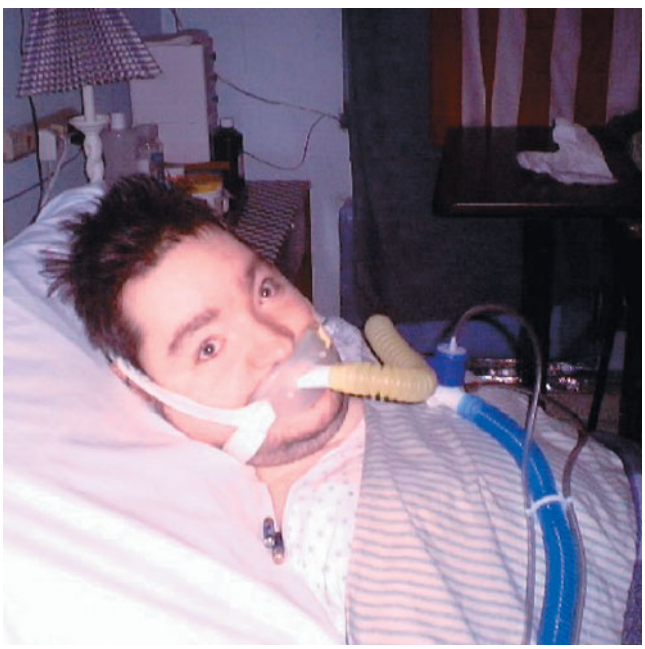

Figure 94-2 A 37-year-old with Duchenne muscular dystrophy, continuously dependent on mouth piece/lip seal intermittent positive pressure ventilation (IPPV) since age 12, is seen here using lip seal IPPV for nocturnal ventilatory support.

three times daily. Deep insufflations can also be delivered via manual resuscitator with the expiratory valve blocked.

The primary objectives of lung expansion therapy are to increase voice volume and MIC, maximize CPF, improve pulmonary compliance, prevent atelectasis, and master noninvasive IPPV. Occasionally the VC also increases with increases in MIC. Should the situation arise, anyone who can air stack can be extubated to noninvasive IPPV. This is extremely important for avoiding tracheostomy because such patients can be easily extubated without being ventilator weaned.

There is some evidence that inflation measures are helpful in promoting lung growth and chest wall development in children. While infants can not air stack, nocturnal use of high span (IPAP – EPAP > 10 cm H_2O) BiPAP has been demonstrated to prevent pectus excavatum and promote lung and chest wall growth for infants with spinal muscular atrophy (SMA), all of whom have paradoxical breathing when not using it.

Goal 2: Maintain Normal Alveolar Ventilation

Noninvasive Ventilation

BiPAP is not optimal for patients with neuromuscular disorders, because one can not air stack using pressure-cycled ventilators or fully expand the lungs with the machines currently on the market. IPPV from volume-cycled machines can be delivered via lip seals, nasal, or oral-nasal interfaces for ventilatory support during sleep. The patients can usually be trained and equipped in the outpatient and home settings.

Patients requiring around-the-clock support use simple 15- or 22-mm angled mouth pieces that they grab with their teeth for IPPVs (Fig. 94-3) during the day. To use mouth piece IPPV, adequate neck rotation and oral motor function are necessary to grab the mouth piece and receive IPPV without insufflation leakage out of the mouth or nose. In addition, the patient must open the glottis and vocal cords, dilate the hypopharynx, and maintain airway patency to receive the air.

When the lips are too weak to grab a mouth piece, the patient can use an IAPV or continue nocturnal nasal IPPV into daytime hours (Fig. 94-4). In the latter case, nasal interfaces are alternated to vary skin pressure. Inconspicuous nasal interfaces that permit the use of eyeglasses can also be used.

Although oronasal interfaces are popular in some centers, we have rarely found them to be necessary. Closed systems are unnecessary provided that ventilatory drive is not blunted by oxygen therapy, sedative medications, or excessive daytime hypercapnia, all of which can result in excessive air leakage out of the nose or mouth when using the open systems of mouth piece or nasal ventilation. If necessary, one can provide an essentially closed system of ventilatory support by using a lip seal device and placing cotton pledgets in the nostrils and sealing the nostrils with a Band-aid. Even patients with little or no measurable VC can be safely ventilated day and night by open systems of nasal or oral ventilation.

While noninvasive ventilation can be used for continuous long-term ventilatory support, the benefits derived from its part-time, usually nocturnal, use appear to be due to some combination of respiratory muscle rest, increasing tidal volumes and alveolar ventilation, improving blood gases, lung compliance, and chemotaxic sensitivity, and possibly by improving ventilation-perfusion matching by reducing atelectasis and small airway closure. To accomplish optimal rest, high volumes or pressure spans are used for all patients; that is, assist-control mode at volumes of 800 to 1500 ml for adults and inspiratory to expiratory-positive airway pressure spans of 13 to 17 cm H_2O for BiPAP users. Patients vary the volume of air taken in from ventilator cycle to ventilator cycle to vary

Figure 94-3 Sixty-six-year-old post-polio survivor who has been using noninvasive ventilation for 60 years, including 57 years of intermittent positive pressure ventilation via an angled mouth piece fixed adjacent to the sip and puff controls of her motorized wheelchair.

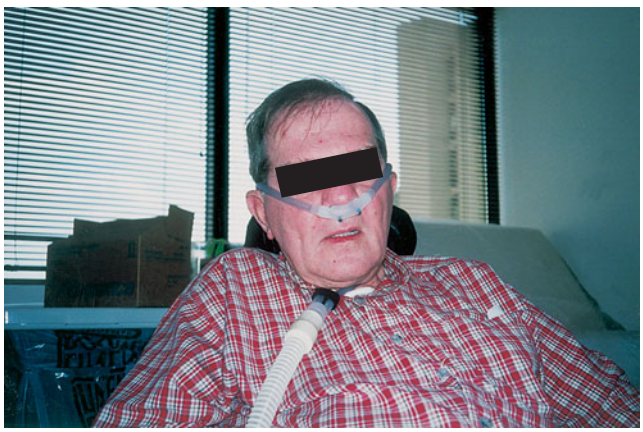

Figure 94-4 Fifty-one-year-old man with amyotrophic lateral sclerosis and no ventilator-free breathing ability using daytime nasal intermittent positive pressure ventilation.

tidal volume, speech volume, and cough flows, as well as air stack and provide lung expansion.

Complications of Noninvasive IPPV

Besides orthodontic deformities and skin pressure from the interface, other potential difficulties include allergy to the plastic lip seal or silicone interfaces (∗ 5 percent for nonsilicone interfaces), dry mouth (65 percent), eye irritation from air leakage (about 24 percent), nasal congestion (25 percent) and dripping (35 percent), sinusitis (8 percent), nose bleeding (4 to 19 percent), gum discomfort (20 percent), and gum receding from nasal interface or lip pressure, maxillary flattening in children, aerophagia, and, as for invasive ventilation, barotrauma. Occasional patients express claustrophobia. Switching to lip-delivered IPPV can relieve most if not all difficulties associated with nasal IPPV; however, it is more difficult to speak when using lip-delivery devices.

Abdominal distention tends to occur sporadically. It can be decreased by pressure limiting volume-cycled ventilators or at times by switching from one ventilator style to another. It is relieved as the air passes as flatus once the patient sits up in the morning or by "burping" of a gastrostomy tube if present. Barotrauma can occur with invasive or noninvasive ventilation, but is rare with the latter for patients with neuromuscular disorders.

Goal 3: Facilitate Clearance of Airway Secretions

Chest percussion and vibration can help mobilize deep airway secretions, but they are not substitutes for coughing. Cough can be assisted manually or by mechanical means.

Manually Assisted Coughing

Manually assisted coughing requires substantial lung inflation attained by air stacking or a deep lung insufflation. This is followed by an abdominal thrust applied as the glottis opens. If the VC is under 1.5 L, air stacking or insufflation is especially important before the abdominal thrust. Whereas the bulbar-innervated muscles, as well as inspiratory and expiratory muscles are needed for spontaneous coughing, only bulbar-innervated muscle function is required for assisted coughing. This is because airway pressure changes and abdominal thrusts substitute for inspiratory and expiratory muscles, but there is nothing noninvasive that can substitute for the function of the glottis.

Manually assisted coughing requires a cooperative patient, good coordination between the patient and care giver, and adequate physical effort and often frequent application by the care giver. When inadequate, and especially when inadequacy is due to difficulty air stacking or diminished glottic strength, the most effective alternative is mechanically assisted coughing (MAC).

Mechanically Assisted Coughing

The combination of mechanical in-exsufflation with an abdominal thrust is a MAC. Mechanical insufflator-exsufflators deliver deep insufflations followed immediately by deep exsufflations. The MAC cough volumes normally exceed 2 L at flows of 10 L/s. Insufflation to exsufflation pressures of +40 to –40 cm H_2O delivered via oronasal interface or adult tracheostomy or translaryngeal tubes with the cuff inflated are usually most effective. However, machine pressures are secondary. What is important is to fully expand and then fully and rapidly empty the lungs.

Whether via the upper airway or via indwelling airway tubes, routine airway suctioning misses the left main stem bronchus about 90 percent of the time. This explains high rates of left lower lobe pneumonia. MAC, on the other hand, provides the same exsufflation flows in both left and right airways without discomfort, fatigue, or airway trauma and it can be effective when suctioning is not.

Indications for MAC

MAC predominantly takes the place of the inspiratory and expiratory muscles. Thus, the patients who need MAC are those whose inspiratory and expiratory muscles are too weak for effective coughing but whose bulbar-innervated muscle function can maintain adequate airway patency but not permit sufficient air stacking for assisted CPF over 5 L/s. This is typical of most patients with neuromuscular disease. On the other hand, MAC is not usually necessary for patients with intact bulbar-innervated muscle function such as those with spinal cord injury, as they can usually air stack sufficiently such that with a properly applied abdominal thrust (assisted) CPF can exceed 6 L/s. These flows are more than adequate to clear the airways without MAC. MAC can not be used to avert tracheostomy very long if bulbar-innervated muscle function is inadequate to prevent airway collapse or continuous aspiration of saliva as is often the case in advanced bulbar ALS.

The Oximetry Feedback Respiratory Aid Protocol

This protocol consists of using inspiratory and/or expiratory aids in combination with pulse oximetry feedback to maintain patients' room air oxyhemoglobin saturation (Sp_{O_2}) greater than 94 percent. The protocol is most important during respiratory tract infections and when extubating patients with little or no ventilatory capacity. Noninvasive IPPV and MAC with oximetry feedback have averted hundreds of hospitalizations for patients with DMD, SMA, ALS, and other neuromuscular conditions. On the other hand, tracheostomy is indicated when saliva is continuously aspirated and the Sp_{O_2} remains below 95 percent despite optimal use of noninvasive IPPV and MAC. This is the only indication for tracheotomy in patients with neuromuscular disorders and it occurs in advanced bulbar ALS patients and in very few other situations. Without tracheostomy most patients with ALS whose Sp_{O_2} baseline has decreased below 95 percent despite respiratory aids will be deceased within 2 months.

NONINVASIVE VS. TRACHEOSTOMY IPPV OUTCOMES

No one has done a controlled study comparing outcomes of long-term noninvasive vs. invasive ventilation. However, a great deal can be inferred from what is already known. In a recent study, 25 patients with ALS became dependent on noninvasive IPPV, including 13 who became continuously dependent for 19.7 ± 16.9 months without developing acute respiratory distress or oxyhemoglobin desaturation. For another 76 patients the daytime Sp_{O2} baseline persistently decreased below 95 percent 78 times because of some combination of alveolar hypoventilation and airway secretions. For 41 patients the baseline was corrected by some combination of noninvasive IPPV and MAC for 11.1 ± 8.7 months before desaturation reoccurred for 27. Of the latter, 11 underwent tracheotomy, 14 died in less than 2 months, and two were again corrected by the addition of MAC to noninvasive IPPV. Thirty-three of the 35 patients for whom the Sp_{O_2} could not be normalized required tracheotomy or died within 2 months. The difference between the patients who could be spared respiratory failure from those who could not was that the latter had significantly poorer glottic function with no ability to air stack or generate measurable assisted CPF. We have decannulated ALS patients with no ventilator-free breathing capacity who have survived as much as 10 years using continuous noninvasive IPPV before requiring tracheotomy. Once bulbar ALS patients undergo tracheostomy for ventilatory support, survival has been reported to be about 5 years before most patients die from complications related to their tracheostomies.

Infants with SMA type 1 have 70 percent mortality by 6 months of age and 90 percent by 24 months of age from respiratory failure. In a recent study of 80 such patients, all of whom developed respiratory failure before 24 months of age, the protocol extubation (Table 94-2) success rate was

Table 94-2

Protocol for Extubation in Neuromuscular Diseases

Oxygen administration limited to achieve Sp_{O_2} of ~95%, no higher
Mechanically assisted coughing used via the endotracheal tube up to every few minutes as needed to fully expand and quickly empty the lungs to reverse oxyhemoglobin desaturations due to airway mucus accumulation, when there is auscultatory evidence of secretion accumulation, and on patient demand. Tube and upper airway are suctioned following use of expiratory aids.
Ventilator weaning attempted without permitting hypercapnia
Extubation whether or not the patient is ventilator weaned when meeting the following criteria: Afebrile and normal white blood cell count No supplemental oxygen required to maintain Sp_{O_2} >94% for >24 h Chest radiograph abnormalities cleared or clearing Respiratory depressants discontinued with no residual effects Airway secretions normal and suctioning required <1–2x/8 h Coryza diminished sufficiently to permit use of nasal ventilation
Extubation to continuous high span BiPAP or noninvasive IPPV via mouth/nasal interface, no supplemental oxygen
Oximetry feedback used to guide the use of MAC, postural drainage, and chest physical therapy to reverse desaturations below 95% due to airway mucus With CO_2 retention or ventilator synchronization difficulties, nasal interface leaks are eliminated. For small children with rapid breathing rates who are using high span BiPAP, the inspiratory ramp may need to be shortened or the IPAP decreased. Back-up BiPAP rates may need to be set at one-half the child's breathing rate to capture every other breath. Synchrony may also improve by switching to using a more trigger-sensitive volume cycle ventilator. Persistent oxyhemoglobin desaturation despite eucapnia and aggressive MAC can indicate impending severe respiratory distress and need to reintubate.
Following reintubation the protocol is used for a second trial of extubation to nasal IPPV or high span nasal BiPAP. Once extubation is successful and Sp_{O_2} remains greater than 94% in ambient air, the patient weans him- or herself to the preintubation regime of ventilator use by taking fewer and fewer mouthpiece IPPVs as tolerated and as presented in Fig. 94-3.

87 percent by comparison to 6 percent by conventional extubation approaches. Hospitalization rates for the noninvasively managed patients fell from 1.6 per year up to age 3 to 0.04 per year after age 5. Four such patients are currently over 10 years of age using nasal ventilation up to 24 hours a day. Only five of 80 underwent tracheotomy because of severe bradycardias in two, bronchomalacia in two, and persistent desaturations due to saliva aspiration in one. SMA type 1 patients who undergo tracheotomy can also have long-term survival.

In another study of 91 ventilator users with DMD, 51 went on to require continuous noninvasive IPPV for 6.3 ± 4.6 (range to 25) years. None of the 34 full-time noninvasive IPPV users who had access to MAC died from respiratory complications, whereas three died from severe cardiomyopathy. Five patients with no breathing capacity were extubated or decannulated to continuous noninvasive IPPV, and five became continuously dependent on noninvasive IPPV for 1 year or more without ever being hospitalized. It has previously been reported that DMD patients undergoing tracheotomy tend to have a prolongation of survival of about 7 years but also have a tendency to die from complications related to invasive mechanical ventilation.

Although both noninvasive and invasive interventions can prolong survival, noninvasive IPPV is overwhelmingly preferred by patients over tracheostomy for speech, sleep, swallowing, comfort, appearance, security, use of GPB, and overall. One study also demonstrated a 200 percent cost savings by using noninvasive ventilatory support methods for patients with no ventilator-free breathing ability by facilitating community placement with personal care attendants rather than nursing care or long-term institutionalization. Despite the benefits of noninvasive interventions, few clinicians are aware that they can be used instead of tracheostomy IPPV and even fewer are familiar with all of the techniques available. As stated, however, when bulbar-innervated musculature is completely dysfunctional, tracheostomy can offer further prolongation of survival. A review of the criteria for successful use of noninvasive ventilatory support can be found in Table 94-3.

Table 94-3

Criteria for Successful Use of Noninvasive Ventilatory Support for Neuromusculoskeletal Disorders

Patient cooperative and no use of heavy sedation or narcotics
No substance abuse or convulsions
Cough flows (with or without manual or mechanical assistance) sufficient to eliminate airway debris and maintain baseline Sp_{O_2} >94%
No mechanical obstacles to using IPPV interfaces (e.g., facial fractures or interfering devices)

GLOSSOPHARYNGEAL BREATHING

Both inspiratory and, indirectly, expiratory muscle activity can be assisted by glossopharyngeal breathing. This technique involves the glottis capturing air and propelling it into the lungs. One breath usually consists of 6 to 9 gulps of 60 to 100 ml each. Glossopharyngeal breathing (GPB) can provide an individual with no inspiratory muscle function with normal ventilation throughout daytime hours without using a ventilator, and safety in the event of ventilator failure during sleep. The safety and versatility afforded by GPB are vital to avoiding tracheostomy or removing one in favor of using noninvasive aids for neuromuscular ventilatory failure. About 65 percent of patients with functional bulbar-innervated musculature have been reported to be able to use GPB to increase tidal volumes.

EXTUBATION AND DECANNULATION

Intubation is a clinical decision based on the clinician's perception of need for invasive respiratory management. Intubation is often avoidable by using noninvasive ventilatory support and manually and mechanically assisted coughing. If needed, however, it is often delayed for fear of unsuccessfully extubating the patient. This misconception occurs because effective approaches to both avoid intubation and extubate unweanable patients are not widely used. It is because of the ability to successfully extubate ventilator dependent patients to noninvasive respiratory muscle aids that chronic tracheotomy can be averted for the great majority of patients with neuromuscular disease.

As for any patient presenting with respiratory distress, patients with neuromuscular disorders conventionally receive supplemental oxygen along with bronchodilators, mucolytics, chest physical therapy, and possibly, sedation, but not noninvasive IPPV or MAC. Oxygen therapy and sedation often result in respiratory arrest. Once intubated, the same ventilator weaning parameters used for patients with lung disease are often used to guide subsequent extubation (i.e., resting minute ventilation, maximum voluntary ventilation, tidal volume, VC, maximum inspiratory pressure, arterial-alveolar oxygen gradient on 100 percent oxygen, and ratio of dead space to tidal volume). The large number of parameters signals their lack of efficacy. This is because most of them relate to inspiratory rather than expiratory function.

Most physicians feel that intubated patients need to be weaned from ventilator use before they can be extubated, whereas patients with neuromuscular disorders can be routinely extubated to noninvasive IPPV despite little or no measurable VC. Postextubation CPF are a sensitive

parameter to predict successful extubation because they best reflect bulbar-innervated muscle integrity and, therefore, the ability to eliminate airway secretions. Preextubation generation of peak expiratory flows, as well as a measure of expiratory muscle function has been shown to be useful in predicting success in extubating patients with primarily respiratory impairment.

In patients with lung disease, ventilator weaning attempts are conventionally done at the cost of hypercapnia. However, for patients with neuromuscular disorders the extent of hypercapnia is directly associated with subsequent pulmonary complications and death. For patients with neuromuscular disorders, "weaning schedules" can cause anxiety because the patient is not ready to breathe autonomously, or the schedule may be too conservative, delaying respiratory muscle reconditioning.

Because an Sp_{O_2} of 90 to 95 percent is acceptable for most lung disease patients, patients with neuromuscular disorders are often extubated without concern for their ability to maintain normal Sp_{O_2} in ambient air. An Sp_{O_2} in ambient air less than 95 percent indicates that there is still hypoventilation, airway mucus, or residual lung disease. Further, they are often extubated to CPAP or inappropriately low span BiPAP and cough aids are not used. Once extubation fails, the clinician feels justified in recommending tracheotomy. Instead of conventional extubation approaches that may be appropriate for patients with lung diseases for whom "permissive hypercapnia" might be acceptable, a more appropriate approach for patients with primarily ventilatory impairment is presented in Table 94-2. It is because of the success of this protocol that tracheotomy can be averted for the great majority of patients with neuromuscular disorders.

INSPIRATORY AND EXPIRATORY AIDS AND SURGICAL ANESTHESIA

Prevention or correction of spinal deformities is crucial to maintain quality of life for patients with neuromuscular disorders. Surveys of neuromuscular disease clinics indicated that most children with neuromuscular scoliosis were not undergoing spinal instrumentation and fusion. As a result, the ability to sit is often lost. Scoliosis can also decrease the effectiveness of the IAPV. Clinicians avoid surgery because of fear of respiratory complications. However, respiratory complications are preventable when patients are trained in noninvasive IPPV and MAC before undergoing general anesthesia and are extubated to these interventions postoperatively, as described in Table 94-2.

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PART

XIII

Sleep and Sleep Disorders

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95

The Stages of Sleep

Adrian R. Morrison

Approximately 45 years ago, two reports published within a few years of each other revolutionized our thinking about sleep and wakefulness. In 1949, Moruzzi and Magoun reasoned, on the basis of results with electrical stimulation of the brain stem, that its central core, the reticular formation, contained the elements essential for arousal and, consequently, wakefulness. Previously the view had been that various stimuli operated on the cerebrum via the "classic" long sensory pathways to arouse the individual. Moruzzi and Magoun recognized that the multisynaptic complexity of the reticular formation lay at the heart of consciousness.

Nonetheless, the idea persisted, until 4 years later, that only wakefulness required active participation of the nervous system. At that time, Aserinsky and Kleitman reported periods during sleep in which the EEG resembled that of wakefulness. They also observed the rapid eye movements that give this stage of sleep its name, rapid eye movement (REM) sleep, and reported that vivid dreams occurred then. Clearly, more than a simple withdrawal of sensory influences had to be involved in the changes from wakefulness to sleep. As a result of this insight, the dominant view of sleep shifted from regarding it as a *passive* process to the belief in *active* processes that still prevails. Kleitman had previously been a proponent of the earlier view, arguing that it was the mechanism of wakefulness requiring explanation, not sleep.

Sleep disorders medicine began to emerge as a clinical specialty just 30 years ago. Thanks to the earlier recognition of the "curious" state of REM and then a considerable amount of basic research aimed at unraveling its mechanisms and those of sleep in general, various medical specialties began to recognize that serious disease can accompany this seemingly peaceful portion of daily life. Previously, sleep was almost exclusively an interest of psychiatrists. Of course, pulmonary physicians now play a major role in sleep disorders medicine.

This chapter focuses on the mechanisms underlying the daily alternation of sleep and wakefulness. Emphasis is placed on emerging ideas about the organization of a largely hidden portion of our lives, particularly ideas that push us beyond conventional thought. Physician readers of this chapter should keep in mind the tremendous debt that sleep disorders medicine owes to animal-based research and that such research has been a particular target of animal rights activism.

WHAT IS SLEEP?

Sleep is a period of bodily rest characterized by reduced awareness of the environment, a species-specific posture, and for most species, a particular sleep place. During each period of sleep, mammals cycle between two phases, non–rapid eye movement sleep (NREM) and REM: NREM always precedes a bout of REM. In humans, the cycle length averages 90 min, although NREM and REM are not evenly distributed through the night (Fig. 95-1). Cycle length varies directly with brain weight; hence, the family dog or cat cycles between NREM and REM more frequently, about every 25 minutes, as well as having multiple sleep periods.

The physiological characteristics of the two phases of sleep are dramatically different. Figure 95-2 illustrates the appearance of the human electroencephalogram (EEG) during the four stages of NREM in which there are lower-frequency EEG waves than in wakefulness. In other mammals, NREM is not as well individuated into different stages, but the

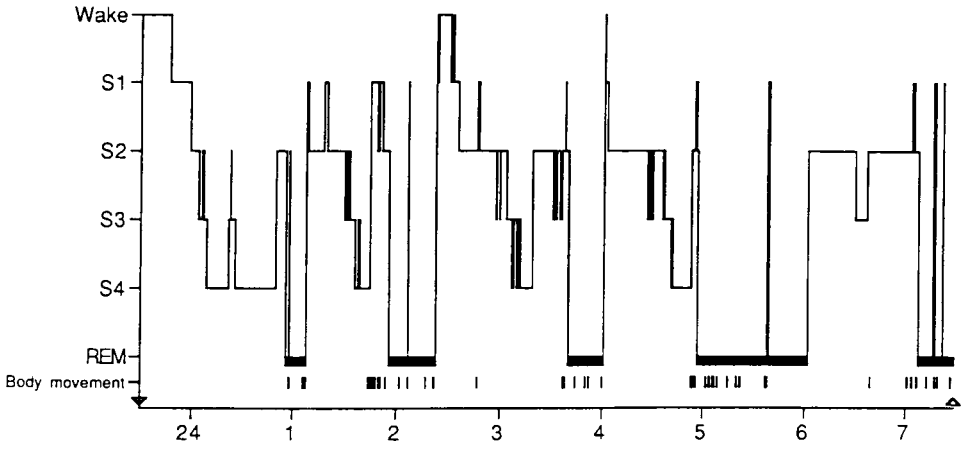


Figure 95-1 The progression of sleep stages across a single night's sleep of a normal young adult. The histogram was drawn on the basis of continuous recordings scored in 30-second epochs. *(From Carskadon MA, Dement WC.: Normal human sleep: An overview, in Kryger MH, Roth T, Dement WC (eds):* Principles and Practice of Sleep Medicine, *4th ed. Philadelphia, Elsevier Saunders, 2005, p 13, with permission.)*

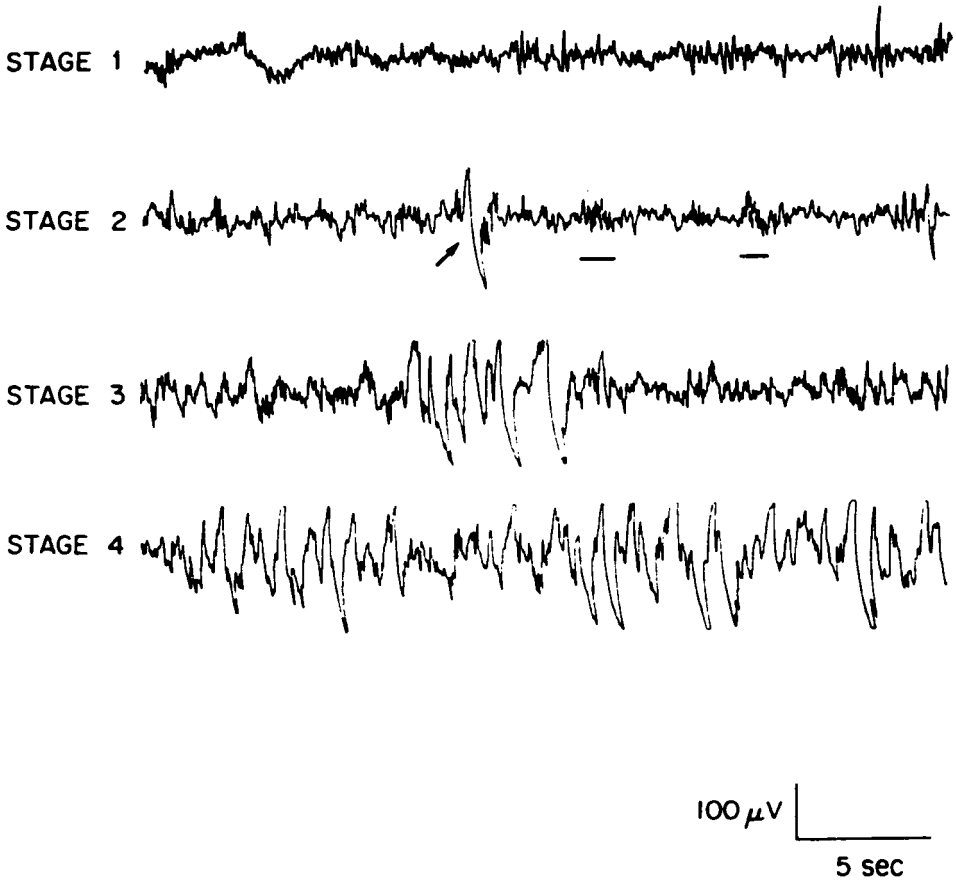


Figure 95-2 Electroencephalographic tracings recorded from a normal young adult demonstrating the four stages of NREM sleep. In the stage 2 recording, the arrow points to a characteristic K complex and the underlining to sleep spindles. *(From Carskadon MA, Dement WC.: Normal human sleep: An overview, in Kryger MH, Roth T, Dement WC (eds):* Principles and Practice of Sleep Medicine, *4th ed. Philadelphia, Elsevier Saunders, 2005, p 13, with permission.)*

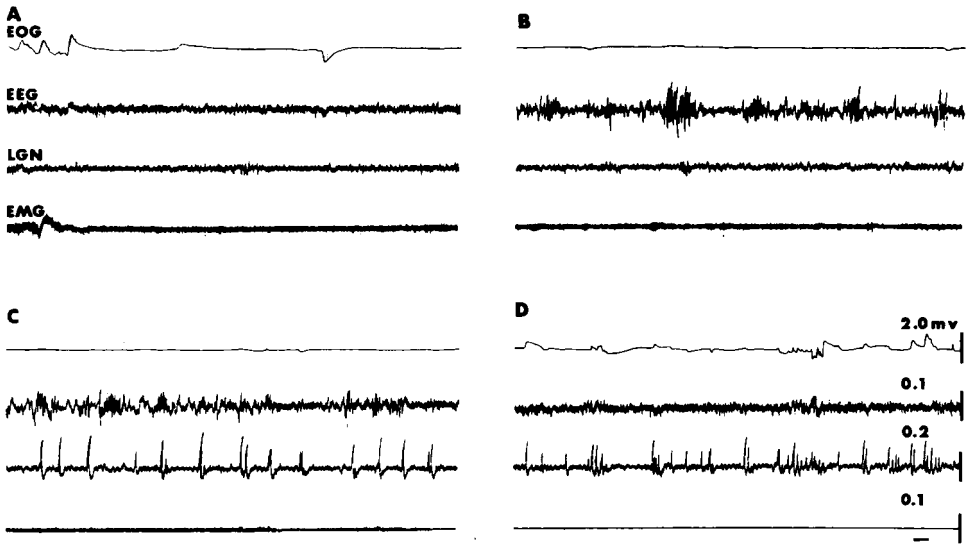


Figure 95-3 Characteristics of the states of sleep in the cat: *A.* Quiet wakefulness. *B.* NREM. *C.* Transition to REM. *D.* REM. EOG = eye movements; EEG = electroencephalogram; LGN = recordings of spontaneous PGO waves in the lateral geniculate body in (*C*) and (*D*); EMG = electromyographic recordings in the dorsal cervical muscles. Note the decreasing muscle tone at the end of the transition period and throughout REM. Time = 1 s. *(From Morrison AR: Brainstem regulation of behavior during sleep and wakefulness, in Sprague JM, Epstein AW (eds):* Progress in Psychobiology and Physiological Psychology, *vol 8. New York, Academic Press, 1979, p 91, with permission.)*

largest-amplitude, lowest-frequency waves occur as the animal approaches REM. A most striking feature is the similarity in appearance of the waking and the REM EEG patterns in humans and animals: low-amplitude, high-frequency waves (Fig. 95-3*A*).

Another event that characterizes REM can be detected in animals with deeply implanted electrodes. Just before and during REM, large-amplitude waves appear in recordings from the lateral geniculate body (Figs. 95-3*C*, *D*). They are termed ponto-geniculo-occipital (PGO) waves, after the sites in which they were first recorded. Rather than being part of a REM-generating mechanism, as first thought, they appear to be another sign of the "peculiar" brain alertness that is an essential feature of REM. These waves are discussed further in The Nature of REM.

Behaviorally, REM is recognized by body twitches, rapid eye movements, and irregularity in rate and depth of respiration. Electromyographic (EMG) recordings of postural muscles reveal a striking generalized atonia, the result of the postsynaptic inhibition of spinal motor neurons by glycine. Brain stem excitatory barrages using a glutamatergic substance briefly overcome this inhibition, leading to the muscle twitches. The source of the inhibitory glycine is either local or produced by neurons in the medullary inhibitory region. The latter, in turn, are excited by several pontine pathways employing such neurotransmitters as acetylcholine, glutamate, and corticotrophin releasing factor. Bilateral, pontine lesions in cats and rats eliminate the atonia of REM, which permits expression of alert-like behavior in REM. "REM without atonia" led directly to the recognition of REM sleep behavior disorder. NREM is characterized by behavioral quiescence with residual muscle tone and very regular, deep breathing. A further distinction is a marked suppression of hypothalamic regulation of homeostasis in REM (see Autonomic Regulation during Sleep).

Many aspects of sleep have been experimentally manipulated in animals (cats and rats in particular), with the result that we have a much greater understanding of the mechanisms that might be altered in human sleep pathology now than we did even 20 years ago. A feature linking birds and mammals is their homeothermy. Because hypothalamic control of thermoregulation is suspended in REM, converting mammals briefly into poikilotherms, it may be that poikilotherms (i.e., fish, amphibians, and reptiles), do not have the means or the "need" to express this or other features of REM.

The echidna, a monotreme (a nonplacental, nonmarsupial mammal), has always complicated the picture because there was no evidence for REM. Siegel et al. found that the echidna's brain stem neural activity presented a composite picture of the two phases during sleep; that is, the decreased discharge rate of NREM and the increased variability of firing rate of REM were accompanied by EEG synchronization. Thus, NREM and REM may have differentiated later from this primordial state in mammals.

Just as sleep is not uniform among different groups of animals, its characteristics also vary with age. Human infants, for example, sleep in a polyphasic pattern for much of the time. During the first year of life, their sleep consolidates into one major period with shorter naps. In parallel fashion, REM, which occupies a large portion of sleep at birth—as much as 90 percent in some species—decreases to about 25 percent of total sleep time as wakefulness increases with maturity. This percentage remains relatively constant into old age, although the total amount of sleep decreases. However,

because neural activity in infant animal sleep resembles that of the undifferentiated sleep state of the primitive echidna, we may question whether it is appropriate to speak of a very high REM percentage in newborns.

WHY SLEEP?

Unlike other behaviors, the actual function of sleep remains a subject for debate. Thinking in broad terms, some have suggested that energy is saved when an animal has nothing better to do or that there is a survival value for certain prey species to nestle out of harm's way. Other aspects of life to which sleep contributes, according to some, are consolidation of memory and improved learning. Of course, one feels better or restored after a night's sleep; but what has been restored, and how?

A possible way out of the dilemma is to focus on sleep not as a *behavior* (like feeding, which happens only during wakefulness), but as a *state* that can subserve multiple functions (just as the waking state does). Indeed, the dramatic physiological differences between NREM and REM suggest this, and the many theories of the function of sleep tacitly acknowledge the idea: They generally present a hypothesis accounting for only one phase. In a tightly reasoned article, Rechtschaffen illustrates the weaknesses of all claims for a particular function, leaving us somewhat stymied. Certainly, the survival value of a stage of sleep, REM, in which an animal is depressed sensorially, paralyzed, and poorly regulated homeostatically is a real mystery. The reduced homeostatic regulation of normal REM may rest vital, undetermined processes in small animals.

AUTONOMIC REGULATION DURING SLEEP

Pulmonologists will be particularly interested that two major changes in autonomic regulation occur during sleep. One of them is predictable or at least not surprising: an increase in parasympathetic activity over that in the sympathetic system. The second is truly remarkable, though—suppression if not abolition of homeostatic regulation by the hypothalamus in REM.

When an animal passes from wakefulness to NREM, the metabolic and behavioral demands on the body are obviously reduced. The heartbeat becomes slower and more regular. This is one sign that parasympathetic tone has increased; cutting the sympathetic nerves to the heart has little effect, indicating that central parasympathetic neurons increase their activity in sleep. Respiration slows and becomes more regular in NREM, but the normal compensatory mechanisms remain unchanged other than a moderate reduction in sensitivity to CO_2 and O_2. Normal thermoregulatory mechanisms—such as panting, shivering and appropriate vascular changes—occur as well.

In REM, the organization of autonomic regulation is quite different. Although local and brain stem reflexes may still be operational, hypothalamic control is not. This has been most completely demonstrated in the case of thermoregulation. Hypothalamic cooling and heating during REM is ineffective in eliciting responses normally associated with heat gain (increased metabolic rate) and heat loss (panting).

The suppression of thermoregulation in REM has been demonstrated further in a very graphic way. The atonia of REM can be eliminated with small pontine lesions; allowing organized movements to occur in REM (see The Nature of REM). Cats with such lesions shiver during wakefulness and NREM but cease shivering as soon as they enter REM without atonia. They also leave their protective curled posture and lose piloerection. Furthermore, they are actually more sensitive to cold and heat than normal animals during wakefulness, which further emphasizes the disruption of thermoregulation that occurs during REM.

These indirect measures have been supplemented by direct recordings of single thermosensitive hypothalamic neurons during different behavioral states. Cold- and warm-sensitive neurons either increase or decrease their rate of firing as a response to hypothalamic cooling or warming during wakefulness and NREM, but the majority loses its sensitivity in REM. Thus, the preoptic hypothalamic drive of thermoregulatory effectors is lost in REM.

Alterations in respiratory control occur during REM, and there is evidence that the hypothalamus no longer modulates lower reflexes. Electrical stimulation in the hypothalamus that elicits inflation- and deflation-like effects during wakefulness and NREM will no longer do so in REM; in contrast, vagal stimulation remains effective, indicating that the brain stem circuits are not altered in REM. Tone in upper airway muscles is diminished during NREM and virtually absent during REM; the atonia during REM of the upper airway and intercostal muscles imposes a considerable burden on respiration. The respiratory rhythm is disrupted by irregularities in rate and depth of respiration due to the excitatory barrages responsible for muscle twitches in postural muscles. Ventilatory responses to hypercapnia are depressed, and, compared to NREM, the arousal threshold is increased.

Activity in the sympathetic nerves of cats drops drastically during REM, although there are phasic increases that accompany rapid eye movements and muscle twitches. As a consequence, paradoxical responses in skin temperature occur, due to passive reductions in vasoconstrictor or vasodilator tone upon entrance into REM (e.g., the skin will warm in a cool environment after the animal enters REM due to relaxation of the constricted skin vessels). Not all vascular beds are passive in REM: A spinal reflex triggered from muscle afferents induces vasoconstrictor activity in hind-limb muscle beds, thereby reducing hypotension due to atonia in these muscles. Blood pressure increases during REM in rats and humans. It seems that the blood pressure decrease earlier reported in cats is reversed if sufficient time for recovery from surgery is permitted. In all species the same central mechanisms are probably operative during REM, but the eventual

patterns may depend on species-specific differences in feedback loops and autoregulation.

SUBSTRATE AND PHYSIOLOGICAL MECHANISMS OF SLEEP

Research in the earlier part of this century pointed to the diencephalon as the region critical for the organization of the sleep-wake cycle. This view was supported by: (1) the association of insomnia or somnolence with pathological changes in the anterior or posterior hypothalamus after encephalitis in humans described by von Economo; (2) elicitation of sleep in cats by electrical stimulation of various limbic structures; and (3) the results of experimental hypothalamic lesions in rats that corroborated the human disease observations. Yet until the discovery of REM, the prevailing opinion pictured sensory inflow as the governing factor.

In 1962, emphasis shifted to the hindbrain because of an important experiment designed to determine the area of the brain that plays the predominant role in REM regulation. Jouvet found that even after removal of the brain rostral to the pons (i.e., decerebration), major elements of REM continued to appear periodically; indeed, rapid eye movements and atonia even overcame decerebrate rigidity. Transection caudal to the pons eliminated all signs of REM. In addition to the active inhibition of the motor neurons there is as well a withdrawal of facilitation by pontine locus ceruleus noradrenergic neurons and the serotonergic brain stem raphé neurons.

The early decerebration experiments led researchers to neglect the forebrain for a number of years in favor of the pons in their search to understand the mechanisms of REM and, indeed, sleep in its entirety. However, two observations led us to propose that the initiation of REM in *intact* animals might well require interactions among forebrain and hindbrain mechanisms. (1) Decerebrate cats can be induced to enter a REM-like state by a number of stimuli not normally sleep-promoting, such as passing a stomach tube, inserting a rectal probe, opening the mouth, and hypothermia. Consequently, the brain stem, lacking modulation by rostral structures, appears to be in an unstable, supersensitive state. (2) In the normal cat, homeostatic mechanisms usually regulated by the hypothalamus are suppressed during REM, and the same could be argued for the decerebrate cat. Clearly, a central reorganization in the hypothalamus and/or other rostral structures must take place at or before the transition from NREM to REM. Given the decerebrate cat's abnormal propensity to enter REM, midbrain transection might well serve as a substitute for the suppression of forebrain control that we argued precedes natural REM.

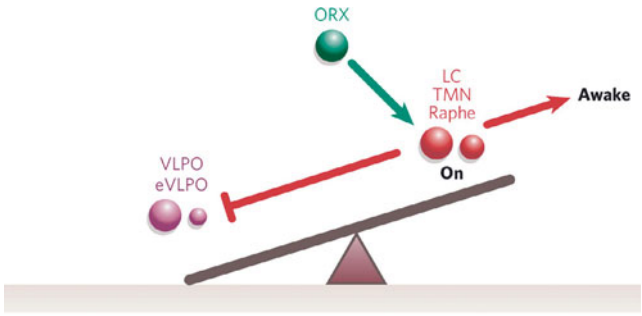
These ideas did not deny the important role played in REM by the caudal brain stem, but implied that full understanding of the mechanisms initiating and maintaining REM would require a more global outlook. A variety of investigations have since revealed interesting effects of forebrain manipulations of REM. Shifting attention to the forebrain in seeking a fuller understanding of REM mechanisms and sleep in general has recently paid huge dividends.

The forebrain, of course, is involved in sleep regulation, as the early studies of brains from those with encephalitis indicated. Many lesion, stimulation, and unit recording studies in the basal forebrain have demonstrated its importance for the onset of sleep (i.e., NREM). The suprachiasmatic nucleus has a role in the timing of sleep occurrence. And a group of neurons in the hypothalamic ventrolateral preoptic nucleus (VLPO) has gained prominence in recent years as the so-called sleep switch. These neurons are located in the region where lesions described by von Economo resulted in insomnia.

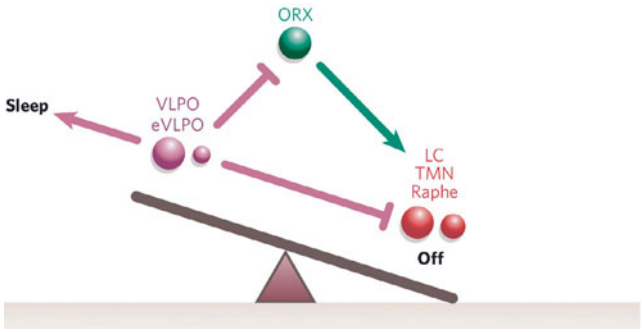
VLPO consists of a dense cluster of cells and a more extended part, the former concerned with NREM and the latter with REM. Its neurons project to all relevant nuclei participating in arousal in the hypothalamus and brain stem. VLPO neurons are sleep active; and lesions of the cluster reduce NREM primarily; while lesions of the extended portion decrease REM. They use the inhibitory transmitters, GABA and galanin, and in turn, they are inhibited directly by noradrenaline and serotonin and indirectly by histamine.

Saper proposes that this arrangement of mutually inhibitory systems constitutes a flip-flop switch that promotes rapid transitions between behavioral states (Fig. 95-4 *A*). We do not spend much time in transitions as a result. Often, switching states rapidly is a good thing, of course: Think of awakening rapidly to a danger signal. Figure 95-5 diagrammatically illustrates the switch from NREM to REM when hypothalamic control is lost and brain stem control of REM takes over. Cats with REM without atonia demonstrate this dramatically if placed in the cold: Although they shiver violently and maintain a tightly curled position in NREM, they cease shivering immediately and lose piloerection and the curled posture the moment they enter REM. The same occurs when orienting—an immediate cessation of shivering and increase in brain temperature as in REM.

However, there is the problem of instability with such a switch. Figure 95-4 *B* illustrates the introduction of a modulatory influence by a newly discovered group of hypothalamic neurons with widespread projections that contain two closely related neuropeptides called orexins or hypocretins, the terminology depending on the research group. Their absence or degeneration has been shown to accompany narcolepsy in knockout mice and dogs and humans with naturally occurring disease. (One characteristic of narcolepsy is the rapid transition from alert wakefulness to REM and particularly one component, cataplexy, with sudden emotional stimuli or situations as well as dozing off during the day and waking up more often at night.) They project to the various brain stem neurons involved with the sleep as well as the cerebral cortex and serve to balance the activities of competing groups of neurons. (See Fig. 95-4 legend for a complete explanation.) Orexin/hypocretin neurons are particularly active during exploration of the environment, and orexin/hypocretin levels collected via microdialysis are significantly higher in



A



B

Figure 95-4 A schematic diagram of the flip-flop switch model. During wakefulness (A), the monoaminergic nuclei inhibit the ventrolateral preoptic nucleus (VLPO), thereby relieving the inhibition of the monoaminergic cells and that of the orexin (ORX) neurons, cholinergic pedunculopontine (PPT), and laterodorsal tegmental nuclei (LDT). Because the VLPO neurons do not have orexin receptors, the orexin neurons serve primarily to reinforce the monoaminergic tone, rather than directly inhibiting the VLPO on their own. During sleep (B), the firing of the VLPO neurons inhibits the monoaminergic cell groups, thereby relieving their own inhibition. This also allows it to inhibit the orexin neurons, further preventing monoaminergic activation that might interrupt sleep. The direct mutual inhibition between the VLPO and the monoaminergic cell groups forms a classic flip-flop switch, which produces sharp transitions in state, but is relatively unstable. The addition of the orexin neurons stabilizes the switch. eVLPO, extended ventrolateral preoptic nucleus. *(From Saper CB, Scammel TE, Lu J: Hypothalamic regulation of sleep and circadian rhythms.* Nature *437:1257, 2005, with permission.)*

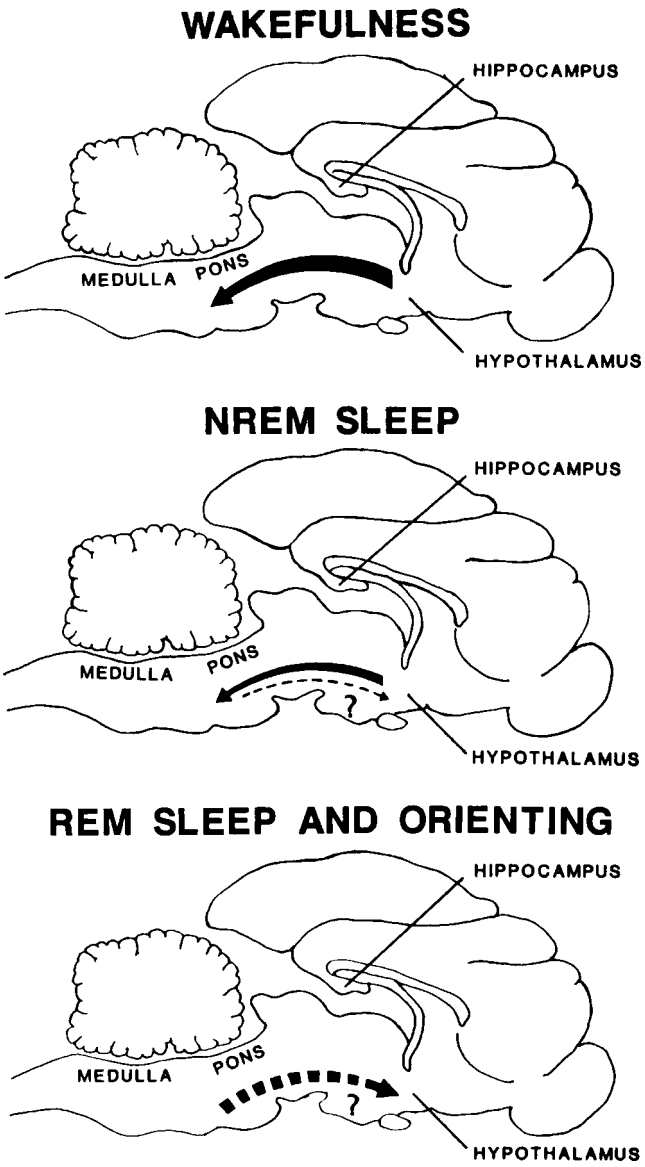


Figure 95-5 Diagrammatic representation of the changing control from the forebrain as an individual passes from NREM to REM when hypothalamic control is suppressed. The same shift in control may occur briefly during orienting in wakefulness. *(From Morrison AR: Brainstem regulation of behavior during sleep and wakefulness, in Sprague JM, Epstein AW (eds):* Progress in Psychobiology and Physiological Psychology, *vol 8. New York, Academic Press, 1979, p 91, with permission.)*

active waking than in quiet waking. These observations led to the proposal that a more general role is to facilitate the arousal and motor activity that underlies any motivated behavior.

The identification of the monoamines, noradrenaline and serotonin, as transmitters with widespread connections extending to the cerebral cortex, following Jouvet's decerebration experiments actually reinforced the attention on the pons as the key region for regulating all of sleep. A series of experiments involving destruction of these neurons and/or pharmacological manipulations led to the hypothesis that serotonin regulates NREM and noradrenaline, REM. Although the monoamine hypothesis of sleep regulation stimulated a number of important experiments, it eventually had to be abandoned because recordings of serotonergic and noradrenergic neurons revealed that these neurons begin to reduce their firing rates when cats pass from wakefulness to NREM, becoming almost totally inactive during REM. Thus, their roles can only be permissive (i.e., allowing REM to occur as a result of their inactivity).

Another transmitter, acetylcholine, clearly plays an active role in REM processes. Many studies have demonstrated that acetylcholine and agonists (e.g., carbachol), will induce REM when injected into the dorsal pons. A cluster of cholinergic neurons in the dorsal pons and midbrain are the

natural source of the cholinergic stimulation. Two effects are clear: They excite directly and indirectly the neurons in the medullary inhibitory area that are responsible for the postsynaptic inhibition of spinal motor neurons in REM, and they induce the changes in thalamic neurons that contribute to the waking pattern of the EEG. At the same time, noradrenergic and serotonergic neurons are inhibited by GABA-containing neurons. Cholinergic neurons in the medulla with ascending projections also appear to play a facilitatory role in the generation of REM.

Cholinergic stimulation of thalamocortical neurons by mesopontine cholinergic cells changes them from the burst-firing mode that underlies the EEG spindles and slow waves that characterize NREM to a tonic-firing mode with an increased transfer function. Cholinergic neurons in the basal forebrain play a parallel role in the cortex. In both sites adenosine induces sleep via a postsynaptic inhibitory effect, long counteracted by drinkers of caffeine-containing coffee. Evidence is also mounting that glutamatergic systems play a parallel role in EEG activation: Because noradrenergic neurons in the pontine locus coeruleus also change the firing mode of thalamocortical neurons in parallel with the nearby mesopontine cholinergic neurons and glutamatergic neurons, their silence in REM is possibly an important feature distinguishing mental activity of wakefulness from REM. In terms of maintaining wakefulness and counteracting sleep-promoting activity of the anterior hypothalamus, histaminergic projections from the posterior hypothalamus play a significant role.

Although EEG patterns allow us to detect the various sleep stages, they do not as accurately reflect the type of mental activity occurring during sleep as some still present it. Initially, REM was equated with dream sleep, and many still accept this convenient distinction. The similarity of the REM EEG pattern to that of wakefulness and the vividness of REM dreams (bizarre, perhaps, but still waking-like) make this a tidy classification. Unfortunately (for the sake of simplicity), mental activity is frequently reported from NREM awakenings, and it can resemble REM dreams, although REM and NREM mental activity can be discriminated on the basis of perceptual vividness and thematic coherence. (The earliest experiments finding few or no dreams in reports from NREM awakenings were designed in ways that were biased against collection of NREM dreams.) Furthermore, stage 1 NREM and REM have similar EEG patterns, yet reports of mental activity are quite different.

The elements within the various patterns of neural activity underlying the dramatically different EEG patterns of NREM and REM that determine dreaming in humans remain uncertain. A recent candidate is the fast, spontaneous EEG rhythm between 20 and 40 Hz observed during attentive waking behavior and REM and also during the depolarizing phases of slow brainwave oscillations occurring in NREM. Because the mesopontine cholinergic neurons that induce fast rhythms are spontaneously active in REM and are responsible for PGO waves (a sign of alerting, remember), they may provide the conditions that make the REM dream invariably vivid. However, the dangers of relating specific electrophysiological events to complex mental activities should be obvious.

How the caudal brain stem cholinergic neurons normally affect the full expression of REM is not known. At first blush, they do not seem to require the rostral brain: Decerebrate cats spontaneously exhibit REM atonia and the pontine component of PGO waves, and carbachol injection is also effective in decerebrate cats. Absence of noradrenaline must be a factor, because noradrenergic blockers also induce the REM state in the same way that cholinergic agonists do. A reduction of serotonergic influence is likely a factor as well. Recent experiments by Chase and colleagues suggest that GABA gates the appearance of natural REM versus wakefulness as well as REM induced by the cholinergic agonist, carbachol, in the nucleus pontis oralis (NPO). GABA agonists injected in NPO induce prolonged episodes of wakefulness; GABA antagonists lead to extended REM; and preinjection of the $GABA_A$ agonist, muscimol, will block the induction of REM by carbachol.

In concluding this section, it should be noted that rarely have workers considered the possibility that sleep changes thought to be effects of manipulating specific sleep mechanisms might be secondary to changes in thermosensitivity, other sensory thresholds, blood gases, etc.

THE NATURE OF REM

Earlier, we observed that a various answers have been proposed for the question "What does REM do for the individual?" but no one asks "Why does REM occur in the form that it does?" In other words, can one make physiological sense out of the characteristics observed or is there no coherent organization? As a seemingly disparate assemblage, one finds the REM EEG resembling the waking EEG: the almost total paralysis, the ineffectual muscle twitches, the rapid eye movements, and, of course, the depression of homeostasis. A mechanistic explanation brings order out of this assortment and also leads to a broader view of the pontine tegmentum, a region that has assumed so much importance in sleep research.

The premise is that the brain in REM resembles to a surprising degree the brain of an individual during alert wakefulness when he or she orients to a novel or unexpected stimulus. From this point of view one can begin to make sense of the apparently unrelated features of REM—in particular, the reticular activation, atonia, and depressed homeostasis.

To begin with, certain features are common to REM and alert wakefulness: the EEG pattern; synchronous waves recorded from the hippocampus, called theta rhythm; an increase in brain temperature during orienting and REM; and suppression of panting and shivering in both of the latter two states. Two additional observations made in the laboratory reinforce this line of reasoning.

1. As briefly noted, the atonia of REM can be eliminated in cats by small lesions in the pontine tegmentum that destroy a complex of cells and fibers that normally excite the medullary inhibitory area of cats. In such animals, behavior during REM consists largely of orienting, searching, or startle unassociated with any obvious external stimuli. Depending on lesion site, some cats can even walk during REM without atonia, although their axial and hind limb support does not equal that of waking. REM without atonia completely replaces normal REM—permanently in some cases; while in others there is gradual recovery to a more normal-appearing REM. Other than the lack of skeletal muscle paralysis, REM without atonia is identical to normal REM.
2. The PGO waves that normally appear spontaneously just prior to and throughout REM in recordings from the lateral geniculate body of cats can be elicited by loud sounds in NREM and REM. These waves occur in wakefulness after stimulation with sound, and others have reported that intracellular recordings from geniculate neurons are the same during the spontaneous waves and those induced by auditory stimuli or electrical stimulation of the reticular formation. Their occurrence is associated with an increase in information transfer through the lateral geniculate body.

Taken together, these observations support the concept of an "alert" brain in REM. This counterintuitive idea becomes less so if one is open to the suggestion that in REM, the brain is focused upon itself and the world of dreams. Interestingly, though, cats show the same degree of orientation to an external sound source in REM without atonia as they do when awake.

In addition, we have proposed a linkage between the "alert" brain and atonia in REM on the basis of a behavioral observation and a concept: The observation is that when an awake animal orients to an unexpected stimulus its ongoing behavior ceases for an instant; the concept is that nature is a parsimonious organizer, very often using the same structures and mechanisms in slightly different ways for various tasks. The respiratory system is a good example of the latter, for the airway and lungs are used for respiration, phonation, and temperature regulation.

Therefore, the extreme motor inhibition in REM can be explained in a mechanical way as an inevitable link between an exaggerated, continuing state of "orienting" and the suppression of motor activity. Moreover, the brain seems to employ the same structures and mechanisms in both wakefulness and REM, but not identically, of course (Fig. 95-5). Rather than global activation during alert wakefulness, one should see in the brain stem reticular formation selective activation of neurons associated with specific movements, not driving them but modulating the set of muscle contractions and relaxations for movement from any posture in response to a sudden stimulus. There are, in fact, such neurons. Thus, I suggest that the dorsal pons, the focus of so much attention from sleep researchers, is probably more generally involved in any behaviors dependent upon abrupt input into the reticular formation.

ACKNOWLEDGMENTS

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96

Changes in the Cardiorespiratory System During Sleep

Allan I. Pack

As outlined in Chapter 98, sleep occurs in distinct states classified broadly as non–rapid eye movement (NREM) sleep and rapid eye movement (REM) sleep. These occur in a temporally organized fashion across the sleep period. There are alterations in autonomic regulation during sleep. This chapter presents additional information on alterations in cardiopulmonary function.

CHANGES IN CARDIOVASCULAR CONTROL DURING SLEEP

In NREM sleep, heart rate slows and blood pressure drops. These changes are not particularly large, being most marked in the deepest stage of NREM sleep, i.e., stage 4 (slow wave sleep). The reduction in heart rate is of the order of 5 to 10 percent, with the fall in mean blood pressure being typically about 10 percent. In NREM sleep there is reduction in sympathetic outflow as is revealed by the seminal studies of Somers et al. using microneurography to record sympathetic bursts in the peroneal nerve in healthy humans during wake and in the different stages of sleep (Fig. 96-1). Thus, the balance of parasympathetic/sympathetic activity is altered during NREM sleep, with the parasympathetic being dominant. This results in alteration in heart rate variability during sleep. The high-frequency component of this heart rate variability is said to reflect parasympathetic activity, while the low frequency component is related to sympathetic activity. Thus, during NREM sleep there is an increase in the high-frequency component compared with wakefulness and a quite marked reduction in the low-frequency component of heart rate variability.

Changes in REM sleep are different. During this stage of sleep there is a return of sympathetic activity such that heart rate and blood pressure return to wakefulness levels. This has been shown directly by sympathetic nerve activity in humans (Figs. 96-1 and 96-2). Thus, during REM sleep the high- and low-frequency component of heart rate variability are the same as in wakefulness.

During REM sleep there is also phasic activity that occurs in bursts. These phasic bursts of activity result in rapid eye movements and hence the name for the state. Phasic bursts of activity can lead to both brief periods of increases in heart rate and periods of decrease. These have pathophysiological significance. During surges of heart rate, there are also increases in coronary blood flow. But these can be mismatched such that the increased delivery of blood flow is insufficient to meet the extra myocardial demands consequent to the increase in heart rate. Moreover, in animal models of severe coronary stenosis, phasic decreases in coronary arterial blood flow are found when heart rate increases. Such changes may play a role in the known diurnal rhythm of timing of reported acute cardiac events in humans. Episodes of slowing of heart rate can also occur. At the extreme, brief episodes of asystole in phasic REM sleep have been described in otherwise healthy adults.

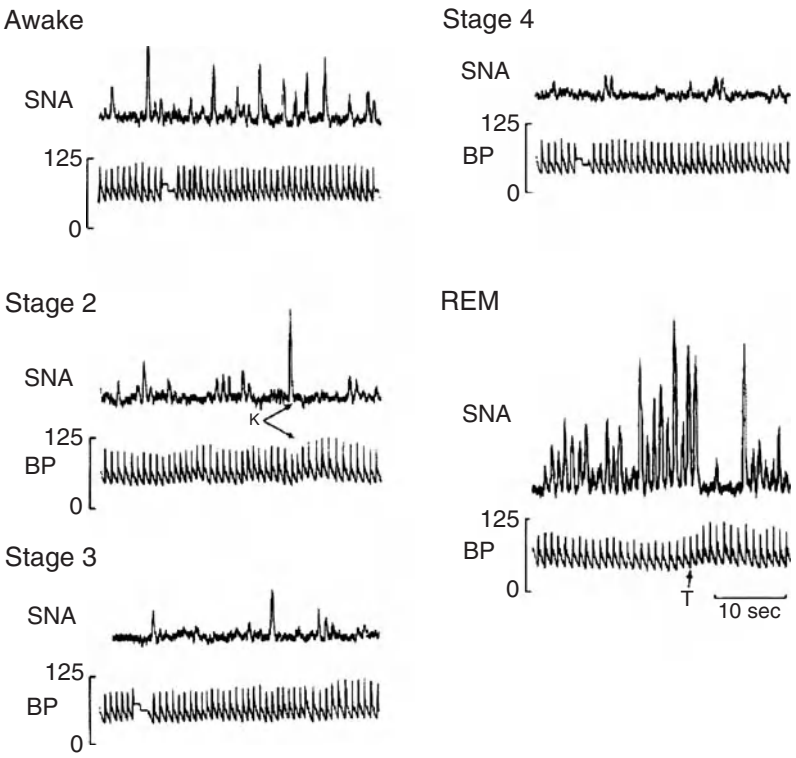

Figure 96-1 Alterations in recorded bursts of sympathetic nerve activity (SNA) and blood pressure in wakefulness, different stages of non–rapid eye movement sleep (stages 2, 3, and 4), and rapid eye movement (REM). With deepening of NREM sleep, there is progressive loss of sympathetic activity, which is virtually absent in slow wave sleep (stage 4). Sympathetic activity returns in REM but is highly variable. *(From Somers VK, Dyken ME, Mark AL, et al.: Sympathetic-nerve activity during sleep in normal subjects.* N Engl J Med *328:303, 1993, with permission.)*

CHANGES IN VENTILATION AND ITS CONTROL WITH SLEEP

As with the cardiovascular system, there are important changes in ventilation during sleep. These, too, are different in NREM and REM sleep. During NREM sleep ventilation declines. The various studies in this area have been summarized by Krieger et al. All studies have reported this decrease, although the magnitude of change varies from study to study (see summary in Fig. 96-3). In general, there is a decline in tidal volume while the change in respiratory rate is more variable (see Table 1 in Krieger J et al., 1990). Ventilation in REM sleep is also consistently less than in wakefulness; some studies report a small increase in ventilation in REM compared with NREM sleep (0.9 to 7.1 percent), while other studies

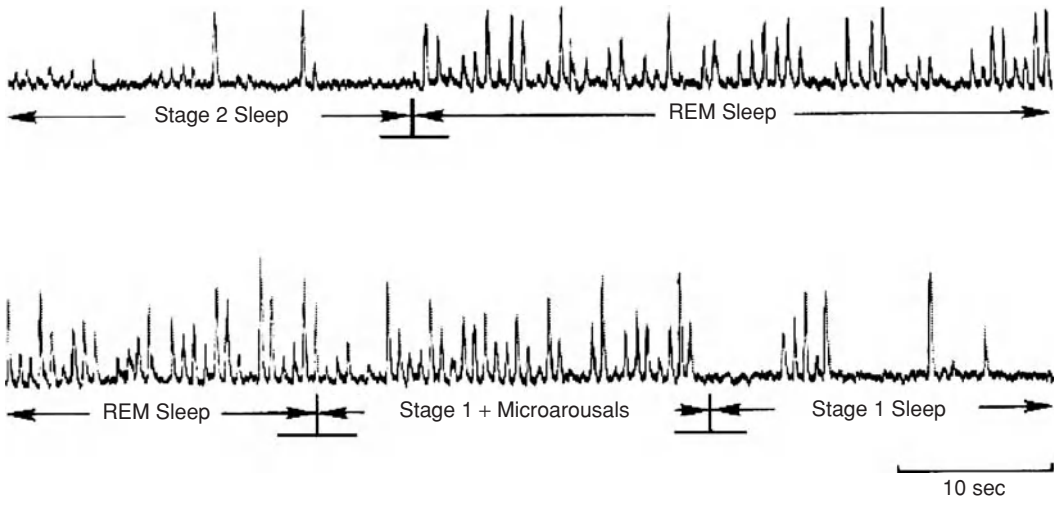

Figure 96-2 Changes in recorded sympathetic nerve bursts in a healthy human during transitions between different sleep stages. There are more bursts, i.e., more sympathetic activity, in REM sleep compared with stage 2 NREM sleep *(top panel)* and more activity in stage 2 sleep when it is transitional with many microarousals than when fully established *(bottom panel). (From Somers VK, Dyken ME, Mark AL, et al.: Sympathetic-nerve activity during sleep in normal subjects.* N Engl J Med *328:303, 1993, with permission.)*

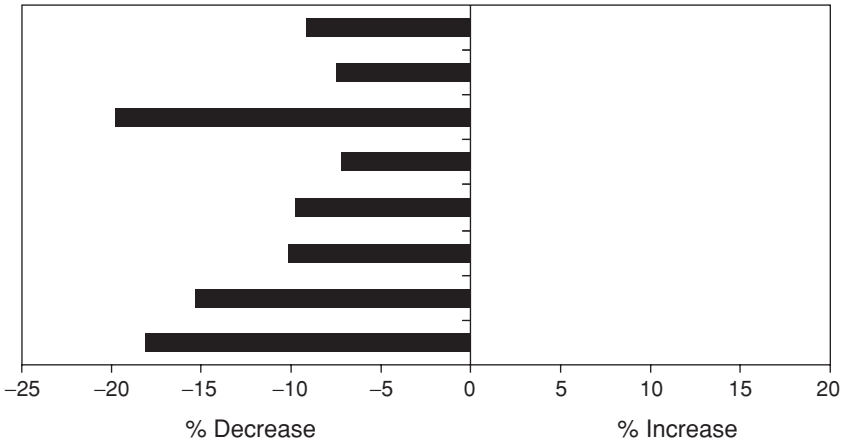

Figure 96-3 Percentage change in minute ventilation from wakefulness to NREM sleep in several different studies. There is some variation between studies in the magnitude of the drop in ventilation in NREM sleep, but all studies show a decline. *(Krieger J, Maglasiu N, Sforza E, et al.: Breathing during sleep in normal middle-aged subjects.* Sleep *13:143, 1990.)*

report a further decrease (−1.1 to −10.8 percent). This variability is likely related to the variability of ventilation in REM sleep itself. As in the cardiovascular system, there are changes in ventilation in association with the phasic events of REM sleep. Both acceleration and slowing of respiratory rate are found as are declines in ventilation. These effects seem to vary between subjects (Fig. 96-4).

The changes in NREM sleep in normal humans are largely the result of increases in upper airway resistance. This resistance progressively increases going from stage 1 to stage 3/4 NREM sleep (Fig. 96-5). This increase in resistance is associated with decreases in upper airway muscle activity in muscles such as the genioglossus and in the soft palate. While an increase in upper airway resistance is the major mechanism, it is, however, not the only mechanism since even in laryngotomized subjects with tracheostomies, thereby bypassing the upper airway, P_{CO_2} increases in NREM sleep compared to wakefulness.

The relative importance of the increase in upper airway resistance reflects different neural control of upper airway muscles and the respiratory pump muscles such as the diaphragm. The former is much more coupled to state, i.e., wake and sleep, while the latter, the diaphragm, is more affected by chemical control rather than variations in state (Fig. 96-6). This is why clinically we are typically talking about obstructive sleep apnea while central sleep apnea is relatively rare. Recent evidence suggests that a major neurotransmitter responsible for the state-dependent change in upper airway motoneuron activity controlling upper airway dilator muscles is noradrenaline.

Sleep also alters the ventilatory response to hypoxia and hypercapnia. The ventilatory response to hypoxia declines in NREM sleep compared to wakefulness. It declines further in REM sleep. Likewise, the slope of the ventilatory response to carbon dioxide is reduced in NREM sleep compared to wakefulness and further reduced in REM sleep. However, there is

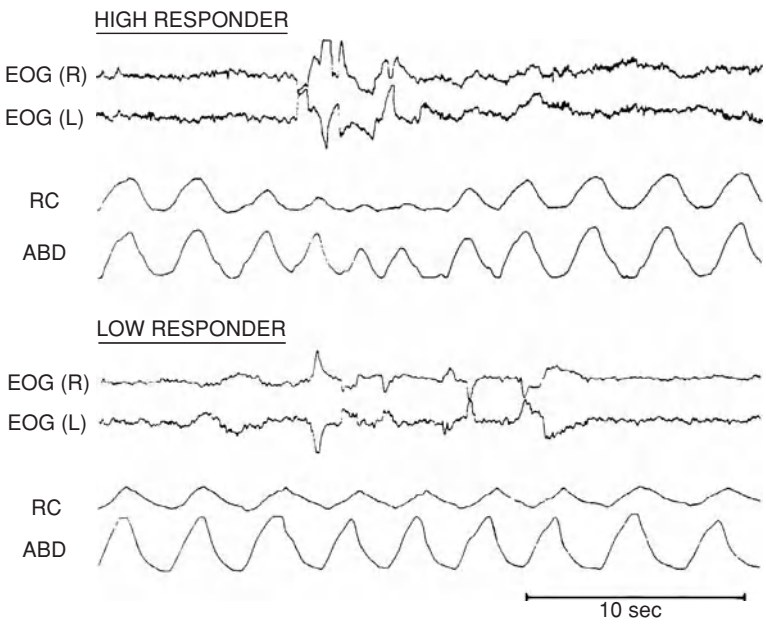

Figure 96-4 Changes in respiration during REM sleep. The data shown are for two normal healthy adults. The top traces are right and left electro-oculogram [(EOG(R) and EOG(L)] that show phasic eye movements during REM sleep. The bottom traces are ribcage (RC) and abdominal (ABD) motion. The subject in the top panel (labeled High Responder) has a marked fall in ribcage and to a lesser extent abdominal motion in association with the eye movements. The subject in the bottom panel (labeled Low Responder) has little alteration in ventilatory movements during these phasic eye movements. *(From Neilly JB, Gaipa EA, Maislin G, et al.: Ventilation during early and late rapid-eye-movement sleep in normal humans.* J Appl Physiol *71:1201, 1991, with permission.)*

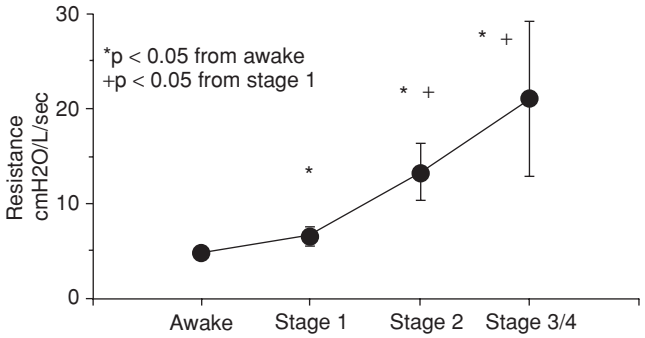

Figure 96-5 Upper airway resistance increases progressively on going from wakefulness to the deeper stages of NREM sleep. *(Data from Tangel DJ, Mezzanotte WS, White DP: Influence of sleep on tensor palatini EMG and upper airway resistance in normal men.* J Appl Physiol *70:2574, 1991, with permission.)*

no compelling evidence that there is alteration in central neural response to chemical stimuli since there is, as outlined, a change in upper airway resistance that will alter the increase in ventilation produced by increases in the neural output to the diaphragm.

As a consequence of these changes in ventilation and its control, Pa_{CO_2} rises, typically from its normal value of 40 mmHg by a few mmHg in NREM sleep. The magnitude of this increase in Pa_{CO_2} is a function of the responsiveness of the system to CO_2 during wakefulness; subjects with low ventilatory responses to CO_2 have larger increases in Pa_{CO_2} during NREM sleep than do subjects with high responsivity (Fig. 96-7).

Parallel to this increase in Pa_{CO_2}, the Pa_{O_2} falls. In normal persons, who are operating on the flat part of the oxygen saturation curve, the Pa_{O_2} does not fall to a level where significant desaturations occur. However, in persons with low Pa_{O_2} during wakefulness, who operate closer to the "knee" of the oxygen saturation curve, this fall in Pa_{O_2} during sleep may lead to a significant hypoxemia. For example, patients with chronic obstructive pulmonary disease may require supplemental oxygen during sleep but not during wakefulness.

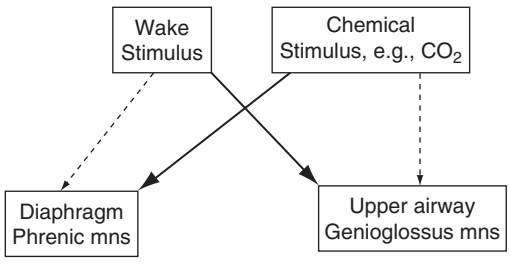

Figure 96-6 Schematic diagram illustrating the relative role of the "wakefulness drive" to breathe and that related to the chemical control system determined by P_{CO_2} and P_{O_2}. The diaphragm is only little affected by the wakefulness drive *(dashed line)* and is predominantly responding to chemical stimuli *(thick line)*. In contrast, upper airway motoneurons, such as genioglossus, are more affected by the "wakefulness stimulus" coupled to sleep state.

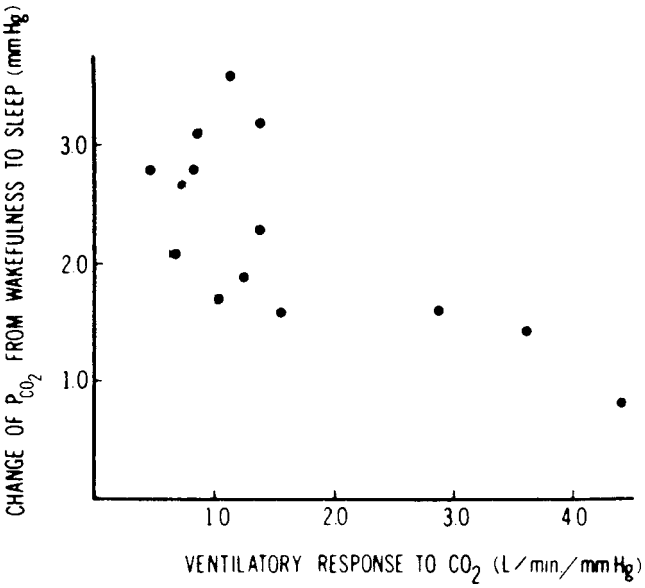

Figure 96-7 Relationship between the increase in P_{CO_2} that occurs in normal subjects in going from wakefulness to stages 1 and 2 NREM sleep and the CO_2 ventilatory response in wakefulness. Persons with the lowest ventilatory responses show the largest change in P_{CO_2} in going to sleep. *(From Gothe B, Altose MD, Goldman MD, et al.: Effect of quiet sleep on resting and CO_2-stimulated breathing in humans.* J Appl Physiol *50:724, 1981, with permission.)*

Another major change that occurs during NREM sleep is an increase in the CO_2 apnea threshold. This apnea threshold is the Pa_{CO_2} at which there is insufficient chemical drive and ventilation ceases. During wakefulness, Pa_{CO_2} can be reduced by assisted ventilation to values as low as 20 mmHg and rhythmic ventilation will be maintained; thus, the CO_2 apnea threshold during wakefulness is extremely low. In contrast, during NREM sleep, the Pa_{CO_2} needs be reduced only to values close to the normal awake Pa_{CO_2} (38 to 40 mmHg) and ventilation will cease. Thus, the normal increase in Pa_{CO_2} that occurs during NREM sleep is often necessary to maintain rhythmic ventilation.

This NREM sleep–related increase in apnea threshold has profound implications. In situations in which ventilation is stimulated—for example, by hypoxia—Pa_{CO_2} may be reduced below the apnea threshold typical for normoxic conditions, creating a state of increased vulnerability to central apneas. It is likely that unexplained central apnea during sleep occurs in association with hypocapnia. If this is the mechanism for these apneas, increase in the Pa_{CO_2} should abolish them. This has been demonstrated in idiopathic central apnea. Relative hypocapnia is also a risk factor for development of Cheyne-Stokes respiration in patients with congestive heart failure.

The specific cellular and neurochemical mechanisms for this NREM sleep–related change in the apnea threshold are currently unknown. Conceptually, however, it may be considered within the same category as the so-called wakefulness stimulus for breathing. Brain stem neuronal groups, such as

the locus ceruleus and raphe nuclei, in which the major transmitters are norepinephrine and serotonin, respectively, decrease their activity with sleep. Since both these transmitters have important excitatory effects at various levels of the central respiratory control system, these neuronal groups likely represent major components of the wakefulness stimulus.

AROUSAL DURING SLEEP

During sleep various sensory stimuli, including auditory and tactile, can lead to a sudden change in sleep state to a lighter stage of sleep or complete wakefulness. Arousal can be detected with abrupt changes in the electroencephalogram. Arousal also results in an increase in heart rate and blood pressure as well as an increase in ventilation. So-called subcortical or brain stem arousals can arise, including in patients with obstructive sleep apnea, i.e., when there is an abrupt change in cardiopulmonary variables but no change in the electroencephalogram. As would be anticipated from the discussion of the wakefulness stimulus, arousals produce much more marked increases in activity of upper airway muscles than in diaphragm.

Respiratory stimuli can also lead to arousal during sleep. Such stimuli include airway occlusion, increased upper airway resistance, hypoxia, and hypercapnia. Isocapnic hypoxia is, however, a poor stimulus to arousal. Subjects can remain asleep without interruption even with an Sa_{O_2} at 70 percent. It appears that the major respiratory stimulus to arousal is the degree of respiratory effort. Arousal occurs at a relatively constant increased respiratory neural output, i.e., respiratory effort that is independent of the causes of this increased effort.

PERIODICITIES OF VENTILATION IN LIGHT NREM SLEEP

Periodic (oscillatory) ventilation is more likely to occur during light NREM sleep (stages 1 and 2) than in slow-wave sleep (stages 3 and 4). This is highly relevant to the problem of obstructive sleep apnea; most apneas occur in stages 1 and 2 sleep. If a subject with sleep apnea is able to enter stages 3 and 4 NREM sleep, regular ventilation resumes and apneas are less likely to occur. Oscillatory ventilation is also typically observed during hypoxia, as in lung disease or at high altitude, and in certain cardiovascular diseases.

Ventilation may be periodic because of particular dynamic properties of the chemical feedback system that controls respiration. As in any feedback system, the critical determinants of this unstable (oscillatory) behavior are the overall response (gain) of the control system and the time delay (phase lag) between the plant and the controller. For the respiratory system, the plant is the gas exchange apparatus in the lung; the controllers are the chemoreceptors, peripheral and central; and the controlled variables are the arterial blood-gas tensions Pa_{CO_2} and Pa_{O_2}. Thus, in the case of the respiratory control system, this time delay is that between the lung and the sensors, the peripheral and central chemoreceptors.

The importance of this delay is illustrated in Fig. 96-8 for a situation in which a disturbance to the ventilatory control system leads to a change in Pa_{CO_2}. If there is no delay,

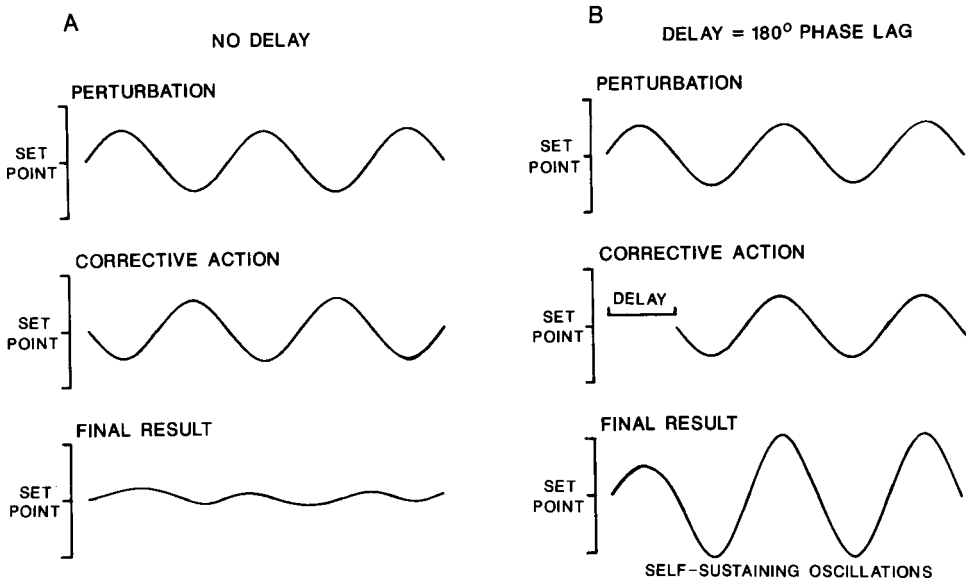

Figure 96-8 Implications for a control system with a delay between the plant and the control system. The left panel (*A*) shows how a control system will respond to a sinusoidal perturbation when there is no delay. The perturbation is essentially neutralized. The right panel (*B*) shows how a control system acts if it has a delay that results in the corrective action being 180 degrees out of phase with the perturbation. In this case, the controller's action acts to sustain, and not to neutralize, the original sinusoidal perturbation.

the control system responds immediately to this perturbation by adjusting ventilation to correct the change in Pa_{CO_2} (Fig. 96-8*A*). In contrast, if there is a delay in the feedback loop, the controller may act to sustain the cyclical disturbance (Fig. 96-8*B*); this is because during the time it takes the altered Pa_{CO_2} level to reach the sensor, the controller may make an inappropriate correction. For example, when the Pa_{CO_2} in the blood leaving the lung is low, the controller should respond by reducing ventilation, returning the Pa_{CO_2} to the regulated value. If, however, the delay is such that by the time the low Pa_{CO_2} signal reaches the sensor, the Pa_{CO_2} of the blood leaving the lung is already higher (e.g., due to the presence of an external perturbation or already existing oscillations, as in Fig. 96-8*B*), the controller will act incorrectly to reduce ventilation and further increase the Pa_{CO_2}. Such a situation promotes self-sustaining periodic ventilation. Thus, the time delay determines not only whether periodic ventilation will or will not occur, but also the period of this oscillation.

Periodic ventilation would not occur if the control system failed to respond, or responded weakly, to these perturbations. Thus, the gain of the response of the system is as important as the magnitude of the delay in determining whether unstable operation of the ventilatory control system will occur. This gain is usually defined as the product of the response of the controller (the change in ventilation per unit change in Pa_{CO_2}—i.e., CO_2 *sensitivity*) and the gain of the plant (the change in Pa_{CO_2} per unit change in ventilation—i.e., the *plant gain*). Overall loop gain is the product of these.

Periodic breathing occurs in clinical situations, particularly in hypoxic subjects (e.g., patients with lung disease) and normal sojourners at high altitude: Hypoxia increases the gain of the response of the controller, making the system more unstable. The period of the oscillations in ventilation induced by hypoxia is on the order of 20 seconds—i.e., much shorter than those typically seen in patients with obstructive sleep apnea. Abnormally increased circulatory time, which prolongs the delay between the lung and chemoreceptors, can also produce an unstable system and ventilatory periodicities. This mechanism is likely to be responsible, at least in part, for the ventilatory oscillations that occur during sleep in patients with severe congestive heart failure (Cheyne-Stokes respiration).

In addition to these mechanisms that are related to instability of the chemical control system for ventilation, *state instability* can produce sleep-related oscillations in ventilation; state instability is defined as periodic changes in the stages of sleep that cause discrete and periodic changes in the level of the wakefulness stimulus to ventilation. As discussed in the preceding section, at the onset of sleep, there are decreases in ventilation and increases in upper-airway resistance that cause an increase in Pa_{CO_2}; the increase in Pa_{CO_2} may, in turn, directly or indirectly interfere with the normal progression of the sleep cycle. For example, an abrupt change in sleep state may occur as a result of airflow limitation and increased respiratory effort, leading to an awakening to a lighter stage of sleep—i.e., to an arousal. Upon arousal, ventilation increases, upper-airway resistance decreases, and Pa_{CO_2} drops. The subject returns to sleep, and the whole cycle may repeat itself. This state instability is more likely to arise if the ventilatory response to CO_2 is low, since the Pa_{CO_2} increases more at sleep onset and is more apt to drive the level of respiratory effort to a point at which an arousal from sleep occurs. The period of ventilatory oscillation caused by this mechanism is longer than that seen with chemical instability—i.e., around 60 to 90 seconds. This mechanism, we believe, predominates in producing the sleep apnea syndrome and periodic breathing in patients with low ventilatory responses to CO_2 (e.g., patients with hypothyroidism, in whom central and obstructive apneas are common).

CIRCADIAN CLOCKS IN THE CARDIOVASCULAR SYSTEM AND LUNG

While much is known about the physiology of cardiopulmonary changes during sleep, recently attention has turned to changes in molecular mechanisms. In the late 1990s the discovery of the molecular components that produce circadian clocks led to study of expression of circadian clock genes in many different organs. Surprisingly, functioning clocks were not only found where they were expected, i.e., in the suprachiasmatic nucleus of the hypothalamus—the site of the circadian clock—but in many organs. In particular, functioning clocks have been demonstrated in the lung and cardiovascular system. In cardiac myocytes and vascular smooth muscle cells, the clocks are intrinsic to these cells since they maintain a circadian rhythm even when the cells are isolated and in culture (for review, see Young ME, 2006). (Many other cell types have not been as extensively tested to date.) These clocks likely alter the temporal pattern of expression of genes in the relevant organs. Microarray studies indicate that about 10 percent of all genes have a diurnal variation in their expression levels. In heart, there is, for example, diurnal variation of genes promoting fatty acid oxidation. Expression of these genes in rats peaks during the dark phase, i.e., their active period. Expression of genes for K+ channels also exhibit diurnal variation in heart and likely contributes to the altered excitability of cardiac myocyte across the day.

These observations indicate that at a fundamental molecular level the heart and lung at night are not the same as during the day. It seems likely that molecular processes in these organs will also be affected by sleep and sleep deprivation, but this is an area that has not been studied to date, and is likely to be a fruitful area of inquiry.

CONCLUSION

In conclusion, there are major changes in cardiopulmonary function during sleep as compared with wakefulness. These changes are sleep-state specific, being different between NREM and REM sleep. The changes have important

pathogenetic significance. This significance includes the following: the timing across the day of acute cardiovascular events; the periodic breathing that occurs during sleep at high altitude; the neuronal changes that lead to obstructive apnea during sleep; the pathogenesis of Cheyne-Stokes respiration. Currently a new window on changes in the cardiopulmonary system with sleep is opening, i.e., changes at the molecular level. This is likely to lead to new insights that will also have implications for the pathogenesis of disease and treatment.

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Sleep Apnea Syndromes

N. P. Patel • R. J. Schwab

HISTORY OF SLEEP-DISORDERED BREATHING

Sleep-disordered breathing is an extremely common medical disorder associated with important morbidity. Recognition of its relevance in medicine is relatively recent, although clinical descriptions of sleep-disordered breathing were made in the nineteenth century by Hunter, Cheyne, and Stokes. Descriptions of an entity constituting obesity and extreme somnolence were highlighted in the character description of the "fat boy" in Charles Dickens' series, *Posthumous Papers of the Pickwick Club,* first published in 1835. Dickens described Joe, the fat boy, as a loud snorer who was obese and excessively somnolent—the classical description of Pickwickian syndrome. Sir William Osler in 1918 was credited with first linking the relationship between obesity and Pickwickian syndrome. In the mid-twentieth century, further work led to the association of Pickwickian syndrome with alveolar hypoventilation by Burwell and colleagues in 1956, and periodic cessation of respiration by Drachman and Gummit in 1962. Gastaut and associates in 1965 showed that cessation of respiration was due to obstruction of the upper airway, and obstructive sleep apnea was recognized. In 1972, a conference organized by Lugaresi and his Bologna group (Italy) entitled Hypersomnia and Periodic Breathing, served as a springboard for the growth of interest and research in sleep-disordered breathing. Guilleminault et al. coined the terms sleep apnea syndrome and obstructive sleep apnea syndrome in 1976 to underscore that airway obstruction during sleep was not restricted to obese subjects. Over the last 30 years, we have begun to understand the pathogenesis of sleep apnea and have developed effective diagnostic and treatment modalities for this common disorder.

DEFINITIONS OF OBSTRUCTIVE SLEEP APNEA, PICKWICKIAN SYNDROME, CENTRAL SLEEP APNEA, AND THE UPPER AIRWAY RESISTANCE SYNDROME

Sleep-disordered breathing (SDB) is present when there are repetitive episodes of cessation of respiration (apnea) or decrements in airflow (hypopnea) during sleep, associated with sleep fragmentation, arousals, and reductions in oxygen saturation. An apnea can be obstructive (absence of airflow but continued respiratory effort), central (absence of airflow and respiratory effort), or mixed. A mixed apnea starts as a central event and then becomes obstructive during the latter portion of the same episode. A majority of patients with obstructive sleep apnea (OSA) have both obstructive and mixed apneas. A hypopnea is defined as a decrement in airflow of 50 percent or more associated with a 4 percent fall in oxygen saturation and/or electroencephalographic (EEG) arousal. However, there is some debate over the exact definition of a hypopnea. Hypopneas have been shown to produce identical clinical consequences as apneas. A respiratory effort-related arousal event (RERA) is a sequence of breaths characterized by increasing effort leading to an arousal from sleep that does not fulfill criteria for apnea or hypopnea. It should last for at least 10 seconds and is terminated by an arousal.

The apnea/hypopnea index (AHI—the number of apneas plus hypopneas per hour of sleep) is the standard metric used to quantitate the severity of obstructive sleep apnea. Although the AHI has been proven to be superior metric when assessing the overall effect of OSA, it excludes the degree of oxygen desaturation, degree of hypoventilation, and total number of arousals. An AHI greater than 5 to 10 events per hour is indicative of OSA. The obstructive sleep apnea syndrome (OSAS) is said to be present when the AHI is greater than 5 to 10 events per hour and the patient has symptoms of excessive daytime somnolence, unrefreshing sleep, or chronic fatigue. Individuals must fulfill criterion A or B, plus criterion C to be diagnosed with OSAS:

A. Excessive daytime sleepiness that is not explained by other factors
B. Two or more of the following that are not explained by other factors:
   - Choking or gasping during sleep
   - Recurrent awakenings from sleep
   - Unrefreshing sleep
   - Daytime fatigue
   - Impaired concentration
C. Overnight monitoring demonstrates 5 to 10 or more obstructed breathing events per hour during sleep or greater than 30 events per 6 hours of sleep. These events may include any combination of obstructive apnea, hypopnea, or respiratory effort–related arousals.

The clinical implications of patients diagnosed with OSA in the absence of daytime symptoms remains to be clarified. However, patients with an AHI greater than 30 events per hour should be treated regardless of their symptoms. In general, as the AHI increases, so does the severity of symptoms. Three other syndromes (central sleep apnea, obesity-hypoventilation, upper airway resistance syndrome) can either coexist with OSA or present independently.

Central sleep apnea (CSA) is less common than obstructive sleep apnea and is characterized by a transient cessation of rhythmic breathing: The respiratory pump muscles do not receive central input. It is defined as repeated episodes of apnea in the absence of respiratory muscle effort and is observed on the polysomnogram as an absence of nasal-oral airflow and thoracoabdominal excursion. The individual must fulfill A, B, and C to be diagnosed with the central sleep-apnea-hypopnea syndrome.

A. At least one of the following symptoms that is not explained by other factors:
   - Excessive daytime sleepiness
   - Frequent nocturnal arousals/awakenings
B. Overnight monitoring that demonstrates 5 to 10 or more central apneic events plus hypopneic events per hour of sleep.
C. Normocarbia while awake (Pa_{CO_2} less than 45 torr).

A number of etiologies for central sleep apnea have been recognized, of which heart failure and stroke are the most common. Patients with CSA experience sleep fragmentation and can report similar daytime symptoms as OSA patients. (For further discussion of central sleep apnea, see Management of Other Disorders, below.)

Upper airway resistance syndrome (UARS) was first described by Guilleminault et al. in 1993. The advent of nasal cannula–pressure transducer system and esophageal pressure monitoring allowed recognition of increasing negative intrathoracic pressure associated with upper airway flow limitation, resulting in arousals from sleep. UARS is not associated with apneas or significant oxyhemoglobin desaturations. The arousals result in sleep fragmentation and daytime sleepiness. UARS may represent a milder form of the OSA spectrum, although there is debate whether or not UARS patients demonstrate different clinical and upper airway characteristics compared with OSA patients. Further study employing standardized techniques that detect respiratory-related EEG changes are being developed to clarify the incidence and prevalence of UARS as a separate entity. Nonetheless, many patients with the upper airway resistance syndrome also have evidence for concomitant obstructive sleep apnea.

Obesity hypoventilation syndrome (OHS), or the Pickwickian syndrome, also frequently coexists with OSA. It is defined by morbid obesity (body mass index greater than 40 kg/m^2) and chronic hypoventilation with hypercapnia (Pa_{CO_2} greater than 45 mmHg) during wakefulness. OSA patients, in general, do not exhibit hypercapnia during wakefulness as a result of preserved minute ventilation. Characteristic findings observed with obesity-hypoventilation syndrome include awake resting hypoxemia, hypersomnolence, signs of cor pulmonale (right-sided heart failure and lower

extremity edema), and nocturnal hypoventilation. The diagnosis of OHS requires a demonstration of at least a 10 mmHg increment in Pa_{CO_2} during sleep. Patients with obesity hypoventilation syndrome often can be confused with patients with COPD since both of these patients manifest daytime hypercapnia. However, patients with COPD have an obstructive pattern on their pulmonary function studies, whereas patients with OHS usually have a restrictive pattern on their pulmonary function studies. In addition, patients with COPD are usually not morbidly obese.

SPECTRUM OF DISEASE

Therefore, obstructive sleep apnea should be considered as a continuum of disease, i.e., a spectrum of abnormalities from snoring to obesity-hypoventilation syndrome (Fig. 97-1). Although common, snoring should not be considered normal; it is often the first manifestation of SDB and may be associated with deleterious effects (see the following). This concept of a continuum of abnormality is important since it is likely, although not proved, that the natural history of disease follows this continuum. Significant weight gain or loss, and other comorbidities such as heart failure may be factors that move an individual along this continuum of SDB. Weight gain is an important risk factor for sleep apnea and the Pickwickian syndrome. Acutely, an individual may change position on the continuum for a number of reasons. Alcohol may worsen the degree of SDB by preferentially suppressing the activity of upper airway dilator muscles. Alcohol, sedatives, or hypnotics can cause normal individuals to snore during sleep and turn a patient who snores into a one with obstructive apnea during sleep. Weight loss moves patients along the continuum in the opposite direction.

PATHOGENESIS OF OBSTRUCTIVE SLEEP APNEA

The pathogenesis of OSA involves both an anatomic and a neurologic component. The upper airway is an extremely complicated structure performing several different physiologic functions, including vocalization, respiration, and deglutition. The upper airway extends from the posterior margin of the nasal septum to the larynx and has a paucity of rigid bony support. It is divided into four anatomic regions:

1. Nasopharynx: between nares and hard palate
2. Retropalatal: between hard palate and caudal margin of the soft palate
3. Retroglossal: between the caudal margin of the soft palate and base of the epiglottis
4. Hypopharynx: from the base of the tongue to the larynx

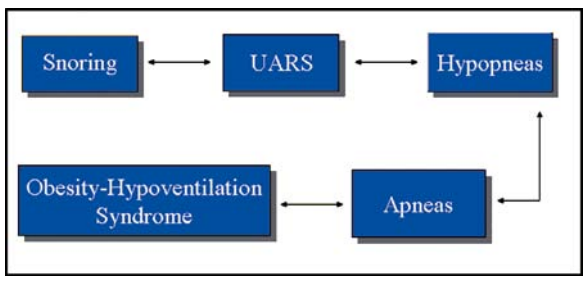

Figure 97-1 Spectrum of sleep-disordered breathing.

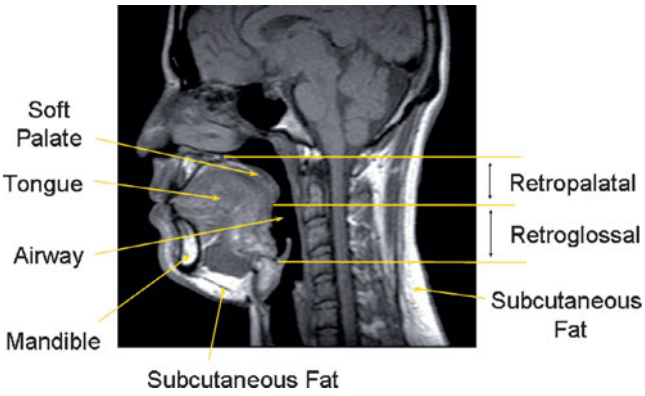

Figure 97-2 Mid-sagittal magnetic resonance image (MRI) in a normal subject demonstrating the anatomic regions of the upper airway and relevant craniofacial and soft tissue structures. The retropalatal (RP) region is defined from the level of the hard palate to the distal margin of the soft palate; the retroglossal (RG) region is defined from the distal margin of the soft palate to the base of the epiglottis. In patients with sleep apnea, obstruction usually occurs in the retropalatal or retroglossal levels or at both locations. *(Reproduced with permission from Schwab RJ, Gupta KB, Gefter WB, et al: Upper airway and soft tissue anatomy in normal subjects and patients with sleep-disordered breathing. Significance of the lateral pharyngeal walls. Am J Respir Crit Care Med 1995;152:1673–1689.)*

Fig. 97-2 displays a mid-sagittal magnetic resonance image (MRI) in a normal subject in which the retropalatal and retroglossal regions are outlined. In addition, this mid-sagittal image highlights the airway, tongue, soft palate, mandible, and subcutaneous fat. The critical lateral upper airway soft tissue structures, i.e., the lateral pharyngeal walls and lateral parapharyngeal fat pads are depicted in Fig. 97-3, which shows an axial MRI of a normal subject in the retropalatal region. In a patient with sleep apnea, collapse of the upper airway occurs most commonly in the retropalatal and retroglossal regions. Although the location of collapse varies among subjects, within a subject it tends to be reproducible from episode to episode. The surrounding tissue and craniofacial structures in the retropalatal and retroglossal regions contribute to the specific morphology of the airway of a given individual. The main contributors of the airway boundaries include the soft palate and tongue anteriorly, the pharyngeal constrictor muscles, lymphoid tissue, parapharyngeal fat pads, and mandibular rami laterally and the pharyngeal constrictor muscles posteriorly. Unfortunately, we do not completely

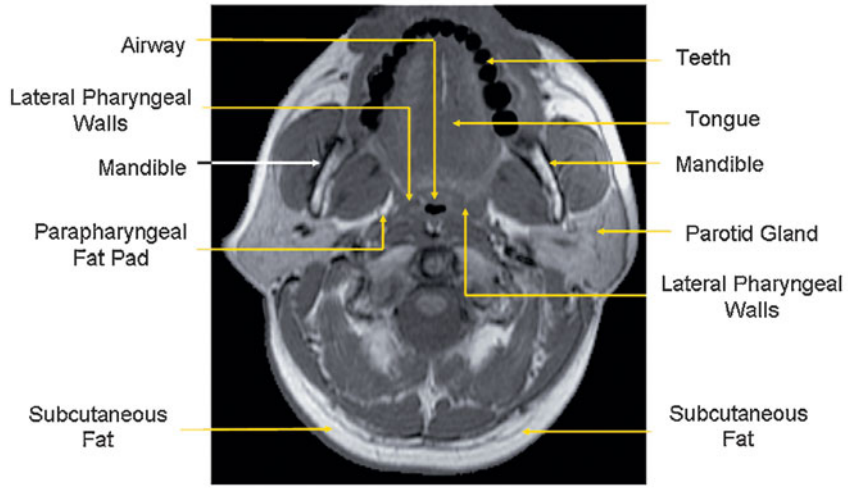

Figure 97-3 Axial MR image at the retropalatal level in a normal subject. The relevant soft tissue and bony structures surrounding the upper airway are highlighted. The tissues immediately lateral to the airway are the lateral pharyngeal walls and the parapharyngeal fat pads.*(Reproduced with permission from Schwab RJ, Gupta KB, Gefter WB, et al: Upper airway and soft tissue anatomy in normal subjects and patients with sleep-disordered breathing. Significance of the lateral pharyngeal walls. Am J Respir Crit Care Med 1995;152:1673–1689.)*

understand the biomechanical relationships between upper airway size and these surrounding structures.

In regard to elucidating the mechanisms leading to obstructive apnea, the focus has been on anatomic and neural factors that influence upper airway patency during wakefulness and sleep.

Anatomic Features That Predispose to Apnea

Airway patency is modulated by physical characteristics and neural mechanisms. The upper airway, unlike the lower respiratory tract, lacks a robust support framework of cartilaginous rings and therefore is at risk for collapse due to: (1) extraluminal tissue pressure exerted by circumferential craniofacial and soft tissue structures; and (2) negative pressure associated with inspiration. The pharyngeal dilator muscles help to maintain upper airway patency. Changes in pharyngeal transmural pressure, defined as the difference between the pressure in the airway lumen and the pressure exerted by tissues surrounding the site of collapse, modulates upper airway size.

An array of imaging techniques including cephalography, nasopharyngoscopy, fluoroscopy, acoustic reflection, computed tomography (CT), MRI, and optical coherence tomography have been employed to better understand the pathogenesis of OSA. Such imaging modalities have examined the upper airway during wakefulness, respiration, and during sleep. OSA subjects demonstrate an excess of upper airway soft tissue for the space within the craniofacial structures that envelop the pharyngeal lumen. Upper airway caliber during wakefulness, in general, is smaller in patients with sleep apnea compared with normal subjects, and the configuration of the upper airway is different in apneics than normals. Patients with sleep apnea have larger tongues and longer soft palates than normal subjects (Fig. 97-4). Habitual snorers with or without OSA also have a generalized narrowing of the pharyngeal lumen compared with normal subjects, whether or not they are obese. Length of the upper airway, using cephalometric and MRI techniques, has been demonstrated to be of significance in men with OSA: A longer airway confers a greater risk of airway lumen collapse compared with normal subjects. The major axis of the normal airway is oriented in the lateral, horizontal dimension. In apneics there is considerable reduction in the lateral diameter of the airway with relative preservation of the anterior-posterior diameter. Thus, in contrast to normals, the apneic patient's airway is oriented more in the anterior-posterior dimension. This configuration has been hypothesized to adversely affect upper airway muscle

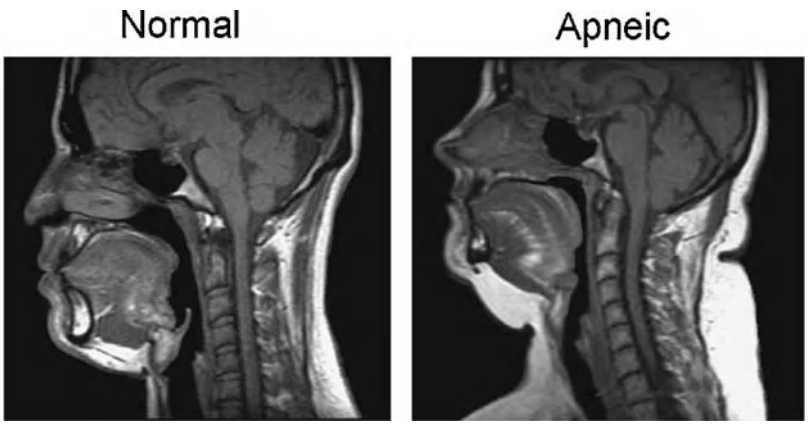

Figure 97-4 Mid-sagittal magnetic resonance imaging (MRI) of a normal subject on the left and a patient with sleep apnea on the right. The upper airway is smaller in both the retropalatal and retroglossal region in the apneic patient. The soft palate is longer in the apneic patient. The tongue is bigger in the retroglossal region in the patient with sleep apnea. The amount of subcutaneous fat (white area at the back of the neck) is greater in the apneic. *(Reproduced with permission from Schwab RJ, Gupta KB, Gefter WB, et al: Upper airway and soft tissue anatomy in normal subjects and patients with sleep-disordered breathing. Significance of the lateral pharyngeal walls. Am J Respir Crit Care Med 1995;152:1673–1689.)*

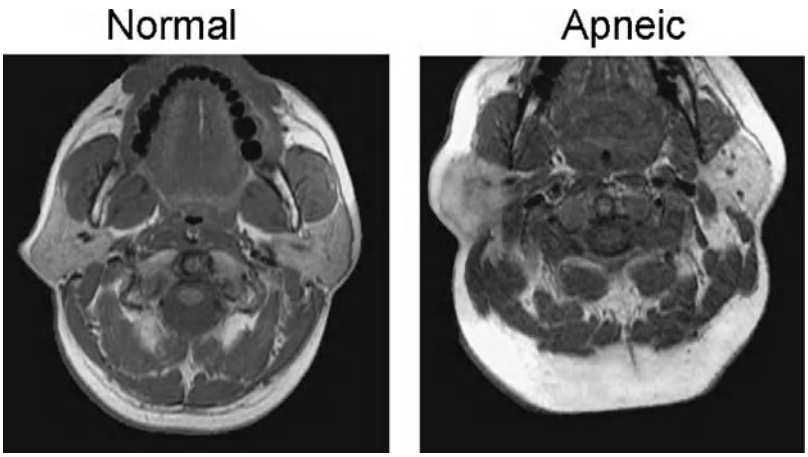

Figure 97-5 Axial magnetic resonance imaging (MRI) in the retropalatal region of a normal subject (left) and a patient with sleep apnea (right). The upper airway is smaller in the lateral dimension in the patient with sleep apnea. The lateral pharyngeal walls are larger in the patient with sleep apnea compared with the normal subject. The apneic patient has more subcutaneous fat than the normal subject. *(Reproduced with permission from Schwab RJ, Gupta KB, Gefter WB, et al: Upper airway and soft tissue anatomy in normal subjects and patients with sleep-disordered breathing. Significance of the lateral pharyngeal walls. Am J Respir Crit Care Med 1995;152:1673–1689.)*

activity and therefore predispose the apneic subject to airway closure during sleep.

This lateral narrowing of the airway indicates that soft tissue structures lateral to the airway (lateral pharyngeal walls and lateral parapharyngeal fat pads) may be important in modulating airway dimensions (Figs. 97-3 and 97-5). Enlargement of the parapharyngeal fat pads solely explaining the obesity-related narrowing of the airway in apneics, has fallen out of favor based on detailed MRI and CT studies. However, increased thickness of the lateral pharyngeal walls has been reported to explain narrowing of the apneic airway by imaging studies (Fig. 97-5). Fat deposition in the parapharyngeal fat pads, in the tongue, and under the mandible in the submental region may all be important in reducing upper airway caliber. Imaging studies have also demonstrated that the total volume of fat surrounding the airway is greater in apneic than in BMI-matched normal subjects, suggesting that fat deposition in the neck plays a role in the pathogenesis of OSA. Indeed, neck circumference is a strong predictor of sleep apnea based on population studies. A number of other soft tissue abnormalities also have been shown to narrow the upper airway in patients with sleep apnea when compared with normals, including an increase in the volume of the tongue, soft palate, and lateral walls surrounding the pharynx. The larger the volume of the lateral pharyngeal walls, tongue, and total soft tissue (Fig. 97-6), the greater is the likelihood of developing OSA.

Other factors important in mediating upper airway narrowing/soft tissue enlargement in apneics include genetics, gender, pharyngeal dilator muscle dysfunction, soft tissue edema (secondary to snoring/apnea-related trauma), airway tissue properties (surface tension), vascular perfusion, and posture of the individual (supine versus lateral). Recumbency decreases lung volume and traction on the airway. Muscular dysfunction and soft tissue edema are thought to be consequences rather than primary causes of OSA.

Finally, variation in craniofacial morphology influences upper airway configuration. For example, retroposed mandible and reduced hyoid-mandibular plane distance have been associated with higher risks of apnea. This is further discussed under Risk Factors for Sleep Apnea, below.

The upper airway's static characteristics during wakefulness in relation to apnea risk have been discussed. However, the dimensions of the airway are dependent on the phase of respiration. Dynamic upper airway imaging with CT, MRI, and nasopharyngoscopy has characterized the airway's geometrical changes into three phases (Fig. 97-7). In inspiration upper airway area is relatively constant, inferring a balance between muscle dilator activity and negative airway lumen pressure. In early expiration, the activity of airway dilator muscles decreases, intraluminal pressure rises, and the airway maximally widens. At end-expiration upper airway dimensions decrease. Therefore, the upper airway is at risk for collapse in both inspiration and expiration.

Neural Modulation of Upper Airway Patency

During sleep, the balance in transpharyngeal pressure shifts toward collapse as a consequence of reduced upper airway dilator muscle activity in both normals and patients with sleep apnea. MR images indicate that the upper airway of normal subjects without sleep apnea narrows during sleep (Figs. 97-8 and 97-9). The neural control of these muscles is complex and involves several neurotransmitters (serotonin, noradrenaline, thyroid releasing hormone, Substance p, and aminobutyric acid) that are also influenced by sleep. The most widely studied upper airway muscle is the genioglossus. Three neural mechanisms have been shown to be operative with regard to genioglossus muscle activity. First, negative airway pressure detected by laryngeal mechanoreceptors activates the genioglossus via increased hypoglossal nerve discharge. Second, genioglossus activation has been observed to precede diaphragmatic activation and development of negative intraluminal pressure due to input received from the respiratory control center in the medulla via respiratory neurons. Therefore, loop gain, a measure of stability or instability of a system controlled by feedback loops, can induce obstructive apneas. If central respiratory drive waxes and wanes, so does the pharyngeal muscle activity. Third, neural mechanisms modulating arousal (serotonergic and noradrenergic neurons) have a tonic excitatory influence on the genioglossus activity.

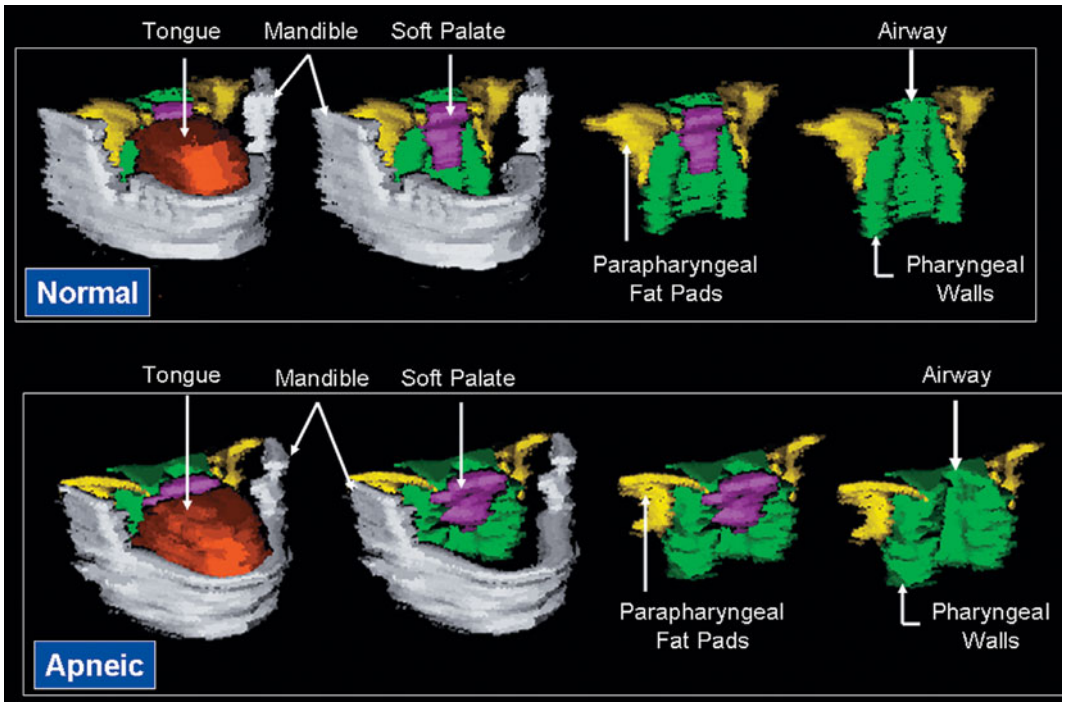

Figure 97-6 Volumetric reconstruction of axial magnetic resonance (MR) images in a normal subject (top panel) and a patient with sleep apnea (bottom panel). The mandible is depicted in gray, the tongue in orange/rust, the soft palate in purple, the lateral parapharyngeal fat pads in yellow and the lateral/posterior pharyngeal walls in green. Both subjects had an equivalent body mass index (32.5 kg/m^2). Upper airway caliber is greater in the normal subject than in the patient with sleep apnea. The tongue, soft palate, and lateral pharyngeal walls are all larger in the patient with sleep apnea than in the normal subject. *(Reproduced with permission from Schwab RJ, Pasirstein M, Pierson R, et al: Identification of upper airway anatomic risk factors for obstructive sleep apnea with volumetric magnetic resonance imaging. Am J Respir Crit Care Med 2003;168:522–530.)*

To summarize the neural modulation of pharyngeal muscle activity, there exists local input (negative intraluminal pressure), respiration-related input (medulla), and arousal state input (serotonin raphe cells). During NREM sleep, both the tonic and phasic activation of airway dilator muscles decreases during inspiration: This is a consequence of diminished local mechanoreceptor feedback loop activity. In REM sleep, these changes in the airway dilator muscle activity can be further depressed. In fact, during phasic REM activity, muscle action can be completely suppressed. Therefore, it is not unexpected that airway closures (or apneas) occur more commonly during REM sleep.

The Apneic Event

Occlusion of the airway results in a range of immediate physiologic disturbances. The continued ventilatory efforts in spite of episodic reduction/cessation in ventilation, combined with repetitive, intermittent hypoxemia and arousals form the basis for a cascade of downstream perturbances. Breathing efforts during an obstructive apnea create large swings in intrathoracic pressures that compromise left ventricular (LV) filling in consequence to rising afterload and preload. Intermittent hypoxemia is associated with increased production in reactive oxygen species, oxidative stress, and an inflammatory state. Surges in the sympathetic nervous system that occur secondary to apnea, hypoxia, hypercapnia, and arousal result in increased peripheral resistance and cardiac stimulation, which in turn lead to increases in blood pressure and heart rate.

Cessation of apnea occurs with an arousal to a lighter stage of sleep or wakefulness. The factors responsible for arousal most likely involve chemical (hypoxia) and mechanical stimuli (increased respiratory effort against an occluded airway). Arousal mechanisms, when adversely affected by alterations in chemosensitive systems or ingestion of alcohol and hypnotics, can lead to prolongation of apnea.

EPIDEMIOLOGY AND RISK FACTORS

Estimations of prevalence of OSA in the general population are variable and dependent on the population studied, methods used to measure sleep, and threshold employed to define normal from abnormal. In the United States, the prevalence has been reported to be 4 percent (up to 9 percent) in men and 2 percent (up to 4 percent) in women between the ages of 30 and 60. The prevalence of moderate to severe OSA associated with sleepiness has been estimated to be 0.5 to 1.5 percent in middle-aged men with an average BMI of 24.9 to 27.1. A Spanish study of a sample of 38- to 70-year-old subjects (male and female) noted a prevalence of 7 and 14 percent, respectively; however, the current actual prevalence may be substantially

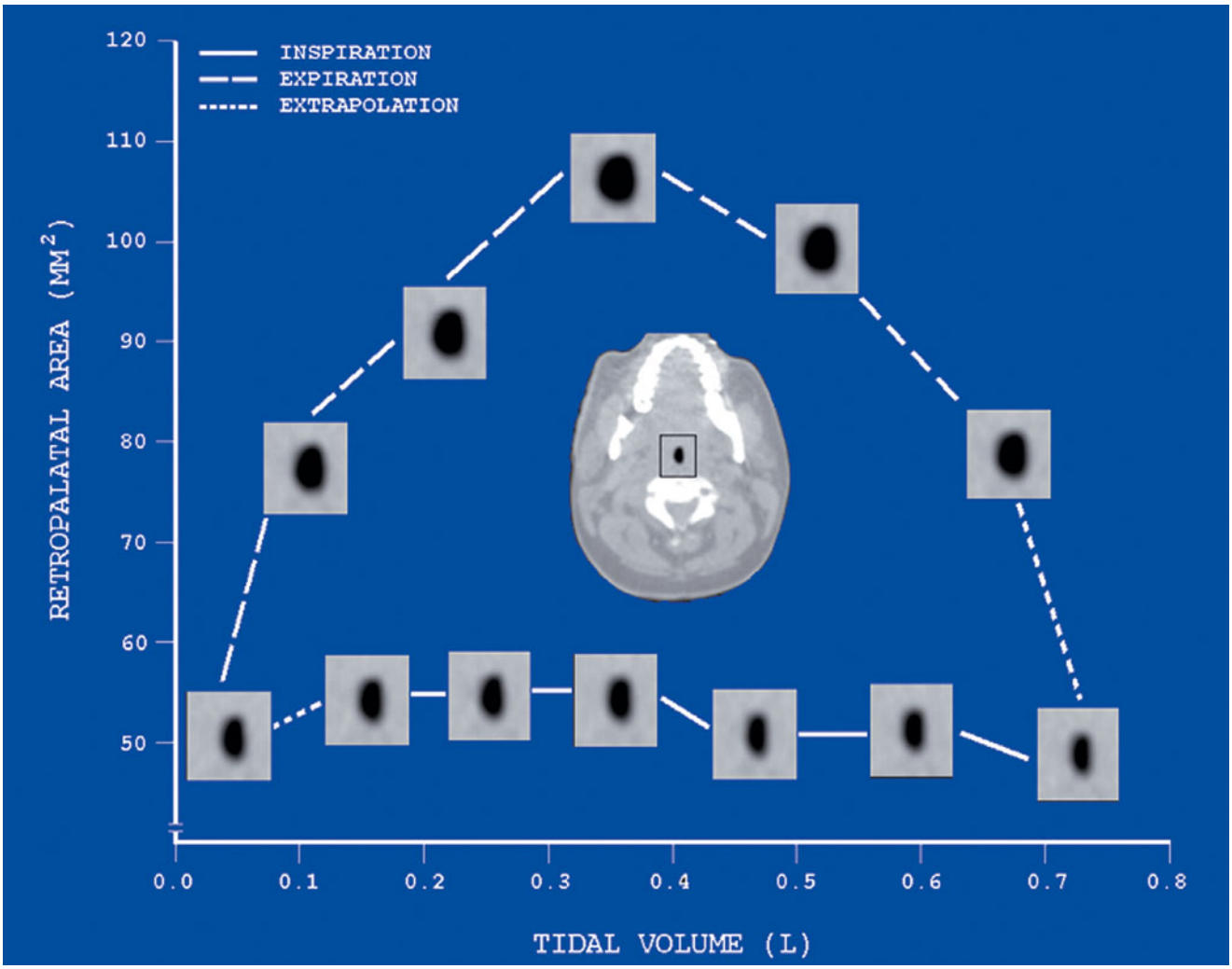

Figure 97-7 Changes in upper airway area as a function of tidal volume during the respiratory cycle using cine CT (computed tomography). Airway caliber is relatively constant in inspiration. Airway size increases in early expiration and decreases in late expiration. *(Reproduced with permission from Schwab RJ, Gefter WB, Hoffman EA, et al: Dynamic upper airway imaging during awake respiration in normal subjects and patients with sleep-disordered breathing. Am Rev Respir Dis 1993;148:1385–1400.)*

higher. Young et al. estimated that among middle-aged adults, 93 percent of women and 82 percent of men with OSA have not been clinically diagnosed. Thus, sleep apnea is exceedingly common and is a significant public health issue that will likely continue to become more common in parallel with its increasingly prevalent risk factors, notably obesity and older age. By consensus, the following criteria are used to define mild, moderate, and severe sleep apnea. (However, it should be noted that this classification system does not use oxyhemoglobin desaturation nadir or EEG arousals.)

Mild sleep apnea, AHI: 5 to 15 events per hour
Moderate sleep apnea, AHI:15 to 30 events per hour
Severe sleep apnea, AHI greater than 30 events per hour

Risk Factors for Sleep Apnea

Several risk factors exist for OSA (Table 97-1). Epidemiologic studies demonstrate the prevalence of OSA to be two to three times higher in men than women. The reasons are not entirely clear but appear to be related to hormonal influence. Postmenopausal women are at higher risk for OSA than are premenopausal women. Hormone replacement therapy may reduce the risk of OSA in postmenopausal women; however, this therapy is problematic due to the increased risk of cardiovascular disease and carcinoma of the breast and uterus. Comparing men with postmenopausal women, the incidence of OSA is reportedly similar. Gender differences in the prevalence of OSA may also be related to body fat distribution. Men exhibit a more central fat distribution, including the neck, thereby increasing the risk for narrowing and closure of the upper airway. However, it is not clear that men have larger parapharyngeal fat pads surrounding their upper airway than women.

Numerous studies have shown correlations between the prevalence of OSA syndrome and obesity. The majority of these investigations were cross-sectional. Important longitudinal studies have demonstrated that obesity increases

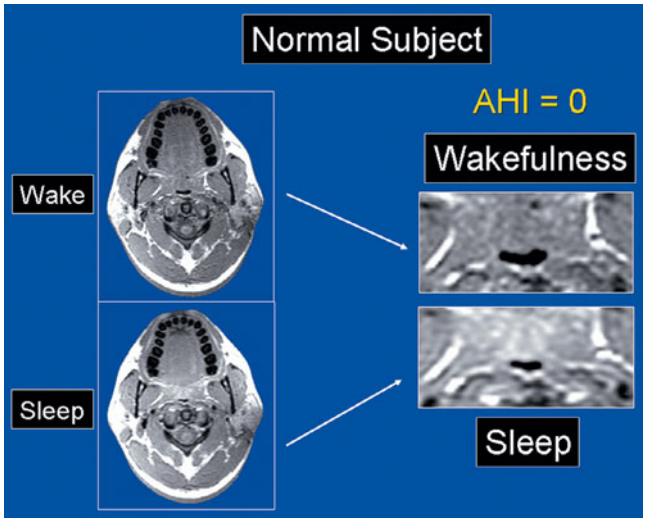

Figure 97-8 State-dependent magnetic resonance imaging (MRI) in the retropalatal region of a normal subject (AHI = 0 events/hour). Airway area is smaller during sleep in this normal subject. The state-dependent change in airway size is secondary to reductions in both the lateral and anterior-posterior airway dimensions. *(Reproduced with permission from Trudo FJ, Gefter WB, Welch KC, et al: State-related changes in upper airway caliber and surrounding soft-tissue structures in normal subjects. Am J Respir Crit Care Med 1998;158:1259–1270.)*

the rate of progression of OSA, and weight gain further accelerates disease progression. Although obesity is the most common risk factor for OSA, sleep apnea also occurs in non-obese subjects. In non-obese patients craniofacial features such as retroposed mandible, micrognathia, and narrowing of the hard palate are the primary risk factors for apnea. The importance of craniofacial morphology's contribution to apnea risk is supported by observations in Asian patients with apnea who have shorter maxillae and mandibles and smaller anterior-posterior facial dimensions, and lower BMI than whites. Soft tissue abnormalities such as tonsillar and adenoidal hypertrophy are important risk factors for apnea in children. Nasal abnormalities, including septal deviation and allergic rhinitis, also increase apnea risk.

Table 97-1

Risk Factors for Obstructive Sleep Apnea

Gender (male/female 2:1)
Obesity (>120% ideal body weight)
Neck size (collar size >17 inches in males, >15 inches in females)
Upper airway anatomy Macroglossia Lateral peritonsillar narrowing Elongation/enlargement of the soft palate Tonsillar hypertrophy Nasal septal deviation Retrognathia, micrognathia Narrowing of the hard palate Class III/IV modified Mallampati airway
Specific genetic diseases, e.g., Treacher Collins, Downs syndrome, Apert's syndrome, Achrodorophsia, etc.
Genetic factors
Endocrine disorders—hypothyroidism, acromegaly
Alcohol, sedative or hypnotic use

The effect of age is complex. Population studies illustrate higher prevalence of OSA with increasing age, peaking in the fifties and sixties. However, older individuals have lower rates of apnea and snoring. Reduced recognition of sleep problems by the elderly and a survivor effect are potential reconciling explanations for this paradox.

Evidence is accumulating that genetic factors may be involved in the pathogenesis of sleep apnea. The phenotypic risk factors arise from changes to upper airway structure: (1) alteration in craniofacial structures; (2) enlargement

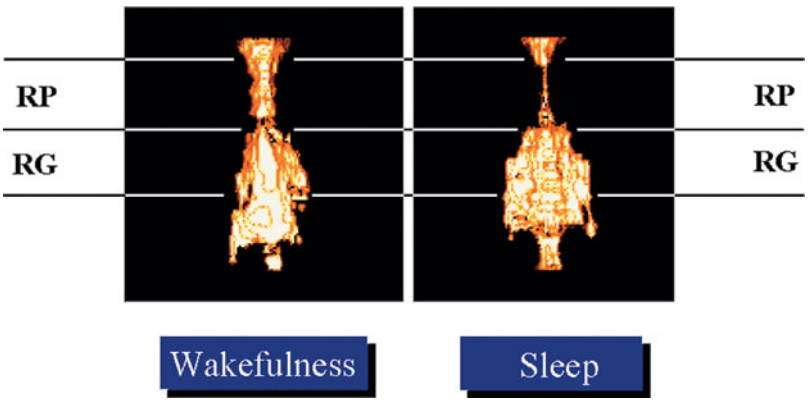

Figure 97-9 Volumetric state-dependent airway imaging in a normal subject using magnetic resonance imaging (MRI). Airway volume during sleep is smaller in the retropalatal (RP) region but not the retroglossal (RG) region. Such images suggest that the upper airway during sleep does not narrow as a homogenous tube. Nonetheless such images indicate that the upper airway of subjects without sleep apnea narrows during sleep. *(Reproduced with permission from Trudo FJ, Gefter WB, Welch KC, et al: State-related changes in upper airway caliber and surrounding soft-tissue structures in normal subjects. Am J Respir Crit Care Med 1998;158:1259–1270.)*

of important upper airway structures (tongue, soft palate, and lateral pharyngeal walls); and (3) modification to regional fat distribution. These factors may operate in concert or alone to increase the risk of apnea. On a chromosomal level, several disorders (Treacher-Collins syndrome, Down's syndrome, Apert's syndrome, and Pierre Robin syndrome) are associated with craniofacial and/or upper airway soft tissue abnormalities that confer increased risk of sleep-disordered breathing. In the Cleveland Family Study, inheritance patterns of sleep apnea in whites and blacks have demonstrated a recessive mode of inheritance, with a single major gene accounting for 20 percent of the variance. Absent of specific chromosomal or mendelian genetic disorders, familial clustering of OSA has been reported such that first-degree relatives of index cases with sleep apnea are significantly more likely to have SDB than first-degree relatives of controls. Furthermore, heritability of craniofacial abnormalities (retroposed mandible, inferior displaced hyoid bone) and upper airway soft tissue structure (volume of the tongue, lateral pharyngeal walls, and total soft tissue) has been demonstrated in first-degree relatives and siblings, respectively.

Heritability accounts for 40 to 70 percent of the variance in body mass index based on studies of population, twins, and adoption. Moreover, regional fat distribution also has a genetic component. The close association of obesity and OSA and the well-known genetic basis of obesity lead to the following questions. First, is the familial aggregation of OSA simply related to the genetics of obesity? Second, do both these conditions share common susceptibility genes? The former is clearly not the case based on a persistence of significant familial aggregation after controlling for BMI. The latter may be partially true, although it is unlikely that susceptibility genes for OSA are exclusively the same genes mediating obesity. The strong effect of obesity on OSA pathogenesis suggests that any genetic alteration predisposing to obesity might also be regarded as an "apnea gene."

Endocrine disorders can also be accompanied by apnea. Hypothyroidism, especially myxedema, is associated with an increased prevalence of obstructive and central sleep apnea via alteration in muscle function and blunted ventilatory response, respectively. Macroglossia associated with hypothyroidism contributes to the higher frequency of sleep-disordered breathing in this population. Sleep apnea syndrome is more common and often severe in acromegalic patients, presumably related to a large tongue narrowing the upper airway.

Alcohol, which reduces the upper airway tone, and sedatives or hypnotics, which reduce the arousal mechanism, also exacerbate OSA. Each of these risk factors needs to be considered in the assessment of a patient with OSA. It is important address why an individual has developed sleep apnea. Routine testing with fiberoptic techniques, radiological airway imaging, and thyroid function testing is not recommended for every patient. However, they should be considered in patients in whom the origin of the sleep apnea is not entirely clear.

Table 97-2

Clinical Presentation of Obstructive Sleep Apnea

Loud, habitual snoring
Witnessed apneas
Nocturnal awakening
Gasping or choking episodes during sleep
Nocturia
Unrefreshing sleep, morning headaches
Excessive daytime sleepiness
Automobile or work-related accidents
Irritability, memory loss, personality change
Decreased libido
Impotence

Clinical Presentation

The diagnosis of sleep apnea is not difficult to make and can be suggested from the history. Patients with sleep apnea complain of symptoms during the daytime and/or nighttime (Table 97-2). Although not common, patients may report difficulties falling asleep at night. Frequent nocturnal awakenings related to repetitive airway obstruction leads to sleep fragmentation. Patients may report snorting or gasping, choking, diaphoresis, and restlessness related to airway obstruction. Nocturia is fairly common and thought to be secondary to atrial naturetic peptide release in response to apnea-related right atrial stretch. A sensation of choking or dyspnea is reported in up to 30 percent of patients and may be due to increased pulmonary wedge pressure associated with enhanced right heart filling amid apneic events.

Bed partners are crucial informants of nocturnal events. A detailed history from bed partners is imperative in all cases of suspected or undiagnosed sleep apnea. Snoring is the cardinal complaint reported by the bed partner. Typically, the snoring is loud, nightly, and has existed for many years. Snoring may be so disruptive that partners may be driven to sleep in another room. A bed partner may report a witnessed apnea that is often followed by loud snorts or gasps at the end of apneic episodes. This can be extremely concerning to the partner and serve as the trigger to seek medical attention. Occasionally, during the arousal that terminates the apneic event, the bed partner may witness arm flailing, other gross movements, or strange behavior.

Repetitive apneic events are not conducive to restorative sleep. OSA patients experience a reduction in slow wave sleep (stage 3 and 4 or delta) and REM compared with normal age-matched controls due to apnea-related sleep fragmentation. Thus, individuals with sleep apnea are not refreshed upon waking in the morning. Morning headache is a less common manifestation of sleep apnea. If reported, one must consider the possibility of hypercapnia secondary to obesity-hypoventilation syndrome.

Excessive daytime sleepiness is a chief clinical consequence among patients with OSA. Typically the excessive daytime sleepiness of apneics occurs following meals, while sitting in a car as a passenger, watching television, reading, and during conversation. Driving is particularly problematic in patients with sleep apnea. It is imperative to inquire about drowsy driving. It is not only risky to the patient but also to others on the road. Such patients may report falling asleep at red lights, drowsiness while driving, and in extreme cases motor vehicle accidents. In general, daytime sleepiness directly relates to the severity of sleep apnea. A standard instrument (Epworth Sleepiness Scale) is a useful tool to assess the degree of self-rated sleepiness (Table 97-3). A value above 10 is considered abnormal. The Epworth Sleepiness Scale (scored 0–24) is usually elevated in sleep apnea patients, indicating a propensity to fall asleep. The scale has been reported to correlate with the degree of physiologic sleepiness as measured by the multiple sleep latency test if the score is greater than 16. It is important to appreciate that the presence of excessive daytime sleepiness is neither a necessary nor sufficient condition for OSA: Many patients with AHI greater than 5 do not report daytime sleepiness and many subjects report sleepiness in the absence of sleep apnea (often secondary to sleep deprivation).

Sleep apnea can also manifest symptoms related to cognitive impairment. Inattention and deficits in memory and concentration often affect ability to function at work. Fear of sleepiness may limit an individual's willingness to integrate socially. Moreover, patients with sleep apnea and/or spouses can report irritability, depressive symptoms, and personality change. Sexual dysfunction, either decreased libido or impotence, is a common complaint for men.

Physical examination of the patient with suspected OSAS focuses on neck circumference, obesity (BMI greater than 28 kg/m^2), visualization of the pharynx to assess crowding, and soft tissue dimension (enlargement of the tongue, tonsils, lateral peritonsillar tissue, uvula, and palate), abnormalities of the shape and size of the craniofacial structures (retrognathia, micrognathia, cross-bite, narrowing of the hard palate, and dental malocclusion), and measurement of blood pressure. Neck circumference greater than 40 cm predicts OSA with a sensitivity of 61 percent and specificity of 93 percent, regardless of gender. In a historical cohort analysis of 422 subjects presenting to a sleep clinic, anatomic abnormalities were assessed by physical examination using predefined criteria. Analysis showed increased risk of OSA in patients with lateral narrowing of the airway (odds ratio equals 2.5; 95 percent confidence interval 1.6 to 3.9), tonsillar enlargement (odds ratio 2.0; 95 percent confidence interval 1.0 to 3.8), and enlargement of the uvula (odds ratio equals 1.7; 95 percent confidence interval 1.2 to 2.9).

Table 97-3

Epworth Sleepiness Scale

In contrast to just feeling tired, how likely are you to doze off or fall asleep in the following situations? (This refers to your usual life in recent times. Even if you have not done some these things recently, try to work out how they would have affected you.) Use the following scale to choose the most appropriate number for each situation:

0 = Would never doze
1 = Slight chance of dozing
2 = Moderate chance of dozing
3 = High chance of dozing

Situation	Chance of dozing
Sitting and reading	_____
Watching TV	_____
Sitting inactive a public place (i.e. a theater or a meeting)	_____
As a passenger in a car for an hour without break	_____
Lying down to rest in the afternoon when circumstances permit	_____
Sitting and talking to someone	_____
Sitting quietly after lunch without alcohol	_____
In a car, while stopping for a few minutes in traffic	_____

Source: Johns MW: A new method for measuring daytime sleepiness: The Epworth sleepiness scale. Sleep *14:540–545, 1991.*

Screening for Sleep Apnea

Inexpensive tools have been developed to assess the likelihood of apnea. Standardized questionnaires such as the multivariable apnea prediction (MAP) and simple tests, such as overnight pulse oximetry, have been evaluated. Three questions in the MAP pertaining to nighttime events have been shown to have excellent predictive power for the presence of sleep apnea. The three questions follow the same form. During the past month, have you had, or have you been told about, the following symptom: snoring or gasping; loud snoring; or breathing stops, choking or struggling for breath? The frequency of occurrence is indicated as follows: never (0); rarely, less than once per week (1); once or twice per week (2); three or four times per week (3); five to seven times per week (4); or don't know. The total symptom score

Table 97-4

Conditions in which Sleep Apnea Should be Suspected

Systemic hypertension
Obesity
Myocardial infarction
Cerebrovascular accident
Pulmonary hypertension
Type II diabetes mellitus
Nocturnal cardiac arrhymthmias
Driver involved in a sleep-related automobile crash
Preoperative anesthesia evaluation

is computed and then combined with age, sex, and BMI to calculate a pretest likelihood of apnea. Such questionnaires are extremely useful to screen for sleep apnea, especially when coupled with further sleep apnea questioning and measurement of neck circumference. The situations where sleep apnea should be considered in evaluating patients are outlined in Table 97-4. Questions pertaining to sleep disorders should be performed in the review of systems of all patients.

Oximetry (Fig. 97-10) also can be used to screen for sleep apnea. Typically, patients with sleep apnea manifest a sawtooth pattern on nocturnal oximetry. However, overnight oximetry does not detect apneas, hypopneas, or arousal in the absence of significant oxygen desaturation, rendering the sensitivity of the test suboptimal. In addition, it has been shown that abnormal ambulatory overnight oximetry testing based on initial suspicion by general internists frequently does not lead to a sleep medicine referral or patient visit in the sleep clinic.

DIAGNOSIS

The diagnosis of OSA is established by polysomnography, i.e., a sleep study. Four types of polysomnography (PSG) based on supervision and diagnostic equipment can be employed. An "attended PSG," a level I study, records the following variables while the subject is asleep: electroencephalogram (EEG) to monitor sleep states, electrooculogram (EOG) for monitoring eyes, electromyogram (EMG) for muscle tone (all three of these variables help to distinguish REM [muscle atonia, rapid eye movements, saw tooth waves on the EEG] from NREM sleep); respiratory airflow by nasal probe and differential pressure transducer; respiratory effort (e.g., by bands placed around the chest and abdomen); arterial oxygen saturation; and EMG of the anterior tibialis muscles to monitor for the presence of periodic leg movements during sleep (Fig. 97-11). Measurements obtained from such instruments are integrated to record sleep stage and the presence of apneas, hypopneas, and snoring-related arousals. The AHI is calculated from the number of apneas plus hypopneas per hour. Level II and III studies are unattended studies and are

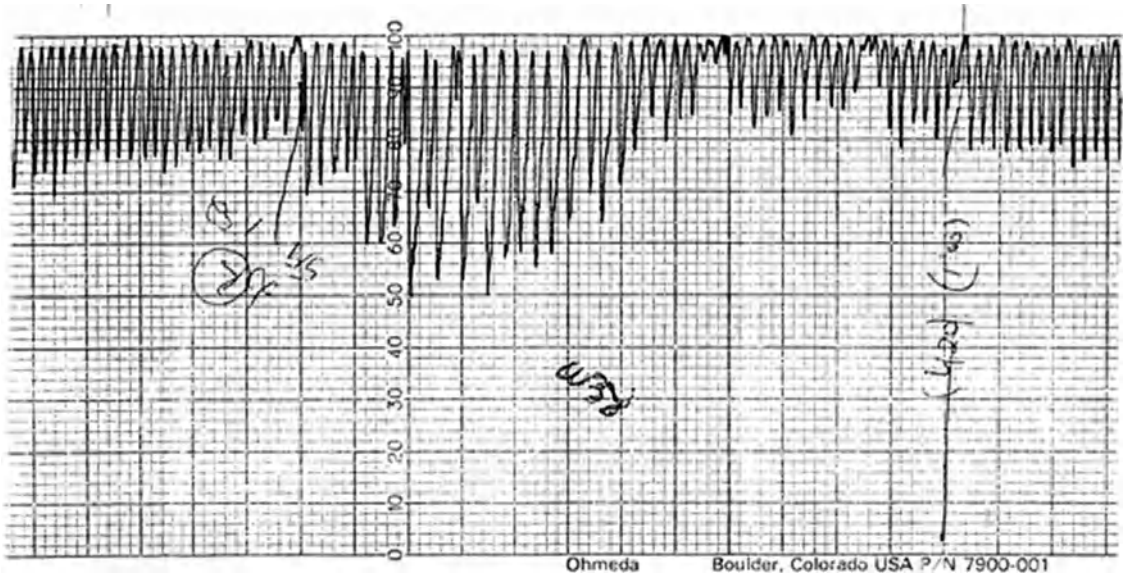

Figure 97-10 Nocturnal oximetry pattern in a patient with obstructive sleep apnea. This patient manifests recurrent oxyhemoglobin desaturations which are most severe in REM sleep. Oximetry calibrated from 0 to 100 percent. Paper speed each small line one minute; each dark black line 5 minutes.

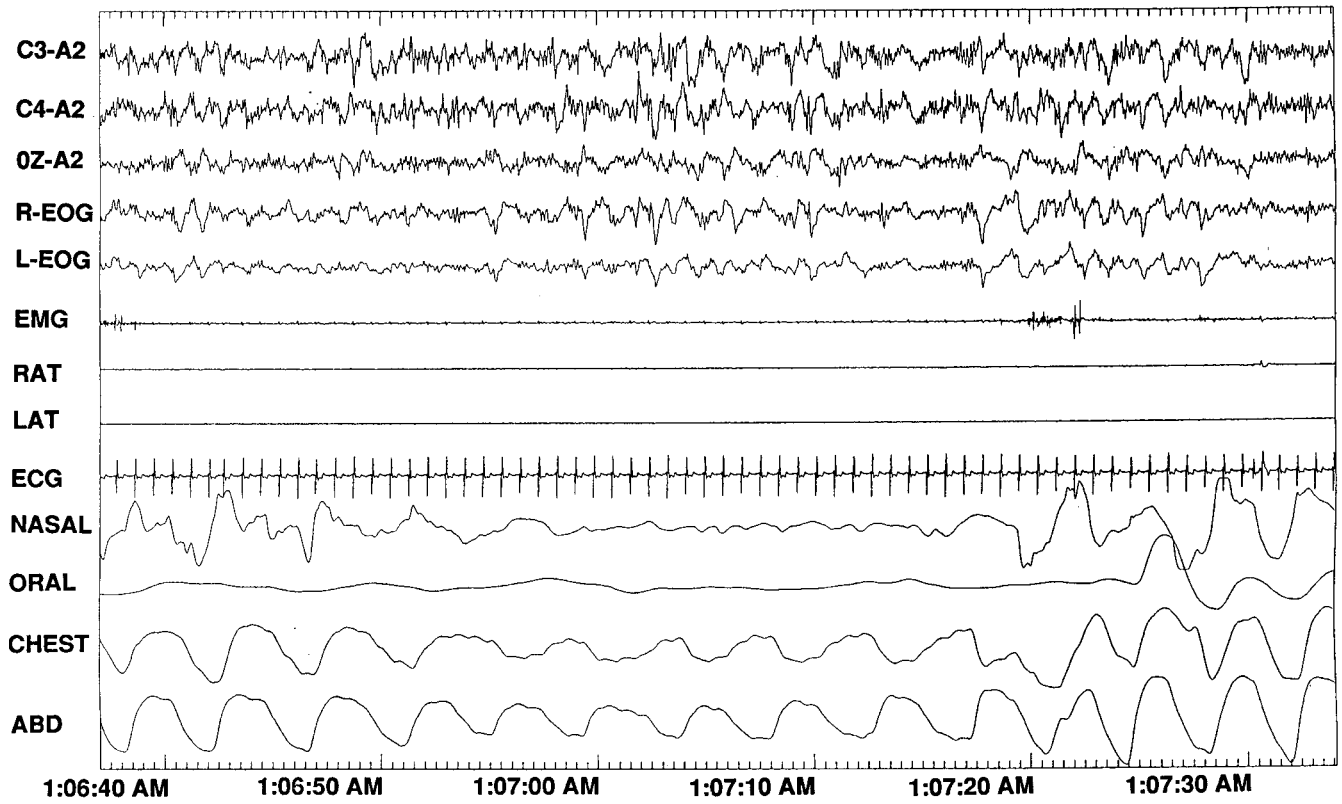

Figure 97-11 Example of an obstructive apneic episode in a patient with sleep apnea syndrome in stage 2 sleep. The polysomnography traces from the top down are as follows: three EEG channels (C3-A2, C4-A2, OZ-A2); two EOG channels (R and L); submental electromyogram (EMG); right and left anterior tibialis EMG (RAT, LAT), electrocardiogram (EKG); nasal and oral airflow; chest and abdominal motion (chest & abd). During the apneic episodes, there is abnormal airflow (both oral and nasal) with paradoxical motion of the rib cage and abdomen. At the end of the apneic episode there is a burst of EMG activity at the arousal. Following the arousal, respiration resumes with synchronous movements of the rib cage and abdomen.

differentiated by the number of variables measured. The former is a complete non-attended home study and measures the same parameters as a level I study. The latter is a partial home study that typically includes measurement of airflow, respiratory effort, pulse, and sleep position. No information is available on sleep staging; therefore, stage-related events are not detectable. A level IV study is a very limited home study that may measure only one or two parameters, such as pulse rate and oximetry.

A typical diagnostic polysomnogram (PSG) entails a whole night of recording during sleep. Patients found to have sleep apnea return on a subsequent night for a second sleep study during which the level of CPAP (continuous positive airway pressure) necessary to abolish SDB events is determined by titration. A "split night" study combines the diagnostic and treatment studies into one night (Figs. 97-12 and 97-13). The scientific rationale for split-night polysomnography is that the AHI in the first half of the night is indicative of the whole night of study; in addition, split-night studies are more cost effective and efficient than two-night studies. The evidence assessing the split-night strategy is comprised predominantly of case series and case control studies in severe OSA patients. Based on this current evidence, split-night polysomnography appears to be a legitimate alternative to full-night titration studies in specific settings. Patients with a high pretest probability for OSA are more likely to be accurately diagnosed and titrated with a split-night study, especially if greater than 3 hours of sleep are recorded. An absence of REM sleep and/or less than 3 hours of sleep recorded during a split-night study can lead to significant underestimation of sleep apnea severity. Split-night polysomnography is effective in approximately 78 percent of patients. Certain patients may require a second night study to optimize CPAP therapy. Concerns over suboptimal CPAP titration and poorer CPAP adherence, due to reduced contact with sleep staff, have been expressed with regard to split-night studies.

To increase patient access and reduce costs related to diagnosis, portable polysomnography has been designed so that studies may be performed unattended in the patient's home. Many investigators have reported comparable results with portable studies to "in-lab" polysomnography. However, specific comparisons between in-lab and portable studies are difficult because of variation in definition of events, parameters measured, and threshold of events to diagnose sleep apnea. The portable monitor often

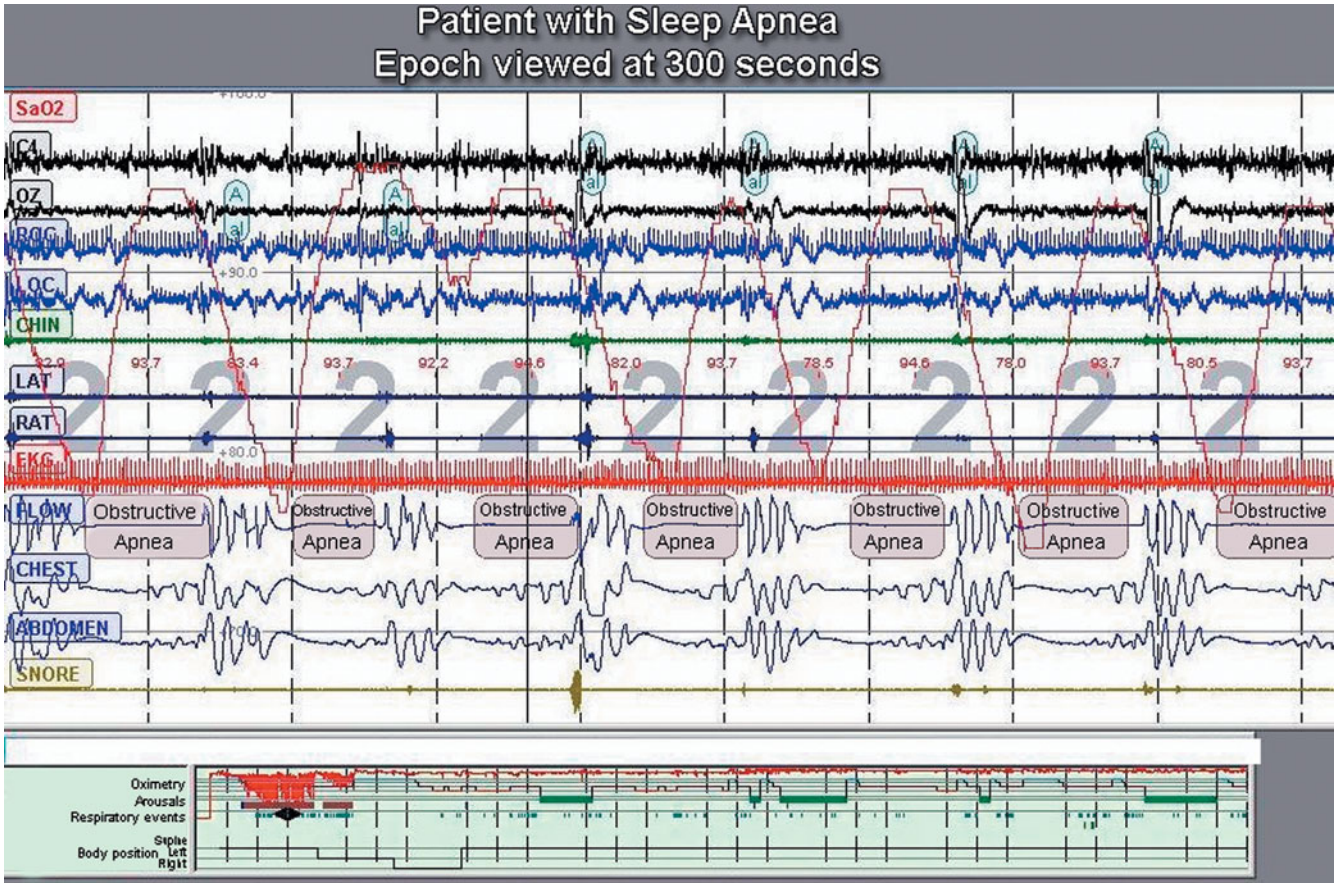

Figure 97-12 Example of a sleep study epoch from a split night sleep study in a patient with severe apnea. The epoch is viewed at 300 seconds. This patient has recurrent apneic events associated with oxyhemoglobin desaturations (recurrent dips in the red line). At the bottom of the figure is a hypnogram displaying the sleep data from the entire night. The black arrow in the hypnogram shows the time frame for the specific epoch displayed in the top portion of the figure. Later on in the night the patient is started on CPAP and the recurrent apneas and oxyhemoglobin desaturations are abolished (the recurrent desaturations: red lines noted in the hypnogram resolve). C4 and OZ are EEG leads; ROC and LOC are the right and left ocular leads); RAT and LAT are the right and left anterior tibialis electromyograms; Sa_{O_2} is the oximetry lead.

does not measure several elements that may be recorded by polysomnography: sleep stage, sleep position, and respiratory-related arousals. The underestimation of RERAs reduces the sensitivity of the portable study: A negative study cannot confidently exclude OSA. The American Sleep Disorder Association (ASDA) states that unattended recordings are acceptable only when the following conditions are met:

1. Clinical symptoms are severe and indicative of sleep apnea, and the initiation of treatment is urgent and standard polysomnography is not available.
2. The patient cannot be studied in the sleep laboratory.
3. Recordings are intended for follow-up studies in which the diagnosis has been previously established and therapy has been initiated.

Although unattended studies (levels II and III) may prove to be cost effective and more patient friendly, Medicare and Medicaid do not recognize portable systems as legitimate means of testing at this point in time, even though some health maintenance organizations have begun to recognize these portable monitoring systems in their diagnostic algorithms. Many different portable monitoring devices are available; however, a majority has only been validated in patients with a high pretest probability of sleep apnea. Most devices correlate closely with in-lab polysomnogram findings, although concerns about misclassification and failure in detecting sleep apnea have been reported.

In-lab polysomnography represents the gold standard for diagnosing sleep apnea. However, excessive focus on the significance of elevations in AHI to diagnose OSA hampers the assessment and diagnosis of such patients. Patients may exhibit similar AHI, but experience dramatically different quality of sleep and outcomes. Oxygen desaturation, number of arousals, and apnea/hypopnea length are examples of other important variables not reflected by the AHI. Furthermore, it is not the AHI itself but the consequences (hypertension, myocardial infarction, stroke, cardiac arrhythmias, excessive daytime sleepiness) of sleep apnea that are of paramount importance.

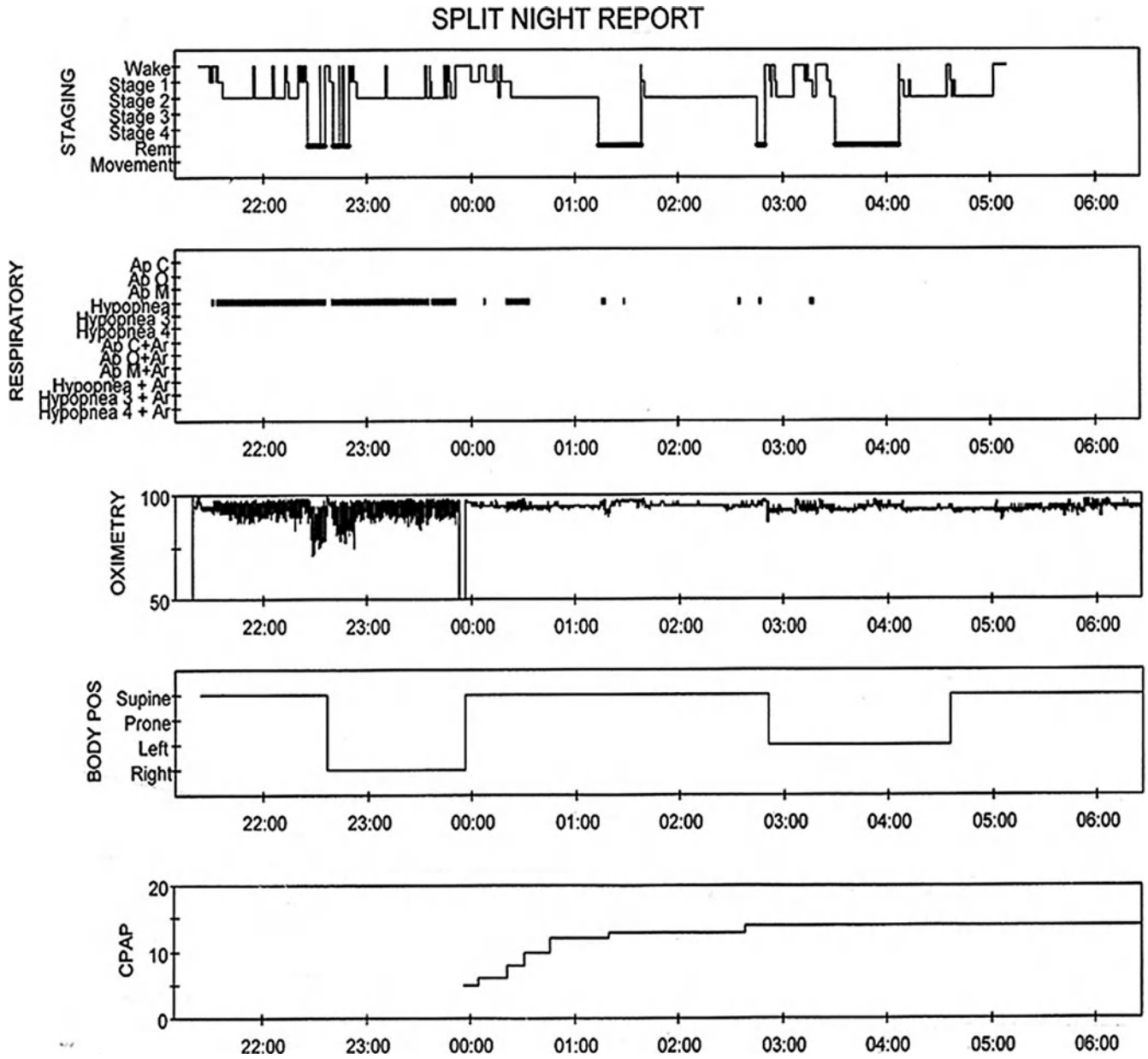

Figure 97-13 Split night hypnogram in a patient with obstructive sleep apnea. The patient has frequent hypopneas with recurrent oxyhemoglobin desaturations until he is started on CPAP at midnight. The CPAP was titrated to 14 cm H_2O, which abolished the hypopneas and oxyghemoglobin desaturations.

The AHI events can be stratified by a subject's position of sleep and stage of sleep (NREM vs. REM). In general, obstructive events are most severe in the supine position and during REM sleep. REM-related apnea is common in premenopausal women.

CONSEQUENCES OF SLEEP APNEA

The number of recognized associations with sleep apnea has increased considerably and can be categorized broadly into neurocognitive and cardiovascular consequences. Fig. 97-14 is a simplified representation of three principal disturbances associated with apnea during sleep, the proposed downstream pathophysiological mechanisms, and reported clinical consequences. We acknowledge that this is not a complete depiction of all that is known, and that many factors operate in a complex interplay that can jointly augment health risk. For instance, hypertension is known to increase the risk of stroke and coronary artery disease. In addition, hypoxia and compromised breathing efforts during apnea are also believed to be stimuli for arousal from sleep. Nevertheless, the scheme provides a basic framework for the reader to understand the operative sequelae of apneic events and how they may interact.

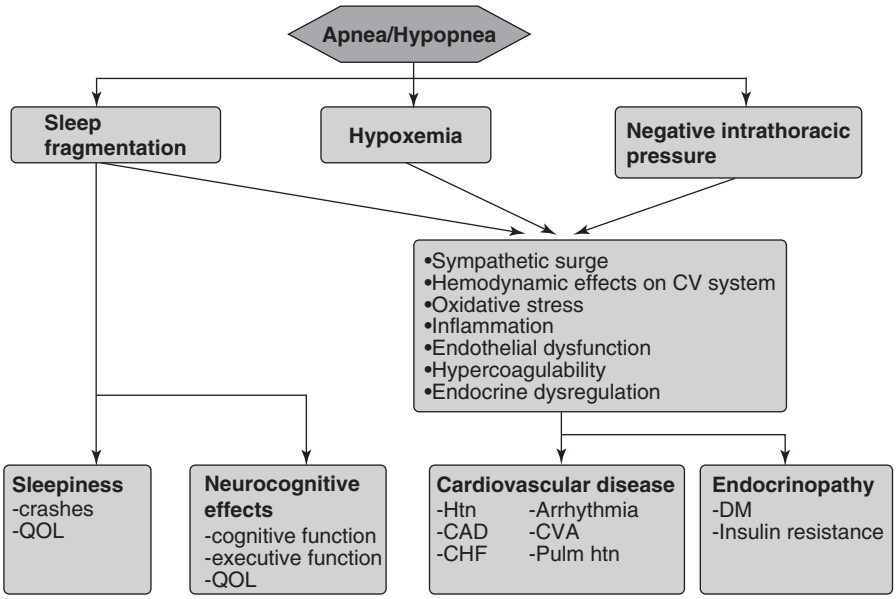

Figure 97-14 Flow chart of the proposed pathophysiologic mechanisms and consequences of obstructive sleep apnea. *Abbreviations:* CV, cardiovascular; QOL, quality of life; Htn, hypertension; Pulm htn, pulmonary hypertension; CHF, congestive heart failure; CVA, cerebrovascular accident; DM, diabetes mellitus.

Neurocognitive Consequences of OSA

Excessive daytime sleepiness and sleep fragmentation associated with sleep apnea lead to diminished cognitive function affecting attention/alertness, learning and memory, and executive function. Such adverse effects lead to a poorer quality of life as revealed by general instruments, such as the Short Form-36. Treating such patients is associated with improvement in vitality using the SF-36.

A dramatic consequence of sleep apnea and its associated daytime sleepiness is the increased risk of motor vehicle accidents. A recent meta-analysis reported the average odds ratio for subjects with sleep apnea syndrome for having a crash at 2.5. Sleep apnea patients have been shown to be as impaired in driving skills as are those with blood alcohol concentrations in excess of legal limits. These findings raise important issues for practitioners in deciding about driving safety. A majority of the United States lacks explicit laws stating that such patients should be reported to the department of transportation. Texas, California, and all Canadian provinces require physicians to notify state motor vehicle authorities of patients diagnosed with sleep apnea. It is unclear if such a reporting system will have the desired effect of reducing crashes or whether it will discourage persons with sleep apnea from seeking treatment for fear of losing their drivers' license. The ATS (American Thoracic Society) recommends that patients be reported to their state department of transportation only if they have been involved in a motor vehicle accident caused by falling asleep at the wheel or if they refused treatment for sleep apnea. Documentation of appropriate counseling to patient about the dangers of driving is also recommended. Transfer of responsibility to the patient is imperative after recommendations for treatment and safe driving practices have been undertaken.

Cardiovascular Consequences of OSA

A number of cardiovascular consequences of sleep apnea have been reported. These are discussed individually, although they share common and complex pathophysiology. Obstructive apneas result in intermittent but recurrent hypoxia, repetitive arousal, and large swings in pleural pressure. These processes lead to an array of maladaptive mechanisms: sympathetic surges, oxidative stress, inflammation, vascular endothelial dysfunction, metabolic dysregulation, and mechanical effects on the heart and vessels. Each of these physiologic responses to apnea has been the focus of detailed research and requires further reading beyond the scope of this chapter. Nevertheless, it is evident that sleep apnea can induce physiological processes that are conducive to the development of cardiovascular disease. Markers of inflammation such as tumor necrosis factor-α and C-reactive protein are also elevated in OSA. Overall, currently available literature supports a strong relationship between sleep apnea and cardiovascular disease.

Hypertension

Data for the cardiovascular risk of OSA are most compelling for systemic hypertension. A canine model of sleep apnea demonstrated that intermittent occlusion of a tracheostomy leads to the development of hypertension. Large cross-sectional studies have showed that OSA is associated with hypertension. In the Sleep Heart Health Study, the odds ratio for the presence of hypertension in the highest category of AHI (greater than 30 events/hour) was 1.37 compared with the lowest category AHI (less than 1.5 events/hour). The Wisconsin Sleep Cohort Study, a prospective population-based study conducted by Peppard et al., demonstrated an

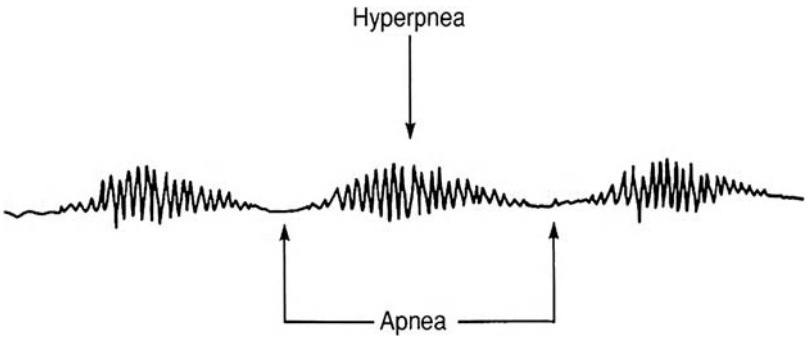

Figure 97-15 Example of Cheyne-Stokes respiration, a pattern of periodic breathing in which intervals of hyperpnea alternate with intervals of apnea. Respiration waxes and wanes in a crescendo-decrescendo pattern. Normally the hyperpneic phase of Cheyne-Stokes respiration is longer than the apneic phase.

increased risk of incident hypertension in patients with OSA, even at low levels of severity (AHI 5–15 events/hour). Independent of BMI, the odds ratio was 2.0 for mild (AHI 5–15 events/hour) and 2.9 for more severe sleep apnea (AHI greater than or equal to 15 events/hour) over a 4- to 8-year follow-up period.

The prevalence of sleep apnea is high in patients with drug-resistant hypertension. Logan studied subjects with hypertension who were all taking optimal doses of at least three antihypertensive agents and found an OSA prevalence of 83 percent, with a mean AHI of 25 events per hour. There are also data showing improvements in blood pressure in randomized trials with CPAP. In these studies blood pressure was significantly lowered not only in patients with resistant hypertension, but also in patients with relatively mild hypertension. Two randomized placebo-controlled trials in which placebo consisted of subtherapeutic levels of CPAP, demonstrated that several weeks to months of CPAP resulted in a significant reduction in daytime blood pressure between 1.3 to 5.3 mmHg. This may appear to be a modest improvement; however, drawing upon literature using conventional antihypertensive agents in the non–sleep apnea population, a 5 mmHg drop in diastolic blood pressure is associated with a 42 percent reduction in stroke and 14 percent reduction in coronary artery disease within a 5-year period. The beneficial effects of CPAP on hypertension, however, should not detract from emphasis on conventional pharmacologic methods of lowering blood pressure.

Other Cardiovascular Consequences of Sleep Apnea

A number of cardiovascular outcomes are adversely affected by sleep apnea. The Sleep Heart Health Study, a study of approximately 6000 subjects, demonstrated that the presence of OSA (AHI greater than 11 events/hour) was associated with a 2.39 odds ratio ($p = 0.002$) for congestive heart failure, 1.27 ($p = 0.004$) for coronary artery disease, and 1.58 ($p = 0.03$) for stroke. The Nurses Health Study demonstrated that self-reported snoring at baseline was an independent risk factor for the development of coronary artery disease 8 years later, after controlling for confounding variables. Marin and associates reported data from a non-randomized controlled observational study of sleep clinic subjects and a community sample of healthy subjects without OSA with a mean follow-up 10 years. Untreated severe (AHI greater than or equal to 30 events/hour) OSA patients had a 2.9-fold increased rate of fatal cardiovascular events after adjusting for confounding variables. Gami reports an alteration in the day-night pattern of sudden cardiac death in individuals with obstructive sleep apnea, i.e., more deaths occurred at night from midnight to 6 AM as compared with the general population. In fact, the risk of sudden death was increased with increasing severity of sleep apnea; individuals with an AHI greater than pr equal to 40 events/hour were more than 2.5 times more likely to experience sudden cardiac death during these nighttime hours than those without OSA.

OSA is also associated with systolic and diastolic heart failure. Among CHF patients with diastolic dysfunction and preserved systolic function, OSA was found in 35 percent of subjects. Cheyne-Stokes respiration (Fig. 97-15) and central sleep apnea (CSA-CSR) is a less common form of sleep-disordered breathing usually demonstrated in patients with congestive heart failure. Cheyne-Stokes respiration (CSR) is characterized by periodic breathing in which apnea and hyperpneas alternate with ventilatory periods. Sympathetic neural drive is increased when compared with heart failure patients without CSA. CSA occurs as a result of CHF-related fluctuation in alveolar ventilation, changes in sleep state and hypoxemia. Such physiologic circumstances lower the Pa_{CO_2} below a highly sensitive apnea threshold leading to breathing cessation that persists until Pa_{CO_2} rises above the threshold required to stimulate breathing. This is typically 4 to 5 mmHg above normocapnia. CSR-CSA is important, as it has been shown to be associated with poorer outcome in CHF patients. It should be noted that the prevalence of CSA is less now than in the past. This is most likely related to the relatively recent widespread use of beta-blocker agents in the management of heart failure patients.

Sleep apnea is also associated with arrhythmias. A majority of the arrhythmias are benign (bradycardia/tachycardia [bradycardia during the apnea and tachycardia during the arousal], atrial and ventricular ectopy), especially if the cardiac substrate is normal. However, all types of cardiac arrhythmias (e.g., heart block, nonsustained ventricular tachycardia, atrial fibrillation) have been reported. Data from the Sleep Heart Health Study have shown that patients with OSA had a higher prevalence of non-sustained ventricular tachycardia, complex ventricular ectopy, and atrial fibrillation. Using a validated screening tool, a high prevalence of OSA in patients

with atrial fibrillation has been reported. These results support an earlier study by that showed higher 1-year recurrence rates of atrial fibrillation in untreated OSA patients compared with subjects who were treated with CPAP.

OSA is common in patients who suffer a stroke, with a prevalence of 60 to 80 percent. The largest trial examining the relationship demonstrated that those subjects with an AHI greater than 11 events/hour were 1.58-fold more likely to have reported a history of stroke compared with those with an AHI less than 1.4 events/hour. More recently, an observational cohort study that excluded subjects with prior history of stroke or myocardial infarction, reported that OSA patients had a statistically significant increased risk (hazard ratio, 1.97; 95 percent confidence interval) for stroke or death, after adjusting for demographic and vascular factors.

Investigations of OSA patients at night have demonstrated elevations of transmural pulmonary artery pressure at the termination of apneas. The mechanisms postulated are hypoxia, hypercapnia, and intrathoracic pressure swings related to apnea. Therefore, the question is: Do nighttime elevations lead to pulmonary hypertension in the daytime? Pulmonary hypertension has been reported to be a complication of OSA, although studies are disparate with respect to their inclusion criteria. In general, patients with OSA and pulmonary hypertension tended to be older, heavier, and have worse lung function compared with patients with OSA and without pulmonary hypertension. A majority of studies employ a lower threshold (mean pulmonary artery systolic greater than 20 mmHg) for diagnosis of pulmonary hypertension, thereby overestimating the true association. Sleep apnea appears to be associated with, at worst, mild daytime pulmonary hypertension. However, in patients with pulmonary hypertension sleep apnea needs to be investigated since the nocturnal hypoxemia associated with the apneas can exacerbate the pulmonary hypertension. Treatment of OSA with CPAP likely is associated with a decrease in pulmonary artery pressures, but randomized trials need to be performed to confirm this.

Finally, the relationship between SDB and metabolic derangements such as insulin resistance has received increasing attention. A ninefold increase in the prevalence of metabolic syndrome has been reported in OSA subjects compared with controls. A subgroup matched by BMI with controls demonstrated an approximately 40 percent absolute increase in the prevalence of metabolic syndrome ($p < 0.001$). OSA and the metabolic syndrome share common pathophysiologic profiles; OSA is associated with disturbance in all of the main components of the metabolic syndrome: central obesity, hypertension, insulin resistance, and dyslipidemia. The relationship, whether synergistic or one syndrome leading to the other, remains to be clarified. However, considerations of OSA as a fifth component of the metabolic syndrome merit future work.

Type II diabetes has been associated with sleep apnea also. Several cross-sectional and case-controlled studies report an association between SDB and the development of diabetes. Treatment with CPAP has not uniformly been shown to improve glucose tolerance or insulin resistance. Although these studies suggest an association, the question remains whether diabetes is a cause and/or consequence of SDB.

CPAP therapy for OSA patients has been examined in multiple studies for various cardiovascular disorders. Intervention trials employing CPAP have shown improved outcomes with respect to hypertension, left ventricular ejection fraction, diastolic dysfunction, cardiovascular events, and mortality. Further supporting evidence can be derived from improvements in serum markers, such as C-reactive protein and interleukin-6, which have been associated with cardiovascular morbidity.

Economic Consequences of OSA

Sleep apnea poses a sizeable economic burden on society. It is a common condition, under-recognized and under-treated. OSA subjects have been demonstrated to utilize health care resources at approximately twice the rate of controls as far back as 10 years prior to diagnosis. Estimates of the total economic cost that sleep apnea confers upon society are sparse, however, a recent analysis estimated the burden of sleep disorders in the United States to be $109 billion based on a US population of 293 million in 2004.

Limited numbers of sleep laboratories, sleep physicians, and sleep technologists coupled with cost of equipment and reimbursement issues have created a "bottleneck" effect in which global demand for sleep medicine services exceeds capacity. Nevertheless, cost-effective ratio analysis by Ayas shows that addressing diagnosis and treatment of sleep apnea is economically attractive.

TREATMENT

First-line therapy for sleep apnea syndrome remains medical. The medical treatment options are listed in Table 97-5.

Table 97-5

Medical Treatment of Obstructive Sleep Apnea

General measures
Avoidance of alcohol, sedatives, and hypnotics
Weight loss
Specific measures to increase upper airway caliber
Position therapy
Positive airway pressure
CPAP
Bilevel systems
Auto-CPAP
Oral appliances

General Measures

Patients with sleep apnea should avoid alcohol, sedatives, and hypnotics. Alcohol and benzodiazepines reduce upper airway muscle tone and increase the severity of snoring and apneas. Hypnotics and sedatives also depress the arousal mechanisms, thereby prolonging the apneas and causing greater oxygen desaturations.

Maintaining a consistent bedtime and wake-up time as part of good sleep hygiene also is important in sleep apnea patients. Sleep deprivation can reduce hypoxic and hypercapnic respiratory drive and prolong apnea duration. Sleep fragmentation can be minimized by avoiding ingestion of stimulants (e.g., caffeine), alcohol, sedatives, and night exercise.

Weight Loss

Weight loss should be recommended in all overweight patients with OSA. Decreasing body weight is a logical target to reduce OSA burden but also to improve a range of health outcomes and quality of life. Weight loss theoretically mitigates the collapsibility of the airway by reducing the extraluminal pressure associated with excess soft tissue and by reducing the encroachment conferred by enlarged airway structures such as the tongue and soft palate. The extent of weight loss and degree of improvement are not always directly related, although it has been shown that a 1 percent change in weight is associated with a 3 percent change in AHI. In cases of dramatic weight loss by extreme dieting or surgery, OSA severity is improved and in some patients abolished. Dietary weight loss remains challenging; therefore, achieving and maintaining a target body weight is difficult. Bariatric surgery, as a potential treatment modality for sleep apnea, has shown impressive short-term improvement in OSA severity and should be considered in apneics with a BMI greater than 35 mg/kg^2. However, recurrences of OSA after several years have been described in the setting of only modest weight gain.

Pharmacologic Treatment

An extensive list of pharmacologic agents has been investigated with obstructive sleep apnea, including antidepressants, respiratory stimulants, central nervous system stimulants, and hormones. Most results have been inconclusive, based on the strength of data or disappointing outcomes.

Selective serotonin reuptake inhibitor agents such as paroxetine (Paxil) and fluoxetine (Prozac) have been shown to increase genioglossal muscle activity and decrease REM sleep (apneas are more common in REM), although this has not translated to a reduction in AHI in apnea patients. Protriptyline (Vivactil), an agent that decreases the amount of REM sleep, has inconsistently shown positive effects on symptoms and apnea burden. Anticholinergic side effects such as dry mouth, constipation, and urinary retention can be troublesome and limit its consideration to the occasional patient whose apnea is primarily REM related.

Several respiratory stimulants, including acetazolamide (Diamox), medroxyprogesterone (Provera), theophylline (Theo-Dur), doxapram (Dopram), and almitrine (Doxil) have been investigated. These agents are primarily centrally acting, except theophylline and medroxyprogesterone, which are arguably the most widely studied. Theophylline is reported to confer salutatory effects on the airway musculature and diaphragm at lower doses and central respiratory center stimulation at higher doses, indicating a differential effect on the respiratory system based on the dose. When compared with CPAP treatment, both theophylline and medroxyprogesterone, have demonstrated inferior efficacy. Nevertheless, many authors have reported variable improvement in apnea index with use of these agents.

Caffeine, modafinil, nicotine, and cannabinoids have been studied based on their actions on various central excitatory pathways; however, there are no data supporting improvement in apnea index.

The key point is that pharmacotherapy does not significantly improve apnea index, but several agents (hypnotics, benzodiazepines, narcotics) are well known to worsen sleep-disordered breathing. Inquiry about these medications, especially benzodiazepines, is important when evaluating patients with sleep apnea.

Oxygen Therapy

Oxygen has a limited role in the treatment of sleep apnea syndrome. Although oxygen desaturation may be mitigated by the delivery of oxygen, arousal threshold consequently may be delayed, thereby prolonging apnea and exacerbating the overall sleep fragmentation. Patients with coexisting obstructive lung disease can manifest respiratory acidosis as a consequence of supplemental oxygen. Thus, oxygen alone does not have a role in the treatment of OSA. However, it can be useful in patients who experience significant reductions in nocturnal oxyhemoglobin independent of apneas to avoid cardiovascular complications.

Nasal Dilators

External and internal nasal devices have been proposed as a treatment for snoring and sleep apnea by increasing nasal cross-sectional area and reducing nasal resistance. However, since snoring and apnea originate predominantly in the retropalatal or retroglossal region, nasal dilators are not effective in treating patients with OSA. Existing data do not support their use; however, treatment of nasal congestion symptoms with humidification and nasal steroids is important in patients who develop rhinitis associated with nasal CPAP treatment.

Specific Medical Therapies

Position Therapy

Sleep in the supine position is more conducive to airway obstruction by virtue of gravity's effect on the tongue. Polysomnography often demonstrates position-dependent sleep apnea with a high AHI in the supine position but not

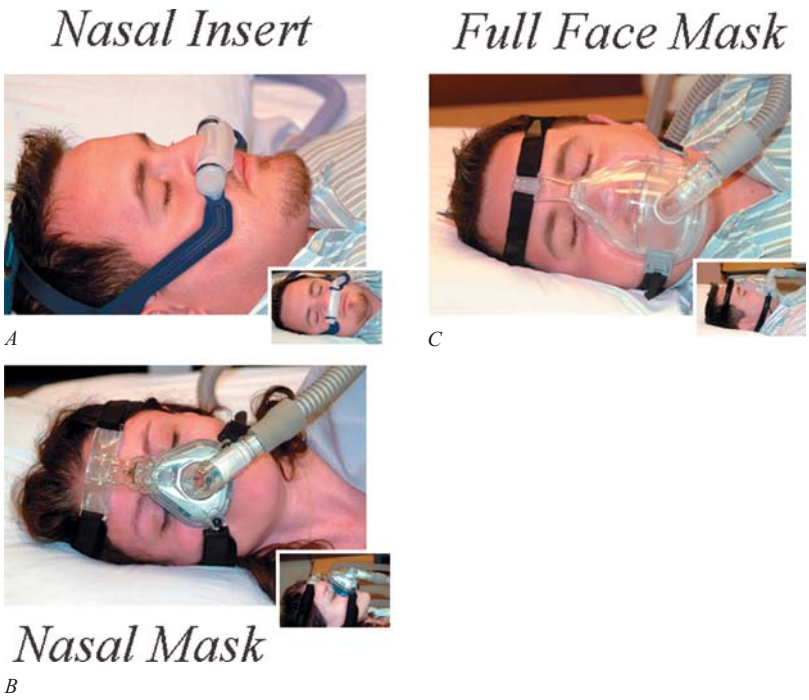

Figure 97-16 Examples of subjects connected to a CPAP unit wearing three different CPAP interfaces: *A*. the subject is wearing a nasal inserts which fit directly into the nostrils; (*B*) the subject is wearing a nasal CPAP mask; and (*C*) the subject is wearing a full face mask (nose and mouth are both covered). With all three types of interfaces it is essential to ensure a good seal with minimal leaks.

in the lateral position. For patients with position-dependent sleep apnea, symptoms may be alleviated by promoting sleep in the lateral decubitus position. This can be accomplished by sewing pockets for tennis balls to the back of night attire. Devices to train people to sleep in the lateral position have been described. Raising the head of bed angle to between 30 and 60 degrees has been studied; however, it is unclear if its effects reach beyond promoting airway stability to actually reducing AHI.

Pharyngeal Muscle Stimulation

This treatment modality is still in the developmental research stage. The strategy is to electrically stimulate the hypoglossal nerve to enhance phasic activity of the upper airway pharyngeal dilator muscles, thereby increasing airway patency during sleep. More studies need to be performed with this modality.

CPAP

Sullivan first described the use of nasal CPAP to treat OSA (see examples of subject wearing CPAP in Fig. 97-16), and it has remained the treatment of choice for patients with sleep-disordered breathing. CPAP can be applied through a nasal mask, nasal inserts, or a full-face mask (covers the nose and mouth). The full-face mask should be used in patients who breathe through their mouth during sleep. (Typically these patients complain of a dry mouth in the morning.) CPAP has the advantage of being noninvasive and has been shown to reduce the number of apneic and hypoxic episodes during sleep. It also reduces daytime sleepiness and improves neuropsychiatric function in patients with OSA. CPAP is indicated in all patients with an AHI greater than 30 events/hour and in those patients with an AHI of 5 to 30 events/hour with associated symptoms, including excessive daytime sleepiness, impaired cognition and mood disorders, insomnia, and cardiovascular disorders (hypertension, ischemic heart disease, CVA). CPAP operates by providing a pneumatic splint for the airway, thereby preventing collapse during sleep, when upper airway muscle dilator activity is reduced. The effect of CPAP on upper airway caliber and the surrounding soft tissue structures is shown in Figs. 97-17 to 97-20. CPAP increases airway caliber in the retropalatal and retroglossal regions; in particular, it increases the lateral dimensions of the airway and thins the lateral pharyngeal walls. Technologists determine the optimal pressure during a titration polysomnography. Typically, 5 to 20 cm H_2O is the pressure needed to abolish apneas, snoring, and oxyhemoglobin desaturation in all positions and during REM sleep.

CPAP is usually applied through a nasal mask or nasal pillows, which insert into the nostrils (Fig. 97-16). It is important to ensure that the patient has a well-fitting interface with the CPAP machine absent of air leaks. Mouth leaks render CPAP ineffective, since the high flow through the nose generated by the CPAP unit escapes through the mouth. In such situation, full-face masks that cover the mouth and nose can be helpful (Fig. 97-16). Heated humidity is used very frequently with the prescription of CPAP therapy. It has been shown to successfully ameliorate side effects of CPAP listed in Table 97-6, but this has not translated into uniform improvements in adherence to CPAP.

Over the last 15 to 20 years, the CPAP equipment and masks have become increasingly user friendly. The machines are smaller, portable, and quieter, and also allow data capture of patient adherence and CPAP efficiency. It is important that CPAP adherence is followed. CPAP masks have improved profoundly so the prospect of using CPAP has become much less daunting. It is important to note that patients

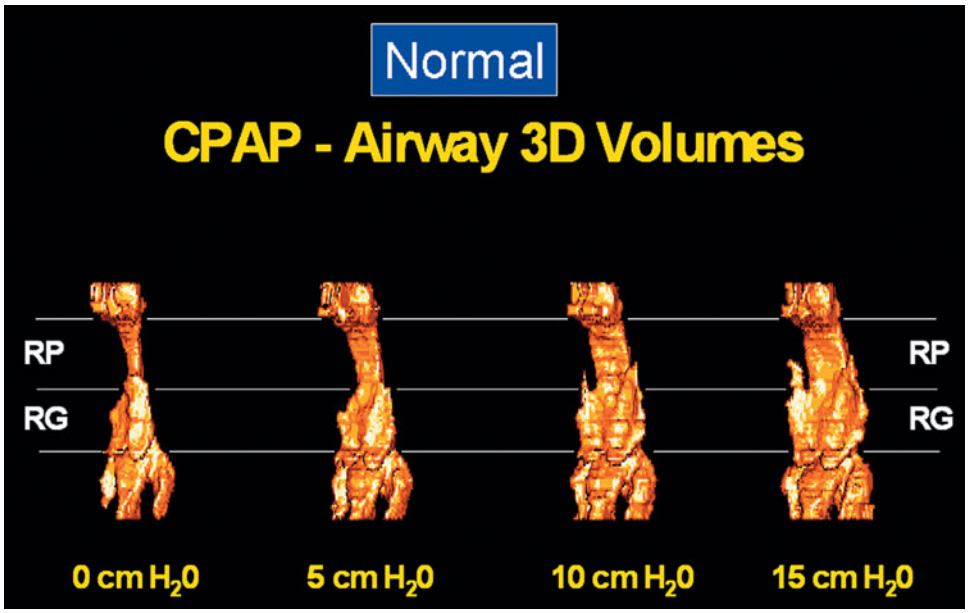

Figure 97-17 Three-dimensional surface renderings of the upper airway from magnetic resonance images in a normal subject with progressively greater continuous positive airway pressure (CPAP) (0–15 cm H_2O). Upper airway volume increases significantly in both the retropalatal (RP) and retroglossal (RG) regions with higher levels of CPAP. *(Reproduced with permission from Schwab RJ, Pack AI, Gupta KB, et al: Upper airway and soft tissue structural changes induced by CPAP in normal subjects. Am J Respir Crit Care Med 1996;154:1106–1116.)*

often have a preconceived prejudice against CPAP therapy, as they may have previously seen or used older masks. Hospital CPAP masks are often few in choice and usually of the older type.

Other strategies to improve patient comfort include the ramp device and devices that reduce pressure in expiration, such as C-flex (Respironics, Murrysville, PA) or EPR (expiratory pressure relief, ResMed Corp., Poway, CA). CPAP units with a ramp device achieve target CPAP pressures with gradual increases over 15 to 45 minutes, allowing sleep onset at a more comfortable pressure level; however, improvement in CPAP use has not been demonstrated. Furthermore, overuse of this option by repeated resetting of the ramp during the night has been reported. C-flex or EPR are algorithms designed to improve patient comfort by reducing CPAP during early exhalation. Some institutions operate "mask clinics" concomitantly with sleep clinics so that patients with OSA can be fitted for a CPAP mask immediately after the sleep

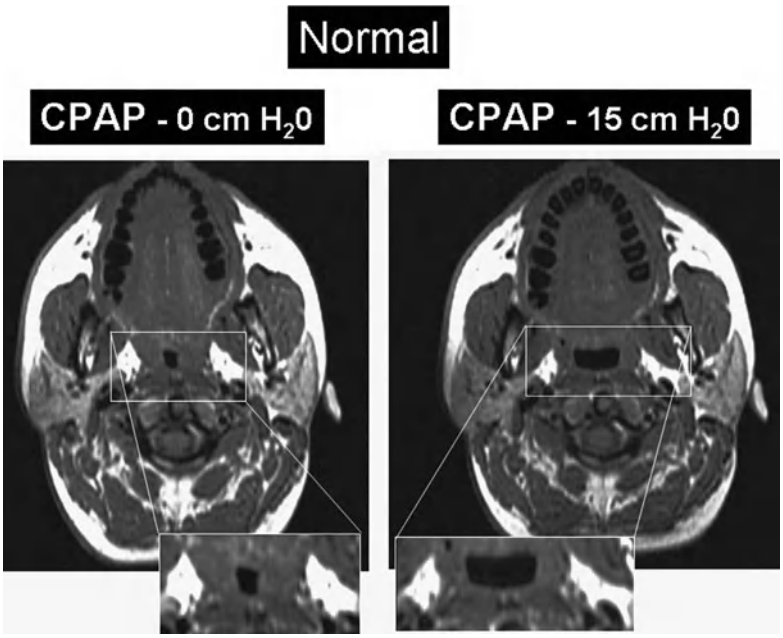

Figure 97-18 Axial retropalatal magnetic resonance imaging in a normal subject (same subject as Fig. 97-17) at two levels of continuous positive airway pressure (CPAP) (0 and 15 cm H_2O). Airway area is significantly greater at 15 cm H_2O than without CPAP. The increase in upper airway caliber with the application of CPAP is predominantly in the lateral dimension. *(Reproduced with permission from Schwab RJ, Pack AI, Gupta KB, et al: Upper airway and soft tissue structural changes induced by CPAP in normal subjects. Am J Respir Crit Care Med 1996;154:1106–1116.)*

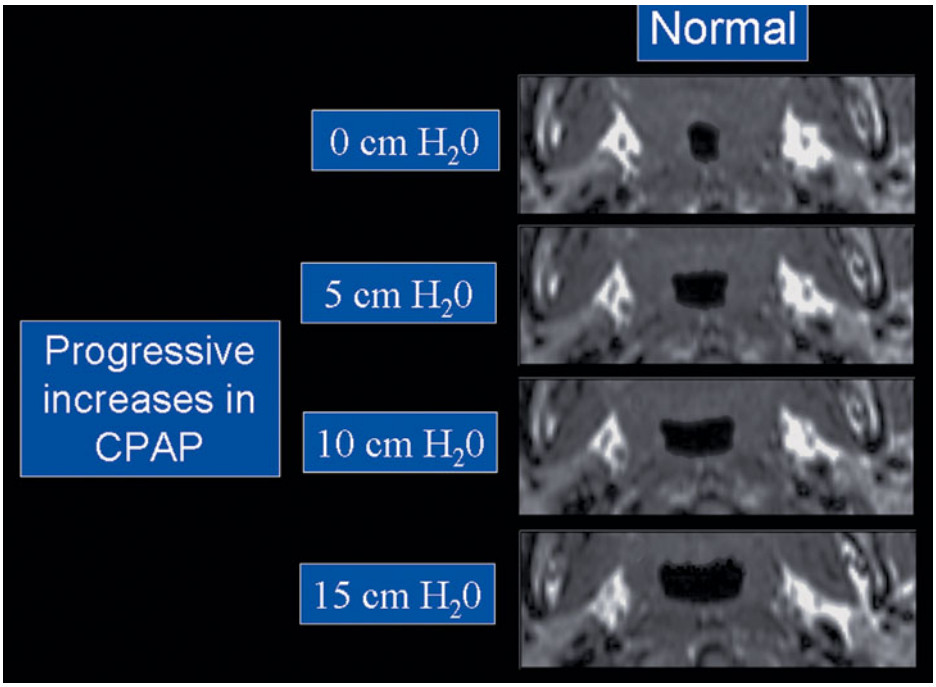

Figure 97-19 Axial retropalatal magnetic resonance imaging (MRI) in a normal subject (the same subject as in Figs. 97-17 and 97-18) with continuous positive airway pressure (CPAP) ranging from 0 to 15 cm H_2O. With increasing CPAP there is a progressive increase in the size of the upper airway, particularly in the lateral dimension (the anterior-posterior dimensions of the airway do not change significantly with CPAP). There is little movement of the parapharyngeal fat pads (white structures lateral to the airway) but progressive thinning of the lateral pharyngeal walls. *(Reproduced with permission from Schwab RJ, Pack AI, Gupta KB, et al: Upper airway and soft tissue structural changes induced by CPAP in normal subjects. Am J Respir Crit Care Med 1996;154:1106–1116.)*

specialist consultation. No outcome data are available on this emerging strategy.

CPAP use is associated with few serious side effects. Common side effects are listed in Table 97-6. Most of these side effects can be alleviated. Nasal irritation and rhinitis are treated with heated humidification and consideration of a nasal steroid spray. Claustrophobia may be relieved by in some case by changing the type of mask. Aerophagia can be ameliorated by altering body position or mask type. Serious adverse effects are uncommon but include reports of severe epistaxis, meningitis, and pneumocephalus.

Adherence to CPAP therapy is variable and ranges in most studies from 60 to 85 percent. Estimates from a number of studies suggest that patients use the treatment, on average, for 4 to 5 hours per night. Weaver et al. have reported that patterns of CPAP usage declare themselves within the first weeks

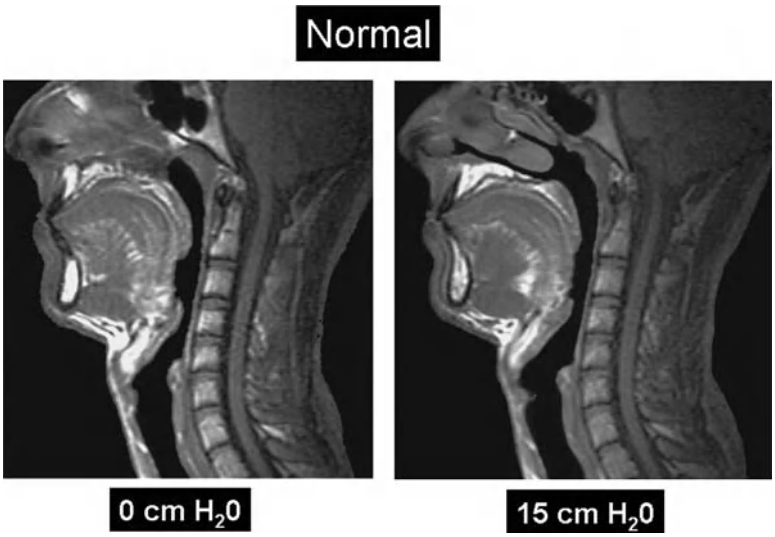

Figure 97-20 Mid-sagittal magnetic resonance imaging of a normal subject (the same subject as in Figs. 97-17 to 97-19) at two levels of continuous positive airway pressure (0 and 15 cm H_2O). There is very little increase in airway caliber with the application of CPAP since CPAP does not significantly affect the anterior-posterior structures. *(Reproduced with permission from Schwab RJ, Pack AI, Gupta KB, et al: Upper airway and soft tissue structural changes induced by CPAP in normal subjects. Am J Respir Crit Care Med 1996;154:1106–1116.)*

Table 97-6

Complications Associated with CPAP
Nocturnal arousals
Rhinitis, nasal irritation, and dryness
Aerophagia
Mask and mouth leaks (dry mouth in morning)
Facial skin discomfort
Difficulty with exhalation
Claustrophobia
Chest and back pain

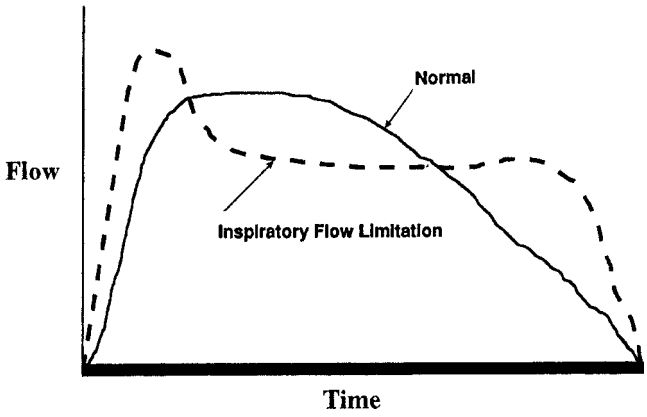

Figure 97-21 Schematic diagram showing the normal pattern of airflow during inspiration and that which occurs when there is inspiratory flow limitation. In the latter the flow quickly reaches a level that is maintained relatively constant throughout inspiration. This pattern of airflow can be detected by computers built into auto-CPAP units.

of therapy with "consistent users" (CPAP greater than 90 percent of nights per week) and "intermittent users" (skipped CPAP use 1 or more nights per week). This pattern, established in the first week, has been reported to remain stable at 1 to 3 months for both groups of patients. Reported predictors for long-term CPAP therapy include snoring history, AHI, and Epworth Sleepiness Score. Regular use in the first 3 months of CPAP therapy appears to be strongly indicative of long-term use. The appropriate CPAP dose (duration and pressure level of CPAP therapy) required for an acceptable outcome remains to be clarified. It is imperative that patients continue to be followed regularly even though they may be long-term users of CPAP. "Perceived benefit" has been shown to be a strong predictor of CPAP use; therefore, it is the health care provider's responsibility to re-emphasize this.

In addition to CPAP, positive airway pressure can be delivered via bi-level systems and automatically titrating systems. Bi-level machines may be used when patients report difficulty with exhaling against positive airway pressure. Bi-level systems allow independent adjustment of inspiratory and expiratory pressure. However, the bi-level systems are more expensive and evidence is lacking in terms of better adherence and treatment outcomes when compared with CPAP. There is limited evidence that patients with coexisting lung disease or respiratory acidosis demonstrate improved gas exchange with the use of bilevel positive airway pressure compared with CPAP.

Autotitrating CPAP, or auto-CPAP, adjusts CPAP throughout the night by detection of airway flow, snoring, apneas, inspiratory flow limitation (Fig. 97-21), and airway vibration (snoring). Each auto-CPAP unit uses a different algorithm for abolishing apneas. Currently auto-CPAP devices are used in patient homes as treatment or the sleep laboratory to determine the ideal CPAP setting to be used at home by the patient's conventional fixed-pressure CPAP unit. Popularity for their use is growing among patients and physicians since the auto-CPAP units can be used to evaluate patients who are having difficulty tolerating conventional CPAP. The auto-CPAP devices can determine the optimal CPAP setting, quantify a mask leak, and measure patient adherence. Nonetheless, patient adherence does not appear to be significantly improved with chronic use of auto-CPAP. However, the cost of one auto-CPAP unit is one-third the cost of one in-laboratory study, and investigators have reported effective therapy with empirical pressures set between 8 and 12 cm H_2O.

Intraoral Devices

Although CPAP represents the gold standard for treating OSA, many patients are intolerant of it because of the described side effects. During the last decade, increasing attention has focused on the intraoral devices as an alternative treatment to CPAP. Dentists have become more attuned and involved in the treatment of OSA, resulting in the growth of research in this field and the formation of the Academy of Dental Sleep Medicine (ADSM). From a patient perspective, based on randomized trials, the oral appliance is a reasonable option. The effectiveness compared with CPAP appears to be the central issue, particularly for patients with severe OSA. A recent report by the AASM updated recommendations for the use of oral appliances for the treatment of snoring and OSA based on the literature.

The oral appliances have undergone considerable evolution in their design, comfort, and effect on airway structures in the past three decades. The tongue retaining device (TRD) developed in the 1980s by Samelson was designed to maintain the tongue in a forward position during sleep. Two other types of devices are palatal lifting devices and mandibular advancing devices, the latter being the most studied (see example of mandibular advancing device, Fig. 97-22).

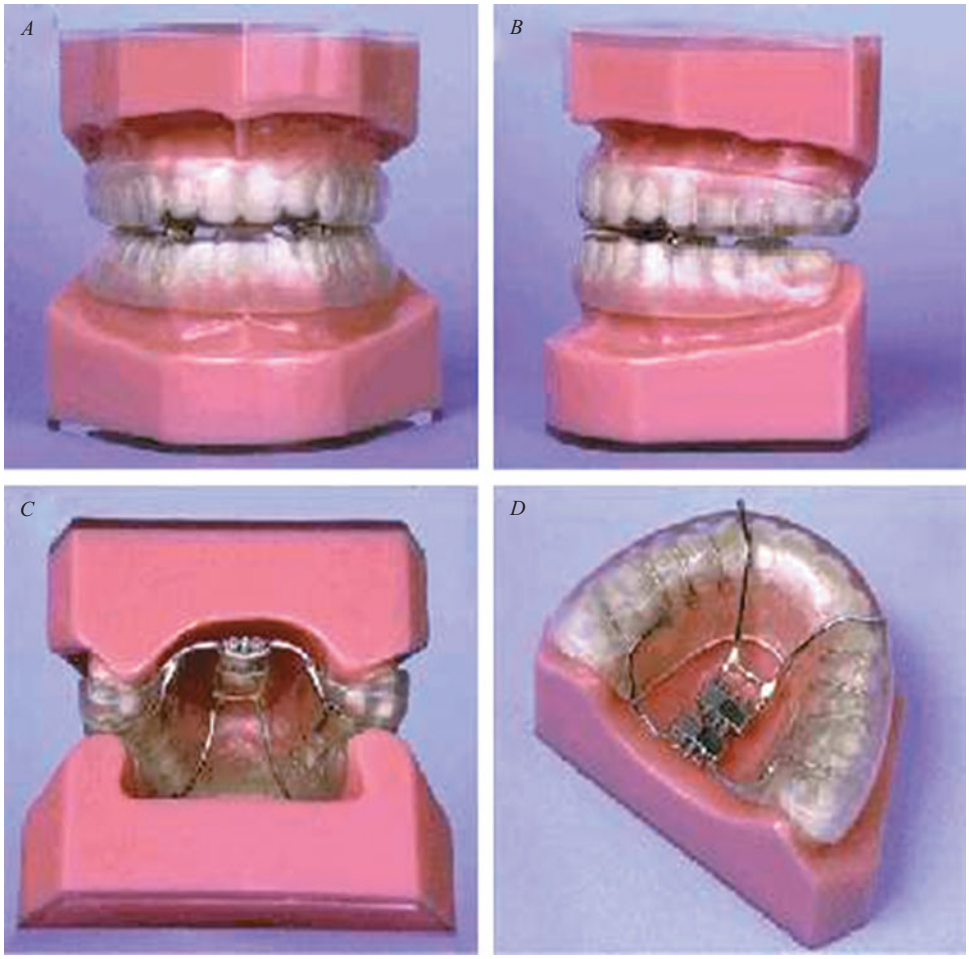

Figure 97-22 Example of an adjustable mandibular repositioning device (Klearway appliance, University of British Columbia, Vancouver, Canada). This device fits on the upper and lower teeth; it is worn during sleep and results in anterior motion of the mandible with consequent enlargement of the airway. The appliance is adjusted until the sleep disordered breathing improves.

Oral devices aim to alter the position of the upper airway structures, thereby enlarging airway caliber or reducing its collapsibility. Cephalometry has confirmed that mandibular advancing devices increase upper airway dimensions, and it has been proposed they may also increase the tone of the upper airway, thereby opposing its tendency to collapse. The devices produce downward rotation and advancement of the mandible to increase the size of the posterior airway space predominantly in the anterior-posterior orientation. However, recent studies have reported increases in the lateral dimension of the upper airway, suggesting that the biomechanical changes induced by oral appliances are complicated.

A number of devices are presently available for snoring and/or sleep apnea and only some these are approved by the Food and Drug Administration (FDA). Many devices are custom-made for the client following a dental or maxillofacial surgery consultation. In choosing an oral device, attention to its adjustability (modifiable over time), titratability (ability to alter jaw position by adjusting the appliance), and provisions for temporomandibular joint support, tooth coverage, and jaw mobility are important.

The effectiveness of oral devices on treating snoring and OSA has been investigated in a multitude of studies. In general, snoring is improved or eliminated; however, this is mostly based on subjective reporting by the bed partner. The degree of improvement in apnea is variable when assessing outcome in terms of AHI. In patients with AHI greater than 20 events/hour, a substantial percentage do not benefit at all. Approximately 50 to 70 percent of all patients with sleep apnea may respond. Response, although indicative of a significant (50 percent) decrement in AHI, does not necessarily mean abolishment of apnea. Success with these devices appears to be heavily related to attention to the adjusting and titrating of the device once in situ. Achieving adequate mandibular advancement influences the extent of improvement in respiratory events. When compared with CPAP, oral devices have demonstrated inferior outcomes, although patient adherence has been higher in many cases. Studies indicate that oral devices may provide better outcomes when compared with surgery, and therefore should be considered as a less invasive option.

Side effects of the oral devices include excessive salivation, dental misalignment, and jaw pain or damage. Jaw

pain, a consequence of muscular activation in response to mandibular repositioning, is of concern but usually subsides with time. Mandibular repositioning devices should be used cautiously in patients with temporomandibular joint syndrome.

At present, oral devices are indicated for patients with primary snoring, or mild-to-moderate OSA where weight loss and CPAP have not been viable options, and for those who are not surgical candidates. Severe OSA patients should have a trial of CPAP first based on lower success rates with oral appliances. Patients treated with an oral device are recommended to have follow-up polysomnography and dental visits.

Surgical Treatment of OSA

Nasal CPAP, as discussed, is the first-line treatment for OSA. However, tolerance of CPAP, particularly in the long term, is challenging for many patients. Weight loss, a strategy known to decrease or eliminate apnea in obese patients, is difficult to maintain. Oral appliances may not be effective or tolerated. Surgery becomes a reasonable consideration when the preceding scenarios are present or the patient presents with particular anatomic defects, such as tonsillar hypertrophy.

A variety of surgical options are available to correct abnormalities in the upper airway that lead to obstruction during sleep (Table 97-7). It is important to appreciate that opting for surgery represents a difficult undertaking. The upper airway is an extremely complex structure with a variety of soft tissue and bony structures contributing to the overall airway morphology. The upper airway not only facilitates exchange of gas between the lungs and atmosphere, but is also crucial in the functions of speech and deglutition. Alterations in airway structure, by nature of surgery and its associated inflammation and scarring, can alter the ability of the airway structures to maintain these vital functions. Therefore, selecting the appropriate sleep apnea patient and suitable surgical approach are critical.

Table 97-7

Surgery for Obstructive Sleep Apnea
Nasal surgery (septoplasty, sinus surgery, and others)
Tonsillectomy ± adenoidectomy
Uvulopalatopharyngoplasty (UPPP)
Laser assisted uvulopalatoplasty (LAUP)
Radiofrequency volumetric tissue reduction
Linguaplasty
Genioglossus and hyoid advancement (GAHM)
Sliding genioplasty
Maxillo-mandibular advancement osteotomy
Tracheostomy

Selection of a suitable candidate can be achieved through evaluations examining clinical, fiberoptic, and radiologic information. Height, weight, and neck circumference are thought to influence the surgical outcome. Physical examination of the head and neck region is often supplemented with nasopharyngolaryngoscopy to assess for anatomic abnormalities such as deviated nasal septum, turbinate hypertrophy, palatal/uvula elongation, tonsillar enlargement, and enlargement of the tongue/lateral walls. Craniofacial abnormality, such as retrognathia and narrowing of the hard palate, should also be noted on examination. The use of the Muller maneuver (voluntary inspiration against a closed mouth and obstructed nares) permits visualization of the upper airway structures during a simulated apneic event. CT and MRI can also be employed to provide detailed information about structural dimensions preoperatively and postoperatively. Lateral cephalography offers a less costly imaging technique to provide information concerning craniofacial structures prior to and after upper airway surgery.

The leading objectives for presurgical evaluation are to identify the primary site of obstruction (although obstruction may not be in only one site) and assess the risk of surgery and anesthesia. Compromise of the airway in the perioperative period is potentially a serious complication. Sedatives (e.g., benzodiazepines), opioid analgesics, inhalation anesthetic agents, and propofol are examples of medications commonly used in the pre-, peri or postoperative period that inhibit upper airway muscle activity and can worsen sleep disordered breathing. Tracheal intubation may prove challenging by virtue of the anatomical features of apneic subject's pharyngeal configuration (patients with sleep apnea usually have a high Mallampati score, making intubation difficult). The supine position during surgery potentiates airway obstruction secondary to the effect of gravity on the tongue and soft palate position. In addition, surgery of the upper airway may compromise the upper airway caliber due to edema, hematoma, and inflammation.

The postoperative transitioning period when a patient emerges from general anesthesia, and is extubated requires extra vigilance in OSA patients. Residual effects of neuromuscular blockade and sedatives, and ongoing postoperative narcotics for pain are capable of compromising airway patency. CPAP should be immediately available postoperatively and used in the postoperative period. Regular CPAP therapy should be strongly emphasized along with an instruction to bring patient's own CPAP equipment into the hospital.

The level of obstructive site influences the type of surgical procedure to be performed (Table 97-7). Fiberoptic laryngoscopy or imaging can be used to classify the obstruction of the airway at the oropharyngeal (type I), oropharyngeal

and hypopharyngeal (type II), and hypopharyngeal (type III) levels.

Surgical Approaches

UPPP is the most common surgical procedure for adult OSA. It was introduced into the United States in 1981 by Fujita and colleagues. UPPP entails removal of excessive mucosa and tissue from the palate and palatopharyngeal arch. The underlying musculature of the palate is left intact, and uvula is shortened or amputated. The tonsils, if present, are removed at the time of this procedure, and the remaining mucosa is trimmed and sutured together. The overall aim is to widen the oropharyngeal aperture. Successful treatment is reported in only approximately 40 to 50 percent of patients. The surgical outcomes are better in patients with retropalatal obstruction compared with retroglossal obstruction. Therefore, patients with obstruction in the hypopharyngeal region would not experience large benefits from this procedure.

Potential complications of UPPP include velopharyngeal insufficiency related to over-resection, odynophagia, dysphagia, disturbance in taste, numbness of the tongue, pharyngeal discomfort, and nasopharyngeal stenosis. Hemorrhage after UPPP occurs in 2 to 4 percent of patients. Despite the wide range of complications and side effects, in practice UPPP is generally well tolerated and uneventful. However, patients who undergo UPPP often have a difficult time tolerating CPAP after surgery because surgical reduction of the soft palate can lead to mouth leaks at relatively low levels of CPAP.

A modified version of the UPPP is the uvulo-palatal flap procedure. This involves suspending the uvula superiorly toward the hard-soft palate junction following a limited resection of the uvula, lateral pharyngeal wall, and mucosa. The intended result is a widening of the oropharyngeal airway similar to the UPPP. The uvulo-palatal flap is reported to be as efficacious as the UPPP and associated with less pain.

Laser assisted uvuloplasty (LAUP) is an office-based procedure that addresses snoring. The procedure involves removal of the uvula and a part of the soft palate with a carbon dioxide laser. The procedure is conducted under local anesthesia and lasts approximately 15 minutes. Although painful, overall it is well tolerated by patients and has a low reported incidence of complications. Nonetheless LAUP can result in dysphagia and the creation of the "silent" (non-snoring) apneic. A success rate of 90 percent is reported in reducing snoring. Many studies have examined LAUP as a treatment for OSA patients; however, these studies are hindered by methodologic and statistical limitations. Currently, LAUP is not recommended as a treatment option for OSA by the American Academy of Sleep Medicine.

Radiofrequency volumetric tissue reduction, a minimally invasive technique, has been employed to treat turbinate hypertrophy and reduce the size of the base of the tongue. Long-term results limited to one study of 18 patients with OSA showed mixed outcomes. It may be useful as an adjunctive treatment to other surgical techniques.

Genioglossus advancement (GA) with hyoid myotomy, sliding mortise genioplasty, mandibular osteotomy, and maxillo-mandibular advancement osteotomy are among the procedures that can be used in patients whose examination and cephalometric analysis are consistent with abnormalities of the craniofacial skeleton. All of these procedures effect an anterior advancement of the "bony cage" (maxilla, mandible, hyoid) to enlarge the upper airway. Therefore, the leading aim is to achieve a larger-caliber airway. It is common for genioglossus advancement to be performed concurrently with other OSA surgical therapies, for example UPPP, to optimize upper airway caliber. The success of such combinations has been variable ranging from 23 to 77 percent. Risks associated with GA include the potential need for tracheostomy perioperatively, fractured mandible, infection, hematoma, and injury to the genioglossal muscle.

Maxillomandibular advancement has been shown to be an effective surgical treatment for OSA in selected patients (i.e., those with retrognathia, and base of tongue obstruction), but this surgery is extensive. Maxillomandibular expansion, distinct from maxillomandibular advancement, is a procedure consisting of a series of limited osteotomies. The aim, using a technique of distraction osteogenesis, is to widen the constricted maxilla and mandibles by performing osteotomy followed by a process of bone lengthening. This technique is a less invasive surgery than maxillomandibular advancement and has been shown to reduce the severity of OSA. However, patients must endure the requirement of having the distractors in situ for several months.

Other procedures listed in Table 97-7 are designed to increase airway caliber or to improve CPAP compliance. Treatment of nasal obstruction by surgical means has proved helpful in some patients, especially by allowing the patient to better tolerate CPAP. The most common nasal surgical procedure is septoplasty and turbinate reduction. These procedures can lead to subjective improvement in nasal patency and a reduction in nasal CPAP requirement. Selected patients who demonstrate macroglossia are candidates for a tongue reduction, although this procedure is usually performed in conjunction with another surgical procedure.

Tracheostomy is virtually 100 percent effective in eliminating apnea. Its use in bypassing the upper airway was first described in "Pickwickian" patients. Despite its high efficacy, it requires changes in lifestyle and is associated with negative impact on patients' quality of life. Tracheostomy is generally reserved for patients with severe OSA who have failed medical or surgical therapy and who manifest severe complications such as malignant arrhythmias without treatment. Tracheostomy can be performed as a temporary measure for high-risk subjects undergoing surgery.

Surgery represents a viable therapeutic option for the carefully selected OSA patient (those who fail CPAP/oral appliances, have tonsillar hypertrophy, or nasal septal deviation). Meticulous preoperative assessment by examination, nasopharyngoscopy, and radiologic imaging can help to identify the likely area of upper airway obstruction. Many surgeons have adopted a staged approach performing limited

procedures such as UPPP and/or GA before proceeding to maxillomandibular advancement. This may be fruitful for some patients by sparing them initial extensive surgery. However, staging may add the unnecessary burden of surgical procedures when the abnormality could have been corrected with a single operation from the outset.

The role of surgical treatment of OSA is likely to evolve in the near future. Improvements in our understanding of airway anatomy should allow better selection of candidates. State-dependent airway imaging technology should increasingly allow the surgeon to view the patient's airway configuration during sleep, thereby enhancing their ability to target the upper airway structures causing the apneas.

MANAGEMENT OF OTHER DISORDERS

Obesity-Hypoventilation Syndrome

The definition and presentation of the obesity hypoventilation syndrome (OHS) has been discussed. A majority of patients with OHS have concomitant OSA. Recent evidence reports significant morbidity and likely early mortality associated with OHS if left untreated. The prevalence is anticipated to increase in parallel with the obesity epidemic; therefore, it is important to recognize the disorder since effective treatment modalities exist. In order to establish the diagnosis, it must be demonstrated in the appropriate clinical setting, that a patient develops nocturnal increments of greater than 10 mmHg in Pa_{CO_2} (for diagnostic features, refer to Table 97-8).

Table 97-8

Diagnostic Features of Obesity-Hypoventilation Syndrome

Morbid obesity
Daytime symptoms of hypercapia Chronic fatigue Morning headache
Right sided congestive heart failure/cor pulmonale with lower extremity edema unresponsive to diuretics
Laboratory findings Hypercapnia during wakefulness (Pa_{CO_2} > 45 torr) Hypoxemia during wakefulness and sleep (Sa_{O_2} < 90%) Greater than a 10 torr increase in Pa_{CO_2} during sleep Respiratory acidosis during sleep (pH < 7.3) Nocturnal oximetry demonstrating persistent oxyhemoglobin desaturation Polysomnography demonstrating concomitant obstructive sleep apnea or evidence of hypoventilation

Oxyhemoglobin desaturations detected by nocturnal pulse oximetry can provide a clue to the diagnosis, particularly the pattern (Fig. 97-23). In a morbidly obese patient, the diagnosis of OHS can be missed if attention is only focused on the oxygen saturation. During wakefulness patients with OHS manifest hypercapnia and can be confused with patients with COPD. Patients with sleep apnea do not manifest daytime hypercapnia. Further diagnostic clues include compensatory metabolic alkalosis in response to chronic hypercapnia and hypoxia-related secondary erythrocytosis. The pathophysiology of OHS is multifactorial and appears to involve a complex interplay of abnormalities in central respiratory drive, respiratory mechanics, sleep-disordered breathing, and leptin sensitivity. Patients with OHS usually have evidence for right-sided heart failure (lower extremity edema), cor pulmonale, and pulmonary hypertension.

The treatment strategy for OHS begins with weight loss, which improves pulmonary function, central ventilatory drive, and concomitant OSA. However, it should not be used as the only strategy, as it is difficult to achieve and maintain. Nocturnal non-invasive ventilation, the treatment of choice, has been demonstrated to correct daytime and nighttime hypoxemia and hypercapnia, ameliorate sleep fragmentation, allow for respiratory muscle rest, reduce pulmonary artery pressures, and improve right ventricular function. These physiologic improvements have been shown to translate to improvement in symptoms, notably excessive daytime somnolence, headache, energy levels, dyspnea, and leg edema. Noninvasive ventilation (NIPPV) may be delivered via volume- or pressure-cycled modes such as bilevel systems. The former appears to be the preferred modality, as it ensures adequate minute ventilation. Regardless, the goal is to achieve normocapnia, preferably over several nights to avoid acute metabolic alkalosis. Use of oxygen alone in OHS patients may worsen hypoxemia and hypercapnia. CPAP therapy may not achieve the required goals in OHS patients due to a failure of airway patency, inadequate inspiratory pressures, patient intolerance, and most importantly an absence of necessary ventilatory support.

Other medical therapy for OHS includes the use of progesterone to stimulate hypercapnic sensitivity, and improve ventilation. The routine use of progesterone is not recommended due to an absence of effect upon apnea index and sleepiness, and the lack of long-term data showing efficacy.

However, gastric bypass surgery should be considered in OHS patients with a BMI greater than 35 kg/m^2. Bariatric surgery has been shown to improve postoperative weight, sleep apnea, and pulmonary physiology.

Central Sleep Apnea

Central sleep apnea (CSA), characterized by repetitive episodes of apnea in the absence of respiratory effort, is caused by an altered ventilatory motor output (Fig. 97-24). CSA has been described as a physiologic process in normal subjects (especially children and the elderly), as a manifestation of breathing instability in a number of medical conditions

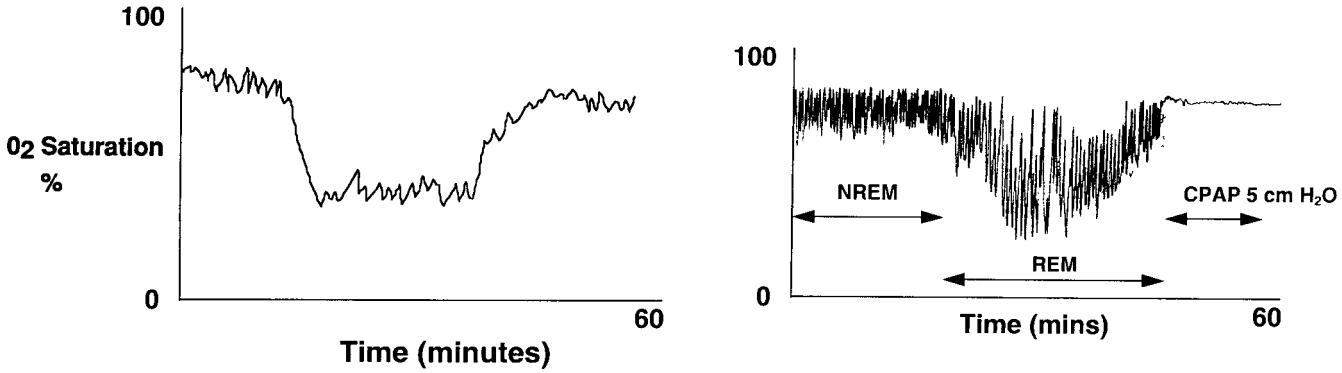

Figure 97-23 Example of typical tracings of oxygen saturation in a patient with obesity-hypoventilation syndrome (left panel) and obstructive sleep apnea (right panel). The former shows an episode of sustained desaturation. In obstructive sleep apnea there are frequent episodic desaturations (saw tooth pattern) that are more profound in REM sleep and abolished by CPAP.

(e.g., Cheyne-Stokes respiration in congestive heart failure and high altitude), or as an association with a variety of neurologic diseases, including Shy-Drager syndrome, CVA, myasthenia gravis, neuromuscular disease, bulbar poliomyelitis, brain stem infarction, and encephalitis. In general, the neurologic disorders associated with CSA lead to the hypercapnic type of CSA in contrast to the non-hypercapnic periodic breathing associated with heart failure, high altitude or hypothyroidism. The latter group manifests an increased chemo-responsiveness that elicits instability of the ventilatory control system.

The initiation of a central apneic event, in most patients, commences with a decrement in arterial P_{CO_2} below the "apneic threshold" (below 35 mmHg), resulting in reduced ventilatory motor output. The causes of hypocapnia include: sleep-state changes, hypoxia, and fluctuation in minute ventilation

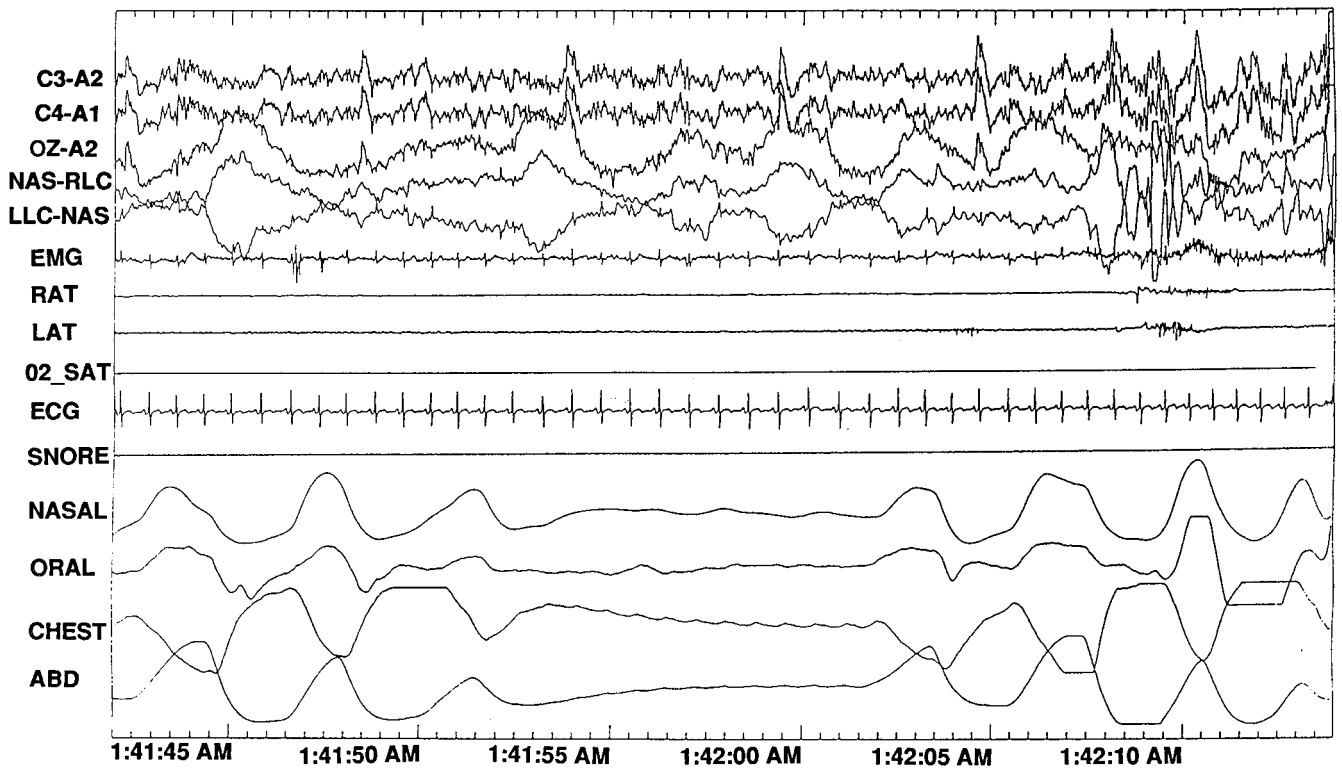

Figure 97-24 Example of a central apnea. The polysomnography traces from the top down are as follows: three EEG channels (C3-A2, C4-A2, OZ-A2); two EOG channels (NAS-RLC and LLC-NAS); submental EMG (EMG); right and left anterior tibialis EMG (RAT, LAT), oxyhemoglobin saturation (O_2 SAT), electrocardiogram (EKG); snoring channel (SNORE), nasal and oral airflow; chest and abdominal motion (chest and abdomen). During the apneic episodes, there is abnormal airflow (both oral and nasal) without rib cage and abdomen motion. At the end of the apneic episode there is a burst of EMG activity at the arousal.

that may be related to heart failure. In patients with hypercapnic CSA, the central drive to breathe is reduced. With sleep onset, a loss of already compromised wakefulness drive to breathe leads to central apnea.

Clinical presentation of CSA patients depends on the type. In the more common non-hypercapnic form, associated sleep fragmentation leads to symptoms that are similar to OSA patients: sleep fragmentation, daytime sleepiness, and poor nocturnal sleep. In patients with hypercapnic CSA, presenting symptoms may include those associated with the underlying disease, sleepiness, morning headache, leg edema, and dyspnea. Hypoxemia due to respiratory failure in these patients can lead to secondary polycythemia or cor pulmonale.

Diagnosis of CSA is established by polysomnography demonstrating repetitive apnea in the absence of thoracic-abdominal excursion. A range of therapeutic options exists depending on the etiology and comorbidity. Oxygen therapy has been shown to improve Cheyne-Stokes respiration in patients with congestive heart failure; however, long-term data showing improved outcomes are lacking. CPAP may be successfully employed in patients who suffer mixed apnea (central and obstructive) or central apneas associated with congestive heart failure. Pharmacologic therapy with heart failure regimens, including beta blockade and angiotensin-converting enzyme inhibitors, improves heart failure status and reduces CSA. The hypercapnic CSA patient is likely to require nocturnal noninvasive ventilation in the form of pressure-cycled mode with a bi-level system and a backup respiratory rate. Although this approach in such a patient appears intuitive, there is a paucity of evidence that supports its use. Pharmacologic approaches to patients with CSA include the use of acetazolamide and theophylline. Although both agents demonstrate improvements in CSA without adverse effects, an absence of high-level evidence precludes their routine use.

Upper Airway Resistance Syndrome

The UARS is characterized by abnormal respiratory effort, nasal airflow limitation, minimal or no oxygen desaturation (greater than 90 percent oxygen saturation), and frequent sleep arousals in the absence of obstructive apneas (Fig. 97-25). Controversy regarding its status as a distinct entity has existed since its first description in adults. It is believed by some experts that physicians are overlooking the syndrome since esophageal monitoring is usually necessary to diagnose this syndrome. UARS is thought to be part of the spectrum of sleep-related disordered breathing beginning with snoring and ending with apnea. The UARS patient in contrast to

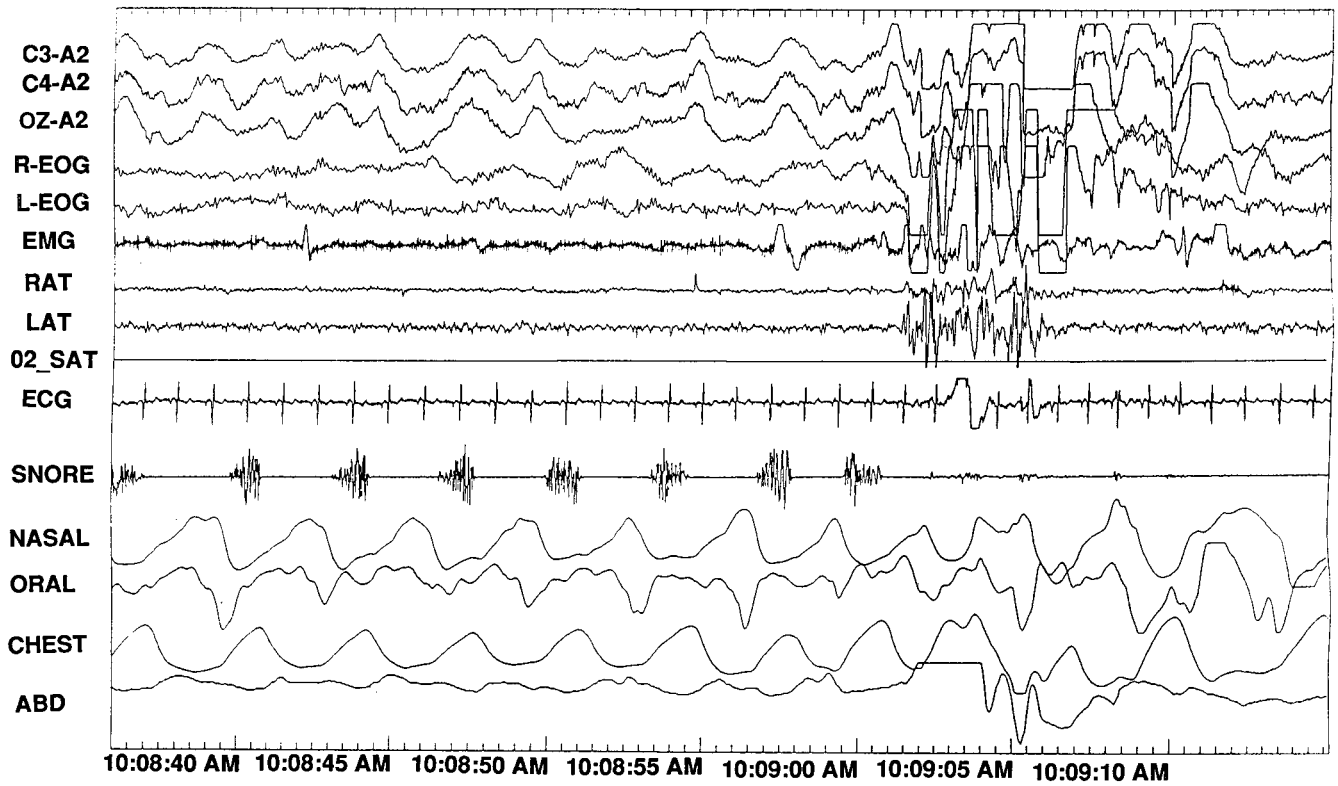

Figure 97-25 Example of an episode of upper airway resistance in a patient with upper airway resistance syndrome. The traces are similar to those in Fig. 97-24. Particular attention should be paid to snoring channel (SNORE). At the beginning of the trace there is snoring present on each inspiration. Toward the end of the trace there is an obvious arousal with movement artifact on the EEG/EOG traces and activity recorded on both right (RAT) and left (LAT) anterior tibialis EMG. With the arousal there is some increase in airflow but the most obvious change is the abolition of snoring as a consequence of the reduction in upper airway resistance.

an OSA subject may present with somatic symptoms such as headaches, insomnia, irritable bowel syndrome, psychiatric morbidity such as depression, attention deficit disorders, and a tendency to feel light-headed. Although relatively invasive, the esophageal balloon remains the gold standard for detecting periodic increases in respiratory effort (UARS) as an indirect measure of airflow obstruction. Other noninvasive strategies are currently being developed.

Based on a recent retrospective cohort study, diagnosing UARS is important. Untreated diagnosed UARS patients over a 4-year period were found to have increased symptoms of daytime fatigue, insomnia, depression, increased sleep disturbance reported by patient and polysomnogram, and increases in the use of hypnotic medication. A majority of UARS patients were denied CPAP by third-party payers during the period of the study (1995–1998). First-line treatment for UARS patients is CPAP, although Medicare does not currently recognize UARS alone as an indication for it. Most patients with UARS also manifest some level of sleep apnea. Patients with concomitant complaints of chronic insomnia or psychosomatic symptoms have benefited from concurrent cognitive behavioral therapy. Other therapeutic modalities for UARS include oral appliances, radiofrequency reduction, nasal septoplasty, and upper airway or craniofacial surgery. Further work is required to understand the medical outcomes of treating UARS patients.

Pulmonary Diseases during Sleep

Pulmonary disorders can deteriorate during normal sleep and especially in patients with concomitant sleep apnea. Normative circadian changes elicit increases in bronchial hyperresponsiveness (increased vagal tone), airway inflammation, and a decrement in lung function, which can contribute to asthma. Supine posture during sleep, interruptions in medication administration, exposure to bed allergens, and gastroesophageal reflux disease (GERD) are also factors that can precipitate asthma. Snoring may trigger bronchospasm by irritation of receptors at the glottic inlet and laryngeal area that are believed to effect bronchoconstrictive reflex activity. Furthermore, snoring or apnea is likely to worsen gastroesophageal reflux, which in turn, is known to exacerbate asthma. Studies addressing subjects with nocturnal asthma and OSA have shown symptom improvement with CPAP use. In fact, asthmatic patients who fail expectant improvement with optimal medical therapy or who manifest primarily nocturnal asthma should be considered for evaluation of sleep apnea, particularly if snoring is present.

In regard to patients with COPD, hypoxemia and hypoventilation can both develop during normal sleep. Normal subjects may experience a decrement in up to 10 mmHg of Pa_{O_2} during sleep. However, COPD patients who exhibit daytime hypoxemia, experience profound declines in Pa_{O_2}, especially in REM, that are proportional to the baseline wakeful oxygen partial pressure. Hypoxemia is multifactorial, and mechanisms include reduced functional residual capacity (decreasing oxygen reserve), increased airway resistance, decreased respiratory muscle function, altered chemosensitivity, alveolar hypoventilation, and ventilation-perfusion mismatch. The coexistence of COPD and OSA is relatively common. In this so-called overlap syndrome, patients are at increased risk of pulmonary hypertension and respiratory failure related to progressive nocturnal hypoxemia. It is important to recognize that a wide variety of lung diseases, including interstitial lung disease, cystic fibrosis, restrictive lung disease, and chest wall disease, can place patients at risk for hypoxemia during sleep. This is related to operating on the steep segment of the sigmoid-shaped oxygen dissociation curve while awake.

Polysomnography is not recommended in COPD patients unless clinical features implicate coexistent OSA. Oxygen therapy is unlikely to be sufficient in patients who suffer the overlap syndrome: Either CPAP with oxygen or nocturnal ventilation is usually required. The latter is appropriate when there is concomitant hypercapnia, although its use remains controversial in the literature.

CONCLUSION

The field of sleep medicine has undergone a period of great change in the last few years. In particular, significant advances have been made in the diagnosis, consequences, and management of sleep apnea. Prospective studies such as the Sleep Heart Health Study have provided stronger evidence for OSA as a causal element in a variety of cardiovascular disorders. The economic ramifications of undiagnosed subjects with sleep apnea are beginning to be understood. An "access" issue for patients to sleep services now looms: Greater public and medical attention to sleep disorders have resulted in a 12-fold increase in the volume of referrals for sleep studies over the last decade in the United States. However, in spite of the steep growth of infrastructure to diagnose and treat OSA, access to such services remains a sizable problem, and demand overwhelms capacity. Strategies (including portable systems, auto-titrating CPAP, and day CPAP titration) are rapidly being developed to expedite sleep study throughput and subsequent therapy. In spite of the encouraging progress, we acknowledge that many subjects remain undiagnosed and untreated for a variety of reasons. It is our hope that continued high-quality research and practice will engender further understanding and treatment of patients with OSA.

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98

Differential Diagnosis and Evaluation of Sleepiness

Charles F. P. George • Meir H. Kryger

Excessive daytime sleepiness is a common problem affecting large segments of the population. Although estimates depend on how sleepiness is defined (e.g., sleeping too much vs. falling asleep in the daytime), about 16 percent of adults experience sleepiness that affects their daytime function, and there is increasing evidence that sleepiness plays a part in both industrial and road traffic accidents. The National Highway Traffic Safety Administration estimates that 100,000 automotive crashes per year are fatigue related. These sleepiness-related accidents contribute to 71,000 injuries and 1500 deaths per year. Over the past two decades, research has provided increased understanding of obstructive sleep apnea (OSA), among other sleep disorders. With the recognition that symptomatic sleep apnea alone affects about 1 in 20 people, and increasing awareness of sleep disorders by the general public, respiratory physicians, by necessity, are dealing more and more with sleep apnea and other sleep disorders. In recognition of the need for training pulmonary physicians in sleep disorders, in 1994 the American Thoracic Society published recommendations for training in sleep medicine (available through the ATS office, currently in revision by the American Thoracic Society 2006). It is clear, therefore, that pulmonary physicians need to better understand and treat excessive daytime sleepiness whatever its cause.

THE PHENOMENON OF SLEEPINESS

Sleepiness is both a subjective and an objective phenomenon, a constellation of sensations and a physiological state with stereotypical behaviors. As such, it is sometimes difficult to define, and its measurement (see below) depends on the circumstances. Sleepiness may be expressed as feeling sleepy, fatigued, or tired; sleeping too much; or fighting to maintain alertness. Sleepiness can be reflected by any or all of the following: heaviness of the eyelids, mild burning or itching of the eyes, difficulty keeping the eyes open, heaviness in the arms or legs, reluctance to move, loss of initiative, loss of interest in surroundings, and difficulty with concentration. These sensations are accompanied by behavioral changes such as rubbing the eyes, yawning and stretching, and nodding the head, and by generally reduced motor functions such as speech, facial expression, and body movement. Indeed, the average sleepy person often exhibits a face with a glazed, blank, or even "dopey" expression.

Sleepiness may also be considered a physiological state like hunger or thirst. Just as hunger and thirst are physiological states that occur with fasting and are satisfied by eating and drinking, sleepiness is produced by sleep restriction or

deprivation and is reversed or satisfied by sleep. The factors that produce and influence sleepiness are detailed below; they include such obvious factors as time since last asleep, previous amount of sleep, continuity of sleep, and normal 24-hour circadian influences. Environmental stimuli influence this state and can determine, up to a point, whether or not this sleepy tendency will be manifested. For example, heavy meals, warm rooms, boring lectures, or monotonous tasks are usually considered soporific activities or situations. In these situations, a person might feel sleepy and, perhaps, might fall asleep. Yet the environmental factors themselves do not cause the sleepiness; they only allow it to be expressed. Equally, the same degree of physiological sleep tendency might go unnoticed when environmental stimulation occurs in the form of a life-threatening situation. In other words, the degree to which sleepiness is experienced or evident in behavior is determined by the underlying physiological sleep tendency (or the need for sleep) and environmental factors, which interact to make manifest the sleep tendency or sleep propensity.

While it is accepted that sleepiness is a physiological state, the physiological substrates of this state have not been identified. Neurotransmitters such as serotonin, acetylcholine, histamine, and the catecholamines have been implicated in the sleep/wake mechanism along with a variety of other sleep-inducing substances, including adenosine through its inhibition of wakefulness-promoting neurons. While much research is ongoing, the understanding of the neurochemicals responsible for sleep, sleepiness, and loss of alertness are still far from clear.

QUANTIFYING SLEEPINESS

The sensation of sleepiness is often difficult to quantify, as are other subjective symptoms, such as pain or shortness of breath. All of these subjective sensations mean different things to different people, and are modified by factors including motivation, external stimulation, and competing needs. What constitutes extreme sleepiness for one person may be only mild sleepiness for another and depend on the situation in which it occurs. Sleepiness has different dimensions with both feelings of perceived sleepiness as well as self-estimates of sleepy behavior, which are different in passive vs. active situations. The notion of a sleepiness trait, a composite of sleep need, sleepability, and other individual difference factors has been proposed to explain individual dissimilarities in sleepiness. This idea is supported by the finding of a hereditary component to self-reported overall alertness that is independent of self-reported sleep timing and duration.

Subjective Measures of Sleepiness

Subjective reports may be used to quantify sleepiness, but statements such as "I feel sleepy" and "I feel very sleepy" often do not distinguish between feelings caused by a high physiological sleep tendency and those resulting from muscular fatigue, depressed mood, or a general lack of energy. Thus, several subjective sleepiness scales have been developed. The Stanford Sleepiness Scale (SSS), the first to receive widespread use, is a seven-point self-rating scale ranging from 1 (alert, wide awake) to 7 (almost in reverie, sleep onset soon). It is brief, simple to use and measures current degree of sleepiness. It has been shown to correlate with the performance of mental tasks and demonstrate changes in sleepiness with sleep loss. However, there are no normative data and results often depend on the duration of prior sleepiness. For example, unlike normal persons who are experimentally sleep deprived, patients with more chronic sleep deprivation (e.g., sleep apnea) cannot be accurately tested with the SSS. Some patients who have an obvious overwhelming physiological sleep tendency may claim to be only mildly sleepy, yet fall asleep before your eyes. This was first observed in the early 1970s, and was a stimulus for that group to develop more objective measures of sleepiness (see below). It is clear that over a period of months or years, many sleep apnea patients lose their frame of reference with regard to normal alertness and cannot distinguish major changes in sleepiness. Thus, the subjective report of sleepiness (using the SSS) by people who are chronically and severely sleep deprived is not reliable.

The Karolinska Sleepiness Scale (KSS) is a nine-point scale ranging from 1 (very alert) to 9 (very sleepy, fighting sleep, making an effort to keep awake), with verbal descriptions of every second point. Like the SSS, the KSS requires the subject to integrate and translate a number of sensations to a continuum that is fairly abstract despite the verbal description. Ratings obtained with these scales may be affected by the situation in which the scale is presented (at rest or during performing a task) and how the subject relates his or her perception to that particular time or place. Nonetheless, both the SSS and KSS show high correlations with performance. The KSS was also found to be strongly related to EEG and electro-oculographic signs of sleepiness.

The Epworth Sleepiness Scale (ESS; Table 98-1) was designed to measure sleep propensity in a single, standardized way and is based on questions relating to eight situations, some known to be very soporific. The questions are self-administered, and subjects are asked to rate on a 0 to 3 scale how likely they are to doze off in the situation based on their usual habits. The ESS tries to overcome the fact that people have different daily routines, some facilitating and others preventing daytime sleep. ESS scores have shown significant correlations with mean sleep latency in the MSLT (see below) and have distinguished groups of patients with disorders of excessive sleepiness such as narcolepsy, OSA, and idiopathic hypersomnolence. It has also correlated significantly with the apnea/hypopnea index (AHI). The ESS has a high test-retest reliability and a high level of internal reliability in normals and patients with sleep apnea. Further work examining the utility of measuring sleepiness in different situations using the ESS suggests that individual measurements of sleep propensity (i.e., sleepiness) entail three components of variation: a general characteristic of the subject (the average sleep propensity), a general characteristic of the situation

Table 98-1

The Epworth Sleepiness Scale

NAME: _____

Today's Date: _____ Your age (years) _____

Your sex (male = M; female = F) _____

How likely are you to doze off or fall asleep in the following situations, in contrast to feeling just tired? This refers to your usual way of life in recent times. Even if you have not done some of these things recently, try to work out how they would have affected you. Use the following scale to choose the *most appropriate number* for each situation.

0 = would *never* doze
1 = *slight* chance of dozing
2 = *moderate* chance of dozing
3 = *high* chance of dozing

Situation	*Chance of dozing*
Sitting and reading	_____
Watching TV	_____
Sitting inactive in a public place (e.g., in a theater or at a meeting)	_____
As a passenger in a car for an hour without a break	_____
Lying down to rest in the afternoon when circumstances permit	_____
Sitting and talking to someone	_____
Sitting quietly after a lunch without alcohol	_____
In a car, while stopped for a few minutes in the traffic	_____

in which the sleepiness or sleep propensity is measured (its soporific nature), and a third component that is specific for both subjects and situation.

Objective Measures of Sleepiness

The Multiple Sleep Latency Test (MSLT) has been developed and standardized as an objective, reliable, and reproducible measure of physiological sleep tendency. Performed at intervals throughout the day, the MSLT measures the time to sleep onset, as determined by the EEG. This test is based on the assumption that, given the proper surroundings, physiological sleep tendency will be expressed; it has an intuitive appeal in that if one patient is more sleepy than the other, the sleepier patient should fall asleep more quickly. Patients are instrumented to record the EEG, electro-oculogram (EOG), and electromyogram (EMG); they are put in a quiet, darkened, temperature-controlled room, and are asked to lie quietly, close their eyes, and try to fall asleep. Naps are scheduled at 2-hour intervals, with 20 minutes allowed for sleep to occur; the average sleep latency of the naps represents the result of the MSLT. Both clinical and research protocols exist for conducting the MSLT. Since sleepiness follows a circadian rhythm (see below), one nap is insufficient to document and quantify daytime sleepiness. Accordingly, a minimum of four and a maximum of six naps are recommended. The MSLT is a reliable, reproducible test that has been validated in a number of sleep deprivation experiments in normal subjects and a variety of clinical conditions with patients who have disorders such as narcolepsy and sleep apnea and is useful for documenting treatment response. An important advantage of the MSLT is that patient motivation cannot counteract the effects of previous sleep loss on sleep latency. That is, while most people can be motivated to compensate for reduced performance after sleep deprivation, motivation cannot overcome an increased pressure for sleep, particularly when the patient is in bed in a darkened room.

An alternative to the MSLT is the Maintenance of Wakefulness Test (MWT). This is a variation on a theme in which subjects sit in a chair in a darkened room and are requested to remain awake for 20 (or 40) minutes. This test was developed on the assumption that the ability to fall asleep and the ability to stay awake are two separate phenomena. The MWT has undergone further tests of validity, but has been criticized for lack of a standardized protocol with 20-, 30-, and 40-minute tests reported. Recent practice parameters suggest using a 40-minute four-trial protocol when assessing whether or not a patient can stay awake in a situation of personal or public safety.

While both MSLT and MWT require observer recognition of EEG changes, *quantitative* computerized *analysis of EEG* have been proposed as an alternate and more sensitive objective measure of sleepiness. Increased EEG delta activity with sleep deprivation and decreased alpha activity just before sleep onset are two possible metrics. However, these have yet to be translated into clinically useful tests. The Alpha Attenuation Test (AAT) has been validated in sleep-restricted normals and in patients with narcolepsy and correlates strongly with the MSLT. Compared to the MSLT, the AAT has the advantage of being fast (it requires only 6 minutes of recording),

minimally intrusive, easily administered, and a purely objective measure of sleepiness. While these features make the AAT a valuable tool in lab and field research, its utility in clinical settings has yet to be determined.

The Oxford SLEep Resistance Test (OSLER test) was designed as a low cost alternative designed to reproduce many of the features of the MWT, but without the labor-intensive, continuous technician monitoring of EEG. Subjects respond to a light-emitting diode mounted on the wall, which flashes for 1 second every 3 seconds. If there is no response after seven consecutive stimuli, the subject is deemed to be asleep and the test is ended. Limited data are available for this metric. The original study compared OSLER sleep latency with MWT latency in 10 OSA patients and 10 control subjects, done on separate days. Two other studies involving small numbers of sleep disorders center patients and/or normal subjects before and after sleep deprivation have demonstrated excellent agreement between the two measures and suggest that the OSLER could be an alternative to measuring sleepiness. In a study of heart failure patients receiving adaptive ventilation for treatment of Cheyne-Stokes respiration, improvement in OSLER scores followed improvement in nighttime sleep. Despite these promising results, there are no large-scale studies using the OSLER, and the main limitation of this test is its dependence on patient cooperation.

Performance and Vigilance Tests

Measurements of performance after sleep loss reflect daytime sleepiness, since most people report decreased performance after a sleepless night. Previously it was felt that only performance tests that were prolonged and monotonous were sensitive to sleep loss. However, the work of Dinges—using his Psychomotor Vigilance Task (PVT)—demonstrates that if the signal rate is high and the response measure sufficiently sensitive, repetitive tasks of only 10-minute duration will expose the limits of performance in sleepy persons. Performance decrements resulting from sleep deprivation (or sleep disorders such as sleep apnea) can be observed in such a task if results are analyzed over time. This time-on-task or vigilance decrement may be observed as evidence of fatigue even in well-motivated subjects with adequate prior sleep, and it manifests itself as a shallow decline in performance as time-on-task increases. When the subject is sleep deprived, it is impossible to sustain attention long enough to maintain peak performance throughout the entire task. Sleep loss increases the rate of decline in and number of lapses in performance and the PVT has become the most widely used measure of neurobehavioral performance. It has been validated with the SSS and MSLT. Recent work using this test has demonstrated consistent individual differences in neurobehavioral deficits from sleep loss, which suggest differential trait vulnerability to sleepiness.

Other tests of sustained attention and performance have been developed, many to assess simulated driving performance. Using a divided attention driving task, sleep apnea patients have been shown to perform poorly, and in some cases, equal to or worse than normals impaired by alcohol. Nonetheless sleepiness as measured by MSLT accounts for less than 25 percent of the variance in tracking performance. Thus, while the effects of sleepiness on performance may occur in a dose-dependent fashion in normals, performance decrements in patients who are sleepy because of an underlying sleep disorder may be accounted for by factors other than sleepiness.

FACTORS AFFECTING SLEEPINESS

Sleepiness is determined by the quantity of sleep and the quality and type of sleep, interacting with circadian rhythms or drugs that patients may be taking.

Sleep Quantity

The amount of nocturnal sleep has a strong relationship to the degree of daytime sleepiness. Partial or total sleep deprivation is followed by increased daytime sleepiness in normal persons. Furthermore, sleep restriction will become cumulative over time and lead to increasing daytime sleepiness.

The effect of sleep restriction on sleep latency is shown in Fig. 98-1. When the sleep of young adults was reduced by 2 hours a night on consecutive nights, sleepiness (as measured by the MSLT) progressively increased over 7 days. Even as little as 1 hour per night of sleep loss will accumulate over time and lead to daytime sleepiness—a fact generally not appreciated. Each person has a certain biologic sleep need, and the specific amount varies from one subject to the next. Regardless of cultural or environmental factors, most adults sleep 7 to 8 hours per day, but the old adage that we must sleep 8 hours each night is not true for everyone. Some people require more than 8 hours, and others less; even conjoined twins show an independence of sleep needs. In the absence of pathology, normal human sleep length varies between 6 and 9 hours, although some people require less. It would be ideal to require a minimum amount of sleep to allow maximum productivity in work and adequate time for social pursuits. Indeed, some investigators believe that Western society predisposes to sleep deprivation. With economic and social constraints—the latter leading to voluntary sleep restriction—the sleep period is the time most encroached on, potentially leading to daytime sleepiness. This is highlighted in the National Sleep Foundation's annual Sleep in America Poll.

Voluntary sleep restriction or insufficient sleep causes daytime sleepiness. Among all prominent features differentiating this group of patients with insufficient sleep from those with narcolepsy was the report, obtained from the sleep history, of a disparity between the amount of sleep on weekdays and that on weekends. People with insufficient sleep typically have a much longer sleep period on weekends (by 2 hours or more).

Most patients consider their weekly sleep loss trivial and assume that it is recovered on weekends. However, while

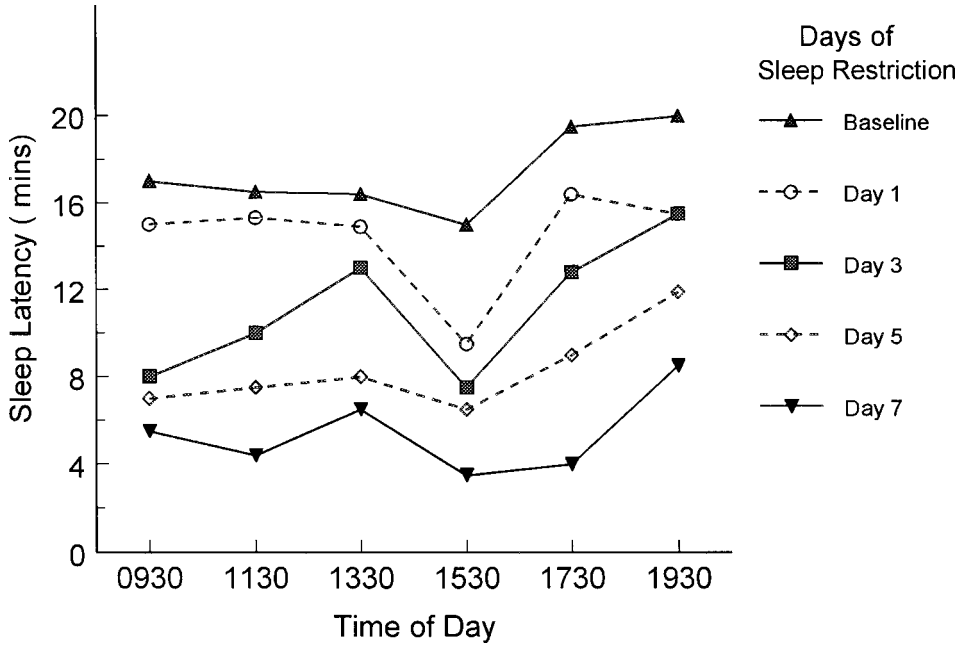

Figure 98-1 Average daily sleep latency test scores for young adults when nighttime sleep was reduced by 2 hours a night for 7 consecutive nights. *(Adapted from Dement WC, Carskadon MA: An essay on sleepiness, in Boldy-Moulinier M (ed),* Actualitiés en Médécine Expérimentale, en Hommage au Prof D Passouant. *Montpellier,* Euromed, *1981, pp 47–71.)*

recovery from a single experimental sleep restriction occurs in a couple of nights, it is not likely that repeated episodes of sleep deprivation can be compensated for in just one night. A study of a large group of normal subjects without complaints of daytime sleepiness has shown that young subjects (particularly college students) had shorter sleep latencies than did older subjects. Within the group of 120 young subjects, 12 healthy, nonsmoking men aged 21 to 35 years, had a mean sleep latency of less than 6 minutes on MSLT testing, while another 12 had an MSLT of greater than 16 minutes. These subjects had baseline testing and then extended their sleep period time from 8 to 10 hours over 6 days. Repeat testing on days 1, 3, and 6 showed stepwise increases in MSLT and performance testing for both subgroups. These data support the notion that chronic voluntary sleep restriction produces objective sleepiness that may or may not be perceived by the subject.

Sleep Quality

Sleep quality is perceived to be abnormal when sleep is decreased or discontinuous. Disrupting sleep continuity—i.e., causing arousal from sleep, either experimentally or by sleep disorders—affects the quality of sleep and results in increased physiological sleep tendency. An arousal can be defined as a brief (3 to 15 seconds) speeding up of the EEG, or as a burst of alpha activity occasionally accompanied by transient increases in skeletal muscle tone. These typically do not result in awakening as defined by standard sleep staging criteria or behavioral indicators. Sleep studies can identify various causes of arousal, such as recurrent obstructive apnea, leg movements, or pain, in some but not all cases. A common exception is the patient with chronic obstructive pulmonary disease (COPD) who has frequent arousals from sleep in the absence of obstructive apnea or leg movements. Patients with COPD often experience oxygen desaturation during sleep, and this is a potential stimulus for arousal. However, arousal frequency is unchanged when supplemental oxygen is given and desaturation is prevented, so the stimulus is still undefined. Nonetheless, compared with age-matched controls, COPD patients have discontinuous sleep and poor sleep efficiency (defined as percentage of time actually asleep in bed). This might be expected to lead to daytime sleepiness, but the sleep latency of COPD patients has not yet been measured systematically.

Auditory stimuli presented externally to normal subjects during sleep can produce arousal; repetitive presentation of such stimuli can produce daytime sleepiness. Several studies have shown decreased performance and increased sleepiness the day after repetitive arousal, with the degree of daytime sleepiness related to the frequency of nocturnal sleep disruption. Not surprisingly, the shortest sleep latency occurred after the most fragmented nocturnal sleep. This increased sleepiness will result even if the stimulus is only sufficient to produce EEG signs of arousal, without full wakefulness.

Circadian Rhythms

If sleep latency is measured every 2 hours over a complete 24-hour day, a biphasic pattern of sleep tendency becomes obvious (Fig. 98-2). This demonstrates that there are two peaks and troughs of sleepiness over a 24-hour period. Not surprisingly, the times of increased sleepiness are during the nocturnal hours and during the daytime hours (in the midafternoon

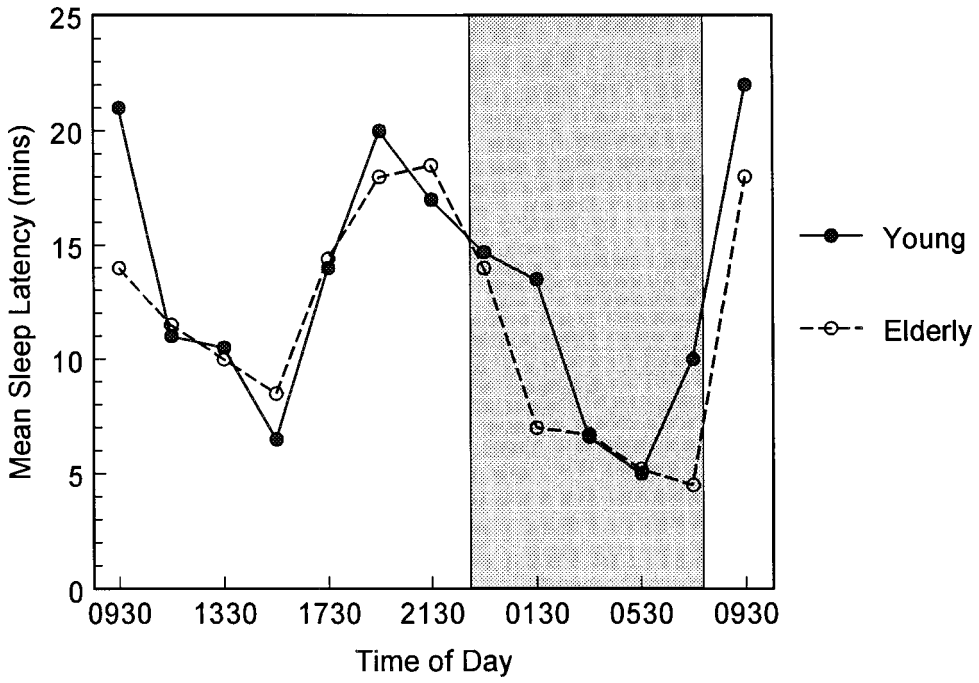

Figure 98-2 Sleep latency (mean) as a function of time of day for young subjects (filled circles) and elderly subjects (open circles). *Stippled area* denotes nighttime sleep period. *(Adapted from Richardson GS, Carskadon MA, Orav EJ, et al.:* Sleep *5:882–92, 1982.)*

between 2 and 4 p.m.). This circadian rhythm of sleepiness is present in all age groups, although the time of the peak rhythm may vary. The circadian rhythm of sleepiness is similar to other circadian rhythms in that it possesses an endogenous periodicity that can be affected by environmental influences that fine tune or entrain the rhythm. Even in the absence of these environmental cues (e.g., awakening time, alarm clock, degree of light or darkness, food and stimulants, social contact), rhythms show a persistent periodicity. The circadian rhythm of temperature is extremely stable. Temperatures fall in the late afternoon, are lowest during the middle of the sleep period, and rise before morning awakening. The temperature rhythm synchronizes most closely with sleepiness. Although the amplitude of body temperature and sleep latency rhythms differ considerably, no other biologic rhythms correlate so well in time.

Two other examples of the influence of circadian rhythms on sleepiness are obvious. The first is that associated with shift work, and the second is due to transcontinental travel (jet lag). Workers with a normal nocturnal sleep period and a previously stable circadian sleepiness rhythm suddenly will have a trough of sleepiness during the middle of their night work period. They will attempt to stay awake, while the circadian influences will promote sleep. Not surprisingly, performance may suffer.

Medications

Drug effects on sleep can be significant and can either promote sleep and sleepiness or increase wakefulness and alertness. Not surprisingly, sedative drugs increase sleepiness. Benzodiazepine hypnotics are widely used to help people get to sleep at night. Many objective studies confirm the ability of hypnotics to shorten sleep latency at bedtime. When given during the day, they will promote sleep. However, the daytime carryover effect of nocturnal sedation is not always recognized. This effect occurs most commonly with long-acting benzodiazepines, but it may occur with other medications as well. Alcohol consistently shortens sleep onset and produces sedation, whether given at night or during the day. Drugs that produce sleepiness include antihistamines, which are used in allergy and pulmonary practice. Many of the early H_1 antihistamines, such as diphenhydramine and chlorpheniramine, have been shown to reduce the MSLT. Some newer antihistamines, such as terfenadine and astemizole, do not produce objective sleepiness. The more lipid-soluble drugs (e.g., diphenhydramine and chlorpheniramine) penetrate the central nervous system more easily and therefore are more likely than less lipid-soluble drugs to produce sedation. Other medications with high lipid solubility have been reported to produce daytime sedation; the most common of these are the beta blocker drugs. There are no controlled, objective studies of sleep latency with this type of drug, and sleepiness from these medications is based on reports of side effects.

The effect of a particular drug in producing sleepiness also depends on the background level of sleepiness or alertness. When ethanol or caffeine is given to normal sleeping young men in the morning, one might expect ethanol to produce daytime sleepiness and caffeine to increase sleep latency during the day. Subjects are consistently sleepier after ethanol than after caffeine ingestion, but fully rested subjects (those

having spent 11 hours in bed) do not show sleepiness after taking ethanol. In other words, the sedative effects of drugs such as alcohol can be enhanced by increased background sleepiness. Thus, a driver who is sleepy to start with may be as vulnerable after just one or two drinks as a previously alert driver who has become legally intoxicated.

Stimulants such as amphetamine, methylphenidate, and modafinil increase alertness. These are most often used in the treatment of narcolepsy but are also used, quite inappropriately, by truck drivers trying to keep awake when driving over long distances. It is our anecdotal experience that many sleepy truck drivers actually have sleep apnea and are not particularly helped by stimulant medications. Caffeine, probably the most widely used stimulant, can reduce daytime sleepiness and transiently increase alertness. Excessive caffeine intake also paradoxically may cause a degree of daytime sleepiness. This occurs when caffeine levels persist into nocturnal hours and promote difficulties with sleep onset and increased awakenings during sleep.

PREVALENCE OF EXCESSIVE DAYTIME SLEEPINESS

Prevalence rates for sleepiness depend greatly on the type of questions addressing sleepiness. Are you sleeping too much vs. are you falling asleep during the daytime vs. does your sense of sleepiness impair your daytime activities all result in widely different prevalence rates. Also men tend to report sleepy behavior while women report feelings of excessive daytime sleepiness, again contributing to variable prevalence. Prevalence of sleepiness also varies with the population examined. Of 2552 Finnish army recruits, 9.5 percent answered affirmatively when asked, "Do you consider yourself more sleepy during the daytime than your friends or work mates?" In addition, "daytime sleepiness" was reported by 16.2 percent of 1138 male subjects aged 18 to 23 years in a questionnaire distributed in Milan. The prevalence of excessive daytime somnolence was investigated in 58,162 draftees in the French army; 14.1 percent reported occasional daytime sleep episodes, 3.8 percent reported one or two daily episodes, and 1.1 percent reported more than two daily episodes. Of the total sample, 5 percent considered the sleep periods to be affecting their lives. A multivariate analysis showed five independent factors related to excessive daytime sleepiness: use of hypnotics, sleep difficulties, irregular sleep/wake schedule, snoring, and hours of sleep. In a recent study of 1066 Brazilian residents, sleepiness causing impairment at least three times per week was 10 percent in men and 21 percent in women, with rates increasing in low-income and unemployed.

The Wisconsin Sleep Cohort study was the first to formally determine the prevalence of sleepiness as a function of sleep apnea. This landmark study demonstrated that at least 2 percent of middle-aged women and 4 percent of middle-aged men had OSA and symptoms of excessive daytime sleepiness. More recent estimates suggest that about 1 in 20 (5 percent) have symptomatic sleep apnea. While there may have been other causes for the daytime sleepiness besides OSA, it is clear that sleep apnea is responsible for a great deal of the daytime sleepiness in North America.

EVALUATING THE SLEEPY PATIENT

Approach and Differential Diagnosis

Keeping in mind the factors that determine daytime sleepiness, the sleep history can be individualized and can be very helpful in narrowing the differential diagnosis (Table 98-2). One should always question the patient about his or her nocturnal sleep, looking specifically at sleep onset time, sleep period time, number of awakenings, and time of rising in the morning. Sleep onset phenomena such as sleep paralysis and hypnagogic hallucinations often suggest a diagnosis of narcolepsy, although these sometimes occur in apneics who are severely sleep deprived. A history of loud snoring or stopped breathing during sleep is suggestive of sleep apnea, particularly if the snoring is cyclical rather than continuous, with periods of loud snoring or snorting alternating with quiet intervals. Since insufficient sleep may be the cause of sleepiness, it is important to ask if there is any difference in the amount of sleep required during the week compared with

Table 98-2

Common Causes of Persistent Daytime Sleepiness

Obstructive sleep apnea and other sleep-disordered breathing conditions (e.g., neuromuscular weakness with nocturnal respiratory failure)
Narcolepsy/cataplexy syndrome
Sleep-related movement disorders (e.g., periodic limb movement disorder, bruxism, etc.)
Depression
Postviral fatigue
Head injury
Metabolic, toxic, and drug-induced hypersomnolence
Idiopathic hypersomnolence
Insufficient sleep
Circadian rhythm sleep disorders

that on weekends. Equally important is whether the patient has any changes in subjective sleepiness on weekends or holidays compared with weekdays.

In some instances, more information will be obtained from the spouse (or bed partner) or from a sleep/wake diary, since not all people are aware of the severity of their sleepiness. Moreover, patients may not understand the importance of good sleep hygiene; the diary can serve as a reminder for patients to be diligent about it.

In estimating the degree of daytime sleepiness, it is useful to ask when and during what activities the patient experiences sleepiness. Is the patient sleepy on awakening in the morning, or is it only by midday? Does the patient fall asleep while doing things or only when inactive? Driving to and from work are important times when sleepiness may become obvious, particularly while the person is waiting at a railroad crossing or stoplight. Episodes of automatic behavior, related to "microsleeps," often occur while one is driving. Do patients nap during the day, and if so, is the nap refreshing? Many patients with sleep apnea are still sleepy or foggy after a nap, whereas patients with narcolepsy most often feel refreshed immediately upon awakening.

Since drugs can have a profound effect on sleep and sleepiness, a careful drug history is mandatory in the assessment of sleepiness. The clinician must remember to include queries not only about drugs that specifically affect sleep (hypnotics, sedatives, or other psychoactive medications) but also about substances that may not be considered to have any effect on sleep or waking. In particular, alcohol is a known precipitant or exaggerating factor for sleep apnea; patients will often report that they feel much worse the day after ingesting alcohol despite having had a nonintoxicating dose.

Apart from a general physical exam, one should pay particular attention to the size of the jaw, face, and upper airway, looking for obvious skeletal abnormalities—particularly retrognathia or micrognathia. One then carefully examines the upper airway, looking for nasal obstructions such as a deviated nasal septum or inflammatory allergic polyps; then, one examines the oropharynx, looking at the size of the tongue, the position of the soft palate, and the size of the uvula; finally one examines the larynx to rule out upper-airway tumors or other obstructing lesions. While the typical sleep apnea patient will be the obese plethoric man with a thick neck, it is important to remember that examination of the awake, upright airway may bear no relationship to what happens when the patient is supine and asleep. Thus, the diagnosis of sleep apnea usually is confirmed by nocturnal polysomnography.

The patient who has a history of snoring and daytime sleepiness but has no sleep apnea during his or her nocturnal study must undergo an objective measure of daytime sleepiness, because some patients who claim to have substantial daytime somnolence are simply looking for compensation. Also, some OSA patients will remain sleepy despite adequate treatment of their apnea, and an additional sleep disorder may coexist. Again, daytime quantification of sleepiness will be necessary. The only disadvantage of the MSLT is that it is an inefficient test. Compared with objective measurements of airflow (i.e., an FEV_1), which take seconds to perform and interpret, the MSLT takes almost a whole day and provides only one piece of information. Until better tests are developed and validated, however, the MSLT will continue as a standard, albeit time-inefficient, objective measure of daytime sleepiness.

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PART

XIV

Surgical Aspects of Pulmonary Medicine

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99

Perioperative Care of the Patient Undergoing Lung Resection

Robert J. Cerfolio

The postoperative care of any patient who undergoes pulmonary resection starts long before the incision is made and is comprised of three main areas. The first is patient selection, the second is the actual operation itself, and the third is postoperative care. This chapter briefly reviews some of the specific elements that go into these three areas. In addition, it discusses the incidence, prevention, and treatment of some of the most common postoperative problems that continue to vex thoracic surgeons around the world.

PATIENT SELECTION

Perhaps the best way to minimize postoperative complications is to operate only on young healthy patients. Unfortunately, thoracic surgeons like most other surgeons are now presented with older and sicker patients than in the past. The median age of our society has increased and so have their comorbidities. We are increasingly challenged with larger

tumors in older patients with smaller pulmonary reserve. As the bar for the upper age limit has risen the basement for the acceptable FEV1% and Dl_{CO}% has fallen. In the third millennium there are few, if any, absolute contraindications to pulmonary resection based on chronological age or pulmonary function.

MORBIDITY AND MORTALITY

During the perioperative period, many factors contribute to pulmonary compromise. Estimates of the overall surgical mortality for pulmonary resection range in large series from 2 to 4 percent. The estimated mortality increases with the size of the resection—from less than 1 percent for a wedge resection of the lung, to 2 to 3 percent for a lobectomy, and 6 to 8 percent for pneumonectomy.

The morbidity associated with elective pulmonary resection is also high. Complications have been reported to occur in 36 to 75 percent of patients undergoing pneumonectomy and 41 to 50 percent of patients after pulmonary lobectomy. Most complications are minor and include air leak, atrial fibrillation, and atelectasis. However, a significant number are major; these most commonly include pneumonia, aspiration, respiratory failure, myocardial infarction, bronchopleural fistula, and pulmonary embolus.

PREOPERATIVE ASSESSMENT AND OPTIMIZATION

Lung Function

Assessment of the patient's risk for pulmonary resection starts preoperatively in the clinic. One important but difficult factor to quantify is the patient's desire to undergo the work required to recuperate from a thoracic surgical procedure. The importance of walking and deep breathing after lung resection cannot be overstated. A study performed by the Lung Cancer Study Group suggested that the patient's attitude toward his or her malignancy was the best indicator of long-term survival. A patient who appears to be unwilling to participate in his recovery should be allowed ample opportunity to explore reasonable alternative therapies, such as radiation. Moreover, if this attitude persists, it may be best not to operate at all.

A large number of studies have examined preoperative pulmonary function tests in an attempt to delineate the risk to a patient. In a study of 476 patients operated on over 12 years, only three of seven preoperative risk factors for morbidity and mortality were found to carry a significant association with mortality. These risks included age over 60 years, pneumonectomy, and the presence of ventricular premature contractions on the preoperative electrocardiogram. All risk factors analyzed together accounted for only 12 percent of the risk of mortality.

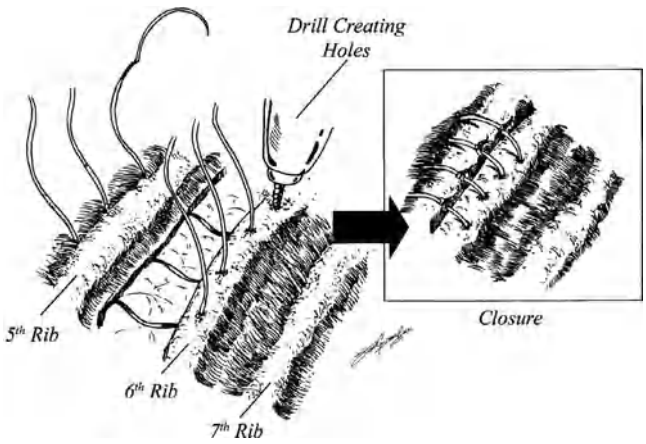

Figure 99-1 Drilling holes in the bottom rib, thus enabling sutures to be placed through it.

At the time of the initial visit, an attempt to establish the amount and character of sputum production, the presence or absence of an effective cough, and a patient's ability to climb a flight of stairs of fixed height help provide an idea of a patient's ability to undergo surgery. Patients with preoperative arterial hypercapnia are apt to have pulmonary hypertension and are poor candidates for pneumonectomy, but they may be able to tolerate a lobectomy. Pulmonary function tests, in particular the FEV_1 percent and the Dl_{CO}%, in combination with lobar perfusion scans, allow prediction of the postoperative predicted or post-resectional FEV_1% (Fig. 99-1). A post-resectional FEV_1% less than 40 percent of predicted is cause for concern. A study of the Dl_{CO}% in 165 patients who underwent lung resection identified it as the most important indicator of postoperative pulmonary complications or death. Another study focused on the maximal oxygen consumption (MVO_2). A MVO_2 of 20 ml/kg per min was associated with the fewest chance of complications, whereas an MVO_2 under 15 ml/kg per min was associated with a 75 percent of the postoperative morbidity.

Optimization of Preoperative Pulmonary Function/Smoking Cessation

Many patients who are to undergo elective pulmonary resection are current smokers. A variety of medical therapies are designed to improve pulmonary function. Optimization of pulmonary function begins first and foremost with smoking cessation. Even a short period of abstinence from cigarettes can improve the effectiveness of mucociliary transport. Heavy smokers also maintain high levels of carboxyhemoglobin that interfere with oxygen transport and delivery to peripheral tissues. However, the optimal time after smoking cessation for elective thoracotomy is still unknown. Studies of patients undergoing abdominal surgery and coronary artery bypass surgery suggest that 8 weeks of abstinence is necessary to achieve a significant decrease in pulmonary complications,but this type of delay is often not practical in patients with lung cancer.

In patients with evidence of reversible airway obstruction on pulmonary function tests, or symptoms suggestive of airflow obstruction, nebulized albuterol appears to be of benefit. Mycostasis, if present, may warrant the addition of mucolytics such as N-acetylcysteine. However, this medicine may also lead to certain side effects, such as increased mucus production and bronchoconstriction. Similarly, although the condition of patients with reversible airflow obstruction generally improves with steroids, prednisone or other corticosteroids should be added reluctantly because of their adverse effects on wound healing and wound infection. If steroids are necessary, the dosage in the postoperative period should be minimized. Patients who produce purulent sputum should be treated with oral antibiotics directed at the organism identified and surgery delayed until the infection is eradicated.

PERIOPERATIVE FACTORS REDUCING LUNG FUNCTION

Despite the wide variety of pathologies and types of operative procedures performed by thoracic surgeons, the postoperative course is often quite predictable. We have published on the techniques and specific steps that enable patients to be "fast-tracked" after both elective pulmonary resection and esophageal resection. These clinical pathways and/or computerized algorithms lead most importantly to safe results, high patient satisfaction, and only a 3- to 4-day length of stay after pulmonary resection. Early ambulation and aggressive pulmonary rehabilitation are cornerstones for successful fast-tracking. The physiological consequences of decreased activity and lack of changes in posture form a background for the pathophysiological processes caused by the underlying illness and the surgical procedure.

Bed Rest and Respiratory Function

In normal adults, mismatches between alveolar ventilation and blood flow are small. In bedridden postoperative patients, however, ventilation and perfusion are badly matched. The zones of the upright lung are considered elsewhere in this volume. Placing a normal patient in a recumbent position leads to changes in all lung volumes except the tidal volume. In a normal person, a change from the upright to supine position decreases the vital capacity by 2 percent, total lung capacity by 7 percent, closing volume by 10 percent, residual volume by 19 percent, expiratory reserve volume by 46 percent, and functional residual capacity (FRC) by 30 percent. The decrements in volume that accompany changes to other than the supine position are small. In normal subjects, the FRC decreases by only 17 percent after a move from the upright to the lateral decubitus position. The closing volume has been shown to be relatively independent of posture. However, the FRC decreases by about 20 percent in the supine position—an amount that may be sufficient to cause the closing volume to exceed the end-tidal volume, thereby resulting in closure of basilar alveoli. These alveoli remain closed for the initial portions of the next inhalation, while the ventilation is shunted to the open apical alveoli.

It is interesting that these changes might be less in patients with chronic pulmonary disease. Thus, in patients with chronic airflow obstruction, a decrease in FRC of only 3.5 percent accompanied a move from the upright to supine position and a decrease of only 1.9 percent accompanied the move from the supine to lateral decubitus position. Finally, although arterial oxygen saturation decreased significantly in supine normal subjects, it did not do so in patients with significant airflow obstruction.

The degree to which the described changes affect gas exchange has been only partly studied. In normal young males after 10 days of bed rest, Pa_{O_2} decreased by 9 mmHg and the alveolar-arterial difference in Po_2 by 10 mmHg, without change in Pa_{CO_2}. Such changes, which would probably not be important in normal young people, might take on greater significance in a patient with chronic obstructive pulmonary disease (COPD).

Bed Rest and Cardiac Function

Upon standing, approximately 500 ml of blood shifts from the upper to the lower body. When lying down, the central venous return increases, resulting in a decrease in heart rate, peripheral vasodilation, increased renal blood flow, and diuresis. Within an average of 24 hours the diuresis causes a 5 percent decrease in plasma volume, which continues to fall by 10 percent in 6 days and 20 percent in 14 days.

A wide variety of experimental subjects and protocols have been used to examine the cardiovascular effects of prolonged immobilization. Orthostatic intolerance is common after prolonged bed rest. This is attributable, at least in part, to the depletion in intravascular volume noted in the preceding. This may be compounded by an increase in venous pooling in the lower extremities because of an increase in venous compliance after bed rest. Prolonged recumbency also blunts cardiac responsiveness to rapid changes in posture. Bed rest increases the resting heart rate by 4 to 15 beats a minute. After prolonged bed rest, the increase in heart rate during exercise is more pronounced. For example, normal volunteers experienced an increase in heart rate to approximately 129 beats a minute during submaximal exercise; after bed rest, the same exercise drove the heart rate to approximately 165 beats a minute.

Alterations in Lung Function Secondary to Surgery

In addition to the physiological consequences of inactivity described in the preceding, the thoracic surgery patient also experiences major alterations in chest wall compliance. The pain and discomfort of deep breathing also lead to an increase in the work of breathing that is independent of the amount of resected lung. Manipulation of the lung and re-expansion of the lung leads to pulmonary "bruising." Microscopic or

even macroscopic areas of atelectasis persist. Fluid or blood clots in the pleural cavity may compress the lung parenchyma. Inhalational anesthesia depresses mucociliary transport. Mechanical changes alter the work of breathing. Thoracotomy alone was found to decrease chest wall compliance to 47 percent of preoperative levels and to increase work of breathing to 143 percent of preoperative levels. As a result, vital capacity and oxygen saturation fall significantly in the first few postoperative days. Pain, among other factors, leads to diminished cough. Cough pressures were found to decrease to 29 percent of preoperative levels after surgery and to increase only to 50 percent of preoperative levels by the seventh postoperative day.

Cardiac Stress Test

Since many patients are smokers and elderly, we prefer to perform a preoperative stress test in most patients prior to thoracotomy. Previously undiscovered or unsuspected coronary artery disease should be determined, anatomically identified, and corrected prior to elective thoracotomy.

RESECTION

Extubation and Postoperative Supplemental Oxygen

Almost every patient undergoing lung resection should be extubated in the operating room and is brought to the recovery room breathing spontaneously. Reintubation in the immediate postoperative period is rare. If prolonged intubation is anticipated, however, the double-lumen endotracheal tube should be replaced by a single-lumen endotracheal tube of sufficient size to permit the introduction of an adult bronchoscope. For extubation, standard criteria are followed: vital capacity more than 10 ml/kg, respiratory rate less than 30 breaths per minute, and normal arterial blood gases.

Supplemental oxygen is supplied in the postoperative period if the patient's arterial oxygen saturation, measured by pulse oximetry, is less than 92 percent, either at rest or during exercise. We prefer sending patients directly to the floor and have not used the intensive care unit after lobectomy since 1998. Many centers have adopted a similar practice; however, patients must have 24-hour cardiac-rhythm and pulse oximetry monitoring in these specialized units. Nurses need to have chest tube training. These types of floors allow the patient's family to stay in close proximity at all times. This offers significant psychological support to most patients; if the family is attentive and intelligent, as most are, they also can act as an invaluable part of the patient's care and add another level of patient protection.

Pain Control

A thoracotomy is a painful procedure. This is probably secondary to trauma and/or compression of the intercostal nerve. We have evaluated ways to reduce the pain of

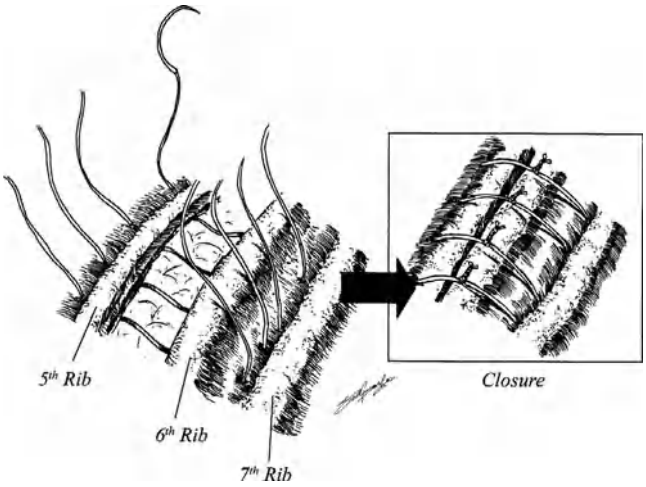

Figure 99-2 Standard pericostal sutures.

thoracotomy using prospective randomized studies. We have completed four such trials and have published three. One study showed that drilling holes in the bottom rib, thus enabling sutures to be placed through it rather than around the ribs, helps avoid entrapment of the lower intercostal nerve (Fig. 99-1) and this simple technique reduces the pain compared with the standard pericostal sutures (Fig. 99-2). Another study examines the use of an intercostal muscle flap. This flap is harvested prior to rib retraction (Fig. 99-3) so as to avoid retractor injury to the intercostal nerve, which runs in the muscle flap. This study also showed significant benefit and further reduction of pain. Both positive studies showed reduction in postoperative pain in the hospital and a lessening of a decrease in the tidal volume immediately postoperatively. In addition, there was less pain at 3 months, both early and up to 12 weeks postoperatively. Simple techniques such as these, as well as video-assisted procedures that help prevent or limit the amount of pain are important.

The key to pain control, like all postoperative complications, is prevention. Postoperative pain that is not controlled early reduces the ability to breath and cough and increases respiratory complications. Moreover, the best way to reduce late or chronic pain is to aggressively treat early pain. Most patients should receive a thoracic epidural prior to thoracotomy and/or a patient-controlled analgesic (PCA) intravenous device to help control it. Recently, some surgeons have tried subpleural catheter systems that infuse local anesthetics in the paravertebral area as well. The complications associated with epidural opiates are numerous and include pruritus, ileus, urinary retention, and respiratory depression. Epidural analgesia is most useful in the young patient with poor pulmonary function. We have avoided it in elderly patients, those who become somnolent, or those who have a rising carbon dioxide level on arterial blood gas. The use of nonsteroidal agents such as oral ketorolac in addition to narcotics is helpful as well and should be given immediately in the operating room and continued for a few days to help prevent pain. It should be avoided in those with marginal renal function. After postoperative day 2 or 3, the epidural should be

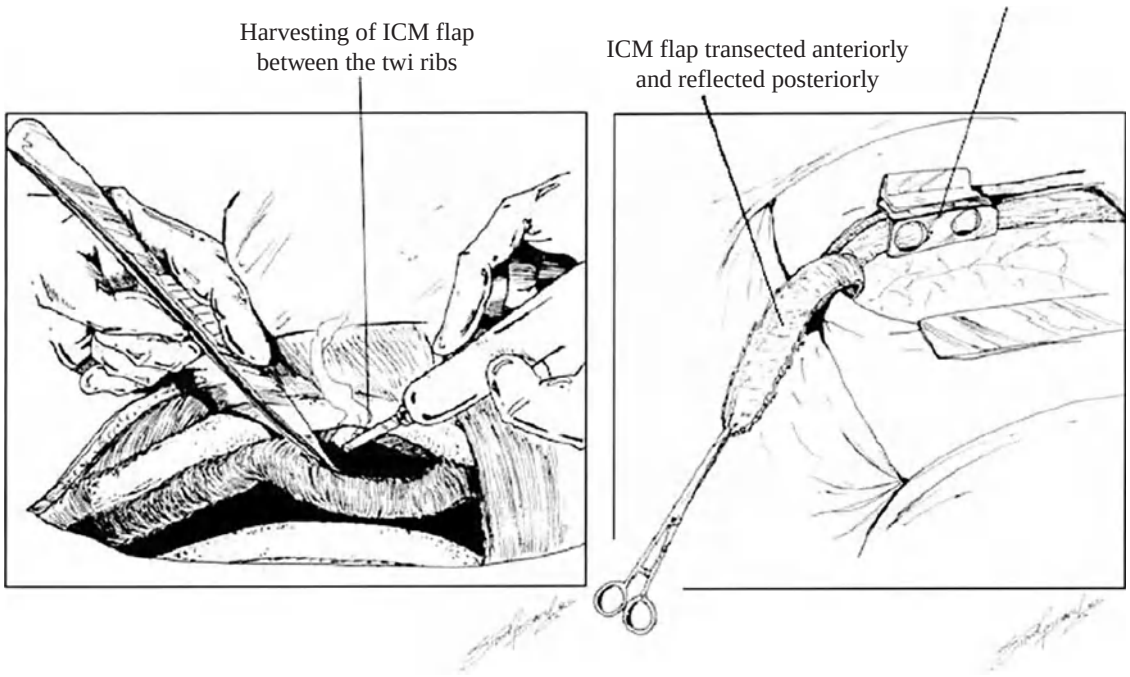

Figure 99-3 Muscle flap harvested prior to rib retraction.

removed and oral agents such as Tylox or Percocet should be added. Treating pain using a combination of different classes of agents is helpful.

Antibiotics

Wound infection following thoracotomy is rare. This may be due to the large amount of musculature contained in the chest wall. However, infectious complications such as pneumonia are not uncommon following lung resection, and prophylactic antibiotics are often given in an attempt to reduce the incidence of these complications. Currently, it is recommended that a broad-spectrum antibiotic, such as cefazolin, be administered within 1 h of the skin incision, and continued for 24 to 48 h. Subsequent antibiotic administration should be based on clinical factors such as fever, radiographic infiltrates, leukocytosis, and sputum Gram stain and culture results. There is no need to provide antibiotic coverage simply because a chest tube is in place.

A study that examined the relationship between pulmonary flora and postoperative infections found that *Haemophilus influenzae* was the most common organism identified from sputum at the time of surgery and that the risk of pneumonia in culture-positive patients was 10-fold that of patients with culture-negative secretions. However, the cultured organisms were sensitive to the antibiotic that was administered, suggesting that the administration of antibiotics may be less important than careful pulmonary toilet in preventing postoperative pneumonia.

Fluids, Electrolytes, and Oral Intake

A routine lung resection is not associated with large fluid losses intraoperatively or sequestration of volume in the third space postoperatively. Most patients should leave the operating room relatively euvolemic. Administration of intravenous fluids consisting of 5 percent dextrose and 0.45 percent normal saline at 50 to 75 ml/h until the patient begins to take oral fluids is usually adequate to maintain intravascular fluid volume. Oral intake should be resumed as soon as the patient is able to take fluids by mouth, but strict aspiration precautions cannot be overemphasized. Urine output should be maintained at 0.5 to 1 ml/kg of body weight an hour to preserve renal function. Oliguria, which is often overtreated by surgical residents, should be tolerated in patients who have undergone elective pulmonary resection. Some surgeons practice aggressive diuresis with the goal of reducing secretions. However, it is not clear that a lower volume of thick, tenacious secretions is preferable to a higher volume of thin secretions that are more readily cleared. Ideally, diuresis should be guided by measurements of intravascular volume. Measurements of central venous pressure correlate poorly with intravascular volume. Many surgeons are reluctant to insert Swan-Ganz catheters into patients after lung resection, particularly after pneumonectomy, because of the possibility of disruption of a pulmonary artery closure. Even if a Swan-Ganz balloon-tipped catheter has been safely introduced into a patient postoperatively, the data should be interpreted with caution because the inflated balloon may have occluded a significant portion of the remaining pulmonary vascular bed, thereby artificially increasing right ventricular after load and decreasing cardiac output. In our practice the measurement of central venous pressure is rarely if ever used and a Swan is reserved for a patient in the intensive care unit that is hypotensive, oliguric, and hypoxic.

Blood transfusion is not necessary unless the patient's hemodynamics and overall clinical scenario call for it. Some

believe that a hematocrit less than 24 percent is an indication for transfusion, but we prefer to use the Hb level, which is less affected by dilution. A decision should be made on each individual patient's situation and a knee-flex reaction to any specific level should be avoided. Transfusion of 250 ml of packed red blood cells increases the intravascular volume by 750 to 1000 ml, because of the movement of extravascular volume into the intravascular space due to plasma oncotic forces. The increase in intravascular volume may be more dangerous than a low hematocrit. Furthermore, the intraoperative administration of blood is probably immunosuppressive and may be associated with a decrease in frequency of 5-year disease-free intervals.

COMPLICATIONS AFTER LUNG RESECTION

Air Leak or Alveolar Pleural Fistula/Chest Tube Management

An alveolar pleural fistula (APF), more commonly known as an air leak, is probably the most common complications after elective pulmonary resection. It is defined as a communication between the pulmonary parenchymal distal to a segmental bronchus and the pleural space. Factors that increase the incidence of air leak include: emphysema, steroids or other medical conditions that slow wound healing, bilobectomy compared with lobectomy, poor chest tube placement, and operations that do not employ techniques that help prevent air leaks. The latter include: pleural tents, pericardial buttressed stapled lines, fissure-less surgery, and checking for air leaks prior to closing.

Chest tubes are commonly placed after thoracotomy to drain blood, serum, and air from the pleural space. The ideal number, type, or size of a chest tube to place after elective pulmonary resection is controversial. There are little data to suggest that one practice is better than another; however, recently several prospective randomized studies have shown that one chest tube works as well as two. After routine lobectomy we have changed our practice based on these studies and now only use one chest tube in patients who do not have a large untreatable air leak or a large fixed pleural space deficit after lobectomy. We use a 28-French soft catheter that is difficult to kink. The advantage of one tube is that it may cause less pain and morbidity, but this advantage is theoretical.

Recently, a great deal of scientific research has been devoted to the best management of chest tubes after pulmonary resection. Until 1998 there were few if any objective data concerning the best setting (i.e., suction or water seal) for chest tubes after lung surgery and most practices were opinions based on where one trained and who one believed. We and others have studied this process using prospective randomized studies. We have developed a classification system for air leaks so as to be able to study air leaks objectively with scientific rigor. The summary of our work is that we prefer to connect the tubes to suction for the night of surgery and then convert to water seal the next morning, especially in patients who have an air leak. If patients have no leak but have a pneumothorax, we prefer suction. In patients with an air leak, we prefer water seal unless there is a pneumothorax, in which case we prefer –10 cm of suction (instead of –20). However, Brunelli, who has carefully and critically studied the problems of air leaks after the pulmonary resection process, prefers water seal during the day and some suction at night. Marshall has corroborated our findings in a prospective randomized study of her own and found that air leaks are best treated by placing chest tubes on water seal instead of suction in the postoperative setting. Brunelli did not find a statistical advantage for water seal; however, he did identify a trend in patients who did not undergo pleural tenting favoring water seal over suction. Thus, the best treatment of most air leaks appears to be water seal in most patients so long as they do not develop a pneumothorax or subcutaneous air on seal.

We have also studied the use of daily chest radiographs, which most surgeons perform to ensure the effective removal of air and fluid from the pleural space. These films, which are labor intensive, costly, and wake the patient in the early morning hours, are not needed if the patient does not have an air leak or other clinical problems. If the postoperative chest roentgenogram in the recovery room after surgery has no significant pathology and the patient is not hypoxic, an everyday early morning chest x-ray is not needed. If a patient develops subcutaneous emphysema and hypoxia and there is a pneumothorax, then suction should be added. We have also studied the problem of air leaks in patients with a concomitant pneumothorax and found that the least amount of suction (usually –10 cm of water) needed to alleviate the pneumothorax or subcutaneous air is best. Other daily management techniques should include "stripping" the tubes in the attempt to remove clots, examining all connections to ensure their integrity, and maintaining appropriate water levels in all drainage bottles. If the leak continues after postoperative day 4, then the patient may be discharged home on a Heimlich valve or a similar device such as an Atrium Express (Atrium USA, Hudson, NH). The chest tube can be removed after 2 weeks even if the air leak remains. A discharge PA and lateral x-ray should be performed prior to leaving, which serves as an important baseline film for later comparisons.

Occasionally, massive subcutaneous emphysema may occur if either the loss of air from the lung into the pleural cavity exceeds the drainage capacities of the chest tube or the tube is positioned away from the site of the air leak (Fig. 99-4). The latter condition is much more common than the former. If this occurs, chest tubes should be examined for patency. Occasionally, a tube will be found to be clamped or twisted by the bed or IV pole, at the skin level or in the subcutaneous fat. If a tube is occluded because of a plug, the tube should be stripped; if this fails to re-establish patency, the tube should be opened and suctioned, using sterile technique, with a nasotracheal suction catheter. Some surgeons irrigate an occluded tube with sterile saline, but because of the possibility of

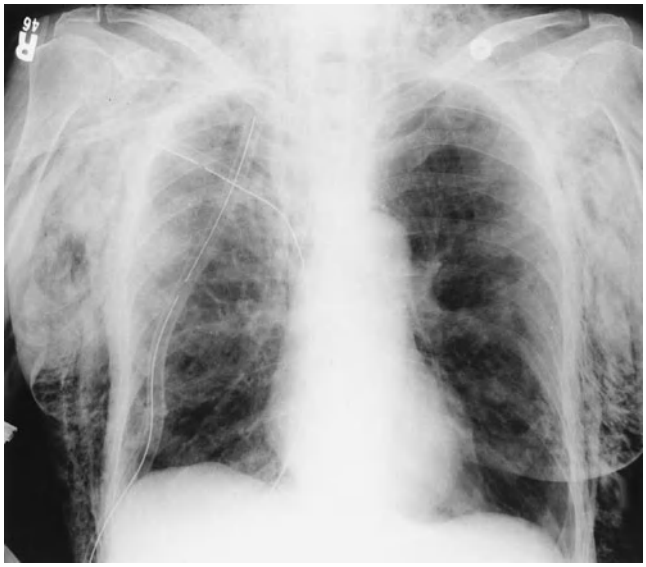

Figure 99-4 Massive subcutaneous emphysema following a pulmonary resection.

infectious contamination this should only be used as a last resort. If all methods fail to re-establish patency of a chest tube, the tube should be removed and a new one inserted.

Although uncomfortable and disfiguring, massive subcutaneous emphysema is rarely life threatening. However, two dangerous situations can arise. First, in patients with tracheostomies, the tube can be displaced into the subcutaneous tissues if the skin is elevated up and away from the tracheal opening. Second, circumferential massive lifting of the skin around the thorax can lead to restriction of normal outward excursions of the rib cage excursion, limiting tidal volume—as in the case of limitation imposed by circumferential eschar in a burn patient. Such emergency situations may require the placement of small skin incisions, usually in an infraclavicular location. We have only had to perform these incisions a few times. In both instances, the patient's eyelids were so swollen with air that the patient could not see. This technique should be reserved for this scenario when the chest tube is in good position, on high (–40 cm of water) suction and patent, and the subcutaneous air is not decreasing.

Postoperative Chest Tube Management

Postpneumonectomy space drainage is managed differently from postlobectomy drainage. After pneumonectomy, the position of the mediastinum is a major concern. Shift of the mediastinal structures either into the pneumonectomy cavity or toward the residual lung can lead to either hemodynamic or respiratory compromise. To allow "balancing" of the mediastinum after a pneumonectomy, most surgeons leave a single chest tube in the pleural cavity. This tube can be removed in the operating room after the patient has been returned to the supine position and is hemodynamically stable. We prefer to leave the tube in overnight attached to a special pneumonectomy balanced drainage system The tube can removed the morning of POD #1 if there is no bleeding.

Amount of Chest Tube Drainage

For resections other than pneumonectomy, chest tubes are removed when there is no air leak and fluid output has decreased. The maximum amount of drainage per day has not been studied. Many surgeon use less than 200 ml a day, but there are no data that higher volumes cannot be accepted. We currently remove tubes with 450 cc per day and this has been a safe cutoff value in over 4000 thoracotomies. Perhaps even a higher number can be used. One needs to ensure there is no blood, chyle, or cerebrospinal fluid prior to removal of the tube as described in the following sections. Removal is performed while the patient executes a Valsalva maneuver. Some argue that it may be best to remove the tube when the patient takes a deep breath out and holds it, as opposed to a deep breath in and holds it. There are little data to suggest the best way to perform chest tube removal, and we are currently performing a prospective study to help answer this question. An occlusive dressing is maintained over the site for 36 hours. Patients should be advised that it is not uncommon to have additional drainage after tube removal.

If the chest tube output in the first several hours after surgery is greater than 200 cc/hour for more than a few hours or if clinically suspected, bleeding must be ruled out. Early surgical re-exploration, before the patient leaves the recovery room, is our preference if the patient's coagulogram (INR, PTT, and platelet count) is normal.. Each individual patient's clinical scenario should be considered. Confirmation that the drainage is blood can be obtained by simple visual inspection of the effluent or, if needed, the effluent can be sent for a confirmatory hemoglobin and/or hematocrit level.

High Output Chest Tube States (Chylothorax, Subarachnoid-Pleural Fistula)

Chylothorax/Subarachnoid Pleural Fistula

A chylothorax is diagnosed when a milky white chylous effusion occurs out of the chest tube in a patient after enteral intake. It consists of intestinal lymphatic fluid (lymphocytes, immunoglobulins, and enzymes) and fat (fat-soluble vitamins, chylomicrons, and triglycerides). Once the patient starts to eat, the diagnosis is obvious. However, the diagnosis should be expected in a patient who is not eating, has a stable hemoglobin and hematocrit, and whose chest tube output is high but the cause is unexplained. The diagnosis is made by sending the effluent for analysis. A triglyceride level greater than 110 mg/dl or a positive Sudan fat stain helps secure the diagnosis. The incidence of a chylothorax has been reported to be about 1 to 2.4 percent after lobectomy, and 0.7 to 1 percent after pneumonectomy.

The treatment of a chylothorax depends on the level of the injury. Most commonly after pulmonary resection, a chylothorax occurs from engorged lymphatics in patients who have positive mediastinal (N2) nodal disease who have

undergone an aggressive nodal dissection. It is also seen in patients who have received neoadjuvant therapy for N2 nodal disease and have undergone a complete thoracic lymphadenectomy. The best treatment of most patients is to make them NPO and ensure the chest tube volume decreases. A medium-chain triglyceride (MCT) diet should then be instituted as well. In this situation re-operation is less helpful, even if fibrin glue is applied to the draining nodal basins, because the lymphatic channels are engorged with obstructed lymphatics from cancer. Radiation has been used successfully in this situation. The patient may be discharged home with the tube in place on the MCT diet for 2 weeks. Finally, we challenge the patient with fatty meals for 2 days. If chest tube output is decreased, the chest tube is removed. However, if the output volume remains high despite compliance on a MCT diet, then complete cessation of all oral intake is needed and total parental nutrient is required. Nutritional parameters should be tested and the white blood cell count monitored. Persistent chylothorax can lead to neutropenia, infection, and malnutrition. Less frequently, a chylothorax following pulmonary resection occurs due to injury to the main thoracic duct. If there is an injury to the main thoracic duct (best determined from a lymphangiogram) or from a high chest tube output greater than 800 c/day, then early re-operation with duct ligation and pleurodesis is best.

Subarachnoid Pleural Fistulas

Subarachnoid pleural fistulas are unusual. The incidence of a subarachnoid pleural fistula after thoracic surgery is very low, but several cases have been reported. They occur most often after trauma but may also complicate thoracic surgical procedures if dissection in the costovertebral angle or excessive traction avulses a thoracic nerve root from its dural sleeve. The most common setting for this to occur is during resection of malignancies invading either the posterior chest wall or vertebral column. However, retraction of the ribs for exposure during a standard posterolateral thoracotomy may generate sufficient traction to avulse a nerve root. The presence of a communication between the subarachnoid and pleural spaces allows for the bidirectional movement of cerebrospinal fluid and pleural fluid: During inspiration, low intrathoracic pressure draws cerebrospinal fluid into the thorax; during expiration, the elevated thoracic pressure forces air and potentially contaminated material outward into the subarachnoid space. A chest tube placed next to the fistulous tract may increase loss of cerebrospinal fluid. As a result, patients may develop headaches, meningismus, paresis, seizures, hemorrhagic infarcts, and obtundation leading to death. Cerebrospinal fluid analysis may be bizarre, owing to the entry of serosanguineous fluid into the subarachnoid space.

The diagnosis of a communication between the subarachnoid and pleural spaces is suggested by visualization of a pneumocephalus on skull radiographs. More specifically, the fistulous communication may be delineated by contrast CT myelography. The time between thoracotomy and clinical diagnosis of the fistula ranges from 5 to 8 weeks. The unpredictable nature of the neurologic sequelae mandates that surgical closure of the dura be carried out as soon as the diagnosis is confirmed via re-operation and application of glues and a muscle flap.

Atrial Fibrillation

Atrial fibrillation is another very common complication after pulmonary resection. The incidence varies due to inconsistent definitions. Its incidence ranged from 12 to 20 percent in several large series, with over 500 patients each with a peak onset on postoperative day 2.

Risk factors for postoperative atrial fibrillation include advanced age (greatest for those more than 70 years old), amount of lung resected, clamshell incision, history of congestive heart failure, and type of pulmonary resection (right-sided pneumonectomy). The incidence is also dependent on the type of pulmonary resection performed. Other identified risk factors for the development of postoperative atrial fibrillation include male gender, previous cardiac arrhythmia, or intraoperative blood transfusions.

The ideal treatment of atrial fibrillation is prevention. A prospective randomized trial from Sloan Kettering showed that prophylactic diltiazem reduced the overall incidence of atrial fibrillation after standard and intrapericardial pneumonectomy. The treatment of postoperative atrial fibrillation depends on the patient's ventricular rate and hemodynamic status. If the patient is unstable, transfer him or her to the intensive care unit and obtain an urgent cardiology consultation. Electrical cardioversion may be needed. However, the vast majority of patients are hemodynamically stable despite a rapid ventricular rate. These patients are best treated with a calcium channel blocker. Often a drip can be used while the blood pressure is carefully monitored. The use of digitalis has fallen out of favor, but this safe and time-tested drug slows the ventricular rate, although it may not restore normal sinus rhythm. More recently, amiodarone has been shown to be effective in the treatment of supraventricular arrhythmias; it is safe even in elderly patients and often restores normal sinus rhythm.

Pneumonia

Pneumonia remains a vexing problem following pulmonary resection. Although the incidence at our institution has been reported to be as low (2.2 percent)in one series, we have reported much higher rates (7–9 percent) in other series. Deslauriers et al. in 1994 and Duque et al. in 1997 reported incidences ranging up to 6 percent. When pneumonia occurs, it wreaks significant morbidity. Risk factors include preoperative hospital stay, immunocompromised state, procedure type (pneumonectomy > lobectomy), compromised pulmonary reserve, smoking, and atelectasis.

Atelectasis, a risk factor for the development of pneumonia, is a common complication after pulmonary surgery itself, as shown by Deslauriers and Ginsberg. Fortunately, most

atelectasis is platelike, discoid, or linear and is subsegmental and has little clinical consequence in the patient with adequate pulmonary reserve. However, atelectasis that is segmental or greater may cause clinical demise and usually requires bronchoscopy. Risk factors for this type of atelectasis are poor cough, impaired pulmonary function, inadequate pain control, diaphragmatic dysfunction, chest wall instability, and sleeve resection. The clinical sequela of this type of atelectasis is ventilation/perfusion mismatch that leads to hypoxemia, impaired alveolar macrophage function, and often pneumonia.

Again, prevention is the best treatment. Chest physiotherapy with vibratory percussion, frequent spirometry exercises, ambulation at least three to four times daily, and secretion control is the mainstay of prevention. Ambulation not only decreases the risk of deep venous thrombosis, but also it helps rehabilitate the patient. It changes pulmonary blood flow and helps improve areas of ventilation/perfusion mismatch. Respiratory treatments entail mist inhalation to loosen secretions, inhaled nebulized bronchodilator, and chest percussion with postural drainage. Pain control allows for deep cough and facilitates adequate mobilization of secretions.

Despite these techniques, sometimes a new infiltrate develops. Sputum cultures should be obtained and broad-spectrum antibiotics started. Although Tobin et al. in 1984 showed that up to 30 percent of new infiltrates in the intensive care unit prove not to be pneumonia, a missed pneumonia in a postoperative patient has high morbidity. Once the culture results are available with a sensitivity panel, the antibiotics should be narrowed to treat the offending organism. This helps prevent the selection of fungus or other resistant organisms. Often there is no evidence of an infiltrate but the patient develops a productive cough, fever, and/or elevated white count. Since the radiological findings of an infiltrate often lag behind a clinical pneumonia, especially in the dehydrated patient, broad-spectrum antibiotics with fungal prophylaxis should be started. If all the cultures are negative, then the antibiotics can be stopped. However, if the infiltrate worsens or if the patient's clinical course deteriorates, bronchoalveolar lavage should be performed to help identify the pathogen and direct antibiotic coverage.

Postoperative Somnolence from Epidural Analgesia

Epidural analgesia has been one of the most important advances in general thoracic surgery in the last decade. It reduces respiratory complications by allowing patients to breathe deeper, walk sooner, and better mobilize secretions. It has allowed us to operate on older and sicker patients. These advantageous effects, however, have resulted in a dual-edged sword. By enabling us to safely operate on older, sicker, and weaker patients with less cardiopulmonary reserve, it has "raised the bar" to such heights that there are now few, if any, patients who cannot tolerate a thoracotomy, wedge resection, or segmentectomy.

Complications from epidural analgesia include accidental entry into the subarachnoid space, hematoma, urinary retention, itching, nausea, and respiratory depression. A "wet tap" can occur when the needle or catheter accidentally enters the subarachnoid space. The former should be immediately recognized by the one placing the epidural. The latter is recognized when the test dose given after insertion results in numbness in the chest area. The most significant and common complication from epidural analgesia is the over-narcotized patient. This is not uncommon and needs to be swiftly recognized and treated. New-onset somnolence may have several etiologies (stoke, intracranial abnormalities, electrolyte imbalances, sundowning, etc.); however, the epidural should not be overlooked as a potential cause. Often, a patient's family members aggressively deliver the analgesia. Clinical staff should discourage this practice. If the patient cannot deliver his or her own pain medicines or does not understand how to use the machine, he or she is a poor candidate for PCA units and should not have one. In this case, traditional pain medicines should be delivered by the nursing staff.

If the patient is somnolent from excessive narcotic analgesia, we prefer to arouse her or him with external stimuli. A chest rub or aggressive bedside maneuvers can quickly wake a patient up, and this helps establish the diagnosis and can eliminate other potential causes. A reliable calm family member in the room can also be helpful, and often one-on-one nursing may be needed. If external stimulation fails, if the patient's oxygen saturations remain low or an arterial blood gas continues to show hypercapnia despite aggressive pulmonary toilet and incentive spirometry, then we prefer to give one-fourth amp of intravenous naloxone (hydrochloride, Endo Labs, Chadds Fords, PA). A higher dose can result in too much rebound pain. If the patient does not awaken after this, a higher dose can be administered after other causes of the new-onset somnolence have been ruled out. This patient is best transferred to the intensive care unit. If the patient arouses with Narcan, we eliminate the epidural basal rate and/or remove the epidural altogether, depending on the situation and postoperative day.

Aspiration

Aspiration is a devastating complication after pulmonary surgery. The incidence is often underestimated because pneumonia may be caused by silent (unsuspected) aspiration. Risk factors for an acute aspiratory event include age (the incidence is greater in elderly patients), altered mental status, and weak and/or sleepy patients. It commonly occurs in the CT scanner because patients are often febrile, weak, and sick (which is why they are often sent to the scanner) and then have to lie flat for considerable lengths of time. It can also occur in a healthy patient who is preparing to go home following an uncomplicated postoperative course. It can take this type of joyous moment and within a few days end with sepsis, multiorgan system failure, and death. Therefore, one's guard against aspiration can never be lowered; its occurrence

must be aggressively avoided. Patients should be instructed to eat only when wide awake and sitting upright at 90 degrees in bed or a chair. Family members should be discouraged from "helping feed the patient to get him or her stronger," especially if the patient is sleepy.

Once aspiration occurs, patients quickly desaturate. Continuous pulse oximetry monitoring until discharge helps signal this event and leads to a quick diagnosis. The diagnosis can be made by history if the patient is still alert or by a family member if he or she was present at the time of the aspiration event. Treatment depends on the patient's clinical status. Most patients should have a nasogastric tube placed, a chest radiograph taken, an arterial blood gas drawn, and other lab work performed. If the patient is in extreme respiratory distress, immediate intubation with bronchoscopy with lavage and cultures should be performed. Broad-spectrum antibiotics should be started immediately, hemodynamics maximized to help perfuse and protect end-organs, and patient should be transferred to the intensive care unit.

Pulmonary Edema

One of the biggest obstacles facing the surgeon who has performed a pulmonary resection is convincing inexperienced anesthesiologists, nurses, residents, and fellows that patients do not require and should not have the "traditional" amount of fluids that most other postsurgical patients need. Pulmonary surgery does not cause large fluid shifts, as does intraperitoneal surgery. Moreover, expansion and deflation of the lung secondary to double lumen tube anesthesia, intraoperative barotrauma and volutrauma to the alveoli, and surgical manipulation of the lung all lead to pulmonary damage and edema. Therefore, the guiding standard to treat pulmonary edema is the principle of prevention. The true incidence is difficult to gauge because of the different etiologies and definitions. The tendency to give the patient large volumes of fluids after epidural placement because of hypotension from the sympathectomy effect must be avoided. This difficult task is only accomplished by continued communication among the surgeons; the rest of the surgical service; and the pain and anesthesia nurses and residents who continually rotate through these services. We prefer the use of alpha agonists such as phenylephrine if mean arterial blood pressure falls after epidural dosing in the patient who is to undergo pulmonary resection after one 250-cc bolus of fluids.

However, despite "running the patient dry," some patients still develop pulmonary edema. Obviously, one needs to ensure that the cause is not cardiac insufficiency. Diuretics remain the mainstay of treatment and the sodium level can be used as a judge of the patient's fluid status. Other factors that need to be considered include the patient's weight gain since surgery, the chloride level, and the urinary osmolarity if diuretics have not been given yet. The more commonly used central venous pressure and/or pulmonary capillary pressure are not needed in most patients unless they are "wet" on chest roentgenogram, hypoxic, hypotensive, and oliguric. If the patient continues to deteriorate, echocardiography should be performed to assess both right and left ventricular function and the patient should be transferred to the intensive care unit for placement of a Swan-Ganz catheter. Blood cultures and appropriate scans should be performed to rule out occult infection and "leaking capillary membranes" from sepsis. If high-dose diuretics are not successful, the patient may have adult respiratory distress syndrome. Management of this complication is discussed elsewhere in this volume.

Right Ventricular Failure

It is possible that some patients with postoperative complications after lung resection experience an acute exacerbation of pulmonary arterial hypertension that leads to right ventricular failure and a decrease in cardiac output. Several reports suggest this possibility. One study, based on the use of thermodilution catheters, found that the right ventricular end-diastolic volume increased from 153 to 177 ml, and that the right ventricular ejection fraction decreased from 45 to 36 percent in the first few postoperative days. Another, using echocardiography, found that patients who developed supraventricular arrhythmias after lung resection had a significant increase in the velocity of the tricuspid regurgitant jet, whereas those who underwent lung resection without arrhythmias did not. A third study of patients undergoing pneumonectomy was unable to find any hemodynamic variable or pulmonary function test that augured early morbidity. It did, however, indicate that a right ventricular ejection fraction of less than 35 percent, pulmonary vascular resistance greater than 200 dyne · s/cm^5, and a pulmonary vascular resistance/right ventricular ejection fraction ratio equal to or greater than 5.0 indicated long-term cardiopulmonary disability. No studies have been reported of patients suffering severe complications, such as pneumonia, in the remaining lung after pneumonectomy to determine whether right ventricular failure is a component of cardiopulmonary dysfunction.

A better understanding of the alterations in right ventricular function might lead to modification in patient management. For example, the anesthetic technique might be altered. In a recent study concerning ventilation of one lung, the administration of propofol was associated with sustained decrease in right ventricular ejection fraction and mean cardiac output as compared with the administration of isoflurane. The use of proper anesthetic agents might minimize the additive effects of hypoxic pulmonary vasoconstriction and surgical resection of the pulmonary vascular bed. In principle, numerous therapies are available to lessen the burden on the right ventricle in the postoperative period. Among the agents proposed are nitric oxide, adenosine, calcium channel blockers, dopamine, and mechanical devices. However, none of these has yet been put to the test.

Early Bronchopleural Fistula

A bronchopleural fistula (BPF) is defined as a communication between a lobar or segmental pulmonary bronchi and

the pleural space. It is different from an alveolar pleural fistula. This difference is not just one of semantics, but also centers around treatment since an alveolar pleural fistula almost never requires a re-operation, whereas a BPF almost always does. A BPF can present as an early complication but more commonly is a late one. The incidence of a BPF has been reported to be 4.5 to 7 percent after a pneumonectomy(8.6 percent if right pneumonectomy and 2.3 percent for left pneumonectomy), about 1 percent after a lobectomy,and 0.3 percent after a segmentectomy. However, a bronchopleural fistula after lobectomy that was performed for cancer is very rare. Risk factors for a BPF are divided into patient characteristics and intraoperative techniques. The former include: infectious etiology, preoperative radiation, type of procedure (right pneumonectomies have the greatest incidence), immunocompromised state such as history of solid organ transplant, and comorbidities such as diabetes. Intraoperative technique risk factors include: surgeon inexperience, a long stump, leaving lymph nodes on the bronchus, and injuring the arterial blood supply to the bronchus.

When a BPF presents as an early complication, the patient develops a new large air leak he or she did not have before. It usually is a continuous leak as described by the RDC classification system of air leaks. Treatment should be immediate recognition, which requires a high index of suspicion any time the air leak suddenly increases. Usually it can be confirmed with bronchoscopy; however, this test can be falsely negative, as a small BPF can be missed. If the diagnosis remains in question, a Xenon ventilation scan can be performed. (This is difficult if the patient is intubated.) The Xenon gas can be seen escaping the airway, traversing the pleural space, and going into the chest tube and drainage system. This secures the diagnosis. Once diagnosed, the BPF should be treated with reoperation using muscle flaps or omentum as further described elsewhere in this volume.

Postpneumonectomy Pulmonary Edema

Postpneumonectomy pulmonary edema is a rare but lethal complication of pneumonectomy. For several reasons, the patient who has undergone pneumonectomy is thought to be at increased risk of pulmonary edema. First, although the removal of one lung is well tolerated if the pulmonary vasculature is normal, if preexisting pulmonary vascular disease is present, the reduced pulmonary vascular bed may be unable to accommodate the cardiac output without an inordinate increase in pulmonary arterial pressure. Second, disruption of lymphatics associated with mediastinal lymph node dissection may interfere significantly with the clearance of fluid from the lung. In the presence of these two predisposing factors, overzealous administration of fluid may lead to the formation of lethal pulmonary edema.

The clinical presentation of postpneumonectomy pulmonary edema is that of a relatively uneventful initial 24- to 48-h postoperative period, followed by a relentlessly increasing need for respiratory support, usually culminating in death within 24 to 48 h. The pulmonary edema progresses despite aggressive efforts to effect diuresis and other supportive measures (Fig. 99-5). Current therapy is directed at limiting the administration of fluids perioperatively and providing supportive measures if the complication should arise.

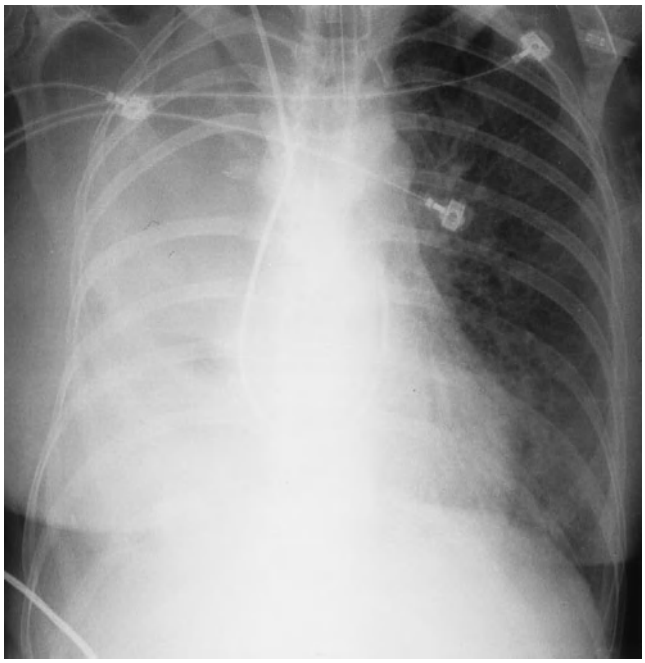

Figure 99-5 Postpneumonectomy pulmonary edema with onset 48 h after extrapleural pneumonectomy. There is a diffuse interstitial infiltrate present that was heralded by the insidious development of hypoxemia in this otherwise healthy 60-year-old woman.

Postpneumonectomy syndrome is a rare complication manifested by cough and dyspnea on exertion that usually follows right pneumonectomy. It is due to progressive mediastinal shift with compression of the left mainstem bronchus by the vertebral column. The underlying cause of this complication of pneumonectomy is herniation of the contralateral lung into the vacant pleural space, causing compression of the mainstem bronchus between the aorta, pulmonary artery, or vertebral column (Fig. 99-6). Repair is directed toward repositioning and stabilizing the mediastinum in the midline by a combined procedure of cardiopexy and placement of pliable, variable-volume tissue expanders into the empty pleural space. Cardiopexy alone probably provides insufficient protection against recurrence. Before surgical repositioning, it can be difficult to assess whether significant tracheomalacia is present in the compressed segment. Persistent airway narrowing and symptoms of obstruction following correction of mediastinal shift may require placement of an airway stent or reoperation for resection of the affected bronchial segment.

Empyema

Empyema is an uncommon complication after pulmonary resection. It is most often seen in patients who have undergone pneumonectomy. It is estimated to occur in about 2 to 16 percent of post-pneumonectomy patients. In a study by

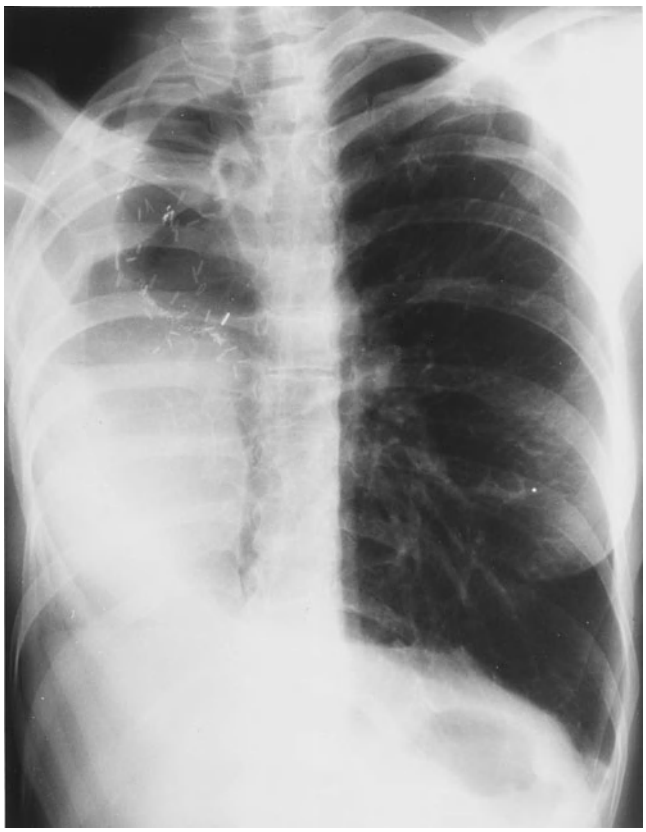

Figure 99-6 Marked shift of the mediastinum with hyperinflation of the left lung and tethering of the left mainstem bronchus over the vertebral column, characteristic of postpneumonectomy syndrome.

Varela, empyema was the most common cause of recidivism after pulmonary resection (18/727), 2.5 percent of patients. The primary risk factor has been cited to be pneumonectomy with an associated BPF. Less commonly cited risk factors include anatomic extent of disease (no association with stage I cancer, some association with stages II and III cancer), degree of surgical manipulation, and a compromised immunological host.

The treatment is control of the pleural space. This can be established by chest tube placement, video-assisted thoracoscopic approach, or most commonly a redo thoracotomy with a muscle flap. If there is any question that an early BPF is the cause of the early empyema, then redo thoracotomy with muscle or omental harvesting is mandatory to not only drain the empyema and decorticate the lung, but to also buttress the open bronchus.

Pulmonary Insufficiency

Despite preoperative tests and pulmonary preserving techniques, pulmonary insufficiency can still occur after pulmonary resection. The inability to extubate a patient immediately after the operation (which should be extremely rare) is a poor prognostic sign. The difficulty usually arises on postoperative day 2 or 3 secondary to pneumonia, poor cough effort, or pulmonary edema.

The patient often begins to develop signs of respiratory distress prior to seeing an infiltrate on chest roentgenogram. Sputum cultures should be obtained and immediate broad-spectrum antibiotics should be started. These should be tailored to the cultures and sensitivities reported later. Pulmonary mechanics must be maximized; this includes minimal intravenous fluids, aggressive chest physiotherapy, continuous respiratory treatments with bronchodilators, incentive spirometry, frequent ambulation with physical therapy, control of secretions, and nutritional support. If the patient can not clear his or her own secretions, then nasal tracheal suction should be used to "encourage" coughing. Nasal tracheal suctioning via a nasal trumpet or even mini-tracheostomy affords the surgeon other methods to help clear the airway and avoid recurrent atelectasis and pneumonia.

If the patient is somnolent, she or he needs to be aroused and treated as described in the preceding. Arterial blood gases should be performed to rule out hypercapnia. If this fails, mini-tracheostomy can be performed to manually suction the upper airways, and bronchoalveolar lavage should be used to obtain sputum samples to identify the offending organisms.

Renal Insufficiency

It is not uncommon for patients to have a increase in their creatinine level after pulmonary resection. Most patients are elderly and thus have reduced renal reserve, and many are hypotensive with the epidural and the low amount of fluids administered. Thus, early recognition of this problem entails checking the creatinine level on all patients who create less than 0.5 mg/kg per hr of urine. Treatment is early recognition, the removal of renal toxic agents such as Toradol (ketoconazole), and the gentle rehydration of the patient.

Postoperative Hemorrhage

The incidence of postoperative hemorrhage after elective general thoracic surgical procedures in a non-coagulopathic patient is extremely low, almost unheard of. We, like most general thoracic surgeons, have limited this complication and currently have an incidence of 0.3 percent (7 patients in our last 2400 thoracotomies) that require re-exploration for bleeding. In all circumstances, bleeding was from a small vessel (or the bronchial artery in one patient). This low incidence, shared by many others, is achievable by having the attending surgeon present during the entire opening and closing of the chest. The pulmonary artery should be handled with meticulous care, and it should be carefully dissected. We prefer double ligation or stapling. The vein can be safely handled with a stapler as well. Prior to chest closure, the major vascular structures in addition to all other sites of surgical dissection should also be re-examined to ensure hemostasis. The inferior pulmonary ligament, which usually contains a small artery, should be checked. We perform a complete lymph node resection in all patients with bronchogenic carcinoma;

therefore, all lymph node stations are potential sites of postoperative bleeding. This is especially true of the #7, subcarinal area. There is a large artery that feeds the subcarinal lymph nodes that comes off the carina. It should be visualized and ligated. This is often difficult to do, especially on the left side. Excessive cauterization should be avoided, especially in the aorta-pulmonary window lymph node area on the left and the paratracheal area on the right, to avoid injury to the recurrent laryngeal nerves. Bleeding can also occur from the pulmonary parenchyma, especially after wedge resection. This area needs to be re-evaluated prior to chest closure. The surface of the undercut rib both anteriorly and posterior should be carefully examined also. Finally, the chest tubes sites and pericostal sutures sites (if used instead of the preferred intracostal sutures) should be examined from inside the chest before closure. The branches of the bronchial artery that can spasm and later bleed should be identified and clipped or tied if dissected.

If a patient is having excessive postoperative bleeding of greater than 200 ccs/hr (i.e., blood loss alone; not chyle, cerebrospinal fluid, or transudative effusion) for 2 to 4 consecutive hours, a coagulogram should be preformed. This panel of blood work includes an INR, PT, PTT, and platelet count. Any abnormalities should be corrected. If the mediastinum and/or pleural space do not have retained clots, and the coagulogram is abnormal, reoperation can be avoided if the underlying problem is corrected and the bleeding slows down. However, if there is residual clot in either space, this often leads to a local consumptive coagulopathy and the patient will continue to hemorrhage until the clot is fully evacuated, either via the chest tubes or usually by reoperation.

Pulmonary Torsion

During a pulmonary resection, an extensive dissection is usually performed around the hilum for division of the pulmonary vessels. In addition, after an upper lobectomy, the inferior pulmonary ligament is divided to allow the lower lobe to rise within the pleural space to obliterate the residual apical space. Unfortunately, on rare occasions the increased mobility of these structures can lead to torsion of all or part of the residual lung, causing venous outflow obstruction and, possibly pulmonary gangrene. The right middle lobe is at greatest risk, especially after a right upper lobectomy, since the right middle lobe fissure-like connection to the right lower lobe is often diminutive. This complication should be avoidable by the surgeon, who should prevent it by tacking the middle to the lower lobe prior to closing the chest. However, it can still occur. Any portion of residual lung can be affected (Fig. 99-7). To reduce the risk of middle-lobe torsion, sutures or staples are used to secure the middle lobe to the remaining right lower lobe or upper lobe after lobectomy.

Pulmonary torsion may be suggested by the radiographic finding of consolidated lung, in association with fever, leukocytosis, and purulent occasionally bloody sputum. Bronchoscopy may be helpful if a twisted bronchus can be demonstrated. The treatment is immediate surgical exploration with re-rotation of the affected lung, followed by fixation to surrounding structures. If the lung is not viable, lobectomy or complete pneumonectomy may be required.

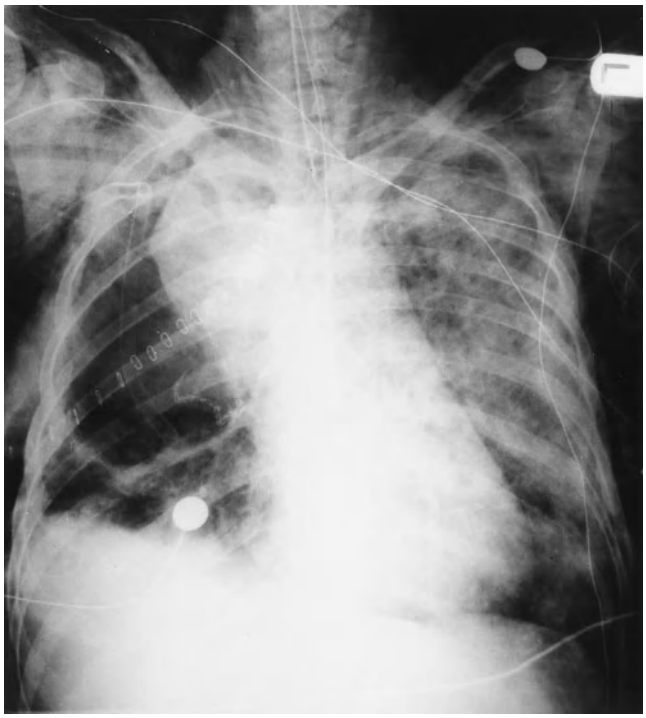

Figure 99-7 Consolidation of the right middle lobe caused by torsion following right upper lobectomy.

Recurrent Laryngeal Nerve Injury

In a patient with lung cancer, the recurrent laryngeal nerves are vulnerable to injury because of either direct invasion by malignancy or injury during surgical dissection. The left vagus nerve is at greater risk than the right because of its course from the neck down into the left aspect of the mediastinum and across the aortic arch before giving off the left recurrent laryngeal nerve at the level of the inferior border of the aortic arch (Fig. 99-8). The nerve passes around the ligamentum arteriosum and "recurs" along the left tracheoesophageal groove. If either nerve is injured, unilateral vocal cord dysfunction results in hoarseness, an increased risk of aspiration, and marked decrease in the effectiveness of cough and the ability to clear secretions. Neurapraxia may resolve within weeks or last for 6 to 9 months. For the patient with limited pulmonary reserve who has undergone surgery with its attendant postoperative transient decrease in pulmonary function, vocal cord paralysis can be a devastating problem and may mean the difference between recovery and respiratory failure secondary to aspiration.

Surgical correction of unilateral vocal cord paralysis is becoming increasingly popular. Techniques include injection of Gelfoam for temporary medialization, Teflon for permanent medialization, or surgical placement of a hand-crafted silicone elastomer implant. The success rate, as measured by

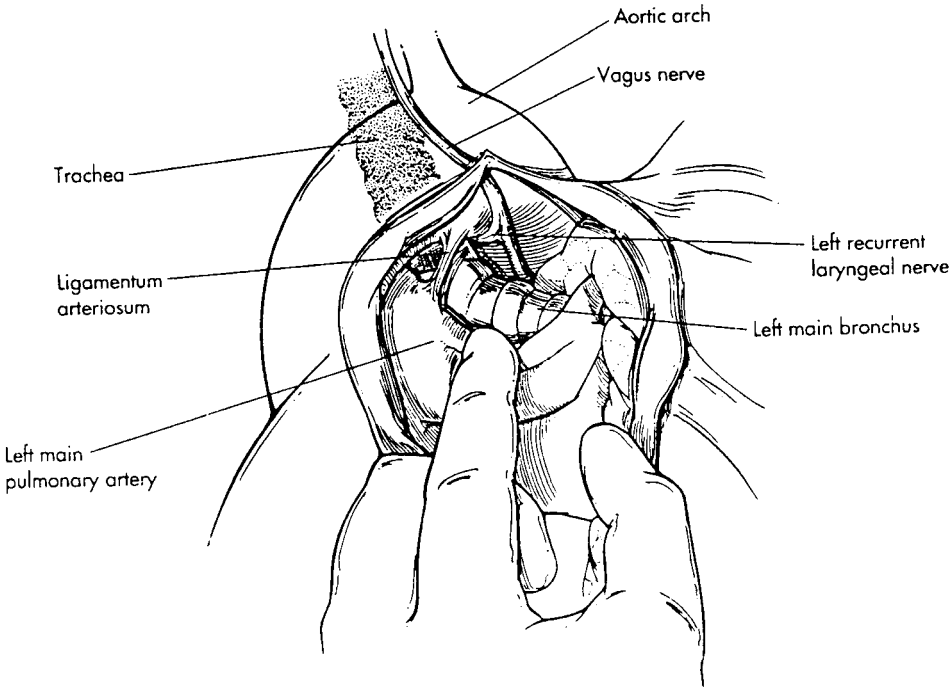

Figure 99-8 Location of the left recurrent laryngeal nerve as it takes its origin from the vagus nerve at the level of the aortic arch. Note its position relative to the ligamentum arteriosum.

symptomatic improvement in dysphonia, aspiration, or incidence of pneumonia, exceeds 90 percent.

Pulmonary Herniation

Herniation of the lung outside of the chest is uncommon but can occur in immunocompromised thin patients. The patient complains of a bulge with coughing or sneezing and a CT scan diagnoses the pulmonary parenchyma in an extrathoracic position. Treatment is surgical re-closure and approximation of the ribs.

CONCLUSION

The key to the management of postoperative complications is full understanding of the cardiopulmonary physiologic changes that occur after pulmonary resection, either using thoracotomy or video-assisted techniques. Despite careful patient selection, meticulous operation, and hypervigilant postoperative care, many of the described complications occur. Early recognition secondary to a high index of suspicion along with prompt treatment leads to the minimization of the morbidity of these unwanted postoperative events.

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Thoracic Trauma

Larry R. Kaiser • Francis W. DiPierro

Chest trauma can be classified as either blunt or penetrating. *Blunt injury* most commonly results from motor vehicle accidents but may also result from falls or beatings. *Penetrating injuries* are the result of stab or gunshot wounds and occasionally of impalement.

The approach to diagnosis and treatment of injuries to the chest depends greatly on the mechanism of injury that influences the incidence and type of associated injuries. Most, if not all, gunshot wounds of the chest require thoracotomy for management, whereas blunt injury usually is managed nonoperatively. The possibility of associated injuries, especially to the abdomen, must also be kept in mind and thoroughly investigated prior to initiating a treatment plan. This is especially important for penetrating injuries that occur in the so-called intermediate zone, in which the chest, abdomen, or both may be involved. An injury of the anterior chest in the fifth intercostal space may not involve intrathoracic structures, but the damage may be confined solely to the abdomen.

The type of weapon as well as the site of injury is particularly important. The physician managing a penetrating chest injury needs to know what type of knife was used because it is crucial to know the length of the blade to assess the possibility of visceral injury in either the chest or abdomen. Likewise for gunshot wounds, it is important to know the type of gun used to better address the potential extent and severity of the resultant injury. Often a determination of the type of gun may be made based on the appearance of the bullet seen on radiographic studies.

Physicians managing patients with chest injuries must be prepared to make quick but accurate judgments and decisions and to act on them. With the development of trauma systems in most cities, more critically injured patients are surviving long enough to make it to the hospital, and the time spent prior to taking the patient to the operating room may make the difference between survival and mortality. The thoracic surgeon should be involved as soon as the patient arrives in the emergency room, although many chest injuries do not require operation.

INITIAL MANAGEMENT

Ensuring Airway Patency and Breathing

The initial goal in resuscitation of any patient sustaining a traumatic injury is to establish adequate oxygenation and ventilation. Of primary importance is the establishment of a patent airway. Objects commonly found obstructing the

This chapter has been slightly modified from the version that appeared in the third edition of *Fishman's Pulmonary Diseases and Disorders.*

airway following chest trauma include the patient's tongue, teeth, blood, secretions, or vomitus. Foreign objects as well as intrinsic laryngeal tissue, as in laryngeal fracture, can also obstruct the airway. As initial management, an oropharyngeal or nasopharyngeal airway can be inserted to maintain patency of the airway. Endotracheal intubation may be performed for apnea, to protect the airway from blood or secretions, or for hyperventilation in cases of severe head trauma. In cases of severe maxillofacial injury, a tracheostomy may need to be performed.

Once patency of the airway has been established, it must be verified that breathing is adequate. The patient's chest is fully exposed and inspected for evidence of rise and fall with respiration. In the intubated patient, a carbon dioxide monitor can be connected to the endotracheal tube to establish that gas exchange is adequate and that the tube is properly situated. Mechanical ventilation may be instituted as necessary.

Emergency Department Interventions

Once adequate oxygenation and ventilation have been established, the primary resuscitation effort must rule out other life-threatening chest injuries. Simple, open, and tension pneumothoraces, hemothoraces, and pericardial tamponade are injuries that require immediate attention.

Simple Pneumothorax

Simple pneumothorax is created when a tear in the pleura allows entry of air into the pleural space with resultant loss of negativity in intrathoracic pressure. If an injury to the lung parenchyma produces an airleak, the air accumulates in the pleural space with each breath markedly increasing intrathoracic pressure, thereby shifting the mediastinum toward the opposite hemithorax (Fig. 100-1). This so-called tension pneumothorax is immediately life threatening because of the limitation of vena caval blood flow, which results in hypotension, tachycardia, and cardiac arrest.

Treatment of simple pneumothorax requires insertion of a chest tube into the pleural space under sterile conditions, usually through the fifth or sixth intercostal space in the anterior axillary line, and connection of the tube to suction. In cases of tension pneumothorax, the pressure is initially relieved by placement of a standard 16-gauge needle in the anterior second intercostal space in the midclavicular line. This maneuver is followed by placement of a chest tube for definitive management.

Tension Pneumothorax

The diagnosis of tension pneumothorax should always be considered in a patient who has sustained penetrating chest trauma. It is less likely to occur after blunt trauma. In this circumstance, the likelihood of its occurrence increases with the severity of the injury to the chest wall (e.g., when rib fractures puncture the lung parenchyma). A high index of suspicion for tension pneumothorax should be maintained, while remembering that insertion of a large-bore needle into the second intercostal space may result in injury to the lung if the diagnosis is incorrect.

Clinical findings that support the diagnosis of tension pneumothorax include hypotension, absent breath sounds on the involved side with tympany on percussion, tracheal deviation toward the opposite side, and difficulty in mechanically ventilating the patient because of high airway pressures. Once the diagnosis of tension pneumothorax is suspected, treatment should be initiated immediately without waiting for chest radiograph confirmation. A rush of air exiting via the needle confirms the diagnosis as treatment is initiated. It should always be kept in mind that not every pneumothorax that results from trauma is a tension pneumothorax.

Pneumothorax and Open Chest Wound

When a pneumothorax is associated with an open chest wound after penetrating trauma, initial management is designed to restore a seal to the thoracic cavity. This is accomplished by applying a sterile occlusive dressing to the wound immediately followed by placement of a chest tube. The dressing allows some air to escape from the pleural space but does not allow air from the outside to enter.

Hemothorax

Both blunt and penetrating injuries of the chest may be associated with hemothorax, but this finding is far more common following penetrating trauma. Absence of breath sounds over the injured hemithorax and dullness to percussion are the characteristic physical findings. When the quantity of blood in the chest is small, the chest radiograph, which is usually taken as an anteroposterior film while the patient is supine, may only show haziness on the involved side (Fig. 100-2). On rare occasion, hemothorax, which is usually the result of injury to the lung parenchyma, can reproduce the physiological

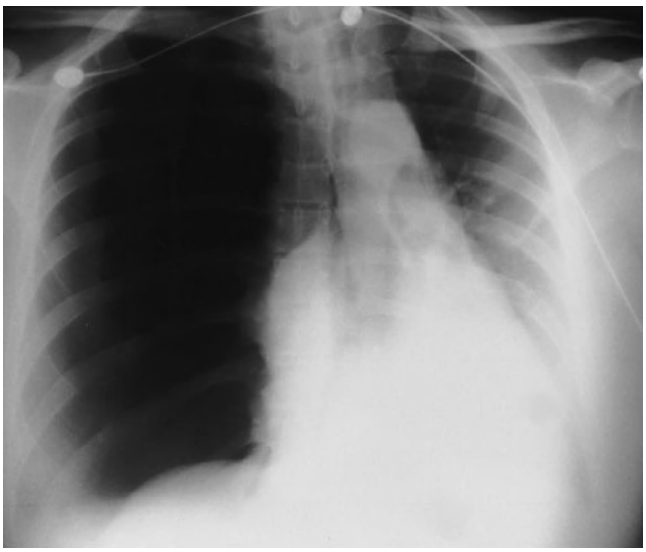

Figure 100-1 Right tension pneumothorax. Note the marked shift of the mediastinum to the left and the total absence of lung markings on the right.

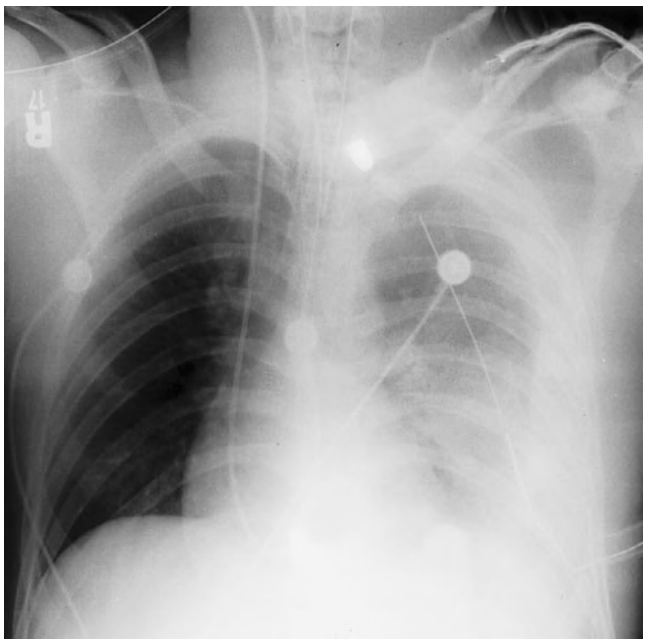

Figure 100-2 Hemothorax following a penetrating wound to the left chest showing the characteristic haziness seen on a supine film. The blood has been incompletely drained despite placement of a large-bore chest tube.

disturbances of a tension pneumothorax by increasing intrapleural pressure. Injury to the pulmonary artery or veins or the aorta is usually fatal before the patient reaches the hospital, but occasionally these patients do reach the emergency room. This type of massive exsanguination is usually obvious because of the clinical findings, and immediate transfer to the operating room is mandatory for any chance to save the patient's life.

For the more common type of hemothorax, which is due to lung parenchymal injury, a large-bore (36 Fr or greater) chest tube should be inserted, and blood volume replacement should be initiated simultaneously. Additional therapeutic maneuvers are based on the documentation of continued blood loss. Depending upon the extent of parenchymal injury, bleeding may have ceased by the time the chest tube is inserted. Thus, after the accumulated blood has drained, little if any further drainage will occur. If blood continues to drain, and the patient is hypotensive and tachycardic in spite of volume replacement, exploration of the chest is indicated. An intraabdominal injury should be ruled out; if suspected, the appropriate procedures should be initiated. Even in the hemodynamically stable patient, if blood continues to drain from the chest tube at a rate of greater than 200 ml/h for 2 or 3 h, the patient should be surgically explored. Following chest tube insertion, if the decision is made to observe the patient, a chest radiograph should be repeated within several hours of the insertion to ensure that blood is not accumulating in the chest.

Cardiac Injury

Penetrating injury to the chest may involve not only the pulmonary parenchyma but also, not infrequently, the heart. Many patients with these injuries live long enough to make it to the hospital despite evidence of cardiac tamponade, which can be managed temporarily by massive replacement of blood volume. Cardiac tamponade results when the intrapericardial pressure becomes high enough to impede the low-pressure venous return to the heart resulting in circulatory collapse. Aspiration of as little as 10 to 20 ml of blood from the pericardial space often relieves intrapericardial pressure sufficiently to restore adequate circulation until the patient can be transported to the operating room for definitive repair of the inciting injury to the myocardium, usually the right atrium or ventricle. On rare occasion, blunt chest injury may cause cardiac tamponade. However, although myocardial rupture secondary to blunt trauma is usually fatal, an occasional patient with rupture of the atrium survives to reach the emergency room.

Emergency Room Thoracotomy

Occasionally, a patient with a penetrating injury to the chest who arrives at the emergency department loses vital signs soon after arrival. A thoracotomy performed in the emergency room allows immediate control of an exsanguinating thoracic injury and enables open cardiac massage while the patient is being transported to the operating room. The decision to perform an emergency room thoracotomy is a difficult one and requires consideration of the time required to transport the patient to the operating room in the particular hospital. Indications for emergency room thoracotomy vary from institution to institution. In general, emergency center thoracotomy is indicated in patients with exsanguinating chest injury who become pulseless after arrival but in whom some myocardial electrical activity persists. The procedure is rarely indicated in the patient who arrives without vital signs, since the success rate in resuscitating these individuals is dismal. Application of a clamp across the thoracic aorta, open cardiac massage, and simultaneous volume replacement are all performed once the chest is opened to restore blood flow to the brain and heart. If the hemorrhage originates in part from the pulmonary hilum, a vascular clamp or the surgeon's hand can be placed across the hilum. In addition, for penetrating cardiac wounds, the pericardium is opened and the injury repaired.

The survival rates for patients undergoing emergency center thoracotomy is less than 10 percent. Feliciano and coworkers reported an 8.1 percent survival rate with 335 emergency center thoracotomies performed over a 7-year period. In most series, the procedure has been successful most often in patients with stab wounds as opposed to gunshot wounds and in patients in whom the injury is confined to the chest.

BLUNT THORACIC TRAUMA

Tracheobronchial Injuries

Isolated injury to the tracheobronchial tree is unusual because of the proximity of other major structures, specifically,

the great vessels. However, it does occur occasionally. Tracheal disruption may follow blunt injury to the neck and is usually identified by the presence of subcutaneous emphysema. Intuitively, it is not obvious how an individual can survive after complete disruption of the cervical trachea. However, survival is due to the pretracheal fascia, which ensheathes the trachea and is stout enough to preserve sufficient integrity of the airway to allow air to pass into the distal trachea, albeit with some difficulty.

The more common injury to the tracheobronchial tree that results from blunt trauma is disruption of a mainstem bronchus, usually resulting from sudden deceleration either as a result of a motor vehicle accident or fall. Since the left mainstem bronchus and carina are tethered by the aortic arch, sudden deceleration of this fixed structure may result in a tear or total disruption of either the right or left main bronchus. Blunt injuries causing tracheobronchial disruption are often associated with simultaneous injuries to adjacent structures including the great vessels (especially the descending thoracic aorta), esophagus, manubrium, mandible, and cervical spine. Usually such coincident injuries are fatal. Those patients with a tracheobronchial injury who do survive long enough to reach the hospital usually have only the isolated injury, implying individuals with other injuries have already died in the field. The isolated tracheobronchial injury occurs most often in young people in whom the blood vessels, including the aorta, are somewhat more compliant than the tracheobronchial tree, so that these vessels remain intact despite trauma to the chest, which disrupts the tracheobronchial tree.

How tracheobronchial injuries present clinically depends on the type of injury. Rupture of the airways resulting from blunt trauma commonly presents with subcutaneous emphysema, although this manifestation may be too subtle to appreciate by clinical examination. Other associated findings include hemoptysis, respiratory distress, change in voice, pneumothorax, or hemothorax. Pneumothorax is only present if the airway rupture communicates with the pleural space, a circumstance that does not always occur because of the dense, fibroconnective tissue around the carina and mainstem bronchi. In fact, more commonly, the only finding, even in the presence of complete bronchial disruption, is the presence of deep cervical or mediastinal air that is only appreciated on the chest radiograph (Fig. 100-3). The diagnosis of airway rupture has to be suspected if the small amount of mediastinal or cervical emphysema displayed by the chest radiograph is to be detected by physical examination. Detection of mediastinal or cervical emphysema is rendered more difficult by the rarity of tracheobronchial injuries (i.e., no more than 2 to 3 per year) seen in major trauma centers.

As noted, pneumothorax may follow bronchial disruption, but the evidence of an airway injury is usually not apparent until after a chest tube is placed. When suction is applied to the chest tube, the patient may become significantly more dyspneic, a situation which is only relieved by discontinuing the suction. Also, as a consequence of the large air leak, the lung expands incompletely despite increasing suction. Although the combination of these findings almost ensures the diagnosis, bronchoscopy should always be done even if suspicion is low that the airway is injured. Bronchoscopy clearly delineates the injury and confirms the location, information that is crucial for planning the operative approach.

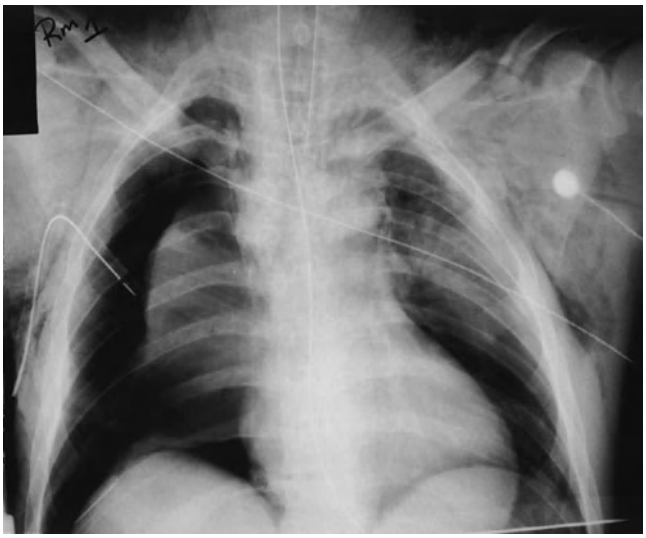

Figure 100-3 Traumatic rupture of the right main bronchus following a motor vehicle accident. This radiograph demonstrates the classic findings of a pneumothorax that fails to resolve despite chest tube placement and subcutaneous and mediastinal air. Often the findings are more subtle.

Management of the patient with tracheobronchial injury begins with making sure that the patient has a reliable airway. In patients with suspected injury to the cervical or mediastinal trachea, intubation of the trachea beyond the injury is performed under direct vision under bronchoscopic guidance. If airway injury is not suspected, blind endotracheal intubation may suffice but may result in further problems. Tracheostomy should be avoided if at all possible. In patients with unilateral bronchial injury, intubation of the opposite main bronchus is desirable.

Airway Ruptures

Airway ruptures occur in transverse, longitudinal, or combined directions. The most common tracheal injury occurs between tracheal rings. Longitudinal injuries occur along the membranous portion of the airways. Most tracheobronchial ruptures occur within 2.5 cm of the carina, and the trachea or bronchi may be completely disrupted.

The principles of managing airway rupture include debridement of devitalized tissue and primary repair for tracheobronchial injuries. Lesions of the distal trachea, carina, and the right mainstem bronchus are approached via a right thoracotomy. This approach also provides excellent exposure of the proximal left main bronchus, but the way in which an injury on the left should be managed is greatly influenced by the bronchoscopic findings. A partial disruption of the proximal left mainstem bronchus is usually approached by way of a right thoracotomy with mobilization of the carina.

Complete disruption on the left usually should be managed by way of a left thoracotomy. Exposure of the proximal left main bronchus from the left side is difficult because of the aortic arch. Often the arch must be encircled and retracted superiorly in order to gain adequate exposure. Division of the ligamentum arteriosum also facilitates exposure of the left main bronchus at its origin.

The bronchus is either repaired or reanastomosed with sutures so as to be airtight. Rarely is pulmonary resection required, although lobectomy may have to be carried out if a lobar bronchus is involved. Pneumonectomy should never be required unless the lung parenchyma has been virtually destroyed. In cases involving complex injuries to the distal trachea, carina, or mainstem bronchi, providing adequate oxygenation and ventilation during the operation without the use of cardiopulmonary bypass may be difficult, but this is distinctly unusual. Usually the airway is managed just as it is in elective carinal or main bronchial sleeve resections, scrupulously avoiding the use of extracorporeal oxygenation and systemic heparinization.

Pulmonary Contusion

Pulmonary contusion occurs during blunt thoracic trauma as the force of impact is transferred through the chest wall to the lung parenchyma. The anatomic manifestation of contusion is disruption of alveolar-capillary interfaces and resultant collection of blood and protein in the interstitium and alveoli. Both the physiologic derangements and the presentation of patients with this type of injury are variable and range from asymptomatic to severe hypoxia and the need for mechanical ventilation. This variability in presentation reflects the fact that contusion often occurs with associated injuries that require resuscitative measures, which can add to the anatomic insult. Also, the extent of the contusion may be quite variable.

In a classic series of experiments, Trinkle and colleagues studied the effects of crystalloid versus colloid resuscitation on the severity of pulmonary contusions in dogs. To mimic the clinical situation in which pulmonary injury is often associated with significant blood loss from associated injuries, the dogs also underwent blood loss that called for restoration of blood volume. Crystalloid intravenous fluid resulted in more severe pulmonary damage than did the use of colloidal solutions. In addition, mechanical ventilation and furosemide therapy decreased the severity of the pulmonary lesion. Hence, in patients suspected of having extensive pulmonary contusion, restoration of blood volume using crystalloid should be accomplished carefully to avoid increasing the injury.

In addition to associated injuries, preexisting medical conditions greatly influence the course of patients with pulmonary contusions. Patients with chronic obstructive pulmonary disease, heart failure, or renal failure are predisposed to shunting in the involved segment of lung parenchyma and should be mechanically ventilated at the first suggestion of systemic hypoxemia. Similarly, the degree of pulmonary vascular reactivity influences the severity of injury from pulmonary contusion and the subsequent clinical course. Pulmonary vasoconstriction occurs after pulmonary contusion, apparently serving to reduce that intrapulmonary shunt created by perfusing injured, poorly ventilated parenchyma. Patients unable to vasoconstrict adequately experience larger shunt fractions than do those with more reactive pulmonary vasoconstriction. Although the value of classifying patients as "good vasoconstrictors" or "bad vasoconstrictors" is not clear, the distinction may help to determine treatment strategies, including the decision to abandon conservative management and proceed with limited pulmonary resection.

Pulmonary laceration often complicates pulmonary contusion. In the transfer of energy to the chest wall during blunt trauma, shear forces are often generated that are capable of tearing the lung. Although most lacerations resolve spontaneously, elastic recoil of the lung can extend the laceration and form a cavity or a pulmonary pseudocyst. Potential complications of these cysts include infection, abscess formation, hemoptysis, air leak, adult respiratory distress syndrome (ARDS), and death. Although secondary infection of these pseudocysts is rare, it does occur and is treated in the same way as uncomplicated lung abscesses with sputum culture, directed antibiotic therapy, and pulmonary toilet. Failure of an infected pseudocyst to respond requires either surgical drainage and debridement or drainage via a percutaneous catheter introduced with the guidance of computed tomography (CT).

The findings on chest radiograph in pulmonary contusion range from small nodular patchy infiltrates to frank consolidation involving a significant portion of the pulmonary parenchyma (Fig. 100-4). These findings become evident

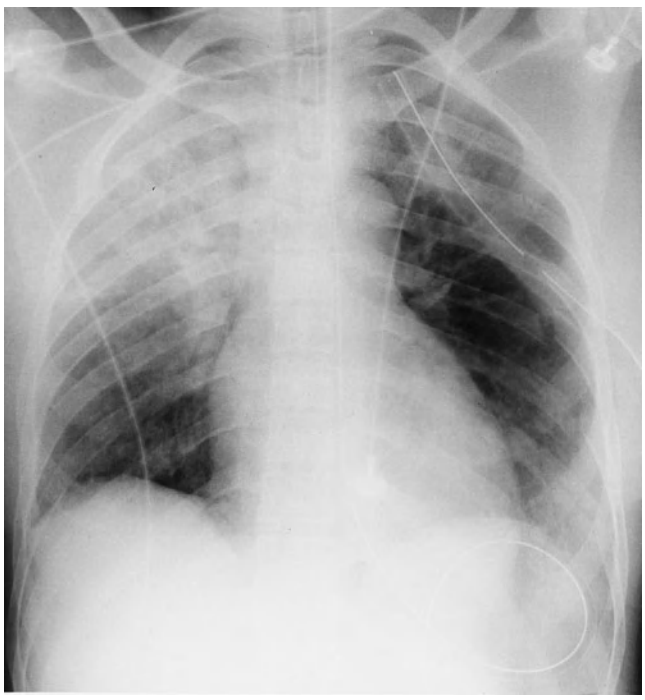

Figure 100-4 Right pulmonary contusion following blunt chest trauma associated with left-sided rib fractures.

within a few hours of injury in the classic presentation of pulmonary contusion. The usefulness of the chest radiograph in the management of contused lung is limited by the time lag between the appearance of abnormalities in gas exchange and the appearance of the injury on chest radiograph. Nonetheless, the chest radiograph is valuable in following resolution. Chest CT scans define the extent of injury more accurately than do chest radiographs and can allow rapid classification and quantification of pulmonary parenchymal damage.

The management of pulmonary contusion consists mainly of adequate analgesia and pulmonary toilet along with supplemental oxygen as needed. Endotracheal intubation and mechanical ventilation may be required depending on the extent of the contusion and the presence of associated injuries. Avoidance of overhydration is particularly important. Serial chest radiographs can be used to follow the course of a pulmonary contusion until it resolves, although clinical evidence of improved gas exchange is really the bottom line as far as the patient is concerned.

Rib Fracture and Flail Chest

Blunt trauma to the chest may fracture ribs or produce flail chest.

Rib Fracture

The designation "simple rib fracture" usually refers to a nondisplaced fracture of a rib without injury to the lung or pleura. The most common mechanism for simple rib fractures is direct impact such as occurs in a fall or in a motor vehicle accident. Clinically, simple rib fractures may present with manifestations ranging from pain isolated to the involved rib to pneumonia secondary to splinting and hypoventilation caused by the pain. This latter circumstance is more likely in the elderly patient with osteoporosis, obstructive pulmonary disease, or malnutrition. Point tenderness is present over the fracture site, and a step-off may be palpated at the point where the fractured ends overlap. However, the physical findings are often more subtle.

Physical examination in the awake patient is usually sufficient to make the diagnosis of rib fracture. Chest radiographs obtained during the initial evaluation of a trauma patient in the emergency room usually are anteroposterior views taken with the patient supine, and rib fractures are often missed. Since the management of isolated simple rib fractures consists of analgesia and pulmonary toilet, attempting to ensure a radiographic diagnosis with oblique views or special rib views may not be necessary. In patients with underlying lung disease, the anteroposterior chest radiograph is most useful in establishing the absence of associated injuries, such as pulmonary contusion and pneumothorax.

The management of rib fractures may, at times, be dictated in part by which ribs and how many are injured. Fracture of the first or second ribs requires significant force and can be associated with major vascular or nerve injury as a result of the proximity of these ribs to the subclavian vessels and the brachial plexus. Although fractures of these two ribs are not necessarily an indication for an arteriogram, certain associated injuries do require angiographic study. Abnormalities in pulse or in the neurologic examination of the upper extremities or a hematoma at the base of the neck should prompt an arteriogram. Other indications include palpable displacement of the first rib and a widened mediastinum on the chest radiograph. Fracture of the lower ribs may be associated with injury to the liver or spleen.

Regardless of etiology, all rib fractures caused by trauma require repeated chest radiographic examinations to screen for radiographic evidence of pulmonary contusion or other complication such as hemothorax. Pulmonary complications of rib fractures can result from pain and splinting and include retained secretions, atelectasis, ventilatory failure in patients with limited pulmonary reserve, and empyema.

The cornerstone of the management of rib fractures is the management of secretions. This can only be accomplished by adequate analgesia. Options for analgesia with rib fractures include narcotics and intercostal nerve blocks.

Rib fractures often accompany other injuries. In a series of 711 patients with rib fractures evaluated over a 5-year period, 94 percent had associated injuries, 32 percent had a pneumothorax or hemothorax, 26 percent had a pulmonary contusion, and 12 percent died. Thus, information underscores the importance of knowing the mechanism of injury and the high likelihood of additional injuries either in the chest or elsewhere.

Flail Chest

Flail chest is an even better indicator of extensive injury. It occurs when a section of the chest wall becomes unstable because of multiple rib fractures (Fig. 100-5). This segment moves paradoxically with respiration causing respiratory embarrassment. There has been a continuing debate regarding whether the segmental, paradoxical chest wall motion or the underlying lung contusion is responsible for the ventilatory

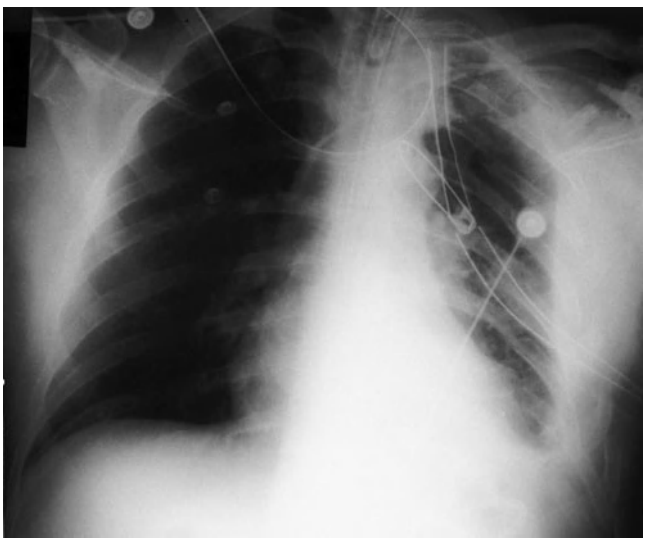

Figure 100-5 Left flail chest following blunt trauma.

abnormalities seen in these patients. The force of the injury required to cause a flail segment causes a significant contusion, and it is likely that the contused lung contributes most significantly to the derangement in gas exchange.

Because of the evolving views concerning the pathophysiological mechanism, the treatment of flail chest has changed dramatically over the years. The early approach reflected the belief that the chest wall deformity was responsible for the ventilatory compromise and consisted of external stabilization of the chest wall with sandbags. Operations were also performed for internal fixation of the flail segment. Subsequently, internal pneumatic stabilization with positive pressure ventilation was used in a further effort to prevent the paradoxical chest wall motion produced by spontaneous respiration. Patients were intubated and ventilated even when gas exchange was reasonable.

In time, more attention was directed toward the underlying pulmonary contusion as the significant pathophysiological mechanism. Trinkle tested this concept by treating one group of chest trauma patients with flail chest using positive-pressure ventilation while treating a second group with a standard pulmonary contusion, which included restriction of fluids and relief of pain. Length of hospitalization was shorter and incidence of complications significantly less in the group treated without mechanical ventilation.

Current treatment for flail chest avoids mechanical ventilation until mandated by standard criteria. There is no physiological reason to institute positive-pressure ventilation solely to prevent paradoxical chest wall motion. Management is directed toward the pulmonary contusion and control of pain. Continuous epidural analgesia has proved to be an excellent adjunct in the overall management of these patients, since the relief of pain lessens splinting, improves chest wall mechanics, and decreases the risk of atelectasis and pneumonia. Aggressive pulmonary toilet and secretion management are also important in the overall management of these patients.

If a segment of the chest wall is completely disrupted, operative fixation may provide a necessary adjunct. In this injury, the bellows mechanism of the chest is severely disordered by the major skeletal deformity, which consists of complete separation of the ribs from each other with maintenance only of the integrity of the overlying skin. In this injury, the flail is severe, and operative repair with wire stabilization of the flail segment and reconstruction of the chest wall is often necessary for restoration of the bellows.

Sternal Fracture

Sternal fracture most commonly occurs during motor vehicle accidents in which there is direct impact of the anterior chest on the steering wheel. Paramedics often report damage to the steering wheel in accidents that produce these injuries. Sternal fractures also are occasionally associated with single or multiple costochondral dislocations. The association of these two injuries can lead to flail chest with paradoxical motion of the sternum during spontaneous respiration. Other injuries associated with sternal fracture include flexion injuries of the vertebral column, tracheobronchial rupture, aortic disruption, and myocardial contusion or rupture. Isolated sternal injury is a relatively rare injury, since the force required to fracture the sternum usually results in other injury, which is often fatal.

When first seen, the awake, conversant patient with a sternal fracture often complains of pain. Inspection of the chest wall often reveals ecchymosis or abrasion of the skin overlying the sternum; a chest wall deformity may be visible. Palpation of the sternum and costochondral junctions may reveal point tenderness and a crepitance or step-off over the fracture. Sternal fractures are difficult to detect on anterior or oblique films. Patients suspected of having a sternal fracture should have lateral views with a specific request for sternal views. In the patient with multiple injuries who is unable to tolerate many diagnostic studies, the diagnosis can be made based safely on physical examination. Sternal fractures most commonly extend either through the body of the sternum or occur at the junction of the manubrium and body.

Simple undisplaced sternal fractures require no treatment. Displaced fractures with overlapping fragments may require operative reduction, debridement, and direct wire fixation. Claviculosternal dislocations may compress the structures traversing the thoracic inlet including the trachea, major vessels, and brachial plexus. Treatment of the sternal fracture may need to be delayed depending on the presence of other associated injuries.

Diaphragmatic Injury

Injury to the diaphragm should be considered in any penetrating or blunt injury to the chest, abdomen, or lower back. The injury is easily detectable at the time of laparotomy but is often overlooked in the heat of the moment when dealing with intraabdominal hemorrhage (Fig. 100-6). When a diaphragmatic injury is noted, primary suture repair of the rent usually suffices, but occasionally repair with prosthetic mesh is required. Regardless of etiology, all diaphragmatic injuries should be repaired because there is a significant risk of incarceration and possible strangulation of abdominal viscera through the hernia as well as pulmonary compromise secondary to compression.

In those patients who do not undergo emergency laparotomy, the diagnosis can be delayed for several months or even years. Diaphragmatic injuries can occur with penetrating injuries as well as from blunt trauma, although the injuries incurred from a blunt mechanism tend to produce larger rents in the diaphragm. Patients with missed diaphragm injuries often complain of midepigastric pain or symptoms of bowel obstruction as abdominal viscera herniate into the chest. Examination may reveal a scaphoid abdomen without significant tenderness to palpation. Auscultation of the chest may reveal bowel sounds. The chest radiograph shows what appears to be an elevated hemidiaphragm, hydrothorax, hydropneumothorax, an air-fluid level, and evidence of abdominal viscera. These findings are most often seen on the left side because, after right-sided diaphragmatic injuries,

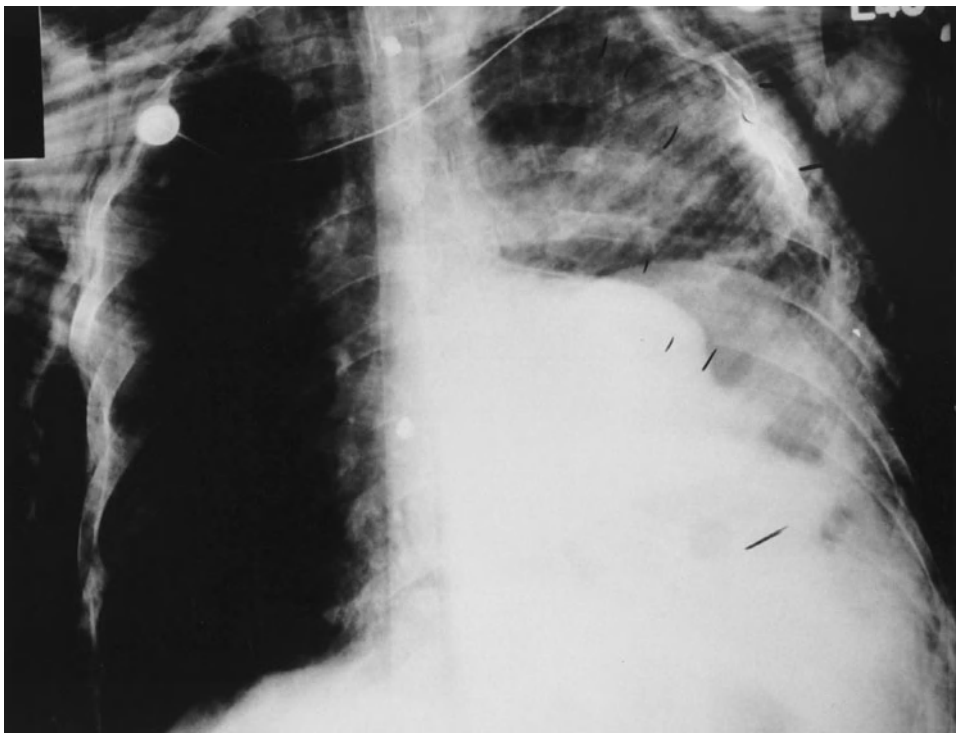

Figure 100-6 Ruptured left hemidiaphragm following a motor vehicle accident. Note the subcutaneous emphysema and the loss of diaphragm contour on the left. The contents of the left side of the abdomen are in the left chest.

the liver protects the abdominal viscera from herniating into the right chest. Occasionally, the liver itself may herniate after right-sided injuries. An easy diagnostic test is the introduction of a nasogastric tube. If the tube coils into the left chest, the diagnosis of gastric herniation through the diaphragmatic injury is made, and operation is indicated for repair of the diaphragm and restoration of the abdominal contents into the abdomen. Similarly, an upper gastrointestinal series or barium enema can be performed to evaluate the viscera with respect to herniation into the chest. If the diagnosis is made relatively quickly after herniation, the abdominal approach can be used for repair. If the diagnosis is made before incarceration but well after the initial herniation, the repair is performed through the left chest, since there are often adhesions to the lung as a result of chronic inflammation. As mentioned, almost all these injuries occur on the left side with only the occasional diaphragmatic injury seen on the right.

PENETRATING INJURY OF THE LUNG

Penetrating injuries of the lung occur from stab or gunshot wounds. An occasional impalement injury may also be seen. The degree of injury sustained by the lung ranges from small lacerations caused by knife injuries to massive destruction with shotgun blasts (Fig. 100-7). In addition, the type of firearm used defines the amount of injury. Specifically, high-velocity missiles such as those used during wartime and, more recently in urban areas, are more likely to produce severe damage than the typical low-velocity missiles used by civilians. High-velocity bullets create a blast effect, producing a large temporary cavity within the tissues hit by the bullet. Although it may not be evident initially, the ultimate extent of

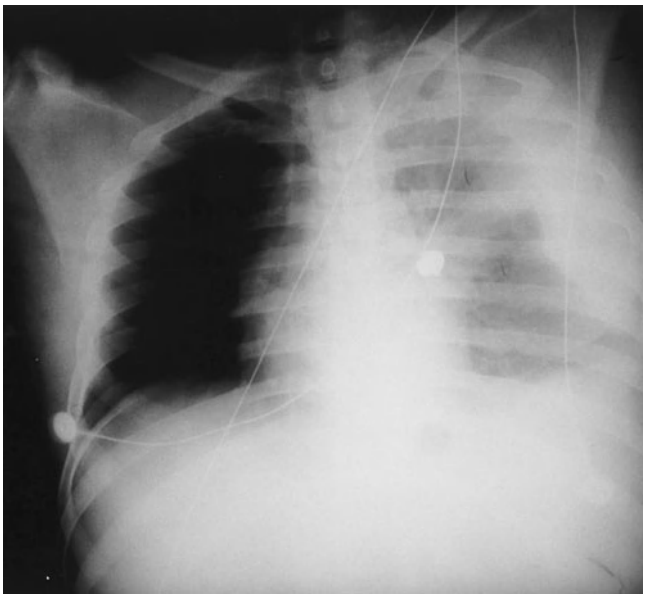

Figure 100-7 Gunshot wound to the left chest demonstrating a large hemothorax present on admission to the emergency room prior to chest tube placement. The amount of blood in the chest and continued drainage of blood determine whether exploration of the chest is indicated.

injury caused by such forces is often extensive because of the associated pulmonary contusion from the blast effect. Low-velocity bullets are more likely to produce wounds that have a cross-sectional area about the size of the bullet and the blast effect is relatively less than that produced by high-velocity bullets.

In a series of 1168 patients with penetrating injuries to the thoracic cavity, only 6 percent of these required operative repair of pulmonary parenchymal or hilar injuries. Of 384 patients with gunshot wounds, 283 (74 percent) were managed with chest tubes alone. Similarly, of 784 patients with stab wounds to the thorax, 602 (77 percent) required only a chest tube. Mortality for those requiring only a chest tube was 0.7 percent. In contrast, mortality for those with hilar injuries was 30 percent, and for those with injuries requiring lung resection, mortality was 28 percent. Thus, most civilian penetrating thoracic injuries can be managed with tube thoracostomy alone because of relatively minimal injury to lung parenchyma. Hilar injury or significant parenchymal injury requiring resection carries a high mortality.

The management of penetrating thoracic injury begins with placement of a chest tube. One indication for operation in such patients is an initial drainage of 2 L or more of blood. Clinical signs are particularly important. The patient who remains hypotensive following volume replacement should be explored. In those with less initial drainage, continuing drainage of 150 to 200 ml of blood every hour for 3 to 4 h is another indication for operation. Additional indications include hemoptysis, shock, and cardiac tamponade. Options for treatment include direct suture repair of the lung, wedge resection, or formal anatomic resection, such as lobectomy. Great effort is made to preserve pulmonary parenchyma, and resection is reserved for those cases where there is significant destruction of lung tissue or injury to a pulmonary artery. Everything possible is done to avoid pneumonectomy which, in this situation, is associated with mortality greater than 60 percent.

ARDS AFTER CHEST TRAUMA

The adult respiratory distress syndrome often complicates chest trauma, and its clinical manifestations are similar to those that occur in patients with adult respiratory distress syndrome (ARDS) after insults that do not involve trauma. Several injuries and their sequelae have been implicated in the etiology of ARDS. Among these are the following clinical factors often found in the chest trauma patient: sepsis syndrome, pulmonary contusion, aspiration of gastric contents, multiple emergency transfusions, and multiple major fractures. In addition, the risk of ARDS has been found to be most closely related to the number of risk factors present (18 percent with one factor, 85 percent with three or more factors). Hence, any chest trauma patient admitted with clinical risk factors of ARDS should be followed closely so that appropriate treatment can be administered promptly. In addition, although these risk factors are only associated with ARDS rather than causative, they should receive prompt treatment with the goal of minimizing any potential causative role they could have.

Mechanically Assisted Ventilation

As with other etiologies, the mainstay of treatment of ARDS in the patient with chest trauma revolves around the use of assisted ventilation (see Chapter 153), i.e., volume ventilation and positive end-expiratory pressure (PEEP). By increasing the number of ventilated alveoli, thereby increasing the functional residual capacity (FRC), the shunt fraction ($\dot{Q}s/\dot{Q}t$) is decreased, and arterial oxygenation improves. The target usually established for the $\dot{Q}s/\dot{Q}t$ ratio is less than 0.2. The goals of this scheme for ventilatory management are to adjust the fraction of inspired oxygen (Fi_{O_2}) and the level of PEEP to the lowest values capable of supporting adequate oxygenation. In the rare patient with severe chronic lung disease, bronchopleural fistula, or such severe ARDS that oxygenation using this approach is not successful, high-frequency jet ventilation, extracorporeal membrane oxygenation (ECMO), and simultaneous independent lung ventilation remain as options.

High-Frequency Jet Ventilation

In high-frequency jet ventilation, a small cannula is inserted into the airway and brief high-pressure jets of air are used to ventilate the lungs. As the jet of air enters the bronchus it pulls air along by the Venturi effect, thereby determining the inspiratory volume. Typical ventilator settings include tidal volumes of 1 to 3 ml per kg and rates of 100 to 200 breaths per minute. The advantage of this mode of ventilation is the avoidance of the high-peak airway pressures produced by PEEP. Results obtained with this technique have not been consistent from clinic to clinic. Hurst and colleagues used both high-frequency jet ventilation (HFJV) and the related high-frequency percussive ventilation (HFPV) in trauma patients with injury to multiple organ systems. This combination combines the mechanism of HFJV with the ability to change airway pressure phasically. They found that HFJV improved CO_2 elimination more effectively than did the intermittent mandatory ventilation/continuous positive airway pressure (IMV/CPAP) mode of ventilation. In addition, HFPV improved Pa_{O_2} and reduced Pa_{CO_2} at lower peak, mean, and end-expiratory pressures. In contrast, Albelda and co-workers studied the use of HFJV in patients with bronchopleural fistulae and found no clear benefit with the technique in these patients. The utility of HFJV in chest trauma patients remains to be completely elucidated, but it is available as an option in patients with severe barotrauma from PEEP.

Extracorporeal Membrane Oxygenator

Yet another option in the chest trauma patient with recalcitrant ARDS is extracorporeal membrane oxygenator

(ECMO). This technique is not yet used routinely in adult patients with severe ARDS. One reason that ECMO has produced variable results in this population is that these patients often have major multiorgan system dysfunction in addition to their pulmonary dysfunction. If these other conditions are not corrected, the likelihood of survival is low despite the ability to oxygenate and ventilate using ECMO. The role of ECMO in the adult population with ARDS remains to be defined.

Ventilation of Each Lung Separately

Simultaneous ventilation of each lung separately involves the use of one separate ventilator for each lung using a double lumen endobronchial tube. The ventilators can function in either synchronous and asynchronous modes. The technique is used in conditions of unilateral severe lung disease, such as postunilateral lung transplantation or unilateral severe pulmonary contusion.

CONCLUSION

For purposes of classification, a distinction must be made between blunt and penetrating trauma to the chest, yet the management of many of these injuries, no matter what the cause, is similar. An injury confined to the chest most often results in a favorable outcome; the difficulty lies in the fact that most chest trauma is associated with other injuries. Many multiple-injury patients with chest trauma never make it to the hospital. Those who do must be managed by a team of individuals consisting of trauma and thoracic surgeons as well as physicians trained in critical care. The initial management of patients with thoracic trauma often requires quick and accurate decision making such as in the case of the patient who presents with a tension pneumothorax. It behooves all physicians who deal with critically ill patients to be familiar with the care of patients with chest trauma.

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101

Lung Transplantation

John C. Wain

Lung transplantation has been used as a successful therapeutic intervention for a variety of end-stage pulmonary parenchymal and vascular diseases over the past 25 years. Advances in recipient and donor selection, surgical technique, and postoperative management have improved early survival. The criteria for the use of either isolated lung transplantation or heart–lung transplantation continue to be defined, with the role for heart–lung transplantation lessening over the past decade. A relative shortage of donor organs has been the major constraint on wider application of this treatment. In addition, chronic rejection in the pulmonary allograft, manifested as obliterative bronchiolitis, remains a major obstacle to long-term patient survival.

HISTORY

Pioneering efforts in experimental lung transplantation were undertaken in the 1940s and 1950s. Demikhov performed a variety of experiments involving transplantation of pulmonary lobes and heterotopic heart–lung transplantation in dogs. These experiments demonstrated the technical feasibility of such procedures. In addition, the heart and the lung in heart–lung grafts pursued different functional courses, foreshadowing the differing rates of rejection of the heart and lungs that were seen in combined heart–lung transplants performed clinically more than three decades later. Metras reported the results of left-lung transplantation in the dog and presciently emphasized technical factors that are now used clinically for isolated lung transplantation. Subsequent experimental studies showed that the transplanted lung could provide ventilation for the recipient.

Clinical lung transplantation was undertaken first by Hardy in 1963. The procedure consisted of a left single-lung transplant performed for a carcinoma of the left lung that involved the hilum. The patient survived for 18 days, dying of renal failure and malnutrition. This effort demonstrated that a transplanted lung could function for the short term in a patient and stimulated further clinical and experimental efforts. Between 1963 and 1978, however, at least 38 attempts were made at isolated lung transplantation, and only one patient survived to hospital discharge. This particular patient

This chapter has been slightly modified from the version that appeared in the third edition of *Fishman's Pulmonary Diseases and Disorders.*

had undergone a right single-lung transplant for silicosis; he developed a bronchial anastomotic stricture and succumbed to sepsis and chronic rejection 8 months after transplantation. The remaining patients in this 15-year experience all died postoperatively. The major cause of mortality beyond the first postoperative week in these patients was bronchial dehiscence. In addition, most of the patients were greatly debilitated at the time of the procedure, frequently ventilator dependent or in a state of multisystem and multiorgan failure, hindering their ability to survive. It was appreciated that in many of these patients, the available immunosuppressive regimens, which relied on high-dose corticosteroids (2 mg/kg of prednisone per day), significantly compromised postoperative healing of the bronchus and further potentiated the adverse effects of preexisting conditions.

The problem of bronchial healing was related to the relative ischemia of the donor bronchus, which followed revascularization of the lung graft without reestablishment of bronchial circulation. One technical approach to this problem was the development of a procedure for combined heart–lung transplantation, allowing for maintenance of collateral bronchial circulation from the coronary circulation and mediastinal tissues. Although the operation was performed primarily for patients with end-stage cardiac failure due to pulmonary hypertension, the initial report of successful heart–lung transplantation demonstrated the feasibility of this approach in obtaining healing of the airway and confirmed the ability of the transplanted lung to provide long-term respiratory function. Subsequently, heart–lung transplantation has been performed for numerous pulmonary parenchymal diseases, including emphysema and bilateral septic lung disease, such as cystic fibrosis.

An alternative technique for improving bronchial healing was to optimize the bronchial–pulmonary collateral circulation by limiting the length of the donor bronchus and to revascularize the bronchial circulation extrinsically by wrapping the anastomosis with omentum. In addition to these technical measures, the avoidance of high-dose steroid immunosuppressive regimens, made possible by the use of cyclosporine and the application of growth factors, was shown to improve bronchial anastomotic healing. These advances, combined with the selection of well-conditioned recipients with pulmonary fibrosis, whose pathophysiology favored perfusion and ventilation of the allograft, culminated in the clinical success of isolated single-lung transplantation. Further efforts were made to perfect a technique for isolated double-lung transplantation to expand this approach to patients with bilateral septic lung disease. The initial clinical success of an en bloc double-lung transplant procedure was tempered by a significant incidence of bronchial anastomotic complications. However, further modification of the technique, by either direct bronchial revascularization or bilateral sequential single-lung transplantation, has provided satisfactory results.

It has since been shown that despite initial concerns about the physiology of allograft ventilation, isolated single-lung transplantation is also appropriate for patients with end-stage chronic obstructive pulmonary disease (COPD). Isolated single- and double-lung transplantation has also been successfully applied to patients with primary pulmonary hypertension or Eisenmenger's syndrome (with correction of the congenital shunt), for whom combined heart–lung transplantation was initially devised. As the utility of isolated lung transplantation for these pulmonary diseases has been demonstrated, the need for heart–lung transplantation has diminished.

RECIPIENT SELECTION

General Considerations

The evaluation of a potential candidate for lung transplantation should include a complete assessment of cardiopulmonary function and the patient's general health in addition to a thorough evaluation of psychosocial status. A battery of screening tests are required, as well as evaluation by members of the transplant team, including pulmonologists, cardiologists, thoracic surgeons, psychiatrists, and social workers (Table 101-1). Contingent on the patient's status, this evaluation can be completed in many instances on an outpatient basis. A coordinated review of the results of these studies by the multidisciplinary transplant team serves to assure that the best candidates are accepted as potential transplant recipients.

Indications

Lung transplantation is a treatment of last resort. Potential recipients should be patients with an end-stage pulmonary parenchymal or vascular disease who have a limited life expectancy and for whom no effective alternative therapy is available. The life expectancy of potential recipients is related to both the underlying disease process and the degree of reduction in activities of daily living resulting from the disease, with significant secondary alterations in the patient's psychosocial status. The variable rates of progression of the diseases for which lung transplantation is performed and the variety of supportive therapies available dictate that many specific criteria are related to a specific disease state.

Careful consideration is required before patients with preexisting osteoporosis are accepted for transplantation. In addition, chronic steroid immunosuppressive therapy causes bone loss in all patients and exacerbates the complications of prior osteoporosis.

Immunologic study of potential transplant candidates includes assessment of ABO status and cross-matching for transfusion. All patients are currently matched to donors by ABO status, most commonly with ABO-identical donors; virtually all patients require some transfusion in the perioperative period. MHC status is also assessed preoperatively, primarily for use in studies of postoperative outcome, such as the effect of HLA–DR mismatching or donor–recipient microchimerism on chronic rejection. Screening for sensitization to HLA antigens is also done at some centers. Pregnancy, blood transfusion, or prior transplantation can lead to HLA sensitization. Before transplantation, potential

Table 101-1

Recipient Evaluation for Lung Transplantation

Hematology
Complete blood count with differential, platelet count, PT, PTT, ESR
Chemistry
Na, K, Cl, CO_2, BUN, Cr, glucose, osmolality, uric acid, Ca, P, Mg, total protein, albumin, globulin, amylase, bilirubin (direct, indirect), alkaline phosphatase, SGOT, LDH, CPK, triglycerides, cholesterol, HDL/LDL
Renal function
Urinalysis, 24 h for calcium and creatinine
Endocrine
TSH, LH, FSH, vitamin D, testosterone (males), estradiol (females)
Infectious disease
Sputum (Gram's stain, C+S, fungal smear and culture, AFB smear and culture), CMV, hepatitis B (antigen/antibody), hepatitis C, herpes, varicella, EBV, HIV, rapidplasma reagin, toxoplasma PPD, mumps, *Candida* skin tests
Immunology
ABO blood type and cross match, MHC typing, HLA sensitization (PRA screen)
Radiology
Chest radiograph (AP, lateral), high-resolution chest CT scan, quantitative V/Q scan, quantitative bone density, abdominal ultrasonography, sinus CT*
Cardiology
ECG, echocardiogram with pulse Doppler imaging, right heart catheterization, left heart catheterization†
Pulmonary
Pulmonary function tests (spirometry, lung volumes, DLCO), Baird level II exercise test‡

* *Septic lung disease.*
† *If > 50 years of age, coronary artery disease or LVEF <45%.*
‡ *Excluding patients with pulmonary hypertension.*

recipients who show a response of more than 15 percent to the panel of antigens require a direct lymphocytotoxic crossmatch with any potential donor before transplantation.

Contraindications

Absolute contraindications to lung transplantation include *bone marrow failure* and *hepatic cirrhosis,* the latter to be distinguished from reversible hepatic dysfunction due to right heart failure, which resolves following lung transplantation (Table 101-2). In exceptional circumstances, combined liver and lung transplantation may be contemplated, although the risks of such a procedure are likely to be prohibitive. An *active malignancy precluding long-term survival,* which in the case of most solid tumors implies a disease-free survival beyond 5 years, is also an absolute contraindication. Because of the current limited supply of donor lungs, other significant life-limiting disorders also stand as a proscription against lung transplantation (Table 101-3).

A host of additional factors may be considered relative contraindications to lung transplantation. The age of the recipient may be a significant factor in view of the limited number of donor organs and the presumed subclinical organ dysfunction associated with the aging process that increases the potential for postoperative complications. As the latter factor is variable, a "physiological age" rather than a strict chronologic criterion is appropriate. The type of transplant procedure also influences the significance of age as a contraindication. (Isolated single-lung transplantation is more suitable for older patients because of its lower risk.) Other contraindications are evidence of psychosocial instability that would preclude compliance with the necessary posttransplant regimens and active use of tobacco products during the wait for transplantation. Obesity or cachexia can increase the risk for perioperative morbidity. The same is true of the continued need for high doses of steroid therapy (e.g., more than 20 mg of prednisone per day).

Respiratory failure requiring mechanical ventilation before transplantation also increases the likelihood of complications. Most centers will not consider a new patient for evaluation who is completely ventilator dependent or has acutely deteriorated and become ventilator dependent. However, patients who have a chronic need for partial ventilatory assistance or those who have been accepted as transplant candidates and require assisted ventilation because of progression of their native disease may still be considered potential recipients for a limited time. Prolonged mechanical ventilation results in colonization of the lower respiratory tract with significant microbiologic pathogens and a degree of deconditioning and protein wasting that significantly increases the perioperative risk of transplantation.

Chronic renal disease may affect eligibility for lung transplantation. All immunosuppressive regimens have some element of renal insufficiency as a complication of therapy, as do many of the antimicrobial regimens required for the management of these patients. As with irreversible hepatic dysfunction, combined renal and lung transplantation may

Table 101-2

Absolute Contraindications for Lung Transplantation	Relative Contraindications for Lung Transplantation
• Malignancy in the last 2 years, with the exception of cutaneous squamous and basal cell tumors. In general, a 5-year disease-free interval is prudent. The role of lung transplantation for localized bronchioalveolar cell carcinoma remains controversial. • Untreatable advanced dysfunction of another major organ system (e.g., heart, liver, or kidney). Coronary artery disease not amenable to percutaneous intervention or bypass grafting, or associated with significant impairment of left ventricular function, is an absolute contraindication to lung transplantation, but heart-lung transplantation could be considered in highly selected cases. • Non-curable chronic extrapulmonary infection including chronic active viral hepatitis B, hepatitis C, and human immunodeficiency virus. • Significant chest wall/spinal deformity. • Documented nonadherence or inability to follow through with medical therapy or office follow-up, or both. • Untreatable psychiatric or psychologic condition associated with the inability to cooperate or comply with medical therapy. • Absence of a consistent or reliable social support system. • Substance addiction (e.g., alcohol, tobacco, or narcotics) that is either active or within the last 6 months.	• Age older than 65 years. Older patients have less optimal survival, likely due to comorbidities, and therefore, recipient age should be a factor in candidate selection. Although there cannot be endorsement of an upper age limit as an absolute contraindication (recognizing that advancing age alone in an otherwise acceptable candidate with few comorbidities does not necessarily compromise successful transplant outcomes), the presence of several relative contraindications can combine to increase the risks of transplantation above a safe threshold. • Critical or unstable clinical condition (e.g., shock, mechanical ventilation or extra-corporeal membrane oxygenation). • Severely limited functional status with poor rehabilitation potential. • Colonization with highly resistant or highly virulent bacteria, fungi, or mycobacteria. • Severe obesity defined as a body mass index (BMI) exceeding 30 kg/m^2. Severe or symptomatic osteoporosis. • Mechanical ventilation. Carefully selected candidates on mechanical ventilation without other acute or chronic organ dysfunction, who are able to actively participate in a meaningful rehabilitation program, may be successfully transplanted. • Other medical conditions that have not resulted in end-stage organ damage, such as diabetes mellitus, systemic hypertension, peptic ulcer disease, or gastroesophageal reflux should be optimally treated before transplantation. Patients with coronary artery disease may undergo percutaneous intervention before transplantation or coronary artery bypass grafting concurrent with the procedure.

SOURCE: *Orens JB, Estenne M, Arcasoy S, et al.: International guidelines for the selection of lung transplant candidates:* J Heart Lung Transplant *25:745–755, 2006.*

be considered, but the potential risks of the procedure, particularly in the context of the shortage of donor lungs, require careful consideration. In most patients, severe preexisting renal insufficiency is a contraindication for lung transplantation.

Severe peripheral vascular disease may be a limiting factor in selecting candidates because of the occasional need for cardiopulmonary support in the perioperative period by either partial cardiopulmonary bypass (CPB) or extracorporeal membrane oxygenation (ECMO) via the femoral or subclavian routes. Peripheral vascular disease is also frequently associated with significant coronary or aortic disease, which may greatly increase the morbidity and mortality of the lung transplant procedure. Finally, transplantation in patients with gangrenous changes in the extremities due to peripheral vascular disease is contraindicated because of the potential for systemic spread of the infectious process during immunosuppression.

Infectious diseases have a profound effect on the morbidity and mortality of lung transplantation. Colonization of the respiratory tract with potential pathogens in patients with end-stage pulmonary disease requires careful assessment of anatomic changes in the airways and determination of antimicrobial susceptibility. Significant anatomic abnormalities that preclude mechanical drainage of secretions in either the upper or lower respiratory tract should be dealt with preoperatively (e.g., drainage of chronic sinusitis in patients with cystic fibrosis) or at the time of the transplantation (e.g., removal of the lung containing a focal area of bronchiectasis). Most bacterial flora in transplant candidates have a pattern of antibiotic sensitivity that can be identified preoperatively to define a perioperative antibiotic regimen. For example, lung transplant

Table 101-3

Contraindications to Lung Transplantation

Absolute contraindications
Bone marrow failure
Hepatic cirrhosis
Active malignancy precluding long-term survival
Other life-limiting condition
Relative Contraindications
Physiological age
>65 for single-lung transplantation
>60 for bilateral-lung transplantation
>55 for heart–lung transplantation
Psychosocial instability
Tobacco use within 6 months
Weight outside acceptable range (obesity or cachexia)
Prednisone use >20 mg/day or 40 mg q.o.d.
Mechanical ventilation
Intrinsic renal disease
Significant peripheral vascular disease
Symptomatic osteoporosis
Severe chest wall deformity
Sputum with panresistant bacteria or Aspergillus
Active hepatitis B or C infection

patients harboring gram-negative bacilli preoperatively were found to be at risk for post–lung transplant pneumonia, demonstrating the importance of preoperative identification and a plan for eradication of potential pathogens. However, *Pseudomonas cepaciae,* a pathogen found in approximately 15 percent of patients with cystic fibrosis, is often highly resistant to antimicrobials and is a relative contraindication to transplantation unless a suitable pattern of antibiotic sensitivity can be identified before transplantation. *Aspergillus fumigatus* and other *Aspergillus* species are also common pathogens in the sputum of patients with septic lung disease or COPD. Interestingly, the presence of organisms in donor lungs is not a predictor of post–lung transplant pneumonia.

Viral diseases in a potential lung transplant recipient can also have a significant impact on the outcome of transplantation. Active hepatitis B or C in the lung transplant candidate increases both early and late mortality because of the effect of hepatic dysfunction on perioperative complications and the accelerated progression of these diseases in patients requiring chronic immunosuppression. Cytomegalovirus (CMV), a DNA-type virus that is incorporated into the host genome, can cause both systemic illness and pneumonitis in immunosuppressed patients. Therefore, the serologic CMV status of the recipient is an important determination to make before transplantation. Duncan and Dummer found that CMV infection developed in 54% (32/59) of patients who underwent heart-lung ($n = 52$), double lung ($n = 7$), and single lung ($n = 2$) transplantation and survived for more than 30 days, and that CMV infection was more common in patients who had been CMV seropositive preoperataively (95%) than those who had been seronegative preoperatively (38%). While some centers prefer to match donor and recipient CMV status as a strategy for minimizing perioperative complications, the use of preemptive prophylactic ganciclovir therapy has been shown to eliminate CMV disease in transplant patients. However, some strains of CMV are resistant to ganciclovir, and because the occurrence of CMV disease is a significant risk factor for morbidity and mortality, ongoing surveillance for CMV based on antigenemia assays and transbronchial lung biopsy is required.

Posttransplant Therapy

Although most post–lung transplant infections are caused by bacteria, the highest mortality is associated with fungal infections, pointing to the critical nature of appropriate perioperative and postoperative antibiotic regimens.

Postoperatively, patients require an aggressive rehabilitation program to complete their immediate recovery and achieve maximum functional capacity. Severe preexisting osteoporosis or severe chest wall deformity may complicate these efforts, owing to difficulties with bone fractures, pain management, and ambulatory status. Close attention to bone density and calcium homeostasis is required postoperatively in all lung transplant patients on chronic steroid therapy. Most of them benefit from calcium supplementation and/or alendronate to offset the steroid effect.

As physical rehabilitation is an important component of posttransplant therapy, it is important that all potential recipients be able to participate in such a *rehabilitation program.* Although most patients with parenchymal diseases also engage in a preoperative rehabilitation program, patients with pulmonary vascular disease cannot do so because of the considerable risks of such preoperative therapy. For these patients, participation in rehabilitation programs is generally deferred until after the transplant procedure. However, an appropriate psychological and emotional context can be promoted by regular preoperative participation in a patient support group (Table 101-4).

Table 101-4

General Indications for Lung Transplantation

End-stage pulmonary parenchymal and/or vascular disease
Projected life expectancy <2 years
NYHA class III or IV functional level
Rehabilitation potential
Disease-specific mortality exceeding transplant-specific mortality over 1–2 years

Table 101-5

Disease-Specific Considerations for Lung Transplantation

Chronic Obstructive Pulmonary Disease (COPD)

Guidelines for referral

BODE index exceeding 5.

Guidelines for transplantation

Patients with a BODE Index of 7 to 10 of at least 1 of the following:

- History of hospitalization for exacerbation associated with acute hypercapnia (P_{CO_2} exceeding 50 mmHg).
- Pulmonary hypertension or cor pulmonale, or both, despite oxygen therapy.
- FEV_1 of less than 20% and either DLCO of less than 20% or homogenous distribution of emphysema.

Cystic Fibrosis/Bronchiectasis

Guidelines for referral

- FEV_1 below 30% predicted or a rapid decline in FEV_1—in particular in young female patients.
- Exacerbation of pulmonary disease requiring ICU stay.
- Increasing frequency of exacerbations requiring antibiotic therapy.
- Refractory and/or recurrent pneumothorax.
- Recurrent hemoptysis not controlled by embolization.

Guideline for transplantation

- Oxygen-dependent respiratory failure.
- Hypercapnia.
- Pulmonary hypertension.

Idiopathic Pulmonary Fibrosis/ Nonspecific Interstitial Pneumonia (NSIP)

Guideline for referral

- Histologic or radiographic evidence of UIP Irrespective of vital capacity.
- Histologic evidence of fibrotic NSIP.

Guideline for transplantation

Histologic or radiographic evidence of UIP and any of the following:

- A DLCO of less than 39% predicted.
- A 10% or greater decrement in FVC during 6 months of follow-up.
- A decrease in pulse oximetry below 88% during a 6-MWT.
- Honeycombing on HRCT (fibrosis score of > 2).

Histologic evidence of NSIP and any of the following:

- A DLCO of less than 35% predicted.
- A 10% or greater decrement in FVC or 15% decrease in DLCO during 6 months of follow-up.

Pulmonary Arterial Hypertension

Guideline for referral

- NYHA functional class III or IV, Irrespective of ongoing therapy.
- Rapidly progressive disease.

Guideline for transplantation

- Persistent NYHA class III or IV on maximal medical therapy.
- Low (<350 meter) or declining 6-MWT.
- Falling therapy with intravenous epoprostenol, or equivalent.
- Cardiac index of less than 2 liters/min/m^2.
- Right atrial pressure exceeding 15 mmHg.

Sarcoidosis

Guideline for referral

NYHA functional class III or IV.

Guideline for transplantation

Impairment of exercise tolerance (NYHA functional class III or IV) and any of the following:

- Hypoxemia at rest.
- Pulmonary hypertension.
- Elevated right atrial pressure exceeding 15 mmHg.

Lymphangioleiomyomatosis (LAM)/ Pulmonary Langerhans Cell Histiocytosis (Eosinophilic Granuloma)

Guideline for referral

NYHA functional class III or IV.

Guideline for transplantation

- Severe impairment in lung function and exercise capacity (e.g., VO_2 max $< 50\%$ predicted).
- Hypoxemia at rest.

SOURCE: *Orens JB, Estenne M, Arcasoy S, et al.: International guidelines for the selection of lung transplant candidates:* J Heart Lung Transplant. *25:745–755, 2006.*

Specific Disease States

The rate of progression of the specific diseases is an important factor in the timing of the evaluation and selection of potential transplant recipients (Table 101-5). The most common indication for lung transplantation is *obstructive lung disease,* with COPD accounting for 38 percent of all lung transplants and emphysema due to α_1-antitrypsin deficiency accounting for 8 percent of all lung transplants. Patients with these diseases, who demonstrate chronic airway obstruction on pulmonary function tests, tend to remain relatively stable for long periods. Although lung transplantation provides marked symptomatic and functional palliation for these patients, it remains to be proved that lung transplantation improves survival. The FEV_1 after administration of a bronchodilator is an excellent predictor of the severity of the disease and is useful, along with assessment of resting Pa_{O_2} and Pa_{CO_2}, in estimating survival before transplantation. The recently devised BODE index that incorporates multiple factors (B, body mass index; O, obstruction as indicated by the FEV_1 as percent predicted; D, degree of dyspnea; and E, exercise capacity) appears to be more accurate in predicting survival in individuals with COPD than the FEV_1 only. Accordingly, calculation of the BODE index is now included in the international guidelines for referral and transplantation for COPD (Tables 101-6 and 101-7). Death during the wait for transplantation is rare in these patients, occurring in less than 5 percent of cases. This may be due in part to two factors: their participation in a graduated rehabilitation program while they await transplantation, which may maintain or even increase the patients' functional capacity, and the institution of oxygen therapy, which improves survival in patients with obstructive lung disease. Supplemental oxygen should be started early and continued throughout the pretransplantation period, along with serial assessments of oxygen consumption based on estimates obtained from the 6-min walk test.

Restrictive lung diseases are the indication for lung transplantation in 22 percent of patients who undergo lung transplantation. The most common cause is idiopathic pulmonary fibrosis (IPF), which accounts for 19 percent of lung transplant patients, whereas a variety of interstitial lung diseases with mixed physiological characteristics account for the remainder (Table 101-6).

The end-stage fibrotic lung is characterized by severe destruction of gas exchange units, distortion and dilatation of the airways with development of cystic lesions, and replacement of the lung with nondistensible fibrous tissues. The work of breathing in these patients may be increased five times above normal because of the increased elastic load. The vital capacity in patients with pulmonary fibrosis is severely reduced, as is the functional residual capacity (FRC), which is a better indicator of disease severity than total lung capacity. Dead-space ventilation is increased, and may actually increase further during exercise. A marked reduction in diffusing capacity is always present, commonly with some degree of alveolar hyperventilation; as the disease becomes increasingly severe, hypercapnia occurs during exercise and later at rest. Extensive intrapulmonary shunting of blood flow is seen, resulting in hypoxemia and, in later stages, pulmonary hypertension. Progression of the disease may be variable, but patients often deteriorate precipitously and severely, developing progressive hypoxemia and pulmonary hypertension. As a result, the mortality of these patients while they await transplantation is more than 20 percent. Criteria for considering IPF patients for of transplantation include severe dyspnea, forced vital capacity (FVC) less than 50 percent of predicted, resting arterial hypoxemia or hypercarbia, and pulmonary hypertension. However, a downhill clinical course despite adequate medical therapy is the best individual indication for transplantation.

Because airway obstruction is frequently a component of the lung disease in some patients with interstitial lung disease, an FEV_1 of less than 30 percent of predicted may be an additional useful criterion. Two other factors in patients with

Table 101-6

Disease-Specific Indications for Lung Transplantation

Obstructive lung disease—a BODE index of 7–10
Chronic obstructive pulmonary disease
α_1-Antitrypsin deficiency
Restrictive lung disease
Idiopathic pulmonary fibrosis—FVC <50% predicted, Pa_{O_2} < 50 mmHg, Pa_{CO_2} > 45 mmHg
Pulmonary artery hypertension
No response to steroid therapy
Interstitial lung disease
Sarcoidosis
Desquamative interstitial pneumonitis
Lymphangioleiomyomatosis
Chemotherapy- or radiation therapy–related fibrosis
Collagen vascular disorders with primarily pulmonary involvement
Eosinophilic granuloma or histiocytosis X
Alveolar microlithiasis
Septic lung disease
Cystic fibrosis—FEV1 < 30% predicted, FVC ≤ 40% predicted, Pa_{O_2} < 60 mmHg, room air
Bilateral bronchiectasis
Hypogammaglobulinemia
Postinfectious (childhood measles, pertussis, postpneumonia, or tuberculosis)
Immotile cilia syndrome—Kartagener's syndrome
Allergic bronchopulmonary aspergillosis
Pulmonary vascular disease
Primary pulmonary hypertension—symptomatic disease
Eisenmenger's syndrome

Table 101-7

The BODE Index for COPD

	Points on BODE Index*			
Variable	0	1	2	3
FEV_1 (%) of predicted)†	≥65	50–64	36–49	≤35
Distance walked in 6 min (m)	≥350	250–349	150–249	≤149
MMRC dyspnea scale‡	0–1	2	3	4
Body-mass index$	>21	≤21		

* *The cutoff values for the assignment of points are shown for each variable. The total possible values range from 0 to 10. FEV_1 denotes forced expiratory volume in one second.*

† *The FEV_1 categories are based on stages identified by the American Thoracic Society.*

‡ *Scores on the modified Medical Research Council (MMRC) dyspnea scale can range from 0 to 4, with a score of 4 indicating that the patient is too breathless to leave the house or becomes breathless when dressing or undressing.*

$ *The values for body-mass index were 0 or 1 because of the inflection point in the inverse relation between survival and body-mass index at a value of 21.*

SOURCE: *Celli BR, Cote CG, Marin JM, et al: The Body-mass index, airflow obstruction, dyspnea, and exercise capacity index in chronic obstructive pulmonary disease.*

interstitial lung disease are also important: many of these diseases are systemic, and the effects of the disease on extrapulmonary organs may result in a sufficient number of relative contraindications to exclude the patient from consideration for transplantation; and a number of these diseases, including sarcoidosis and lymphangiomyomatosis, have been shown to recur in the lung graft, underscoring the need for particularly cautious screening of such patients as potential candidates for transplantation.

Septic lung disease, including cystic fibrosis and other types of bronchiectasis, accounts for approximately 20 percent of patients undergoing lung transplantation. Candidates with focal or unilateral disease can often be managed with medical treatment or surgical resection of the affected area. In most patients, however, the disease is bilateral or systemic, and the natural history is one of recurrent infection and progressive pulmonary failure. It is important to attempt to establish a cause of the bronchiectasis before transplant evaluation, because of the impact of systemic diseases on management before and after transplantation (Table 101-6). Cystic fibrosis can be diagnosed with a sweat test or from genotyping. Serum immunoglobulin levels should be measured and a careful assessment for evidence for a systemic illness—such as rheumatoid arthritis, ulcerative colitis, or immotile cilia syndrome—should be undertaken. Primary infectious causes, such as tuberculosis and allergic bronchopulmonary aspergillosis, should be identified and treated appropriately before transplantation. Finally, any suggestion of aspiration as a primary or secondary factor demands further investigation, including a barium swallow to rule out gastroesophageal reflux.

Many of these patients demonstrate significant short-term improvements in response to aggressive medical therapy, which includes postural drainage, intravenous and inhaled antibiotics, and nutritional supplementation. Once medical therapy has been optimized, however, a pattern of more frequent hospitalizations for "clean-outs," continued weight loss, and progressive functional impairment is indicative of a patient who has a limited life span and should be given priority for transplantation. Cystic fibrosis patients with an FEV_1 under 30 percent of the predicted value, a Pa_{O_2} under 55 mmHg, or a Pa_{CO_2} greater than 50 mmHg have a 2-year mortality of 50 percent; the FEV_1 appears to be the most sensitive predictive factor. Any patient with septic lung disease who manifests these criteria should be further evaluated as a potential transplant recipient. While the patient is awaiting transplantation, close medical follow-up is required, and all of the patient's therapeutic regimen (e.g., postural drainage, DNAse therapy) should be continued. Serial study of sputum microbiology is important for assessing changes in flora. Aerosolized broad-spectrum antibiotic therapy (e.g., colistin 150 mg via nebulizer twice a day) reduces the bacterial load while minimizing the potential for renal toxicity; in some cases, it may transiently improve functional capacity. In the event of progressive hemoptysis, bronchial artery embolization can provide adequate short-term control of the bleeding without significantly compromising technical aspects of the transplant procedure. Finally, institution of nasal ventilation in the patient who is approaching respiratory failure has been shown to prolong viability without adversely affecting the outcome of transplantation. Application of these measures generally ensures that fewer than 20 percent of cystic fibrosis patients will die while awaiting lung transplantation. However, because of the shortage of donor organs and the variability in the progression of the disease, donation of a lung

from a dying related donor may warrant consideration for some patients. Initial results of this approach, using bilateral isolated lobar transplants from two donors, have been encouraging for patients with cystic fibrosis, without entailing donor mortality or significant morbidity.

Pulmonary vascular disease, either primary pulmonary hypertension (PPH) or secondary pulmonary hypertension due to Eisenmenger's syndrome, accounts for 4 to 5 percent of patients requiring isolated lung transplantation and approximately 25 percent of patients requiring heart–lung transplantation. The criteria for identifying patients who may require transplantation relate to the risks of death due to the underlying disease. On the basis of data from the National Heart, Lung, and Blood Institute registry, it is apparent that a NYHA class III or IV functional status, an elevated central venous pressure, a decreased cardiac index, and an elevated *mean* pulmonary artery pressure correlate with a poor prognosis. Episodes of near-syncope, syncope, or near-death, which tend to occur later in the course of the disease, are also associated with mortality. It should be noted, however, that alleviation of symptoms or physiological abnormalities by medical therapy using high-dose calcium channel blockers or prostacyclin infusions in PPH patients may significantly modify the natural history of the disease. Therefore, symptomatic patients with PPH who do not respond to medical therapy are the ones best considered for transplantation. Although identical data concerning the natural history of patients with Eisenmenger's syndrome are not available, similar clinical criteria and evidence of a declining functional status associated with progressive right heart failure are indications for transplantation in these patients.

The decision about whether a patient should undergo isolated lung transplantation or heart–lung transplantation may be difficult. However, with the relative shortage of suitable heart–lung donor blocs, and a mortality of 20 to 25 percent among patients with significant pulmonary hypertension who are awaiting lung transplantation, an increasing number of patients with pulmonary vascular disease have undergone isolated lung transplantation. The results with isolated lung transplantation are similar to those with heart–lung transplantation for pulmonary vascular disease provided that there is no significant left ventricular dysfunction [i.e., absence of cardiomyopathy, left ventricular ejection fraction (LVEF) at least 45 percent], that right ventricular *diastolic* function is maintained (i.e., right ventricular end-diastolic (RVEDP) of 15 mmHg or under), and that there are no incorrectable structural abnormalities. Of interest, the presence of severe right ventricular systolic dysfunction [i.e., right ventricular ejection fraction pressure (RVEF) of 20 percent or less] does not appear to affect the results of isolated lung transplantation, and the severe tricuspid regurgitation and pulmonary valvular regurgitation that are present in virtually all patients preoperatively resolve almost immediately after isolated lung transplantation. Patients with Eisenmenger's syndrome who have a shunt defect that can be corrected at the time of transplantation are also candidates for isolated lung transplantation. Heart–lung transplantation is primarily limited to patients with either significant biventricular dysfunction (e.g., severe valvular cardiomyopathy) or incorrectable congenital heart defects.

TRANSPLANT PROCEDURE SELECTION

Except for patients with bilateral septic lung disease or severe pulmonary arterial hypertension, single-lung transplantation (SLT) is optimal for the majority of end-stage pulmonary diseases that require transplantation. SLT is associated with a shorter wait for donor lungs before transplantation and a lower morbidity and mortality rate after transplantation than other lung transplant procedures performed for the same recipient diagnoses. The surgical mortality for SLT ranges from 3 to 10 percent, relating to the specific transplant indication, the presence or absence of pulmonary hypertension, and the intraoperative need for cardiopulmonary bypass.

Double-lung transplantation (DLT) is the procedure of choice for patients with bilateral septic lung disease, such as cystic fibrosis, or for patients with pulmonary arterial pressures that are at near-systemic levels from either primary or secondary causes. Some centers also favor the use of DLT for patients with emphysema who are less than 50 years of age. Typically, however, surgical mortality is higher for DLT than for SLT, ranging from 10 to 15 percent. Surgical mortality is probably higher because of the number of patients with septic lung disease treated by DLT—patients who are at greater risk for complications. Notably, at most large centers, perioperative morbidity from other than infectious complications, including acute graft failure and bronchial dehiscence, is similar for SLT and DLT. For patients with pulmonary vascular disease, DLT is favored over SLT for patients with the higher levels of pulmonary artery (PA) pressures (e.g., systolic PA at least 90 mmHg or mean PA at least 65 mmHg) and more advanced right ventricular dysfunction (e.g., RVEF 20 percent or less).

Combined heart–lung transplantation (HLT) has been used successfully for virtually all end-stage pulmonary diseases that require transplantation. However, with the perfection of the techniques of SLT and DLT and in light of the significant limitations in supply of donor organs, the use of HLT has focused on patients with significant refractory right ventricular *diastolic* dysfunction (e.g., RVEDP more than 15 mmHg), significant intrinsic left ventricular dysfunction, or Eisenmenger's syndrome and irreparable shunt defects. The surgical mortality for HLT at large centers is about 15 percent; typically, it is higher than the surgical mortality for SLT or DLT for similar disease states (Table 101-8).

DONOR SELECTION

The most significant factor limiting wider application of lung transplantation is the supply of donor organs. Unlike other

Table 101-8

Indications for Specific Lung Transplant Procedures

Single-lung transplantation (SLT)
Obstructive lung disease
Restrictive lung disease
Unilateral septic lung disease
Primary pulmonary hypertension
Eisenmenger's syndrome with a correctable shunt defect
Double-lung transplantation (DLT)
Obstructive lung disease (patient <50 years old)
Bilateral septic lung disease
Primary pulmonary hypertension
Eisenmenger's syndrome with a correctable shunt defect
Combined heart–lung transplantation (HLT)
Refractory right ventricular end-diastolic dysfunction (RVEDP <15 mmHg)
Significant intrinsic left ventricular dysfunction (LVEF <45%)
Significant coronary artery disease, not amenable to nonsurgical interventions
Eisenmenger's syndrome with an irreparable shunt defect

solid organs used for transplantation, the lung is exposed, before brain death, to environmental contamination, including both microbiologic pathogens and toxic substances, which may significantly impair its functional capabilities. The microbiologic aspects of this exposure are accentuated by the endotracheal intubation that is a necessary aspect of donor management. In addition, aspiration of oropharyngeal or gastric contents is a common occurrence during the events preceding brain death.

Nearly half of all comatose patients develop pneumonia within 1 week of intubation, probably owing to a combination of these factors. Brain death itself may also lead to neurogenic pulmonary edema. In cases of trauma that lead to brain death, significant injury to the thorax may occur, or the volume replacement required for the resuscitation of these patients may limit the suitability of the lungs for subsequent transplantation. As a result, only about 25 percent of cadaveric organ donors are potential lung donors.

Criteria for lung donation are meant to identify donors with evidence of good gas exchange in the absence of infection of the airways or parenchyma (Table 101-9). A donor age of less than 60 years and a history of smoking for less than 20 to 30 pack-years are important. Both increasing age and prolonged tobacco use are known to correlate directly with anatomic alterations in the pulmonary parenchyma—which, despite preservation of gas exchange function in the donor, may result in impaired graft function in the recipient. Chest radiograph should reveal a normal lung on the side of the proposed lung donation. Unilateral pneumonia or parenchymal trauma does not preclude use of the contralateral lung for transplantation in most circumstances. No major thoracic surgery should have been performed on the side of proposed donation, not only because of potential technical limitations but also because such a history usually suggests either a major anatomic abnormality (e.g., prior lobectomy) or pathology (e.g., malignant neoplasm), which would preclude donation.

Finally, the size of the donor lungs, based on direct measurement or correlated to body surface area as estimated by donor height, is a useful parameter for one to use when selecting lungs for a particular recipient. Generally, the donor lungs should be within 25 to 30 percent of the *predicted* size of the recipient's lungs. Since most recipients have significant abnormalities in lung volume, the predicted size of an ideal recipient lung, estimated from the recipient's body surface area, should be used for comparison. A donor lung larger than these measurements can be volume reduced at the time of transplantation, whereas a donor lung smaller than these measurements usually should be avoided.

Adequate gas exchange has been defined as a Pa_{O_2} greater than 300 mmHg on mechanical ventilation, with an Fi_{O_2} of 1.0 and positive end-expiratory pressure (PEEP) at least 5 cm H_2O. Minute ventilation should be adjusted to achieve normocarbia, with a tidal volume of 10 to 15 ml/kg and an appropriate respiratory rate. If a unilateral pulmonary process is present, however, a lower Pa_{O_2} may be acceptable because of the possibility of mixing of venous blood from the two lungs at the level of the left atrium. In this circumstance, intraoperative evaluation of unilateral gas exchange by sampling from the ipsilateral pulmonary vein for determination

Table 101-9

Characteristics of a Suitable Lung Donor

Age <60 years
Cigarette smoking <30 pack-years
No significant prior thoracic surgery on the side of the donor lung
Normal chest radiograph of the donor lung
Adequate gas exchange of the donor lung Pa_{O_2} > 300 mmHg on FIO_2 1.0, PEEP ≥5 cm Pv_{O_2} > 450 mmHg on FIO_2 1.0, PEEP ≥5 cm
Bronchoscopic evaluation demonstrating absence of mucosal inflammation
No significant pulmonary trauma or anatomic abnormalities

of P_{O_2} can be used to determine that the prospective donor lung is satisfactory.

All lung donors have some evidence of colonization of the lower respiratory tract by potential pathogens owing to the requisite endotracheal intubation, which bypasses the defense mechanisms of the upper airway. A distal tracheitis is uniformly present after 72 h of intubation. Therefore, a sputum Gram's stain revealing polymorphonuclear leukocytes or multiple bacterial forms does not necessarily imply invasive infection. For this reason, bronchoscopy is a critical step in the evaluation of any potential lung donor. Bronchoscopy allows inspection of the large airways for the presence of aspirated debris as well as assessment of the character of the secretions and status of the bronchial mucosa. A finding of diffuse bronchial mucosal inflammation is significant, even if only a limited amount of aspirated debris or secretions are present. However, purulent secretions without significant mucosal inflammation in the presence of a clear chest radiograph and preserved gas exchange generally indicate a suitable lung for donation. A potassium hydroxide smear for fungal organisms is also a part of the routine evaluation of the lung donor, although as with the Gram's stain, the mere presence of fungal organisms does not preclude lung donation. In most cases, the presence of potential pathogens in the donor sputum by either Gram's stain or fungal smear requires preemptive modification of the recipient's antimicrobial regimen if such lungs are used for transplantation. At some centers, this treatment is begun by the administration of intravenous or aerosolized antimicrobial therapy to the donor before extraction of the lungs.

The donor evaluation is completed by intraoperative inspection of the pleural space and lung. Occasionally, unsuspected parenchymal trauma is evident in the form of a bloody pleural effusion or pulmonary contusion. The donor lung also should be studied for evidence of unsuspected bullous disease or mass lesions. Excisional biopsy and intraoperative pathologic evaluation of any parenchymal mass lesion should be carried out. Finally, the anesthesiologist should be directed to maintain adequate tidal volumes and PEEP during intraoperative ventilation to preserve optimal function of the donor lung before its removal.

The appropriateness of a potential lung donor always should be interpreted in the context of the recipient's disease and clinical status. Older patients, patients with diseases such as COPD (in whom lung transplantation may be largely palliative), and patients with a sudden clinical deterioration, such as those who have recently been placed on mechanical ventilation, may all benefit from transplantation with a lung that does not fulfill all the criteria of an optimal donor lung. Most frequently, the criteria relating to cigarette smoking and Pa_{O_2} are breeched in these circumstances. The results have generally been satisfactory in such recipients, suggesting that the use of these "compromised" lung donors may partly address the problem of donor organ shortage. It has also been shown that the effect of the functional status of the donor lung is most significant in the first 24 h after transplantation, and that subsequent graft function depends primarily on factors related to the recipient. However, the potential effects of using compromised lung on long-term issues, such as the incidence of rejection, is not known. In addition, these studies have underscored that patients with pulmonary hypertension, who are the most difficult to manage postoperatively, are best served by transplantation with noncompromised lungs from optimal donors.

LUNG PRESERVATION

The ideal method of pulmonary preservation has not yet been identified. With current techniques, however, satisfactory graft function can be obtained after ischemic intervals as long as 6 to 8 h. As with other vascularized solid organs used for transplantation, the lung consists of a heterogeneous population of cells, of which the vascular endothelial cell appears to be the most sensitive to ischemia. Ischemic injury to the pulmonary vascular endothelium increases its permeability and results in pulmonary edema, the common end point for assessment of injury in models of pulmonary preservation techniques. Hypothermia is the major method used clinically to limit ischemic injury to these cells. The lung also has some unique biologic and physical characteristics that distinguish it from other solid organ transplants: Although it has an absolute requirement for aerobic metabolism, the lung is capable of using ambient oxygen for the metabolism of glucose, even during the ischemic state. In addition, the effective size of the pulmonary vascular bed and thermal conductivity of the lung can be manipulated by the state of lung inflation. Current clinical methods of lung preservation make use of these characteristics to optimize graft function following an ischemic interval.

Two techniques are currently being used for lung preservation, core cooling and hypothermic flush perfusion. *Extracorporeal core cooling* (ECC) is a technique that has been used primarily for procurement of heart–lung donor blocs, commonly in conjunction with multiorgan procurement at abdominal sites. ECC consists of systemic heparinization of the donor and institution of full CPB by means of a transpericardial approach. The donor is cooled to 15°C (rectal temperature). Ventricular fibrillation typically develops during this maneuver, and the heart is decompressed through the left ventricle. CPB is then discontinued, and the heart–lung bloc is harvested and transported in a cold ischemic state with the lungs inflated. No flush solutions are used, although the lungs are essentially being flushed by cooled autologous blood during the time of CPB. Safe ischemic times of 6 h or more have been reported with adequate pulmonary function. It is of interest that while oxygenation in lungs preserved by ECC appears to be somewhat less optimal than in those preserved by hypothermic flush techniques, the pulmonary vascular resistance upon reperfusion of the lungs following ECC is generally lower than that seen upon reperfusion of lungs obtained by flush techniques.

Hypothermic flush perfusion is the method most commonly used for pulmonary preservation in clinical practice. This technique consists of flushing the pulmonary vasculature with a cold solution after systemic heparinization of the donor, followed by extraction and transport of the lungs inflated with 100 percent oxygen. A low-potassium dextran solution is used.

The state of inflation of the lungs is important in obtaining optimal perfusion of the pulmonary vasculature by the flush solution, for the effects both of rapid cooling and of direct cellular preservation by the solution itself. Intraoperatively, maintaining a tidal volume similar to that used during the initial donor assessment is important. The addition of PEEP during the procurement procedure maintains FRC and the desired state of inflation of the donor lungs. PEEP also increases the intra-alveolar release of surfactant, minimizing pulmonary compliance abnormalities after implantation of the donor lungs. Ventilation is continued throughout the period of lung perfusion to maintain the effective size of the pulmonary vascular bed. Maintenance of an Fi_{O_2} of 1.0 during the procurement is also useful, particularly at the time of lung extraction, to provide an oxygen-rich ambient environment for metabolic activity of the lung during the ischemic interval. The lungs are extracted and transported in a state of inflation that approximates end-tidal inspiration. Some consideration should be given to the fact that the donor lungs may be transported by aircraft, in which a fall in atmospheric pressure may result in further inflation of the lungs. Overinflation of the donor lungs is to be avoided, as this leads to increased capillary permeability and postimplantation pulmonary edema.

The administration of prostanoids, either prostaglandin E_1 (PgE_1) or prostacyclin, into the pulmonary circulation before flush perfusion has been shown to improve lung preservation. The mechanism of action of prostanoids includes dilation of the pulmonary vasculature, allowing for better distribution of the flush solution, and decreased leukocyte adhesiveness, which can abrogate the initial events of reperfusion injury. Most commonly in North America, PgE_1 is used as a bolus (500 μg) into the pulmonary circulation, with or without the addition of similar amounts of PgE_1 directly to the flush solution. The use of prostanoids in combination with intracellular flush solutions has been shown to provide pulmonary preservation equivalent, if not superior, to that with the use of extracellular-type flush solutions alone.

Most flush solutions are administered at a temperature of 4°C, while topical cooling is carried out by filling of the pleural cavity with iced crystalloid solution. After extraction, the lungs are immersed in crystalloid and packed in ice, resulting in a transport temperature of 1 to 4°C. Some studies have shown that lung preservation is superior when a more moderate hypothermia with a temperature of 10°C is used. However, because of the concerns regarding the deleterious effects of flush and storage temperatures greater than 10°C, and the difficulties in maintaining this temperature during the procurement procedure, clinical flush perfusion continues to be performed at the lower temperature ranges.

Experimental work has identified numerous adjuncts to the techniques currently used for pulmonary preservation that have the potential for prolonging ischemic intervals. A significant part of the lung injury seen after ischemia has been shown to be due to the phenomenon of reperfusion, which is initiated by leukocyte adhesion to endothelial cells and the production of oxygen-derived free radicals and peroxides. Measures that diminish this response, in addition to the use of prostanoids, include donor leukocyte depletion, the administration of antibodies to block adhesion molecules, the use of inhaled nitric oxide, and the inclusion of oxygen radical scavengers, such as superoxide dismutase or catalase, to the flush solution. In addition, methods of increasing the resistance of cells to ischemic injury, such as the induction of heat shock proteins, have been shown to be beneficial in other organs and may be of some use in lung preservation. Evidence of the effect of these manipulations on tolerable ischemic intervals in clinical lung transplantation awaits additional study.

TECHNIQUES OF LUNG TRANSPLANTATION

Anesthetic Management

Proper perioperative management of the recipient is crucial to obtain the best outcome following lung transplantation. Close cooperation and understanding between the anesthesiology and surgical teams are essential. An appreciation of the unique aspects of the physiology of the various types of lung transplant recipient is also important. Patients with COPD have reduced expiratory flow rates, air trapping, and increased lung volumes. In advanced states, chronic pulmonary artery hypertension develops and leads to cor pulmonale in 10 to 40 percent of patients. These patients are usually oxygen dependent, dyspneic, orthopneic, and quite anxious. Following endotracheal intubation, extreme care should be taken to allow adequate expiratory time for emptying of the lungs, avoiding the cardiovascular instability caused by "pulmonary tamponade" due to progressive air trapping in the lungs and reduction of ventricular filling. Tension pneumothorax due to rupture of bullae can also occur but is relatively uncommon. Patients with *restrictive lung disease* have progressive fibrosis of the lung tissue, with secondary hypoxemia and progressive pulmonary hypertension. Patients with these diseases have an increased work of breathing and are oxygen dependent and extremely dyspneic before transplantation. Many of these patients have evidence of cor pulmonale at the time of transplantation and can not tolerate occlusion of the pulmonary artery during implantation of the donor lung without the support of cardiopulmonary bypass. Careful and repeated assessment of filling pressures and cardiac output is required to allow prompt interventions in such patients.

Patients with *septic lung disease* demonstrate primarily the abnormalities in pulmonary function seen in patients with

obstructive airway disease. However, these recipients have excessive copious purulent secretions, which can exacerbate air trapping and also contribute to marked V/Q abnormalities—particularly during single-lung ventilation. Careful management of double-lumen endotracheal tubes to avoid contamination of the contralateral lung graft and attention to bronchopulmonary hygiene to avoid obstruction of the lumens of these tubes are needed in these patients. Finally, recipients with *pulmonary vascular disease* who present for transplantation have marginally compensated cor pulmonale and are extremely dyspneic and anxious. Patients with PPH become oxygen dependent late in the course of their disease, although oxygen is commonly administered to these patients to lessen the hypoxic contribution to their pulmonary hypertension. For this reason, oxygen therapy should be continued throughout the time of preoperative preparation and line placement to avoid abrupt right heart dysfunction. Because these patients have normal pulmonary mechanics, they generally tolerate mechanical ventilation well. Patients with Eisenmenger's syndrome are well adapted to chronic hypoxemia. In these patients, supplemental oxygen does not reverse the hypoxemia and may even worsen arterial hypoxemia by eliciting systemic vasodilatation and increasing right-to-left shunting.

All lung transplant procedures should be performed with CPB available on standby. However, CPB is best avoided in cases of septic lung disease or when there are known extensive intrapleural adhesions, to avoid excessive bleeding complications. No specific preoperative factors can be used to predict the need for CPB—with the exception of either PPH or Eisenmenger's syndrome, for which CPB is requisite for the procedure. For other lung transplant recipients, assessment of the need for CPB is best made intraoperatively by trial clamping of the pulmonary artery, followed by assessment of hemodynamic parameters, oximetry, and if available, ventricular function testing by transesophageal echocardiography. Progressive deterioration in these parameters requires unclamping of the pulmonary artery and an attempt to optimize factors such as preload, inotropic support, Pa_{O_2}, Pa_{CO_2}, and pulmonary vascular resistance. If repeat trial clamping of the pulmonary artery is still not tolerated, plans for CPB are made. Typically, cannulation after systemic heparinization is via the femoral vessels for SLT and via a transpericardial approach for patients undergoing DLT or HLT.

Single-Lung Transplantation

The approach to SLT requires an initial decision regarding the side of implantation. Most commonly, the native lung with the least pulmonary function based on preoperative V/Q scans is excised. In some patients, however, specific technical factors, such as a prior pleurodesis, may override this factor. When the function of the two lungs is equal or when the need for CPB is anticipated, the right side is preferred because of the greater ease of surgical exposure and the institution of CPB via the ascending aorta and right atrium. A right-sided approach also facilitates exposure for closure of intracardiac defects in patients with Eisenmenger's syndrome. Despite the potential differences in size of the right and left hemithorax, there does not appear to be any long-term difference in outcome following right or left SLT.

Most often, exposure for SLT is via a generous posterolateral thoracotomy through the fifth intercostal space or the bed of the excised fifth rib. When elective CPB via the right hemithorax is planned, the use of a fourth interspace may facilitate placement of the cannulae. The ipsilateral groin is included in the surgical field in the event that cannulation of the femoral vessels is required for partial CPB. Although the use of femoral sites for cannulation requires repair of the vessels after removal of the cannulae, it does provide a site for additional venous drainage with use of intrathoracic cannulation sites. Femoral cannulation sites also provide access for conversion to ECMO support if acute graft failure occurs immediately after implantation. Occasionally, when the repair of an associated intracardiac defect requires an anterior approach, a median sternotomy may be used for right SLT in patients with Eisenmenger's syndrome.

The donor lung is prepared for implantation and then wrapped in sponges soaked with cold crystalloid solution and placed into the hemithorax. The bronchial anastomosis is performed first. Although a variety of techniques have been described, the essential points are to minimize the length of both the donor and recipient bronchi to preserve collateral blood supply and achieve some degree of anastomotic overlap. The smaller bronchus, most commonly the donor bronchus, is telescoped into the larger bronchus with either a technique of interrupted sutures or a combination of running sutures on the membranous wall and interrupted sutures on the anterior wall in a figure-eight or horizontal mattress fashion. Polyfilament absorbable suture (e.g., 4-0 polyglactin) or monofilament suture, either absorbable (e.g., polydioxanone) or nonabsorbable (e.g., polypropylene), may be used. The anastomosis is then covered by either local peribronchial tissue or local pedicled flaps of thymic tissue or pericardial fat (Fig. 101-1).

The order of the vascular anatomoses can vary even though the pulmonary artery anastomosis is frequently the more technically difficult to perform. A continuous 5-0 polypropylene suture is used for each anastomosis, leaving the ends untied for de-airing upon reperfusion of the lung. For the pulmonary artery anastomosis, the length of the donor and recipient vessels requires careful assessment to avoid kinking. For the left atrial anastomosis, the confluence of the recipient pulmonary veins is incised to create a left atrial cuff. Occasionally, dissection in the interatrial groove is required to allow more proximal placement of the vascular clamp on the recipient left atrium (Fig. 101-2). After completion of these anastomoses, the lung is gently reinflated. Perfusion of the lung graft is then reestablished, initially in an antegrade fashion, evacuating air via the left atrial suture line. The atrial clamp is removed, with the atrial suture line under a fluid level to prevent entrainment of air into the left heart. Ventilation of the donor lung is resumed, and after a few minutes to allow the vascular suture lines to adapt to the distention caused by

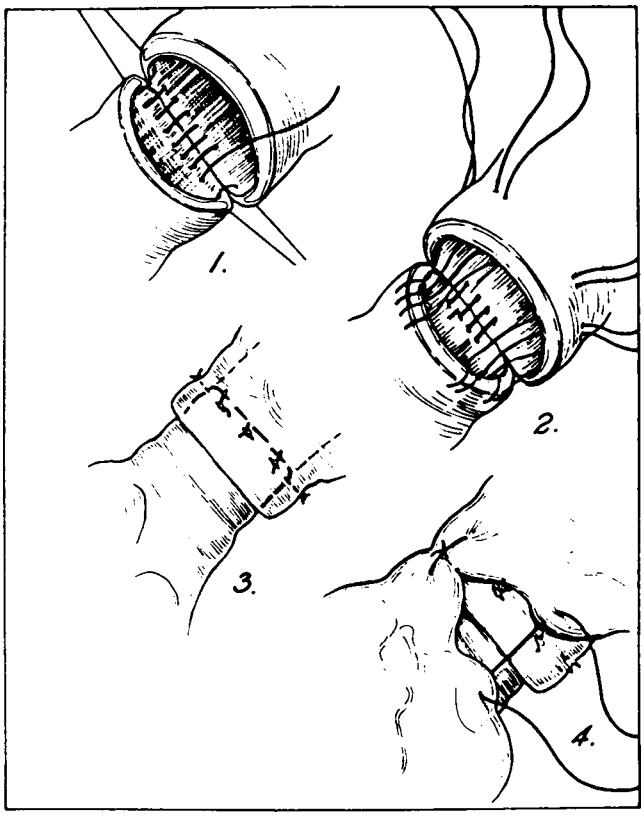

Figure 101-1 Bronchial anastomosis for lung transplantation. A technique of approximation using stay sutures at the junction of the cartilaginous and membranous walls is shown. A running suture is used for the membranous wall *(1)*, followed by an interrupted suture technique of horizontal mattress sutures on the cartilaginous wall to achieve telescoping of the donor into the recipient bronchus *(2)*. Significant anastomotic overlap is achieved with this technique *(3)*, with additional anastomotic coverage obtained by approximation of peribronchial and mediastinal tissues about the site *(4)*. *(From Pearson FG:* Thoracic Surgery. *New York, Churchill Livingstone, 1995, with permission.)*

increased flow, these suture lines are secured. Hemostasis is then obtained, two chest tubes are placed, and the chest is closed in a standard fashion. Following reintubation with a single-lumen tube, flexible bronchoscopy is completed to inspect the bronchial anastomosis and clear the airway of blood or residual secretions.

Double-Lung Transplantation

The most frequently performed DLT procedure is that of bilateral sequential SLT. This procedure has a significantly lower incidence of bronchial complications than the en bloc DLT procedure, and is technically less difficult to perform than en bloc DLT with simultaneous bronchial artery revascularization. The exposure for bilateral sequential lung transplantation is via bilateral anterolateral thoracotomies through the fourth or fifth intercostal space, connected by a transverse sternotomy—the so-called clam shell incision (Fig. 101-3). The incision provides adequate exposure for mobilization of intrapleural adhesions, even after previous pulmonary resections or pleurodesis, and also provides excellent access for institution of CPB and correction of intracardiac defects. In most patients, the entire incision is made at the beginning of the procedure, and both lungs are completely mobilized. For patients with emphysema who undergo DLT, however, the contralateral hemithorax may be left closed until after the first lung graft is implanted; this sequence minimizes the tendency to overinflation of the native lung that may occur during the initial implantation procedure. The mobilization and pneumonectomy of the native lung and the implantation of the lung graft are conducted in the same manner as described for SLT. Thymic and anterior mediastinal tissue on a superiorly based vascular pedicle may be mobilized for coverage of the bronchial anastamoses.

Living related lung transplantation is most commonly performed as a bilateral sequential transplant procedure using the clam shell incision. Cardiopulmonary bypass is instituted electively after the recipient native lungs are mobilized. Each of the donor lobes is implanted at the recipient hilum. Typically, there is little discrepancy in size between the *lobar* bronchus and pulmonary vein of the donor (usually an adult) and the *main* bronchus and left atrium of the typical pediatric recipient. The order of the anastomoses (bronchus first) and the technique are the same as for cadaveric SLT and DLT. Overinflation of the lobar graft is more likely than with a cadaveric allograft and may contribute to postoperative pulmonary edema. A marked size discrepancy between the lobar allograft and the recipient hemithorax is uncommon; if present, the descrepancy should be treated conservatively (e.g., by avoiding chest tube suction rather than by aggressive surgical measures such as thoracoplasty). In all cases, sufficient remodeling of the thorax or hyperinflation of the lobar grafts will occur to obliterate any residual pleural space.

Heart–Lung Transplantation

Either a standard median sternotomy or a clam shell incision may be used for HLT. The latter provides better access for mobilization of intrapleural incisions and is particularly useful for recipients with septic lung disease or prior pulmonary procedures. Following institution of CPB, the lungs are removed by an extrapericardial approach using successive stapling of the bronchovascular structures at the pulmonary hila.

The donor right atrium is incised from the inferior vena cava to the right atrial appendage. Inspection is made for the presence of an atrial septal defect and adequate closure of the superior vena cava. The donor bloc is positioned by passing the lungs into the pleural spaces via the retrophrenic pedicles. If a tracheal anastomosis is used, the posterior pericardium is incised between the ascending aorta and superior vena cava to expose the distal trachea and, after the donor and recipient tracheas have been trimmed, a distal tracheal anastomosis is performed. Some centers prefer bilateral bronchial anastomoses at the mediastinal pleural reflection, using a telescoping technique as described for SLT. This approach obviates dissection in the posterior mediastinum and may be associated

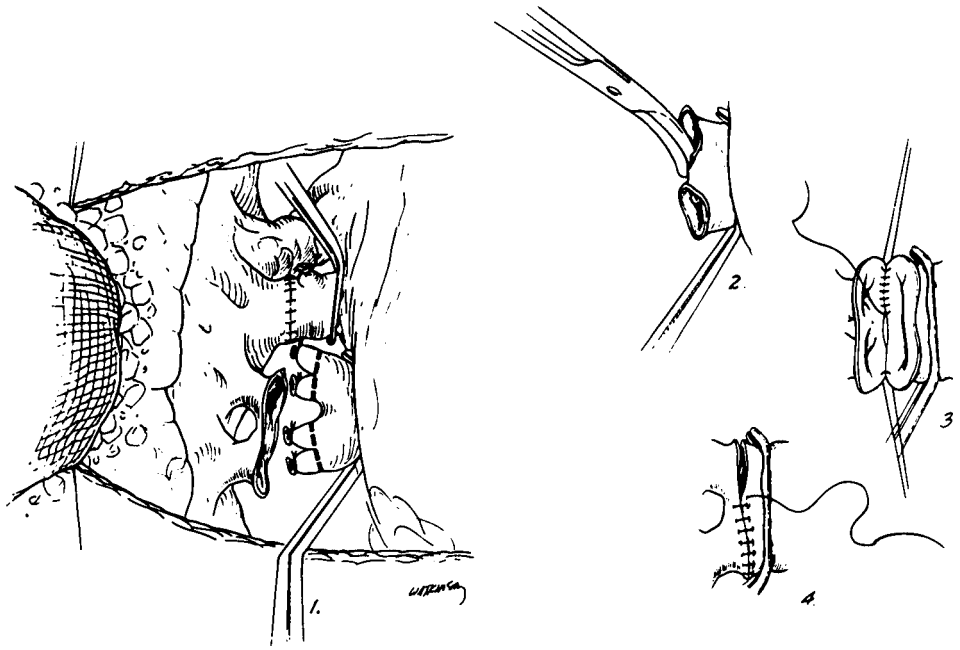

Figure 101-2 Implantation of the donor lung at the right hilum. *1*. The bronchial anastomosis is performed first, followed by the vascular anastomoses. A clamp is placed on the proximal pulmonary artery, and the anastomosis is performed distal to the first upper-lobe arterial branch in the recipient, which has been ligated. A clamp is placed on the left atrium intrapericardially. *2*. After excision of the pulmonary vein stumps, the confluence of the pulmonary veins is incised to create a cuff of left atrium for anastomosis. *3*. Atrial anastomosis is performed with a running monofilament suture following approximation with stay sutures superiorly and inferiorly. *4*. On completion of the anastomosis, the sutures are left untied until lung reinflation and antegrade reperfusion is completed to evacuate air from the donor vasculature. *(From Shields TW:* General Thoracic Surgery. *Philadelphia, Lea & Febiger, 1994, with permission.)*

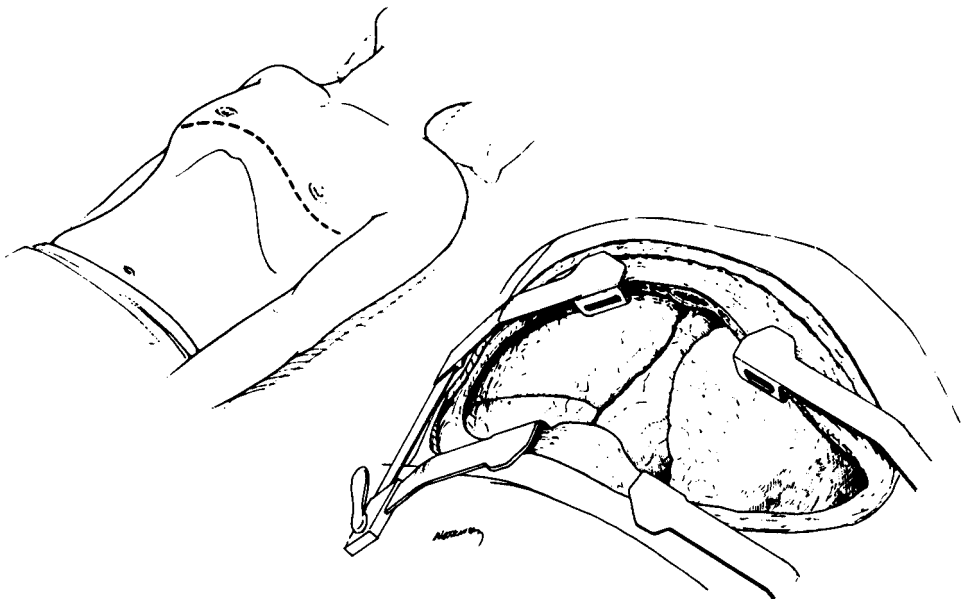

Figure 101-3 Approach to double-lung transplantation. The clam shell incision is used, consisting of bilateral anterior thoracotomy with transverse sternotomy, defined by the line of the inframammary crease. Entrance into the chest is through either the fourth or fifth intercostal space, followed by placement of bilateral rib retractors. *(From Shields TW:* General Thoracic Surgery, *Philadelphia, Lea & Febiger, 1994, with permission.)*

with fewer anastomotic complications. The right atrial anastomosis is completed, followed by the aortic anastomosis. The aortic cross clamp is removed, and after reinflation of the lungs, the heart is de-aired via the pulmonary artery and left ventricle. After defibrillation, the patient is weaned from CPB.

POSTOPERATIVE MANAGEMENT

Ventilation

In most cases, ventilatory management folllows standard criteria. The Fi_{O_2} is adjusted to maintain a Pa_{O_2} greater than 65 mmHg. Standard volume ventilation is used, with a tidal volume of 12 to 15 ml/kg and PEEP of 5 to 7.5 cm H_2O. Significant barotrauma due to increased airway pressures is extremely uncommon after lung transplantation, and higher airway pressures may have a beneficial effect in minimizing postoperative pulmonary edema. Transition from volume ventilation to pressure ventilation before extubation may be useful to decrease the work of breathing and serves to minimize differences in compliance between the native lung and allograft following SLT. Appropriate management of postoperative pain is also helpful in weaning these patients from the ventilator. Extubation is performed when the mental status of the patient is normal and the patient has achieved a reasonable rate of ventilation and spontaneous tidal volume, typically 48 to 72 h after the procedure. Maintaining good bronchopulmonary hygiene, with frequent endotracheal aspiration of secretions and physiotherapy, is important in achieving and maintaining extubation in these patients.

Patients with emphysema who undergo SLT are an exception to the above guidelines. These patients require particular attention to airway pressures and to the compliance difference between the allograft and the native lung. Hyperinflation of the native lung may not only result in compromise of cardiac filling but also interferes progressively with ventilation of the allograft. Efforts to control hyperinflation of the native lung include use of slightly lower tidal volumes (9–12 ml/kg) accompanied by higher respiratory rates to preserve minute ventilation and lower levels of PEEP (1–3 cm H_2O). Positioning of the patient with the native lung down may further increase the impedance of that hemithorax and limit hyperinflation, although increased blood flow to the native lung induced by this maneuver may require adjustment of ventilatory parameters to maintain normocarbia. In rare circumstances, when significant edema has occurred in the allograft, independent lung ventilation using a double-lumen endotracheal tube may be needed.

In patients with significant pulmonary hypertension who undergo lung transplantation, the postoperative pulmonary hemodynamics are unique. In these patients, the right ventricle has been conditioned to generate peak systolic pressures against a markedly elevated pulmonary vascular resistance (PVR). Following lung transplantation, the PVR abruptly decreases to near-normal levels, accompanied by improved ventricular hemodynamics. Minimal catecholamine stimulation occurs when the patient awakes from anesthesia or is weaned from a ventilator, causing the right ventricle to respond by generating peak systolic pressures similar to those that existed preoperatively. The resultant abrupt increase in pulmonary artery pressure, in combination with increased capillary permeability due to ischemia and reperfusion injury and the absence of lymphatic continuity, causes fluid to accumulate rapidly in the donor lung. Typically, this pulmonary edema is very rapid in onset and results in hypoxia that elicits additional increase in pulmonary artery pressure. Preemptive treatment for this condition is necessary and requires maintenance of a high degree of sedation, or even of muscle paralysis, in the first 3 to 5 days after surgery. Following this period, patients can be awakened cautiously and weaned from the ventilator with standard methods while cardiac output, blood gases, and pulmonary artery pressures are closely monitored.

Fluid Management

The goal of fluid management after lung transplantation is to minimize the accumulation of edema fluid in the implanted lung while maintaining optimal cardiac function. As previously noted, the effects of ischemia, reperfusion injury, and lymphatic discontinuity all contribute to a tendency to develop pulmonary edema in the lung graft. Pulmonary artery pressures and pulmonary capillary wedge pressures need to be kept as low as possible after surgery without compromising ventricular preload. For most patients, a reduction in PVR almost immediately after lung transplantation results in improved right ventricular and, secondarily, left ventricular performance. However, some inotropic support may be required in patients who have preexisting right ventricular hypertrophy, particularly when pressure overload of the right ventricle occurs during the implantation procedure or following CPB.

Antimicrobial Therapy

Bacterial prophylaxis entails the use of vancomycin for prophylaxis against gram-positive organisms in combination with a broad-spectrum antibiotic to provide appropriate coverage for organisms identified preoperatively from the sputum of the recipient. Recipients who have been recently hospitalized, and therefore exposed to respiratory therapy equipment, or those with cystic fibrosis, require specific antibiotic coverage against *Pseudomonas* species, based on susceptibility data. For cystic fibrosis patients, ongoing surveillance of sputum flora and determination of antibiotic sensitivities are important in the waiting period before transplantation so that an appropriate multidrug antimicrobial regimen can be developed for perioperative use. The addition of antimicrobial inhalation therapy, using either tobramycin or colistin, can have additive effects in the management of *Pseudomonas.* Postoperative antibacterial coverage should be modified if pathogens not already covered by the recipient-specific regimen are found in the sputum of the donor.

Routine prophylaxis for fungal organisms is useful when preoperative recipient sputum cultures have demonstrated the presence of *Aspergillus* species at any time before the transplant procedure, when there has been evidence of heavy overgrowth of yeast (e.g., *Candida*) in the donor sputum culture, or when cytolytic induction immunosuppression is used. In the case of *Aspergillus,* prophylactic therapy requires the use of amphotericin B; in the latter instances, fluconazole or low-dose ketoconazole therapy is effective.

The occurrence of herpes simplex infection, including mucosal ulceration and pneumonitis, has been eliminated by the routine use of acyclovir prophylaxis after lung transplantation. However, CMV infection remains a significant problem following lung transplantation. The incidence of CMV infection after lung transplantation is related to the preoperative CMV status of both the donor (D) and the recipient (R). A discordant CMV status between donor and recipient may result in either primary infection of the donor lungs by the recipient (in the case of D+/R+) or the more serious circumstance of primary systemic CMV infection (in the case of D+/R+). In either case, the incidence of acute and chronic rejection and mortality are higher than among patients in whom CMV status is concordant. For this reason, many centers prefer to match D and R status. However, the use of ganciclovir prophylaxis has been shown to eliminate the incidence of primary disease and to improve the outcome of CMV-disparate lung transplants. *Pneumocystis carinii* infection in lung transplant patients has been eliminated by the routine use of trimethoprim-sulfamethoxazole beginning 1 week after surgery.

Nutrition

Maintaining optimal nutrition in the postoperative period is a useful adjunct for improving surgical outcome. When prolonged ventilatory support is required, the use of intravenous hyperalimentation or, preferably, enteral alimentation via a nasogastric feeding tube is mandatory. Patients with cystic fibrosis have a malabsorptive syndrome, which requires resumption of preoperative pancreatic enzyme supplementation. These patients have difficulty absorbing medications such as cyclosporine—a circumstance that may be improved by the intake bof bile salts (e.g., ursodeoxycholic acid 330 mg with each cyclosporine dose).

Immunosuppression

The induction of a state of relatively nonspecific immune suppression by pharmacologic means has been the key to successful clinical lung transplantation. While the ideal method would be to achieve specific, permanent tolerance of the allograft without the need for chronic medication, this is not possible at present. As a result, although the current regimens lead to satisfactory control of most acute rejection processes, the combined side effects of these medications and their incomplete ability to control chronic rejection in the lung account for the major long-term morbidity and mortality associated with lung transplantation.

The immunosuppressive regimens used for lung transplantation are based on the successful protocols that have evolved for renal and heart transplantation. Virtually all centers use a three-drug regimen for immunosuppression (a calcineurin inhibitor, cell-cycle inhibitor, and steroids), with the hope of obtaining additive effects in terms of immune suppression while limiting drug toxicities. Most lung transplant programs use steroids as part of the regimen for the induction of immunosuppression. However, some centers have used cytolytic therapies such as daclizumab, basiliximab (anti-CD25), Campath (anti-CD52), OKT3, and anti-thymocyte globulin for this purpose. These therapies are typically initiated within 24 hours of transplantation, and are typically combined with the usual triple-drug regimen of steroids, a calcineurin inhibitor, and a cell-cycle inhibitor.

Cyclosporine remains the mainstay of immunosuppression for lung transplantation. Intravenous administration is usually begun before the graft is implanted and continued postoperatively, provided renal function remains satisfactory. Subsequent conversion to oral dosing is completed when gastrointestinal function is normal. Blood levels of cyclosporine correlate with immunosuppressive effects and toxicity. Whole blood levels of 350 to 400 ng/ml or serum levels of 150 to 200 ng/ml are considered therapeutic. Nephrotoxicity, the major side effect of cyclosporine, results from vasoconstriction of the afferent glomerular arteriole.

Azathioprine, a purine analog, is converted to several purine metabolites, including 6-mercaptopurine, in red cells and hepatocytes. These purine metabolites have a variety of inhibitory effects on hematologic cell proliferation, with a somewhat greater effect on T cells than B cells. Azathioprine is begun at a dosage of 2 to 2.5 mg/kg per day and adjusted downward to maintain a white blood cell count of more than 4000 cells/ml. The dosage is the same for both the intravenous and oral routes. If necessary, azathioprine may be omitted for several days without significant compromise of its immunosuppressive effect.

Corticosteroids have a variety of effects on the immune response, mediated by the interaction of the steroid with a high-affinity cytoplasmic receptor. Steroids affect both inflammation and immunity, and modulate lymphocyte-, mononuclear phagocyte–, and antigen-presenting cell functions. Prednisone, prednisolone, and methylprednisolone are all synthetic derivatives of cortisol that are used clinically for transplant patients. Intraoperatively, methylprednisolone is administered before reperfusion of the lung graft. Postoperatively, in the absence of cytolytic induction therapy, moderate-dose corticosteroid therapy is used in combination with cyclosporine and azathioprine for induction immunosuppression. An oral dose of prednisone (0.5 mg/kg per day) is usually begun on postoperative day 5 to 7. Although corticosteroids have profound inhibitory effects on wound healing, their use in this fashion in the immediate postoperative period has not adversely affected the outcomes of lung transplantation.

Various antilymphocyte antibody preparations, so-called cytolytic therapies, have been used in clinical lung transplantation. Both polyclonal preparations, such as antilymphocyte globulin and antithymocyte globulin (ATG), and a murine monoclonal antibody to the CD3 complex of human lymphocytes (OKT3) have been used. Initially, it was believed that strict avoidance of corticosteroids was needed in the early postoperative period to assure satisfactory healing of the bronchial anastomosis. As a result, cytolytic therapy was thought to be necessary to induce immunosuppression before the initiation of steroid therapy in the second postoperative week. The subsequent demonstration that moderate-dose corticosteroid therapy was well tolerated immediately after lung transplantation, as described, as well as concerns regarding the risks of cytolytic therapy, resulted in most centers' reserving the use of these agents for the treatment of refractory acute rejection.

The two most significant concerns regarding the use of cytolytic therapy have been the increased incidence of CMV disease and the incidence of posttransplant lymphoproliferative disorder (PTLD). CMV disease can be effectively eliminated by several strategies, including matching of D/R CMV status and the use of prophylactic ganciclovir. The incidence of PTLD may also be minimized by the use of ganciclovir, which has additional effects against the Epstein-Barr virus (EBV), the likely cause of PTLD in most cases.

Tacrolimus (FK-506) is a macrolide compound with a mechanism of action similar to that of cyclosporine through an immunophilin protein called the FK-binding protein (FKBP). Tacrolimus has been used for induction immunosuppression as part of a three-drug regimen with azathioprine and steroids and as a rescue therapy for patients with refractory rejection on a standard three-drug regimen (cyclosporine, azathioprine, and steroids). Toxicity is similar to that of cyclosporine and includes reversible renal dysfunction, hypertension, and neurotoxicity. New-onset diabetes mellitus has also been reported. Hypertrichosis and gingival hyperplasia have not been seen with tacrolimus. In a randomized trial in lung transplant patients of three-drug regimens containing either cyclosporine or tacrolimus, the incidence of postoperative fungal infections was higher in patients receiving tacrolimus.

Sirolimus (rapamycin) is an analog of tacrolimus that also binds to MTOR (mammalian target of rapamycin). It inhibits the response of T lymphocytes to IL-2 and other cytokines but does not inhibit IL-2 production. Rapamycin has been shown to reverse ongoing rejection and prolong graft survival in animal models. However, rapamycin has been associated with airway anastamotic dehiscence (a major complication) when used for immunosuppression early posttransplant. Although the drug does not cause nephrotoxicity, a major toxicity is necrotizing vasculitis of the gastrointestinal tract. Concurrent cyclosporine administration increases the potency of rapamycin, suggesting that it may be used in combination with cyclosporine to lower the overall toxicity of a multidrug immunosuppressive regimen. Mycophenolic acid inhibits de novo purine synthesis by inhibiting the conversion of inosine monophosphate to xanthine monophosphate. Since lymphocytes depend almost exclusively on de novo purine synthesis, mycophenolic acid selectively inhibits their replication, including the formation of cytotoxic lymphocytes and both primary and secondary antibody formation. Mycophenolic acid has been shown to reverse acute rejection that is resistant to both corticosteroids and OKT3. It appears to have primarily gastrointestinal side effects, including nausea, gastritis, and ileus, without significant myelosuppressive toxicity.

Rejection

Lung grafts contain a large population of immunocompetent cells, including lymphocytes and macrophages within the parenchyma, hilar and pulmonary lymph nodes, and bronchus-associated lymphoid tissue (BALT). Most of these cells are memory T cells. A prominent interaction occurs between donor and recipient immune cells during the early period after implantation. Analysis of cells obtained by bronchoalveolar lavage (BAL) during the first month after transplant demonstrates donor-specific lymphocyte proliferation, suggesting in vivo mixed lymphocyte reactivity at a time when both donor and recipient immune-competent cells are present. Subsequently, rapid replacement of donor lymphocytes and macrophages occurs. By 90 days after transplantation, most of the intraparenchymal cells are of recipient origin and BALT has been markedly depleted.

In view of these rapid and profound changes in immune cell populations, it is not surprising that rejection is common in lung allografts and that, in the case of heart–lung grafts, lung rejection may occur more frequently than, and independent of, rejection of the heart (Table 101-10). A protocol of routine transbronchial biopsy of the lung for identification of histologic evidence of lung rejection is usually recommended for both heart–lung and isolated-lung transplants because of the likelihood of rejection that may occur with minimal clinical symptoms. Typically, surveillance bronchoscopy is performed at 3 weeks, 6 weeks, 3 months, 6 months, 9 months, and 12 months after surgery. Bronchoscopy and biopsy are, of course, also performed for clinical symptoms or for changes in lung spirometry such as a decrease in FEV_1.

Acute rejection (AR) is characterized by perivascular and subendothelial mononuclear cellular infiltrates (Fig. 101-4). Airway inflammation, a lymphocytic bronchitis or bronchiolitis, may also be seen as a component of AR. Clinically, the patients manifest dyspnea, low-grade fever, hypoxemia, and pulmonary infiltrates on chest radiograph. Flexible bronchoscopy with BAL and transbronchial biopsy are the most useful methods of differentiating AR from infection. BAL is most useful in excluding infection and is not generally helpful in confirming rejection. The transbronchial biopsy is assessed with a standard histologic grading of AR based on the degree of perivascular infiltrate, with an additional category for assessing the degree of airway inflammation (Table 101-10). Although the severity of the perivascular process determines the "grade" of AR, the bronchial inflammation may

Table 101-10

Working Formulation for Classification and Grading of Pulmonary Allograft Rejection

Acute rejection—[with/without (B)]
Grade A0, None
Grade A1, Minimal
Grade A2, Mild
Grade A3, Moderate
Grade A4, Severe
Airway inflammation—lymphocytic bronchitis/ bronchiolitis
B0, no airway inflammation
B1, minimal airway inflammation
B3, moderate airway inflammation
B4, severe airway inflammation
BX, ungradeable because of sampling problem, infection, tangential cutting, etc.
Chronic airway rejection—bronchiolitis obliterans
Active
Inactive
D. Chronic vascular rejection—accelerated graft vascular sclerosis

SOURCE: *Yousem SA, Berry GJ, Cagle PT, et al.: Revision of the 1990 working formulation for the classification of pulmonary allograft rejection: Lung Rejection Study Group.* J Heart Lung Transplant *15:1–15, 1996.*

be a significant factor in predicting the later development of chronic rejection that involves the airways.

Because the incidence of AR in the first 3 weeks after lung transplantation exceeds 90 percent at most centers, antirejection therapy is usually administered empirically for transplant recipients with the appropriate clinical syndrome, even in the absence of confirmatory biopsy findings, if no infectious cause is found by BAL. The initial treatment of AR is by the administration of a brief course of high-dose corticosteroids (e.g., methylprednisolone 500 mg intravenously every day for 3 days). Ganciclovir prophylaxis (5 mg/kg twice a day, tapered over 6 weeks) is necessary for all patients with CMV-disparate D/R status when antirejection therapy is initiated. In most patients, symptomatic and radiographic improvement is seen within 48 h. Thereafter, the maintenance dose of steroids is usually increased for several weeks and then slowly reduced to prerejection levels. As a rule, it is not necessary to repeat transbronchial biopsy to confirm resolution of the AR unless symptoms or radiographic abnormalities persist. Occasionally, some patients with persistent findings require a second course of steroids, either as previously administered or as a slightly longer course of oral therapy (e.g., "recycling" beginning with prednisone 200 mg a day and then a dosage reduced by 40 mg a day to return to a maintenance dose 10 mg a day higher than the dose on which rejection occurred). For the rare patient in whom these methods do not bring about resolution of the process, repeat bronchoscopy for BAL and transbronchial biopsy are recommended to confirm the diagnosis. If persistent AR is identified, cytolytic therapy with OKT3 or ATG should be considered.

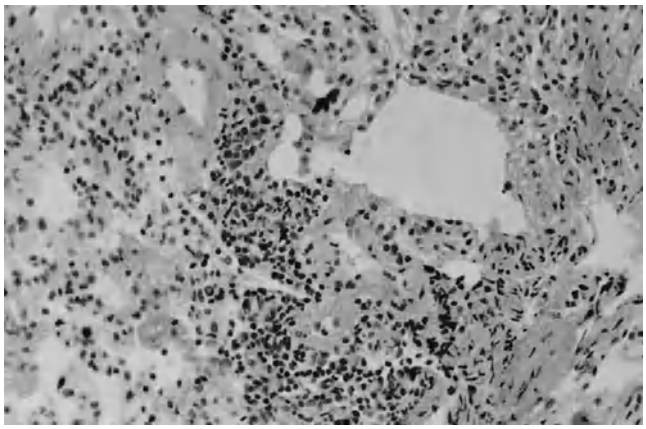

Figure 101-4 Lung allograft rejection—acute rejection, grade 2. Acute rejection is characterized by lymphocytic infiltration about pulmonary vessels. Grading of the rejection process is based on the extent of the lymphocytic infiltration into the surrounding lung parenchyma.

Chronic rejection (CR) in the lung may affect either the pulmonary vasculature or the airway. Occasionally, accelerated sclerosis of the pulmonary arteries and veins may be encountered in lung allografts. These changes are analogous to the CR identified in many isolated cardiac allograft recipients. In fact, when this type of CR is identified in the lungs of HLT recipients, it appears to correlate with similar changes in the coronary arteries of these patients.

More typically, CR in the lung is manifested by obstructive changes in the small airways. Clinically, progressive dyspnea occurs, although a gradual decline in FEV_1 or in expiratory flow rates often precedes symptoms. Histologically, this process is identified as bronchiolitis obliterans and consists of dense eosinophilic scarring of the membranous and respiratory bronchioles (Fig. 101-5). Further progression of this process leads to worsening dyspnea and bronchiectasis with secondary infection. Although this form of CR is uncommon in the first 3 months after lung transplantation, up to 50 percent of patients develop it within 2 years, and the mortality at 3 years after diagnosis is 40 percent or higher. Risk factors for the development of this process include episodes of severe AR, three or more episodes of mild AR, and, in some centers, the occurrence of CMV disease. Some studies have suggested that the use of OKT3 for induction immunosuppression or the use of tacrolimus as part of a three-drug immunosuppressive regimen has been associated with a lower incidence of CR of the lung involving the airways.

The term *bronchiolitis obliterans syndrome* (BOS) has been used to identify patients with CR of the lung involving the airways. Progressive symptoms and an unexplained fall in expiratory flow rates are the hallmarks of this process. Because of sampling limitations of transbronchial biopsy, some

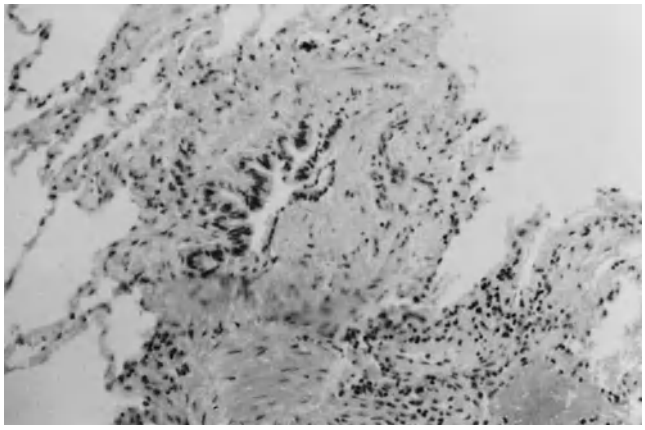

Figure 101-5 Lung allograft rejection—obliterative bronchiolitis. Chronic rejection in the lung most commonly involves the small airways, resulting in obliterative bronchiolitis. Dense submucosal scarring occurs and may completely obstruct the lumen of small airways. The process may be categorized as active or inactive, depending on the degree of associated inflammation.

patients with CR may not have histologic proof of bronchiolitis obliterans despite a course of progressive deterioration. Therefore, the diagnosis of BOS is based on symptoms and objective changes in pulmonary function and does not require histologic evidence of bronchioitis obliterans (Table 101-11). The clinical condition of patients with BOS is graded on a scale from 0 to 3. Although some patients with BOS will remain stable within a given grade, most demonstrate evidence of disease progression. Some evidence suggests that augmented immunosuppression may stabilize the BOS process, particularly if initiated early in its evolution. Treatment is usually directed to patients with symptomatic BOS (grades 1–3). Augmented corticosteroid therapy, including the use of inhaled steroids, cytolytic agents, and tacrolimus, has been used for this purpose. Whether one type of therapy offers a specific advantage over another in the treatment of this syndrome is not yet clear.

Table 101-11

Staging Classification of Bronchiolitis Obliterans Syndrome

Stage	Severity	FEV_1 (%5 baseline)
0	No symptoms	>80%
1	Mild	66–80%
2	Moderate	51–65%
3	Severe	≤50%

All stages may be subcategorized according to the presence (subcategory a) or absence (subcategory b) of histologic evidence of bronchiolitis obliterans.

Management of progressive BOS in its later stages is mostly palliative. At its most advanced stage, BOS is essentially an acquired form of septic lung disease, and management is similar to that required for other patients with septic lung disease awaiting lung transplantation. Salvage therapies such as total lymphoid irradiation and extracorporeal photopheresis have met with limited success. Retransplantation has been performed for some patients with BOS. The results demonstrate a significantly increased perioperative mortality for such patients. One-year survival is approximately 45 percent, less than half that for primary lung transplantation. Approximately 40 percent of patients surviving retransplantation develop recurrent BOS by 3 years—an incidence similar to that following primary lung transplantation.

Complications

Surgical Complications

Major technical complications following lung transplantation have become increasingly rare with improvements in surgical technique and perioperative management. *Postoperative hemorrhage* requiring reexploration is very uncommon with the use of the clam shell incision to improve operative exposure for patients requiring DLT or HLT and with the routine use of aprotonin infusions during CPB to diminish fibrinolysis. *Pulmonary artery obstruction* can occur as a result of anastomotic stenosis, kinking, or extrinsic compression. In these patients, persistent pulmonary hypertension and unexplained hypoxemia may be evident. Attention to anatomic factors, such as the length of donor and recipient pulmonary arteries and division of the pericardial attachments surrounding the donor pulmonary artery, as well as awareness of the potential for a flap wrapping the bronchial anastomosis to compress the adjacent anastomosis, helps to avoid these problems. *Left atrial anastomotic obstruction* can also occur because of faulty anastomotic technique or extrinsic compression by clot, pericardium, or an omental flap. This problem results in more severe abnormalities than pulmonary artery obstruction, including marked pulmonary hypertension and ipsilateral pulmonary edema. Diagnostic methods for these vascular anastomotic complications include routine intraoperative measurement of anastomotic gradients and transesophageal echocardiography, which is particularly helpful in assessing the left atrial anastomosis. Postoperatively, diagnostic measures include contrast angiography and ventilation/perfusion scanning. Reoperation and correction of the anastomosis are indicated if clinical compromise is apparent, which is particularly likely if there is significant left atrial anastomotic obstruction.

Some transplanted lungs demonstrate *acute graft dysfunction,* even without evidence of vascular anastomotic complications (Table 101-12). As many as 20 percent of patients have severe early abnormalities of lung function, with rapidly progressive pulmonary edema, persistent pulmonary hypertension, and a markedly diminished pulmonary compliance that occurs rapidly after graft implantation. This process is to be differentiated from the "reimplantation response" that

Table 101-12

Recommended Grading System for Primary Graft Dysfunction (PGD)

Grade	Pao_2/Fio_2	Radiographic Infiltrates Consistent with Pulmonary Edema
0	>300	Absent
1	>300	Present
2	200–300	Present
3	<200	Present

SOURCE: *Christie JD, Carby M, Bag R, et al: Report of the ISHLT Working Group on Primary Lung Dysfunction, part II: Definition.* J Heart Lung Transplant, *24:1454–1459, 2005.*

is seen in almost all patients 36 to 96 h after transplantation and consists of perihilar and peribronchiolar edema *without* significant abnormalities in gas exchange. In some patients, acute graft dysfunction is due to unsuspected abnormalities in the donor lung, such as aspiration or contusion, whereas in others it may be due to inadequate pulmonary preservation. However, no cause has been identified. Management includes evaluation of the vascular anastomoses, to rule out a potentially correctable technical complication, and maintenance of oxygenation using volume ventilation and PEEP. In most patients, regardless of the supportive measure required, the process resolves over several days.

Pleural space complications are not uncommon after lung transplantation, although they are usually of minor significance. *Pneumothorax* may occur on either the side of a lung graft or on the side of a native lung. Pneumothoraces that arise from the lung graft are of greatest concern because of the possibility that airway dehiscence communicates with the pleural space. Fortunately, this is a rare occurrence. Nonetheless, flexible bronchoscopy is always indicated for diagnostic purposes in patients presenting with this problem. In most patients, placement of a chest tube with reexpansion of the lung limits the process acutely.

More commonly, pneumothorax is the result of rupture of a bullous lesion in an emphysematous native lung after SLT. Conservative management with intercostal tube drainage is indicated. Occasionally, pneumothoraces are noted after DLT when a significant size discrepancy exists between the donor lungs and recipient thorax. In these patients, the space resolves spontaneously in a short time and specific interventions are not required. *Pleural effusions* are common after lung transplantation, particularly when a significant size disparity exists between the donor lungs and the thorax. Continued chest tube drainage following the primary procedure is not indicated as a preventive measure for these effusions and may actually lead to secondary infection and empyema. Management of these effusions is best done conservatively, with diuretic therapy and dietary salt restriction. Invasive measures, such as thoracentesis and tube drainage, are indicated only for effusions complicated by a delayed pneumothorax, for enlarging effusions, or for large effusions that persist for more than 4 weeks after surgery.

Airway complications have been significantly less common in the recent experience with lung transplantation. Bronchial ischemia is the most common cause of postoperative airway complications. The most common methods of lung transplantation do not provide direct revascularization of the bronchial arterial circulation, and the donor bronchus must rely entirely on collateral perfusion from the pulmonary circulation in the initial postimplantation period. Airway ischemia at this time leads to mucosal ulceration followed by progressive mural necrosis. Localized bronchomalacia is frequently present adjacent to this region. A spectrum of abnormalities, ranging from anastomotic dehiscence to submucosal fibrosis, may occur as a result. Most commonly, partial anastomotic dehiscence occurs, followed by formation of granulation tissue and eventually some degree of anastomotic stenosis.

The reduced incidence of these complications has been attributed to methods of anastomosis that limit the length of the donor bronchus, minimizing the amount of airway for which collateral perfusion is required. Most anastomotic techniques emphasize trimming the donor bronchus to within two rings of the upper-lobe orifice and the preservation of peribronchial tissues containing the collateral circulation. Telescoping the bronchi and covering the anastomosis with vascularized tissue are also useful adjunctive measures. The use of omentum does not appear to be a critical factor in most cases, although in patients who require prolonged mechanical ventilation because of graft dysfunction or in whom anastomotic dehiscence develops, the presence of an omental wrap helps to minimize the morbidity caused by these complications. The effect of improved methods of lung preservation and of more specific immunosuppression on the decrease in airway complications is difficult to quantitate, but these factors are probably of some importance in the reduced incidence of this problem.

The overall incidence of airway complications in all lung transplant patients is 15 to 20 percent. In approximately half of these patients, the diagnosis is made from endoscopic surveillance alone, and healing occurs without further treatment or secondary complication. In the rest, the airway complication requires more specific management and may lead to secondary complications. Of these patients, 70 percent require anastomotic dilatation or stent placement and 20 percent develop a bronchopleural fistula that requires a chest tube and perhaps reoperation. Death due to extensive airway necrosis or secondary infectious complications occurs in 10 percent of patients who develop symptomatic airway complications.

Another complication following lung transplantation is *myocardial infarction,* which is usually due to pressure overload during the implantation procedure and can be prevented in most patients by prompt initiation of CPB. Postoperative

management of these patients is similar to the routine management of patients with myocardial ischemia; it consists of the judicious use of nitrate therapy, reductions in preload and afterload, and observation for dysrhythmias. *Atrial dysrhythmias* are also common, as with other types of cardiothoracic surgery, and are managed in a similar fashion. Transplant patients are also prone to significant *gastrointestinal complications,* whose manifestations may be obscured by the anti-inflammatory effects of immunosuppressive therapy. Hepatobiliary and pancreatic complications are especially common after intrathoracic transplantation, particularly when CPB has been required. Preventive measures include laparoscopic cholecystectomy for patients with symptomatic biliary disease before transplantation. Postoperatively, continued surveillance of pancreatic exocrine function, bilirubin, and liver function tests is indicated to allow prompt diagnosis and intervention for specific abnormalities. In view of the surgical stress and use of corticosteroids in these patients, all patients should receive H_2-blocking agents and antacid therapy postoperatively to prevent upper gastrointestinal hemorrhage.

Infectious Complications

Lung transplant patients have several unique attributes that account for a rate of infectious complications that is higher than the rate for other transplant recipients. Before implantation, the donor lung may contain significant pathogens, owing to the changes in lung defense mechanisms that follow intubation and brain death. After the transplant, the lung allograft continues to be exposed both to the external environment and sites in the upper respiratory tract, such as the sinuses, that may contain significant pulmonary pathogens. Finally, the lack of a cough reflex and a disturbed pattern of mucociliary clearance in the donor lung after the transplant predispose to pulmonary infection. An aggressive approach to the evaluation of all new pulmonary infiltrates, in either the lung graft or the native lung, is required in these patients. Flexible bronchoscopy with BAL or protected brushing is needed for proper diagnosis of pulmonary infections after lung transplantation. BAL specimens from both lungs should be routinely sent for Gram's stain, fungal smear, and acid-fast bacilli smear as well as for culture of these organisms. In addition, analysis of BAL for *P. carinii, Legionella* species, and viral assays is required.

Bacterial pneumonia is the most commonly acquired infection after lung transplantation. Pneumonia occurs most frequently within 2 months of transplantation and is usually due to gram-negative bacilli. Diagnosis made with bronchoscopy and treatment with antibiotics administered intravenously lead to prompt resolution in most cases. Depending on the organism, aerosolized antimicrobial therapy, in addition to intravenous therapy, may be helpful. Potential native sources of contamination of the respiratory tract should be evaluated, particularly in patients with cystic fibrosis or recurrent pneumonias. Chronic sinusitis is common in cystic fibrosis patients and acts as a source of contamination of the lower respiratory tract. Careful otolaryngologic evaluation and sinus drainage are indicated in selected patients. Gastroesophageal reflux is common in both cystic fibrosis patients and patients with COPD and can lead to recurrent aspiration pneumonias in dependent regions of the lungs. In most patients, conservative treatment with elevation of the head of the bed and the administration of promotility agents, in addition to the H_2-blocking agents taken by most transplant recipients, control the reflux. In patients who have undergone SLT, the native lung may occasionally be a site of graft contamination or, more commonly, may become the site of pneumonia or a lung abscess. Standard therapy is recommended for such cases, although a localized area of anatomic abnormality in the native lung (e.g., focal bronchiectasis) may require surgical excision if it proves to be the source of recurrent infection.

Viral infections can be a major source of morbidity or mortality for lung transplant patients. Previously, *herpes simplex virus* infection was an occasional cause of tracheobronchitis or pneumonitis following lung transplantation. The use of prophylactic acyclovir or ganciclovir has eliminated these infections. *Respiratory syncytial virus* (RSV), which can cause pneumonitis and bronchiolitis in immunosuppressed patients, has been more frequently identified in lung transplant patients during the time of peak community infection (from November to March). Treatment of RSV requires the use of aerosolized ribavirin and RSV hyperimmune globulin. Although successful treatment of the acute disease has been reported, a major issue remains regarding the potential for later development of obliterative bronchiolitis following RSV infection.

Cytomegalovirus, a member of the human herpesvirus family, is the second most frequent cause of infection in the lung transplant patient and the most important opportunistic infection that occurs in these patients. Following infection with CMV, the virus remains in a latent state in the body; evidence of the infection can be identified from a positive serologic assay. Approximately 80 percent of adults are seropositive for CMV. Immunosuppression can cause reactivation of the latent virus and shedding of CMV into both the urine and sputum. Viremia may also be detected in more advanced cases of reactivation disease. CMV infection of a lung transplant recipient can occur either from reactivation of latent virus or direct transmission to the patient. Direct transmission, which occurs by the transfusion of blood products obtained from seropositive donors into seronegative recipients, has been essentially eliminated by administration of blood products only from seronegative donors to seronegative recipients.

The incidence of CMV infection in the lung transplant recipient is related to the serologic status of both donor and recipient. Recipients who are seronegative for CMV and receive seronegative lungs should never develop CMV infection, provided they are protected from transmission of the virus by transfusion. CMV should never be found in their sputum. Alternatively, recipients who are seropositive for CMV and receive lungs from seropositive donors rarely develop CMV infection because of their preoperative immunity. However, these patients shed CMV in their sputum when the latent virus is reactivated by immunosuppression. When a seropositive

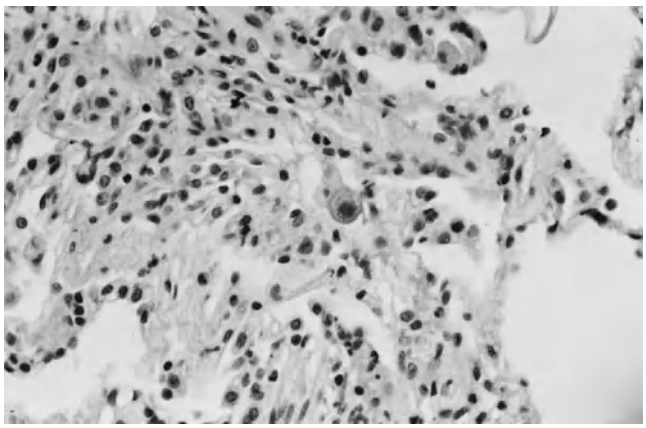

Figure 101-6 Cytomegalovirus (CMV) pneumonitis. A characteristic cytotrophic change in the pulmonary parenchyma is seen with invasive CMV infection.

recipient receives a lung from a seronegative donor, reactivation of the recipient's CMV can cause CMV pneumonitis in the lung graft. This is an invasive infection, with evidence of viral-induced cytotrophic changes in the pulmonary parenchyma in addition to the presence of CMV in the sputum (Fig. 101-6). In these cases, CMV pneumonitis is generally well treated with a course of ganciclovir (5 mg/kg intravenously twice a day for 4 weeks). Conversely, when seronegative recipients receive lungs from a seropositive donor, reactivation of the CMV in the donor lung can cause a primary infection of the recipient. Primary CMV infection of an immunosuppressed host, such as the recipient of a lung transplant, is a potentially fatal systemic illness associated with viremia, pneumonitis, hepatitis, encephalitis, retinitis, and enterocolitis. Such patients require both ganciclovir (5 mg/kg intravenously twice a day) and CMV hyperimmune globulin (10 g intravenously every month) for prolonged courses of therapy until the disease is eradicated.

Ganciclovir administered prophylactically three times weekly was found to be as effective as daily administration for up to 3 months after lung transplantation in the prevention of CMV infection. Ganciclovir is also effective therapy for CMV in patients with pneumonitis or primary infection, but the occurrence of CMV infection in these patients can lead to significant morbidity. CMV infection seems to elicit acute graft rejection in many instances, requiring a complicated treatment plan to balance the need for augmented immunosuppression against adequate treatment of the infection. Primary CMV infection was associated wth 54 percent mortality, which in turn was associated with a high rate of pulmonary superinfections during the first year after transplantation. In addition, CMV disease in some series appears to be a risk factor for the subsequent development of BOS, the most common cause of late mortality following lung transplantation. Many centers strive to match donor and recipient CMV status to minimize the potential for these problems. When precise donor–recipient matching is performed, the use of ganciclovir is reserved for cases of invasive CMV disease—i.e., CMV pneumonitis or primary infection with viremia. Other centers, however, have demonstrated the efficacy of a prophylactic regimen of ganciclovir (5 mg/kg intravenously twice a day, tapered over 6 weeks) in minimizing the incidence of CMV disease, even when donor–recipient CMV mismatching occurs. In these preemptive regimens, ganciclovir is used for all patients who are at risk for CMV disease during the induction of immunosuppression and whenever immunosuppression is augmented to treat acute rejection. This approach has led to an improvement in survival for patients with disparate donor–recipient CMV status. Relapse rates remain high, however, and the best approach to the management of the lung transplant patient with a mismatched donor–recipient CMV status remains to be determined.

Neoplastic Complications

Immunosuppression increases the risk of development of neoplasms after lung transplantation. The risk applies to a specific group of solid tumors, including squamous cell cancers of the lip and skin, Kaposi's sarcoma, soft tissue sarcomas, carcinomas of the vulva and perineum, and hepatobiliary tumors. Transplant recipients are not at increased risk for developing the more common cancers encountered in the general population, such as carcinoma of the lung, breast, colon, or prostate, and some of the newer agents, such as mycophenolate mofetil and sirolimus may have antitumor properties, although they have yet to be studied long-term to determine whether they will reduce malignancy-related mortality.

The most common malignancy seen after lung transplantation is a type of B-cell lymphoid proliferation known as *posttransplant lymphoproliferative disorder* (PTLD). PTLD represents a morphologically diverse group of polyclonal lymphoid proliferations. The pathogenesis of PTLD appears to be related to EBV infection of B lymphocytes that are stimulated to proliferate by the recipient's immunosuppression. Clinically, a distinction can be made between patients presenting with PTLD within 1 year after transplantation and those presenting with PTLD at later times. The early patients tend to have localized disease that responds to a temporary reduction in immunosuppression; their long-term prognosis is excellent. Patients who present after 1 year usually have disseminated disease that does not respond to reduced immunosuppression and requires cytotoxic chemotherapy for treatment. The mortality from lymphoma in these patients is 70 percent. Epstein-Barr virus seronegative patients with high levels of immunosuppression have such a high risk for lymphoproliferative disorder as to preclude transplantation in some cases. Of interest is that the use of ganciclovir for prophylaxis against CMV disease in lung transplant patients may also help to control the incidence of PTLD, since ganciclovir also has significant activity against EBV. Future trials to assess the impact of ganciclovir therapy on the incidence of PTLD are planned. Rituximab and chemotherapy have been shown to be effective in EBV-positive patients with PTLD who fail or do not tolerate reduction in immunosuppression, however, although rituximab is well tolerated, chemotherapy is associated wth marked toxicity.

RESULTS

Survival

Mortality following lung transplantation has decreased significantly over the past decade. The cause of this reduction is probably multifactorial—i.e., the result of technical improvements in the procedure, of improved recipient selection and preoperative management, and increasing experience in perioperative management of these patients. In most recent series, surgical mortality following lung transplantation has been between 10 and 15 percent. The surgical mortality of DLT ranges from 15 to 20 percent as compared to that of SLT, which is usually 10 percent or less. This difference is attributable, in large part, to the increased likelihood of postoperative infectious complications in patients with septic lung disease who require DLT. Surgical mortality after HLT is usually slightly higher than for patients undergoing DLT, probably owing to the more advanced disease state of patients who require HLT. Most centers have not noted a marked difference in surgical mortality for patients undergoing SLT for different diseases, although preoperative pulmonary hypertension in these patients usually increases the risk of perioperative morbidity.

Infection is the major cause of early mortality in lung transplant recipients, accounting for 30 to 45 percent of deaths. The likelihood of pulmonary infection is greatest in the first 100 days after transplantation, before recipient defense mechanisms (e.g., cough) are restored. Risk factors for infection during this period include a positive sputum culture from the donor, a lower Pa_{O_2} in the donor lung (under 350 mmHg), a prolonged ischemic time (greater than 6 h), recipient age greater than 40 years, and CMV disease as the result of donor–recipient mismatching without ganciclovir prophylaxis. Postoperative graft failure with diffuse alveolar damage may also contribute to early mortality in as many as 15 percent of patients. Improved surgical techniques, preservation solutions, and donor management strategies have reduced the incidence of primary graft dysfunction. Cardiovascular decompensation is the third leading cause of early death. In most cases, this process occurs in the clinical setting of adult respiratory distress syndrome and persistent pulmonary hypertension with secondary cardiac dysfunction. Coronary artery disease or myocardial infarction is uncommon in these patients.

Long-term survival data indicate a cumulative survival rate of 70 to 80 percent at 1 year. Survival curves can vary significantly beyond 1 year, depending on the disease for which transplantation was performed. Patients with emphysema and those with pulmonary vascular disease appear to have a survival advantage over patients with restrictive lung disease or septic lung disease, in whom infectious complications or recurrence of native disease in the lung graft is more common. By 3 years, survival ranges from 75 percent in the former group to 55 percent in the latter group. At this interval, BOS begins to have a significant impact on survival as well, leading to an overall survival rate of only 50 percent at 5 years. Causes of death in this period include infection, which has another peak of increased incidence throughout the second postoperative year, and BOS, which can be identified in half of the patients who survive to 3 years. Malignancy, usually PTLD, is the third most common cause of late mortality following lung transplantation.

Functional Results

Most patients surviving lung transplantation experience a highly significant improvement in their functional capability over their preoperative state. Typically, patients can resume an exercise program without oxygen supplementation by 6 weeks after transplantation. However, in some patients who require muscular paralysis for management of postoperative graft failure, a demyelinating process may delay full recovery for 2 to 3 months. Survivors of primary graft dysfunction are frequently left with significant functional deficits.

Improvements occur regardless of the native disease that led to transplantation. Unless BOS occurs, functional capacity based on the standards of reproducible exercise testing remains stable for at least 3 years. Controversy exists over the potential benefit of SLT as compared to DLT for younger patients with emphysema. Although the results of spirometry are obviously better in DLT recipients, exercise tolerance is similar initially in the two groups. Whether a significant later advantage exists for DLT recipients that would offset the increased perioperative risk of the procedure remains to be seen. Similarly, functional results following SLT or DLT for pulmonary vascular disease demonstrate little objective difference between the two approaches. However, DLT may provide a slight advantage in patients in whom preoperative pulmonary artery pressures approach systemic levels, because such an approach provides the maximum reduction of pulmonary vascular resistance. In addition, because the allograft receives up to 95 percent of the blood flow in these patients after SLT, the development of BOS, even at grade 1, has profound functional implications. The development of BOS in patients who have undergone DLT for pulmonary vascular disease causes less immediate hemodynamic compromise because the partition of blood flow between the two lungs is similar.

Retransplantation

Pulmonary retransplantation has been undertaken with increasing frequency in recent years. Retransplantation is used either as a method to correct an acute complication, such as graft failure or diffuse airway necrosis, or as a treatment for a chronic process in the graft, such as BOS or airway stenosis. At the present time, BOS appears to be the most common indication. A variety of approaches have been used, including redo ipsilateral SLT, contralateral SLT, and DLT following either SLT or DLT. These are technically challenging procedures, with a surgical mortality of nearly 50 percent. Factors contributing to a more favorable outcome include an ambulatory status before retransplantation, the use of ABO-identical grafts, and prior institutional experience with

retransplantation; notably, retransplantation with a CMV-seronegative donor has also been associated with a favorable outcome. The long-term results of retransplantation are much worse than those of initial lung transplantation. One-year survival is about 45 percent, and 2-year survival is about 35 percent. BOS occurs with a frequency similar to that seen with primary lung transplantation and can be identified in one-third of patients 2 years after retransplantation.

SUMMARY

Significant progress has been made in the development of techniques of lung transplantation for all types of end-stage pulmonary diseases. Isolated lung transplantation has been applied with increasing success to the entire group of patients, including those with pulmonary vascular disease. A shortage of donor organs, however, remains the most significant obstacle to wider use of this method of treatment. Techniques of donor lung preservation and implantation allow ischemic intervals of 6 to 8 h for reasonable postoperative function. Surgical mortality is 10 to 15 percent, slightly lower for SLT and slightly higher for DLT and HLT. Functional results in survivors of the operation are excellent. Infection remains a significant source of morbidity and mortality in both the early and late postoperative periods. However, the most significant impediment to long-term survival is the development of chronic rejection in the lung allograft, manifested as BOS, in half of the patients by 5 years after transplantation. Further measures to prevent or treat this malady are critical to improving long-term survival rates following lung transplantation.

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PART

XV

Neoplasms of the Lungs

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CHAPTER

Genetic and Molecular Changes of Human Lung Cancer

Jeffrey A. Kern • Geoffrey McLennan

Lung cancer is the phenotypic consequence of an accumulation of genetic changes in airway epithelial cells that result in unrestrained cellular proliferation. The genetic and molecular changes that typify lung cancer are complex and not yet fully understood. There continue to be advances in knowledge and, with this, a better understanding of how the changes might contribute to the cancer phenotype, with possible diagnostic and therapeutic measures arising from this understanding. Initial studies in the 1960s were performed using cytogenetics, and they allowed for developments in molecular biology to unravel some of the mystery of oncogenes. Although oncogenes were very much at the leading edge in the 1980s, in the early 1990s tumor suppressor genes (recessive oncogenes or antioncogenes) added immensely to our understanding of tumorigenesis. Currently much interest is focused on the influence of these genetic factors on the cell cycle and on programmed cell death, or apoptosis. Underlying all this is the influence of environmental factors, especially cigarette smoke exposure, on any genetic susceptibility to lung cancer.

What is to be gained from understanding molecular and genetic changes in the development of lung cancer? We firmly believe that analysis of these factors will have a profound effect on diagnosis, histologic typing, the development of novel treatment strategies and therapeutic agents, prediction of response to therapy, and assessment of risk of relapse and long-term survival. Because of this, much effort has been expended translating newly discovered molecular and genetic changes into clinically useful information. Indeed, recent studies have begun to achieve this goal, with the realization that some genetic changes can identify patient subsets with differing prognoses and therapeutic responses, and with the

This chapter has been slightly modified from the version that appeared in the third edition of *Fishman's Pulmonary Diseases and Disorders.*

design of novel therapeutic agents targeting the defect. In this chapter we review recent knowledge in molecular genetics as it relates to small cell lung cancer (SCLC) and non–small-cell lung cancer (NSCLC).

GENETIC SUSCEPTIBILITY TO LUNG CANCER

Many epidemiologic studies have demonstrated that some cancers are clustered in families, suggesting that susceptibility to the cancer may be inherited. Lung cancer, however, is most commonly thought of as a cancer that is determined solely by the environment. Certainly, the risks of lung cancer associated with cigarette smoking and in certain occupations, such as uranium mining and shipbuilding, are well established. On the basis of clinical findings, however, differing susceptibilities for tumor formation due to these environmental agents have often been postulated. Demonstrated epidemiologic differences between NSCLC in never-smokers and smokers, as well as differing survival outcomes, for instance, suggest that the pathogenesis and behavior of NSCLC progression may be different for the two groups.

Epidemiologic evidence for an increased familial risk of lung cancer was first noted in the early 1960s. In the largest study to date, a 2.4-fold increased risk of lung cancer was identified in relatives of lung cancer patients. This familial risk is supported by data from the Utah Population Database. More than one-third of all cancer cases in Utah were examined for a relationship with their genealogic record. These data also identified a familial clustering of lung cancer. Other studies have identified a gender disparity, with women at greater risk of developing lung cancer through familial factors than men. Epidemiologically, this is most likely to occur in women who do not have a history of heavy smoking, who have a younger age at onset of the disease, and who have squamous cell carcinoma.

More recent studies of familial risks or genetic susceptibility to lung cancer have demonstrated a chromosomal linkage between lung cancer and lung function, as well as overlap in candidate genes for these outcomes and a fivefold increase in breast cancer risk for first-degree relatives of women with a positive family history of early-onset lung cancer. Specific genetic polymorphisms have also been associated with lung cancer risk.

Modeling of the familial clustering data suggests a mendelian pattern of codominant inheritance, the result of a rare autosomal gene. This model suggests that carriers of this gene have a young age at lung cancer onset, with a risk 2245-fold greater in nonsmoking individuals homozygous for the affected gene. In this model, the putative lung cancer gene accounts for 69 and 47 percent of the cumulative incidence of lung cancer in patients up to 50 and 60 years old, respectively, and is involved in 22 percent of all lung cancers in persons up to age 70. Significantly, random environmental factors do not explain this familial clustering. Further segregation analysis of smoking-associated malignancies has demonstrated that 62 percent of the population appear to be genetically susceptible to smoking-associated lung cancers. Though mathematically compelling, the physical existence of such a lung cancer susceptibility gene has not yet been demonstrated.

Acquired Genetic Changes

Not all lung cancers have a heritable basis. Thus, other explanations must exist for cancers that arise as sporadic or nonfamilial cases. These tumors are not due to germ line mutations or a cancer susceptibility gene that would result in a heritable cancer, but must be due to acquired somatic genetic alterations. The first persuasive evidence that cancer could be attributed to discrete, noninherited, genetic elements was the observation by Rous in 1911 that a cell-free filtrate from a chicken sarcoma could induce sarcomas in other chickens. The cancer-causing element was ultimately found to be a virus, the Rous sarcoma virus, and its oncogenic potential was demonstrated to result from a specific gene called v-*src,* which was identified as a mutated cellular gene. Since the discovery of this oncogene, more than 50 different cellular oncogenes have been discovered and found to have critical roles in human cancer development.

There are two classes of oncogenes, *dominant oncogenes* and *recessive oncogenes,* or *tumor suppressor genes.* Oncogenes are derived from normal cellular genes called proto-oncogenes. The encoded protein product of a proto-oncogene often plays an important role in cell signaling, or cell growth regulation. These genes can become activated by mutation, chromosomal translocation, amplification (gene duplication manyfold in the genome), or transcriptional dysregulation, resulting in the production of an abnormal protein or an overabundance of the normal protein. These activated proto-oncogenes are now called oncogenes, and their protein products are oncoproteins. Proto-oncogenes and oncogenes are named with a three-letter designation (e.g., *myc*). The same three-letter code, nonitalicized and starting with a capital letter, denotes the protein product (e.g., Myc). The prefix v, as in v-*src,* refers to an oncogene of viral origin. The corresponding cellular proto-oncogene is given the prefix c (c-*src*). In their activated form, the oncogenes provide a growth advantage for the expressing cell. Laboratory, clinical, and epidemiologic observations suggest that more than one genetic or biochemical event is needed to transform normal cells into malignant cells. Thus, the further accumulation of critical events in a cell population with a growth advantage results in tumorigenesis. Once a cell becomes transformed into a malignant cell (i.e., no growth restraint), other events are required for malignant cells to proliferate successfully, especially the provision of new blood vessels (angiogenesis) to create a favorable environment for growth. The interactions between the genetic changes in the cell nucleus and the changes necessary in the cell environment such as blood supply, nutrition, and extracellular matrix are only just beginning to be studied. However, these interactions are likely to be critical to conferring the various degrees of malignancy.

In practical terms, proto-oncogenes fall into five categories: growth factors, receptors for growth factors or hormones,

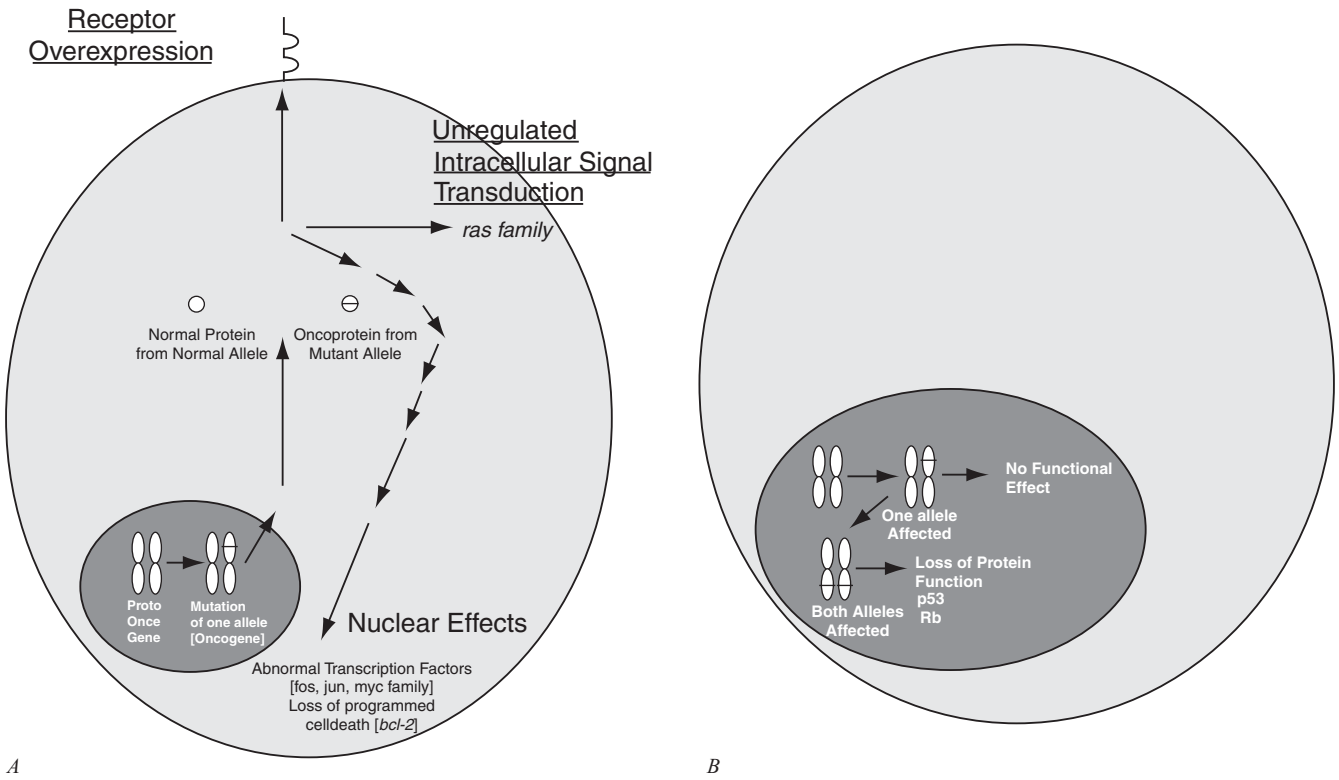

Figure 102-1 The role of dominant oncogenes and recessive oncogenes in human lung cancer. *A*. Dominant oncogenes require activation of only one allele. The resultant oncoprotein functions abnormally or is overproduced. Shown here are oncogenes and oncoproteins known to be active in lung cancer. *B*. Recessive oncogenes require two mutations, resulting in the actual loss or loss of function of the encoded protein. Shown here are recessive oncogenes known to be associated with lung cancer.

intracellular signal transducers, nuclear transcription factors, and cell cycle control proteins. Thus, it is understandable that an oncogene, through the action of its corresponding oncoprotein, can have a profound effect on cell growth.

Dominant oncogenes are relatively easily identified, since they have a genetically dominant role in converting a nontransformed cell to a transformed (malignant) cell. In this instance, only one of the two alleles carrying a specific gene needs to be affected. The concept of dominant oncogenes and the resulting oncoproteins is illustrated in Fig. 102-1 *A*. This figure also highlights oncogenes that have been noted so far in lung cancer.

Evidence for a second class of genes active in tumor formation—recessive oncogenes or tumor suppressor genes—has been much more difficult to establish. The earliest evidence for the existence of tumor suppressor genes in cancer genesis was from somatic cell genetic studies in which normal and tumor cells were fused. Surprisingly, the resultant hybrid cells were often not tumorigenic, an unexpected finding if a dominant oncogene was involved. If transformation was due to a dominant oncogene supplied by one member of the hybrid, the presence of normal genetic information supplied by the other member should have no effect on transformation. This led to the notion that the tumor cell had lost genetic information from both the maternal and paternal alleles of a critical genetic locus, which was replaced by the normal cell in the hybrid.

A second line of evidence for the existence of tumor suppressor genes was provided by studies of the genetics and natural history of pediatric tumors—in particular, retinoblastoma. It was proposed by Knudson that the development of retinoblastoma could be explained by the acquisition of two mutations (i.e., one mutation in both alleles of the same genetic locus). For each gene locus, the human genome has two gene copies, one maternal and one paternal. One mutation was proposed to be present in a parent's germ line and therefore abnormal in all somatic cells of the affected subject at birth. With the acquisition of a second mutation in the remaining normal allele, the protein product encoded by the affected gene became functionally inactive, and the retinoblast cell underwent malignant transformation. After elegant cytogenetic and molecular genetic analysis, it was determined that one allele of the retinoblastoma gene (*Rb*) was inactivated in the inherited form of retinoblastoma as hypothesized. On inactivation of the other retinoblastoma allele, a retinoblastoma developed. In the nonfamilial form of retinoblastoma, somatic mutations in both alleles of the retinoblastoma gene are acquired after birth. The acquisition of two events in the correct alleles is, of course, much less likely than the single event required for the heritable form of the disease, making sporadic retinoblastoma much rarer. Thus, for tumors to develop as a result of tumor suppressor oncogene abnormalities, both maternal and paternal alleles must be mutated/inactivated before the malignant phenotype is evident. Therefore, the

name recessive oncogenes or tumor suppressor genes was developed. The concept of recessive oncogenes is shown in Fig. 102-1 *B*, which also highlights recessive oncogenes found in lung cancer.

Many genetic regions containing suspected tumor suppressor genes have been discovered by examination of DNA obtained from malignant and normal cells from the same patient for loss of alleles, i.e., loss of heterozygosity (LOH). The two alleles of a gene locus, one maternal and one paternal, are often polymorphic and thus distinguishable through genetic techniques. However, the heterozygous pattern often found in normal tissue, due to alleles inherited from two parents, is not seen if one allele is lost or mutated. If a mutation is present in the remaining allele, the loss of the other allele unmasks the mutation, resulting in the outgrowth of cells that have lost the function of the affected gene, as in the example of retinoblastoma. In lung cancer, many such allelic losses in specific chromosomal regions have been identified. However, outside of the retinoblastoma and the *p53* gene, the presumed target of the losses (i.e., specific putative tumor suppressor genes) has not been identified.

MOLECULAR CHANGES

Cytogenetic Changes

Chromosomal changes are informative in tumors, as they point to a discrete area in the genome to examine for mutated or lost growth regulatory genetic information. Initially, chromosomal changes were discovered by examination of chromosomes in a dividing cell with microscopy. This tedious task, known as cytogenetics, began our genetic understanding of many malignant changes, beginning with the Philadelphia chromosome in 1960. In lung cancer, karyotypic or cytogenetic changes in SCLC have been repeatedly demonstrated, with consistent deletions of the short arm (p) of chromosome 3 (3p), especially 3p21-25, suggesting a tumor suppressor gene at that site. Also, losses cytogenetically of the long arm (q) of chromosomes 5, (5q21), 13 (13q14), and 17 (17q13) have been described cytogenetically. The last two sites contain the *Rb* and *p53* suppressor loci. In addition, in NSCLC numerous chromosomal abnormalities are seen on cytogenetic study, most frequently (in descending order) in 3p14, 3q21, 19q13, 11p15, 1q11, 7q11, 1q21, 3p23, and 3p21. A recent meta-analysis of chromosomal imbalances reports identification of affected genes that may contribute to SCLC and NSCLC development and progression. Other findings point out the many chromosomal defects in NSCLC that are likely to contribute to the pathogenesis of the disease, and new dominant and recessive oncogenes are likely to be discovered.

Dominant Oncogenes

Myc Family

The *myc* family of proto-oncogenes encode nuclear proteins that have DNA-binding properties and are thought to be active in the regulation of transcription. There are three members of this family, *c-myc* (chromosome 8q24), N-*myc* (chromosome 2p23-24), and L-*myc* (chromosome 1p32). Activation of this family of proto-oncogenes in lung cancer occurs by gene amplification and overproduction of the normal protein product. Amplification of all members of this family has been found in SCLC. In any single tumor, however, only one member of the family has been reported amplified at a time. Amplification of two or all three members simultaneously has not been found. The *myc* genes encode three related cell cycle–specific nuclear phosphoproteins. It is likely that the *myc* genes, which are highly conserved over large phylogenic distances, are important in normal cell growth and differentiation, embryo genesis, and apoptosis. Clinically, c-*myc* gene amplification has been related to a more malignant course in SCLC. N-*myc* gene overexpression in SCLC has been correlated with a poor response to chemotherapy and a more aggressive clinical course. L-*myc* is also overexpressed in some patients with SCLC, but without apparent clinically significant effects. However, the L-*myc Eco*R1 polymorphism has been shown to be a marker of tumor prognosis in lung cancer. Understanding this abnormality has led to the possibility of targeting c-*myc* as a new form of therapy. Exposure of an SCLC cell line expressing L-*myc* to L-*myc* antisense DNA inhibited cell growth in a dose-dependent manner, perhaps suggesting a therapeutic opportunity as well as providing insight into function. *Myc* gene amplification also occurs in NSCLC. In a recent study, c-*myc* amplification was found in 48 percent of NSCLC, but amplification of L-*myc* and N-*myc* was uncommon. Unfortunately, the presence of c-*myc* amplification in NSCLC does not appear to have any clinical significance. It is emerging that there is clearly complex regulation of *myc* expression, and *myc* appears to regulate the expression of other proto-oncogenes. For example, c-*kit* expression may be regulated by c-*myc* when cells expressing c-*myc* do not express c-*kit.*

Ras

There are three *ras* proto-oncogenes, H-*ras,* K-*ras,* and N-*ras.* These genes code for closely related 21-kD guanosine triphosphate (GTP)–binding proteins, called p21ras, which are functionally related and have structural similarities to G proteins. These proteins are localized to the inner side of the cell membrane and participate in signal transduction. Specific K-*ras* point mutations are relatively common in NSCLC, especially in adenocarcinomas. These mutations result in a single amino acid change in the protein, causing a marked reduction in its intrinsic GTPase activity, and the protein remains in an active GTP-bound state. Thus the protein is fixed in the "on" position and cannot turn off. Once acquired, these mutations appear stable, being present both in the primary tumor and in metastases, as is the case with most of the genetic mutations, although the *ras* abnormalities have been best studied in this regard. H-*ras* and N-*ras* mutations appear to be rare in human lung cancers. As the sensitivity of assays increases, the incidence of K-*ras* mutations continues

to increase, occurring in up to 56 percent of lung cancers. It is interesting that K-*ras* mutations have been noted in bronchial biopsies from smokers with no evidence of lung cancer, and they can be found in sputum samples up to 1 year before the clinical diagnosis of lung cancer, raising the question of their use as premalignant markers. Indeed, examination of the distribution of K-*ras* mutations in established tumors suggests that these changes occur at an early stage in the development of the malignancy.

The carcinogen causing the K-*ras* mutation is not known, but K-*ras* mutations are closely associated with cigarette smoke exposure. Whether this is a causative factor or only an association is unclear. Clinically, the presence of a K-*ras* mutation in an adenocarcinoma is an independent portent of poor survival, which two recent meta-analyses have confirmed. However, one study indicates that for patients with completely resected NSCLC, K-*ras* mutations in combination with p53 mutations may only be a weak prognostic marker. Nonetheless, the presence of this discrete molecular change has led to the design of a new treatment strategy. Tumor growth in cell lines containing a K-*ras* mutation is markedly reduced by a K-*ras* antisense RNA construct introduced by a retroviral vector. Thus, a better understanding of this molecular change in lung cancer has led to the recognition of an important negative prognostic factor, possible premalignant marker, and novel therapeutic approach.

Ras Protein

The protein product of the *ras* gene (p21ras) has been demonstrated also to be an independent prognostic factor in defining survival in NSCLC. Subjects whose tumors had a high level of p21ras expression had shorter survival than those whose tumors were p21ras negative. How this finding relates, if at all, to the known *ras* gene mutations in lung cancer and whether it provides information independent from them are unclear. Of great interest is the recent observation that inhibition of p21ras activity may be a viable treatment strategy by interfering with a posttranslational lipid modification of the molecule necessary for its function. With use of the farnesyltransferase inhibitor (FTI276), growth of a human lung cancer characterized by a K-*ras* mutation was inhibited in an animal host in a dose-dependent manner.

Tumor Suppressor Genes

Retinoblastoma Gene

The retinoblastoma gene, located on 13q, was the first tumor suppressor gene to be identified, owing to its importance in the genesis of hereditary retinoblastoma. It encodes a 105,000-Da nuclear phosphoprotein (pRB) that is a regulator of cell division. pRB's phosphorylation status is key to a cell's progression through the cell cycle. pRB is underphosphorylated in G1, is heavily phosphorylated in late G1 just before S phase, but reverts to an unphosphorylated state just before G0. pRB in its unphosphorylated state binds to the E2F family of transcription factors, not allowing the E2F-induced transcription of genes important to cell cycle progression. This results in a block of S phase entry, ultimately causing cell division to stop. pRB isolated from tumors is often mutated, resulting in a functionally inactive protein unable to bind E2F or to be regulated by phosphorylation. Thus, cellular proliferation becomes unregulated. *Rb* gene inactivation may promote cell division by other measures as well, such as shortening telomere length. In addition, differential regulation of the pRB protein may occur in SCLC versus NSCLC; pRB may be inhibited by p16 (a cyclin-dependent kinase inhibitor) in SCLC, but not in NSCLC, indicating the complex relationships that exist in genetic abnormalities and are increasingly being demonstrated. However, the relationships between various common gene abnormalities have been assessed in lung cancer, and generally there is no clear or regular association of one gene defect with another. Although resectable NSCLS may show distinct patterns of TSG inactivation, no clear correlate has been established with respect to pRB, among other abnormalities.

Defects in the *Rb* gene or in pRB are almost universal in SCLC but are seen in only 30 percent of NSCLC. No relationship to clinical survival has been found. The central importance of pRB in growth regulation has been shown by reconstitution of the *Rb* gene into SCLC lines. This suppresses their growth, without the requirement for correction of other genetic abnormalities. This finding perhaps points to another potential therapeutic strategy.

p53 Gene

Initially, *p53* was thought to be a dominant oncogene, as the p53 protein was detected at very high levels in cancers. However, it is now realized that wild-type p53 is a regulator of cell growth, and mutations in the *p53* gene produce either a dysfunctional or no p53 protein. The mutant protein has a much longer half-life than the wild type, resulting in the high levels that are seen in transformed cells. The *p53* gene is located on chromosome 17p. *p53* Gene abnormalities are common in lung cancer, usually as a point mutation, which has been detected in exhaled breath condensate. The encoded protein (p53) is probably a nuclear transcription factor, and it is a tumor suppressor factor by mechanisms that are not yet fully elucidated. p53 Regulates cell growth at the G1-S phase interface of the cell cycle and plays a role in inducing apoptosis, or programmed cell death, in cells with damaged DNA. Mutations in *p53* appear to be associated with exposures to environmental substances such as cigarette smoke but are not correlated to resectable NSCLCs. Abnormalities in *p53* expression do not appear to be associated with prognosis in mixed lung tumors, but they may confer a worse prognosis in patients with stage I adenocarcinomas. A meta-analysis of published studies shows that p53 alteration is more likely as overexpression (protein) than mutation (DNA), and less likely in adenocarcinoma than in squamous cell carcinoma; and confirms that it is a significant marker of poor prognosis. It has been demonstrated in an animal model that wild-type *p53* can be transduced into lung cancer tumor spheroids with

a retroviral vector. If the tumor cells were homozygous for a mutant *p53*, there was significant growth inhibition after transduction and expression of wild-type p53, with apoptosis induced in the cellular spheroids. This raises the possibility of a novel therapeutic approach to lung cancers that have a *p53* gene mutation. A recent study has shown that intratumoral injections of Ad5CMV-p53 have been linked to clinical benefits for advanced NSCLC patients, including specific p53 transgene expressions.

9p

LOH on the short arm of chromosome 9 (9p) occurs in more than 50 percent of NSCLC, and in SCLC there are abnormalities in the same region (9p21-22) in approximately 58 percent of cases. Of interest is that 9p contains the interferon and the methylthioadenosine phosphorylase genes. These genes are deleted or rearranged in 36 to 43 percent of all lung tumor types and, while not themselves tumor suppressor genes, are probably adjacent to a putative tumor suppressor gene. This gene has recently been identified as the multiple tumor suppressor 1/cyclin-dependent kinase-4 inhibitor (*MTS 1/CDK4I*) gene and is inactivated in NSCLC. When the *MTS1* gene encoding $p16^{INK4}$ is introduced into human lung cancer cell lines not expressing the gene, tumor proliferation is inhibited in vivo and in vitro. These tumor cells are growth arrested in G1 just before S phase. This also raises the notion that such a gene may be a suitable gene therapy candidate in selected lung tumors. Similarities between mutations in HER2 and EFR genes with respect to tumor type, mutation type, and patient subpopulations (smokers versus never smokers) suggest similar etiologic factors. The mutual exclusivity shown between EGFR, HER2, and K-*ras* mutations suggests different pathways to lung cancer in smokers and never smokers.

5q

There have been further observations on the LOH involving 5q, which has been observed in 29 percent of NSCLC. 5q LOH correlates with tumor progression and poor survival. In SCLC, 5q LOH is even more frequent, being found in more than 80 percent of cases. This locus is in the region of the adenomatous polyposis coli (*APC*) gene associated with colorectal cancers, suggesting that a lung cancer tumor suppressor gene is present at this site and is associated with these lung carcinomas.

Other Proto-Oncogenes and Oncoproteins

Several other oncogenes in lung cancer appear to exert their effects through the overproduction of the normally encoded protein, not through a mutant gene or the production of an abnormal protein. The overproduction suggests a regulatory defect in transcription of the gene or gene amplification. The genes and protein products commonly affected in this manner are c-erbB-1 and c-erbB-2, both receptor tyrosine kinases; c-src, a nonreceptor tyrosine kinase; c-kit, c-met, and c-fms, also receptor tyrosine kinases; c-fos and c-jun, nuclear transcription factors; p40TAK, a protein kinase; and RAF1, a serine kinase. At least two of these oncoproteins—namely, c-kit in SCLC and c-erbB-2 in NSCLC—are increased without detectable gene amplification.

c-erbB-1

This membrane-bound proto-oncogene encodes a 170,000-Da tyrosine kinase growth receptor that is the epidermal growth factor receptor (EGFR). The proto-oncogene, through its protein product, functions in the normal lung to stimulate epithelial cell proliferation and promote airway maturation during development. Overexpression of the proto-oncogene has been found in NSCLC, especially the squamous cell subtype, in 65 to 90 percent of reported cases. The mechanism for this is complex, as overexpression of c-erbB-1 alone does not result in transformation of cultured NIH3T3 cells. However, transformation of these cells does occur in the presence of the c-erbB-1 ligand (epidermal growth factor, transforming growth factor-α). Analysis of c-erbB-1's ability to transform airway epithelial cells has not been performed, so it is not clear whether c-erbB-1 overexpression is causative or simply associated with human lung cancer. The use of c-erbB-1 overexpression as a clinical prognostic marker is controversial, with some studies showing an association with poor survival, while others do not.

c-erbB-2

This proto-oncogene is in the c-erbB-1 family of membrane-bound tyrosine kinase receptors; thus it is related to c-erbB-1 structurally and in amino acid sequence. The encoded protein, called p185c-erbB-2 or HER2, also is expressed in normal lung respiratory airway epithelial cells and may play a role in normal lung epithelium growth and differentiation. HER2 is coproduced with EGFR in many lung adenocarcinomas and almost certainly contributes to sustained cell growth. This oncoprotein also co-localizes with integrin alpha 6 beta 4 at cell-cell junctions in a lung cancer cell line, suggesting one mechanism of action—namely, control of the tyrosine phosphorylation at these sites. Overexpression of HER2 has been demonstrated in 34 percent of adenocarcinomas, and its presence is associated independently with a poor prognosis in this cell type. This association of HER2 with prognosis has been independently confirmed, together with the finding that EGFR expression does not show any survival effect. Of further interest is the demonstration of measurable serum levels of HER2 in 27 percent of adenocarcinomas, with an increased level in subjects with more advanced disease, suggesting a possible role as a systemic tumor marker. Both of these c-erbB proteins have extracellular domains, making them attractive targets for specific antibodies, either for diagnosis or therapy. However, therapeutic agents directed against this target may also interfere with normal epithelial turnover. Overexpression of c-erbB-2 in normal airway epithelial cells in vitro does not result in their transformation, suggesting that overexpression of c-erbB-2 alone does not result in tumor formation. The prognostic value of p53 and c-erbB-2 immunostaining and preoperative serum levels of CEA and CA125 has also been evaluated in NSCLC patients with resectable tumors,

indicating poor prognosis and likelihood of relapse. With the identification that the receptor complex actually consists of a heterodimer consisting of HER2 and another member of the erbB family, HER3, transformation may require both to be present to form the correct heterodimeric receptor for the specific activating ligand, Heregulin.

fos

The c-*fos* gene encodes a transcription factor active in cell proliferation and differentiation. Increased expression of c-*fos* is seen in NSCLC, especially the squamous cell subtype. In this study, c-Fos proteins were found in 41 percent of squamous cell lung tumors. c-Fos immunoreactivity has also been demonstrated in mucosal biopsies of the airways from asthmatic subjects, suggesting a role in normal inflammation. Its role in lung cancer remains indeterminate.

jun

c-*jun* Encodes an oncoprotein that functions as a transcriptional regulator. This product (c-Jun) associates with the c-*fos* product (c-Fos) to form a nucleoprotein transcription complex that interacts with AP-1 control elements. c-Jun is another oncogene product that is overexpressed in squamous cell lung cancer. In this study, expression of c-*jun,* c-erbB-1, and c-*fos* were all associated with a poor prognosis. C-*myc* and c-erbB-2 overexpression did not have any survival effect. This study is one of the few studies that has examined the coexpression of a variety of oncogenes; it is a demonstration that, in the future, clinical studies might be necessary to define the interaction of the various oncogenes and protein products, rather than just examining these aspects in isolation. The role of c-*jun* in the development of lung cancer is largely unclear. However, a recent study has shown that when c-*jun* was inducted into a bronchial epithelial cell line, in contrast to c-*fos* and c-*myc,* its disregulated expression may be involved in anchorage independence in the process of lunch carcinogenesis.

src

The c-*src* protein (pp60) was identified as the Rous sarcoma virus transforming region *(src);* it is expressed in both SCLC and NSCLC but not in histologically uninvolved lung tissue. The importance of this remains uncertain.

THE PROGRESSION OF NORMAL AIRWAY EPITHELIUM TO MALIGNANT EPITHELIUM

As described thus far, many genetic alterations can be found in lung cancers. The current evidence suggests that many events, both genetic and epigenetic, are necessary for the transformation of normal cells to neoplastic cells. It is logical to postulate that with the accumulation of these events, the involved cell(s) would have characteristic genetic, biochemical, and morphologic changes. How many events are necessary for the malignant transformation of a lung epithelial cell and in what order they occur in lung cancer constitute an area of intense research. Colorectal carcinogenesis provides a useful paradigm for understanding this process. Further, it may be directly relevant to lung cancer, since embryologically the lung develops from the foregut, and both organs are constantly exposed to external carcinogens. In addition, the emerging association of lung cancer with known colorectal cancer genes is of great interest.

Colorectal Carcinogenesis

Morphologically, colorectal carcinomas arise from preexisting adenomas, which in turn arise from areas of hyperproliferative mucosa or mucosa with abnormal tissue architecture. Thus, normal mucosa undergoes changes that result in proliferative or structural changes and forms microadenomas. With progression, the microadenoma becomes an early adenoma, an intermediate adenoma, a late adenoma, and finally a carcinoma. Through molecular genetic analysis of colorectal tissue at these defined morphologic stages, certain genetic alterations have been found to occur at a high frequency. These studies have become the basis for assigning a multistep pathway of genetic alterations that correspond to the mucosal phenotypic changes, summarized in Fig. 102-2.

Many studies have been performed on patients with familial adenomatous polyposis. These patients suffer from an autosomal dominant disorder resulting in diffuse colon polyp formation, and they are at increased risk for developing colorectal carcinoma. In this syndrome, germ line mutations (thus inherited) in the *APC* gene are believed to be responsible for the epithelial hyperproliferation found in the initial stage. In patients who do not have this inherited defect, LOH on chromosome 5q and/or somatic mutations of the *APC* gene may play a role in the early stages. LOH involving chromosomes 18q and 17p and mutations in the *DCC* (deleted in colorectal carcinoma) and *p*53 genes occur more frequently at later stages of tumorigenesis and are infrequent in early-stage tumors. Mutations in the K-*ras* gene occur during the transition of early adenomas to intermediate adenomas. It should be made clear that the order of genetic changes is probably not invariant. It is the composite of changes rather than the specific sequence that is of importance. In addition, changes are likely to be carcinogen dependent; therefore, changes found in colorectal carcinomas may not be directly associated with pulmonary tumorigenesis. Finally, not all alterations may exist within a tumor. Thus the accumulation and interaction of numerous genetic events determine the histology and clinical phenotype of the tumor. This paradigm, while attractive, is a working model; it does not take into account quantitative alterations in levels of oncogene expression or the effect of growth factors, the surrounding connective tissue, tissue oxygenation, or angiogenesis factors. Although the model is logical and is supported by histologic and genetic studies, it is likely to be incomplete and perhaps simplistic.

Can this model be applied to the development of lung cancer? It probably can, with some similarities and many important differences. Lung cancer is also thought to develop through many stages of histologically defined epithelial

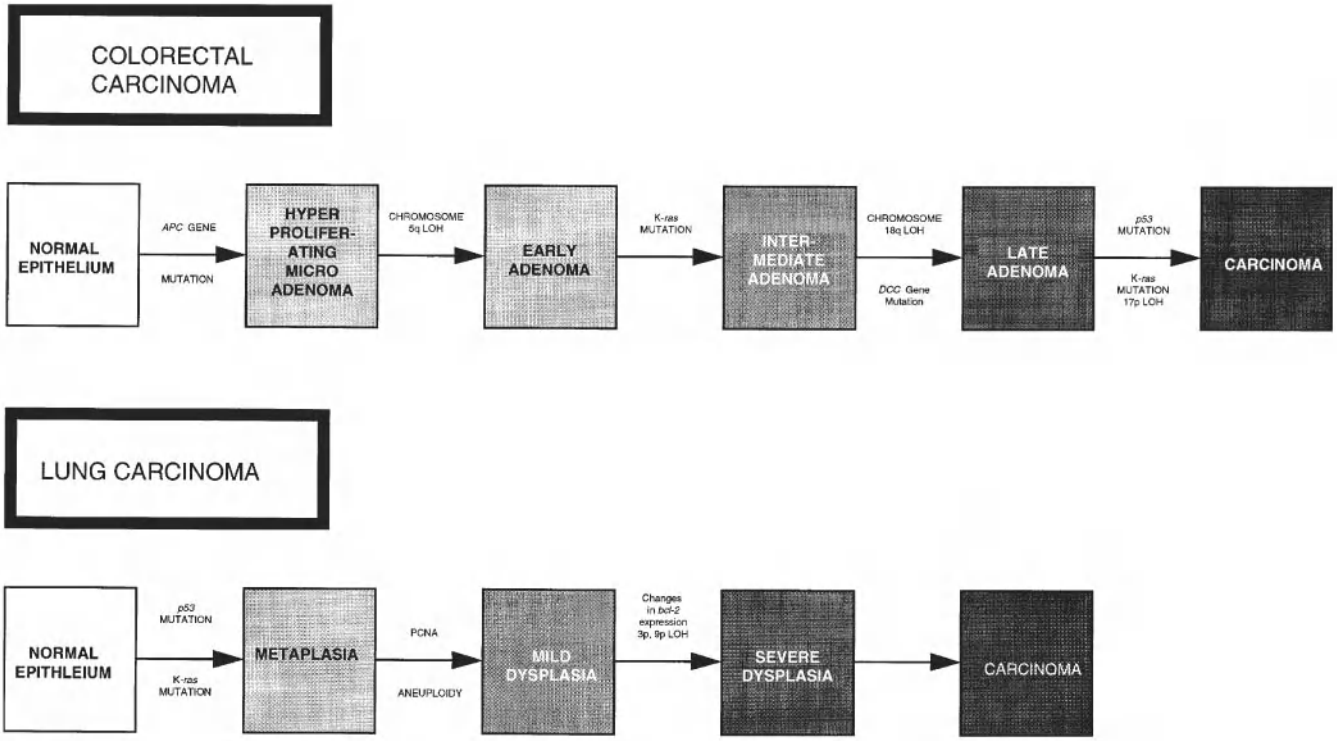

Figure 102-2 The multistage carcinogenesis model for colorectal cancer is shown in the top panel. This model has been reasonably validated for colorectal cancer and demonstrates a progressive series of genetic events. In contrast, the evolution of lung cancer (shown in the bottom panel) using the same multistage carcinogenesis approach is less well studied. Lung cancer, as indicated in the text, is more complex because of the different cell types and because peripheral lung tumors are not easily studied. Nevertheless, it is emerging that lung cancer also is likely to exhibit a series of defined genetic events that confer specific phenotype expression.

changes. The earliest changes include squamous metaplasia, followed by dysplasia, carcinoma in situ, and microinvasive and invasive cancer. While no longitudinal studies have definitely implicated the metaplastic and dysplastic lesions as premalignant, there is strong circumstantial evidence to support the notion that epithelial dysplasia represents an early stage in the development of bronchogenic carcinoma. In a study of 14,414 male smokers, the presence of atypical squamous metaplasia on cytologic examination of the sputum was considered an indicator of a modest elevation in the risk of bronchogenic carcinoma. And the development and application of an 80-gene biomarker distinguishing smokers with lunch cancer from those without lung cancer has demonstrated that gene expression in cytologically normal epithelial cells can serve as a biomarker for the disease. Perhaps the strongest factor making this link is the dose-response relationship between the number of cigarettes smoked per day and the frequency of dysplastic lesions in the bronchial epithelium. These changes are most evident in pulmonary squamous cell carcinomas, as has been assessed using serial sections around minute squamous cell carcinomas; but they are not as clear in lung adenocarcinomas, owing to the inability to readily access, screen, and study areas of the peripheral lung from which these tumors usually arise. There is reasonable evidence, however, that a sequence of morphologic changes occur in the bronchial mucosa, consistent with a multistage model of carcinogenesis for lung cancer development.

It is of great interest, therefore, to examine whether genetic changes occur in a stepwise fashion in the bronchial epithelium to correlate with the morphologic changes. This area is currently being defined, and extensive information is not yet available. However, the limited information that is available leads to the conclusion that stepwise accumulation of genetic changes also occurs in lung cancer. Not surprisingly, the events and their timing differ from the colorectal carcinoma paradigm, undoubtedly reflecting differences in the epithelium, microenvironment, and carcinogen exposure. The most studied molecular change has been in *p53* expression. In several analyses of preneoplastic lung lesions and lung neoplasms, alterations in the immunohistochemically defined levels of *p53* expression (which implies a mutation in *p53*) occur early, with *p53* abnormalities found in metaplastic and mild to moderate dysplastic lesions (10–30 percent of cases). The frequency of *p*53 alterations jumps to more than 60 percent in severe dysplasia and as high as 80 percent in carcinomas. Further molecular changes have been the LOH of 3p and the LOH of chromosome 9p, described at the severe-dysplasia stage. Hyperproliferation is evident during early dysplasia, when proliferating cell nuclear antigen (PCNA), a marker of cell proliferation, is found in 33 percent of samples, as opposed to 25 percent of normal airway

epithelium samples. This increases to 40 percent in severe dysplasia and to more than 85 percent at the carcinoma in situ stage. This study suggests that hyperproliferation is quickly followed by DNA aneuploidy and then p53 immunoreactivity. Genetic instability is evident early in the natural history of bronchogenic cancer, with DNA aneuploidy found in 8 percent of samples with mild dysplasia, 33 percent with severe dysplasia, and 100 percent of samples with carcinoma in situ. K-*ras* mutations have not been studied as completely as *p*53, but they have been shown to occur early in the course of lung tumorigenesis, at least in adenocarcinomas.

The information necessary to construct as complete a paradigm for pulmonary tumorigenesis as has been done for colorectal carcinogenesis is not available, although it is clearly being derived. Fig. 102-2 provides a summary of our current understanding. It is clear that changes in specific oncogenes can be associated with specific phenotypes, giving credence to this paradigm. The ability to identify dysplastic airway lesions at bronchoscopy will create the opportunity to obtain a better collection of samples for analysis. However, there is evidence of hyperproliferation in preneoplastic pulmonary epithelium, *p53* mutations, and genetic instability. The molecular paradigm for lung cancer is very complex because of the unclear familial genetics of the disease, the large number of carcinogens that may play a role in pulmonary tumorigenesis, and the variability in the malignant phenotypes that can be expressed (small cell vs. large cell vs. squamous cell). And unlike the situation with colon carcinoma, early events in the airway have not been as easily detected macroscopically, reducing the possibility of obtaining tissue. Also, surveillance bronchoscopies for early detection of lung cancer are not recommended, even in known at-risk patient groups.

THE IMPACT OF MOLECULAR GENETIC CHANGES ON THE CELL CYCLE

We have identified a number of genetic changes that have been found in lung cancer and proposed a multistep paradigm of lung cancer development. It is not clear, however, whether these molecular-genetic events are causative or simply associated with lung cancer. Are these events directly responsible for the genesis of lung cancer? The answer to this question is unknown, but there is evidence to suggest that some of these events may have a direct role in pulmonary tumorigenesis. At the simplest level, malignant transformation represents either the loss of regulated growth or the loss of programmed cell death (apoptosis). Therefore, if the genetic changes that occur in lung cancer affect growth regulation or apoptosis, a causative role may be implied.

Recently, much has been learned about events that regulate cell growth. In addition, all oncogenes and the genetic changes described in this chapter have an impact on cellular growth regulation. Within this framework, many of the genetic changes we have discussed affect the cell cycle. EGFR and HER2 are membrane-bound receptors that can initiate signaling and transmit a growth signal; p21 ras is also active in intracellular signaling pathways related to cell proliferation. Fos, Jun, and Myc are nuclear transcription factors that could control growth regulatory genes. The tumor suppressor genes provide the best examples of the effect of genetic changes on the cell cycle.

The cell cycle is divided into distinct periods—the G1 period (preparing for DNA synthesis), S phase (DNA synthesis), G2 period (postsynthesis), and M (mitosis). At various points in the cell cycle, there are checkpoints at which the cell has the ability to assess itself and determine whether it is ready to progress to the next phase of the cell cycle. These checkpoints are under the influence of both positive and negative regulators. If the function of a negative regulator is lost, or if a positive regulator is overexpressed, the cell may progress to the next portion of the cell cycle at an inappropriate time. Perhaps the most important checkpoint is the G1-to-S transition. At this time the cell must determine the integrity of its DNA before replication, so as not to replicate any DNA defects into the genetic code. If regulation of this checkpoint is lost, or a mutation inadvertently replicates in an important growth regulatory gene before it can be repaired, uncontrolled cell growth may result.

The Rb protein is a key regulator of the passage of cells through the G1 period. pRB function is regulated by its phosphorylation status. During the G1 period, pRB is primarily hypophosphorylated. Thus, the growth suppressive form of pRB is thought to be the hypophosphorylated form. In late G1, pRB goes through successive phosphorylations that inactivate its ability to suppress cell proliferation. The phosphorylation of pRB is regulated by a complex consisting of two subunits—a cyclin and a cyclin-dependent kinase (cdk). Specifically, the D type cyclins (D1, D2, D3) complex with and activate cdk4 and cdk6, which mediate the phosphorylation of pRB. The cyclin/cdk complexes themselves are under regulation by a series of small protein inhibitors (p15, p16, p21, and p27). How is the phosphorylation of pRB important in regulation of the cell cycle? While this is still currently being defined, it appears that in its unphosphorylated state, pRB binds and sequesters specific proteins necessary for cell cycle progression. The bound proteins include members of the E2F family of transcription factors, which are necessary for the expression of many genes active in DNA replication (DNA polymerase-α, PCNA). Thus, pRB binding to E2F prevents transcription from promoters containing E2F sites. Upon pRB phosphorylation, E2F is released, activating transcription. E2F DNA binding sites have been noted in a number of genes critical for cell entry into S phase. Thus, mutations of pRB that interfere with E2F binding, or affect pRB phosphorylation by cdk4 or cdk6, may result in unrestrained entry into S phase.

The G1-to-S transition is also a p53-regulated checkpoint. Structurally, p53 has hallmarks of a transcription factor; it has a sequence-specific DNA binding domain, and its amino terminus has a transcriptional activation domain. p53 Has a role in DNA repair through one of its transcriptional targets, Gadd45. In response to DNA damage, p53 levels rise,

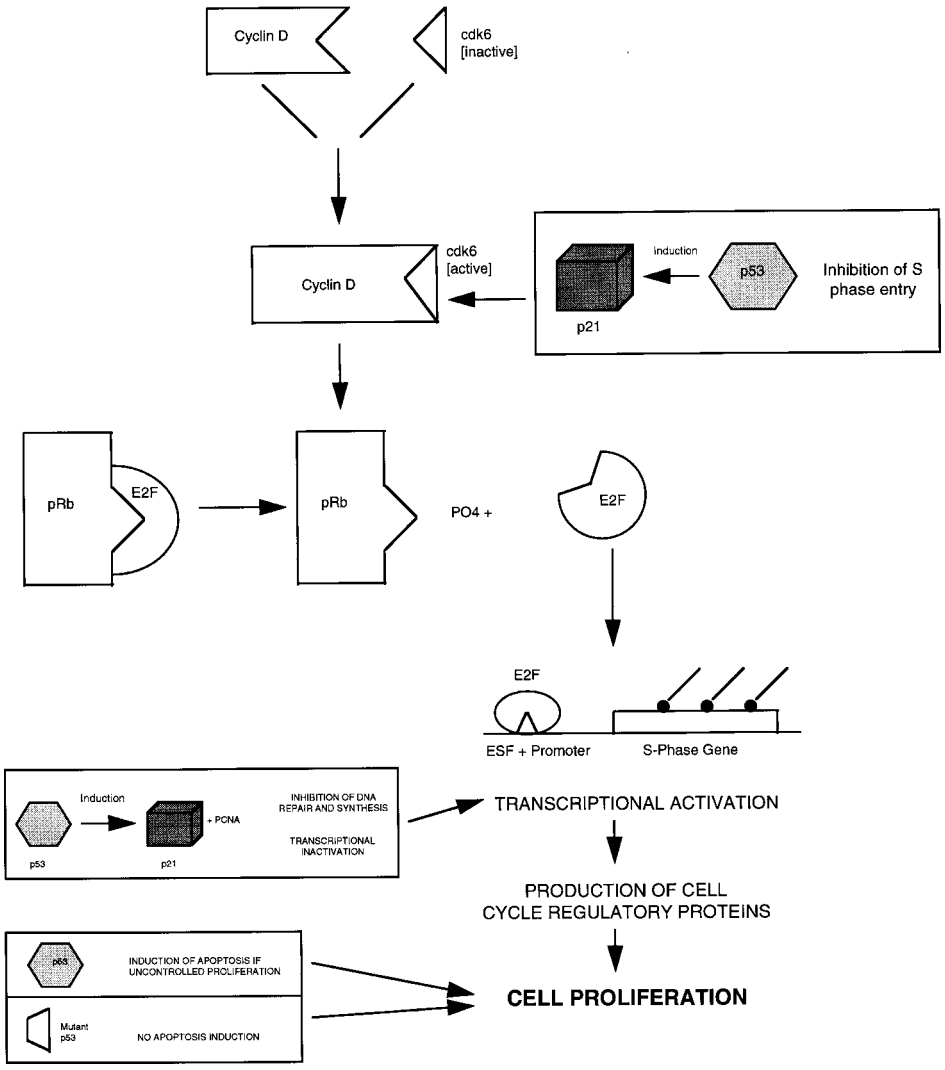

Figure 102-3 Tumor suppressor genes are thought to act on the cell cycle. Several different pathways of activity have been identified. The retinoblastoma protein (pRb) undergoes phosphorylation, allowing E2F to interact with its promoter, leading to transcriptional activation and the production of cell cycle regulatory proteins. p53 Can act by inhibiting S phase entry through the induction of p21, by inhibition of DNA synthesis or repair through interaction with p21 and PCNA, or by inducing apoptosis.

resulting in the transcriptional induction of the cdk inhibitor p21. p21 Causes an accumulation of unphosphorylated pRB, which in turn causes G1 arrest; p53 levels also rise in response to hypoxia. The p53 rise consequent on DNA damage not only seems to arrest the growth of the cell, thereby preventing transmission of the abnormal DNA, but under hypoxic conditions, it appears that the rise in p53 triggers apoptosis. In tumors that have a mutant *p53* gene, resulting in a functional loss of p53, control of cell cycle progression or apoptosis may be lost, leading to unrestrained cell growth.

Apoptosis is probably regulated by *p53* through a further mechanism. In the face of pRB inactivation or ectopic expression of E2F, entry into S phase is uncontrolled. In such cells, if there is a wild-type p53 background, apoptosis ensues. In a mutant p53 background, apoptosis does not occur; uncontrolled cell proliferation ensues, with the ultimate result being neoplastic transformation. Thus, p53 regulates both cell cycle progression and apoptosis with a key role in protecting cells from duplicating damaged DNA. These interactions are summarized in Fig. 102-3.

These two genes and the effects their mutations have on cell growth regulation illustrate how genetic events may play a direct role in tumor formation through deregulating cell growth. p53 And Rb have a clear impact on cell cycle regulation; however, many other genetic events found in lung cancer potentially have an impact on cell growth. p21 Ras plays a role in signaling and in its mutant form may provide an unregulated growth stimulus signal; the *myc* family of oncogenes are believed to be transcriptional activators and in a mutated form perhaps provide unregulated transcription of genes important in the cell cycle; mutant or high-level expression of growth factor receptors or their ligands may result in a continuous growth stimulatory signal. Clearly, when more is understood about the function of these genetic events

in lung cancer, it is likely that they will be found to have an effect on the cell cycle. In addition, many currently undescribed changes will be identified in known cell cycle genes and their encoded proteins, leading to a further understanding of genetic events occurring in pulmonary tumorigenesis.

These changes provide discrete therapeutic targets for the development of new treatments of this devastating disease. Many of these therapeutic targets have already been the subject of in vivo and in vitro experiments to assess the effects on tumor growth and differentiation. For instance, a recent study of the role of p53 in growth inhibition and apoptosis has shown that it may be a factor in determining sensitivity to treatment by gefitinib, by regulating Fas expression in NSCLC. Morover, restoration of p53 by a Cre-loxP-based strategy, controlling the tumor suppression gene in vivo, has led to apoptosis in lymphoma and suppression of cell growth in sarcomas. Other studies have shown similar promise. Other experiments that have been described in association with the description of the particular oncogene or oncoprotein are summarized in Fig. 102-4. In all instances so far reported, there has been a measurable effect on tumor growth. It is therefore possible that major changes in the therapy of lung cancer will occur in the future with the use of these approaches either as single agents or, more likely, as part of a combined-modality therapy. This molecular approach to therapy will probably be combined with a molecular evaluation of the population most at risk, so that effective screening programs can be established. This, together with increasing efforts to reduce environmental exposures such as those from tobacco smoke, should help to bring the epidemic of deaths from lung cancer under control.

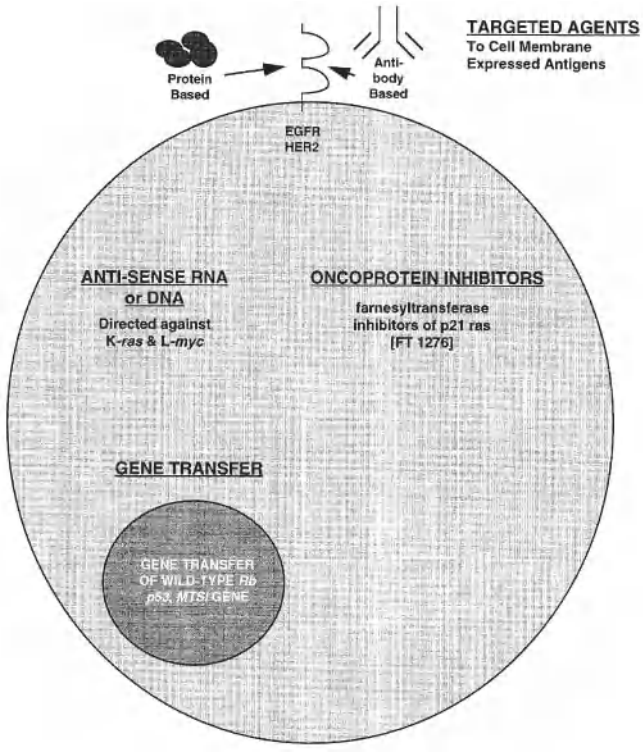

Figure 102-4 The potential sites for therapeutic targets are shown. Opportunities exist to target the extra cellular domain of EGFR and HER2, by either proteins or specific antibodies. Antisense RNA and DNA are currently being directed against K-*ras* and L-*myc* in cell culture studies, and specific oncoprotein inhibitors are also being tested for antitumor activity. Finally, gene transfer of several tumor suppressor genes is undergoing laboratory study, especially the transfer of the wild-type *Rb* and *p53* gene.

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The Solitary Pulmonary Nodule: A Systematic Approach

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The radiographic finding of a solitary pulmonary nodule, formerly known as a *coin lesion,* has long challenged the clinician. At the heart of the dilemma, the question remains unchanged: "Is it malignant or benign?" Bronchogenic carcinoma is the most common malignancy found in solitary pulmonary nodules, and it remains the leading cause of cancer death in the United States. When faced with a solitary pulmonary nodule, the clinician and the patient usually have one of three choices: (1) observe it with serial chest computed tomography (CT); (2) perform additional diagnostic tests (imaging and/or a biopsy); or (3) remove it surgically.

The proper choice depends on radiographic appearance, epidemiology, assessment of surgical risk, and patient preferences. Surgical resection of an early solitary malignant lesion still represents the best chance for cure. On the other hand, unnecessary resection of benign nodules exposes patients to the morbidity and mortality of a surgical procedure. The aim of this chapter is to review what we know about the solitary pulmonary nodule to formulate a diagnostic approach to this often controversial problem. The goal is to arrive at a systematic approach that will promptly identify and bring to surgery all patients with operable malignant nodules while avoiding thoracotomy in patients with benign nodules.

DEFINITION

A solitary pulmonary nodule is defined as a single discrete pulmonary opacity that is surrounded by normal lung tissue that is not associated with adenopathy or atelectasis. Previously there was controversy as to what constituted the upper size limit for defining a solitary pulmonary nodule. Some early series included lesions up to 6 cm in size. However, it is now recognized that lesions larger than 3 cm are almost always malignant, so current convention is that solitary pulmonary nodules must be 3 cm or less in diameter. Larger lesions should be referred to as pulmonary masses and should be managed with the understanding that they are most likely malignant; prompt diagnosis and resection are usually advisable.

INCIDENCE AND PREVALENCE

The frequency with which a solitary pulmonary nodule is identified on chest radiography is on the order of 1 to 2 per thousand chest radiographs. Most of these are clinically silent, and about 90 percent are noted as an incidental finding on radiographic examination. The prevalence of malignancy in nodules varies widely, depending on the patient population; thus, many case series may not be directly comparable. Surgical series in the era before computed tomography (CT), including both calcified and noncalcified nodules, reported an overall malignancy rate of 10 to 68 percent. A Veterans Administration Armed Forces Cooperative Study in 1963 reported an overall 35 percent malignancy rate in a cohort that included a significant number of young military recruits (about half of them under age 50). Infectious granulomas were found in 53 percent. When those over the age of 50 were studied, a 56 percent malignancy rate was noted, with a 30 percent incidence of granulomas. Of those under the age of 35, only three patients had a malignancy, one of which was a primary lung carcinoma. Series that have used chest CT to screen out benign-appearing calcified nodules show much higher overall malignancy rates: 56 to 100 percent. A series of 360 patients from the Minneapolis Veterans Administration Medical Center, which used CT scan to exclude benign nodules, showed an overall malignancy rate of 79 percent, with an increase from about 60 percent in the early 1980s to 100 percent from 1990 to 1994. This population included mostly male smokers aged about 65. A smaller series (40 patients), referred to the outpatient practice of a pulmonologist in an urban university hospital from 1990 to 1993, had a 53 percent malignancy rate. The mean age was 65, 83 percent were smokers, and sex distribution was almost equal.

Younger patients from areas where granulomatous diseases such as tuberculosis, histoplasmosis, and coccidioidomycosis are endemic can be expected to have a lower malignancy rate. In an Air Force Medical Center study from Illinois of 137 patients, only 22 (16 percent) had a malignancy. Granulomas were diagnosed in 103 patients (75 percent); 53 of them were attributable to histoplasmosis endemic to the area. Most of these patients (77 percent) were under age 45, and no malignant nodules were diagnosed in patients less than 35 years of age. This series predated the use of chest CT.

MALIGNANT SOLITARY PULMONARY NODULES

Risk factors for malignancy have been identified from studies of large series of solitary pulmonary nodules and include patient age, smoking history, nodule size, and prior history of malignancy. Age is one of the most consistent risk factors. In a series of 370 indeterminate solitary pulmonary nodules, the incidence of malignancy increased from 63 percent for patients aged 45 to 54, to 74 percent for those aged 54 to 64, and continued to rise with age to 96 percent for those above the age of 75. These findings correlate with those of previous studies, which also show that malignancy is very rarely found in patients under the age of 35.

Smoking is closely correlated with the development of lung cancer, particularly squamous and small cell carcinoma. The Surgeon General's report of 1964 and subsequent studies have demonstrated that the risk of lung cancer increases with the duration of smoking and the number of cigarettes smoked. Average smokers have about a 10-fold risk and heavy smokers a 20-fold risk of developing lung cancer when compared with nonsmokers. Smoking is responsible for about 85 percent of the cases of bronchogenic carcinoma. Cessation of smoking reduces this risk after 10 to 20 years, but it now appears that former smokers have a slightly higher risk of cancer throughout their lifetimes.

Nodule size is closely correlated to risk of malignancy. Several series have demonstrated an increased incidence of malignancy with increasing nodule size. Nodules larger than 3 cm are malignant 80 to 99 percent of the time, whereas those under 2 cm in size are malignant in 20 to 66 percent of cases.

A history of current or prior extrapulmonary malignancy greatly increases the probability that a nodule is malignant. Depending on the series, 33 to 95 percent of such nodules have proved to be malignant—most represent metastases but some second primaries. The most common histologic types of metastatic nodules are adenocarcinomas of colon, breast, kidney, head and neck tumors, sarcoma, and melanoma.

Primary bronchogenic carcinoma is the most common malignant tumor that presents as a solitary pulmonary nodule. Histologically, adenocarcinoma and squamous cell carcinoma make up the majority; of the two, adenocarcinoma is the more common. Less frequent as a solitary pulmonary nodule is the bronchioloalveolar cell carcinoma. Small cell carcinoma that presents as a solitary pulmonary nodule is rare. Other rare primary lung tumors that may present as solitary pulmonary nodules are bronchial carcinoids (1–5 percent), which are usually peripherally located; lymphomas; hemangioendotheliomas; and sarcomas.

Metastases may present as solitary pulmonary nodules in patients who have known primary malignancies or in whom the presence of primary malignancy is unknown. In up to 40 percent of such patients, who manifest only a single nodule on chest radiograph, CT scan may show other nodules that are not disclosed by plain chest radiograph. Even though the lesion is solitary, in patients with an established diagnosis of cancer, up to 95 percent of these nodules are malignant upon resection. Because of this high likelihood of malignancy, a nodule in a patient with an established diagnosis of cancer should be treated differently from other solitary nodules. Assuming no other obvious metastatic spread, one should consider proceeding directly to biopsy. Even in the presence of a known malignancy, some of these nodules may represent a second primary pulmonary malignancy that is similar

in histologic appearance. Immunohistochemistry and other confirmatory marker studies may be indicated to determine the nature of the nodule. A solitary pulmonary nodule in a patient with a history of malignant disease should be removed so long as there is no other evidence of recurrent or metastatic disease.

BENIGN SOLITARY PULMONARY NODULES

Benign solitary pulmonary nodules are more common in the young and in nonsmokers. They include both infectious and noninfectious granulomas, benign tumors such as hamartomas, vascular lesions, and rare miscellaneous conditions (Table 103-1).

Hamartomas are the most common benign tumors presenting as solitary pulmonary nodules. They are believed to be developmental malformations composed mainly of cartilage, fibromyxoid stroma, and adipose tissue. Our review of six series of resected solitary pulmonary nodules since 1974 shows that 192 of 3802 nodules (5 percent) were histologically proved hamartomas. In a series of 215 hamartomas resected at the Mayo Clinic, the peak incidence was in the seventh decade of life; male-to-female ratio was 1:1; and the average size was 1.5 cm, although some were as big as 6 cm. Most hamartomas were asymptomatic (97 percent), and 17 percent were noted to grow slowly on serial radiographic examination. They may be identified radiographically by a pattern of "popcorn" calcification, which is often intermixed with areas of low attenuation on CT scan representing fat deposits within the nodule. CT appearance is diagnostic in about 50 percent of hamartomas.

Infectious granulomas make up more than 90 percent of all benign nodules. They arise as a result of healing after infection from a variety of organisms. The offending agents vary, depending on geographic location. Among the most common causes are histoplasmosis, coccidioidomycosis, and tuberculosis. Other, less common causes are dirofilariasis (dog heartworm), mycetoma, echinococcal cyst, and ascariasis. A history of exposure is important in establishing a possible infectious origin. Clues such as prior travel history, places of residence, occupation, and pets may be invaluable in some instances.

Noninfectious granulomas sometimes occur as solitary pulmonary nodules in systemic diseases such as sarcoidosis, in which nodules are not invariably accompanied by hilar adenopathy; rheumatoid arthritis, usually in patients with active disease who often have subcutaneous nodules; and Wegener's granulomatosis.

Miscellaneous causes of solitary pulmonary nodules have been described. Some of the more common conditions are lung abscess; rounded or spherical pneumonia; pseudotumor (Fig. 103-1), which represents fluid in an intralobar fissure; hematomas after thoracic trauma or surgery; and fibrosis or scars resulting from the resolution of infectious or inflammatory process. Rarer conditions presenting as solitary pulmonary nodules include silicosis, bronchogenic cyst, amyloidosis, pulmonary infarct, and vascular anomalies. Arteriovenous malformations may present as solitary pulmonary nodules. They may grow slowly and have a characteristic appearance on contrast-enhanced CT scan.

Table 103-1

Differential Diagnosis of Solitary Pulmonary Nodules

Malignant tumors
Bronchogenic carcinoma (adenocarcinoma, large cell, squamous, small cell)
Carcinoid
Pulmonary lymphoma
Pulmonary sarcoma
Plasmocytoma
Solitary metastases (colon, breast, kidney, head and neck, germ cell, sarcoma, thyroid, melanoma, others)
Benign tumors
Hamartoma
Adenoma
Lipoma
Infectious granulomas
Tuberculosis
Histoplasmosis
Coccidioidomycosis
Mycetoma
Ascaris
Echinococcal cyst
Dirofilariasis (dog heartworm)
Noninfectious granulomas
Rheumatoid arthritis
Wegener's granulomatosis
Sarcoidosis
Paraffinoma
Others
Miscellaneous
BOOP
Abscess
Silicosis
Fibrosis/scar
Hematoma
Pseudotumor
Spherical pneumonia
Pulmonary infarction
Arteriovenous malformation
Bronchogenic cyst
Amyloidoma

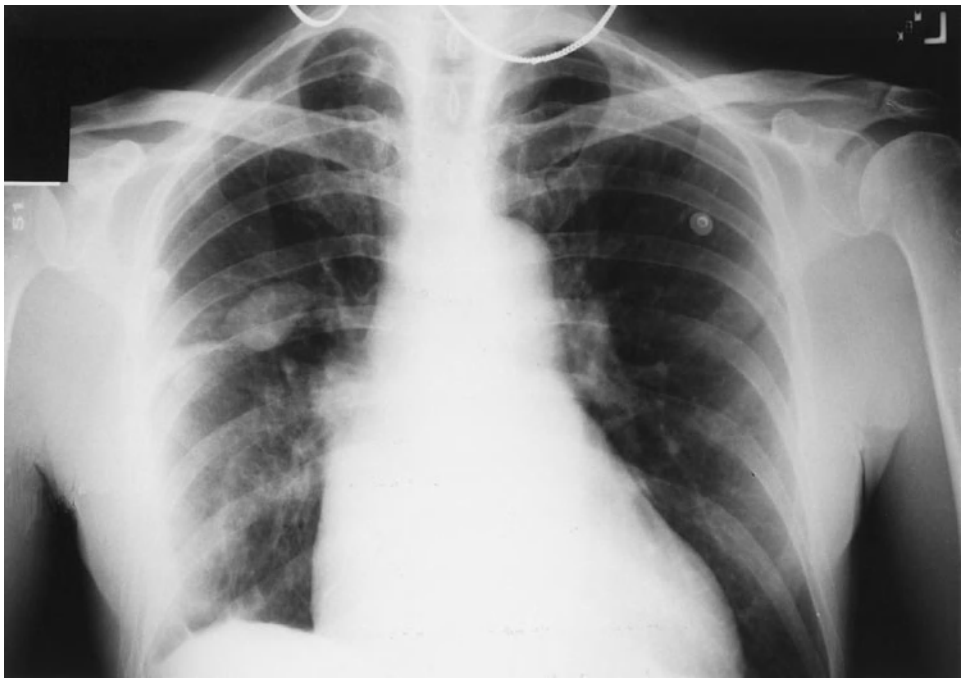

Figure 103-1 Pseudotumor. Fluid in a fissure, the result of both pleural disease and fluid overload, has the appearance of a pulmonary mass.

IMAGING TECHNIQUES

Imaging techniques are often helpful in distinguishing benign from malignant causes of solitary pulmonary nodules, and as such they play a key role in their evaluation and management. During the last decade, rapid advances in both CT and positron emission tomography (PET) have dramatically changed the diagnostic approach to the solitary pulmonary nodules. However, this does not mean that these techniques should be used indiscriminately. Cost-effective strategies to manage solitary pulmonary nodules require that we understand the performance characteristics (sensitivity, specificity), strengths, and weaknesses of each of these technologies, so that they can be applied properly. The primary technologies that need to be considered are plain chest radiography, CT, and PET.

Plain Chest Radiography

Most solitary pulmonary nodules are discovered on routine plain chest radiograph while asymptomatic. Malignant nodules are usually identifiable on chest radiograph by the time they are 0.8 to 1 cm in diameter, although nodules 0.5 to 0.6 cm are seen occasionally. Most are identified on posteroanterior (PA) projection, but some are seen only on lateral projection, so standard PA and lateral chest radiography should be obtained whenever possible. When a nodule can be seen only on one projection, the clinician should question whether it is truly in the lung parenchyma. Structures overlying the skin of the chest wall—such as leads used for cardiac monitoring, nipple shadows, skin lesions, bone lesions, and pulmonary vessels on end—can all mimic pulmonary nodules. Once it has been ascertained that a true nodule exists, the first step is to make every effort to obtain previous radiographs for comparison. A nodule that has remained stable, with no increase in size, for 2 years, is very probably benign and warrants no further investigation. Conversely, a nodule that was not present on a comparable radiograph within the past 2 months is unlikely, having grown so rapidly, to be a malignancy. On rare occasions, small cell carcinoma may present as a solitary pulmonary nodule with a doubling time of less than 30 days.

Newer techniques, such as digital chest radiography, which uses computerized postprocessing to enhance radiographic images, can improve the detection of nodules over normally radiopaque areas of the thorax, such as the mediastinum and the diaphragm. This is accomplished by means of computerized algorithms (e.g., adaptive spatial filtering) that selectively change enhancement patterns over the areas of interest, making previously unseen nodules visible.

Standard and Computed Tomography

Standard tomography was once used extensively in the evaluation of solitary pulmonary nodules, and it can be very useful in determining their exact location and characteristics. With the advent of CT, however, this technique is now seldom used, and few radiologists are being trained to use the technique.

CT has replaced plain tomography as a more sensitive tool in the evaluation of solitary pulmonary nodules. CT is indicated when one is assessing indeterminate nodules less than 3 cm in diameter or in staging of larger lesions. It

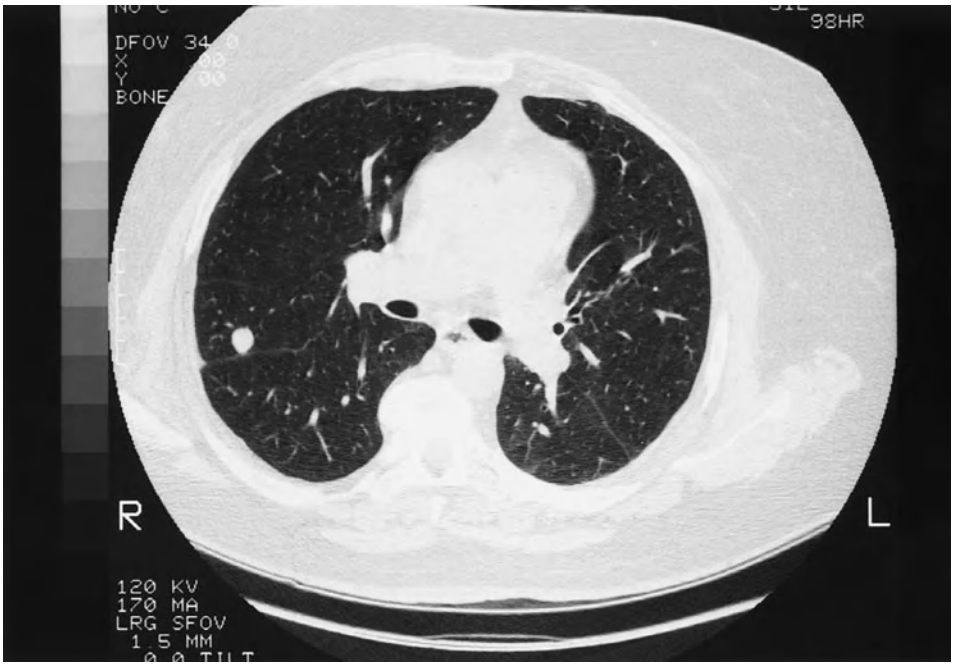

Figure 103-2 Noncontrast CT shows a round 1-cm nodule, with relatively high radiographic density, proven on resection to be a granuloma.

can pinpoint the exact location of the nodule and provide three-dimensional images of the lesion. Thin-section high-resolution CT (HRCT) can better define the borders and the nodule's relation to adjacent structures, such as vessels and the pleura. It is more sensitive than standard tomography in detecting calcification patterns, and it can detect fat within a nodule—which, when coupled with calcification, is highly suggestive of a benign hamartoma. In up to 40 percent of cases, previously unseen synchronous lesions can be seen. CT may be useful in looking for hilar or mediastinal adenopathy, and in evaluating accessibility of nodules for biopsy or resection.

HRCT can quantify calcification in nodules even when they are not readily visible to the naked eye. Nodules with higher radiographic density are more likely to be benign (Fig. 103-2). This technique has been suggested for indeterminate nodules smaller than 3 cm in diameter. Nodules that are bigger than 3 cm or that have suspect characteristics in the right clinical setting (e.g., an older smoker, spiculated borders) should be considered for biopsy or resection. Because it is difficult to standardize radiographic density on CT when a nodule is being examined for occult calcification, a phantom model is constructed to mimic the patient's chest, nodule size, and location. Benign nodules usually have a density greater than 164 Hounsfield units. Therefore, the reference nodule is created with a known density greater than this—at about 185 Hounsfield units. The patient's nodule density is measured with HRCT and is compared with the reference phantom. If the patient's nodule is denser than the phantom, it is very probably benign and can be observed with sequential conventional radiographs. If it is less dense than the reference phantom, it remains indeterminate and further workup is indicated. It should be noted that in a study of 85 nodules that were classified as having a high probability of benignity by the means of the 185 Hounsfield units cutoff, eight of them (9 percent) proved to be malignant on biopsy or resection. The CT reference phantom technique can be a helpful adjunct in the evaluation of the solitary pulmonary nodule, but it is helpful in only about 30 percent of cases, with 70 percent of nodules evaluated remaining indeterminate. CT densitometry has not achieved widespread clinical use.

Another CT technique that may be helpful is incremental dynamic CT, which uses serially increasing doses of iodinated IV contrast to look for enhancement of nodules. Although malignant nodules enhance more than benign ones, benign lesions, such as hamartomas and tuberculomas, may also enhance. In centers with expertise with this methodology, the sensitivity and specificity of the test are good. However, few centers at the present time are using this approach. The development of faster multidetector scanners has also had a great impact on the evaluation of pulmonary nodules. The ability to scan a large area with a single breath hold, thereby eliminating respiratory artifact, has increased the ability of radiologists to reconstruct images at different intervals and thicknesses. This also has increased the ability detect smaller subcentimeter nodules, down to 1 to 2 mm in size.

Positron Emission Tomography

Newer imaging methods, such as PET, can be used to differentiate noninvasively between malignant and benign nodules. PET takes advantage of the fact that tumor cells have an increased glucose uptake and metabolism. A d-glucose analog labeled with a positron-emitting fluorine-18 radioisotope

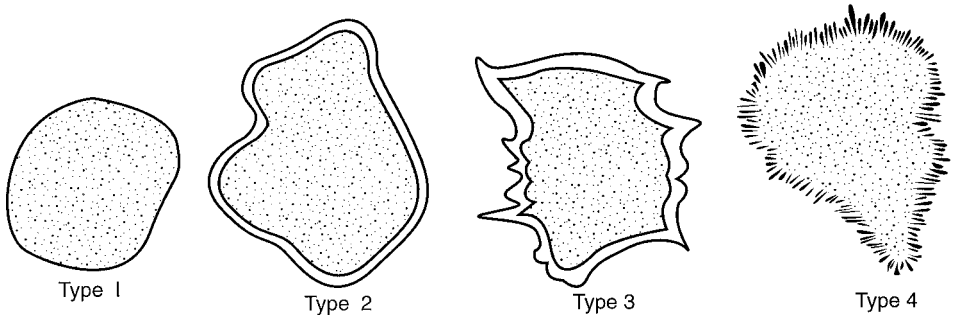

Figure 103-3 Characteristic appearance of nodule IV is edges. Type I is sharp and smooth, type II is lobulated, type III has irregular undulations, and type IV is grossly irregular with many spiculations. *(Based on data of Siegelman SS, Khouri NF, Leo FP, et al: Solitary pulmonary nodules: CT assessment.* Radiology *160:307–312, 1986.)*

(FDG) is injected into the patient, and uptake by the nodule is then measured. Malignant nodules have a higher uptake of FDG. A meta-analysis of 13 studies involving 450 patients estimated the sensitivity of PET to be 94.3 percent with a specificity of 83.3 percent.

However, PET appears to be less sensitive for lesions less than 1 cm in size, so its use should be limited to those lesions 1 cm or greater in size. Although there is limited preliminary evidence that PET may be useful for lesions as small as 8 to 10 mm in size, there are still too many false-negatives reported to make PET useful for these types of lesions outside of a clinical trial at the current time. False-negative findings have also been seen in patients with bronchioloalveolar cell carcinoma, carcinoids, and mucinous adenocarcinomas. False-positives have been seen in patients with granulomatous infections, such as tuberculosis or endemic fungi, as well as in patients with inflammatory conditions, such as rheumatoid arthritis and sarcoidosis. Theoretically, false-positive results can also be caused by uncontrolled hyperglycemia.

DISTINGUISHING BETWEEN BENIGN AND MALIGNANT NODULES

The goal of management algorithms for solitary pulmonary nodules is to bring to surgery all patients with potentially curable disease while avoiding unnecessary surgery in those who do not need it. As such, distinguishing between benign and malignant nodules is critical. Assessing image characteristics from a PET scan at a given moment in time is one method to help distinguish benign from malignant pulmonary nodules. However, there are other methods that can help the physician with this critical step. These include assessment of a nodule's shape and calcification pattern, the nodule's growth rate, and assessment of the probability of malignancy based on epidemiologic risk factors.

Nodule Shape and Calcification Patterns

Certain shapes make a nodule more likely to be malignant. Although nodules may appear to be spherical on plain chest radiograph, further study by CT may disclose irregular borders and shapes. The borders of benign nodules are often well circumscribed, with a rounded appearance. On the other hand, malignant nodules tend to have irregular, lobulated, or spiculated borders (Fig. 103-3). A malignant nodule may have pleural tags or tails extending from its body (Fig. 103-4), or a notch may be present in the border of the nodule (Rigler's sign). None of these radiographic signs is entirely specific for malignancy.

Calcification is generally an indication of benignity in a solitary pulmonary nodule. Infectious granulomas tend to calcify with central, diffuse, or stippled patterns (Fig. 103-5). Laminar or concentric calcification is characteristic of granulomas caused by histoplasmosis. Popcorn calcification, when present, is suggestive of a hamartoma. Eccentric calcification patterns should make one suspicious for malignancy. It should be noted that, in general, 6 to 14 percent of malignant nodules exhibit calcification. When present, calcifications are usually eccentric and few. Benign patterns of calcification (central, diffuse, laminar, or popcorn) are very rare in malignant nodules. In one study of 1267 solitary pulmonary nodules, only seven malignant nodules (0.6 percent) had a benign calcification pattern. Most nodules with a benign calcification pattern can be observed with serial CT scans.

Rapid advances in CT technology have also led to more precise characterization of the morphology of lung nodules. Small nodules can be visualized by high resolution CT (HRCT) with thin (approximately 1 mm) slices through the target nodule, allowing for a higher degree of resolution and more precise description of their morphology. It is now appreciated that nodules may be characterized as solid, partly solid, or pure ground-glass opacities (defined as focal densities in which underlying lung morphology is preserved). This is particularly useful for categorizing small nodules (less than 1 cm) since these categories can help to distinguish benign from malignant nodules. The percentage of pure ground-glass opacities that are malignant varies significantly in the literature, from 18 percent to almost 60 percent. For subcentimeter nodules, the likelihood of malignancy was similarly high in partly solid lesions, but much lower (less than 10 percent) in solid nodules.

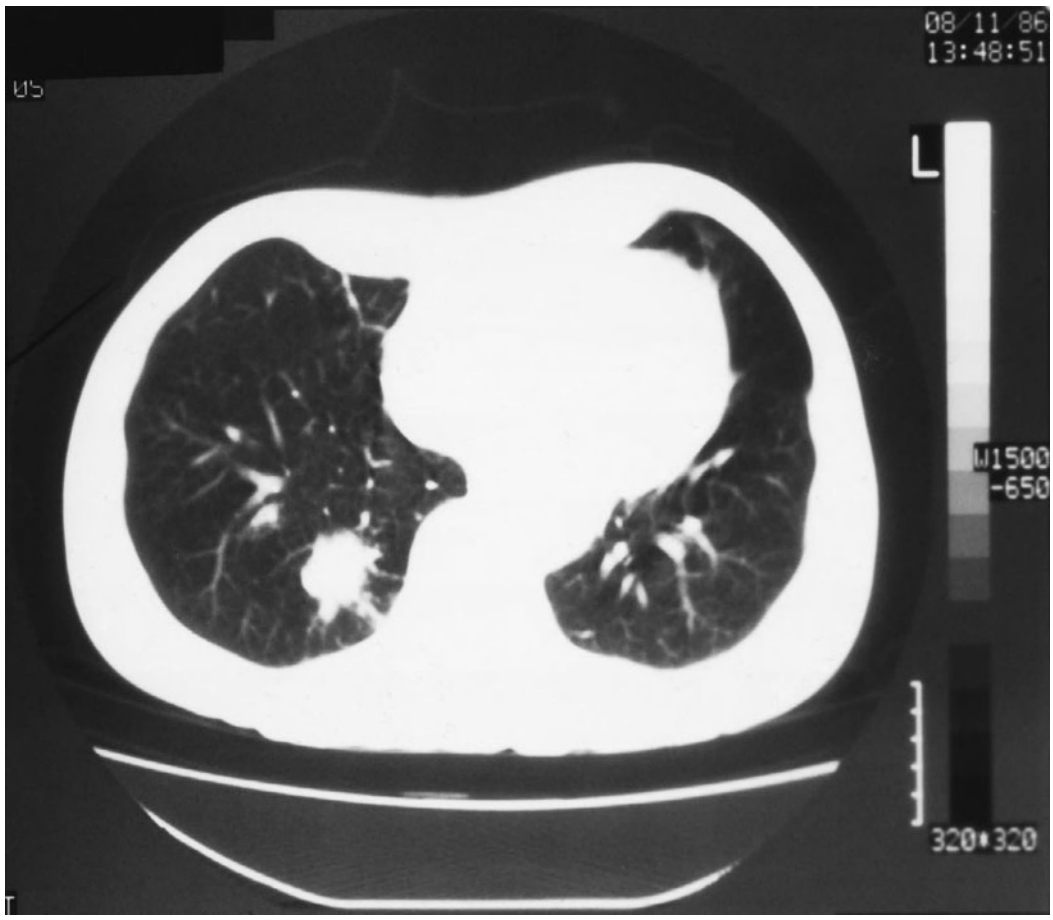

Figure 103-4 Three-centimeter mass with irregular borders and pleural tag highly suggestive of malignancy—proven adenocarcinoma.

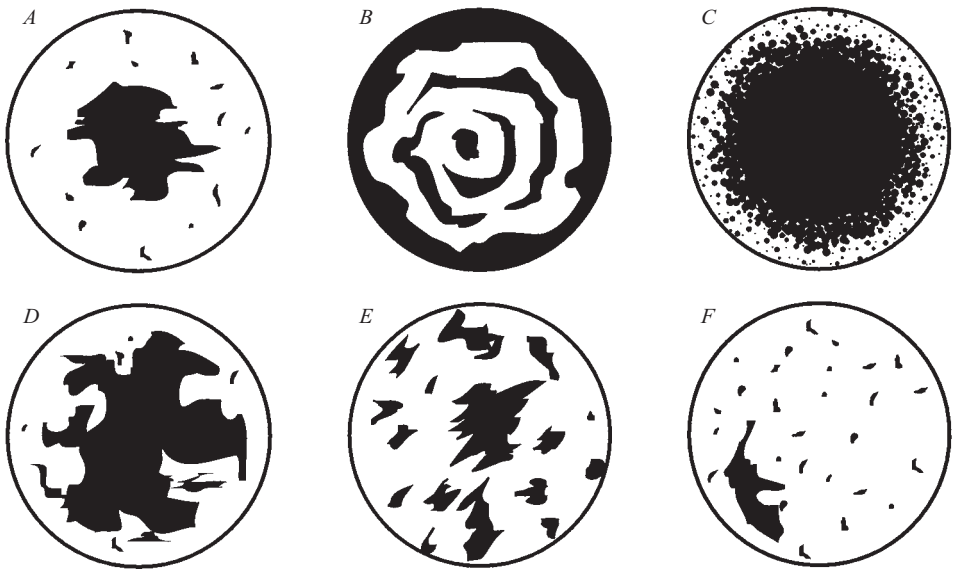

Figure 103-5 Patterns of calcification in nodules. *A*. Central. *B*. Laminated. *C*. Diffuse. *D*. Popcorn. *E*. Eccentric. Patterns A, B, C, and D generally indicate a benign process; E and F suggest malignancy. *(Based on data of Lillington GA: Management of solitary pulmonary nodules.* Dis Mon *37:271–318, 1991.)*

Ground-glass nodules may represent either atypical adenomatous hyperplasia (AAH) or true bronchioloalveolar cell carcinoma. In contrast, partly solid or solid nodules usually represent adenocarcinoma, but can also be caused by squamous cell carcinoma or small cell carcinoma. When a pure ground-glass opacity starts to grow and becomes more solid, demonstrating a replacement growth pattern, this is highly suspicious for adenocarcinoma. Of note, observed growth rates are often very slow for malignant ground-glass opacities, intermediate for partly solid nodules, and relatively fast for solid nodules.

Assessment of Nodule Growth Rate and Frequency of Follow-up Imaging

Assessing a nodule's growth rate can further assist in distinguishing between benign and malignant nodules, provided serial images over time are available for comparison. Determination of nodule growth is based on the assumption that nodules are more or less spherical. Growth of a sphere must be considered in three-dimensional volume, not in two-dimensional diameter. The formula for volume of a sphere is $4/3(\pi)r^3$, or $1/6(\pi)D^3$, where r = radius and D = diameter. A nodule originally 1 cm in diameter whose diameter is now 1.3 cm has actually more than doubled in volume. Similarly, a 2-cm nodule has doubled in volume by the time its diameter reaches 2.5 cm. A nodule that has doubled in diameter has undergone an eightfold increase in volume. When old radiographs are available, growth rate and nodule *doubling time* (i.e., the time for a nodule to double in volume) can be estimated. Accepting the assumption that a tumor arises from serial doublings of a single cancerous cell, we can estimate that it will take 27 doublings for it to reach 0.5 cm, the smallest lesion detectable on chest radiography. By the time a nodule is 1 cm in diameter, it represents 30 doubling times and about 1 billion tumor cells. Depending on the exact growth rate, this theoretical 1-cm nodule has probably existed for years before it is detected, as malignant bronchogenic tumors have doubling times estimated at between 20 and 400 days. The natural history of a tumor usually spans about 40 doublings, whereupon the tumor is 10 cm in diameter and the patient has usually died. Squamous and large cell tumors have an average doubling time of 60 to 80 days. Adenocarcinomas double at about 120 days, and the rare small cell carcinoma that presents as a solitary pulmonary nodule can have a doubling time of less than 30 days. A nodule that has doubled in weeks to months is probably malignant and should be removed when possible.

Benign nodules have doubling times of less than 20 days or more than 400 days. A nodule that doubles in size in less than 20 days is usually the result of an acute infectious or inflammatory process, whereas those that grow very slowly are usually chronic granulomatous reactions or hamartomas. Such nodules can be observed with serial radiographs.

Nodule growth rate and doubling times become clinically relevant when we have to decide how often to order follow-up imaging when observing a solitary pulmonary nodule. The question often arises whether observing a solitary pulmonary nodule for an extra 3 to 6 months increases the likelihood of metastatic disease, since that nodule has probably been growing for years. There is no convincing empiric evidence to support this hypothesis. Whether delays longer than 3 to 6 months are safe is unknown. However, estimating this hazard of delay is clinically relevant, since the optimal frequency of serial CT follow-up imaging to monitor nodules for growth is predicated on limiting this hazard of delay. The question is, how frequently do follow-up scans need to be done to minimize the hazard of delay while containing costs and avoiding excessive radiation exposure?

Traditional practice, based on little empiric evidence, recommended that when a careful observation strategy was warranted, repeat CT scans be done at 3, 6, 12, and 24 months. However, more recent data from lung cancer screening trials using CT imaging suggest that a less aggressive practice may be reasonable in some patients with very small nodules. Therefore, decisions about the frequency and duration of follow-up for patients with solitary pulmonary nodules need to consider multiple dimensions of the problem, including clinical risk factors, nodule size, the probable growth rate as reflected by CT morphology, the limits of imaging technology resolution and volume measurement (especially at sizes less than 5 mm), radiation dose, surgical risks, patient preferences, and cost. All of these can affect the optimal frequency of CT follow-up significantly. For example, in patients who are not considered to be surgical candidates due to other comorbidities, such as severe emphysema, the utility of follow-up CT imaging is questionable and less aggressive approaches, such as no imaging at all, are reasonable.

Given this framework, it is reasonable to apply more recent expert consensus-based guidelines to help guide the frequency of follow-up CT imaging for the solitary pulmonary nodule. For follow-up studies, imaging should be performed with the lowest possible radiation dose that provides adequate imaging (with current technology between 40 and 100mA). The key variables that determine optimal imaging frequency are surgical risk, size, and lung cancer risk. For patients who are potential surgical candidates with no lung cancer risk factors, the frequency of repeat CT imaging is:

- Nodule size $\leq$ 4 mm: No follow-up needed.
- Nodule size > 4 mm but less then 6 mm: Re-evaluate in 12 months. If there is no change, then no additional follow-up is warranted.
- Nodule size $\geq$ 6 to 8 mm: Follow in 6 to 12 months and then again at 18 to 24 months if there is no change.
- Nodule size > 8 mm: Traditional schedule with serial CT imaging at 3, 6, 12, and 24 months if there is no change.

For patients who are potential surgical candidates with one or more lung cancer risk factors, the frequency of repeat CT imaging is:

- Nodule size $\leq$ 4 mm: Once at 12 months, no additional imaging if there is no change.

- Nodule size > 4 mm but < 6 mm: Initially at 6 to 12 months, and if no growth repeat again at 18 to 24 months if there is no change.
- Nodule size ≥ 6 to 8 mm: Initially at 3 to 6 months and then again at 9 to 12 months, and then again at 24 months if there is no change.
- Nodules size > 8 mm: Traditional schedule with serial CT imaging at 3, 6, 12, and 24 months if there is no change.

It should also be noted that controversy remains regarding how long follow-up should be continued. Although traditional teaching has recommended observing lesions for a maximum of 2 years, it is now recognized that for some lesions longer follow-up may be warranted. Long doubling times have been observed in malignant lesions that presented as ground-glass nodules or as partially solid nodules. As a consequence, longer follow-up extending over years may be appropriate in some special instances, especially if there is an antecedent history of lung cancer. For most nodules, 2 years of follow-up without evidence of growth is sufficiently long to warrant discontinuation of CT imaging.

Estimating Probability of Malignancy

Several authors have attempted to develop mathematical models to estimate the probability of malignancy of indeterminate solitary pulmonary nodules. Using clinical and radiographic characteristics of malignancy derived from the literature, these authors have analyzed some combination of the following malignant risk factors by Bayesian, neural network, and other methods to obtain a mathematical estimate of the probability of malignancy: nodule size, location, growth rate, margin characteristics, age of the patient, smoking history, prevalence of malignancy in the community, and occult calcification on CT densitometry.

For example, in the Bayesian approach, each risk factor for a particular patient and nodule is assigned a likelihood ratio of malignancy derived from published data. In one model, overall prevalence of malignancy, diameter of the nodule, patient's age, and smoking history were considered. The likelihood ratios for malignancy of each of these factors were then multiplied to provide odds of malignancy, which are then converted into a percent probability of cancer (pCa). Three different management strategies are followed, depending on the calculated pCa. If the pCa is under 5 percent, careful observation with follow-up imaging is recommended; if the pCa is more than 60 percent, immediate resection of the nodule is warranted; if the pCa is between 5 and 60 percent, percutaneous needle aspiration biopsy is equal to or slightly preferable to resection. In a computerized neural network model that uses nonlinear mathematics to analyze input data, risk factors for malignancy were used and compared with the results of Bayesian analysis. The authors found that their neural network was not as accurate as Bayesian analysis in predicting malignancy.

One of the problems with these and other methods is the quality of the input data (i.e., the likelihood ratios), which may not be representative of all patient populations. In addition, Bayesian analysis presupposes that the likelihood ratios for a particular risk factor are not affected by the presence or absence of any other factor. It is not clear that this is true of the likelihood ratios. Therefore, although mathematical models to predict probability of malignancy may seem attractive, the complexity of the issue once again leaves us with an uncertain answer. This may explain why the described methods are not in widespread clinical use.

However, assessment of the pretest probability of malignancy is central to optimal strategy selection making when managing solitary pulmonary nodules. Although these formulas and neural networks may lack precision on an individual patient level, they can serve to inform decision making as to what risk factors to pay attention to and how important they are relative to each other. Risk factors associated with a low probability of malignancy include diameter less than 1.5 cm, age less than 45 years, absence of tobacco use, having quit for 7 or more years, and a smooth appearance on radiography. Risk factors associated with a moderately increased risk of malignancy include diameter 1.5 to 2.2 cm, age 45 to 59, smoking up to 20 cigarettes per day, being a former smoker within the last 7 years, or a scalloped edge appearance on radiography. Risk factors associated with a high risk of malignancy include a diameter of 2.3 cm or greater, age greater than 60 years, being a current smoker of more than 20 cigarettes per day, a history of prior cancer, and a corona radiate or spiculated appearance on radiography.

BIOPSY TECHNIQUES

The issue of whether it is useful to biopsy an indeterminate solitary pulmonary nodule and, if so, how to do it remains controversial. Most experts agree that in certain clinical circumstances, a biopsy procedure is warranted. For example, in a patient who is at high surgical risk, it may be useful in establishing a diagnosis and guiding decision making. If the biopsy reveals malignancy, it may convince a patient who is wary of surgery to undergo thoracotomy or thoracoscopic resection of a potentially curable lesion. Another indication for biopsy may be anxiety to establish a specific diagnosis in a patient in whom the nodule seems to be benign. Some chest physicians argue that all indeterminate nodules should be resected if the results of history, physical examination, and laboratory and radiographic staging methods are negative for metastases. Others argue that this last approach exposes patients with benign nodules to the risks of needless surgery. In such cases, a biopsy procedure sometimes provides a specific diagnosis of a benign lesion and obviates surgery.

Once it has been decided to biopsy a solitary pulmonary nodule, the choice of procedure is a matter of debate, but includes fiberoptic bronchoscopy, percutaneous needle

aspiration, thoracoscopic biopsy (usually with video assistance), and open thoracotomy.

BRONCHOSCOPY

Traditionally, bronchoscopy has been regarded as a procedure of limited usefulness in the evaluation of solitary pulmonary nodules. Studies have shown variable success rates, with an overall diagnostic yield of 36 to 68 percent, in nodules greater than 2 cm with bronchoscopic biopsy, brushings, and washings. In general, the yield for specific benign diagnoses has ranged from 12 to 41 percent.

For smaller nodules, the sensitivity of bronchoscopy is significantly worse. For example, for nodules larger than 2 cm in diameter, a sensitivity as high as 68 percent (average 55 percent) can be obtained. However, this dropped to 11 percent for nodules smaller than 2 cm. Location also matters: nodules located in the inner or middle one-third of the lung fields have the best diagnostic yield; nodules in the outer one-third have a much lower diagnostic yield and as such are probably best approached with percutaneous needle aspiration if biopsy is needed.

Another characteristic of solitary pulmonary nodules to consider when deciding on the role of bronchoscopy is the nodule's relation to neighboring bronchi (Fig. 103-6). Tsuboi and colleagues described four types of tumor–bronchus relationships: (1) the bronchial lumen is patent up to the tumor; (2) the bronchus is contained in the tumor mass; (3) the bronchus is compressed and narrowed by the tumor, but the bronchial mucosa is intact; and (4) the proximal bronchial tree is narrowed by peribronchial or submucosal spread of the tumor or by enlarged lymph nodes. The presence of types I and II, a bronchus leading to or contained within the body of a nodule or mass on HRCT, has subsequently been termed a *positive bronchus sign*. When a bronchus sign is present on HRCT, the diagnostic yield of fiberoptic bronchoscopy can be as high as 60 to 90 percent. With a negative bronchus sign, the yield drops to 14 to 30 percent. Signs and symptoms of airway involvement (cough, hemoptysis, localized wheezing), although rare in solitary pulmonary nodules, increases diagnostic yield when present.

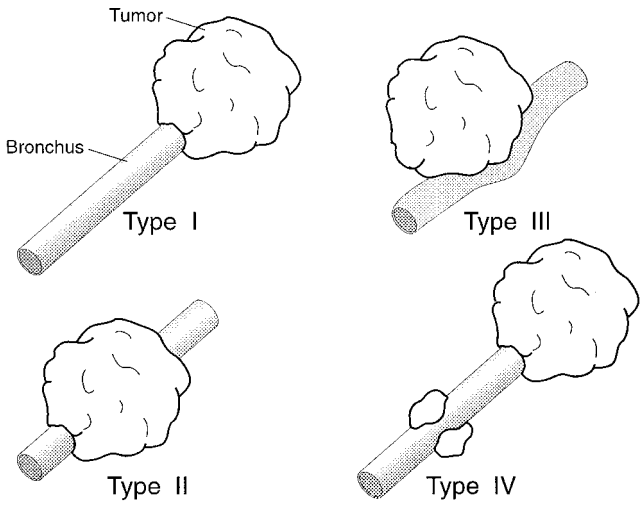

Figure 103-6 Schematic illustration of tumor–bronchus relationships (see text). *(Based on data of Tsuboi E, Ikeda S, Tajima M, et al: Transbronchial biopsy smear for diagnosis of peripheral pulmonary carcinomas.* Cancer *20:687–698, 1967.)*

After an extensive evidence based review of the various studies, it was concluded that bronchoscopy can play a role in the evaluation of the solitary pulmonary nodule under rare circumstances but that most of the time bronchoscopy is not the best choice. In those cases in which there is an air-bronchus sign, or in cases in which there are very central lesions abutting the large airways, bronchoscopy may be of use. Similarly, if there is a suspicion for unusual infections, such as tuberculosis or fungal infections, then bronchoscopy may be warranted. However, for most patients bronchoscopy does not play a major role. It should also be mentioned that routine preoperative staging bronchoscopy is of no value in asymptomatic patients with a solitary pulmonary nodule smaller than 3 cm because it has not been shown to alter management decisions.

Percutaneous Needle Aspiration

Percutaneous needle aspiration can be performed under fluoroscopic or CT guidance, the choice often depending on the availability and experience of the operator. It is most useful as the initial procedure in peripheral lesions, in the outer third of the lung, and in lesions under 2 cm in diameter. It can establish the diagnosis of malignancy in up to 95 percent of cases and can establish specific benign diagnosis (granuloma, hamartoma, infarct) in up to 68 percent of patients. The use of larger-bore biopsy needles—such as a 19 gauge, which provides a core specimen in addition to cytology—improves the yield for both malignant and benign lesions. The major limitation of percutaneous needle aspiration is its high rate of pneumothorax (10–35 percent overall); pneumothorax is more likely when lung parenchyma lies in the path of the needle (Fig. 103-7). Of these pneumothoraxes, 5 to 10 percent require drainage with a chest tube. Because of the high rate of pneumothorax and its possible complications, the following patients should not undergo percutaneous needle aspiration: those with limited pulmonary reserve (e.g., FEV_1 under 1 L); those with bullous emphysema or blebs in the needle path; and postpneumonectomy patients. Other general contraindications are: bleeding diathesis, inability to hold breath, and severe pulmonary hypertension. Bronchoscopy can sometimes be used when percutaneous needle aspiration is contraindicated. The two procedures can be used successfully in a complementary fashion.

THORACOTOMY AND THORACOSCOPY

Lobectomy using either open thoracotomy or video-assisted thoracoscopic surgery with lymph node resection and staging remain the standard of care for stage I bronchogenic

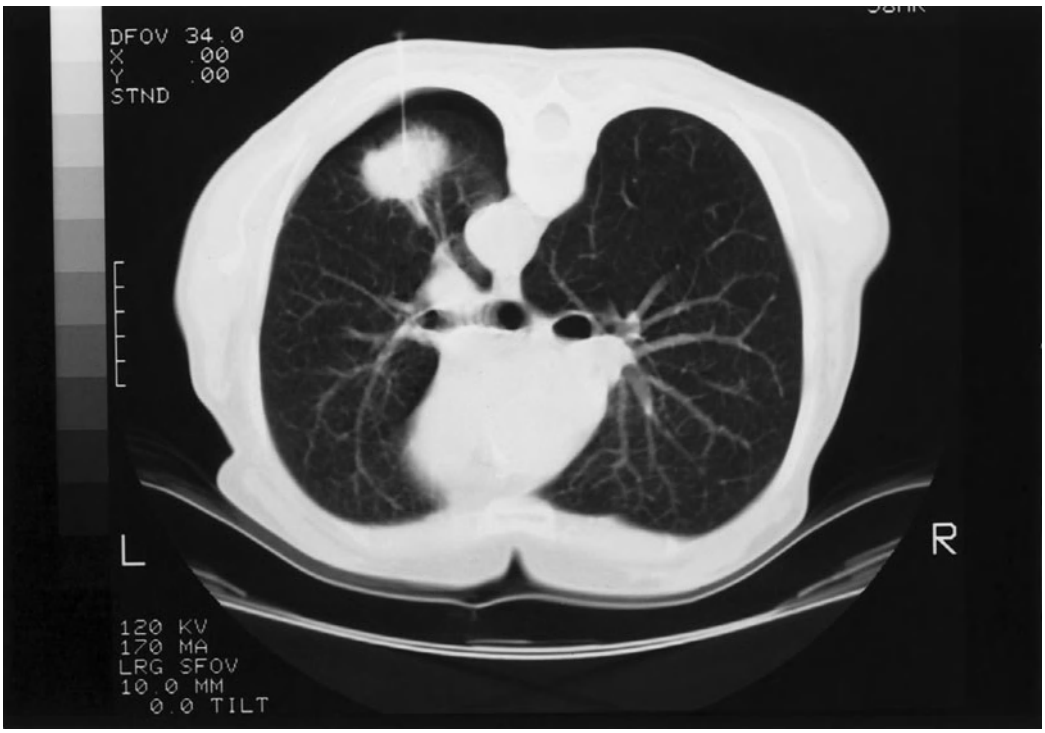

Figure 103-7 Malignant nodule during CT-guided aspiration showing development of pneumothorax.

carcinoma, the most common malignancy among solitary pulmonary nodules. Nodules greater than 3 cm in diameter have a more than 90 percent chance of being malignant, and in the face of a negative metastatic workup and adequate pulmonary reserve, indeterminate nodules of this size should be resected. Smaller nodules that remain indeterminate after appropriate radiographic evaluation and possibly biopsy (bronchoscopic and/or percutaneous needle aspiration where indicated) either can be resected or observed with close serial CT follow-up. The decision depends on the patient and physician, who must educate the patient on the alternatives and possible consequences.

Thoracotomy has a reported mortality of 3 to 7 percent. It is higher in patients over age 70 and those with malignancy. These patients usually have other coexisting illnesses, such as chronic obstructive pulmonary disease (COPD), and coronary artery disease. The mortality risk increases with the extent of the procedure. In one series by Ginsberg and coworkers, the mortality was 1.4 percent for wedge resection, 2.9 percent for lobectomy, and 6.2 percent for pneumonectomy. More recent observational studies of lung cancer surgery reported similar 30-day mortality rates. Of note, this study indicated that there may be a relationship between volume of surgeries performed and outcome. Hospitals that performed the highest volume of lung cancer surgeries had lower 30-day mortality than those that had the lowest volume (3 vs. 6 percent).

VATS uses fiberoptic telescopes and miniaturized video cameras to facilitate biopsies and resection. VATS represents a complementary approach to traditional thoracotomy and can be very useful in some patients. This approach still requires general anesthesia but does not require a full thoracotomy incision or spreading of the ribs. VATS allows the experienced surgeon to identify and wedge out peripheral nodules in many cases with minimal morbidity and mortality. In a series by Mack and colleagues, 242 nodules were resected with no mortality and minimal morbidity. Average hospital stay was 2.4 days. Video-assisted thoracic surgery can spare some patients with benign nodules the risks of open thoracotomy and can be useful for wedging out nodules in patients who have limited pulmonary reserve who cannot otherwise tolerate a lobectomy. However, in a significant percentage of cases conversion from VATS to a mini-thoracotomy is still required.

However resection is performed, whether by VATS or thoracotomy, lobectomy remains the procedure of choice for malignant solitary pulmonary nodules. Wedge excisions or segmental resections for smaller cancers have been evaluated, but the role of these limited pulmonary resections in the management of lung cancer remains controversial. The Lung Cancer Study Group evaluated this in a study of 276 patients with T1 N0 lesions that were strictly staged to prove N0 status. Patients were randomized to lobectomy or limited resection. In patients undergoing limited resection, there was an observed 75 percent increase in recurrence rates ($p = 0.02$, one-sided) attributable to an observed tripling of the local recurrence rate ($p = 0.008$ two-sided), an observed 30 percent increase in overall death rate ($p = 0.08$, one-sided), and an observed 50 percent increase in death with cancer rate ($p = 0.09$, one-sided) compared with patients undergoing lobectomy ($p = 0.10$, one-sided was the predefined threshold for statistical significance for this equivalency study). Because of the higher death rate and locoregional recurrence rate

associated with limited resection, lobectomy has been recommended as the surgical procedure of choice for patients with peripheral T1 N0 non-small cell lung cancer.

For patients with insufficient pulmonary reserve to tolerate a lobectomy, segmentectomy or wedge resection remains a viable alternative. In addition, whether or not very small malignant lesions, less than 2 cm in size, can be managed with segmentectomy, radiation, or some combination thereof, remains controversial and is the subject of ongoing research. At the present time, it is reasonable to recommend lobectomy for all patients with malignant solitary pulmonary nodules who have sufficient pulmonary reserve to tolerate the procedure, with consideration of segmentectomy for those patients with inadequate pulmonary function to tolerate a lobectomy.

DIAGNOSTIC APPROACH

As is often the case in medicine, it is unwise to presume that an infallible algorithm can be provided for the evaluation of all solitary pulmonary nodules. Since no consensus can be reached on the basis of available data, the best that can be done is to offer recommendations. The pathway to be taken and final decision rest on the individual physician and patient. Individual patient preferences also play a key role. A 30-year-old nonsmoker, the mother of two children, with an indeterminate lesion, may not be willing to "observe with serial CT scans" and demand a resection; in contrast, a 75-year-old smoker with mild COPD and a lesion that seems to be malignant may decide to leave well enough alone and ignore it. The following recommendations represent one possible approach to this complex clinical problem (Fig. 103-8).

1. On discovering a solitary pulmonary nodule, the clinician should determine whether it is a true solitary nodule, spherical, and located within the lung fields. CT imaging should be part of the initial evaluation.
2. A thorough history and physical may provide clues about the nodule's possible cause. (A history of tuberculosis in an asymptomatic patient suggests granuloma, whereas weight loss and adenopathy point toward malignancy.) Most of the time, solitary pulmonary nodules are asymptomatic. The history should include an assessment of risk factors for cancer, including smoking history, occupational exposures, exposure to endemic fungi, and any history of prior malignancy. Patient risk preferences should be obtained as part of the discussion.
3. If it is established that the nodule is truly solitary, and a benign pattern of calcification is present, the nodule is considered benign and no further workup is necessary. Follow-up with serial CT imaging may be warranted based on the size of the lesion and risk factors for cancer as described.
4. All prior chest radiographs and CT images should be obtained and compared with the present images.
   - If prior chest radiographs are available, and the nodule has remained unchanged for 2 years or longer, no further workup is necessary. Follow-up with serial CT imaging may be warranted if there is a concern for a slow-growing bronchioloalveolar cell carcinoma or there are other risk factors for cancer, as described.
   - If the nodule has grown and the doubling time is more than 20 days but less than 18 months, it is considered malignant and should be resected. If the doubling time is more than 18 months, consideration of a slow-growing bronchioloalveolar cell carcinoma or a carcinoid is warranted and, depending on the patient's preferences and surgical risk, a biopsy procedure may be useful to provide further reassurance to the patient. Alternatively, the nodule may be benign and close serial CT follow-up is also reasonable, perhaps every 2 to 3 months for the first year and every 6 months for the next year.
   - If old chest images are available but the nodule was not present on prior radiographs, an upper-limit doubling time is calculated. The assumption is made that a 0.8-cm nodule was present but not yet detectable in the last available radiograph, and the doubling time is then calculated. If the doubling time is again less than 18 months, it is considered to be malignant and resected. If the doubling time is more than 18 months, the nodule remains indeterminate. Nodules for which previous radiographs are unavailable are also indeterminate.
5. The physician should arrive at an estimate of the probability of malignancy based on the history, physical, and CT imaging characteristics.
   - Those with a low probability (less than 10 percent) of malignant disease, such as those that have been demonstrated to be stable on serial CXR for 2 years or more, have a characteristic benign calcification pattern, or are present in patients less than 35 years of age in the absence of other risk factors, can be observed with serial CT scans depending on their size. The follow-up would be as described, with surgery for those with evidence of progression.
   - Those with a high probability of malignant disease who are surgical candidates should be considered for staging followed by VATS/thoracotomy. Examples are a new nodule of large size in an older patient with a heavy smoking history and a spiculated pattern on CXR. Staging would include a PET scan plus investigation of any other symptoms. PET scanning in these instances is primarily to look for mediastinal and extrapulmonary disease, since 4 to 20 percent of patients without evidence of lymph node enlargement on CT have nodal or extrapulmonary disease. When the probability of

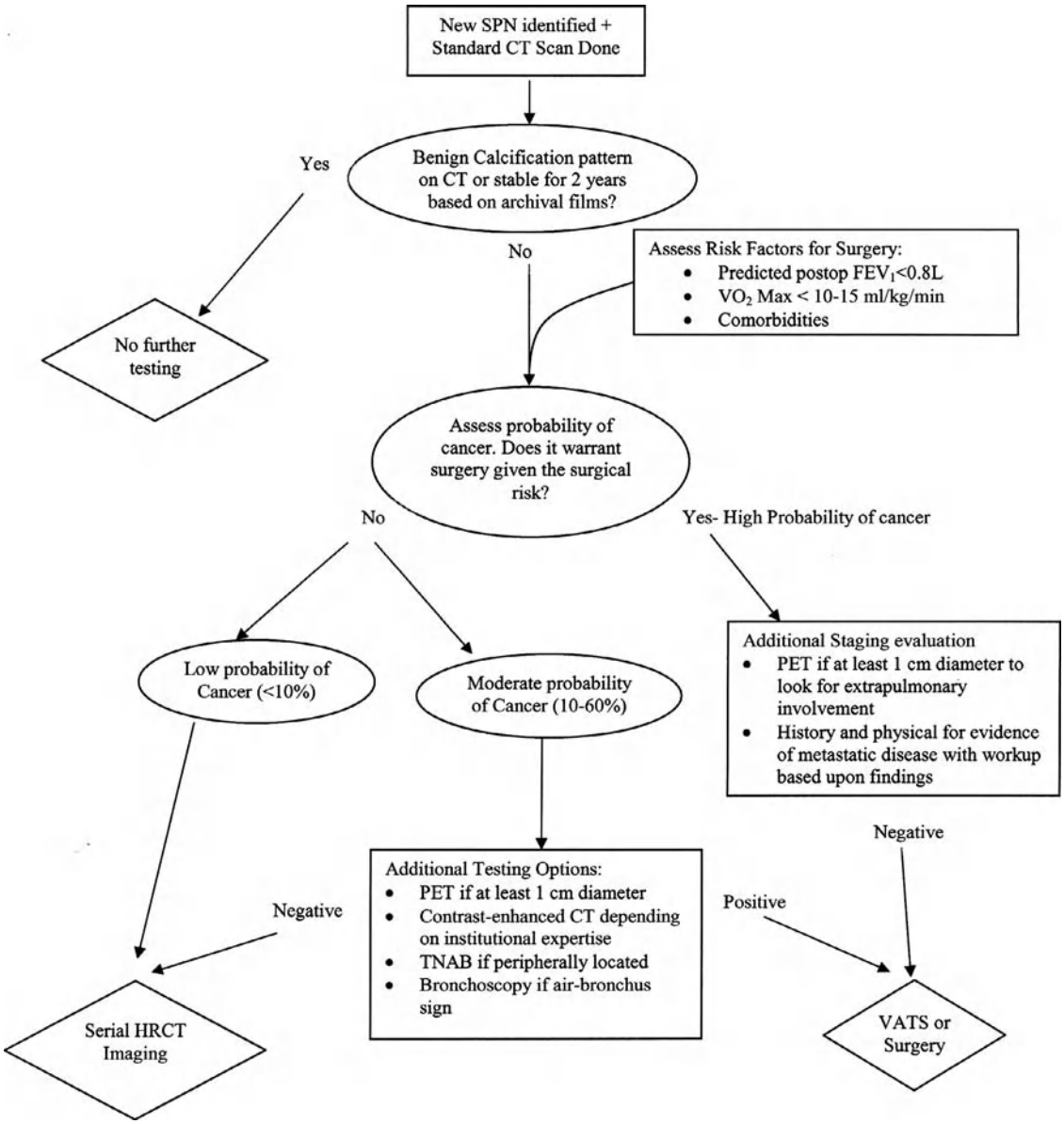

Figure 103-8 An approach to the solitary pulmonary nodule.

malignant disease is this high, even if the PET scan is completely negative, biopsy or resection is warranted. Note that PET in this instance is more of a staging tool (determine extent and respectability of cancer), rather than a diagnostic tool (determine whether or not there is cancer present).

- The third category, which many patients fall into, consists of those patients who are surgical candidates with nodules with a moderate probability (10–60 percent) of cancer. These nodules are considered indeterminate. After a standard evaluation including chest radiographs and CT scanning, 70 to 75 percent of nodules that remain indeterminate are malignant. The management of these nodules remains controversial. PET scanning for those with nodules measuring 1 cm or greater in size is warranted. Transthoracic fine-needle aspiration, bronchoscopy if there is an air-bronchus sign, or a contrast-enhanced CT are reasonable options. If the results are positive, then surgery is clearly warranted whereas a specific benign diagnostic result (example: core biopsy demonstrates hamartoma or bronchoscopy demonstrates tuberculosis) is usually sufficient to guide management. However, a nonspecific nondiagnostic result should be interpreted with caution. Depending on the patient's preferences, surgical risk, and probability of cancer, VATS/thoracotomy or careful follow-up CT imaging may be warranted.

6. The probability thresholds that define "low," "moderate," and "high" probability are not arbitrary but rather are determined by multiple factors, including

the patient's preferences, estimates of the effectiveness of surgery, the risks of surgery in those with and without disease, the long-term consequences of surgery, estimates of the hazard of delay, the patient's comorbidities, the range of alternative diagnostic tests and their performance characteristics (sensitivity and specificity), and the range of alternative treatments.

- "Low" probability in this case means that after considering all these factors, the probability of cancer is sufficiently low that the best strategy is careful observation with serial CT follow-up. "High" means that after consideration of all these factors, the best strategy is VATS/thoracotomy. "Moderate" means that one of the available diagnostic studies has sufficient discriminatory power to change what would be done in the absence of that test, either toward careful observation if the result is negative or surgery if the result is positive.
- Many decision analysis studies of solitary pulmonary nodules have been published over time, and the probability thresholds that define the low, moderate, and high probability groups vary among studies. In part, this is because the available technologies and treatments have changed over time, so these probability thresholds also vary over time. As new diagnostic and treatment alternatives become available, these thresholds need to be periodically reassessed. However, even if technology were unchanging, patient preferences vary significantly, so defining a single "optimal" answer is not feasible.
- Given these constraints, all of the decision analyses published are fairly consistent, with low probability being approximately 10 to 12 percent or less, and high probability being approximately 60 to 72 percent. However, these recommendations are just estimates. Their value lies not in their precision, but in the systematic approach that they promote and the recognition that careful assessment of the probability of cancer is critical to determining optimal strategy.

7. Noncalcified nodules greater than 3 cm and of indeterminate stability are likely to be malignant and should be resected if the patient has adequate pulmonary reserve and staging CT and PET imaging do not suggest mediastinal or distant metastatic disease. If there is no evidence of extrapulmonary disease but CT or PET suggest mediastinal nodal disease, bronchoscopy with transbronchial needle aspiration (with or without endobronchial ultrasound) is probably the most cost-effective initial approach. In select patients when the anatomic location makes it feasible, endoscopic ultrasound–guided aspiration is an alternative. If bronchoscopic transbronchial needle aspiration is non-diagnostic, mediastinoscopy is warranted. Importantly, enlarged lymph nodes (greater than 1 cm) on CT or a PET scan that shows nodal involvement is not sufficient to rule out surgery as an option; a biopsy should still be obtained in such instances to determine whether the patient does indeed have metastatic disease.

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The Pathology of Non–Small Cell Lung Carcinoma

Leslie A. Litzky

As a broad diagnostic category, non–small-cell lung carcinoma (NSCLC) comprises about 80 percent of all lung cancers. The World Health Organization (WHO) classification of lung tumors is the most frequently used system for categorizing these lung tumors. There have been two significant revisions of this classification in the intervening years since the 1981 revision and the previous edition of this book. Within the modified 2004 WHO classification, there are seven major categories of malignant non–small cell epithelial lung tumors (Table 104-1). Squamous cell carcinoma, adenocarcinoma and large cell carcinoma have traditionally been grouped as non–small cell lung carcinoma (NSCLC) in research studies and for treatment purposes. This practice is becoming less common as details about the biologic behavior and/or response to different therapeutic drugs emerge. This chapter focuses on these major histological subtypes, as well as carcinoid tumors, sarcomatoid carcinoma, and salivary gland tumors. Small cell carcinomas, as well as other unusual tumors, both benign and malignant, are covered in separate chapters.

THE 1999 AND 2004 WORLD HEALTH ORGANIZATION CLASSIFICATION OF LUNG TUMORS—MAJOR REVISIONS

Pathologic assessments are continually refined to reflect changes in surgical and medical management, as well as to incorporate an improved understanding of basic tumor biology. Once the diagnosis of malignancy has been made, the pathologic evaluation of non–small cell carcinoma has typically focused on histological subtyping and determining the extent of disease. Histological classification is essentially

Table 104-1

WHO Classification of Malignant Epithelial Non–Small-Cell Lung Tumors

Major Subtype	Variants
Squamous cell carcinoma	Papillary Clear cell Small cell Basaloid
Adenocarcinoma	Adenocarcinoma, mixed type Acinar adenocarcinoma Papillary adenocarcinoma Bronchioloalveolar carcinoma Solid adenocarcinoma with mucin production
Adenosquamous carcinoma	
Large cell carcinoma	Large cell neuroendocrine carcinoma Basaloid carcinoma Lymphoepithelioma-like carcinoma Clear cell carcinoma Large cell carcinoma with rhabdoid phenotype
Sarcomatoid carcinoma	Pleomorphic carcinoma Spindle cell carcinoma Giant cell carcinoma Carcinosarcoma Pulmonary blastoma
Carcinoid tumor	Typical carcinoid Atypical carcinoid
Salivary gland tumors	Adenoid cystic carcinoma Mucoepidermoid carcinoma Epithelial-myoepithelial carcinoma

SOURCE: *Data from Travis WD, Brambilla E, Muller-Hermelink, HK, et al: Tumours of the Lung, in Travis WD, Brambilla E, Muller-Hermelink HK, et al (eds),* Pathology and Genetics of Tumours of the Lung, Pleura, Thymus and Heart. *WHO Health Organization Classification of Tumours, vol 10. Lyon, France, IARC Press, 2004.*

predicated on the assumption that the quantitative predominance of a particular histological pattern reflects distinctive biologic characteristics. There remains great expectation that developments in other disciplines such as molecular biology may have a profound impact on tumor categorization, as well as on prognosis and treatment. Whether basic research in molecular biology and other fields will substantiate or modify the currently accepted histological classification is an actively debated question. The 1999 revisions introduced significant changes in the classification and nomenclature of malignant epithelial lung tumors from the previous 1981 WHO classification. These changes reflected the substantial amount of pathologic observation and translational research that had ensued in the intervening eighteen years. The 2004 revision made some minor changes in nomenclature but preserved the overall classification scheme that had been established in 1999. Major changes in the 1999 revision included the introduction of new variants of squamous cell carcinoma, adenocarcinoma, and large cell carcinoma, as well as new or refined definitions for bronchioloalveolar carcinoma and solid adenocarcinoma. The 1999 revisions also incorporated the long anticipated consensus on neuroendocrine tumor nomenclature and classification criteria as well as consensus on biphasic and pleomorphic tumor nomenclature and classification criteria. Although it is beyond the scope of this chapter, it is worth noting that 1999 WHO revisions also added and defined two other preneoplastic processes—atypical adenomatous hyperplasia (AAH) and diffuse idiopathic neuroendocrine cell hyperplasia (DIPNECH)—to the previously recognized squamous dysplasia/carcinoma in situ. Finally, it should be recognized that in some circumstances, notably bronchioloalveolar carcinoma and carcinoid tumors, the 1999/2004 revisions require a very detailed histological examination of a resected specimen for definitive diagnosis.

The 2004 WHO classification of lung tumors was the first edition to extensively summarize the molecular biology of different tumor subtypes. Nevertheless, the main purpose of the current 2004 WHO classification, as in previous editions, is to provide reproducible criteria to pathologists worldwide by using recognizable architectural patterns and individual cellular features that can be appreciated by routine light microscopy and standard hematoxylin and eosin stained slides. The use of ancillary techniques, such as immunohistochemistry or molecular biology, is not required in most instances, thereby making the classification accessible to all pathologists for diagnosis and for fostering consistency in treatment and research protocols. Although this approach might be open to some criticism, it should be noted that the incorporation of data from ancillary studies such as immunohistochemistry or molecular has broad implications, not the least of which is the expense of the laboratory tests, which would require additional time, special equipment, and technical expertise. Criteria for the interpretation of some of these tests have yet to be well defined and it will only be possible to address definitively the clinical significance of these markers within the confines of prospectively designed, large clinical studies with standardized laboratory analysis and rigorous follow-up.

GENERAL CONSIDERATIONS IN HISTOLOGICAL CLASSIFICATION

Tumor classification and associated generalizations pertaining to tumor type are often made to seem relatively

straightforward but, in practice, it is always a challenge for any proposed scheme of histopathological classification to ensure the reproducible recognition of tumor subtypes. In order to understand some of these difficulties in lung tumor subclassification, it is worth recalling that all of the epithelial tissues in the lung are derived from an endodermal outpouching lined by a single layer of cuboidal cells that in turn differentiate to form the many different epithelial lining cell types and secretory cells. It is therefore not surprising that many epithelial tumors show a mixture of different cell types at both the light microscopic and ultrastructural level. This overlap extends to the presentation of antigens and cell products. As is often true of any classification scheme, distinctions can be somewhat arbitrary and before proceeding to a general discussion of histological subtypes, it is also appropriate to consider the factors that led to variability or lack of specificity in the classification of lung tumors. Roggli outlines two different aspects of variability in his analysis. As mentioned, one component is that of histopathological variability within a particular tumor due to divergent pathways of differentiation. It is well recognized that lung cancers frequently show histologic heterogeneity and that almost 50 percent of lung carcinomas exhibit more than one of the major histological types. A second component is that of interobserver or intraobserver variation in the application of a particular histopathological classification scheme. Factors that affect interobserver/intraobserver variability, in both published studies and in general practice, include the extent of tumor sampling and the field-to-field variation, the source of the material (i.e., biopsy vs. surgical vs. autopsy), the number of observers, the number of cases studied, and the manner in which the cases are evaluated. In an older study that looked at diagnostic consensus, overall interobserver agreement was obtained in 76 percent of cases. Consensus was best for small cell carcinomas (72.5 percent), intermediate for adenocarcinomas and squamous cell carcinomas (56 and 48 percent, respectively), and very poor for large cell carcinomas (about 5 percent). Agreement was also quite poor for further tumor subtyping within a specific tumor type such as bronchioloalveolar carcinoma within adenocarcinoma. It should be noted that this study was published prior to the major criteria revisions in the 1999 WHO classification, some of which were specifically aimed at improving consensus in subtype diagnoses such as bronchioloalveolar carcinoma.

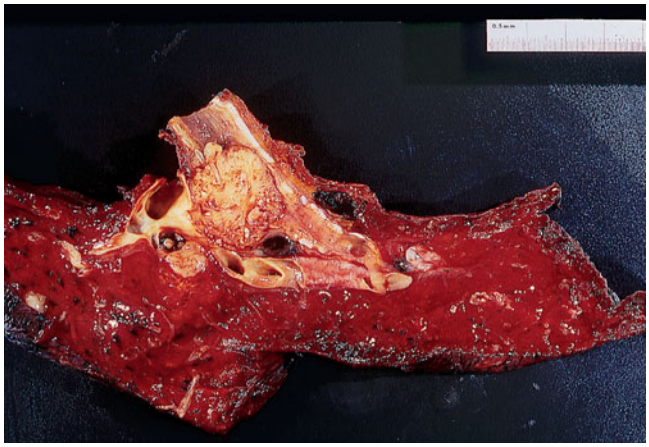
The practical impact of this variability is the resultant discrepancy that occurs occasionally between the cytologic and surgical pathological diagnosis or the final findings at autopsy. Recognition of histological heterogeneity depends to a great extent on sampling techniques that may, in turn, have implications for protocol design and prognosis. Similarly, interpretative disagreements following a second review do arise and should be viewed with appropriate circumspection as to clinical significance. In one study of lung cancer heterogeneity, there was no significant difference in survival between patients with homogeneous, as compared with heterogeneous tumors, when differences in stage were considered. The interobserver agreement for small cell carcinoma is also worth noting and underscores the fact that lung tumor heterogeneity may confound a clear-cut pathologic distinction between non–small cell and small cell carcinoma. From a therapeutic point of view, the recognition of any small cell component has significant clinical relevance, but interpretative disagreements as to whether the tumor is a combined small cell carcinoma or a pure small cell carcinoma may not.

Lung carcinomas are classified according to the best differentiated component, and pathologists assign a degree of differentiation to tumors that show differentiation, such as squamous cell carcinoma and adenocarcinoma. This is also known as histological grading and it is an assessment as to how much the tumor cells phenotypically resemble a normal cell type, such as a squamous cell or a glandular cell. Histological grading should not be viewed as a histogenetic determination, i.e., that a tumor is derived from a specific cell of origin, such as a squamous cell, or that the tumor cell has "dedifferentiated" from a cell of origin. There are three histological degrees of differentiation: well differentiated, moderately differentiated, and poorly differentiated. As a group, lung cancers tend to be poorly differentiated, but many lung tumors show a wide variation in differentiation. Even if a tumor is largely undifferentiated but contains focal squamous cell carcinoma or adenocarcinoma, it would be classified as a poorly differentiated squamous cell carcinoma or adenocarcinoma. It is not clear that reporting precise percentages in terms of areas of well, moderate, and poor differentiation improves prognostic accuracy. Some tumors, such as small cell carcinoma or sarcomatoid carcinoma, are poorly differentiated by definition.

SQUAMOUS CELL CARCINOMA

Adenocarcinoma replaced squamous cell carcinoma as the leading lung cancer cell type among both men and women in the United States by the 1990s. Nevertheless, this histological subtype of squamous cell carcinoma is still very strongly correlated with cigarette smoking and is seen more commonly in men. About two-thirds of squamous cell carcinomas occur centrally, where involvement of a mainstem, lobar, or segmental bronchus may be demonstrated (Fig. 104-1*A*). As would be expected from an endobronchial growth pattern, squamous cell carcinomas frequently are associated with bronchial obstruction and postobstructive pneumonia. Cavitation is seen more frequently in squamous cell carcinoma than in the other histological subtypes (Fig. 104-1*B*). Squamous cell carcinomas may also present as a peripheral nodule and there is some recent evidence to suggest that the proportion of peripheral squamous cell carcinomas is increasing in at least some populations (Fig. 104-1*C*).

By the 1999/2004 WHO classification, squamous cell carcinoma is defined as a malignant epithelial tumor showing keratinization and/or intercellular bridges. Keratinization may be in the form of squamous pearls or individual cells with



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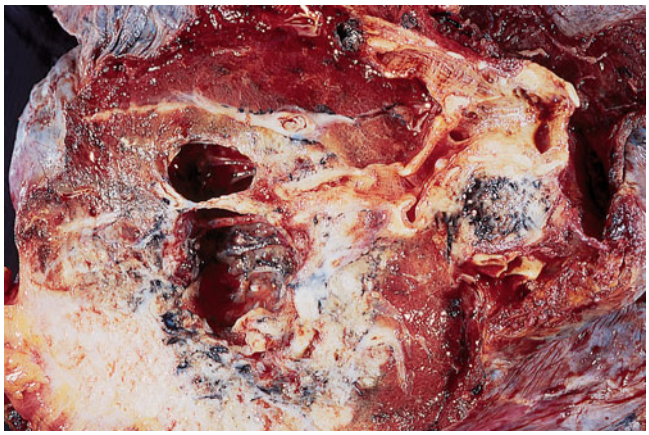

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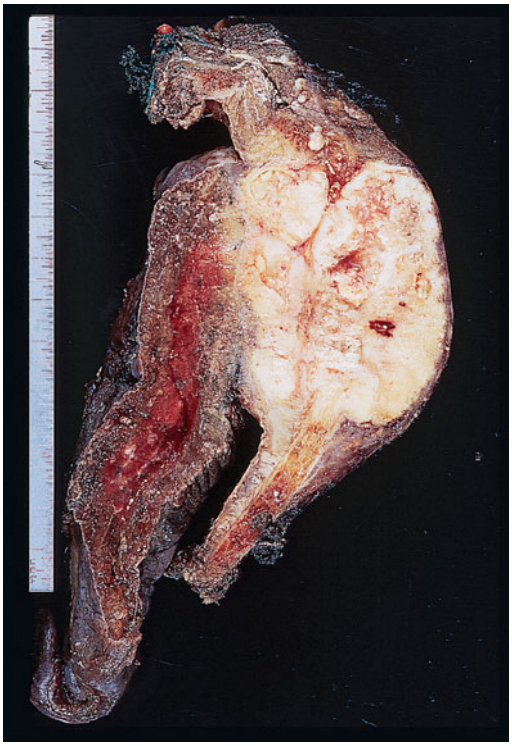


C

Figure 104-1 *A*. Large endobronchial squamous cell carcinoma with atelectasis and obstructive pneumonitis. *B*. Cavitation within a squamous cell carcinoma. *C*. Right upper lobectomy with chest wall resection for squamous cell carcinoma.

dense eosinophilic cytoplasm. Intercellular "bridges" are seen in paraffin sections due to cell shrinkage caused by fixation and correspond to the desmosomal attachments that can be appreciated ultrastructurally (Fig. 104-2 *B* and *C*). A desmoplastic (i.e., fibrotic) response is often associated with the invasive nests of tumor cells (Fig. 104-2 *A*). As noted with the other histological types, squamous cell carcinomas often show significant areas of histological heterogeneity. There are four histological variants with the 1999/2004 WHO classification of squamous cell carcinoma: papillary, clear cell, small cell, and basaloid patterns. On occasion, a tumor may consist entirely of one of these variants, but it is more common for these patterns to be focal. A familiarity with these variant patterns is useful for the practicing pathologist, but at the current time there is no evidence that these variant patterns have any clinical significance. The *papillary variant* is characterized by an exophytic growth pattern and papillary cores. The classic tumor cells of a squamous cell carcinoma are large and polygonal with eosinophilic cytoplasm, but in the *clear cell variant*, as the name suggests, cells with clear cell cytoplasm can be seen (Fig. 104-2*D*). In the basaloid variant, the nests of tumor cells have prominent peripheral palisading and have less cytoplasm toward the periphery, but the more centrally located cells have more obvious keratinization. In the *small cell variant* of squamous cell carcinoma, the tumor cells are relatively smaller and can have granular nuclear chromatin, but there is some chromatin variation with more coarse or vesicular chromatin and prominent nucleoli. A careful search shows cytoplasmic evidence of squamous differentiation in the form of focal keratinization or intracellular bridges.

Although not invariably demonstrated, it is easiest to identify a trend in tumor progression with this histological subtype. Sampling of a resected specimen typically shows changes in the adjacent bronchial mucosa ranging from squamous metaplasia to dysplasia to carcinoma in situ. If identified, the presence of an in situ component helps to differentiate a primary squamous cell carcinoma from a metastatic lesion. At the present time, there is no other conclusive means of differentiating a primary pulmonary squamous cell carcinoma from a metastasis, but there is a tendency for metastatic tumors from the head and neck to be better differentiated (i.e., show more extensive keratinization) than their primary pulmonary counterparts.

Electron microscopy demonstrates the presence of tonofilaments and desmosomes in squamous cell carcinomas.

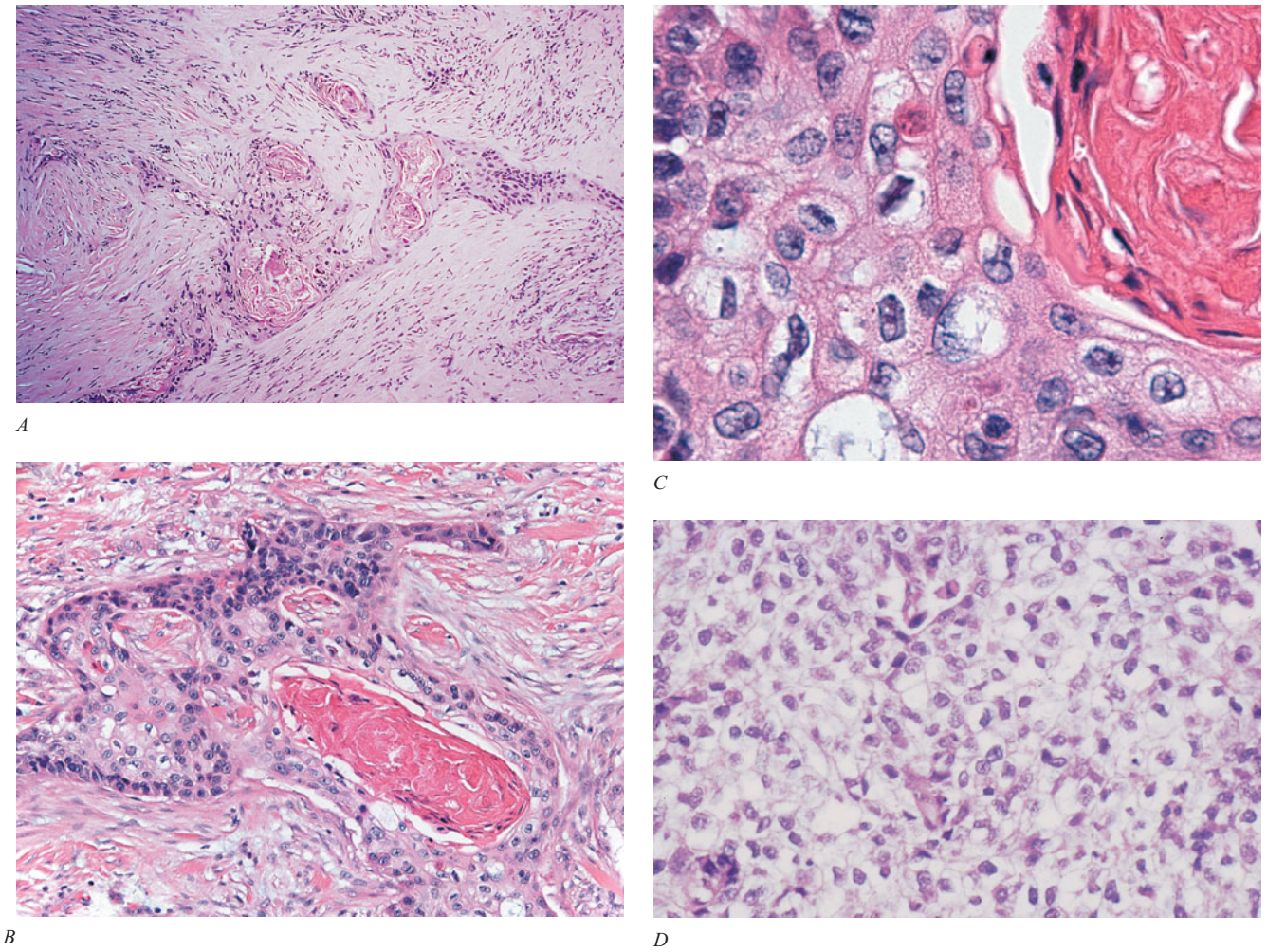


Figure 104-2 *A*. Desmoplastic response with nests of infiltrating squamous cell carcinoma (H&E, 200×). *B*. Squamous cell carcinoma with keratinization and intracellular bridges (H&E, 200×). *C*. High power view of keratinization and intercellular bridges (H&E, 400×). *D*. Tumor cells with clear cytoplasm from a squamous cell carcinoma (H&E, 400×).

However, these findings are non-specific and may also be present in adenocarcinomas. There continues to be a considerable amount of active research focused on an immunohistochemical panel or a molecular profiling technique that would reliably distinguish a primary squamous cell carcinoma of the lung from other primary sites.

ADENOCARCINOMA, INCLUDING BRONCHIOLOALVEOLAR CARCINOMA

Within the United States, epidemiologic studies have now demonstrated that adenocarcinoma is the most frequently diagnosed histological type of lung cancer. Adenocarcinoma is also the most frequently diagnosed subtype in women, as well as in non-smokers, although most patients with adenocarcinoma are smokers. It is generally believed that most likely explanation for the increased proportion of adenocarcinoma among smokers relates to the shift to low-tar filter cigarettes during the 1960s and 1970s.

A majority of adenocarcinomas arise in the periphery of the lung and are typically associated with puckering of the overlying pleura or parenchymal scarring (Fig. 104-3). It was initially assumed that all these lesions represented a tumor arising in an area of preexisting fibrosis. A number of studies subsequently challenged this view and presented various lines of evidence to support the hypothesis that the scarring represents a desmoplastic response to the tumor. It is likely that both observations are correct and that the etiology of the tumor-associated fibrosis depends on the clinical circumstances. There are well-documented cases of adenocarcinoma occurring in patients with diffuse pulmonary fibrosis, remote infarcts, tuberculomas, and within emphysematous bullae.

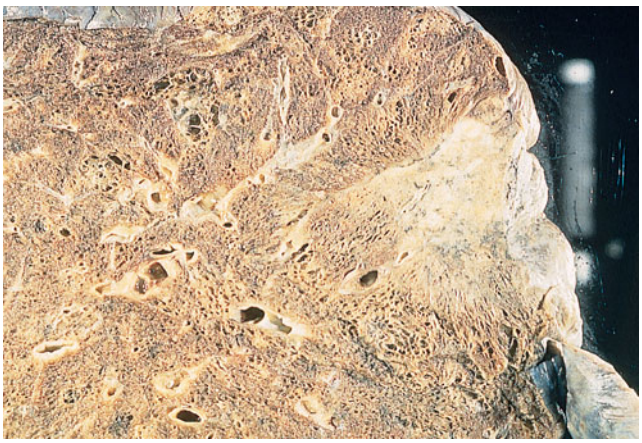


Figure 104-3 Peripheral adenocarcinoma of the lung with pleural puckering.

The histological appearance of adenocarcinomas is extremely diverse and this histological heterogeneity presents a significant problem when the differential diagnosis includes metastasis or malignant mesothelioma. In addition, this histological heterogeneity has always made reproducible subclassification with primary pulmonary adenocarcinomas extremely difficult. Small adenocarcinomas (typically less than 2 cm) are more likely to consist of one histological pattern, but even small adenocarcinomas can contain more than one histological subtype. This practical problem was to a great extent resolved by the 1999 WHO revision, which introduced, for the first time, a *mixed* subtype, to the four previously recognized subtypes of *acinar, papillary, bronchioloalveolar,* and *solid.* The 1999/2004 WHO classifications also recognize five relatively uncommon variants: *fetal adenocarcinoma, mucinous ("colloid") carcinoma, mucinous cystadenocarcinoma, signet ring adenocarcinoma,* and *clear cell adenocarcinoma.*

Acinar adenocarcinomas consist of irregularly contoured but nonetheless recognizable glandular structures and are often associated with a desmoplastic stroma (Fig. 104-4*A* and *B*). The *papillary variant* is illustrated in Fig. 104-4*C*. The presence of cytoplasmic vacuoles suggests the *solid variant* of adenocarcinoma, which then may be confirmed by a special stain for mucin (Fig. 104-4*D*). The 1999/2004 WHO classification requires that be there five or more mucin-positive cells in at least two high-power fields for the diagnosis of *solid adenocarcinoma with mucin production.* This criterion was adopted because it is not uncommon for squamous cell or large cell carcinomas to have focal mucin droplets. By definition, given the solid pattern of the tumor, solid adenocarcinomas are poorly differentiated. Some of the other rare variants such as signet ring carcinomas and cystic mucinous tumors resemble other solid organ malignancies and may be very difficult to distinguish as primary lung cancers.

The distinction between peripheral adenocarcinomas with extensive pleural involvement, diffuse carcinomatous involvement of the pleura by metastatic tumor, and malignant mesothelioma may be problematic. Some carcinomas grow in a manner virtually identical to malignant mesothelioma, with extensive pleural involvement and limited parenchymal invasion. Clinically, radiographically, and macroscopically, these tumors are indistinguishable from malignant pleural mesothelioma. The histological appearance may be equally confusing, requiring the use of immunohistochemical stains.

A strict definition for bronchioloalveolar carcinoma (BAC) was adopted in the 1999 revision and retained in the 2004 revision. The definition requires that the tumor have a pure lepidic growth pattern without evidence of stromal, vascular, or pleural invasion. The term "lepidic" means that the proliferation of tumor cells should line the alveolar walls in a uniform manner, using the alveolar walls as a supporting stroma. It should be noted that prior to the 1999 revision, pathologists widely varied in their assessments, with some allowing for more histological variability in the definition. Adenocarcinomas with a minor, usually central, and often more poorly differentiated glandular component along with a peripheral bronchioloalveolar pattern are frequently encountered. In instances in which the peripheral BAC component predominated, it had been a common practice to designate the tumor either as a BAC or an "adenocarcinoma with a BAC pattern." This term of "adenocarcinoma with a BAC pattern" should be avoided and the current WHO nomenclature should be adhered to, whatever its shortcomings. The stricter definition prevailed in the revisions because of studies that demonstrated that small (less than 2.0 cm) solitary tumors with a pure lepidic growth pattern had a 100 percent 5-year survival. Although it is true that this strict definition has improved the reproducibility of the diagnosis, application of the criteria, specifically defining stromal invasion, are still somewhat problematic in practice. Many adenocarcinomas have areas of fibrosis due to alveolar wall collapse or septal fibrosis. This is not considered to be true invasion, but this assessment can be difficult. Histological criteria for true invasion include single cell infiltration, a fibromyxoid stromal response, high-grade cytology, and a cribriform or acinar growth pattern. Some experts have suggested the use of elastic or trichrome stains to help highlight parenchymal disruption but consensus protocols for finding and defining invasion—other than submitting the entire lesion for histological examination—have not yet been published. A second issue is what to do about tumors with areas of focal or "minimal" invasion, which are now subsumed under the "mixed" subtype of pulmonary adenocarcinomas. There are a number of studies that have argued for a quantitation of the lepidic growth pattern and the area of invasion within these mixed adenocarcinomas. Some of these studies have focused on a cutoff of less than 5 mm of invasion as a way of defining a "minimally invasive adenocarcinoma." However, a consensus on the clinical meaning of this type of minimal invasion, how to accurately and reproducibly measure it, how significantly it affects an individual patient's prognosis, and whether there

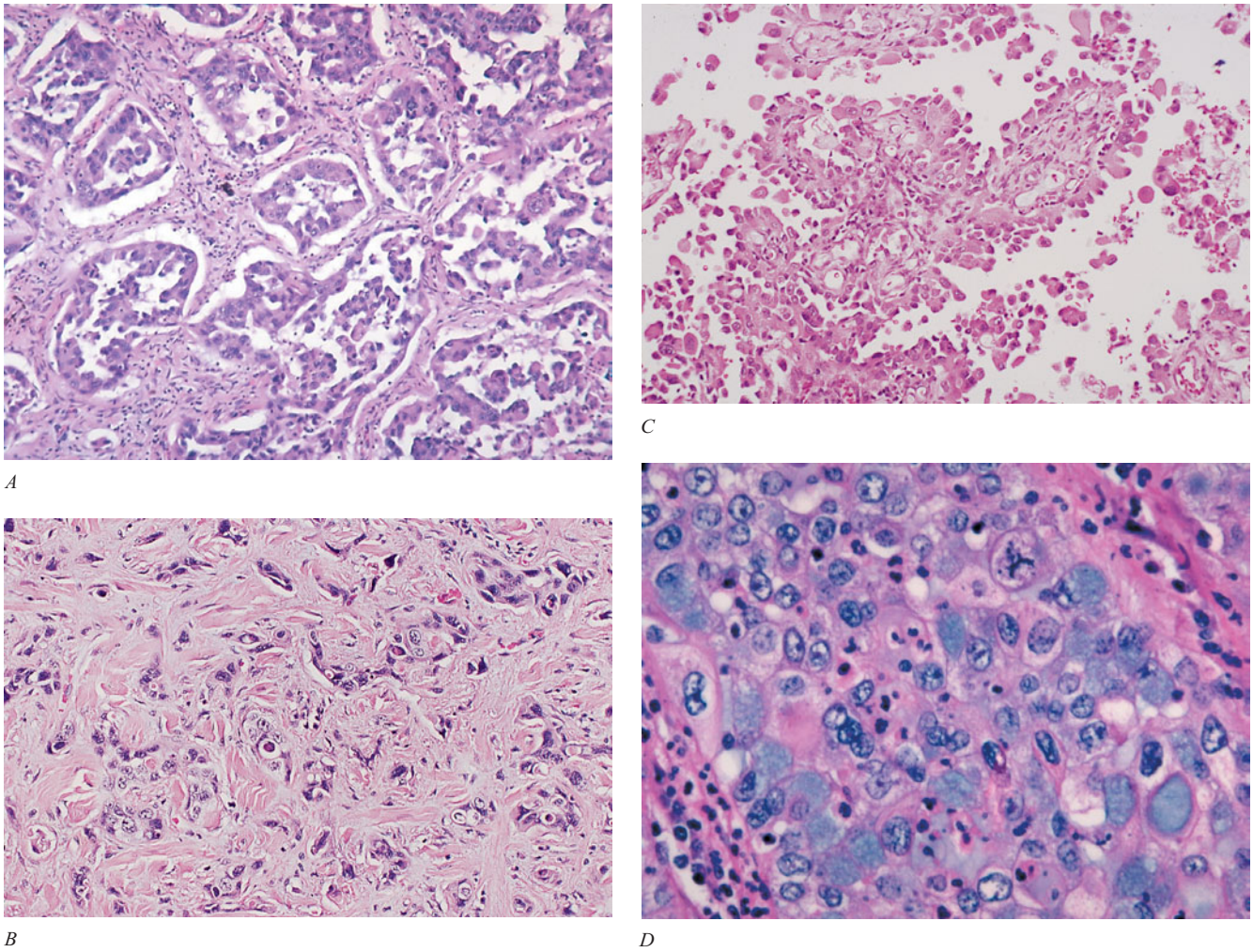
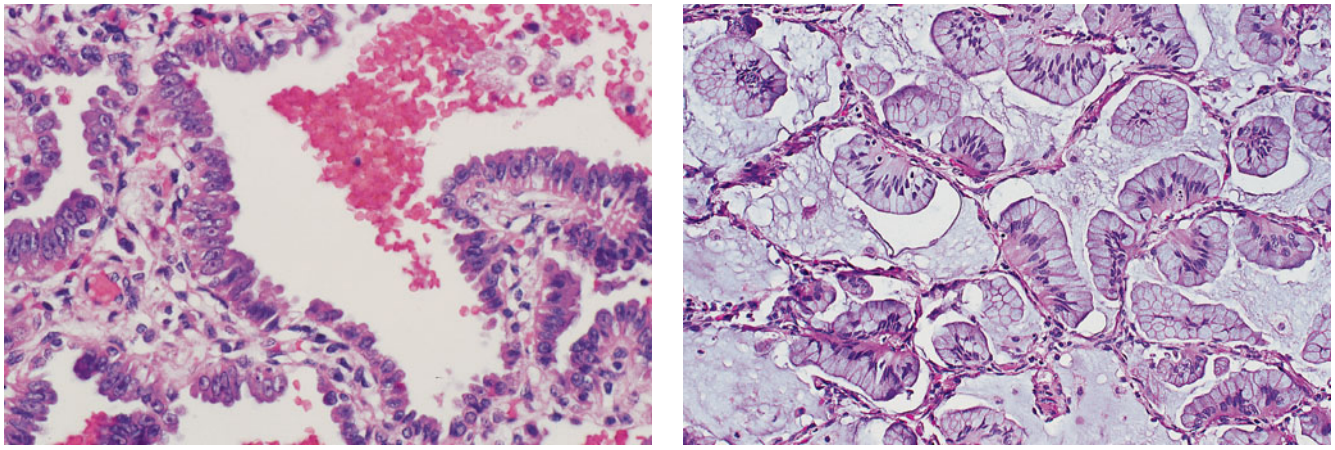


Figure 104-4 *A*. Moderately differentiated adenocarcinoma, acinar pattern, with recognizable gland formation (H&E, 200×). *B*. Poorly differentiated adenocarcinoma, acinar pattern. Within the desmoplastic stroma, the tumor forms occasional small, irregularly shaped glands with mucin vacuoles (H&E, 400×). *C*. Adenocarcinoma, papillary pattern. Malignant cells are arranged on the surface of fibrovascular cores (H&E, 400×). *D*. Adenocarcinoma, solid growth pattern with mucin production (H&E, 400×).

is any geographic variability in these outcomes has not been clearly established. Another issue is how to classify patients for treatment purposes when they have had a very small sampling of their tumor—either by bronchial washings, transbronchial biopsy, or fine needle procedures. It is clear that the final diagnosis of BAC can only be rendered on a full histological examination of the resection specimen. For smaller samplings, it is recommended that the diagnosis be stated as "adenocarcinoma, possible bronchioloalveolar carcinoma," but this leaves opens the issue of clinical management in patients who will not undergo resection. This uncertainty may be problematic as more specific treatment protocols for specific tumor subtypes are introduced, unless some compromise, possibly using radiographic correlation, is made.

Histologically, BACs are divided into two major subtypes: *nonmucinous* and *mucinous*. A rare *mixed nonmucinous and mucinous* or *indeterminate* subtype is also recognized in the 1999/2004 revisions. The more common nonmucinous type consists of cuboidal, columnar, or so-called "hobnail" cells with apical nuclei (Fig. 104-5*A*). The mucinous type shows goblet cell differentiation, i.e., tall columnar cells with abundant apical pale mucinous cytoplasm and basally located nuclei (Fig. 104-5*B*). Other mucinous carcinomas, particularly of pancreatic ovarian origin, may metastasize to the lung and grow in a bronchioloalveolar pattern. It has become increasing apparent that the two cell types do have some distinctive clinical and radiographic correlations. The pure ground-glass opacities without a solid component that are now commonly detected on high resolution CT scans and that prove to be a tumor on resection are strongly correlated with the non-mucinous subtype. Most solitary BACs are also of the non-mucinous type. A diffuse pneumonic infiltrate has a significantly worse survival when compared with unifocal and multifocal patterns. The mucinous subtype



A *B*

Figure 104-5 *A*. Bronchioloalveolar carcinoma, non-mucinous type. Malignant cells uniformly line thickened alveolar septa. *B*. Bronchioloalveolar carcinoma, mucinous type. Tall columnar cells with abundant mucinous cytoplasm line the alveolar septa (H&E, 400×).

is more frequently associated with this diffuse pneumonic pattern.

The ultrastructural appearance of adenocarcinomas can be quite heterogeneous but electron microscopy can still be useful in some problematic cases. In contrast to malignant mesotheliomas, which have long microvilli, these cells have short, uniform microvilli and prominent rootlets with a fuzzy glycocalyx. As discussed in the general section on immunohistochemistry, there are multiple antibodies that will stain adenocarcinomas of the lung. Many of these antibodies (CEA, MOC31, B72.3, LeuM1, and BerEP4) recognize glycoproteins and are not specific for the lung. Clara cell antigen and surfactant apoprotein antibodies are commercially available but have limited diagnostic utility. Until relatively recently, it was believed that TTF-1 was specific for lung and thyroid, but there is now evidence that this antibody stains a wider variety of tumors. The sensitivity of TTF-1 staining is also quite variable depending on the adenocarcinoma subtype. For example, TTF-1 stains a much lower percentage of mucinous bronchioloalveolar carcinomas.

ADENOSQUAMOUS CARCINOMA

This tumor consists of well-defined squamous carcinoma and adenocarcinoma components, with each component comprising at least 10 percent of the whole tumor. The areas of glandular and squamous differentiation may be located in different areas of the tumor or may be intimately admixed. In the past, different criteria had been used for this histological subtype and these differences in definition, in addition to its low incidence, have made it extremely difficult to compare survival rates with other non–small cell carcinomas. The SEER data show an overall 21 percent 5-year survival rate. The current 1999/2004 WHO criteria of 10 percent should foster more uniformity in future studies.

LARGE CELL CARCINOMA

Large cell carcinomas account for a little less than 10 percent of all lung cancers. Large cell undifferentiated carcinoma (LCC) is defined in the 1999/2004 WHO classification as "an undifferentiated malignant epithelial tumor that lacks the cytologic features of small cell carcinoma and glandular or squamous differentiation". The cells typically have large nuclei, prominent nucleoli, and a moderate amount of cytoplasm (Fig. 104-6). As is evident from this description, this tumor is defined more by what it is not than what it is; therefore, for all practical purposes, it is a diagnosis of exclusion. The practical implication of this definition is that the diagnosis of LCC, as with BAC, requires examination of the entire tumor to rule out areas of squamous or glandular differentiation. The

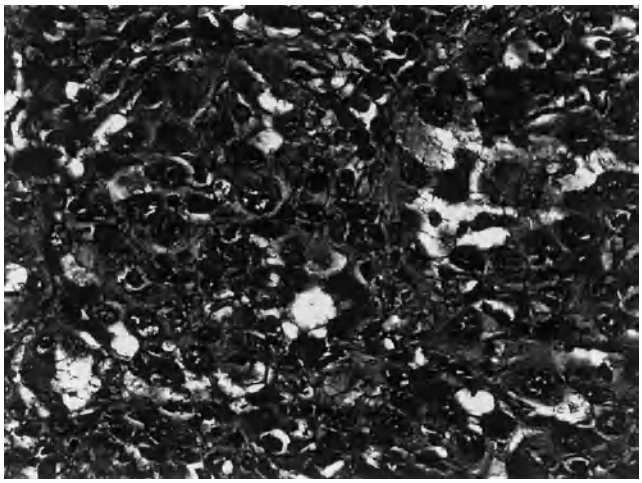
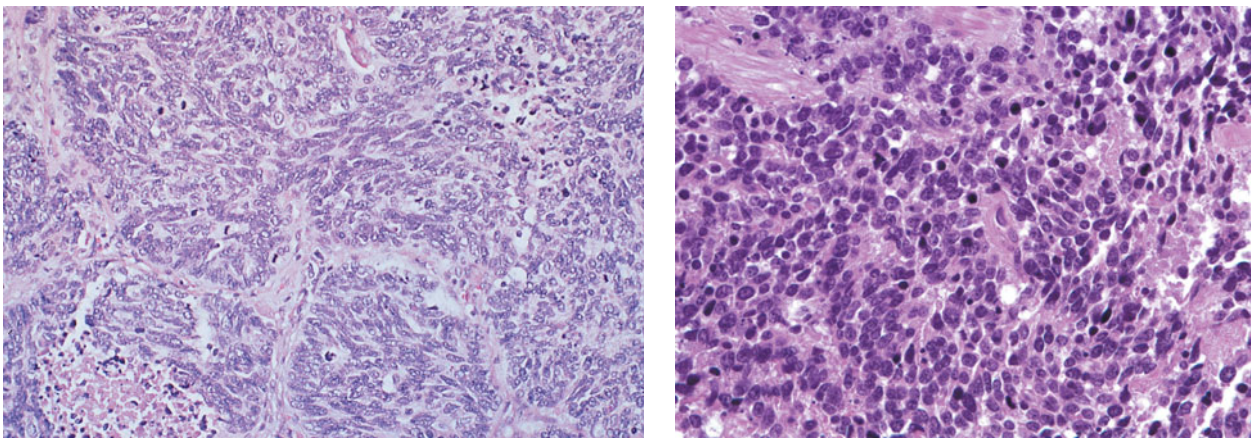


Figure 104-6 Large cell carcinoma of the lung. There is no obvious squamous differentiation in the form of keratinization or intercellular bridges and a mucin stain was negative (H&E, 400×).

WHO criteria are based on conventional microscopy, the occasional use of mucin stains, and the required use of immunohistochemistry for one variant (large cell neuroendocrine carcinoma). On electron microscopy, many large cell carcinomas show focal ultrastructural features consistent with adenocarcinoma or a poorly differentiated squamous cell carcinoma. Melanoma and malignant large cell lymphomas also can mimic large cell carcinoma, typically requiring the use of immunohistochemistry to exclude these diagnoses. The major change in the 1999/2004 revisions was to expand the number of variants included within the category of large cell carcinoma and transfer others, namely giant cell carcinoma and spindle cell carcinoma, into the sarcomatoid carcinoma category. The large cell carcinoma variants include *large cell neuroendocrine carcinoma, combined large cell neuroendocrine carcinoma, basaloid carcinoma, lymphoepithelioma-like carcinoma, clear cell carcinoma, and large cell carcinoma with rhabdoid phenotype.*

Large Cell Neuroendocrine Carcinoma of the Lung

Large cell neuroendocrine carcinoma (LCNEC) is defined as "a large cell carcinoma showing histological features such as organoid nesting, trabecular, rosette-like and palisading patterns that suggest neuroendocrine differentiation and in which the latter can be confirmed by immunohistochemistry or electron microscopy" (Fig. 104-7*A*). The cells are relatively large in size, often polygonal in shape, with moderate to abundant cytoplasm. The nuclear chromatin ranges from vesicular to finely granular. Nucleoli are frequent and often prominent (Fig. 104-7*A*). The presence of nucleoli tends to be a critical feature in the separation from small cell carcinoma (Fig. 104-7*B*) but some LCNECs lack this criterion. Mitoses should be greater than 10 mitoses/10 high power fields. As mentioned previously, neuroendocrine differentiation must be demonstrated by ancillary techniques such as immunohistochemistry. Chromogranin and synaptophysin are the two stains that are most frequently used and are considered to be more specific that neuron-specific enolase (NSE). In order for a tumor to be designated as an LCNEC, the tumor must have both neuroendocrine morphology and positive staining. Tumors that otherwise look like squamous cell carcinomas, adenocarcinomas, or large cell carcinomas but have focal neuroendocrine staining have been termed "non–small cell lung carcinoma with neuroendocrine differentiation" (NSCLC-ND). Although this designation appears in the literature, particularly in studies that have sought to determine whether NSCLC-ND has a worse prognosis or differs in its response to chemotherapy, it is actually not formally part of the WHO classification. In 1991, Travis and coworkers first proposed criteria for this entity, which was considered to be histologically distinct from other tumors with neuroendocrine differentiation such as atypical carcinoids or small cell carcinoma. A great deal of controversy ensued over the following decade and continues to some extent. One controversy, which centered around the reproducibility of the diagnosis of LCNEC as well as other neuroendocrine tumors, was addressed by a study that demonstrated substantial agreement, at least among experienced lung pathologists. In this study, a majority consensus diagnosis was achieved for 50 percent of the cases of LCNEC, which is no worse than other categories of lung tumors. The second controversy focused on the clinical significance of the diagnosis, particularly in relationship to small cell carcinoma. It has been very clear from multiple studies that both tumors are aggressive and have a very poor prognosis. From an epidemiologic perspective, both tumors are associated with heavy tobacco use, both tumors share a loss of Rb and both tumors can occur in combination with other non–small cell lung cancers. *Combined large*



A *B*

Figure 104-7 *A*. Large cell neuroendocrine carcinoma. The tumor cells are arranged in large organoid nests with numerous mitoses and necrosis (H&E, 200×). *B*. Comparison of large cell neuroendocrine carcinoma (left) with small cell carcinoma (right) at same magnification. The large cell neuroendocrine cells are larger, with a lower nuclear-cytoplasmic ratio, and the chromatin is coarsely granular (H&E, 400×).

cell neuroendocrine carcinoma refers to a large cell neuroendocrine carcinoma with components of another non–small cell carcinoma such as, for example, squamous cell carcinoma or adenocarcinoma.

Basaloid Carcinoma of the Lung

In the 1999/2204 WHO revisions, pure primary basaloid carcinoma of the lung is considered to be a variant of large cell carcinoma. The basaloid histological features in lung carcinomas are similar to those also seen in other extrapulmonary sites such as the head and neck or cervix. Basaloid cells are typically described as relatively small monomorphic cuboidal to fusiform cells with moderately hyperchromatic nuclei, finely granular chromatin, absent or focal nucleoli, scant cytoplasm, and a high mitotic rate. Intercellular bridges and/or individual cell keratinization should not be present. The tumor cells are usually arranged in lobular, trabecular or palisading growth patterns (Fig. 104-8). Since these types of histological patterns can also be seen in neuroendocrine tumors, immunohistochemical stains for neuroendocrine markers should be negative or extremely focal. These tumors are reported to be consistently positive for cytokeratin 903 as well as negative for TTF-1. Unlike the other variants of large cell carcinoma that are more likely to occur as peripheral tumors, basaloid carcinomas usually develop in proximal bronchi and have a central endobronchial component. About 50 percent of cases have associated carcinoma in situ. If the basaloid component is less than 50 percent and combined with a non–small carcinoma such as squamous cell carcinoma, the tumor is classified as squamous cell carcinoma (basaloid variant).

Other Variants of Large Cell Carcinoma

Lymphoepithelial-like carcinomas are extremely rare in the United States but represent 1 percent of all lung cancers in China. The histological features in lung carcinomas are similar to those also seen in other extrapulmonary sites such as the head and neck. Large malignant cells with prominent nucleoli are arranged in nests within a lymphoid-rich stroma. Epstein-Barr virus EBER-1 RNA has been demonstrated to be present in the large tumor cells. The *clear cell carcinoma variant* consists of a pure clear cell carcinoma without evidence of squamous or glandular differentiation. *Pure large cell carcinoma with rhabdoid phenotype*, i.e., a large cell carcinoma with cells showing prominent eosinophilic cytoplasmic globules, is extremely rare.

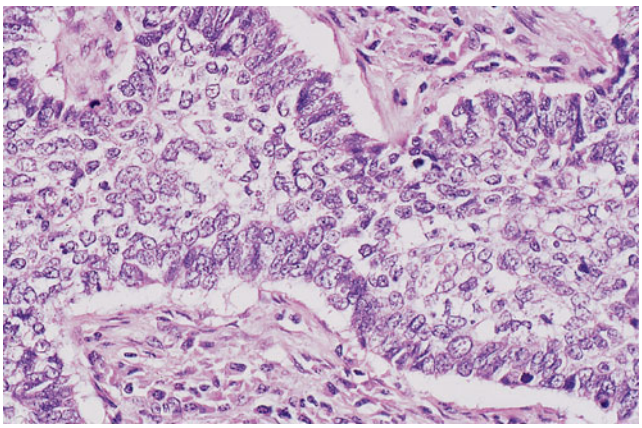


Figure 104-8 Basaloid carcinoma of the lung. The tumor cells are relatively small with hyperchromatic nuclei and scant cytoplasm. Note the tendency of the tumor cells to palisade at the periphery of the tumor nest (H&E, 400×).

SARCOMATOID CARCINOMA

Tumors that have sarcoma-like elements such as malignant spindle or giant cells or have a sarcomatous component that consists of a neoplastic but differentiated connective tissue phenotype such as neoplastic bone, cartilage, and striated muscle have been described in many primary organ sites, including the lung. The proliferation of terms in past literature and even the variations in nomenclature that have characterized revisions in the WHO classification have generated a disproportionate degree of confusion when compared with the actual incidence of these relatively rare lung tumors. Various terms in the literature have included spindle cell carcinoma, sarcomatoid carcinoma, carcinosarcoma, pleomorphic carcinoma, giant cell carcinoma, and pulmonary blastoma. The 1999 revision established a minimum requirement of 10 percent for certain elements, such as spindle cells or giant cells, for a tumor to be appropriately classified. The most recent 2004 WHO revision has settled on the term *sarcomatoid carcinoma* to categorize these tumors, which are by definition poorly differentiated non–small cell carcinomas that have a histological appearance that suggests mesenchymal differentiation. The current variants of sarcomatoid carcinoma include *pleomorphic carcinoma, spindle cell carcinoma, giant cell carcinoma, carcinosarcoma,* and *pulmonary blastoma.* It is now accepted that these variants are merely the phenotypic variations that can occur within the spectrum of epithelial-derived lung tumors. Careful sampling of these tumors usually demonstrates an identifiable component of squamous cell carcinoma, adenocarcinoma, or large cell carcinoma. The rarity of these tumors and previous confusion in terminology have made it difficult to characterize clinical characteristics and outcome. These tumors have no distinguishing radiologic features and have been reported in both central and peripheral locations. With the exception of pulmonary blastoma, which appears to be most frequent in the fourth decade and occurs equally in women and men, the other variants occur primarily in men in the sixth and seventh decade and have the same general association with tobacco use as other more common lung tumors. In a large series that was based on current WHO criteria and was analyzed according to stage, sarcomatoid carcinomas had a worse prognosis than conventional non–small cell carcinomas at surgically curable stage I.

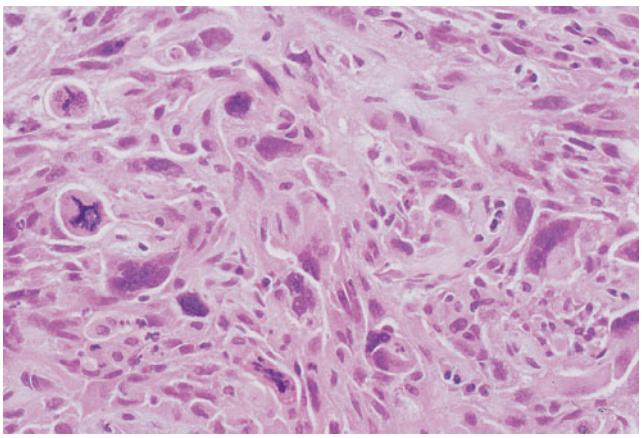


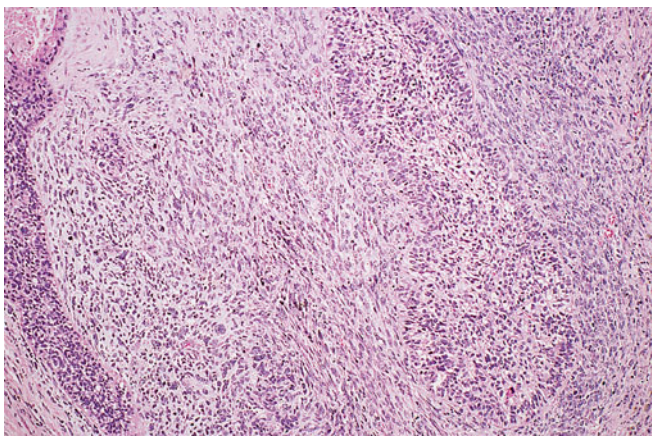
Figure 104-9 Pleomorphic carcinoma of the lung. The spindle cell and giant cell component in this large cell carcinoma comprise at least 10 percent of the tumor (H&E, 400×).

Pleomorphic carcinoma is defined as a poorly differentiated non–small cell carcinoma containing spindle cells and/or giant cells. As mentioned, the spindle cell and/or giant cell component should comprise at least 10 percent of the tumor (Fig. 104-9). *Spindle cell carcinoma* and *giant cell carcinoma* are terms that are reserved for the extremely rare instance in which the tumor is shown to consist entirely of spindle cells or giant cells, respectively. In the pathology literature, tumors that contain cells with a neoplastic but differentiated connective tissue phenotype are said to have "heterologous elements." *Carcinosarcoma* refers to a lung tumor that has recognizable heterologous elements such as rhabdomyosarcoma, osteosarcoma, or chondrosarcoma (Fig. 104-10*A* and *B*). Rather than terminology, the more significant issues confronting the pathologist are exclusion of metastasis from another site and avoiding the misdiagnosis of a primary pulmonary sarcoma.

Pulmonary blastoma is a biphasic tumor that contains a primitive epithelial component that resembles well-differentiated fetal adenocarcinoma and a primitive mesenchymal stroma, which occasionally has foci of osteosarcoma, chondrosarcoma, or rhabdomyosarcoma. The term pulmonary blastoma had been used historically to describe tumors that have been reported in all age groups. Manivel et al. argued that the childhood intrathoracic tumor was a distinct clinicopathologic entity that differed from the adult type, particularly in the absence of a carcinomatous component and its variable anatomic location. They proposed the alternate nomenclature of *pleuropulmonary blastoma* for these pediatric tumors, which occur almost exclusively in children of 6 years of age or younger, and this has been preserved in the 1999/2004 WHO revisions as a distinctly separate entity in the classification of soft tissue tumors. *Pulmonary blastoma* mainly occurs in adults. Although uncommon, pulmonary blastomas composed exclusively of embryonal-like epithelial and mesenchymal elements do occur. Adult tumors consisting entirely of malignant primitive glandular epithelium have also been described and are termed fetal adenocarcinomas, a variant of adenocarcinoma. Pulmonary blastomas have a histologically distinct, more embryonic appearance resembling fetal lung, with primitive cellular stroma and distinctive "endometrioid"-type glands (Fig. 104-11*A* and *B*).

CARCINOID TUMORS

Pulmonary carcinoid tumors represent about 1 to 5 percent of all lung malignancies. The 1999/2004 WHO revisions recognize two distinct subtypes of well-differentiated neuroendocrine tumors, typical carcinoid tumor and atypical carcinoid tumor. Both tumors are recognized by their low-power architectural pattern and characteristic cytologic features that are familiar to pathologists and are similar in appearance to carcinoid tumors that occur in other primary sites such as the gastrointestinal tract. However, in contrast to the term "well-differentiated neuroendocrine carcinoma" that is gaining in



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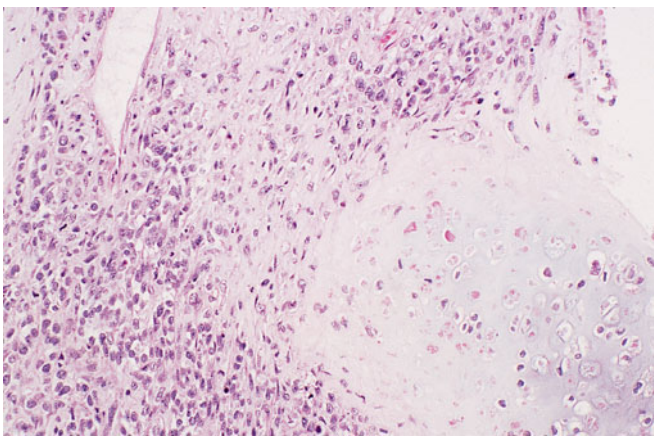
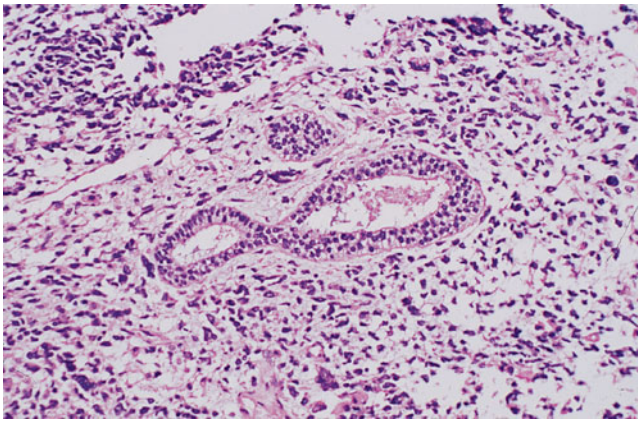


B

Figure 104-10 *A*. Carcinosarcoma showing a mixture of sarcoma (center) and carcinoma (periphery) (H&E stain, 100×). *B*. Same tumor with focus of histologically malignant cartilage (H&E stain, 200×).



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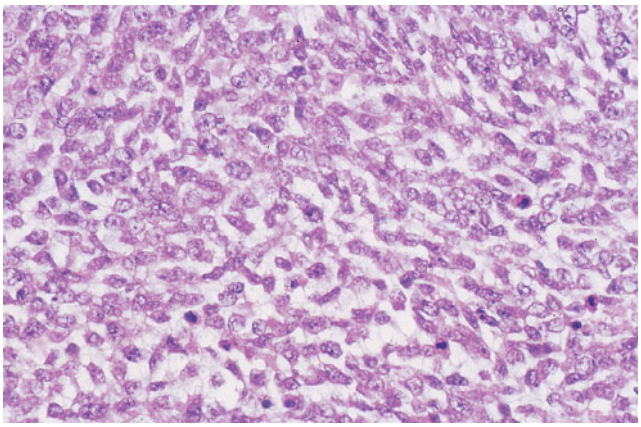


B

Figure 104-11 *A*. Pulmonary blastoma, showing a characteristic endometrioid-type gland, composed of cells with clear cytoplasm and basally oriented nuclei (H&E, 200×). *B*. Malignant stroma in a pulmonary blastoma (H&E, 400×).

popularity in extrapulmonary sites, carcinoid tumor has been retained in lung tumor classification because of its familiarity to clinicians and because of the well-established clinical behavior associated with the terminology. In the intervening years between the 1981 WHO revisions and the 1999/2004 revisions, there was a significant amount of debate regarding the diagnostic criteria for these lesions, the most appropriate nomenclature, and their clinical behavior within the broader context of pulmonary neuroendocrine tumors. It has been intellectually appealing to try to view neuroendocrine tumors as a continuous spectrum, with carcinoid tumors at one end and small cell carcinoma, as an aggressive tumor with neuroendocrine differentiation, at the other end. Numerous research studies have suggested that this is likely not the case and it is best to regard each tumor as a unique entity with set diagnostic criteria and a generally predictable clinical course. As will become clear in the discussion of these tumors that follows, it may be impossible to separate an atypical carcinoid from a typical carcinoid tumor on the basis of a small biopsy specimen. This distinction should not affect initial surgical management but it may significantly impact on subsequent prognosis.

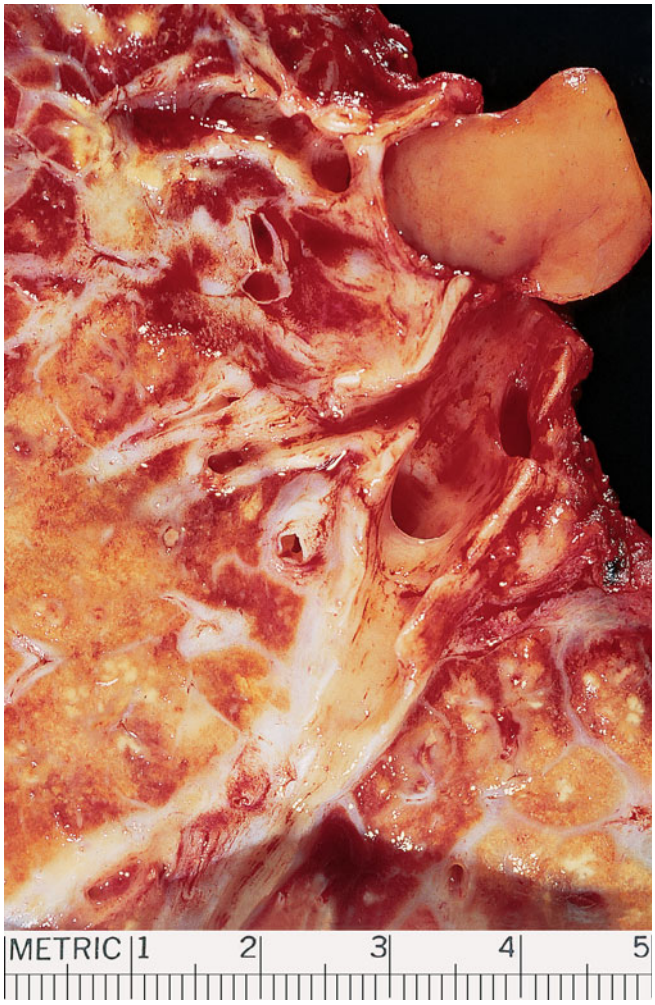
Typical Carcinoid

Typical carcinoid tumors can be divided into central and peripheral variants. Both variants can be asymptomatic but central carcinoids, which characteristically grow as an endobronchial mass, may present clinically with recurrent pneumonias or hemoptysis. There is a roughly equal incidence among males and females, with a wide age range at presentation. Typical carcinoid tumors are not associated with tobacco use, but there is a rare association with MEN1 syndrome. The association of bronchial carcinoid tumors with carcinoid syndrome is extremely unusual and typically occurs in the presence of widespread metastatic disease. Cushing's syndrome due to ectopic production of ACTH is similarly rare.

Central carcinoids grossly appear as yellow or fleshy, polypoid masses (Fig. 104-12). The tumor usually has a significant exophytic endobronchial component but the tumor can infiltrate between cartilaginous rings to extensively involve the bronchial submucosa. The tumor cells form diverse patterns such as organoid nests, trabeculae, insular islands, ribbon, or rosette-like arrangements. Carcinoids can also have papillary, sclerosing, follicular, and glandular patterns. The tumor cells are generally uniform in appearance and have a low nuclear:cytoplasmic ratio with round to oval nuclei and eosinophilic cytoplasm (Fig. 104-13). The tumor cells have characteristic neuroendocrine tumor chromatin that is finely granular or classically described as "salt and pepper."

Peripheral carcinoids are frequently subpleural and can be associated with a scar (Fig. 104-14*A*). Unlike the cells of central tumors, which are usually round or polygonal in shape, the tumor cells of peripheral carcinoids tend to have prominent spindle cell features (Fig. 104-14*B*). These fusiform cells have less cytoplasm than central tumors, but this feature should not be considered a sign of atypia. There is a subset of patients with one or more peripheral carcinoid tumors who have multiple tumorlets (small neuroendocrine cell proliferations less than 0.5 cm) and diffuse idiopathic pulmonary neuroendocrine cell hyperplasia (DIPNECH). In these patients, it is believed that the neuroendocrine cell hyperplasia represents a preneoplastic condition. The most significant complication for this subset of patients is airway fibrosis, which can progress to severe obstructive lung disease and require lung transplantation.

The pathologic attributes of these tumors have been examined in numerous histological, immunohistochemical, and molecular studies. The only consistent prognostic indicators have proved to be mitotic rate and necrosis. The current 1999/2004 WHO criteria for the diagnosis of carcinoid tumor require fewer than 2 mitoses per 10 high-power fields of viable tumor and no necrosis. Cytologic atypia, increased cellularity, and lymphovascular invasion are not predictive features. Although carcinoid tumors have an excellent prognosis with reported 5-year survival rates of 87 to 100 percent, it is critical to understand that typical carcinoids are low-grade but malignant tumors. Hilar and mediastinal lymph



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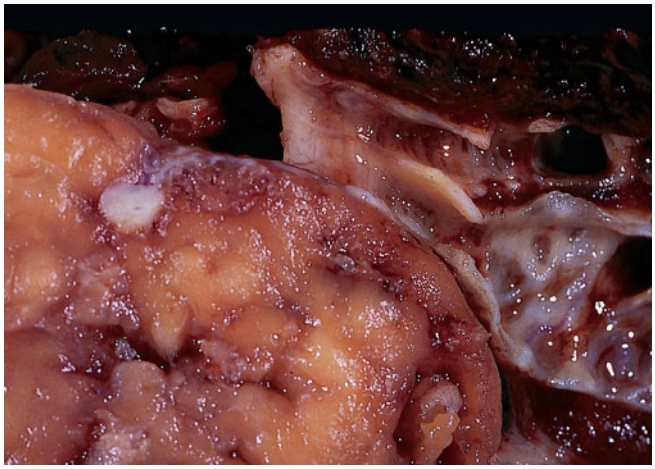

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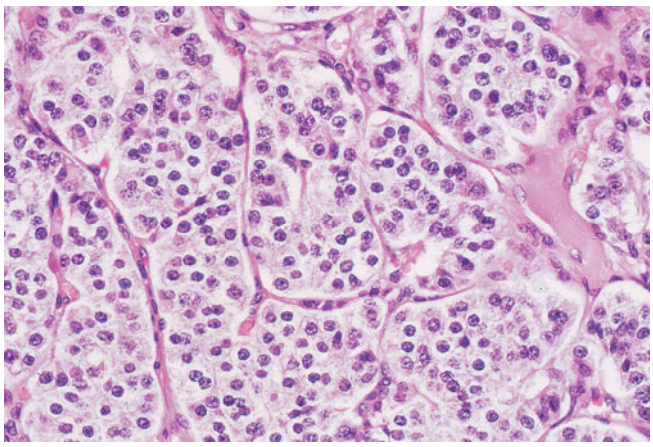
Figure 104-12 *A*. Large endobronchial carcinoid. *B*. Endobronchial carcinoid. Grossly, the tumor is yellow, fleshy, and vascular.

node metastases occur in 5 to 10 percent of cases, but do not necessarily indicate a poor prognosis. There are currently no histological characteristics that reliably predict which typical carcinoid tumors will behave more aggressively and go on to develop systemic disease.

Atypical Carcinoid

The term "atypical carcinoid" was first introduced by Arrigoni et al. in 1972. Twenty-three tumors were described that appeared to have a general resemblance to carcinoid tumors but that also had a focally disorganized growth pattern, areas of tumor necrosis, increased mitoses, and cellular pleomorphism. Dissension was immediately generated by the use of the word "atypical," given the aggressive biologic behavior in their series with 30 percent dead of disease at 3 years, a 70 percent incidence of metastases, and a mean survival of 27 months. Many other terms were introduced into the literature in the 1980s as more published reports detailing this entity appeared. Other terms used include malignant carcinoid, well-differentiated neuroendocrine carcinoma, peripheral small cell carcinoma of lung resembling carcinoid tumor, and Kulchitsky cell carcinoma II. The tumors described in these papers have been a heterogeneous group. This is in, in part, due to the subjective interpretation of features such as "architectural distortion." In defending atypical carcinoids as a distinct clinicopathologic entity, Travis et al. emphasized that the overall architecture should be that of a recognizable carcinoid tumor with a predominantly organoid growth pattern. Following numerous studies, the most reliable criteria for the reproducible diagnosis of these tumors and separation of typical carcinoid from atypical carcinoid proved to be mitotic rate and necrosis. In the 1999/2004 WHO revisions, an atypical carcinoid tumor is defined as a carcinoid tumor with between two and 10 mitoses per 10 high-power fields and/or with foci of necrosis. The necrosis in these tumors is usually punctate (Fig. 104-15) and one should be careful to exclude the possibility of a large area of necrosis that is secondary to a previous needle biopsy. Although cytologic atypia, lymphovascular invasion, nucleoli, increased cellularity, and disorganized architecture may be seen, these features are not a part of the classification system. In published reports of this entity, the gender distribution and age at presentation overlap with that of typical carcinoids. Like



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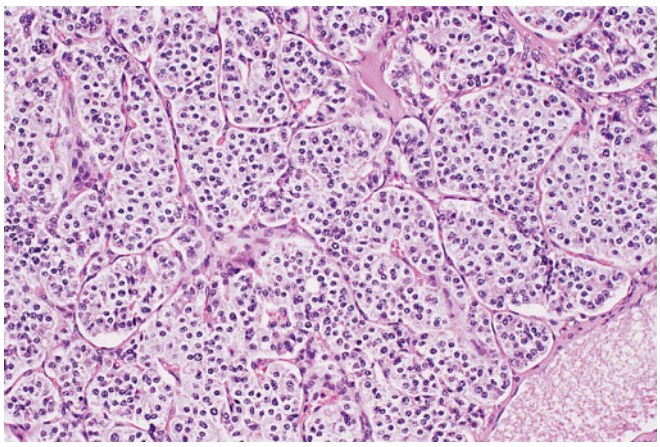

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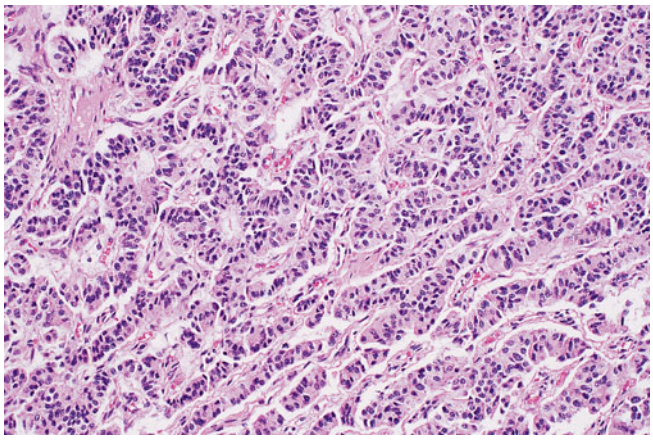
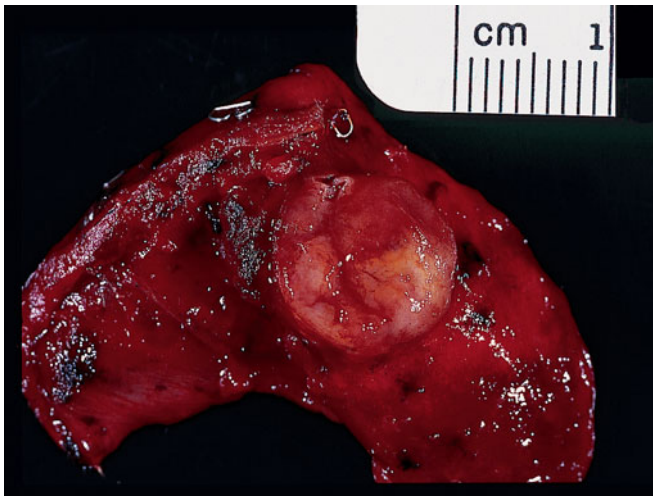


C

Figure 104-13 *A*. Cytologic features of carcinoid tumor with small, uniform cells. The nuclei are round to oval with a "salt and pepper" chromatin pattern (H&E, 400×). *B*. Carcinoid tumor, nested pattern of carcinoid tumor (H&E, 200×). *C*. Carcinoid tumor, ribboned pattern in carcinoid tumor (H&E, 200×).

typical carcinoid tumors, atypical carcinoid tumors can occur centrally as well as in the periphery. It is appropriate to consider atypical carcinoid tumors as an intermediate grade malignant tumor with an increased capacity for progression. Atypical carcinoids have a higher incidence of lymph node metastases at presentation and, in contrast to typical carcinoids, nodal disease is a negative predictor of survival. A tumor size of 3.5 cm or greater and a higher mitotic rate are also poor prognostic indicators. The overall 5- and 10-year survival rates for atypical carcinoid are reported as 61 to 73



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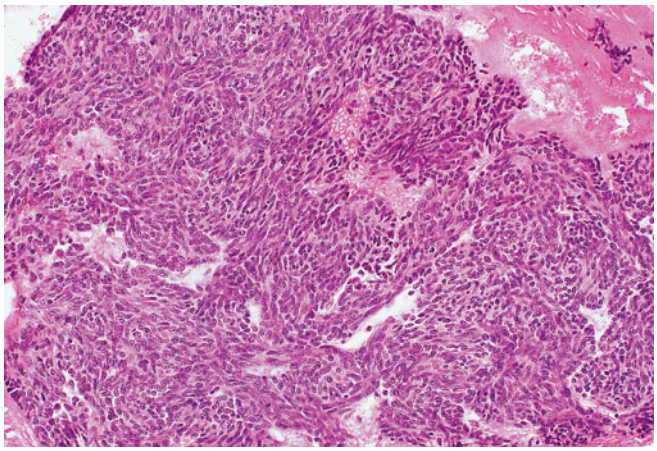

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Figure 104-14 *A*. Peripheral carcinoid. *B*. Peripheral carcinoid with prominent spindle cell features (H&E, 200×).

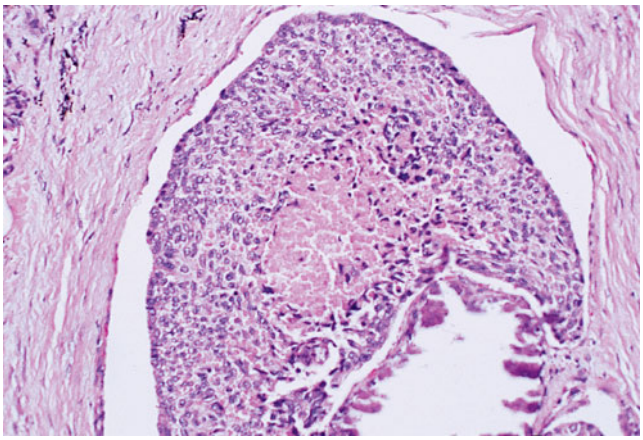


Figure 104-15 Central necrosis in an atypical carcinoid tumor (H&E, 200×).

percent and 35 to 59 percent, respectively. Chemotherapy and radiation have not been demonstrated to be efficacious.

SALIVARY GLAND TUMORS

Mixed seromucinous glands are found in the tracheal and large bronchial submucosa and are believed to give rise to a variety of salivary gland-like tumors, histologically indistinguishable from their major salivary gland counterparts. The 2004 WHO revision recognizes three major subtypes of malignant salivary gland tumors: mucoepidermoid carcinoma, adenoid cystic carcinoma, and epithelial-myoepithelial carcinoma. There is also a category of other rare malignant salivary gland tumors that includes malignant mixed tumors and acinic cell carcinoma. It is considered quite likely that some tumors diagnosed as adenocarcinomas (usually of acinar subtype) are actually of bronchial gland origin because their histological features are not sufficiently distinctive to confirm bronchial gland origin. Salivary gland carcinomas represent less than 1 percent of all lung carcinomas, with mucoepidermoid carcinoma and adenoid cystic carcinoma being the most common subtypes. Although relatively uncommon, their distinctive morphology, growth pattern, and clinical presentation make these two salivary gland-type tumors of the lung an important subgroup of non–small cell lung carcinoma.

Adenoid Cystic Carcinoma

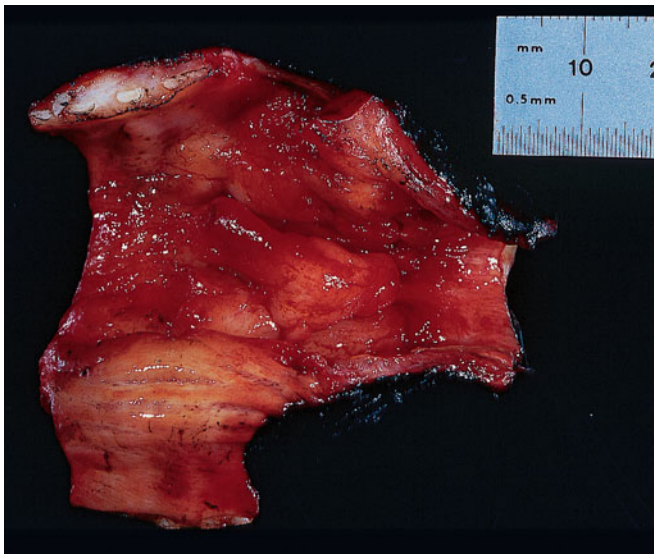
Adenoid cystic carcinoma is the most common of the tracheobronchial gland tumors. Patients range in age from 18 to 82 at presentation and the incidence is equal among men and women. The vast majority of cases originate intraluminally and the typical presenting symptoms such as wheezing, progressive dyspnea, stridor, cough, and hemoptysis reflect this intraluminal tumor growth. Unlike carcinoid tumors and mucoepidermoid carcinomas, which usually present as intraluminal endophytic masses, adenoid cystic carcinomas have a more variable growth pattern. Some tumors are grossly nodular with minimal invasion of the bronchus, whereas others have a mixed nodular/infiltrative or predominantly infiltrative growth pattern (Fig. 104-16*A* and *B*). More infiltrative tumors appear as small nodules within the airway or cause a generalized constriction of the airway. There may be lymph node involvement, usually by direct extension, and higher-grade tumors have a tendency to radially spread into the adjacent parenchyma rather than along the airways.

The microscopic level of invasion nearly always exceeds that which is grossly apparent. Negative resection margins often are difficult to achieve. Complete resection may be quite difficult and can require multiple frozen sections to confirm clear surgical margins. The tumor cells are small with a relatively high nuclear/cytoplasmic ratio but nuclear pleomorphism and mitoses are rare. Characteristic mucinous cysts of varying size are present within the tubular and cribriform patterns (Fig. 104-16*C*). Poorly differentiated tumors have a significant component of solid tumor nests. As is characteristic of their salivary gland counterparts, adenoid cystic carcinomas are notorious for perineural spread. Long-term survival can be achieved with adequate resection but local recurrence may occur even late (greater than 10 years) following resection. The most common site of disseminated disease is the lung parenchyma, but extrathoracic metastases have been reported.

Mucoepidermoid Carcinoma

Mucoepidermoid carcinomas account for approximately 0.1 to 0.2 percent of lung cancers. Patients with this tumor may be asymptomatic, but it is common for patients to present with symptoms of bronchial obstruction due to the tumor's characteristic endobronchial location. These symptoms include wheezing, cough, and hemoptysis, and patients may present with postobstructive pneumonia. The age at presentation varies, but almost half of patients with mucoepidermoid carcinoma occur in patients under 30 years of age. There is no significant association with tobacco use. A chest radiograph often reveals a solitary, centrally located mass with distal pneumonia or atelectasis.

Mucoepidermoid carcinomas usually arise from segmental and subsegmental bronchi, but can involve the trachea as well. They range in size from a few millimeters to up to 6 cm and grow as polypoid masses with a tan or gray surface (Fig. 104-17*A* and *B*). On cross-section, the tumor may appear more mucoid or cystic than the more common non–small cell carcinomas of the lung. Histologically, mucoepidermoid tumors are separated into low- and high-grade tumors. The tumors are composed of a mixture of mucin-secreting cells, squamous cells, and what are termed "intermediate cells." The intermediate cells have a polygonal shape and eosinophilic cytoplasm, but lack obvious squamous or glandular differentiation. The mucinous component consists of well-differentiated glands, with both intracellular and extracellular mucin (Fig. 104-17*C*).



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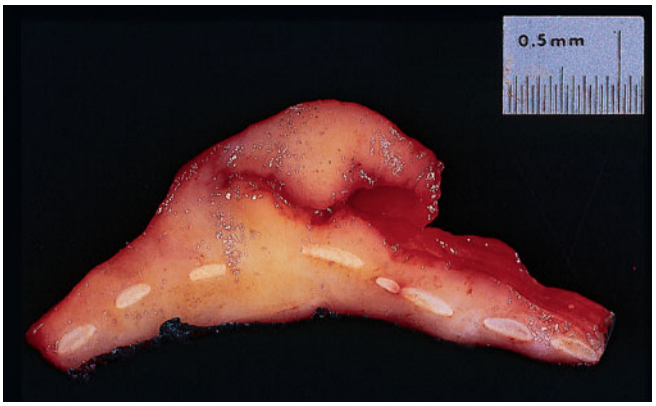

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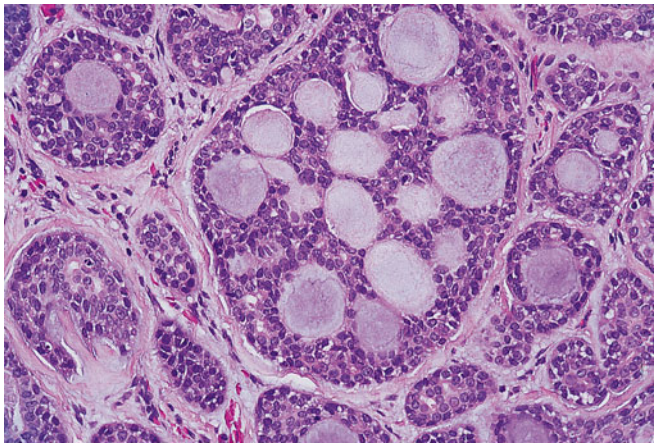
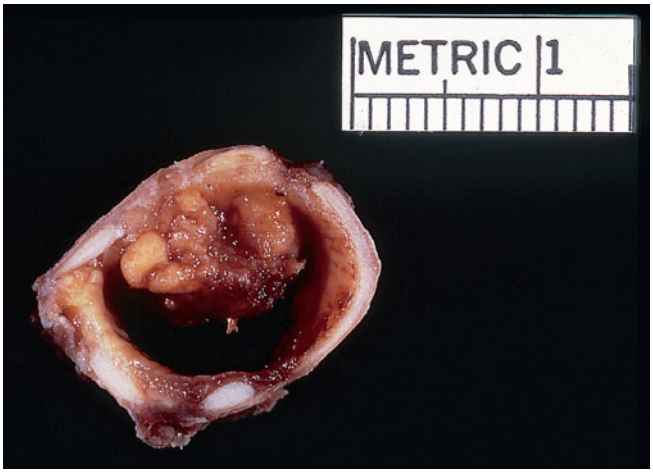


C

Figure 104-16 *A.* Carinal resection for adenoid cystic carcinoma with a mixed infiltrative and nodular pattern of growth within the submucosa. *B.* Same adenoid cystic carcinoma in cross-section, illustrating the extensive diffuse involvement of the submucosa with infiltration beyond the cartilage. *C.* Cribriform growth pattern of adenoid cystic carcinoma (H&E, 200×).

In low-grade tumors, the cells have minimal pleomorphism, rare mitoses, and minimal necrosis. Suggested criteria for high grade tumors include an increased mitotic rate (average of 4 per 10 high-power fields), necrosis, and nuclear pleomorphism. High-grade mucoepidermoid carcinomas may be difficult to distinguish from adenosquamous carcinomas. High-grade mucoepidermoid carcinomas still retain a characteristic admixture of mucin-containing cells, squamoid cells, a central endobronchial location, and transitional areas from low-grade mucoepidermoid carcinoma. There should be no keratinization, squamous pearl formation, or in situ squamous cell carcinoma: features, which if present, are consistent with a diagnosis of squamous or adenosquamous carcinoma.

The clinical behavior of these neoplasms had been controversial, mainly due to past ambiguities regarding the definition of high-grade mucoepidermoid carcinomas and their distinction from adenosquamous carcinomas. In an analysis of 58 cases, Yousem and Hochholzer separated mucoepidermoid tumors into low- and high-grade tumors using criteria formulated for mucoepidermoid tumors of the salivary glands. In this study, there was no evidence of disease following complete surgical excision for 41 patients with low-grade tumors and an average follow-up of 4 years. Of 13 patients with high-grade mucoepidermoid carcinomas, 3/13 patients died of metastatic disease, but 8/13 were alive without evidence of disease at a median follow-up of 31 months. Almost all of the tumors reported in patients younger than 30 years have been low-grade tumors, which are mostly endobronchial and have an excellent prognosis. There is a low reported incidence of lymph node metastases (about 2 percent). Local recurrence has been reported with incomplete excision and adequate excision may require a lobectomy, bronchoplastic procedure (sleeve lobectomy), or pneumonectomy. High-grade tumors, which tend to invade the adjacent lung parenchyma, are associated with an older population and carry a worse prognosis. High-grade mucoepidermoid carcinomas tend to behave in a manner similar to the more common non–small cell carcinomas.



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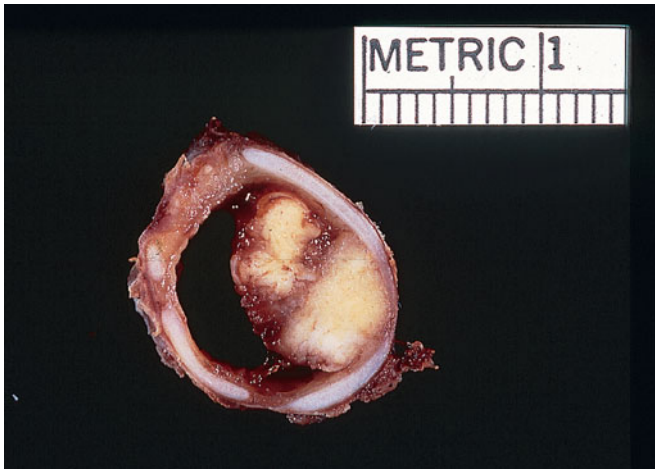

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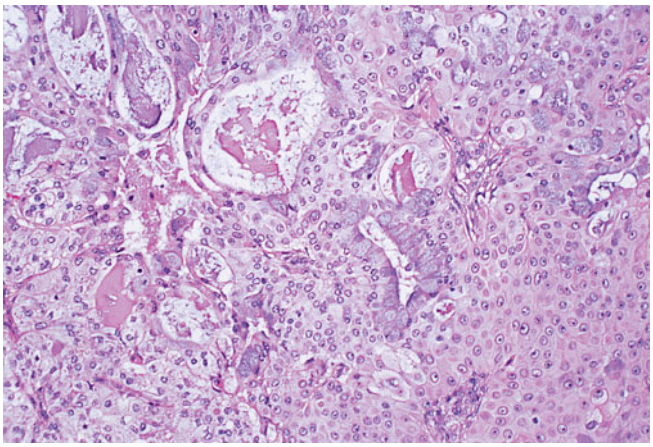

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Figure 104-17 *A*. Left main-stem bronchus resection for endobronchial mucoepidermoid carcinoma. *B*. Same mucoepidermoid carcinoma tumor in cross-section, demonstrating an attachment to the bronchus but invasion is limited to the superficial portion of the submucosa. *C*. Mucoepidermoid carcinoma. There are both well-differentiated mucinous glands (left) and intermediate cells (right) that have a polygonal shape and abundant eosinophilic cytoplasm (H&E, 200×).

ANCILLARY STUDIES

The lung is a common site for both primary tumors and metastases and the pathologist must consider a broad differential diagnosis when analyzing a cytologic or tissue preparation. Ancillary studies typically are used to narrow the differential diagnosis or demonstrate differentiation. It is a general principle of laboratory diagnosis that the sensitivity and specificity of any test depends on the pretest prevalence of the disease. The appropriate use of ancillary studies is grounded in a well-formulated differential diagnosis based on the tumor's histological appearance. The clinician contributes greatly by providing a complete clinical history, which helps direct the diagnostic work-up and avoid unnecessary tests.

HISTOCHEMICAL STAINS

The most commonly used histochemical stains are those that demonstrate intracellular mucins—periodic acid-Schiff (PAS) after diastase and mucicarmine—and are characteristic of adenocarcinomas. As discussed in the chapter on the pleura, stains for neutral mucins are often used to distinguish adenocarcinoma from epithelial mesothelioma. Alcian blue staining with hyaluronidase treatment had been used to distinguish the acid mucin of mesothelial cells from the epithelial mucin associated with adenocarcinomas, but its use has largely been supplanted by immunohistochemistry. Mucin stains are also typically performed on poorly differentiated carcinomas, which appear as solid carcinomas lacking glandular differentiation but prove to have numerous mucin-positive tumor cells and therefore would be best classified as adenocarcinomas, solid type.

Immunohistochemistry

Immunohistochemistry is based on a primary antigen-antibody reaction and a secondary antibody-enzyme complex that interacts with a chromogen for a microscopically visible color reaction. Since its introduction into diagnostic pathology in the early 1980s, immunohistochemistry has become an integral part of tumor diagnosis. Unfortunately, there are very few antibodies that approach 100 percent sensitivity and specificity. As experts on immunohistochemistry have emphasized, it is diagnostically irrelevant to speak of overall

sensitivity and specificity for a particular antibody. Rather it is more appropriate to speak of relative sensitivity and specificity within a particular differential diagnosis. This requires clinical interaction and morphologic expertise in generating a differential diagnosis in addition to critical assessment of the immunohistochemical results with appropriate controls.

Immunohistochemistry is often used in the work-up of an undifferentiated large cell carcinoma, usually to exclude melanoma and lymphoma, which can mimic a highly pleomorphic epithelial tumor. Within this differential diagnosis of an undifferentiated tumor comprised of large cells, cytokeratin antibodies such as AE1/3, CAM 5.2, and pancytokeratin are used to support the diagnosis of carcinoma. Cytokeratin antibodies least focally stain most non–small cell carcinomas of all histological subtypes, in addition to a wide variety of carcinomas from other primary sites. There are, however, potential pitfalls. Cytokeratin antibodies stain benign bronchial and alveolar epithelia, which can be entrapped within tumors and lead to a false-positive interpretation. Reactive mesothelial cells and malignant mesotheliomas are cytokeratin positive as well. Cytokeratin positivity, usually focal, also has been demonstrated in sarcomas and melanomas. S100, HMB45, and melanA are markers of melanocytic differentiation. Although sensitive, S100 is less specific for melanoma and stains other tumors, including those of neural origin and some adenocarcinomas of both primary pulmonary and extrapulmonary origin, such as the breast. Leukocyte common antigen (LCA), CD30 (for Ki-1 positive large cell lymphomas), and B and T cell markers are the immunohistochemical stains most frequently used to exclude lymphoma. As discussed in the section on malignant mesothelioma, there are antibodies to glycoproteins such as CEA, MOC31, B72.3, LeuM1, Bg8, and BerEP4, which stain a high percentage of adenocarcinomas, including adenocarcinomas of the lung. Different staining patterns of epithelial membrane antigen (EMA) immunoreactivity have been reported as a means of distinguishing malignant mesothelioma from adenocarcinoma, but others have disputed the utility of EMA for this purpose.

The biggest challenge within immunohistochemistry remains the differential diagnosis of pulmonary primary from metastatic disease. There are only a limited number of instances in which immunohistochemical stains are useful in differentiating a pulmonary primary from a metastatic tumor. Outside of thyroglobulin for the majority of thyroid tumors and prostate-specific antigen for the majority of prostatic adenocarcinomas, most other antibodies have too much overlap in specificity to be conclusive. There has been some more qualified success in some instances when the differential diagnosis includes other common solid organ malignancies such as breast or gastrointestinal carcinomas. Staining with a panel of antibodies to bolster one's diagnostic certainty in the differential diagnosis of primary lung carcinoma versus metastasis can certainly enhance diagnostic accuracy. Fundamentally, however, this type of immunohistochemical analysis remains an exercise in probabilities and may not be sufficient for certain clinical circumstances. It is most often the case that new markers are introduced into the literature with initial reports of high sensitivity and specificity. After a time, with additional studies and incorporation into daily practice, more exceptions appear. A good example is thyroid transcription factor (TTF-1). On average, TTF-1 stains about 75 percent of primary pulmonary adenocarcinomas, although the percentage is lower in more poorly differentiated tumors, some subtypes of adenocarcinoma, better differentiated neuroendocrine tumors, and squamous cell carcinomas. It was initially believed that the only extrapulmonary tumor that was as frequently positive for TTF-1 was thyroid carcinoma. Now there are reports of TTF-1 positivity in extrathoracic tumors that would not be expected—such as ovarian epithelial tumors—making the marker less specific than was initially asserted. Whether "molecular profiles" will be able to improve diagnostic accuracy remains to be seen. For the present, the fundamental lesson is that there is no substitute for a good clinical history, thorough physical examination, and high-quality radiographic studies.

CONCLUSION

In addition to the clinicopathologic features and histological subtyping of non–small cell carcinoma, recent changes and current controversies in tumor classification have been reviewed. The pathologist makes a critical contribution to the management and treatment of lung carcinoma, but the final pathologic interpretation should not be rendered in a clinical vacuum. It is incumbent upon the clinician caring for the patient to be sure that the pathologist has the benefit of complete clinical information. This should include symptoms at presentation, radiographic findings, and past medical history, particularly as it relates to prior malignancies. The inclusion of the pathologist as an integral part of what is now commonly a multidisciplinary evaluation for a thoracic malignancy enhances the quality of care for the individual patient, as well as refining the general practice of thoracic oncology.

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Part I: Treatment of Non–Small-Cell Lung Cancer
Surgical

Larry R. Kaiser

Lung cancer is a clinical problem of the twentieth century, having been virtually unrecognized until the early part of this century. It is a disease for which the cause is known in the majority of cases yet despite that knowledge the incidence in women continues to rise, while it has leveled off for men. Thus it is both a travesty and an indictment against us as a society that lung cancer is the leading cause of death from cancer in both men and women despite our knowledge that cigarette smoking causes the disease. The treatment of lung cancer has evolved from a single modality, surgery, to a multimodality approach that calls upon the skills of numerous specialists. Not many years ago an operation was all that could be offered to a patient, and it has taken a considerable amount of time to recognize that not only is an operation not for everyone but may be contraindicated in many situations. It has remained for students of the disease—surgeons, and medical and radiation oncologists—to define the role that surgery should play in the modern management of lung cancer. Surgery was and is the cornerstone of management in this disease, and surgeons continue to assume a leading role in the diagnosis and treatment of patients with lung cancer.

DIAGNOSIS

It is illustrative to consider the route taken by most patients prior to being referred to a surgeon and the qualifications that the surgeon should ideally possess to contribute optimally to the management of the patient with lung cancer. Patients with lung cancer either present with symptoms or are found inadvertently to have an abnormal chest radiograph when the film has been done for some other reason. The symptomatic patient sees his or her primary care physician, who may initiate further evaluation or more likely refer the patient to a pulmonary physician. Rarely is a patient referred

This chapter has been slightly modified from the version that appeared in the third edition of *Fishman's Pulmonary Diseases and Disorders.*

directly to the surgical specialist for evaluation of an abnormal chest radiograph, although this does occur with greater frequency in certain communities. From the surgeon's viewpoint how should a patient with a presumed lung cancer be evaluated? How likely is it for a given patient to have a lung cancer? We look at smokers differently than we look at nonsmokers when evaluating an abnormal chest radiograph. Certainly lung cancer is seen in nonsmokers, but we are much less suspicious in this group than in smokers, in whom an abnormal chest radiograph is lung cancer until proved otherwise. If a previous chest radiograph is available, the first move should be to compare it with the current film. A lesion present on a previous film markedly diminishes, but does not eliminate, the probability that the current finding represents a lung cancer.

The Symptomatic Patient

Patients present with symptoms either referable to the chest or related to the presence of metastatic disease. The initial evaluation should be directed toward an explanation of the symptoms. A complete discussion of the clinical presentation is available in Chapter 104. Patients with evidence of metastatic disease still require a tissue diagnosis. The method employed to obtain the tissue diagnosis should have the highest probability of success. Whereas bronchoscopy has a high likelihood of yielding a diagnosis in the patient who presents with cough or hemoptysis, it is less likely to be successful when the lung findings are confined to multiple small nodules. Often transthoracic needle biopsy may have the highest yield, and bronchoscopy is not required. When a patient presents with presumed metastatic disease that is accessible, such as a palpable supraclavicular lymph node, a needle aspirate, done in the office, likely will be all that is required both to diagnose and stage the patient. Again, there is no need to bronchoscope such a patient unless specifically indicated. A percutaneous biopsy of an adrenal lesion may also provide both a diagnosis and stage. Too often extra procedures are performed that add no useful information to the subsequent management of the patient. Unfortunately the only question of significance in the patient with metastatic disease is the differentiation between small cell and non–small-cell lung cancer (NSCLC), and this difference, although intuitively of great importance, is actually of minimal significance, since the chemotherapy, if indicated, is quite similar for both diseases. Yet it seems important to know the histology if for no other reason than to be able to discuss the prognosis with the patient. What is important in this early phase of the management of a patient with presumed metastatic lung cancer is to select a procedure that is likely to yield the most information with regard to both histologic type and stage and avoid unnecessary procedures in these individuals who have a limited life expectancy. Rarely is it necessary in the patient with metastatic disease to subject them to a procedure any more invasive than a needle biopsy or bronchoscopy. Occasionally mediastinoscopy may be required to obtain enough tissue and very rarely video thoracoscopic excision of a lung nodule, but a so-called exploratory thoracotomy really has no place in the management of these patients.

The Asymptomatic Patient with Abnormal Chest Radiograph

Usually patients who are asymptomatic present with a solitary pulmonary nodule since those with an infiltrate or consolidation of a lobe rarely are without some symptom or sign of disease. The real question in this situation comes down to whether the nodule is malignant. A chest computed tomographic (CT) scan should be performed to determine if the nodule is solitary as well as to assess the status of the mediastinum, liver, and adrenals. The role of percutaneous needle biopsy of the solitary pulmonary nodule remains controversial. Bronchoscopy in this situation adds little and is probably not indicated. One approach in certain patients, namely nonsmokers with a small nodule, is to follow the lesion over a period of time. A repeat chest radiograph in 4 to 6 weeks to assess a change in size of the nodule is a reasonable alternative as long as the patient can tolerate the uncertainty that the nodule may prove to be a carcinoma. If the lesion has increased in size, then excision is carried out. No change in size warrants continued observation with repeated chest radiographs. Conversely, in a smoker in whom there is a high probability that the nodule is malignant, excision is justified in most cases no matter the result of a needle biopsy. A negative biopsy does not negate the fact that a suspicious nodule remains; if the biopsy is positive it only confirms what we already suspected, but the patient has been exposed to the risk of the needle biopsy, namely, a 30 percent incidence of pneumothorax with a need for a chest tube in one-half of cases. The problem remains that a negative needle biopsy is of little help. Some positive information has to be obtained, such as cartilage or fungal elements, for the biopsy to be definitive in order to prevent an operation. To really understand and use a negative needle biopsy to guide therapy we need to know not just what percentage of patients with negative needle biopsies prove to have cancers, but also what percentage of needle biopsies are negative when performed in patients in whom there is a high suspicion of cancer. A recent study from the University of Toronto, where essentially all patients with pulmonary nodules undergo needle biopsy, shows that 6 percent of patients with a negative needle biopsy ultimately prove to have a cancer (T. Todd, personal communication).

The role of needle biopsy has been further diminished by the development of video thoracoscopy, which in a relatively minimally invasive fashion, allows for the excision of a pulmonary nodule and a definitive diagnosis. If the nodule proves to be benign, video thoracoscopic excision both makes the diagnosis and treats the problem. If the nodule is malignant, the procedure may be immediately converted to the appropriate anatomic pulmonary resection, most commonly lobectomy. Needle biopsy is useful for the patient who insists on having a diagnosis of malignancy prior to going to the operating room. The argument that needle biopsy should be performed to rule out small-cell carcinoma is weak, since

in the absence of mediastinal adenopathy, extremely rare for a small cell, a solitary nodule should be excised even if the needle biopsy suggests the diagnosis of small cell carcinoma by histology. All the preceding notwithstanding, needle biopsies continue to be performed almost routinely despite the current concern regarding costs.

STAGING

A discussion of noninvasive staging is beyond the scope of this chapter and is dealt with elsewhere in this volume; however, the role of invasive staging and specific procedures utilized deserve mention. In discussing stage, distinction must be made between *clinical* and *pathologic* stage. The former is based solely on noninvasive imaging studies, whereas the latter depends on actual histologic material obtained either by invasive staging studies or at the time of the surgical resection. A clinical stage is no more or less than an assumption, which is only as good as the noninvasive studies employed. A chest CT scan provides excellent visualization of the contents of the superior mediastinum. However, size of the lymph nodes remains the only criterion on which to base a judgment as to whether tumor is present in these nodes. There are no other specific criteria either on CT or magnetic resonance imaging (MRI) by which to make such a judgment. The sensitivity and specificity of CT depends on the size cutoff arbitrarily determined to separate a positive finding from a negative one. The smaller the size chosen, the greater the specificity, but at the expense of the sensitivity. A larger size increases the sensitivity but decreases the specificity. In the author's clinic, 1.5 cm is used as the threshold for determining whether a patient should have a mediastinoscopy performed. It has to be realized, however, that even though a size criterion has been determined, problems remain both in the subjectivity in measuring 1.5 cm on CT and the thickness of the slices utilized in performing the scan.

Mediastinoscopy provides a great deal of information about the lymph node status of the superior mediastinum and is the gold standard for the assessment of the mediastinal lymph nodes. The procedure has a false-negative rate of less than 10 percent, far better than CT, but has the disadvantage of being an invasive procedure. As the resolution of CT scans has improved, performing routine mediastinoscopy on all patients with lung cancer must be questioned when the procedure may be applied selectively based on the size of the lymph nodes seen on the CT. This avoids a needless operation in over 80 percent of patients. There are nodal stations that cannot be accessed by standard cervical mediastinoscopy. These include the aortopulmonary window (level 5), a common site for lymph node involvement in left upper lobe tumors, and the posterior subcarinal space (level 7). However, the anterior subcarinal space, usually representative of the contents of the posterior subcarinal space, is accessible to mediastinoscopic biopsy, and involved lymph nodes in the aortopulmonary window in the absence of other lymph node disease carries a prognosis equivalent to N1 (hilar) disease.

Mediastinoscopy is performed through a small (2-cm) incision made in the neck 1 cm above the sternal notch. The area explored by mediastinoscopy, the superior mediastinum, is palpated first by inserting a finger along the anterior aspect of the trachea which also serves to develop the space and facilitate insertion of the mediastinoscope (Fig. 110 I-1). Obviously involved lymph nodes often may be palpated, but palpation alone is insufficient, since intranodal disease may be present that can only be identified if representative biopsies of the important nodal stations are taken following insertion of the mediastinoscope. Of major importance are the ipsilateral nodes, but just as important is the status of the contralateral

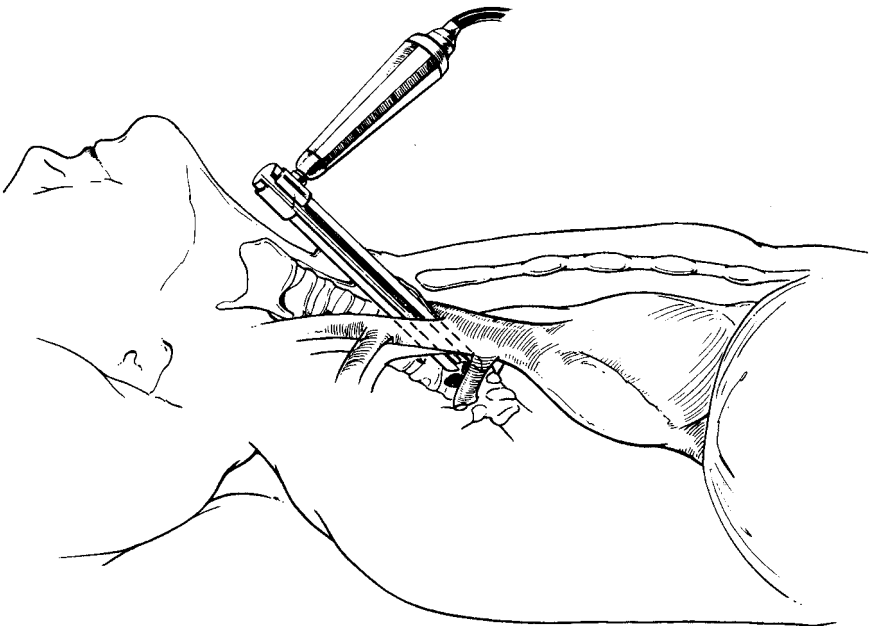

Figure 105 I-1 Mediastinoscope in place demonstrating the superior mediastinal plane.

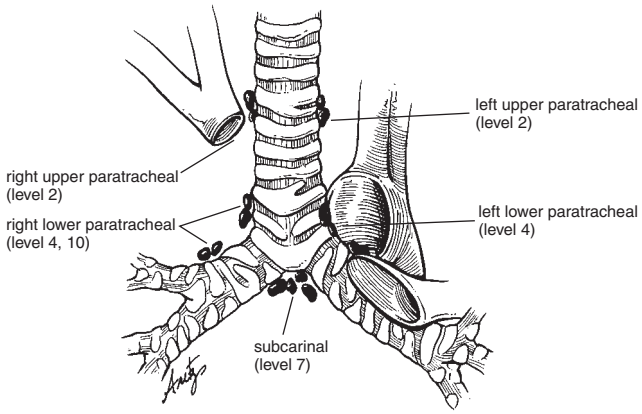

Figure 105 I-2 Lymph node stations accessible by cervical mediastinoscopy. For consistency the levels should be labeled with the appropriate number when submitted to surgical pathology.

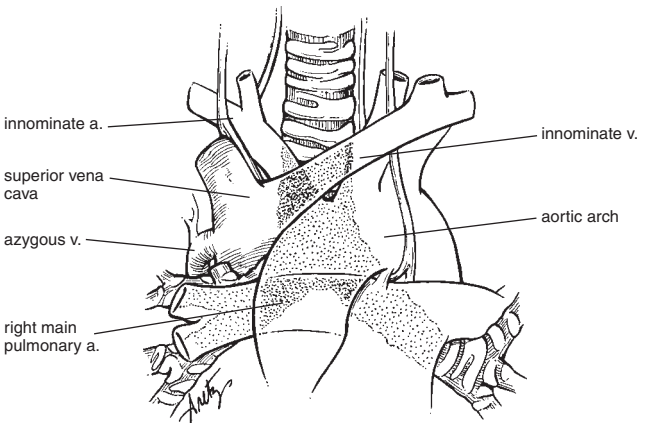

Figure 105 I-3 The relationship of major vascular structures potentially encountered during mediastinoscopy to the trachea and main bronchi.

lymph nodes, especially in left lower lobe lesions, in which right paratracheal lymph nodes are commonly involved. Despite notions to the contrary, left-sided lymph nodes are readily accessible at mediastinoscopy but are somewhat more difficult to identify. In fact the left paratracheal lymph nodes are much more easily sampled at mediastinoscopy than at left thoracotomy because of the location of the aortic arch relative to the left mainstem bronchus. Because of this we have a much lower threshold for performing mediastinoscopy for left-sided lesions.

Nodal stations most frequently sampled include levels 2 (upper paratracheal) and 4 (lower paratracheal) on the right, level 3 (pretracheal), level 7 (subcarinal), and level 4 on the left (Fig. 110 I-2). Because the left level-4 lymph nodes occur at a slightly higher location, it is identifying separate level 2 nodes on the left can be difficult. It is not necessary always to sample all nodal stations; if there are nodes obviously involved, these, along with contralateral nodes, are all that are necessary to adequately stage the patient. This makes it sound very simple to carry out the procedure, but in fact mediastinoscopy is a technically demanding procedure that is performed correctly and thoroughly only by those who have been well-grounded in the techniques. It is a difficult procedure to teach, and the close proximity of a number of major vascular structures makes it daunting even to the experienced practitioner. The vessels include the inominate artery, aortic arch, superior vena cava, azygous vein, and right main pulmonary artery. Unfortunately none of these structures is easily seen, and success requires that the operator know where they are located to avoid injury (Fig. 110 I-3). The left recurrent laryngeal nerve and esophagus are also subject to injury. Many surgeons have had disastrous experiences with mediastinoscopy and have great hesitation about performing it despite the wealth of information obtained when it is performed properly. These are usually the same clinicians who downplay the importance of the procedure in staging lung cancer and seek to avoid it. A surgeon attempting to practice thoracic surgery without the ability to perform a complete and thorough mediastinoscopy is at a great disadvantage, which unfortunately is passed on to patients. This inability usually results in the performance of many thoracotomies that otherwise could be avoided.

Although mediastinoscopy is the mainstay of invasive staging for lung cancer, other procedures provide additional information that often complements that obtained at mediastinoscopy. The aortopulmonary window, a common site of nodal spread from tumors of the left upper lobe, may be reached with a parasternal mediastinotomy, or so-called Chamberlain procedure. An incision is made over the left second costal cartilage, the cartilage is excised, and the pleural reflection is swept laterally to access the aortopulmonary window in an extrapleural plane. The involvement of lymph nodes at this level (level 5) in the absence of other nodal disease is associated with a 5-year survival that approaches 50 percent if the disease can be completely resected at thoracotomy, a survival that is almost identical to that seen with N1 (hilar) disease. The rationale, then, behind performing parasternal mediastinotomy either is to assess resectability or document mediastinal nodal disease to justify placing the patient into an experimental protocol of neoadjuvant chemotherapy, radiation therapy, or both.

Similarly, video thoracoscopy aids in the staging of lung cancer, although not in lieu of mediastinoscopy, which offers an opportunity to sample nodes on the right and left through one incision, but as an adjunct. Nodes inaccessible by mediastinoscopy, including the aortopulmonary window (level 5), subcarinal (level 7), and inferior pulmonary ligament (level 9) are easily sampled utilizing video thoracoscopy. This technique also visualizes the pleural space, especially useful in the patient with a pleural effusion and negative fluid cytology, so as to rule out diffuse pleural involvement and prevent an unnecessary thoracotomy. Other nodules seen on CT scan that may have an impact on treatment planning also may be excised and defined histologically prior to formal thoracotomy. Video thoracoscopic examination has not proved particularly useful in assessing resectability of a tumor when there is a question because of presumed invasion of an adjacent

mediastinal structure. Usually the ultimate decision regarding resectability of a locally invasive lesion must be made at the time of thoracotomy when the lesion itself may be palpated and the dissection conducted under greater control. A logical progression from the less invasive to the more invasive procedures guided by the imaging studies often results in the patient being spared a procedure from which there will be no significant benefit.

Any discussion of staging presupposes that the information obtained will be used in the decision regarding therapy. It is of no use obtaining information and subjecting the patient to the risk of an additional procedure unless the information obtained is utilized. Discovering at mediastinoscopy that there is N2 disease and still proceeding on to thoracotomy makes little sense. Why bother with the mediastinoscopy? This introduces the concepts of operability and resectability, two terms that are *not* synonymous, although mistakenly used as such. Any staging study or procedure, invasive or noninvasive, contributes to the decision regarding operability but usually has no bearing whatsoever on resectability. A patient who has bone metastases is *inoperable,* by definition, since the local control achieved by removing the primary tumor has no effect at all on the fact that the patient already has disseminated disease. Removing the primary tumor, although an extremely difficult concept to convey to the patient and family, offers nothing in terms of survival and only subjects the patient to the morbidity of the operation. This same patient, although *inoperable,* may have an eminently *resectable* lesion. *Resectability* is a surgical determination made by the surgeon at the time of the operation. Staging studies have little to do with determining resectability, the exception being the finding of gross extranodal disease at mediastinoscopy that both defines operability and, for the most part, precludes resection. Finding diffuse pleural studding at video thoracoscopy does not define resectability, since the primary tumor easily may be resected, but it does prove inoperability, since removing the tumor will add nothing to the overall outcome. Operability may also be determined by coexisting medical problems such as heart disease, although the patient may have a resectable primary tumor. The two terms refer to decidedly different concepts; *resectability* is a surgical term whose use should be confined to surgeons. Unless you are the one doing the resecting, how can you know what is resectable and what is not? The recognition of this concept would go a long way toward allowing patients to obtain a complete assessment of their disease followed by the institution of appropriate treatment. For a nonsurgeon to decide, based on imaging studies, what is *resectable* and then institute treatment without referring the patient to a thoracic surgeon at least for consultation does a disservice to the patient.

SURGICAL TREATMENT OF LUNG CANCER

Many patients undergo very little in the way of a staging evaluation prior to operation. The type and extent of the staging evaluation depends on a number of clinical factors. At a minimum patients should have a recent chest radiograph and CT scan of the chest. Most, but not all, should have a recent set of pulmonary function studies. The decision to search for disseminated disease with a bone scan and brain CT or MRI is a difficult one, and precise criteria to define when they should be obtained do not exist. A complete discussion of this issue may be found in Chapter 104. The practice in this clinic is to obtain a complete evaluation of the extent of disease if there is any reason at all to do so. This includes any organ-specific or nonspecific signs or symptoms. Nonspecific signs include weight loss, easy fatigueability, or anemia; organ-specific signs include bone pain, elevated liver enzymes, or localizing neurologic findings. If any of these findings are present, a complete evaluation is obtained, not just the study pointed to by the organ-specific complaint. Any patient with a history of malignancy should have a complete extent of disease workup, as should the patient who is at a higher risk for operation, such as an individual with multiple medical problems or borderline pulmonary function. As well, any patient with locally advanced disease in whom the indications for operation are being extended (i.e., N2 disease) or the nonsmoker with a lung mass should have disseminated disease ruled out. The aim is to avoid operating on a patient who proceeds to manifest disseminated disease within 1 year of operation, a finding that ideally should have been identified preoperatively.

Recognizing that operation is the best treatment for early-stage disease, it is important that the appropriate procedure be performed. Lobectomy remains the definitive resection for most lung cancers, since it is an anatomic resection that removes the regional lymph nodes located along the lobar bronchus. Doing less than a lobectomy must be considered a compromise, although a non-anatomic wedge excision is tempting for small primary tumors. Not only does a wedge excision not include the lobar bronchus, precluding evaluation of lobar lymph nodes, but it provides only a minimal parenchymal margin. The Lung Cancer Study Group (LCSG) addressed the question of lobectomy versus limited resection for T1N0 lesions (tumor lass than 3 cm, negative lymph nodes) in a prospective randomized trial. The early analysis of the data demonstrated an increased incidence of local recurrence in the limited resection group but no difference in survival. The final analysis revealed superior survival for patients in the lobectomy group. Other studies have looked retrospectively at patients undergoing limited resection, which includes segmental resection, and have demonstrated long-term survivors, but the LCSG study stands alone as the only randomized trial.

For patients in whom lobectomy is not feasible, a lesser resection offers the best alternative, although admittedly it is a compromise. Patients in this category are those with borderline pulmonary function or those who have had previous pulmonary resections. Whenever possible the lesser resection should be an anatomic segmental resection, which takes the segmental artery and vein as well as the segmental bronchus with its accompanying lymph nodes (Fig. 110 I-4).

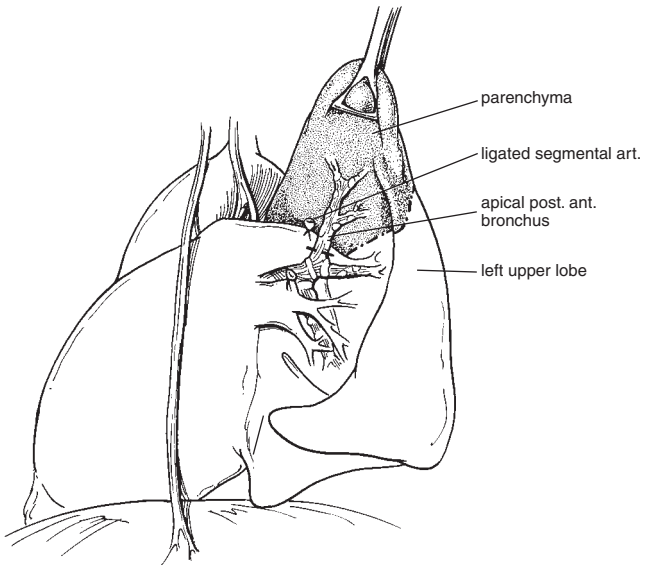

Figure 105 I-4 Segmental resection. The example shown here is the resection of the apical-posterior segment of the left upper lobe. The segmental pulmonary arterial branch is shown ligated and divided. The segmental bronchus has been dissected out and is the next structure to be divided.

A classic segmental resection is a relatively difficult operation, and many surgeons do not possess a significant amount of experience in performing this procedure. The prototype segmental resections include the lingular resection and resection of the superior segment of the lower lobe, but any lung segment may be removed anatomically. The key to segmental resection is the identification of the segmental artery, which, once ligated and divided, reveals the location of the segmental bronchus that is taken next. The segmental vein is divided last, and the parenchyma is divided with a stapler or "stripped" as described.

With the development of video thoracoscopic techniques and the simplicity of wedge resection via this approach, there has been renewed interest in utilizing this technique for T1N0 lung cancers. Based on the LCSG data this should be avoided, and patients who are found to have a cancer should be offered the best possible procedure, which, to the best of present knowledge, is a lobectomy. Wedge resection is, at best, a compromise, and patients who otherwise could tolerate an anatomic resection are not well served by having less done. There have also been several reports of tumor growing in thoracoscopic incision sites when lung cancers have been pulled through these small incisions.

Depending mainly on the location of the tumor, more extensive and complex resections than lobectomy may be required. The determination as to when to perform pneumonectomy is made at the time of operation, rarely preoperatively. Recognizing that even today pneumonectomy carries a perioperative mortality of at least 5 percent, we do everything possible to avoid removing an entire lung. There are only a few absolute indications for performing pneumonectomy for the experienced surgeon. These include such proximal involvement of the main pulmonary artery that it is difficult to place a clamp on the artery, endobronchial tumor so extensive as to preclude sleeve resection, and involvement of the confluence of the pulmonary veins or of the left atrium. There is reason for concern if a surgeon is performing an abundance of pneumonectomies. A "difficult" fissure, unless tumor involves the artery in the fissure, is not an indication for pneumonectomy, nor is tumor crossing a fissure an absolute indication. Pneumonectomy, technically, is an easier operation to perform than lobectomy, requiring very little dissection and only several applications of the stapler. Sleeve resections, or bronchoplastic procedures, are technically more demanding procedures that result in the same bronchial resection as a pneumonectomy, yet preserve lung tissue. The prototypical bronchoplastic procedure is the right upper lobe sleeve resection, in which the main bronchus is divided just proximal to the right upper lobe takeoff and the bronchus intermedius is divided just distal to the upper lobe bronchus (Fig. 110 I-5). The right upper lobe, with tumor present at the lobar orifice, is thus removed with a portion of the mainstem bronchus, and the bronchus intermedius is anastamosed to the mainstem bronchus. Thus the proximal bronchial division occurs essentially at the same site as if a pneumonectomy had been performed. Other sleeve resections are possible on both the right and left side, all result in lung conservation and are associated with long-term survival equivalent to pneumonectomy, depending on the indications.

Even with proximal involvement of the pulmonary artery, partial resection or sleeve resection of the artery is possible to avoid removal of the entire lung. A patch angioplasty with pericardium may be utilized if a significant enough portion of the anterior wall of the artery is taken so as to narrow it. Alternatively a segment of the artery may be removed

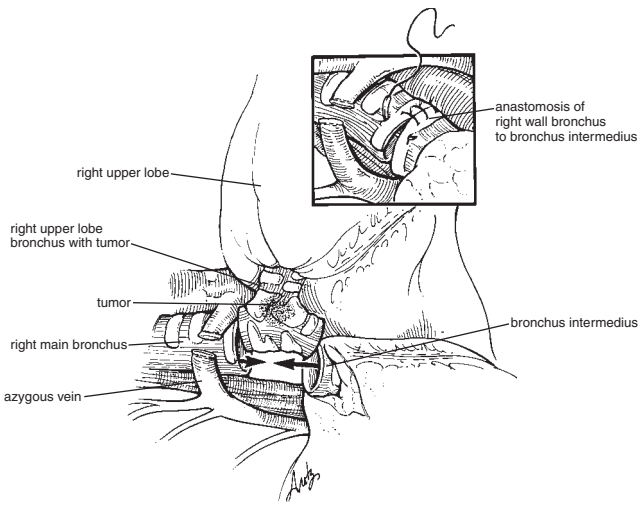

Figure 105 I-5 Right upper lobe sleeve resection. The right main bronchus has been divided just proximal to the right upper lobe takeoff where the tumor is located. The bronchus intermedius has been divided just distal to the right upper lobe bronchus. The bronchus intermedius is anastamosed to the right main bronchus (inset).

and an end-to-end anastamosis completed. Sometimes a pneumonectomy must be done, but the complete thoracic surgeon always looks to see if alternatives exist while preserving the principles of the cancer operation and not compromising margins. With any lung-conserving procedure, the margins of the resection should be sent for frozen section confirmation that no tumor is present.

A complete pulmonary resection requires more than simply excision of the tumor and the surrounding lung parenchyma, whether lobe or entire lung. The operation is incomplete without excision of lymph nodes to complete the staging assessment. We perform a mediastinal lymph node dissection even if mediastinoscopy has been performed. This procedure—when, at least on the right side, the entire contents of the superior mediastinum are removed—is the only one that assures complete lymph nodes staging. The hilar and peribronchial lymph nodes are removed with the lobectomy or pneumonectomy specimen but must be specifically searched for by the pathologist. Any sampling procedure of mediastinal lymph nodes depends on how the nodes to be sampled are chosen. The failure to include mediastinal lymph nodes as part of a resection results in incomplete information. Not only must the mediastinal lymph nodes be removed as part of the resection, but also they should be labeled according to their location in the mediastinum.

Having removed the mediastinal lymph nodes, it is not uncommon to find microscopic disease in a node that grossly appears normal. Finding tumor in mediastinal lymph nodes portends a significantly worse prognosis and at least prompts thought regarding postoperative treatment. Postoperative adjuvant therapy, usually radiation therapy, has not improved survival. Currently patients with disease found in mediastinal lymph nodes (25–30 percent, 5-year survival) following a complete resection may be entered into a national randomized protocol that compares postoperative radiation therapy alone with concurrent chemotherapy and radiation therapy (ECOG 3509).The drugs employed, cis-platinum and VP-16, are both active agents in NSCLC and are reasonably well tolerated. Patients with N1 disease (hilar, peribronchial, and segmental nodes) are also eligible for treatment on this adjuvant protocol.

The designation *locally advanced* includes a wide variety of lesions that extend outside of the lung parenchyma, whether by direct extension or nodal involvement to involve other structures within the hemithorax. Certain criteria need to be fulfilled before considering extending the indications for resection, since the intent is to maximize survival. The most obvious criterion is the exclusion of disseminated disease; thus, it is vital to complete an extent-of-disease evaluation before embarking upon a complex resection in which the indications for resection have been extended.

N2 Disease

Classically the involvement of mediastinal lymph nodes with tumor precluded any attempt at surgical resection, since most of these patients died within 2 years due to the development of disseminated disease. Utilizing mediastinoscopy, mediastinal lymph node involvement may be detected prior to thoracotomy, saving the patient a needless operation. Contralateral nodal disease, which carries a significantly worse prognosis than ipsilateral disease, may also be detected at mediastinoscopy and if found usually takes the patient out of the realm of operative intervention even if combined with neoadjuvant therapy. Perhaps the first recognition that a subset of patients with mediastinal lymph node involvement could benefit from surgery came from the work of Martini, who was able to completely resect 151 patients out of approximately 500 with N2 disease. Many of these patients were treated with postoperative radiation therapy. For the group of completely resected patients he found a 28 percent 5-year actuarial survival and subsequently a 26 percent absolute survival. All the patients with N2 disease, resected or not, were identified at the time of thoracotomy, as mediastinoscopy was not performed. Breaking the patients down into two groups yields those staged as N0 or N1 preoperatively, and those with bulky disease, so-called clinical N2, noted either on preoperative chest radiograph or at bronchoscopy when carinal splaying was noted. Those patients thought to have N0 or N1 disease preoperatively had a 35 percent 5-year survival, and those with clinical N2 disease had 0 percent 5-year survival. Fewer than 10 percent of patients with clinical N2 disease could be completely resected.

In recognition that patients with bulky N2 disease not only had a low rate of resectability but also a poor long-term outlook, an attempt was made to improve the resectability rate and, it was hoped, survival in this patient group by employing preoperative chemotherapy. There was a 77 percent response rate to the chemotherapy regimen of velban and cis-platinum with 10 percent complete responders. Sixty-five percent of patients who underwent operation were able to have a complete resection, a significant improvement over the rate able to be resected when no preoperative therapy was employed. Keep in mind that patients entered into this trial were those with bulky mediastinal disease. The overall survival was 28 percent at 3 years and 17 percent at 5 years, with a median survival of 19 months. Patients who were able to undergo a complete resection had a mean survival of 27 months and 3- and 5-year survival of 44 and 26 percent, respectively. Multiple other nonrandomized phase II trials of preoperative therapy have been carried out in patients with N2 disease utilizing chemotherapy alone or chemotherapy combined with radiation therapy.

Resections following preoperative therapy can be extremely difficult and hazardous because of the fibrosis that often results as a response to the therapy. This is especially significant when there has been a response in involved lymph nodes, since the nodes are intimately associated with the pulmonary artery and its branches, often making resection quite tricky. It is particularly important to have proximal control of the pulmonary artery prior to undertaking a resection in a patient with N2 disease who has received preoperative therapy, and resections of this type ideally should only be undertaken

Table 105 I-1

Summary from Randomized Trial of Chemotherapy plus Surgery versus Surgery Alone for Stage IIIa Disease

	Chemo + Surgery	Surgery Alone
Median survival (est)	64 months	11 months ($p < 0.008$)
2-Year survival (est)	60%	25%
3-Year survival (est)	56%	15%

Source: From Roth JA, Fossella F, Komaki R, et al. A randomized trial comparing perioperative chemo therapy and surgery with surgery alone in resectable stage III A non–small-cell lung cancer. J Natl Cancer Inst *86: 673–680, 1994.*

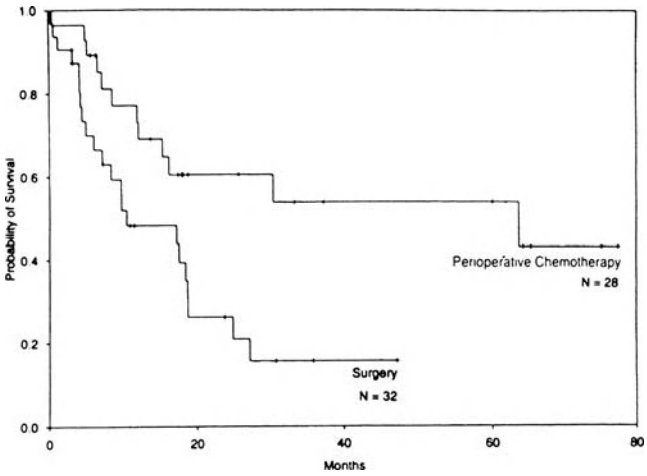

Figure 105 I-6 Time to death for all patients by treatment group, surgery alone versus chemotherapy plus surgery from the Roth trial. *(From Roth JA, Fossella F, Komaki R, et al.: A randomized trial comparing perioperative chemotherapy and surgery with surgery along in resectable stage IIIA non-small-cell lung cancer.* J Natl Cancer Inst *86:673–680, 1994, with permission.)*

by a surgeon with experience in dealing with complex resections.

Two prospective, randomized trials have been completed demonstrating the superiority of preoperative neoadjuvant therapy followed by operation compared with operation alone in patients with N2 disease. Unfortunately neither of these trials dealt solely with a population of patients with N2 disease, as they both included patients with T3 disease. Roth and colleagues randomized 28 patients to a combined therapy group who received three cycles of preoperative chemotherapy with cyclophosphamide, etoposide, and cis-platinum followed by operation, and 32 patients underwent operation without preoperative therapy. Results of the trial are summarized in Table 110 I-1. Significant survival advantage was conferred upon those who received preoperative therapy (Fig. 110 I-6). Median survival in the surgery-only group was 11 months versus 64 months in the combined therapy group ($p > 0.008$). This is all the more interesting considering that fewer than 40 percent of the patients in each group were able to have a complete resection. (39 vs. 31 percent, combined vs. surgery alone). This trial is notable for several reasons. It clearly demonstrates an advantage to neoadjuvant therapy in a group of patients with locally advanced disease. Survival in the surgery-only group was significantly shorter than expected, making the survival difference between the groups more striking. Excluded from the trial were patients with left lung tumors and left paratracheal disease, as these patients were felt to be unresectable, so there is some selection bias to the study population. However, one must be impressed by the significant difference in survival observed in this randomized trial.

Likewise, Rosell randomized 60 patients with stage IIIa disease, 25 of whom had N2 disease who received chemotherapy followed by an operation. Nineteen patients with N2 disease underwent operation as their only therapy. As in the Roth trial there was a significant survival benefit in the group that received combination therapy (median, 26 vs. 8 months, $p<0.001$).

There is a suggestion that a preoperative regimen incorporating radiation therapy and chemotherapy may be more efficacious than either modality alone. In a phase II trial the Southwest Oncology Group studied concurrent induction chemotherapy with cis-platinum and etoposide in both stage IIIa and IIIb patients. Complete resection was accomplished in 74 percent of patients. Although there was an 8 percent incidence of postoperative death, no tumor was found in 22 percent of the resections. Median survival was 13 months, and 2- and 3-year survival was 37 and 27 percent, respectively. Patients with a pathologic complete response in the lymph nodes had a 30-month median survival compared with 10 months for those with persistent lymph node disease ($p < 0.0005$).

Despite the numerous studies addressing preoperative therapy, whether chemotherapy alone or combined with radiation therapy, the question as to what role surgical resection plays in the outcome of patients with N2 disease remains unanswered. To date no conclusive studies have proved that operation is superior to radiation therapy in controlling local disease in these patients. One reason for this is the difficulty in accruing patients on a study in which the randomization chooses between a surgical and nonsurgical arm. A study addressing this question, Radiation Therapy Oncology Group (RTOG) 89-01, accrued fewer than 80 patients in the 4 years it was open. Currently there is an ongoing intergroup phase III randomized trial (RTOG 9309) for patients with N2 disease comparing concurrent chemotherapy (cis-platinum, vinblastine) and radiation therapy followed by surgical excision or additional radiation (total 61 Gy over 6 weeks).

Thus, although there is a suggestion that neoadjuvant therapy results in improved survival when compared with surgery alone, this has not been confirmed in a phase III

randomized, large multi-institutional trial. There is evidence, however, that 60 to 75 percent of patients with lymph node disease as the only site of spread respond to the preoperative regimens, a significantly greater response than when the same regimens are used in patients with disseminated disease, and over half of these patients go on to resection. Between 10 and 20 percent of patients resected have no evidence of disease found on histologic examination of the resected material. The activity of the neoadjuvant regimen in this patient population cannot be denied. Whether surgical excision is required or radiation is an acceptable modality for local control remains to be determined. Of great importance is the consideration of quality of life in patients undergoing these combined regimens, an area that has not been adequately addressed. The quality of life measurement tools are available to incorporate into future studies so that additional information should be forthcoming. Toxicity from these preoperative regimens can be substantial, especially if there is an element of postobstructive pneumonia. In the SWOG trial, two deaths resulted from the preoperative regimen, and 13 percent of patients experienced grade 4 or greater acute toxicity. The overall treatment-related mortality was 15 percent in the neoadjuvant study from Toronto. This further underscores the importance of confining multimodality therapy for N2 disease to controlled trials as opposed to routine community use, despite the current enthusiasm.

CHEST WALL RESECTION

Approximately 5 percent of lung cancers involve the chest wall by direct extension. This involvement may be limited to the parietal pleura or may invade the endothoracic fascia, intercostal muscle, or ribs. Chest wall involvement by direct extension is *not* a contraindication to resection unless vertebral bodies are invaded, and even then, under some circumstances, resection may still be completed. Chest wall pain is the most sensitive predictor of chest wall involvement in a patient with a peripheral lung lesion in which there is a question of chest wall invasion. Neither CT scan nor MRI can distinguish between abuttment and invasion unless there is gross invasion of bone. The radionuclide bone scan may be negative with chest wall involvement, especially if only the parietal pleura and muscle are involved. Lesions involving parietal pleura or other chest wall structures are staged as T3 primary tumors, but often definitive staging cannot be accomplished until the time of operation.

As with any lung cancer it is important to rule out disseminated disease prior to considering operation in a patient with chest wall involvement. It is particularly important to assess the mediastinum in these patients, since mediastinal lymph node involvement is the single best prognostic indicator. Three-year survival approaches zero in patients with chest wall and mediastinal lymph node involvement, underscoring the importance of invasive mediastinal lymph node staging, usually with mediastinoscopy, prior to considering thoracotomy in this patient group. Conversely, greater than 50 percent 5-year survival can be expected in patients with chest wall involvement with negative mediastinal lymph nodes as long as the resection margins are negative.

The operation performed in a patient with suspected chest wall involvement begins by assessing the pleural space to rule out diffuse pleural disease and then defining whether the chest wall is invaded. Prior to beginning the chest wall resection it is important to assess the hilum of the lung to ensure that the findings do not preclude resection. It is disconcerting to resect a large chunk of chest wall only to find that there is such extensive disease at the pulmonary hilum as to preclude parenchymal resection. Often one finds only adherence with no evidence of invasion, and this is established by beginning the resection in the extrapleural plane, thus separating the parietal pleura from the endothoracic fascia in the area of the lesion. If this plane is easily developed, something that is very clear to the experienced surgeon, it may be that the parietal pleura are not invaded. If there is any question at all about invasion when attempting to develop the extrapleural plane, then chest wall resection is performed (Fig. 110 I-7). Ideally the chest wall resection is performed in continuity with the parenchymal resection, that is the portion of chest wall resected remains attached to the underlying lung. The chest wall resection should include at least one rib and preferably two above and below the area of chest wall invaded. Three- to five-cm margins should also be taken anteriorly and posteriorly. The intent is to achieve negative margins, so the resection should be wide; there is little if any additional morbidity to taking a somewhat larger piece of chest wall.

Once the chest wall block is totally mobilized, the lobectomy and mediastinal lymph node dissection are completed. A mediastinoscopy should have been performed earlier, but a lymph node dissection should be done for complete staging. A posterior chest wall defect is reconstructed with polypropylene mesh, and a defect in the anterior chest wall should be reconstructed with a sandwich of methylmethacrylate cement and polypropylene mesh. Posteriorly the defect is covered additionally by the scapula, but anteriorly the rigid fixation provided by the methyl methacrylate and mesh eliminates any paradoxical motion that might interfere with mechanics of breathing. Interference with the mechanics of breathing is much less likely to occur with posterior defects.

Chest wall resection adds little if any additional morbidity to a pulmonary resection. Patients tend to have the chest tubes in a few days longer following chest wall resection because of increased fluid drainage. Pain in the early postoperative period is best controlled with a thoracic epidural catheter, which allows patients to be comfortable enough to maintain a good cough for clearance of secretions. There is no evidence that patients undergoing chest wall resection are subject to more pain than those who have a simple lobectomy. If the cough is ineffective, then secretion retention is aggressively managed with periodic bronchoscopies.

Postoperative treatment for patients who have undergone chest wall resection with pulmonary resection remains controversial. The most important consideration is

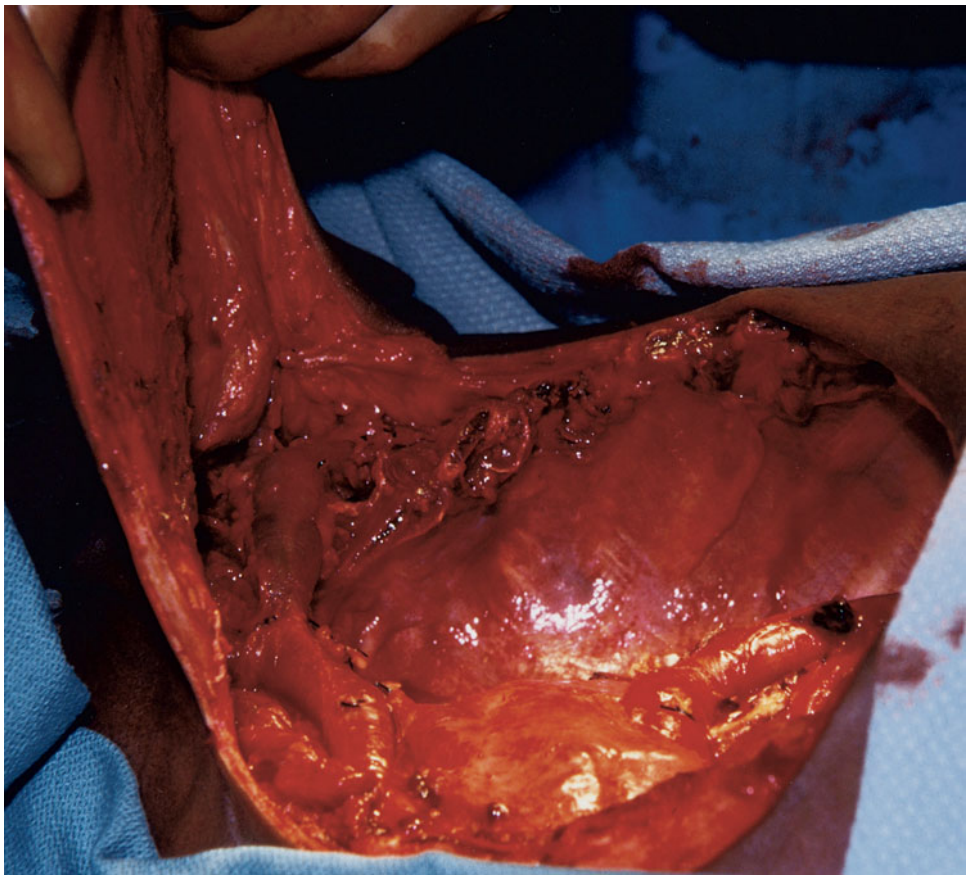

Figure 105 I-7 Operative photograph showing the defect left after resection of the left upper lobe in continuity with the anterior chest wall. This anterior defect requires reconstruction with prosthetic mesh and methylmethacrylate cement.

the attainment of negative resection margins at the time of operation. The surgeon should never think that a few close margins or even a small amount of gross disease left behind can be "cleaned up" by the radiation oncologist. Anything less than a complete resection is associated with poor long-term survival. With negative surgical margins is there a role for radiation therapy? Currently no evidence exists that postoperative radiation therapy prolongs survival in this patient group, but local recurrence may be problematic. Thus there may be a role for radiation therapy in some of these patients—in particular those with disease close to the spine, in whom local recurrence presents major management problems.

Tumors Involving the Mediastinum by Direct Extension

Some centrally located primary tumors may involve structures in the mediastinum by direct extension (Fig. 110 I-8). The assessment of this involvement, whether there is true invasion or just abuttment and adherence, cannot be determined until the findings are seen intraoperatively and then often only as the dissection proceeds. The presence of a central tumor that appears on CT scan to be close to the mediastinum is not justification for making a judgment of unresectability, especially if the judgment is being made by someone other than a surgeon. This is a judgment that can only be made intraoperatively, since no imaging modality readily distinguishes abuttment from invasion. There may be other reasons why the patient should not be operated on, but it is dangerous to simply assume that a lesion is unresectable. The distinction between a T3 tumor involving the mediastinum and a T4 tumor depends on the mediastinal structure invaded. Tumors invading structures such as the phrenic nerve, mediastinal pleura or fat, the pericardium, or the diaphragm that may be readily removed are classified as T3 primary tumors and as such are in the stage IIIa group, which also includes mediastinal lymph node involvement and tumors involving chest wall. T4 primary tumors involve those structures that usually are not considered to be resectable, such as aorta, left atrium, superior vena cava, trachea esophagus, or vertebral bodies. There are occasions when tumors involving these structures are resected, most commonly with lesions involving the vena cava or left atrium. Rarely, if ever, is a portion of aorta resected for excision of a lung tumor, but a lesion may involve only the muscular coat of the esophagus and thus may be amenable to

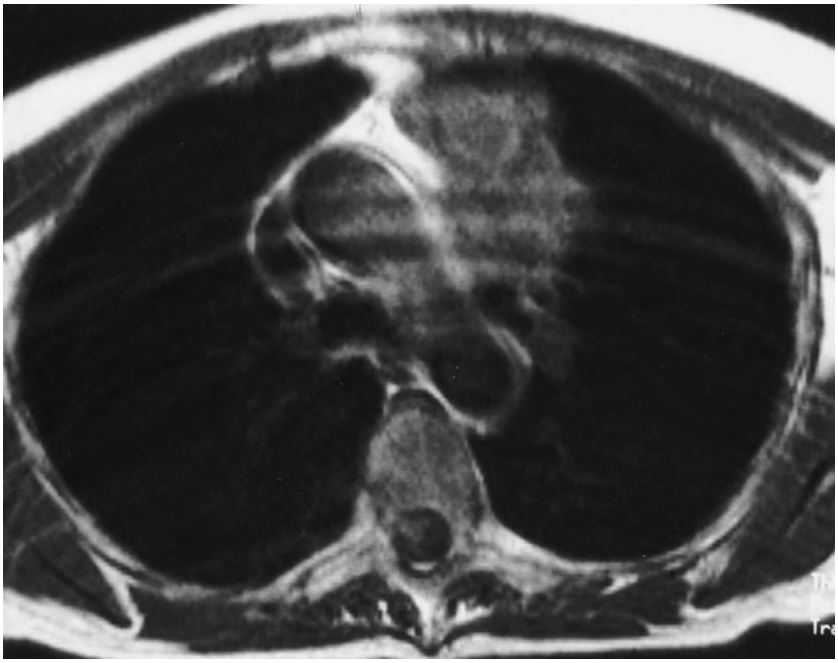

Figure 105 I-8 MRI scan showing a primary lung tumor involving the aorta by direct extension (T4 primary). The distinction between abuttment and invasion often cannot be made until the findings are seen at operation. MRI is no better at delineating invasion than CT.

resection. What is important to recognize, however, is despite the seeming ability to remove some of these invasive lesions, the prognosis for long-term survival is dismal. For T4 lesions, fewer than 10 percent of patients are alive at 5 years. From the viewpoint of the surgeon, although certainly recognizing the poor long-term survival with these tumors, in the absence of mediastinal lymph node involvement it is difficult to simply back out and leave the tumor in place when it is possible to resect the lesion with minimal morbidity, such as when a portion of vena cava or piece of left atrium is all that is necessary to complete a resection. Extensive involvement of one of these structures is an absolute contraindication to resection.

It is illustrative to discuss the situation of a patient who presents with the new onset of hoarseness and is found to have a paralysis of the left vocal cord. Almost always a tumor will be found in the left chest, usually the left upper lobe. In fact the acute onset of left vocal cord paralysis should be assumed to be from a cancer of the lung until proved otherwise. A benign problem causing a left vocal cord paralysis is distinctly unusual. Rarely, if ever, is hoarseness due to right vocal cord paralysis because of the position of the right recurrent laryngeal nerve, which "recurs" around the right subclavian artery above the apex of the chest. Conversely, the left recurrent nerve is in a position of great vulnerability, since it arises after the vagus nerve crosses the aortic arch and recurs around the ligamentum arteriosum (Fig. 110 I-9). The left recurrent nerve may be involved either by a primary tumor, which encases the vagus nerve as it crosses the aortic arch, or more commonly by lymph node disease in the aortopulmonary window. Because of the depth of the aortopulmonary window, there can be gross mediastinal lymph node involvement and a sheet of tumor with minimal plain radiographic evidence, since tumor underneath the aortic arch is not easily seen. CT scan usually confirms extensive involvement. Involvement of the left recurrent laryngeal nerve represents a contraindication to operation, since rarely are these lesions able to be completely resected. Left recurrent laryngeal nerve involvement should exclude patients from participating in neoadjuvant trials as well. The only exception is the occasional situation in which the primary tumor involves the vagus nerve as it crosses the aortic arch, a situation that may prove to be resectable and justifies exploration.

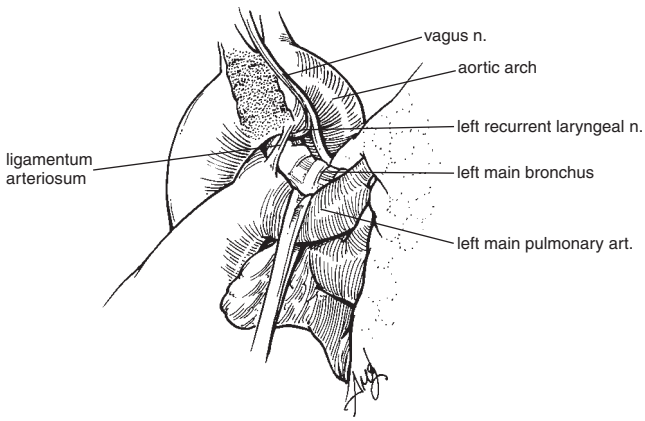

Figure 105 I-9 The anatomy of the aortopulmonary window showing the relationship of the left recurrent laryngeal nerve to the aortic arch and ligamentum arteriosum. The nerve is easily damaged in this location. Hoarseness may result from tumor involvement of the nerve in this location or from involvement of the vagus nerve at the level of the aortic arch proximal to the location where the recurrent laryngeal nerve originates.

Palliative Resections

There is essentially no role for palliative resections in the modern management of NSCLC. Morbidity resulting from the primary tumor usually may be managed using modalities other than operation. There probably is no justification for operation if less than a complete resection is anticipated. At the present time there is no role for surgical "debulking" in the management of the patient with unresectable disease. With the newer treatment planning modalities available, radiation therapy can be given accurately and in high doses to patients who are inoperable or unresectable. Patients with hemoptysis or postobstructive pneumonia may benefit from laser excision of the endobronchial disease combined with external beam radiation therapy and endobronchial placement of radioactive sources. Laser excision may be combined with stent placement to maintain open an obstructed bronchus or trachea. Chest wall pain usually is readily controlled by a course of radiation therapy.

RESULTS OF TREATMENT

Postoperative Complications

Major improvements in perioperative care of patients undergoing thoracic surgical procedures have led to decreased morbidity and mortality when compared with only 10 to 20 years ago. Improved preoperative evaluation of patients has allowed us to identify risk factors associated with morbidity and address these early on. Experience with lung transplantation has shown that deconditioned patients benefit from at least a 6-week period of pulmonary rehabilitation, and selected patients with otherwise operable disease may be placed in a rehabilitation program prior to undergoing operation. Quantitative perfusion lung scans have allowed us to better select borderline patients for pulmonary resection, especially when pneumonectomy is a possibility. This information has all but eliminated the "pulmonary cripple" as a result of a lung resection. Recent experience with bilateral lung volume reduction surgery demonstrates that patients with severe emphysema and hyperinflation actually benefit from the resection of nonfunctional pulmonary parenchyma and has fueled the realization that no matter how poor the pulmonary function studies, many of these patients may be candidates for resection. The further refinement of lung-conserving procedures and the use of minimally invasive techniques such as video thoracoscopy along with better perioperative pain management provided by continuous epidural administration of narcotic have provided the incentive for us to operate on many patients previously thought not to be candidates because of poor pulmonary function. A greater recognition of the importance of preoperative teaching of postoperative maneuvers such as coughing and the use of chest physiotherapy given by expertly trained individuals also has contributed to decreasing respiratory complications. With the ascent of a class of formally trained cardiothoracic surgeons who confine their practice to general thoracic surgery, as distinct from cardiac surgery, have come dedicated inpatient units to care for patients undergoing pulmonary resections.

Postoperative Mortality

Recent analyses identify that modern 30-day operative mortality from pulmonary resections should be less than 4 percent. Lobectomies and lesser resections should have a mortality between 1 and 2 percent, and pneumonectomies still carry a mortality of 6 to 7 percent. The mortality rate is directly proportional to increased age, associated diseases, and the extent of resection. Respiratory complications, not surprisingly, are the most common cause of postoperative mortality in patients undergoing pulmonary resection. Cardiac complications also account for a significant percentage of mortality, and technical problems such as hemorrhage, bronchopleural fistula, and empyema account for a small but significant percentage of complications leading to death.

Postoperative Morbidity

Approximately 30 percent of patients undergoing pulmonary resection sustain a postoperative complication, of which approximately two-thirds are minor and the other one-third nonfatal major complications. The most common complication is supraventricular arrhythmia, which occurs in up to 20 percent of patients, depending on how closely patients are monitored. Most of these respond to simple pharmacologic manipulation and rarely are hemodynamically significant at onset. With appropriate treatment the rhythm reverts to sinus rhythm quickly, and patients may be taken off the antiarrhythmic drugs usually after 1 month. Other minor complications include postoperative air leaks lasting greater than 7 days and atelectasis. Major nonfatal events most commonly are respiratory related, with patients developing significant infiltrates and pneumonitis. A small percentage of patients require reintubation in the postoperative period for respiratory failure usually related to the development of an infiltrate. There are no definitive predictors for postoperative pulmonary complications, although significant risk factors for major complications include age greater than 60 years, FEV_1 less than 2 L, weight loss greater than 10 percent, associated systemic disease, and extent of disease. Pulmonary complications can be minimized with meticulous attention to postoperative respiratory maneuvers, including chest physiotherapy and preoperative teaching.

Other complications of pulmonary resection include wound infections and disturbances in mental status, especially in older patients. Fortunately, Postpneumonectomy complications are unusual, but the most common one is empyema with or without a bronchial stump leak.

Prognosis Following Resection

Prognosis following pulmonary resection has been well analyzed, and results are summarized in Table 110 I-2.Prognosis

Table 105 I-2

5-Year Postoperative Survival by TNM Stage Based on Data from Lung Cancer Study Group Trials

	Squamous Cell Adenocarcinoma	
Stage	**($n = 549$),%**	**($n = 572$)%**
Stage I		
T1NO	83	69 ($p = 0.02$)
T2NO	64	57
Stage II		
T1N1	75	52 ($p = 0.04$)
T2N1	53	25 ($p < 0.01$)
Stage IIIa		
T1-2N2	46	35
T3N0	37	21

depends mainly on TNM stage, a classification that was revised as recently as 1986. Short of disseminated disease, prognosis mainly depends on the status of the regional lymph nodes. Prognostic data are only as good as the sampling done at the time of operation, and lymph node dissection is the only sure way to ascertain definitively the status of the lymph nodes. Histologic type also has some prognostic significance but to a lesser extent, and histologic grade, according to present knowledge, has little prognostic significance. The presence of neuroendocrine features in what is otherwise an NSCLC, however, may have prognostic significance.

Sites of Recurrence

Patients with lung cancer die of disseminated disease, and it is a distant site that most commonly is the first site of recurrent disease. Over 30 percent of patients with adenocarcinomas develop brain metastases, a percentage significantly higher than for patients with squamous carcinoma. Other common sites of metastatic disease include bone, lung, liver, and adrenals. Patients with higher-stage disease have a significantly greater likelihood of developing disseminated disease. This recognition has led to the neoadjuvant treatment regimens in patients with N2 disease. Local recurrence occurs, most commonly associated with distant disease. Isolated local recurrence is a rare phenomenon but sometimes is amenable to resection. This underscores the importance of a complete resection at the time of the initial operative procedure. Sites of local recurrence that may cause problems include the chest wall (pain), superior vena cava (SVC syndrome), and involvement of the left recurrent laryngeal nerve (hoarseness and swallowing problems). Symptomatic local recurrence is often treated with radiation therapy, and chemotherapy is employed for some patients who develop disseminated disease, while recognizing that cure is usually not possible in patients who have developed distant disease.

Postsurgical Follow-up

Recognizing that essentially no patient is cured once distant disease is present might raise the question of why patients should be followed at all after pulmonary resection. Is there an advantage to recognizing the development of distant disease early rather than late? Actually there may be some advantage, especially when it comes to preventing some of the morbidity that may accompany disseminated disease if treatment begins early. Also the occasional patient presents with an isolated local recurrence that may be amenable to surgery. Perhaps most important is the sense of comfort patients derive from knowing that they are being closely followed by their physician or surgeon, especially if the follow-up is done in a cost-efficient manner it is difficult to fault.

Since most local recurrences occur within the first 2 years following resection, patients should be seen every 3 months, with a chest radiograph as the only diagnostic study. There is absolutely no need to obtain a CT scan as a follow-up study, and no blood tests are of any use in following these patients. Further studies are ordered based on patient complaints or findings elicited by a careful history and physical examination in addition to the chest radiograph. Between years 2 and 5, patients are seen every 6 months, and after 5 years on a yearly basis. Usually the development of disseminated disease is obvious as patients relate the history of problems since their last visit. Imaging studies tend only to confirm the clinical impression, and then a decision regarding further treatment needs to be made.

FUTURE DIRECTIONS

The role of surgery in the management of NSCLC has been well defined and remains the standard therapy for patients with localized disease. The challenge for all who deal with lung cancer is the problem of disseminated disease. Perhaps the better way to deal with the problem is to identify causes of the disease in addition to the already well-defined risk of cigarette smoking. Thus far a "lung cancer susceptibility" gene has not been demonstrated; however, based on the recent explosion of knowledge related to breast cancer, the identification of one or more genes involved in the genesis of certain lung cancers is at hand. Cigarette smoking has been identified as a major risk factor, yet only a small percentage of patients who smoke develop lung cancers. Efforts to identify such susceptibility genes have been hampered by the relative lack of families with a genetic predisposition. The issue of smoking as a risk factor only serves to confound the search.

Molecular markers to identify patients at increased risk of developing recurrent disease are also desperately needed.

Once identified, these patients would begin adjuvant therapy designed to prevent recurrence in this high-risk group, sparing those patients who are at lower risk. This further underscores the need for better adjuvant therapy, since none exists at present. Targeting specific factors that control lung cancer development or specific receptors on lung cancer cells seems a more sensible strategy than that utilized by currently available antineoplastic agents. Major strides have been and continue to be made in the molecular biology and genetics of tumors, and we can expect lung cancer to be the beneficiary of some of these developments.

In the meantime refinements in surgical techniques and perioperative management of patients with lung cancer have allowed greater numbers of patients with localized and locally advanced disease to benefit from operative intervention. Many patients with mediastinal lymph node disease previously thought not to be operative candidates now are able to be operated upon with improved survival after a course of neoadjuvant therapy. Other patients with pulmonary function so compromised that it precluded resection now are often considered for resection using the minimally invasive techniques developed within the previous few years aided by better pain management and postoperative chest physiotherapy. It's safe to say that surgery will continue to play a major role in the management of patients with NSCLC.

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105

Part II: Treatment of Non–Small-Cell Lung Cancer
Chemotherapy

Ranee Mehra • Joseph Treat

Approximately 45 percent of patients with non–small-cell lung cancer (NSCLC) have evidence of advanced stage disease when first seen by a physician. Such data have led to the assumption that NSCLC is generally a systemic disease and that relatively few patients have localized disease that is amenable to a surgical approach alone. Unfortunately, patients with disseminated disease are rarely cured despite our best efforts. In the most favorable prognostic group, those with T1N0 disease (i.e., up to 25 percent) are destined to fail within 5 years after surgery. Therefore, since even patients with localized disease are likely to develop disseminated disease, systemic therapy is an important component of therapy.

Historically, single cytotoxic chemotherapeutic agents have achieved only minimal response rates in NSCLC, so regimens that entail combinations of drugs have evolved as first-line standard therapy—if any therapy can be designated as "standard" in this disease. Definition of the role of chemotherapy in the treatment of this disease continues to evolve. In addition, the development and study of molecular targeting agents have added more treatment options for NSCLC, especially in the advanced stage setting.

CRITERIA FOR REPORTING RESULTS

Several criteria are used in assessing the efficacy of chemotherapy. One of these is response rate based on radiographic criteria. Response is measured as the percent of decreasing tumor size; the decrease is qualified in terms of being complete (total disappearance by radiologic or physical examination) or partial. A partial response is defined as either a 50 percent reduction in the product of the largest dimensions of the lesion without any new lesions (WHO criteria), or as a 50 percent reduction in the sum of the largest dimension of all target lesions without any new lesions (RECIST criteria). Responses are almost always partial in NSCLC.

Although response rates are important in the assessment of new agents or combinations, response rates that are reported by a single institution on the basis of a nonrandomized trial (without a "standard" comparison arm) should be interpreted with caution. A high response rate determined in this way may call attention to an active new agent or combination, but in the last analysis, efficacy can be demonstrated

only by larger randomized trials. Many factors influence the response rate in single-arm phase II trials. These include patient selection in terms of performance status, extent of disease, weight loss, and symptoms. Sicker patients, with extensive disease and a worse performance status, tend to be left out of these trials.

Once a new active drug or combination has been identified, a larger randomized trial is necessary to determine whether it offers advantages over a previously established regimen. Although response rates are still being reported, survival is the major end point in treating NSCLC by chemotherapy. Small improvements in survival (e.g., additional 10 weeks), although statistically significant, are of dubious biologic and clinical significance. In addition, quality-of-life indices that are standardized and reproducible are now available as part of the evaluation of clinical benefit. It seems likely that future clinical trials will include quality of life and cost analysis as measurable end points.

It is also important at this point to distinguish between *efficacy* and *effectiveness*. A particular regimen may demonstrate *efficacy* within the confines of a limited clinical trial conducted at academic institutions by interested and committed investigators who have a large cohort of patients from which to choose for the study. The extent to which the results of such a trial, based on a selected group of patients, is applicable to the general population is often unpredictable. An *efficacious* regimen administered within the confines of a limited clinical trial by dedicated investigators may prove not to be *effective* when applied to a larger population and administered by a multitude of clinicians. This dichotomy between *efficacy* and *effectiveness* needs to be kept in mind when one is evaluating results of any clinical trial. It is especially important, however, when one is looking at results of trials of therapeutic methods in advanced malignant disease, in which the response rates are modest at best.

LOCALIZED NON–SMALL-CELL LUNG CANCER

Early Stage Disease

Surgery remains the best option for patients with localized disease who do not have overwhelming medical contraindications to a lobectomy or pneumonectomy. Staging is central to the therapeutic approach to NSCLC. This entails determination of the extent of invasion of the mediastinal lymph nodes. Mediastinoscopy is the procedure of choice for sampling mediastinal lymph nodes before a thoracotomy. As for all surgical interventions for thoracic malignancy, complete nodal sampling or lymph node dissection is an integral part of the procedure. Staging of a patient with localized lung cancer is feasible only if the status of the mediastinal lymph nodes is ascertained. Reliance on noninvasive imaging alone may be inadequate for accurate assessment of the mediastinum (Figs. 105 II-1 and 105 II-2).

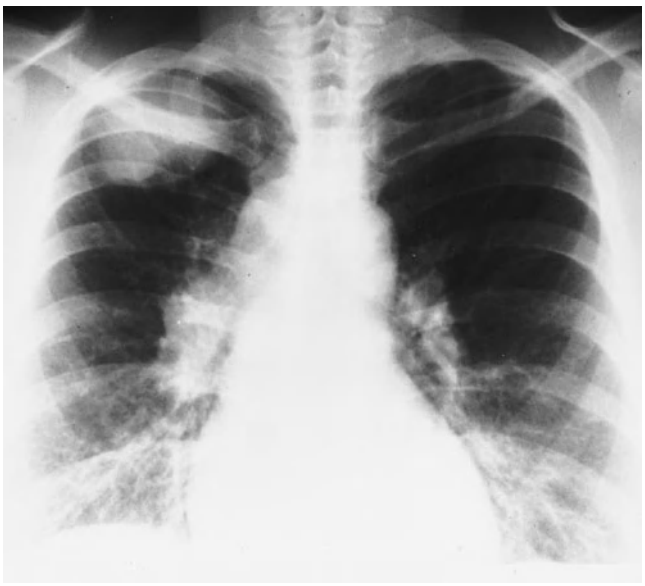

Figure 105 II-1 Chest radiograph of a 60-year-old female smoker who presented with increasing cough. The film shows a large right upper-lobe mass with obvious mediastinal and hilar adenopathy. Ipsilateral mediastinal lymph node involvement was confirmed by mediastinoscopy. An extent-of-disease evaluation failed to demonstrate any evidence of disseminated disease. The patient was treated in a protocol setting with preoperative chemotherapy.

Role of Adjuvant Chemotherapy

It is well recognized that despite complete resection, most patients with locally advanced NSCLC will, at some time, develop disseminated disease. As noted, the risk of developing disseminated disease can be predicted, with some accuracy,

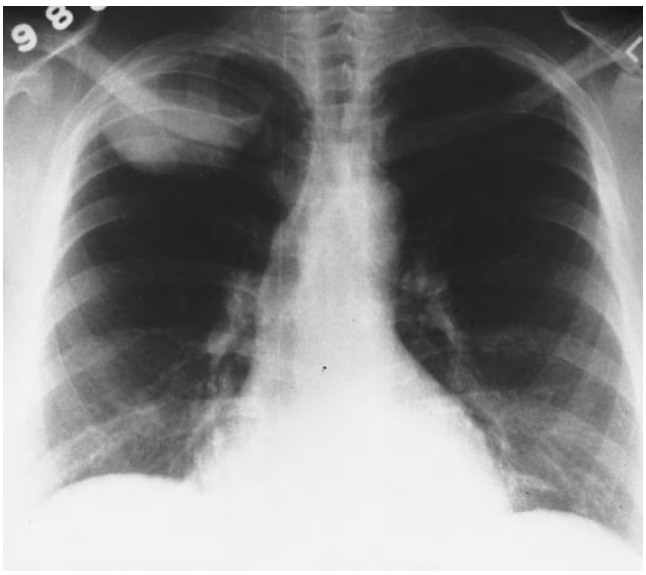

Figure 105 II-2 Chest radiograph of the same patient as in Fig. 105 II-1 following two cycles of chemotherapy. Note the minimal effect on the primary tumor, but the considerable decrease in size of the nodal metastatic disease. The patient subsequently went to surgery and was able to have a complete resection.

Table 105 II-1

Randomized Trials for Adjuvant Chemotherapy

Number of Patients	Overall Stage	Therapy	Survival (months)	1 Yr	Survival (%) 2 Yr	3 Yr	5 Yr	Reference
1867	IA, IB, II, III	Observation Chemo			66.7 70.3*	44.5*	40.4	IALT Arriagada R, Bergman B, et al., 2004
344	IB–T2N0	Obs Chemo	78 95	94 94	84 90	71 79*	57 59	CALGB 9633 Strauss GM, Maddaus MA, Johnstone DW, Johnson EA, et al., 2004; Strauss GM, Maddaus MA, Johnstone DW, et al., 2006
482	IB, II (no T3N0)	Obs Chemo	73 94				54 69*	NCIC JBR10 Winton T, Livingston, R, et al., 2005
840	IB-IIIA	Obs Chemo	43.7 65.7*					ANITA Douillard JY, Rosell R, et al., 2006

* *Statistically insignificant.*

on the basis of the stage of the disease determined at the time of the initial resection. However, the value of the staging information depends on the completeness of the staging procedures carried out at the time of resection. Even with stage I disease, as many as 20 percent of patients die of disseminated disease within 5 years. With stage II disease, less than 50 percent of patients are alive at 5 years; with stage IIIA N2 disease, at best 30 percent of patients are alive at 5 years. These numbers make clear the need for some additional therapy to improve on the overall survival achieved by surgery.

To this end, there has been an emergence of a body of data to better define the role of chemotherapy in the adjuvant setting. The rationale behind this approach is to treat patients who are deemed to be at high risk for recurrence and dissemination of disease in the hope of eliminating micrometastatic disease. Early trials to study adjuvant chemotherapy have been negative, possibly either due to the use of less effective chemotherapy regimens, the increased morbidity of treatment with fewer supportive care options, or the lack of statistical power. However, interest in studying adjuvant chemotherapy reemerged with presentation of a meta-analysis in 1995 in which 52 randomized trials were reviewed. The authors concluded that the trials that compared cisplatin–based chemotherapy to no chemotherapy favored the used of chemotherapy with an absolute benefit at 5 years of 5 percent. Since then, more homogeneous trials randomizing patients to surgery versus surgery followed by platinum-based chemotherapy have been conducted. These studies are outlined in Table 105 II-1.

International Adjuvant Lung Cancer Trial

The International Adjuvant Lung Cancer Trial (IALT) randomized 1867 patients with stage I, II, or III NSCLC to observation or chemotherapy after they had undergone a surgical resection of their tumor. The two groups were evenly matched with regard to age, sex, stage, performance status, type of surgery, and histologic subtype. The chemotherapy regimen used consisted of cisplatin 80, 100, or 120 mg/m^2 offered on one of four different schedules with vindesine, vinblastine, vinorelbine, or etoposide. Patients were treated with three or four cycles. Of the various choices, the combination of cisplatin and etoposide was used to treat nearly 50 percent of the patients. Due to the lack of consensus regarding the used of adjuvant radiotherapy, this was allowed with the choice being left available to individual practitioners. When offered, radiation was given after chemotherapy in the group randomized to postoperative treatment. Radiation was planned for about 30 percent of the patients of the trial, with two-thirds of these having N2 disease. It was actually delivered to slightly more patients in the control group compared with the chemotherapy group (28 vs. 23 percent). Overall,

the results favored the use of adjuvant chemotherapy, with a hazard ratio (HR) for death of 0.86 (0.76–0.98). At five years, the group that received chemotherapy had a statistically significant improvement in survival of 44.5 versus 40.4 percent. The toxicities associated with chemotherapy included the expected risks of neutropenia and nausea/vomiting. However, seven patients died due to chemotherapy-related acute toxicities. In general though, this positive trial provided an absolute benefit in 5 years that was consistent with the meta-analysis and provided support for the use of a cisplatin doublet in the adjuvant setting.

Retrospectively, tissue samples collected from patients on IALT have been analyzed by immunohistochemistry (IHC) to assess which biomarkers may predict for a response to cisplatin therapy. Specifically, investigators have assayed for the enzyme excision repair cross-complementation group 1 (ERCC1). Cisplatin acts by directly binding to DNA and forming platinum-DNA adducts, which prevents DNA replication. It is known that the presence of ERCC1 is associated with cisplatin resistance due to the activation of DNA repair mechanisms. To study this in the context of the IALT results, 761 tumor samples from that trial were assayed for ERCC1 expression by IHC; half of these patients received chemotherapy and the remainder were in the control group. Of the tumors analyzed, 44 percent were ERCC1 positive. Expression was more common in patients over the age of 55 and those with squamous cell histology. Interestingly, there was a benefit from adjuvant chemotherapy in patients with ERCC1-negative tumors, with a statistically significant improvement in overall survival and disease-free survival due to chemotherapy (HR 0.65). In contrast, patients with ERCC1-positive tumors did not achieve a survival benefit from adjuvant chemotherapy compared with the control group. Among patients in the control group, those with ERCC1-positive tumors had an increased survival compared with patients with ERCC1-negative tumors. Although these results are intriguing, ERCC1 is currently not routinely tested in the clinical setting, and its use as a predictive marker for cisplatin-based adjuvant therapy needs to be validated in a prospective clinical trial.

CALGB 9633

The Cancer and Leukemia Group B (CALGB) conducted a trial to test the benefit of adjuvant chemotherapy in only stage IB (T2N0) patients. Other studies have included these patients along with those with more advanced disease, and in subset analyses the true benefit of chemotherapy after surgery in this population has been questioned. Originally, this study was intended to enroll 500 patients. However, due to poor accrual, this number was modified and in the final analysis 344 patients were treated. Patients randomized to the chemotherapy arm received carboplatin AUC 6 and paclitaxel 200 mg/m^2 every 3 weeks for four cycles. This study has been provocative in that it was initially reported to be a positive trial with a statistically significant survival advantage in 2004, after a median follow-up of 34 months. This prompted the study to be terminated early, and the NCCN practice guidelines adopted the use of adjuvant chemotherapy in stage IB patients. Since then, when the results were updated after longer follow-up in 2006, the difference in 5-year survival between the chemotherapy and observation arms (59 vs. 57 percent) was no longer statistically significant. However, the 3-year survival difference still remains statistically significant, and there is a trend favoring a benefit in overall survival in the patients who received chemotherapy. Despite this, the routine practice of treating patients with stage IB disease can no longer be endorsed. In a subset analysis of the updated results, there was a statistically significant benefit in overall and disease free survival in patients with tumors over 4 cm in size who received chemotherapy. This benefit was not shared in those with tumors less than 4 cm in size. Therefore, in practice, many oncologists choose to treat patients with larger tumors, based on this subset analysis. The analysis of this study is still preliminary, as it has not met its planned target of 150 events for a final statistical analysis. Therefore, there will be much interest as the follow-up and data further mature. Currently, the reason why the results are negative to date is an active area of debate, and it is not known if this is due to the population of patients being treated, the choice of a carboplatin-based regimen rather than cisplatin, or the abridged number of patients who were treated.

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In this intergroup study, 482 patients with stage IB or II (excluding T3N0) NSCLC were randomized to either surgery or surgery followed by four cycles of chemotherapy. Again, the treatment studied included cisplatin (50 mg/m^2 days 1 and 8) and vinorelbine (25 mg/m^{2}weekly); one cycle was 4 weeks. This also was a positive study, with the 5-year survival favoring the chemotherapy group (69 vs. 54 percent), as well as a statistically significant improvement in disease-free and overall survival. Toxicity was associated with this regimen with two treatment-related deaths and over 70 percent of patients experiencing either grade 3 or 4 neutropenia. Other toxicities included fatigue, anorexia, and vomiting.

ANITA

The most recent study of interest is the Adjuvant Navelbine International Trialist Association study (ANITA), in which 799 patients with stage IB, II, or IIIA NSCLC were randomized to four cycles of chemotherapy or observation after surgery. Similar to the other trials, the chemotherapy regimen consisted of cisplatin (100 mg/m^2, day 1) and vinorelbine (30 mg/m^2, weekly) for a 4-week cycle. The choice of radiotherapy was left to the discretion of the treating physicians, and in the final analysis 24 percent of patients in the chemotherapy arm and 33 percent of patients in the observation arm received radiation. Patients who were randomized to chemotherapy had a significant improvement in overall survival to 66 months, compared with 44 months in the

control group. At 5 years, the absolute benefit in survival was 8.6 percent, and in a subset analysis this benefit seemed to be mainly noted in stage II and IIIA patients. This result is tempered by the occurrence of seven chemotherapy-related deaths.

Future Directions

Adjuvant cisplatin doublet chemotherapy is currently the standard of care for stage II and IIIA patients. The role of adjuvant treatment of stage IB patients has yet to be defined more clearly, but based on subset analyses it is possible that patients with tumors greater than 4 cm will benefit from chemotherapy. Given the now-negative results of the CALGB 9633 study, carboplatin cannot be recommended as a standard choice for adjuvant treatment. Hopefully future studies will provide further data to guide the therapy of stage IB patients. Also, although molecularly targeted agents have been studied in the advanced disease stage (as detailed in the following), the utility of these agents in the early stage setting is unknown. To begin to answer this question, the current large intergroup effort that is underway will randomize patients with stage IB (greater than 4 cm), II, and IIIA NSCLC to a cisplatin–based doublet either with or without the anti-angiogenesis agent bevacizumab.

Role of Adjuvant Radiotherapy

Research conducted by the Lung Cancer Study Group on patients with either stage II or IIIA disease who had undergone resection of a squamous cell carcinoma showed that those who received postoperative radiation therapy (without chemotherapy) had a significantly lower incidence of local recurrence to the ipsilateral lung or mediastinum than those receiving no postoperative radiation. There was especially a benefit in patients with N2 disease. However, the decreased incidence of local recurrence with radiation has not been shown to translate into a survival benefit. This result should not be surprising, since patients with lung cancer die of disseminated disease and one would not expect treatment with postoperative radiation therapy—like surgery, a local modality—to prevent the development of disseminated disease. With trials that support the use of adjuvant chemotherapy in stage II and IIIA disease, adjuvant radiotherapy alone is not considered to be the standard of care. The Eastern Cooperative Oncology Group (ECOG) conducted a trial in which patients were randomized to postoperative radiotherapy or radiotherapy (RT) and chemotherapy (cisplatin/etoposide). However, there was no benefit in overall survival or local control with the addition of chemotherapy to RT. Thus, concurrent postoperative chemoradiotherapy is also not considered to be a standard treatment approach. Sequential RT after adjuvant chemotherapy in patients with N2 disease is currently an area of controversy. Although this approach is recommended by some practitioners, it has not been validated in a prospective, randomized study.

LOCALLY ADVANCED NSCLC

The term *locally advanced* includes several different presentations of primary lung cancer, but all have in common the absence of disease outside of the chest. Some of these lesions are eminently resectable, others marginally resectable, and others out of the realm of resectability. Included in this group of lesions are those with mediastinal lymph node involvement (N2 disease), direct extension into certain mediastinal structures (T3), direct extension into the chest wall (T3), and certain endobronchial lesions.

Lesions that directly invade the mediastinum but affect structures that are not usually considered resectable (e.g., aorta, esophagus, and vertebral bodies) are classified as T4 and are considered to be stage IIIB. The distinction between IIIA and IIIB lesions is important, since prognosis is significantly worse for the latter lesions. The distinction between a T3 and T4 primary often cannot be made on the basis of preoperative imaging and depends on a determination made at thoracotomy. As indicated, mediastinal lymph node invasion can be determined before thoracotomy by way of mediastinoscopy, which also allows contralateral mediastinal lymph nodes to be sampled. Contralateral nodal invasion indicates N3 disease, which also falls within the unresectable stage IIIB classification.

Many studies in which patients with locally advanced disease were treated with chemotherapy, radiotherapy, or a combination of the two have relied on noninvasive determination of the extent of the disease. Thus, on the basis of enlarged mediastinal lymph nodes seen on a computed tomographic (CT) scan, patients were assumed to have N2 disease and were treated without histologic documentation of mediastinal lymph node impairment. Such studies are seriously flawed. For meaningful interpretation, accurate histologic staging has to be included as an entry criterion for any study of locally advanced disease.

About 40,000 cases of stage IIIA and IIIB disease occur per year in the United States. The best treatment approach to locally advanced disease has not yet been determined. A wide array of combined modality approaches have been used in stage IIIA patients (particularly those with N2 nodes). These include varying combinations of chemotherapy, radiation, and surgery. Unfortunately, some T3 patients have been included in many of these trials—again complicating interpretation of the results (Fig. 105 II-3).

Radiation Therapy Alone

Prior to the development of regimens with chemotherapy and chemoradiotherapy, radiation therapy alone was the standard treatment for patients with N2 disease. This practice resulted in a 5-year survival of about 5 percent. This form of treatment was based largely on a clinical trial begun in 1973 by the Radiation Therapy Oncology Group (RTOG 73-01). This study looked at different doses of radiation (4000, 5000, or

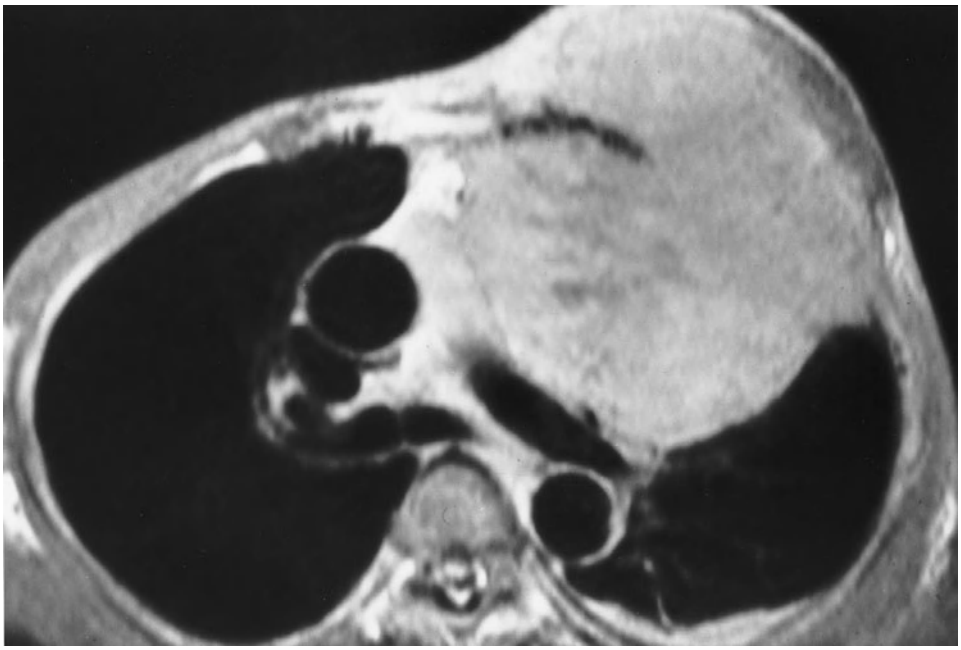

Figure 105 II-3 MRI scan of a patient with locally advanced disease invading the chest wall and at least abutting the mediastinum. At exploration, the lesion was found not to be invading the mediastinum and was completely removed with a lobectomy and chest wall resection.

6000 cGy), as well as split-course versus continuous therapy at 4000 cGy. Interpretation of this study is difficult because of the relatively poor quality of the CT scan images available at that time and the lack of histologic evidence of N2 disease before entry into the study. Nonetheless, this trial did demonstrate responsiveness at the higher doses of radiation and improved survival at 3 years for the 6000-cGy arm. At 5 years, all treatment arms were associated with a 5 percent survival. Today, after accurate staging, many of these patients would be eligible for combined modality treatment that consists of chemotherapy and radiation therapy, with or without surgery.

Another historic study, conducted by the Southwestern Oncology Group, randomized patients to radiation alone (6000 cGy), single-agent chemotherapy with vindesine, or concurrent vindesine and radiation therapy. The median survival and percentage of patients alive at 5 years were 8.6 (3 percent), 10.1 (1 percent), and 9.4 months (3 percent), respectively. This study underscore the lack of effect of radiation as a single modality as well as the lack of improvement when a single drug is added to radiation therapy. Since combination chemotherapy that includes cisplatin provided longer survival than did any single agent, in subsequent studies combination chemotherapy was added to radiation therapy in the attempt to improve results.

Chemotherapy Followed by Radiation Therapy: Randomized Trials

Several prospective, randomized studies have compared radiation therapy alone and radiation therapy in sequence with chemotherapy. Mattson's team reported a series of "inoperable" patients randomized to receive either radiation alone (5500 cGy) or chemotherapy (cyclophosphamide [Cytoxan], doxorubicin [Adriamycin], and cisplatin) followed by radiation. Patients were entered in this trial if they had disease confined to the hemithorax or mediastinal lymph nodes. Thus, patients with N1 disease and presumed T3 disease were included and analyzed together. There was no statistically significant difference in median survival times (10.2 vs. 10.9 months) or in long-term survival for the study groups as a whole. The study was flawed because of the inclusion of patients with different disease stages, a lack of histologic documentation of the stage of disease, and the use of a smaller than usual dose of cisplatin.

The North Central Cancer Treatment Group randomized patients to radiation alone (6000 cGy) versus chemotherapy (intravenous methotrexate, intravenous doxorubicin, intravenous cyclophosphamide, and oral lomustine) followed by radiation and additional chemotherapy. Again, no difference in median survival or long-term outcome could be demonstrated between the two treatment groups. Failure to obtain a benefit from chemotherapy may be due to the absence of cisplatin from this chemotherapy regimen.

In contrast, reports of cisplatin-based regimens do indicate an advantage for combined chemotherapy and radiation. Le Chevalier and associates randomized 353 patients to radiation alone (6500 cGy) or to cisplatin-based chemotherapy followed by radiation. One-, 2-, and 3-year survival rates all favored the combined therapy arm (51, 21, and 12 percent versus 41, 14, and 4 percent, respectively). However, using repeat biopsies, the study found only a 17 percent incidence of

local control in the radiation arm and a 15 percent incidence of local control in the chemotherapy and radiation arm.

In a trial conducted by the Cancer and Leukemia Group B (CALGB), 155 patients were randomized to either radiation alone (6000 cGy) or a cisplatin-based regimen followed by radiation. The median survival favored the combination therapy arm (13.8 vs. 9.7 months). The results at 1 and 2 years were so striking for the combined therapy group that the study was terminated early—a decision that subsequently prompted considerable criticism. The 3- and 5-year survival rates also favored the combination therapy (25 and 19 percent) over radiation therapy alone (11 and 7 percent). However, the intrathoracic failure rate was very high. Unfortunately, the study was limited to patients with a high performance status and less than 5 percent weight loss in the 6 months before enrollment in the trial. Limiting a study to the most favorable patients begs the question of the applicability of the results to the general group of patients with locally advanced lung cancer, many of whom have a decrease in their performance status and have lost considerable weight.

A study seeking to confirm the CALGB report was initiated by the RTOG, which randomized patients to the same two arms, in addition to a third arm using hyperfractionation radiation (69.6 cGy twice daily) as the only treatment modality. This study, RTOG-88-08, demonstrated that chemotherapy combined with radiation was indeed superior in the patients with good performance status (i.e., loss of weight of less than 5 percent in the previous 3 months). Analysis at 1 year showed the median survival to be statistically longer for those in the combined chemotherapy and radiation arm. At 3 years' follow-up, however, no difference in survival (14 percent) was found between the chemotherapy and radiation arm and the hyperfractionated arm. Both of these treatment regimens were better than standard radiation alone.

Concurrent Chemotherapy and Radiation Therapy

The rationale for concurrent therapy (i.e., chemotherapy given during a course of radiation therapy) is based on the concept that some drugs or drug combinations (notably cisplatin) may act synergistically with radiation. The trade-off, however, is an increase in toxicity and a regimen that is not well tolerated by all potentially eligible patients.

Several studies have tested the concept of concurrent therapy by combining frequent dosing of cisplatin with radiation. One such study, conducted by the European Organization for Research and Treatment of Cancer (EORTC), randomized 331 patients to radiation alone or to radiation with cisplatin given on either a daily or weekly schedule. At 2 years, 26 percent of patients treated with concurrent radiation and daily cisplatin were alive, in contrast to only 13 percent survival in the group receiving radiation alone. When given on a weekly basis with radiation, the cisplatin did not confer any advantage over radiation alone. In contrast, several older studies have failed to demonstrate an advantage for concurrent therapy in locally advanced disease (Table 105 II-2). It seems though, that the greatest advantage with concurrent chemotherapy and radiation therapy is seen at the 2- and 3-year marks.

Currently, with more experience with combined modality therapy, concurrent platinum chemotherapy and radiation therapy is the treatment of choice for patients with locally advanced, inoperable disease, provided their performance status and co-morbidities do not limit their ability to withstand the toxicities associated with this approach. This is based on data using platinum based chemotherapy regimens in conjunction with radiation. The RTOG conducted a three-arm trial (9410) in which 610 patients with unresectable NSCLC were randomized to sequential chemotherapy (cisplatin/vinblastine) followed by conventional RT, concurrent chemoradiotherapy with the same regimen, and concurrent chemotherapy with hyperfractionated RT. Median and 4-year survival were improved in the concurrent chemoradiotherapy arm with conventional RT, compared to sequential therapy and concurrent therapy with hyperfractionated RT (14.6, 17, 15.2 months, and 12, 21, 17%, respectively). Based on small phase II trials conducted by the Southwest Oncology Group (SWOG), a favored regimen for concurrent therapy utilizes cisplatin (day 1, 8, 29, 36) and etoposide (days 1–5, 29–33) with conventional RT. In one of these trials, this was followed by two cycles of consolidation cisplatin and etoposide with results of a median survival of 15 months and a 5-year survival of 15 percent. A subsequent trial used the same combined treatment regimen, but then used docetaxel for consolidation. This yielded a median survival of 26 months and a 3-year survival of 37 percent. However, a recent randomized study in which patients received cisplatin, etopiside, and radiation, either with or without consolidation docetaxel, failed to show a benefit from consolidation treatment. This is the first and only study of consolidation therapy after concurrent therapy and radiation. Another favored regimen utilizes low dose carboplatin and paclitaxel with radiation, followed by consolidation therapy with the same agents, resulting a median survival of 16 months, but again, this has only been studied in non-comparative phase II studies. As is described, it is unclear how combined chemoradiotherapy compares to induction chemotherapy followed by surgery or chemoradiotherapy followed by surgery. At the present time, this is a matter of institutional preference as well as based on the characteristics of individual patients.

Chemotherapy Followed by Surgery

Neoadjuvant therapy, also referred to as *induction therapy,* has been applied to the treatment of NSCLC as well as to treatment of many other solid tumors. It entails treating patients with chemotherapy even though there is no clinical evidence that the primary cancer has spread. Lung cancers are particularly attractive targets for neoadjuvant therapy because even though many present as locally advanced disease confined to the chest, patients run a considerable risk of developing distant disease within a short time. Neoadjuvant therapy affords a unique opportunity to assess the sensitivity of the cancer

Table 105 II-2

Randomized Trials in Stage III Disease: Radiation Alone vs. Radiation and Chemotherapy

Number of Patients	Therapy	Median Survival	1 Yr	2 Yr	3 Yr	Reference
155	RT	9.6	40	13	11	Dillman RO, Seagren SL, et al., 1990
	RT/CT	13.8	55	26	23	
353	RT	10	41	14	4	Le Chevalier T, Arriagada R, et al., 1991.
	RT/CT	12	51	21	12	
238	RT	10.2	41	17		Mattson K, Holsti, L.R., et al., 1988
		RT/CT	10.9	42	19	
331	RT		46	13	2	Schaake-Koning C, van den Bogaert W, et al., 1992.
	RT/CT		54	26	16	
			44	19	13	
95	RT	11				Soresi E, Clerici M, et al., 1988
	RT/CT	16				
240	RT	46	45	13	2	Blanke C, Ansari R, et al., 1995
	RT/CT	43	43	18	5	

to the drug regimen. This information may be useful in the postoperative period when the possibility of adjuvant therapy is under consideration. Moreover, preoperative neoadjuvant therapy may render resectable a tumor that would otherwise be regarded as unresectable. Another consideration is that the required dose-intensive regimens are apt to be tolerated better before than after surgery. Finally, neoadjuvant therapy may allow for improved drug delivery to the preserved vasculature of the tumor, and thus decrease the prospect of developing drug resistance. However, the possibility exists that delaying surgery may be disadvantageous. In patients with locally advanced disease who are at high risk for developing disseminated disease, the delay imposed by the administration of chemotherapy provides an additional period of observation during which a nonresponder may manifest distant disease, thereby precluding surgery.

There have been two phase III randomized trials of neoadjuvant chemotherapy in patients with locally advanced lung cancer (stage IIIA). Some patients had N2 disease alone; while others had T3N0 disease. In contrast to results in patients with disseminated NSCLC in whom the response to chemotherapy at best approaches 30 percent, 60 to 70 percent of patients with locally advanced disease responded favorably. Also, in both trials, the median survival was improved in the group of patients who received neoadjuvant treatment. The explanation for this difference in responsive may be the better overall status of patients who are regarded as candidates for surgery and the smaller tumor burden that these patients bear. Alternatively, qualities inherent in the primary tumor that differ from those in tumor that has metastasized may contribute to a better response to chemotherapy. Currently, there is no way of assessing the response of micrometastatic disease other than the disease-free interval after resection and survival.

Another experience with neoadjuvant chemotherapy for NSCLC was reported from the Memorial Sloan-Kettering Cancer Center. The study was prospective but nonrandomized. It included 41 patients with "clinical N2" disease defined as bulky mediastinal adenopathy that could be seen on the conventional chest radiograph or was manifested at bronchoscopy by widening of the carina. Patients received a cisplatin-based regimen plus mitomycin. The overall response rate was 77 percent; 19 of the patients achieved a complete response that was confirmed by histologic examination. Seventy-five percent of patients were able to undergo resection, even though resectability based on previous experience would have been anticipated to be about 10 percent. It must be emphasized that these patients had bulky mediastinal lymph node disease, not lymph nodes that appeared grossly normal but in whom disease was subsequently detected. The authors concluded that the results obtained paralleled those noted in neoadjuvant studies with other solid tumors in that response rates to chemotherapy were high, and complete resection rates were high after response to chemotherapy. They

identified response to chemotherapy as a significant prognostic indicator for survival; complete response was associated with prolonged survival.

Chemotherapy and Radiation Followed by Surgery

Various theoretical considerations have led to trials of chemotherapy and radiation followed by surgery (tri-modality therapy): (1) tumor cell subpopulations in locally advanced NSCLC may respond differently to radiation and chemotherapy, and cells resistant to one treatment method may be sensitive to the other; (2) chemotherapy may promote the emergence of radiosensitive cells, thereby increasing the total number of cells killed by continued radiation treatments; and (3) induction of cell cycle synchronization by certain drugs may increase cell killing by radiation and induce recruitment of tumor cells in G_0.

The Southwest Oncology Group conducted a trial (8805) using the cisplatin/etoposide regimen that they had developed with concurrent radiotherapy; the trial included both stage IIIA and IIIB patients. All 126 patients underwent mediastinoscopy for histologic evaluation of mediastinal lymph nodes. The response rate to the preoperative therapy was 59 percent, with 29 percent having stable disease. The resection rate was 85 percent in the stage IIIA patients, and 80 percent in the stage IIIB patients. The 3-year survival was similar in both stage IIIA and IIIB patients at 27 and 24 percent, respectively. The absence of tumor in the mediastinal nodes at the time of surgery was associated with improved survival. Failure was more common in distant, rather than locoregional sites, with the occurrence of brain relapses in 26 patients.

It remains to be proved that surgery is a necessary part of the treatment of these patients. The high response rate to chemoradiotherapy in the high-performance patients entered into these clinical trials raises the question of whether chemotherapy and radiation (RT) might be able to achieve a similar end point with regard to local control. A large intergroup study (0139) addressed this question. In this trial, 396 patients with stage IIIA, pathologic N2 disease were randomized to either concurrent chemotherapy with cisplatin/etoposide and RT to 4500 cGY followed by surgery or the same chemotherapy regimen with RT to higher doses of 6100 cGy. The patients who were randomized to surgery had a statistically significant improvement in progression free survival (12.8 vs. 10.5 months), but while there was a trend toward an improvement in overall survival in the surgery group, this was not statistically significant. Patients who seemed to do better were those who had a lobectomy rather than a pneumonectomy, as well as those who had obtained a pathologic response in the mediastinal nodes. Although there was no significant benefit in overall survival, surgery is still often offered to medically fit patients after induction chemoradiotherapy.

In summary, major issues remain concerning the sequence and number of treatment methods for locally advanced disease. Although some permutation of combined modality treatment is clearly needed in patients with locally advanced disease, we currently do not have data in the form of randomized control studies that compare the efficacy of the varying combinations of chemotherapy, radiation and surgery. In patients who can tolerate the added toxicity, combined concurrent chemoradiotherapy is more effective than sequential therapy. Although it has not been proven that surgery after induction chemoradiotherapy confers a survival benefit compared to definitive chemoradiotherapy, surgery is still a preferred approach in many institutions if patients can tolerate tri-modality treatment. As far as whether induction treatment should consist of chemotherapy alone or combined with radiation, this is an unanswered question at this time.

Future Directions

The next large intergroup effort plans to determine if increasing the dose of radiation in combination with chemotherapy will decrease the rate of local failure. In order to answer this question, patients will be randomized to either 6400 cGy or 7400 cGy. Also, trials are underway to determine if prophylactic cranial irradiation after definitive treatment of a locally advanced tumor will decrease the occurrence of brain metastases. Finally, the integration of biologic molecular targeting agents into combined modality treatment of locally advanced disease will certainly be studied in the future. Currently, the CALGB is sponsoring a randomized phase II study in which patients with unresectable disease are randomized to chemoradiotherapy with or without the epidermal growth factor receptor (EGFR) targeting monoclonal antibody, cetuximab.

ADVANCED-STAGE NSCLC

The goal of chemotherapy in advanced-stage disease is palliation, since with few exceptions, disseminated lung cancer, like most other solid tumors, is essentially impossible to cure. Among the issues that have been raised with respect to the relative value of chemotherapy in patients with disseminated disease are the response rate, survival data, cost-effectiveness, and the quality of life.

Prognostic criteria play an important role in analyzing and constructing clinical trials. For example, patients with a poor performance status (spending more than 50 percent of time in bed, significant weight loss) are much less likely to respond to chemotherapy than those with a better performance status. Especially in patients with a poor prognosis, it is important to assess the effect of treatment-related toxicity on overall quality of life and the cost effectiveness of therapy.

Several of the older studies that randomized patients with disseminated disease to receive either best supportive care or systemic chemotherapy had mixed results. In addition,

several meta-analyses have reviewed studies that randomized patients to best supportive care or chemotherapy. One of these meta-analyses that did detect a significant benefit in survival from chemotherapy reviewed 52 randomized trials comparing chemotherapy with best supportive care. There was a 10 percent absolute improvement in survival in 1 year, and a median survival improvement of 2 months. Another more recent review indicated a similar benefit. These data can be used to make the case for or against systemic chemotherapy (i.e., that the patients did live longer when treated or that the 2 to 3 additional months of survival had little biologic significance).

An issue of great concern in this setting is the balance between obtaining a survival benefit with palliation of cancer related symptoms and the toxicity associated with systemic chemotherapy. Most of the studies have included only the higher performance status patients—which calls into question the general applicability of the results. Whether to treat a patient with disseminated disease using chemotherapy or to treat symptoms as they arise often comes down to the judgment of the medical oncologist balanced against the wishes of the patient. Patients with a poor performance status can be expected to have a worse response to chemotherapy than those with relatively good performance status; therefore, they are often not offered chemotherapy.

First-Line Chemotherapy

For patients of adequate performance status, the standard first-line chemotherapy recommendations currently consist of a platinum or non-platinum–based doublet. Numerous randomized studies have been conducted that compare the benefits of single agent versus doublet regimens. A meta-analysis that reviewed 65 of these trials found a significant benefit in response and median survival with a cytotoxic doublet. There was no survival benefit with the addition of a third cytotoxic agent at the time of this analysis. Although there are several cisplatin or carboplatin backbone doublets to consider, carboplatin tends to be favored in the palliative setting due to its better toxicity profile. A large study that was conducted by ECOG randomized 1207 patients with advanced disease to either cisplatin/paclitaxel, cisplatin/gemcitabine, cisplatin/docetaxel, or carboplatin/paclitaxel. The median survival among all four treatment groups was 7.9 months, with a 1-year survival of 33 percent and a 2-year survival of 11 percent. There was no clear survival benefit with any one regimen compared with the others. Those with an ECOG performance status of 2 tended to do worse. Carboplatin/paclitaxel did seem to have a slightly better toxicity profile. Hence, this is a common regimen in use, but the other doublets are acceptable as well.

Two randomized phase III studies have addressed the use of non-platinum–based regimens in first line treatment. The first, by Kosmidis et al., randomized patients to paclitaxel and gemcitabine versus paclitaxel and carboplatin. The study showed similar efficacy with respect to median survival, 1-year survival and response rate. Both regimens were well tolerated. The largest study to address the role of non-platinum doublets randomly allocated 929 patients to carboplatin/paclitaxel (CP), carboplatin/gemcitabine (CG), or gemcitabine/paclitaxel (GP). Again, the results indicated similar efficacy in all three arms. There were differences in toxicities in that anemia and thrombocytopenia were more common in the CG arm, although peripheral neuropathy and alopecia were more common in the paclitaxel containing groups. For chemotherapy naïve patients, treatment choices tend to be heavily dependent on a patient's co-morbidities and the toxicity profile of each regimen.

The issue of how to treat the elderly and those with a poor performance status is an issue of ongoing debate. There are data to suggest that single agent chemotherapy, such as vinorelbine or docetaxel, does palliate symptoms and result in a modest survival benefit. However, there are situations when it is reasonable to defer chemotherapy.

Anti-angiogenesis Therapy

The generation of new vasculature from existing vessels has an important role in tumor pathogenesis. Tumor growth beyond a certain size depends on the development of new blood vessels at the growing edge, a process that depends on the vascular endothelial growth factor receptors (VEGFR1/2) and the ligand vascular endothelial growth factor (VEGF). Anti-angiogenic agents are thought to inhibit tumor growth by several mechanisms: (1) blocking the formation of new blood vessels needed to sustain growth; (2) blocking tumor metastasis; and (3) enhancing drug delivery to tumors by normalizing tumor blood flow and reducing tumor interstitial pressure.

Bevacizumab is a monoclonal antibody that targets VEGF. It has demonstrated efficacy in the treatment of colorectal cancer, among others. In a pivotal trial conducted by ECOG, 878 patients with stage IIIB or IV NSCLC were randomized to carboplatin/paclitaxel or carboplatin/paclitaxel/bevacizumab in the first-line setting. In the group that was randomized to bevacizumab (BV), after the chemotherapy had been completed, the BV was continued until progression. Given the risk of potentially fatal bleeding that has been noted with this agent, patients with brain metastases, a history of hemoptysis, on therapeutic anticoagulation, and with squamous cell tumors were excluded from this trial. Also, given the known toxicities of hypertension and thromboembolic events with BV, those with uncontrolled hypertension and active cardiovascular disease were also excluded. There was a 2-month improvement in median survival with the addition of BV (12.3 vs. 10.3 months), which was statistically significant. Although this is a modest benefit, this trial did generate excitement in that a biologically targeting agent yielded a statistically significant survival benefit in this disease. Despite the entry criteria, there were 15 treatment related deaths in the chemotherapy plus BV group, with 5 being from pulmonary hemorrhage. Thus, it is important to consider the risks of this agent in determining if a patient is eligible for BV therapy.

Table 105 II-3

Advanced NSCLC Second-Line Randomized Trials

Number of Patients	Therapy	Median Survival	1 Yr	Reference
104	D BSC	7.5 4.6	37 11	Shepherd FA, Dancey J, et al., 2000
373	D 75 I/V	5.6 5.6	32 19	Fossella FV, De Vore R, et al., 2000
571	D Pem	10.2 8.3	30 30	Hanna N, Shepherd FA, et al., 2004
731	Placebo E	4.7 6.7		Shepherd FA, Rodrigues Pereira J, et al., 2005

D = docetaxel; E = erlotinib; I = Ifosfamide; Pem = pemetrexed; V = vinorelbine.

Second-Line Therapy

Ultimately, patients with advanced disease will progress after receiving first-line therapy. There are several options to consider in the second-line setting. Docetaxel was one of the first agents approved for this indication. In the first trial of interest, 104 previously treated patients were randomized to docetaxel every 3 weeks at 100 mg/m^2, 75 mg/m^2 or to supportive care. Docetaxel therapy resulted in an improvement in median survival (7.5 vs. 4.6 months) and 1-year survival (37 vs. 11 percent). The lower dose of docetaxel was better tolerated. In another study, 373 patients who progressed after platinum therapy were randomized to docetaxel at one of two schedules, ifosfamide or vinorelbine. Treatment with docetaxel at 75 mg/m^2 was associated with a higher response rate as well as an improvement in 1-year survival. Interestingly, there was no difference in overall survival between the four groups (Table 105 II-3).

Pemetrexed, an antifolate, is a relatively new addition to the available agents in the second line setting. In the phase III registration trial, 571 patients were randomized to docetaxel or pemetrexed. The survival data was similar in each arm with a median survival of 8.3 and 7.9 months for pemetrexed and docetaxel, respectively. The 1-year survival was 29.7 percent in both groups. Although the survival data with pemetrexed were not improved compared to docetaxel, it was better tolerated with a significant decrease in the incidence of grade 3 or 4 neutropenia and febrile neutropenic events.

EGFR Inhibitor Therapy

Another biological target of considerable interest is the epidermal growth factor receptor (EGFR). The EGFR is a transmembrane tyrosine kinase receptor with an extracellular, transmembrane and intracellular domain. Following ligand binding, the EGFR is activated by either homodimerization with another EGFR, or via heterodimerization with another member of this type 1 receptor tyrosine kinase (RTK) family. EGFR stimulation results in activation of signal transduction pathways for PI3-Akt and Ras-Raf-MEK-MAPK.

There are several EGFR inhibiting agents in varying stages of development. To date, the small molecule agents, such as gefitinib (Iressa) and erlotinib (Tarceva), have played a greater role in the treatment of NSCLC than the EGFR targeting antibodies. Gefitinib initially obtained provisional FDA approval based on encouraging results from a phase II study. However, when it was studied in the larger phase III Iressa Survival Evaluation in Lung Cancer (ISEL) trial, in which 1692 patients were randomized to gefitinib versus placebo, the results were negative with no detected survival benefit. In subset analyses, patients who never smoked and were of Asian origin seemed to have a greater benefit to therapy. There are several theories as to why this trial was negative. For one, it is possible that a subtherapeutic dose of gefitinib was used. Also, this was a large study with a heterogeneous population and did not enrich its entry criteria to include the subsets of patients who may benefit from this type of treatment. Subsequent analyses of tumor samples from this trial indicate that high EGFR gene copy number, increased EGFR expression, and EGFR mutations are related to higher response rates. Although Asian patients seemed to respond in the original study, a recent trial in Japan in which patients were randomized to gefitinib or docetaxel failed to show a benefit with gefitinib.

As data to support the use of gefitinib in NSCLC were diminishing, erlotinib emerged as the small molecule tyrosine kinase inhibitor of EGFR of choice. In a large multicenter trial, 731 patients with stage IIIB or IV disease who were previously treated with first or second-line therapy were randomized to

either erlotinib or placebo, in a 2:1 randomization favoring erlotinib. Patients with an ECOG performance status of 0, 1, 2, and 3 were eligible. The response rate to erlotinib was 8.9 percent, with an overall survival of 6.7 versus 4.7 months in the placebo arm. In addition, there was an improvement in cancer-related symptoms in patients who received erlotinib. This was a significant survival benefit, and based on this study, erlotinib obtained FDA approval in the second-line setting. A small percentage of patients required dose reductions or were taken off of therapy due to drug-related toxicity. Although overall erlotinib is well tolerated, it can cause a characteristic rash, which seems to be a class effect. Other side effects are diarrhea and a low risk of pneumonitis. In a subset analysis of this study, patients who had an increased likelihood of a response included those who were never smokers, of Asian origin, female, or who had the adenocarcinoma histology. This is a consistent finding with this class of agents. Currently, the small benefit seen with EGFR inhibitors is limited to their use as a single agent. Several trials in which either gefitinib or erlotinib were combined with platinum-based chemotherapy have all been negative, with no improvement in survival.

Although data are emerging that EGFR copy number and expression levels can predict for a response to erlotinib, currently these are not tested routinely in the clinical setting. Similarly, in analyzing tumors from patients who have had a remarkable response to EGFR inhibitors, investigators have detected the presence of EGFR somatic mutations. The more common ones characterized are in exon 19 or 21, but there are likely others as well. These mutations may be involved in the pathogenesis of lung cancer in never-smokers, and can predict for sensitivity for EGFR inhibitor therapy. Again, assays for mutations are still in the realm of research and are not routine clinical tests.

Future Directions

The integration of agents that target signal transduction and other biologically relevant pathways are beginning to make an impact in the care of patients and in the design of future trials for NSCLC. Although responses and survival benefits are currently modest, one avenue of research is to combine multiple agents with nonoverlapping mechanisms of action and toxicity profiles to have obtain a greater clinical benefit. Also, the early investigations of multikinase targeting small molecule agents, such as sorafenib, sunitinib, and ZD6474 indicate that these agents may have activity in NSCLC. There are also currently trials underway to study the safety and effectiveness of bevacizumab in patients with treated brain metastases, and squamous cell cancers that have already initiated treatment with the hope that this would serve to reduce the risk of bleeding in these patients. Finally, now that the number of biologic agents in development is increasing at a faster pace, future research will focus heavily on learning more about patterns of resistance and determining which biomarkers will predict for responsiveness to each agent and regimen.

CONCLUSION

Chemotherapy has an established role in the adjuvant therapy of stage II and IIIA NSCLC. Randomized clinical trial data demonstrate improved median and long-term survival when antineoplastic agents are used as part of a multimodality approach. The next step in the development of adjuvant regimens will be to add molecular targeting agents; these trials are already underway.

Response rates to chemotherapy are higher in patients with localized disease than in those with disseminated disease. Some of these differences may be related to tumor burden or overall performance status. Questions that need to be addressed in future and ongoing trials include the optimal sequence for various modalities and the best modalities for each situation in locally advanced disease.

For advanced-stage NSCLC, there is now a growing list of active agents. However, especially for heavily pretreated patients and those with a poor performance status, response rates and overall prognosis are still limited. There are data to suggest though that cytotoxic and now biologic agents can modestly increase survival and improve a patient's quality of life. However, even in the most recent phase III trial with bevacizumab in the advanced setting, the median survival barely increased over the 1-year mark. Thus, there is still considerable room for improvement. Cost analyses will have to continue to be a matter of consideration, as the newer agents are especially expensive. However, with the development of molecular agents and the future potential to select treatment options based on genomic and protenomic profiles, there is cautious optimism that the treatment of this disease will take a new direction with more hope in the future.

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Part III: Treatment of Non–Small-Cell Lung Cancer
Radiation Therapy

Mitchell Machtay

Most patients with lung cancer receive radiotherapy as part of their treatment, either as initial management or later in the course of their disease. This may include thoracic radiotherapy and/or irradiation of sites of metastatic disease. Thoracic radiotherapy (RT) for non-small cell lung carcinoma is usually categorized as follows:

- Neoadjuvant = preoperative
- Adjuvant = postoperative
- Definitive = cure without surgery as treatment goal; with or without chemotherapy
- Palliative = directed at relief of thoracic symptoms

There is some overlap in these categories with respect to the goals of treatment. For example, most patients treated with definitive intent are not cured but do achieve palliation of intrathoracic symptoms. Similarly, a few patients originally considered to be technically unresectable may have a dramatic response to irradiation and/or chemotherapy, and the goal of treatment may then change from palliative to neoadjuvant or definitive intent. The size of the primary lesion, stage, and total dose of radiation are important factors in determining local control. A summary of radiotherapy for lung cancer is provided in Table 105 III-1.

Utilization of thoracic radiotherapy as part of the therapeutic regimen and the therapeutic goal of the therapy depends not only on tumor related-factors such as stage but also on patient-related factors such as pulmonary reserve and performance status. All these factors need to be considered when deciding whether to irradiate. Although radiotherapy might be appropriate for a patient with a postoperative forced expiratory volume (FEV_1) of 2.0 l and pathologic stage T2N2M0 disease with a close margin, the same treatment would be problematic in a patient with pathologic stage T1N1 disease and a postlobectomy FEV_1 of 1.1 l who has had a series of postoperative complications. Of course, such clearcut cases usually are the exception rather than the rule in clinical oncology. Table 105 III-2 lists the relative contraindications to thoracic radiation for lung cancer.

Table 105 III-1

Summary of Radiotherapy for Lung Cancer: Indications and Treatment

Type	Indication(s)	Dose*
Preoperative (with chemotherapy)	Pancoast tumor; clinical N2	45–50 Gy
Postoperative	N2 disease; T4 tumors; selected T3 and/or N1 disease; Incomplete resection	50–66 Gy (depends on surg-path findings)
Definitive medically inoperable	T1-2NO-1 not surgical candidate or refuses surgery	60–74 Gy (conventional fractionation) or 40–60 Gy (accelerated hypofractionation with stereotactic techniques)
Definitive unresectable (with chemotherapy)	Selected stage III patients; performance status high	56–74 Gy
Palliative unresectable	Other stage III and IV patients with local symptoms	20–50 Gy with accelerated hypofractionation (2.5–4 Gy fraction size)
Small cell (with chemotherapy)	Limited stage with good performance status	45–55 Gy or Gy in 1.5 Gy bid fractionation

** (1.8–2 Gy once daily fractionation unless otherwise indicated.)*

Finally, it must be remembered that the prognosis for most patients with non–small-cell lung carcinoma (NSCLC) is poor with standard therapy, and a concerted effort should be made to enter patients into clinical trials that are investigating new treatments or combinations of treatments for this disease.

Table 105 III-2

Relative Contraindications to Thoracic Radiotherapy (RT) for Lung Cancer

Prior high-dose thoracic radiotherapy
Connective tissue disease
FEV_1 < 800 cc
Tracheobronchial-esophangeal fistula
Projected RT fields to include >35% of normal lung volume (i.e., >40% of normal lung volume is projected by 3-D treatment plan to receive > 20 Gy).
Projected RT fields to include >50% of heart volume
Patient expected to be noncompliant with treatment or follow-up visits

MANAGEMENT OF NON–SMALL-CELL LUNG CANCER

Surgery, irradiation, and chemotherapy are all used in the treatment of lung cancer. Surgical resection remains the primary curative modality and may be the only treatment required in early stage disease if all the cancer is removed. The local failure rate in stage I patients after lobectomy or pneumonectomy is less than 10 percent. With such a low incidence of local failure the addition of postoperative irradiation is unnecessary if resection margins are negative. Unfortunately, most patients present with unresectable or marginally resectable disease. The addition of radiation and chemotherapy is aimed at decreasing the unacceptably high frequency of failure due to local and distant spread that occur with surgery alone. However, progress has been slow, and the overall survival of patients with locally advanced lung cancer has only risen modestly over the past 20 years.

Neoadjuvant Therapy

The current use of preoperative radiotherapy in the management of NSCLC falls into two categories: (1) as part of neoadjuvant chemoradiotherapy for N2 (IIIA) disease; and (2) as part of neoadjuvant chemoradiotherapy for superior sulcus (Pancoast) tumors (T3-4NxM0). For patients who are otherwise surgical candidates but are found at mediastinoscopy to have positive mediastinal lymph nodes (N2 disease), it is not

clear whether neoadjuvant chemoradiotherapy is superior to neoadjuvant chemotherapy; either is an acceptable option.

In most institutions, preoperative chemoradiotherapy is standard management for Pancoast tumors. However, based on the surgical-pathologic findings, modern imaging techniques, including magnetic resonance imaging (MRI) of the spine and brachial plexus, have made it possible for selected patients to undergo surgery first followed by adjuvant treatment.

Conceptually, it has become attractive to attempt to convert patients with bulky mediastinal nodal disease to patients with microscopic mediastinal nodal disease, thereby rendering them candidates for surgical resection. A large number of phase II clinical trials have been conducted utilizing induction chemotherapy or induction chemoradiotherapy in patients with bulky mediastinal adenopathy ("clinical" stage N2 disease). These include both single-institution studies (e.g., from Memorial Sloan-Kettering Cancer Center) and multi-institutional cooperative group studies (e.g., from the Southwest Oncology Group [SWOG]). These studies clearly show significantly improved outcomes with neoadjuvant treatment as opposed to historical controls treated with local therapy alone. Several randomized trials have confirmed a benefit to induction chemotherapy prior to surgery. It is far less clear, however, what the optimal local therapy is for these patients, despite several large and well publicized phase III randomized trials. Options include chemotherapy followed by surgery; chemoradiotherapy followed by surgery; and definitive chemoradiotherapy alone. The median and 5-year survival rates for all of these three options appear to be similar. There is the suggestion that induction chemotherapy followed by pneumonectomy (particularly right pneumonectomy) may be excessively toxic, with some studies reporting treatment-related mortality rates above 20 percent. In contrast, induction therapy (chemotherapy or chemoradiotherapy) followed by lobectomy appears to be well tolerated, and retrospective studies show encouraging outcomes.

Chemoradiotherapy followed by thoracotomy is an intensive treatment with considerable morbidity and mortality. Its use should be limited to patients with excellent cardiac and pulmonary reserve and a high performance status. Preferably this combination should be used in the context of a prospective clinical trial. Only patients with reasonable expectation of benefit should receive this form of aggressive management; thorough staging workups for metastatic disease (CT scans of the chest, abdomen, and brain, and bone scan) should be performed prior to the start of preoperative treatment and in the "window" period (i.e., after this therapy has been administered and before surgery). Lesions that are suspected of being distant metastases should be investigated by tissue biopsy. The radiotherapy dose should be moderate, approximately 45 to 50 Gy, with standard fractionation (1.8–2 Gy once daily). An interval of approximately 3 to 8 weeks between completion of irradiation and surgery is advised to minimize the risk of difficulties in wound healing. Bronchial stump reinforcement at the time of surgery is strongly encouraged. As noted, right pneumonectomy after neodjuvant chemoradiotherapy has a high mortality rate and should be avoided.

Preoperative radiotherapy carries with it the potential disadvantage of limiting the ability to give additional radiotherapy if tumor proves to be unresectable or if residual disease remains after resection. After 45 Gy preoperatively, only about 30 Gy of additional irradiation can be safely administered postoperatively. Thus, it may be preferable to defer additional radiotherapy (reirradiation) unless or until there is clear evidence of local progression. Chemotherapy may be offered, although in general, the patient left with residual or unresectable disease after preoperative chemoradiotherapy has a poor chance for long-term disease-free survival.

Adjuvant Therapy

The primary tumor-related factors in considering postoperative radiotherapy (PORT) are the pathologic stage and the completeness of the surgery. Based on its proven and very dramatic efficacy in decreasing the risk of local-regional recurrences, PORT is generally considered to be the standard of care for patients with resected mediastinal node-positive (N2) NSCLC. Based on the Lung Cancer Study Group Trial in patients with N2 disease, which suggested a longer relapse-free survival in this subgroup, the presence of N2 disease would seem to favor PORT. There is no role for PORT for T1-2N0 tumors completely resected by lobectomy or pneumonectomy and a dubious role for PORT for T1-2N1 tumors. In fact, there is the suggestion of a slight detrimental effect of postoperative radiotherapy on overall survival. It is less clear whether radiotherapy should be administered after a wedge resection, although in selected patients, the high local failure rate after this procedure suggests a possible role for adjuvant radiotherapy, particularly the placement of intraoperative brachytherapy sources via a catheter-based mesh. Phase II data suggest that the combination of wedge resection + brachytherapy results in local failure rates below 5 percent, comparable to that of lobectomy.

Whether postoperative irradiation has any impact on survival is debatable. Although many retrospective studies have shown a survival benefit to PORT, randomized trials have not. In fact, a highly publicizied meta-analysis of randomized trials of surgery alone vs. surgery + PORT showed a detrimental effect of PORT on survival. This negative effect of PORT was very strong for stage I disease and modest for stage II disease; there was no evidence of any detrimental effect of PORT in stage III disease. The reason for excess deaths in the PORT arm were not explained, though likely attributable to radiation-induced cardiopulmonary toxicity. It should be noted that the randomized trials included in the PORT meta-analysis all used radiotherapy techniques that would be considered grossly outdated by modern standards.

Future studies of PORT should foucs on stage III disease and selected stage II disease. The majority of patients with node-positive resected NSCLC probably harbor micrometastatic disease outside of the thorax and thus adjuvant

chemotherapy is appropriate. However, the risk for potentially very morbid local-regional recurrence also exists in these patients. Further research is needed to better identify which patients are at very high risk for local-regional recurrence and thus most likely to benefit from PORT. If more effective therapy to prevent distant disease is developed, then the improvement in local control may lead to consistent significant increases in survival.

If PORT is going to be used, meticulous radiotherapy treatment planning is essential in order to minimize risks of toxicity. Radiotherapy fields should be relatively modest in size, yet include the high risk regions of the bronchial stump, ipsilateral hilum and the portion(s) of the mediastinum considered high risk for regional recurrence. If resection margins are negative and if there is no chest wall invasion, there is no reason to irradiate the "tumor bed"; doing so would only increase toxicity by irradiating that portion of remaining lung that has filled into the space left by the lobectomy. A radiation dose of 50 to 55 Gy using a standard fractionation schedule (1.8–2 Gy per day) should provide excellent local and regional control. Higher doses may be reasonable if resection margins are compromised and the patient has excellent underlying cardiopulmonary function.

Patients who undergo incomplete resection (gross residual disease) or suffer local recurrence after surgery alone have a poor prognosis, although radiation is usually used in an attempt to maximize local control. These patients should be considered to have the equivalent of locally advanced, nonoperative NSCLC and treated accordingly, potentially with definitive intent (see the following).

Definitive Therapy (Locally Advanced, Nonoperative NSCLC)

Patients who do not have demonstrable distant metastases but are not candidates for surgery because of locally advanced stage and/or medical inoperability are often referred for radiation therapy, with or without chemotherapy. Patients with malignant pleural or pericardial effusions, although technically still having stage IIIB disease, should not be considered candidates for curative treatment and should be offered appropriate palliative measures, which may include surgical intervention (pericardial window or thoracoscopic sclerosis), chemotherapy, or moderate-dose palliative radiotherapy to bulky central disease. Combined chemotherapy and radiotherapy has not been well studied in patients with medically inoperable stage I disease. Definitive radiotherapy alone remains the standard treatment for these patients.

Patients with "medically inoperable" stage I NSCLC treated with radiotherapy have a significantly improved prognosis compared with locally advanced "technically unresectable" stage II/III NSCLC. This is one major argument in favor of intervention with radiotherapy prior to disease progression to stage III. Relatively small radiotherapy fields can be safely used for most patients with stage I disease, and high doses can be administered. A traditional radiotherapy course consists of 60 to 70 Gy in conventional fractionation

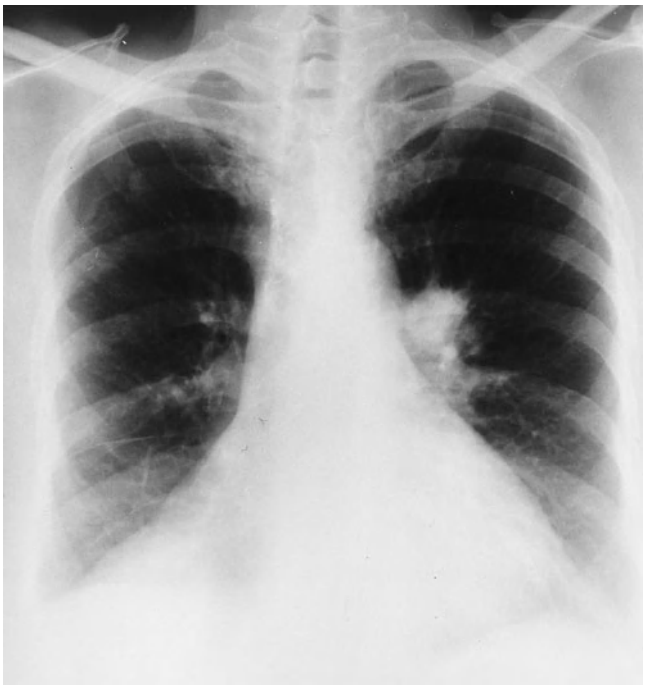


Figure 105 III-1 Pre-radiotherapy chest radiograph of a patient with a medically inoperable T2N0M0 non–small cell lung carcinoma of the left hilar region.

(1.8–2 Gy once daily). However, there is recent interest in more aggressive radiation fractionation schedules (which are also usually more convenient for these patients), given via high-technology radiation treatments often referred to as stereotactic radiotherapy (SRT). This may consist of three sessions of 20 Gy each (60 Gy total), a dose of radiation that is generally considered uniformly ablative of malignant cells. A recent report suggests that SRT offers extremely high local control rates approaching those achievable with lobectomy. However, long-term data are still pending, and at this time relatively few centers carry great expertise in this highly complex treatment.

For other nonoperable (stage IIIA and IIIB) patients, combined chemotherapy and radiation therapy is often considered an alternative to radiotherapy or supportive care alone. The most important factor to consider in selecting patients for combined modality therapy, which has considerable toxicity and a high level of patient time, commitment, and expense, is their performance status. In general, intensive chemoradiotherapy should be limited to patients whose Karnofsky scores are 70 percent or greater. Significant weight loss, defined in most cooperative group trials as greater than 5 percent, is also a relative contraindication to aggressive combined modality therapy. Although age itself is not a contraindication to combination therapy, intensive regimens should be applied cautiously in patients more than 70 years old. Of note is that in most of the trials utilizing chemoradiotherapy, the median age averaged 60 years. Although large tumor size is not a contraindication to definitive treatment, larger tumors generally result in a larger portion of normal

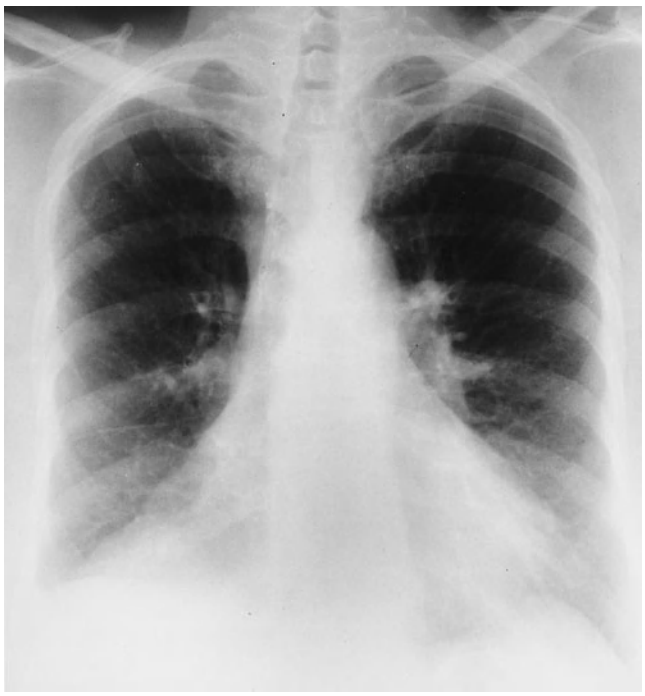


Figure 105 III-2 Chest radiograph 1 month after definitive radiotherapy for the patient shown in Fig. 105 III-1.

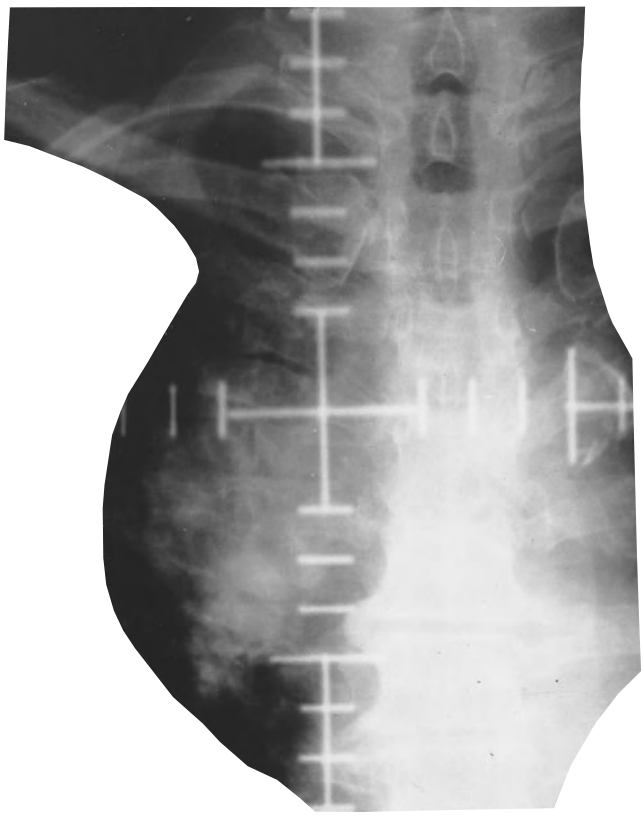


Figure 105 III-3 Simulation (radiation planning) film for "radical en bloc" radiotherapy for a patient with T4N2M0 non–small-cell lung carcinoma of the right hilar region. The actual area being irradiated is inside the yellow boundaries. All other areas are shielded via primary collimation, secondary multileaf collimation and/or lead alloy blocks.

tissue (lung, heart, and esophagus) being included in a radiotherapy portal, and the resultant high-dose irradiation may carry an unacceptable risk of complications. The location of the tumor (e.g., proximity to the heart and/or extensive involvement of the right lower lobe of the lung) and the patient's pulmonary reserve may also influence the decision regarding definitive irradiation. Supraclavicular adenopathy (N3 disease) is not an absolute contraindication for definitive therapy, although its presence is a poor prognostic indicator.

In recent years, there has been increasingly strong evidence that concurrent chemoradiotherapy is better than sequential induction chemotherapy followed by radiotherapy. A sizeable number of randomized trials have addressed this topic, and most show a clear benefit in local-regional control, median survival, and 2- and 3-year survival in favor of concurrent therapy. Long-term toxicity rates appear similar between sequential versus concurrent chemoradiotherapy; however acute toxicity (especially esophagitis) is markedly increased with concurrent therapy. The conventional dose fractionation schedule used for definitive irradiation is 60 to 66 Gy in standard fractionation (1.8–2 Gy once daily). The maximum tolerated dose of irradiation is probably higher than that for small to medium-sized tumors in which the amount of normal tissue in the field is low. Several institutional and cooperative group prospective phase I/II studies suggest that in combination with concurrent chemotherapy, the highest "safe" dose of thoracic radiotherapy is 74 Gy. A randomized trial comparing 60 Gy vs. 74 Gy is under development.

For many years, the fields to be treated in the definitive therapy of NSCLC have followed the Halsted principle

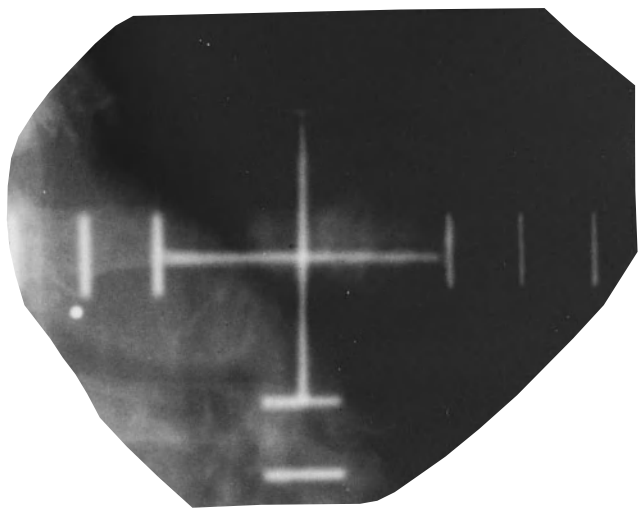


Figure 105 III-4 Radiotherapy simulation film (highly magnified, compared with Fig. 105 III-3) for the patient with medically inoperable NSCLC shown in Figs. 105 III-1 and 105 III-2. The area being irradiated is inside the yellow boundaries. CT-assisted radiation dosimetry revealed the amount of normal lung tissue in the treated field to be under 15 percent.

of "radical en bloc" loco-regional therapy. The typical radiotherapy field, encompassed the primary tumor (with approximately 2-cm margin), both the ipsilateral and contralateral hila, and the entire mediastinum from the thoracic inlet to a point at least 5 cm below the carina. Elective supraclavicular nodal irradiation was also typically used for upper lobe cancers. This usually results in a field size measuring approximately 16 by 20 cm, which incidentally irradiates a large amount of normal tissue. With this technique, it has been estimated that greater than 30 percent of a patient's normal lung tissue is exposed to a dose of irradiation expected to cause permanent fibrosis and nonfunction.

Because of these issues, in recent years, there has been a trend toward smaller field size in definitive radiotherapy, encompassing gross disease with an appropriate margin and fewer areas of "prophylactic" nodal stations. This evolution has been accelerated by improvements in pre-radiotherapy imaging (e.g., PET scan–based treatment planning) and the addition of chemotherapy to control microscopic disease. The use of smaller field sizes does appear to make radiotherapy better tolerated and offers the possibility for higher doses of radiotherapy in combination with chemotherapy. A concern about local failure just outside of the irradiated volume (also known as "marginal miss") with these newer techniques exists; however, the risk of this kind of failure appears to be relatively low compared with central local or distant failure. Most studies show that the risk for a marginal miss recurrence is between 5 and 10 percent, compared with 30 to 60 percent risk for central local recurrence and/or distant metastases.

Through advances in chemoradiotherapy over the past 20 years, there have been improvements in the prognosis for locally advanced, unresectable NSCLC, as reviewed in Table 105 III-3. With supportive care alone (i.e., antibiotics, expectorants, oxygen, etc.) it has been shown that only about 5 percent of patients are alive at 2 years, with an expected survival less than 6 months. Single agent radiotherapy improves the median survival to about 9 months, with approximately 20 percent 2-year survivors. Sequential induction chemotherapy followed by radiotherapy further improves these values to approximately 14 months and 33 percent, whereas concurrent chemoradiotherapy increases these values to 17 months and 40 percent. Several phase II studies incorporating newer chemotherapy agents/schedules with modern radiotherapy have reported median survivals of about 2 years, with approximately 20 percent chance for 5-year survival. Clearly a portion of these gains are related to patients selection and stage migration, particularly with the widespread use of PET scan–based staging.

Improvements in supportive care are also likely valuable contributors. However, the improvements in the prognosis for stage III nonoperative NSCLC are well documented by large, prospective randomized trials and should be considered valid. It must be stressed that the trials in which the outcomes were positive involved patients with good performance status, absence of malignant effusion(s), and minimal weight loss. Not all patients with presumed unresectable disease would benefit from highly aggressive concurrent chemoradiotherapy.

Current and future research consists primarily of optimizing radiation techniques and integrating new molecularly targeted therapies into the treatment of locally advanced NSCLC. As noted, there has been a paradigm shift away from large-field/medium-dose radiotherapy toward small-field/high-dose radiotherapy. This will hopefully continue to improve the therapeutic ratio of radiotherapy while making it more feasible to introduce new agents with less worry about excessive overlapping toxicities. Preclinical data suggest a benefit from combining radiotherapy with agents that target

Table 105 III-3

Review of Relative Efficacy of Various Treatments for Locally Advanced Nonoperative but Non-metastatic Non–Small-Cell Lung Carcinoma

Treatment	Approximate Local Response Rate (%)	Approximate Median Survival (mo)	Approximate 3-Y Survival Rate (%)
RT alone—40 Gy	45	8	8
RT alone—50–60 Gy	60	9	10
RT alone—70 Gy	70	11	15
Sequential chemo followed by RT (60 Gy)	70	14	25
Concurrent Chemo–RT (60 Gy)	80	17	35

Adapted from data from multiple prospective trials of the Radiation Therapy Oncology Group (RTOG) and other clinical trials.

signal transduction and/or angiogenesis pathways. Clinically, while this approach has been validated in some extrathoracic tumor sites (e.g., head and neck cancer), it is still investigational in lung cancer.

Palliative Therapy

The goal of treatment in patients with advanced malignancies is to preserve the quality of life. This may require intervention with a potentially morbid treatment in order to relieve the patient of an unpleasant complication of the disease.

Palliative radiation therapy is most often used in situations in which the patient's quality of life is, or could be, substantially compromised. Situations in which treatment is commonly applied include locally advanced disease with hemoptysis, dyspnea, or obstructive pneumonia and metastatic disease.

Although response rates to chemotherapy have improved, radiotherapy remains the mainstay of palliative therapy for distressing local symptoms of lung cancer. The selection of patients for palliative radiotherapy is often more difficult than is the selection for adjuvant or definitive treatment, since the goals may be less well defined. The presence of a large lung cancer in and of itself is not an indication for palliative radiotherapy, particularly when a patient has been shown to have distant metastases with minimal, or no, local symptoms. Fairly clear situations that call for palliative thoracic radiotherapy include the superior vena caval syndrome, hemoptysis, and significant pain.

Cough, often due to partial bronchial obstruction, is frequently palliated by radiotherapy. Atelectasis is rarely reversed by radiotherapy, although consideration should be given to irradiation in order to prevent refractory postobstructive atelectasis and pneumonia when impending obstruction of a mainstem or lobar bronchus is identified by bronchoscopy. A summary of the response rate (partial relief) of symptoms is shown in Table 105 III-4.

The palliative role of external irradiation in endobronchial disease has been evaluated in patients with inoperable NSCLC. Hemoptysis was relieved in 76 percent of patients, obstructive pneumonia in 59 percent, cough in 55 percent, chest pain in 50 percent, and dyspnea in 37 percent. Significant toxicity occurred in less than 6 percent of patients; radiation pneumonitis was the most common adverse reaction.

Palliative radiotherapy generally involves lower total doses and smaller fields than does definitive radiotherapy. Larger daily fraction size is used (2.5–4 Gy once daily) in the attempt to achieve relatively rapid palliation and minimize the number of trips to the radiotherapy department. In addition, late radiotherapy complications (which are related to larger fraction size) are less relevant in this patient population. There is no standard palliation regimen, and treatments have ranged from a single fraction of 10 Gy (a very popular European regimen) to a full course of 60 Gy in standard 2 Gy once daily fractions. A typical compromise palliative radiotherapy schema in the United States is to deliver 3 Gy times 10 fractions (30 Gy total), which may be followed by a second similar course of treatment, either after a 1- to 2-week break or later, at the time of further local progression.

Table 105 III-4

Response Rate to Palliative Radiotherapy (RT)

Symptom	Response Rate (%)
Atelectasis	20
Cough	35–65
Dyspnea	35–50
Hemoptysis	75–85
Pain	50–75
SVC syndrome	60–80
Weight loss/anorexia	30–50
Vocal cord paralysis	5
Overall symptomatic response	60–75

SVC = superior vena cava.

After full-course external beam irradiation, patients commonly develop symptoms associated with recurrent disease. In this situation, additional external radiotherapy may not be possible. If the primary cause of the distressing symptom(s) is endobronchial disease, the patient may be a candidate for endobronchial irradiation. This treatment can be given over a short period of time and because of its highly localized nature, it rarely causes radiation esophagits or pneumonitis. Endobronchial irradiation typically uses an Iridium-192 source, with a depth penetration that is superior to current laser or photodynamic treatments. However, it does carry the risk of massive hemoptysis (presumably the result of tumor lysis with bronchovascular fistula); this risk is between 5 and 10 percent.

Finally, radiotherapy plays an important role in the palliation of metastatic sites, including brain and bone metastases. Whole-brain irradiation, to a dose of 30 Gy in 10 fractions, is appropriate therapy for multiple brain metastases. In addition to palliating neurologic symptoms in many patients, it marginally improves survival compared with steroids alone. In addition, patients with solitary brain metastases appear to benefit from a combination of whole-brain irradiation plus either surgical resection or stereotactic radiosurgery boost.

For bony metastases, most patients achieve at least partial pain relief from a typical palliative dose of 30 Gy in 10 fractions. The appearance caused by disfiguring metastases to the skin, subcutaneous tissues, and/or lymph nodes can be

improved by similar modest dosages of irradiation. Occasionally, pain from adrenal metastases can be palliated with radiotherapy in patients in whom the radiotherapy field would not include an excessive amount of liver, kidney, or bowel.

LIMITED-STAGE SMALL-CELL LUNG CARCINOMA

Thoracic Radiation

It is now generally accepted, based on the results of two meta-analyses, that combined chemotherapy and thoracic radiotherapy is superior to chemotherapy alone in the treatment of limited-stage small-cell lung carcinoma. However, the best way to combine these treatments remains controversial. Concurrent chemoradiation at the start of therapy appears to be superior to "consolidative" radiotherapy at the end of all chemotherapy, although this comes at the expense of increased toxicity. A possible advantage of delayed radiotherapy is that chemotherapy usually shrinks bulky hilar/mediastinal tumor, allowing smaller and potentially less toxic radiotherapy portals to be used.

In general, for patients with high performance status and good cardiopulmonary function, concurrent chemoradiotherapy (with etoposide and cisplatin) at the start of treatment represents the standard of care in the United States at this time. Although low doses of radiotherapy (less than 40 Gy) appear to be less effective in local control, it is unclear whether increasing the dose above 45 to 50 Gy improves outcome. Radiotherapy fractionation appears to be more important in small cell lung cancer than in NSCLC; a large randomized trial showed that 1.5 Gy bid (to 45 Gy total) was superior to 1.8 Gy qd (also to 45 Gy total). Both local control and overall survival were improved with bid radiotherapy, although esophageal toxicity was significantly increased. The increased toxicity of bid radiotherapy, as well as its inconvenience to patients, has limited its widespread acceptance and alternative radiotherapy fractionation schedules are under study. For example, an RTOG trial showed that a new regimen of 61.2 Gy over 5 weeks had an 18-month survival rate of 82 percent.

Prophylactic Cranial Irradiation

The role of prophylactic cranial irradiation (PCI) remains controversial. Its use should be considered only for patients thought to be in complete remission after chemoradiotherapy. PCI dramatically reduces the risk of brain metastases and offers a modest but real improvement in survival (approximately 5 percent absolute gain). The primary argument against the use of PCI is the high incidence of neurocognitive deficits in long-term survivors after PCI. These deficits may range from subtle abnormalities that are demonstrable only by sophisticated neuropsychologic testing and/or high-resolution imaging all the way up to progressive dementia. Many studies critical of PCI have included patients who received relatively high doses of PCI and/or received PCI with concurrent chemotherapy. Moreover, recent neurocognitive studies of patients with newly diagnosed small cell lung cancer have shown deficits before any treatment was administered, suggesting that at least some of the problem with neurocognitive deficits is due to a paraneoplastic syndrome.

When given, PCI should be delivered at least 2 to 3 weeks after all chemotherapy has been completed. In order to minimize the risk and severity of late sequelae, a whole-brain dose of 2.5 Gy in 10 fractions (25 Gy) or 2 Gy in 15 fractions (30 Gy) is recommended. Aside from alopecia and fatigue, acute toxicity from this treatment is minimal. Steroids are not usually needed for PCI (in contrast to their use when treating brain metastases). If steroids are required, however, extreme care must be taken in tapering them, since rebound radiation pneumonitis may develop (from the patient's prior thoracic radiotherapy).

TOXICITY OF THORACIC RADIOTHERAPY

Toxicity from radiotherapy occurs both as *acute* side effects, generally defined as those occurring during or within 90 days after the completion of a course of irradiation, and *late* effects, which do not develop until at least 90 days after the completion of irradiation. Although some of the same factors that predict acute effects also increase the likelihood of late effects, the acute effects themselves do not necessarily lead to the late, long-term complications. In general, most injuries from irradiation are a consequence of localized damage to tissue within the irradiated portal. However, some effects are more generalized (e.g., fatigue, immunosuppression, and the rare complication of diffuse adult respiratory distress syndrome [ARDS]). The *grade* of radiation toxicity is generally reported on a 1 to 5 scale, with grade 1 toxicity representing mild effects (e.g., dyspnea on exertion) and grade 5 representing fatal toxicity.

In the treatment of thoracic malignancies, where high irradiation doses and large fields are often used, the organs of greatest concern for both acute and late complications are the lung, esophagus, and heart. Significant dermatologic toxicity has been virtually eliminated by the use of megavoltage equipment. Likewise, with modern treatment planning techniques, spinal cord complications should be extremely rare. Other structures at risk for injury by thoracic irradiation include the brachial plexus, the tracheobronchial tree, the great vessels, the ribs, and the sternum. Although many complications of thoracic irradiation are manageable, the most important prospect is prevention through sophisticated treatment planning and appropriate selection of patients for treatment.

Lungs: Acute Complications

Radiation pneumonitis and pulmonary fibrosis are the most common serious complications of thoracic irradiation. Radiation pneumonitis represents acute/subacute lung injury. It

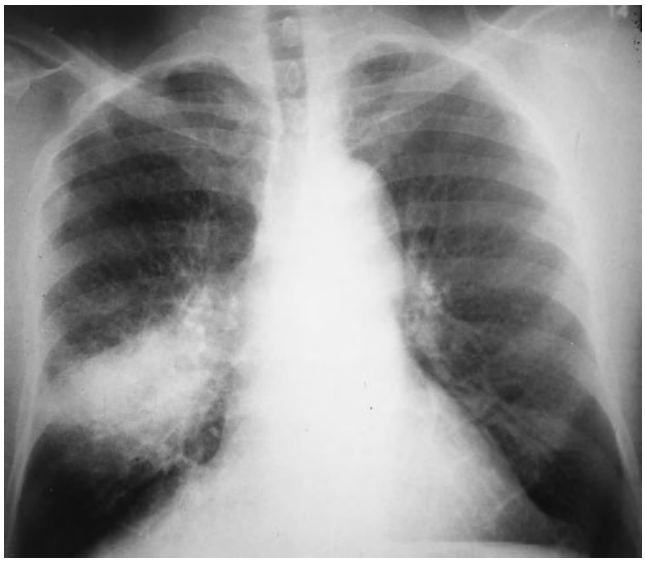


Figure 105 III-5 Preradiotherapy chest radiograph of a patient with limited-stage small cell carcinoma of the right lower lobe.

usually occurs from 1 to 4 months after irradiation, although it may occur during a course of particularly intensive radiotherapy, often when combined with chemotherapy. Dyspnea is the most characteristic symptom, although cough, low-grade fever, and pleuritic chest pain often are also present (Figs. 105 III-5 to 105 III-7).

Although infiltrates outside of the radiation portal do not completely rule out radiation pneumonitis, they make the diagnosis less likely. Regardless of the radiographic appearance, community-acquired pneumonia and opportunistic infections as well as progressive malignancy can mimic radiation pneumonitis. Therefore, appropriate testing and

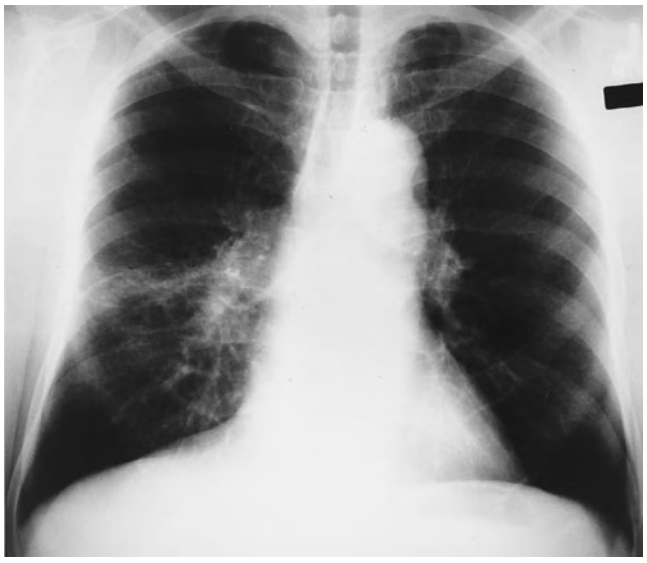


Figure 105 III-6 Chest radiograph 1 month after definitive radiotherapy and chemotherapy for the patient shown in Fig. 105 III-5.

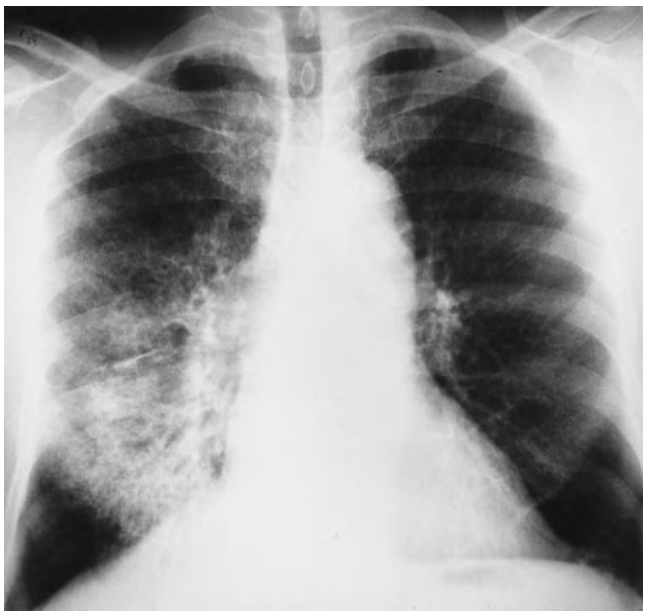


Figure 105 III-7 Chest radiograph 4 months after completion of radiotherapy for the patient shown in Figs. 105 III-5 and 110 III-6. He presented with severe dyspnea on exertion. Radiographic infiltrates conform to the shape of his radiation portal. He responded promptly to steroids but soon developed fatal brain metastases.

consultation with the patient's radiation oncologist are indicated before empiric corticosteroids are begun. Mild cases should be treated supportively, reserving steroids for more severe symptoms. For severe radiation pneumonitis, prednisone 20 mg, three times per day, for approximately 2 weeks is used; tapering is done slowly (i.e., during the subsequent 2 to 4 weeks). Whether antibiotics should be used in addition to corticosteroids is controversial.

The incidence of serious (greater than or equal to grade 3) radiation pneumonitis ranges from 5 to 15 percent, and the risk depends on several variables. The most important factor appears to be the amount of normal lung tissue irradiated (see Advances in Radiation Therapy: Technical Planning and Delivery of Radiation). The total radiotherapy dose prescribed for the tumor appears to be somewhat less important, since virtually any dose used for the definitive or palliative treatment of lung cancer devitalizes the lung tissue within the treated portal. Other factors that appear to increase the risk of radiation pneumonitis include radiation dose per fraction (i.e., larger fraction size increases the risk) and tumor location (i.e., lower lobe lesions have a higher risk). The use of chemotherapy (particularly the anthracyclines, methotrexate, bleomycin, and mitomycin) and poor pulmonary function before treatment also increase the risks of serious damage to the lungs by radiation.

On rare occasion, a patient develops an adult respiratory distress syndrome shortly after irradiation. The chest radiographs reveal diffuse infiltrates both within and outside of the radiotherapy portal. It has been hypothesized that a severe autoimmune response may be involved: Whereas mild

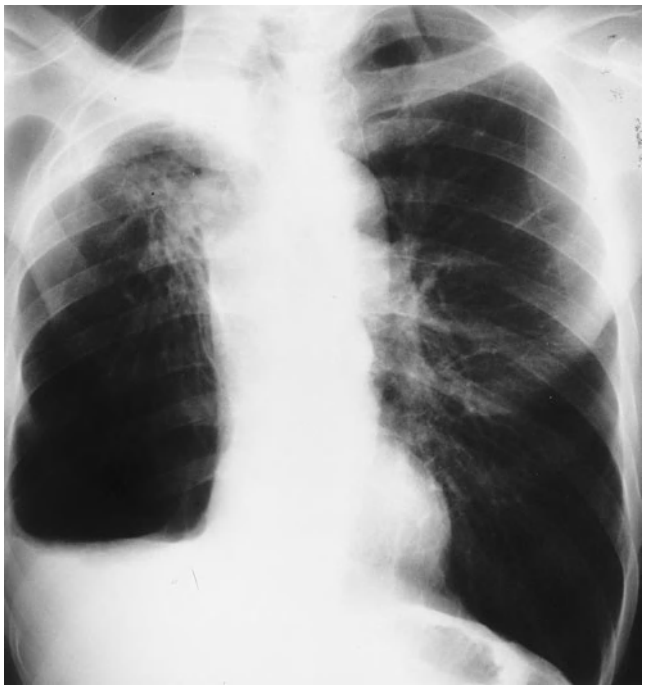


Figure 105 III-8 Chest radiograph of a patient 6 years after definitive radiotherapy for stage III unresectable non–small-cell lung carcinoma. radiation fibrosis in the right upper lobe with mediastinal shift to the treated side and an ipsilateral pleural effusion and thickening is evident. Patient remained asymptomatic.

and moderate radiation injury becomes manifest only in the irradiated portion of lung, a severe autoimmune response results in generalized bilateral lung injury.

Lungs: Late Complications

The *late complication* of radiation fibrosis develops from 3 to 18 months after radiotherapy. Essentially 100 percent of patients irradiated for lung carcinoma with high doses of radiation develop radiologic evidence of radiation fibrosis in the portion of the lung that was heavily irradiated (Fig. 105-III-8). The major difficulty is in distinguishing between fibrosis and residual, or recurrent, tumor. In clinically significant radiation fibrosis, there is usually a progressive decrease in the Dl_{CO}, which may be combined with a more modest decrease in the FEV1, reflecting the restrictive nature of radiation fibrosis.

Severe symptoms from radiation fibrosis are uncommon in patients who were irradiated to modest-sized radiation fields. However, established fibrosis does not respond to corticosteroids or any other therapy. Longitudinal studies in Hodgkin's disease patients suggest some recovery of lung function at approximately 3 years, after treatment. It is less clear if lung cancer patients, who are far older and more chronically ill than most lymphoma patients, can expect appreciable recovery.

Esophagus

Most patients receiving moderate- to high-dose radiotherapy for lung cancer experience an acute mucositis of the esophagus that is similar to that seen on other epithelial surfaces after radiation therapy. With standard radiotherapy (60 Gy in standard fractionation) this mucositis is almost always self-limited and usually responds to topical agents, such as sucralfate slurry or "magic mouthwash" combinations (e.g., antacid, viscous lidocaine, and diphenhydramine) with or without non-opiod and/or mild opioid pain medications. However, with more intensive radiotherapy or with concurrent chemotherapy, the incidence of grade 3 esophagitis is higher, the recovery period is longer, and the need for aggressive pain management is greater.

Esophageal stricture is a late complication and its incidence is likely to increase as there are more long-term survivors following thoracic radiotherapy. The risk of esophageal stricture is strongly related to the dose to the esophagus, approximately 1 percent with 50 Gy, 10 percent with 60 Gy and may be as high as 50 percent with 70 Gy. It is likely that the concurrent use of chemotherapy potentiates this effect. Most cases of radiation esophageal stricture respond well to endoscopic dilatation although the procedure may have to be repeated. More severe complications, such as esophageal fistula or perforation, fortunately, are rare.

Heart

Acute effects of radiotherapy on the heart during treatment are extremely uncommon, although effects related to the tumor itself (e.g., atrial fibrillation due to lung cancer invading the pericardium) are relatively common. Radiation pericarditis may occasionally occur during a course of treatment but, in general this is a subacute or late complication, developing several months to years after irradiation. The presentation is similar to that for other causes of pericarditis, and as in the case of radiation pneumonitis, distinguishing between radiation pericarditis and tumor progression can be difficult. Most cases are self-limited and are treated supportively with antipyretics, analgesics, and occasionally with antiarrhythmic agents. Pericardiocentesis for tamponade is rarely required. Occasionally, severe constrictive changes may develop, leading to signs and symptoms of heart failure and necessitating pericardiectomy.

The risk of symptomatic radiation pericarditis is about 5 percent when doses of 60 Gy are administered to one-third of the heart. However, considerably lower doses (35–40 Gy) can induce this disorder when a large part of the heart is in the treatment field (e.g., radiation therapy for Hodgkin's disease or for tumors in the left lower lobe). In addition to the risk of radiation pericarditis, irradiation has increased long-term morbidity and mortality from heart disease in patients cured of Hodgkin's disease, seminoma, and breast cancer, presumably due to accelerated coronary artery disease.

Long-term cardiac complications of radiotherapy are rarely encountered in patients with lung cancer, since few patients survive long enough to manifest these effects. Furthermore, it can be difficult or impossible to distinguish between a cardiac event due to prior mediastinal irradiation and a cardiac event that is unrelated to radiation, since the risk of coronary artery disease is high in the older, heavy smoker who develops lung cancer.

ADVANCES IN RADIOTHERAPY

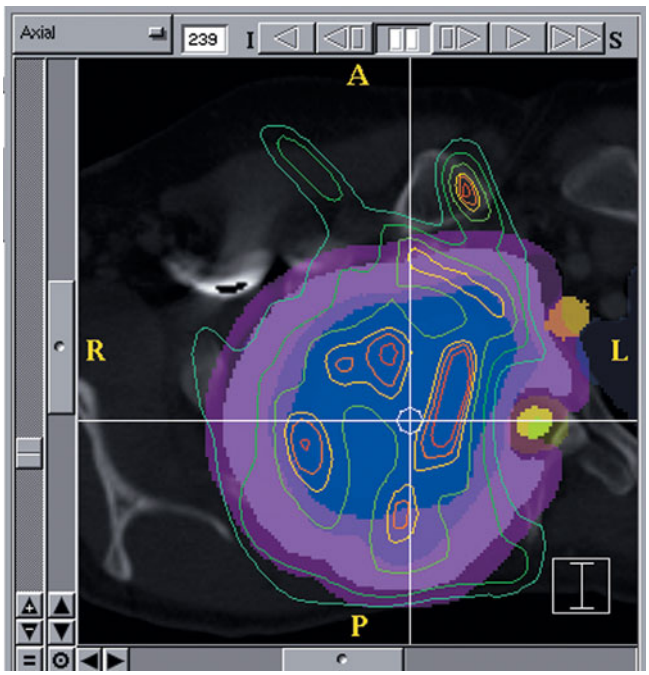
Radiation Dose-Fractionation Modulation

As the understanding of the relationship between radiation and cellular kinetics has grown, mathematical models have been developed that allow us to predict the responses of both normal tissue and tumor to radiation. This capability has led to many creative new fractionation schemes designed to maximize the destruction of tumor while minimizing damage to normal tissue. The difference in cellular kinetics between tumor cells and normal cells makes these new schemes possible and attractive. Both tumor cells and normal cells are injured by radiation; however, normal cells usually have a greater ability to repair this damage than do the tumor cells and can repopulate more between fractions. *Hyperfractionation* utilizes multiple daily fractions in an effort to reduce the late effects in normal tissue without decreasing tumor control. The overall treatment time is the same as conventional schedules, but multiple smaller fractions are given each day, and total doses are increased. By giving multiple smaller fractions, the normal tissues are able to repair a greater percentage of the damage during the course of treatment; this may allow higher total cumulative doses of radiotherapy to be safely administered.

Accelerated treatment administers a larger total dose of radiation per day and also decreases the overall treatment time. The nominal final dose of radiotherapy may be similar to (or even somewhat less than) that of conventional treatment. Accelerated treatment may be given via hyperfractionation (e.g., 1.5 Gy bid) or as hypofractionation (e.g., 4 Gy qd). It is designed to reduce the amount of tumor repair and repopulation that occurs during treatment of rapidly dividing tumors and, therefore, improve local control. Much of the data on modified patterns of fractionation come from patients treated for cancers of the head and neck. In patients with epithelial neoplasms, both accelerated fractionation and hyperfractionation increase local-regional control. As noted, acclerated hyperfractionation was superior to standard treatment for limited stage small cell lung cancer. Data for NSCLC are less clear; although as noted, extreme accelerated hypofractionation (stereotactic irradiation) appears to be beneficial for medically inoperable stage I disease.

Technical Planning and Delivery of Radiation

Complementing the advances in dose-fractionation schedules in radiotherapy are the advances in technical planning and delivery of radiotherapy. Specifically, three-dimensional (3D) conformal radiation therapy, which includes newer techniques such as intensity modulated radiation therapy (IMRT), proton beam radiotherapy, and stereotactic radiotherapy (SRT), is used in efforts to improve local control while minimizing toxicity. Utilizing three-dimensional planning of both the tumor and surrounding normal tissue, the radiation beam(s) can be precisely conformed and modulated to the shape and size of the tumor volume (Fig. 105 III-9). Powerful computer software allows for detailed analysis of anticipated radiation dose/volume distributions, so that adjustments in the treatment plan can be made if necessary (Fig. 105 III-10).



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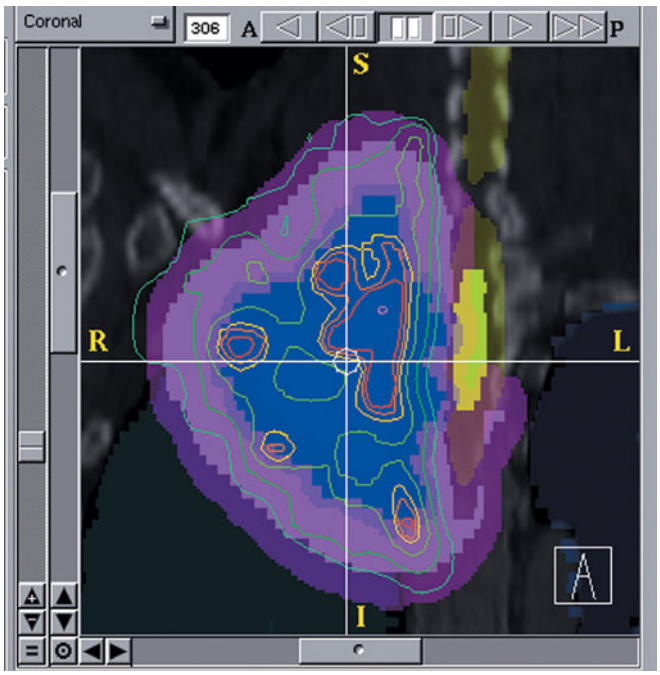

B

Figure 105 III-9 High technology radiation therapy involves the design of multiple conformal radiation beams directed in 3-dimensional space from various angles and using variable field shapes and intensities. These slides illustrate the radiation dosimetry for a patient with a pancoast tumor (T4N2M0) of the right upper lobe (A = axial view of radiation treatment planning CT scan; B = coronal view). The spinal cord is (relatively) spared from maximal radiation doses.

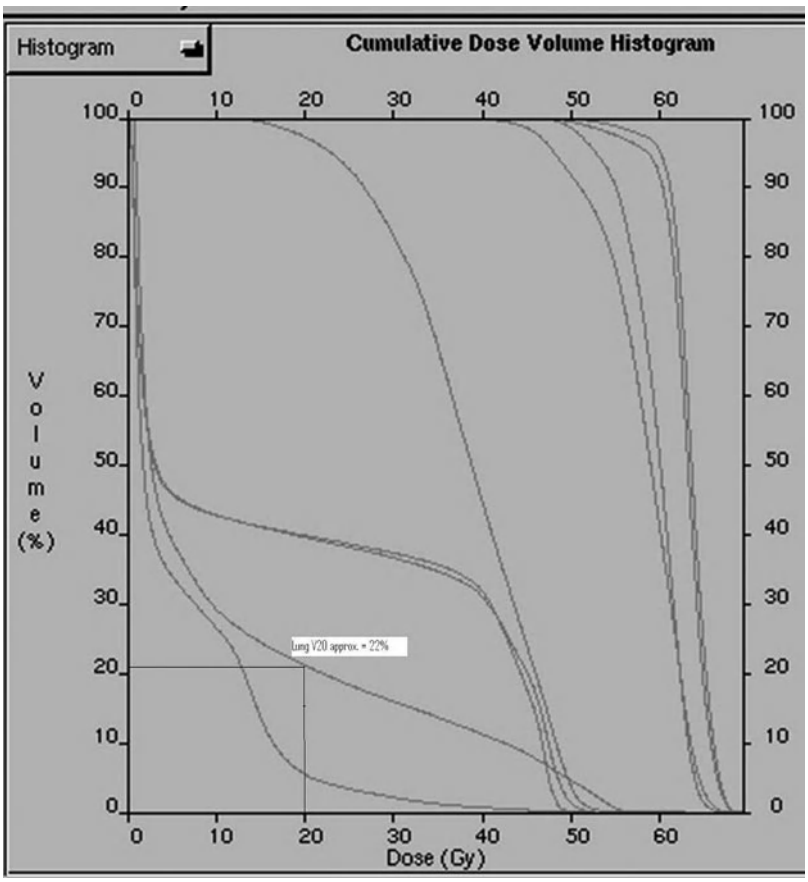

Figure 105 III-10 This figure illustrates the cumulative radiation dose volume histogram plots for the patient from Fig. 105 III-9. This graph includes the DVH curves for multiple normal organs (lung, heart, esophagus, spinal cord) as well as DVH curves for the tumor itself and electively irradiated targets adjacent to the gross tumor. The degree of radiation exposure to the normal lung tissue is expressed as The lung V20, the percent of the patient's total lung volume that receives a dose of at least 20 Gy, which is expected to devitalize that portion of lung. In this case the V20 is approximately 20 percent, which is generally considered a "safe" amount of radiation lung exposure and low risk for clinical radiation pneumonitis.

This information includes comprehensive dose volume histograms (DVHs), which quantitatively plot the volume of a given organ (or tumor/target) receiving a given dose of radiation. DVH analysis has demonstrated a powerful relationship between the risk of radiation pneumonopathy and the amount of lung tissue irradiated to a certain threshold dose, usually considered to be 20 Gy in most studies.

In the future, these techniques may simultaneously allow a higher dose to the tumor and lower dose to normal tissues such as the spinal cord, esophagus, and normal lung tissue, offering an improved therapeutic ratio. As noted, dose escalation studies have determined maximum tolerated doses of radiotherapy for standard 3-D conformal radiotherapy. It is likely that higher doses will be achievable with IMRT, proton beam radiotherapy, and SRT, particularly as better technology is developed to account for intratreatment tumor motion due to respiration.

Combined Modality Therapy/Radiosensitizers

The rationale for combining radiotherapy with other anticancer treatments is twofold: first is the hope that the non-radiotherapy treatment can sterilize tumor cells located outside of the radiation field (this is also known as spatial cooperation). Second and more intriguing to radiation oncologists is the hypothesis that these other treatments act as radiosensitizers, turning a sublethal dose of radiation into a lethal dose of radiation. Both concepts apply to standard cisplatin-based polychemotherapy. However, the toxicity of combined chemoradiotherapy appears to be at the limites of acceptability. Thus newer and better drugs and drug schedules are needed. Regarding standard chemotherapy, one modern technique is to combine the benefits of both sequential and concurrent chemoradiotherapy. Specifically this involves several cycles of very intense chemotherapy alone before or after concurrent chemoradiotherapy, in an effort to eradicate distant metastases; this may allow the use of less toxic dose schedules of chemotherapy during radiotherapy.

As noted, conventional chemoradiotherapy is suboptimal against lung cancer, so newer, better targeted agents are needed to complement current treatment. As of the writing of this chapter, two molecularly targeted agents are approved for systemic therapy for stage IV NSCLC, specifically the anti-EGFR small molecule drug erlotinib and the anti-angiogenic humanized antibody bevacizumab. These and other compounds are currently undergoing testing in phase I and II studies in combination with radiotherapy for stage III disease.

SUMMARY

External beam radiotherapy plays a major role in the treatment of lung cancer. It improves local control and enhances curability in patients with marginally resectable NSCLC. Patients with medically inoperable NSCLC have a good

chance for durable local control with high-dose radiotherapy, particularly with modern technology. In patients with unresectable NSCLC, radiotherapy (combined with chemotherapy) maximizes the median survival and offers occasional cure. Aggressive thoracic radiotherapy with chemotherapy and prophylactic cranial irradiation offers potentially curative treatment for limited stage small-cell lung cancer, once considered a universally fatal disease. Finally, radiotherapy often provides good palliation for patients with incurable and/or metastatic lung cancer.

APPENDIX

Glossary of Terms Related to Radiation Therapy

Adjuvant: Generally refers to postoperative therapy. However, chemotherapy given after definitive radiotherapy would also be considered adjuvant.

Blocks: Thick shields made of a leadlike alloy that can be shaped for each patient to block portions of their anatomy that would otherwise fall into the radiation field. These heavy physical devices have been largely replaced by mutlileaf collimators installed directly into the gantry of modern linear accelerators.

Brachytherapy: Radiotherapy given in the form of radioactive sources placed directly into or around a patient's tumor. This may be given interstitially (sources imbedded directly into tissue) or intracavitary (sources laid into a cavity such as a bronchus).

cGy (centigray): A modern basic unit of radiotherapy dose. One Gy (Gray) = 100 cGy.

Conedown: Shrinking the field size sometime during the course of radiotherapy, to take advantage of the decreasing size of tumor during treatment and minimize the amount of toxicity of treatment. For example, a patient may begin radiotherapy with a large treatment plan/field irradiating half of his or her hemithorax, and then have a conedown midway through treatment to a small field only irradiating the gross tumor itself.

Conformal radiotherapy: The use of extremely sophisticated imaging studies and dosimetry to design radiation fields that *conform* precisely to the shape of a patient's tumor. Conformal radiotherapy usually uses smaller safety margins around a patient's tumor, a larger number of fields, and less prophylactic radiotherapy of clinically uninvolved lymph node areas.

Consolidative: Refers to radiotherapy given after a maximal or complete response to chemotherapy.

Course: A series or program of radiation treatments or fractions with a specific goal in mind for a patient (e.g., a 7-week course of daily radiotherapy to the lung for attempted cure).

Definitive: Refers to radiotherapy given with the intention of cure without surgery. May be given with other nonsurgical treatment such as chemotherapy.

Dosimetry: The process of optimizing the radiotherapy fields and dose by calculating the radiation dose to be received by a tumor and/or normal tissues in a radiation field. Physicists and "dosimetrists" work with the radiation oncologist in comparing possible radiation treatment plans with the goal of maximizing the radiation dose to the tumor while minimizing dose to normal tissue, often requiring sophisticated computer programs.

Endobronchial irradiation: A form of brachytherapy in which radioactive sources are placed directly into a bronchus using a hollow catheter threaded into the diseased area via bronchoscopy.

External beam radiotherapy (x-ray therapy): Radiotherapy given from a machine (usually a linear accelerator) which produces a high-energy x-ray beam that is then aimed at a patient's tumor and/or suspected tumor areas.

Field: An area at which a radiotherapy beam is directed, usually described as a rectangular shape, in cm (e.g., 10 × 14 cm). Blocks are often used to further customize the shape of a field. A single fraction of radiotherapy may include multiple fields, typically two to four, although extremely high-technology conformal radiotherapy may include 6 to 20 fields.

Fraction: A single radiation therapy session, usually given over 1 to 5 min. A fraction may consist of one or multiple fields, and any dose, as prescribed by the radiation oncologist. Most courses of radiotherapy involve one fraction per day, Monday through Friday, over 1 to 7 weeks, although an infinite number of possible fractionation schedules are possible.

Gy (Gray): The SI modern basic unit of radiotherapy dose; 1 Gy = 100 cGy = 100 rad. One Gy = 1 joule per kilogram of absorbed energy.

Hyperfractionation (see also *fraction*: The delivery of two or more radiation fractions per day, generally given with a 4- or more hour interval between fractions.

Intensity Modulated Radiation therapy (IMRT): An advanced form of 3-D conformal radiotherapy in a very large number of small radiation beams of variable intensity are used instead of a small number of larger radiation beams. This offers potentially better conformal dosimetry than standard 3-D XRT. However, it may result in a larger volume of normal lung tissue receiving small to medium doses of irradiation; this is of unknown clinical significance.

Karnofsky score: A performance status scale commonly used in oncology to measure a patient's level of independent function. Scores range from 10 (moribund) to 100 (asymptomatic, able to work full-time). Karnofsky score has been shown to be highly predictive of survival in lung cancer.

Neoadjuvant: Generally refers to preoperative therapy. However, chemotherapy prior to definitive radiotherapy would also be considered neoadjuvant.

Palliative: Refers to therapy given with the goal of relieving distressing symptoms, without any anticipated effect on survival.

Prophylactic: Refers to radiotherapy given to a site at which there is no known tumor but which is considered to be at high risk for harboring occult "microscopic" disease, such as lymph node areas.

Proton beam radiotherapy: Proton beam radiotherapy uses all of the same principles as standard x-ray (photon beam) radiotherapy, but requires a far more sophisticated accelerator to produce radiation. Proton beam radiotherapy may offer significantly more conformal radiotherapy dosimetry than standard XRT.

Rad: Basic unit of radiotherapy dose; terminology not changed to the SI units (cGy and Gy).

Radiation Therapy Oncology Group (RTOG): A National Cancer Institute–sponsored multicenter clinical trials cooperative group which performs studies related to radiation therapy, including many lung cancer studies.

Radiosensitizers: Drugs or other treatments which increase the cellular response to radiotherapy. Many chemotherapy drugs and molecularly taregeted agents have radiosensitizing properties.

Safety margin: A margin of "normal-appearing" tissue which is added onto the visible tumor area for the purposes of radiation planning. Typically 1.5 to 2 cm in all dimensions is added, to account for microscopic extension of tumor cells and the possibility of slight patient motion during treatment. The most significant motion variable in the treatment of lung cancer is tumor motion due to normal breathing (particularly in the superior-inferior direction due to diaphragmantic motion).

Simulation: A detailed planning session for radiation therapy that simulates but does not actually deliver a radiation treatment. Simulation consists of immobilization of the patient in an appropriate position for radiation therapy, marking the patient's skin, localizing the area to be treated under fluoroscopy, taking radiographs of the area to be treated, and taking measurements of the patient's contour for dosimetry purposes.

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Small Cell Lung Cancer: Diagnosis, Treatment, and Natural History

Kevin Palka • David H. Johnson

Small cell lung cancer (SCLC) is a tumor of extremes. Untreated, it is one of the most highly virulent malignancies known, with a life expectancy best measured in days to weeks. On the other hand, it displays exquisite chemosensitivity, resulting in partial or complete responses in the vast majority of cases. Unfortunately, although many patients can be rendered free of clinical evidence of disease, most quickly relapse and die from this malignancy. Over the past 20 years, little progress has been made in prolonging survival in this disease, despite trials using newer chemotherapeutic agents. This chapter reviews several aspects of the diagnosis, natural history, and best current therapies for SCLC.

EPIDEMIOLOGY

Lung cancer remains the leading cause of neoplastic death in American men and women. In 2006 estimates called for 174,470 cases of newly diagnosed lung cancer (92,700 men and 81,770 women) and 162,460 deaths (90,330 in men and 72,130 in women) from this disease. However, for the first time in 50 years, the incidence rate in men is declining, whereas the incidence rate in women has reached a plateau after a long period of increase. The National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) suggest that small cell lung cancer (SCLC) currently represents approximately 14 percent (roughly 24,000 cases) of lung cancers in the United States, a decline from the peak of approximately 17 to 20 percent in 1986. In the United States and Europe, SCLC constituted about 77,000 of the 550,000 lung cancers diagnosed in 2004. Between 1985 and 2000 there was a significant increase in the percentage of women and patients over 70 years of age who were diagnosed with SCLC. Of note, national health surveillance studies have demonstrated that non–African Americans have improved survival rates compared with African Americans.

Like all other lung cancers, SCLC is linked to a variety of environmental risk factors. By far the strongest association is with the use of tobacco: Up to 98 percent of SCLC patients have a history of smoking. In most populations the incidence of SCLC rises with increasing tobacco exposure in a dose-dependent fashion, making the overall risk for smokers

approximately 15-fold higher than for nonsmokers. Occupational risks for SCLC include exposure to bischloromethyl ethers, nickel, vinyl chloride, asbestos, cadmium, and radon daughters (in uranium miners). Other types of radiation exposure also appear to be significant risk factors, with an increased incidence of SCLC in atomic bomb survivors and patients (typically those with breast cancer or Hodgkin's lymphoma) exposed to therapeutic irradiation. Industrial nations in general have an increased incidence of SCLC, possibly secondary to higher levels of air pollutants.

HISTOPATHOLOGIC CLASSIFICATION

A number of different histologic classification schemes have been proposed for SCLC over the past 80 years beginning with Bernard's initial report published in 1926 in which he described the epithelial nature of this "mediastinal tumor." Bernard's "The Nature of the 'Oat Cell Sarcoma,"' was a four-subtype morphologic classification. Although the first World Health Organization (WHO) small cell classification included only two subtypes (oat cell and polygonal), the categorization published by WHO in 1967 returned to the original four: fusiform, polygonal, lymphocyte-like, and "other." Subsequent modifications were suggested by pathologists in the Working Party for Therapy of Lung Cancer, and in 1981 WHO changed the lymphocyte-like subtype to the oat cell classification, and combined fusiform and polygonal cell types into the intermediate cell type classification. In 1988, citing lack of differences in biologic behavior among the various subtypes within the WHO classification scheme, the Pathology Committee of the International Association for the Study of Lung Cancer (IASLC) recommended discarding the terms "oat cell" and "intermediate" and substituting the terms "pure small cell carcinoma" (more than 90 percent of small cell cancers) and "variant" histology. The latter contains large cell elements (including *mixed*, a combination of small and large cells, and *combined*, an admixture of small cells with defined non–small cell adenocarcinoma or squamous cell carcinoma elements).

More recently, the WHO joined with the IASLC pathology panel to develop a revised classification of lung and pleural tumors. In the updated classification schema neuroendocrine tumors are viewed as a spectrum extending from low-grade typical carcinoid to intermediate-grade atypical carcinoid to high-grade neuroendocrine tumors, including large cell neuroendocrine carcinoma (LCNEC) and SCLC. Because of differences in clinical behavior, therapeutic implications, and epidemiologic context, these tumors have been presented separately in the WHO revised classification. Using only very objective criteria (mitosis and necrosis), there is substantial inter-observer reproducibility for subclassification of pulmonary neuroendocrine tumors, with the most common disagreement involving LCNEC vs. SCLC. Although, IASLC had proposed to recognize a variant form of SCLC called mixed small cell-large cell carcinoma, this variant was not retained in revised WHO classification. Instead, SCLC is now described with only one variant: "SCLC combined," when at least 10 percent of the tumor bulk is made of an associated non–small cell component. SCLC presents a proliferation of small cells (less than 4 lymphocytes in diameter) with unique and strict morphologic features, scant cytoplasm, ill-defined borders, finely granular "salt and pepper" chromatin, absent or inconspicuous nucleoli, frequent nuclear molding, and a high mitotic count (Fig. 106-1). The category of combined

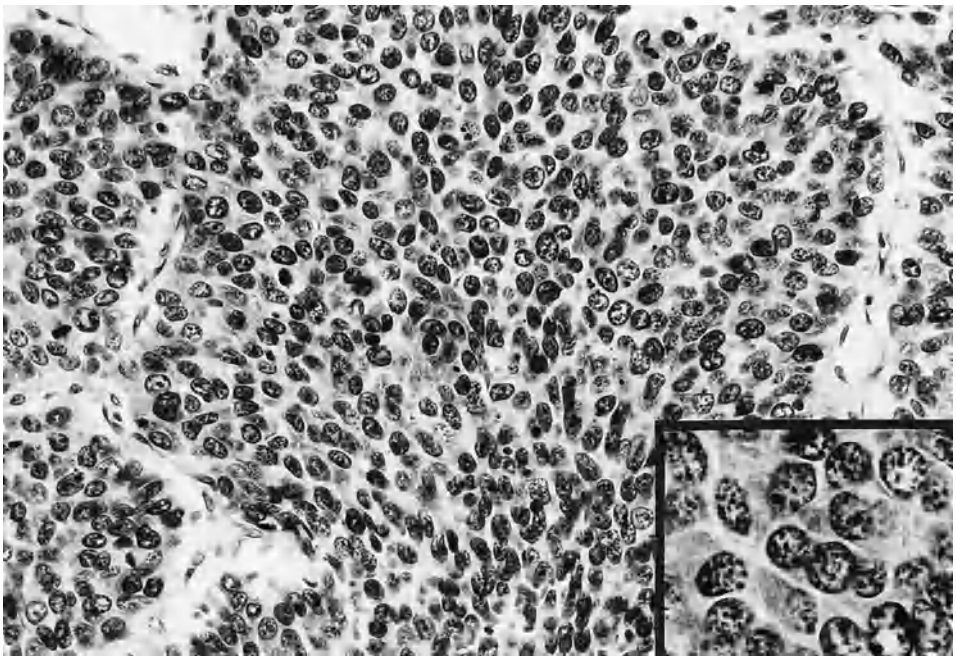

Figure 106-1 Photomicrograph of pure small cell carcinoma, demonstrating a homogeneous cell population with salt and pepper chromatin and moderately prominent nucleoli (H&E, 250×; inset 400×). *(Courtesy of Dr. Michael T. Lomis, Vanderbilt University.)*

small cell carcinoma includes cases with a mixture of small cell and large cell or any other non–small cell component. Importantly for the clinical significance of the diagnostic signature, any case showing at least 10 percent of SCLC is diagnosed as SCLC combined, even if the tumor has a heterogeneous sarcomatous component. SCLC alone is reserved to tumors with pure SCLC histology. SCLC associated with LCNEC is diagnosed as SCLC combined with LCNEC. Thus, there are currently three histologic categories: classical small cell cancer, large cell neuroendocrine cancer, and combined small cell cancer. The clinical significance of dividing small cell cancer into these histologic subtypes is controversial as there appears to be no significant survival difference between LCNEC and SCLC when stratified by stage (see Prognosis). Regardless, pathologists must be cautious in making a diagnosis, since poor fixation can make small cell components appear to be large cells, and crush artifact can give large cells a small cell appearance.

TUMOR BIOLOGY

Most cancers arise as a consequence of genetic abnormalities caused by exposure to environmental carcinogens. *Activation* of a dominant oncogene or *inactivation* of a tumor suppressor gene can both lead to the development of a malignant phenotype. In SCLC the most common genetic abnormalities include loss of chromosomal material associated with inactivation of specific tumor suppressor genes. This frees the cells from the normal growth constraint imposed by the gene products, resulting in unrestrained growth of the cancer cell.

The chromosomal abnormalities most commonly associated with SCLC include loss of a portion of the short arm of chromosomes 3, 9, 11, and 17. Deletions in 3p are found in nearly all (90 percent) SCLC tumors and cell lines. Three tumor suppressor genes of particular interest are located in this region: the fragile histidine triad gene (FHIT) at 3p14.3 encoding the enzyme diadenosine triphosphate hydrolase, the RAS effector homologe (RASSF1A) at 3p21.3 encoding a microtubule-binding protein, and the RARB gene at 3p24 encoding the retinoic acid receptor β. All three gene products are important in cell cycle control or induction of apoptosis; the detailed mechanisms of which are outside the scope of this chapter. The retinoblastoma gene (RB1) at 13q14.11 encodes a nuclear protein involved in cell-cycle progression, and inactivating mutations of this gene are found in more than 90 percent of SCLC. Transfection of a normal *Rb* gene into tumor cell lines with defective retinoblastoma genes causes normal Rb protein production in the tumor cells and reverses malignant phenotype. Mutations of the TP53 gene at 17p13.1, the most common gene abnormality in all human cancers, are found in 75–80 percent of SCLC (Table 106-1).

Dominant oncogene abnormalities are less common in SCLC. For example, overexpression of *myc* oncogene through gene amplification is seen in approximately 25 percent of SCLC patients. The *myc* oncogenes *c-myc, n-myc,* and *l-myc*

Table 106-1

Genetic Abnormalities in SCLC

Gene	Chromosome	Protein	Frequency
Fragile histidine triad (FHIT)	3p14.3	Diadenosine triphosphate hydrolase	~90%
RAS effector homologue (RASSF1A)	3p21.3	Microtubule binding protein	~90%
Retinoic acid receptor β (RARB)	3p24	Retinoic acid receptor β	~90%
Retinoblastoma (RB1)	13q14.11	Nuclear protein involved in cell-cycle progression	~90%
TP53	17p13.1	p53: multifunctional transcription factor	75%–80%
c-myc/N-myc/L-myc (amplification)	8q24/2p24-25/1p34-35	Nuclear DNA-binding phosphioproteins	~25%
K-ras (point mutation)	12p11-12	G-protein regulator of cellular signal transduction	Rare
c-kit receptor	4q12	Transmembrane receptor tyrosine kinase	70%

are closely related nuclear DNA-binding phosphoproteins involved in gene regulation. In two retrospective studies, the presence of *myc* DNA amplification in tumor cell lines and *myc* family DNA amplification was associated with shortened survival in SCLC patients. In laboratory studies, transfection of myc into a SCLC cell line was found to be associated with faster growth, a greater cloning efficiency in soft agarose, altered cell structure, and altered histology in athymic nude mice. These findings connote a more aggressive form of SCLC in association with *myc* amplification. Mutations in ras are mainly observed in NSCLC and rarely in SCLC. It is interesting to note that the mutation is most commonly seen in adenocarcinomas and primarily in subjects with a smoking history. Like *myc* amplification, *ras* mutation in NSCLC is associated with a worse prognosis.

SCLC has long been associated with the production of numerous peptides, including ADH, ACTH, and calcitonin. The autocrine growth promotion potential of these peptides was first proposed almost 25 years ago. The classic autocrine agent in SCLC is gastrin-releasing peptide (GRP), a mammalian analog of the amphibian hormone bombesin. SCLC cells produce GRP, as well as neuromedin B, which bind to one of three receptors (GRP receptor, neuromedin B receptor, and bombesin receptor subtype 3) to active the autocrine-simulated growth loop. A murine anti-bombesin monoclonal antibody directed against GRP has been shown to inhibit the growth of SCLC in vitro and in a mouse model. Unfortunately, no clinically usable antibody is currently available. A second autocrine growth loop involves the c-kit receptor, which is found in the majority of gastrointestinal stromal tumors (GIST), as well as up to 70 percent of SCLC tumors. The ligand stem-cell factor is produced by small cell cancers, which in turn binds to the c-kit receptor to stimulate cell growth. The tyrosine kinase inhibitor imatinib, although effective in GIST, was not shown to have any antitumor activity in two phase II trials, and is not an option for treatment at present. Elevated levels of IGF-1 have been detected in more than 90 percent of SCLC tumors and cell lines, and receptors for IGF-1 are found on SCLC cell lines, suggesting autocrine growth activity.

NATURAL HISTORY

The natural history of untreated SCLC is early dissemination and death. Unlike NSCLC, it is always considered a systemic disease at diagnosis, even if it appears clinically confined to the chest. Postmortem exams performed on patients who died from other causes shortly after the "complete" surgical resection of their SCLC have demonstrated identifiable metastases in up to 70 percent of cases. Evidence of distant spread can be found in virtually any organ system. The most common sites of involvement, however, are the liver, bone and bone marrow, and central nervous system (Table 106-2). This pattern of spread dictates how the search for metastatic disease is made (see Staging).

Table 106-2

Extent of Disease at Presentation

Limited stage disease	25%–30%
Extensive stage disease	70%–75%
Metastatic sites:	
Liver	25%–30%
Bone	25%–40%
Bone marrow	20%
Adrenal	5%–30%
Brain	10%
Extrathoracic lymph nodes	5%
Subcutaneous masses	5%

Patients with SCLC have a short lifespan if therapy is not instigated in a timely fashion. The median survival for untreated patients is 4 to 6 months if they have disease that is apparently confined to the chest, and 5 to 9 *weeks* if they present with metastatic disease. With therapy, survival improves significantly (see Treatment). Chemotherapy with or without irradiation can extend median survival to an average of 14 to 20 months for those with thorax-confined disease and 7 to 10 months for those with more extensive spread. At 2 to 3 years, a consistent 10 to 25 percent of limited-stage patients will still be alive, although cure is not guaranteed even in these relatively long-term survivors (see Late Complications). Recent trials indicate that 2-year survival may be as high as 40 percent for aggressively treated limited-stage patients. Two- to three-year survival remains a dismal 1 to 2 percent for those with metastatic disease.

DIAGNOSIS

The diagnosis of SCLC is usually not difficult (see also Histopathologic Classification). The gross specimen often reflects a central lesion arising from a major bronchus and extending into the nearby pulmonary parenchyma. Necrosis and hemorrhage are often present. The classic oat cell form of small cell cancer consists of sheets of heavily staining "blue" cells with scant cytoplasm, hyperchromatic nuclei, and non-prominent nucleoli. In general, any subtype of description of "small cell carcinoma" includes cells double the size of a small lymphocyte, with salt-and-pepper chromatin, nuclear molding, and areas of necrosis (Fig. 106-1). Inflammatory response and desmoplastic reactions are usually absent. Although biopsy specimens are ideal, cytologic specimens alone are often sufficient for diagnosis, with a sensitivity of 60 to 90 percent and a specificity of greater than 95 percent.

Difficulty occasionally arises in distinguishing small cell carcinomas from lymphomas, other neuroendocrine tumors (e.g., atypical carcinoids), and poorly differentiated non–small cell cancers. The presence of "crush artifact" is more common in SCLC than NSCLC, but it can be present in lymphomas. If additional review fails to reveal subtle glandular or epidermoid differentiation, tests beyond light microscopy may be necessary to establish the diagnosis. Electron microscopy can be useful in this setting, particularly with large cell neuroendocrine cancers, revealing dense neurosecretory granules.

Immunohistochemistry plays an important role in the diagnosis of SCLC. Nearly all small cell cancers are positive for the epithelial markers keratin, epithelial membrane antigen, and BER-EP4. (Non-Hodgkin's lymphoma is suggested by antibodies against the common leukocyte antigen, with negative epithelial markers.) Given their neuroendocrine derivation, many of the tumors will stain positively for one of a variety of neuroendocrine markers, with neuron-specific enolase and chromogranin A being the two most common. Other neuroendocrine markers that can be found include dopa decarboxylase, calcitonin, Leu-7, CD56 (neural cell adhesion molecule [NCAM]), gastrin releasing peptide (GRP), and insulin-like growth factor-I (IGF-I). One or more of these markers can be found in approximately 75 percent of SCLCs. However, negative neuroendocrine markers should not deter one from diagnosing SCLC.

STAGING

Staging a cancer defines the anatomic extent of the tumor, helps determine prognosis, and guides treatment options. Although the TNM staging system can be used for SCLC, most authorities prefer a simpler two-stage system, which reflects not only the systemic nature of the disease at diagnosis, but also the beneficial role of radiotherapy in early-stage cancer. This two-stage system has been found to have independent prognostic implications for patients with SCLC.

As originally proposed by the Veterans Administration Lung Cancer Study Group, the staging system places patients with disease that can be confined to a single, tolerable radiation portal in the limited stage category (25–30 percent of all patients with SCLC): *all others* are defined as extensive stage (70–75 percent) (Table 106-2). Unlike pulmonary adenocarcinoma, isolated pleural effusions are uncommon in SCLC. Controversy exists over the staging of an ipsilateral pleural effusion, which technically could be confined to a single radiation portal, although most authorities consider this to be extensive disease. Similar controversy exists for supraclavicular and contralateral hilar adenopathy.

Clinical conditions, such as the superior vena cava (SVC) syndrome, are not strictly encompassed by this two-stage system. Many authorities do not believe SVC syndrome automatically places the patient into the extensive-stage category, because it does not significantly change the prognosis of those treated with combination chemotherapy. Some authors have even proposed a "very limited" stage, which purports to define a group of patients without any mediastinal adenopathy (18.5 percent of limited-stage patients, and approximately 6 percent of all SCLC patients) who have long-term survival much beyond that normally seen for those who are "conventionally limited."

A full history and physical examination, complete blood count with platelet analysis, and blood chemistries (including liver function tests, lactate dehydrogenase, and alkaline phosphatase) should be performed after diagnosis. Tests such as mediastinoscopy, which may or may not be necessary for diagnosis, are not required for staging once the diagnosis has been made. Current guidelines call for computed tomography (CT) scans of the chest to assess for adenopathy, contralateral parenchymal disease, and pleural effusion. Liver metastases occur in roughly 25 percent of SCLC patients, and adrenal metastases in 5 to 30 percent; therefore, the initial CT of the chest should be extended caudally to include the liver and both adrenal glands.

Patients with any neurological abnormality should immediately undergo MRI or CT of the brain and MRI of the spinal cord, as 80 to 90 percent of these SCLC patients have disease in the central nervous system. Radionuclide bone scans are called for in any patient with bony pain. As 25 to 40 percent of patients have bony metastases on presentation, and most of these patients are asymptomatic with normal serum alkaline phosphatases, a bone scan can be considered an integral part of the staging workup.

Positron emission tomography (PET) scans have recently been show to have utility in SCLC. SCLC is fluorodeoxy-D-glucose (FDG) avid at both primary and metastatic sites. PET appears to be more sensitive and specific than CT scans in detecting non–brain distant metastases, but less sensitive than MRI or CT in detecting brain metastases. Approximately 10 percent of limited stage patients can be upstaged to extensive stage disease through the use of PET scans, and therein lies the best defined clinical utility for this modality. Nonetheless, the U.S. Centers for Medicare & Medicaid Services (CMS) does not consider SCLC an appropriate indication for PET scanning.

Histologic bone marrow examination has historically been deemed to be of value in the initial evaluation of otherwise limited SCLC. Unless significantly low, hematologic variables do not reliably predict bone marrow metastases, and leukoerythroblastic changes on peripheral smear are usually seen only with extensive marrow involvement. However, fewer than 5 percent of patients have bone marrow involvement as their only metastatic disease, and stage is rarely altered (less than 2 percent) on the basis of bone marrow biopsy alone. Thus this test is not routinely performed if other blood parameters are normal. Although the true incidence of marrow metastases is probably much higher than that reported from series using histologic examination alone, there is no proof that immunostaining with monoclonal antibodies or doing cell cultures to detect microscopic bone

marrow involvement will meaningfully change treatment planning.

CLINICAL PRESENTATION

No aspect of the clinical presentation of SCLC distinguishes it from NSCLC or even from neoplasms metastatic to the lungs. However, the duration of symptoms of small cell cancer tends to be very short, due to the rapid dissemination of the disease. The typical patient is a middle-aged or elderly smoker who presents with symptoms attributable to their pulmonary and mediastinal disease: cough, dyspnea, chest pain, hoarseness, and/or hemoptysis. Because of the usual endobronchial location of the tumor, patients often have accompanying postobstructive pneumonia.

Constitutional symptoms may include weakness, anorexia, weight loss, and, rarely, fever. Symptoms may also arise from distant metastases, including headache or seizures in patients with central nervous system (CNS) disease, and abdominal or bone pain with hepatic and osseous metastases, or from regional disease with attendant superior vena cava obstruction, manifesting as facial fullness, upper extremity swelling, headache, and dysphagia. In rare instances, patients present with symptoms from a paraneoplastic syndrome. The more common of these rare presentations are inappropriate secretion of antidiuretic hormone (SIADH) and other causes of hyponatremia, Cushing's syndrome, Lambert Eaton syndrome, and other paraneoplastic neuropathies or neurologic disorders.

Physical exam may yield only the stigmata of chronic obstructive pulmonary disease, or it may demonstrate lymphadenopathy, hepatomegaly, bone tenderness, or neurologic findings. Signs of the superior vena cava syndrome include venous distention of the neck and chest wall, cyanosis, facial plethora, and upper extremity edema.

A chest radiograph typically demonstrates a central mass (75 percent of patients) with or without hilar nodal involvement (Fig. 106-2). Postobstructive atelectasis and pneumonia are very common with small cell lung cancer, but cavitation on chest radiograph suggests the alternative diagnosis of squamous cell lung cancer.

Laboratory evaluation reveals mild abnormalities of liver function (usually elevated alkaline phosphatase, and less commonly SGOT, SGPT, or bilirubin) and/or elevated lactate dehydrogenase in about 50 percent of patients. Leukopenia and thrombocytopenia are unusual and hardly ever seen in the absence of widespread disease at a number of sites beside the bone marrow.

Two special situations warrant brief discussion. Organ involvement from SCLC obviously can lead directly to failure of that organ, but this neoplasm can also cause problems in an indirect fashion. For example, hepatic insufficiency from frank neoplastic involvement, based on the clinical picture of jaundice and abnormal liver function, is a well-described phenomenon to those who treat SCLC, and usually signals a poor outcome. If the same clinical picture is a result of extrahepatic biliary obstruction from nodal metastases, also well described in the literature, the patient has a better prognosis than one with diffuse liver replacement.

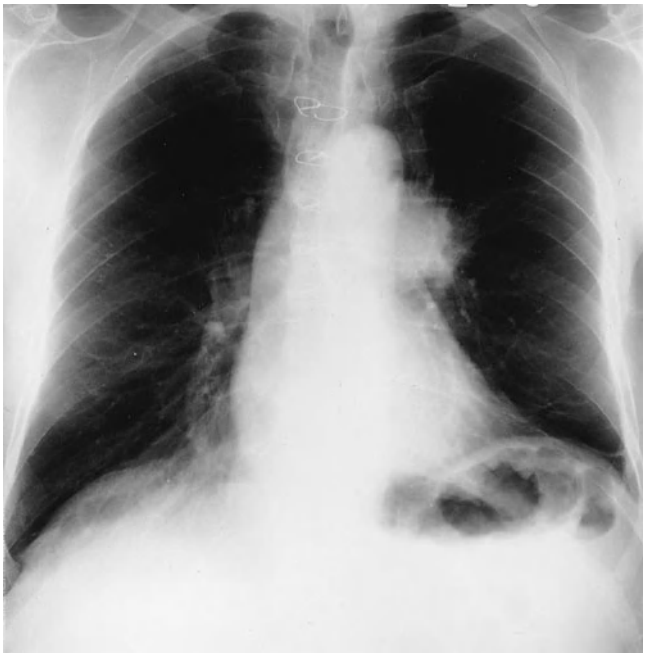

Figure 106-2 Chest radiograph of a patient with small cell lung cancer, demonstrating a left hilar mass extending into the (anterior) upper lobe. *(Courtesy of Dr. Russell DeVore, Vanderbilt University.)*

Pancoast's syndrome, with ptosis, anhydrosis, facial edema, and sensory neuropathic pain and functional loss, is more commonly associated with NSCLC, but it has also been reported in patients with small cell disease. Obtaining a tissue diagnosis from an apical pulmonary mass is thus mandatory before radiotherapy or other treatment is started.

PARANEOPLASTIC PHENOMENA

Many of the symptoms of lung cancer can be attributed to mass effect and direct impingement upon vital organs. However, tumor cells can act at a distance by secreting various biologically active agents, including antibodies, hormones, and other proteins. These so-called paraneoplastic phenomena can be seen in any type of lung cancer, but historically are most frequently associated with small cell lung cancers (Table 106-3). Most of these paraneoplastic phenomena can be placed into endocrine or neurologic categories.

Ectopic adrenocorticotropic hormone (ACTH) production by small cell carcinoma has been a well-recognized phenomenon since 1928. The secretion of ectopic ACTH

Table 106-3

Common Paraneoplastic Phenomena in SCLC

Syndrome	Biologically Active Agent	Laboratory Finding	Frequency
SIADH	Antidiuretic hormone (ADH)	Hypo-osmolar hyponatremia	10%–15% in limited 30% in extensive
Cushing's	Ectopic adrenocorticotropic (ACTH)	Hypercortisolemia	1.6%–4.5% with clinical syndrome ~50% with elevated cortisol levels
Humoral hypercalcemia	Calcitonin	Elevated calcium Low-Normal PTH-rP	10% with hypercalcemia 50% with elevated calcitonin
Lambert-Eaton myasthenic syndrome (LEMS)	IgG auto-antibodies to P/Q-type voltage gated calcium channels	Positive antibody titers	~5%
Paraneoplastic cerebellar degeneration	Auto-antibodies against cerebellar Purkinje cells	anti-Yo antibodies	~2%
Paraneoplastic encephalomyelitis	Neuronal nuclear antibody Type 1	anti-Hu (ANNA-1) antibodies	Antibodies present in ~25% of pts

results in bilateral adrenocortical hyperplasia and hyperfunction, leading to the clinical manifestations of Cushing's syndrome. Cushing's syndrome from small cell carcinoma differs slightly from Cushing's disease (the same syndrome produced by a pituitary adenoma) in that the onset of symptoms in the former is usually abrupt. When signs and symptoms do occur, they tend to be those associated with acute hypercortisolism: hypokalemic alkalosis, hypertension, hyperglycemia, and rarely edema and muscle wasting. The features of chronic steroid overexposure seen in Cushing's disease, such as the "buffalo hump," striae, and moon facies, are usually absent. Neuroendocrine tumors of the lung, including small cell carcinoma (27 percent) and pulmonary carcinoids (21 percent) represent about half of the cases of ectopic ACTH-producing tumors. As such, SCLC is the most common malignancy associated with Cushing's syndrome. Although hypercortisolemia has been documented in up to 50 percent of SCLC cases, only 1.6 to 4.5 percent of SCLC patients have clinical Cushing's syndrome. The effect of Cushing's syndrome on survival is unclear, although some investigators hold that its onset heralds a more aggressive tumor behavior. Lethal infections, particularly those caused by fungi, often complicate the clinical course. Treatment with standard medications, such as metyrapone and ketoconazole, is largely ineffective due to extremely high cortisol levels. Some patients require bilateral adrenalectomy. Effective treatment of the underlying SCLC is generally the best treatment for Cushing's syndrome.

The syndrome of inappropriate antidiuretic hormone (SIADH), with its resultant euvolemic, refractory, hypo-osmolar hyponatremia, is a common SCLC-associated paraneoplastic disorder. Indeed, SCLC is estimated to represent about 80 percent of all ADH-secreting tumors, and is the most common malignant cause of acute or chronic SIADH. The incidence of hyponatremia ranges from 10 to 15 percent in patients with limited disease, and around 30 percent of patients with extensive stage disease. Roughly 25 percent of SCLC patients are estimated to have symptomatic SIADH at the time of diagnosis. As with other paraneoplastic syndromes, the best therapy for SIADH is effective treatment of the underlying SCLC. Vanderbilt University researchers demonstrated resolution of SIADH in 16 of 17 patients with SCLC 8 to 28 days after treatment with chemotherapy. The authors discussed temporizing measures for the hyponatremia while awaiting the effects of chemotherapy: They suggested that strict fluid restriction alone would maintain the serum sodium above 128 mEq/L in all patients. The use of demeclocycline, and agent that blocks the action of vasopressin at the level of the renal tubule, is another possible adjunctive measure. The starting dose is 150 mg orally four times a day (600 mg total), but the daily dosage may need to be increased to 1200 mg. Despite previous suggestions to the contrary, SIADH does not worsen the prognosis for SCLC patients, especially in the age of modern chemotherapy.

Although humoral hypercalcemia of malignancy is common in NSCLC patients, particularly those with

squamous cell cancers, it is extremely unusual in SCLC. Serum calcium is elevated at presentation in only 10 percent of patients, although serum calcitonin levels are elevated in up to half of patients. The rare patients with hypercalcemia have been found to have inappropriately normal (i.e., not suppressed) levels of parathyroid hormone-related protein (PTH-rP). The precise mechanism for the hypercalcemia is unclear, although these patients almost always have extensive bone or marrow involvement. Local destruction of bone is not a satisfying hypothesis, however, as the vast majority of SCLC patients with bony involvement have normal calcium levels.

Neurologic paraneoplastic syndromes are frequently reported. These are often the result of production of antibodies that react with both the small cell cancer cells and with normal host tissue. Well-described syndromes include the Lambert-Eaton myasthenic syndrome (LEMS) and cerebellar degeneration. Less frequent abnormalities include subacute sensory neuropathy, autonomic disturbances, myelopathies, progressive encephalopathy, and a visual paraneoplastic syndrome. Nonspecific neurologic findings that may be related to ectopic hormone or antibody production include generalized weakness and anal sphincter dysfunction. LEMS is a result of IgG autoantibodies directed against presynaptic P/Q-type voltage-gated calcium channels. These antibodies are estimated to occur in 5 percent of patients with SCLC. Clinically, the syndrome presents with proximal muscle weakness, usually in the lower extremities, occasional autonomic dysfunction, and rarely with cranial nerve symptoms. As contrasted with patients with myasthenia gravis, strength improves with serial effort, and the weakness associated with LEMS improves over the course of the day. Plasma exchange and intravenous immunoglobulin can provide short-term benefit, whereas 3,4-diaminopyridine (which enhances the release of acetylcholine from presynaptic terminals), prednisone, and azathioprine can provide limited long-term benefit. Some patients who respond to chemotherapy have resolution of the neurologic abnormalities, and this is the initial treatment of choice.

The neuronal nuclear antibody type 1 (also called anti-Hu and ANNA-1), is associated with SCLC and a paraneoplastic encephalomyelitis or sensory neuropathy. These antibodies have been found in up to 25 percent of SCLC patients. As with voltage-gated calcium channel antibodies, the presence of anti-Hu antibodies does not correlate with neurological symptoms, nor with an improved prognosis. Initially these two antibodies were thought to be associated with improved survival. Given that the diagnosis of the neurological syndrome often predates the diagnosis of SCLC, this may be reflective of lead-time bias, rather than an upregulated immune response.

Paraneoplastic cerebellar degeneration (PCD), manifesting with ataxia, dysarthria, and nystagmus, is also commonly associated with SCLC, as well as ovarian malignancies and lymphomas. Antibodies that react against cytoplasmic proteins of cerebellar Purkinje cells are often found in these patients. One such antibody, anti-Yo, attacks the cdr2 proteins in the Purkinje cells. Treatment may include steroids, plasmapheresis, and chemotherapy.

Finally, elevations of gonadotropins, gastrin, β-melanocyte–stimulating hormone, and prostaglandins have all been described in SCLC patients. None has contributed significantly to a defined clinical syndrome.

EXTRAPULMONARY SMALL CELL CARCINOMA

The knowledge that small cell cancers can arise from tissues other than the lungs has existed since 1930. Extrapulmonary small cell cancer (EPSCC) remains relatively rare, representing 2 to 4 percent of diagnosed small cell cancers, with an estimated 1000 cases occurring annually in the United States. EPSCC has been described as arising in a wide variety of tissues, most commonly in the uterine cervix, gastrointestinal tract (esophagus and colon), upper airway and salivary glands, and genitourinary organs (prostate). The cell of origin of the extrapulmonary cancer is thought to be a totipotent stem cell that can differentiate into either epithelial cells or neuroendocrine (and thus, small cell cancer) elements. EPSCC has been recognized to be a distinct clinical entity, and can be distinguished from metastatic SCLC without a clear pulmonary primary site by the lack of deletion of chromosome 3p in the former. Ectopic hormone production is extremely rare, and the extrapulmonary variety of small cell cancer has a weaker correlation with smoking than SCLC.

Staging of EPSCC is similar to the staging of small cell pulmonary tumors. Limited disease is still defined as that confined to a small anatomic compartment, and extensive disease as that extending beyond locoregional lymph nodes. Most authorities would perform the same staging evaluation on these patients as on those with SCLC.

Due to the paucity of cases, the optimal treatment of EPSCC is not clearly defined. Surgery has been shown to be curative in certain patients with disease confined to the organ of origin. Unfortunately, as with SCLC, tumors tend to clinically aggressive with early dissemination. Combined chemoradiotherapy can be used for limited stage disease. Extensive stage EPSCC responds to platinum-based chemotherapies in approximately 75 percent of the cases, but these responses are generally short-lived. In one series of 81 patients at the Mayo clinic, disease-free and overall survival at 5 years was 13 percent.

PROGNOSTIC FACTORS

A variety of pretreatment factors have been reported as having value in predicting therapeutic outcomes for patients with small cell carcinoma. Since the aggressiveness of therapy may depend on this perceived outcome, it is important to determine before treatment how a patient is *likely* to do. The

strongest and most consistent prognosticators from nearly all studies have been stage of disease (limited vs. extensive) and Karnofsky performance status at presentation. The importance of stage has already been mentioned. In general, extensive-stage patients have a lower chance of achieving a complete response to chemotherapy, shorter median survival times, and a much smaller chance of being cured. However, patients with extensive-stage disease, by virtue of having a single site of metastasis (especially in soft tissue, bone, or brain), often behave more like limited-stage patients and should be treated accordingly. Within the extensive-stage group, having an increasing number of affected sites, especially if these include bone marrow or abdominal disease, carries a worse outlook.

The performance status or ability of the patient to carry out normal daily activities has a profound effect both on the ability to tolerate chemotherapy and the efficacy of those drugs administered. In general, patients with poor performance status have a lower chance of response to chemotherapy and a higher chance of having clinical toxicity. However, poor performance status does not automatically exclude patients from receiving aggressive treatment, unlike non–small cell lung cancer. The occasional bedridden patient can experience clinical improvement and even be cured with chemotherapy. Similar to performance status, substantial weight loss (usually qualified as at least 10 percent of total body weight) is an independent prognostic factor for an adverse outcome. As seems logical, achieving complete remission with chemotherapy in general portends a better outcome than being nonresponsive or having only a partial response. Similarly, relapse from remission clearly heralds short survival.

In many epidemiologic studies, female gender has been suggested to be a favorable prognostic factor in patients with SCLC. Women have a higher likelihood of responding to chemotherapy and obtaining a complete response. Their overall survival is also better than that of male patients. Variance in other epidemiologic factors, such as age (in the absence of poor performance status) and race, does not seem to be of consistent importance.

The continued use of tobacco is an adverse prognostic factor. Second malignancies, often smoking related, are a significant cause of death in long-term survivors of SCLC. Chronic tobacco use puts these patients at risk for chronic obstructive pulmonary disease and ischemic heart disease, which worsen with continued tobacco exposure. These two conditions represent significant sources of morbidity and mortality in patients with SCLC both during and after treatment.

Abnormalities in various laboratory parameters have long been held to have prognostic value. For example, a high serum lactate dehydrogenase, suggestive of more bulky disease, is an independent predictor of poor outcome for extensive-stage disease. In an analysis of the Southwest Oncology Group Small Cell Cancer Data Base, Albain and colleagues determined that good performance status, female sex, younger age (less than 70 years), white race, and normal serum lactate dehydrogenase were independent predictors for better survival. In extensive-stage patients, normal serum lactate dehydrogenase was the best predictor, followed by having a single metastatic focus of disease and receiving intensive combination chemotherapy. Hypoalbuminemia, hyponatremia, elevated alkaline phosphatase, and leukocytosis have been associated in various studies with poor prognosis. The serum tumor marker neuron-specific enolase (NSE) is more often elevated in extensive-stage than in limited-stage patients. Diagnostic specificity of this marker, however, is only 40 to 70 percent in limited SCLC, but specificity reaches to 80 to 100 percent in extensive disease. The baseline value increases in proportion to the number of metastases and baseline values and values after chemotherapy correlate with overall survival. Nonetheless, measurement of this parameter has not proved clinically useful. Moreover, serum NSE levels can also be elevated in NSCLC and smokers.

Histologic classification is of prognostic significance. Previously some investigators reported longer survival with the so-called "oat cell subtype" than with tumors of the non–oat cell subtype. However, it is now known that there is not much biologic or prognostic difference among the subtypes of pure small cell carcinoma. The importance of mixed elements by histology, including large cell neuroendocrine carcinoma (LCNEC) component, is less clear. LCNEC is considered to be a variant of non–small cell lung cancer, with a relative insensitivity to chemotherapy. In a study of intensive treatment of 375 patients with SCLC, Hirsch and colleagues noted a median survival of 168 days for those with pure SCLC (of various non–large cell subtypes) versus 280 days for those with tumors with any large cell features. Data from an Eastern Cooperative Oncology Group publication, however, point to a different conclusion. ECOG investigators examined all patients with the diagnosis of variant histology (small cell with large cell elements) placed on an ECOG chemotherapy protocol. They found that variant histology actually was rare (less than 10 percent of cases) and did not lead to lower response rates or a shorter median survival. Taken as separate entities, Japanese investigators have recently demonstrated that LCNEC and SCLC have roughly the same prognosis.

TREATMENT

Surgery

The role of surgery for SCLC has come full circle in the past four decades. The disease has been thought of as systemic from the outset, and chemotherapeutic treatment has long been standard. In the mid-twentieth century, however, the British Research Medical Council randomized patients with SCLC to surgery or thoracic radiation. The patients on the surgical arm had worse survival, but neither arm did particularly well, with less than 5 percent of patients alive at 5 years. Subsequently, The VA Surgical Oncology Group entered more than 2000 patients in a study looking at the role of adjuvant chemotherapy after resection of NSCLC. One

hundred forty-eight patients with SCLC were incidentally entered in the study, and early-stage patients enjoyed superior survival.

Surgery for early stage small cell carcinoma, particularly those cancers presenting as small single pulmonary nodules, may be more appropriate, as these tumors may be biologically distinct from advanced disease. For example, in a retrospective study, Roswell Park Cancer Institute investigators identified a small number of SCLC patients with "isolated" lesions. These patients did not receive "prompt" diagnosis or treatment of their cancers. Moreover, extremely slow growth of the tumors was documented, ranging from 14 to 40 months, and no lymph node involvement or metastatic disease was found at the time of surgery. Thus, this experience is not characteristic of SCLC in general. Nonetheless, other studies of resection for patients with T1N0M0 tumors have suggested a 50 to 80 percent 5-year survival rate, although it is extremely rare for patients to fall into this category. In the early 1990s University of Toronto investigators reviewed a 15-year surgical experience with SCLC at that institution. They reported that resection improved control at the primary site, and a significant proportion of patients with stage I (N0) disease achieved long-term survival and cure with combined modality therapy, including surgery. Moreover, stage II and IIIa patients had survival durations similar to stage IIIa non–small cell lung carcinoma treated surgically.

There may be other circumstances in which one might consider employing surgery with or without systemic therapies in selected patients with SCLC. First, small cell cancer treated with chemoradiotherapy still has a high local recurrence rate. Surgery for other thoracic malignancies, particularly esophageal cancer, affords significant improvement in local control, even when added to radiotherapy. Second, surgery immediately puts the patient into a "no clinical evidence of disease" category, and both chemotherapy and radiotherapy work better on small-volume or microscopic disease. Finally, many mixed histology SCLCs contain large cell elements that may be less responsive to irradiation or chemotherapy. NSCLC is notoriously resistant to chemotherapy, and surgery is the best curative option for this disease. Therefore, an argument could be made for resection of residual disease after chemotherapy, especially if the remaining element represents a non–small cell fraction. There has been one randomized study testing this role for surgery in SCLC. The Lung Cancer Study Group gave limited-stage patients standard chemotherapy for five cycles, followed by PCI and thoracic irradiation; the patients were also randomized to receive or not receive surgery. It is interesting to note that 9 percent of patients who did undergo surgery had residual non–small cell elements. Actuarial 2-year survival was identical on the two arms at 20 percent; thus, no survival benefit was demonstrated for surgery. However, this study excluded patients who would have fallen into the extremely limited T1N0M0 or T2N0M0 non–small cell staging schema—the ones who had shown the most benefit from surgery in earlier studies. Thus this trial does not definitively exclude a role for postinduction surgery in SCLC, although admittedly such an approach is likely to be exceedingly uncommon in clinical practice.

In summary, the benefits of surgical resection in SCLC are mainly seen in patients with TNM stage I disease with peripheral tumors and no nodal involvement, and who are able to tolerate the procedure. Adjuvant chemotherapy should be offered postoperatively.

Chemotherapy

Unlike non–small cell lung cancer (NSCLC), SCLC is classically associated with exquisite chemosensitivity. Ironically, however, the survival of patients with metastatic NSCLC is actually quite comparable with that of SCLC patients with extensive-stage (ES) disease following platinum-based therapies. Nonetheless, in some quarters, the perception persists that SCLC is more "chemo-sensitive" than NSCLC. In limited-stage (LS) disease, chemotherapy combined with thoracic radiation achieves a response in over 80 percent of patients, and a complete response in the range of 40 to 60 percent. In ES disease, the response rate is lower (60–80 percent), with a rate of complete response around 15 to 35 percent. Chemotherapy has been shown to improve survival compared with supportive care. In LS disease, median survival in treated patients is 15 to 20 months, with 5-year survival rates of 10 to 13 percent. The median survival for ES patients treated with chemotherapy remains at 7 to 9 months, with few long-term survivors.

Early studies from the 1940s and 1950s showed nitrogen mustards had activity against anaplastic lung cancer, which presumably included cases of SCLC. In the late 1960s, a large VA Lung Cancer Study Group trial demonstrated the survival benefit of treatment with cyclophosphamide, an alkylating agent. As responses to single agents were rare, the focus changed to combinations of drugs, each with independent activity against SCLC. When given in combination, these drugs had synergistic activity, and lowered the likelihood of complete tumor resistance. Until the mid-1980s the combination of cyclophosphamide, doxorubicin (Adriamycin), and vincristine (CAV) was commonly used as first-line therapy. Currently, the two-drug regimen of etoposide and cisplatin (EP) is the standard of care for SCLC chemotherapy. A large randomized trial demonstrated that an EP regimen conferred a significant survival benefit compared with the traditional CAV regimen in LS disease. The median survival in the EP arm was 14.5 months, compared with 9.7 months in the CAV arm. Hematological toxicity was diminished with EP, and this combination was more easily combined with radiation. The EP regimen is typically given every 3 weeks for four to six cycles. Although additional cycles of chemotherapy (i.e., using maintenance chemotherapy) may prolong time to progression, there is no survival benefit to extending chemotherapy past six cycles of induction chemotherapy.

In ES disease, the EP regimen has never shown a survival benefit over CAV, yet EP remains the standard of care due mainly to an improved side-effect profile. Likewise, carboplatin appears to be as effective as cisplatin when used

in combination with etoposide, and is often better tolerated by patients. A recent Phase III trial in Japan suggested that irinotecan plus cisplatin is superior to EP. The response rate (84 vs. 66 percent), median survival (12.8 vs. 9.4 months), and 2-year survival rate (19.5 vs. 5.2 percent) were significantly higher in the irinotecan group. However, an attempt to confirm these results in the United States failed to show any improvement in survival in a non-Japanese patient population. This may be due to genetic or unrecognized molecular differences between the two patient populations as seen in the markedly different mutational rates of the epidermal growth factor receptors in NSCLC. Oral topotecan plus cisplatin was recently shown to be similar to EP in first-line therapy of ES SCLC in a non-inferiority study. The authors suggest oral topotecan is also more convenient, but this is conjectural. Moreover, maintenance therapy with topotecan following standard EP therapy failed to demonstrate a survival benefit.

Based on the extant literature, it appears the optimal therapy for a majority of SCLC patients is EP with the addition of thoracic radiotherapy for those with limited stage disease [vide infra]. Treatment beyond four to six cycles in unwarranted in the first-line setting. There is little support for the use of dose intensification or so-called "dose dense" therapy as a course of routine treatment. Furthermore, the need for expensive supportive care drugs such as colony-stimulating factors or erythropoietin is greatly diminished if one uses EP at standard dosing.

Thoracic Radiotherapy

As with chemotherapy, SCLC is clearly sensitive to irradiation. Radiation therapy as a single modality leads to a response rate of 75 percent in LS disease, and has been noted to cure as many as 5 percent of these patients. Initial clinical trials combining radiotherapy with chemotherapy yielded mixed results. For the most part, these early trials demonstrated a decrease in local recurrence coupled with significant host toxicity but no clear survival benefit. However, a 1992 meta-analysis of 13 prospective, randomized trials showed that combined chemoradiotherapy in LS disease provides a 5 percent survival benefit at 2 and 3 years post-treatment when compared with chemotherapy alone. However, several key questions relating to the optimization of thoracic radiotherapy (TRT) remain unanswered, including volume of irradiation, optimal total dose, fractionation, timing, and sequencing of radiation. Regarding optimal timing, concurrent treatment administered early, meaning within the first two cycles of induction chemotherapy, appears to yield the greatest survival benefit. Early concurrent radiotherapy comes with a cost in the form of increased toxicity to the patient, mainly severe esophagitis and greater myelosuppression. The optimal fractionation and dose of TRT also are unknown. ECOG investigators conducted a randomized trial of twice-daily radiation therapy combined with the EP regimen that yielded significantly improved median (23 vs. 19 months) and 5-year (27 vs. 11 percent) survival compared with once-daily radiation treatments. Nonetheless, the oncology community has not embraced this approach. Rather, most radiation oncologists tend to increase the total dose of radiotherapy under the assumption this has biological equivalent results; however, data supporting this supposition are lacking.

Radiation serves a purely palliative role in ES disease, and can be used for symptomatic control in bony, pulmonary, and CNS metastases. Certain ES patients may benefit from prophylactic cranial irradiation, as well.

Prophylactic Cranial Irradiation

The need for prophylactic cranial irradiation (PCI) in patients with LS SCLC had long been an area of controversy until the late 1990s. This issue is critical in the management of limited stage disease for two key reasons: the CNS has long been considered a sanctuary site from many chemotherapeutic agents, and the brain is a common site of metastasis in this cancer. Limited stage SCLC successfully treated with induction chemoradiotherapy is estimated to have a 50 to 67 percent chance of relapse in the brain, with one-third of these patients having disease solely in the CNS. A meta-analysis of seven randomized trials published in 1999 demonstrated a significant benefit to PCI. Patients who received PCI were 5.4 percent more likely to be alive at 3 years, had a 54 percent reduction in the risk of brain metastases, and a 25 percent increase in disease-free survival.

Current guidelines recommend PCI for all patients with a good performance status who have attained remission after induction chemoradiation. This includes patients with extensive-stage disease in complete remission, although the benefit for this subset of patients is not as clear. PCI should be given sequentially, rather than concurrently, to avoid additional toxicity. Typically patients receive 25 to 36 Gy in 10 to 18 fractions. Although there is concern that PCI can lead to late cognitive impairment, patients randomized to PCI or observation showed no detectable difference in post-treatment cognitive impairment or quality of life at 1 year post treatment.

Second-Line Chemotherapy

The majority of SCLC patients treated with first-line chemotherapy demonstrate tumor shrinkage but most eventually relapse. The time course after treatment is important when considering further treatment options. Those patients who relapse within 3 months of completing treatment are considered to have "refractory" (chemoresistant) disease, which responds to second-line treatments less than 10 percent of the time. Recurrence beyond 3 months is classified as "sensitive" relapsed (chemosensitive) disease. Patients with chemosensitive disease respond much better to second-line agents (30–40 percent response rate), and achieve a median survival of approximately 6 months. In the United States, the topoisomerase I inhibitor topotecan is currently the only drug approved for second-line treatment. Intravenous topotecan used as a single agent has a response rate of 11 to 37 percent.

Modest response rates have been shown with the use of single agents such as irinotecan, paclitaxel, docetaxel, vinorelbine, and gemcitabine. These responses are rarely durable.

Recently, targeted therapy has made a significant impact in the treatment of certain cancers, most importantly in colorectal and renal cell cancers. In NSCLC, anti-angiogenic drugs directed at vascular endothelial growth factor (i.e., bevacizumab) and tyrosine kinase inhibitors (i.e., erlotinib and gefitinib) are currently in use. Certain targeted therapies, including inhibitors of c-kit, matrix metalloproteinases, farnesyl transferase, proteosomes, and the mammalian target of rapamycin (mTOR) have been investigated in SCLC. To date, the results of these trials have been negative. Targeted therapies are currently under investigation in SCLC, and these agents may provide the most hope for future treatment options.

Treatment in Patients with Poor Performance Status

As the percentage of the population over 65 years old continues to grow rapidly, it is common to encounter older patients with SCLC. Oncologists have been taught that because of poor bone marrow, renal and hepatic reserves, elderly cancer patients do not tolerate chemotherapy as well as their younger counterparts. Curative chemotherapy is often not even attempted in the elderly for other malignancies, such as acute myelogenous leukemia. Additionally, given the lengthy smoking history in the majority of SCLC patients, many suffer from the cardiovascular and pulmonary sequelae of smoking, which diminishes performance status. Although it is true that elderly patients are, as a group, less able to tolerate chemotherapy, for those who do receive full-course treatment, survival is equal compared with comparable-stage younger patients. Single-agent etoposide has been compared with combination chemotherapy in this subset of patients. Combination therapy provided a survival advantage and a better side-effect profile. Therefore, combination chemotherapy, often substituting carboplatin for cisplatin, remains the standard treatment for elderly and poor–performance-status patients.

LATE COMPLICATIONS

The treatment of SCLC can cause more morbidity than the neoplasm itself. Both radiotherapy and chemotherapy cause side effects specific to the agent used. Irradiation can have early (esophagitis, pneumonitis, superficial skin burns) and late (pulmonary fibrosis, late cardiac disease, myelitis) toxicities. Chemotherapy toxicities depend on the specific regimen used, but they generally include alopecia, nausea and vomiting, and myelosuppression. Bone marrow suppression can lead to life-threatening bleeding episodes (from thrombocytopenia), but more commonly is associated neutropenic fevers, and occasionally fatal infections. Series have demonstrated that episodes of febrile neutropenia occur in roughly 30 percent of treated patients, documented infection in 5 to 15 percent, and fatal infection in 7 percent. Prevention of infection in patients treated with chemotherapy with or without irradiation has received significant attention: Measures have included prophylactic use of antibiotics and granulocyte colony-stimulating factor (GCSF). Recently, a large randomized trial showed that GCSF in addition to chemotherapy led to a reduction of the number of episodes of neutropenic fever and documented infections. Many oncologists do not agree that this is a cost-effective measure, however.

Given the tobacco abuse and older age of the vast majority of the SCLC patients, it is not surprising that cardiovascular, cerebrovascular, and pulmonary diseases are extremely common in this population. Thus, a large portion of long-term small cell lung cancers succumb to these other diseases. Up to one-third of all long-term surviving patients, especially those who continue to smoke, have recurrence of their small cell cancer, or more rarely, develop new small cell lung tumors. Other aerodigestive cancers, particularly NSCLC, are extremely common, leading some investigators to propose trials of chemoprevention agents in long-term survivors of small cell cancer. Finally, patients with SCLC have an increased risk of developing hematologic malignancy. Secondary leukemias are believed to be related to treatment, especially if chemotherapy with alkylating agents was employed. Some of these post-treatment leukemias have also shown a deletion of chromosome 3, suggesting an underlying predisposition or common ancestor cell to both cancers, instead of a secondary leukemia arising from alkylating chemotherapy-induced genetic damage. Overall, the risk of second cancer in 2-year SCLC survivors is probably as high as 50 percent, making long-term surveillance mandatory in these otherwise cured patients.

CONCLUSION

Small cell lung cancer is distinct from the other three major histologic varieties of pulmonary malignancies, which tend to behave similarly and are lumped together under the generic rubric "non–small cell lung cancer." It is biologically more active, secreting multiple hormones and neural markers, resulting in a number of paraneoplastic syndromes. It is thought of as a systemic disease, and treatment nearly always includes chemotherapy. Although the tumor is highly responsive to chemotherapy, and survival is markedly prolonged with drug treatment, the complete eradication of SCLC remains a relatively rare event. Long-term survivors are still subject to a host of morbid cardiopulmonary conditions, as well as second malignancies and recurrence of their small cell cancer. Over the last 30 years, clinical trials have made little progress in prolonging the survival of SCLC patients, especially when compared with trials involving tumors such as renal cell carcinoma and colorectal cancer. In the era of targeted therapies, there is hope that a new anti-angiogenic drug, monoclonal antibody, or small molecule tyrosine kinase inhibitor may show promise in clinical trials in the treatment of this aggressive and often fatal cancer.

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107

Primary Lung Tumors Other Than Bronchogenic Carcinoma: Benign and Malignant

Reshma Biniwale • Steven M. Keller

Bronchogenic carcinoma represents the overwhelming majority of pulmonary neoplasms; however, a great variety of tumors originate in the lung. Benign neoplasms of the lung (Table 107-1) comprise less than 1 percent of all resected lung tumors, and non-bronchogenic primary pulmonary malignancies (Table 107-2) account for 3 to 5 percent of all lung tumors. Numerous classifications of these rare tumors have been devised, although none are widely accepted. Due to the disparate histogenesis of these varied tumors, it is best to discuss them individually.

BENIGN TUMORS

Mucous Gland Adenoma

Mucus gland adenoma, also known as bronchial cystadenoma, originates in the bronchial submucous glands and presents as an exophytic endobronchial mass. The tumor occurs in the segmental or lobar bronchi and symptoms are due to obstruction or hemorrhage. Histologically, mucous-filled acini are lined by well differentiated mucous-secreting cells, without any evidence of invasion. Radiologically, they appear as coin lesions on chest radiograph, or as an "air-meniscus" sign on computed tomography (CT) scan. Treatment is endoscopic local excision. However, lobectomy may be required if the distal lung is destroyed.

Squamous Papilloma

Juvenile-onset recurrent respiratory papillomatosis (RRP) is associated with a bronchial papilloma in 5 percent of patients. Tracheobronchial extension of RRP is causally related to a previous tracheotomy in 92 percent of cases. Radiologically, it appears as a pulmonary nodule with central cavitary necrosis or as pneumatoceles. Histologically, papillomata consist of stratified squamous epithelium with a fibrovascular core. Parakeratosis and koilocytosis are typical. Infection with

Table 107-1

Benign Tumors of the Lung

Solitary Tumors	Other Solitary Tumors	Multiple Tumors
Epithelial tumors	Alveolar adenoma	Benign metastasizing leiomyoma
Clara cell adenoma	Pulmonary paraganglioma—chemodectoma	Lymphangioleiomyomatosis
Mucous gland adenoma	Glomus tumor	Cystic fibrohistiocytic tumors
Oncocytoma	Nodular amyloid	
Squamous papilloma	Pleomorphic adenoma—mixed tumor	
Soft tissue tumors	Pulmonary meningioma	
Cavernous hemangioma	Sclerosing hemangioma—pneumocytoma	
Chondroma	Sugar tumor—benign clear cell tumor	
Fibroma fibrous polyp	Teratoma	
Fibromyxoma		
Inflammatory pseudotumor—fibrous histiocytoma, fibroxanthoma, plasma cell granuloma		
Granular cell myoblastoma		
Hamartoma		
Leiomyoma		
Lipoma		
Neurilemoma—schwannoma		
Neurofibroma		
Pulmonary hyalinizing granuloma		

HPV 11 rather than HPV6 is associated with a more severe course of RRP. Sporadic malignant transformation is seen after radiotherapy. Local endoscopic excision is the treatment of choice. Solitary bronchial papillomas are rare and affect adults in their fifth to seventh decade. They may cause obstructive bronchiectasis, which may necessitate resection of distally destroyed lung.

Cavernous Hemangioma

Cavernous hemangiomas are extremely rare primary neoplasms of the lung, found in all age groups and may be single or multiple. They may be asymptomatic, or present with symptoms of hemoptysis, respiratory distress, or congestive heart failure. Histologically, they consist of flattened endothelial cells lining dilated vascular spaces. These cells stain positive for anti-von Willebrand factor antibody and CD34, identifying them as endothelial in origin. The treatment of choice for solitary lesions is surgical excision.

Chondroma

Chondromas of the lung may be solitary or multiple, unilateral, or bilateral, and are usually asymptomatic slow-growing tumors. The association of multiple peripheral pulmonary chondromas with gastric stromal sarcoma and extraadrenal paraganglionomas has been described as the "Carney triad." The majority of tumors present at a young age (7–48 years), and 85 percent occur in females. Microscopically, they consist of benign cartilaginous tissue, although Carney also described foci of mature bone, and stellate mesenchymal cells in a myxoid stroma. Lung-sparing resections are curative in 44 percent, the rest develope new chondromas. Recently, MRI-guided laser thermotherapy has been described for ablation of multiple chondromas.

Intrapulmonary Fibroma/Fibrous Tumor

Intrapulmonary fibrous tumors are usually found in a subpleural location. They are diagnosed following resection of an asymptomatic lung mass found on routine radiography. The lung is the most common location of these tumors, but they may also be found in the retroperitoneum, mediastinum, and parietal surfaces of abdominal viscera. Histologically, interlacing bundles of spindle cells without nuclear atypia are seen in a collagenous stroma. Tumor cells are immunoreactive for vimentin but not keratin, desmin, or actin, suggesting fibroblastic differentiation from a submesothelial origin. Treatment is parenchyma-sparing resection.

Inflammatory Pseudotumor (Plasma Cell Granuloma)

Inflammatory pseudotumor of the lung (also known as fibrous histiocytoma, fibroxanthoma, and plasma cell granuloma) is the most common benign lung tumor in children,

Table 107-2

Rare Primary Malignant Neoplasms of the Lung

Blastoma
Carcinoid tumors
Carcinosarcoma
Epithelioid hemangioendothelioma (IVBAT)
Malignant lymphoreticular disorders Hodgkin's disease Non-Hodgkin's lymphoma Plasmacytoma
Malignant melanoma
Malignant germ cell tumors Malignant teratoma Choriocarcinoma
Salivary gland-type tumors Adenoid cystic carcinoma Mucoepidermoid carcinoma Acinic cell tumor
Sarcoma Chondrosarcoma Osteosarcoma Soft tissue sarcoma
Miscellaneous Ependymoma, malignant Ewing's sarcoma Lymphoepithelioma
Pseudomesotheliomatous carcinoma

although it is also commonly found in adults. Patients are usually symptomatic, presenting with cough, fatigue, or weight loss. Previously thought to be an unchecked inflammatory response to viral/foreign antigens, inflammatory pseudotumor has been confirmed to be of neoplastic origin with evidence of rearrangement of the anaplastic lymphoma kinase gene on chromosome 2p23, resulting in the expression of ALK-1 protein. Inflammatory pseudotumor is locally aggressive, and can be multifocal, relapse, and even metastasize. Radiologically, inflammatory pseudotumor presents as a large pulmonary mass or nodules closely related to the airways without evidence of mediastinal adenopathy. Histologically, plasma cells and spindle cells are seen with varying degrees of mitosis, necrosis, and vascular invasion. Inflammatory pseudotumor stains for vimentin, actin, and epithelial membrane antigen. Transbronchial/transthoracic biopsy often reveals mixed inflammatory cells with predominantly plasma cells in a background of fibroblastic proliferation, granulation tissue, and histiocytes with nuclear atypia. Thus, both fine-needle aspiration and frozen section are nonspecific and complete resection is necessary for establishing a diagnosis. Incomplete resection can result in recurrence, which can be treated with re-resection. Symptoms, incomplete resection, as well as large size are predictors of mortality. Steroids, chemotherapy, and radiation therapy are controversial in the treatment of inflammatory pseudotumors.

Granular Cell Myoblastoma

Granular cell tumors are uncommon benign neoplasms that are thought to arise from Schwann cells. Usually discovered incidentally on a chest radiograph, they are endobronchial in location and multicentric. Peribronchial extension is seen in half the tumors. However, distant metastases have not been reported. They occur equally in men and women, with a median age of 42 years. Microscopically, sheets of granular cells with abundant lysosomes that stain positive with periodic acid-Schiff stain are present. Tumor cells also stain positive for S-100 and myelin basic proteins. Large tumor size, necrosis, increased mitosis, and p53, as well as Ki-67 immunoreactivity are consistent with malignant change. Treatment consists of local excision, either endoscopically (laser) or by sleeve resection. Larger resections are reserved for postobstructive bronchiectasis or abscess. Up to 13 percent of granular cell tumors coexist with other neoplasms such as esophageal, renal, and lung carcinoma.

Hamartoma

Hamartomas (mesenchymomas) are the most common benign tumors of the lung. They are derived from peribronchial mesenchyme, are slow-growing, present in adulthood, and have a 3/1 male predominance. Most are detected incidentally as peripheral round nodules on a chest radiograph, only 20 percent are endobronchial. The classic popcorn calcification is seen only in 30 percent of hamartomas. Cavitations are due to the fat content. Histologically, they consist of cartilage, fat, bone, connective tissue, and smooth muscle cells surrounding clefts lined by bronchial epithelium. Fine-needle aspiration has a high false-positive rate and low accuracy in diagnosing hamartomas. Malignant transformation is rare. Therefore, small peripheral hamartomas may be safely observed. Excision is indicated for obstructive symptoms or if the diagnosis is in doubt (Fig. 107-1). Parenchyma sparing resection should be performed. Recurrences are rare, although hamartomas may be associated with increased risk of developing other primary lung cancers.

Leiomyoma

Primary solitary leiomyoma accounts for 2 percent of all benign lung tumors and may present as pulmonary obstruction, or as an asymptomatic peripheral radiographic nodule.

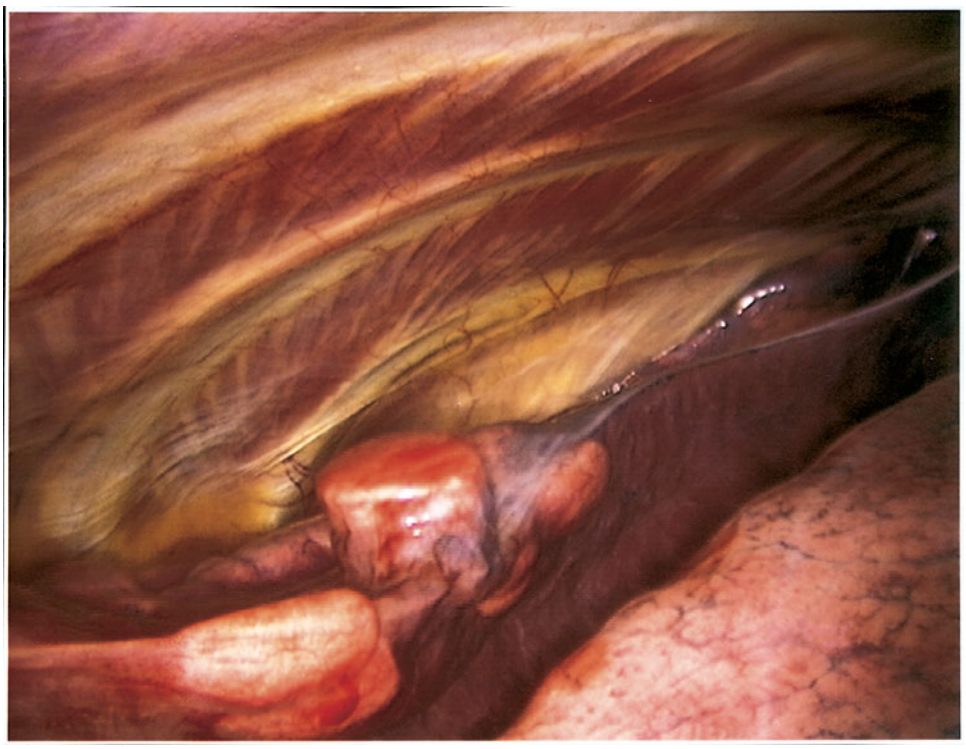


Figure 107-1 Pulmonary hamartoma seen at thoracoscopy. The tumor is easily visualized in a subpleural location. Incising the overlying pleural allows the lesion to be "popped" out.

Patients are typically in their fourth decade. The tumor is slightly more common in women. Surgical resection is the treatment of choice, although laser resection of endobronchial tumors offers prolonged palliation. Benign metastasizing leiomyoma consists of multiple pulmonary nodules of well-differentiated smooth muscle, resulting from hematogenous spread from a benign uterine leiomyoma. These tumors are ER and PR positive and respond to hormonal therapy.

MALIGNANT TUMORS

Pulmonary Blastoma

Pulmonary blastomas are divided into three subgroups: Biphasic pulmonary blastoma (BPB), well-differentiated fetal adenocarcinoma (WDFA), and pleuropulmonary blastoma (PPB). WDFA contains neoplastic epithelial glandular elements in an endometrial pattern without mesenchymal malignancy. PPB is a dysontogenic neoplasm having mesenchymal malignant elements (liposarcoma, rhabdomyosarcoma, or chondrosarcoma) without epithelial malignancy. BPB contains both epithelial and mesenchymal malignant elements, which mimic fetal lung. PPB is further subclassified as type I (purely cystic), type II (cystic and solid), and type III (purely solid). PPB occurs in infants and young children, WDFA and BPB occur in young adults, with a mean age of 35 years. All three are fast-growing symptomatic tumors that present in the periphery of the lung with a predilection for lower lobes. Radiologically they appear as large solitary smooth masses (Fig. 107-2). Fine-needle aspiration is usually non-diagnostic due to extensive necrosis and lack of cellular material. Neoadjuvant chemotherapy has been used to downstage the tumors before surgical resection. Adjuvant cisplatinum based chemotherapy is combined with local radiation for control after resection. Poor prognostic factors are large tumor size, mediastinal or pleural involvement, and nodal metastasis. CNS is the commonest site of distant metastasis followed by bone. Mutations of p53 gene are seen more frequently with BPB and PPB than with WDFA, suggesting a worse prognosis. Types II and III PPB have an overall survival of 42 percent at 5 years, despite multimodality treatment.

Carcinoid

Carcinoid tumors are malignant neuroendocrine tumors arising from Kulchitsky (APUD system) cells and are classified by the World Health Organization into typical (TC) and atypical carcinoids (AC) on the basis presence of necrosis and greater than 2 mitosis per 2 square mm. Mean age at presentation is 55 years, but AC are seen in significantly older patients with a history of smoking. Seventy-five percent of carcinoids are central, endobronchial, and present commonly with postobstructive pneumonia, hemoptysis, or wheezing. Uncommonly, carcinoids may present with paraneoplastic syndromes such as Cushing's syndrome due to ectopic ACTH

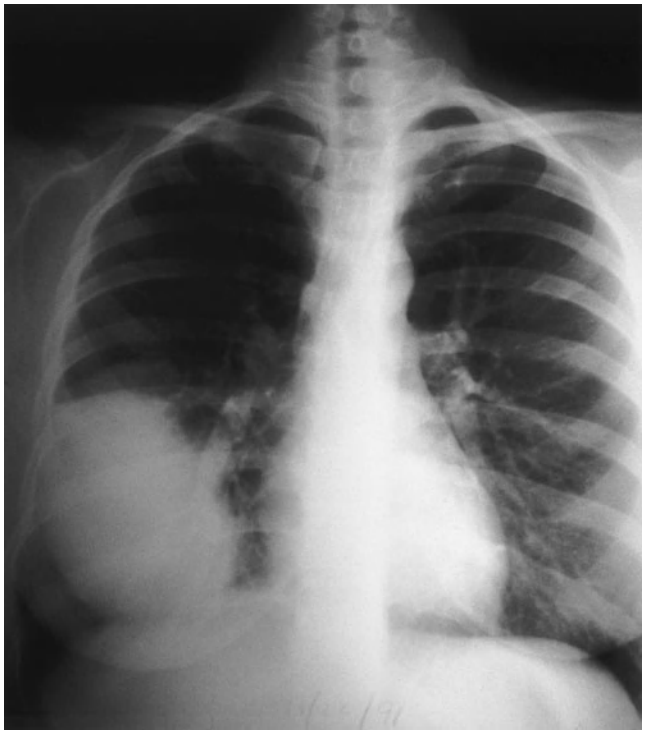


Figure 107-2 Chest radiograph demonstrating a pulmonary blastoma. The lesion presented as a large mass in the right lower lobe of a 25-year-old nonsmoking woman.

production, or even acromegaly from ectopic GH and insulin-like growth factor-1 production.

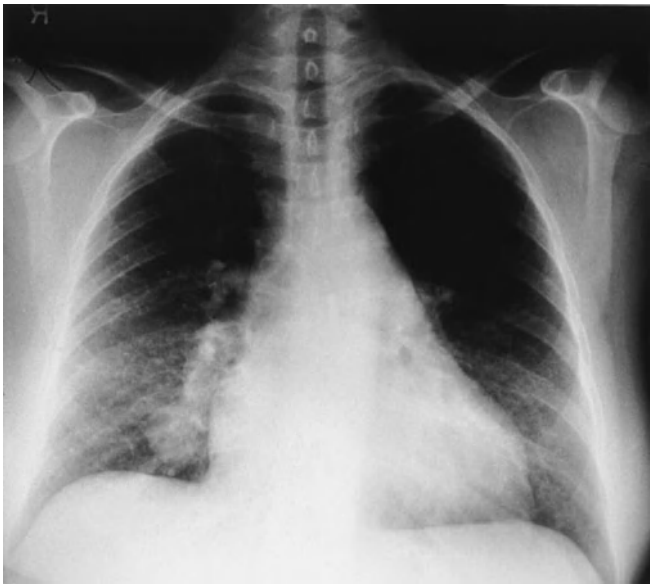
Bronchoscopy frequently demonstrates a polypoid pinkish/yellow mass with intact overlying epithelium. Brushings and washings are usually nondiagnostic. Endobronchial biopsy is diagnostic in 51 percent of patients, but may precipitate a carcinoid crisis. Carcinoids are characterized by an organoid growth pattern with uniform cells containing finely granular eosinophilic cytoplasm and nuclei with a fine chromatin pattern. Radiologically, carcinoids present as solitary nodules (30 percent), infiltrates (60 percent), and as calcified nodules (30 percent) (Fig. 107-3). CT scan reveals a well-defined central tumor deforming an airway with punctate calcification and homogenous contrast enhancement with or without hilar lymphadenopathy. Carcinoids demonstrate high signal intensity on T2-weighted MRI. FDG-PET scans, however, have a high false-negative rate, as carcinoids are hypometabolic. Somatostatin receptor scintigraphy can be used in detecting occult primary tumors, staging, and localization of metastatic disease. Chromosome analysis shows evidence of 11q and 3p deletion in AC, with loss of 18q in metastatic carcinoid. Overexpression of p53 and loss of heterozygosity of 11q13 is seen in AC, which correlates with tumor aggressiveness. Five percent of patients with MEN I syndrome have associated sporadic carcinoids. Inactivation of the MEN I gene is seen in 67 percent of TC, and 25 percent of AC.

Treatment of choice for TC is surgical resection. Lobectomy and lymph node dissection is preferred because 20 percent of TC and 60 percent of AC are associated with nodal metastases. Bronchoplastic sleeve-resection for central lesions of early stage TC is preferable to pneumonectomy. Cis-platinum and etoposide-based chemotherapy is indicated for unresectable disease as well as metastases. However, the response rate is only 22 percent with a median survival of 20 months. Bio-therapy with interferon alpha and octreotide is used for the treatment of carcinoid syndrome with symptomatic relief in 70 percent of patients. Liver embolization can be used to debulk liver metastases in symptomatic patients. Targeted radiotherapy with radiolabeled octreotide or MIBG remains investigational.

Recurrence-free survival is commonly seen in TC. Tumor histology and nodal status are the main predictors of mortality. Completeness of resection, symptoms, and age are also significant prognostic factors. Five-year survival following complete resection of TC and AC is 87 to 100 percent and 44 to 77 percent, respectively. Survival decreases to 25 to 69 percent in the presence of nodal metastases. There is no correlation between tumor size and presence of nodal involvement. Sixty-three percent of patients with nodal mediastinal nodal metastases develop distant metastases, most commonly in the liver. Carcinoid syndrome occurs rarely (2 percent) and results from release of 5HT. Urinary 5HIAA is used to monitor disease activity in patients with carcinoid syndrome.

Carcinosarcoma

Carcinosarcoma is a biphasic tumor consisting of carcinomatous and sarcomatous elements containing differentiated cartilage, bone, or skeletal muscle. This tumor is seven times more common in males than females. The median age of presentation is 65 years. The upper lobes are affected in 60 percent of cases. Carcinosarcomas are divided into two groups: central endobronchial and peripheral solid parenchymal (Fig. 107-4). Symptoms of airway obstruction or postobstructive pneumonia are common. However, one-third of all patients are asymptomatic. These tumors eventually invade the mediastinum and chest wall, causing pain. Carcinosarcomas are firm, rubbery, or fleshy masses with areas of necrosis and cavitation. The carcinomatous elements are squamous cell carcinoma (46 percent), adenocarcinoma (31 percent), and adenosquamous carcinoma (19 percent). The sarcomatous elements are rhabdomyosarcoma (51 percent), chondrosarcoma, and osteosarcoma. The carcinomatous elements are often displaced to the periphery, suggesting rapid growth of the central sarcomatous elements, which form the bulk of the tumor. Immunohistochemical staining for keratin is positive for both the epithelial and mesenchymal components, suggesting that carcinosarcomas are of a monoclonal epithelial origin that has undergone sarcomatoid metaplasia. Metastases are found in lymph nodes, bone, kidney, liver, and lung and commonly contain only one of the components of the primary tumor. Complete surgical resection is usually possible and the 5-year survival rates ranges from 21 to 49 percent. Endobronchial location and tumor stage do not correlate with survival. However, tumor size greater than 6 cm is associated with poor survival.



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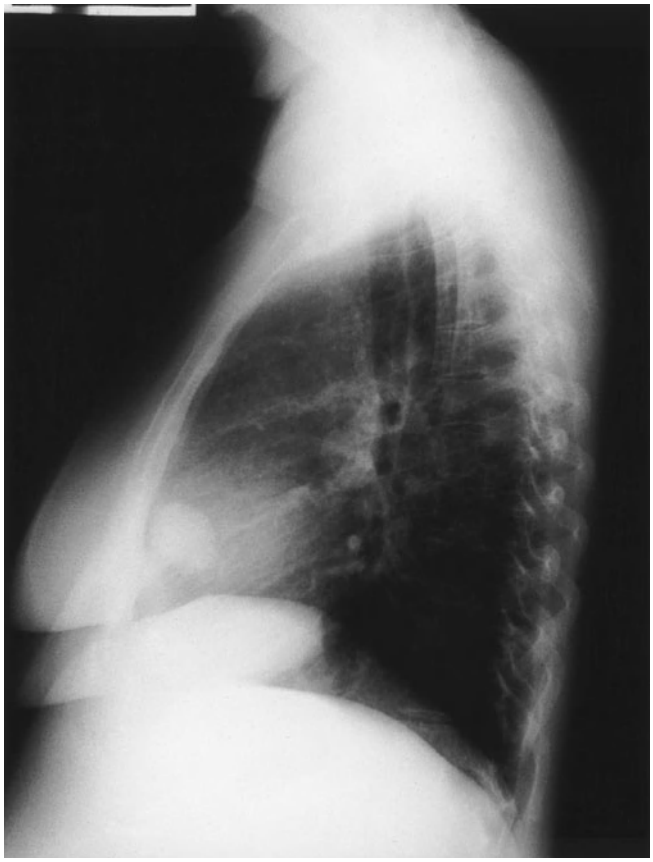

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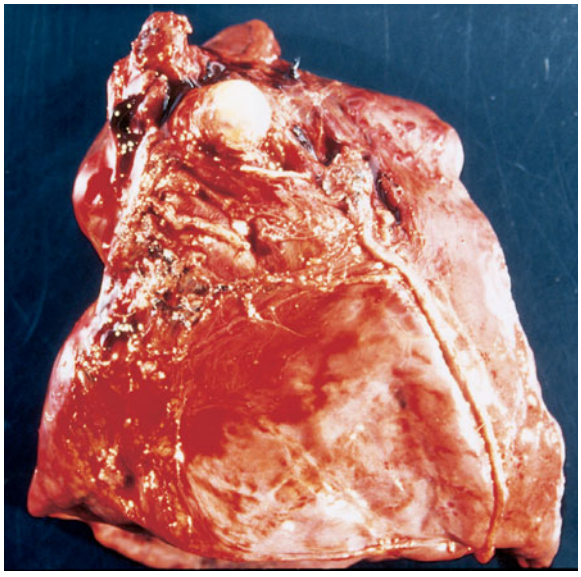
Figure 107-3 Solitary nodule presenting in a young asymptomatic woman. *A*. PA chest radiograph. *B*. Lateral film. The lesion was excised and found to be a typical carcinoid tumor with no evidence of mitoses or necrosis.



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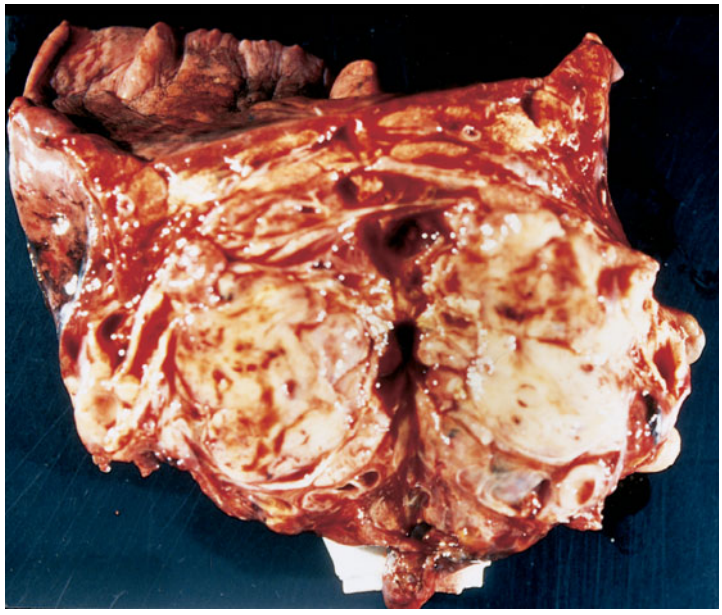

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Figure 107-4 Carcinosarcoma. *A*. Endobronchial component of a carcinosarcoma. *B*. The parenchymal component of the same tumor bisected.

Epithelioid Hemangioendothelioma

Originally named intravascular bronchoalveolar tumor (IVBAT), this neoplasm has since been demonstrated to be of endothelial origin on the basis of immunohistochemical staining for factor VIII–related antigen and CD34. Epithelioid hemangioendothelioma is best considered a low-grade sarcoma and is usually multicentric in origin. It is a disease of young women, with 80 percent of cases seen in women under the age of 40 years. Patients are usually asymptomatic, although they may present with respiratory symptoms. Multiple perivascular nodules less than 1cm in diameter or diffuse thickening of interlobular septae are present on CT scan. Microscopically, epithelioid hemangioendothelioma consists of eosinophilic cells forming trabeculae or nests with characteristic central acellular sclerotic areas and lymphovascular and bronchiolar invasion. Pleural, intravascular, and endobronchial spread is associated with a poor prognosis, as are liver and lymph node metastases. Complete resection is the treatment for localized tumors. Diffuse tumors have been treated with chemotherapy, interleukin-2 and interferon-α2b with mixed results. Radiation is ineffective and is used only for palliation of bone pain. Partial spontaneous regression also has been reported occasionally.

Lymphomas

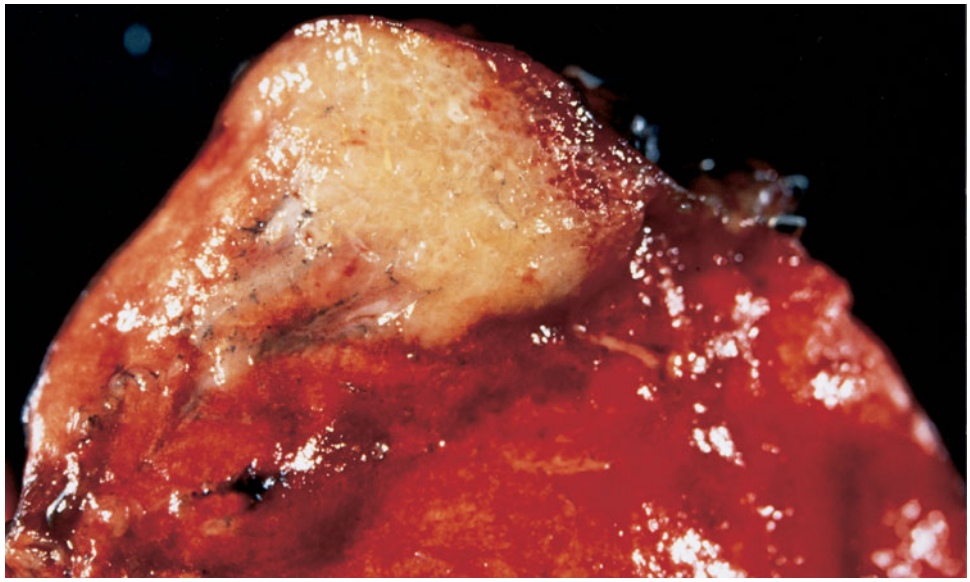
Primary pulmonary lymphomas (PPL) are rare neoplasms accounting for less than 1 percent of all lung cancers. Criteria used for diagnosis of primary pulmonary lymphoma include involvement of the lung with or without mediastinal involvement, and absence of extrathoracic lymphoma at the time of diagnosis or for 3 months thereafter.

Primary pulmonary B cell non-Hodgkin's lymphoma (NHL) is also known as MALT (mucosa-associated lymphoid tissue) or BALT (bronchus-associated lymphoid tissue) and accounts for up to 80 percent of PPL. This is a low-grade small B lymphocyte lymphoma that is associated with a 5-year survival greater than 80 percent. The tumor is thought to arise due to chronic inflammation secondary to smoking, infection or autoimmune disease (Sjögren's). Age of onset is 50 to 60 years, with equal distribution between the sexes. Half of the patients are asymptomatic on presentation. Pulmonary manifestations include cough, dyspnea, and hemoptysis. Extrapulmonary symptoms such as fever and weight loss occur in less than 25 percent of patients. Radiologically, a localized alveolar opacity with blurred margins is seen associated with air bronchograms. CT demonstrates bilateral multifocal disease in 70 percent of cases. CT-guided biopsy is diagnostic in 25 percent. Bronchoalveolar lavage is diagnostic if it shows lymphocytic alveolitis with greater than 10 percent of the total cells being B lymphocytes. Microscopically MALT PPL is defined as a lesion containing: small lymphoid cells, lymphoepithelial lesions showing migration of lymphoid cells from the marginal zone to bronchiolar epithelium, reactive follicular hyperplasia, and rare blastic cells (Fig. 107-5). Immunohistochemistry demonstrates B-cell phenotype (CD19, CD20) and monoclonality. Bone marrow biopsy may show involvement in 25 percent of cases. Evaluation of other mucosal sites with endoscopy, ENT examination, and CT scan of salivary and lacrimal glands should be performed. Serum immunoelectrophoresis will reveal a monoclonal gammopathy (IgM) in 20 to 60 percent of patients. Elevated β2 microglobulin is associated with a poor prognosis. Solitary tumors should be removed. Long-term surveillance is necessary due to late local or systemic relapse after resection. Chemotherapy is recommended for residual, bilateral, progressive, or recurrent disease. Various regimens, including CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone) have been used with success.

High-grade PPL NHL-B, also known as large B-cell lymphoma, accounts for up to 15 percent of PPL. Immunosuppression, HIV infection, and Sjögren's syndrome are underlying disorders often associated with large B-cell lymphomas. These lymphomas are usually found in the elderly and commonly present with either pulmonary or systemic symptoms. A solitary lung mass often associated with a pleural effusion is present. Bronchoscopy may reveal infiltrative stenosis. Transbronchial biopsy is often diagnostic. Microscopically, large blast-like lymphoid cells with frequent mitosis, necrosis and bronchovascular invasion are seen. Survival is poorer than in small B-cell lymphomas, especially in those with underlying disorders. Resection is followed by combination chemotherapy. Progression of disease and recurrence occurs earlier and more commonly than in small B-cell lymphoma.

Lymphomatoid granulomatosis (LG) also known as an angiocentric immunoproliferative lesion (AIL) is rare. The age of onset is around 50 years. Almost all patients present with either pulmonary or systemic symptoms. Radiologically, multiple bilateral ill-defined nodular opacities, mainly affecting the lower lobes, are seen. These opacities can cavitate and disappear secondary to infarction of the granulomatosis lesions. Extrapulmonary involvement is seen mainly in the CNS, skin, ENT, or renal systems. Neurological deficits can be central, cranial nerve affection, or peripheral neuropathies. Skin lesions are erythema or nodules with or without ulceration. Arthralgia and ocular and gastrointestinal manifestations have also been reported. Microscopically, an angiocentric lymphocytic infiltrate is seen mixed with occasional large blastic cells, which compresses the lumen of arterioles and erodes into bronchioles. Immunohistochemistry demonstrates the B-cell origin of the lymphocytes, which also express EBV LMP protein. Initial assessment should include brain MRI, CT scan of the abdomen for renal or lymphoid involvement, and a bone marrow biopsy. Localized LG should be removed. Combination chemotherapy is reserved for diffuse disease. Radiotherapy is useful in CNS involvement. Despite aggressive therapy the prognosis remains poor and median survival is about 4 years. Poor prognostic factors include early age of onset, CNS involvement, hepatosplenomegaly, leucopenia, fever, anergy, and predominant blast cells with necrosis on biopsy.

NK/T cell primary pulmonary lymphoma is an extremely rare diagnosis with only 13 cases reported in the



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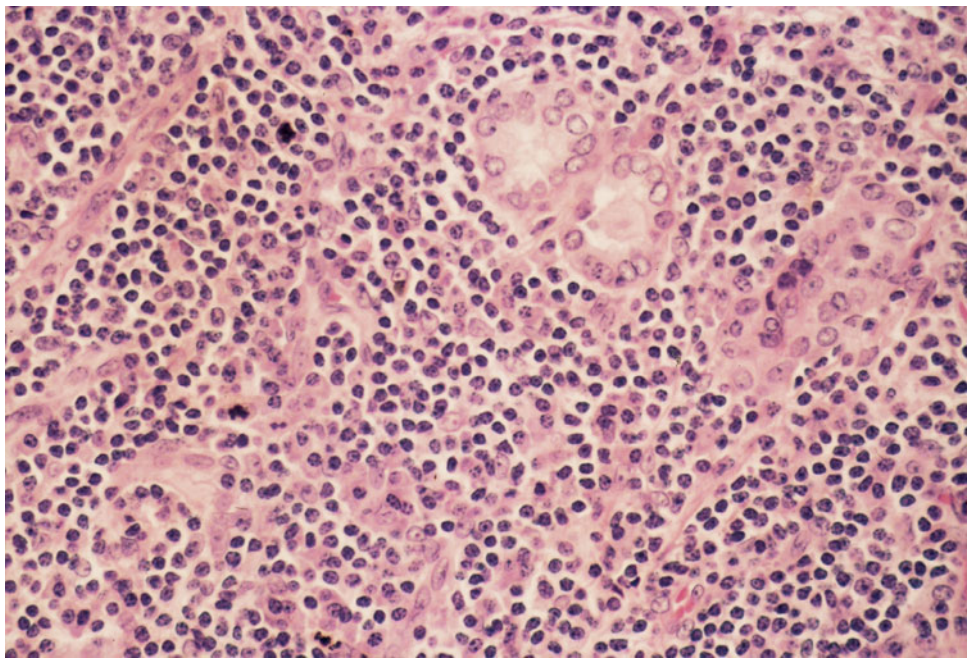

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Figure 107-5 Pulmonary lymphoma (BALT). *A*. Gross appearance of a BALT following wedge excision. *B*. Microscopic appearance of the same BALT lesion showing the lymphoid cells along with some residual epithelial elements.

world. Patients are elderly; females are twice as commonly affected as males. Radiographically, bilateral diffuse nodularities are seen. Diagnosis requires an open lung biopsy and immunohistochemistry, which reveals T-cell markers. Microscopically, homogenous cells with architectural effacement and dysplasia are seen. Monoclonality of the T cells is demonstrated by TCR gene rearrangement. Prognosis is very poor despite surgical resection and CHOP based chemotherapy.

Primary pulmonary Hodgkin's lymphoma is also very rare with 61 reported cases. There is a bimodal age distribution with peaks in the third and sixth decades. Most patients are female. Symptoms may be pulmonary or systemic. Radiologically, multinodular and massive parenchymal involvement is seen with occasional cavitation. Bronchoscopy and BAL are inconclusive, and often open biopsy is required to confirm the diagnosis. The most frequent histologic subtype is the nodular sclerosing variety. Combination chemotherapy, radiation, and surgery are the common modalities of treatment. A poor prognosis is predicted in patients with multilobar or bilateral disease.

Plasmacytoma

Plasmacytomas are tumors arising from monoclonal plasma cells. The diagnostic criteria for extramedullary plasmacytoma are biopsy-proven plasma cell proliferation, absence of bone marrow infiltration and absence of osteolytic lesions, renal failure, and hypercalcemia. The average age of presentation is 54 years, with equal distribution between males and females. Plasmacytomas commonly present as a hilar mass, but lobar consolidation or bilateral diffuse infiltrates with air bronchograms may also be seen. Serum electrophoresis reveals an M-protein spike, which usually consists of IgG κ chains, and correlates with the tumor burden. Treatment is surgical resection, but chemotherapy with melphalan and prednisolone has been used with good results. The 5-year survival rate is 40 percent. These tumors need to be distinguished from marginal zone B-cell lymphomas of MALT origin. Forty percent of patients develop multiple myeloma; therefore, surveillance with serum and urine electrophoresis, bone marrow biopsy, skeletal bone survey and clinical monitoring is necessary.

Malignant Melanoma

Primary pulmonary melanoma is an extremely rare lung tumor for which several theories have been suggested: aberrant migration of melanocytes from the primitive foregut, melanogenic metaplasia of bronchial epithelium, or melanocytic differentiation of neuroendocrine precursor Kulchitsky cells. Jensen and Egedorf first suggested the clinical criteria for the diagnosis of primary pulmonary melanoma: no previously removed skin or ocular melanomas, solitary tumor, morphology compatible with a primary tumor, no melanoma in other organs at surgery, and no evidence of primary tumor elsewhere on autopsy. Histopathological criteria include junctional change with nesting of malignant cells beneath bronchial epithelium, and invasion of bronchial epithelium in an area without ulceration. Aggressive resection is the treatment of choice and offers the best chance for cure. Chemotherapy and immunotherapy is used for widespread disease.

Malignant Germ Cell Tumors

Malignant teratoma and choriocarcinoma are the two types of malignant germ cell tumors that arise in the lung. Teratomas show elements from all three germ layers. Half of the primary pulmonary teratomas are malignant. Patients present with cough, hemoptysis, or chest pain. The most specific symptom, trichoptysis, is rarely present. Radiologically, the mass may show calcification with peripheral radiolucency. Resection is the treatment of choice. Adjuvant chemotherapy is usually a combination of cis-platinum, bleomycin, and etoposide.

Choriocarcinomas are usually seen in women or elderly men who present with symptoms of feminization. The commonest symptom is cough with hemoptysis. Various theories have been postulated to explain the origin of choriocarcinomas of the lung. Neoplastic transformation of misplaced primordial germ cells, spontaneous regression of an occult genital primary leaving behind pulmonary metastatic lesions, neoplastic transformation of placental emboli at the time of delivery or abortion, and neoplastic transformation of somatic neoplastic cells, have all been postulated. These tumors manifest as the choriocarcinoma syndrome: bleeding from the primary lung lesion and elevation of β-HCG. Differentiation from a large cell carcinoma producing ectopic human chorionic gonadotropin can be done by immunohistochemistry, which shows staining for thyroid transcription factor (TTF)-1 (a marker of pulmonary origin) and not for β-HCG. Histologically, cytotrophoblastic cell nests are seen covered by syncytiotrophoblasts, with evidence of widespread necrosis and hemorrhage, and a lack of fibrovascular stroma. Surgical resection is recommended, followed by adjuvant chemotherapy. Choriocarcinomas are unresponsive to radiation, unlike their gestational counterparts. Distant metastases can occur in the contralateral lung, brain, and kidney.

Salivary Gland-Type Tumors

Adenoid cystic carcinoma (ACC) is the most common salivary-gland tumor found in the lung. It is believed to arise from ductal/myoepithelial cells of bronchial submucosal glands. Centrally located ACC arises in the trachea or mainstem bronchi and presents as an exophytic endobronchial mass causing obstructive symptoms. Overlying mucosa is often grossly normal. Peripheral ACC is uncommon. Males and females are equally affected. Histologically there are three subtypes: cribriform, tubular, and solid. ACC are slow-growing neoplasms that exhibit centripetal spread in the airways as well as perineural growth. Therefore, extensive resections are required. These tumors are extremely radiosensitive and local recurrences or residual disease may be treated with radiation. Following complete resection, 5- and 10-year survivals of 91 and 76 percent, respectively, have been reported.

Mucoepidermoid carcinomas usually arise in mainstem bronchi or the proximal portion of the lobar bronchi. The right bronchial tree is more commonly affected in children. Patients present with symptoms of obstruction due to a polypoid endobronchial mass. Bronchoscopic biopsy is diagnostic. Three histological grades have been defined (low, intermediate, and high) based on the presence of cystic spaces, cell type (mucous cells, intermediate cells, and epidermoid cells), cellular pleomorphism, and mitosis. Complete resection with mediastinal lymph node dissection is the treatment of choice. High-grade tumors are more common in adults and may invade adjacent structures, lymph nodes, vascular, and perineural spaces. Incomplete resection is more likely in high-grade tumors, and postoperative chemoradiation may be necessary. High-grade tumors are uniformly fatal in 11 to 28 months.

Acinic cell tumors (Fechner tumors) are usually found in the salivary glands, and hence a diligent search for an extrathoracic primary is essential. Symptoms vary and are determined by whether the tumor is central endobronchial or peripheral in location. Microscopy demonstrates a pattern

resembling a neuroendocrine tumor and may need to be differentiated from the more common carcinoid tumor. Acinic cell tumors are slow-growing and recurrence or metastases after complete excision has not been reported.

Sarcomas

Primary pulmonary sarcomas are rare tumors, accounting for less than 0.5 percent of all lung tumors. Mean age at presentation is 53 years, with a slight predominance in males. A history of smoking or previous radiation exposure may be present. Usual symptoms are chest pain and cough. Sarcomas appear as large (mean diameter 5 cm), solitary peripheral or hilar nodular opacities usually located in the upper lobes. Bronchoscopy may show either extrinsic compression or a polypoid endobronchial mass. The variety of soft tissue pulmonary sarcomas reflects the range of mesenchymal tissue found in the lung (Table 107-3). The most common primary pulmonary sarcoma is leiomyosarcoma (30 percent), followed by malignant fibrous histiocytoma and synovial sarcoma. Histological subtypes can be differentiated on the basis of immunohistochemical markers such as vimentin, desmin, actin, and epithelial membrane antigen. Treatment is wide resection with mediastinal lymph node dissection. Residual disease is treated with radiotherapy or reresection. Recurrences can be resected with good results. Ifosfamide-based chemotherapy has also been used in the neoadjuvant and adjuvant setting for positive margins or positive lymph nodes. Median survival is 48 months and 5-year survival is 38 to 69 percent. Size and grade do not correlate with increased mortality. Incomplete resection is associated with poor survival.

Table 107-3

Primary Soft Tissue Sarcomas of the Lung

Leiomyosarcoma
Spindle cell sarcoma
Rhabdomyosarcoma
Malignant fibrous histiocytoma
Angiosarcoma
Fibrosarcoma
Malignant hemangiopericytoma
Neurogenic sarcoma
Synovial sarcoma
Kaposi's sarcoma
Liposarcoma

Chondrosarcomas of the lung can occur either within central bronchi or peripherally in the lung parenchyma. Tumors consist of islands of chondroid and osteoid with foci of mineralization within sheets of small hyperchromatic mesenchymal cells. Chondrosarcomas are slow growing and rarely metastasize. Complete resection is usually curative.

Osteosarcomas of the lung present with cough or hemoptysis and appear as large cavitating masses. These are rapidly growing tumors with a poor prognosis. Recurrence is seen in 50 percent of patients after resection. The majority of patients succumb within months from metastases to the lung, liver, lymph nodes and bone. The role of adjuvant therapy for the treatment of this tumor is still unproved.

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Extrapulmonary Syndromes Associated with Lung Tumors

Bruce E. Johnson • John P. Chute

Lung cancers are the most common tumors associated with paraneoplastic syndromes. The paraneoplastic syndromes can be classified into endocrine, hematologic, and neurologic syndromes. Endocrine and hematologic syndromes associated with lung tumors are listed in Table 108-1.

The endocrine syndromes are characterized by the ectopic production of biologically active peptide hormones by tumor cells that bind to receptors in adjacent or distant organs, giving rise to a clinical syndrome. The ectopic adrenocorticotropic hormone (ACTH) syndrome, the hyponatremia of malignancy, and hypercalcemia of malignancy are examples of this model. In order to establish the diagnosis of an endocrine paraneoplastic syndrome, the following criteria should be met: (1) a decrease in the level of the hormone after treatment of the tumor; (2) demonstration of hormone synthesis and secretion by tumor cells in vitro; (3) high concentrations of the hormone in the tumor; and (4) an arteriovenous gradient in hormone levels across the tumor bed.

Lung cancers also produce extrapulmonary syndromes by other mechanisms. Hematologic syndromes develop in

This chapter has been slightly modified from the version that appeared in the third edition of *Fishman's Pulmonary Diseases and Disorders.*

Table 108-1

Endocrine and Hematologic Syndromes Associated with Lung Tumors

Syndrome	Tumor	Proteins/Cytokines
Hypercalcemia of malignancy	Non–small-cell	Parathyroid hormone–related peptide Parathormone
Hyponatremia of malignancy	Small-cell Non–small-cell	Arginine vasopressin Atrial natriuretic peptide
Ectopic ACTH syndrome	Small-cell Carcinoid tumors	Adrenocorticotropic hormone Corticotropin-releasing hormone
Acromegaly	Carcinoid tumors Small-cell	Growth hormone–releasing hormone Growth hormone
Granulocytosis	Non–small-cell	G-CSF GM-CSF IL-6
Thrombocytosis	Non–small-cell Small-cell	IL-6
Thromboembolism	Non–small-cell Small-cell	Unknown

patients with lung cancer through the production of cytokines by tumor cells that activate progenitor cells in the bone marrow. Neurologic syndromes, such as encephalomyelitis and subacute sensory neuropathy, are caused by the induction of antibodies directed against proteins expressed by the lung cancer cells and antigens present on cells in the nervous system.

Although lung cancers produce and express various hormones, many (e.g., the gastrin-releasing peptide) do not cause a clinically evident syndrome. Other peptide hormones, such as ACTH precursors, are translated into prohormones, which are not processed into mature peptides. As a result, levels of the immunoreactive proteins in plasma are increased without a clinical syndrome.

This chapter focuses on the extrapulmonary syndromes that are encountered in clinical practice. An understanding of the extrapulmonary syndromes is important for several reasons: (1) the syndrome is often the presenting feature of the underlying cancer; (2) the course of the endocrine and hematologic syndromes usually parallels the course of the lung cancer, although the neurologic syndromes frequently do not; and (3) appropriate treatment of the extrapulmonary syndrome often reduces the patient's morbidity and may allow definitive treatment of the cancer. In general, definitive treatment of the underlying tumor by surgical resection, radiotherapy, or chemotherapy is the most effective form of therapy for the paraneoplastic syndrome.

HYPERCALCEMIA OF MALIGNANCY

Hypercalcemia is the most common paraneoplastic syndrome. Approximately 1 percent of patients with lung cancer have hypercalcemia when first seen, but 10 to 20 percent of patients develop hypercalcemia during the course of their disease. Lung cancer is the most common solid tumor associated with hypercalcemia, accounting for 30 to 40 percent of all paraneoplastic cases. Hypercalcemia is commonly seen in patients with squamous cell carcinoma of the lung, uncommonly in patients with adenocarcinoma, and very rarely in patients with small-cell lung cancer.

Hypercalcemia in patients with lung cancer is usually not caused by local osteolytic effects of bony metastases. Most cases of hypercalcemia in patients with lung cancer are caused by the ectopic production of parathyroid hormone–related peptide (PTHrP) by tumor cells (humoral hypercalcemia of malignancy).

Biology

Ectopic production of PTHrP accounts for 80 to 90 percent of humoral hypercalcemia of malignancy in patients with lung cancer. The PTHrP gene expresses three messenger RNAs (mRNAs); these encode for three distinct peptides, which differ at the COOH-terminal region (Fig. 108-1). Eight of the first 13 amino acids in PTHrP are homologous with PTH, so

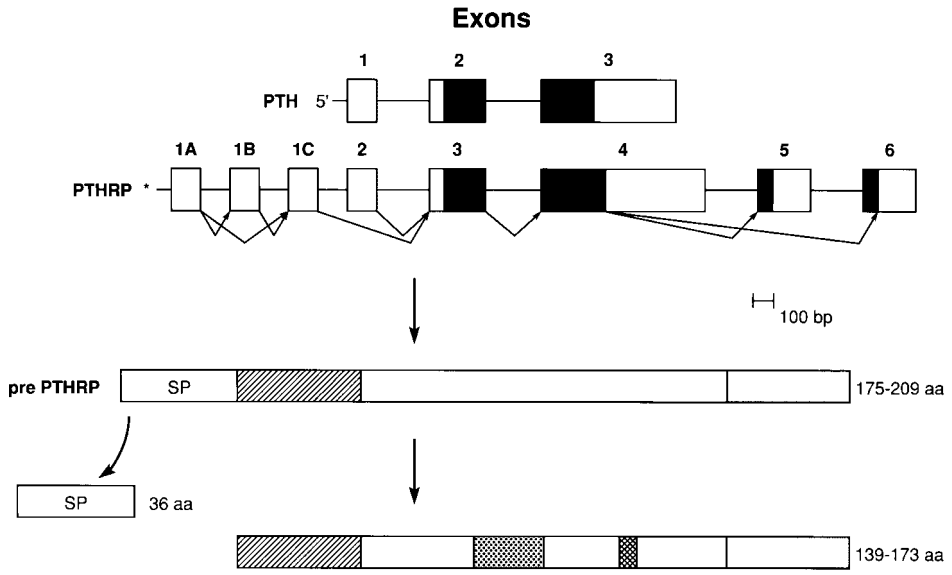

Figure 108-1 Parathyroid hormone and parathyroid hormone–related peptide. The human PTH gene has three exons, which constitute the protein-coding segments. The protein coding segments are represented by the black boxes. The PTHrP gene is more complex, with eight exons. Through alternative splicing, three different isoforms of mRNA can be produced. These isoform mRNAs encode the pre-PTHrP proteins, which vary in size from 175 to 209 amino acids (aa). Thirty-six amino acids are removed from the amino terminal end as the signal peptide. Three different PTHrP molecules are produced, with 139 to 173 amino acids. The rectangular region at the carboxy terminal represents the different lengths of PTHrP. The N-terminal region (aa 1–34) mimics the classic PTH-like function (hatched box). The midregion (aa 67–86) of the peptide stimulates placental calcium transport (shaded box). The C-terminal region (aa 107–111) inhibits osteoclastic bone resorption (double hatched box).

similar functional activity is shared between the two peptides. PTHrP messenger RNA and peptides have been demonstrated in cancer cells from patients with lung cancer and hypercalcemia. PTHrP has been shown to bind to PTH receptors in the bone and kidney, causing increased osteoclastic bone resorption, decreased bone formation, and decreased calciuria, leading to hypercalcemia. Levels of 1,25-dihydroxyvitamin D_3 are suppressed in patients with PTHrP-induced hypercalcemia but are raised in patients with primary hyperparathyroidism. This difference occurs because renal α-hydroxylase activity is low in PTHrP-induced hypercalcemia, unlike primary hyperparathyroidism. PTH production by lung cancer cells has also been described, but it is a very rare cause of humoral hypercalcemia.

Other factors that cause bone resorption have been identified in the plasma of patients with lung cancer, including transforming growth factor-α and a vitamin D metabolite. These are very rare, however, and their causative role in hypercalcemia has not been shown conclusively.

Diagnosis

The early symptoms of hypercalcemia include thirst, malaise, fatigue, anorexia, polyuria, constipation, nausea, and vomiting. As the hypercalcemia becomes increasingly severe, confusion, lethargy, coma, and death can occur. The demonstration of an increased concentration (greater than 10.5 mg/dl) of calcium in the serum of a patient with non–small-cell lung cancer should suggest this paraneoplastic syndrome.

When hypercalcemia is identified in a patient with lung cancer, other potential causes of elevated serum calcium should be excluded. Thiazide diuretics, vitamin D or lithium administration, hyperthyroidism, and sarcoidosis are potential causes. A PTH radioimmunoassay should be performed because up to 10 percent of hypercalcemia in patients with cancer is caused by primary hyperparathyroidism. Bone scintiscan should be obtained to exclude bone metastases, and a PTHrP level should be determined. An elevated PTHrP level in the absence of bone metastases establishes the diagnosis of humoral hypercalcemia of malignancy caused by ectopic PTHrP.

Treatment

As with other paraneoplastic syndromes, treatment of the underlying cancer is the most effective method of treating the humoral hypercalcemia associated with lung cancer. Patients in whom lung cancer cannot be eradicated can be treated with intravenous saline plus furosemide diuresis. Subcutaneous calcitonin has a rapid onset of action and is most useful in severe cases. Mithramycin and long-acting biphosphonates, such as pamidronate, are effective for long-term control of hypercalcemia. Corticosteroids exert their effect through inhibition of dihydroxyvitamin D_3 synthesis and therefore have less effect in patients with elevated PTHrP.

This syndrome usually develops in patients with advanced progressive cancer. Therefore, reversal of hypercalcemia should be undertaken only when there is some hope

for control of the underlying cancer. It may be inappropriate to treat hypercalcemia in patients with far-advanced lung cancer, having them regain consciousness only to die of their underlying disease.

HYPONATREMIA OF MALIGNANCY

Hyponatremia is a frequent complication in patients with cancer. More than 90 percent of cases occur in patients with small-cell lung cancer. Ten to 15 percent of patients with small-cell lung cancer and 1 percent of patients with non–small-cell lung cancer present with hyponatremia. Most of these cases are caused by the ectopic production of arginine vasopressin (AVP). This subset of hyponatremia is recognized as the *syndrome of inappropriate antidiuretic hormone* (SIADH). Ectopic production of atrial natriuretic peptide (ANP) may also play a role in the hyponatremia of malignancy, but the exact contribution of this hormone remains to be defined.

Biology

AVP is a 9–amino acid peptide normally produced by the neurohypophysis. The peptide binds to receptors in the kidney to reduce the excretion of free water. When plasma osmolality exceeds 280 mOsmol/kg, the release of arginine vasopressin from the pituitary increases, causing the kidney to retain more free water and maintain fluid and osmolar balance. In patients with small-cell lung cancer, ectopic production of AVP causes hyponatremia by inhibiting free-water excretion in the distal tubule of the kidney. Arginine vasopressin mRNA is expressed in small-cell lung cancer cells, and the peptide is translated and secreted (Fig. 108-2). Levels of AVP in plasma are increased.

A subgroup of patients with small-cell lung cancer and hyponatremia have been identified in whom the cancer and the cancer cell lines do not produce ectopic arginine vasopressin. The tumors from these patients express ANP mRNA, secrete the peptide, and have high levels of ANP in their plasma. ANP is the leading candidate to be the natriuretic factor that Bartter and Schwartz proposed in their original description of SIADH. Further investigation into the precise role of ANP in patients with small-cell lung cancer and hyponatremia of malignancy is ongoing.

Diagnosis

In patients with lung cancer, hyponatremia is most frequently diagnosed as a laboratory abnormality in the absence of significant symptoms. The symptoms associated with acute hyponatremia do not typically occur because the syndrome develops over a prolonged period in concert with the growth of the lung cancer. The symptoms of mild hyponatremia (more than 120 mEq/ml) include headache, difficulty concentrating, nausea, weakness, and fatigue. Patients who develop a more acute hyponatremia may manifest confusion, lethargy, seizures, coma, and death.

In patients with lung cancer, nonmalignant causes of hyponatremia—including diuretic use, renal disease, cardiac dysfunction, hypoadrenalism, thyroid disease, and dilutional hyponatremia—should be considered in the initial evaluation. Medications that can induce SIADH include the chemotherapeutic agents cisplatin, vincristine, cyclophosphamide, and melphalan, along with narcotics, which are

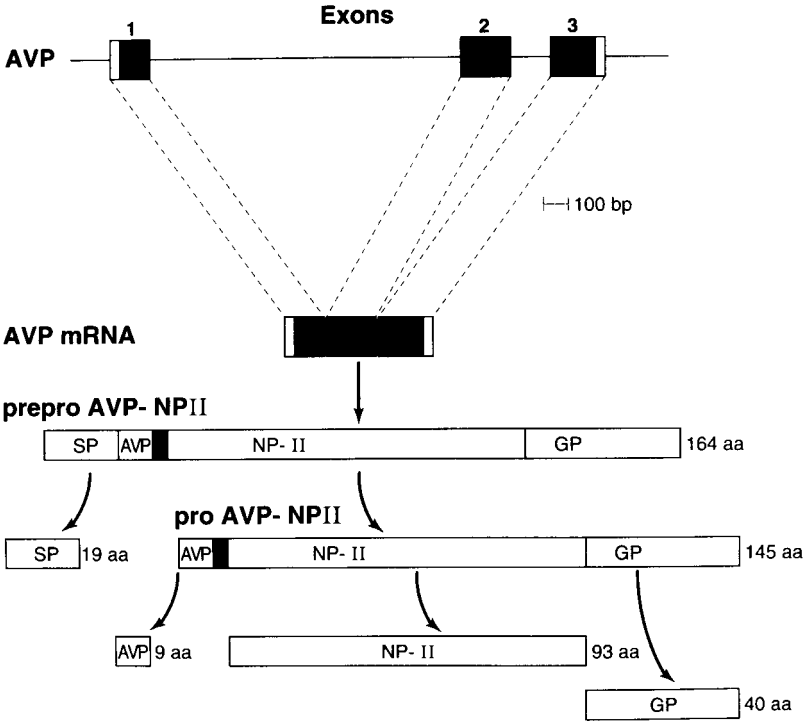

Figure 108-2 Arginine vasopressin. The three exons of the human AVP gene rise to a 700-base arginine vasopressin mRNA. The mRNA is translated into a 164-amino acid (aa) preprohormone with a 19–amino acid amino terminal signal peptide (SP). The signal peptide is cleaved, giving rise to a 145–amino acid prohormone. This prohormone is processed into the AVP nonapeptide (AVP), a 93–amino acid neurophysin (NP), and a 40–amino acid glycoprotein (GP). The black portions of the boxes represent the protein-coding portion of the gene and mRNA.

commonly used in patients with lung cancer. The subgroup of hyponatremic patients with the diagnosis of SIADH should satisfy the following criteria: (1) plasma hypoosmolality (under 280 mOsmol/kg); (2) osmolality of urine greater than serum (usually over 500 mOsmol/kg); (3) persistent urinary excretion of sodium in the absence of diuretics (more than 20 meq/l); (4) absent signs of volume depletion; and (5) normal renal, adrenal, and thyroid function.

Treatment

The initial therapy for hyponatremia caused by lung cancer is treatment of the underlying malignancy. This requires chemotherapy and/or radiotherapy for patients with small-cell lung cancer and surgery for non–small-cell lung cancers. In many patients, despite an initial tumor response to chemotherapy, the syndrome of hyponatremia persists or recurs after the cancer regrows. In these patients, the short-term treatment for mild hyponatremia is fluid restriction of 500 ml per day. Many patients with cancer cannot tolerate this level of fluid restriction for extended periods, so other treatments are usually required. Demeclocycline is the medication of choice for chronic management of SIADH in patients with small-cell lung cancer. When given in doses of 600 to 1200 mg orally per day, demeclocycline blocks the action of AVP on the renal tubule, inducing a diabetes insipidus that will correct the hyponatremia in most patients. Lithium and phenytoin also can be used to inhibit the effects of AVP on the renal tubule, but administration of these agents is limited by their neurologic side effects.

In patients who present with severe, symptomatic hyponatremia, the intravenous administration of 3 percent hypertonic saline, along with the intravenous administration of furosemide, is recommended. The intravenous administration of furosemide rapidly causes an increase in the net free-water clearance. This method has been used successfully in patients with small-cell lung cancer. It can increase the concentration of sodium in serum from 120 to 133 mEq/l in 6 to 8 h. Overly rapid correction of the level of sodium in serum (more than 2 mEq/h) in patients with hyponatremia has been associated with a central pontine myelinolysis. Therefore, frequent measurements of serum sodium during treatment with hypertonic saline are required to avoid this complication.

ECTOPIC ACTH SYNDROME

Cushing's syndrome was first recognized in a patient with lung cancer caused by the ectopic production of ACTH. Twenty to 30 percent of Cushing's syndrome is caused by biologically active ACTH, which is produced by nonpituitary neoplasms. Lung cancers are the most common neoplasms that cause ectopic ACTH production and Cushing's syndrome, accounting for 50 percent of all cases. Small-cell carcinoma accounts for 80 to 90 percent of cases associated with lung cancers, but carcinoid tumors (10 percent) and bronchial adenocarcinomas (5 percent) have also been reported to produce biologically active ACTH. Although one-half of all cases of ectopic ACTH production are caused by small-cell carcinoma, fewer than 3 percent of patients with small-cell lung cancer have Cushing's syndrome at the time of diagnosis.

Biology

Most cases of ectopic ACTH syndrome associated with lung cancers are caused by ectopic production of ACTH by the tumor. The precursor gene, pro-opiomelanocortin (POMC), is expressed in the cancer cells, and a 241–amino acid prohormone is translated and then cleaved into ACTH (39 amino acids), melanocyte-stimulating hormone, and opiatelike hormones (Fig. 108-3). The ACTH binds to receptors in the adrenal gland, causing them to produce excessive glucocorticoid and mineralocorticoid hormones.

A small number of patients with small-cell lung cancer or bronchial carcinoids have been reported to produce corticotropin-releasing hormone (CRH), thereby causing Cushing's syndrome. CRH is a 41–amino acid normally produced in the paraventricular nuclei of the hypothalamus, which stimulates the release of ACTH from the pituitary. In patients with small-cell carcinoma or bronchial carcinoid, CRH is produced by the cancer cells, thereby stimulating ACTH production by the pituitary gland and causing Cushing's syndrome.

Diagnosis

Ectopic ACTH production occurs with equal frequency in males and females—unlike Cushing's syndrome, which has an 8:1 female preponderance. Patients who have slow-growing tumors (carcinoids) often present with the clinical features of Cushing's syndrome: truncal obesity, moon facies, striae, polyuria, and polydipsia. In contrast, patients with small-cell lung cancer often present with other signs of mineralocorticoid and glucocorticoid excess due to the rapidity of tumor growth: edema, weakness, hypertension, and hypokalemic alkalosis.

The diagnosis of ectopic ACTH syndrome is established by the demonstration of increased 24-h excretion of urinary free cortisol (more than 400 nmol a day), increased plasma cortisol level (more than 600 nmol/l), and increased plasma ACTH level (over 22 pmol/l), which do not decrease in response to the administration of high-dose dexamethasone. Bronchial carcinoids are an exception because, in some tumors, ACTH and cortisol levels have been suppressed by dexamethasone. In patients in whom the dexamethasone suppression test does not establish the diagnosis of ectopic ACTH production, a CRH stimulation test or bilateral inferior petrosal vein sampling will provide the definitive diagnosis. After CRH infusion, pituitary tumors release increased amounts of ACTH, whereas pituitary-independent lung tumors should not. Similarly, in pituitary-dependent Cushing's syndrome, petrosal vein sampling will reveal a gradient between the level

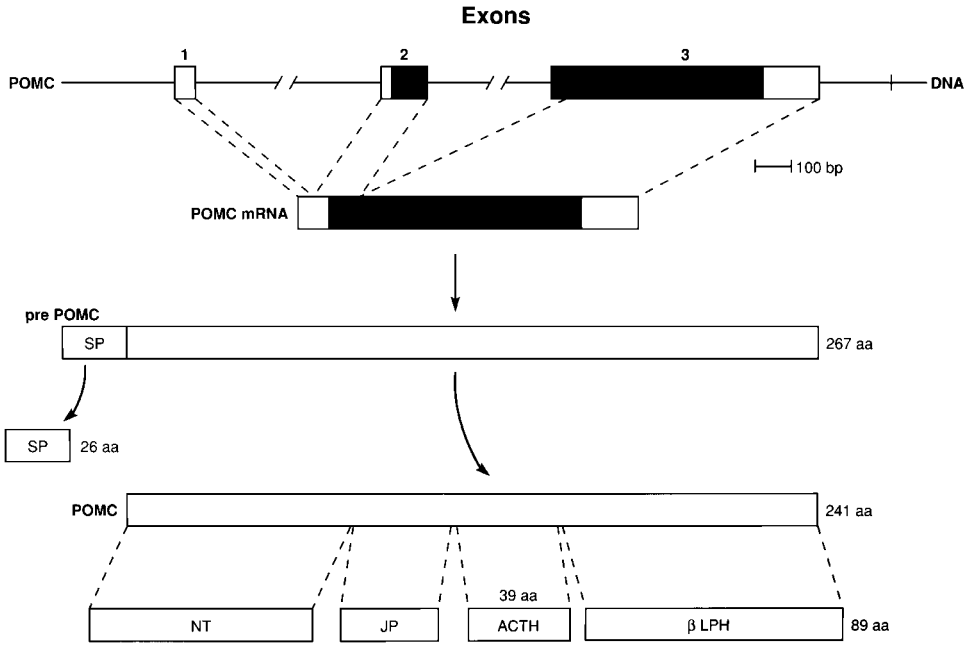

Figure 108-3 Pro-opiomelanocortin. The three exons of the POMC gene give rise to a 1072-base POMC mRNA. The mRNA is translated into a 267-amino acid pre-POMC with a 26–amino acid amino terminal signal peptide (SP). The signal peptide is cleaved, creating the 241–amino acid POMC. The POMC peptide is cleaved into many products, including the N-terminal peptide (NT), the joining peptide (JP), a 39–amino acid mature ACTH, and β-lipotropin (BLPH). The molecules can also undergo further processing. The black portions of the exons represent the protein-coding portion of the gene and mRNA.

of ACTH in the petrosal vein and the peripheral concentration. In contrast, patients in whom ACTH is ectopically produced demonstrate no gradient between the petrosal vein and the peripheral blood.

Treatment

Management of a patient with lung cancer and ectopic ACTH syndrome requires therapy directed at both the underlying tumor and the hypercortisolism. The treatment for a patient with ectopic ACTH production is to remove the source of the ACTH. This requires combination chemotherapy, with or without irradiation, for patients with small-cell lung cancer and surgical resection and/or radiation for patients with carcinoid tumors. Chemotherapy for patients with small-cell lung cancer and ectopic ACTH syndrome has been only minimally successful. Patients often have a poor response to chemotherapy and are susceptible to early infection and death. Early control of a patient's glucocorticoid excess is beneficial and may reduce the morbidity of treatment.

When removal of the ectopic source of ACTH is not possible, medical therapy directed at decreasing adrenal secretion may be successful. Ketoconazole is an imidazole derivative that inhibits steroidogenesis at both adrenal and gonadal sites. A recent review of medical therapy for ectopic ACTH syndrome suggests that ketoconazole may be the most effective and least toxic agent available. Metapyrone and aminoglutethimide also have shown limited success by inhibiting adrenal steroid synthesis. Octreotide, a somatostatin analogue, can suppress ectopic ACTH production and has been reported to be useful in some of these patients.

In some patients, the clinical signs and symptoms of ectopic ACTH production develop before the development of a clinically obvious lung cancer. In these cases, symptomatic management of hypercortisolism is undertaken and periodic imaging studies are performed because these patients may have a slow-growing carcinoid tumor that will be amenable to surgical resection.

ACROMEGALY

Carcinoid tumors of the lung and intestine are responsible for 70 percent of cases of ectopic acromegaly. Ectopic production of growth hormone–releasing hormone (GHRH) by tumor cells can be demonstrated in most patients, whereas a minority of tumors produce growth hormone.

Biology

The ectopic production of GHRH or GH by lung cancers has been demonstrated to cause acromegaly. In most cases, the GHRH gene is expressed by the cancer cells, and a 40– or 44–amino acid peptide is produced. This peptide is secreted into the circulation and binds to receptors in the pituitary gland, causing the production of excessive amounts of GH. GH then

mediates its effects through GH receptors in soft tissue and by stimulating the production of insulinlike growth factor–1 (IGF-1).

Immunoreactive GHRH can be identified in many bronchial carcinoids and small-cell lung cancers, but acromegaly occurs in a minority of these patients. Ectopic GHRH production may not cause clinically evident acromegaly because: (1) the tumor produces inadequate amounts of GHRH to cause the clinical syndrome; (2) the hormone is synthesized but not secreted; or (3) the rapid progress of the malignancy prevents the full development of clinical features of acromegaly.

Diagnosis

The earliest features of GH excess are hypertrophy of the extremities and face (forcing increased glove, shoe, and ring size), thickened leathery skin, prominent skin folds, increased skin pigmentation, and hair growth. Bony changes, hypertension, and diabetes mellitus are later, less common findings.

The presentation of a patient with a lung mass and signs of acromegaly should raise suspicion of the paraneoplastic syndrome of acromegaly. This is particularly true if the lung tumor is a carcinoid. The diagnosis is established by the presence of increased levels of GHRH and IGF-1 in the patient's plasma, the absence of a pituitary tumor, and the demonstration of GHRH or GH in tumor tissue by immunohistochemistry or mRNA expression studies. Because coincidental pituitary tumors and solid tumors have been described, patients who have lung cancer in association with low GHRH levels and high GH and IGF-1 levels should undergo magnetic resonance imaging (MRI) to exclude a pituitary tumor.

Treatment

The treatment of choice for ectopic acromegaly is removal of the GHRH- or GH-secreting tumor. This can often be achieved in patients with lung carcinoid tumors. Radiation therapy has also been effective. Patients with ectopic acromegaly whose tumors cannot be removed or irradiated should undergo medical therapy using the somatostatin analogue octreotide or bromocriptine. Bromocriptine acts by inhibiting GH release by the pituitary; octreotide lowers both GH and IGF-1 levels in plasma and also appears to inhibit GHRH release by tumors. Clinical abatement of acromegalic features has been reported in patients treated with octreotide.

HEMATOLOGIC SYNDROMES

Most hematologic syndromes associated with lung tumors are not as well characterized as the endocrine syndromes, because the ectopic hormone responsible for the syndrome has not been identified in most tumor tissues. In many of the hematologic syndromes, such as granulocytosis and thrombocytosis, clinical sequelae are often absent. As with the endocrine paraneoplastic syndromes, the most appropriate therapy for the hematologic syndromes is the treatment of the underlying neoplasm.

Granulocytosis

Non–small-cell lung cancer is the most common cancer associated with granulocytosis. Twenty percent of patients with non–small-cell lung cancer have granulocytosis, with absolute white blood counts ranging from 10,100 to 25,000 (normal range is 4000 to 10,000).

Although granulocyte colony–stimulating activity can be demonstrated in serum and/or urine in 80 percent of patients, the specific peptide hormone causing the syndrome has not been identified. Tumor production of granulocyte colony–stimulating factor (G-CSF), granulocyte-monocyte colony–stimulating factor (GM-CSF), and interleukin-6 (IL-6) has been shown in a minority of patients.

Virtually all patients with lung cancer who present with tumor-associated granulocytosis are asymptomatic. The diagnosis is suggested by the presence of an increased white blood count in which neutrophils predominate without immature forms, in the absence of nonneoplastic causes. An increased leukocyte alkaline phosphatase score and a normal bone marrow are consistent with this diagnosis.

Thrombocytosis

Thrombocytosis is common in patients with lung cancer, afflicting 40 percent of patients with both non–small-cell and small-cell tumors.

The pathogenesis of thrombocytosis in patients with lung cancer has not been definitively elucidated. IL-6, which is a cytokine for megakaryocytes, has been demonstrated in cell lines from patients with lung cancer and thrombocytosis, and increased levels of IL-6 have been demonstrated in the plasma of such patients. The recent identification of the thrombopoietin gene should lead to a better understanding of the role of this protein in paraneoplastic thrombocytosis.

Patients with thrombocytosis are nearly always asymptomatic and do not have an increased incidence of thromboembolism. The diagnosis of cancer-associated thrombocytosis is suggested by an increased platelet count (above $500{,}000/mm^2$) in a patient with newly diagnosed lung cancer. A primary myeloproliferative disorder can be excluded only by a bone marrow biopsy.

Thromboembolism

Twenty percent of patients with lung cancer develop venous thromboembolism during the course of their disease. Twenty percent of patients who present with recurrent idiopathic venous thrombosis are found to have an underlying diagnosis of cancer. The spectrum of causes of thrombosis in patients with lung cancer is broad, including disseminated intravascular

coagulation (DIC), Trousseau's syndrome (recurrent migratory venous thrombophlebitis), nonbacterial thrombotic endocarditis, and obstruction of great vessels. Surgical procedures and chemotherapy have also been demonstrated to increase cancer patients' risk of thrombotic complications.

The treatment for venous thrombosis in patients with lung cancer depends on the underlying hematologic diagnosis. If the patient has an isolated venous thrombosis in the absence of DIC or Trousseau's syndrome, oral warfarin therapy is appropriate with the aim of an international normalized ratio two to three times normal. If there are recurrent thromboses, long-term subcutaneous heparin is more efficacious than warfarin.

NEUROLOGIC SYNDROMES

Neurologic dysfunction as a paraneoplastic manifestation of lung cancer was first described more than 30 years ago. Encephalomyelitis, cerebellar degeneration, retinopathy, opsoclonus/myoclonus, and the Lambert-Eaton syndrome have all been associated with lung tumors, most commonly small-cell lung cancer. Most of these neurologic paraneoplastic syndromes appear to be caused by an autoimmune response directed at antigens that are shared by the cancer cells and normal neural tissue. Unlike that of the endocrine and hematologic syndromes associated with lung cancer, the clinical courses of the neurologic syndromes are typically independent of the course of the underlying disease. The autoantibodies associated with each neurologic syndrome are listed in Table 108-2.

Encephalomyelitis/Subacute Sensory Neuropathy

The paraneoplastic syndrome of encephalomyelitis/subacute sensory neuropathy was initially discovered in a patient with small-cell lung cancer. Currently, more than 70 percent of cases of paraneoplastic encephalomyelitis are diagnosed in patients with small-cell lung cancer. A specific antibody, anti-Hu, which reacts with the HuD antigen expressed by lung cancer cells and neuronal tissues, has been associated with the development of this syndrome.

Biology

The anti-Hu antibody is an IgG antibody found in the sera of patients with sensory neuropathy and encephalomyelitis. This antibody reacts with 35- to 40-kD neuronal nuclear antigens in the cerebral cortex, brain stem, cerebellum, spinal cord, and dorsal root ganglia, and it reacts with surface proteins on some small-cell lung cancer cells. The HuD gene has been mapped to the chromosome 1p region and appears to be a marker of neuroendocrine differentiation in these cells.

Diagnosis

The clinical features of this syndrome are diverse. One-half of patients undergo progressive sensory loss in the hands and feet. Others present with a limbic encephalopathy characterized by memory loss, behavioral changes, and seizures. Focal myelopathy with weakness, brain stem signs (nystagmus, dysarthria), and autonomic nervous system dysfunction also occur in patients with this syndrome. These clinical signs and symptoms can antedate the diagnosis of lung cancer, so a full evaluation for occult cancer in patients who present with encephalomyelitis or subacute sensory neuropathy is warranted. CT scans are typically normal in these patients, but MRI studies may show increased T2 signal in affected areas of the brain. Pathologic examination of brain biopsies show inflammatory infiltrates and neuronal destruction in the brain stem, hippocampus, spinal cord, and dorsal root ganglia. The demonstration of anti-Hu antibodies in a patient with encephalomyelitis and a diagnosis of small-cell lung cancer establishes the diagnosis.

Treatment

Treatment of the encephalomyelitis/subacute sensory neuropathy syndrome associated with lung cancer is treatment of the primary tumor. Immunosuppressive therapy with

Table 108-2

Neurologic Syndromes Associated with Lung Cancer

Syndrome	Tumor	Antibody	Antigen
Encephalomyelitis/subacute sensory neuropathy	Small-cell	Anti-Hu	Hu-D antigen: 35- to 40-kD neuronal nuclear protein
Cancer-associated retinopathy	Small-cell	Antirecoverin	23-kD protein specific to photoreceptor cells (recoverin)
Lambert-Eaton syndrome	Small-cell	Anti-P/Q channel	P/Q-type calcium channel

corticosteroids and plasmapheresis directed at removal of the offending immunoglobulin from the patient's serum have been shown to be effective in only 10 to 20 percent of patients. Patients who are severely affected by the anti-Hu syndrome can die from neurologic sequelae (e.g., cardiovascular collapse) rather than from the underlying lung cancer.

Paraneoplastic Cerebellar Degeneration

A syndrome of cerebellar degeneration has also been noted in patients with small-cell lung cancer. This is believed to be a variant of the paraneoplastic cerebellar degeneration (PCD) observed in patients with gynecologic and breast tumors. In patients with gynecologic tumors and PCD, a specific anti-Purkinje cell antibody called anti-Yo has been identified that binds to 34- to 38-kD and 62- to 64-kD proteins in the cytoplasm of Purkinje cells. Patients with small-cell lung cancer and cerebellar degeneration have anti-Hu antibodies in their sera and do not have the anti-Yo antibody. These patients are considered to have the anti-Hu syndrome and frequently go on to develop encephalitis or sensory neuropathy.

Opsoclonus and Myoclonus

Opsoclonus is a disorder consisting of involuntary rapid conjugate eye movements in vertical and horizontal directions. It is often associated with myoclonus in patients with solid tumors. This syndrome of opsoclonus/myoclonus has been associated with both small-cell and non–small-cell lung cancer in numerous case reports, but less is known about this syndrome than about the syndrome of paraneoplastic encephalomyelitis/subacute sensory neuropathy.

A specific antibody called anti-Ri has been identified that binds to 55-kD nuclear proteins expressed in the dentate nucleus. Although this antibody is considered to be the cause of the opsoclonus/myoclonus syndrome in patients with gynecologic tumors, the antibody has not been demonstrated in patients with lung cancer.

The anti-Hu antibody has been identified in some patients with small-cell lung cancer and opsoclonus/myoclonus. As in patients with the anti-Hu antibody and cerebellar degeneration, patients who have opsoclonus and the anti-Hu antibody may have a variant of the encephalomyelitis/subacute sensory neuropathy syndrome. Patients who present with lung cancer and opsoclonus should be evaluated for the anti-Hu antibody.

CANCER-ASSOCIATED RETINOPATHY

Cancer-associated retinopathy is a rare paraneoplastic syndrome that occurs predominantly in patients with small-cell lung cancer. Many autoantibodies have been identified in patients with this disorder; they bind to a photoreceptor-specific protein called recoverin.

Biology

Retinal ganglion cells and their processes are characteristically lost in this disorder because of the autoantibodies that bind to recoverin, a 23-kD photoreceptor-specific protein found in rods and cones as well as in small-cell lung cancer cells. The autoantibodies that cause the cancer-associated retinopathy specifically bind to the recoverin protein and do not recognize other retinal proteins.

Diagnosis

The clinical triad of photosensitivity, ring-scotomata visual field loss, and attenuation of retinal arteriole caliber is considered highly suggestive of cancer-associated retinopathy. The typical patient presents with symptoms of rapid visual loss, night blindness, and color loss. On physical examination, most patients show visual field deficits, disk pallor, and cells in the vitreous body, along with arteriolar narrowing.

Demonstration of the antirecoverin antibody in a patient with signs of retinopathy establishes the diagnosis. As with paraneoplastic cerebellar degeneration, cancer-associated retinopathy is often the first sign of an occult carcinoma. Therefore, an evaluation for lung cancer should be performed in all patients who present with this syndrome.

Treatment

In contrast to those with the other paraneoplastic neurologic syndromes, more than half of patients with cancer-associated retinopathy have been reported to respond with visual improvement after systemic steroid therapy. Treatment of the primary tumor without immunosuppressive therapy has not been shown to cause visual improvement in patients with cancer-associated retinopathy. Most of these patients develop progressive visual loss and blindness within 18 months.

LAMBERT-EATON SYNDROME

The Lambert-Eaton syndrome afflicts fewer than 2 percent of lung cancer patients but has been reported in up to 5 percent of patients with small-cell lung cancer. Sixty percent of all patients who present with the Lambert-Eaton syndrome have small-cell lung cancer.

Biology

In patients with Lambert-Eaton syndrome and small-cell lung cancer, an IgG autoantibody has been identified that binds to calcium channels in motor and autonomic nerve terminals, thereby inhibiting acetylcholine release. This antibody also binds to the 58-kD synaptic vesicle protein synaptotagmin, which is present in small-cell lung cancer cells. Recent evidence suggests that the P/Q calcium channel is the specific target of these antibodies. The antibody binding of the

P/Q calcium channel weakens the neuromuscular signal, and neurologic dysfunction follows. It has also been postulated that these autoantibodies induce the production of acetylcholinesterase, which would also diminish the neuromuscular signal.

Diagnosis

Clinical features include weakness of the pelvic girdle and thigh, fatigue, dry mouth, dysarthria, dysphagia, blurred vision, and muscle pain. Unlike the situation with myasthenia gravis, muscle strength improves with exercise and does not improve significantly with the administration of anticholinesterases (e.g., edrophonium). Electromyography performed in these patients demonstrates increased muscle action potential with repeated nerve stimulation. In patients with the Lambert-Eaton syndrome, IgG autoantibodies should be demonstrable in serum.

Treatment

Treatment of the underlying small-cell lung cancer with chemotherapy can effectively treat the associated Lambert-Eaton syndrome. For patients whose neuromuscular status does not improve with chemotherapy, immune modulation with azathioprine (2.5 mg/kg per day), plasma exchange, or intravenous γ-globulin (400 mg/kg per day for 5 days) has been shown to induce remissions. 3,4-Diaminopyridine in doses of 10 to 100 mg a day has also been used successfully to bring about short-term control of this syndrome.

CONCLUSION

The paraneoplastic syndromes have long fascinated and perplexed oncologists, and only in recent years have the molecular bases for these syndromes been appreciated. Not only has this new knowledge led to more effective palliation of symptoms, but it may also offer new clues to the pathogenesis of malignancy. The presence of signs and symptoms that suggest a paraneoplastic syndrome should prompt a search for malignancy.

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Pulmonary Metastases

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Pulmonary metastasis represents the dissemination of cancer cells with establishment of local residence in the pulmonary parenchyma. Recent advances in technology have allowed basic science to further elucidate not only the cellular and metastatic signature, but also the metastatic cascade. Krishnan describes a six-step model of the metastatic cascade involving intravasation, resistance to anoikis, evasion of the immune system, extravasation, dormancy, and proliferation. Matrix metalloproteases, up-regulated by cancer cells, have the ability to degrade the extracellular matrix, allowing the cells access to the vasculature. Krishnan states, "Loss of cell-cell or cell-matrix interaction triggers the activation of the caspase proteases, the hallmark of cell death." Metastatic cancer cells that do not undergo apoptosis survive through the development of homotypic as well as heterotypic interactions, thereby resisting anoikis (apoptotic cell death when a cell loses interaction with the extracellular matrix). These cells can avoid immunosurveillance through down-regulation of antigens as well as production of immunosuppressive cytokines. Extravasation requires interaction of metalloproteases and degradation of extracellular matrix along with the addition of basement membrane to cell adhesion molecules (CAM). Metastases may remain dormant for many years, becoming clinically relevant only when turned on by angiogenesis controls, immune mediated growth suppression, or other mechanisms. The process of neovascularization leads to proliferation. Potential therapeutic strategies include anti-VEGF monoclonal antibody, tyrosine kinase inhibitors, and the anti-EGFR antibody cetuximab.

However, the presence of metastatic disease connotes a negative prognosis for the patient. SEER (Surveillance Epidemiology and End Results) Cancer statistics review (1975–2003; Table 109-1) shows 5-year survival rates for patients with colon and rectal carcinoma sink to 9.1 percent versus 90.5 percent for patients with distant versus localized disease. Five-year survival rates for breast cancer are reduced from 97.5 to 24.2 percent when the patient develops distant disease. Five-year survival from esophagus cancer is reduced from 29.4 to 2.5 percent when the patient goes from localized to distant disease. The SEER report shows similar trends for lung, pancreas, melanoma, and stomach cancer. Despite improvements in multimodality therapy for oncologic disease, survival from metastatic disease remains poor. However, multiple retrospective observational studies demonstrate a survival benefit for carefully selected patients who present with pulmonary metastasis and who can tolerate complete resection of all metastatic disease.

In 1882, Weinlechner performed the first lung resection for pulmonary metastasis. The principles established by Alexander and Haight in 1947 regarding a controllable

Table 109-1

Five Year Survival Data by Primary Cancer Site

Primary Histology	Distant Disease	Local Disease
Lung	2%	59%
Breast	21%	100%
Colon and rectum	8%	96%
Pancreas	1.7%	17%
Melanoma	15.1%	97.6%
Stomach	2.8%	60%

primary site of malignant disease, and the absence of extrapulmonary metastasis in conjunction with a medically fit patient remain cornerstones of surgical management decisions regarding patients with pulmonary metastasis. Furthermore, the international registry of lung metastases in 1997 developed a model of prognostic grouping, based on resectability, disease-free interval, and number of metastases. Resectable patients with isolated solitary pulmonary metastasis and prolonged disease-free interval of more than 36 months had a median survival of 61 months compared with resectable patients with a disease-free interval of less than 16 months and multiple metastases (greater than 1). In 2007, Petersen and colleagues reviewed their experience with 1720 patients with pulmonary metastatic melanoma and corroborated the above, noting that the number of pulmonary nodules, disease-free interval, and presence of extrathoracic metastasis are significant prognostic factors.

Metastasectomy has always and continues to be controversial. The current salient issues include: patient selection, operability and resectability, tissue histology, disease-free interval, number of metastasis, presence of extrathoracic disease, the role of mediastinal lymph node evaluation, open versus thoracoscopic approach, unilateral versus bilateral assessment, and the role of removal of radiographic disease versus palpable disease.

PATIENT SELECTION, OPERABILITY, AND RESECTABILITY

Patients presenting with pulmonary metastatic disease often are evaluated by the thoracic surgical oncology team in a similar manner to a primary lung cancer patient. After establishing that the metastatic burden is confined to the lungs and that the primary site is controlled or controllable, cardiac risk assessment and pulmonary functional assessment should be performed. Patients who can tolerate resection of all pulmonary metastases are recommended to undergo pulmonary metastasectomy. Patients with metastatic colorectal cancer to liver and lung are an exception to the requirement of no extrathoracic metastatic disease. Such patients can benefit from hepatic and pulmonary metastasectomy with anticipated 30 to 44 percent 5-year survival.

TISSUE HISTOLOGY, DISEASE-FREE INTERVAL, AND NUMBER OF METASTASES

Sarcoma

Following the principles previously outlined, pulmonary metastasectomy for osteosarcoma and soft tissue sarcoma can lead to 43.6 percent (range 22.6–43.6 percent) 5-year survival. Repeat metastasectomy also has prolonged 5-year survival. Pfannschmidt et al. reported on pulmonary metastasectomy in 50 patients with soft tissue sarcoma who underwent systematic hilar and mediastinal lymph node dissection. Lymph node metastases were identified in 24 percent ($n = 12$). Survival was decreased in the patients with lymph node involvement, but was not statistically significant. Currently, routine mediastinal and hilar lymph node evaluation for patients with metastatic soft tissue sarcoma to the lungs cannot be recommended and needs further trials.

For sarcomas, a disease-free interval of more than 1 year and primary tumor necrosis greater than 98 percent following neoadjuvant chemotherapy have been shown to correlate with improved survival following pulmonary metastasectomy.

Colorectal Carcinoma

Five-year survival rates between 35 and 45 percent can be achieved with pulmonary metastasectomy for colorectal pulmonary metastasis. Elevated CEA levels greater than 10 as well as regional hilar and mediastinal lymph node involvement are negative prognostic indicators. Saito et al. stated in 2002:

> Five-year survival was 53.6% for patients without hilar or mediastinal lymph node metastasis, versus 6.2% at 4 years for patients with metastases ($p < 0.001$). Five-year survival of patients with a prethoracotomy carcinoembryonic antigen level less than 10 ng/mL was 42.7%, versus 15.1% at 4 years for patients with a carcinoembryonic antigen level 10 ng/mL or greater ($p < 0.0001$).

Therefore, it seems prudent that routine mediastinal as well as hilar nodal sampling should be considered for patients undergoing pulmonary metastasectomy for colorectal metastasis. Prolonged disease-free interval has not consistently correlated with improved outcome. Multiple pulmonary metastases (greater than 3 lesions) have been shown to negatively affect survival.

Metastatic Melanoma

Petersen and colleagues reviewed the Duke experience with 1720 patients who experienced metastatic pulmonary melanoma. Overall 5-year survival was 6 percent. Nodular histology of the primary tumor, two or more metastases, disease-free interval less than 5 years, and the presence of extrathoracic metastasis were associated with poorer prognosis. Similar to the international registry of lung metastases, prognostic grouping was performed. Five-year survival decreased from 26 percent to 11 percent to 4 percent to 2 percent as associated risk factors increased from 0 to 1 to 2 to 3 or more. They performed unilateral thoracotomy in 255 patients undergoing resection, thoracoscopy in 40 patients, and bilateral thoracotomy in 23 patients. Wedge resection was the most frequent type of resection.

Non-Seminomatous Germ Cell Tumors

Non-seminomatous germ cell tumors disseminate along the course of the thoracic duct, leading to mediastinal metastases as well as pulmonary metastases. Cisplatin-based chemotherapy is the primary treatment, with surgical salvage for residual disease. The majority of patients with residual disease have either conversion to mature teratoma (59 percent) or necrotic tumor (15 percent). Pulmonary metastasectomy is associated with prolonged survival in patients with metastatic non-seminomatous germ cell tumors, from 59 to 82 percent 5-year survival. The presence of an increase in elevated tumor markers (AFP and B-HCG), viable tumor cells, incomplete resection, four or more metastases, and pulmonary as opposed to mediastinal metastases negatively affect survival. The disease-free interval has not been shown to affect survival.

Breast Carcinoma

Complete resection of pulmonary metastatic breast cancer can be accomplished in 77 to 84 percent of patients. Although 5-year survival following pulmonary metastasectomy secondary to breast carcinoma approaches 38 to 50 percent, effective medical oncologic management is preferred over surgery for initial treatment. Disease-free intervals greater than 36 months are associated with improved survival following metastasectomy. If the size of the largest metastasis is greater than 20 mm, there is negative impact on survival.

Although multiple metastatic lesions have not been shown conclusively to affect survival negatively, treatment of the solitary pulmonary nodule in a patient with a history of breast carcinoma remains a challenge. This is particularly true because the ability to distinguish a solitary metastasis from primary lung carcinoma may not be possible. Thus, solitary pulmonary nodules should be treated as primary lung carcinoma until proved otherwise. When treated as a primary lung cancer, the planned resection is different and includes mediastinal lymphadenectomy or nodal sampling.

Other Cancers Metastatic to the Lungs

Prolonged 5-year survival following pulmonary metastasectomy may be realized for renal cell carcinoma, uterine cancer, hepatocellular carcinoma, and head and neck cancers.

EXTENT OF AND APPROACH TO RESECTION

The goal of pulmonary metastasectomy is to accomplish a complete (R0) resection while using optimal pulmonary conservation techniques (i.e., wedge resection). Dowling, et al. at University of Pittsburgh reported the first use of video-assisted thoracic surgery (VATS) for pulmonary metastasectomy in 1992. Subsequent to that report, many centers routinely perform VATS pulmonary metastasectomy. Ketchedjian et al. argue that VATS metastasectomy should be limited to two or fewer metastases located in the outer one-third of the lung and be resectable by VATS. Opponents of VATS or a minimally invasive approach to pulmonary metastasectomy argue that it is necessary to perform bimanual palpation of the lung to assess for additional metastases not identified on preoperative radiographic evaluation. Complete resection (R0) rendering the patient pathologically free of metastatic disease can be accomplished by this approach. McCormack et al. from Memorial Sloan-Kettering Cancer Center (MSKCC) performed VATS metastasectomy of all radiographically identified nodules (inclusion criteria were no more than two unilateral nodules) followed by immediate conversion to thoracotomy and bimanual palpation. They found that additional malignant nodules were present in 10/18 (56 percent) of their patients. Helical CT was used in 2 of 18 patients. They concluded that VATS was an inadequate surgical option for resecting all disease (R0 resection). Despite the fact that pulmonary metastases are hematogenous in origin, mandatory exploration of the radiologically negative hemithorax is not the standard approach for these investigators and was not performed in this experimental cohort. Of the International Registry of Lung Metastases database of 5206 patients who had metastasectomies, 4572 (88 percent) patients underwent R0 resections: 2.4 percent had residual microscopic disease (R1), and an additional 9.7 percent had residual macroscopic disease (R2). Of the 88 percent of patients who underwent an R0 resection, only 2 percent had minimally invasive approach or thoracoscopy and 58 percent had a monolateral thoracotomy. Based on pathological assessment, single metastases were identified in 46 percent of patients. Radiologic accuracy for unilateral thoracotomy was 75 percent; underestimation of tumor burden occurred in 16 percent. If one were to extrapolate the data from MSKCC regarding the finding that bimanual palpation reveals additional metastases in 56 percent of the patients, one would expect a lower percentage of solitary metastasectomy to have been performed in the international registry group. This is not the case. Repeat metastasectomy in the international registry was associated with 44 percent 5-year survival

("remarkably good"). As we learn more about the metastatic cascade, it seems plausible that metastatic dormancy, avoidance of immunosurveillance through antigen down-regulation, and production of immunosuppressive cytokines may be partially responsible for the good results achieved with VATS metastasectomy as well as unilateral thoracotomy for pulmonary metastasectomy.

With evolving technology, such as 64 slice CT scanners, the ability to detect smaller lesions will continue to improve. The improvement in PET scans to detect probable mitotic activity continues to gain better resolution at lower levels. Use of intraoperative ultrasound as well as wire-guided localizations, in conjunction with minimally invasive techniques, will allow surgeons to identify and remove metastatic nodules not previously identified radiographically, but appreciated on bimanual palpation. Radiologic complete resection is merging with complete resection of all palpable disease. Thus, consideration for a new paradigm may be warranted. Now is the time to establish the category of radiographic complete resection (R-R0). Such an approach would require postoperative surveillance CT scans and possibly PET scans at 3-month intervals following resection.

ROLE OF MEDIASTINAL NODAL EVALUATION AND EFFECT ON OUTCOME

Routine mediastinal and hilar nodal sampling is not performed uniformly. Although the International Registry of Lung Metastases found a 4.6 percent incidence of lymph node metastases, only 5 percent of patients underwent mediastinal lymph node evaluation. Autopsy studies of patients with non-pulmonary carcinoma demonstrate a 33 percent incidence of mediastinal lymph node metastases. Since there is a trend toward decreased survival when mediastinal or hilar lymph node metastases are present, Pfannschmidt and colleagues have attempted to elucidate further the incidence as well as impact of mediastinal lymph node metastases. They reported on pulmonary metastasectomy in 50 patients with soft tissue sarcoma who underwent systematic hilar and mediastinal lymph node dissection. Lymph node metastases were identified in 24 percent ($n = 12$). Survival tended to be decreased in the patients with lymph node involvement, but was not statistically significant from those without nodal metastasis. Routine mediastinal and hilar lymph node evaluation for patients with metastatic soft tissue sarcoma to the lungs currently cannot be recommended and needs further study.

Also, Pfannschmidt et al. evaluated mediastinal lymph nodes in 167 patients undergoing metastasectomy for colorectal carcinoma spread to the lungs. Lymph node metastasis was identified in 19.1 percent of patients. Five-year survival decreased from 38.7 to 0 percent when nodes were involved ($p < 0.03$). At the current time, mediastinal lymph node evaluation should be considered for all patients undergoing pulmonary metastasectomy secondary to colorectal carcinoma prior to pulmonary metastasectomy. Mediastinal node involvement should be considered a contraindication to metastasectomy.

Pfannschmidt et al. later evaluated 191 patients with pulmonary metastases secondary to renal cell carcinoma and found a 29.8 percent incidence of lymph node metastases. Despite a significant decrease in 3-year survival from 55.4 to 31.4 percent for patients with mediastinal or pulmonary lymph node metastases ($p = 0.0038$), prolonged survival is seen in patients with pulmonary and thoracic nodal metastatic renal cell carcinoma. Therefore, the presence of mediastinal adenopathy in these patients is not a contraindication to metastasectomy.

For other histology, further investigation is warranted to evaluate the role of mediastinal lymph node evaluation, mediastinal lymph node dissection, mediastinal lymph node impact on survival, and the decision to proceed with pulmonary metastasectomy.

ISOLATED LUNG PERFUSION

Isolated lung perfusion is a technique designed to allow the delivery of a variety of agents to the pulmonary parenchyma with minimal systemic exposure. Currently, tumor necrosis factor-α, doxorubicin, melphalan, cisplatin, and other agents have been studied. The pharmacokinetics of these agents as well as systemic agent leakage have been studied. Despite extensive study, isolated lung perfusion remains an investigational modality that may help in the multimodality approach to cancer. It may play a role in tumor reduction, conversion of unresectable patients to resectable, and ultimately survival.

CONCLUSIONS

Pulmonary metastasectomy can be performed in selected patients with acceptable long-term survival, when other treatment options are not available. Patients must meet the tenets of controllable primary disease, no extrathoracic disease (colorectal and germ cell tumors may be exceptions), and have sufficient cardiac and pulmonary reserve to tolerate complete resection. Mediastinal lymph node evaluation prior to pulmonary metastasectomy should be performed on all patients with a primary colorectal cancer. Positive mediastinal nodal metastases, secondary to colorectal carcinoma, are a contraindication to pulmonary metastasectomy. The finding of positive mediastinal lymph node involvement for sarcoma, as well as for renal cell carcinoma, does not support routine mediastinal nodal evaluation for these patients. Routine mediastinal nodal evaluation prior to pulmonary metastasectomy for other primary tumors

needs further investigation and should be considered for mediastinoscopy or transtracheal, transbronchial fine-needle aspirate.

Since repeat pulmonary metastasectomy has been shown to have good survival, patients who undergo pulmonary metastasectomy must undergo routine surveillance CT and/or PET-CT scanning to identify recurrent disease at 3-month intervals. Minimally invasive approaches to pulmonary metastasectomy produce similar survival to open approaches and enable the surgeon to perform a complete radiologic resection (R-R0). A minimally invasive approach to pulmonary metastasectomy in conjunction with serial radiographic follow-up and repeat metastasectomy is essential for achieving a complete pathological response.

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110
CHAPTER

Lymphoproliferative and Hematologic Diseases Involving the Lung and Pleura

Douglas B. Flieder

Lymphoproliferative disorders of the lung and pleura comprise a varied but rare group of localized and diffuse processes that span the morphologic gamut from reactive to neoplastic and include several peculiar lesions that do not fit conventional definitions of either hyperplasia or neoplasia. Although most diagnoses are based on light microscopy, immunohistochemical and molecular investigations are practically *de rigueur*. Nomenclature and classification schemes have undergone drastic changes over the past quarter century and current definitions appear reasonable. Malignant lesions are best classified according to the current World Health Organization (WHO) scheme. This chapter presents the clinicopathologic features of primary and secondary pulmonary and pleural hematolymphoid lesions.

ANATOMY AND HISTOLOGY OF THE PULMONARY LYMPHOID SYSTEM

Pulmonary lymphatics are divided into two interconnecting channels that drain to peribronchial, hilar, and/or mediastinal lymph nodes and eventually into the thoracic duct, right lymphatic duct, and subclavian veins. One system drains through

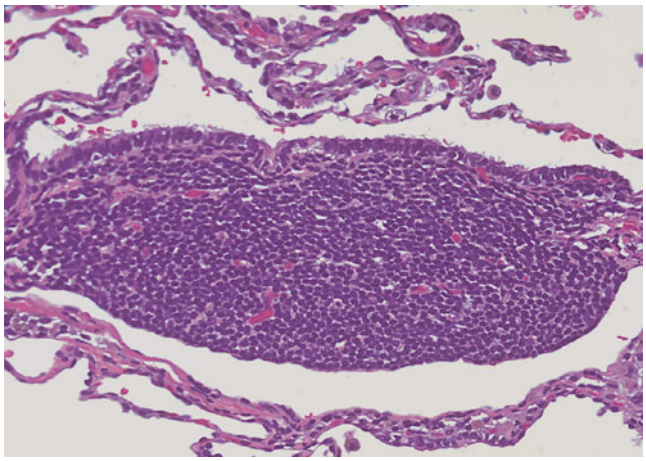


Figure 110-1 Bronchus-associated lymphoid tissue. The submucosal collection of lymphoid cells is intimately associated with overlying bronchiolar epithelium. Hematoxylin and eosin, 40× original magnification.

the visceral pleura around the lung into mediastinal lymph nodes and the other drains from central lung parenchyma to peribronchial and hilar lymph nodes. The lymphatics communicate at lobar, lobular, and pleural boundaries and thus serve each other as potential collaterals. Although not usually obvious in histologic sections of normal lung, lymphatics are prominent in disease states ranging from pulmonary edema to lymphangitic carcinoma. In the latter, lymphatic channels distended with malignant cells are apparent within the visceral pleura, interlobular septa, and adventitia of arteries, veins, and bronchioles. Of note, alveolar septa do not contain lymphatic channels. All lymphatics contain valves and flat endothelial cells line the discontinuous basal lamina. Larger lymphatics contain smooth muscle and collagen.

Small submucosal aggregates of lymphoid cells are often prominent at bronchial bifurcations and near distal respiratory bronchioles (pulmonary microtonsils) and represent bronchus-associated lymphoid tissue (BALT) (Fig. 110-1). Whether humans are born with this specialized secondary lymphoid system, or whether the aggregates of B lymphocytes, T lymphocytes, HLA-DR+ interdigitating cells, follicular dendritic cells, and lymphoid follicles with an overlying flattened and attenuated specialized epithelium develop in response to antigenic stimulation is controversial. Viruses, connective tissue disorders, tobacco use, and obstructive pneumonia are just a few pathologic processes known to induce BALT (Table 110-1). Unlike typical lymph nodes that rely on afferent lymphatics for antigen retrieval, BALT is integrated into lung tissue and antigen is sampled directly from the bronchial and bronchiolar lumens through specialized "lymphoepithelia." Immunoglobulins, most notably IgA, are synthesized and secreted by lymphocytes directly into airway lumens. Amazingly, this system appears capable of mounting a competent adaptive immune response. In addition, BALT B-lymphocytes circulate and "home" to other mucosal sites such as the conjunctiva, salivary glands, stomach, and intestines to create a common mucosal immune system, the mucosa-associated lymphoid system (MALT). Thus, responses induced in one location can be replicated at other sites. Malignant lymphomas arising in one MALT location can secondarily involve other MALT sites. Bronchus-associated lymphoid tissue appears to be the origin of many of the primary pulmonary lymphoid lesions.

Intrapulmonary lymph nodes (IPLs) may be part of the pulmonary immune system and may also be induced by antigenic stimuli rather normal embryologic development. Autopsy studies suggest a prevalence of 18 percent, and although many are related to bronchi of the first few orders, peripheral subpleural locations are not uncommon. In this age of high-resolution computed tomography (HRCT) and lung cancer screening programs, up to 80 percent of reported cases occur in men with histories of tobacco use and almost 35 percent of cases are multiple. These up to 2.0 cm round to angulated sharply circumscribed subpleural opacities are found along interlobular septa or within major and minor fissures and histologically resemble classic lymph nodes with

Table 110-1

Diseases Associated with Hyperplasia of Bronchus-Associated Lymphoid Tissue

Autoimmune diseases
Allergy such as asthma
Autoimmune hemolytic anemia
Celiac sprue
Hashimoto's thyroiditis
Myasthenia gravis
Pernicious anemia/ agammaglobulinemia
Primary biliary cirrhosis
Rheumatoid arthritis
Systemic lupus erythematosus
Sjögren's syndrome
Transverse myelitis
Immunodeficiency syndromes
Common variable immunodeficiency
Unexplained childhood immunodeficiency
Virus-associated
Epstein-Barr virus
Hepatitis viruses
Human immunodeficiency virus
Drug-induced forms
Allogeneic bone marrow transplantation
Dilantin
Infections
Chylamydia
Mycoplasma
Tuberculosis
Familial

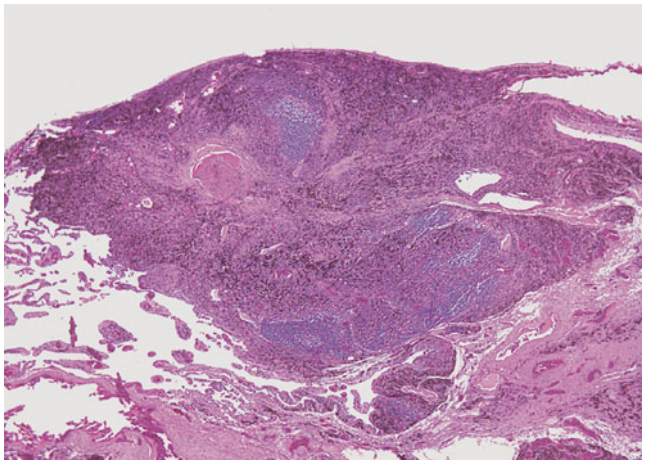


Figure 110-2 Intrapulmonary lymph node. Subpleural lymph nodes often accumulate carbon pigment and become fibrotic. The radiologic differential diagnosis includes carcinoma while a fine needle aspirate sample may mimic malignant lymphoma. Hematoxylin and eosin, 4× original magnification.

well-developed cortical and medullary areas. Sinus histiocytes frequently contain abundant anthracosilicotic pigment and silicotic nodules with calcifications may form (Fig. 110-2). In patients with chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL), IPLs may be involved and, rarely, primary lung carcinoma or carcinoma from a nonpulmonary site can metastasize to IPLs. Most importantly, IPLs can be clinically, radiographically and cytologically mistaken for malignancy. Although fine-needle aspirates can exclude the possibility of carcinoma, an erroneous diagnosis of lymphoma might be considered.

GENERAL CONSIDERATIONS

Although internists, pulmonologists, and radiologists often diagnose pulmonary diseases on the basis of clinical and radiographic findings and rely on tissue samples merely for confirmation, lymphoid lesions of the lung are often unsuspected diagnoses rendered by pathologists. Yet clinical and radiologic studies are essential in the interpretation of all lesions. Often, light microscopic considerations can be excluded purely on the basis of radiographic findings. For example, whereas pulmonary lymphomas can be localized or diffuse, lymphoid interstitial pneumonia (LIP) is always bilateral and diffuse.

Pulmonary lymphoid lesions almost always require wedge biopsies or excisions for diagnosis. Although fine-needle aspirate biopsies and transbronchial biopsies supplemented with ancillary studies may suffice for a diagnosis of malignant lymphoma, architectural and cytologic variability necessitates generous sampling. Such is especially the case, as cellular monotony is not the sole criterion for malignancy. Whereas sheets of uniform cells may be diagnostic of lymphoma, many malignant processes such as Hodgkin's lymphoma (HL) and T-cell lymphoma are polymorphous and admixed with inflammatory cells. Secondary changes and biopsy-related artifacts may also confound the interpretation of a small sample.

Larger samples also allow for low-magnification pattern recognition. A "lymphatic distribution" may be seen in non-lymphoid processes such as sarcoidosis, yet is most striking in lymphoproliferative lesions reflecting the homing of lymphoid cells to endogenous pulmonary lymphatic routes. Although malignant lymphoid processes usually obliterate underlying lung architecture, diffuse alveolar septal expansion with lymphoid cells without a beaded lymphangitic pattern tends to represent an inflammatory rather than neoplastic process.

In addition to histologic examination, immunophenotyping is routinely performed and has become indispensable in diagnosing and classifying lymphoid lesions of the lung. Immunohistochemical studies can be reliably performed on formalin-fixed, paraffin-embedded tissue, whereas flow cytometry is useful for demonstrating immunoglobulin light-chain restriction. Aberrant antigen expression by either method also allows for subclassification. Polymerase chain reaction (PCR) may be required in up to 20 percent of cases to prove clonality. Either rearrangement of the immunoglobulin heavy-chain gene joining region (J_H) or the T-cell receptor γ-chain gene (TCR-γ) can be investigated. Lastly, chromosomal abnormalities indicative of specific lymphomas such as t(14;18) translocation and bcl-2 gene rearrangement in follicular lymphoma or t(11;14) translocation and cyclin D1 (bcl-1) gene rearrangement in mantle cell lymphoma may be helpful.

Given the complex evaluation required of these lesions, it is incumbent upon the clinician to deliver the fresh tissue sample to the pathologist along with his or her concern for lymphoma. Although formalin-fixed or B5 fixed, paraffin-embedded samples may suffice for diagnosis and immunohistochemical evaluation, cell suspensions and fresh-frozen tissue are required for flow cytometry, cytogenetics, and many molecular studies.

Lastly, although clonality indicates malignancy, clonality in pulmonary lymphoid lesions may not predict clinical outcome. Many pulmonary lymphomas have long indolent courses with 10-year survival rates of more than 80 percent yet lymphoid interstitial pneumonia, a polyclonal process, is progressive with one-third of affected patients dying of end-stage pulmonary fibrosis.

REACTIVE LYMPHOID PROCESSES

Although the terminology used to describe inflammatory processes of the lung has remained relatively static over the past 20 years, immunohistochemistry and molecular genetic analysis have redefined diagnostic criteria. Processes arising from BALT include nodular lymphoid hyperplasia (NLH), follicular bronchitis/bronchiolitis (FB/FBB), diffuse lymphoid hyperplasia (DLH), and LIP. Pulmonary hyalinizing granuloma is included in this section for historical reasons

only. Although the lesions are best considered either localized or diffuse, clinicopathologic entities including Castleman's disease can manifest with either distribution.

Localized Reactive Lymphoid Processes

Nodular Lymphoid Hyperplasia

Known to previous generations of pulmonologists and hematopathologists as "pseudolymphoma," this reactive process was recognized as a form of BALT hyperplasia in the mid 1980s. Although once quite common, ancillary studies have convincingly demonstrated that most cases were actually low-grade lymphomas. Thus NLH is now considered a legitimate but exceedingly rare polymorphous nodular lymphoid lesion of the lung. Neutrophilic microabscesses and foreign body giant cells found in several reported lesions indicate that the lesion may be the result of an inflammatory stimulus. Interestingly, immunohistochemical studies have documented B-cell lymphomas of BALT within preexisting reactive masses of BALT, such that one could, in the most general sense, consider NLH a precursor lesion.

Most affected individuals are middle-aged with a nearly equal gender incidence. Patients are usually asymptomatic, although a small percentage may have autoimmune diseases such as systemic lupus erythematosus or Sjögren's syndrome, or polyclonal hypergammaglobulinemia. Lesions most often appear as solitary subpleural radiographic nodules with air bronchograms, but several nodules or localized infiltrates can be seen, the latter finding serving as a reminder that the distinction between nodular and diffuse processes is arbitrary. Up to one-third of cases feature regional lymphadenopathy.

Excised tan-white rubbery to firm nodules measure from 0.6 to 6.0 cm. Histologically, the well-demarcated lesions may feature slight extension along alveolar septa and central scarring. Normal lung parenchyma is overrun by large reactive germinal centers with well-preserved mantel zones, and lymphoepithelial lesions are not seen (Fig. 110-3). Interfollicular areas are filled with plasma cells and mature lymphocytes. The follicles are clearly reactive with a variety of cell types, mitoses, and tingible body macrophages. Regional lymph nodes often feature reactive follicular hyperplasia.

Immunohistochemical studies demonstrate a mixture of B- and T-cells. The B-cells express both κ and λ light chains, i.e., lack light chain restriction. Aberrant B-cell staining for CD5, CD23, or CD43 is not seen, and the germinal centers do not stain with BCL-2. Immunoglobulin heavy chain gene rearrangement or evidence of t(14,18) breakpoints is not observed. These ancillary findings are of the utmost importance since light microscopy alone may not differentiate NLH from an extranodal marginal zone B-cell lymphoma of MALT. The latter usually features infiltrative growth, but may have reactive follicles and polytypic plasma cells with only a focal monotypic cell population.

Surgical excision is usually curative, although a small percentage of patients develop local recurrences at the original surgical site. Neither systemic spread nor death has been reported.

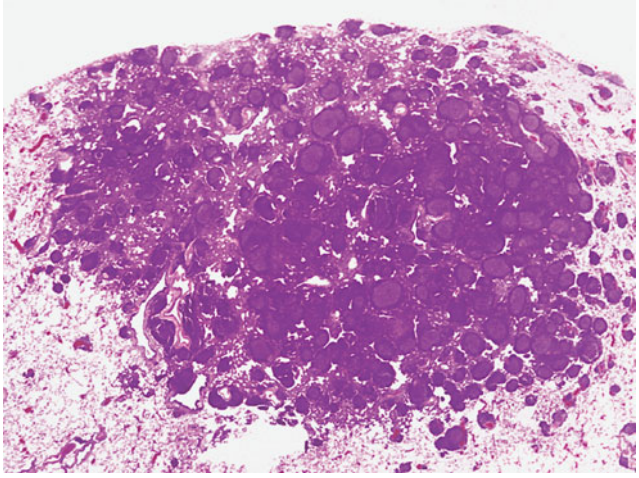


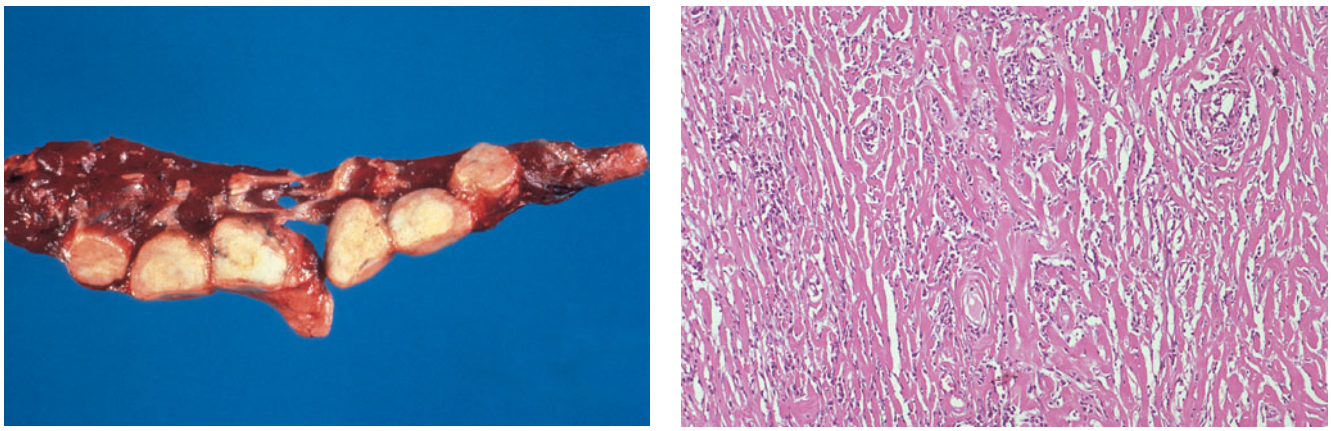
Figure 110-3 Nodular lymphoid hyperplasia. The lesion is composed of benign reactive germinal centers. Although radiographically nodular, germinal centers spill out into surrounding lung. Immunohistochemistry is required to exclude a diagnosis of malignant lymphoma. Hematoxylin and eosin, 1× original magnification.

Pulmonary Hyalinizing Granuloma

Pulmonary hyalinizing granuloma (PHG) is not a lymphoid lesion per se, but an ever-present lymphoid component allows for its discussion in a hematolymphoid chapter. This peculiar fibrosing process shares clinicopathologic and morphologic features with sclerosing mediastinitis, inflammatory pseudotumor of the orbit, Riedel thyroiditis, and idiopathic retroperitoneal fibrosis. In fact, approximately one-fourth of cases feature concomitant mediastinal or retroperitoneal disease. The etiology is unknown; however, probably represents either an autoimmune phenomenon or exaggerated host response to mycobacteria or fungi.

Age at presentation ranges from 24 to 77 years and women are affected twice as often as men. Most patients present with mild symptoms including cough, shortness of breath, fever, and fatigue but up to 25 percent of reported individuals are asymptomatic. Laboratory studies include positive antinuclear antibodies, rheumatoid factor, antineutrophil cytoplasmic antibodies, and Coombs'-positive hemolytic anemia. Skin testing usually demonstrates exposure to *Mycobacterium tuberculosis* or *Histoplasma capsulatum,* but cultures and stains for microbes are negative. Radiographs reveal less than 4.0 cm bilateral and multilobar ill-defined homogeneous nodules that resemble metastases. Unilateral and solitary cases measuring up to 15 cm have been reported. Although not common, focal central irregular calcification may suggest metastatic bone-forming neoplasms. Central cavitation is rare.

Lesions are sharply circumscribed white-tan rubbery masses composed of irregular concentric whorls of hyalinized collagen encasing vessels and airways (Fig. 110-4*A*). The center of the lesion is paucicellular, whereas peripheral thick collagen bands are separated by mature T-lymphocytes, plasma cells, fibroblasts, and occasional giant cells (Fig. 110-4*B*).



A *B*

Figure 110-4 Pulmonary hyalinizing granulomas. *A*. Multiple well-circumscribed tan firm nodules can compromise respiratory function. *B.* Pink hyalinized collagen bands encircle vessels. Scant benign lymphoid infiltrates percolate between the collagen. Hematoxylin and eosin, 10× original magnification.

Blood vessels may feature transmural inflammation without necrosis. Microscopic calcifications can be seen, but granulomas are not present despite the designation PHG. The tumoral interface with lung parenchyma features reactive germinal centers, whereas adjacent lung may feature organizing pneumonia and hyperplasia of BALT. The morphologic differential diagnosis includes rheumatoid nodule, amyloidosis, Wegener's granulomatosis, malignant lymphoma, inflammatory myofibroblastic tumor, and infections. Clinicians should not be comfortable with a diagnosis of PHG rendered on anything less than a completely removed lesion.

Pulmonary hyalinizing granuloma tends to enlarge slowly and does not recur after surgical resection. However, growth of unresected or unresectable nodules can lead to respiratory compromise.

Amyloidosis and Light-Chain Deposition Disease

Immunoglobulin light chains can accumulate in many tissues in different forms, depending on the underlying condition and particular organ cytoskeleton. Clinically recognizable disease in the lung can manifest as tracheobronchial disease, solitary or multiple nodules, or in a diffuse interstitial parenchymal pattern. Most cases of diffuse light chain deposition in the lung are part of multiorgan involvement, associated with plasma cell dyscrasia, have dismal clinical outcomes and are not discussed further in this section.

Solitary and multiple amyloidoma are seen most often in older individuals, with a mean age of 67 years. Central and solitary lesions are often incidental findings but airway or visceral pleural distortion may produce cough, hemoptysis, or pleuritic chest pain. A radiographic diagnosis can be suggested when calcification or ossification is noted (20–50 percent of the time); otherwise, the clinical impression is that of a neoplasm.

Serum or urine monoclonal proteins are found in 10 percent of patients, and this lung pathology may be associated with lymphoproliferative diseases such as benign monoclonal gammopathy of undetermined significance, Sjögren's syndrome, Crohn's disease, NLH, lymphoid interstitial pneumonia, extranodal marginal zone B-cell lymphoma of MALT, or multiple myeloma. Solitary amyloidoma without underlying blood dyscrasias probably represent a hyperimmune response to unknown antigens.

Waxy hard gritty and yellow-tan nodules measure up to 15 cm and are composed of amorphous eosinophilic hyaline material that obliterates lung parenchyma but spares many arterioles (Fig. 110-5). Lymphocytes, plasma cells, and multinucleated giant cells percolate through the amyloid, but the infiltrate is most dense at the periphery of the nodules. Calcification and ossification with secondary marrow space formation is common. Congo red staining examined by polarizing microscopy reveals lesional apple-green birefringence. Immunohistochemical studies usually demonstrate λ

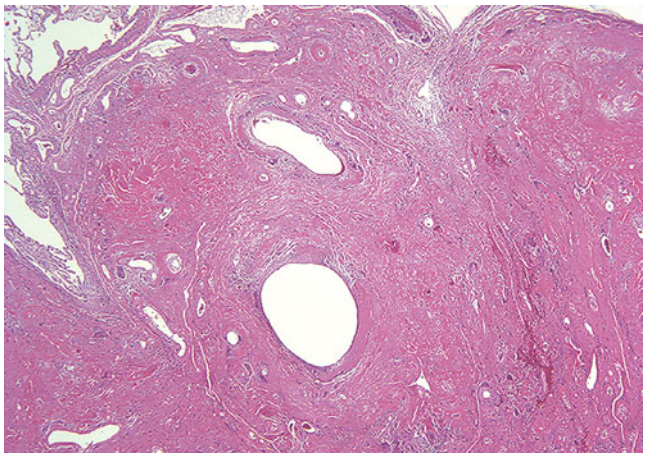


Figure 110-5 Nodular amyloidosis. Amorphous pink material replaces airspaces and overruns airways. In the absence of Congo red apple-green birefringence one should consider the possibility of nodular light chain deposition. Hematoxylin and eosin, 4× original magnification.

light-chain composition and negative immunoreactivity for amyloid A and transthyretin. Plasma cells are most often polytypic; however, small foci of monoclonal plasma cells within foci of polytypic plasma cells have been identified. Ultrastructurally, amyloid is composed of disorderly nonbranching hollow-core 8- to 10-nm fibrils. These extracellular deposits of chemically diverse proteins form a three-dimensional twisted β-pleated sheet.

Surgical excision is curative, but patients should be screened for underlying monoclonal B-cell proliferations including multiple myeloma and overt B-cell malignancies.

In stark contrast to nodular amyloidosis, nodular deposition of light chain deposition disease (LCDD) is associated with an underlying blood dyscrasia or renal failure in more than 50 percent of affected individuals. Most patients have free κ monoclonal light chains (IgG, IgA, and IgM in decreasing order) in their urine or serum. The clinical and light microscopic appearance of LCDD is similar to amyloid, and one might mistake a case lacking the characteristic Congo red staining as simply a poorly stained example of amyloid. These light chain deposits are composed of amorphous granular or globular electron dense material. One should consider this entity when dealing with a non-amyloidotic deposit given its strong association with lymphoid malignancies.

Diffuse Reactive Lymphoid Processes

Although NLH most likely represents a local response to an extrinsic stimulus and is clinically relevant owing to its radiographic appearance as a coin lesion and morphologic similarity with extranodal marginal zone B-cell lymphoma of MALT, the diffuse lymphoid hyperplasias FB/FBB and LIP represent a continuum of BALT hyperplasia often seen in patients with systemic diseases (Table 110-1). The extent of lung involvement is due in large part to host immune factors. Although thoracoscopic or open lung biopsies are required to establish these "diagnoses" and exclude other processes, including interstitial lung diseases and malignant lymphoma, morphology does not suggest etiology.

Follicular Bronchitis/Bronchiolitis and Diffuse Lymphoid Hyperplasia

Diffuse lymphoid hyperplasia *restricted* to the walls of airways and peribronchial tissue is often seen in individuals with bronchiectasis, chronic infections, and chronic obstructive pulmonary diseases, including asthma. The pattern may manifest as pulmonary disease in those with connective tissue diseases, congenital or acquired immunodeficiencies, and bone marrow transplantation, or as a hypersensitivity reaction. When the process spreads along lymphatic routes of the pulmonary lobule some prefer the designation DLH instead of FB/FBB.

Those with connective tissue disease are usually in their forties and most often suffer from rheumatoid arthritis (RA) or Sjögren's syndrome. Patients with immunodeficiency syndromes such as acquired immunodeficiency syndrome (AIDS), common variable immunodeficiency, IgA deficiency, and Evan's syndrome present in childhood, whereas a poorly defined subgroup with hypersensitivity syndromes is usually in their sixth decade of life. Those with DLH may also suffer with chronic low-grade infections such as *Mycoplasma, Chlamydia,* or Epstein-Barr virus (EBV).

Individuals present with dyspnea, cough, and fever; some may have recurrent pneumonia or weight loss. Pulmonary function tests reveal a restrictive pattern in most cases, but obstructive or normal patterns have been reported. Those with RA often have a very high rheumatoid factor on the order of 1:640 to 1:2560. Peripheral eosinophilia may be noted in those with hypersensitivity syndromes. Arterial blood gases show arterial hypoxia with a widened $AaPO_2$ gradient and hypocapnia. Chest radiographs feature bilateral diffuse reticular and nodular opacities, whereas high-resolution CT show up to 12-mm centrilobular and peribronchial nodules with or without areas of ground-glass opacity.

Gross pathology demonstrates numerous minute (1- to 2-mm) nodules adjacent to airways. Microscopically, nodular aggregates of B-cell rich lymphocytes and plasma cells with reactive germinal centers expand bronchial and/or bronchiolar submucosa and budge into and permeate overlying epithelium (Fig. 110-6). Rare T cells wander beyond the follicles into adjacent alveolar septa. Smaller airway lumens are distorted and narrowed predisposing to mucostasis and subsequent infections. Lymphoid follicles along interlobular septa and beneath the pleura represent a more diffuse form of lymphoid hyperplasia and warrant the descriptive diagnosis DLH.

Treatment with corticosteroids has variable results since this lung pathology is essentially a manifestation of an underlying disease. Those with peripheral eosinophilia are reportedly steroid responsive.

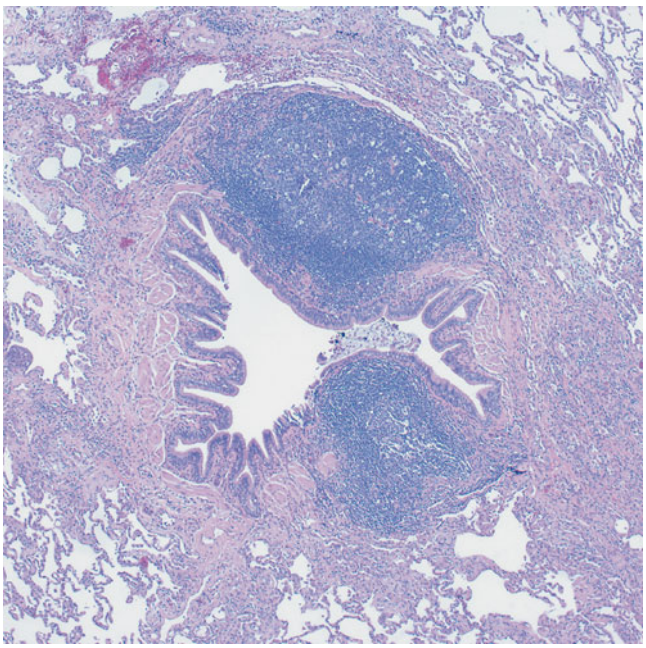
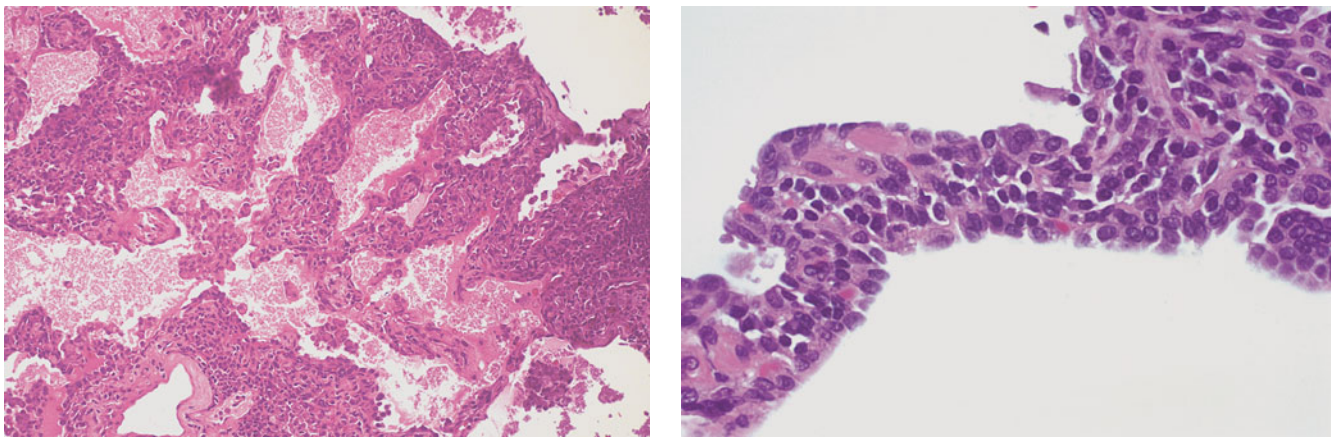


Figure 110-6 Follicular bronchitis/bronchiolitis. Reactive germinal centers expand airway submucosa and compress the lumen. Mucus accumulation often leads to infection and bronchiolectasis. Alveolar parenchyma is spared. Hematoxylin and eosin, 4× original magnification.



A *B*

Figure 110-7 Lymphocytic interstitial pneumonia. *A.* Diffuse alveolar septal expansion with lymphocytes is usually a manifestation of underlying disease. Hematoxylin and eosin, 50× original magnification. *B.* Benign lymphocytes and plasma cells interfere with gas exchange. The morphologic differential diagnosis includes *Pneumocystis* infection. Hematoxylin and eosin, 60× original magnification.

Lymphocytic Interstitial Pneumonia

Although LIP is included in the American Thoracic Society/European Respiratory Society (ATS/ERS) classification of idiopathic interstitial pneumonias, this multi-factorial but rarely idiopathic process represents the most florid BALT hyperplasia and may be difficult to differentiate from DLH and low-grade malignant lymphoma. Almost all patients with LIP have immunologic disorders, dysproteinemias, or viral infections, including EBV and, especially in children, human immunodeficiency virus (HIV). The age and sex distribution reflect these different populations. This clinicopathologic process is exceedingly rare in the HIV-negative population, in which patients are usually middle-aged Caucasian women, but represents a pulmonary manifestation of chronic graft-vs.-host disease in bone marrow transplant patients. A strong association with Sjögren's syndrome is also noted.

The clinical presentation is that of interstitial lung disease with cough and/or dyspnea in addition to symptoms and signs related to underlying diseases. More than 60 percent of patients have dysproteinemias which can precede the onset of LIP or occur any time during the clinical course. Most are hypergammaglobulinemia, yet 10 percent of cases have a hypogammaglobulinemia. A monoclonal spike on serum immunoelectrophoresis suggests a diagnosis of lymphoma rather than LIP. Pulmonary function tests reveal reduced lung volumes and lowered diffusing capacity for carbon dioxide (D_{LCO}), and hypoxia is common. Bronchoalveolar lavage (BAL) analysis shows an increased percentage of lymphocytes.

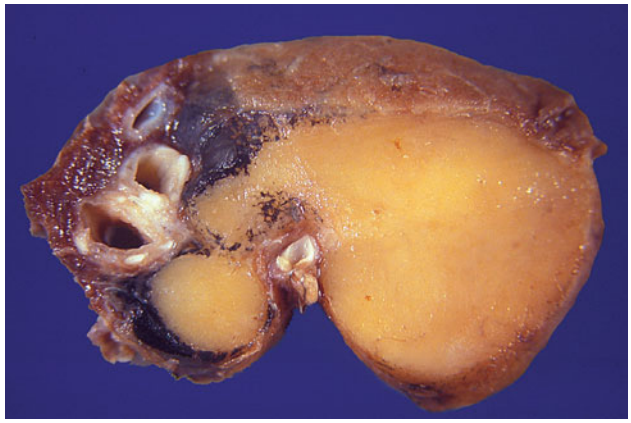
Chest radiographs feature bilateral reticular and nodular opacities, ground-glass opacities, and parenchymal consolidation with lower lung zone predilections. Computed tomography demonstrates diffuse ground-glass opacities, ill-defined centrilobular nodules, bronchovascular and interlobular thickening, and scattered less than 3.0 cm thin-walled cysts. Lymphadenopathy is more commonly seen than fibrosis and honeycomb lung.

The lungs are typically firm and tan-gray and end-stage cases feature honeycomb change with subpleural cysts. Although the radiographs and gross appearance suggest parenchymal consolidation, histologically LIP shows a diffuse prominently *interstitial* infiltrate of small lymphocytes, plasma cells, larger mononuclear cells, and histiocytes (Fig. 110-7*A*). Although these infiltrates are centered on airways, vessels, and interlobular septa, and include peribronchiolar lymphoid follicles, infiltration into alveolar septa is always present and distinguishes LIP from FB/FBB and DLH (Fig. 110-7*B*). Small non-necrotizing granulomas, reactive germinal centers, and infiltration into overlying respiratory epithelium are often seen, whereas lymphocytes frequently spill into alveolar spaces. In long-standing lesions, hyaline, collagen, or even amyloid widens the interstitium leading to honeycomb fibrosis.

The lymphoid follicles largely consist of cytologically bland B cells, whereas the interstitial lymphocytes are mostly T cells. This pattern suggests that the lung can function like a giant lymph node. Immunoglobulin heavy chain restriction or gene rearrangement is lacking. In addition to malignant lymphoma, nonspecific interstitial pneumonia-pattern interstitial lung disease (NSIP) and infections including *Pneumocystis* should be excluded.

Given the rarity of the process, controlled treatment trials have not been undertaken. Corticosteroids are the primary therapy in addition to other immunosuppressive agents, such as cyclophosphamide and chlorambucil with variable results. One-third of patients have resolution, one third stabilize and the remaining third progress. Non-responders usually die of therapy-related infections, but occasional individuals die of end-stage pulmonary fibrosis. Lymphomatous change is very unusual; older reports of such most likely represented malignant lymphomas from the start.

In patients with HIV infections or AIDS, LIP is part of a spectrum of pulmonary lymphoid proliferations with virtually identical morphologies, but differing clinical



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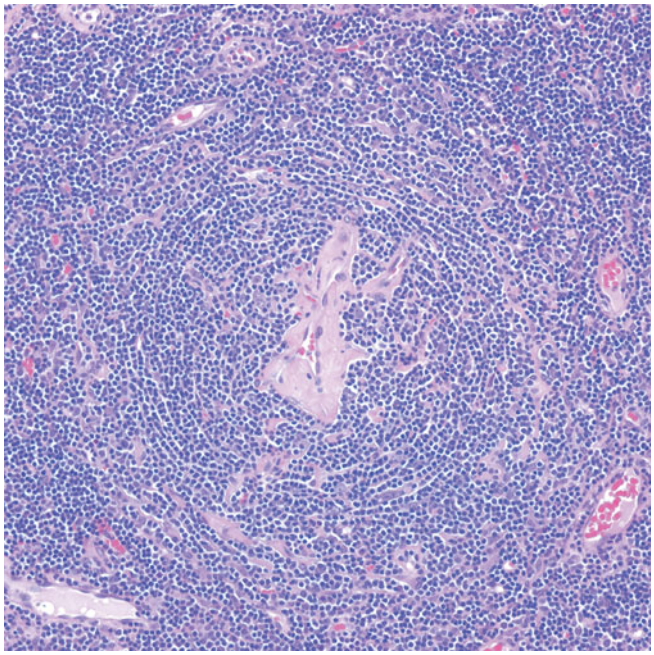


B

Figure 110-8 Solitary Castleman's disease. *A.* Involved peribronchial lymph nodes are often mistaken for pulmonary parenchymal disease. Airway and vessel distortion may cause symptoms. *B.* Solitary lymph nodes and rare lung lesions feature hyaline-vascular morphology. Small germinal centers are penetrated by hyalinized venules. The follicle mantle zone rings the burnt-out center in an onionskin pattern. Hematoxylin and eosin, 20× original magnification.

presentations. Individuals with so-called *diffuse infiltrative lymphocytosis syndrome* (DILS) featuring sicca syndrome with increased numbers of circulating CD8+ T-cells in the blood, generalized lymphadenopathy and enlarged parotid glands, are at high risk of developing LIP.

Lymphocytic interstitial pneumonia is most common is HIV-positive children and is a CDC category B indicator condition in children younger than age 13. In fact, up to 17 percent of HIV-positive children have LIP. Most present in their second or third year with lung infiltrates, failure to thrive, and increasing respiratory distress. The chest radiograph shows a diffuse micronodular or linear interstitial pattern with hilar and mediastinal widening. Therapy is uncertain, response to steroids is unpredictable, and mean survival is 33 months.

In HIV-positive adults, LIP is quite rare, and tissue sampling is required for diagnosis. Most patients present with generalized lymphadenopathy and polyclonal hypergammaglobulinemia. Bronchoalveolar lavage samples feature lymphocytes with CD8+ cells comprising up to 90 percent of the lymphoid cells. Histologically, the lymphoid infiltrates are predominantly T cells with few plasma cells. Germinal center formation is not a frequent finding. HIV-positive adults with LIP rarely die of the process, but rather of other AIDS-related diseases.

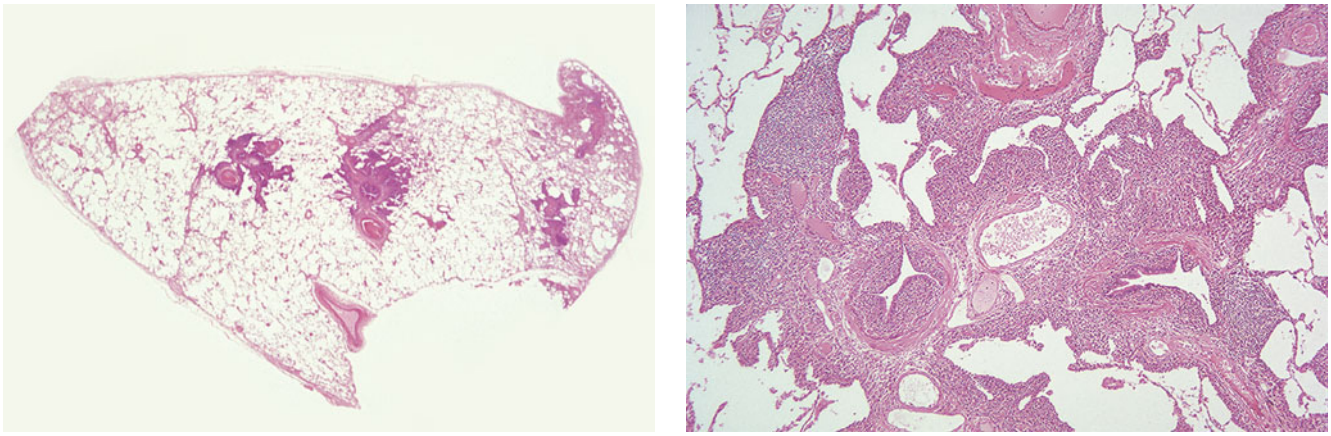
Castleman's Disease

Castleman's disease (CD), the eponymous term for angiofollicular lymph node hyperplasia, encompasses two clinically and pathologically distinct entities. Solitary lesions usually feature hyaline-vascular (HV-CD) morphology, whereas multicentric disease always has a plasma cell pattern (PC-CD).

Solitary CD is an uncommon form of lymphoid hyperplasia that usually presents as an incidental mediastinal mass in asymptomatic young to middle-aged individuals of either gender. Pleural, chest wall, and extrathoracic involvement have been reported, but pulmonary parenchymal disease is a true rarity and most reported cases likely represent nodal rather than true pulmonary disease (Fig. 110-8*A*). Solitary HV-CD lesions are usually asymptomatic or rarely cause pressure-related symptoms.

Ninety percent of solitary CDs feature hyaline-vascular morphology, whereas the remainder are the plasma cell variant. Hyaline-vascular Castleman's disease lymph nodes are enlarged and feature prominent lymphoid follicles with small atrophic germinal centers penetrated by hyalinized venules with plump endothelial cells originating in the interfollicular zone (Fig. 110-8B). Expanded mantle zones have concentric rings of lymphocytes imparting an onionskin appearance. The solitary plasma cell variant only involves lymph nodes and has not been reported in the lung. Lymph nodes are hyperplastic with enlarged germinal centers and sheets of interfollicular plasma cells. Surgical extirpation is both diagnostic and therapeutic since clinical suspicion of malignancy requires excision and excision results in the disappearance of any symptoms.

Multicentric Castleman's disease (MCCD) is best considered a virus-driven polyclonal lymphoproliferative process that shares virtually no features with solitary CD. In general, MCCD presents in the fourth and fifth decades of life but earlier in HIV-positive individuals. Signs and symptoms include fever, sweating, malaise, anemia, lymphadenopathy, hepatosplenomegaly, ascites, and pleural and pericardial effusions; all attributed to Kaposi's sarcoma herpesvirus/human herpesvirus 8 (KSHV/HHV8) induction of interleukin-6. Laboratory abnormalities include an elevated erythrocyte sedimentation rate, polyclonal hypergammaglobulinemia, and bone marrow plasmacytosis that may lead to pancytopenia. A chronic demyelinating polyneuropathy may present as part of POEMS syndrome (Crow-Fukase disease). Patients



A *B*

Figure 110-9 Multicentric Castleman's disease. *A.* The bronchocentric nature of this KSHV/HHV8-driven systemic process is apparent at scanning microscopy. Hematoxylin and eosin, 1× original magnification. *B.* The lymphoplasmacytic infiltrate is confined to the pulmonary interstitium. Honeycomb change may develop. Hematoxylin and eosin, 10× original magnification. *(Glass slides courtesy of Dr. J. English, University of British Columbia and Vancouver Hospital, Vancouver, BC.)*

may also develop non-Hodgkin's lymphoma. HIV-positive patients with MCCD have a greater likelihood of pulmonary involvement.

Histomorphology correlates with high-resolution CT scan findings of peribronchovascular interstitial thickening and centrilobular nodules (Fig. 110-9*A*). Polyclonal peribronchiolar lymphoplasmacytic infiltrates with focal extension into interlobular and alveolar septa may rarely be associated with honeycomb change (Fig. 110-9B). Polymerase chain reaction and in situ hybridization with a KSHV probe is almost always positive in lung samples including bronchoalveolar lavage fluid. Although MCCD shares many features with LIP, the plasma cell-rich nature of the infiltrate and presence of KSHV discriminate between the two.

Treatment is primarily nonsurgical but survival beyond 5 years is rare. Although splenectomy may provide brief relief from hematologic symptoms, chemotherapeutic regimens with or without immunotherapy, including anti-IL-6 and anti-CD20 monoclonal antibodies, appear to induce the longest remissions. Highly active anti-retroviral therapy is also utilized in the HIV-positive population.

MALIGNANT LYMPHOID LESIONS

Within the hematopathology field, past decades will probably be best remembered for the myriad of classification schemes and ever-changing nomenclature. Thankfully, the current WHO classification represents a consensus list of lymphoid neoplasms that appear to be distinct clinical entities. Although complex, this scheme is reproducible among trained pathologists. Diagnoses are based on clinical, morphologic, immunophenotypic, and genetic features and not simply on morphologic, immunophenotypic, or even clinical subtleties. B-cell neoplasms, T- and NK-cell neoplasms, and Hodgkin's lymphoma are subgrouped according to lineage and stage of differentiation. Within this general context one can understand the practicality of a seemingly cumbersome diagnosis, such as pulmonary extranodal marginal zone B-cell lymphoma of MALT type, given the belief that these lymphomas arise from acquired BALT.

Primary Pulmonary Non-Hodgkin's Lymphoma

Although more than half of patients with nodal lymphoma have lung involvement, primary pulmonary lymphomas comprise less than 0.5 percent of primary lung neoplasms. Furthermore, the most common primary lung lymphoma, marginal zone non-Hodgkin's lymphoma of MALT origin, represents less than 10 percent of extranodal lymphomas. Non-Hodgkin's lymphomas are considered lung primaries when the lung is the major site of disease at the time of diagnosis. Thus, up to 20 percent of these lung lymphomas involve hilar and/or mediastinal lymph nodes. Pulmonary lymphomas have a range of morphologies and clinical aggressiveness such that separating the tumors into low- and high-grade categories is a dangerous oversimplification. Although most lung non-Hodgkin's lymphomas differ from nodal lymphomas and are thought to have their origin in BALT, traditional nodal non-Hodgkin's lymphomas, such as follicle center lymphoma, mantle cell lymphoma, diffuse large B-cell lymphoma, peripheral T-cell lymphoma, and $CD30^+$ anaplastic large cell lymphoma, also present as pulmonary primaries (Table 110-2).

Extranodal Marginal Zone B-Cell Lymphoma of MALT Type

Recent recognition that most primary pulmonary lymphomas arise from BALT revolutionized our thinking about extranodal lymphoid lesions. This hypothesis suggests that some degree of lymphoid hyperplasia is a necessary precondition for the development of these lymphomas and explains

Table 110-2

Lymphoid neoplasms commonly involving the lungs

- B-cell neoplasms
  - Mature B-cell neoplasms
    - Chronic lymphocytic leukemia/small lymphocytic lymphoma
    - Lymphoplasmacytic lymphoma
    - Plasma cell myeloma
    - Extraosseous plasmacytoma
    - Extranodal marginal zone B-cell lymphoma of mucosa-associated lymphoid tissue (MALT-lymphoma)
    - Nodal marginal zone B-cell lymphoma
    - Follicular lymphoma
    - Mantle cell lymphoma
    - Diffuse large B-cell lymphoma
    - Intravascular large B-cell lymphoma
    - Burkitt lymphoma/leukemia
  - B-cell proliferations of uncertain malignant potential
    - Lymphomatoid granulomatosis
    - Post-transplant lymphoproliferative disorder
- T-cell and NK-cell neoplasms
  - Mature T-cell and NK-cell neoplasms
    - Mycosis fungoides
    - Sézary syndrome
    - Peripheral T-cell lymphoma, unspecified
    - Angioimmunoblastic T-cell lymphoma
    - Anaplastic large cell lymphoma
- Hodgkin lymphoma
  - Classical Hodgkin lymphoma
    - Nodular sclerosis classical Hodgkin lymphoma
    - Lymphocyte-rich classical Hodgkin lymphoma
    - Mixed cellularity classical Hodgkin lymphoma

the association with inflammatory and autoimmune processes as well as the common finding of reactive germinal centers in lymphomas of BALT. These relatively indolent lymphomas must be discerned from both reactive processes, including NLH and LIP as well as more aggressive lymphomas.

Patients tend to be in their fifth through seventh decades of life with a slight male preponderance. Those younger, including children, almost always have preexisting immunosuppression such as HIV infection. Most individuals are asymptomatic and are noted to have an abnormality on a routine chest radiograph; however, dyspnea, cough, hemoptysis, and shortness of breath reflect extensive disease causing airway constriction, poor compliance, and atelectasis. "B" symptoms are rare. Mean lymphocyte counts are typically normal and peripheral blood does not show a leukemic phase, whereas a monoclonal gammopathy, usually IgM, is noted in up to 30 percent of patients.

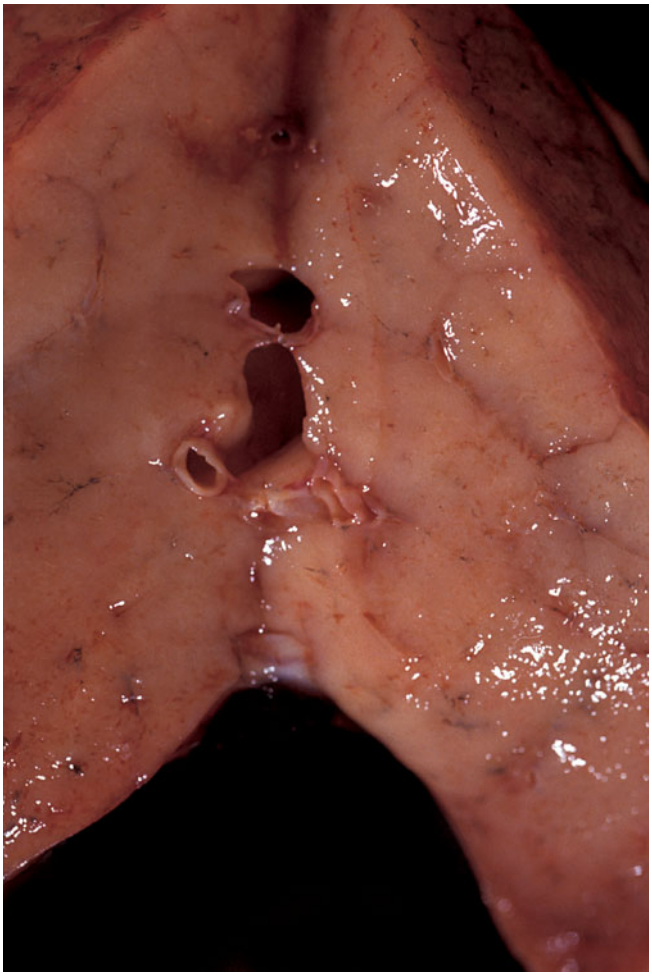
Chest radiographs and HRCT scans show either peripheral or perihilar solitary or multiple masses or alveolar opacities with air bronchograms. Cavitation, calcification, and pleural effusions are very rare, whereas hilar adenopathy is present in less than 25 percent of cases. The interval between the finding of a radiologic abnormality and definitive pathologic diagnosis has a mean of over 5 years, demonstrating the tendency of this tumor to remain localized for a long period. Thus, it is not surprising that up to 80 percent of individuals present with stage I disease.

Grossly, nodular areas vary from 2.0 to 20 cm and are tan and fleshy. Underlying lung architecture may be preserved (Fig. 110-10*A*). At low magnification these lymphomas appear as diffuse infiltrates surrounding reactive follicles with peripheral tracking along bronchovascular bundles and interlobular septa (Fig. 110-10*B* and *C*). Invasion of bronchial cartilage and visceral pleura are common. At high magnification, the small lymphoid cells may have round nuclei with little cytoplasm (centrocyte-like) or irregular nuclear contours and abundant clear cytoplasm (monocytoid differentiation) (Fig. 110-10*D*). Plasmacytic differentiation is also common. Scattered larger cells (immunoblasts) can also be seen. Malignant cells often infiltrate reactive germinal centers (follicular colonization) as well as bronchial, bronchiolar, and alveolar epithelium (lymphoepithelial lesions). This latter finding is seen in up to 90 percent of cases, but is not a useful diagnostic criterion. Secondary features include fibrosis, sclerosis, and amyloid and sarcoidal granulomas. Involved mediastinal lymph nodes feature typical morphology of nodal marginal zone B-cell non-Hodgkin's lymphoma.

When light microscopic features favor a diagnosis of this lymphoma, all available ancillary studies should be utilized to make a definitive diagnosis. The neoplastic cells are monoclonal B cells, which may be identified with CD20 or CD79a stains. Light chain restriction is present in all cases with equal κ and λ percentages; however, amplification of the immunoglobulin heavy chain gene from paraffin sections with the PCR detects monoclonality in only 60 percent of tumors. Fifty to 60 percent of marginal zone B-cell lymphoma of MALT type demonstrate t(11;18), whereas t(1;14) or trisomy 3 may also occur.

The differential diagnosis includes NLH, LIP as well as pulmonary involvement with a variety of different malignant lymphomas, such as lymphoplasmacytoid lymphoma/immunocytoma. These distinctions are of paramount importance and the surgical pathologist or hematopathologist has the necessary tools to make a correct diagnosis.

Pulmonary marginal zone B-cell lymphomas of MALT are indolent tumors with 85 to 95 percent 5- and 10-year survival rates. In several studies, median survival was not reached at 10 years. Thus, patients with resectable disease are treated with resection, but those with diffuse lung involvement may be followed and treated with chemotherapy with or without anti-CD20 antibodies. Patients with systemic symptoms at



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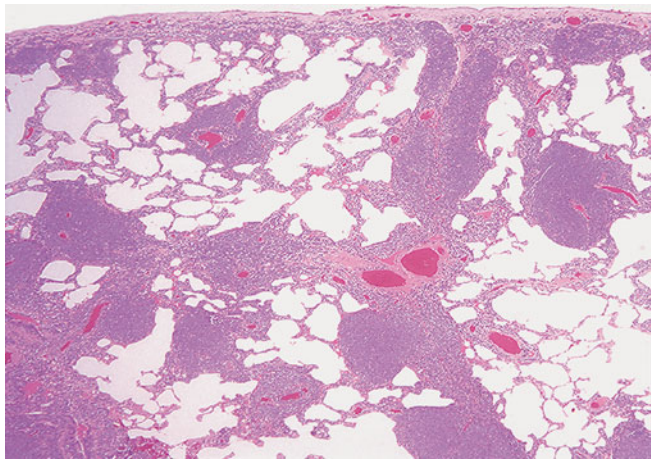

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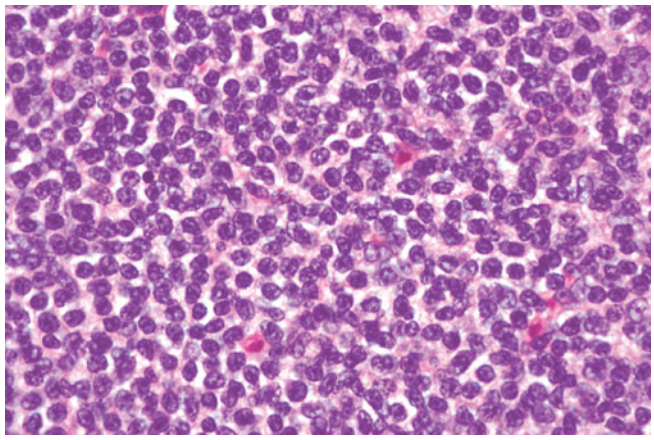

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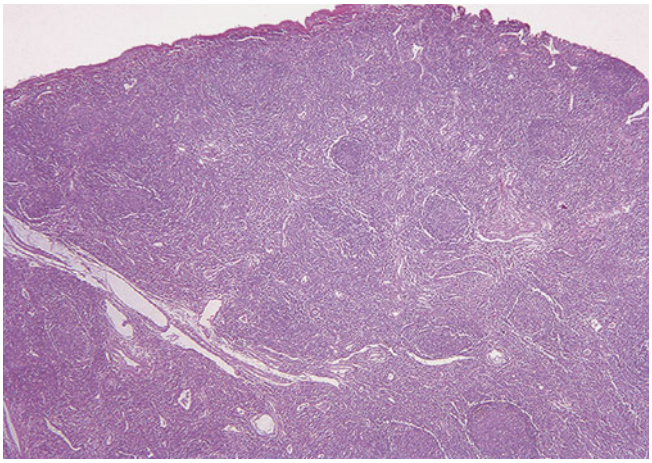


B

Figure 110-10 Extranodal marginal zone B-cell lymphoma of MALT type. *A.* Tan fleshy tumor fills alveolar spaces but preserves lobular architecture. *B.* Malignant lymphoid cells overrun lung tissue. Germinal centers are usually prominent. Hematoxylin and eosin, 4× original magnification. *C.* Malignant lymphoma often tracks along lymphatic pathways beyond the dominant mass lesion. If such a region was sampled the differential diagnosis would include diffuse lymphoid hyperplasia. Involvement of visceral pleura suggests the malignant nature of the process. Hematoxylin and eosin, 4× original magnification. *D.* Most pulmonary marginal zone B-cell lymphomas of MALT type are composed of small monotonous round (centrocyte-like) B-lymphocytes. Hematoxylin and eosin, 40× original magnification.

presentation may have a worse prognosis. Lymphoma recurs in the lungs or in other MALT sites such as salivary gland, orbital, or gastrointestinal tract in almost half of patients, and up to 15 percent of patients experience transformation of their lymphomas into more aggressive and usually deadly forms including diffuse large B-cell non-Hodgkin's lymphoma (DLBCL).

Other Non-Hodgkin's Lymphomas

Non-Hodgkin's lymphomas other than extranodal marginal zone B-cell lymphomas originating in the lung are very rare and comprise less than one-fourth of primary lung lymphomas. These tumors represent a heterogeneous group consisting primarily of DLBCL with fewer cases of follicle center cell lymphoma, and rare examples of mantle cell lymphoma,

lymphoplasmacytic lymphoma/immunocytoma, Burkitt's lymphoma, anaplastic large cell lymphoma, and peripheral T-cell lymphomas. The latter almost always represent secondary involvement by systemic lymphoma rather than lung primaries. Rare AIDS-related primary pulmonary B- and T-cell lymphomas related to severe immunodeficiency containing EBV RNA have also been described. Of note, only primary pulmonary DLBCL appears to arise from BALT and is also weakly associated with both fibrosing interstitial lung diseases and collagen vascular diseases.

Although each lymphoma subtype has particular morphologic features, primary pulmonary DLBCL is best characterized. Patients are usually adults but younger individuals with immunodeficiency states may be affected. Unlike those with extranodal marginal zone B-cell lymphomas of MALT, most patients present with shortness of breath, fever, chest pain and hemoptysis and often develop extrapulmonary lesions and paraneoplastic syndromes shortly after diagnosis. Restrictive physiology is often observed while imaging studies reveal solitary or multifocal nodules or infiltrates measuring at least 3.0 cm. Cavitation and pleural effusions are frequently seen and regional lymph nodes are involved in up to 50 percent of cases.

Resected lesions are white-tan and fleshy with areas of necrosis. Histologically, largely necrotic nodules or striking lymphangitic growth with parenchymal destruction are accompanied by inflammatory infiltrates. Infarction is not uncommon. Sheets of malignant mitotically active B cells are two to four times the size of normal lymphocytes (Fig. 110-11). Vascular infiltration and pleural involvement are common features and airway destruction leads to postobstructive pneumonia. Residual BALT hyperplasia and low-grade marginal zone lymphoma may be seen at the periphery of the mass.

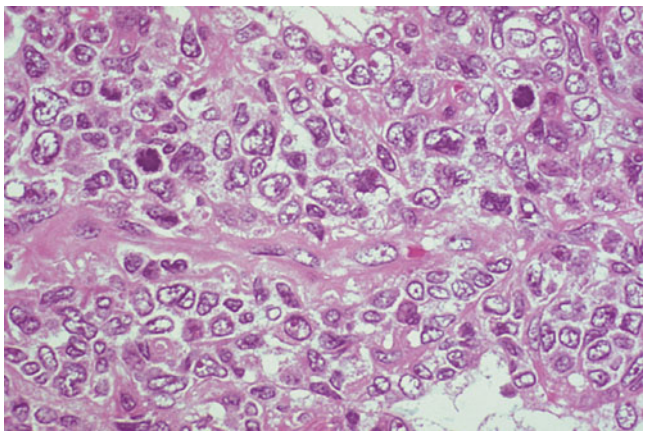


Figure 110-11 Diffuse large B-cell lymphoma. This lymphoma is composed of large cells with irregular nuclear features and significant mitotic activity. The B-cell phenotype is demonstrated by flow cytometry or immunohistochemistry. This lymphoma not only looks more aggressive than marginal zone B-cell lymphoma of MALT type, but also follows an aggressive clinical course. Hematoxylin and eosin, 40× original magnification.

Neoplastic cells express pan-B antigens CD20 and CD79a. Monotypic immunoglobulin light chain expression can be demonstrated with frozen tissue samples.

Although the cytologic atypia and necrosis in these lymphomas make it easy to distinguish them from benign lymphoid processes and extranodal marginal zone lymphomas, confusion with poorly differentiated carcinomas or Hodgkin's lymphoma can occur.

Localized DLBCL is potentially curable with surgery and Adriamycin-based chemotherapy, but 5-year survival rates do not surpass 60 percent and the median survival is only 3 years. Only half of HIV-positive patients achieve clinical remission and those remissions usually last only 6 months.

Lymphomatoid Granulomatosis

Lymphomatoid granulomatosis (LYG) is one of the most confusing lesions in all of human disease. The original investigators were not certain whether this lung-based process, which also involves the central nervous system, skin and other organs, was a malignant lymphoma or a variant of Wegener's granulomatosis. Since that time erroneous ideas concerning its etiology and histogenesis have muddled the entity even further. We now recognize LYG as an EBV-driven B-cell lymphoproliferative disorder arising in individuals with either obvious or clinically undetected defects in cell-mediated and perhaps also humoral immunity. In many ways, LYG is similar to posttransplant lymphoproliferative disorders (PTLD) with a spectrum of clinical behaviors.

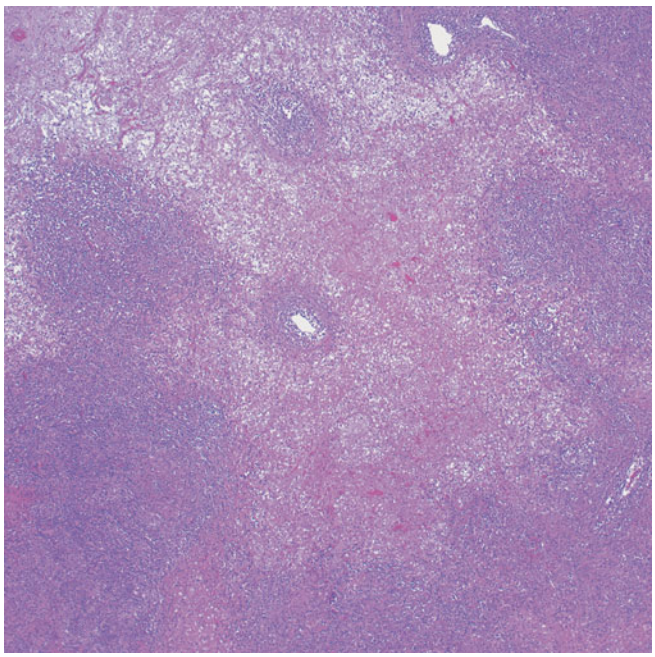
Although quite rare, LYG has characteristic clinical features. Patients usually present in the fifth or sixth decades of life but children and the elderly can be strickened. Men are affected two to three times as often as women. Dyspnea, cough, chest pain along with fever, and malaise and weight loss are the most common presenting complaints and up to 40 percent of patients also have skin nodules, ulcers, rashes, peripheral neuropathies, or other symptoms referable to central nervous system involvement. Gastrointestinal, musculoskeletal, or nodal involvement is uncommon, whereas a diagnosis following resection of an asymptomatic solitary lung nodule is very rare.

Laboratory findings can include either leukocytosis or leukopenia and elevated serum IgG or IgM. Cerebrospinal fluid may have abnormal protein and glucose levels. Serologies for autoimmune diseases are negative but evidence of EBV infection has been reported.

Radiographically, up to 70 percent of patients show bilateral middle and lower zone lung nodules as large as 10 cm. Coalescence and cavitation are often seen. Nonspecific reticulonodular infiltrates as well as solitary infiltrates or masses are less common findings. Pleural effusion is present in up to one-third of patients.

Macroscopically the lungs and other affected organs contain yellow-white well-demarcated masses with either solid or granular textures (Fig. 110-12*A*). Microscopically LYG is composed of nodular lymphoid infiltrates centered

A



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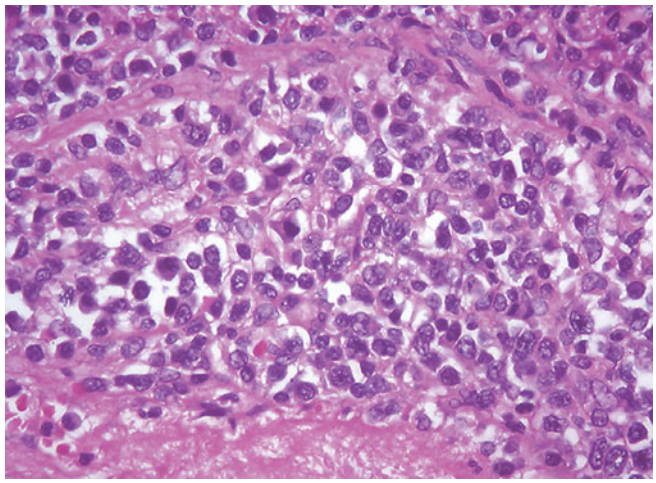


C

Figure 110-12 Lymphomatoid granulomatosis. *A.* Most lesions are well circumscribed with central necrosis. However, this macroscopic appearance is not pathognomonic for LYG. *B.* Lung parenchyma often features irregular areas of necrosis with preserved vessels. Hematoxylin and eosin, 4× original magnification. *C.* The lymphoid infiltrate expands a vessel wall. Morphology does not suggest lymphoma yet cytologic atypia is noted. This grade II lesion was treated with combination chemotherapy but clinical remission was not achieved. Hematoxylin and eosin, 60× original magnification.

on lymphatic routes including bronchovascular bundles. As the lesions increase in size, blood vessels are encircled, infiltrated, and perhaps occluded but not obliterated by the process (Fig. 110-12*B*). The infiltrate and nodules are composed of a heterogeneous population of small, intermediate and large lymphocytes (Fig. 110-12*C*). The large cells are in the minority but can be very atypical or pleomorphic, stain as B cells ($CD20^+$ and $CD79a^+$) and are EBV-infected according to PCR and in situ hybridization studies. CD30 positivity is also noted in infected monoclonal cells. The smaller and more numerous cells stain as T cells ($CD3^+$, $CD4^+$, and/or $CD8^+$). Secondary features include interstitial and consolidative pneumonia. Despite its designation, granulomas are not seen.

Depending on the relative number of EBV-infected cells one observes more necrosis and a more aggressive clinical course. The grading system is based on the number of atypical large EBV-infected cells (Table 110-3). Grade 1 lesions probably include cases of so-called *benign lymphocytic angiitis* and *granulomatosis,* whereas grade 3 proliferations are alternatively considered a subtype of diffuse large cell lymphoma (DLCL). Given the complex histologic features of LYG and need to identify scattered large cells in an inflammatory mass, diagnosis and accurate grading almost always requires a surgical lung biopsy.

Although similar to T-cell–rich B-cell lymphomas such as angiocentric nasal NK/T-cell lymphoma and PTLDs, the former entity lacks EBV-infected monoclonal B cells and the latter lacks the angiocentricity of LYG. Other diagnostic considerations include Hodgkin's lymphoma and necrotizing inflammatory conditions.

The natural history is variable and clinical behavior ranges from indolent to aggressive. Spontaneous remissions and therapy-induced remissions occur but more than

Table 110-3

Histologic and *In Situ* Hybridization Grading of Lymphomatoid Granulomatosis

Grade 1
Angiocentric polymorphous infiltrate without atypia or necrosis
Rare Epstein-Barr virus infected cells (<5 per high-power (40×) field)
Grade 2
Angiocentric predominantly polymorphous infiltrate with occasional large or atypical lymphoid cells and parenchymal necrosis
Scattered EBV-infected cells (5–20 per high-power (40×) field)
Grade 3
Angiocentric and destructive monomorphous infiltrate with widespread necrosis
Sheets of EBV-infected cells (>20 per high-power (40×) field)

60 percent of patients die with a median survival of 14 months. Although most organ systems can be involved, lymphoid tissue including the spleen is only involved in the 25 percent of patients who develop grade 3 lesions. Hemophagocytic syndrome is related to systemic EBV infection rather than bone marrow involvement. Histologic grade correlates with outcome. Most patients have either grade 1 or 2 disease but only one-third of those with grade 1 lesions progress to grade 3/malignant lymphoma, whereas two-third of those with grade 2 lesions develop grade 3/malignant lymphoma. Asymptomatic patients or those with minimal disease and grade 1 or 2 histology may be observed; those with symptomatic grade 1 or 2 histology require treatment with corticosteroids or single or multiagent chemotherapy. Clinically aggressive grade 1 and 2 and all grade 3 lesions are treated as DLCL with combination chemotherapy. Therapies targeting EBV-bearing B-cells (interferon-$\alpha 2\beta$) or reactive T cells (i.e., cyclosporine) as well as stem cell transplantation, have been reported.

Intravascular Lymphomatosis

Intravascular lymphomatosis (IVL) is a rare non-Hodgkin's lymphoma characterized by lymphoma cells only in the lumina of small vessels, particularly capillaries. Although IVL most often manifests with neurologic or dermatologic manifestations, individuals in their fifth to seventh decades of life may complain of fever, dyspnea, cough, chest pain, or present with respiratory failure. Hypoxia and decreased diffusion capacity are seen and radiographs demonstrate reticulonodular infiltrates, whereas CT scans can show patchy ground glass opacities.

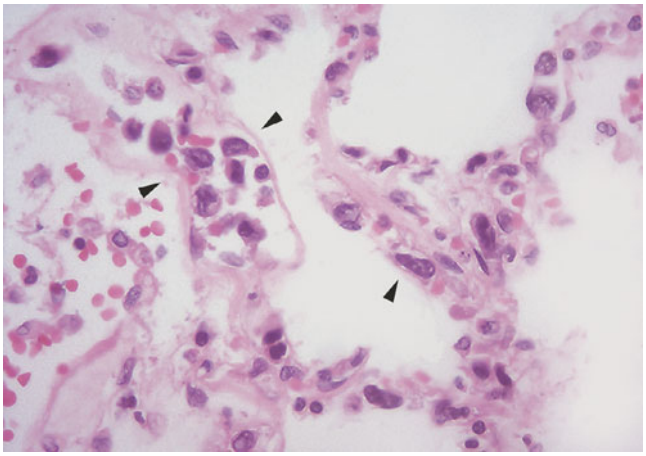


Figure 110-13 Intravascular large B-cell lymphoma. Malignant lymphoid cells remain confined to vascular channels (arrowheads). Hematoxylin and eosin, 60× original magnification.

Low magnification histology demonstrates a diffuse interstitial process resembling cellular interstitial pneumonia yet higher magnification reveals large cells with prominent nucleoli confined to arteries, veins, lymphatics, and especially capillaries (Fig. 110-13). Fibrin thrombi may be noted.

Although most reported cases of IVL are B-cell lymphoma ($CD19^+$, $CD20^+$, $CD79a^+$) and the WHO classifies the process as intravascular large B-cell lymphoma, a T-cell phenotype associated with EBV has been described. Although the intravascular nature of the lymphoma is not understood, absence of adhesion molecules CD54 (I-CAM-1) and CD29 ($\beta_1$integrin) may prevent neoplastic cell–endothelial cell interactions and extravascular spread.

Half of cases are diagnosed at autopsy yet a diagnosis is possible on thoracoscopic and even transbronchial biopsies. Immunohistochemical stains are necessary to discern IVL from metastatic carcinoma, malignant melanoma, and leukemia. Although prognosis is poor, complete remission and long-term survival can be achieved with prompt diagnosis and aggressive combination chemotherapy.

Hodgkin's Lymphoma

Primary pulmonary HL is very rare. This is in part due to the requirement that, unlike non-Hodgkin's lymphoma, regional lymph nodes be free of disease in order to qualify as a lung primary.

Primary pulmonary HL shows the usual bimodal age distribution of systemic HL but the age is slightly older with a mean of 42 years. Women outnumber men by 1.5 to 1. Symptoms include cough, dyspnea, hemoptysis, and chest pain and one-third of patients experience B symptoms. Radiographs demonstrate reticulonodular and linear infiltrates or multiple nodular lesions. Solitary lesions and consolidation are also seen. Upper lobe disease is most common, whereas atelectasis and cavitation are frequently observed.

Tumors have a multinodular white firm macroscopic appearance and histologically grow along lymphatic routes in the lung. As small nodules coalesce, central necrosis becomes apparent. Visceral pleura is often infiltrated while bronchial involvement can result in plaque-like nodules, polypoid endobronchial masses, or airway collapse. Within the WHO histological classification of HL, one cannot be certain if nodular lymphocyte predominant HL and the four subtypes of classical Hodgkin's lymphoma all involve the lung. Nodular sclerosis and mixed cellularity subtypes of HL are more commonly seen than lymphocyte rich, whereas lymphocyte depleted has not been reported in primary pulmonary HL. Diagnosis requires the identification of Reed-Sternberg cells or variants (usually $CD15^+$ or $CD30^+$) within the appropriate inflammatory background. Central necrosis, granulomatous inflammation, and vascular permeation by the polymorphous infiltrate are commonly seen.

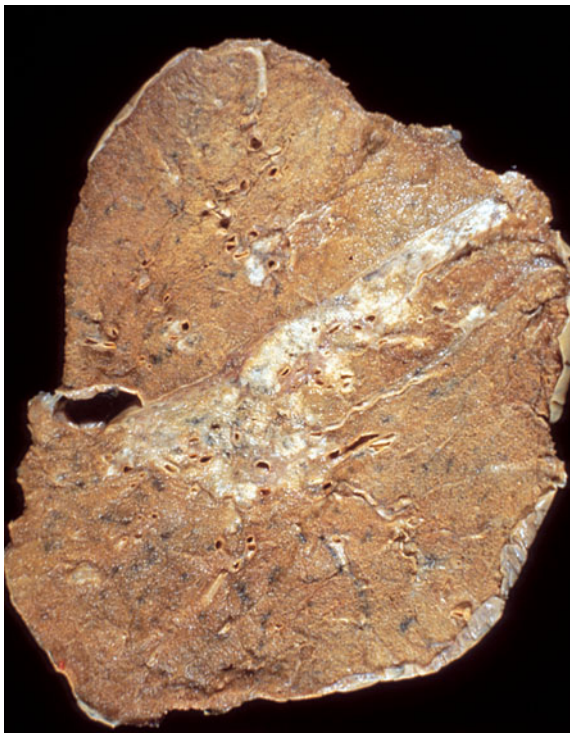
The morphologic differential diagnosis includes inflammatory and malignant processes. Infections, Wegener's granulomatosis, and sarcoidosis as well as poorly differentiated carcinomas, LYG, and a variety of non-Hodgkin's lymphomas must be considered. The non-neoplastic entities can be discerned histologically, whereas the neoplasms require at least immunohistochemical studies.

The prognosis for patients with primary pulmonary HL is variable. Although individuals with all types and stages of HL have a 5-year survival of almost 75 percent, small patient group studies suggest only a 50 percent 2-year disease-free period for this subgroup of clinical stage IE disease. Relapses occur in the lung and elsewhere and appear associated with multiple lobe involvement, pleural invasion, cavitation, and presence of B symptoms.

Secondary Lymphoma Involving the Lung

Secondary lung involvement with nodal and extranodal lymphomas is significantly more common than primary pulmonary lymphoma. Lung involvement with common nodal and disseminated lymphomas surpasses 50 percent during life and at autopsy. Clinical and radiologic features may suggest an infectious process, but tissue samples demonstrate a lymphangitic pattern of disease (Fig. 110-14A). Patchy infiltrates and endobronchial masses are, however, not uncommon.

Morphology does not usually allow for distinction between primary and secondary lung disease. For example, pulmonary involvement with nodal marginal zone lymphoma is indistinguishable from primary pulmonary extranodal B-cell lymphoma of MALT. Thus, clinical history and review of previous diagnostic material are necessary for proper diagnosis. Secondary lymphomas involving the lung can also transform to more aggressive histology with increased numbers of large



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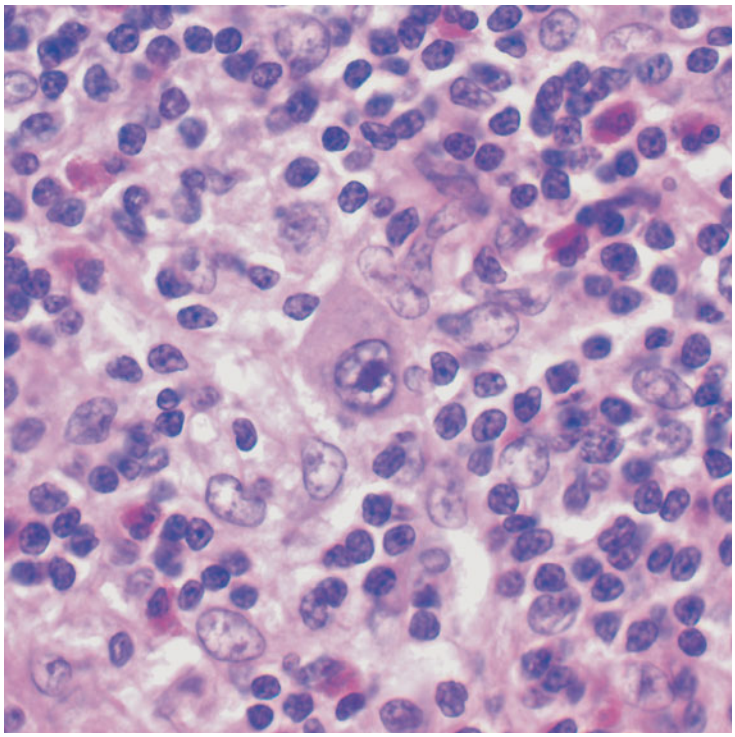


B

Figure 110-14 Lung involvement with Hodgkin's lymphoma. *A.* The striking lymphangitic distribution of this dense white tumor indicates secondary pulmonary involvement. *B.* A uninucleate Reed-Sternberg cell with typical prominent nucleolus (center) is surrounded by lymphocytes and eosinophils. Hematoxylin and eosin, 60× original magnification.

cells. This phenomenon is not infrequently seen in samples from patients with CLL/SLL.

Several particular systemic lymphoproliferative disorders that may present with significant lung pathology warrant additional discussion.

Mycosis fungoides may involve the lung after dissemination of cutaneous disease or as part of the Sézary syndrome and is the second most common extracutaneous site after lymph nodes. Clinical and radiographic features often mimic pneumonia or even acute respiratory distress syndrome with nodular and diffuse disease. Tissue samples demonstrate airspace and interstitial infiltrates along lymphatic routes in addition to occasional granulomas, extensive vascular infiltration, and necrosis. Cells range from small with irregular twisted nuclei to large with prominent nucleoli.

The lungs are also frequently involved with angioimmunoblastic T-cell lymphoma. Although originally described as a reactive process (angioimmunoblastic lymphadenopathy with dysproteinemia), this malignant disease in the lung can be mistaken for interstitial pneumonia. However, the lymphatic distribution of atypical "clear" cells with indented nuclei admixed with immunoblasts, plasma cells, and histiocytes should be distinguished from HL.

Pulmonary involvement with HL is recognized at presentation in more than 10 percent of patients with mediastinal or extrathoracic disease, 50 percent of patients have relapses in the lung and almost 60 percent are noted to have pulmonary involvement at autopsy. Unlike primary pulmonary HL, secondary involvement rarely manifests with large nodules, whereas infiltrates often surround blood vessels and may feature greater numbers of atypical cells and fewer inflammatory cells than in primary HL (Fig. 110-14*B*).

Plasmacytoma/Multiple Myeloma

Extraosseous plasmacytomas most often affect the upper respiratory tract. Primary plasmacytomas of the lung are exceedingly rare; patients are usually in their fifth and sixth decades of life and asymptomatic. Cough, dyspnea, and hemoptysis have been reported. Unlike multiple myeloma, individuals may lack a serum M-protein or Bence Jones light chains in the urine. Radiographs demonstrate a midlung or hilar solitary mass, but peripheral lesions amenable to transthoracic needle aspiration biopsy occur.

Tumors range from 2.5 to 8.0 cm and most often involve a major bronchus with occasional involvement of regional lymph nodes. Histologically, sheets of plasma cells including binucleate forms overrun lung parenchyma and bronchial cartilage (Fig. 110-15). Fibrous bands course through the tumor and amyloid or light chain may be associated with the neoplasm. κ and λ light chains as well as IgG, IgA, and IgD can be expressed immunohistochemically or produced as M-proteins by the tumor. The pathologist must discriminate between plasmacytoma and marginal zone lymphoma with plasmacytoid features as well as inflammatory myofibroblastic tumor.

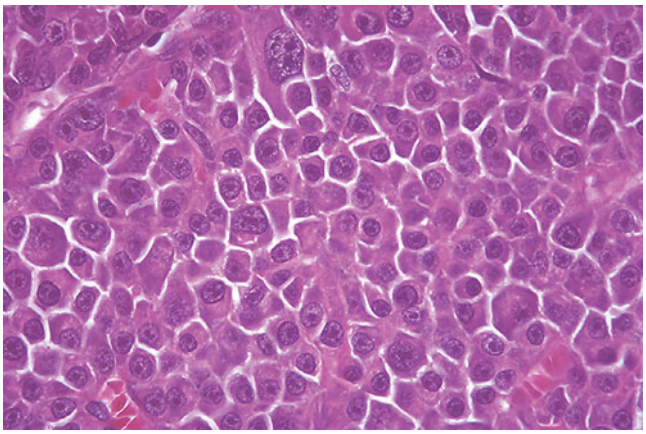


Figure 110-15 Plasmacytoma of lung. Sheets of plasma cells usually form a solitary nodule. Cytologic atypia is often seen. Since this lesion is less common than pulmonary involvement with multiple myeloma, clinical correlation is always required. Hematoxylin and eosin, 40× original magnification.

Although the natural history of this rare tumor is not well delineated, it appears that cases are either cured with either surgical excision or radiation therapy, or evolve into multiple myeloma. The presence or absence and amount of M protein may mirror tumor burden and clinical course while an increase or decrease in levels may be associated with recurrence or successful treatment. An overall 5-year survival of 40 percent has been reported.

Pulmonary involvement with multiple myeloma is more common than pulmonary plasmacytoma. Lung involvement may be nodular or have a diffuse lymphangitic pattern. Nodular or diffuse amyloid deposition may accompany the neoplastic cells. Intracytoplasmic crystalline casts similar to those seen in the kidney are occasionally observed.

POSTTRANSPLANT LYMPHOPROLIFERATIVE DISORDER

PTLD is a lymphoid proliferation or lymphoma that develops as a consequence of immunosuppression in solid organ or bone marrow allograft recipients. Eighty percent of cases are associated with EBV infection in the setting of decreased T-cell immune surveillance; the etiology of EBV negative PTLD is unknown. Most cases are of host origin while approximately 10 percent of cases are of donor origin. Those of donor origin are more common in lung and heart-lung transplantation patients due to the presence of donor BALT in the lungs.

Allograft and extranodal MALT sites including Waldeyer's ring, lung and gastrointestinal tract, are usually involved and incidence varies based on type of allograft and immunosuppression regimen. One percent of renal transplant patients but almost 20 percent of lung transplant recipients are stricken. In solid organ transplants

treated with azathioprine PTLD develops after years but those treated with cyclosporine A often present within weeks of transplantation.

Approximately 10 percent of PTLDs manifest with pulmonary lesions. Individuals may be asymptomatic or present with constitutional symptoms. In lung transplant patients, organ failure may occur. Radiographs demonstrate nodular or diffuse reticulonodular infiltrates, solitary nodules, or multiple mass lesions with or without regional lymphadenopathy.

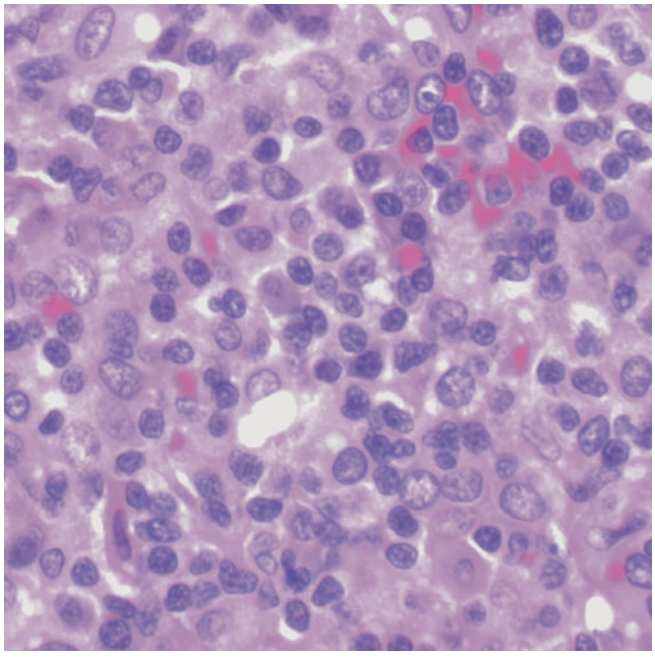
Morphologic categories of PTLD include early lesions, polymorphic PTLD, monomorphic PTLD, Hodgkin's lymphoma, and Hodgkin's lymphoma-like PTLD (Table 110-4). Most proliferations are B-cell processes, although T-cell lesions are seen. Early lesions usually involve lymph nodes and Waldeyer's ring rather than lung; lymphoid tissue is hyperplastic with either sheets of plasma cells or paracortical expansion with immunoblasts. The latter resembles infectious mononucleosis morphology. Polymorphic and polyclonal proliferations feature mixtures of small lymphocytes, plasma cells, and immunoblasts and may progress to monomorphic monoclonal proliferations with sheets of large transformed cells resembling aggressive lymphoma (Figs. 110-16*A* and *B*). In fact, the monomorphic monoclonal proliferations are subclassified according to lymphoma classification. Hodgkin's lymphoma and Hodgkin's lymphoma-like PTLD are very rare and purportedly similar to methotrexate-related HL. The morphologic findings may be difficult to differentiate from allograft rejection; immunophenotyping is essential, whereas molecular genetic testing for clonality and in situ hybridization studies for EBV may be necessary. For these reasons, tissue procurement rather than fine-needle aspiration biopsy is preferred for diagnosis.

Treatment starts with reductions in immunosuppression despite the risk of losing the allograft. Early lesions

Table 110-4

Posttransplant Lymphoproliferative Disorders

Early lesions
Reactive plasmacytic hyperplasia
Infectious mononucleosis-like
Polymorphic PTLD
Monomorphic PTLD
B-cell neoplasms
Diffuse large B-cell lymphoma
Burkitt's/Burkitt-like lymphoma
Plasma cell myeloma
Plasmacytoma-like lesions
T-cell neoplasms
Peripheral T-cell lymphoma, unspecified
Hodgkin's lymphoma and Hodgkin's lymphoma-like PTLD



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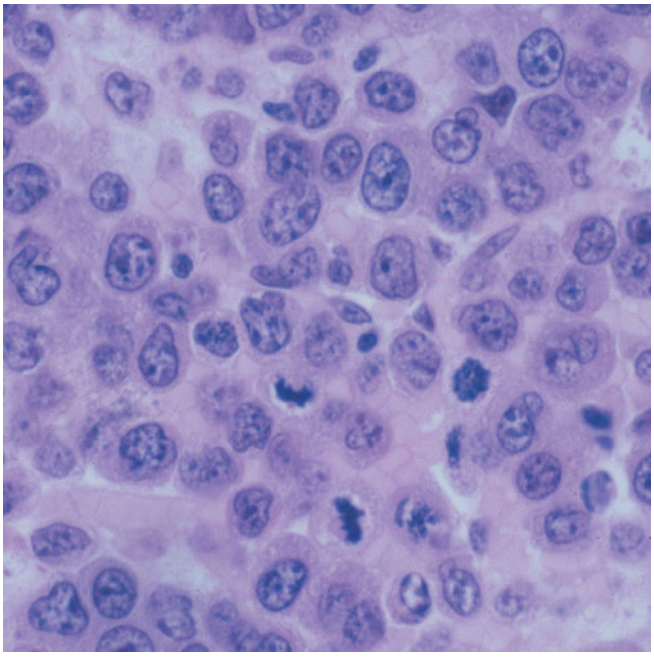

B

Figure 110-16 Posttransplant lymphoproliferative disorder. *A.* This polymorphic lesion features small and large lymphocytes admixed with plasma cells. Hematoxylin and eosin, 60× original magnification. *B.* Monomorphic lesions are often comprised of large atypical cells with numerous mitoses. According to the WHO scheme this lesion is classified as a diffuse large B-cell lymphoma. Hematoxylin and eosin, 60× original magnification. *(Photomicrograph courtesy of Dr. A. Chadburn, Weill Medical College of Cornell University, New York, NY.)*

usually regress while only a proportion of polymorphic and monomorphic PTLD respond. Neither morphology nor molecular characterization of the PTLD can predict response to reduction in immunosuppression. Non-responders are then treated with cytotoxic chemotherapy and perhaps radiation therapy. Anti-CD20 antibody therapy plays a limited role. Although early diagnosis with prompt reduction of immunosuppression followed by cautious chemotherapy administration has improved the prognosis of patients with PTLD, mortality rates in solid organ transplants and bone marrow transplant recipients are 60 and 80 percent, respectively.

LEUKEMIC INFILTRATES INVOLVING THE LUNG

Significant lung involvement with leukemia affects less than 10 percent of individuals but secondary effects of leukemia or therapy including infections, alveolar proteinosis, leukemic cell lysis pneumopathy, hemorrhage, and chemotherapy toxicity afflict most leukemia patients. Leukemic lung infiltration is often found at autopsy or as an "incidental" finding in a tissue sample demonstrating an infectious process, and only causes symptoms in those patients with high (40 percent or greater) blast counts.

Cough, dyspnea, and hemoptysis may precede the leukemia diagnosis for months or develop suddenly. Bronchiolar involvement producing asthma-like symptoms has been reported. Radiographic findings run the gamut from localized to diffuse infiltrates.

All leukemia subtypes can involve the lung but acute myeloid leukemia, acute lymphoblastic leukemia, and CLL/SLL are most often seen. Infiltrates are predominantly restricted to the pulmonary lymphatic distribution and rarely form micronodules (Fig. 110-17). Bronchiolocentricity may be mistaken for bronchiolitis. Infiltrates can be subtle and chloroacetate esterase and myeloperoxidase stains may be useful in diagnosis and subtyping. Leukemic counts greater than 200,000/μm cause capillary leukostasis with resultant thrombosis. Pulmonary edema, infarct, and diffuse alveolar damage may result.

Patients with agnogenic myeloid metaplasia (myelofibrosis) occasionally have pulmonary manifestations. Diffuse and nodular foci of extramedullary hematopoiesis usually follow lymphatic routes and associated fibrous tissue can form large nodules. Interstitial fibrosis can result and may be mistaken for a primary chronic fibrosing interstitial pneumonia.

In addition to acute complications of leukemia, patients undergoing bone marrow transplantation for leukemia may experience a variety of pulmonary complications including pulmonary edema, diffuse alveolar damage/acute respiratory distress syndrome, bacterial, fungal, and viral infections and graft-vs.-host disease. Acute graft-v.-host (GVH) rarely involves the lung but lymphocytic bronchiolitis, LIP, constrictive bronchiolitis, and pulmonary fibrosis are all considered within the spectrum of chronic pulmonary GVH. However, these manifestations may represent cytotoxic chemotherapeutic effect.

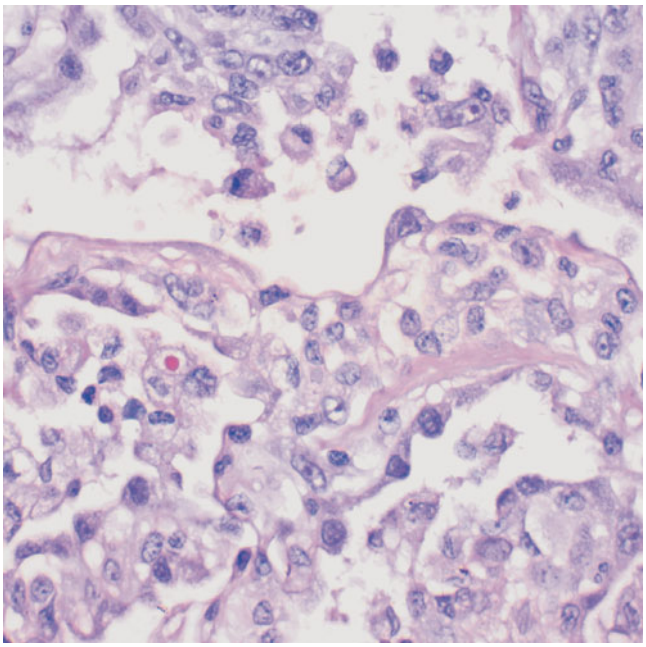

Figure 110-17 Leukemic infiltrate in the lung. Primitive mononuclear cells with clumped chromatin (blasts) expand alveolar septa and spill into air spaces. Although an infectious process was suspected clinically, acute myeloid leukemia represented the only lung pathology. Hematoxylin and eosin, 60× original magnification.

PLEURAL LYMPHOMAS

Disseminated lymphomas frequently affect the visceral pleura and pleural cavity. Non-Hodgkin's lymphomas often invade the visceral pleura while HL often causes pleural effusions due to mediastinal lymph node involvement and secondary lymphatic obstruction. Leukemia and multiple myeloma rarely manifest with pleural involvement. Diagnosis can be established with effusion cytology and parietal pleural biopsies are rarely required.

Primary pleural lymphomas are much less common and only two have been described; primary effusion lymphoma (PEL) and pyothorax-associated lymphoma (PAL). Both are associated with EBV but similarities end there.

Primary Effusion Lymphoma

Primary effusion lymphoma is a rare large B-cell lymphoma that presents as either a pleural, pericardial or peritoneal cavity effusion without a detectable tumor mass. All cases are associated with KSHV/HHV8 and most occur in young to middle-aged HIV-positive homosexual males. Rare cases have been reported in supposedly immunocompetent elderly individuals and HIV-negative cardiac transplant patients. Some

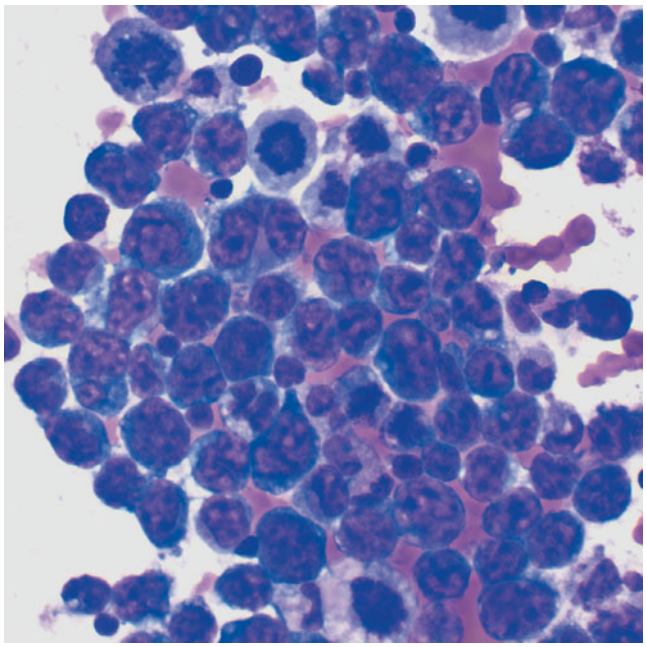

Figure 110-18 Primary effusion lymphoma. This pleural cytology demonstrates a large cluster of pleomorphic cells. This KSHV/HHV8 associated lymphoma is of B-cell origin despite the absence of immunohistochemical staining for B-cell markers. Modified Wright-Giemsa, 60× original magnification.

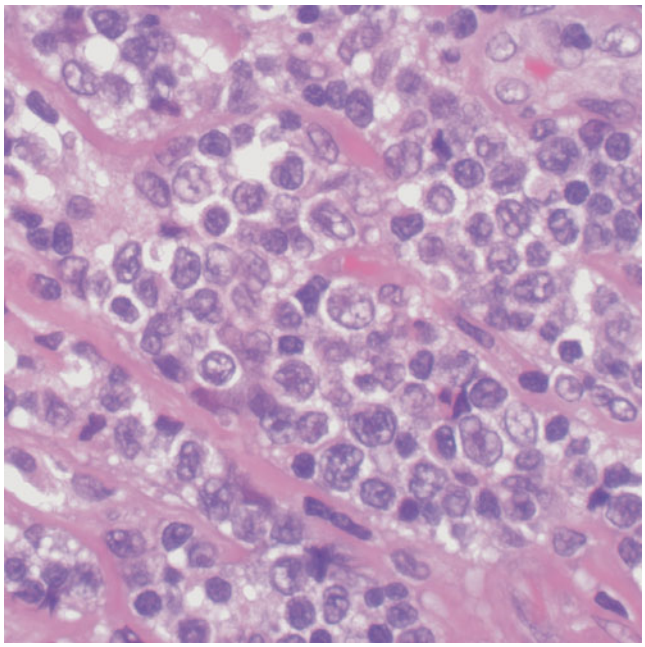

Figure 110-19 Pyothorax-associated lymphoma. Unlike primary effusion lymphoma, this aggressive large cell B-cell lymphoma is pathogenetically linked to EBV and forms a mass lesion. Hematoxylin and eosin, 60× original magnification.

patients have preexisting Kaposi sarcoma and rare cases are associated with MCCD. In addition, most cases are co-infected with EBV but a pathogenetic role for this virus has not been elucidated.

Effusion cytology specimens demonstrate large lymphoid cells with large round to irregular nuclei and frequent multinucleation as well as numerous mitotic figures (Fig. 110-18). Plasma cell features may be prominent and anaplastic cells can be seen. Biopsies feature tumor cells admixed with fibrin. Parietal or visceral pleura invasion is a very rare finding. B-cell lineage is confirmed by immunoglobulin gene rearrangement studies but neoplastic cells rarely express B-cell markers! Leukocyte common antigen (CD45), CD30, CD38, and CD138 (plasma cell-related markers) are expressed. These findings suggest a post-germinal center B cell origin. Two cases with T-cell lineage have been reported.

This lymphoma is extremely aggressive with survival measured in months. Combined antiviral therapy and chemotherapy are offered.

Pyothorax-Associated Lymphoma

Pyothorax-associated lymphoma develops in the pleural cavities of immunocompetent patients with chronic suppurative pleuritis. Most cases arise following long-standing artificial pneumothorax for treatment of tuberculosis or pleuritis secondary to pulmonary asbestosis. Approximately 2 percent of individuals with chronic pyothorax develop PAL. Epstein-Barr virus is strongly associated but the pathogenesis is not clearly understood. It is postulated that immunocompetent cells cannot enter the diseased pleural cavity resulting in local immunodepression facilitating proliferation of EBV-infected lymphocytes.

Patients are often in their sixth to eight decades of life and usually present with chest pain, back pain or shoulder pain and dyspnea. Radiographic studies demonstrate a visceral or parietal pleural mass invading chest wall, lung, pericardium, or diaphragm in the setting of pleural fibrosis and calcification. In contrast to PEL, pleural effusion is not seen.

Biopsy and resection specimens show masses composed of sheets of large atypical lymphoid cells with prominent nucleoli and basophilic cytoplasm (Fig. 110-19). Mitotic figures and apoptotic bodies as well as necrosis abound. Immunohistochemical studies discern this high-grade lymphoma from PEL. Typically lymphoma cells stain for B-cell antigens CD20 and CD79a, plasma cell markers CD38 and CD138 and on occasion a T-cell marker such as CD2, CD3, CD4, or CD7. Immunohistochemistry is positive for EBV, whereas KSHV/HHV8 is absent.

The prognosis for patients with PAL is dismal with most deaths occurring within one year. However, combination chemotherapy and radiotherapy may prolong survival with 5-year survival rates of 20 percent.

CONCLUSIONS

Pulmonary and pleural lymphomas and reactive processes are uncommon entities with rich historical contexts. Current immunohistochemical and molecular methods allow for

accurate reproducible classification. Since most lesions arise from BALT, using this construct to order most lung lymphoid proliferations is very appealing. The wide variety of diseases associated with underlying immunologic disorders is only surpassed by the complexities of the primary lymphoproliferative disorders themselves. Clinicopathologic correlation is required for interpretation of virtually all these lesions. Sound diagnoses combined with improved therapies will hopefully improve patient quality of life and survival.

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PART

XVI

Infectious Diseases of the Lungs

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111
CHAPTER

Pulmonary Clearance of Infectious Agents

Galen B. Toews

The primary function of the lungs is the exchange of gases at a rate required to support tissue metabolism. During gas exchange processes, the lung is exposed to a varied burden of foreign materials, including infectious agents. In addition, the lung is repeatedly exposed to microbes via aspiration of secretions from the upper respiratory tract, particularly during sleep. The lung must defend itself against this potentially hostile environment to perform gas exchange adequately. This group of nonrespiratory functions has been collectively termed *pulmonary host defenses* (Fig. 111-1).

MECHANICAL DEFENSES

Nasopharyngeal Airways

Nasal hairs remove most particulates bigger than 10 μm. Rapid airflow and quick changes in direction of the airstream in the nose favor inertial deposition of large particulates; these particulates are cleared primarily by swallowing, sneezing, or coughing. Mucociliary clearance participates in the removal of particulates from the nasopharynx. Ciliated mucosa is present on the nasal septum and turbinates; mucociliary action sweeps mucus toward the posterior pharynx, where secretions are either swallowed or cleared from the throat.

Conducting Airways

Mucociliary Escalator

Most particulates larger than 2 μm in diameter affect the conducting airways. Mucociliary clearance and coughing are the principal means of mechanical defense (Fig. 111-2). The mucosa of the conducting airways is lined with mucus secreted by goblet cells, bronchial glands, and Clara cells. The mucous blanket is composed of two distinct layers: a watery sublayer, in which most ciliary movement takes place, and

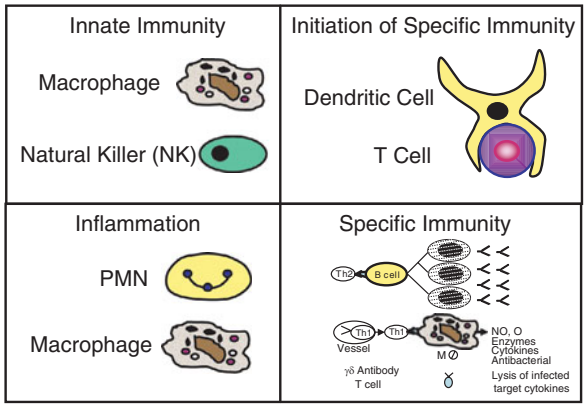

Figure 111-1 Pulmonary immune defenses. Three immune defense systems protect the airways and lower respiratory tract. Alveolar macrophages and pulmonary natural killer cells effectively remove certain microbes. Inflammatory responses, which lead to the recruitment of polymorphonuclear (PMN) leukocytes and monocytes, are crucial for the pulmonary clearance of most microbes. The initiation of specific immune responses requires dendritic cell–T lymphocyte interactions. Specific immune responses are required for effective pulmonary clearance of viruses, encapsulated bacteria, fungi and mycobacteria. The expression of immune responses requires the interaction of Th1 lymphocytes and macrophages and Th2 lymphocytes and B cells.

an upper viscous layer that is just penetrated by the ciliary tip.

Mucus is propelled up the respiratory tract by the pseudostratified ciliated epithelium that lines the conducting airways. Approximately 200 cilia are present on each ciliated cell. Ciliary length is approximately 5 to 6 μm, and ciliary frequency is 12 to 14 beats per seconds. Particulates can be cleared from the trachea with a half-time of 30 minutes and from distal airways with a half-time of hours.

Oxidants impair cilliary function and elastase damages cilia. Interferon (IFN)-γ, tumor necrosis factor (TNF)-α, and interleukin (IL)-1 increase cilia beating by a mechanism that is dependent on nitric oxide. Cigarette smoke adversely affects cells that produce mucus; mucus production is increased, and its biochemical and biophysical characteristics are altered.

Airway Secretion

Airway epithelial cells secrete nonimmune host defense molecules. Iron is an essential ingredient for survival of many microbes. Iron is sequestered in cells or firmly complexes to transport proteins. Microbes compete for this iron with their own transport proteins, known as siderophores. Lactoferrin, found predominantly in the airways, and transferrin, found predominantly in the alveolar spaces, effectively complex any free iron in mucosal secretions, suppressing bacterial growth by making iron difficult for bacteria to obtain.

Lysozyme is secreted in large quantities in human airways (10–20 mg per day). Lysozyme catalyzes the hydrolysis of bonds between constituents of the cell walls of most bacteria and *Cryptococcus neoformans* and *Coccidioides immitis*. Lysozyme inhibits chemotaxis and the production of toxic oxygen radicals by stimulated neutrophils. Airway secretions also contain both serum-derived antiproteases (α1-antitrypsin, α_2-chymotrypsin, and α_2-macroglobulin) and an airway epithelial cell-derived antiproteases (elafin). Elafin is produced by Clara cells in the airway.

INNATE IMMUNITY

Host defenses against invading microbial pathogens consist of two components: innate immunity and acquired immunity. Innate immune recognition occurs via germ-line encoded receptors that recognize conserved structures present on microorganisms (Fig. 111-2).

Innate Immune Recognition

Microbial recognition is problematic because microbes evidence molecular heterogeneity and have high mutation rates. The innate immune system recognizes a broad spectrum of pathogens using a repertoire of invariant receptors that recognize highly conserved microbial molecules including combinations of sugars, proteins, lipids, and distinct nucleic acid motifs. The receptors recognize molecular patterns and have, therefore, been termed pathogen recognition receptors (PRRs). Several hundred receptors accomplish the task of innate immune recognition. The ligands recognized by PRRs are pathogen-associated molecular patterns (PAMP). PAMPs share certain features. PAMPs are invariant structures shared by classes of pathogens, are produced only by microbes, and are essential for microbial pathogenicity or microbial survival. Cells that express PRRs include macrophages, dendritic cells (DCs), mast cells, neutrophils, eosinophils, natural killer (NK) cells, epithelial cells, and fibroblasts.

PRRs can be divided into three classes: secreted, endocytic and signaling receptors. C-reactive protein (CRP), mannan-binding lectin (MBL) and serum amyloid protein (SAP) are secreted pattern recognition molecules. CRP and SAP function as opsonins and bind to Clq to activate the classic complement pathway. MBL binds to mannose residues that are abundant on the surface of many microbes. Macrophage mannose receptor (MMR) interacts with gram-positive and gram-negative bacteria and fungal pathogens and mediates phagocytosis. Macrophage scavenger receptor (MSR) has broad specificity for a variety of ligands including double-stranded RNA, LPS, and lipoteichoic acid. Signaling PRRs induce expression of inflammatory cytokines and co-stimulatory molecules on antigen presenting cells following the recognition of PAMPs. Toll-like receptors (TLRs) are signaling PRRs. Thirteen TLRs have been described in mammals. TLRs differ from one another in ligand specificity, expression patterns, and the genes they induce.

TLR2 recognizes a wide range of microbial products. These include lipoproteins/lipopeptides, peptidoglycan, lipoteichoic acid, lipoarabinomannan, and zymosan. TLR2 forms heterophilic dimers with other TLRs such as TLR1 and TLR6, likely accounting for its ability to recognize numerous

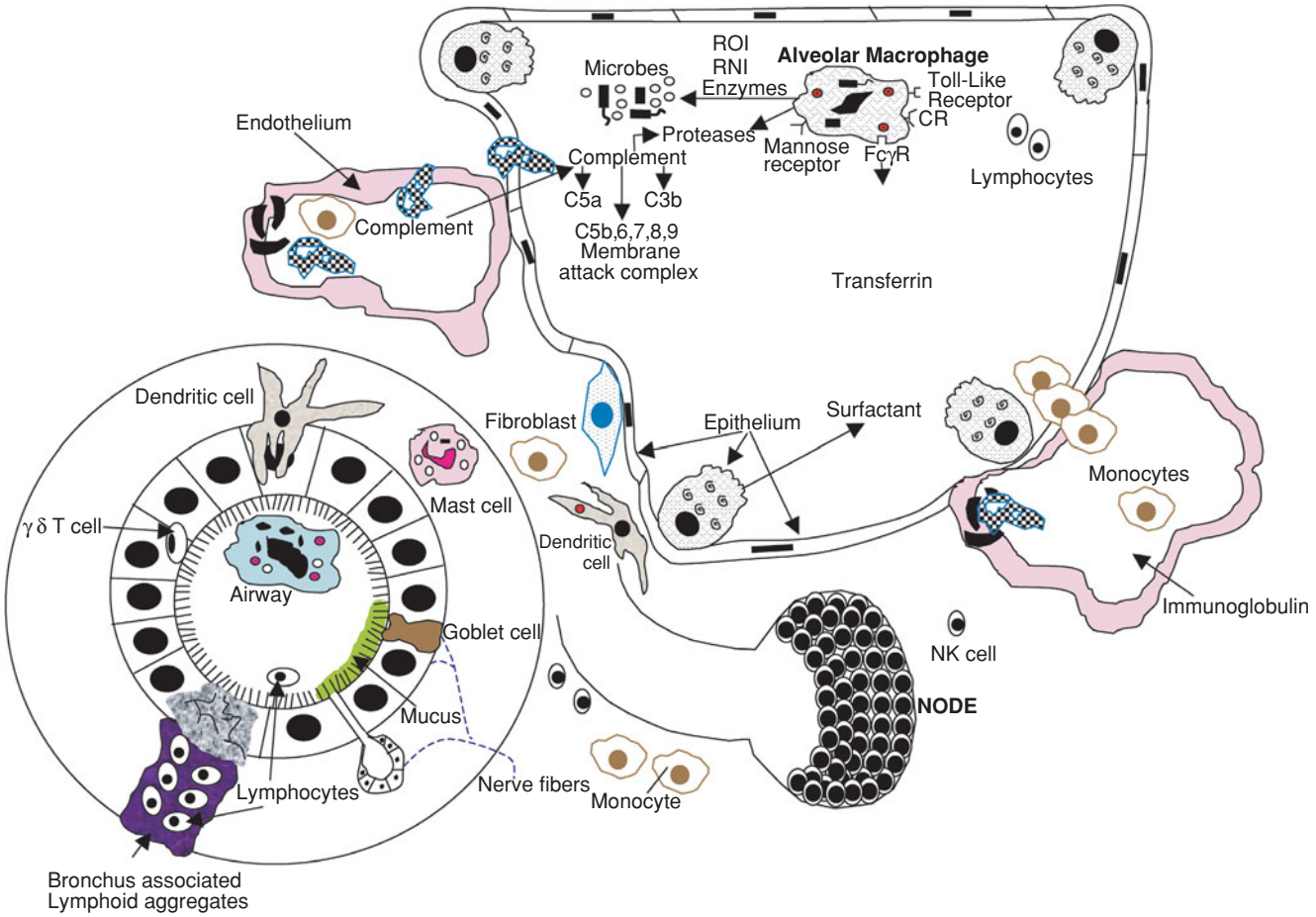

Figure 111-2 Resident defenses of conducting airways and alveoli. Conducting airways are lined by ciliated epithelium, which moves mucus generated by bronchial glands and goblet cells cephalad, where it is expectorated or swallowed. Airway macrophages ingest and kill small inocula of most aspirated and airborne bacteria. The alveolar spaces rely on innate immunity for the clearance of microbes that reach the alveolar surface. Alveolar macrophages are the first line of defense against microbes. Complement, surfactant, and iron-binding proteins are important humoral microbicidal factors.

ligands. TLR4 is an essential receptor for LPS recognition. TLR4 also recognizes endogenous ligands such as heat-shocked proteins and portions of fibronectin, hyaluronic acid, heparin sulfate, and fibrinogen. TLR5 recognizes flagellin, the principal structural component of bacterial flagella. TLR1, TLR2, TLR4, TLR5, and TLR6 are expressed on the surface of cells. TLR7, TLR8, and TLR9 are in the endosomal compartment and TLR3 is intracellular, although its exact location has not been defined. TLR3 recognizes double-stranded RNA (dsRNA) produced by most viruses during their replication. TLR7 and TLR8 are structurally highly conserved proteins and recognize the same ligand in some instances. TLR7 and TLR8 recognize single-stranded RNA (ssRNA) from viruses such as human immunodeficiency virus and influenza virus. TLR9 recognizes unmethylated CpG motifs in bacterial DNA. Mammalian DNA is methylated, whereas bacteria lack CpG methylation enzymes, allowing bacterial recognition.

Alveolar Macrophages

Alveolar macrophages are a heterogeneous population of phagocytes that constitute the first line of defense against microbes that reach the alveolar surface (see Fig. 111-2). Alveolar macrophages are derived from monocytes and proliferating macrophage precursors in the interstitium of the lung. Alveolar macrophages undergo differentiation within the lung. Alveolar macrophages have a life span of months to years. The signals and ligands that modulate monocyte traffic into the normal lung have not been defined.

The microbicidal function of alveolar macrophage is dependent on four critical attributes. Macrophages recognize signals, ingest particulates, secrete mediators, and migrate in response to stimuli (Table 111-1). Macrophages recognize signals in their microenvironment via PRRs and surface receptors capable of binding specific ligands, including complement proteins, immunoglobulins, cytokines, PAMPS, and toxins. Activation of TLRs induces transcriptional activation of inflammatory mediators (TNF-α, IL-1, IL-6, IFN-α, IFN-β), chemokines, costimulatory molecules of T-cell activation (CD80, CD86), and signals that regulate the differentiation of lymphocytes (IL-4, IL-5, IL-10, IL-12), transforming growth factor (TGF-β and IFN-γ). Receptor-ligand interactions allow macrophages to ingest microorganisms and respond to cytokines and proteins.

Table 111-1

Secretory Products of Macrophages

Cytokines, Growth Factors, and Hormones
- Growth factors
  - GM-CSF
  - M-CSF
  - G-CSF
- Proteins involved in host defense and inflammation
  - C1
  - C2
  - C3
  - C4
  - C5
  - Factor B
  - Factor D
  - Properdin
  - C3b inactivation
  - βIH
  - Lysozyme
  - Interferon-γ
  - Fibronectin
  - Lactoferrin
- Cytokines that promote acute inflammation and regulate lymphocytes
  - TNF
  - IL-1α/β
  - IL-6
  - IL-8
  - IL-12
  - GROα/β/γ
  - CTAPIII
  - β-Thromboglobulin
  - IP-10
  - MCP-1
  - MIP-1α
  - MIP-1β
- Cytokines that inhibit acute inflammation and lymphocyte responses
  - IL-10
  - TGF-β_1, -β_2, -β_3
  - IL-1 receptor antagonist

Reactive Oxygen Intermediates
- O_2^-
- H_2O_2
- $OH^{\cdot}$

Reactive Nitrogen Intermediates
- $NO^{\cdot}$
- NO_2
- NO_3

Enzymes Active in Microbicidal Activity and Inflammation
- Acid hydrolases
- Acid phosphatases
- Cathepsins
- Cytolytic proteinase
- Hyaluronidase
- Lysozyme
- Phospholipase A_2
- Plasminogen activator

Inhibitors of Enzymes
- α_1-Antiprotease
- α_2-Macroglobulin
- Inhibitors of plasminogen
- Inhibitors of plasminogen activator
- Lipomodulin

Lipids Active in Host Defense and Inflammation
- PGE_2
- $PGF_2\alpha$
- Prostacylin
- Thromboxane A_2
- Leukotrienes B, C, D, and E
- Mono-HETES
- Di-HETES
- PAF
- Lysophospholipids

Macrophages express two distinct receptors for the third component of complement. Complement receptor 1 (CR1) preferentially binds C3b and complement receptor 3 (CR3, Mo-1, MAC-1, CD11b/18) is a member of the β_2 integrin family. CR3 is essential for migration of leukocytes functioning in cell-cell and cell-substrate adhesion. Genetic deficiency in the CD18 complex causes recurrent life-threatening infections.

Three Fcγ receptors recognize the Fc domain of immunoglobulin G (IgG). All FcRs function as signal-transducing molecules. FcγRI, FcγRII, and FcγRIII trigger both phagocytosis and cytolytic responses. Patients who lack FcγRI have no increased susceptibility to infection.

The redundancy of the three FcγRs may confer a selective advantage. The mannose receptor binds mannose and mediates phagocytosis of yeasts, zymosan particles, and *Pneumocystis carinii* (see Fig. 111-2).

Phagocytosis follows recognition of the microbe. Particle engulfment requires engagement of specific receptors and the generation of transmembrane signals that induce movement of the phagocyte plasma membrane over a ligand-coated particle. Phagocytosis requires sequential,

circumferential interaction of phagocyte surface receptors with complementary ligands on the surface of the particle.

The ingested microbe is initially contained within a phagosome that subsequently fuses with lysosomes. TLR stimulation is linked to phagosomal maturation. Resident alveolar macrophages require activation for microbicidal killing. Activation stimuli include microbial products, inflammatory cytokines and plasma proteins. IFN-α and/or IFN-β provide priming signals to augment macrophage microbicidal activity. GM-CFS is a potent stimulator of macrophage activation. Interactions with microbes lead to production of IFN-γ by NK cells.

Both oxidative and nonoxidative processes are used to kill ingested microbes. Alveolar macrophages have less antimicrobial activity than monocytes. Loss of granular peroxidase and a decrease in the magnitude of the respiratory burst account for a portion of the decline. Resident alveolar macrophages contain minimal myeloperoxidase (MPO): the MPO-H_2O_2-halide system is lest robust in resident macrophages than in recruited macrophages.

Microbes are also killed by macrophage-dependent nonoxidative mechanisms, including proteases, lysozyme, and defensins. Defensins are a multiple-member family of broad-spectrum cytotoxic peptides that kill many gram-positive organisms (*S. aureus, S. epidermidis, Streptococcus*) and gram-negative species (*Escherichia coli, Pseudomonas aeruginosa, Klebsiella pneumoniae*). Defensins also kill fungi and inactivate certain viruses. Defensins are present in the alveolar macrophages of some species.

NK Cells

NK cells are present within the lung. Active NK cells are located primarily in the interstitium of the lung. Pulmonary NK cells play a proactive role in influenza infections and in fungal infections. Engagement of TLRs induces macrophages to produce IL-12 and TNF-α which induce IFN-γ production by NK cells. Early IFN-γ activates macrophages and enhances their microbicidal activity.

Complement

Normal alveolar lavage fluids contain a functional alternative complement pathway. C3b, has opsonic activity and promotes receptor-mediated phagocytosis of microbes by macrophages. C5a is a chemoattractant for PMNs.

Alveolar Epithelial Cells

Alveolar epithelial cells secrete proteins important in innate immune responses. SP-A and SP-D are members of the collectin family. SP-A facilitates alveolar macrophage and type 2 alveolar epithelial cell uptake of microbes. SP-A increases secretion of GM-CSF, promotes movement of alveolar macrophages and regulates macrophage oxidant production. SP-D mediates agglutination of gram-negative bacteria.

INFLAMMATORY RESPONSES

A dual phagocytic system involving resident alveolar macrophages and recruited polymorphonuclear leukocytes (PMN) is required for the clearance of bacteria from the lower respiratory tract. Recruitment of PMNs into the alveoli is initiated by the generation of chemotaxins within the alveolar space (Fig. 111-3). A super-gene family of chemotactic cytokines, chemokines, possesses high degrees of specificity for inflammatory cells; accordingly they play important roles in the selective recruitment of blood-borne leukocytes to sites of inflammation. CXC, CC, C, and CX_3C chemokine families have been characterized. CXC chemokine family members (IL-8, MIP-2, GRO, ENA-78, NAP2) are chemotaxins for PMN. The CC family (MCP-1-4, RANTES, MIP-1α and MIP-1β) are chemotaxins for macrophages, lymphocytes, basophils, eosinophils, and mast cells. Lymphotoxin is a C chemokine family member and fractalkine is a CX_3C chemokine.

Activation of TLRs on innate immune cells induces transcriptional activation of inflammatory genes. TLR activation induces TNF-α and IL-1, both of which induce gene expression and secretion of CXC chemokines from endothelial cells, fibroblasts and pulmonary epithelial cells. Macrophages also generate leukotriene B4, a potent chemotactic substance. Sentinel dendritic cells and macrophages also produce IL-23 within a few hours after exposure to LPS and microbial products. This triggers rapid (hours) production of IL-17 from tissue resident α/β, $\gamma\delta$, and NK T cells. IL-17 promotes production of IL-1, IL-6, TNFα, and CXC chemokines from fibroblasts, epithelial cells and endothelial cells. Mice lacking the receptor for IL-17 evidence blunted G-CSF and MIP-2 responses, decreased neutrophil recruitment, have larger bacterial burden and worsening mortality in a murine model of *Klebsiella pneumoniae* infection. The alveolar capillary membrane is a dynamic assembly of innate immune cells that generate chemokines required to recruit specific inflammatory cells during microbial insults.

Neutrophils ingest microbes by phagocytosis. Effective killing requires products of granule constituents and molecular oxygen. Hydrogen peroxide and reactive oxygen intermediates are involved in neutrophil mediated killing. The MPO-H_2O_2-halide system is a crucial participant in oxygen-dependent killing by neutrophils. Granule components are also crucial in PMN mediated microbial killing. Lactoferrin chelates iron and lysozyme hydrolyzes bacterial cell walls. Cathepsin G, elastase and cationic proteins found in azurophil granules kill bacteria. Human neutrophils contain defensins which kill gram-positive and gram-negative bacteria and fungi.

ADAPTIVE IMMUNE RESPONSES

Microbial infections that elude the innate defense mechanisms and inflammatory responses generate a threshold

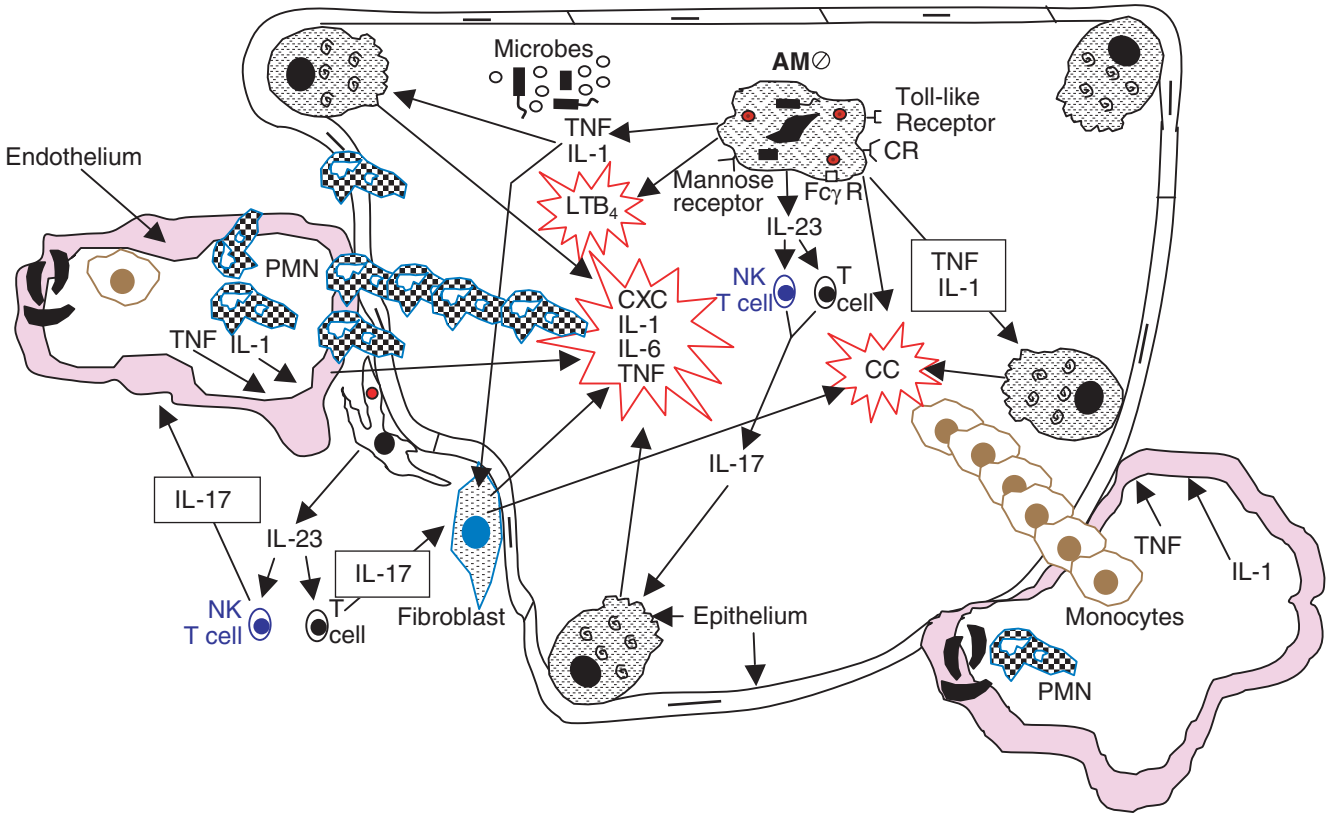

Figure 111-3 Initiation of inflammatory responses in the lower respiratory tract. Chemotaxins are generated sequentially following the entry of bacteria or bacterial products into the alveolus. LPS stimulates alveolar macrophages to produce TNFα, IL-1β, IL-8, and leukotriene B4. TNFα and IL-1β induce gene expression and production of chemokines by epithelial cells and fibroblasts present in the alveolar-capillary wall and induce the expression of adherence molecules on inflammatory cells and endothelial cells. Microbes induce dendritic cells and macrophages to produce IL-23. IL-23 induces resident lymphocytes and monocytes to produce IL-17. IL-17 induces production of IL-1, IL-6 and CXC chemokines by parenchymal cells.

dose of antigen, which is needed to trigger adaptive immune responses. Adaptive immune responses consist of two major effector systems, antibody- and cell-mediated immunity, which are generated by antigen specific B and T lymphocytes, respectively. B and T lymphocytes rearrange their Ig and T-cell receptor (TCR) genes to maintain approximately 10^{11} different clones of B and T lymphocytes that express distinct antigen receptors. B lymphocytes recognize native antigens including carbohydrates, proteins, and simple chemical groups. T-lymphocyte receptors recognize only peptides derived from protein antigens bound to cell-surface proteins from the major histocompatibility complex (MHC). Clones of lymphocytes are triggered by antigen-presenting cells (APCs) to proliferate and differentiate into effector cells. Antigen-specific lymphocytes remain expanded after elimination of an infection (memory lymphocytes). Memory lymphocytes provide a more rapid response to a second exposure to antigen.

Antigen-specific immune responses require at least 7 to 10 days for their development; this time is required for the proliferation and differentiation of antigen-specific T and B lymphocytes. During the development of specific immune responses, pathogens may continue to grow in the host or be held in check by innate and inflammatory mechanisms. The generation of specific immune responses to infectious antigens can be divided into three phases: the afferent phase, central control/processing phase, and efferent phase.

Afferent Immune Response

Antigen presenting cells (APCs) provide an essential link between innate and adaptive immunity (Fig. 111-4). DCs are the most potent APC for T cells. DCs are bone marrow-derived cells which take up residence in peripheral tissues at epithelial borders throughout the mammalian host where they become specialized for recognition of pathogens and microenvironmental tissue damage. DCs signal the presence of "danger" to cells of adaptive immunity.

Two broad subsets of DC have been identified: myeloid DC (mDC) and plasmacytoid DC (pDC). mDC express CD11c, CD11b, varying levels of MHC class II and costimulatory molecules (CD40, CD80, and CD86). Human pDC express blood DC antigen (BDCA)2, whereas murine pDC express CD11c, GR-1, and B220. mDC contribute to a variety of T-cell responses or tolerance and pDC have been implicated in antiviral immunity and in murine models of asthma.

DC exist in both immature and mature forms. Immature DC are concerned mainly with antigen capture.

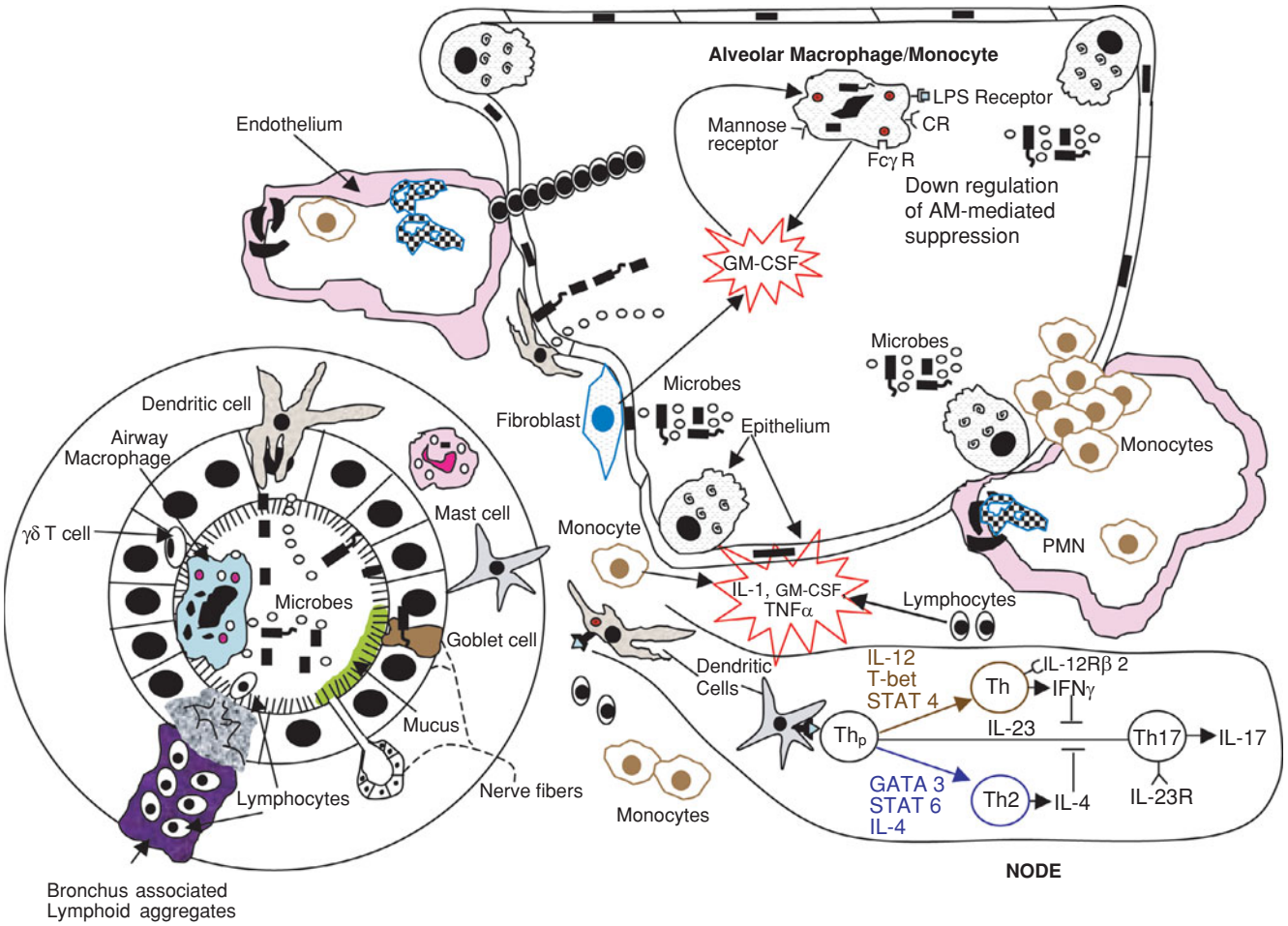

Figure 111-4 Initiation of specific immune responses in the lung. Dendritic cells located in the interstitium of the lung and in the airway epithelium function as sentinel antigen-presenting cells. Dendritic cells reside in close contact to airway epithelial cells, alveolar epithelial cells, and interstitial macrophages. Following exposure to microbial antigens, DC differentiation occurs as a result of exposure to cytokines produced by cells of the innate immune system (macrophages) and cytokine produced as a result of injury to epithelial cells. Differentiated DC migrates to local nodes and present antigen to naive T lymphocytes. The control of CD4 T-lymphocyte subset differentiation occurs via complex, cross-regulatory interactions mediated by lymphokines. The development of CD8 effector cells and plasma cells usually requires cognate interactions with DC4 regulatory T lymphocytes.

DC are mobilized from bone marrow precursors to peripheral blood in response to pulmonary inflammation. Monocytes contribute to the pool of newly recruited DC through transendothelial migration in which peripheral blood monocytes differentiate into tissue DC after crossing the vascular endothelium. CCR2 is a critical receptor in the recruitment of DC during inflammatory responses. CCR6 mediates recruitment of DC specifically to the airways and alveolar space in response to macrophage inhibitory protein (MIP)-3α secreted by respiratory epithelial cells.

DC maturation is dependent on sensing of infection which may occur either directly by detection of pathogen products using TLRs or indirectly through exposure to endogenous danger signals such as material released from damaged cells. Ingested antigens are rapidly processed by one of two pathways. The endocytic pathways processe protein antigens obtained from the extracellular space in phagolysosomes converting them to small polypeptides. The polypeptides are loaded on to MHC class II molecules to prime DC for further presentation to MHC class II restricted, CD4+ T helper lymphocytes. The endogenous pathway processes peptides from the intracellular environment and loads them onto MHC class I molecules for presentation to MHC class I restricted, CD8+ T cells. Mature DC up regulate MHC class II and costimulatory molecules allowing a phenotype focused on antigen presentation and the stimulation of naïve T cells.

DC maturation is accompanied by changes in the expression of chemokine receptors. CCR1, CCR2, CCR5, and CCR6 are down regulated. CCR7 expression is enhanced allowing DC to respond to chemokine gradients of secondary lymphoid tissue chemokines (SLC/CCL21) and Epstein-Barr virus–induced molecule1 ligand chemokine (ELC/CCL19) emanating from local lymphatics and draining lymph nodes. Mature DC leave the local inflammatory environment carrying their antigenic load to draining lymph nodes. DC–T-cell interactions within the draining lymph node are complex.

T-cell stimulation, proliferation, and activation result if antigen recognition occurs. Induction of Th1, Th2, Th17, or T-regulatory responses may be the end result.

The engagement of TLRs on DCs leads to increased expression of MHC-peptide complexes and co-stimulatory molecules as well as the production of immunomodulatory cytokines, all of which have a profound effect on T-cell priming and differentiation. Triggering of the T-cell receptor (TCR) occurs following an interaction with an antigen/MHC complex and provides "signal one" to the T cell. T-cell maturation results in upregulation of important co-stimulatory molecules. Specifically, DC increase the expression of B7.1 (CD80) and B7.2 (CD86), which bind CD28 on T cells providing "signal two" to activate antigen specific T cells.

T-cell responses to pathogens are heterogeneous; three subsets of CD4 T helper cells have been defined on the basis of the cytokines they produce. Interleukin-12 (IL-12) is an innate immune response cytokine that drives Th1 polarization. IL-12 production by DC is tightly controlled, requiring a priming signal provided by microbial products or IFN-γ and an amplifying signal provided by T cells through CD40 ligand (CD40L). Cues other than IL-12 drive T-cell differentiation. IL-23, which shares the p40 chain with IL-12 but pairs with a unique p19 chain, drives differentiation of inflammatory T cells capable of secreting large amounts of TNF and IL-17. TLR3 and TLR4 potently act in synergy with endosomal TLR7, TLR8, and TLR9 in the induction of IL-12 p70 and IL-23. The amounts of IL-12 and IL-23 induced by synergistic signaling are 50- to 100-fold higher than those induced by optimal concentrations of single agonists, leading to enhanced and sustained Th1-polarizing capacity. Since pathogens express several TLR agonists that may engage different TLRs at different times and in distinct cellular compartments, it is likely that "combinatorial codes" may exist by which DC discriminate pathogens for which a Th1 response is desirable. IL-12 activation of STAT4 is necessary for differentiation of naive T cells into IFN-γ–producing Th1 cells. IFN-γ activates STAT1 and subsequently T-bet. T-bet activation is required for IL-12Rβ_2 expression and IL-12 responsiveness. Th1 responses are characterized by the strong expression of IFN-γ, IL-2, and TNF-α. These cytokines in concert with simultaneous interactions between DC, Th1 cells, and CD8+ T cells result in the generation of antigen specific cytoxic T lymphocytes. The net result of the Th1 response is the generation of activated Th1 and cytotoxic T lymphocytes necessary for macrophage activation and effective cell-mediated immunity against predominantly intracellular pathogens.

Th2 responses are characterized by T-cell production of IL-4, IL-5, IL-10, and IL-13 as well as systemic IgE production and tissue eosinophilia. This response results in humoral immunity–mediated through interactions among DC, Th2 cells, and B cells. Th2 cell development is dependent on the transcription factors GATA3, STAT6, and IL-4.

It is increasingly evident that IL-23 has unique roles in regulating immunity. Whereas IL-12 drives classic Th1 responses characterized by IFN-γ production, IL-23 drives a T-cell population that produces IL-17 (Th17 cells). IL-17 is a proinflammatory cytokine that induces G-CSF, GM-CSF, monocyte chemoattractant protein 1 (MCP-1), macrophage-inflammatory protein-2 (MIP-2), IL-6, IL-8, neutrophil chemokine growth-related oncogene-α and PGE_2. The production of IL-17 by antigen-specific Th17 cells within a local tissue environment is important for both rapid recruitment of neutrophils to sites of acute infection and for continuous neutrophil recruitment. IL-23 induces IL-17 production in both CD4+ and CD8+ T cells.

Regulatory T Cells

The immune system possesses various mechanisms to control and regulate the immune system to prevent and minimize reactivity to self-antigens or an overexuberant response to a pathogen. Avoidance of damage to the host is achieved by active suppression mediated by regulatory T (Treg) cell populations. Naturally occurring CD4+ CD25+ T reg cells are the best characterized subset. These cells represent 5 to 10 percent of the CD4+ T lymphocytes in healthy adult mice and humans. No characteristic stable surface marker has been ascribed to Treg cells. The forkhead/winged helix transcription factor, Foxp3, is specifically expressed by CD25+ Treg cells as well as CD25– T cells with regulatory activity. Foxp3 is thought to program the development and function of this subset of T cells. Naturally occurring Tregs suppress T cell proliferation by cell contact, membrane or soluble TGF-β and by secreted IL-10. A second population of regulatory T cells that produce IL-10 and secrete TGF-β have been described (IL-10 T reg). These cells are derived in culture and also express CD25. This second type of regulatory T cell also inhibits naïve T-cell proliferation in vitro and suppresses experimentally induced autoimmune disease. These cells are Foxp3 negative. IL-10 Tregs suppress T cells via cell contact mediated mechanisms and secreted IL-10.

Efferent Immune Responses

Migration of Effector Cells to the Lung

Antigen specific T cells must migrate via the blood stream to peripheral sites of ongoing infection (Fig. 111-5). Chemokine receptors are used, some of which are specific for Th1 cells. A subset of recruited DC remains in the lung rather than migrating to draining lymph nodes. These recruited nonmigratory pulmonary DC present antigen to newly recruited T cells to drive T-cell polarization and stimulate cytokine release. Cytokines produced by specific CD4 and CD8 lymphocytes play a central role in the recruitment of inflammatory mononuclear phagocytes and other effector lymphocytes. Monocytes and NK cells are recruited into the complex peripheral infectious environment.

Efferent T Cell Mediated Responses in the Lung

Viral Infection

Viruses including influenza, parainfluenza, respiratory syncytial virus, Hantavirus, coronavirus (severe acute respiratory

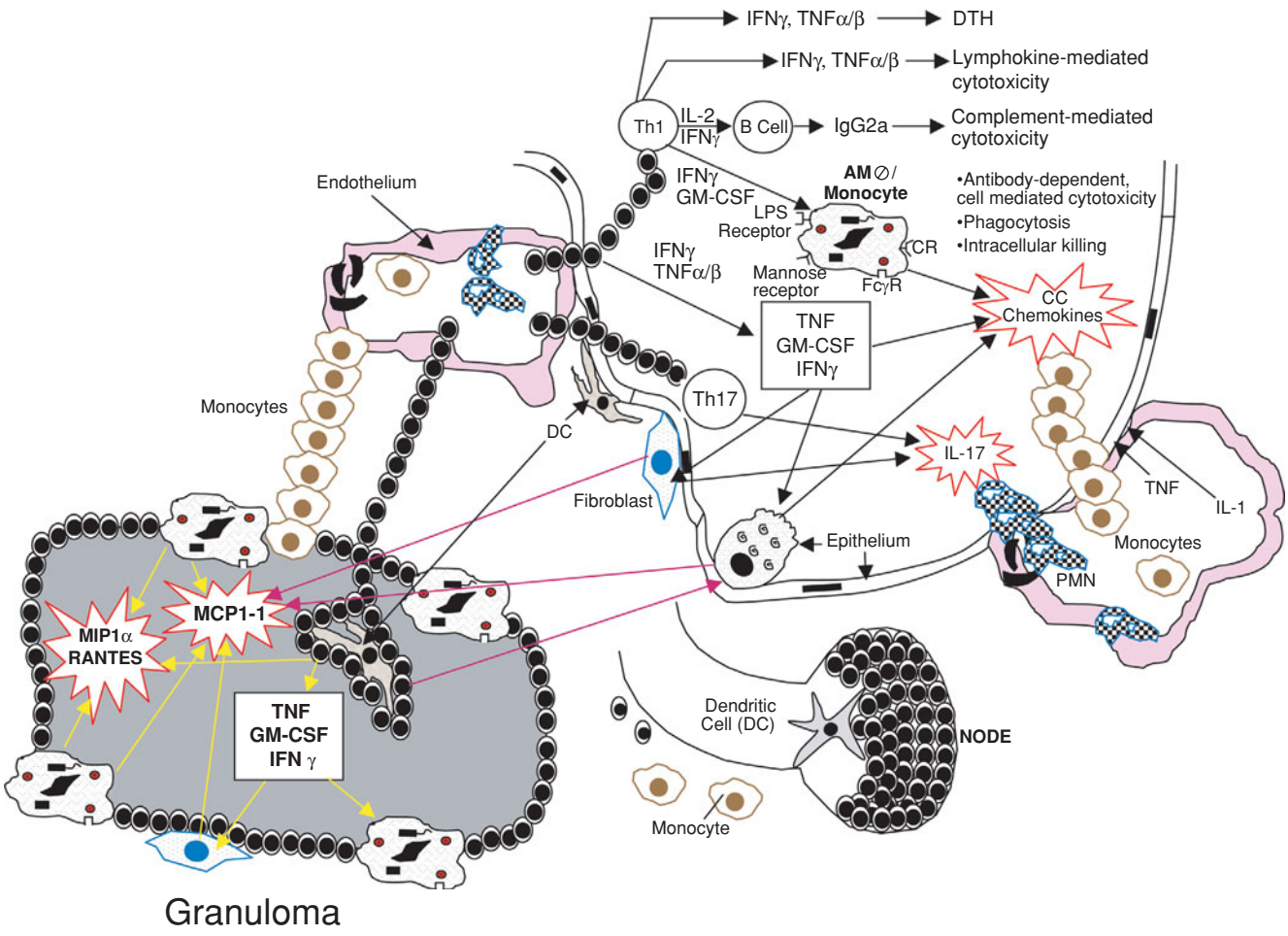

Figure 111-5 Expression of specific immune responses in the lower respiratory tract. Activated T lymphocytes recirculate from draining regional lymph nodes and enter sites of microbial multiplication via a series of highly regulated events involving cytokines and adherence molecules expressed on both lymphocytes and endothelial cells. Activated Th0 or Th1 lymphocytes are stimulated by resident antigen-presenting cells to produce high levels of IFN-γ, GM-CSF, and TNF, which recruit and activate monocytes from the circulation. Adherence receptor ligand interactions between monocytes and endothelial cells are important in their recruitment. A unique subset of mononuclear cell chemotaxins (MIP-1α, MCP-1) are probably active in recruitment of mononuclear phagocytes. Recruited, activated mononuclear phagocytes are crucial to the clearance of certain pathogens. Th17 cells produce IL-17, which induces parenchymal cells to produce TNF-α, IL-1, IL-6, and CXC chemokines. These proinflammatory cytokines are important for continuous neutrophil recruitment during chronic infections.

syndrome), herpesvirus, and CMV cause significant pulmonary disease. Viruses are intracellular pathogens; the killing of virally infected cells by MHC class I restricted cytotoxic CD8 T lymphocytes (CTL) is required. CTL kill target cells by two mechanisms. Cytolytic mediators, including perforins and granzymes, are released from cytoplasmic granules. Perforins induce pore formation and osmotic cell lysis and granzymes are proteases that activate cell caspases, resulting in apoptosis. Killing of virally infected cells can also result from the direct induction of apoptosis by ligation of Fas by Fas ligand, which is up regulated and present on CTL.

The development of cell-mediated immunity to viral infections precedes by mechanisms presented earlier, but may also precede locally within the lung. Lymphotoxin knockout mice that lack lymphoid organs are capable of generating antigen-specific CD4+ T-cell responses. Priming occurred in bronchus-associated lymphoid tissue (BALT), a submucosal lymphoid tissue found in the major bronchi. Localized priming of the cell-mediated immune response may play a crucial role in viral host defense.

Memory T-cell responses are important in certain viral illnesses and following administration of antiviral vaccines. Two subsets of memory T cells have been defined. Effector memory T cells are found within the lung, are short lived, retain markers of activation, and have effector functions; these cells lack expression of lymphoid trafficking molecules CCR7 or CD62L. Central memory T cells reside predominantly within lymphoid organs, persist for long periods of time, and express CCR7 and CD62L.

Intracellular Pathogens

Numerous strains of bacteria and certain fungi have evolved the capacity to invade and survive within host leukocytes, primarily macrophages, to evade recognition and elimination by innate immune responses. Cell-mediated immunity is required to successfully eradicate these microbes. Cytokines produced by CD4 and CD8 T lymphocytes play a central role in the activation of microbicidal function in phagocytic cells (see Fig. 111-5). IFN-γ produced by both CD4 and CD8 T lymphocytes is the most important macrophage activating factor. Macrophage activation is further enhanced by TLR stimulation and by inflammatory cytokines such as TNF-α and GM-CSF. Activated macrophages kill microbes. Intracellular microbes are exposed to toxic acid hydrolysis and cationic peptides in phagolysosomes. Expression of inducible nitric oxide synthase results in enhanced nitric oxide synthesis and the synthesis of reactive nitrogen intermediates that have antimicrobial properties. Induction of the respiratory burst results in generation of superoxide, hydrogen peroxide, and toxic reactive oxygen intermediates. The induction of macrophage apoptosis in response to intracellular infection has been shown to be of importance in blocking cell-to-cell spread of certain intracellular infections.

Granuloma formation is an important mechanism of host defense to intracellular microbes (see Fig. 111-5). The recruitment of monocytes and lymphocyte populations to the site of infection is required for granuloma formation. Macrophages coalesce into large, epithelioid and multinucleated giant cells. DC, CD4+ T lymphocytes, and CD8+ lymphocytes form a loose meshwork that serves to contain microorganisms. Granulomas are sites of ongoing production of inflammatory cytokines, including TNF-α, IFN-γ, and chemokines capable of recruiting additional effector cells.

Efferent B Lymphocyte–Mediated Immune Responses in the Lung

Immunoglobulins are a major protein constituent of the fluid that lines the luminal surface of conducting airways and alveolar lining fluid. Effector functions for antibodies include opsonization, complement fixation, antibody-dependent cellular cytotoxicity (ADCC), agglutination and neutralization (Fig. 111-6). Approximately 20 percent of the total protein

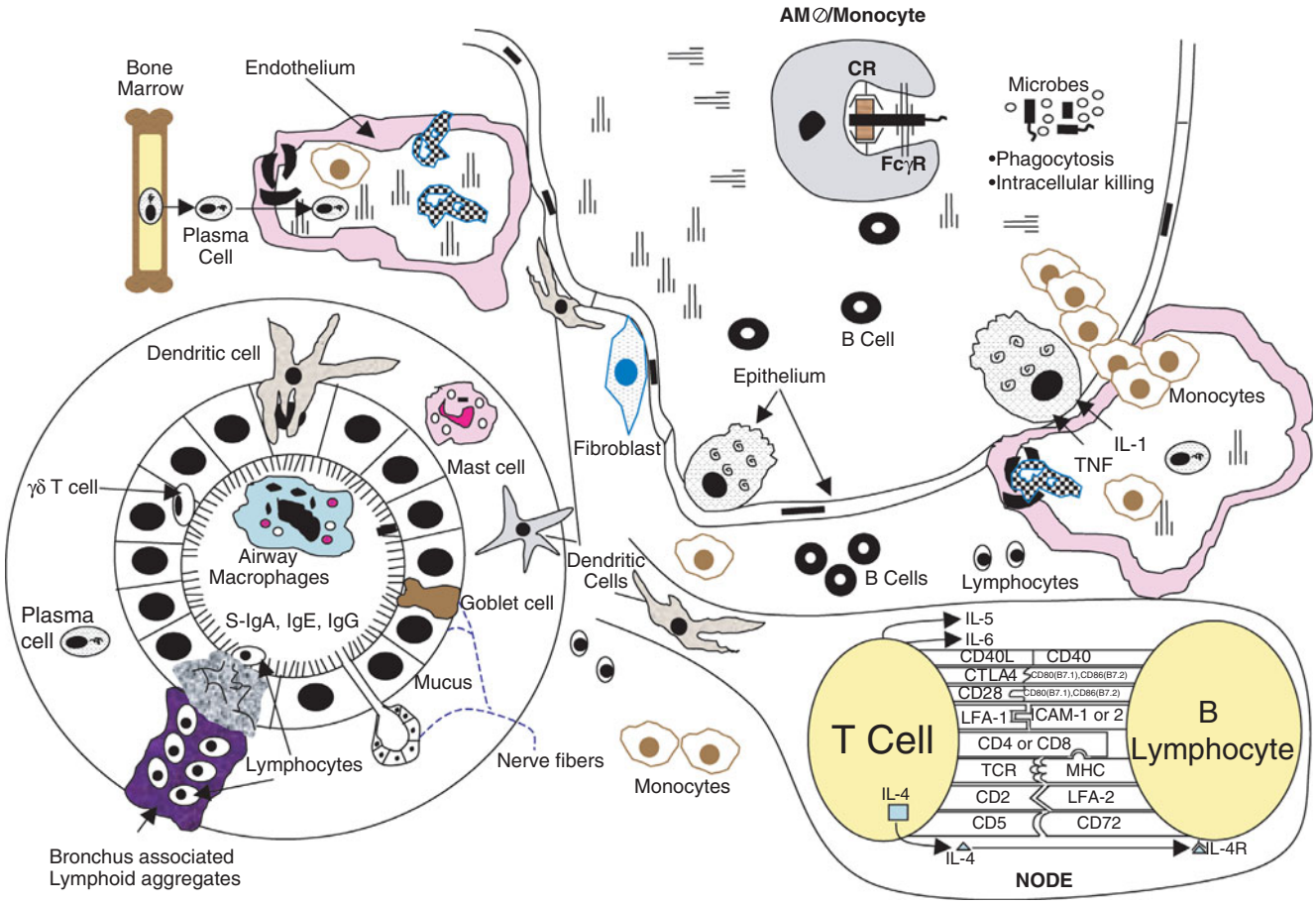

Figure 111-6 Expression of B lymphocyte–mediated immune responses in the lower respiratory tract. Initial events in B-lymphocyte proliferation and differentiation occur in T lymphocyte–dependent areas of regional lymph nodes. Proliferation, somatic hypermutation, and selection occur within the lymphoid follicle. B lymphocytes then migrate to bone marrow and to the lung, where they undergo differentiation to mature antibody-producing plasma cells. Serum antibody that gains access to the alveolar spaces of uninflamed lungs is present in large amounts during intra-alveolar infections processes. Antibodies neutralize pathogens and their toxins, activate complement, and function as opsonins to enhance macrophage recognition and ingestion of extracellular pathogens.

present in bronchoalveolar lavage fluid consists of IgG, IgM, and IgA. IgA is the predominant immunoglobulin in secretions of the trachea and major bronchi while both IgG and IgE are present as well. IgG is the predominant immunoglobulin in alveolar lining fluid.

Humans produce more IgA than any other Ig class. The secretory IgA found in external secretions consists of two molecules of IgA that are held together by a joining chain and by a secretory component, a glycoprotein produced by epithelial cells. The role of IgA in pulmonary defenses remains enigmatic. The usual specificity of IgA antibodies is antiviral. Specific IgA antibodies against hemagglutinating antigen have been isolated from patients infected with influenza A. IgA may also be important in inhibiting bacterial adherence to the respiratory epithelium; it may also serve as an antitoxin, since specific IgA against *Bordetella pertussis* toxin has been isolated from the respiratory secretions of patients with pertussis. Although IgA is believed to fix complement poorly, IgA1 antibodies from volunteers vaccinated with meningococcal polysaccharide vaccine induced classic complement pathway–mediated killing of group C *Neisseria meningitis*. Finally, IgA may also have a role as an opsonin, since human alveolar macrophages bear Fc receptors that bind either IgA1 or IgA2. Certain bacteria elaborate proteases that digest IgA; these proteases may provide a selective colonization advantage to the microbes.

Specific antibody is an important ingredient in lower respiratory tract defenses against extracellular microbes. Extracellular bacteria possess polysaccharide capsules that allow them to evade phagocytic cells. Antibodies function as: (a) opsonins that allow phagocytes to recognize and ingest microbes via the involvement of Fc receptors; (b) activators of complement, which enhances opsonization and leads to direct lysis of some bacteria; and (c) as neutralizing antibodies that neutralize pathogens or their toxins by binding to microbes or their products, thereby preventing injury to cells.

The role of antibody in resident bacterial defenses in the lower respiratory tract is uncertain. Immunoglobulins are clearly present in the epithelial lining fluid of the lower respiratory tract. Systemic immunization enhances pulmonary clearance of *P. aeruginosa, P. mirabilis,* and *H. influenzae*. Enhanced clearance correlates with the appearance of antibodies in serum and bronchoalveolar lavage fluid, which are directed against the organisms. Antibody specificities of serum and alveolar antibodies are identical. Thus, it seems likely that alveolar antibodies are derived in large part from serum.

Serum IgG can clearly gain access to the alveolar space in normal subjects and during inflammation when large changes in alveolar permeability occur. Serum IgG can clearly and directly enhance bacterial clearance from the lower respiratory tract, since intravenous injection of a murine IgG monoclonal antibody specific for a cell surface–exposed epitope of nontypable *H. influenzae* resulted in enhanced pulmonary clearance. Accordingly, it seems likely that direct airway immunization would not be required to obtain protective antibodies in the lung.

CONCLUSION

Infections are the most likely evolutionary driving force for the development of a complex system of pulmonary host defenses. A coordinated response of many different cells is required for the lung to clear pulmonary pathogens. An increasingly complex and potentially injurious cascade of host responses is mobilized following pulmonary microbial challenges (Table 111-2). Although the interactions of microbes

Table 111-2

Pulmonary Host Defense-Microbe Interactions

Host Mood	Defense Mechanism	Timing	Microbial Behavior
Content	Mechanical: Epithelial barrier Mucociliary escalator	Continuous	Commensal
Irritated	Innate Immunity: Macrophages, NK cells, γ/δ T lymphocytes	Hours–days	Replication in the airway and alveolar space
Interested	Inflammation: Macrophages/PMN	Minutes–hours	Invasion
Angry	Antigen-specific immunity: DC; CD4, CD8 T lymphocytes; B lymphocytes	3–7 days	Tissue invasion/replication in phagocytes
Hysterical	Immunopathology: Macrophages; CD4, CD8 T cells; NK cells, B cells		Dissemination to many tissues

in the host are invariably complex, models of pulmonary infection have provided crucial information regarding the regulation of inflammatory and immune responses. These insights should eventually allow the development of rational strategies regarding vaccination and immunotherapy. The use of animal models offers the possibility of understanding the mechanisms that regulate immune responses sufficiently well so that the response to a specific antigen could be controlled. A more complete understanding of host defense would allow the stimulation of deficient responses and the suppression of harmful responses to microbial pathogens and other antigens that enter the lung.

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112

Approach to the Patient with Pulmonary Infection

Jay A. Fishman

I. THE PATIENT WITH PNEUMONIA

Pneumonia is a common cause of infection-related mortality and is one of the most important challenges in clinical medicine. Inappropriate treatment of pulmonary infection contributes to poor clinical outcomes and to the emergence of antimicrobial resistance. Pneumonia is defined as inflammation of the pulmonary parenchyma caused by an infectious agent. The clinical syndrome of pneumonia may include fever or hypothermia, sweats, rigors or chills, and pulmonary symptoms such as cough, sputum production, dyspnea, pleurisy or pulmonary lesions observed on radiographic examination. The diagnosis and management of pneumonia has been complicated by the discovery of newer pathogens, expanded antimicrobial resistance, increased populations of immunocompromised patients, and by newer diagnostic tools and antimicrobial agents.

Pneumonitis may be due to both infectious and noninfectious causes and only reflects inflammation. A variety of eponyms have been applied to various forms of pneumonia that *may* reflect the epidemiology of the process and the likely causative organisms: aspiration pneumonia, community-acquired, nosocomial pneumonia, immunocompromised host, and atypical pneumonia (Table 112-1). These descriptions coupled with the radiologic appearance are useful in considering empiric therapy while awaiting microbiologic data. Consideration of potential immune deficits in each host will help to define the urgency of empiric antimicrobial therapies. These categories may be misleading, emphasizing the importance of definitive microbiologic diagnosis in optimizing clinical care (Table 112-2). Physical findings may also be unreliable—particularly since reliance on radiologic techniques has displaced the physical examination as an art form. Further, dual processes are common and physical findings are often muted in the immunocompromised host. "Crackles" and rales are "heard" much more often than the actual frequency of pulmonary consolidation. Commonly, radiographic appearances are misconstrued as etiologic diagnoses: consolidation, bronchopneumonia, miliary patterns, nodules, abscesses, fluid collections, pleural effusions, interstitial pneumonitis, and lymphadenopathy. The goal of the

Table 112-1

Categorization of Pneumonia by Clinical Setting

Community-Acquired Pneumonia
- Typical (i.e., classic) pneumonia
- Atypical pneumonia
- Aspiration pneumonia

Pneumonia in the Elderly
- Community-acquired
- Nursing home residents

Nosocomial Pneumonia
- Hospital-associated pneumonia
- Ventilator-associated pneumonia
- Health care facility associated pneumonia

Pneumonia in Immunocompromised Hosts
- Immunoglobulin and complement deficiencies
- Granulocyte dysfunction or deficiency (cyclic neutropenia, chronic granulomatous disease)
- Cellular and combined immune deficiencies
  - Neoplastic disease
  - Solid organ and hematopoietic transplant recipients
  - Untreated HIV infection
  - Immune reconstitution syndromes (AIDS, neutropenia)
  - Severe combined immunodeficiency (SCID) and congenital deficiencies
  - Autoimmune and connective tissue disorders
  - Other immunocompromised patients

Cystic Fibrosis and Anatomic Disorders
- Bronchopulmonary sequestration

Table 112-2

Routine Evaluation of Patients with Suspected Pneumonia

History
- Age
- Community (respiratory viruses, antimicrobial resistance) vs. hospital (ventilator)
- Pace of onset, dyspnea
- Recent infections (postviral pneumonia, endocarditis, aspiration)
- Recent hospitalization or exposure to medical facilities (extended care)
- Underlying conditions (mental status, immunity, cardiopulmonary, medications)
- Exposures (illness, children, institutions, animals, gardens, travel)
- Antimicrobial therapies, home infusion therapy, vaccinations
- Duration of hospitalization or endotracheal intubation

Physical Examination

Laboratory
- Complete blood count with differential counts
- Electrolytes, liver function tests, blood urea nitrogen, creatinine

Radiology
- PA and lateral chest radiograph
- *Consider need for:* Chest CT with contrast, echocardiogram, thoracentesis

Microbiology
- Sputum Gram's is stain, culture and sensitivity (susceptibility)
- Nasal swab (direct immunofluorescence) for respiratory virus panel (influenza, respiratory syncytial virus, parainfluenza, adenovirus)
- Blood cultures (2)

Consider in appropriate setting:
- Pneumococcal urinary antigen
- *Legionella* urinary antigen
- *Histoplasma* urinary antigen
- Acid-fast smear (modified acid-fast smear) and culture
- Acute and convalescent sera *(Mycoplasma, Chlamydophila*, Q fever (*Coxiella burnetti*), *Histoplasma, Coccidioides, Tularemia*)
- HIV status
- Molecular assays (cytomegalovirus, Epstein-Barr virus)

clinician is to define the etiology of pulmonary processes as rapidly as possible so as to facilitate management.

Host Defenses

The presence of pneumonia should be taken as evidence of an immune defect relative to the epidemiological pressure of the microorganisms. A small inoculum of an organism of high intrinsic virulence (adhesion, invasive enzymes, motility, intracellular pathogens) may cause infection in a relatively normal host. Organisms of low virulence should cause infection only if there is an immune or anatomic predisposition to infection or with a high burden of organisms. Microorganisms may reach the lungs via the airways, bloodstream, or lymphatics. Defects in specific components of the immune system (innate and acquired) predispose to specific types of infection (Table 112-3). An important first step in many infections is colonization of the upper airway via adhesion of organisms to

Table 112-3

Infections Associated with Specific Immune Defects

Defect	Common Causes	Associated Infections
Granulocytopenia	Leukemia, cytotoxic chemotherapy, AIDS, drug toxicity, Felty syndrome	Enteric gnr, *Pseudomonas, S. aureus, S. epidermidis,* streptococci, *Aspergillus, Candida* and other fungi
Neutrophil chemotaxis	Diabetes, alcoholism, uremia, Hodgkin's disease, trauma (burns), lazy leukocyte syndrome, CT disease	*S. aureus*, Candida, streptococci
Neutrophil killing	CGD, myeloperoxidase deficiency	*S. aureus, E. coli, Candida, Aspergillus, Torulopsis*
T-cell defects	AIDS, congenital, lymphoma, sarcoidosis, viral infection, CT diseases, organ transplants, steroids	Intracellular bacteria (*Legionella Listeria*, mycobacteria), HSV, VZV, CMV, EBV, parasites
B-cell defects	Congenital/acquired agammaglobulinemia, burns, enteropathies, splenic dysfunction, myeloma, ALL surgery, sickle cell disease, cirrhosis	(*Strongyloides, Toxoplasma*), fungi (*P. carinii, Candida, Cryptococcus*) *S. pneumoniae, H. influenzae, Salmonella* and *Campylobacter spp, Giardia lamblia*
Splenectomy		*S. pneumoniae, H. influenzae, Salmonella spp, Capnocytophaga*
Complement	Congenital/acquired defects	*S. aureus, Neisseria spp, H. influenzae, S. pneumoniae*
Anatomic	IV/foley catheters, incisions, anastomotic leaks, mucosal ulceration, vascular insufficiency	Colonizing organisms, resistant nosocomial organisms

HSV, herps simplex virus; VZV, Varicella zoster virus; CMV, cytomegalovirus; EBV, Epstein-Barr virus.

the epithelial surfaces. These surfaces are normally protected against infection by mechanical clearance of organisms via the nose or oropharynx, local production of complement and immunoglobulin A (IgA), saliva, sloughing of epithelial cells, and bacterial interference by "normal flora". Changes in these surfaces (diminished IgA secretion, changes in production of adhesins, fibronectin, altered lectin binding) predispose to adhesion of microorganisms. Organisms carrying enzymes that can degrade IgA exotoxins, adhesion proteins, or pili are favored in colonizing the respiratory epithelium. Mucociliary clearance may be disrupted by cigarette smoking, viral infection, *Haemophilus influenzae*, or *Mycoplasma pneumoniae* infection. Aspiration can result from altered closure of the glottis (neurological injury, sleep apnea, intubation, alcohol, anesthesia). Once past the glottis, most bacteria and viruses are small enough (up to 2 microns) to reach the alveoli unless impeded by alveolar lining fluid containing surfactant, immunoglobulin G (IgG), complement, and other proteins. Surfactant includes a variety of components that serve to activate alveolar macrophage and neutrophil functions and may serve as an opsonin (SP-A and SP-D) for many types of organism. Organisms surviving the defenses of the upper airway are left to the cellular components of the lower airways including T- and B-lymphocytes, macrophages, and dendritic cells.

Pulmonary defense mechanisms are also disrupted by systemic infections (sepsis), acidosis, hypoxemia, pulmonary edema, malnutrition, uremia, age, and lung injury (acute respiratory distress syndrome, ARDS). Endotoxin and lipopolysaccharide diminish clearance of bacteria from the lungs. Viral infections may diminish neutrophil and macrophage functions, including phagocytosis, chemotaxis, and oxidative metabolism.

General Guidelines for Management of Pneumonia

The individual with pulmonary infection often presents in an ambulatory setting. The evaluation of the patient with possible pneumonia depends on a series of questions that provide clues to management, including the need for hospitalization and selection of antimicrobial agents. Subsequently,

microbiologic data provide the basis for adjusting antimicrobial therapy. The questions include:

1. *Is the process life-threatening?*
   a. Does the patient need to be admitted to the hospital? *Does the patient have supports in the community?* Can he/she manage oral medications, other therapies, and follow-up visits from home?
   b. What is the time course of the process? Is the infection rapidly progressive or gradual? Is there time to delay therapy or diagnostic procedures?
   c. Does the patient need supplemental oxygen, assisted ventilation, surgery, blood products, monitoring, or isolation?
2. *Does the patient have immune deficits?* Could the process be underestimated based on the absence of normal inflammatory responses?
3. *What are the most common infections in the community or hospital or institution where this "infection" was acquired?* In this appraisal, it is helpful to resort to clinical groupings: community-acquired, nosocomial (hospital, ventilator, health care facility), and pneumonia in the immunocompromised patient. Such groupings provide a guide to empiric therapy while evaluation is underway. It is important to understand the incidence of tuberculosis, acquired immunodeficiency syndrome (AIDS), respiratory viral infections, and antimicrobial-resistant organisms (*Pneumococcus, Staphylococcus*) in the community and of antimicrobial resistance in the institution.
4. *What are the gross pathological and pathogenetic features of the pulmonary process?* These may include frank pneumonia, focal infiltrate, lung abscess, chronic cavitary lesion, bronchiectasis, or miliary lesions. As a corollary, since pulmonary infections are occasionally generated by the hematogenous route, rather than by the bronchogenic route, consider possible extrapulmonary processes in the pathogenesis of pulmonary infection.
5. *History:* Are there clues to a specific etiology of infection and to the severity of the illness?
   a. Underlying clinical conditions: Chronic obstructive pulmonary disease (COPD), immune deficits, altered mental status, prior infections.
   b. Epidemiological history (i.e., travel, contacts, exposures, vaccines, medications, prior infections or hospitalizations): Has the patient traveled or does he/she have any hobbies (gardening, hiking, cooking) that might provide an epidemiological clue (Table 112-4)?
   c. Symptoms: Rate of progression, other systemic signs. Prior mild respiratory illness ("the flu") with improvement and then rapid deterioration is suggestive of bacterial superinfection of viral pneumonitis, consistent with *Staphylococcus*

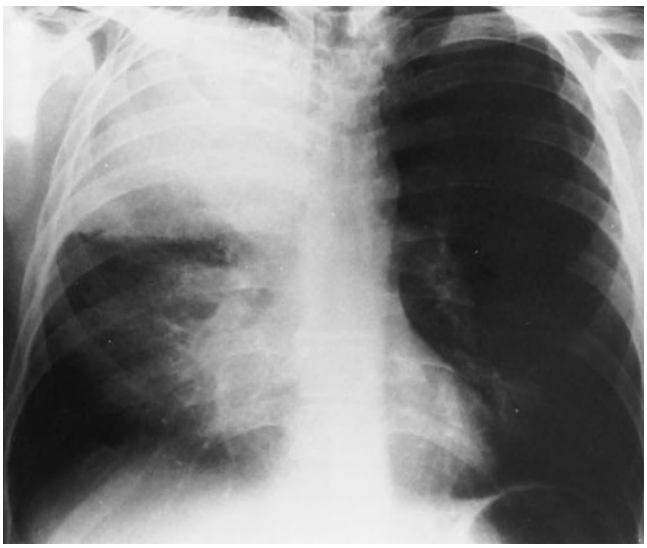
Table 112-4

Epidemiologic Exposures Associated with Pneumonia

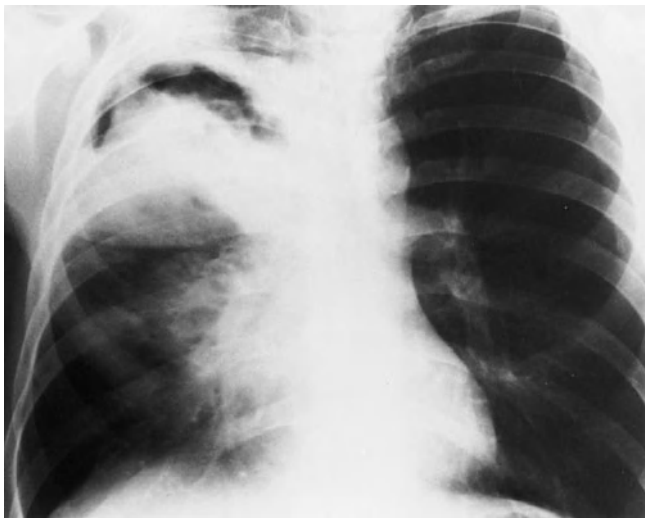
Pathogen	Epidemiology
Anthrax	Bioterrorism; animals, hides, raw wool, goat hair
Brucella sp.	Domestic animals, dairy products, abattoir, veterinarian
Chlamydophila psittaci	Birds: parrots, budgerigars, cockatoos, pigeons, turkeys
Coccidioidomycosis	Southwest United States, Southern California, San Joaquin Valley
Coxiella burnetii	Cattle, domestic animals, cats
Hantavirus	Rodent droppings/urine (virtually all states)
Histoplasmosis	Bird/bat droppings
Legionella	Contaminated aerosols
Leptospirosis	Rodents, animals, water contaminated by animal urine
Melioidosis	West Indies, Australia, Southeast Asia, South Central America—delayed onset post-exposure
Pasturella multocida	Dogs, cats
Plague (*Yersinia, pestis*)	Bioterrorism; squirrels, chipmunks, rabbits, prairie dogs, rats
Paracoccidioides	South America (Brazil)
Q fever	Goats, sheep, cattle, domestic animals (feces, amniotic fluid, placenta, milk)
Rhodococcus	Horses, soil, farms
Severe acute respiratory syndrome/ (SARS)	Endemic regions, nosocomial exposures

aureus or other bacterial infection. The abrupt onset of illness with recurrent (over several days) shaking chills, particularly if associated with mild diarrhea for 1 or 2 days, may suggest Legionnaires' disease. Pneumococcal pneumonia may be associated with a single severe rigor with fever, often with symptomatic herpes labialis. Gastrointestinal symptoms and confusion may occur with any infection but are often notable with pneumococcal pneumonia and Legionnaires' disease. The presence of extrapulmonary signs or symptoms is often a better clue to the nature of infection than are pulmonary symptoms.

6. *Physical examination:* Skin lesions (e.g., furuncles, endocarditis, or gram-negative sepsis), lymph nodes (symmetrical or regional), retinal examination, ear examination (bullous myringitis with *Mycoplasma* infection), periodontal disease or absent gag reflexes (with aspiration pneumonia), ipsilateral chest splinting, and neurological disease (pulmonary-brain syndromes) are often ignored but provide valuable clues. Dullness to percussion, bronchial breath sounds, and egophony (E to A changes) are suggestive of pulmonary consolidation but may be absent. Patients infected with *Pneumocystis carinii*, *Mycoplasma*, or viruses (or severe immune compromise) may have normal chest examinations despite abnormal chest radiographs and marked hypoxemia.
7. *Basic laboratory data:* Many systemic processes are reflected in abnormalities of blood counts, urinalysis, and routine blood chemistries. For example, the presence of mild liver function abnormalities might suggest Q fever, tularemia, miliary tuberculosis, or Legionnaires' disease. The presence of pigmented casts in the urine and markedly elevated serum levels of creatine phosphokinase might focus attention on the possibilities of influenza virus pneumonia, Legionnaires' disease, or a pulmonary infiltrate associated with intravenous drug abuse. Rapid screening tests (e.g., for respiratory viruses) are useful, but have limitations in terms of sensitivity.
8. *Radiology:* All patients with pneumonia merit chest radiography, preferably posterior-anterior and lateral views since portable films are often of limited value. Radiographs allow the physician to assess the severity of pneumonia and to distinguish this process from acute bronchitis; the latter, when infectious, is often viral in etiology. No radiographic findings are specific enough to define the microbial origin of a given pneumonia or pulmonary infiltrate. The only definitive way to obtain a specific etiologic diagnosis is through demonstration of the infecting organism—i.e., by examination of stained smears of sputum and pleural fluid or other biologic materials, by culture of respiratory secretions and blood, by demonstration of nucleic acids or proteins from an infecting microorganism, or by demonstration of an increase in antibody titer against the infecting microorganism. Nonetheless, the radiographic picture, taken along with other clinical information, can favor one or several etiologic agents. Involvement of multiple pulmonary lobes in the process and the presence of a pulmonary effusion are poor prognostic features.
   a. Define the radiographic pattern as either lobar (Fig. 112-1) or segmental consolidation, patchy bronchopneumonia, nodules (large, small, or miliary) (Fig. 112-2), or an interstitial process (Table 112-5). For example, many large, round pulmonary densities in a renal transplant recipient suggest *Nocardia* infection rather than *Pneumocystis* pneumonia, whereas in a heroin addict with cough, fever, and pleuritic chest pain, such densities suggest acute right-sided endocarditis rather than pneumococcal pneumonia.
   b. Compare with prior radiographs: Is the process old or new? Are there multiple processes? Has the patient had surgery in the intervening period? Is the spleen enlarged or absent?
   c. Confounding variables: Is it too early in the process to detect radiologic changes (first 18 to 24 h)? Is the patient neutropenic (early viral or fungal pneumonitis) or otherwise immunocompromised (*P. carinii* pneumonia often occurs with minimal or no findings on plain chest radiographs)? Dehydration is commonly cited as a cause of false-negative radiographs, but, in general, this concept is probably overrated.
   d. Computed tomography (CT) scanning is sensitive to changes unrecognized in plain radiographs and may be useful in guiding invasive procedures.
9. *How can a diagnosis be achieved most expeditiously?* Is this likely to be a viral process that can be diagnosed in the office? Which invasive procedures are done well at your institution?
10. *Examination of clinical specimens* (appropriately stained smear of sputum or pleural fluid, blood buffy coat, skin lesions, throat swabs) often provides a provisional diagnosis. Examination of an appropriately stained smear of sputum can provide a shortcut to diagnosis if the findings are reasonably definitive.
    a. Gram-stained smears provide valuable information regarding the morphology and the tinctorial properties of bacteria (and some fungi) but also about the presence of polymorphonuclear leukocytes and squamous epithelial cells, the latter indicating that the specimen originated in the upper, rather than the lower, respiratory tract (Fig. 112-3).
    b. Other special staining methods, including Kinyoun and modified acid-fast stains for



A



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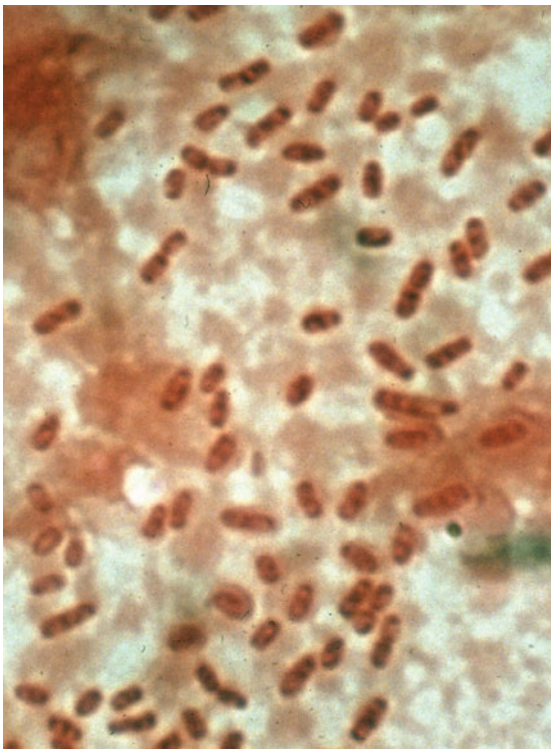


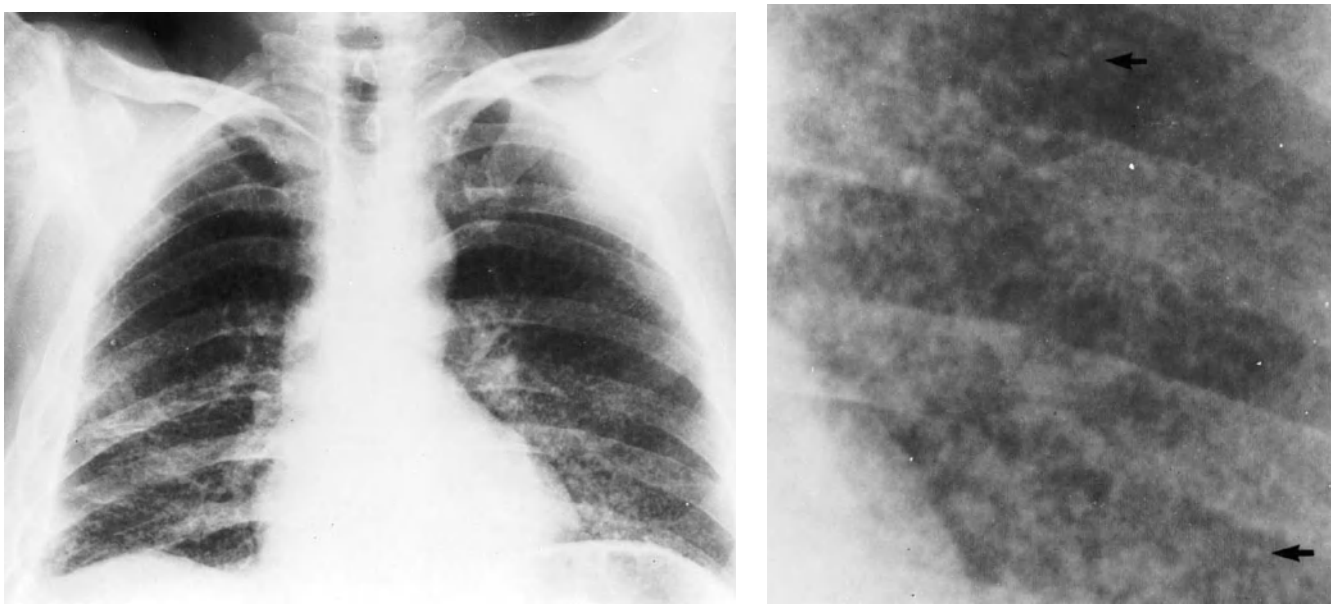
C

Figure 112-1 *A*. Dense lobar consolidation involving right upper lobe and right middle lobe in an alcoholic patient with *Klebsiella pneumoniae* pneumonia. The minor fissure is bulging downward. *(Courtesy of Dr. R. Greene.) B*. Same patient 7 days later. Despite antibiotic therapy, *K. pneumoniae* pneumonia progressed to become a necrotic process with formation of multiple abscesses. *(Courtesy of Dr. R. Greene.) C*. Sputum Gram's stain from patient with *K. pneumoniae* infection reveals gram-negative rod forms with trace of a surrounding capsule.

mycobacteria can provide additional data. *Actinomyces* or *Nocardia* species and Wright-Giemsa or a variant such as Diff-Quik or direct fluorescent antibody staining of induced sputum samples for *P. carinii* or *Legionella pneumophila* may provide a diagnosis.

c. Culture of sputum or blood or other bodily fluids may provide a specific etiologic diagnosis when evaluation of a sputum smear has not supplied a provisional diagnosis. The failure may be caused either because the infecting agent cannot be distinguished from components of the normal upper-respiratory-tract flora which are incorporated in the specimen or because the particular microorganism is not visible on Gram-stained smear (e.g., *Aspergillus* species or *M. pneumoniae*).

d. In some patients, an etiologic diagnosis cannot be made on the basis of initial smears or cultures. In such circumstances, a definitive diagnosis can sometimes be made by alternative means—e.g., urinary antigen tests for *Legionella* or *Histoplasma* infections, antigenemia or nucleic acid polymerase chain reactions for viral processes



A *B*

Figure 112-2 Miliary tuberculosis in a 45-year-old immigrant from Portugal with old calcified tuberculous empyema on the right. *A*. Fine nodularity present in both lungs. *B*. Arrows point to individual miliary lesions, which are more readily visible with added magnification. *(Courtesy of Dr. R. Greene.)*

(Tables 112-2 and 112-6) or, retrospectively, by serologic means, as in psittacosis, Q fever, or adenovirus pneumonia. Screening tests are highly useful for respiratory viruses (nasal swab coupled with immunofluorescence). Induced sputum examinations have a high yield for *Pneumocystis* and mycobacteria.

e. Invasive diagnostic procedures: In patients who are critically ill or unlikely to tolerate invasive infections (immunocompromised hosts, recent major surgery, heart failure, COPD) it is reasonable to consider more invasive diagnostic procedures early in the clinical course. In such patients, only specific etiologic diagnoses can direct appropriate therapy. However, this observation illustrates the tension between empiric therapies and the risks inherent in invasive tests. Empiric antimicrobial therapies carry the risk of obscuring a specific microbiologic diagnosis as well as evoking drug-associated toxicities. Invasive diagnostic procedures are used to obtain uncontaminated lower-respiratory-tract secretions or pulmonary tissue for microbiologic and histologic analysis. The selection of an invasive procedure should be based on the nature of the illness and the likelihood of success for each procedure afforded by the institution. Among the invasive procedures that are available are:

(1) protected specimen brushing (PSB)
(2) plugged telescoping catheter (PTC) sampling
(3) standard bronchoalveolar lavage (BAL)
(4) protected bronchoalveolar lavage (P-BAL or PTC-BAL)
(5) transtracheal aspiration (now uncommon)
(6) fiberoptic bronchoscopy with transbronchial biopsy
(7) needle biopsy of the lung
(8) open lung biopsy via limited or video-assisted thoracotomy.

Important considerations in selecting an invasive procedure include the type and location of the pulmonary lesion, the ability of the patient to cooperate with the required manipulations, the presence of coagulopathies, and experience at the particular hospital in performing the particular procedure.

11. *Antimicrobial therapy:* In practice, initial therapy is empiric and based primarily on clinical clues. The selection of drug(s) for empiric therapy depends on the clinical setting and on the gravity of the pulmonary process. The selection of specific antimicrobial agents is considered in subsequent chapters.

PULMONARY INFECTIONS: PATHOLOGICAL AND PATHOGENETIC FEATURES

Pulmonary infections can be categorized according to distinctive pathological, anatomic, and radiologic features. Some general patterns are presented below for their value in

Table 112-5

Radiographic Features and Differential Diagnosis of Pneumonia in an Immunocompetent Host

Consolidation/Focal opacity	*S. pneumoniae, M. pneumoniae, H. influenzae, C. pneumoniae, Legionella* sp., *S. aureus, M. tuberculosis*, and "atypical" mycobacteria (*M. avium* complex)
Cavitation	*S. aureus*, anaerobic bacteria, *M. tuberculosis*, gram-negative aerobic bacteria, *Aspergillus sp.*, geographic/endemic fungi (*H. capsulatum, C. immitis, B. dermatitidis*)
Interstitial infiltrates	Viruses, *M. pneumoniae, M. tuberculosis*, geographic/endemic fungi, *C. psittaci*
Miliary	*M. tuberculosis*, geographic/endemic fungi, viruses, *M. pneumoniae*
Lymphadenopathy	*M. tuberculosis*, viral , Epstein-Barr virus, cytomegalovirus, rubella), geographic/endemic fungi, *C. psittaci*, cat-scratch disease.

differential diagnosis and are discussed in detail in subsequent chapters.

Bacterial Pneumonia

Bacterial pneumonia commonly results from bronchogenic spread of infection following microaspiration of pharyngeal secretions. Such particles reach terminal airways and alveoli where they initiate infection, which has the anatomic distribution and radiologic appearance of subsegmental, segmental, or lobar consolidation. Pneumonia may be patchy, with a peribronchial and multifocal distribution, and occur in association with aspiration and bronchial plugging, superinfection of preexisting chronic bronchitis, diffuse acute tracheobronchial inflammation (e.g., influenza, parainfluenza), and with specific infecting microorganisms (e.g., oral anaerobic bacteria). The progression of a pulmonary infiltrate or lobar consolidation to parenchymal destruction (necrotizing pneumonia or lung abscess) is usually the consequence of one or more of three factors: the intrinsic virulence of the infecting organism(s), the presence of bronchial obstruction

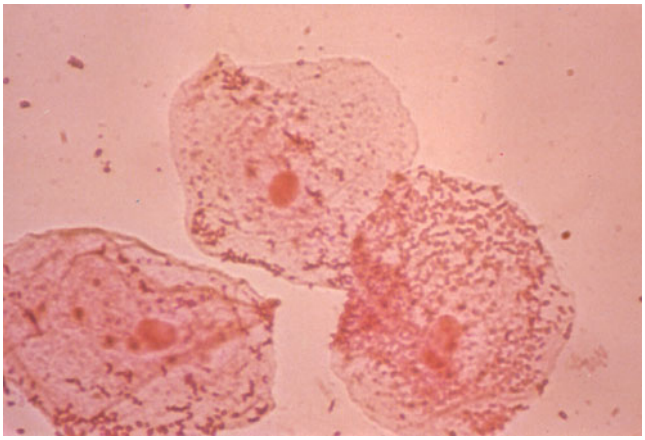


Figure 112-3 Three large oropharyngeal epithelial cells from a specimen of "sputum" that is inadequate for Gram's stain analysis and culture because of its origin in the upper respiratory tract. Note the large number of organisms agglutinated on the surface of the squamous epithelial cells (×400).

or other anatomic abnormality, or immune compromise of the host (Fig. 112-1).

Pneumonia may develop via the bacteremic route rather than the bronchogenic route. The clinical setting and the radiographic pattern usually suggest this type of pathogenesis. The intravenous drug abuser with *S. aureus* bacteremia and acute right-sided endocarditis presents with fever, cough, purulent sputum, a murmur of tricuspid insufficiency, numerous irregular infiltrates, and rounded densities on chest radiograph. Similarly, burn patients with *Pseudomonas aeruginosa* bacteremia and multiple nodular pulmonary densities are apt to have bacteremic *Pseudomonas* pneumonia with pulmonary bacterial arteritis. Septic pulmonary emboli, arising from septic thrombosis of the jugular vein may cause a clinical and radiographic picture suggestive of multifocal bronchopneumonia. On the chest radiograph, however, the lesions are nodular; histologically, they represent septic pulmonary infarcts (following emboli) upon which are engrafted pyogenic infection and abscess formation.

Lung Abscess

A lung abscess is an area of pulmonary infection with parenchymal necrosis. Lung abscesses may be solitary or may occur as multiple discrete lesions. Most often a lung abscess is secondary to aspiration of anaerobic or anaerobic and aerobic organisms which have colonized the upper-respiratory tract and may be associated with periodontal disease (Fig. 112-4). Superinfection of damaged or infarcted lung tissue (e.g., as occurs in aspirational pneumonia after chemical injury and anaerobic superinfection or primary anaerobic infection) progresses to necrosis and to microscopic foci of abscess formation. Confluence of small necrotic foci can either create one or more lung abscesses or lead to a progressively fibrotic, shrunken, and destroyed lobe. *Pulmonary gangrene* is an unusual consequence of severe pulmonary infection characterized by sloughing of a pulmonary segment or lobe. This

Table 112-6

Assays for Viral Agents of Adults

Virus (Type)	Season	Culture/Specimen	Culture Days to Positive	DFA/ Serology	Molecular Amplification*
Influenza A/B (RNA)	Winter	Nasopharyngeal wash/BAL	3–5	+/+	Qual
RSV (RNA)	Fall/Winter	Nasopharyngeal wash/BAL	5–7	+/+	Qual
Parainfluenza(RNA)	Fall/Spring	Nasopharyngeal wash/BAL	5–7	+/+	Qual
Adenovirus (DNA)	All	Nasopharyngeal swab, stool	3–5	+/+	Qual/Quant
Measles (RNA)	All	Conjunct, nasopharyn; BAL, blood, urine	2–15	Fair −/+	N/A
EBV (DNA)	All	PBL-PCR, mono spot, serum	1–7	−/+	Qual/Quant (not well standardized)
CMV (DNA)	All	Blood, urine, BAL, saliva	2 (shell vial)–14	+/+	Qual/Quant antigenemia pp65
VZV (DNA)	All, Spring	Vesicle, throat, BAL, blood	Slow	+/+	Qual/Quant
HSV1, HSV2 (DNA)	All	Vesicle, BAL, blood	1–2	+/+	Qual/Quant (HSV1/2)
SARS Coronavirus (RNA)	All, Spring (Asia)				Qual
Human metapneumovirus (RNA)	All, Spring				Qual

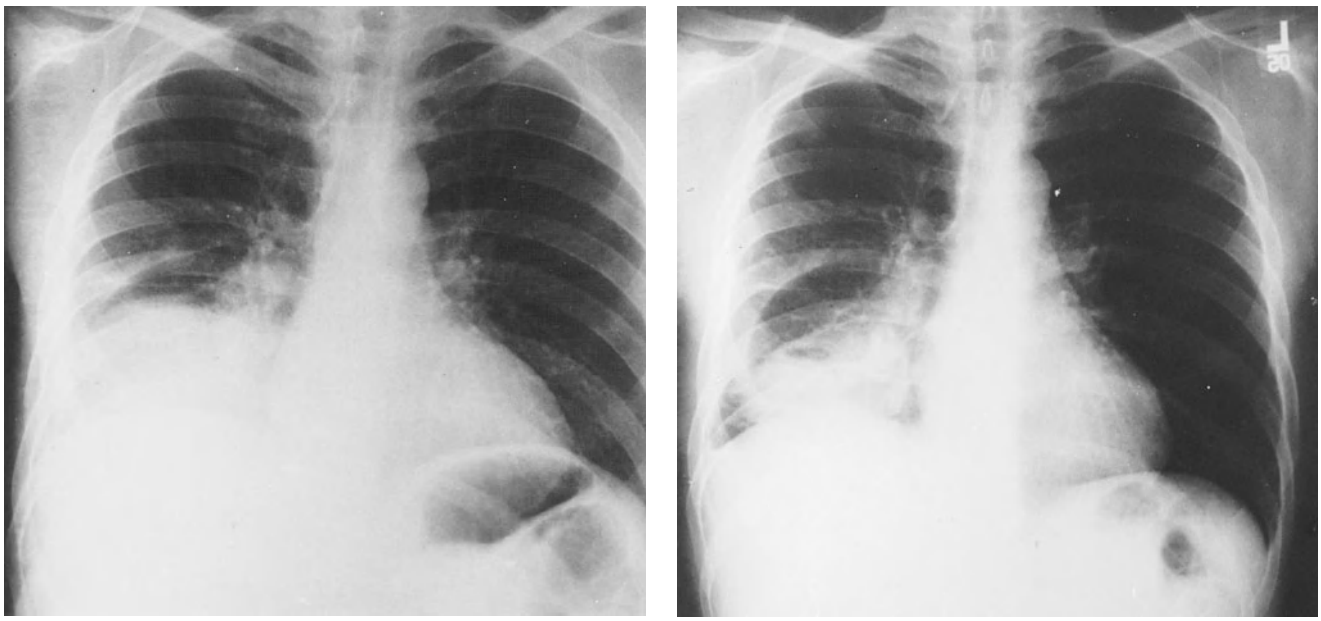
**Qual: qualitative assay; Quant: quantitative assay. Abbreviations: DFA, direct fluorescent antibody; BAL, bronchoalveolav lavage; RSV, respiratory syncytial virus; EBV, Epstein-Barr virus; PBL-PCR, pevipheral blood leukocytes – polymerase chain reaction; CMV, cytomegalovirus; VZV, varicella zoster virus; HSV, herpes simplex virus; SARS, severe acute respiratory syndrome.*

process affects an entire segment or lobe secondary to thrombosis of both bronchial and pulmonary arteries followed by pulmonary infarction. The organism most commonly implicated has been *Klebsiella pneumoniae*, but others which have been implicated include *Streptococcus pneumoniae*, *Escherichia coli*, mixed anaerobes, *H. influenzae*, and *S. aureus*. If there is some degree of ball-valve bronchial obstruction, air may enter while contained pus may fail to drain, producing the radiographic picture of an air-fluid level.

Other causes of lung abscess are (1) progression of a bronchogenic pneumonia due to a pathogen with necrotizing potential (e.g., *K. pneumoniae*, Fig. 112-1) or *Nocardia asteroides* in an immunocompromised patient, (2) bacteremic spread of infection, and (3) septic pulmonary emboli. Lung abscesses complicating necrotizing pneumonia should be distinguished from pneumatoceles; the latter are thin-walled, air-filled structures that often develop early in the course of staphylococcal pneumonia, particularly in infants and young children, and usually disappear over the course of a few months.

Bronchitis and Bronchiectasis

Acute bronchitis is an inflammatory process, usually of viral origin, confined to the bronchi and bronchioles; it does not extend appreciably to surrounding pulmonary parenchyma



A *B*

Figure 112-4 Necrotizing pneumonia, probably secondary to aspiration in a 39-year-old man, smoker and drinker, previously healthy. Onset was with cough, shortness of breath, fever, and right-sided pleuritic pain. Despite antibiotics, signs and symptoms progressed to include high fevers, night sweats, greenish sputum, leukocytosis, and manifestations of hypertrophic osteoarthropathy. *A*. On admission, there was consolidation of right lower lobe, a right hilar mass (or adenopathy), and right pleural effusion. Mediastinoscopy and bronchoscopy revealed no tumor. *B*. Three months later, the process in the right lower lobe is more circumscribed. Right lower lobectomy revealed extensive necrotizing pneumonia, multiple abscesses, and ''reactive" lymph nodes. Postoperatively, the patient was free of signs and symptoms, including hypertrophic osteoarthropathy.

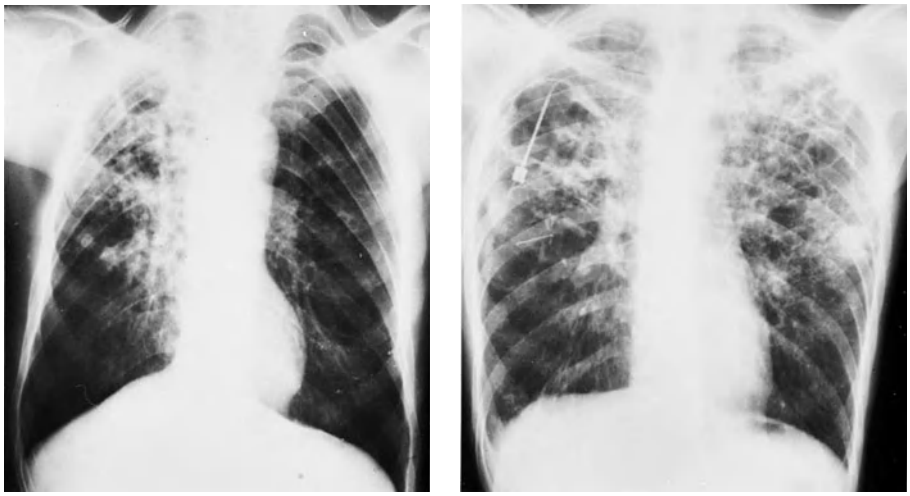
and is not evident on radiographic examination. Purulent inflammatory secretions are common even though there may be no discernible bacterial infection. Such purulent secretions represent bacterial superinfection. The diagnosis of an acute exacerbation of chronic bronchitis is based solely on clinical grounds; the manifestations are increased cough, dyspnea, and enhanced production of purulent sputum, with or without fever, in a patient with COPD. Bacteriologic examination generally reveals large numbers of pneumococci or nontypeable *H. influenzae*, either as infecting organisms or as chronic colonizers of the bronchial tree. Patients with acute exacerbations of chronic bronchitis tend to improve with antimicrobial treatment while those with chronic bronchitis are less likely to improve with therapy.

Bronchiectasis is characterized by destruction of epithelial, elastic, and muscular elements of bronchi, resulting in their irreversible dilatation. The major proximate cause is repeated or chronic bacterial infection. However, predisposition to such infections may be a consequence of a variety of factors, including certain types of prior infection (pertussis, adenovirus, or rubeola infections, necrotizing pneumonia), bronchial obstruction, immunodeficiencies, congenital anatomic lung disease (e.g., congenital tracheobronchomegaly), and other hereditable disorders, such as ciliary dysfunctional states and α_1-antitrypsin deficiency. Currently, cystic fibrosis is the most common predisposing factor for bronchiectasis. As a result of repeated infections, stasis of secretions, and peribronchial fibrosis, bronchi are grossly distorted or completely destroyed. Although pneumonia or lung abscess may accompany recurrent acute infections, exacerbations are usually confined to bronchial and peribronchial tissues.

Chronic Cavitary Disease

Chronic cavitary pulmonary disease is most often due to tuberculosis, but may be seen in α_1-antitrypsin deficiency, echinococcal disease, Wegener's granulomatosis, and other structural disorders. Tuberculosis commonly begins with a focus of pneumonitis, usually in the subapical posterior portion of an upper lobe. This patch of pneumonitis occurs at a latent site of earlier metastatic infection (Simon focus) produced by lymphohematogenous spread from primary pulmonary tuberculous lesions. Progressive caseation necrosis at this site, followed by drainage of caseous material through the bronchial tree, produces a cavity (Fig. 112-5). The cavity is encased in a rigid wall of fibrous tissue.

In addition to pyogenic lung abscess and pulmonary tuberculosis, other pulmonary infections can produce chronic cavities. These include *Nocardia* infections, *Rhodococcus equi* infections, actinomycosis, and chronic primary pulmonary mycoses (particularly histoplasmosis, occasionally coccidioidomycosis, uncommonly blastomycosis). Sporotrichosis can affect the lung and produce thin-walled cavities. Parasitic



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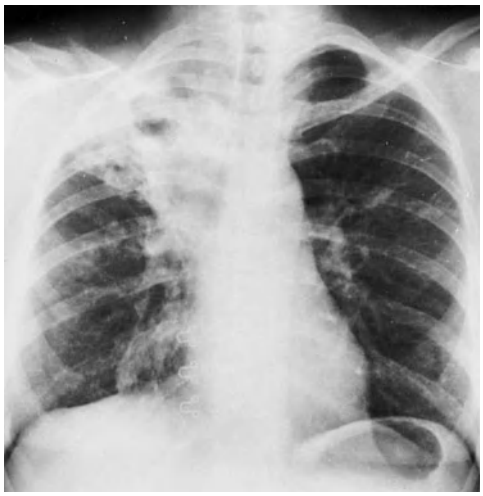


C

Figure 112-5 Tuberculous cavities. In each instance, the organisms were seen on smear and identified by culture. *A.* Fifty-six-year-old African-American man. Cavity amid consolidation. *B.* Seventy-two-year-old African-American man. Bilateral, multiple cavities. *C.* Forty-eight-year-old African-American woman. Spread from original involvement of right upper lobe.

infestation of the lung (paragonimiasis, echinococcosis) can also form cavities.

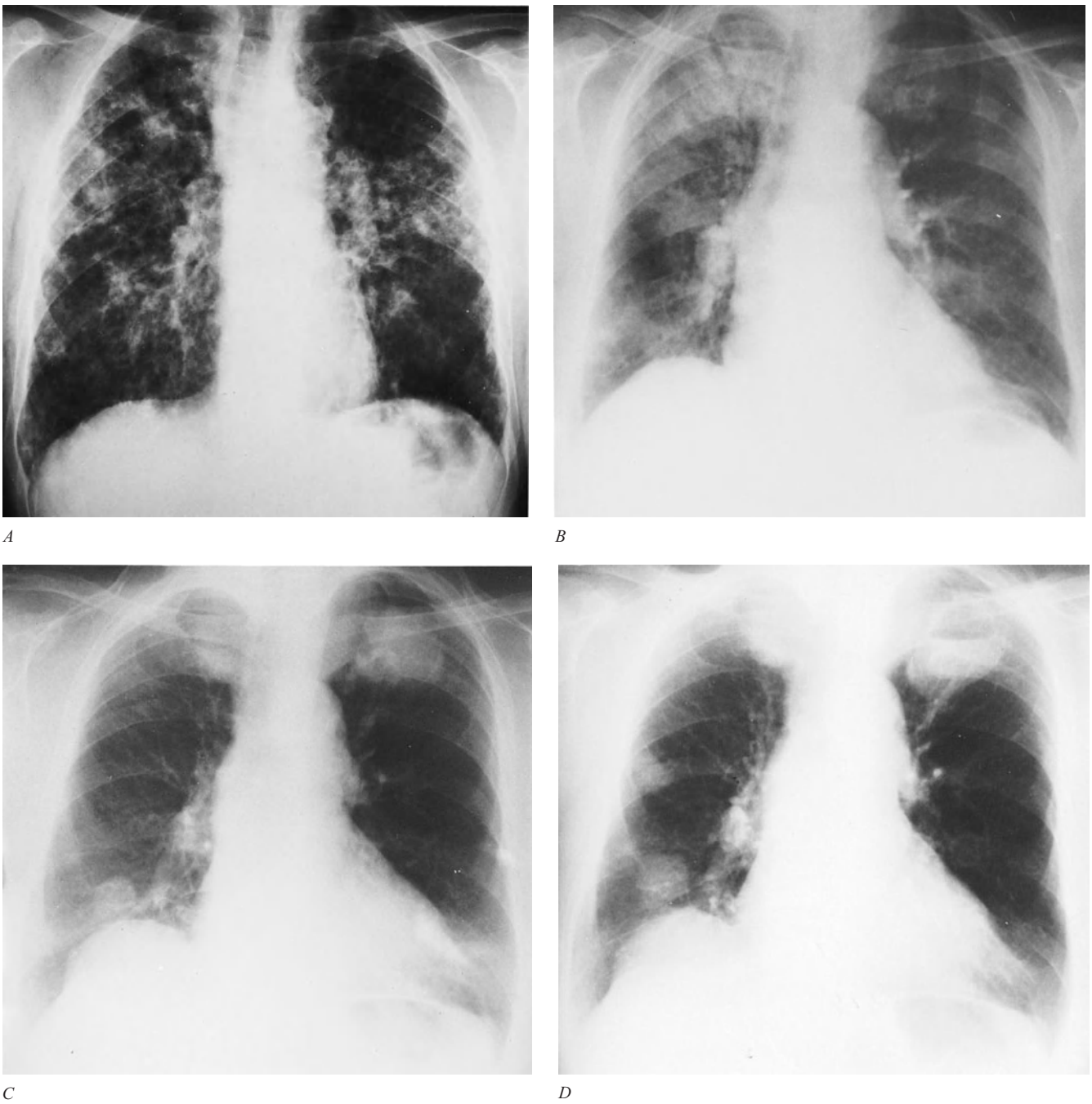
Pulmonary cavities may also occur in noninfectious disorders (e.g., Wegener's granulomatosis, lymphoma or bronchogenic carcinoma, bland pulmonary infarcts, and intrapulmonary nodules of rheumatoid lung disease) (Fig. 112-6). Such cavitary lesions, as well as the cystic lesions that occur in chronic pulmonary sarcoidosis (Fig. 112-7) and in the markedly dilated bronchi of saccular bronchiectasis, can be the sites of *fungus balls.* These represent tangled masses of fungal hyphae and debris lying freely within pulmonary cavities generally as noninvasive saprophytic growths in the immunologically normal host. Most often the mycotic agent is an *Aspergillus* species (usually *A. fumigatus*), and the fungus balls are called *aspergillomas.* Hemoptysis originating from the cavity wall is common and may be severe.

Miliary Lesions

Hematogenous dissemination of tuberculosis can follow initial infection in children or adults. It also can result from breakdown of formerly quiescent sites of pulmonary or extrapulmonary infection. Clinically unexplained fever may be accompanied by miliary lesions (which resemble millet seeds and are very small and uniform in shape) on the chest radiograph; histologically, these lesions are foci of granulomatous reaction (Fig. 112-2). Similar radiographic lesions also occur in the course of hematogenously disseminated bacterial and mycotic infections including cryptococcosis and histoplasmosis.

Viral Infections of the Respiratory Tract

Respiratory viral infections are a major cause of morbidity worldwide. Patients present with cough, sore throat, bronchoconstriction, fever, rhinitis, and suffusion of mucous membranes. The majority of these infections are upper respiratory infections and of significance only as causes of discomfort and as predisposing conditions for infection of the lower respiratory tract. Spread is via aerosolized droplets and hand contamination. The most prominent viral pathogens include rhinovirus and coronavirus for which no specific antimicrobial therapies are available. Commonly, adenovirus,



A *B*

C *D*

Figure 112-6 Wegener's granulomatosis. *A*. Onset with chills and fever in a previously healthy 64-year-old man. Lung biopsy was interpreted as Wegener's granulomatosis. Partial clearing in response to combined chemotherapy (cyclophosphamide and prednisone). *B*. Onset with malaise, headaches, and fever in a previously healthy 62-year-old woman. Bilateral maxillary sinusitis. Widespread nodular pulmonary infiltrates are most marked on the right. *C*. Same patient as *B* after 3 years of intermittent combined chemotherapy. Bilateral large masses. *D*. Same patient as *C*, 2 months later. Necrosis within mass in left upper lobe has produced a fluid level.

parainfluenza virus, respiratory syncytial virus (RSV), and influenza virus may also cause this syndrome. Infections with respiratory viruses occur predominantly in the winter and early spring. Less commonly, reovirus, enteroviruses, metapneumoviruses, and picornaviruses may cause the same symptoms. Of nonviral etiologies, treatable infections with *M. pneumoniae* and *Chlamydophila* (formerly *Chlamydia*) *pneumoniae* also cause significant upper- as well as lower-respiratory infections. The predominant differential diagnoses for these infections include allergic, vasomotor, or atrophic rhinitis or nasal polyposis. These syndromes should be considered in patients with an atopic history and recurrent

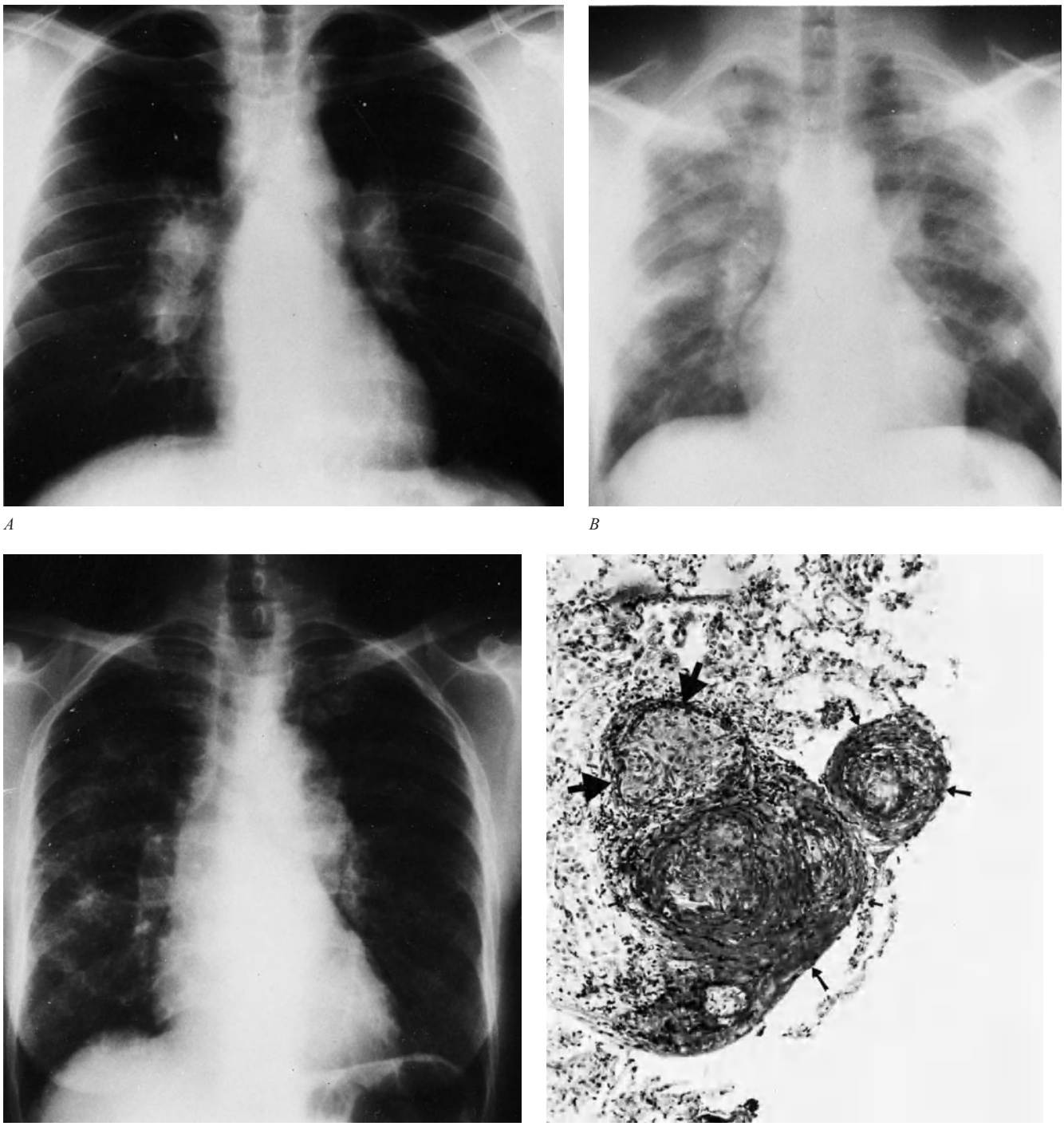


Figure 112-7 *A* to *C*. Chest radiographs illustrating the various stages of sarcoidosis. *A*. Stage I, bilateral hilar adenopathy. *B*. Stage II, bilateral hilar adenopathy with parenchymal infiltrates. *C*. Stage III, parenchymal infiltrates without hilar adenopathy. *D*. Transbronchial lung biopsy from a patient with sarcoidosis. Small arrows indicate granuloma with a surrounding rim of collagen (confirmed by positive trichrome staining). The large arrows indicate a granuloma without a surrounding rim of collagen. (Original magnification ×10.)

upper-respiratory infections. Although these infections are generally self-limited, common complications include sinusitis, otitis and bronchitis, exacerbations of chronic pulmonary disease (chronic bronchitis), asthma, and bacterial superinfection with pneumonia.

Viral Infections of the Lower-Respiratory Tract

Influenza virus is an agent of the family Orthomyxoviridae that may be associated with sizable outbreaks or major epidemics of upper-respiratory infections. Influenza is classified into three subtypes based on antigenic differences: influenza

A, B, and C. Primary influenza viral pneumonia usually occurs in the setting of an outbreak of influenza A infections. It impacts disproportionately on patients with underlying heart disease (mitral stenosis), chronic pulmonary disease, pregnancy, and immunocompromised individuals. Unlike secondary bacterial pneumonia after influenza—a complication that occurs after a period (1 to 4 days) of improvement following typical upper-respiratory illness—primary influenza pneumonia immediately follows typical influenza. Two classes of drugs are available to treat influenza A including M2 matrix protein inhibitors (amantadine and rimantadine) and neuraminidase inhibitors (zanamivir and oseltamivir). Resistance is emerging to both groups. Influenza A infects a wide range of species as hosts, including humans, pigs, birds, horses, and marine animals, whereas influenza B and C are generally restricted to humans. As a result, influenza A may move between host species, risking recombination, mutation (drift), and geographic spread. Pandemic influenza (e.g., avian influenza, H5N1) is most likely to arise in birds as all of the hemagglutinin and neuraminidase variants are carried in that population with viral replication in the gastrointestinal tract and secretion in high titers in feces. The spread of mild variants of H5N1 influenza is common in some Asian populations.

Rarely, viral pneumonia develops in an otherwise healthy person in the course of systemic infection with viruses whose principal impact is extrapulmonary. Pulmonary infiltrates occur in 16 percent of young adults with varicella, but only 2 to 4 percent have clinical manifestations suggestive of pneumonia. Some cases of mild pneumonitis have been observed in patients receiving live varicella vaccine. Pneumonia in children with varicella is more likely to represent bacterial superinfection than primary viral pneumonia. On rare occasions, pulmonary infiltrates develop in patients with clinical infectious mononucleosis; the infiltrates represent atypical pneumonia due to Epstein-Barr virus (EBV).

A novel Hantavirus, Sin Nombre virus, emerged acutely in 1993, in the Four Corners area of New Mexico, Arizona, Colorado, and Utah. Cases had previously been reported worldwide but primarily in the west and southwestern United States. The Hantavirus pulmonary syndrome begins with a 3- to 6-day prodromal period consisting of myalgias and fever, sometimes accompanied by gastrointestinal symptoms. The prodrome is followed by progressive cough, dyspnea, tachycardia, and hypotension. Bleeding may occur. Laboratory findings include hemoconcentration, leukocytosis, and thrombocytopenia. The chest radiograph demonstrates interstitial edema, peribronchial cuffing, and bilateral airspace (bibasilar and perihilar) disease. The picture of pulmonary edema (interstitial and alveolar) is consistent with a diffuse pulmonary capillary leak syndrome. The case fatality rate for the Hantavirus pulmonary syndrome is 50 percent. The principal host for Sin Nombre virus is the deer mouse, and infection is acquired through exposure to this rodent, to rodent excreta, or to contaminated dust.

Severe acute respiratory syndrome (SARS) is a viral respiratory illness that first appeared in southern China in November 2002 before spreading globally. SARS is caused by a previously unrecognized coronavirus, called *SARS-associated coronavirus* (SARS-CoV). SARS-CoV is thought to be transmitted most readily by respiratory droplets. Illness usually begins with a high fever (measured temperature greater than 38.0°C with chills and malaise). Diarrhea occurs in approximately 10 to 20 percent of patients. After 2 to 7 days, SARS patients may develop a dry, nonproductive cough that may be accompanied by hypoxemia or progress to hypoxemia. Ten to 20 percent of cases require mechanical ventilation. Most patients develop pneumonia. The incidence of pneumonia is greatest in immunocompromised individuals. Between November 2002 through July 2003, 8098 people worldwide developed SARS and 774 died. No new cases were reported after July 2003.

Human metapneumovirus (HMPV) is a recently described but ubiquitous virus (Pneumovirinae subfamily, Paramyxoviridae family) which is recognized to be a major cause of acute respiratory infection, particularly in children and in immunocompromised individuals. The virus has phenotypic and clinical characteristics similar to those of RSV, often presenting with bronchiolitis. This virus may co-infect individuals with RSV.

In the immunocompromised host, viral infection is most often due to cytomegalovirus (CMV) or community-acquired respiratory viruses, although varicella zoster and herpes simplex viral pneumonias do occur. In this population, the frequency, duration, and severity of viral illness exceed that of the general population. In the solid-organ transplant recipient CMV pneumonia occurs most often in seronegative (naïve) recipients of donor organs from seropositive (latently infected) individuals. Conversely, in hematopoietic stem cell recipients, the seropositive recipient of seronegative cells is at greatest risk. The syndrome of hypoxia with diffuse, interstitial infiltrates may predispose to, or coexist with, a similar syndrome due to *P. carinii*. This syndrome is most severe in the lung transplant recipient. In contrast, CMV pneumonitis in the hematopoietic transplant recipient (bone marrow transplant) occurs with the activation of CMV in the seropositive recipient of cells from a seronegative donor. With engraftment, the naïve immune system reacts against CMV antigens expressed in the lungs. Superinfection is common; graft-versus-host disease may complicate the differential diagnosis.

Fungal Pneumonia

Fungal pneumonia occurs most often in immunocompromised hosts. However, in the normal host, infection due to the endemic or geographic fungi (*Histoplasma capsulatum, Coccidioides immitis*) or to *Cryptococcus neoformans* may be asymptomatic or may present with systemic signs often confused with acute bronchitis, viral infection, mycobacterial infection, or aseptic meningitis. Otherwise, fungal infection of the lungs is most common with anatomic defects (aspergilloma) or aspiration (*Candida* species) but is otherwise rare in individuals without immune defects. A few syndromes

merit consideration. *P. carinii* causes pneumonia with prominent hypoxia and often few physical or radiologic findings in immunocompromised individuals, particularly those on corticosteroids. Since this infection is easily prevented, consideration should be given to prophylaxis in any individual receiving chronic immunosuppressive therapy or with human immunodeficiency virus (HIV) infection or AIDS unresponsive to antiretroviral therapy.

Aspergilloma was traditionally considered to be a noninvasive colonization of pulmonary cavities. However, gross hemoptysis may complicate management and dissemination may occur at the time of surgical resection. Immune suppression may convert benign disease into invasive infection. Mucormycosis (due to the Mucoraceae family) causes rapidly progressive sinus and lung infection that requires surgical resection for cure. This infection is most common in diabetics. *Fusarium* species typically disseminate via the bloodstream, producing diffuse infiltrates.

Parasitic Pneumonia

Parasitic pneumonia is uncommon without endemic exposures. Pneumonia generally occurs when the normal life cycle of the organism includes the lungs. Infection by *Entaboeba histolytica* causes pleuropulmonary disease as a result of (1) *sympathetic* reaction to an unruptured abscess within the liver; (2) empyema, after rupture of the liver abscess into the pleural space; or (3) parenchymal involvement with abscess, consolidation, or hepatobronchial fistula after rupture of a liver abscess. Amebae that have broached the mucosal barrier are thought to gain entry to the liver via the portal vein. Subsequent liver abscesses can be either purely amebic or mixed bacterial and amebic. Other less common routes exist, including hematogenous spread that can lead to metastatic abscesses of brain, lung, and other organs. *Acanthamoeba* species cause subacute meningoencephalitis or secondary keratitis often after hematogenous spread of dermal or pulmonary disease. Some form of pulmonary complication occurs in 3 to 10 percent of patients with falciparum malaria. Noncardiogenic pulmonary edema can develop suddenly, even after appropriate antimalarial therapy has been instituted and even after parasites are no longer detected on blood smears. Acute acquired infection due to *Toxoplasma gondii* in the immunocompetent host is generally asymptomatic, with cervical lymphadenopathy as the hallmark of disease. It may be confused with mononucleosis caused by EBV or CMV. Fever, malaise, sore throat, and hepatosplenomegaly also occur, and the peripheral blood may manifest atypical lymphocytosis. Rarely, acute acquired disease may present with severe dissemination, marked by pneumonitis, hepatitis, encephalitis, polymyositis, or myocarditis. In the immunocompromised host, acute toxoplasmosis is most often associated with necrotizing encephalitis as a result of brain cyst reactivation, although myocarditis, hepatosplenomegaly, fever, and interstitial pneumonitis are also common. Pulmonary infections due to migrating worms include a Loeffler-like syndrome with *Ascaris lumbricoides*, postobstructive pneumonitis and systemic sepsis due to *Strongyloides stercoralis*, cysts and nodules due to *Echinococcus granulosus*, *Paragonimus westermani*, *Schistosoma* species, and pulmonary eosinophilia in filariasis.

RADIOGRAPHIC FEATURES OF PNEUMONIA

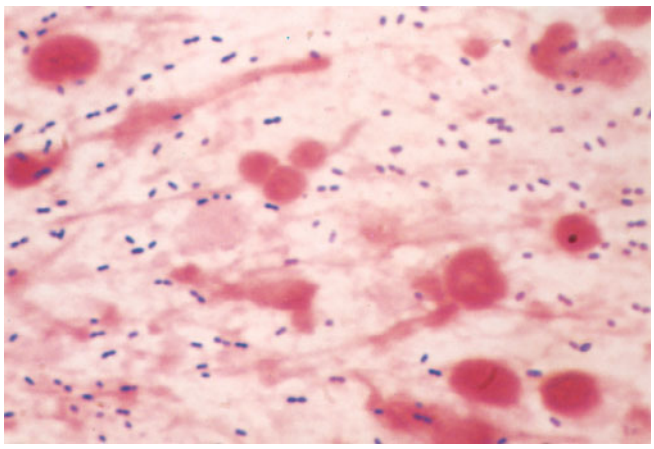
The radiographic features of pneumonia are discussed in detail elsewhere. No radiologic pattern provides a specific etiologic diagnosis. However, the radiographic pattern, combined with clinical and epidemiological information, can narrow diagnostic considerations while microbiologic data are being assembled. Several radiographic patterns can be helpful in categorizing infectious and noninfectious causes: (1) airspace or alveolar pneumonia, (2) broncho- or lobular pneumonia (Fig. 112-1), (3) interstitial pneumonia, and (4) nodular infiltrates. Although the chest radiographs of a particular patient may not fit neatly into one or another of these categories, identification of a predominant pattern can be helpful in directing attention to certain causes.

Alveolar Pneumonia

This form of infiltrate occurs when certain organisms, notably *S. pneumoniae*, induce inflammatory edema in peripheral alveoli. When the extent of the consolidation involves an entire lobe, this is the classic *lobar pneumonia*. But more often the process is not that extensive, although the pathogenesis is the same. An air bronchogram is characteristic. Loss of volume is absent or minimal during the acute stage of consolidation, but some atelectasis may develop owing to obstruction of bronchi by exudate during resolution of the process.

K. pneumoniae is another common cause of community-acquired pneumonia (CAP), which, like pneumococcal pneumonia, shows homogeneous parenchymal consolidation containing air bronchograms. Although *K. pneumoniae* pneumonia classically affects the right upper lobe and produces a dense, homogeneous lobar consolidation with bulging of the fissure, these features are not pathognomonic and cannot be relied on for diagnosis without supportive bacteriologic data (Fig. 112-1). The propensity for *K. pneumoniae* to produce tissue destruction and abscess formation may, in fact, result in a shrunken, rather than an expanded, lobe. Pneumococcal pneumonia may also cause bulging of the fissure, albeit less commonly and less prominently. Extensive alveolar consolidation may occur with a variety of other bacterial causes of pneumonia, including mixed anaerobes of aspiration pneumonia and a variety of gram-negative bacilli implicated in nosocomial pneumonias. Occasionally, an unusual configuration of airspace consolidation, *spherical pneumonia*, occurs, particularly in children, with pneumococcal or *H. influenzae* pneumonia. It has also been reported with Q fever.

In the immunocompromised host, alveolar consolidation on the plain chest radiograph may be delayed and appreciated only by chest CT scan. Among infectious causes, bacterial agents are a major consideration. Common pathogens, such as *S. pneumoniae*, cause infection in this group of patients



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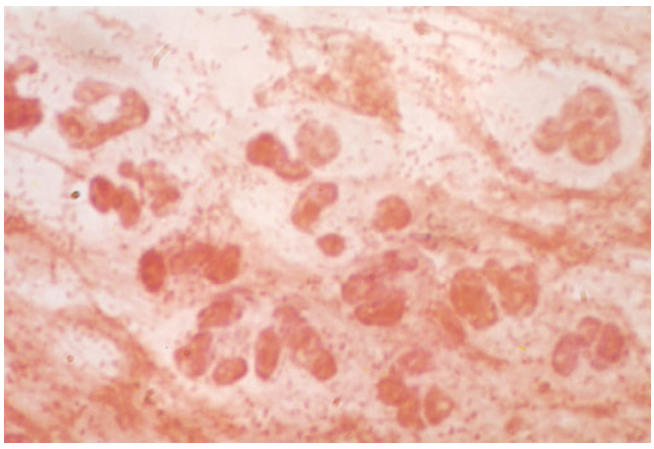

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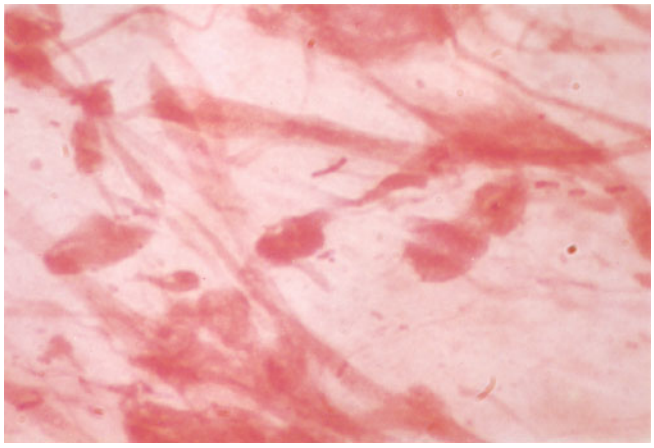

C

Figure 112-8 *A*. Gram-stained smear of sputum from patient with pneumococcal lobar pneumonia (×1000). In this field there are numerous gram-positive, lancet-shaped diplococci and polymorphonuclear leukocytes. *B*. Gram-stained smear of sputum from patient with bronchopneumonia superimposed on chronic bronchitis. This field (×1000) is teeming with gram-negative coccobacilli. Many polymorphonuclear leukocytes are present. *Haemophilus influenzae* was isolated from sputum as the predominant organism. *C*. Gram-stained smear of sputum from patient with lobar pneumonia due to *K. pneumoniae*. In this field (×1000) there are moderate numbers of polymorphonuclear leukocytes and large, thick, gram-negative bacilli. *(A to C Courtesy of H. Provine.)*

which is often of greater severity than in the normal host and with less radiologic evidence for infection. Bacterial superinfection of viral processes (e.g., influenza, CMV) is also common. However, if the consolidation is lobar or multilobar, *L. pneumophila* is an important possibility. Other likely infectious agents are fungi (e.g., *Aspergillus*), *Nocardia*, and *M. tuberculosis*. Less often, viruses alone (e.g., CMV) elicit a predominantly alveolar pattern. Bilateral diffuse involvement with an airspace pattern resembling pulmonary edema is not uncommonly a feature of *P. carinii* pneumonia, but may also reflect viral or noninfectious etiologies.

Bronchopneumonia

In bronchopneumonia, the focus of infection and the inflammatory response is in the bronchi and surrounding parenchyma. Consolidation is segmental in distribution, and involvement is patchy; segmental involvement may become confluent to produce a more homogeneous pattern. Bronchopneumonic patterns are commonly observed in pulmonary infections due to *S. aureus* or nonencapsulated *H. influenzae*. With *S. aureus* infections, macro- and microabscess formation may occur rapidly. Also, pneumatoceles occur during the first week of lung involvement in about half the children with *S. aureus* pneumonia. These cystic spaces are believed to be the consequence of a check valve opening between a peribronchial abscess and an adjacent bronchus.

A bronchopneumonic pattern of consolidation is commonly observed when pneumonia is engrafted on underlying bronchiectasis or chronic bronchitis. In such predisposing circumstances, *S. pneumoniae* infection may produce a bronchopneumonic pattern rather than its usual lobar consolidation (Fig. 112-8). In the presence of underlying emphysema, the radiographic pattern of pneumococcal pneumonia may also be altered from its usual homogeneous pattern to one that contains multiple radiolucencies (representing unconsolidated emphysematous areas) that may be misinterpreted as abscesses.

Segmental bronchopneumonia is the radiographic picture in pneumonia due to *C. pneumoniae* (strain TWAR) or *M. pneumoniae,* and in many viral pneumonias. Any of the bacterial species that cause nosocomial pneumonia can produce a radiographic pattern of bronchopneumonic consolidation.

Interstitial Pneumonia (Peribronchovascular Infiltrate)

A reticular or reticulonodular pattern of infiltration is the radiographic representation of interstitial inflammation—i.e.,

a peribronchovascular infiltrate. In otherwise healthy persons, *M. pneumoniae* is high on the list of community-acquired causes of a radiographic pattern of interstitial pneumonia. In some instances, interstitial infiltration progresses to produce patchy consolidation of airspaces, most often in the lower lobes. Pneumonias due to respiratory viruses sometimes have an interstitial pattern that progresses to patchy segmental consolidation or to diffuse airspace disease that resembles pulmonary edema. A variety of noninfectious causes of interstitial lung disease (e.g., hypersensitivity lung disease, collagen vascular disease, and sarcoidosis) may also produce a reticular pattern on the chest radiograph (Fig. 112-6).

In immunocompromised patients, particularly in those with AIDS, the infectious causes of interstitial pneumonia are broadened to include early *P. carinii* pneumonia and additional opportunistic viral agents (CMV, varicella-zoster, herpes simplex, and probably EBV and possibly HIV). Noninfectious causes of a reticular pattern on chest radiography in an immunocompromised host include drug-induced (bleomycin, methotrexate, etc.) pneumonitis, early radiation pneumonitis, and pulmonary edema.

Nodular Infiltrates

Nodular infiltrates are considered here as well-defined large (greater than 1 cm on the chest radiograph), round focal lesions. Such a lesion may represent small aspirational abscesses (without air-fluid levels), a fungal or tuberculous granuloma, or a lesion of pulmonary nocardiosis. Multiple nodular infiltrates may also represent the necrotic lesions that develop in the lung secondary to the septic vasculitis produced by *P. aeruginosa* bacteremia or the consequences of fungemic spread of candidal infection from an infected intravascular catheter. Infected nodular pulmonary lesions are sometimes caused by septic pulmonary infarcts produced by infected emboli that originate from right-sided bacterial endocarditis, septic thrombophlebitis of pelvic veins, or septic jugular vein phlebitis. On rare occasions, similar nodular lesions are produced by necrotic (but not infected) pulmonary infarctions; primary or metastatic neoplastic lesions may have a similar appearance. Nodular lesions that undergo rapid necrosis with cavity formation can be a feature of Wegener's granulomatosis (Fig. 112-5).

In the immunocompromised patient, nodular infiltrates may be due to bacteremic or fungemic spread of infection, most often as a result of nosocomial infection caused by an infected intravenous catheter. In this type of patient, nodular lesions should bring to mind the possibilities of pulmonary nocardial infection, aspergillosis, or other fungal infections. Tuberculous granulomas in the lungs may develop or enlarge in the immunosuppressed patient. Metastatic neoplasm or lymphoma sometimes presents a similar radiologic picture. Multiple small nodules, larger than miliary lesions but smaller than the gross nodular lesions described above, raise the possibility of varicella-zoster or CMV infection of the lung.

Miliary Pulmonary Disease

Disseminated miliary lesions of infectious nature suggest miliary tuberculosis, histoplasmosis, or blastomycosis in either the normal or immunosuppressed host. In the immunosuppressed patient, a miliary pattern may also occur in disseminated cryptococcal infection or bacteremic spread of bacterial or candidal infection (Figs. 112-2 and 112-4).

Computed Tomography Scanning

In patients with pulmonary infections, CT scanning of the chest may be helpful in certain situations in determining whether pneumonia is necrotizing, consolidation secondary to bronchial obstruction (as by hilar lymphadenopathy or by endobronchial tumor), or if there is a relationship between a pleural effusion or an empyema or loculated fluid collections to parenchymal infections, if bronchiectasis is present, or whether circumscribed pulmonary densities represent a fungus ball within a cavitary lesion, and so forth. When small granulomatous lesions are present, CT scanning can provide information on the extent of the process. When a single nodule is present, CT scanning can assist in determining the best invasive diagnostic approach (needle, open biopsy). In particular, in immunocompromised individuals in which infiltrates are not appreciated on ordinary radiographs (e.g., *P. carinii*) may be demonstrated by CT scanning. This information greatly facilitates invasive procedures such as needle biopsy, video-assisted thoracoscopy, or bronchoscopy.

Noninvasive Diagnostic Studies

Noninvasive studies can provide information indicating the specific microbial cause of a pulmonary infection or can narrow the field of likely etiologic agents.

Direct Examination of the Sputum

Cytologic Examination

Examination of Gram-stained sputum smears can be of major value in pinpointing a bacterial cause of pneumonia and guiding initial and subsequent therapy. The quality of a sample of expectorated or induced sputum sample determines the value of the results that can be expected. Culture of sputum or nasopharyngeal secretions that consists principally of saliva is worthless. Cytologic examination provides an evaluation of the quality of the sample and its suitability for culture and interpretation of a Gram-stained smear made from it. Scanning of Gram-stained smears or application of specific quantitative criteria is helpful in selecting meaningful specimens for bacteriologic evaluation by smear and in culture. Squamous epithelial cells (normally exfoliated from the oropharynx), when present in numbers of 10 or more per low-power ($\times 100$) magnification field, indicate that the specimen is unsatisfactory; culture of such a specimen correlates poorly with results from culture of a transtracheal aspirate (Fig. 112-3). The presence of numerous polymorphonuclear neutrophils on Gram-stained smear (10 to 25 or more per

low-power microscopic field) in the absence of an excessive number of squamous cells (see above) is indicative of a good specimen for bacteriologic evaluation.

Examination of Gram-Stained Smears for Bacteria

The oil immersion fields examined, and the immediately adjacent fields should not contain any squamous cells; each should also contain at least three or four neutrophils (in non-neutropenic hosts). The presence of squamous cells not only indicates that the specimen is derived from the upper-respiratory tract but also may be confusing to the uninitiated because of the large number of bacteria, often gram-positive diplococci, which might be mistaken for *S. pneumoniae*, adherent to the surface of these cells.

A variety of bacterial respiratory tract pathogens have rather characteristic morphologies and strongly suggest an etiologic role when present in a suitable specimen of sputum (or in a transtracheal aspirate) that contains the proper numbers of inflammatory cells. Such organisms include *S. pneumoniae* (gram-positive oval or lancet-shaped diplococci), *H. influenzae* (small, pleomorphic gram-negative bacilli), *Moraxella catarrhalis* (gram-negative, biscuit-shaped diplococci), or the similar-appearing *Neisseria meningitis*, enteric gram-negative bacilli (not distinguishable from one another with respect to species except for large encapsulated rods that are suggestive of *Klebsiella*), and *S. aureus* (large gram-positive cocci in small groups or clusters (Fig. 112-9). Since normal oral flora includes a variety of streptococcal species that are morphologically somewhat similar to *S. pneumoniae*, sputum smears may be misinterpreted. Thus, a definite predominance of gram-positive diplococci in multiple appropriate oil immersion fields needs to be observed in order to implicate *S. pneumoniae* (Fig. 112-7). A quantitative aspect to the evaluation has been suggested: at least 10 gram-positive lancet-shaped diplococci per oil immersion field predict the isolation of *S. pneumoniae* from sputum cultures. With use of these criteria (numbers of polymorphonuclear leukocytes, absence of epithelial cells, and numbers of gram-positive lancet-shaped diplococci), the specificity of Gram's stain for identifying *S. pneumoniae* is 85 percent, with a sensitivity of 62 percent.

Gram-stained smears can be helpful not only in the etiologic diagnosis of community-acquired bacterial pneumonia due to the usual respiratory pathogens but also in supporting a diagnosis of atypical pneumonia when sputum examinations repeatedly show neither neutrophils nor bacteria. Uncommon bacterial species may be implicated in a pulmonary infection on the basis of unusual morphology on Gram-stained smear. For example, irregularly staining, beaded, delicate gram-positive branching filaments suggest either *Nocardia* or *Actinomyces* (Fig. 112-10).

Several organisms, uncommon causes of pulmonary infection, have morphologic characteristics that may mimic other, more common respiratory pathogens. *Pasteurella multocida* and *Acinetobacter* species, both small gram-negative coccobacilli, have each been mistaken in sputum of patients with pulmonary infections for either *H. influenzae* or *M. catarrhalis*, or for a mixture of the two.

Sputum or pleural fluid with foul odor provides evidence of activity of anaerobic organisms in infective processes such as lung abscess, aspiration pneumonia, empyema, and, occasionally, bronchiectasis. In these settings, the findings on Gram-stained smear may corroborate the preliminary diagnosis. Organisms of the *P. melaninogenicus-asaccharolyticus* group are small, gram-negative coccobacilli. *Fusobacterium nucleatum* is a long, tapering, pale-staining gram-negative bacillus with irregularly staining gram-positive internal granules. Purulent secretions or pus from such anaerobic infections contain numerous neutrophils and usually a mixture

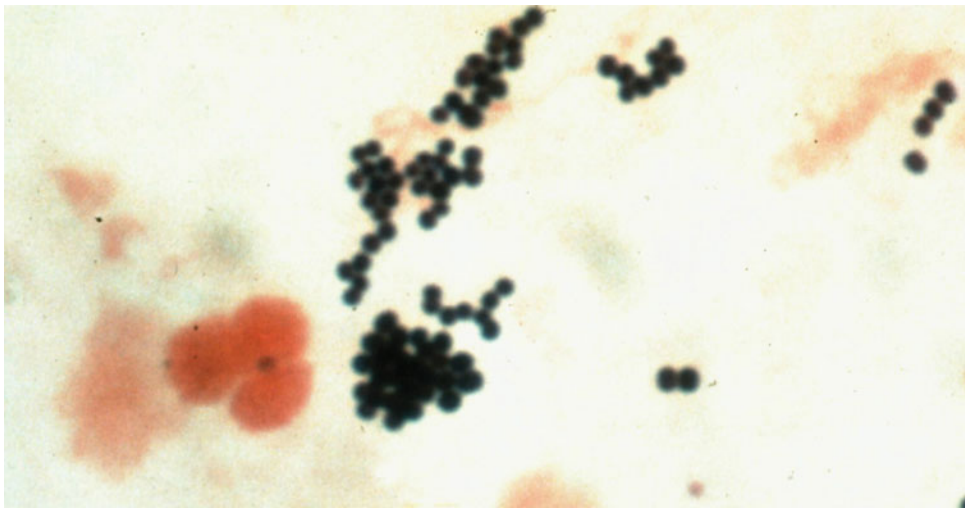

Figure 112-9 *Staphylococcus aureus* on Gram-stained smear from a drug addict with right-sided bacterial endocarditis. In this field (×1000) there are polymorphonuclear leukocytes and clusters of gram-positive cocci. (*Courtesy of H. Provine.)*

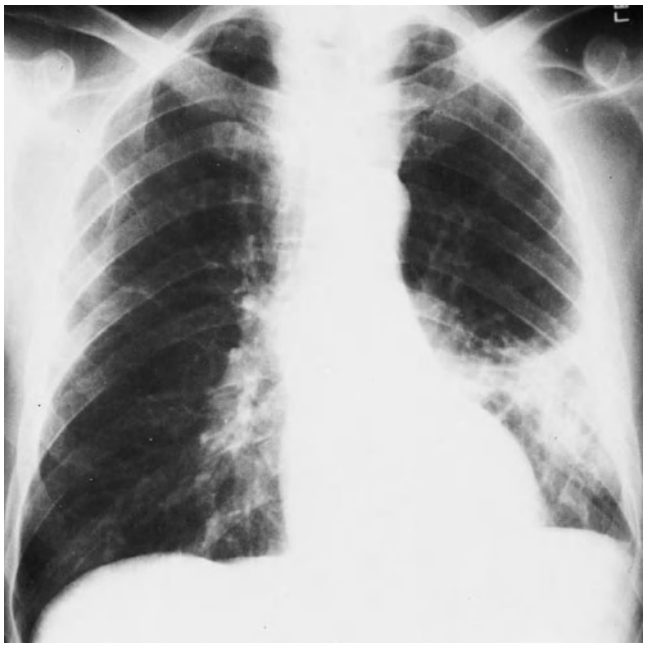

Figure 112-10 Actinomycosis in a 54-year-old chronic alcoholic man with pyorrheic gums who was admitted with signs of brain tumor. Chest radiograph shows mass in left lower lobe. Computed tomography is consistent with brain metastasis. Transthoracic needle aspirate revealed *Actinomyces israelii*.

of bacterial species, including anaerobic and microaerophilic streptococci on stained smear.

Examination of Ziehl-Neelsen or Fluorochrome-Stained Smears for Mycobacteria

The number of new cases of tuberculosis in the United States steadily declined over past decades, reaching a nadir in 1995. During the period 1985 to 1991, the rate of development of new cases (often due to multidrug-resistant strains of *M. tuberculosis*) increased, primarily associated with microepidemics among the urban poor, racial and ethnic minorities, drug abusers, hospital and correctional facility populations, and patients with HIV infection. In patients with AIDS who have access to HAART (highly active antiretroviral therapies), the incidence of tuberculosis is decreasing. Pulmonary tuberculosis in the aforementioned settings may take the form of chronic cavitary tuberculosis or of forms more suggestive of pyogenic or atypical pneumonia—i.e., progressive primary tuberculosis and tuberculous pneumonia. Acid-fast smears of sputum can provide the very first evidence of this disease. Mycobacteria are seen on smears of about 50 percent of specimens that subsequently prove to contain *M. tuberculosis*. Most laboratories currently employ a fluorochrome stain with auramine-rhodamine (mycobacteria fluoresce orange-yellow) for initial examination of sputum or other body fluids. Atypical mycobacteria may be demonstrated on sputum smears of patients, usually older people, with slowly progressive pulmonary disease. In patients with AIDS, disseminated *Mycobacterium avium-intracellulare* infection is usually diagnosed by isolation of the organism from blood culture (lysis centrifugation method) or by histopathological diagnosis on biopsy. However, the organism can be demonstrated on acid-fast smears and culture of respiratory secretions even though there may be little radiographic evidence of pulmonary infection directly attributable to its presence. Modified Ziehl-Neelsen–stained smears are helpful in detecting *Nocardia*.

Fungal Wet Mounts (Potassium Hydroxide, KOH Preparations)

Fungal wet mounts, smears stained with Calcofluor white chemofluorescent agent or phase-contrast microscopy, are employed when epidemiological considerations suggest community-acquired pulmonary mycoses (particularly coccidioidomycosis and blastomycosis). They should be a routine part of evaluation of respiratory secretions and lung biopsy materials from immunocompromised patients in whom additional fungal pathogens (e.g., *Aspergillus* and *Mucor*) may be active. In patients with allergic bronchopulmonary aspergillosis, or with the unexpected detection of *Aspergillus* in sputum, fungal hyphae must be considered in the clinical context of each patient.

Direct Immunofluorescent Microscopy

Direct fluorescent antibody (DFA) staining can be useful in rapid diagnosis of respiratory tract pathogens. DFA staining reagents for *L. pneumophila* are commercially available. Their use is not recommended in examination of sputum specimens because of the presence of cross-reacting species (*Bacteroides* species, *Pseudomonas* species, *Bordetella pertussis*) in the upper-respiratory tract. However, biopsy specimens of lung (needle, bronchoscopic, or surgical), bronchoscopic aspirates, BAL washings, and pleural fluid samples are suitable for DFA staining for *L. pneumophila*. Although a variety of stains (toluidine blue O, methenamine silver, Wright-Giemsa, Diff-Quik, Calcofluor) are useful in identifying *P. carinii* in induced sputa or BAL specimens, or on imprint smears of tissue specimens, the most widely used diagnostic technique utilizes immunofluorescence with monoclonal antibodies against *P. carinii*. Rapid viral diagnosis (RSV, influenza, parainfluenza, adenovirus) by DFA can be applied to specimens from bronchial lavage or brushings or from nasopharyngeal swabs or washings. Anti–*B. pertussis* DFA may be used on nasopharyngeal aspirate smears in the presumptive diagnosis of pertussis.

Giemsa and Other Special Stained Smears for Diagnosis of Pneumocystis Infection

Since *P. carinii* pneumonia is an alveolar process, examination of routinely collected expectorated sputa for *P. carinii* is generally not regarded as rewarding in immunosuppressed patients with neoplastic disease or transplant recipients. In these patients, fiberoptic bronchoscopy and transbronchial biopsy, combined with BAL, provide the highest diagnostic yield. In patients with AIDS, however, induced sputum

examination for *P. carinii* may be helpful. Sputum induction employing aerosolized, hypertonic saline provides a diagnosis in up to 80 percent of patients, particularly if coupled with microscopy of antibody-stained cytocentrifuged specimens. Immunofluorescent assays, with monoclonal antibodies to *P. carinii*, of induced sputum have a sensitivity of 69 to 92 percent, compared with that of 28 to 80 percent for tinctorial stains. Toluidine blue O and methenamine silver stains stain only the cyst (less than 10 percent of the organism burden) and not the trophozoite forms of *P. carinii*. Giemsa and Diff-Quik stain trophozoites and intracystic sporozoites. If results of examination of induced sputum are negative and clinical circumstances warrant further attempts at diagnosis, follow-up bronchoscopy with transbronchial biopsy or BAL is performed. The sensitivity of each of these procedures for diagnosis of *P. carinii* pneumonia is more than 90 percent.

Special Microscopic Examinations

Occasionally, in the setting of apparent pulmonary inflammation with features atypical for infection, microscopic examinations using stains other than Gram's stain may be indicated. For example, Wright-stained smears may show the presence of eosinophils in allergic pulmonary aspergillosis or other causes of pulmonary infiltrates that are accompanied by eosinophilia. Cytologic examination of exfoliated sputum using Papanicolaou's stain may reveal a pulmonary neoplasm. Birefringent calcium oxalate crystals (needlelike in rosettes or arranged like sheaves of wheat) in sputum cytologic specimens have been reported as suggesting pulmonary infection with *Aspergillus* (aspergilloma and, occasionally, invasive aspergillosis).

In the intubated or tracheotomized patient, whose tracheobronchial secretions commonly contain neutrophils and often some bacteria on Gram-stained smears, it may be difficult to distinguish between colonization and nosocomial pneumonia. The presence on light microscopy (×400) of characteristic elastin fibers with split ends (in a drop of tracheal aspirate to which a drop of 40 percent KOH has been added), in the appropriate clinical setting, is a strong indicator of a necrotizing pulmonary infection.

Intense bacteremia sometimes accompanies pulmonary infections, and the etiologic agent may be demonstrable on stained smears of the buffy coat of centrifuged blood: pneumococci have been identified in Gram-stained or Wright-Giemsa–stained smears of buffy coats from splenectomized patients; occasionally, *M. avium-intracellulare* has been found intracellularly in acid-fast stains of buffy coats from patients with AIDS.

Additional special microscopic examinations may be indicated for immunocompromised patients who have patchy pulmonary infiltrates on the chest radiograph. For example, the presence of the hyperinfection syndrome of strongyloidiasis (often accompanied by *E. coli* bacteremia) can be established by the finding of filariform larvae in the sputum and in the stool after the latter is suitably prepared by concentration techniques. Although eosinophilia is often present in patients with strongyloidiasis, it may be absent in the hyperinfection syndrome.

Sputum Cultures

In most patients with the common types of community-acquired and nosocomial bacterial pneumonia, the etiologic diagnosis can be made on the basis of the combined results of a Gram-stained smear of sputum and a proper culture of a suitable exudative portion of a freshly obtained sputum specimen. The criteria for a proper sample of sputum have been noted above. Culture entails streak dilution on blood agar and MacConkey media. Expectorated sputum should not be cultured anaerobically, since contamination with oral anaerobes is inevitable. Because patients with Legionnaires' disease often have little sputum production, most attempts to isolate *Legionella* are limited to specimens obtained either by induced sputum samples, fiberoptic bronchoscopy or lung biopsy, or at thoracentesis. Cultures of such materials are plated on buffered charcoal-yeast extract (BCYE) agar. Occasionally, *Legionella* species can be isolated from sputum with the use of a semi-selective medium, either BCYE or BCYE-containing cefamandole, polymyxin B, and ansamycin. Culture is the most definitive method for diagnosis of *Legionella* infection. Unfortunately, it may take 5 or more days for colonies to appear.

Cultures for mycobacteria are undertaken when clinical circumstances raise the possibility of pulmonary infections due to *M. tuberculosis* or atypical mycobacteria. Similarly, cultures of sputum for primary invasive mycotic agents (e.g., *H. capsulatum*, *Blastomyces dermatitidis*, and *C. immitis*) are dictated by clinical and epidemiological circumstances. In immunosuppressed patients, cultures of sputum are also directed toward uncovering a variety of opportunistic fungi, including *Cryptococcus neoformans*, *Aspergillus* species, and Mucoraceae.

Most hospitals do not have facilities for isolating viruses by tissue culture. This lack poses little problem in dealing with most community-acquired viral pneumonias, for which viral isolation is not necessary and the cost is prohibitive. However, viral isolation from throat washings is warranted in certain circumstances (e.g., to prove the presence of an outbreak of influenza), to establish that an outbreak among young children is due to RSV, and to identify a specific viral agent, such as an adenovirus, as the cause of a serious pneumonia that is not responding to antibacterial therapy. In immunosuppressed patients with pneumonia, a variety of opportunistic viral infections (CMV, RSV, varicella-zoster virus, herpes simplex) are diagnostic considerations. In vitro testing of CMV may provide data regarding susceptibility to antiviral agents. Most viral cultures and susceptibility (for CMV in particular) tests have been replaced by quantitative molecular amplification assays (polymerase chain reaction, PCR) or antigen detection systems (Table 112-6) that are more rapid and cost-efficient than culture systems.

Cultures are grown in cell lines susceptible to the viral infections under consideration in either standard

"tube cultures" or "shell vial" cultures (rapid culture achieved by centrifugation of specimens against the cultured cells). Viral replication in the tissue culture can be confirmed within 48 h after inoculation with use of fluorescent monoclonal antibodies. Because CMV and herpes simplex are frequently present in the oral secretions of immunosuppressed patients, isolation of these viruses is apt to be meaningful only if the materials used for the isolation procedure were obtained either by bronchoscopy with protected specimen brushing (PSB) or with BAL, lung biopsy, or transtracheal aspiration.

Blood Cultures

Blood cultures should always be performed in patients with suspected bacterial pneumonia. Bacteremia occurs in approximately 30 percent of patients with pneumococcal pneumonia. Demonstration of bacteremia in other patients with pneumonia may indicate that the pulmonary infection is secondary to a focus of infection elsewhere (e.g., acute right-sided *S. aureus* endocarditis or *P. aeruginosa* infection of thermal burns). In patients with AIDS and disseminated *M. avium-intracellulare* infection, mycobacterial blood cultures are almost always positive. The lysis centrifugation technique permits ready and rapid isolation of the mycobacterium and quantifies the intensity of the bacteremia. *L. pneumophila* has been isolated with some frequency from automated radiometric blood culture bottles, but blind subculture onto BCYE agar is necessary because growth in the liquid medium does not achieve detectable levels.

Bacterial Antigen Detection in Sputum and Urine

The quellung reaction was extensively used in the pre-antimicrobial agent era to identify *S. pneumoniae* in sputum. It entails the use of light microscopy to detect capsular swelling after pneumococcal antiserum has been added to a loopful of sputum. The occurrence of the quellung reaction was shown to correlate closely with the presence of *S. pneumoniae* in sputum culture—in about 90 percent of the patients.

Pneumococcal antigens may be detected in the sputum of patients with pneumococcal pneumonia by enzyme-linked immunosorbent assay (ELISA), latex particle agglutination, or counterimmunoelectrophoresis. The first two are more readily available. ELISA is the most sensitive method. Antigen detection in sputum may have as high a sensitivity as 70 to 90 percent; but specificity is a problem, with about 20 percent false-positives, probably due in part to the difficulty in distinguishing oropharyngeal contamination and colonization (e.g., in patients with chronic bronchitis without pneumonia). Antigen detection in the urine has been less sensitive, and the sensitivity of antigen detection in the serum has been even lower.

A radioimmunoassay and an enzyme-linked immunoassay for *L. pneumophila* antigenuria are commercially available and provide a means of rapid (under 24 h) diagnosis of *Legionella* pneumonia, particularly in patients without sputum production. The sensitivity of the radioimmunoassay is 89 to 95 percent, and the specificity is very high (estimated at 99 percent). The test is positive despite antimicrobial agent administration, and antigenuria may persist for weeks or months after recovery from pneumonia. It must be remembered that the assay is available only for *L. pneumophila* serogroup 1, and this serogroup is responsible for only 80 percent of *L. pneumophila* infections.

Rapid Viral Diagnosis by Antigen Detection

The need for methods that can rapidly identify viruses stems from the introduction of effective antiviral chemotherapy for several common viral agents. As noted earlier ("Direct Immunofluorescent Microscopy"), DFA can be used to detect viral antigens (adenovirus, influenza A and B, parainfluenza, and RSV, as well as CMV and herpes simplex virus [HSV]) in specimens of bronchial brushings, BAL, or nasopharyngeal washings. Enzyme immunoassay can also be used to detect viral antigens in respiratory secretions. The CMV antigenemia assay detects matrix protein pp65 and can be detected with the use of fluorescent or peroxidase-labeled antibody staining of peripheral blood neutrophils. This assay is semiquantitative. Quantitative and sensitive PCR assays are available for most clinically important viruses (see below, Table 112-6). These are positive days in the advance of antigenemia assays, which are useful in management as well as diagnosis of acute infection. Strict criteria for CMV pneumonia include demonstration of the virus, typical cytologic changes, and absence of other evident pathogens. This is applicable in patients with AIDS, in whom CMV is frequently isolated but in whom CMV rarely causes pneumonia. In contrast, isolation of CMV from BAL fluid in blood or bone marrow transplant recipients with pneumonia is sufficient evidence to make the diagnosis and institute treatment, in view of the high frequency and mortality of CMV pneumonia in these patients.

Serologic Tests

Serologic tests are sometimes of considerable help in establishing the causes of a number of pulmonary infections when the causative agents are difficult to isolate. However, this approach, requiring the demonstration of a fourfold or greater rise in titer between acute and convalescent samples, neither enables rapid diagnosis nor provides assistance in initial selection of antimicrobial therapy. Microimmunofluorescence serologic tests are of value in the diagnosis of psittacosis (*Chlamydophila psittaci*). A fourfold rise in IgG or the presence of IgM antibody indicates recent infection. The indirect immunofluorescent antibody test (fourfold titer rise to 1:128 or higher indicates recent infection) may provide a retrospective diagnosis of Legionnaires' disease, but the antibody rise occasionally may not be demonstrable for 4 to 6 weeks after the clinical onset. Antibodies may persist for months or up to a year or more. Thus, a single titer of 1:256 or higher may reflect a prior *Legionella* infection. Cold agglutinins develop in about half the patients with *M. pneumoniae* pneumonia, but such antibodies occur in other conditions; complement fixation testing is the preferred diagnostic procedure. The

most sensitive and specific serologic test for infection with *C. pneumoniae* is the microimmunofluorescence test. A fourfold rise in IgG titer or an IgM titer of 1:16 or more reflects an acute infection. The complement fixation test is usually used to confirm a diagnosis of Q-fever pneumonia, but microimmunofluorescence, microagglutination, and ELISA have been used to diagnose acute *Coxiella burnetii* pulmonary infection. Tularemic pneumonia can be diagnosed serologically with an agglutination test for *Francisella tularensis*.

Serologic tests are also helpful in the diagnosis of invasive infection due to the primary pulmonary mycotic pathogens. Serum IgM precipitins (latex agglutination, immunodiffusion) appear with primary coccidioidomycosis. Abnormally high complement fixation titers (at least 1:32) are present in most patients who have disseminated infection due to *C. immitis*. A fourfold increase in complement fixation titer to yeast and to mycelial phases of *H. capsulatum* (or possibly a single titer of 1:64 or higher) and the presence of H and M precipitin bands strongly suggest histoplasmosis. Complement fixation tests for blastomycosis lack sensitivity and specificity: titers of at least 1:8 suggest recent or active disease, particularly if precipitins to the A antigen are also present. Cryptococcal antigenemia is detectable from latex particle agglutination in patients with cryptococcal pneumonia or disseminated cryptococcal infection. Sporotrichosis can be diagnosed with a serologic agglutination test when the titer is 1:80 or greater. Pulmonary toxoplasmosis is uncommon in seronegative individuals although acute toxoplasmosis is seen in endemic regions (the Caribbean, France) and after organ transplantation.

Serologic tests (paired acute and convalescent sera) may be helpful for the retrospective diagnosis of infections due to influenza A and B, RSV, adenoviruses, and parainfluenza viruses.

Molecular Diagnostic Testing

A variety of nucleic acid target amplification tests (often PCR) are available for the direct detection of pulmonary pathogens. PCR tests approved by the U.S. Food and Drug Administration can detect *M. tuberculosis* (as distinct from nontuberculosis mycobacteria) directly from sputum and BAL specimens. These tests have shown a sensitivity of 90 to 100 percent in specimens that are acid-fast bacillus (AFB) smear–positive but a sensitivity of only 65 to 85 percent for specimens that are smear negative. Consequently, these PCR assays have been approved for use only on AFB smear–positive specimens. In some major medical centers, PCR assays for detection of *C. pneumoniae* and *M. pneumoniae* on nasopharyngeal or throat swab specimens are available to markedly shorten (by 1 to 2 days) the time required to isolate these organisms by culture (up to 3 weeks). Molecular detection of HSV, adenovirus, CMV, EBV, and other pathogens are used primarily with blood specimens but may also be used in BAL or cerebrospinal fluid samples. The interpretation of such assays used with respiratory secretions is nonstandardized and blood studies are preferred. Molecular amplification is under development for many common pulmonary pathogens including *P. carinii, L. pneumophila,* and *Candida* and *Aspergillus* species. PCR tests are also under development for agents of bioterrorism.

Skin Tests of Delayed Hypersensitivity

The tuberculin skin test is of great importance in the evaluation of a pulmonary infection of unknown origin. The intermediate (5 tuberculin unit) purified protein derivative (IPPD) test should be used if no information is available about previous testing. A positive test does not distinguish between prior and current infection, but in persons who are either less than 35 years old or members of high-risk groups (immigrant, HIV-positive), a positive reaction carries considerable diagnostic weight.

A negative second-strength PPD skin test in a patient who is not anergic is strong evidence against a tuberculous origin of a pulmonary process. However, several caveats are noteworthy: since it may take 4 to 6 weeks for the skin test to become positive, the tuberculin skin test may be initially negative in progressive primary pulmonary tuberculosis, and in the patient who was infected long ago, cutaneous hypersensitivity may wane; in the elderly person, in whom waning has occurred, repeat testing several weeks later may show a positive result (booster effect) even if the original IPPD skin test was negative.

Fungal skin tests do not distinguish between current and past infection; indeed, active disease is often accompanied by a negative skin test. The coccidioidin skin test is the best of the available tests, but the diagnosis of coccidioidomycosis is not excluded by a negative test. Blastomycin and histoplasmin skin tests are of little value because of frequent false-negative results and cross-reactions. Also, the performance of the histoplasmin skin test may falsely elevate antibody levels to the *H. capsulatum* mycelial antigen.

A negative skin test response to a specific antigen must be interpreted in light of possible anergy. A battery of control antigens (mumps, *Candida*, *Trichophyton*, streptokinase-streptodornase) serves to detect such anergy, but these reagents are increasingly unavailable and costly.

Invasive Diagnostic Procedures

In certain circumstances, a more aggressive approach is required to uncover the etiology of pneumonia. This should be considered in any patient with immune deficiency or who is critically ill in whom rapid therapy is critical or in whom drug toxicity may be a major concern (e.g., renal transplant recipients). Such procedures are best done prior to the initiation of antimicrobial therapy. Such an approach may also be required if the patient's condition continues to deteriorate despite empiric antimicrobial therapy. In the immunocompromised patient, early invasive diagnostic approaches are mandated by the large number of etiologic agents that may be responsible, the frequent involvement of many infectious or noninfectious agents in the pulmonary process, the multiplicity of antimicrobial choices available against different organisms, and the rapidity with which clinical deterioration may

preclude further diagnostic and therapeutic actions. Among such invasive diagnostic procedures are bronchoscopy, BAL, open lung biopsy, transthoracic needle aspiration, and video-assisted thoracoscopy (VATS). A choice has to be made for one of several invasive procedures. The choice depends on the experience and skill with the different procedures at a given hospital. Also important in determining the proper procedure are the location and radiographic appearance of the pulmonary lesions. Fiberoptic bronchoscopy using specialized devices to shield against oropharyngeal contamination (protected specimen brushing) is used at some institutions to obtain tracheobronchial secretions for culture in certain acute bacterial pneumonias. A peripheral nodule or cavity (more than 1 cm in diameter) that is readily visualized on conventional (posteroanterior and lateral) radiographs and fluoroscopy, and is in an accessible location, may be aspirated and biopsied by a needle introduced percutaneously. A nodule that is inaccessible to needle aspiration, or a process placed peripherally, where the need for histopathology is not apt to be met by needle aspiration and biopsy, is best approached by open lung biopsy.

Flexible Fiberoptic Bronchoscopy with Lung Biopsy

Fiberoptic bronchoscopy in conjunction with transbronchial lung biopsy provides an etiologic diagnosis in about 50 to 80 percent of immunosuppressed patients who do not have AIDS and in 60 to 90 percent of patients who do have AIDS, in whom *P. carinii*, CMV, and *M. avium-intracellulare* infections are common. Contraindications to transbronchial biopsy include inability of the patient to cooperate, marked hypoxemia, bleeding disorders (particularly those associated with hypoprothrombinemia, thrombocytopenia refractory to platelet transfusion, and uremia), and pulmonary hypertension. In such patients, correction of bleeding tendency and/or open procedures may be preferred. Fiberoptic bronchoscopy combined with transbronchial biopsy and segmental BAL is the usual initial invasive diagnostic procedure in the immunocompromised patient with an undefined diffuse pulmonary process. If this fails to provide a diagnosis, open lung biopsy is indicated.

Tissue specimens are processed for histopathological examination (hematoxylin and eosin stain, tissue acid-fast stains, Gomori's methenamine-silver stain, periodic acid–Schiff stain, tissue Gram's stain, and Dieterle silver stain). Impression smears from tissues are made with sterile slides, which, after appropriate fixation, are stained with Giemsa, Gram, Ziehl-Neelsen, and methenamine silver (for *P. carinii*) stains, as previously described. As indicated, DFA staining for *Legionella* and monoclonal antibody staining for *P. carinii* are performed on separate impression smears. Appropriate cultures are made with tissue obtained either transbronchially or at open lung biopsy.

Bronchoalveolar Lavage

In patients with AIDS, fiberoptic bronchoscopy coupled with wedged, terminal, subsegmental BAL has proved particularly useful, providing a diagnosis in more than 95 percent of cases of *Pneumocystis* pneumonia. BAL alone, without transbronchial biopsy, is often substituted in patients who are thrombocytopenic, on mechanical ventilation, or severely hypoxemic. It should be noted that the yield in non-AIDS immunocompromised hosts is significantly less than in AIDS. Biopsy is often needed in this population. The material obtained by BAL is processed for smear and culture. As indicated earlier, a variety of stains are available for demonstrating the presence of *Pneumocystis* in the cytocentrifuged material. Stained cytocentrifuged BAL specimens can also be helpful in establishing other diagnoses: Papanicolaou's stain is useful in detecting neoplastic cells and in identifying viral cytopathic effects in epithelial cells.

In at least two-thirds of immunosuppressed patients with CMV pneumonia, the diagnosis can be made from the finding of inclusion bodies in cytocentrifuged BAL specimens and with immunofluorescent monoclonal antibody staining. CMV is isolated more often on culture in these patients, but culture alone is not sufficient to establish the diagnosis, since viral isolation may represent only viral shedding in the presence of pulmonary disease due to other causes.

Invasive Diagnostic Testing in Ventilator-Associated Pneumonia

Protected specimen brushing (PSB) with quantitative culture and protected-catheter BAL, also with quantitative culture, have been employed to obtain bacteriologic information while minimizing opportunity for contamination from colonization of the upper airway in patients with ventilator-associated pneumonia (VAP). The role of quantitative diagnostic techniques in the evaluation of patients with hospital-acquired pneumonia (HAP) and VAP remains controversial (discussed below) because of questions of reproducibility and the optimal threshold concentration of bacteria. In at least one study, tracheal aspirate cultures correlated with PSB cultures in patients with VAP, suggesting no added value to use of such an invasive procedure to direct initial therapy. The routine use of such tests requires standardization of techniques at the institutional level.

Percutaneous Transthoracic Needle Lung Biopsy

Percutaneous needle biopsy is often the invasive diagnostic procedure of choice for a sizable (greater than 1 cm) pulmonary nodule or cavity that is located peripherally. The use of smaller-gauge needles has reduced the frequency of pneumothorax as a complication. Diagnostic yields of 60 to 80 percent have been obtained in immunocompromised patients with pneumonia. This procedure has also provided the diagnosis in 70 percent of patients in whom the underlying lesion was granulomatous. The small core of tissue and aspirated fluid is examined by stained smear and culture for various infectious agents (see "Flexible Fiberoptic Bronchoscopy with Lung Biopsy"). Cytologic examination should be done for neoplastic cells. Because of the nature of the specimen, however, histopathological examination is generally fruitless. In patients in whom respiratory status is tenuous, or in whom

lymph node biopsy or sampling of pleural fluid may be desired, VATS or open biopsy may be preferable.

Open Lung Biopsy

Open lung biopsy and more recently VATS, provides the most definitive procedure for histopathological diagnosis in the immunocompromised host. It provides sufficient lung tissue for diagnosis and also makes it possible to sample several different sites. It is particularly suitable for evaluating processes that may not be infectious (e.g., neoplasm such as Kaposi's sarcoma, antineoplastic drug toxicity, drug hypersensitivity, and lymphocytic interstitial pneumonia). Open lung biopsy has provided a specific diagnosis in 60 to 90 percent of non-AIDS immunocompromised patients. Major advantages include specimen size and the ability to control bleeding, air leaks, and the airway. Its disadvantages relate to the thoracotomy: the need for general anesthesia, the inherent delay in preparing the patient for the surgical procedure, the need for intubation, the usual placement of a chest tube, and postoperative splinting due to incisional pain. Some of these complications are decreased in VATS. The mortality from the procedure is about 1 percent. Bleeding is a complication in about 1 percent of patients and delayed pneumothorax in about 9 percent. For the patient in whom the pace of the illness does not allow this sequential approach, open lung biopsy may have to be the first choice. It is also preferred in the patient who is unable to cooperate with fiberoptic bronchoscopy or in whom thrombocytopenia or hypoxemia pose additional problems for transbronchial biopsy.

Processing of lung biopsy specimens should include special stained imprint smears for *P. carinii*, bacteria (including *Nocardia* and mycobacteria), fungi, and viral inclusion bodies; cultures for bacteria, viruses, fungi, and mycobacteria; and tissue sections stained for histology and for infectious agents.

MAJOR CLINICAL SYNDROMES

Community-Acquired Pneumonia

Approximately 1 million people are admitted to the hospital each year for pneumonia. Initial evaluations of pulmonary processes in the outpatient setting revolve around an assessment of whether the individual merits admission to the hospital for management. Clinical judgment is the most important guide to appropriate care. This judgment is based on whether the patient can manage at home (needs oxygen or intravenous antimicrobials, weakness, cannot eat independently or take oral medications, other preexisting medical or psychiatric conditions, substance abuse, home supports) and whether the patient is at risk for disease progression. Many factors have been implicated in risk for death due to pneumonia. These include both common (alcoholism) and less common (immune deficiency) underlying conditions (Table 112-7). The PORT (Pneumonia Outcomes Research Team) Severity Index (PSI) is a quantitative tool that assesses the severity of a patient's illness, prognosis, and the need for hospitalization. This index provides the basis of North American practice guidelines for community-acquired pneumonia (CAP).

Table 112-7

Underlying Conditions Contributing to Adverse Outcomes from Pneumonia

Alcohol consumption
Increasing age
Leukopenia
Congestive heart failure
Coronary artery disease
Diabetes mellitus
Immune compromise
Neurological disease
Active malignancy
Clinical signs including: dyspnea/tachypnea, hypothermia, chills, hypotension, confusion or altered mental status
Laboratory tests: hyponatremia, hyperglycemia, azotemia, hypoalbuminemia, liver function test abnormalities
Radiographic infiltrates and pleural effusions, post-obstructive pneumonia
Microbiology: gram-negative bacilli, *S. aureus*, mixed flora (aspiration), bacteremia

For more than half of the patients with CAP, no causative pathogen can be identified. Up to 15 percent of CAP cases are due to aspiration or mixed bacteria. In most series, 20 to 65 percent are due to *S. pneumoniae* (pneumococcus). Approximately 15 percent of patients have definable, nonbacterial etiologies such as *M. pneumoniae*, *C. psittaci*, or viruses. These atypical pathogens are difficult to diagnose (and therapy, while universal, is often of less than certain value). The atypical pathogens, the pneumococcus and *Legionella* species, and aspirational events account for many of the undiagnosed cases of CAP. Certain uncommon causes may be endemic, in particular geographic niches, including *Coxiella burnetii* (in Nova Scotia) or *Francisella tularensis* in Little Rock, Arkansas. Thus, a major variable is the regional incidence of endemic infections including tuberculosis, and the episodic occurrence of epidemic infections such as outbreaks of influenza virus or Hantavirus.

CAP is a major cause of infectious morbidity and mortality. Depending on the causative organisms, the mortality of CAP ranges from 10 to 15 percent for pneumococcal infection to 60 percent for *P. aeruginosa*. Adverse clinical prognostic factors included co-morbid conditions (neurological or neoplastic disease, cirrhosis, congestive heart failure, respiratory compromise, diabetes, hepatic and renal dysfunction, immune deficiency), bacteremia, and multilobar involvement. *S. pneumoniae* is the preeminent bacterial cause of CAP. *H. influenzae*, usually unencapsulated strains, may produce pneumonia in patients with chronic bronchitis or in the chronic alcoholic. Apart from *S. pneumoniae*, however, the most important pathogen in this type of patient, by virtue of its virulence and special antimicrobial agent susceptibilities, is *K. pneumoniae*. During an outbreak of influenza viral infections, bacterial superinfections often occur, usually in the elderly or in patients with chronic cardiopulmonary disease. Patients with secondary bacterial pneumonia often have up to 4 days of clinical improvement after the initial influenzal illness before the onset of overt pulmonary infection. The superinfecting microorganisms are the pathogens that would ordinarily colonize the upper airways but opportunistically invade a tracheobronchial tree that has been recently damaged. These organisms include *S. pneumoniae*, *H. influenzae*, *S. aureus*, *Streptococcus pyogenes*, *M. catarrhalis*, and *K. pneumoniae*. The use of antimicrobial agents at the time of the initial respiratory infection not only is useless against viral influenza but also may selectively promote the emergence of a more resistant bacterial flora in the respiratory tract. *S. aureus* is a very uncommon cause of CAP. Indeed, the occurrence of several cases of *S. aureus* pneumonia in the community during the winter months is usually a good indicator of the presence of an ambient influenza outbreak. Pneumonia due to *S. pyogenes* is quite uncommon. Usually it occurs as a superinfection in a patient with influenza or as a primary pneumonia in the course of a regional outbreak of group A streptococcal infections (as still occurs from time to time when a new M-antigenic type appears in a community).

Atypical Pneumonia Syndromes and Endemic Mycoses

In the evaluation of patients with CAP, it is often helpful to consider separately a group of patients whose illness is characterized by minimal sputum that does not reveal a predominant microbial etiology on routine smears (Gram's stain, Ziehl-Neelsen) or cultures (including for mycobacteria and *Legionella*). The clinical onset of illness is generally subacute with a radiologic picture consisting of patchy infiltrates or an interstitial pattern than a lobar consolidation. Fever and peripheral leukocytosis are less common or intense than in common bacterial pneumonias. For convenience, this grouping has been designated *atypical pneumonia*.

The entities in the category of atypical pneumonia are heterogeneous (Table 112-8). The syndrome may account for up to 60 percent of cases of CAP. *M. pneumoniae* is the causative agent in about 25 percent of the cases of atypical pneumonia. Respiratory viruses are responsible for about another 30 percent. However, the predominant etiologic agent varies with the season and the prevalence of influenza viruses in the community. This information should direct the initial evaluation (e.g., nasal swab for respiratory viruses).

Chlamydophila pneumoniae (formerly known as *Chlamydia* strain TWAR) is an infectious agent that can be spread from person to person and appears to be responsible for 12 to 21 percent of cases of atypical pneumonia. This form of pneumonia typically occurs in young adults as a sporadic mild pneumonia, but may have enhanced severity when co-infecting individuals with pneumococcal infection. In adults, *M. pneumoniae* pneumonia, in contrast to bacterial pneumonia, often begins insidiously with malaise, fever, and prominent headache. Sore throat is common, but coryza is minimal or absent. Nonproductive cough develops over the next few days and is the hallmark of this disease. Skin rash (erythema multiforme) and bullous myringitis, usually appearing late in the course of illness, are uncommon findings but, when present, do suggest the diagnosis. Mini-outbreaks of *M. pneumoniae* infection in households, schools, and military camps may not be appreciated because of the long incubation period (3 weeks) and variation in clinical presentation.

Q fever, due to *C. burnetii*, is suspected on the basis of epidemiological clues. Transmission of this disease to humans occurs as a result of inhalation of aerosols from surroundings

Table 112-8

Causes of "Atypical Pneumonia"

Mycoplasma *M. pneumoniae*
Chlamydophila *C. psittaci* (psittacosis), *C. pneumoniae*
Respiratory tract viruses Influenza, adenovirus, respiratory syncytial virus, parainfluenza virus
Bacteria *Legionella, F. tularensis, Y. pestis, B. anthracis*
Fungi *Histoplasma, Blastomyces, Coccidioides, Pneumocystis*
Aspiration pneumonitis Sterile or mixed upper respiratory and oral flora
Other viral agents Varicella-zoster, measles, Epstein-Barr virus, cytomegalovirus, metapneumovirus, Hantavirus
Rickettsia *C. burnetii* (Q fever)

contaminated by placental and birth fluids of infected livestock (cattle, sheep, goats), wild rabbits, and domestic animals (cats). Veterinarians, ranchers, taxidermists, and others who handle livestock are at particular risk. Since the incubation period of Q fever is approximately 20 days, a source of exposure may be overlooked. Although the clinical picture resembles that of *M. pneumoniae* pneumonia, the onset may be more abrupt, with chills and high fever. Liver function abnormalities or clinical hepatitis in a patient with atypical pneumonia is suggestive of Q fever. In some geographic areas (Australia, France), hepatitis has been the most frequent clinical presentation of *C. burnetii* infection; in others (Spain, Nova Scotia), pneumonia has been the major presenting sign.

Chlamydia trachomatis causes pneumonia in the newborn but has not been proved to be a cause of pneumonia in adults. *C. psittaci*, the causative agent of psittacosis, is spread to humans by avian species. Although psittacine birds (parakeets, parrots) are the major reservoir, human infection can be acquired from pigeons, sparrows, and turkeys. In a patient with atypical pneumonia, the clinical features that raise the possibility of this etiology are relative bradycardia, splenomegaly and hepatomegaly, and hepatic dysfunction. *C. pneumoniae* produces atypical pneumonia without the usual bird-to-human transmission of *C. psittaci* infection.

Legionella infections (due to *L. pneumophila* and other *Legionella* species) account for 2 to 4 percent of cases of atypical pneumonia. Although *Legionella* is an important nosocomial pathogen, it is also responsible for community-based sporadic cases and major outbreaks. The occurrence of summer outbreaks associated with the use of air conditioners, pooled water, and evaporative condensers should call attention to this possible cause of pneumonia. Various extrapulmonary manifestations are common with Legionnaires' disease including relative bradycardia, diarrhea for 24 h at the onset of illness, confusion and obtundation, mild renal dysfunction (azotemia, microscopic hematuria, proteinuria), acute rhabdomyolysis, and mild hepatic dysfunction. Although many of these manifestations also occur with other pneumonias, the coincidence of several of these features should raise the possibility of *Legionella* infection. This is particularly important in view of the fact that the antimicrobial therapy (macrolides, fluoroquinolones) for Legionnaires' disease differs from that for the more common bacterial pneumonias. The mortality from Legionnaires' disease, if inadequately treated, can be as high as 15 percent. Recurrent chills, which occur over several days in Legionnaires' disease, are rare in pneumococcal pneumonia unless septic complications (e.g., endocarditis and pericarditis) develop. Although the initial radiographic picture of *Legionella* pneumonia is often that of an interstitial, segmental, or bronchopneumonic pneumonia, if the disease is untreated, it progresses to lobar or multilobar consolidation, a picture that mimics pneumococcal or *Klebsiella* pneumonia.

The other noteworthy bacterial types of atypical pneumonia are those due to *F. tularensis* (tularemic pneumonia), *Yersinia pestis* (plague pneumonia), and *Bacillus anthracis* (anthrax pneumonia). These are all singularly uncommon causes of pneumonia, and the principal clues to diagnosis again derive from epidemiological considerations. Exposure to *F. tularensis* comes through contact with tissues of an infected animal (rabbit), animal bites (coyote, cat), inhalation of infectious aerosols, tick or deerfly bites, or ingestion of contaminated water or poorly cooked meat from an infected animal. Ulceroglandular tularemia, or the typhoidal form of tularemia, may be complicated by patchy pulmonary infiltrates. Indeed, it is likely that typhoidal tularemia often represents infection initially acquired via the bronchogenic route. Plague is less common than tularemia in the United States and is strictly localized to southwestern states, including California. The diagnosis should be considered in a person from an endemic area who has a septic illness (septicemic plague) or painful localized lymphadenopathy with fever (bubonic plague) and a history of bites by rodent fleas or of handling tissues of infected animals, such as prairie dogs or coyotes. Pneumonia occurs as a complication in 10 to 15 percent of patients with bubonic or septicemic plague. Primary (inhalation) pneumonic plague is extremely rare and occurs only as a result of exposure to aerosolized particles from an infected animal or following close contact with cases of plague pneumonia. Anthrax pneumonia (inhalation anthrax) is also extremely rare in this country; it is a consequence of the inhalation of anthrax spores during the processing, or use, of goat skin, hair, or wool (usually imported from the Middle East, Asia, or Africa).

The principal clues to the presence of pulmonary mycoses are epidemiological. Thus, the principal endemic areas for histoplasmosis in the Western Hemisphere are in the midwestern United States and Central America. However, disease can be found in other locales and after travel. The organism is present in high concentrations in soil sites where avian, chicken, or bat excrement has accumulated. Movement of soil in such endemic areas by cleaning chicken coops, knocking down old starling roosts, or cleaning out old attics or basements can expose people to high concentrations of airborne spores that, when inhaled, produce an acute pneumonia. Atypical pneumonia in a person with this type of geographic exposure, or in a spelunker, should automatically raise the possibility of histoplasmosis. Blastomycosis occurs throughout most areas of the United States, but the endemic area is principally in the southeastern and south central areas. Rural exposure to soil contaminated with animal excrement appears to be a risk factor. Skin lesions, either verrucous or ulcerative, are the most common extrapulmonary manifestations of blastomycosis and afford a clinical clue to diagnosis. Coccidioidomycosis is endemic in the southwestern United States (California, particularly the San Joaquin Valley, and Arizona) and in neighboring portions of Mexico. Infection is usually acquired in these areas by inhalation of highly infectious arthrospores. Occasionally, major dust storms carry the arthrospores considerable distances from their soil source and produce unexpected outbreaks of infection. Archeological digs sometimes cause infection in those living elsewhere who receive an artifact uncovered in the explorations. Erythema nodosum may be associated with any of the primary

pulmonary mycoses, but most often with coccidioidomycosis. The coincidence of this hypersensitivity skin lesion and an atypical pneumonia syndrome in a person from an endemic area suggests the possibility of one of these pulmonary mycoses.

Paracoccidioidomycosis (South American blastomycosis) is endemic to Brazil (predominantly), and in Colombia, Venezuela, and Argentina. This disease is caused by *Paracoccidioides brasiliensis*. In adults, the manifestations of this disease are mainly pulmonary; radiographs show patchy or confluent areas of consolidation, often bilateral. Cases have occurred in North America and Europe, but in those instances, the patients had previously resided in endemic areas where initial infection presumably had been acquired.

Aspiration Pneumonia

Aspiration pneumonia may occur after an overt episode of aspiration (e.g., of gastric contents) or of bronchial obstruction by a foreign body. More often the predisposing circumstances are clear-cut (e.g., alcoholism, nocturnal esophageal reflux, pyorrhea, a prolonged session in the dental chair, epilepsy, or chronic sinusitis in a patient with absent gag reflex). In these circumstances, since the pneumonia may develop more insidiously than after overt aspiration, the relationship of the developing pneumonia to the predisposing circumstances may not be appreciated at the time. For this reason, specific questioning regarding such possible pathogenetic factors and evaluation of the gag reflex should be part of the examination of any patient with pneumonia.

If untreated, aspiration pneumonia may progress rapidly to a necrotizing process that is usually due to anaerobic organisms. The process may involve a pulmonary segment, a lobe, or an entire lung, with ultimate extension to the pleura ("putrid empyema"); in some patients, the necrotizing pneumonia culminates in lung abscesses. In others, aspiration produces an illness of several weeks' duration that is characterized by malaise, productive cough, and low-grade fever. If a chest radiograph is first taken after several weeks of untreated illness, it may show little, if any, evidence of pneumonia but will clearly identify a well-formed lung abscess.

In community-acquired aspiration pneumonia, bacteriologic studies provide a statistical basis for selecting initial antimicrobial therapy. Anaerobic bacteria are etiologically implicated in about 90 percent of community-acquired aspiration pneumonias and lung abscesses. In 40 to 65 percent of these patients, anaerobic organisms are the sole infecting agents; in 40 to 45 percent, the cause is a mixture of anaerobes and aerobes. The most common anaerobes are *Prevotella melaninogenica*, *Bacteroides* species, *Porphyromonas* species, *Fusobacterium* species, peptostreptococci, peptococci, and microaerophilic streptococci. β-Lactamase–producing *Bacteroides* species, *P. melaninogenica*, and members of the *Bacteroides fragilis* group are present in about 15 percent of cases. *P. melaninogenica* may be the most important contributor in such mixed infections. The aerobic indigenous flora in mixed aerobic-anaerobic infections are *Streptococcus viridans*, *M. catarrhalis*, and *Eikenella corrodens*. A rare form of anaerobic aspiration pneumonia (actinomycosis) that is community-acquired is that due to *Actinomyces israelii*, part of the normal flora in the gingival crevice or may contribute to chronic sinus infection. The direct extension of such a necrotizing pneumonia to the pleura and chest wall is a characteristic finding that strongly suggests the diagnosis of actinomycosis.

Although anaerobic members of the oropharyngeal flora have a preeminent role in community-acquired aspiration pneumonia and lung abscess, occasionally colonizing gram-negative enteric bacilli such as *K. pneumoniae*, *E. coli*, and *Proteus* species may be the cause (notably in alcoholics). Persistence of a necrotizing pneumonia or lung abscess despite antimicrobial therapy that would be expected a priori to be effective raises the possibility of an underlying obstruction, often in the form of bronchogenic carcinoma, particularly if the patient is edentulous.

Pneumonia in the Elderly

CAP in the elderly (over 60 years) primarily affects two populations: one that lives at home and another residing in nursing homes. The latter, from the point of view of oropharyngeal flora and the extent of exposure to antimicrobial agents, is generally considered as a part of "Health Care–Associated Pneumonia" (HCAP), with a predisposition to nosocomial infection (see below) with an increased rate of antimicrobial resistance. The clinical features of pneumonia in the elderly may differ in presentation from that in younger people. Infection has a more gradual onset, with less fever and cough, often with a decline in mental status or confusion and generalized weakness, often with less readily elicited signs of consolidation on examination. Eliciting a deep breath from the patient may be helpful in demonstrating a localized wheeze or rales that might otherwise be undetectable. Among the bacterial causes of CAP in the elderly, *S. pneumoniae* is the most frequent, accounting for 30 to 60 percent of cases. *H. influenzae*, primarily nontypeable strains, is the second most common cause (about 20 percent). *M. catarrhalis* is another cause of pneumonia in this age group, primarily in patients with chronic bronchitis. Aspiration pneumonia due to mixed aerobic-anaerobic flora occurs in this age group, particularly because of the presence of a diminished gag reflex or impaired pharyngeal motor function.

In nursing home residents or persons with recent hospitalizations, increased oropharyngeal colonization with gram-negative bacilli occurs, due to antimicrobial exposure, or exposure to the hospital environment or to other recent patients. Microaspirational events predispose to pneumonia due to species such as *K. pneumoniae, E. coli* and other Enterobacteriaceae, and *P. aeruginosa*. Such gram-negative bacilli have been implicated as the cause in 25 to 40 percent of elderly nursing home residents with pneumonia. *S. aureus* is responsible for 2 to 10 percent of cases of CAP in the elderly overall, more commonly in nursing home residents and during community outbreaks of influenza. Common forms of CAP are also seen in the elderly.

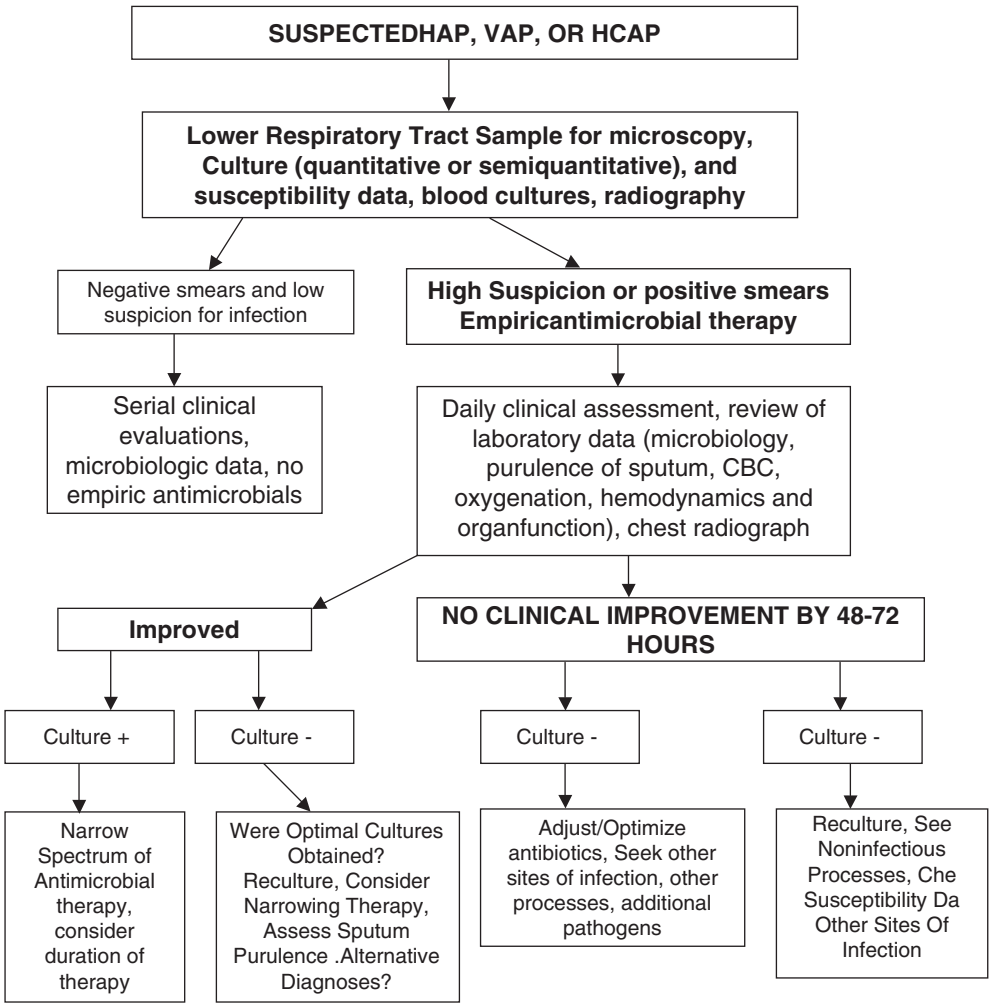

Figure 112-11 Paradigm for the evaluation of patients with nosocomially acquired pneumonia. Careful reassessment of patients on a daily basis is needed to assure an adequate response to therapy. Clinical judgment is the best guide to the use of empiric therapy.

Hospital-Acquired, Ventilator-Associated, and Nonresolving Pneumonias

The hospitalized patient with pneumonia poses the dual challenge of infection with nosocomial pathogens and the presence of concomitant processes—the "sick" patient (Fig. 112-11). Nosocomial pneumonia occurs at a rate of 5 to 10 cases per 1000 hospital admissions. The incidence increases 6- to 20-fold in patients receiving assisted ventilation. Hospital-acquired pneumonia (HAP) develops over 48 hours into hospitalization while VAP occurs more than 48 to 72 hours after endotracheal intubation. HCAP includes patients with infection developing within 90 days of hospitalization, residents in a nursing home or long-term care facility, or those who have had recent exposure to hemodialysis, intravenous antimicrobial therapy, chemotherapy, wound care, or hospital-associated clinics. HAP accounts for up to one-fourth of intensive care unit infections. VAP occurs in up to one-fourth of intubated patients in some series, generally in the first 4 days of intubation.

Early-onset (first 3 days) nosocomial pneumonia is more often due to organisms without antimicrobial resistance including *S. pneumoniae*, *H. influenzae*, and *M. catarrhalis*. Community-acquired atypical pathogens (*Mycoplasma, Chlamydophila*) may also lead to early hospitalization. Beyond 5 days of hospitalization, or in those with recent hospitalization or with prior antimicrobial therapy, infection is more often due to multidrug-resistant (MDR) organisms (*K. pneumoniae*, other Enterobacteriaceae, *Acinetobacter* species, and *P. aeruginosa*) and mortality is increased. Attributable mortality for nosocomial pneumonia approaches 50 percent.

In practice, pneumonia is defined as the presence of a new or progressive radiologic infiltrate coupled with evidence that the infiltrate is infectious in origin—fever higher than 38°C, leukocytosis or leukopenia, and/or purulent secretions. Two out of three criteria are generally considered adequate. Tracheal aspirates will generally contain the offending organism(s) but may be contaminated by upper-tract flora, notably flora associated with tracheobronchitis.

Semiquantitative cultures are used to discriminate between pathogens and commensals. Gram staining of such specimens provides added information about host response (neutrophils and macrophages) and predominant bacterial forms. In immunocompromised hosts, fungal smears and cultures, cultures and microscopy for *Legionella, Nocardia*, and mycobacteria should also be obtained. A good sputum specimen or an aspirate lacking bacteria or inflammatory cells (in a non-neutropenic host) should suggest other diagnoses (nonbacterial or noninfectious). While the majority of HAPs are bacterial, nosocomial infection due to respiratory viruses and *Legionella* species are common. A negative Gram's stain of a good tracheal aspirate has a strong negative predictive value (approximately 94 percent) for VAP.

Some friction exists between strict advocates of microbiologic evaluations and care which is based on clinical expertise. In practice, neither is sufficient, per se. Lower respiratory tract cultures must be obtained prior to the initiation of antimicrobial therapy, but should not delay the initiation of therapy in critically ill patients or in those with evidence of sepsis. Respiratory specimens may be obtained bronchoscopically or nonbronchoscopically, and cultured semiquantitatively or quantitatively, based on local expertise and availability. All patients with nosocomial pneumonia should also have blood cultures, chest radiography, arterial oxygenation levels, and diagnostic thoracentesis if large pleural effusions are present.

The use of semiquantitative cultures and clinical judgment results in the inappropriate use of broad-spectrum antimicrobial therapy in some patients with either minor infections or colonization in the setting of other pulmonary inflammatory processes: drug reactions, cancer, ARDS, congestive heart failure, pulmonary thromboembolus, hemorrhage, or even viral infection. However, depending on the patient mix of the institution (acuity, immune deficits) this approach is generally appropriate.

A narrower spectrum of initial antimicrobial therapy is possible by using quantitative cultures of invasive (endotracheal aspirates, BAL, or PSB specimens) specimens from the lower respiratory tract. Bacterial growth above a predetermined threshold (e.g., 10^4 to 10^5 cfu/ml in BAL or 10^3 cfu/ml for PSB specimen) provides a basis for treatment. Quantitative approaches may suffer from poor reproducibility and the impact of recent antimicrobial therapies (e.g., the use of empiric antimicrobial agents entails the risk of false-negative cultures and under-treatment of specific pathogens or patients). Pneumonia "in evolution" or patchy processes may confound quantitative approaches. This approach risks delays in therapy while awaiting culture data. This reservation is addressed in part by using detection of intracellular organisms (in 2 to 5 percent of cells) on Gram's stained smear as a basis for empiric therapy. Sensitivity and specificity of various methods of collection and analysis vary greatly—but can be standardized within an institution.

Use of appropriate antimicrobial agents initially has a major beneficial impact on patient survival. Prior antimicrobial therapy and colonization patterns must be considered as risk factors for antimicrobial-resistant pathogens. The major pathogens in "hospital-acquired" pneumonia vary among institutions and within hospitals. Thus, empiric therapies must be individualized by institution as well by patient. Initially, broad-spectrum antimicrobial therapy directed at the likely pathogens (by clinical assessment) and at the predominant resistant flora of the given institution is likely to avoid inappropriate selection of agents. This approach must be coupled with "de-escalation" of therapy based on culture data. Initial therapy should utilize appropriate doses of bactericidal therapies (including loading doses). If the patient has recently received antimicrobial therapy, drugs from a different class should be used in initial therapy. In normal hosts, sputum Gram's stains are useful in gauging response to therapy (disappearance of neutrophils) while chest radiographs and oxygenation are helpful in evaluating response to therapy. Reevaluation of antimicrobial selections must be made as microbiologic data become available and the clinical progress of the patient is observed.

MDR pathogens provide special challenges. Risk factors for MDR-infection include recent hospitalization or antimicrobial therapy, exposure to certain clinical environments (dialysis, clinic, home IV therapy), and to immune compromise (Table 112-9). In intensive care units, *Burkholderia* (formerly *Pseudomonas*) *cepacia*, *Stenotrophomonas* (formerly *Xanthomonas*) *maltophilia*, and *Acinetobacter baumannii* (formerly *Acinetobacter calcoaceticus* variant *anitratus*) have been implicated in localized outbreaks of nosocomial pneumonia. Combination therapy for gram-negative bacterial pneumonia is generally reserved for two situations: suspected *Pseudomonas* pneumonia or for the initial therapy of nosocomial pneumonia while susceptibility data are pending. Community- and hospital-acquired *Staphylococcus aureus* is increasingly resistant to methicillin (MRSA). Both vancomycin and linezolid are reasonable alternatives for MRSA in this setting and some preliminary data suggest that linezolid may be advantageous in ventilator-associated infection. Strategies for empiric therapy are discussed in Chapter 115.

Nonresolving pneumonia occurs as a result of inappropriate antimicrobial therapy, superinfection, inadequate host response, obstruction, empyema, noninfectious processes, or recurrent infection. Inappropriate antimicrobial therapy includes inadequate dosing, agents that fail to penetrate infected lung tissue (often aminoglycosides), or the use of agents to which the organisms are or have become resistant. Empyema or loculated infection may occur during the course of appropriate therapy for pneumonia. Relapsed infection is common in intubated patients colonized with resistant microorganisms. Superinfection with resistant organisms (including fungi, *Mycobacterium tuberculosis*) may occur in the hospital setting as well as viral co-infection with community-acquired respiratory viruses. Untreated bacteremia (due to endocarditis, abdominal abscess, catheter-associated infections) or septic pulmonary emboli may cause persistent lung infections. In the compromised host, repletion of antibodies, neutrophils (colony-stimulating factor), treatment of concomitant viral

Table 112-9

Factors in the Emergence of Antimicrobial Resistance

Increase in "high-risk" (immunodeficient) population
Prolonged survival of persons with chronic diseases
Greater severity of illness of hospitalized patients
Newer devices and procedures in use
Increased introduction of resistant organisms from the community
Congregate facilities (e.g., jails, day care centers)
Increased use of antibiotics in animals and agriculture
Physician practices that contribute to inappropriate antibiotic use
Providing antibacterial drugs to treat viral illnesses
Using inadequate diagnostic criteria for infections that may have a bacterial etiology
Providing expensive, broad-spectrum agents that are unnecessary
Prescribing antibiotics at an improper dose or duration • Lack of rapid, accurate diagnostic tests to distinguish between viral and bacterial infections
Selection of antibiotic-resistant genes via abuse of antimicrobial agents • Ineffective infection control and isolation practices and compliance

infections (HIV, CMV), and repeat culturing may assist in management. Obstruction or empyema must resolve to allow resolution of infection. Recurrent infection may be observed if the patient is aspirating, has sinusitis, has a misplaced feeding tube, has airway compromise, or has pulmonary infarction. Additional cultures and radiologic studies (CT scans, decubitus films) may assist in defining lung processes which fail to respond to therapy. Bronchoscopic evaluation and, in selected patients, lung biopsy may assist in management.

NONINFECTIOUS PROCESSES MIMICKING PULMONARY INFECTIONS

The list of noninfectious disorders that mimic pulmonary infections is extensive (Table 112-10). These should be considered in the course of taking the initial history. The likelihood of noninfectious etiologies of pulmonary disease increases if the Gram-stained smear and culture of sputum are unrevealing, if the initial response to empiric antimicrobial therapy proves unsatisfactory, or if radiographic findings are atypical. Similar histologic appearances result from both infectious and noninfectious etiologies. The presence of a maculopapular skin rash, generalized lymphadenopathy, joint or rheumatologic symptoms, and/or peripheral eosinophilia should suggest hypersensitivity. However, as noninfectious and infectious processes often coexist, it is essential to exclude infectious causes of pulmonary dysfunction before treating hypersensitivity reactions. Immunosuppressive agents, notably corticosteroids, reduce inflammation due to both infectious and noninfectious causes.

Drug-Induced Pneumonitis

Noncytotoxic Drugs

Drugs producing pulmonary reactions may be considered in two categories: noncytotoxic and cytotoxic drugs. Noncytotoxic drugs that cause hypersensitivity pneumonitis include antimicrobials, anticonvulsants, diuretics, antiarrhythmics, tranquilizers, and antirheumatic agents (Table 112-11). Among the most common pulmonary reactions are those due to sulfa drugs, phenytoin, nitrofurantoin, and amiodarone. Sulfasalazine (and other sulfonamides) can produce hypersensitivity lung disease that includes cough, fever, dyspnea, and peripheral hazy acinar or diffuse reticular infiltrates on the chest radiograph. Phenytoin can produce hypersensitivity responses in the lungs 3 to 6 weeks after initiation of therapy. Fever, cough, and dyspnea are accompanied by radiographic findings of bilateral acinar, nodular, or reticular infiltrates. Nitrofurantoin can produce two patterns of pulmonary reaction: (1) acute, which occurs within 2 weeks after starting therapy and consists of dyspnea, nonproductive cough, chills, fever, crackles, eosinophilia, and diffuse interstitial or patchy infiltrates (often with pleural effusion); and (2) chronic, which is less common and occurs after months to years of continuous treatment. The picture of the chronic form is one in which exertional dyspnea and nonproductive cough appear gradually and are unaccompanied by fever; the pattern is not that of an acute pulmonary infection but, rather, the pattern of diffuse interstitial pneumonitis or pulmonary fibrosis. Amiodarone may be associated with pulmonary side effects that often occur after 5 to 6 months of therapy. Exertional dyspnea, nonproductive cough, malaise, and fever (in about half the patients) are gradual in onset, over weeks to several months. The radiographic findings include peripheral areas of consolidation that primarily affect the upper lobes. In some instances, coarse reticular interstitial infiltrates are present. Withdrawal of the medication, coupled with the administration of corticosteroids, usually leads to complete resolution. Other common forms of drug-induced hypersensitivity pneumonitis include those due to hydrochlorothiazide and gold salts. Hydralazine, procainamide, and isoniazid are capable of inducing a lupus-like syndrome which may include pleuropulmonary involvement.

Table 112-10

Noninfectious Causes of Febrile Pneumonitis Syndrome (Mimics of Pulmonary Infection)

- Drug-induced pulmonary disease
- Extrinsic allergic alveolitis
- Injury due to inhaled toxic gases, dusts, chemicals
- Acute eosinophilic pneumonia
- Pulmonary infiltrate with eosinophilia ("PIE syndrome")
- Chronic eosinophilic pneumonia
- Interstitial lung disease associated with autoimmune/connective-tissue disorders
  - Systemic lupus erythematosus
  - Polymyositis-dermatomyositis
  - Mixed connective-tissue disease
- Interstitial lung disease associated with pulmonary vasculitis
  - Wegener's granulomatosis
  - Lymphomatoid granulomatosis
  - Churg-Strauss syndrome (allergic angiitis and granulomatosis)
  - Polyangiitis overlap syndrome
- Intersititial lung disease associated with pulmonary airway disease
  - Allergic bronchopulmonary aspergillosis
  - Bronchocentric granulomatosis
  - Bronchiolitis obliterans and bronchiolitis obliterans with organizing pneumonia
- Acute or subacute interstitial pulmonary fibrosis (IPF, Hamman-Rich syndrome)
- Chronic interstitial pneumonias of unknown origin
  - Usual interstitial pneumonia (UIP)
  - Lymphocytic interstitial pneumonia (LIP)
  - Desquamative interstitial pneumonia (DIP)
  - Giant-cell interstitial pneumonia (GIP)
- Pulmonary neoplasms
  - Carcinoma or lymphoma
  - Kaposi's sarcoma in AIDS
- Sarcoidosis
- Pulmonary infarction
- Acute chest syndrome in sickle cell crisis
- Radiation pneumonitis
- Lipoid pneumonia (exogenous or endogenous)
- Acute respiratory distress syndrome (ARDS) associated with:
  - Extrapulmonary sepsis
  - Oxygen toxicity, chemical inhalation or aspiration, or aspiration of gastric contents
  - Pancreatitis
  - Fat embolization
  - Shock of various etiologies
  - Drug overdose
  - Chest trauma
- Pulmonary leukoagglutinin transfusion reactions
- Miscellaneous
  - Pulmonary alveolar proteinosis
  - Plasma cell granuloma
  - Histiocytosis X
  - Idiopathic pulmonary hemosiderosis
  - Goodpasture's syndrome
  - Rheumatic pneumonia (in acute rheumatic fever)

Cytotoxic Drugs

Three clinical and pathological patterns characterize cytotoxic drug–induced pulmonary disease: chronic pneumonitis with pulmonary fibrosis, acute hypersensitivity lung disease, and noncardiogenic pulmonary edema (Table 112-12). A variety of predisposing factors may contribute to the development of these reactions. The cumulative dose of certain drugs (e.g., bleomycin, busulfan, and carmustine) appears to be particularly important. Combined exposures (e.g., Adriamycin and bleomycin) with dual patterns (cardiac failure and pulmonary injury) are common.

Syndrome of Acute or Chronic Pneumonitis with Fibrosis

All cytotoxic drugs capable of inducing pulmonary disease can produce pneumonitis with fibrosis. The clinical manifestations develop over weeks to months and include nonproductive cough, progressive dyspnea on exertion, fatigue, and malaise. End-inspiratory crackles are audible on examination. The radiographic findings are consistent with those of an interstitial inflammatory process and pulmonary fibrosis. Fever is not common in this process except for the disease due to cyclophosphamide; over 50 percent of patients with pulmonary fibrosis due to cyclophosphamide exhibit fever.

Table 112-11

Noncytotoxic Drugs Capable of Inducing a Picture Resembling Pulmonary Infection

Antimicrobial agents
- Nitrofurantoin
- Penicillins, cephalosporins
- Sulfasalazine, other salfonamides
- Minocycline, tetracycline
- Amphotericin B (acting with leukocyte transfusions)
- Para-aminosalicylic acid

Anticonvulsants
- Phenytoin
- Carbamazepine

Diuretics
- Hydrochlorothiazide

Antiarrhythmics
- Amiodarone
- Tocainide

Narcotics
- Heroin
- Methadone
- Propoxyphene
- Cocaine

Anti-rheumatic agents
- Gold salts
- Penicillamine
- Naproxen

Drugs that can induce a lupus erythematosus-like syndrome
- Hydralazine
- Procainamide
- Isoniazid
- Chlorpromazine

Others: Sirolimus

Distinguishing between the effect of the drugs and the underlying disease process is often difficult.

Syndrome of Hypersensitivity Lung Disease

Methotrexate, bleomycin, and procarbazine cause an acute syndrome of dyspnea, nonproductive cough, fever, and occasionally pleuritic chest pain. The presence of blood eosinophilia and a skin rash suggests a hypersensitivity reaction. The radiographic findings include a diffuse reticular pattern and, in some patients, bilateral acinar infiltrates.

Table 112-12

Cytotoxic Drugs Capable of Inducing a Picture Resembling Pulmonary Infection

Acute or Chronic Pneumonitis with Pulmonary Fibrosis
- Antimicrobial agents
  - Bleomycin, mitomycin, neocarzinostatin
- Alkylating agents
  - Busulfan, cyclophosphamide, chlorambucil, melphalan, chlorozotocin
- Nitrosoureas
  - Carmustine (BCNU), semustine (methyl CCNU), lomustine (CCNU), chlorozotocin
- Antimetabolites
  - Methotrexate, azathioprine, mercaptopurine, cytosine arabinoside, 6-thioguanine
- Miscellaneous
  - Vinblastine, VM-26, vindescine

Hypersensitivity Lung Disease
- Antimetabolites
  - Methotrexate
- Antimicrobial agents
  - Bleomycin
- Miscellaneous
  - Procarbazine

Noncardiogenic Pulmonary Edema
- Antimetabolites
  - Methotrexate, cytosine arabinoside
- Alkylating agents
  - Cyclophosphamide
- Miscellaneous
  - VM-26

Extrinsic Allergic Alveolitis (Hypersensitivity Pneumonitis)

Inhalation of organic dusts may produce chills, fever, nonproductive cough, dyspnea, and pulmonary crackles within hours of exposure to organic dusts or vapors. The chest radiograph usually shows bilateral patchy acinar infiltrates, suggestive of pulmonary infection. The history of a specific exposure provides the clue to diagnosis, particularly when such episodes have been recurrent. Farmer's lung is due to hypersensitivity to moldy hay containing *Thermoactinomyces* species and *Micropolyspora faeni*. "Air-conditioner" or "humidifier" lung is associated with exposure to similar moldy antigens stemming from occult microbial growth on air-exchanging systems in offices and homes. In other hypersensitivity pneumonitides, the offending antigens may be avian in origin (pigeon breeder's disease) or due to other environmental fungi which contaminate natural products in industry (e.g., maple bark stripper's lung; moldy sugar cane in bagassosis).

INJURY DUE TO INHALED TOXIC GASES, DUSTS, CHEMICALS Silo-filler's disease is an acute syndrome that mimics acute bacterial or viral pneumonia clinically and radiologically following exposure to nitrogen dioxide. A degenerative interstitial pneumonitis–like picture may result from exposure to organic (e.g., wood, mycotoxin-containing) and inorganic (e.g., silicates, tungsten carbide) dusts. Severe interstitial disease and organizing pneumonia have occurred among workers exposed to aerosols of organic chemicals (designed to polymerize on mixing) used in textile dyeing.

CHRONIC AND ACUTE EOSINOPHILIC PNEUMONIA Chronic eosinophilic pneumonia usually has a course of weeks to months, characterized by fever, night sweats, nonproductive cough, and dyspnea. Pulmonary crackles are variably present. Chest radiographs show a characteristic pattern of peripheral acinar infiltrates that usually involve the upper lobes and resemble the appearance of butterfly pulmonary edema. Peripheral blood eosinophilia is common. Occasionally, chronic eosinophilic pneumonia has an acute onset. Even though the onset in such instances is acute, the course, if untreated (corticosteroids), is prolonged, as in typical chronic eosinophilic pneumonia. Acute eosinophilic pneumonia was initially described as an acute febrile illness with severe hypoxemia, diffuse pulmonary infiltrates, increased numbers of eosinophils in BAL fluid, and prompt response to corticosteroid therapy without relapse. Drug hypersensitivity may be the cause in some instances. A subset has been described with the same acute onset with high fever, a radiologic picture of micronodular and diffuse ground-glass infiltrates, and spontaneous improvement without relapse.

PULMONARY INFILTRATE WITH EOSINOPHILIA The term *pulmonary infiltrates with eosinophilia* (PIE syndrome) is used to encompass a wide range of definable clinical entities such as acute eosinophilic pneumonia, chronic eosinophilic pneumonia, allergic pulmonary aspergillosis, and Churg-Strauss vasculitis (see below). However, PIE syndrome should be used to refer to a syndrome consisting of fleeting pulmonary infiltrates, dry cough and mild wheezing, low-grade fever, and blood and pulmonary eosinophilia. Loeffler's syndrome, a form of PIE, may be associated with parasitic infestation (migration or hypersensitivity) with *Ascaris lumbricoides, Strongyloides stercoralis, Ancylostoma duodenale, Toxocara canis,* and others, or due to drug hypersensitivity. Tropical eosinophilia is a similar syndrome, endemic in India and southern Asia, Africa, and South America, and most likely due to filarial infection.

INTERSTITIAL LUNG DISEASE ASSOCIATED WITH CONNECTIVE TISSUE DISORDERS AND PULMONARY VASCULITIS A variety of connective tissue disorders and vasculitides mimic pulmonary infections. Systemic lupus erythematosus may be associated with transitory infiltrates, interstitial disease, or frank consolidation of a noninfectious nature. Interstitial pneumonitis occurs in 5 to 10 percent of patients with polymyositis and may be mistaken for a pulmonary infection, since pulmonary manifestations and fever may precede muscle weakness.

Three types of vasculitis commonly mimic pulmonary infection. Wegener's granulomatosis involves the lung in approximately 95 percent of cases. Radiologically, the lesions appear as patchy infiltrates or as nodular lesions that may progress to cavities or lung abscesses. Superinfection of Wegener's granulomatosis of the lungs is common. Allergic angiitis and granulomatosis (Churg-Strauss syndrome) occurs in the setting of asthma and peripheral eosinophilia. It characteristically involves the lungs, producing pulmonary infiltrates associated with granulomatous and vasculitic lesions. The polyangiitis overlap syndrome combines some of the characteristic features of classic polyarteritis nodosa and of allergic angiitis and granulomatosis; in some instances pulmonary impairment is a prominent feature.

INTERSTITIAL LUNG DISEASE ASSOCIATED WITH PULMONARY AIRWAY DISEASE Allergic bronchopulmonary aspergillosis, characterized by cough, bronchospasm, fever, and intermittent pulmonary infiltrates, can suggest pulmonary infection, although an accompanying eosinophilia provides a clue to the true nature of the process. Eosinophilia may be absent in patients receiving corticosteroid therapy. Bronchocentric granulomatosis, a necrotizing process of unknown cause affecting small bronchi may be associated with fever in some patients. The pulmonary lesions vary from mucoid impaction to diffuse and nodular infiltrates.

Bronchiolitis obliterans is an occasional complication of pulmonary viral or bacterial infections, cocaine toxicity, drug hypersensitivity, connective tissue disease, inhalation of chemical irritants; or the disease can occur without apparent cause. It is a common presentation of lung injury and chronic rejection of transplanted lungs. It may present with patchy areas of pneumonitis, necrosis of bronchiolar epithelium, and occlusion of terminal airways by granulation tissue. Bronchiolitis obliterans-organizing pneumonia (BOOP) refers to instances in which the presence of organizing inflammatory polypoid masses in distal bronchioles and alveolar ducts is accompanied by a chronic pneumonitis with lipid-laden macrophages. Although many patients with BOOP respond promptly to corticosteroids, occasional patients undergo a rapidly progressive course even with intensive therapy.

CHRONIC INTERSTITIAL PNEUMONIAS OF UNKNOWN CAUSE A variety of interstitial pneumonias, known as usual interstitial pneumonia (UIP), lymphocytic interstitial pneumonia (LIP), desquamative interstitial pneumonia (DIP), and giant cell interstitial pneumonia (GIP), are conditions of unknown origin that are defined on histologic grounds. Most often they present clinically as subacute or chronic processes characterized by progressive dyspnea, cyanosis, nonproductive cough, pulmonary crackles, and a radiographic picture of diffuse reticulonodular infiltrates (more prominent at the lung bases) or a "ground-glass" pattern without fever. Thus, the clinical picture may not suggest pulmonary infection. In some patients, the onset is rapid and accompanied by fever suggesting an acute respiratory infection.

PULMONARY NEOPLASMS Bronchial obstruction by a bronchogenic carcinoma may produce obstructive pneumonia ("drowned lung") or atelectasis. Fever and signs of consolidation/atelectasis may fail to respond to antimicrobial therapy. Recurrent pneumonia in the same portion of the lung should suggest this possibility. Hodgkin's disease and non-Hodgkin's lymphoma may present with fever, cough, dyspnea, and pulmonary lesions suggesting infection. In Hodgkin's disease, a single mass lesion may be present and cavitate, suggesting a lung abscess.

SARCOIDOSIS In the patient with sarcoidosis and interstitial lung disease, fever is uncommon unless hilar adenopathy or other features, such as erythema nodosum, are also present. Consequently, this process is usually not mistaken for a primary pulmonary infection.

PULMONARY INFARCTION Fever, dyspnea, pleuritic chest pain, leukocytosis, and segmental pleural-based infiltrates (and possibly accompanying pleural effusion) of pulmonary infarction suggest the presence of pulmonary infarction due to pulmonary embolus or septic emboli. Similar features are observed with pneumococcal pneumonia. The presence of blood-streaked sputum in this syndrome may suggest the possibility of *S. pyogenes* pneumonia with hemorrhagic tracheobronchitis. Occasionally, multiple round radiographic infiltrates in the lungs of a febrile, dyspneic patient with pulmonary emboli may suggest lung abscesses due to aspiration or septic emboli.

LIPOID PNEUMONIA Exogenous lipoid pneumonia results from inhaling or aspirating fatty materials (oily nose drops, mineral oil). Endogenous lipoid pneumonia (often called "*cholesterol* pneumonia") consists of chronic inflammatory foci containing cholesterol and its esters, derived from destroyed alveolar walls located either behind a bronchial obstruction or in lung parenchyma at a site of chronic suppuration. Sputum, fine-needle aspirates, or BAL specimens may reveal macrophages containing lipoid vacuoles, as demonstrated by fat stains (Sudan, oil red O).

RADIATION PNEUMONITIS The acute phase of radiation pneumonitis usually develops within 3 or 4 months after initiation of radiation therapy. It is characterized by fever, dyspnea, cough, and radiographic changes (infiltrates or ground-glass density) sharply demarcated geometrically to the portal of irradiation rather than to natural pulmonary anatomic divisions. This reaction might be mistaken for a bacterial pneumonia. The late phase of radiation pneumonia, characterized by pulmonary fibrosis, occurs 9 months or more after radiation therapy and is not accompanied by fever.

MISCELLANEOUS MIMICS OF PULMONARY INFECTION Pulmonary alveolar proteinosis usually begins slowly, with dyspnea as the principal symptom. Radiographic features are those of a bilateral diffuse, predominantly perihilar airspace disease. The radiographic, but not the clinical, manifestations may suggest pulmonary infection. Fever is usually absent. However, pulmonary alveolar proteinosis may be associated with hematologic malignancies, which are associated with fever including lymphoma or acute leukemia. In addition, pulmonary alveolar proteinosis is sometimes complicated by pulmonary infections—e.g., nocardiosis (most frequently), cryptococcosis, aspergillosis, tuberculosis, pneumocystosis, and histoplasmosis.

Plasma cell granuloma is a postinflammatory pseudotumor of the lung. The combination of cough, fever, and radiologic changes of atelectasis and consolidation suggests the diagnosis of pulmonary infection associated with bronchial obstruction. This process is very similar to the previously described cholesterol pneumonia.

Eosinophilic granuloma of the lung (pulmonary histiocytosis X) usually is manifested as a noninfectious interstitial pulmonary process with dyspnea and nonprogressive cough. In about 15 percent of patients, however, fever does occur, suggesting the possibility of pulmonary infection. The radiographic findings are those of small nodules and reticulation or honeycombing; these findings in the febrile patient may suggest the diagnosis of miliary tuberculosis, invasive mycotic infection, *Rhodococcus equi*, or viral disease (e.g., varicella-zoster).

ACUTE RESPIRATORY DISTRESS SYNDROME (ARDS) Many unrelated conditions involving the lungs primarily or having their initial impact elsewhere have in common the capacity to cause diffuse damage to the alveolar-capillary membrane and produce noncardiogenic pulmonary edema. The process progresses rapidly with inflammatory cell infiltration and pulmonary fibrosis. Extensive pulmonary infiltrates are evident on chest radiographs. Superinfection of lungs injured by ARDS, often by nosocomial pathogens, is common. Many of the underlying processes that produce ARDS are associated with fever, including pancreatitis, peritonitis, endocarditis, severe thermal injuries, as well as fulminant bacterial or viral infections.

PULMONARY LEUKOAGGLUTININ TRANSFUSION REACTIONS An acute pulmonary reaction may follow receipt of a blood transfusion with which there has been passive transfer of leukoagglutinins and antibodies cytotoxic to recipient lymphocytes. The clinical picture of an abrupt onset of chills, fever, tachycardia, cough, and dyspnea, accompanied by numerous fluffy and nodular perihilar infiltrates on radiograph, may easily be mistaken for an acute pulmonary infection. Pulmonary hemorrhage may also affect such patients, particularly after hematopoietic transplantation.

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The Radiology of Pulmonary Infection

Reginald E. Greene

This chapter aims to provide clinicians with a framework for analyzing images of pulmonary infection by focusing on generic pathogenetic categories that can be identified on computed tomography (CT). The focus is on the role of chest imaging in the diagnosis of pneumonia, the identification of common etiologic classes of infection, and notation of pertinent non-infectious differential diagnoses. A detailed examination of the imaging findings of the entire range of potential causes of lung infection is beyond the scope of this chapter.

IMAGING MODALITIES

Imaging is an essential tool in the management of patients with pneumonia. The main roles of imaging are to independently detect, corroborate, and localize clinically suspected pneumonia, estimate the severity and extent of disease, identify categorical abnormalities that can narrow the range of likely etiological infectious agents, and differentiate pneumonia from non-infectious etiologies that may be responsible for the clinical and imaging findings. Follow-up imaging is used to estimate response to treatment, exclude complications of pneumonia, and document clearing of the initial imaging abnormality. Pneumonias that respond clinically to treatment can often take 8 weeks or more to clear on plain film radiography, and even longer on CT, usually long after the clinical status has returned to normal. Return to an imaging baseline condition is particularly slow in patients with co-morbidity or severe infections.

Plain chest radiography is the basic tool for imaging patients with suspected pneumonia. The findings can justify a working clinical diagnosis and help form the basis for initial management. In some cases atypical or otherwise worrisome findings of plain film radiography point to a need for supplementary CT to rule out complicated infection or other disease. This sequence occurs more often in older patients, and those with co-morbidities than in previously healthy young patients.

CT is the imaging gold standard for evaluation of lung disease in general, and chest infection in particular. It provides the highest level of global specificity and sensitivity for the diagnosis of pneumonia. In a few specific circumstances CT findings may warrant the start of preemptive antimicrobial therapy when etiological, microbiological, or histopathological proof of diagnosis is lacking. The present generation of 4- to 64-slice multidetector CT scanners can provide high-speed, single-breath, volume acquisitions that can be viewed as 2.5 mm or finer reconstructed sections. If these images are obtained after delivery of intravenous iodinated contrast medium, and there is careful control of the patient's breath-hold during the scan, then adequate anatomic detail can be obtained to evaluate the lung, pleura, mediastinum, and great vessels for infection. The categories of imaging findings discussed in this chapter may at times be identifiable on plain film radiography when fully developed, but the basis for their discussion relies on the CT technique.

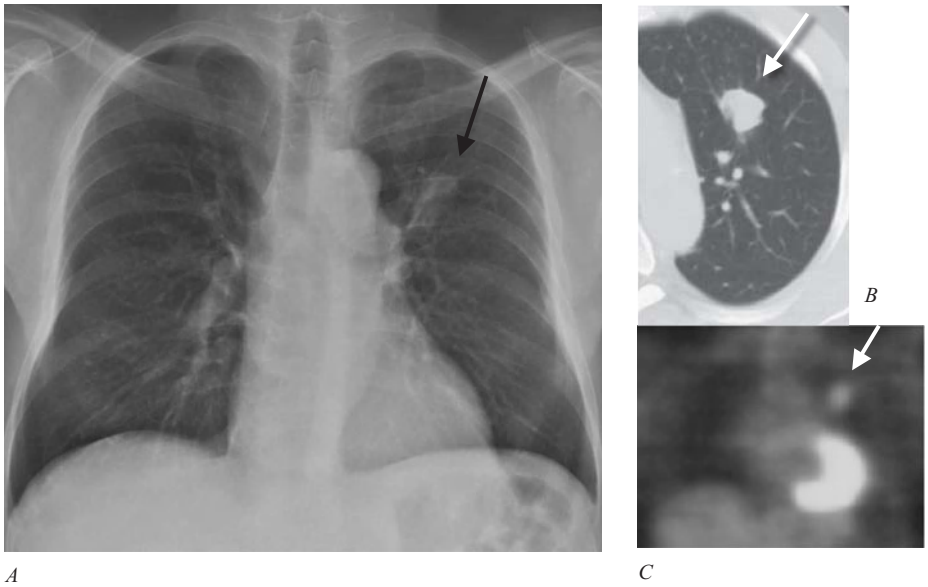


Figure 113-1 18FDG-avid macronodular C. neoformans infection. *A*. Plain chest radiograph with a macronodular opacity in the left upper lobe (arrow) in an asymptomatic mildly immunosuppressed solid organ transplant recipient. *B*. CT scan confirms a well defined macronodule in the left upper lobe (white arrow). *C*. Positron emission tomography (PET) with 18 fluorodeoxyglucose (18FDG) shows normally high metabolic avidity of the cardiac ventricular musculature, and moderate avidity of the left upper lobe nodule due to *Cryptococcus neoformans*.

Other imaging modalities are at present used infrequently for evaluation of suspected pneumonia. Ultrasound is a standard modality for detecting and tapping pleural effusions, but it is not employed in the diagnosis of pneumonia. Magnetic resonance imaging (MRI) is rarely employed to detect or further assess patients with a clinical diagnosis of infection except when critical extension or dissemination is suspected. Positron emission tomography (PET) with 18 fluorodeoxyglucose (18FDG) is increasing used as a sensitive method of detecting metabolically active tumor lesions, but it has yet to find a definable role in clinical evaluation of inflammation and pneumonia. Anecdotal studies of patients with chronic and acute inflammatory lesions and infections have identified a wide spectrum of lung lesions that are 18FDG-avid (Fig. 113-1).

GENERIC LUNG FINDINGS ASSOCIATED WITH PNEUMONIA

Six common imaging categories of pneumonia are discussed, each of which has a distinctive pathogenesis, typical gross pathology, and characteristic imaging findings: the first two are most common: (1) peripheral airspace consolidation pneumonia (lobar pneumonia); and (2) centrilobular and peribronchiolar opacity pneumonia (bronchopneumonia). The next three categories are less common but no less important: (3) nodular pneumonia; (4) micronodular pneumonia (miliary pneumonia); and (5) diffuse lung opacification pneumonia.

Several factors that limit this type of categorical analysis must be recognized; imaging findings vary between patients with pneumonia of the same etiology; imaging findings vary over time as pneumonias evolve, and different categories of imaging findings may be encountered in any single snapshot of a patient with pneumonia. Although no single imaging category can completely characterize a single etiologic kind of pneumonia, it is useful to think in terms of the predominant imaging finding when evaluating the likely pathogenesis and etiology of a likely pneumonia while taking into account the clinical context in which it occurs. One or more types of etiologic agents are more likely than others in each category of pneumonia when the clinical background is taken into account: immunocompetent versus immunocompromised, previously healthy versus having co-morbidity, acquisition of infection inside of the hospital, i.e., nosocomial pneumonia (NP) versus acquisition in the wider community, i.e., community-acquired pneumonia (CAP), and the presence of local epidemic infections.

Peripheral Airspace Consolidation Pneumonia (Lobar Pneumonia)

Overview and Pathogenesis

Peripheral airspace consolidation is a characteristic imaging category of pneumonia that is commonly encountered in all patient groups. It is an especially common primary pneumonia caused by bacteria in previously healthy patients with CAP. It is also called lobar pneumonia because it is often essentially confined to a single peripheral lung region without prominent involvement of the bronchial tree.

The pathogenesis and imaging of peripheral airspace consolidation pneumonia is unique. It is the result of airborne infection initiated by microbes that reach and settle in the peripheral alveolar airspaces. From there the pneumonia spreads into adjacent alveoli by traversing collateral channels of ventilation, such as the pores of Kohn and canals of Lambert. Spread by this way from alveolus to alveolus results in characteristic involvement that parallels the pleural surface, and ultimately extends toward the more central regions of the lung in centripedal fashion. As the infection progresses, gas in the peripheral airspaces is replaced by exudate. This process of accretion tends to preserve or slightly expand without distorting the normal anatomic contours of the affected lung. The relatively unaffected bronchi remain relatively gas filled, and become surrounded by consolidated alveoli. At the leading edge of a consolidation there is generally a patchwork of individually spared and affected lung.

Etiologies

Outside of neonates, *Streptococcus pneumoniae* is the most common bacterial etiology of peripheral airspace consolidation pneumonia, as well as the most common cause of bacterial pneumonia acquired outside of hospitals in previously healthy patients (Fig. 113-2). It accounts for a large fraction of the etiologically proven, bacteremic, life-threatening pneumonias. In CAP and NP of patients with co-morbid conditions, peripheral airspace consolidation may be caused by opportunistic gram-negative enteric bacteria of the Enterobacteriaceae *family* such as, *Klebsiella, Enterobacter*, *Escherichia*, *Citrobacter,* and *Serratia*, as well as by *Legionella pneumophila* (Fig. 113-3). Large peripheral airspace consolidation is also a presenting imaging category in primary tuberculosis, in which case it affects primarily the lower lobes, middle lobes, and/or anterior segments of the upper lobes. It is usually associated with mediastinal lymphadenopathy,

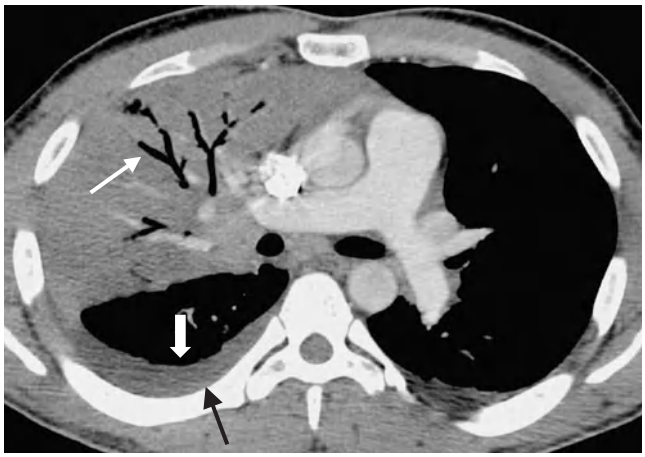


Figure 113-2 Lobar pneumonia due to *S. Pneumoniae* in previously normal host. Severe community-acquired lobar pneumonia with bacteremia due to *S. pneumoniae* in a previously healthy 30-year-old man. There is dense consolidation of the right upper lobe with prominent air bronchograms (white arrow). Layered pleural fluid is present along the right posterior chest wall (black arrow).

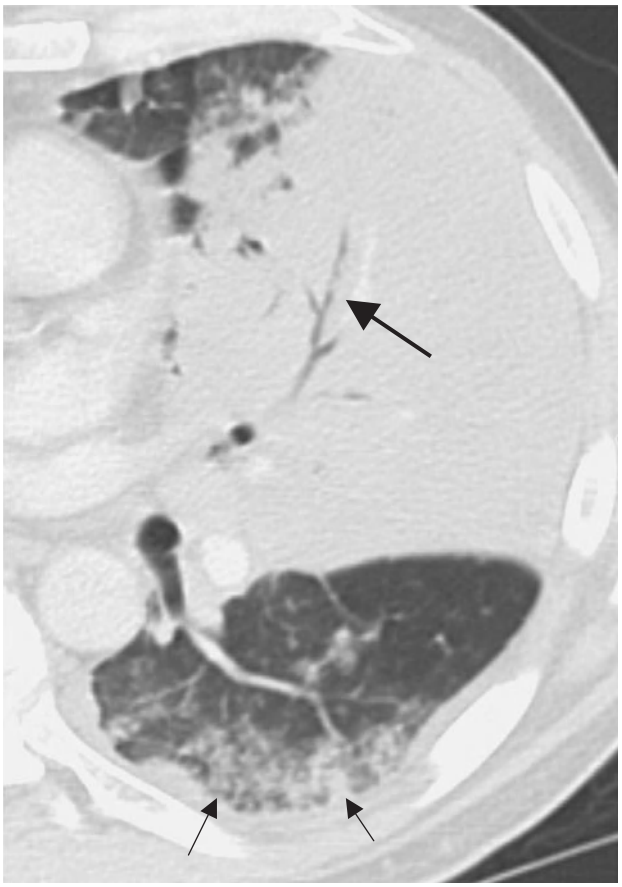


Figure 113-3 Community-acquired lobar pneumonia caused by *Legionella pneumoniae* in patient with co-morbidity. Community-acquired lobar pneumonia caused by *Legionella pneumoniae* in patient with co-morbidity due to chronic granulomatous vasculitis. There is peripheral airspace consolidation (lobar) pneumonia containing prominent air bronchograms (black arrow). There is also patchy "spillover" pneumonia associated with ground glass and tree-in-bud opacities along the posterior chest wall (small black arrows), as well as a small layering pleural effusion.

especially in pediatric patients. Lobar pneumonia can also be a component of the imaging findings in endemic fungal infections, and in immunocompromised patients with invasive fungal infection. Less commonly it can result from a wide variety of viral infections such as adenovirus, Hantavirus, and the coronavirus of severe acute respiratory syndrome (SARS).

Imaging

The characteristic imaging finding of peripheral airspace consolidation pneumonia is opacification of the peripheral airspaces often with visible air-filled proximal conducting airways, i.e., "air bronchograms." Where fully developed, exudate causes complete opacification of the involved lung such that all the underlying pulmonary vasculature of the affected region is totally obscured. Where the consolidation is incomplete the affected lung may exhibit ground-glass opacification, in which case it does not completely obscure underlying vasculature. At the leading edge of spread of infection, there

is generally a patchwork of affected and spared secondary lobules, i.e., lung regions of 10 to 25 mm on a side that are marginated by pulmonary septations. Specific identification of peripheral airspace consolidation is facilitated by recognition of internal air bronchograms that are in most cases identifiable. Atelectasis and significant local loss of lung volume are usually absent.

Peripheral consolidative pneumonia differs notably from bronchopneumonia (which will be described subsequently) in that it primarily affects peripheral airspaces rather than bronchi/bronchioles and peri-bronchial airspaces, and is not usually associated with loss of volume or atelectasis of the affected lung. It differs also from macronodule pneumonia (which will be described subsequently) in that even when large its lung opacification does not tend to substantially distort the pre-infection anatomic shape of the involved area.

The absence of air bronchograms does not per se exclude consolidation; air bronchograms may be absent when consolidation results from central bronchial occlusion or causes exudative impaction of proximal bronchi within the affected lung. Cavitation, necrosis, and pleural effusion are sometimes features of peripheral airspace consolidation pneumonia, particularly when the infection is caused by aggressive or necrotizing bacterium, such as *Staphylococcus aureus*, mycobacteria, and anaerobic enteric bacilli such as *actinomycetes*. The association of lymphadenopathy is common in mycobacterial, endemic fungal, and other less common infections such as tularemia.

Non-Infectious Etiologies

Non-infectious simulators and etiologies of peripheral consolidation include localized aspiration, atelectasis, hemorrhage, hydrostatic edema, alveolar-capillary leak edema, post-obstructive pneumonitis, bronchiolo-alveolar cell carcinoma, lymphoma, and bronchiolitis obliterans organizing pneumonia (BOOP). Air bronchograms are often present in non-obstructive atelectasis in the absence of infection. In such cases of atelectasis is recognized by crowding together of the air-filled bronchi that are be visible within the atelectatic lung. The air bronchograms of pure airspace consolidative pneumonia are normally distributed or splayed apart. Bronchioloalveolar cell carcinoma is suspected by atypical clinical presentation and failure to respond to antibiotic therapy.

Centrilobular and Peri-bronchiolar Opacity Pneumonia (Bronchopneumonia)

Overview and Pathogenesis

Like lobar pneumonia, centrilobular and peribronchiolar opacity pneumonia (bronchopneumonia), a characteristic imaging category of pneumonia that is commonly encountered in all patient groups. It is an especially common imaging category in CAP that follows viral infection. It is also called bronchopneumonia because it is associated with acute infection of the walls of bronchioles that spreads into the peribronchiolar alveoli, and often involves the lung in a patchy multifocal distribution (Fig. 113-2).

Etiologies

Many patients with community-acquired bronchopneumonia have mild and self-limited disease attributable to respiratory viruses, including epidemic influenza, adenovirus, rhinovirus, and respiratory syncytial viruses (RSV) (Fig. 113-3). Some of these viruses can produce more serious primary pneumonia, as well as set the stage for bacterial or other etiology superinfection pneumonia, especially when there are co-morbid conditions. Severe acute respiratory syndrome (SARS), a newly identified coronavirus infection, can produce severe viral pneumonia with a broad spectrum of imaging findings, including bronchopneumonia. Other organisms that commonly cause bronchopneumonia include *Mycoplasma pneumoniae*, *Chlamydia pneumoniae*, *Haemophilus influenzae,* and *Neisseria catarrhalis (Moraxella catarrhalis)*. *Klebsiella pneumoniae, Escherichia coli,* and *Pseudomonas aeruginosa* are also common causes of nosocomial (and ventilator-associated) bronchopneumonia, and of community-acquired bronchopneumonia in patients with co-morbid conditions. These latter pneumonias are associated with necrosis, abscess formation and pleural effusion.

The role of *Staphylococcus aureus* in the etiology of bronchopneumonia in the ventilator-associated milieu pneumonia (VAP) is controversial because airway recovery of the organism is not usually associated with the characteristic imaging signs of CAP caused by that organism in patients without co-morbid conditions, i.e., rapid development and necrosis. The organisms that cause peripheral airspace consolidation pneumonia are not restricted from also causing bronchopneumonia when bronchioles are already inflamed by recent infection.

Imaging

On initial imaging bronchopneumonia is different from lobar pneumonia; it causes centrilobular opacities, as well as peri-bronchiolar opacities rather than affecting subpleural lung as in lobar pneumonia, and it tends to be multifocal and patchy in distribution rather than localized to any one lung region. Centrilobular opacities include centrilobular nodules, and small branching tubular opacities (tree-in-bud opacities), each of which is found within the center of the secondary pulmonary lobule (Fig. 113-4).

Centrilobular nodules are very small well- or ill-defined rounded opacities situated in the center of a secondary lobule (defined by its arterial/bronchial core, and/or straight septal walls with pulmonary veins at its corners). The nodules are usually only in (2–3 mm) in diameter but may grow large enough to fill entire lobules (10–24 mm), at which size they are often considered to be macro-nodules. Because small centrilobular nodules are located at the center rather than at the periphery of the secondary pulmonary lobule, they do not normally abut the visceral pleural surface, but usually stand off about 5 mm from it. Centrilobular nodules are considered

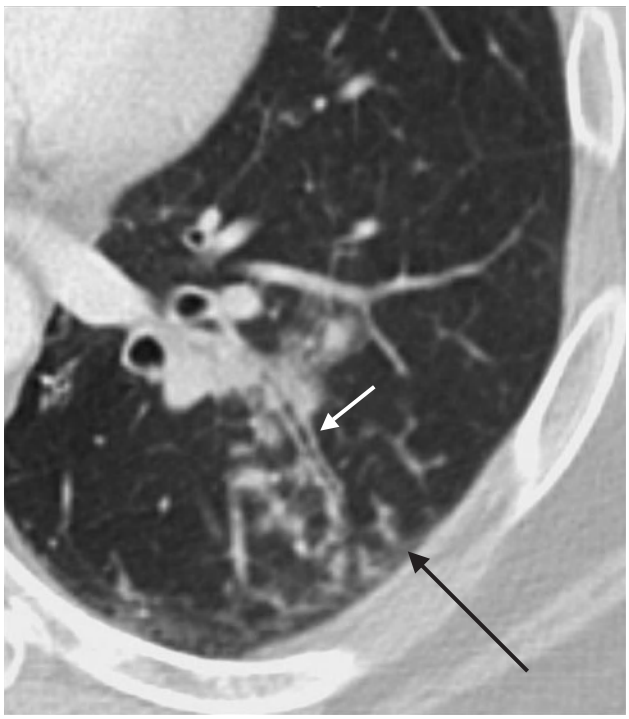


Figure 113-4 Viral bronchopneumonia. Centrilobular and peribronchial opacity pneumonia (bronchopneumonia) after a 1-week viral type prodrome with fever and cough. One of many bilateral patches of bronchopneumonia in the left lower lobe is characterized by branching small tubular opacities (black arrow) attributed to thickened, dilated and impacted bronchioles (tree-in-bud opacities) that simulate game "Jacks," i.e., six-pronged three-dimensional metal crosses with bulbous ends. There is also a thickened bronchial wall leading to, and surrounded by the same tubular bronchiolar opacities (white arrow).

to be axial views of bronchiolar wall thickening, impaction and distention at bifurcations, and may present in clusters. Branching centrilobular tubular opacities (tree-in-bud opacities) are very small cylindrical, branching structures with bulbous ends that equate to longitudinal projection of the bronchiolar thickening, exudative filling, and distention.

Peribronchial and peribronchiolar lung opacities are much larger than centrilobular opacities that develop from the coalescence of affected alveoli that open directly into respiratory bronchioles (Fig. 113-5). When secondary lobular involvement is complete, there is total opacification of a secondary lobule. When local alveolar involvement is incomplete, there may be ground-glass opacification of the lobule such that background vasculature is still visible. In lobar pneumonia, progression of infection tends to spread subpleurally and centripetally. In bronchopneumonia, progression of infection tends to spread centrifugally to affect secondary lobules distributed axially along bronchovascular bundles.

In most cases centrilobular nodules and tree-in-bud opacities are seen in combination. Common infectious etiologies of centrilobular opacities include a wide range of bacterial, mycobacterial, viral, and fungal etiologies that are caused by acute or chronic bronchiolar inflammation/infection.

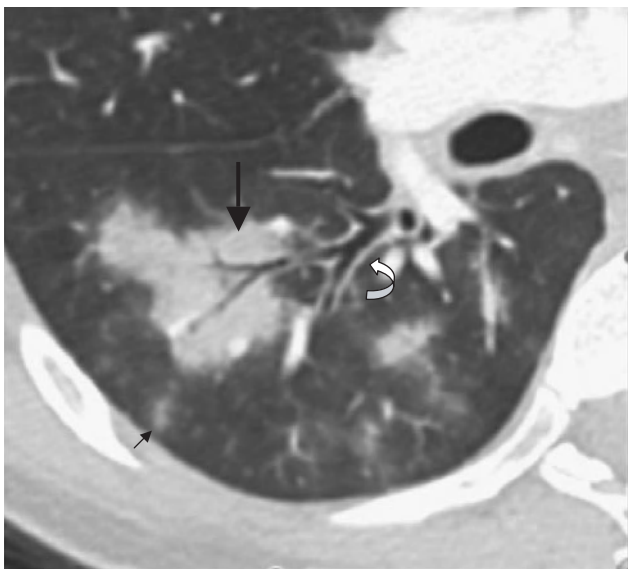


Figure 113-5 Peribronchial consolidation due to viral pneumonia. CT scan one week after onset of fever; cough with a confirmed diagnosis of *Influenza B* and *Mycoplasma pneumoniae*. There are multifocal, bilateral peribronchial consolidations, one of which is in the right lower lobe (large black arrows) with prominent air bronchograms and bronchial wall thickening (curved white arrows). Centrilobular opacities, including nodules (short arrow) and branching tree-in-bud opacities, are also present.

They are also often seen in infectious pneumonias associated with bronchiectasis or cystic fibrosis. In *Mycoplasma pneumoniae* infection, tree-in-bud opacities are a common feature, and are often found in association with centrilobular nodules. In some infections tree-in-bud opacities may be seen as a predominant feature, as in acute bronchiolitis, bronchogenic tuberculosis, and infections by atypical mycobacteria (Fig. 113-6). In patients with HIV infection (CD4 T-lymphocyte count less than 200/mm^3), disseminated bronchogenic tuberculosis, and disseminated atypical mycobacterial infection may be manifested by diffuse tree-in-bud opacities. The high CT attenuation of these opacities is ascribed to caseous necrosis material impacted within bronchioles (Fig. 113-7). In progressive primary or post-primary tuberculosis bronchogenic spread into other regions of the lung occurs when infected liquefied caseous material gains access into bronchial tree to be coughed or expectorated into other lung regions. In addition to centrilobular nodules, tree-in-bud opacities, multiple fluffy 5- to 10-mm "acinar" nodules may be detected adjacent to a source consolidation or cavity.

Regional atelectasis is common imaging finding in bronchopneumonia due to multiple small airway occlusions by exudates. Some infections may produce necrosis, cavitation, pleural effusion, bronchopleural fistula, and empyema.

Post-primary tuberculosis is a centrilobular process that when latent may include scarring, atelectasis, bronchial wall thickening, bronchiectasis, architectural distortion, and local pleural thickening, especially in the lung apices or superior segments of the lower lobes. Active post-primary tuberculosis usually results from reactivation of a dormant

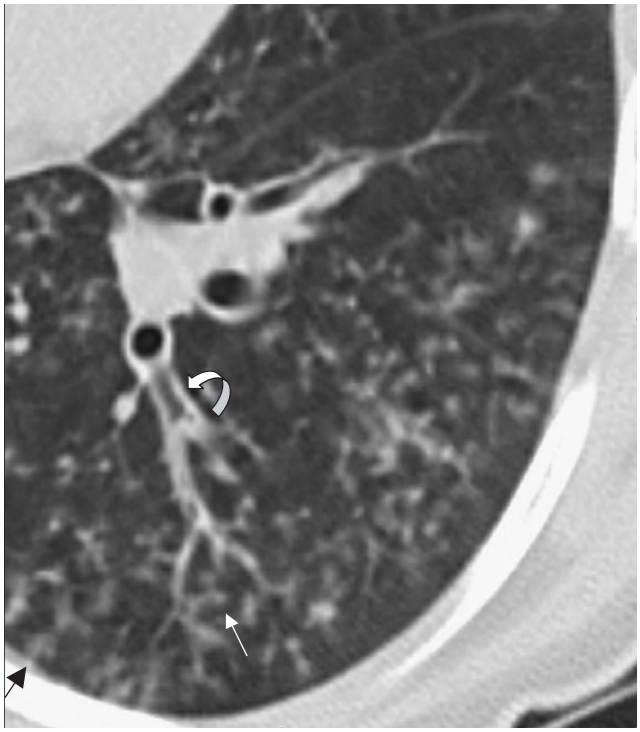


Figure 113-6 Bronchogenic tuberculosis. CT scan with disseminated bilateral high density tree-in-bud opacities (white arrow), centrilobular nodules (black arrow), and bronchial wall thickening (curved arrow) in a patient with advanced HIV infection and bronchogenic tuberculosis.

focus when cellular immunity deficiency lowers specific cellular immunity to tuberculosis, such as in debility or advanced AIDS. Active post-primary tuberculosis begins with ulceration of one or more bronchioles (2- to 4-mm diameter) that progress by coalescing into larger bronchocentric cavities.

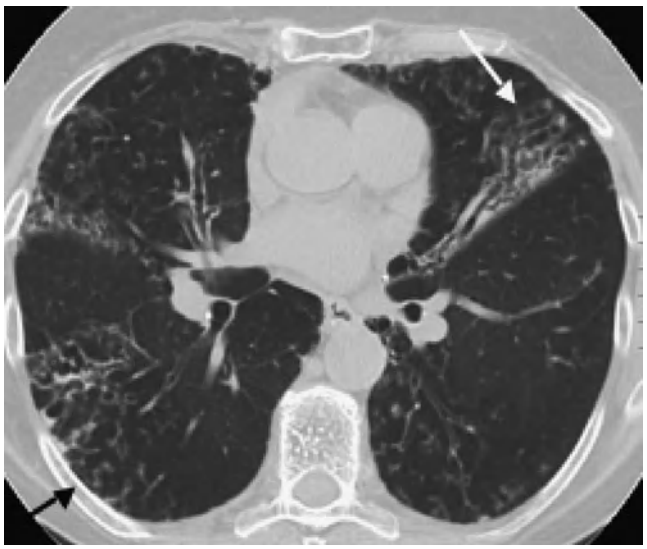


Figure 113-7 Widespread centrilobular opacities and bronchiectasis in chronic *Mycobacterium avium* complex (MAC) infection. CT scan of elderly female with widespread centrilobular opacities, including tree-in-bud opacities (black arrows), and lingular bronchiectasis (white arrow) due to chronic *Mycobacterium avium* complex (MAC) infection.

These cavities indicate activated latent post-primary tuberculosis, and can be detected twice as often, and more accurately differentiated from paracicatricial emphysema and fibrosis by CT than by plain film radiography (Fig. 113-8). Other findings in active post-primary tuberculosis include poorly defined centrilobular 5- to 8-mm nodules, consolidation, and granulomas.

Non-Infectious Etiologies

Non-infectious simulators and etiologies of centrilobular and peri-bronchial opacities include aspiration pneumonia, itself a frequent non-infectious cause of bronchopneumonia, as well as a facilitator of superinfection. Other causes include bronchiolo-alveolar cell carcinoma, non-infectious granulomas due to pneumoconiosis, sarcoidosis, respiratory bronchiolitis, hypersensitivity pneumonitis, bronchiolitis obliterans organizing pneumonia (BOOP), asthma, autoimmune disease, and bronchiolitis obliterans. They can also be found in patients with small mucous airway plugs and other endobronchial disease.

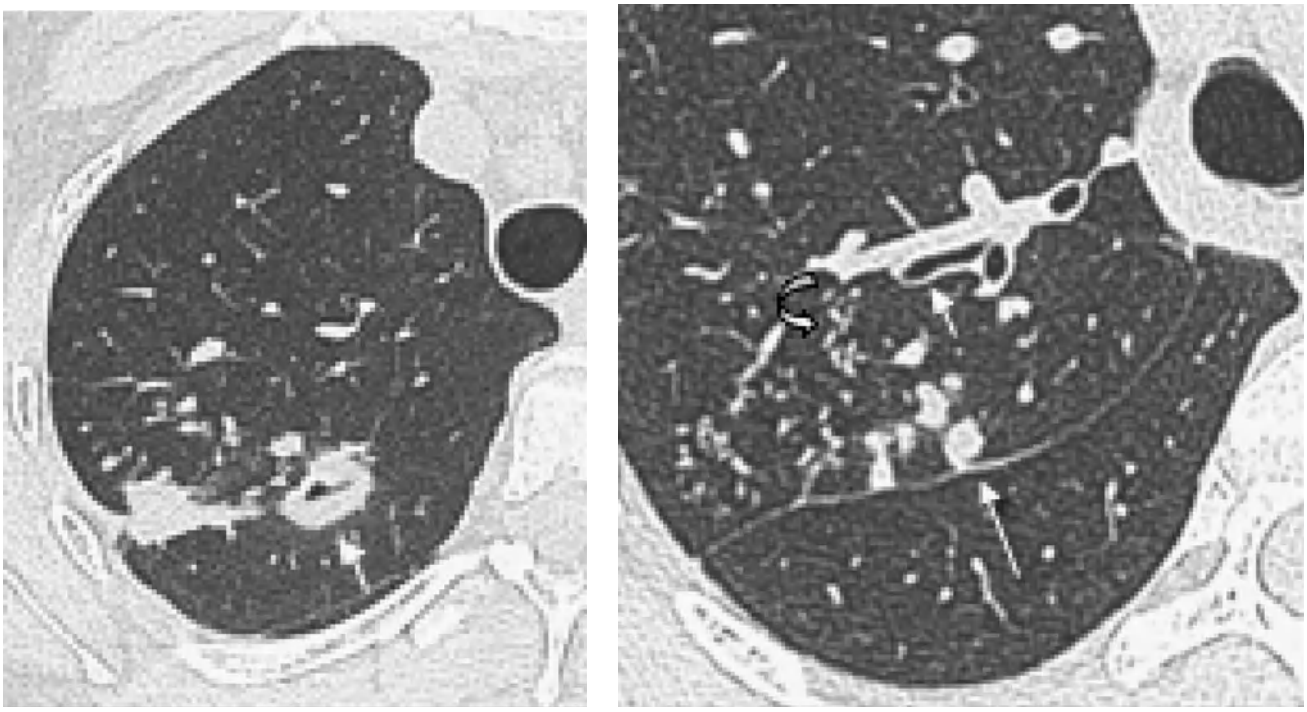
Nodular Pneumonia (Round Pneumonia)

Overview and Pathogenesis

Nodular pneumonia is predominantly made up of circumscribed, ovoid opacities greater than or equal to 1 cm diameter that may at times be quadrilateral shaped and marginated by septal walls. This imaging type of is not as common as the two previously discussed types of pneumonia, but its finding as acute pneumonia may portend aggressive, potentially life-threatening pneumonia. The nodules may be bronchocentric in location, but are often are subpleural whether the portal of entry is by way of the vascular route such as in septic emboli, or via the inhalational route, as in *Staphylococcus aureus* pneumonia and invasive pulmonary aspergillosis (Fig. 113-9). They represent circumscribed foci of pneumonia forming in the distal airspaces or foci of pneumonia forming at the termination of pulmonary arteries.

Etiologies

In a CAP setting, nodular pneumonia is often caused by *Staphylococcus aureus* in which case the lesions tend to enlarge rapidly and cavitate (Fig. 113-10). *S. aureus* is relatively more common among children and infants than among adults. Other causes of round pneumonia include *Actinomycetes*, *Nocardia*, *Aspergillus, Legionella* spp., Q fever, *M. tuberculosis,* and viruses. Among pediatric-aged patients, nodular pneumonia may be due to measles virus. In the nosocomial setting, and in the immunocompromised patient, nodular pneumonia may be due to inhaled or bacteremic seeding of the lungs by gram-negative opportunistic intestinal organisms, opportunistic gram-negative enteric bacteria of the Enterobacteriaceae *family* such as, *Klebsiella, Enterobacter*, *Escherichia*, *Citrobacter,* and *Serratia,* especially when there is bowel distention or obstruction. In patients with mild reduction in defense against infection, such as that due in alcoholism, liver dysfunction, diabetes, wasting or chronic lung



A *B*

Figure 113-8 Centrilobular opacities and cavity in reactivation of latent post-primary tuberculosis. *A*. Non-immunocompromised patient with abnormal nodular opacities characteristic of latent post-primary tuberculosis in the posterior segment of the right upper lobe. The presence of new cavitation of a "tuberculoma" indicates reactivation of latent tuberculosis (white arrow). *B*. More caudally in the same lobe, there are multiple centrilobular opacities indicative of endobronchial spread from the cephalad thick-walled cavity identified in Fig. 113-3*A*. There is a very large centrilobular nodule that approaches the major fissure (long arrow), bronchial wall thickening (short arrow), and many branching centrilobular tubular opacities (tree-in-bud) indicative of bronchiolar thickening, dilatation, and impaction (curved arrow).

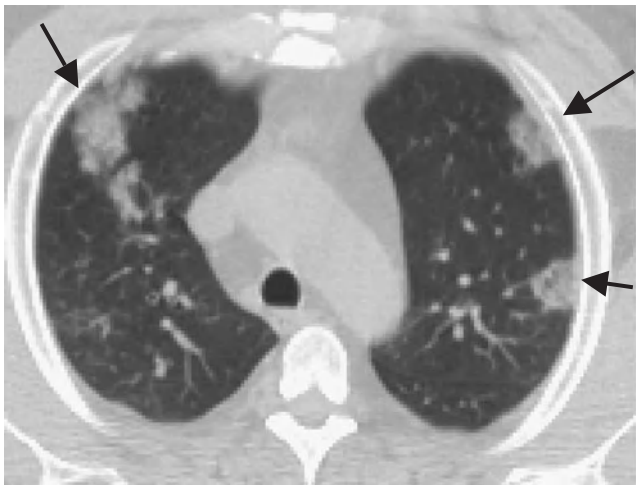


Figure 113-9 Macronodular pneumonia. Multiple subpleural macronodular opacities (arrows) in a patient with acute onset of fever, shaking chills, fever, and cough productive of green sputum likely due to bacterial pneumonia that responded promptly to vancomycin therapy. Respiratory secretions and blood were culture-negative.

disease, and in AIDS patients with CD4+ greater than 200 c/ml, nodular pneumonia is often due to bacterial pneumonia. In severely immunosuppressed AIDS patients with CD4+ less than 200 c/ml, and in solid organ transplant recipients, nodular pneumonia may also be due to mycobacterial or fungal infection, including *Mycobacterium avium complex*

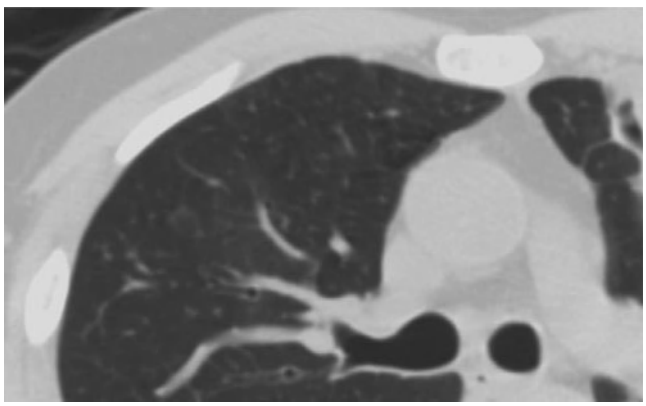


Figure 113-10 Cavitating *Staphylococcal aureus* macronodular pneumonia. Large subpleural mass-like macronodule with multiple gas pockets in this previously normal 39-year-old patient with sputum positive for *S. aureus*. The findings are characteristic of lung abscess before complete excavation.

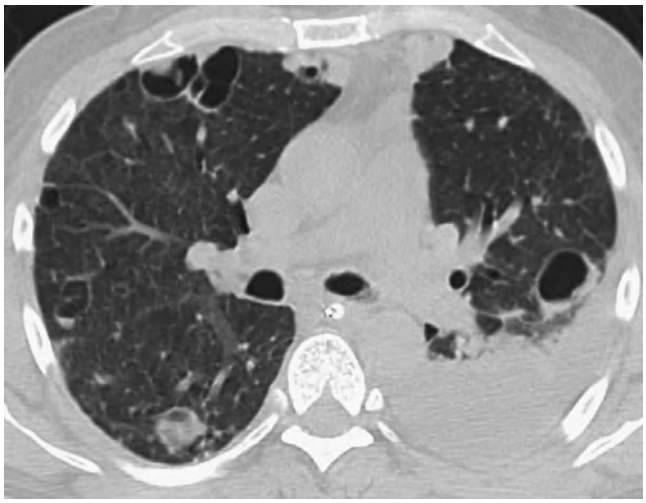


Figure 113-11 Septic emboli. Multiple predominately subpleural nodular opacities of varying sizes and stages in a patient with positive blood cultures for methicillin-resistant *S. aureus* (MRSA) and beta hemolytic *Streptococcus*. These findings are characteristic of septic emboli. There is a wide disparity in the size and stage of infection; some nodules are three times the diameter of others; some nodules are partially solid; others are partially fluid filled; and others are totally gas-filled, and have thin walls. There is a layered left pleural effusion likely due to unroofing of an infected cavity, a common feature.

(MAC), *M. tuberculosis*, *Cryptococcus* sp., *Blastomyces* sp., *Histoplasma capsulatum*, *C. immitis*, or *Aspergillus* spp. (Fig. 113-1). In heart, lung, and other solid organ transplant recipients, nodular pneumonias found shortly after surgery nodular pneumonia is most often due to bacterial infection, especially gram-negative intestinal bacteria. During the initial 3 months after lung transplantation, the risk of CMV pneumonia is high enough that even an uncharacteristic nodular presentation must be considered as possible CMV pneumonia.

Imaging

In intravenous drug abusers nodular pneumonia can indicate septic emboli, particularly when the nodules are multiple, subpleural, and of varying size often from less than 10 mm in diameter to greater than 3 cm. Ultimately, the nodules cavitate late in the course of disease. Sometimes a feeding vessel can be seen extending to a nodule (Fig. 113-11).

Among severely immunocompromised patients with a compatible illnesses suffering from hematological malignancy with severe or prolonged neutropenia, or allogeneic hematopoietic stem cell transplant recipients, the presence of one or "halo signs," i.e., macronodules (greater than or equal to 1 cm) with perimeter of ground-glass, is virtually diagnostic of early angio-invasive pulmonary aspergillosis (Fig. 113-12). Pre-emptive targeted treatment of such patients based on the presence of a halo sign is associated with improved treatment response and outcome. It is notable that 90 percent of such patients with angioinvasive aspergillosis have one or more macronodular lesions with or without halo signs at

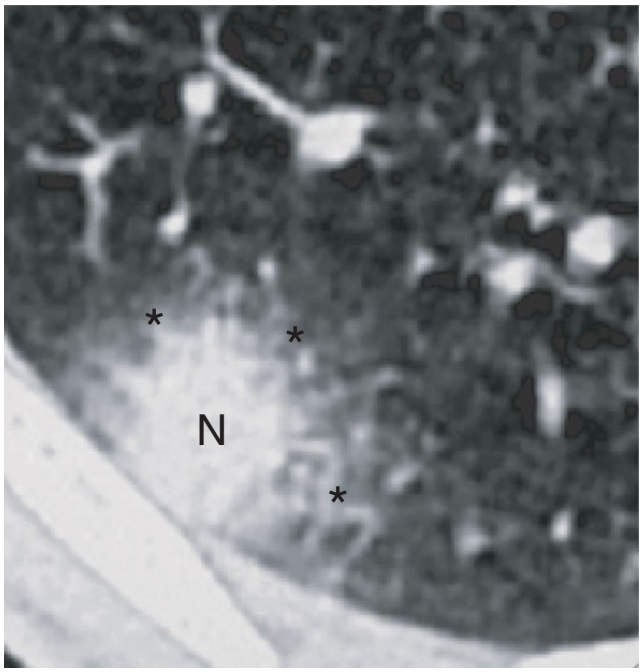


Figure 113-12 Halo sign in angioinvasive aspergillosis. CT scan of patient with hematopoietic malignancy and prolonged neutropenia demonstrating a macronodule (N) surrounded by a halo of ground-glass opacity (*) in a patient with angioinvasive aspergillosis.

presentation. Thus, the absence of at least one macro-nodule argues against the diagnosis of angioinvasive aspergillosis. Although other etiologies, such as mucormycosis, may cause halo signs in this group of patients, the prior probability of such infections is very much lower. The air crescent sign is an indicator of late angioinvasive pulmonary aspergillosis, usually after recovery from neutropenia (Fig. 113-13).

Non-Infectious Etiologies

The most common simulators and non-infectious etiologies of nodular pneumonia include bland pulmonary infarcts, granulomatous vasculitis, primary lung cancer, and pulmonary metastases. Often a biopsy is necessary to make the diagnosis.

Micronodular Pneumonia

Overview and Pathogenesis

Micronodular pneumonias are an uncommon but important group of pneumonias. Micronodules are nodules 9 mm or less in diameter, ill- or well-defined, and of random distribution. The most important infectious etiologies of micronodular pneumonia include: (1) miliary pneumonia; and (2) intermediate micronodular pneumonias. These micronodules are generally diffuse, bilateral, and widely distributed. They are variously distributed along the bronchovascular bundles, interlobular septal walls, and costal and interlobar fissural pleural surfaces.

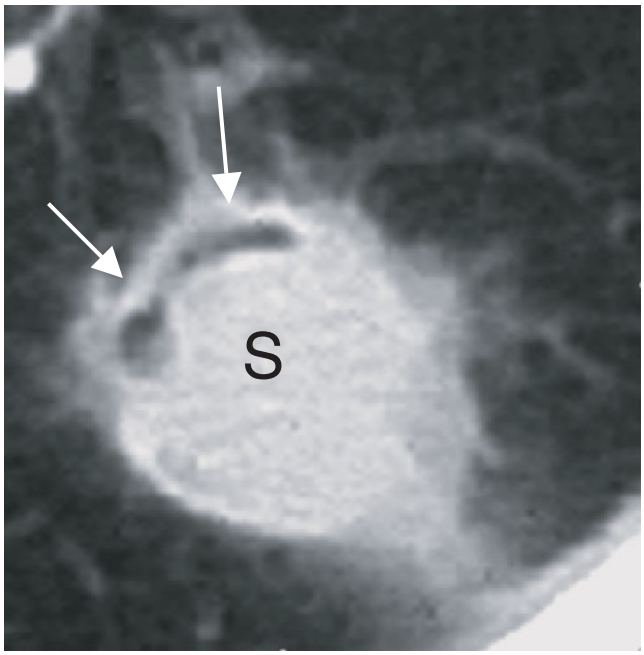


Figure 113-13 Air crescent sign in late angioinvasive aspergillosis. CT scan of patient with hematologic condition late in the course of angioinvasive aspergillosis after recovery from neutropenia demonstrates a cavitary macronodule with an air crescent at 10 to 1 o'clock (arrows) outlining a central necrotic sequestrum (S).

Etiologies

Miliary nodules are random micronodular opacities (1–5 mm) that are associated with a small but important group of disseminated miliary infections, including those caused by disseminated *M. tuberculosis*, non-tuberculous mycobacteria, and fungi (Fig. 113-14).

Imaging

Miliary Nodules

Miliary tuberculosis is the prototypical example of miliary pneumonia that results from lymphohematogenous dissemination. Like bronchogenic tuberculosis, miliary tuberculosis can result from either progressive primary or re-activated post-primary tuberculosis. The numerous 1- to 5-mm randomly distributed nodules of military tuberculosis can usually be detected 3 to 6 weeks after lymphohematogenous dissemination. Some nodules are subpleural in location; some are septal thickening, and some are bronchovascular. Ground-glass opacities may be seen. As the infection progresses, the nodules tend to increase in size and coalesce.

The primary non-infectious etiologies include disseminated hematogenous metastases from cancers of the thyroid, kidney, or the breast. Under other clinical circumstances, miliary nodules may be identified in coal workers pneumoconiosis, silicosis, berylliosis, sarcoidosis and Langerhans' cell histiocytosis, and silicosis, but such nodules tend not to be randomly distributed.

Intermediate Micronodular Pneumonia

These are micronodules are of intermediate size and somewhat larger than those most characteristic of early miliary nodules. They range in average size from 5 to 7 mm. These are often ill-defined. The prototypical viral causes of intermediate micronodule pneumonia are herpes simplex and varicella zoster pneumonias. In the patient with varicella skin lesions, intermediate-sized random lung nodules are virtually diagnostic of varicella pneumonia (Fig. 113-15). This appearance can also be found in hematogenous dissemination of fungal pneumonias, and other late disseminated infections. Intermediate nodules can be caused by bronchogenic tuberculosis, but these are restricted to centrilobular location. Non-infectious causes most often are due to metastatic neoplasms.

Diffuse Opacification Pneumonia

Overview and Pathogenesis

Diffuse opacification pneumonia is a group of pneumonias of variable etiology that may have a diffuse or widespread multifocal bilateral distribution associated with ground-glass opacification, septal widening and/or frank consolidation. Sometimes the lesions are limited to discrete secondary lobules leaving multiple areas of spared lung (Fig. 113-16).

Etiologies

This type of pneumonia can be caused by *Mycoplasma pneumoniae* pneumonia, *Respiratory syncytial virus (RSV), Ebstein-Barr virus (EBV), Herpes Simplex virus (HSV), adenovirus,* and other viruses. These viruses may also cause a wide variety of other imaging types of findings. In pneumonias caused by *Cytomegalovirus (CMV)* diffuse ground-glass opacification heralds a poor prognosis (Fig. 113-17). In *Pneumocystis jiroveci* pneumonia, patchy diffuse ground-glass opacities often demonstrate spared regions, prominent septal thickening, bulla, and thin-walled cysts (Fig. 113-18). Less common causes of diffuse ground-glass attenuation, include infections due to fungi which most often focal or multifocal.

Imaging

The imaging elements of diffuse lung opacification include ground-glass opacification, septal thickening, and a variety of centrilobular airspace opacities. Ground-glass attenuation is intermediate lung opacification that unlike consolidation does not completely obscure underlying pulmonary vasculature. This can result from parenchymal abnormalities that are beyond the spatial resolving power of CT, i.e., alveolar wall inflammation, alveolar wall thickening, partial airspace filling, or a combination of multiple causes, in which extensive bilateral ground-glass opacities progress into complete consolidation. Most infectious causes of diffuse lung opacification may also at different times be multifocal, and less commonly be localized.

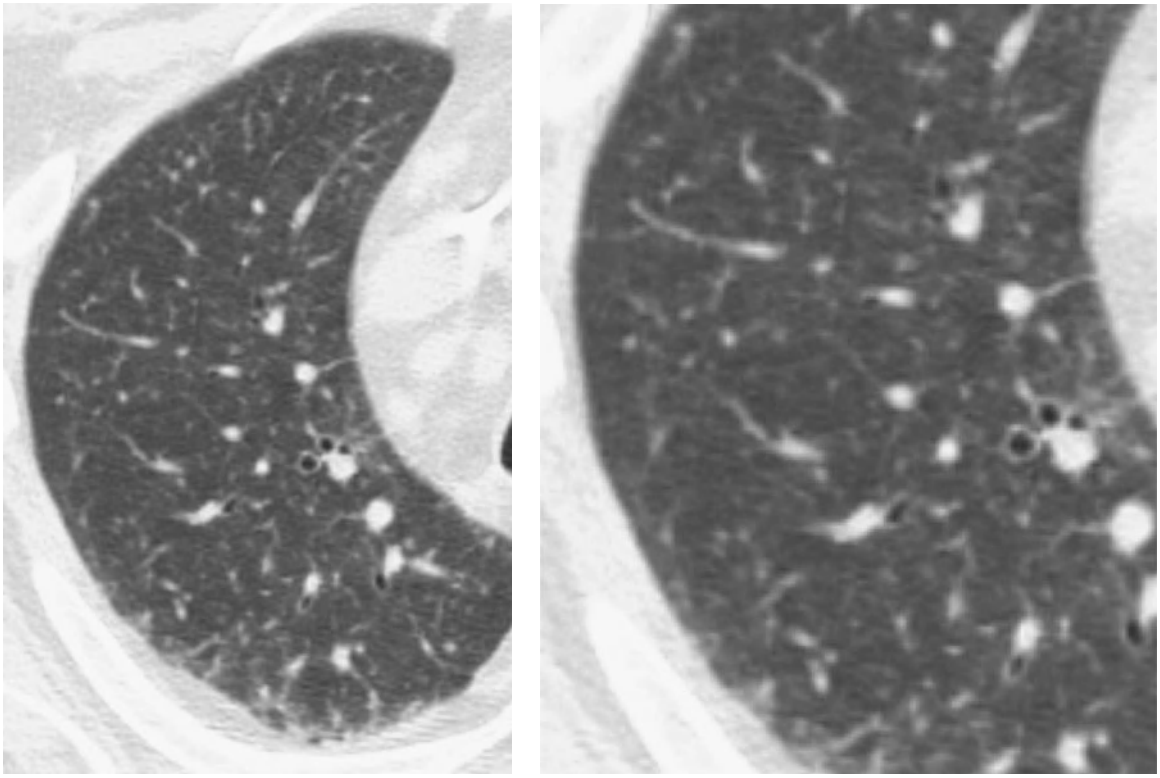


Figure 113-14 Miliary cryptococcal pneumonia. Immunosuppressed 62-year-old man under chemotherapy for metastatic pancreatic carcinoma. Disseminated cryptococcal infection was diagnosed by isolating cryptococcus from bronchoalveolar lavage, and detecting cryptococcus antigen in cerebrospinal fluid. CT scan demonstrates myriad randomly distributed 1- to 3-mm micronodules distributed throughout both lungs. Such miliary micronodules, although not easily distinguished from small end-on vessels on a single CT section, are more obvious when a stack of sections are viewed in rapid succession at which time the micronodules are found to be small spheres, not part of a longitudinal vascular structure.

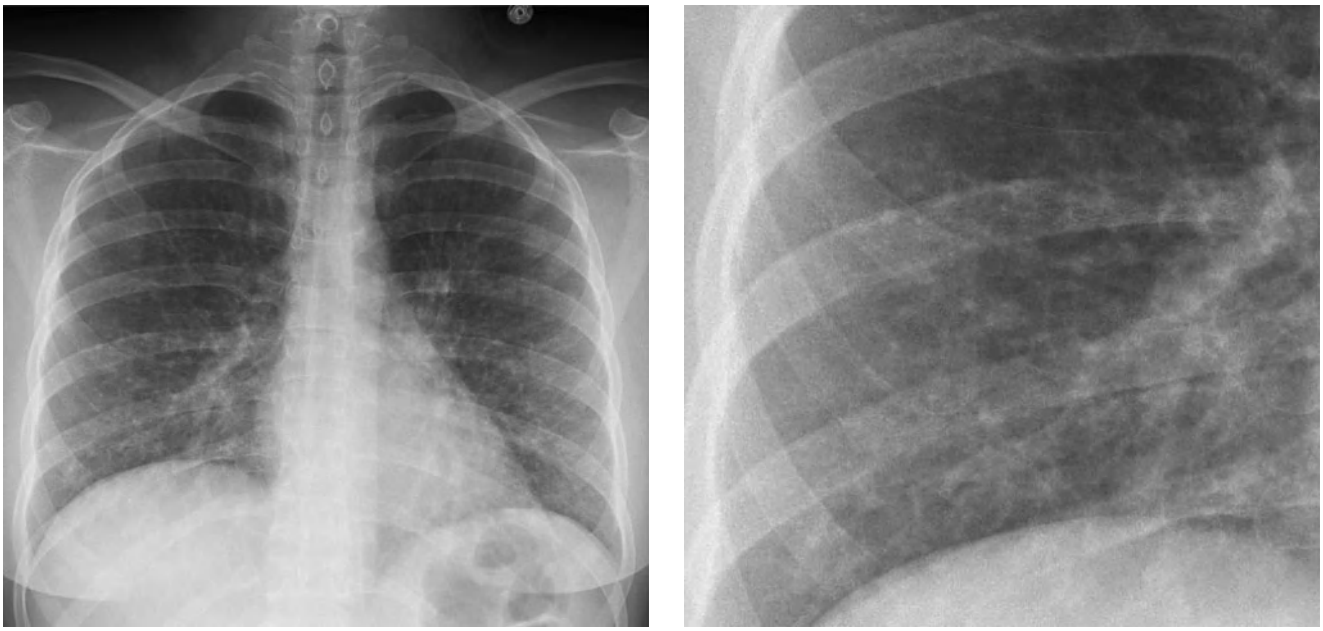
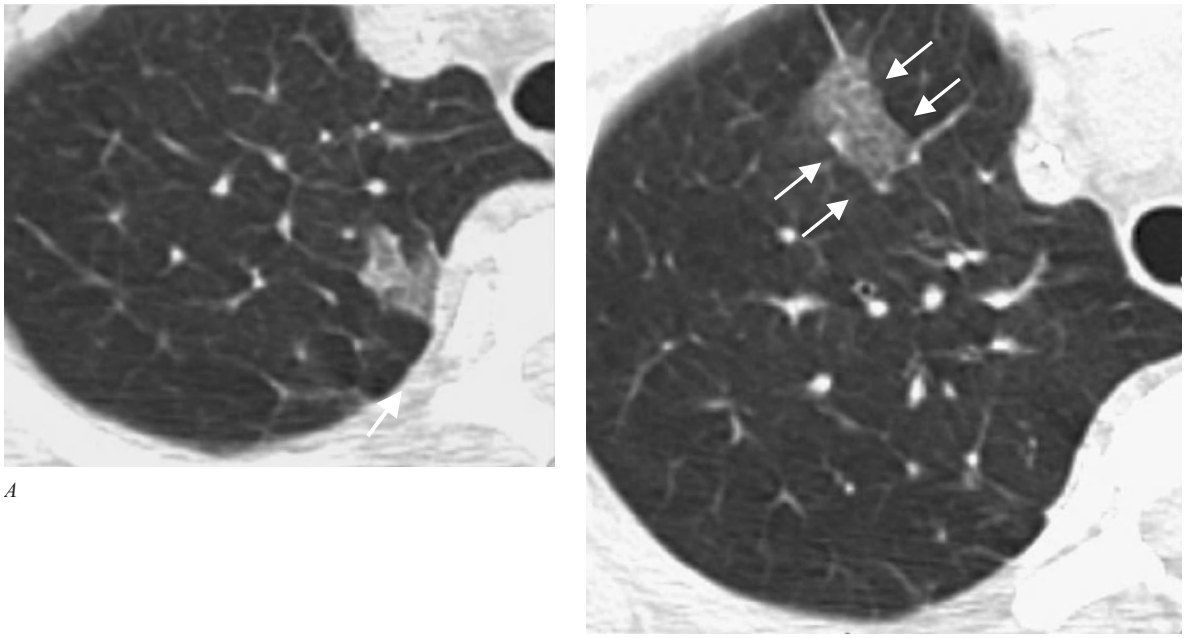


Figure 113-15 Diffuse small nodules in varicella virus pneumonia. Thirty-nine-year-old woman whose son had chickenpox 2 weeks before she developed a new chickenpox lesion on her neck, cough, nausea, vomiting, headache, chills, and malaise. Chest radiograph demonstrates widespread small nodular opacities approximately 5 to 7 mm in diameter. A CT scan was not deemed necessary because of the characteristic radiographic findings of varicella zoster virus (VZV) pneumonia, the skin lesions, and the high clinical likelihood of varicella zoster virus (VZV) infection. The patient rapidly responded to intravenous acyclovir therapy.



A

B

Figure 113-16 Lobular ground-glass opacities in viral pneumonia. Multifocal, bilateral patchy lobular ground glass opacification of secondary pulmonary nodules in the right upper lobe attributed to respiratory syncytial virus (RSV) pneumonia in immunocompromised patient under treatment for metastatic breast cancer. CT scan of the chest demonstrates two of many ground glass opacified secondary pulmonary lobules (*A* and *B*). The flat sides of the lobules indicate the sites of the septal margins of the lobules (arrows). The ground-glass opacity only partly obscures the underlying lung parenchyma.

Non-infectious Etiologies

Non-infectious causes of diffuse opacification include pulmonary edema, drug-induced lung disease, hypersensitivity pneumonia; pulmonary hemorrhage, diffuse aspiration, diffuse alveolar damage, and other diffuse interstitial lung diseases, such as lymphocytic interstitial pneumonia and pulmonary alveolar proteinosis.

Ancillary Findings Associated with Pneumonia

A wide variety of ancillary imaging findings may provide useful additional clues to etiologic causes of pneumonia. These include: atelectasis or other evidence of reduced lung volume; cavitation (which is suggested by lucency within lung

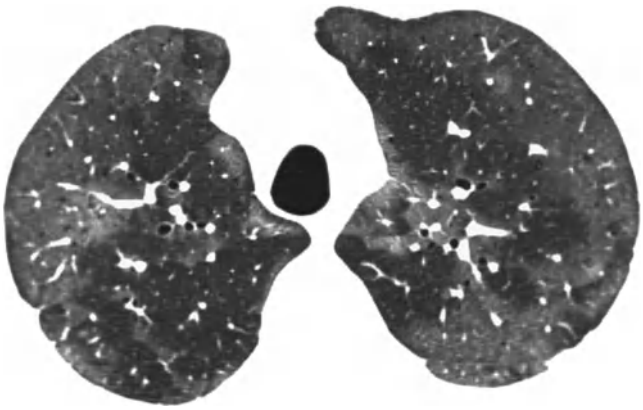


Figure 113-17 Diffuse ground-glass opacity in cytomegalovirus pneumonia. Widespread ground-glass opacity with prominent inter- and intra-lobular septal thickening sparing the anterior lung in an elderly patient with cytomegalovirus pneumonia (CMV) while under radiotherapy for residual chordoma.

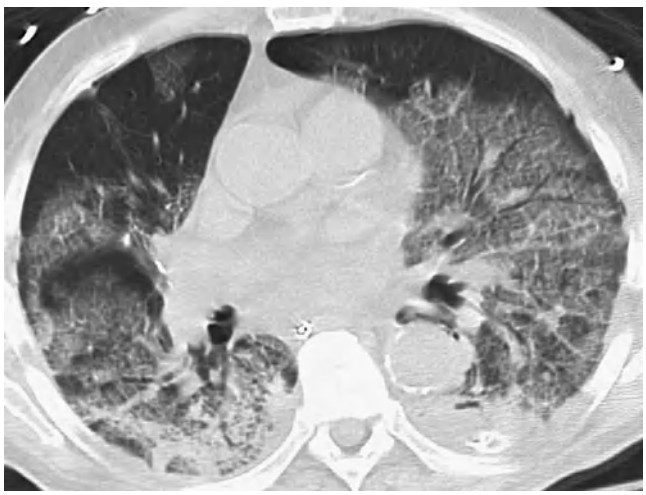


Figure 113-18 Diffuse ground-glass opacity *Pneumocystis jiroveci* pneumonia. Diffuse ground-glass opacification predominantly involving the subpleural (cortical) lung sparing the central lung at the time of first detection of *Pneumocystis jiroveci* pneumonia in a patient with advanced AIDS.

opacity); or pleural effusion (which is suggested by a meniscus contour or smooth thickening of the pleural space); pericardial effusion or pericarditis (which is suggested by pericardial widening or enlargement of the cardiac silhouette); and mediastinal and/or hilar or perihilar lymphadenopathy.

Atelectasis

Atelectasis refers to airlessness of a portion of lung. Crowded air-filled bronchi, and appropriate shift of lung contours toward the area of atelectasis may be diagnostic, e.g., pleural fissures, mediastinum, and diaphragm. When atelectasis is due to total airway occlusion, such as in proximal bronchogenic carcinoma, mucous plug, or aspirated foreign body, air bronchograms are usually absent. Atelectasis is a common feature of bronchopneumonia; it is not usually a prominent feature of peripheral airspace consolidation pneumonia. Atelectasis per se needs to be differentiated from pneumonia.

Bronchiectasis/Bronchiolectasis

Bronchiectasis/bronchiolectasis refers to abnormal dilatation of the airway. It implies air- or fluid-filled and widened tubular, varicose, or cystic. Bronchiectasis is recognized by an airway diameter significantly greater than its paired pulmonary artery. Varicose and cystic bronchiectasis implies destructive pneumonia or other inflammation, such as due to granulomatous pneumonia, or prior radiation therapy. In acute pneumonia, cylindrical, often "reversible" bronchiectasis may be identified.

Cavitation

Cavitation refers to abnormal non-anatomic lucency of lung usually within a lung opacity that makes up its wall. It is often devoid of normal internal vasculature. In uncomplicated bullous lung disease no significant wall thickness is present, and residual internal vasculature may be identified. Necrotizing cavitation may be caused by aspiration or pneumonia due to gram-negative intestinal bacteria, and mixed anaerobic oral flora. Cavitation suggests aggressive bacterial infections infection by bacteria such as *S. aureus* and gram-negative bacilli, and granulomatous infections, such as due to mycobacteria and fungi.

Lymphadenopathy

Lymphadenopathy is inferred on plain film radiography by unilateral or bilateral nodular enlargement of the mediastinum and hilar regions. On plain film radiography these findings often cannot be differentiated from vascular enlargement. Contrast-enhanced CT is much more sensitive than non-contrast CT scan in the detection of lymph node enlargement.

In general, mediastinal adenopathy can be found in a wide variety of different types of pneumonia associated with sympathetic or complicated effusions, but it is especially common in patients with primary infection due to *M. tuberculosis*. The absence of acquired specific cellular immunity to *M. tuberculosis* is responsible for the peripheral airspace consolidation and lymphadenopathy that are characteristic of primary tuberculosis. Lymphohematogenous dissemination results in characteristic mediastinal and hilar adenopathy with low-density necrotic centers, and rim enhancement in contrast-enhanced CT. Lymphadenopathy is also found in atypical mycobacterial infection; fungal infection due to *Histoplasma capsulatum* and *Coccidioidomycosis immitis*; viral infection due to HIV, CMV, and EBV; and bacterial infection associated with sepsis, e.g., pneumonia due to staphylococci, beta-hemolytic streptococci, and tularemia. In *P. jiroveci* pneumonia, lymphadenopathy often calcifies.

Non-infectious causes of hilar and mediastinal lymphadenopathy include bronchogenic carcinoma, lymphoma, sarcoidosis, metastatic cancer, lymphatic spread of tumor, pneumoconiosis, such as due to silica (in which case "eggshell" calcification, small lung nodules, and conglomerate masses may be seen), and interstitial pulmonary fibrosis. In congestive heart failure non-pathologic lymph nodes can significantly enlarge, and reduce in size after diuresis.

Pleural and Pericardial Abnormality

Pleural fluid is identified by abnormal fluid separation of the visceral and parietal pleural surfaces. It is likely to be free flowing if it is gravitationally dependent, and tapers out smoothly against gravity. Uniform meniscal opacity is usually identified in gravitationally dependent lung regions, where it tends to separate the lung from the ribcage. Loculation is suspected when the fluid localizes in non-gravitational regions of the pleural space. Pleural fluid is the only radiographic finding that has thus far been found to be an independent predictor of outcome of CAP pneumonia. For this reason pleural effusion has been incorporated into a Pneumonia Severity Index. Pleural fluid accumulation is more likely to indicate progressive and/or necrotizing pneumonia.

Pleural thickening and empyema are higher than water density on CT. Abnormal enhancement of both the visceral and parietal pleura is an imaging sign of active pleuritis. Empyema fluid may have near-normal water density or increased density. Pleural hemorrhage tends to have high density on non-contrast–enhanced CT studies.

Pneumothorax in the context of pneumonia implies a bronchopleural fistula (BPF) usually from cavitating pneumonia. CT scan can help localize the source of a BPF, as well as detect a small pneumothorax.

Pericardial effusion, when large, can be suspected on plain-film radiography by a new globular cardiac silhouette, short-interval cardiac enlargement, or abnormal fluid density thickness between the visceral and parietal pericardium on the lateral chest radiograph. On CT pericardial fluid can be identified by fluid density (or higher than fluid density in the case of empyema or hemorrhage) within the pericardial sac. Active pericarditis is indicated by abnormal thickening and enhancement of the visceral and parietal pericardium.

CONCLUSIONS

Radiologic imaging is an essential diagnostic tool for the diagnosis and management of pneumonia. Uncommonly, under special clinical circumstances, imaging findings can be virtually diagnostic of a specific etiology of infection. However, in most cases imaging only narrows the range of likely etiologies of pneumonia, and provides insight into its pathogenesis by categorizing its predominant imaging features and integrating these findings into the prior clinical probabilities. Radiologists need to be aware of each patient's pertinent background information to provide insightful opinions regarding imaging findings.

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114

The Pathology of Pulmonary Infection

Richard Kradin

The pathology of lung infection reflects a composite of host-pathogen interactions. Distortions in pulmonary anatomy, decreased mucocilary clearance, and local and systemic abnormalities in cellular and humoral immune response all predispose to pulmonary infection. Although clinical history, radiographic findings, and noninvasive sampling of secretions often establish a diagnosis of infection, only tissue sampling affords the possibility of directly assessing pulmonary infection. As biopsy procedures have become progressively less invasive, there has been a tendency to focus primarily on the identification of the causative infectious agent as the sole end point of the diagnostic process. However, this goal potentially ignores the benefits of evaluating host-pathogen interactions.

This chapter reviews the basics that clinicians and pathologists must know about lung tissue sampling, the optimal diagnostic work-up of the lung biopsy, and the histopathology of infection.

I. THE APPROACH TO TISSUE SAMPLING

The optimal method of sampling infection (Table 114-1) is a function of host immune status, where the infection is located in the lung, and on whether it is localized or diffuse. Infections that cause diffuse pulmonary infiltrates in an immunosuppressed patient with HIV-1 infection often can be accurately diagnosed by the induction of sputum or by bronchoalveolar lavage (BAL). This is particularly true when the microbial burden is large, as it often is in *P. jirocevi* and mycobacterial infections. Noninvasive procedures are less sensitive than biopsy in diagnosing pulmonary fungal infections, e.g., aspergillosis, and do not differentiate between noninvasive and invasive disease. Lung biopsy is also indispensable in distinguishing infection from noninfectious lung injury in patients receiving chemotherapy, radiation, or immunosuppressive agents. Whereas clinicians tend to favor minimally invasive

Table 114-1

Approach to the Isolation of Pulmonary Microorganisms

Expectorated sputum
Induced sputum
Bronchoalveolar lavage
Fine-needle aspirate (1 mm)
Bronchial biopsy (1–3 mm)
Transbronchial biopsy (1–3 mm)
Transbronchial needle biopsy (1 mm)
Video-assisted thoracoscopic biopsy (2–3 cm)
Open-lung biopsy (2–3 cm)

techniques in the sampling of lung tissue, most pathologists favor generous tissue samples. In support of the latter preference, it may be argued that diagnoses based on larger tissue samples are more reliable, afford the opportunity to establish additional treatable diagnoses, and lead to more finely crafted therapeutic interventions.

Transbronchial Biopsy

The optimal approach to lung biopsy depends on the specific clinical features of the case. Sampling error is a serious pitfall in pulmonary pathology. Since the lungs have roughly the surface area of a tennis court, diagnostic accuracy is inversely related to the size of the biopsy. Transbronchial biopsy (TBB) yields tissue fragments of 1 to 3 mm in diameter and preferentially samples peribronchiolar parenchyma of the lung. The TBB is particularly effective in sampling diffuse peribronchiolar granulomatous and neoplastic disorders. Despite limitations imposed by its size, it has a high yield in identifying infection when pulmonary infiltrates are diffuse, e.g., in diffuse alveolar damage due to viral pneumonia but is far less reliable in the diagnosis of localized parenchymal infections.

Despite its advantages, the findings in TBBs are often nonspecific and even misleading. Peripheral lesions in the lung are difficult to sample by TBB and samples obtained by this approach often prove to be nondiagnostic or nonrepresentative. For example, an area of organizing pneumonia can represent a tissue response to a focus of infection or it may reflect noninfectious etiologies, including treatment effects, aspiration, or cryptogenic organizing pneumonia. The findings in a TBB must always be carefully correlated with clinical and radiographic data, but even then there is risk that they will be inaccurately interpreted.

Fine-Needle Aspiration Biopsy

CT-guided fine needle aspiration biopsies have a high yield in the diagnosis of peripheral nodular infiltrates. Samples may be semi-liquid or include a 1-mm core of tissue. The procedures are generally performed with the assistance of a cytotechnologist, so that rapid diagnoses can be proffered at the bedside from the preparation and examination of stained smears. FNA is helpful in isolating the cause of infection and may enable the cytopathologists to suggest the pattern of inflammation based on the types of inflammatory cells, and the presence or absence of fibrin, necrosis, and elastic fibers in the sample. However, the limited sampling often does not provide sufficient tissue to reliably assess the inflammatory response of the host.

Transbronchial Needle Aspiration Biopsy

Transbronchial needle aspiration biopsies of regional lymph node groups generally add little to the diagnosis of pulmonary infection, in part, because nonspecific reactive lymphadenitis is common but also because the procedure yields artifacts that can present diagnostic difficulties for the surgical pathologist. However, they may have a role in diagnosing infection in patients with AIDS, since approximately 50 percent of patients with tuberculous lymphadenitis were successfully diagnosed using this approach.

Video-Assisted and Open Thoracoscopic Biopsy

Video-assisted thoracoscopic lung biopsies have largely replaced procedures involving open thoracotomy. This approach is associated with less overall morbidity and allows direct access to widely separated lung segments. The procedure yields wedge biopsies of 2 to 3 cm with little artifactual distortion. Although it may be bucking the current clinical tide to argue for larger rather than smaller biopsies, the slight potential increase in morbidity associated with VATS lung biopsy is often counterbalanced by less discomfort than TBB, increased diagnostic accuracy, and less doubt concerning the subsequent treatment.

HANDLING OF BIOPSY TISSUES

Proper handling of the lung biopsy is critical for obtaining the highest diagnostic yield from tissue samples (Fig. 114-1). The examination of touch imprints of lung biopsy tissue is a simple way for identifying organisms rapidly. At least 10 touch imprint slides should be prepared from areas of pulmonary consolidation. These can be stained rapidly for bacteria, mycobacteria, and fungi, in the surgical pathology suite or the microbiology laboratory. Concomitantly, portions of

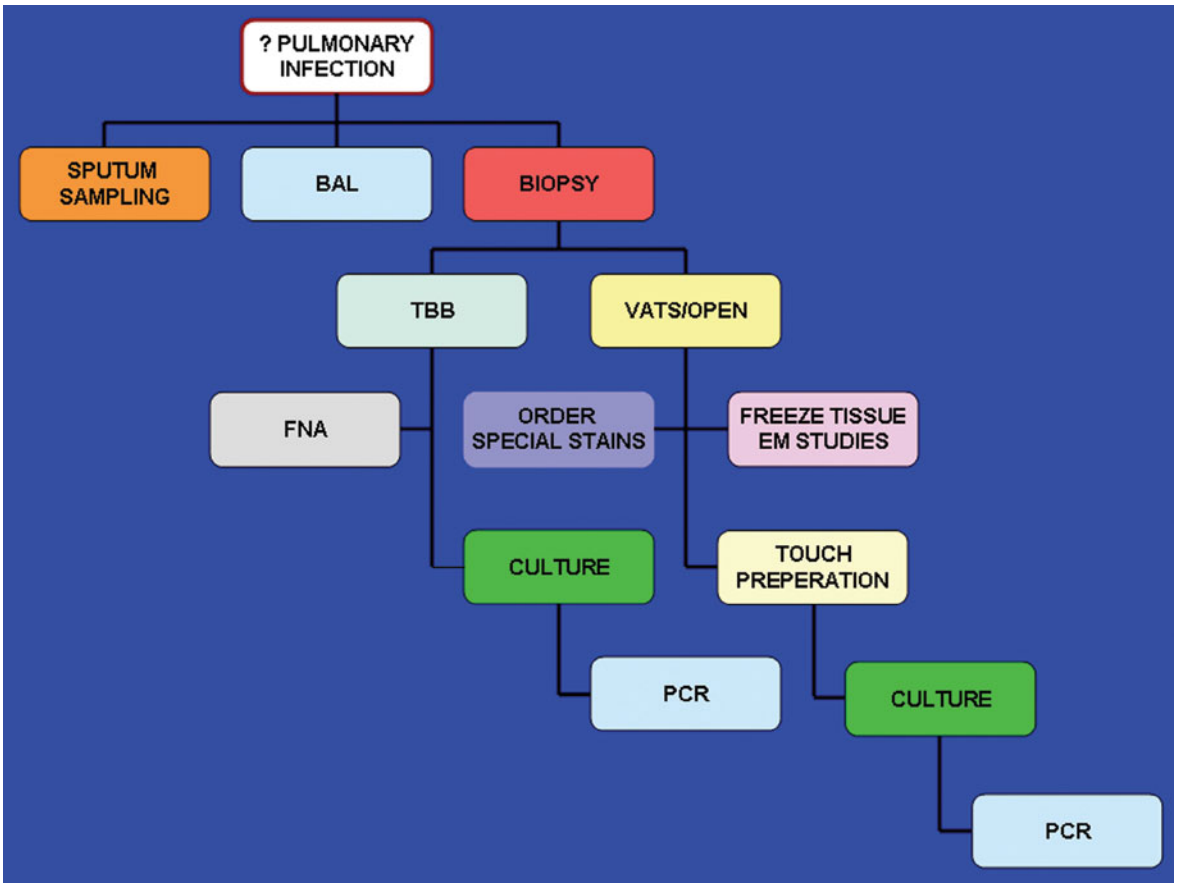


Figure 114-1 The diagnostic work-up of pulmonary infection.

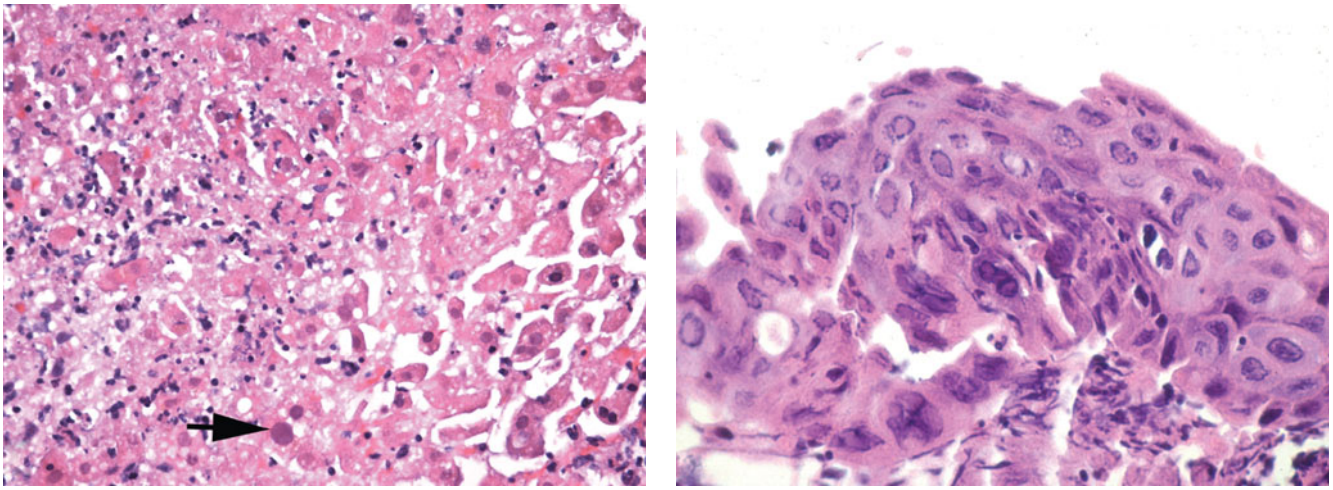
a large biopsy (VATS or open) or separate biopsies (TBB or FNA) should be harvested for culture, ultrastructural analysis, and polymerase chain reaction (PCR) assays. In preparing lung tissue for culture, it should be finely minced rather than crushed, since some hyphal fungi, e.g., *Zygomyces* sp., fail to grow in culture after the tissue has been macerated. For VATS or open lung biopsies, the lung should subsequently be inflated with 5 percent formalin via a 23- to 25-gauge needle, in order to optimize the histology of the paraffin-embedded lung sections.

The pathologist who receives the lung biopsy for processing must ascertain which diagnostic tests were sent by the surgeon and be prepared to harvest additional samples for tests that may have been overlooked. It is substandard care for either a surgeon or a pathologist to place a lung biopsy directly into formalin fixative, without first considering the possibility of infection. If there are doubts concerning which diagnostic tests to order, the amount of tissue required for a test or how best to transport the specimen to the laboratory, brief discussions with the hospital microbiology laboratory or an infectious disease specialist will promptly eliminate them.

Preparing Histopathology Sections

The scarcity of microorganisms in tissue biopsies creates a diagnostic challenge for the pathologist. In addition, previous antibiotic treatment can sterilize inflamed tissues, making it difficult to identify the original cause of the infection in situ. For these reasons, an adequate sample of tissue obtained by biopsy is critical for the microscopic identification of infectious agents. The surgical pathologist must be prepared to review multiple sections in the routine assessment of infection. In some instances, it may be necessary to examine literally scores of sections in order to identify an organism in situ. Too often, busy surgical pathologists may conclude that the diagnosis of infection is primarily in the realm of the microbiology laboratory or that the labor-intensive effort required to identify organisms in situ is not cost effective. This attitude is to be discouraged, since it is incorrect and limits the practice that is required in order to acquire expertise in the identification of microorganisms in situ.

Certainly, if the microbiology laboratory has previously identified the offending pathogen, it may not be necessary to go to extraordinary lengths in order to duplicate its results. But in instances in which cultures were not obtained, or when pathogens require weeks to grow in culture, e.g., mycobacteria, or the organism isolated in the laboratory may represent a commensal or contaminant, the pathologist must be ready to undertake a detailed examination of multiple tissue sections. Since antimicrobial drugs have become increasingly selective, it is currently suboptimal to render a nonspecific



A B

Figure 114-2 *A*. The lung shows a miliary focus of necrosis and fibrin deposition. Intranuclear inclusions (arrow) of herpesvirus-1 are present. *B*. Note the presence of multiple amphophilic intranuclear inclusions of Herpesvirus-1 infection in the trachea of a patient receiving chronic ventilator support.

diagnosis of, e.g., "necrotizing granulomatous inflammation," without a concerted effort to identify the offending pathogen.

The pattern of pulmonary inflammation suggests the primary route of infection in the lung. For example, *Herpesvirus-1* may either show a miliary pattern of fibrinoid necrosis (Fig. 114-2) in patients with viremia, or primarily affect the tracheobronchial epithelium in patients who have been intubated for prolonged periods. Microbes tend to be compartmentalized in inflamed tissues, and substantial effort can be wasted in searching for organisms at high magnification, in areas of the tissue section where they are not likely to be found. For example, mycobacteria and fungi are almost always localized in areas of necrotic tissue, and it is unusual to find them elsewhere in the biopsy. Organisms, such as *Rickettsia* sp. and *Bartonella* sp. are angiotropic, and attention should be focused on foci of perivascular inflammation. Virus tends to target specific areas of the lung and certain types of cells.

Histochemical Stains

A number of histochemical stains are available for the demonstration of microbes in situ and their proper application can yield accurate and specific diagnoses in many cases (Table 114-2). However, the limits of this approach must be recognized, and the gold standard, in most cases, remains the isolation and biochemical or molecular identification of an organism.

Hematoxylin & Eosin

Most of the stains to be discussed in this chapter are widely available in pathology laboratories. However, if only one was to be chosen, it would be the standard hematoxylin and eosin (H&E) stain. Table 114-3 lists the diagnoses that can be established reliably by H&E staining, without the benefit of additional methods. They include cytopathic viral infections, most fungal infections, and all parasites.

Although it is not possible to speciate bacteria into gram-positive or -negative subsets by the H&E stain, bacterial colonies often can be identified by this approach. Most fungi are visible by H&E, with the notable exception of *Histoplasma capsulatum;* and the tinctorial properties of the fungi can be helpful in speciating. For example, the cell walls of *Zygomyces* sp. stain intensely basophilic with H&E (Fig. 114-3), and the yeast of *Candida glabrata* show prominent amphophilic staining.

Tissue Gram Stain

The tissue gram stain (Brown-Hopps and Brown-Brenn) identifies most bacteria and some fungi in tissue sections. It also can be used to demonstrate the spores of microsporidia. Gram-positive organisms stain a deep magenta, whereas gram-negative bacteria are pale pink (Fig. 114-4). For this reason, gram-negative organisms can easily be missed in a low-power cursory screening of gram-stained sections. The phenomenon of gram stain-variability, in which colonies of gram-positive organisms show a range of staining from dark blue to pink, is common and can give the false impression of "mixed flora." In such instances, only culture can reliably distinguish the actual additional presence of gram-negative bacteria. Although most fungi are weakly gram positive, most *Candida* sp. stain intensely positive, a fact that can be used to advantage in their identification.

Gomori Methenamine Silver

Gomori methenamine silver (GMS) is the stain of choice for identifying fungi in tissue sections. Both fungal yeast and

Table 114-2

Histochemical Staining Characteristics of Microbes

Organism	Staining Characteristics
Virus	
Influenza	No cytopathic change
SARS (Coronavirus)	No cytopathic change
Adenovirus	H&E (smudge cells), IHC
Cytomegalovirus	H&E (intranuclear and cytoplasmic inclusions) IHC; PAS and GMS (intracytoplasmic inclusions)
Herpes virus	H&E (intranuclear inclusions); IHC
Measles	H&E (intranuclear inclusions, polykaryons)
Respiratory	H&E (polykaryons); IHC syncytial virus
Parainfluenza	H&E (intracytoplasmic inclusions)
Bacteria	
Gram-positive	Tissue gram, GMS (all)
Gram-negative	Tissue gram, GMS (some)
Legionella	Silver impregnation
Nocardia	Tissue gram, GMS, modified ZN
Actinomyces	Tissue gram, GMS
Mycobacteria tuberculosis	ZN and mod ZN, PCR
Atypical mycobacteria	Mod ZN, ±ZN, PCR
Fungi	
Histoplasma	GMS, PAS
Cryptococcus	H&E, GMS, PAS, mucicarmine; Fontana, IHC
Blastomyces	H&E, GMS, PAS, mucicarmine (weak)
Coccidioidomycosis	H&E, GMS, PAS
Candida	H&E, GMS, PAS, gram-stain; IHC
Aspergillus	H&E, GMS, PAS, IHC
Zygomyces	H&E, GMS, PAS
Pseudeallescheria	H&E, GMS, PAS
Alternaria and dermatiacious fungi	H&E, GMS, PAS, Fontana
Parasites	
Protozooa	H&E, PAS, gram stain (microsporidia); IHC (toxoplasma)
Metazoa	H&E, trichrome stain
Echinococcus	GMS in chitinous wall, modified ZN (hooklets)
Paragonimiasis	Ova birefringent
Schistosomiasis	Lateral and terminal spines stain with modified ZN

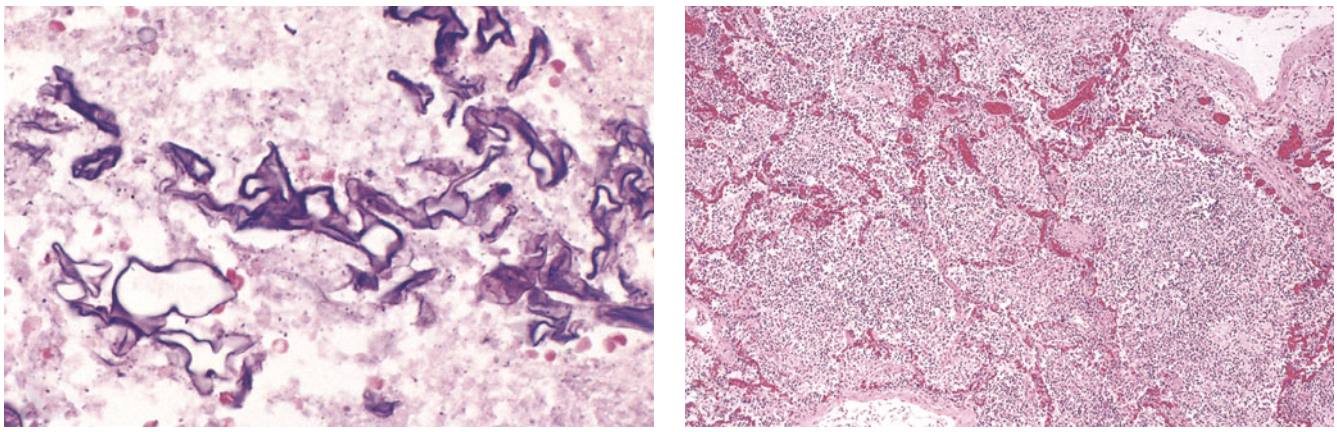
Table 114-3

Microbes That Can Be Identified with H&E Stain

Cytopathic virus
Bacteria in colonies or in "granules"
Most fungi
Parasites

hyphae stain intensely with GMS (Fig. 114-5). However, identification of speciating fungi in tissue sections is a challenging morphologic task (Table 114-4). Identification is based primarily on size, branching pattern, and mode of reproduction. Hyphal organisms, e.g., *Aspergillus* sp., *Pseudallescheria* sp., *Fusarium* sp., and the *Zygomyces* sp. are particularly difficult to distinguish based solely on morphology, especially when fragmented, and immunohistochemical methods or culture confirmation are required (Fig. 114-6). Yeast forms are distinguished by size, pattern of budding, and affinity for special stains.

The GMS stain is generally counterstained with methyl green, which highlights the grey-black staining of fungi.



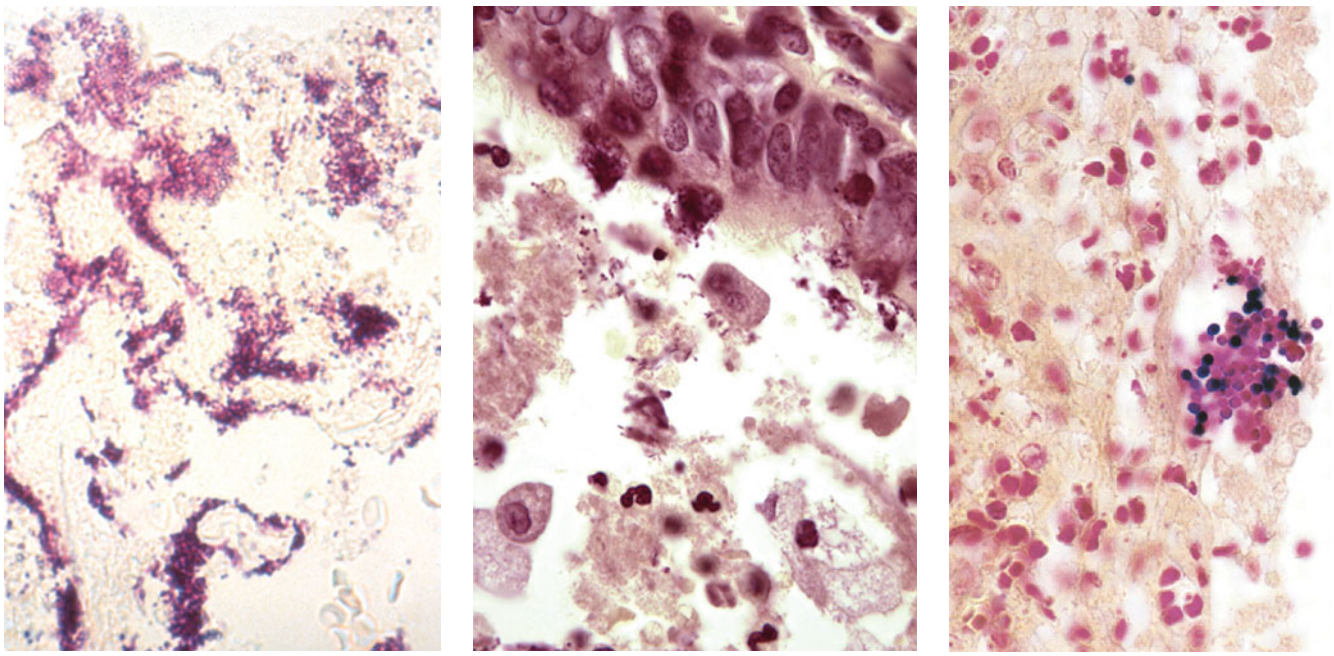
A *B*

Figure 114-3 *A*. The broad pauciseptate ribbon-like hyphae of *Zygomyces* (mucor) stain intensely basophilic with H&E. *B*. The 3 to 4 μM yeast of *C. glabrata* (torulopsis) show amphophilic staining with H&E.

However, this does not allow for optimal visualization of pulmonary anatomic structures or assessment of the inflammatory response of the host. When desirable or necessary, the GMS can be counterstained with H&E. This technique diminishes modestly the sensitivity of fungal identification in situ, but greatly facilitates localization within the lung (Fig. 114-7).

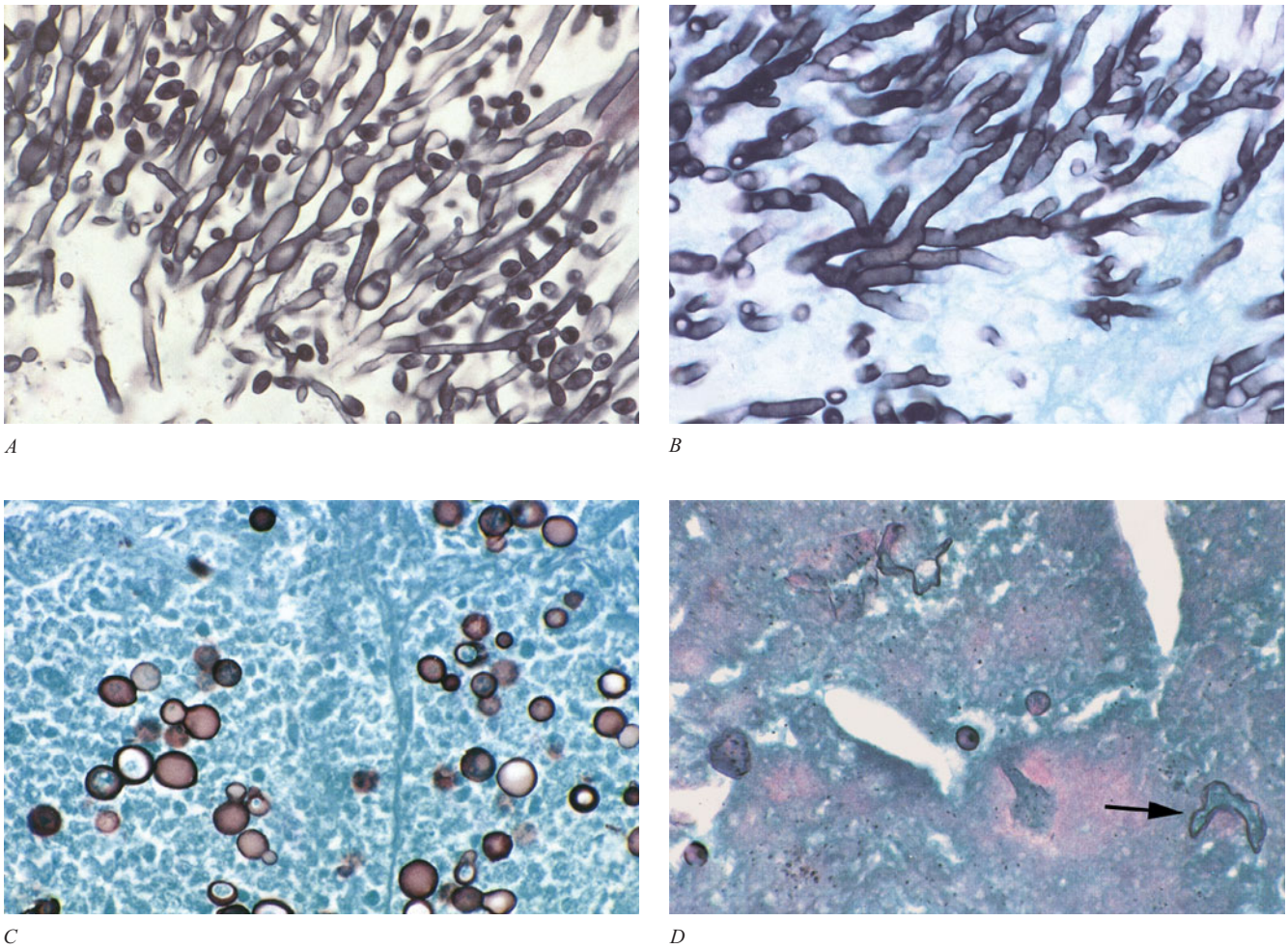
In addition to staining fungi, GMS blackens gram-positive bacteria and some encapsulated gram-negative bacteria, e.g., *Klebsiella* sp. and *H. influenzae*. Unfortunately, the stain also reacts with anthracotic pigment, microcalcifications, and hemosiderin, complicating the distinction between bacteria and nonbacterial structures. The identification of bacteria by GMS should be confirmed and complemented by tissue gram stain.

Most pathologists recognize that GMS reacts with both *Actinomyces* sp. and *Nocardia* sp.; however, this is not a specific feature of these organisms but instead reflects the fact that they are gram-positive filamentous bacteria. The GMS stain adds little to their specific identification but does enhance



A *B* *C*

Figure 114-4 *A*. Colonies of magenta staining gram-positive cocci line the alveoli in a lethal case of streptococcal pneumonia. *B*. Gram-negative rods are seen in the lumen of a bronchiectatic airway in a patient with cystic fibrosis and *Burkholderia cepacia* infection. *C*. The yeast (blastoconidia) of *C. parapsilosis* show gram-variable staining.



A *B*

C *D*

Figure 114-5 *A*. Both pseudohyphae and yeast (blastoconidia) of *Candida albicans* are well demonstrated with GMS. *B*. Septate acute-angle progressively branching hyphae of *Aspergillus fumigatus*. *C*. Yeast forms of *Blastomyces dermatitidis* show broad based single buds and accentuation of thick cell wall with GMS. *D*. GMS shows intact and collapsed cyst walls (arrow) of *Coccidioides immitis*. Endosporulation is not obvious.

their visibility in tissue sections. *Actinomyces* sp. are invariably seen within granules lined by granulohistiocytic inflammation, often highlighted by the eosinophilic staining of the Splendore-Hoepllei phenomenon (Fig. 114-8). *Nocardia* in the lung are rarely localized to granules, and unlike *Actinomyces* sp., they are generally weakly acid-fast positive. GMS reacts variably with mycobacteria. The intracellular inclusions of cytomegalovirus (CMV)-infected cells are GMS-positive and must not be confused with intracellular *Histoplasma capsulatum*.

Periodic Acid Schiff

Many pathologists prefer the periodic acid Schiff (PAS) stain with diastase digestion for the identification of fungal forms. However, PAS should be used primarily to complement GMS, and not as a first-line screening tool, since the latter is more sensitive. However, PAS can add important morphologic details that assist with identification of fungi (Fig. 114-9). PAS stains the cytoplasm of *Entamoeba* intensely but obscures the karyosome, a feature that is required for accurate diagnosis. The PAS stain also demonstrates the intracellular bacilli of *Trophyrema whipelli* (Whipple's disease bacillus).

Silver Impregnation Techniques

Silver impregnation techniques, including the Warthin-Starry, Steiner, and Dieterle stains, are distinguished by their capacity to blacken *all* eubacteria, including mycobacteria. In practice, this stain is used to identify bacteria that cannot be visualized by tissue gram stain. This includes *Legionella* sp., *Bartonella* sp., and spirochetes (Fig. 114-10).

Mucin Stains

Mucicarmine stains *Cryptococcus* sp. (Fig. 114-11). The central organism does not stain and the capsule is stained red. Capsule-deficient variants generally infect hosts who can mount a granulomatous response. When yeast forms meet the

Table 114-4

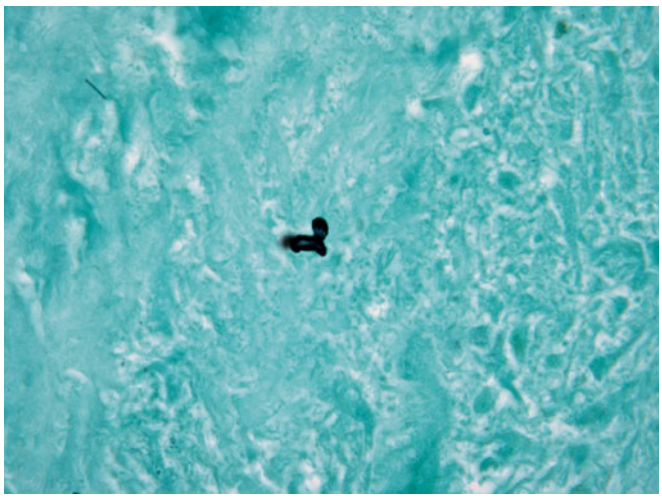
Fungal Identification in Tissue

Organism	Size (Width μM)	Defining Morphology
Histoplasma capsulatum	2–5	Narrow-neck bud
Cryptococcus neoformans	5–20	Narrow-neck bud
Blastomyces dermatitides	15–30	Broad-based bud
Candida glabrata	3–5	Budding, no pseudohyphae
Candida sp.	2–3	Yeast, pseudohyphae, hyphae
Aspergillus sp.	3–5	Acute-angle branching, septate, conidial head
Zygomyces spp.	5–8	Right-angle branching, ribbons, pauciseptate
Pseudallescheria sp.	3–4	Acute-angle branch, septate, terminal chlamydospore, pigmented conidia
Fusarium sp.	4–5	Acute and right-angle branch, septate, narrowed branch points
Coccidioides immitis	20–200	Endosporulation

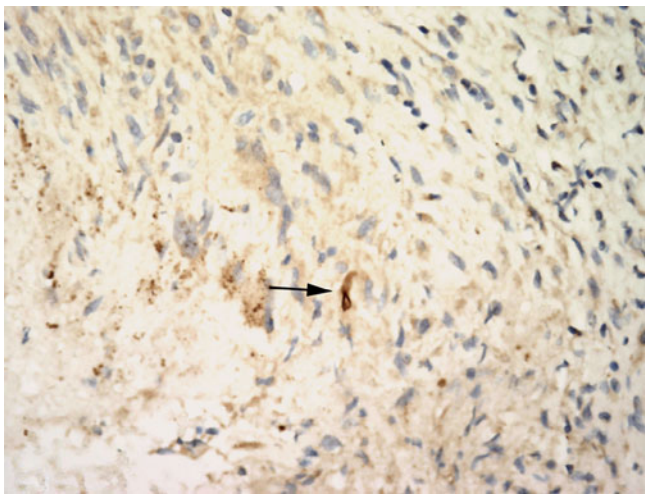
size and morphologic criteria of *Cryptoccocus* on the GMS and PAS stains but do not react well with mucin stains. A Fontana-Masson stain will demonstrate the premelanin substances expressed within the cell wall by all cryptococci. A careful examination of the mucicarmine stain will generally reveal a rim of weak staining, even in the capsule deficient organisms. Fontana-Masson is helpful in demonstrating dermatiacious fungi, when pigment is not convincingly discerned with H&E.

Acid-Fast Stains

The Ziehl-Neelsen (ZN) stain and its modifications are useful in the identification of mycobacteria in tissue sections.



A



B

Figure 114-6 A patient with chronic granulomatous disease and lung nodule. Lung biopsy showed (*A*) fragmented hyphal form with stubby right angle buds that were impossible to speciate with confidence with GMS. *B*. Immunostain for *Aspergillus sp.* was positive (arrow) and the microbiology laboratory isolated *A. terreus*.

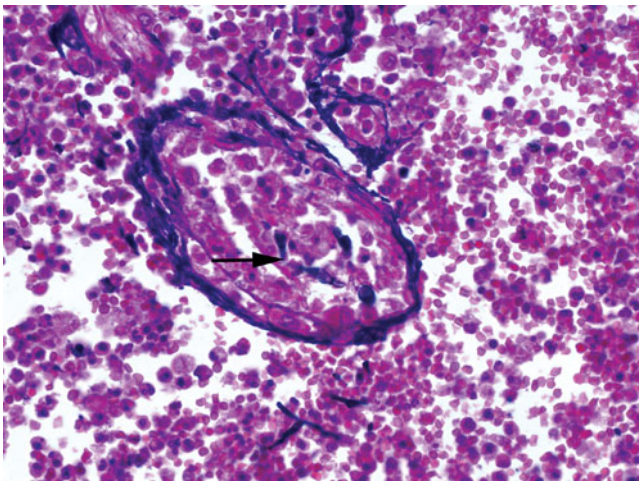


Figure 114-7 Patient with disseminated trichosporon infection. GMS-H&E shows hyphae (arrow) in a blood vessel with surrounding hemorrhage. This preparation is helpful when there is doubt concerning the localization of organisms in the routine GMS-methyl green preparation.

M. tuberculosis stains avidly with ZN. Mycobacterial organisms vary in length and are often curved and beaded (Fig. 114-12). Modifications of the ZN (Fite-Farraco or Putt) can help to identify organisms that fail to stain following strong decolorization by acid. This includes some atypical mycobacteria and *M. leprae.* The morphology of the mycobacteria is generally not diagnostic; however, *M. kansasii* characteristically shows prominent "cross-linking" due to variable uptake of stain. As noted, *Nocardia* sp. generally stain with the modified ZN, a feature that can help to differentiate this organism from *Actinomyces* sp. The hooklets of *Echinococcus* sp. stain with the modified ZN; so do the shells or spines of *Schistosoma* sp.

Immunohistochemical Techniques

A variety of immunohistochemical techniques are currently available for the identification of organisms in tissue (Table 114-5). Unfortunately, the number of commercially available stains for specific organisms is limited. A large panel of specific reagents is available through consultation with the Pathology Division of the Center for Disease Control in Atlanta, GA, or other regional medical centers. Most antimicrobial immunostains can be applied to either frozen or formalin-fixed and paraffin-embedded tissues. Protein nucleotide agglutination (PNA) represents a new and potentially important breakthrough in the localization of microorganisms in tissue sections.

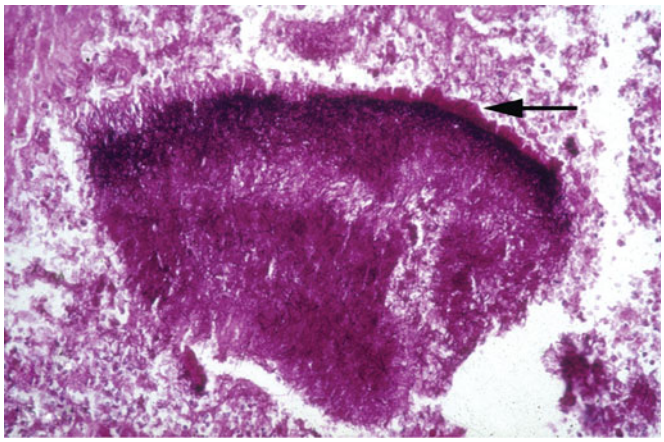
Electron Microscopy

Ultrastructural examination can be adopted for the identification of microbes in tissue. The limiting factors in this approach include sampling and expense. Whereas ultrastructural examination has largely been replaced primarily by immunohistochemistry, it can still assist in the morphologic identification of virus and other organisms. In addition, when questions remain concerning the veracity of light microscopic findings, areas of interest can be excised from the paraffin block and examined by electron microscopy. Most organisms can be identified even though fixation and paraffin embedding procedures may be suboptimal.

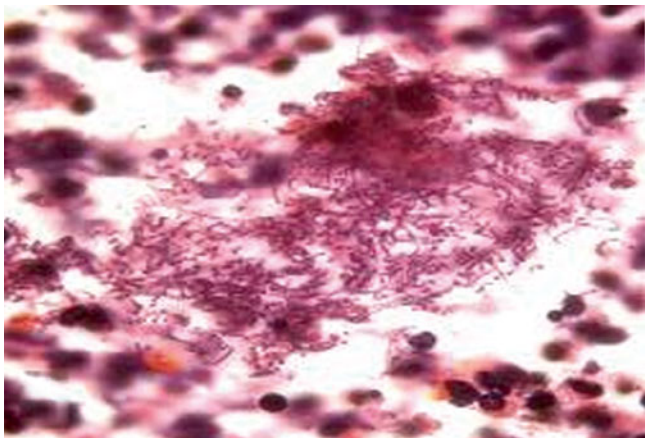
PATTERNS OF PULMONARY INJURY IN INFECTION

Pulmonary Host Response

Before examining the patterns of inflammation that occur in pulmonary infection, it may be helpful to summarize the basic

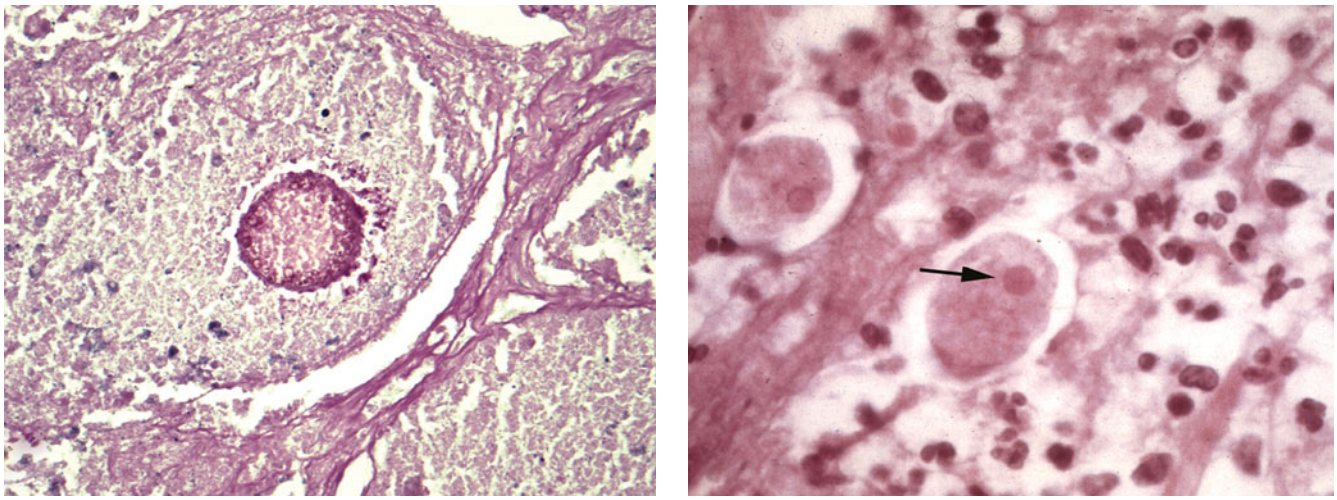


A



B

Figure 114-8 *A.* Granule in patient with *Actinomyces israelli.* To the naked eye, these granules are bight yellow (sulfur granules). Microscopically the gram-positive filamentous organisms are coated with eosinophilic PAS+ material that is deposited on the surface of the granule, i.e., the Splendore-Hoepllei phenomenon. *B.* Loosely adherent gram-positive filamentous organisms are seen *in Nocardia asteroides* pneumonia. *Nocardia* in the lung rarely forms true granules.

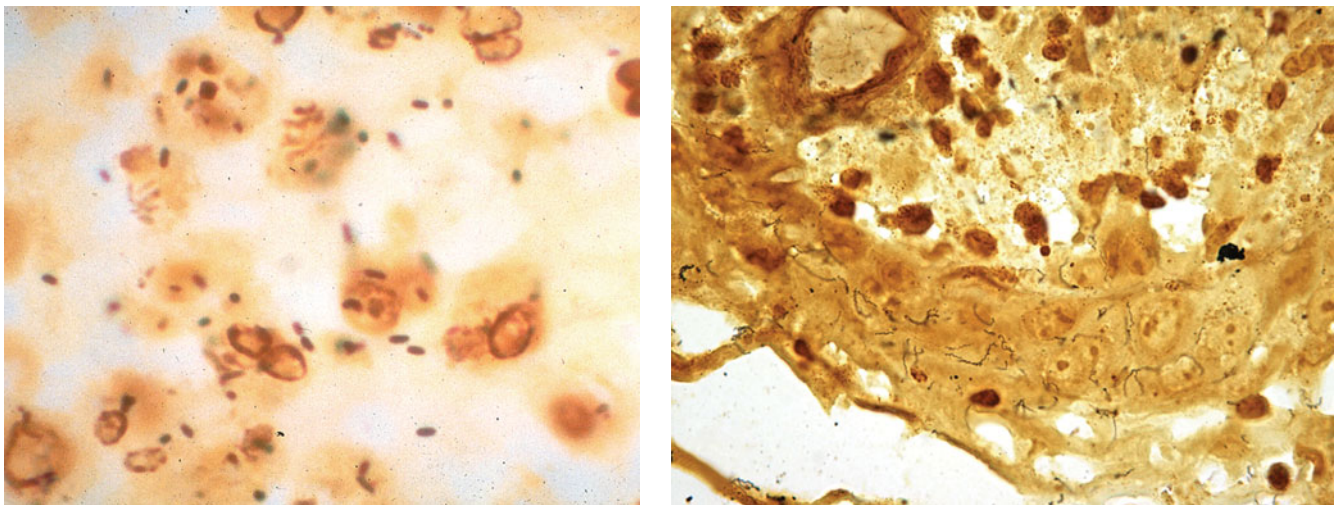


A *B*

Figure 114-9 *A*. PAS shows the cyst wall and endospores of *Coccidioides immitis* to excellent advantage. *B*. The karyosome (arrow) of *Entamoeba histolytica* is well seen in this H&E preparation but can be obscured by PAS.

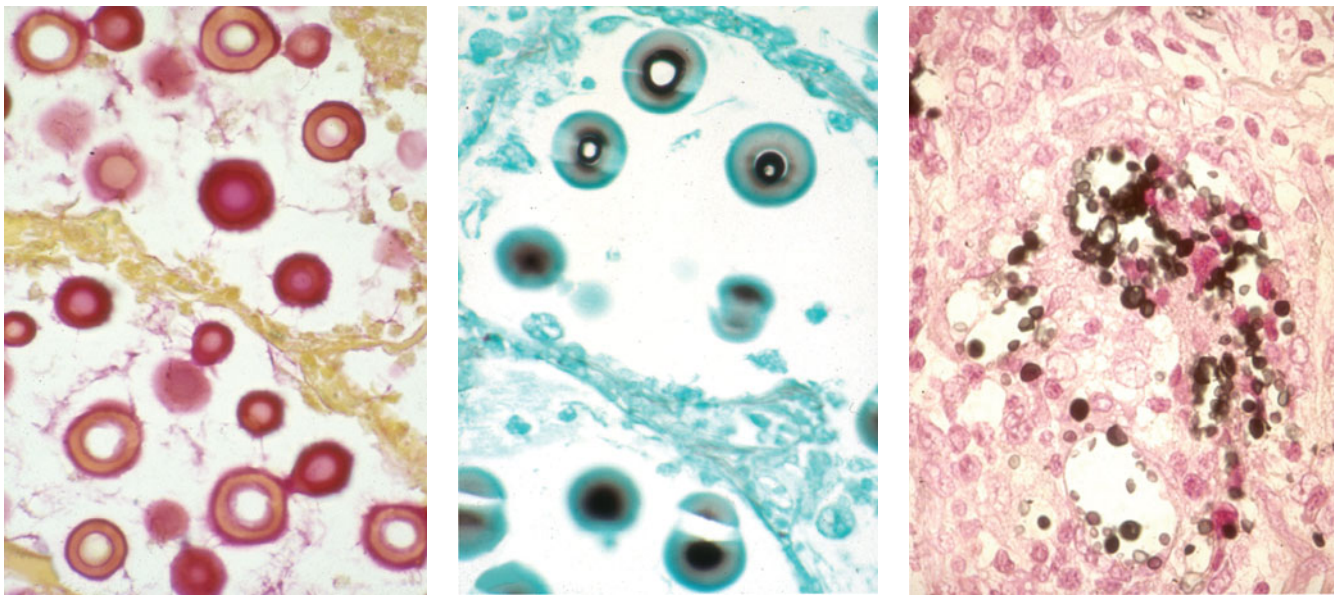
mechanisms of pulmonary host defense. The pulmonary response to infection includes generic elements of both innate and adaptive immunity that are shared by all tissues in their response to a particular infectious agent. However, the morphology of immune responses is modified by the specific microanatomy of the lung.

The lung is an elastic organ, composed of asymmetric dichotomously branching conducting airways that lead to the gas-exchange surfaces. The airways and the alveoli are embedded in a connective tissue matrix that is supplied by two blood circulations. The pulmonary circulation arises from the right side of the heart and carries deoxygenated blood at low mean arterial pressures to the alveolated surfaces, whereas the bronchial circulation arises from branches of the aorta and nourishes the airways and connective tissue stroma of the lung with oxygenated blood at systemic arterial pressures. All new growths within the lung, including fibroinflammatory responses to pulmonary infection, evoke neoangiogenesis from the bronchial circulation, so that areas of infected bronchiectasis, abscesses, and tuberculous cavities are all supplied by the systemic circulation. Deep and superficial systems of pulmonary lymphatics drain the lung from the level of the respiratory bronchioles, respectively, either toward lymph nodes at the hilum or centripetally along



A *B*

Figure 114-10 *A*. The coccobacilli of *Legionella pneumophila* are demonstrated by silver impregnation (Steiner). *B*. A pulmonary syphilitic gumma shows numerous spirochetes with silver impregnation (Warthin-Starry).

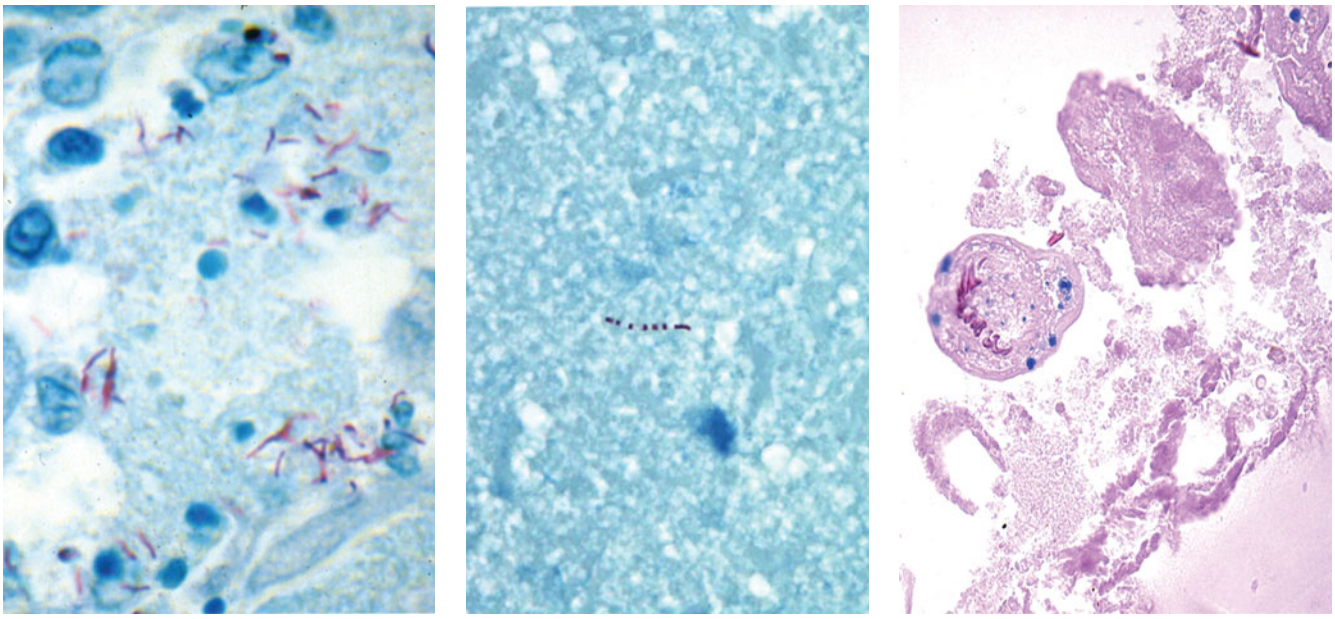


A *B* *C*

Figure 114-11 *A*. The true capsule of *Cryptococcus neoformans* stains red with mucicarmine. *B*. GMS shows the staining of the organism but does not demonstrate the capsule. *C*. Capsule-deficient cryptococci stain with Fontana-Masson. In most cases, careful examination, in retrospect, will reveal a faint mucicarminophilic capsule.

the pleural surfaces before emptying at the hilum. Lymphatic drainage plays an important role in the mechanism of disease. Streptococcal infections rapidly invade the pulmonary lymphatics, which transport bacteria to the pleural spaces to produce empyema. Inhaled anthrax bacilli drain rapidly to the local lymph nodes and lead to rapid dissemination of infection. Mycobacteria and fungi drain to the hilar nodes and, from there, disseminate to extrapulmonary tissues via the blood circulation.

The primary defenses of the airways include the olfactory hairs of the nasal passages and the mucociliary clearance mechanisms of the lower airways. Most microbes are



A *B* *C*

Figure 114-12 The Ziehl-Neelsen stain demonstrates (*A*) *M. tuberculosis*. *B*. *M. kansasii* shows a prominent cross-linked staining pattern. *C*. The hooklets (arrow) of *Echinococcus granulosa* stain with modified Ziehl-Neelsen (Fite).

Table 114-5

Immunohistochemical Stains Commercially Available for Microbe Identification in Paraffin-Embedded Tissues

Fungi	Virus
Aspergillus (genus only)	Herpesvirus-1 (cross-reacts Herpesvirus-2)
Cryptococcus	Varicella-Zoster
Histoplasma	Cytomegalovirus
Candida sp.	Respiratory syncytial virus
Coccidioides immitis	Adenovirus
Pneumocystis jiroveci	Ebstein-Barr (EBER)
Pseudallescheria boydii	*Actinomycetes*
Zygomyces (genus only)	*Actinomyces israelii*
Sporothrix schenkii	*Actinomyces naeslundi*
Trichosporon	Arachnia propionica

small enough (less than 5 μM) to penetrate to the distal gas-exchanging surfaces of the lung. However, the vast majority are excluded by the defenses of the upper airways or deposit along the conducting airways, and are cleared by the mucociliary escalator. Humoral factors, including sIgA and defensins that are released into the airways, limit penetration by microbes. Mucosal dendritic cells trap microbial antigens and carry them to the regional lymph nodes, where they are processed and presented to both T- and B-lymphocytes (Fig. 114-13), affording the potential for specific adaptive anamnestic responses

The gas-exchange surface consists of a fused epithelial-endothelial basement membrane. Disruption or thickening of the gas-exchange surface is deleterious with respect to the diffusion of oxygen and carbon dioxide. For this reason, the surfaces of the alveoli are kept sterile by scavenging alveolar macrophages. These resident alveolar macrophages have the capacity to ingest inhaled particulates and to secrete monokines, including IL-10, that actively suppress local inflammation. Under conditions of health, the prevailing response is one of immunotolerance. However, when the alveolar lining is injured, or the number of invading organisms overwhelms the phagocytotic capacities of resident alveolar macrophages, neutrophils and exudate monocytes are recruited to the sites of inflammation. Even small numbers of virulent pathogens can greatly amplify inflammation via the release by the host of chemokines, cytokines, and complement components. Although this response may increase the clearance of infection, the damage evoked by these factors can injure the lung irreversibly, leading to fibrosis. The lung biopsy affords a unique opportunity to assess the host inflammatory response, in addition to identifying the cause of infection (Table 114-6). It is ultimately, the most accurate mode of determining host immune competence in patients with immune deficits.

Diffuse Alveolar Damage

A number of patterns of inflammation are unique to the lung. The *sine qua non* of acute injury to the alveolar wall is the development of the *hyaline membrane*, composed of an extravascular fibrin coagulum admixed with the necrotic alveolar cell debris. Diffuse alveolar damage (DAD) is the most frequent pathological correlate of the adult respiratory distress syndrome (ARDS), although confluent bronchopneumonia can also yield this syndrome since it is impossible to distinguish DAD from localized acute lung injury in small biopsy specimens, radiographic and clinical confirmation always should be sought.

Virtually all viruses cause DAD. *Influenza* and *coronarvirus* are RNA viruses that yield DAD with no diagnostic cytopathic features (Fig. 114-14). *Herpesvirus, adenovirus, varicella-zoster, measles* and *cytomegalovirus* cause DAD, but also exhibit cytopathic changes that are diagnostic. Immunohistochemical techniques can be used to localize viral proteins within infected cells in situ.

Bacterial, fungal, or parasitic infections rarely cause DAD primarily, although *Pneumocystis jiroveci* is a well-recognized cause. However, the presence of DAD is not limited to infection. Many inhaled toxins also produce DAD, and in patients who are immunosuppressed due to cancer therapy or organ transplantation, distinction can be difficult between DAD due to infection versus radiation, cytotoxic drug therapy, lung implantation injury, and diffuse gastric acid aspiration. Pulmonary infection can complicate DAD due to other causes, and the septic complications of extrathoracic infections can cause DAD.

Bronchopneumonia

Bronchopneumonia is the most common pattern of inflammation caused by inhaled pathogens. Bronchopneumonia begins as infection with inflammation of the membranous small airways and then extends into the surrounding alveolar spaces. Bacterial bronchopneumonia due to pyogenic bacteria, including *S. pneumonia*, *S. aureus*, and *Streptococci* sp., often complicate viral tracheobronchitis, probably reflecting an acquired postviral defect in mucociliary clearance and barrier defense. Virtually all bacteria and fungi and many viruses can cause bronchopneumonia. The inflammatory response evoked by the pathogen is helpful in limiting the differential diagnosis. Both gram-positive and -negative bacterial infections evoke a brisk pyogenic neutrophilic response

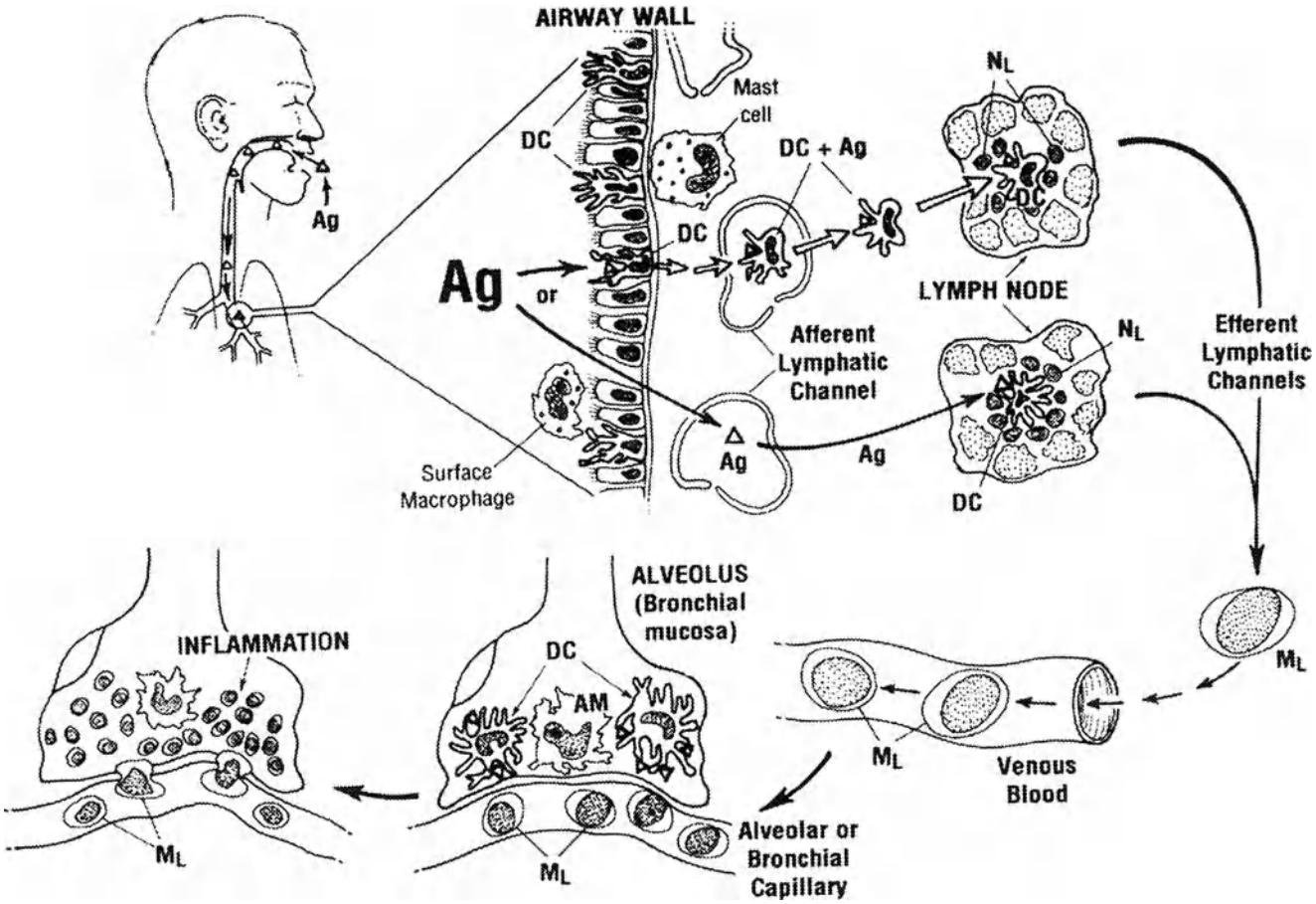


Figure 114-13 The cartoon shows the afferent and efferent pathways of adaptive pulmonary immunity via which entrapped antigens (Ag) are transported by dendritic cells (DC) to regional lymph nodes, presented to T- and B-lymphocytes, and subsequently evoke a cellular anamnestic response by memory lymphocytes (M_L) upon rechallenge. (Adapted from Kradin RL, Robinson BWS (eds.): *Immunopathology of the Lung.* Boston: Butterworth-Heinemann, 1996.)

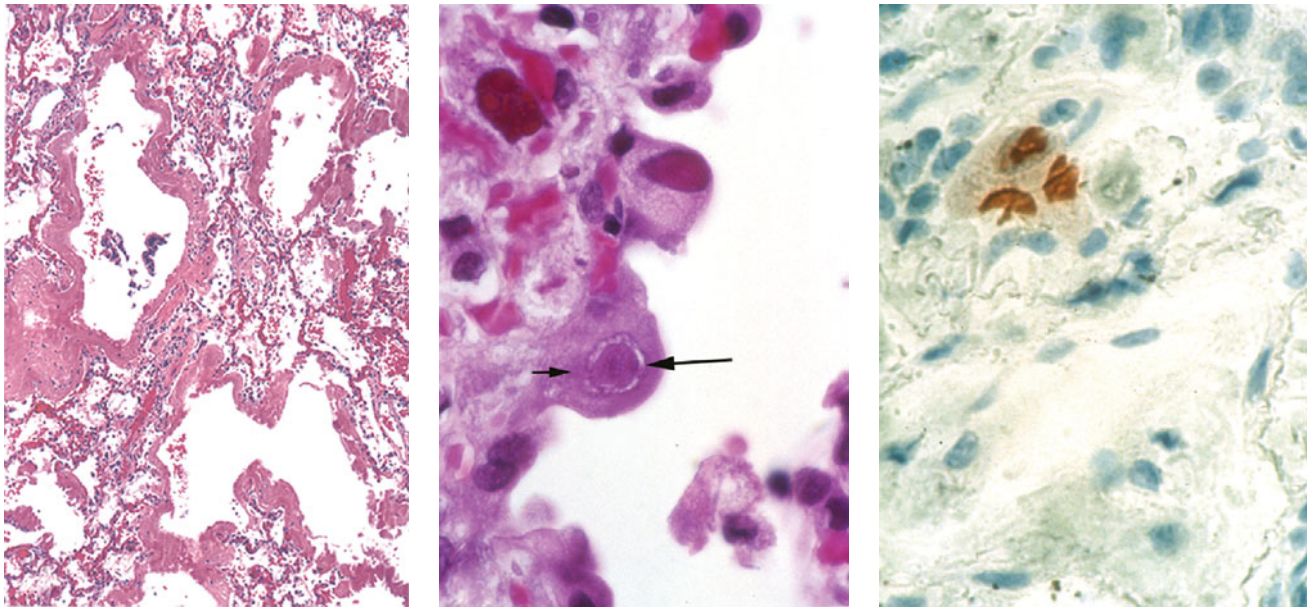
Table 114-6

Tissue Responses to Infection

Type of Inflammation	Example
Exudative inflammation	Pyogenic bacteria
Necrotizing inflammation	Gram-negative bacteria, amebiasis
Granulomatous inflammation	Mycobacteria, fungi
Histiocytic inflammation	*Rhodococcus, Legionella*, Whipple's
Interstitial inflammation	Pneumocystis
Cytopathic changes	Virus
No response	Host anergy

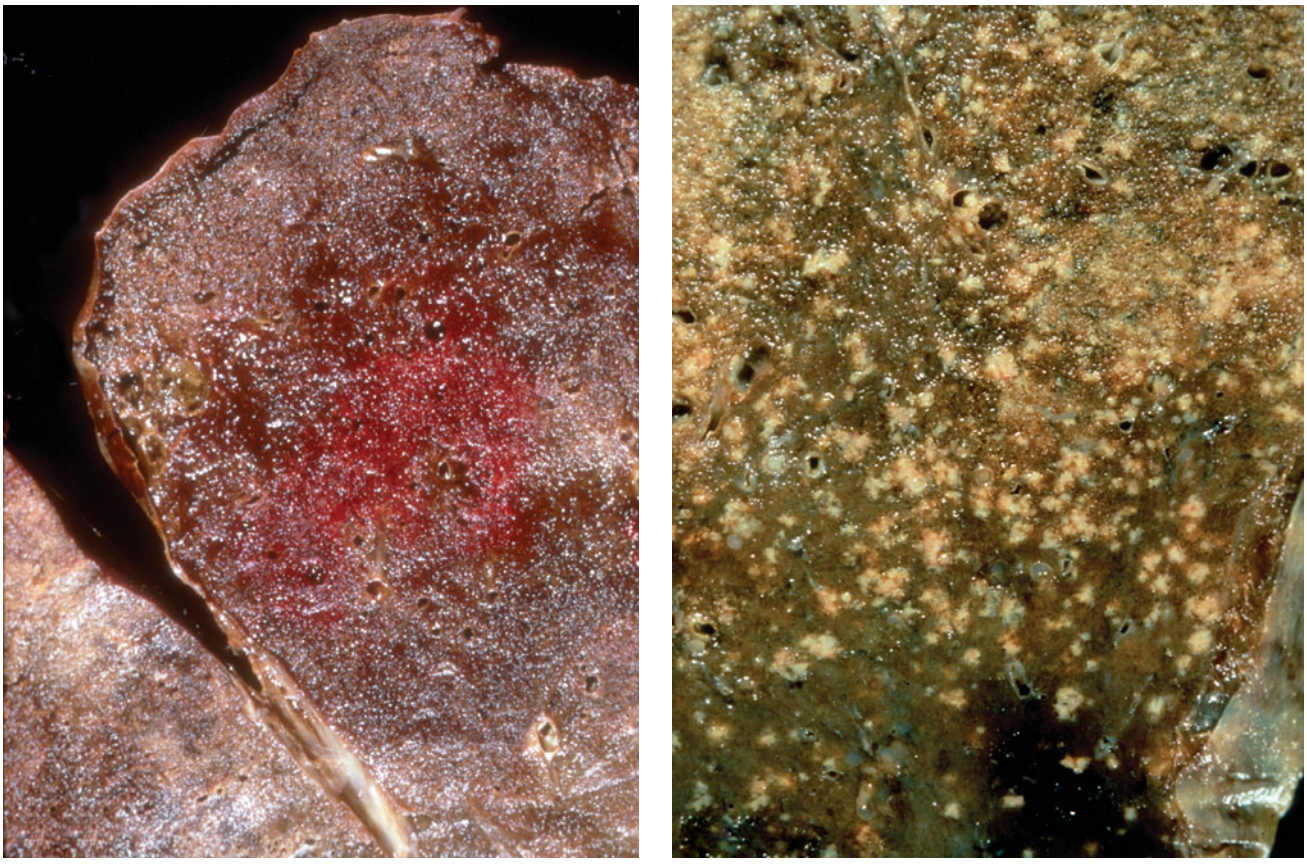
in the lung. *Streptococcal pneumonia* is distinguished by its tendency to produce a non-necrotizing lobar pneumonia, although in the current age of antibiotic treatment, bronchopneumonia is more common. *Klebsiella* sp. classically produces a hemorrhagic lobar pneumonia, with upper lobe predominance (Fig. 114-15). Necrosis of lung tissue with microabscess formation proceeding to cavitation can follow due to infection by aspirated mixed oral flora, *Staphylococcal* sp., *Streptococcal* sp., or gram-negative bacilli.

Herpes simplex virus evokes dense neutrophilic infiltrates in the airways with fibrinoid necrosis and karyorrhexis that histologically mimics bacterial bronchopneumonia (Fig. 114-16). But the presence of characteristic intranuclear viral inclusions distinguishes herpetic from bacterial infection. *Adenovirus* has a propensity to produce ulcerative bronchiolitis and bronchiolitis obliterans organizing pneumonia (BOOP). The characteristic nuclear inclusions disrupt the nuclear membrane to produce diagnostic "smudge cells." Influenza, respiratory syncytial virus (RSV) and parainfluenza viruses can all present as bronchopneumonia with a lymphohistiocytic inflammation or progress to DAD. Mycoplasma and nonvirulent *Chlamydia* produce acute bronchiolitis with



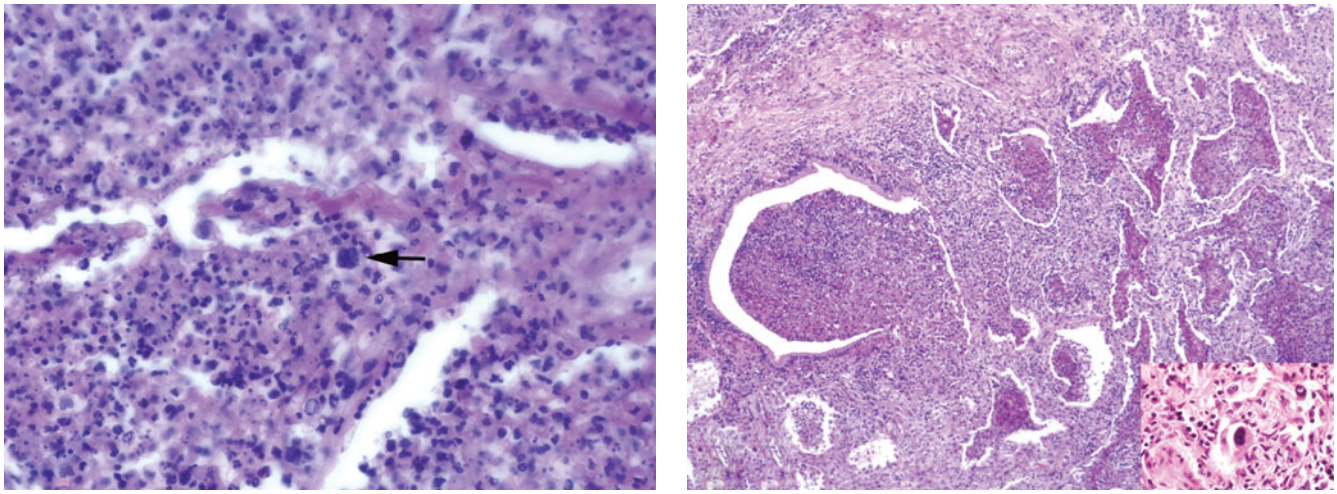
A *B* *C*

Figure 114-14 *A*. The lung in a lethal case of severe acute respiratory syndrome (SARS) shows diffuse alveolar damage with no cytopathic changes. *B*. Cytomegalovirus infection (CMV) with enlarged cell bodies, intranuclear (long arrow) and intracytoplasmic inclusions (small arrow), which are well seen with H&E. *C*. Confirmation can be established by immunohistologic demonstration of nuclear antigen. CMV can produce DAD, bronchopneumonia, or patchy nodular interstitial pneumonitis.



A *B*

Figure 114-15 *A*. Hemorrhagic lobar pneumonia due to *Klebsiella pneumonia*. *B*. Multiple lung abscesses with early cavity formation (arrow) due to methicillin-resistant *Staphylococcal aureus*.



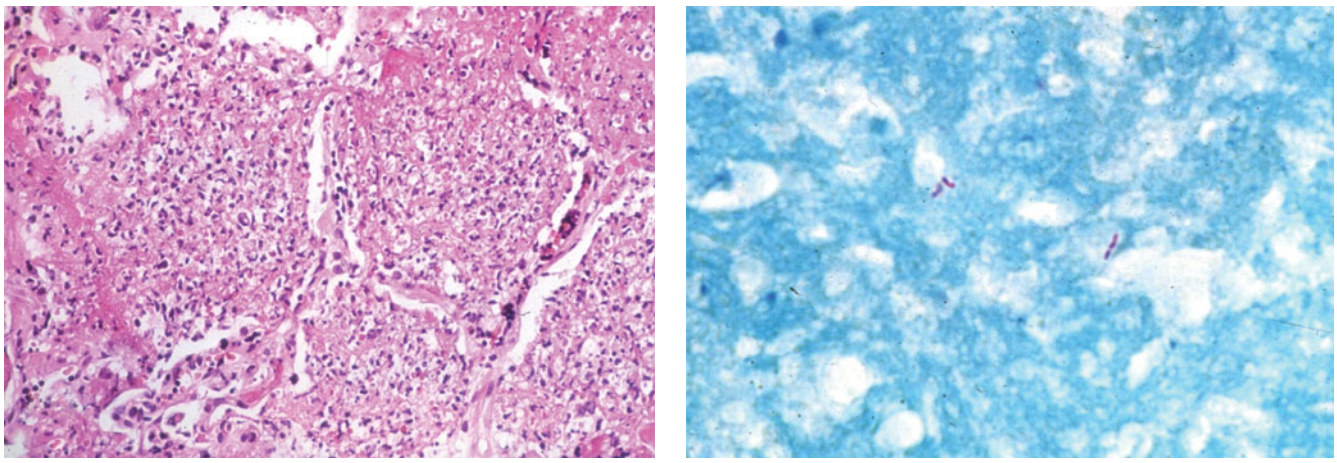
A *B*

Figure 114-16 *A. Herpesvirus-1* bronchopneumonia produces a pyogenic and necrotizing response. Viral inclusions are present (arrow). *B. Adenovirus* causes necrotizing bronchiolitis with surrounding fibrinous pneumonia. A diagnostic "smudge cell" is shown in the inset.

interstitial lymphohistiocytic infiltrates. *Legionella sp.* characteristically exhibits a necrotizing bronchopneumonia with alveolar filling by fibrin and histiocytes (Fig. 114-17). The demonstration of this weakly gram-negative coccobacillus in tissue requires either silver-impregnation techniques or immunohistochemical staining. *L. micdadei* shows positivity on modified Ziehl-Neelsen stains.

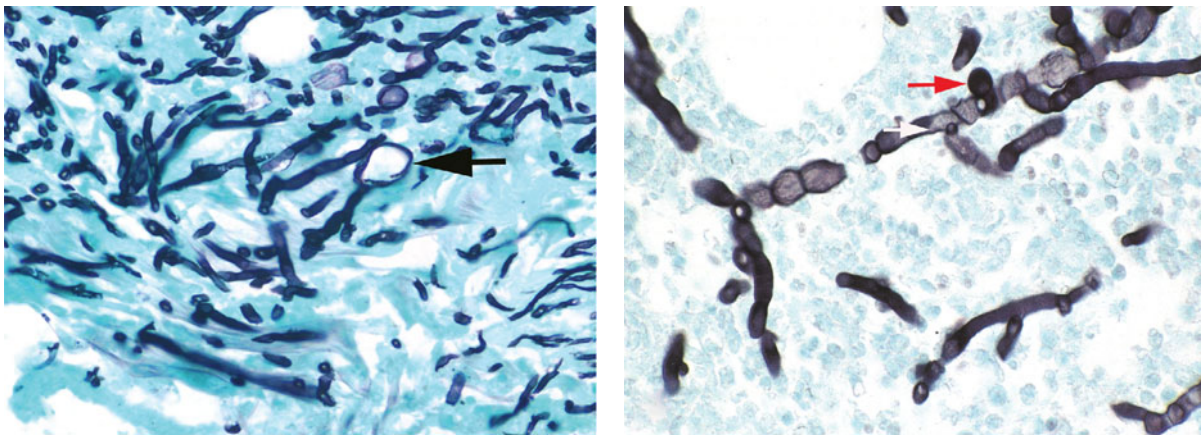
Confluent bronchopneumonia mimicking lobar consolidation is a common finding at autopsy in immunosuppressed patients with fungal infection. Opportunistic molds such as *Aspergillus, Zygomyces, Pseudoallescheria,* and *Fusarium* (Fig. 114-18), often begin as airway infections and then rapidly invade blood vessels. This produces the characteristic gross appearance of a "targetoid" lesion, comprised of central vascular plugging by organisms and surrounding necrotizing fungal pneumonia (Fig. 114-19). Fungal infection due to fungemic spread to the lungs from extrathoracic sites yields a lesion in which the fungi grow radially from a plugged pulmonary arteriole, producing a "sunburst" appearance.

Nematodes that have a larval developmental phase in the lung, e.g., *Ascaris and Strongyloides*, migrate through the airways toward the mouth, where they are either swallowed or expectorated. This process may be associated with wheezing, migratory pneumonia, and blood eosinophilia, a complex of findings termed Loeffler syndrome (Fig. 114-20). The presence of track-like necrotizing granulomatous bronchitis and bronchopneumonia with prominent eosinophilic infiltrates



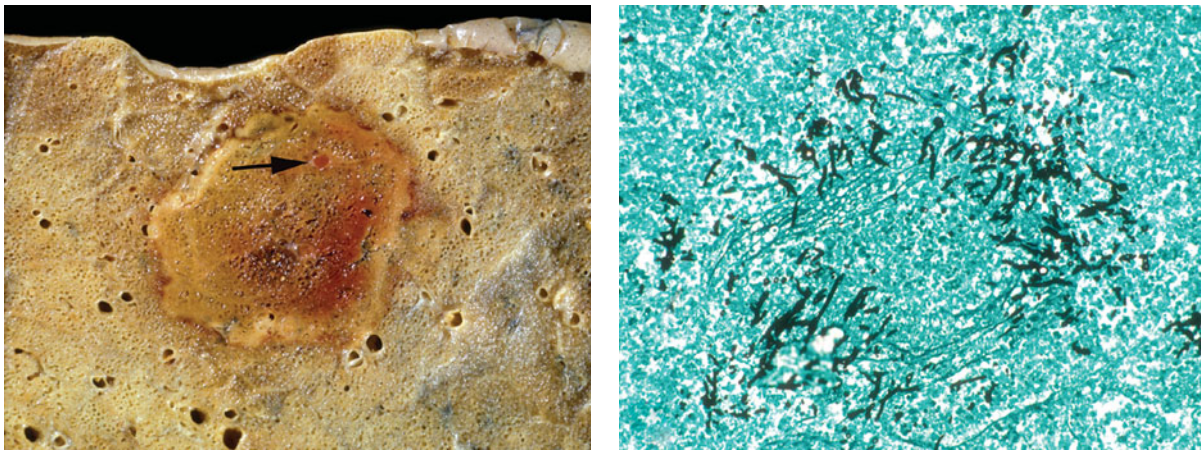
A *B*

Figure 114-17 *A. Legionella pneumophila* characteristically yields a fibrinous and histiocytic bronchopneumonia. Coccobacilli organisms are generally numerous but require silver impregnation for demonstration. *B. L. micdadei* stains with modified Ziehl-Neelsen.



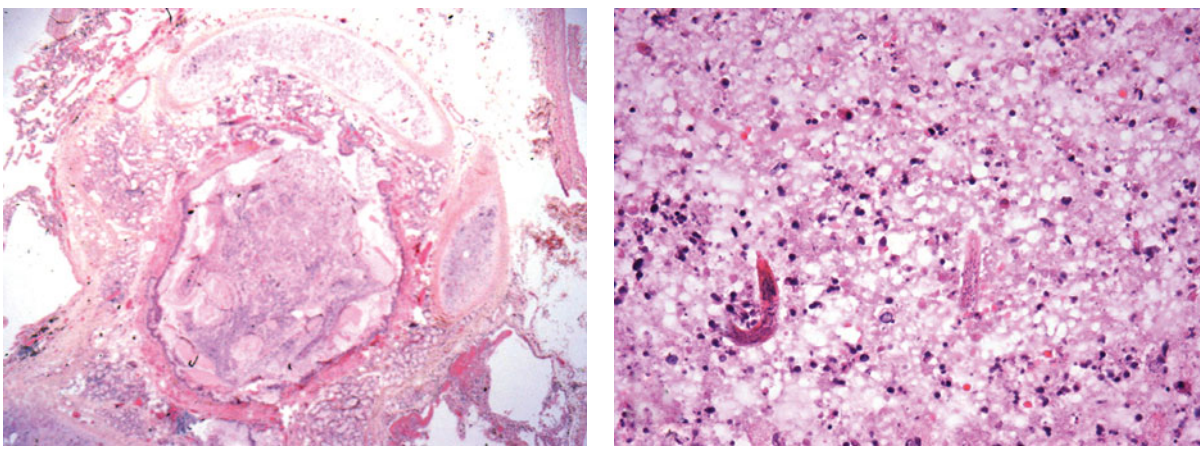
A *B*

Figure 114-18 *A. Pseudallescheria boydii* (*Scedosporium*) at a dehisced anastomotic site of a recent lung transplant. The organism is septate and branching and can be confused with *Aspergillus* sp. In this instance, prominent terminal chlamydospores (arrow), evoking the image of a tadpole, are a distinguishing feature. *B. Fusarium* sp. is septate, shows nonparallel walls, branches predominantly at right angles, and narrows at branch points (white arrow). Blastoconidia can be seen in most cases (red arrow).



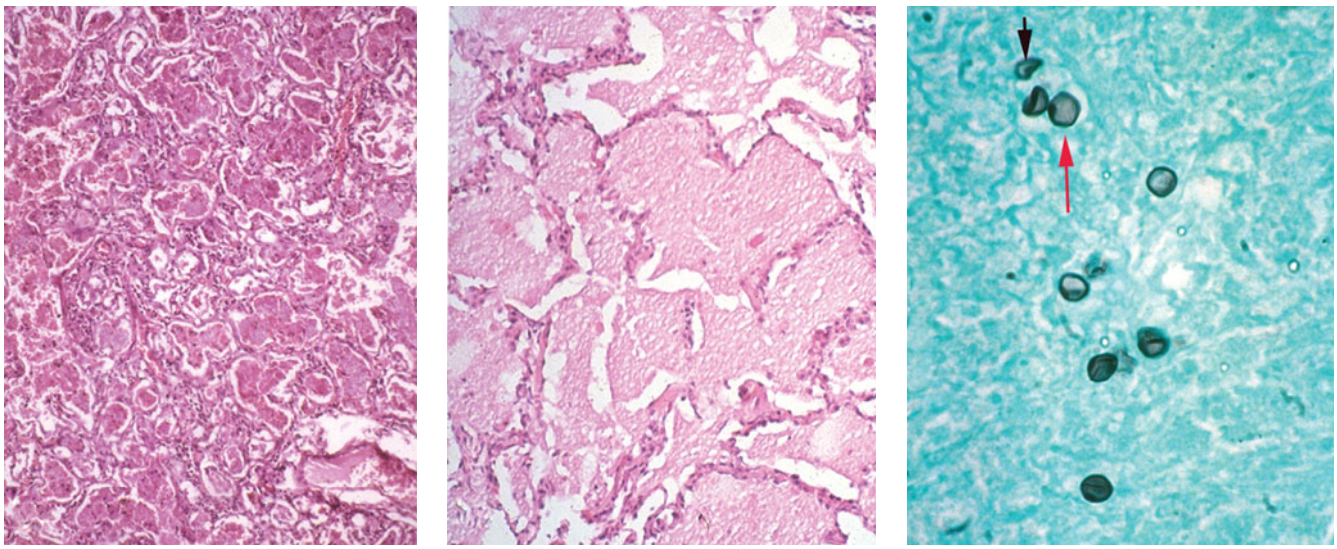
A *B*

Figure 114-19 *A.* Targetoid infarct-pneumonia due to disseminated *Aspergillus fumigatus*. A small vessel is thrombosed (arrow) and the surrounding area shows necrotizing pneumonia. *B.* Branching hyphae of *Aspergillus fumigatus* are seen growing out of a small vessel with GMS.



A *B*

Figure 114-20 *A.* A small airway shows a prominent mucus plug. *B.* High-power reveals larval forms of *Strongyloides.*



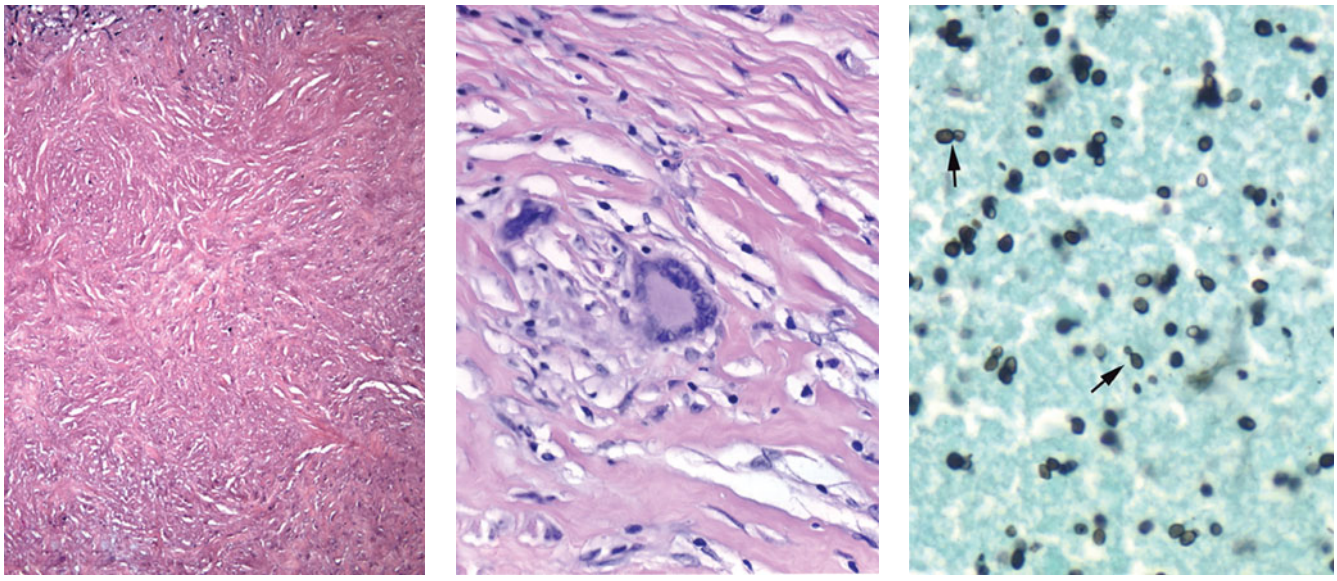
A *B* *C*

Figure 114-21 *A*. The lung in *Pneumocystis jiroveci* pneumonia shows filling of alveolar spaces by eosinophilic frothy material due to the presence of trophozoites. *B*. This appearance can be confused with pulmonary alveolar proteinosis or with fibrinous pulmonary edema (not shown). The organisms of *P. jiroveci* are demonstrated with GMS. Characteristic features include size (4 to 6 μM), absence of budding, "boat"-shaped cysts (white arrow), and pericapsular accentuations (red arrow).

should alert the diagnostic pathologist to the presence of a parasitic pulmonary infection.

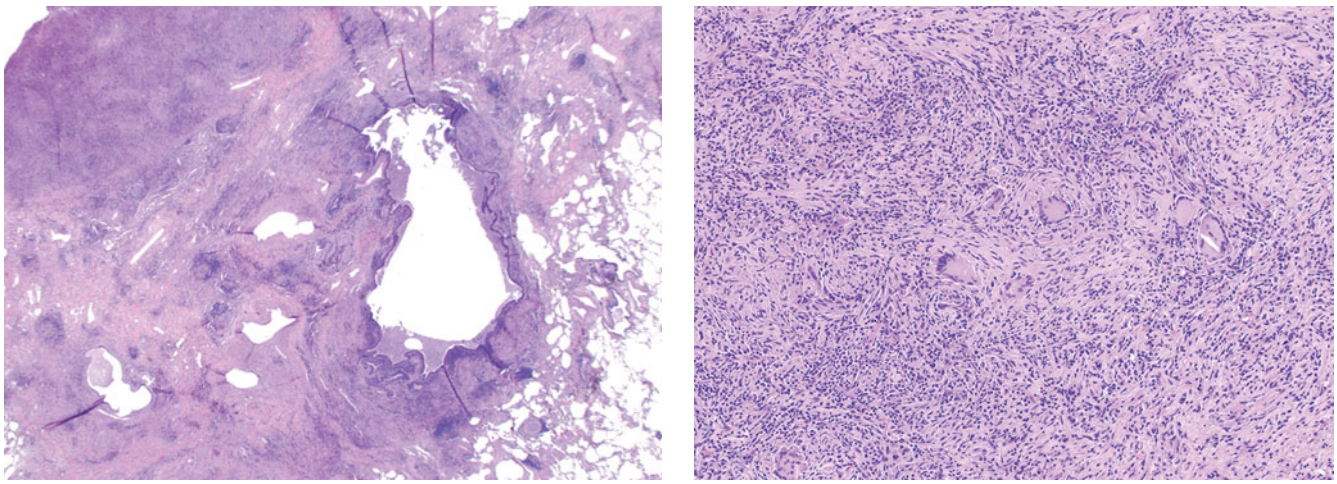
Other Patterns of Inflammation

A variety of other inflammatory reactions are seen in response to infection. *Pneumocystis jiroveci* pneumonia generally shows alveolar filling by a foamy exudate that contains innumerable trophozoites (Fig. 114-21). *Pneumocystis* pneumonia must be morphologically distinguished from pulmonary alveolar proteinosis that also can occur in the immunosuppressed host, as well as from fibrinous pulmonary edema. Necrotizing granulomas and cystic lesions also may be caused by *Pneumocystis* and can easily be mistaken for fungal yeast forms.



A *B* *C*

Figure 114-22 *A*. Chronic infection with *Histoplasma capsulatum* shows a necrotizing granuloma with mummification. *B*. The wall shows a multinucleate giant cell and characteristic paucicellular hyaline fibrosis. The GMS stain reveals multiple 2- to 4-μM yeast, some of which have single narrow-necked buds (arrow).



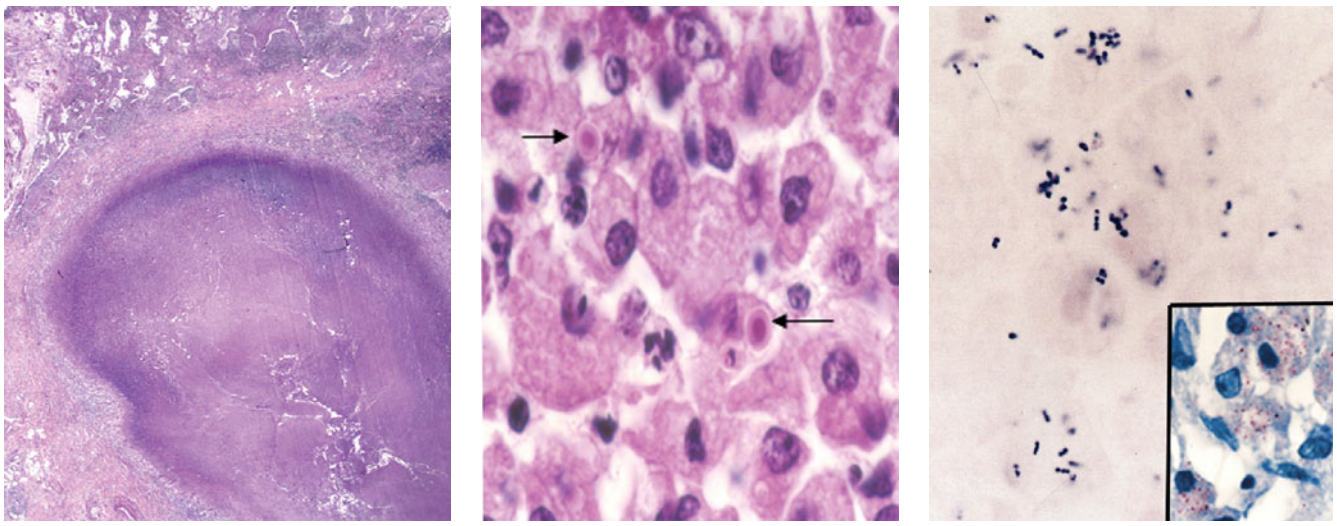
A *B*

Figure 114-23 *A*. A bronchiectatic lung is infected with *Mycobacteria avium/intracellulare* complex (MAC). *B*. The inflammatory response in the non-immunosuppressed host includes primarily non-necrotizing granulomatous inflammation. When areas of necrosis are more prominent, *M. tuberculosis*, or other more virulent atypical mycobacteria, e.g., *M. kansasii*, or an abnormal host response, should be considered.

Granulomatous Inflammation

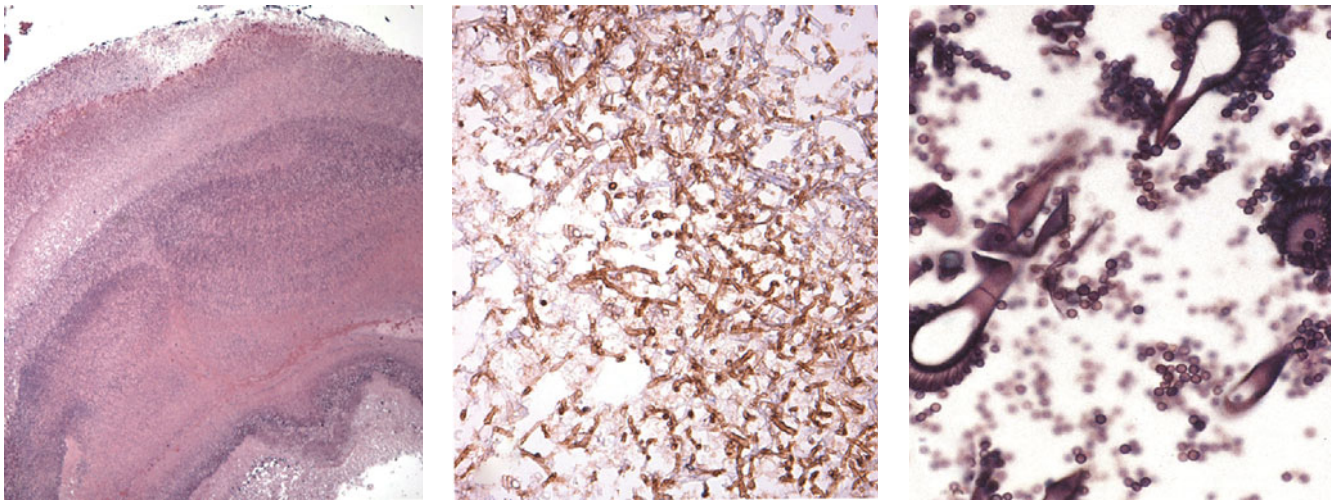
Most necrotizing granulomas in the lung are caused by chronic mycobacterial or fungal infections. However, noninfectious diseases, e.g., Wegener's granulomatosis and rheumatoid nodules, can show comparable morphologic features. *M. tuberculosis* can affect the airways, lung parenchyma, and pleura. Miliary tuberculous granulomas in the lung indicate spread through the pulmonary blood circulation. Tuberculous necrosis destroys the underlying elastic framework of the lung and is generally referred to as "caseous" necrosis, but this term should be restricted to describe the cheesy appearance of the gross lesion. Chronic pulmonary infection with *Histoplasma capsulatum* yields an unusual form of mummifactive necrosis, as well as a dense paucicellular fibrotic response that can, in most instances, be distinguished from tuberculosis (Fig. 114-22). Involvement of regional lymph nodes by *H. capsulatum* can lead to the development of broncholiths or to immune-mediated mediastinal fibrosis.

Atypical mycobacterial infection in the emphysematous or bronchiectatic lung is characterized by a considerable number of non-necrotizing granulomas centered on distorted airways (Fig. 114-23). Necrotizing granulomatous changes



A *B* *C*

Figure 114-24 Patient with HIV-1 infection and (*A*) a cavitary lung nodule due to *Rhodococcus equi*. *B*. The host response includes histiocytic inflammation and small calcified concretions termed Michaelis-Guttmann bodies (arrows). *C*. The organism is a gram-positive coccobacillus that is also positive with the modified Ziehl-Neelsen stain (inset).



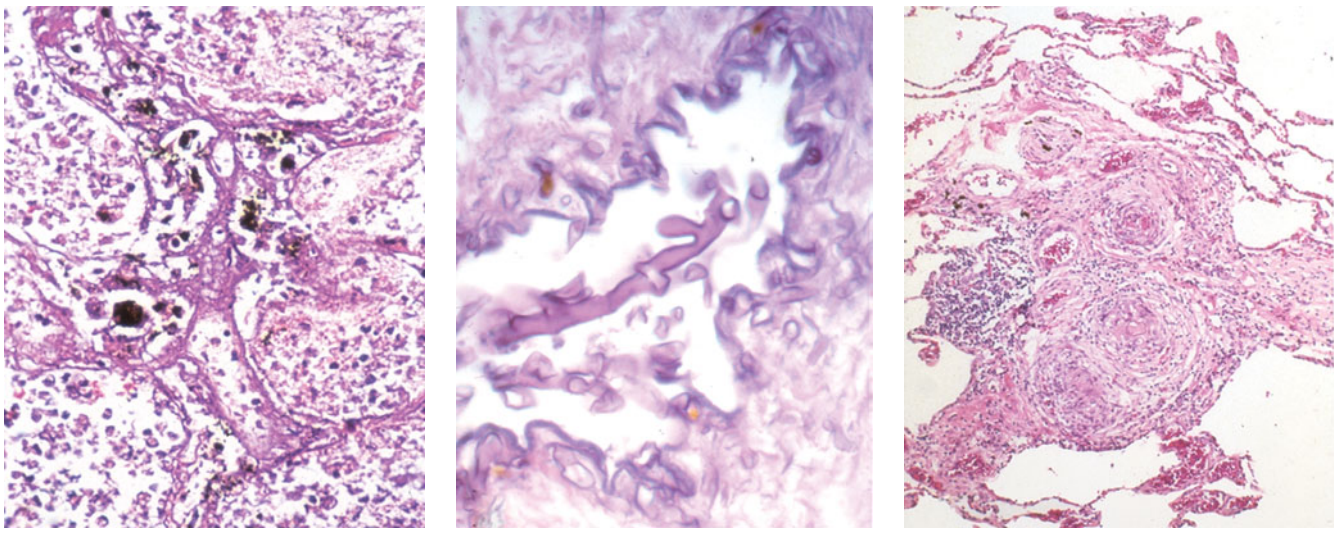
A *B* *C*

Figure 114-25 A fungus ball was identified in an area of cystic bronchiectasis. *A*. The fungus ball shows rings of "zonation" that include distorted fungal mycelial forms. *B*. Specific identification may require immunohistochemical (*Aspergillus* sp.) staining or culture. *C*. Occasionally, the conidial head (fruiting body) is present, which allows for speciation. In this case, the morphology is diagnostic of *Aspergillus fumigatus*.

suggest a more virulent atypical mycobacterial infection, e.g., *M. kansasii* or *M. abscessus*. *Rhodococcus equi*, a gram-positive, weakly acid-fast coccobacillus, can yield necrotizing histiocytic pulmonary inflammation, usually in the immunocompromised host. The host response is distinguished by the presence of microcalcifications termed Michaelis-Guttmann bodies (Fig. 114-24). Amebic pulmonary infection is virtually always the result of extension of a hepatic abscess through the diaphragm. The organisms produce liquefactive necrosis with granulohistiocytic inflammation but no tissue eosinophilia.

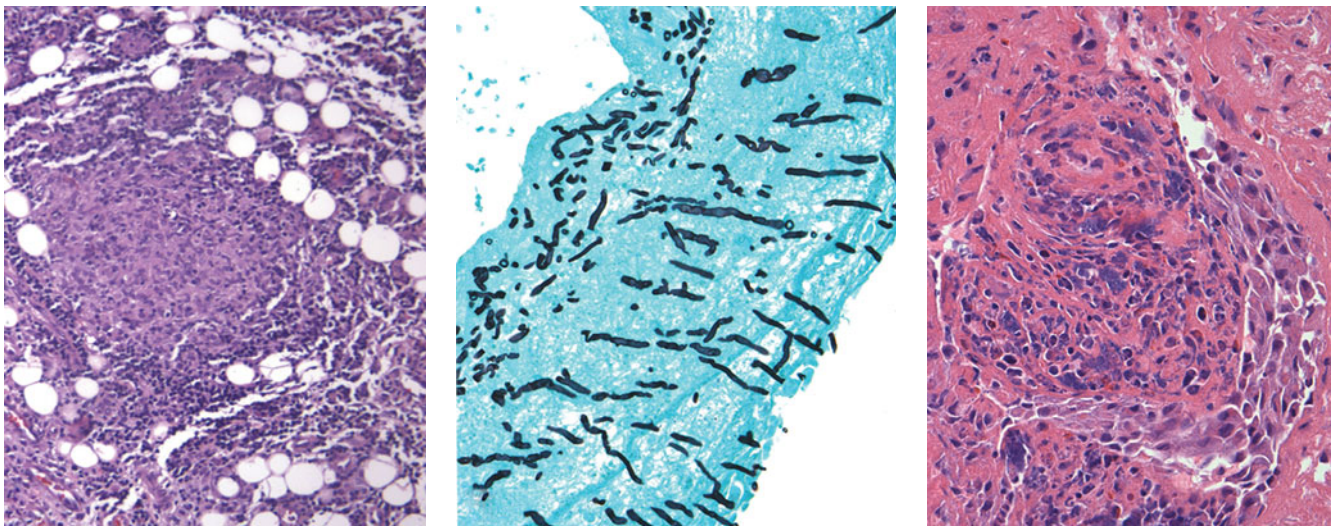
Fungus Balls

Aspergillus, *Pseudallescheria*, and the *Zygomyces* can produce fungus balls within pre-existing areas of lung cystification due to emphysema, old mycobacterial infection, or sarcoidosis (Fig. 114-25). The diagnostic morphologic features of the organisms are distorted by the mycelial growth so that either immunohistological staining or culture is required to establish the specific cause. Occasionally, a conidial fruiting body, which develops only in areas of high oxygen tensions, e.g., a cavity, enables accurate speciation of aspergillus in situ or



A *B* *C*

Figure 114-26 *A. Pseudomonas aeruginosa* pneumonia produces necrotizing microvascular injury. *B*. A small pulmonary vessel contains a club-shaped zygomycosis. *C*. Granulomatous pulmonary arteritis in response to the ova of *Schistosome mansoni*.



A *B* *C*

Figure 114-27 *A*. Tubercle in granulomatous pleuritis due to *M. tuberculosis*. *B*. Eosinophilic pleuritis in patient with *Strongyloides stercoralis*. Although no organisms were identified in the pleura, multiple parasites were identified in the stool. *C*. Multiple *Aspergillus* sp. hyphae are seen with GMS, lining the pleural surface in a young boy with leukemia.

helps to identify the pigmented conidia of *Pseudallescheria boydii*. The presence of birefringent oxalate crystals is particularly common with *A. niger*.

Vascular Inflammation

Blood vessel involvement can occur as a necrotizing vasculitis associated with acute pneumonia in *Pseudomonas* and other gram-negative bacterial infections (Fig. 114-26). Penetration of blood vessels is a dreaded complication of infections by molds, such as *Aspergillus, Pseudallescheria, Fusarium,* and *Mucor* sp., *Rickettsiae* sp., *Bartonella* sp., and spirochetes target blood vessels where they cause endothelialitis. Granulomatous arteritis may be evoked in response to either the ova or larval forms of schistosomes. Unlike the ova of *Paragonimus* sp., schistosome eggs are not birefringent. Pulmonary arterial occlusion with distal ischemic infarction may be caused by the heartworm *Dirofilaria immitis*.

Pleural Infection

Parapneumonic effusions may complicate bacterial pneumonias but are rarely biopsied, unless they lead to empyema or the production of a restrictive rind around the underlying lung. In most instances, an infectious cause has been identified and treated previously, so that identifying viable organisms in situ is uncommon. Mycobacteria, fungi, and parasites yield exudative effusions and necrotizing granulomatous inflammation, and their presence helps to narrow the differential diagnosis, even if organisms are not identified (Fig. 114-27). Tissue eosinophilia may be a clue to the presence of a parasitic infection, but can also occur in fungal and mycobacterial infections, in response to pleural metastases, and following pneumothorax.

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115

Principles of Antibiotic Use and the Selection of Empiric Therapy for Pneumonia

Michael S. Niederman

Antibiotics are the foundation of therapy for respiratory tract infections, but the approach to their use varies with the type of pneumonia present (community acquired, health care–related, or nosocomial), as well as the age of the affected patient, the presence of various co-morbid illnesses and risk factors for infection by specific pathogens, and the severity of the acute illness. For most patients, initial therapy is aimed at a broad spectrum of potential pathogens and is empiric because the infecting pathogen is often not known. Therapy can be more specifically focused on the basis of results of diagnostic tests. In some cases, initial empiric therapy must be continued because no etiologic pathogen is identified. When a pathogen is defined, the term "appropriate" refers to the use of at least one antimicrobial agent that is active in vitro against the etiologic pathogen. The term "adequate" includes not only appropriate therapy, but also the use of that agent in the correct dose, via the right route, given in a timely fashion and with penetration to the site of infection.

Timely and appropriate antibiotic therapy can improve survival in patients with community-acquired pneumonia (CAP) and nosocomial pneumonia [hospital-acquired pneumonia (HAP)], and the benefits are most evident in patients who are not otherwise terminally ill. The term HAP includes pneumonia in nonventilated patients, ventilated patients (VAP), and a new entity health care–associated pneumonia (HCAP). HCAP includes patients coming from nursing homes, those in the hospital for more than 2 days in the past 90 days, those from dialysis centers, or those getting home wound care. Because of their exposure to the health care environment, those with HCAP are at risk for infection with drug-resistant pathogens, and the presence of this entity has blurred the distinction between CAP and HAP, since HCAP patients may reside in the "community," but be infected with organisms very similar to those present in patients with HAP.

In the setting of CAP, effective initial antibiotic therapy is associated with a marked improvement in survival,

compared with ineffective initial therapy, particularly in patients with severe illness. Data on patients with severe CAP provide the most convincing argument for the use of empiric therapy. In several studies, identification of the pathogens causing severe CAP did not lead to an improved survival rate, whereas the use of a broad-spectrum, empiric regimen directed at likely pathogens reduced mortality. In patients with HAP and VAP, survival is improved with the use of antibiotics to which isolated pathogens are susceptible, compared with empiric, nonspecific therapy. In both forms of respiratory infection, the timing of appropriate therapy has also been identified as a determinant of outcome. Patients with CAP have a reduced mortality if initial antibiotic therapy is provided within 4–6 hours of arrival to the hospital. In the treatment of VAP, data show that appropriate therapy should be given as soon as the infection is clinically identified and lower respiratory tract samples have been collected for culture. A delay of at least 24 hours in starting therapy is an important mortality risk factor in VAP.

Even with the use of the correct agents, not all patients recover. The fact that some patients with HAP die in spite of microbiologically appropriate therapy is a reflection of the degree of antibiotic efficacy, as well as a reflection of host response capability (which may have a genetic determination in part), and the fact that not all deaths are the direct result of infection. In some patients with HAP, death is the result of underlying serious illness; the percentage of deaths that occur because of infection, termed the "attributable mortality" of HAP, has been estimated to be as high as 50 to 60 percent. However, the use of timely appropriate antimicrobial therapy can reduce attributable mortality to as little as 20 percent.

In recent years, a number of paradigms for empiric therapy, in the form of guidelines for both CAP and HAP have been developed, but several caveats should be remembered. First, although current guidelines for empiric therapy are evidence based, outcome studies are required to demonstrate their utility in clinical practice.Second, guidelines must be re-evaluated relative to local patterns of antibiotic susceptibility. In the case of CAP, the emergence of penicillin-resistant pneumococcus, community-acquired methicillin-resistant *S. aureus*, and epidemic viral illness (influenza, severe acute respiratory syndrome) may affect the selection of initial therapy, particularly if resistance is prevalent in a specific community. In the setting of HAP, each hospital has its own unique flora and antibiotic susceptibility patterns; a knowledge of such patterns is essential.

This chapter examines the principles underlying antibiotic use, and then discusses the commonly used antibiotics for respiratory tract infections and the principles of empiric therapy for patients with both CAP and HAP.

PRINCIPLES OF ANTIBIOTIC USE

Mechanisms of Action

Antibiotics interfere with the growth of bacteria by undermining the integrity of their cell wall or interfering with bacterial protein synthesis or common metabolic pathways. The terms *bactericidal* and *bacteriostatic* are broad categorizations, and may not apply for a given agent against all organisms, with certain antimicrobials being bactericidal for one bacterial pathogen but bacteriostatic for another. Bactericidal antibiotics kill bacteria, generally by inhibiting cell wall synthesis or interrupting a key metabolic function of the organism. Agents of this type include the penicillins, cephalosporins, aminoglycosides, fluoroquinolones, vancomycin, daptomycin, rifampin, and metronidazole. Bacteriostatic agents inhibit bacterial growth, do not interfere with cell wall synthesis, and rely on host defenses to eliminate bacteria. Agents of this type include the macrolides, tetracyclines, sulfa drugs, chloramphenicol, linezolid, and clindamycin. The use of specific agents is dictated by the susceptibility of the causative organism(s) in a given location to individual antibiotics. However, when neutropenia is present, or if there is accompanying endocarditis or meningitis, the use of a bactericidal agent is preferred. Thus, for most patients with pneumonia, it is not essential to choose a bactericidal agent. One additional consideration is that certain organisms, such as *S. aureus,* can produce toxins, and the optimal agent must be able to not only kill the bacteria, but also inhibit the production of disease-mediating toxins.

Antimicrobial activity is often described by the terms MIC and MBC. The term MIC defines the minimum concentration of an antibiotic that inhibits the growth of 90 percent of a standard-size inoculum, leading to no visible growth in a broth culture. At this concentration not necessarily all the bacteria have been killed. The term MBC refers to the minimum concentration needed to cause a 3-logarithmic decrease (99.9 percent killing) in the size of the standard inoculum, and generally all pathogenic bacteria are killed at this concentration. The MIC is used to define the *sensitivity* of a pathogen to a specific antibiotic, under the assumption that the concentration required for killing (the MIC) can be reached in the serum in vivo. However, these terms must be interpreted cautiously in the treatment of pneumonia, because the clinician must consider the MIC data in light of the penetration of an agent into lung tissues, with some agents achieving higher than serum levels at respiratory sites of infection, and others reaching lower levels.

In recent years, most respiratory infections have been dominated by concerns of antimicrobial resistance, and a new term has emerged, the mutant prevention concentration (MPC). The MPC is defined as the lowest concentration of an antimicrobial that prevents bacterial colony formation from a culture containing greater than 10^{10} bacteria. At lower than MPC concentrations, spontaneous mutants can persist and be enriched among the organisms that remain during therapy. The concept has been most carefully studied with pneumococcus and the fluoroquinolones. In general the MPC is higher than the MIC, implying that it is possible to use an antimicrobial to successfully treat an infection, but not to prevent the remaining organisms (which are not causing illness) from emerging as resistant, and persisting and spreading to other patients.

Penetration into the Lung

The concentration of an antibiotic in the lung depends on the permeability of the capillary bed at the site of infection (the bronchial circulation), the degree of protein binding of the drug, and the presence or absence of an active transport site for the antibiotic in the lung. In the lung, the relevant site to consider for antibiotic penetration is controversial and not clearly defined. Sputum and bronchial concentrations may be most relevant for bronchial infections, whereas concentrations in lung parenchyma, epithelial lining fluid, and cells such as macrophages and neutrophils are probably more important for parenchymal infections. The localization of the pathogen also may be important, and intracellular organisms such as *Legionella pneumophila* and *Chlamydophila pneumoniae* may be best eradicated by agents that achieve high concentrations in macrophages. Local concentrations of an antibiotic must be considered in light of the activity of the agent at the site of infection. For example, antibiotics can be inactivated by certain local conditions. Aminoglycosides have reduced activity at acidic pHs, which may be present in infected lung tissues. In addition, certain bacteria develop resistance by producing destructive enzymes (e.g., β-lactamases), altering the permeability of the outer cell wall, changing the target site of antimicrobial action, or pumping (efflux) of the antimicrobial from the interior of the cell. In all of these conditions, a high local concentration of antimicrobial may help offset the bacterial resistance mechanisms.

The concentration of an antibiotic in lung parenchyma depends on its penetration through the bronchial circulation capillaries. The bronchial circulation has a fenestrated endothelium, so antibiotics penetrate in proportion to their molecular size and protein binding, with small molecules that are not highly protein bound passing readily into the lung parenchyma. When inflammation is present, penetration is further improved. For an antibiotic to reach the epithelial lining fluid, it must pass through the pulmonary vascular bed, which has a nonfenestrated endothelium. This presents an advantage for lipophilic agents, which are generally not inflammation dependent. Agents that are lipophilic and thus inflammation independent for their entry into the epithelial lining fluid include chloramphenicol, the macrolides (including the azalides and ketolides), linezolid, clindamycin, the tetracyclines, the quinolones, and trimethoprim-sulfamethoxazole. Agents that are poorly lipid soluble are inflammation dependent for their entry into the epithelial lining fluid and include the penicillins, cephalosporins, aminoglycosides, vancomycin, carbapenems, and monobactams.

The volume of distribution of an antibiotic reflects the compartment size of its distribution. If this value exceeds 3 L it implies distribution outside of the plasma. The poorly lipid soluble (hydrophilic) drugs diffuse freely into interstitial fluid, but do not penetrate cells. For these agents, only the free, non–protein-bound drug can be distributed out of the plasma. Some lipophilic agents, such as the macrolides and quinolones, are distributed extensively to body tissues, and the serum levels underestimate their effect at sites of infection, an observation that can explain the efficacy of azithromycin, which achieves high intracellular concentrations in phagocytes, can treat pneumonia, but achieves relatively low serum levels. Volume of distribution also can be increased by obesity, and dosing based on ideal body weight may lead to underdosing, although basing doses of hydrophilic antibiotics on total body weight may result in overdosage.

Active transport can facilitate antibiotic entry into lung tissue and phagocytes. Agents that are concentrated in phagocytes in this manner include the macrolides, clindamycin, and the fluoroquinolones. Antibiotics, such as the β-lactams, that are not concentrated in phagocytes by active transport remain in the extracellular space, which constitutes 40 percent of the weight of bronchial tissue; thus, penicillins achieve only about 40 percent of their serum level in lung tissue. Considering all of these factors, some general categories can be established (Table 115-1). Drugs that penetrate well into the sputum or bronchial tissue include the quinolones, newer macrolides and azalides (azithromycin and clarithromycin), ketolides (telithromycin), tetracyclines, clindamycin, and trimethoprim-sulfamethoxazole. On the other hand, the aminoglycosides, vancomycin, and to some extent the β-lactams penetrate less well into these sites. With the use of once-daily aminoglycoside dosing, high peak serum concentrations can be achieved, but the alveolar lining fluid concentration in patients with pneumonia is only 32 percent of the serum level over the first 2 hours, but the two sites have more similar concentrations later in the dosing interval. Since aminoglycosides require high peak concentrations for optimal killing (below), their poor penetration with systemic administration often makes this impossible, suggesting a potential role for delivery by the aerosol route (discussed below).

Table 115-1

Penetration of Antibiotics into Respiratory Secretions

Good Penetration: Lipid Soluble, Concentration Not Inflammation Dependent
Quinolones
New macrolides: azithromycin, clarithromycin
Ketolides (telithromycin)
Tetracyclines
Clindamycin
Trimethoprim/sulfamethoxazole
Poor Penetration: Relatively Lipid Insoluble, Inflammation Dependent for Concentration in the Lung
Aminoglycosides
β-lactams
Penicillins
Cephalosporins
Monobactams
Carbapenems

Antibiotic Pharmacokinetics and Pharmacodynamics

Pharmacokinetics is the study of the absorption, distribution, and elimination of a drug in the body, and the information can be used to describe the concentration in serum. Pharmacokinetics also includes the study of the concentration at other sites of the body, including the site of infection and the relationship between drug concentrations and their pharmacologic or toxic effect. For antibiotics, this means the relationship of antibiotic concentrations at the site of infection, compared with the MIC of the target organism. Pharmacodynamics refers to the action of a drug on the body, including its therapeutic effect.

The way in which an antibiotic reaches the site of infection, considering the frequency of administration and dose administered, can affect its ability to kill bacteria, thus defining a close relationship between pharmacokinetics and pharmacodynamics. Some agents are bactericidal in relation to how long they stay above the MIC of the target organism (time-dependent killing), whereas others are effective in relation to the peak concentration achieved (concentration-dependent killing). If antibiotic killing is time dependent, dosing schedules should be chosen to achieve the maximal time above the MIC of the target organism. Antibiotics of this type include the β-lactams (penicillins and cephalosporins), carbapenems, aztreonam, macrolides, and clindamycin. The rate of killing is saturated once the antibiotic concentration exceeds four times the MIC of the target organism. Therefore, the optimal dosing strategy is to dose often and not let trough concentrations fall below the MIC of the target organism. With these considerations in mind, continuous infusion of β-lactams is under study to optimize treatment with β-lactam agents. In spite of these considerations, for many organisms, the concentration of the antibiotic only needs to be above the MIC for 40 to 50 percent of the dosing interval, and possibly as little as 20 to 30 percent of the interval in the case of carbapenems. For the time-dependent killing drugs listed above, the pharmacodynamic parameter that best predicts clinical efficacy is the time above the MIC.

When killing is concentration dependent, activity is related to how high a concentration is achieved at the site of infection and how great is the AUC, or the "area under the curve" (of drug concentration plotted versus time) in relation to the MIC of the target organism. Alternatively, the action of these agents can be described by how high the peak serum concentration (Cmax) is in relation to the organism MIC. Classic agents of this type include the aminoglycosides and fluoroquinolones, but the ketolides are also concentration-dependent antibiotics. For these types of agents, the optimal killing of bacteria is defined by the ratio of AUC to MIC, often referred to as the area under the inhibition curve, or the AUIC. The target AUIC for gram-negative bacteria is 125 or greater, whereas for most antibiotics that treat pneumococcus, the target value is at least 30. For both the aminoglycosides and quinolones, some studies have shown that efficacy also can be defined by the ratio of peak serum concentrations to MIC (Cmax/MIC), aiming for a target of 12 for quinolones against pneumococcus. Optimal use of these agents would entail infrequent administration but with high doses—the underlying principle behind the once-daily administration of aminoglycosides. With once-daily aminoglycoside dosing regimens, the patient achieves a high peak concentration (maximal killing), and a low trough concentration (minimal nephrotoxicity), relying on the "postantibiotic effect" (PAE) to maintain the efficacy of the antibiotic after the serum (or lung) concentrations fall below the MIC of the target organism. If an antibiotic has a PAE, it is capable of suppressing bacterial growth even after its concentration falls below the MIC of the target organism.

Although most agents exhibit a PAE against gram-positive organisms, a prolonged PAE against gram-negative bacilli is achieved by the aminoglycosides and fluoroquinolones For pneumococcus, a PAE exists for the macrolides/azalides, clindamycin, vancomycin, quinupristin/dalfopristin, tetracyclines, and the oxazolidinones (e.g., linezolid) Most of the agents that kill in a concentration-dependent fashion have a prolonged PAE. Agents with little or no PAE against gram negatives are generally also agents that kill in a time-dependent fashion; thus, they are given several times daily. The β-lactams (including penicillins, cephalosporins, and monobactams) generally have little or no PAE against gram-negatives; one notable exception is imipenem, which has a modest PAE against *Pseudomonas aeruginosa*. In clinical practice, the use of once-daily aminoglycoside dosing has had variable benefits in both efficacy and toxicity, but the advent of this type of dosing regimen follows from an understanding of pharmacodynamic principles.

A phenomenon similar to PAE is termed *postantibiotic leukocyte enhancement* (PALE), which refers to the ability of functioning white blood cells to kill organisms while they are in the postantibiotic phase of growth. Thus, when the patient has functioning neutrophils, the PAE of some agents is extended by their PALE.

Recently, some investigators have suggested that antibiotic therapy be chosen on the basis of another property of certain agents: their ability to stimulate inflammation and cytokine production in response to the presence of the bacterial cell wall lysis products that they generate. It has been known for many years that certain antibiotics liberate bacterial cell wall products that can interact with cytokine-producing cells, stimulating the production of high levels of cytokines such as tumor necrosis factor. In theory, this could lead to the development, or worsening, of the sepsis syndrome in patients immediately after therapy for pneumonia is started, a phenomenon seen in the therapy of *Pneumocystis jiroveci* pneumonia and pneumococcal meningitis, leading to recommendations to use corticosteroids with antibiotics when treating these infections. Other than in these situations, it is unclear if cytokine release is clinically relevant, but bactericidal antibiotics lead to more of a host inflammatory response than bacteriostatic agents; antibiotics that are cell wall active, and kill slowly, have been associated with the greatest cytokine

release. In particular, if an antibiotic has a high affinity for bacterial penicillin-binding protein 3, it may kill slowly and lead to filamentous cell wall products that are potent stimuli for cytokine release. On the other hand, agents that kill rapidly and do not interact with penicillin-binding protein 3 are associated with lower levels of in vitro stimulation of cytokine production by host inflammatory cells. In addition to these considerations, the use of antibiotics that inhibit protein synthesis (linezolid, clindamycin) may have an advantage in toxin-mediated illnesses, such as those caused by certain strains of *S. aureus*, when compared with cell-wall active bactericidal antibiotics.

FEATURES OF SPECIFIC ANTIMICROBIALS USED IN THE THERAPY OF RESPIRATORY TRACT INFECTIONS

Macrolides (Including Azalides) and Tetracyclines

Macrolides are bacteriostatic agents that bind to the 50S ribosomal subunit of the target bacteria and inhibit RNA-dependent protein synthesis. The macrolides traditionally have had good activity against pneumococci, as well as atypical pathogens (*C. pneumoniae, M. pneumoniae, Legionella*), but the older erythromycin-like agents are not active against *H. influenzae*, and have poor intestinal tolerance, so prolonged therapy is difficult. The new agents in this class include azithromycin (also referred to as an azalide) and clarithromycin. These agents have enhanced activity against *H. influenzae* (including β-lactamase–producing strains), although on an MIC basis, azithromycin is more active. Erythromycin is active against *Moraxella catarrhalis,* although the new agents have enhanced activity against this pathogen. Among the new macrolides, azithromycin is more active against not only *H. influenzae* and *M. catarrhalis*, but also *M. pneumoniae* than clarithromycin. On the other hand, clarithromycin is more active against *S. pneumoniae, Legionella,* and *C. pneumoniae.*

Both of the newer agents have better intestinal tolerance than erythromycin and penetrate well into sputum, lung tissue, and phagocytes. Clarithromycin, which has an active 14-hydroxy metabolite that is antibacterial, is administered twice a day orally at a 500 mg dose for 7 to 10 days in the treatment of CAP and acute exacerbations of chronic bronchitis (AECB). A new preparation of extended-release clarithromycin is administered as a 1000 mg dose once daily and has been effective as a 7-day course of therapy for AECB. Azithromycin has a longer half-life than clarithromycin, and concentrates in tissues, achieving very low serum levels when administered orally. The dosing regimen for CAP is usually 500 mg daily for 3 days in outpatients, but a recent extended release preparation allows the administration of 2000 mg as a one-time dose for CAP. For the hospitalized patient, an intravenous preparation of azithromycin is available and is dosed as 500 mg daily, with the duration defined by the clinical course of the patient, but usually for 7 to 10 days. Because of its intravenous administration, the serum levels achieved have been adequate for the therapy of bacteremic pneumococcal pneumonia.

Clinical studies of CAP have consistently shown a benefit of using macrolide therapy, usually in conjunction with a β-lactam, but the mechanism for this favorable effect is not known. Speculation has included the possibility of atypical pathogen co-infection, a possibility supported by studies that have found the benefit of the addition of macrolides to vary over the course of time. Another explanation has been that macrolides have anti-inflammatory effects, which may explain their benefit in improving quality of life in patients with cystic fibrosis. Macrolides have a myriad of other effects, including the interference with "quorum sensing" between bacteria, which could inhibit the in vivo proliferation of *Pseudomonas aeruginosa* after colonization has occurred.

Although macrolides remain an important therapeutic option for community respiratory tract infections, pneumococcal resistance is becoming increasingly common, being present in as many as 35 to 40 percent of all pneumococci, especially in patients who have received an agent of this class in the past 3 months. In addition, macrolide resistance also can co-exist with penicillin resistance, and as many as 30 to 40 percent of penicillin-resistant pneumococci are also erythromycin resistant. The clinical relevance of these in vitro findings remains to be defined. However, there are two forms of pneumococcal macrolide resistance, one involving efflux of the antibiotic from the bacterial cell, and the other involving altered ribosomal binding of the antibiotic. The former mechanism is associated with much lower levels of resistance than the latter, and is present in two-thirds of the macrolide resistant pneumococci in the United States. The latter form of resistance is fortunately less common, because if present, it is unlikely that macrolide therapy for pneumococcal infection would be effective.

The tetracyclines are also bacteriostatic agents that act by binding the 30S ribosomal subunit and interfering with protein synthesis. These agents can be used in CAP because they are active against *H. influenzae* and atypical pathogens, but in the United States pneumococcal resistance to tetracyclines may be approaching 20 percent, and may exceed 50 percent among organisms with high-level penicillin resistance. Photosensitivity is the major side effect, limiting the use of these agents in sun-exposed patients.

Ketolides

This new class of antimicrobials is a semisynthetic derivative of the macrolides, with a 14-member ring structure, and substitution of a keto group at the C3 site. These agents act to inhibit ribosomal protein synthesis in bacteria, by binding to two different sites on the 50S ribosomal subunit, and because of enhanced binding affinity and the binding to multiples sites, may be able to avoid some of the resistance problems associated with the macrolides. In addition, this class

of antibiotics has a poor affinity for the pneumococcal efflux pump. Because of these characteristics, ketolides are active against pneumococci that are macrolide resistant by either the efflux or ribosomal mechanism. Ketolides are also active against *H. influenzae*, but in vitro activity is not quite as high as with azithromycin, and efficacy in AECB is an area that requires further data. In addition, these agents have activity against the atypical pathogens. In clinical trials, one ketolide, telithromycin, has been evaluated and has been dosed at 800 mg daily for 5 days in the therapy of AECB and 7 to 10 days for CAP, with good efficacy. Side effects are primarily intestinal, with nausea and diarrhea occurring in some patients, but visual disturbances, liver function abnormalities (including rare cases of liver failure), and electrocardiographic QT prolongation have been reported.

Trimethoprim-Sulfamethoxazole (TMP-SMX)

This combination antibiotic has been used as a mainstay for the therapy of *P. jiroveci* pneumonia, and in the past was an effective agent for CAP and AECB because of its antimicrobial spectrum, ease of use, and low cost. It has bactericidal activity against pneumococcus, *H. influenzae,* and *M. catarrhalis*, but not against atypical pathogens. Recently, it has become less popular because of the emergence of pneumococcal resistance at rates of at least 30 percent, since 80 to 90 percent of organisms that are penicillin resistant are also resistant to TMP-SMX. The sulfa component of the drug inhibits the bacterial enzyme responsible for forming the immediate precursor of folic acid, dihydropteroic acid. Trimethoprim is synergistic with the sulfa component because it inhibits the activity of bacterial dihydrofolate reductase. TMP-SMX is available in a fixed combination of 1:5 (TMP:SMX), and is dosed as either 80/400 mg or 160/800 mg orally twice a day for 10 days, but the dosage should be adjusted in renal failure. An intravenous preparation is also available. Side effects generally result from the sulfa component and include rash, gastrointestinal upset, and occasional renal failure (especially in elderly patients).

β-Lactam Antibiotics

These bactericidal antibiotics have in common the presence of a β-lactam ring, which is bound to a five-membered thiazolidine ring in the case of the penicillins and a six-membered dihydrothiazine ring in the case of the cephalosporins. Modifications in the thiazolidine ring can lead to agents such as the penems (imipenem, ertapenem, and meropenem), whereas absence of the second ring structure characterizes the monobactams (aztreonam). These agents also can be combined with β-lactamase inhibitors such as sulbactam, tazobactam, or clavulanic acid, to create the β-lactam/β-lactamase inhibitor drugs. These agents extend the antimicrobial spectrum of the β-lactams by providing a substrate (sulbactam, clavulanic acid, tazobactam) for the bacterial β-lactamase, thereby preserving the antibacterial activity of the parent compound. β-Lactam antibiotics work by interfering with the synthesis of bacterial cell wall peptidoglycans by binding to bacterial penicillin binding proteins.

The penicillins used for respiratory tract infections include the natural penicillins (penicillin G and V), aminopenicillins (ampicillin, amoxicillin), anti-*Staphylococcal* agents (nafcillin, oxacillin), anti-*Pseudomonal* agents (piperacillin, ticarcillin), and β-lactam/β-lactamase inhibitor combinations (ampicillin/sulbactam, amoxicillin/clavulanate, piperacillin/tazobactam, and ticarcillin/clavulanate). Among the anti-*Pseudomonal* penicillins, piperacillin is the most active agent.

The cephalosporins span from first to fourth generation. The earlier agents generally were active against gram-positives, but did not extend activity to the more complex gram-negatives, or anaerobes, and were susceptible to destruction by bacterial β-lactamase. The newer generation agents generally are more specialized, with broad-spectrum activity, and more mechanisms to resist breakdown by bacterial enzymes. The second generation and newer agents are resistant to bacterial β-lactamase, but recent data suggest that cefuroxime may not be an optimal pneumococcal agent if resistance is present. On the other hand, the third generation agents such as ceftriaxone and cefotaxime are reliable and active against penicillin resistant pneumococci, whereas ceftazidime is not reliable against pneumococcus, but is active against *P. aeruginosa*. The third-generation agents may induce β-lactamases among certain gram-negatives (especially the *Enterobacteriaceae* spp.), and thus promote the emergence of resistance during monotherapy. The fourth-generation agent, cefepime, is active against pneumococci and *P. aeruginosa*, but is also less likely to induce resistance among the *Enterobacteriaceae* than the third-generation agents.

Imipenem and meropenem are the broadest spectrum agents in this class, being active against gram-positives, anaerobes, and gram-negatives, including *P. aeruginosa*. They have shown efficacy for patients with severe pneumonia, both community-acquired and nosocomial. A non-*Pseudomonal* carbapenem, ertapenem, is also available and has been used effectively in the therapy of CAP. Aztreonam is a monobactam that is so antigenically different from the rest of the β-lactams that it can be used in penicillin-allergic patients. It is only active against gram-negative organisms, having a spectrum very similar to the aminoglycosides.

Fluoroquinolones

These bactericidal agents act by interfering with bacterial DNA gyrase and/or topoisomerase IV, leading to impaired DNA synthesis repair, transcription, and other cellular processes, resulting in bacterial cell lysis. DNA gyrase is only one form of a bacterial topoisomerase enzyme that is inhibited by quinolones, and activity against other such enzymes is part of the effect of a variety of quinolones. The earlier quinolones (e.g., ciprofloxacin and ofloxacin) are active primarily against DNA gyrase, which accounts for their good activity against gram-negatives. The newer agents (gemifloxacin, levofloxacin, and moxifloxacin) bind both DNA

gyrase and topoisomerase IV, and have extended their activity to gram-positives, including drug-resistant *Streptococcus pneumoniae* (DRSP). Resistance to quinolones can occur through mutations in the topoisomerase enzymes, by altered permeability of the bacterial cell wall, or efflux of the antibiotic from the inside of the bacteria. The quinolones kill in a concentration-dependent fashion, and thus optimal antibacterial activity can be achieved with infrequent dosing, and high peak concentrations and high ratios of either AUC/MIC or Cmax/MIC. In addition, because quinolones have a postantibiotic effect (PAE) against both gram-positive and -negative organisms, they can continue to kill even after local concentrations fall below the MIC of the target organism. These properties make the quinolones well suited to infrequent dosing, with the ideal being once-daily dosing, particularly given the relatively long half-life of the newer compounds. The only factor limiting a switch to once-daily dosing for all quinolones is the toxicity associated with high doses of some agents (e.g., ciprofloxacin), particularly concerns related to neurotoxicity and possible seizures.

Two features of quinolones make them well suited to respiratory infections. First, they penetrate well into respiratory secretions and inflammatory cells within the lung, achieving local concentrations that often exceed serum levels. Thus, these agents may be clinically more effective than predicted by MIC values. This may explain the observation that quinolones are often better than other agents in prolonging the "disease-free" interval between exacerbations of COPD, a finding that has been demonstrated for moxifloxacin and gemifloxacin. Second, these agents are highly bioavailable with oral administration and thus similar serum and tissue levels can be reached if administered orally or intravenously. This allows for some "borderline" patients (e.g., nursing home patients) with pneumonia to be managed with outpatient oral therapy and maintain high therapeutic levels in the serum. In addition, the high bioavailability of these agents permits an easy transition from intravenous to oral therapy of inpatients with pneumonia, facilitating early discharge when the patient is clinically improving, and permitting ongoing oral therapy with maintenance of high serum levels.

The fluoroquinolones have excellent antimicrobial activity against β-lactamase–producing *H. influenzae* and *M. catarrhalis,* making them very useful for patients with AECB. However, the newer agents (gemifloxacin, levofloxacin, and moxifloxacin) extend the activity of the quinolones by having enhanced gram-positive activity, as well as by being more active against *C. pneumoniae* and *M. pneumoniae*, compared with older agents. The new agents are also highly effective against *L. pneumophila* and may be the drug of choice for this organism. However, if *P. aeruginosa* is the target organism (as it is in certain patients with CAP, AECB, and HAP), then only ciprofloxacin (750 mg twice-daily orally or 400 mg every 8 hours intravenously) or levofloxacin (750 mg orally or intravenously daily) are active enough for clinical use. Since the older agents, ciprofloxacin and levofloxacin, have borderline activity against the pneumococcus, if they are used for AECB or CAP, the dose probably should be optimized to either 750 mg twice daily of ciprofloxacin for AECB or 750 mg once daily of levofloxacin for CAP or AECB.

Among the newer agents, their in vitro activity against pneumococcus is variable, with the agents listed in the order of most to least active (on an MIC basis) as gemifloxacin, moxifloxacin, and levofloxacin. All of these agents also have long half-lives, generally allowing for once-daily dosing, although the half-lives of these drugs vary from as short as 6 hours for levofloxacin, to as long as greater than15 hours for moxifloxacin and gemifloxacin. The agents also differ in the degree of protein binding, with agents that have a low degree of binding having higher free concentrations in the serum. The relevance of this feature to clinical outcome is uncertain, but agents like levofloxacin and moxifloxacin are not highly protein bound. Although the new agents are highly active against pneumococci, both penicillin-sensitive and -resistant organisms, there is some concern that with widespread use, pneumococcal resistance to these agents will increase, especially since recent data show that many pneumococci (up to 20 percent) have quinolone-resistance determinant genes present, but have not yet developed full resistance. However, with continued selection pressure due to widespread use, this may become an important clinical problem. With this in mind, pneumococci are more likely to be resistant to the agents with the lowest pneumococcal activity, and in parts of Asia pneumococcal resistance to quinolones has already developed at much higher rates than in North America, particularly to levofloxacin, and especially among patients who have been given repeated courses of therapy with this agent. Other risk factors for quinolone resistance among pneumococci are recent hospitalization and residence in a nursing home.

One major distinction among these new quinolones is their profile of toxic side effects. A number of agents have been removed from clinical use because of toxicities such as QT prolongation (grepafloxacin), phototoxicity (sparfloxacin), and liver necrosis (trovafloxacin). The side effects of the other new agents have been acceptable generally, but as with any therapy, the risks of use should be weighed against the benefits. There have been reports of drug-induced hypoglycemia, which may be a quinolones class-effect, but this problem is most common with gatifloxacin and has led to removal of this agent from clinical use. A recent study comparing moxifloxacin with levofloxacin in elderly hospitalized patients with CAP, and a high frequency of heart disease, showed comparable safety, including a low frequency for both drugs, of cardiac arrhythmias and *Clostridium difficile* diarrhea.

In clinical trials, all of the newer agents have been effective in the therapy of AECB with 5 days of therapy. In CAP, therapy is usually for 7 to 14 days, but levofloxacin at 750 mg daily can be used for 5 days. Levofloxacin, but not moxifloxacin, is renally excreted, and thus need dosage adjustment in patients with renal insufficiency. Currently there are no good studies of severe CAP showing efficacy of any of the quinolones as monotherapy, although in both nosocomial pneumonia and AECB, monotherapy has been tested and shown to be effective.

Aminoglycosides

These bactericidal agents act by binding to the 30S ribosomal subunit of bacteria, thus interfering with protein synthesis. Aminoglycosides have primarily a gram-negative spectrum of activity and are usually used in combination with other agents targeting difficult organisms such as *P. aeruginosa* or other resistant gram-negatives. When combined with certain β-lactam agents they can achieve antibacterial synergy against *P. aeruginosa.* Amikacin is the least susceptible to enzymatic inactivation by bacteria, whereas tobramycin is more active than gentamicin against *P. aeruginosa.* Aminoglycosides penetrate poorly into lung tissue, and can be inactivated by acid pHs, which are common in pneumonic lung tissue. Thus, in a clinical trial of nosocomial pneumonia therapy, the use of an aminoglycoside with a β-lactam was no more effective than a β-lactam alone, and the combination regimen was not more effective in preventing the emergence of *Pseudomonal* resistance during therapy than was the monotherapy regimen with a β-lactam. In the treatment of bacteremic *Pseudomonal* pneumonia, aminoglycoside combination therapy may be more effective than monotherapy. Recent meta-analysis has suggested that the use of combination therapy with an aminoglycoside is of limited value, and may simply add to the risk of nephrotoxicity.

As discussed, aminoglycosides kill in a concentration-dependent fashion, and can be dosed once daily to optimize killing while minimizing toxicity (primarily renal insufficiency). In clinical practice, this has not been proved to occur, and once-daily dosing is comparable in efficacy and nephrotoxicity to multiple-dose regimens. When aminoglycosides are used, it is necessary to monitor serum levels to minimize the occurrence of acute renal failure. Peak concentrations correlate with efficacy, but only have meaning with multiple daily doses, and their utility in once-daily regimens has not been established. Trough concentrations are monitored to minimize toxicity and probably should be followed regardless of dosing regimen.

Because of poor penetration into tissues, some investigators have used nebulized aminoglycosides for the therapy and/or prevention of gram-negative pneumonia. This approach is discussed below.

New Agents Active Against Methicillin-Resistant *S. aureus*

In the past several years, methicillin-resistant *S. aureus* (MRSA) has emerged as an important pathogen in patients with nosocomial pneumonia, particularly ventilator-associated pneumonia (VAP), and recently has been described as a potential pathogen in patients with necrotizing post-influenza pneumonia. In the past, vancomycin was the agent used most commonly for this pathogen. However, there have been concerns about the limited efficacy of vancomycin, primarily because of its poor penetration into respiratory secretions. Linezolid the first agent in a new antibiotic class, the oxazolidinones, is active against MRSA, and also may block the production of antibacterial toxins, such as the Panton-Valentine leukocidin, which can be produced by community MRSA strains. The oxazolidinones act to inhibit bacterial protein synthesis, by binding to the 50S ribosomal subunit, and preventing the binding of transfer RNA and the formation of the 70S initiation complex.

Linezolid is not only active against MRSA, but also drug-resistant *Streptococcus pneumoniae*, and vancomycin-resistant enterococci (VRE) (both *Enterococcus faecium* and *Enterococcus faecalis*). The agent has high bioavailability; thus, serum levels are the same with oral or IV therapy. Renal and nonrenal clearance occur, and dosing adjustment is not needed for patients with renal failure. Efficacy has been shown for nosocomial pneumonia and CAP, but one recent analysis suggested that linezolid may be superior to vancomycin for the therapy of VAP that is proved to be caused by MRSA. Side effects are not common and include nausea, diarrhea, anemia, and thrombocytopenia (especially with prolonged use). It is also a weak monoamine oxidase inhibitor.

Quinupristin/dalfopristin has been tested in patients with VAP and was not as effective against MRSA as vancomycin, in spite of good in vitro activity. Several other agents in various stages of development have activity against MRSA, but they are not yet proved to be useful for the therapy of respiratory tract infections. These include daptomycin, which has been shown to be inactivated by pulmonary surfactant, thus explaining its lack of efficacy in pneumonia therapy trials. Tigecycline is available for non-respiratory tract infections, and its efficacy in the therapy of pneumonia is not yet known, although it does have in vitro activity against MRSA and many gram-negatives, including *Acinetobacter* spp., but not *P. aeruginosa.* Other agents currently in development are dalbavancin and telavancin.

Aerosolized Antibiotics for Respiratory Tract Infections

Local administration of antimicrobials has been used in the therapy of bronchiectasis, especially in the setting of cystic fibrosis and the therapy of ventilator-associated pneumonia. This approach is used to enhance the delivery of agents to the site of respiratory infection, especially for antibiotics that penetrate poorly into the lung. Direct delivery of antibiotics is usually achieved by nebulization, and this approach not only achieves high intrapulmonary concentrations, but may do so with low systemic absorption, and thus a reduced risk of systemic toxicity. The majority of studies of inhaled antibiotics have been done in nonventilated patients with cystic fibrosis, and chronic bronchial infection with *Pseudomonas aeruginosa*, and have used nebulized tobramycin, which has been shown to both improve pulmonary function, as well as decrease the density of *P. aeruginosa* in sputum and thus reduce the risk of hospital admission. The use of this approach in mechanically ventilated patients has been proposed for patients with either infectious tracheobronchitis or VAP, since both infections can involve highly resistant gram-negative bacteria, and the local delivery of antibiotics may effectively treat some pathogens that cannot be eradicated by systemic therapy.

In mechanically ventilated patients, local antibiotic administration by instillation or nebulization has been used to prevent pneumonia. In general, this is not a recommended approach, because even when it has been successful, there has been concern about the emergence of multidrug resistant gram-negatives in those who subsequently do develop infection, and these organisms may be difficult to treat. Most studies in this population have involved either the aminoglycosides or polymyxin B. Only one prospective randomized trial has examined the impact of the adjunctive use of locally instilled tobramycin with intravenous agents in the management of VAP. Although the addition of endotracheal tobramycin did not improve clinical outcome compared with placebo, microbiologic eradication was significantly greater in the patients receiving aerosolized antibiotics.

In spite of these data, sporadic small and uncontrolled series have shown that when patients have VAP due to multidrug-resistant *Pseudomonas aeruginosa* or *Acinetobacter* spp., aerosolized aminoglycosides, polymyxin, or colistin may be helpful as adjunctive therapy to systemic antibiotics. One side effect of aerosolized antibiotics has been bronchospasm, which can be induced by the antibiotic or the associated diluents present in certain preparations. A specially formulated preparation of tobramycin for aerosol administration was designed to avoid this complication.

Although the optimal method of administration of aerosol therapy is unknown, most studies have shown that nebulization can be effective and achieve more uniform distribution than direct instillation. When aerosol therapy is used in mechanically ventilated patients, it must be carefully synchronized with the ventilator cycle, and the optimal delivery device is not yet defined. In an animal model, investigators found that using an ultrasonic nebulizer placed in the inspiratory limb of the ventilator circuit, proximal to the "Y-connector," up to 40 percent of the administered dose can be retained in the lung, achieving tissue concentrations ten times higher than can be achieved with comparable doses given systemically, and with minimal systemic absorption. To optimize delivery, inspiratory time may need to be as high as 50 percent of the ventilatory cycle and routine humidification should be stopped during antibiotic administration. In ventilated patients, the ventilator may need to be set with a tidal volume of 8 to 10 ml/kg, with no humidification system in use during the use of the ultrasonic nebulizer which should be set to deliver 8 L/min.

Table 115-2

Common Pathogens Causing CAP in Specific Patient Popoulations (in Order of Decreasing Frequency)

Outpatient, No Cardiopulmonary Disease or Modifying Factors *S. pneumoniae, M. pneumoniae, C. pneumoniae* (alone or as mixed infection), *H. influenzae*, respiratory viruses, others (*Legionella sp., M. tuberculosis*, endemic fungi)
Outpatient, with Cardiopulmonary Disease and/or Modifying Factors* All of the above plus: DRSP, enteric gram-negatives, and possibly anaerobes (with aspiration)
Inpatient, with Cardiopulmonary Disease and/or Modifying Factors* *S. pneumoniae* (including DRSP), *H. influenzae, M. pneumoniae, C. pneumoniae*, mixed infection (bacteria plus atypical pathogen), enteric gram-negatives (which can include *P. aeruginosa*), anaerobes (aspiration), viruses, *Legionella* sp., others (*M. tuberculosis*, endemic fungi, *Pneumocystis jerovici*)
Inpatient, with No Cardiopulmonary Disease or Modifying Factors All of the above, but DRSP and enteric gram-negatives are not likely. These patients are rarely admitted to the hospital.
Severe CAP, with no Risks for *P. Aeruginosa* *S. pneumoniae* (including DRSP), *Legionella* sp., *H. influenzae*, enteric gram-negative bacilli, *S. aureus, M. pneumoniae*, respiratory viruses, others (*C. pneumoniae, M. tuberculosis* endemic fungi)
Severe CAP, with Risks for *P. Aeruginosa* All of the pathogens above, plus *P. aeruginosa*

** Some patients in this category are now classified as having HCAP if they have risk factors such as: hospitalization in an acute care hospital for two or more days within 90 days of the infection; those residing in a nursing home or long-term care facility; those who have received recent intravenous antibiotic therapy, chemotherapy, or wound care within the past 30 days of the current infection; or individuals who have attended a hospital or hemodialysis clinic.*

PRINCIPLES OF THERAPY FOR RESPIRATORY TRACT INFECTIONS

Community-Acquired Pneumonia

Selection of Initial Therapy

Empiric therapy is selected by categorizing patients on the basis of place of therapy (outpatient, inpatient, intensive care unit), severity of illness, and the presence or absence of cardiopulmonary disease or specific "modifying" factors that make certain pathogens more likely (Table 115-2). In the current guidelines for CAP management, patient risk factors for infection with drug-resistant pneumococcus, enteric gram-negatives, and *P. aeruginosa* have been identified. By using these factors, a set of likely pathogens can be predicted for each type of patient and this information can be used to guide therapy. If a specific pathogen is subsequently identified by diagnostic testing, then therapy can be focused. Risk factors, or "modifying factors" that increase the risk of infection with DRSP are: age greater than 65 years, β-lactam therapy within

the past 3 months, alcoholism, immune suppressive illness (including therapy with corticosteroids), multiple medical comorbidities, and exposure to a child in day care. The modifying factors for enteric gram-negatives include residence in a nursing home, underlying cardiopulmonary disease, multiple medical comorbidities, and recent antibiotic therapy. The risk factors for *P. aeruginosa* infection are structural lung disease (bronchiectasis), corticosteroid therapy (greater than 10 mg prednisone per day), broad-spectrum antibiotic therapy for more than 7 days in the past month, and malnutrition. In addition, there are a number of other clinical conditions that are associated with specific pathogens, and these associations should be considered in all patients when obtaining a history. Examples include the association between *S. aureus* and post-influenza pneumonia, *H. influenzae* with underlying COPD, and oral anaerobes with the presence of poor dental hygiene.

Empiric therapy for outpatients with no cardiopulmonary disease or modifying factors should be with a new oral macrolide (azithromycin or clarithromycin) or a tetracycline. Although erythromycin has been used for these patients, its value is limited by its lack of coverage of *H. influenzae*, and a higher frequency of intestinal complications (nausea, vomiting) than with the newer macrolides. Therapy with an anti-pneumococcal quinolone (gemifloxacin, levofloxacin, or moxifloxacin) is not necessary in these outpatients, because they are not at risk for organisms, such as DRSP and enteric gram-negatives. However, outpatients with cardiopulmonary disease and/or modifying factors, should not receive macrolide monotherapy, but should be treated with either a selected oral β-lactam (cefpodoxime, cefuroxime, high-dose ampicillin [3 grams daily] or high-dose amoxicillin/clavulanate [up to 4 g daily]) combined with a macrolide or alternatively, they can receive monotherapy using an oral antipneumococcal quinolone (gemifloxacin, levofloxacin, or moxifloxacin). The ketolide telithromycin also can be used in this population as oral monotherapy for patients at risk for DRSP, but only if the patient has no risk factors for aspiration or for enteric gram-negatives but concerns about lung toxicity have limited its clinical utility.

For the non-ICU inpatient, therapy can be with an intravenous macrolide (azithromycin) alone, provided that the patient has no underlying cardiopulmonary disease, and no risk factors for infection with DRSP, enteric gram-negatives or anaerobes. Although very few patients of this type are admitted to the hospital, macrolide monotherapy has been documented to be effective in this patient population. Since the majority of inpatients have cardiopulmonary disease and/or modifying factors, they should treated with either a selected intravenous β-lactam (cefotaxime, ceftriaxone, ampicillin/sulbactam, or ertapenem) combined with a macrolide, or alternatively, monotherapy with an intravenous anti-pneumococcal quinolone (levofloxacin, or moxifloxacin) can be administered. From the available data, it appears that either regimen is therapeutically equivalent, and although not proved, it may be useful to use these two types of regimens interchangeably, striving for "antibiotic heterogeneity," but being sure to select an agent in a different class from what the patient received in the past 3 to 6 months. Recent data have shown that if patients have received a macrolide, quinolones, or penicillin in the past 3 months, then a subsequent infection with pneumococcus is more likely to be resistant to the agent received in the past, than to other agents. Although oral quinolones may be as effective as intravenous quinolones for admitted patients with moderately severe illness, most admitted patients should receive initial therapy intravenously to be sure that the medication has been absorbed. Once the patient shows a good clinical response, oral therapy can be started. Selected inpatients with mild to moderate disease can be treated initially with the combination of an intravenous β-lactam and an oral macrolide, switching to exclusively oral therapy once the patient shows a good clinical response.

In the ICU population, all individuals should be treated for DRSP and atypical pathogens, but only those with appropriate risk factors (see above) should have coverage for *P. aeruginosa*. As mentioned quinolone monotherapy has not been established as safe or effective for these patients, and monotherapy should not be used in any ICU admitted CAP patient. Those without *Pseudomonal* risk factors, should be treated with a selected intravenous β-lactam (cefotaxime, ceftriaxone, or ertapenem), combined with either an intravenous macrolide or an intravenous quinolone. For patients with *Pseudomonal* risk factors, therapy can be with a two-drug regimen, using an anti-*Pseudomonal* β-lactam (cefepime, imipenem, meropenem, or piperacillin/tazobactam) plus ciprofloxacin or high-dose levofloxacin, or alternatively, with a three-drug regimen, using an anti- *Pseudomonal* β-lactam plus an aminoglycoside plus either an intravenous non- *Pseudomonal* quinolone or macrolide.

Other Therapeutic Issues

In addition to the general approach to therapy outlined above, CAP patients need timely administration of initial antibiotic therapy. Retrospective data have shown a reduced mortality for admitted CAP patients who are treated within 4–6 hours of arrival to the hospital, compared with those who are treated later. However, it is uncertain if these outcomes are related to the timing of therapy or whether the timeliness of antimicrobial administration is a surrogate marker of other relevant factors. In the empiric therapy of CAP, there is a limited need for routine therapy against MRSA; however, a new strain of this organism has been described to cause a severe, necrotizing form of CAP after influenza. Although the frequency of this organism is still low, vigilance is needed to see how common it becomes in the future. The algorithms presented above suggest that all patients should receive empiric therapy that provides coverage for atypical pathogens. As mentioned, this recommendation is based on outcome studies, and may be explained by a high frequency of atypical pathogen co-infection. In fact, even with bacteremic pneumococcal pneumonia, mortality is reduced when a β-lactam is used with a macrolide, compared with when it is used as

monotherapy. Another emphasis of the recommendations for empiric therapy is to use a highly active agent in all patients with risk factors for infection with DRSP. The reason for this recommendation is because if a patient is at risk for infection with DRSP, the use of a highly active agent is not only likely to minimize the risk of treatment failure, but may also rapidly and reliably eradicate pneumococcal organisms that have even low levels of resistance, so that there is less selection pressure for the emergence of organisms with higher level of resistance.

Hospital-Acquired Pneumonia

How to Initiate Responsible Empiric Therapy (Table 115-3)

Many studies have documented that mortality in HAP is increased if initial empiric therapy is incorrect, or if there is a delay in the initiation of therapy. In the American Thoracic Society/Infectious Disease Society (ATS/IDSA)guideline for HAP, the terms "appropriate" and "adequate" therapy were defined. Appropriate refers to the use of an antibiotic that is active in vitro against the identified pathogen, the term "adequate" refers to not only using an antibiotic to which the organism is sensitive, but also using that therapy without delay, in the right doses, having it penetrate to the site of infection, and using combination therapy, if needed. For example, for critically ill patients with normal renal function who were effectively treated for nosocomial pneumonia in clinical trials, the correct doses, of common antibiotics include: cefepime 1 to 2 g every 8 to 12 hours; imipenem 500 mg every 6 hours, or 1 g every 8 hours; meropenem 1 g every 8 hours, piperacillin-tazobactam 4.5 g every 6 hours; levofloxacin 750 mg daily or ciprofloxacin 400 mg every 8 hours; vancomycin 15 mg/kg every 12 hours, leading to a trough level of 15 to 20 mg/L; linezolid 600 mg every 12 hours; and aminoglycosides of 7 mg/kg per day of gentamicin or tobramycin and 20 mg/kg of amikacin. However, it is still a challenge to use antibiotics adequately, without using them too widely, and

Table 115-3

Principles of Antibiotic Therapy for Hospital-Acquired Pneumonia

Prompt empiric therapy: Initiate when there is clinical suspicion of infection
Obtain a lower respiratory tract culture (sputum, tracheal aspirate, protected brush, BAL) prior to initiation of antibiotic therapy. Samples can be obtained bronchoscopically or nonbronchoscopically, cultured quantitatively or semiquantitatively.
Use a narrow spectrum agent for patients only at risk for infection with "core pathogens," and with no risk factors for MDR pathogens. Options include: ceftriaxone, ampicillin/sulbactam, ertapenem, levofloxacin, or moxifloxacin. For penicillin allergiy, use a quinolone or the combination of clindamycin and aztreonam.
Use combination therapy with a broad spectrum regimen, containing at least two antimicrobials in patients with risk factors for MDR pathogens. Specific choices should be guided by a knowledge of local microbiology patterns. Use an aminoglycoside or an antipneumococcal quinolone (ciprofloxacin or high dose levofloxacin), PLUS an anti-*Pseudomonal* β-lactam such as: cefepime, ceftazidime, imipenem, meropenem or piperacillin-tazobactam. If there is concern about MRSA, add either linezolid or vancomycin
Use the correct therapy in recommended doses (see text).
Choose an empiric therapy that uses agents from a different class of antibiotics than the patient has received in the past 2 weeks.
Try to de-escalate to monotherapy after initial combination therapy, after reviewing culture data and clinical response. If *Pseudomonas aeruginosa*, consider stopping the aminoglycoside after 5 days and finish with a single agent to which the organism is sensitive. If a non-*Pseudomonal* infection, switch to a single agent that the organism is sensitive to, using: imipenem, meropenem, cefepime, piperacillin/tazobactam, ciprofloxacin, or high-dose levofloxacin.
The drug of choice for *Acinetobacter* is a carbapenem, but colistin should be oonsidered if there is carbapenem resistance.
Consider linezolid as an alternative to vancomycin in patients with proven MRSA VAP, those with renal insufficiency, and those receiving other nephrotoxic medications (e.g., an aminoglycoside).
Consider adjunctive aerosolized aminoglycosides in patients with highly resistant gram-negative pathogens.

thus promoting antibiotic resistance, which is often driven by antibiotic use. Thus, the guideline emphasizes the need for a "de-escalation" strategy of usage, that generally urges prompt broad-spectrum empiric therapy whenever there is a clinical suspicion of infection, in order to avoid a delay of therapy, combined with a commitment to focus, narrow the spectrum, reduce the duration of therapy, or stop therapy once culture and clinical response information become available. Several studies have shown that it is possible to effectively treat VAP with 6 to 8 days of therapy, provided that the initial therapy is appropriate. The optimal duration of therapy for infections caused by *P. aeruginosa* and MRSA is still uncertain, but prolonged therapy may be no better than short duration therapy, in the absence of bacteremia.

Algorithms for Initial Empiric Therapy

Once there is a clinical suspicion of HAP, the antibiotic choice falls into either a narrow spectrum of therapy or a broad-spectrum regimen, directed at multi-drug resistant (MDR) pathogens. The narrow spectrum approach is used if the patient has a pneumonia that started in the first 4 days of hospitalization and there are no other risk factors for MDR pathogens. Risk factors include recent antibiotic therapy within the past 90 days, immunosuppressive illness or therapy (corticosteroids or chemotherapy), admission to a unit with a high rate of MDR organisms, recent hospitalization for two or more days within the past 90 days, residence in a nursing home or long-term care facility (i.e., the presence of HCAP); or regular visits to a hospital clinic or hemodialysis center. All others receive a broad-spectrum therapy approach.

The narrow spectrum therapy is directed at the "core pathogens," such as non-resistant enteric gram-negatives, pneumococcus,*H. influenzae*, and methicillin-sensitive *S. aureus*. Recommended regimens are usually monotherapy with ceftriaxone, ampicillin/sulbactam, ertapenem, levofloxacin, or moxifloxacin. If the patient is penicillin allergic, a quinolone can be used, or the patient can get the combination of clindamycin and aztreonam. When the patient has risk factors for MDR pathogens, therapy is directed at not only the core pathogens, but also *P. aeruginosa, Acinetobacter* spp., and in many instances MRSA. To provide this spectrum of coverage, patients need to receive at least two, and often three antibiotics. The recommended therapy is to use either an aminoglycoside or an anti-*Pseudomonal* quinolone (ciprofloxacin or levofloxacin) in combination with an anti-*Pseudomonal* β-lactam (cefepime, ceftazidime, imipenem, meropenem, or piperacillin-tazobactam). If there are concerns about MRSA because of risk factors, a high local prevalence, or the presence of gram-positives on a gram stain of lower respiratory tract secretions, then a third agent, either linezolid or vancomycin, should be added.

The use of combination therapy is controversial, and as mentioned, there are limited data to show that the use of an aminoglycoside with a β-lactam is more effective than β-lactam monotherapy. Dual therapy may have value if the patient is neutropenic, or if *Pseudomonal* bacteremia is present, but both situations are uncommon. Thus, the most compelling reason for using empiric combination therapy in patients with suspected MDR pathogens, is to provide a broad enough spectrum of agents to increase the likelihood that the initial therapy was appropriate. Once the organism is identified, it is possible to de-escalate, and if an aminoglycoside was used with a β-lactam, the maximal benefit may have been achieved after 5 days of dual therapy, and thus the aminoglycoside usually can be stopped at that point. Similarly, If a non-resistant gram-negative is identified, therapy can be with a single agent, and the ones that have been shown to be effective for critically ill mechanically ventilated patients are: ciprofloxacin, levofloxacin, imipenem, meropenem, piperacillin/tazobactam, and cefepime. Thus, it is usually possible to de-escalate to monotherapy with one of these agents as soon as culture data become available, or after 5 days of dual therapy with an aminoglycoside, if *P. aeruginosa* has been identified.

Other Principles of Antibiotic Usage for Hospital-Acquired Pneumonia

In general, it is necessary to use an agent as empiric therapy that is in a different class of antimicrobial than the patient has recently received. A number of studies of HAP have demonstrated that recent therapy with an antibiotic (within the past 2 weeks) predicts a greater frequency that pathogens such as *P. aeruginosa* will be resistant to the agents recently used. This applies to β-lactams, as well as to quinolones. In addition, some studies have shown that quinolones promote not only gram-negative resistance to quinolones, but also to β-lactams, and that their use can cause resistance to many types of β-lactam antimicrobials. With this in mind, it may be better not to use quinolones for a first episode of hospital infection, since it may make both β-lactams and quinolones less effective for a subsequent infection. If quinolones are not used for a first episode of infection, there will be more options available if the patient develops a second infection while in the hospital.

In the management of HAP, as clinical and microbiologic data become available, it is often possible to de-escalate therapy in the form of using less drugs, using agents of narrower spectrum, stopping therapy, or reducing the duration of therapy. The key decision point for manipulating therapy is on day 2 to 3 when a decision can be made about whether the patient is improving or not. This decision is made by assessing clinical features such as fever, leukocytosis, purulence of secretions, radiographic patterns, and oxygenation. In general, the best clinical predictor of response is improvement in oxygenation, which usually occurs by day 3 in survivors of VAP, but not in nonsurvivors. If the patient is improving, then cultures should be checked, and efforts made to de-escalate and shorten duration of therapy. In some instances, all signs of pneumonia are gone by day 2 to 3, respiratory cultures are negative and in retrospect, the diagnosis was heart failure or atelectasis, and antibiotics can be completely stopped.

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Vaccination against Pulmonary Infections

Michael S. Simberkoff

Vaccines are an important, often recommended means of preventing pulmonary infections. There are several reasons to encourage their use.

1. Pulmonary infections, such as pneumonia, are associated with substantial morbidity. For example, recent data from the National Center for Health Statistics showed that respiratory diseases accounted for 11 percent of the hospitalizations in the United States during 2003. During that year, there were more than 1.4 million discharges from acute, non-federal health care facilities in the United States with pneumonia as the first diagnosis. The average length of stay for patients hospitalized with pneumonia was 5.5 days. Pneumonia disproportionately affects the elderly. In the study cited above, the rate of hospitalization for pneumonia for those who were 65 years of age or older was 224 per 10,000, over four times the rate in the population as a whole. In another population-based study conducted in the state of Washington, the rate of community-acquired pneumonia was 52.3 cases per 1000 person years among patients older than 85 years of age.
2. Pneumonia and influenza are, overall, the seventh leading causes of death in the United States, ranking behind heart, malignant, cerebrovascular, and chronic lower-respiratory tract diseases, accidents and diabetes mellitus. In 2003, the age-adjusted death rate for pneumonia in the United States was 21.4 per 100,000 population.
3. Pulmonary pathogens are increasingly resistant to commonly used antibiotics, even when acquired in the community. For example, investigators from the Centers for Disease Control and Prevention (CDC) recently reported that 24 percent of the bacteremic pneumococcal strains isolated during 1998 were resistant to penicillin and that 14 percent were resistant to multiple other antibiotics. Both of these numbers increased significantly during the period from 1995 to 1998. There was considerable variation in the prevalence of drug-resistant pneumococcal isolates from different parts of the United States, different age groups, and different racial backgrounds. Drug resistance was most common among the isolates from patients residing in Tennessee and Georgia, from patients who were very young and very old, and from white as compared to black patients.
4. Vaccines that are licensed for use in the United States are remarkably safe. Most produce transient local or mild and infrequent systemic reactions (described below).
5. The licensed vaccines are effective in preventing pulmonary infections and their complications. However, efficacy may vary in different patient populations. Specific examples will be discussed under individual vaccines.
6. Vaccines are generally inexpensive, whereas the pulmonary infections they prevent are often expensive to diagnose and treat. Further, infected patients are often unable to work for extended periods. Thus, use

of vaccines to prevent pulmonary infections is cost-effective for individual patients, employers, insurers, and society.

VACCINES AGAINST BACTERIAL PULMONARY PATHOGENS

A number of microorganisms infect the lungs including a diverse group of bacteria, mycobacteria, mycoplasma, chlamydia, viruses, and some fungi. *Streptococcus pneumoniae* is the most commonly recognized cause of severe community-acquired pneumonia (CAP), occurring in 20 to 50 percent of cases. *Haemophilus influenzae*, *Legionella* species, and *Moraxella catarrhalis* are isolated in 3 to 10 percent of cases.

Vaccines against four pulmonary pathogens are available (Table 116-1). These are the *S. pneumoniae* (pneumococcal) polysaccharide and protein-polysaccharide conjugate vaccines, the *H. influenzae*, type *b* protein-polysaccharide conjugate vaccines, the *Bordetella pertussis* vaccines (whole cell and acellular), and the live bacille Calmette-Guérin (BCG) vaccine.

Pneumococcal Vaccines

The pneumococcal vaccines are designed to elicit protective antibodies against the strains of *S. pneumoniae* that are commonly associated with invasive infection. At present, 83 pneumococcal serotypes are recognized by serological reactions with their capsular polysaccharide. Included among these are 19 serogroups consisting of 2 to 4 antigenically related serotypes. A 14-valent pneumococcal polysaccharide vaccine was licensed in the United States in 1977, a 23-valent polysaccharide vaccine was licensed in 1983, and a 7-valent protein-polysaccharide conjugate vaccine was licensed for use in infants and very young children in 2000.

The Advisory Committee on Immunization Practices (ACIP) recommended use of the 23-valent pneumococcal polysaccharide vaccine for immunocompetent individuals who are 65 years of age and older, for immunocompetent individuals who are between 2 and 64 years of age with chronic cardiac or pulmonary diseases, diabetes mellitus, cerebrospinal fluid leak, functional or anatomic asplenia, or those living in a chronic care facility. ACIP also recommended use of the vaccine for immunocompromised individuals 2 years of age and older, including those with human immunodeficiency virus (HIV) infection; leukemia, lymphoma, multiple myeloma or generalized malignancy; chronic renal failure or nephrotic syndrome; organ or bone marrow transplant recipients; and patients receiving immunosuppressive chemotherapy or corticosteroids. It recommended revaccination for those who were vaccinated at less than 65 years of age where 5 years or more have elapsed since last vaccinations.

Pneumococcal polysaccharides elicit a T-cell independent, B-cell response. Thus, responses to these vaccines are neither prolonged nor does revaccination elicit an anamnestic, booster response. Infants and young children (up to 5 years of age) respond poorly to the pneumococcal polysaccharide vaccine. Therefore, a 7-valent, protein-conjugate vaccine was developed to provide protection for them.

ACIP recommended use of the 7-valent pneumococcal vaccine for all children 23 months of age and younger and for children who are 23 to 59 months of age with chronic cardiac or pulmonary disease, cerebrospinal fluid leak, diabetes mellitus, renal failure or nephrotic syndrome, functional or anatomic asplenia, HIV infection, immuno- or complement

Table 116-1

Vaccines for Bacterial Pulmonary Pathogens

Pathogen	Vaccine	Targeted Population	Frequency
S. pneumoniae	23-valent polysaccharide	Elderly (>65 years of age) Asplenia; chronic pulmonary, cardiac or renal diseases; diabetes; HIV	Administer once; repeat once after 5 years
	7-valent protein-conjugate	Children 2 months to ≤5 years of age	2, 4, 6, and 12–15 months
H. influenzae, type *b*	Protein-conjugate	Children 2 months to <5 years of age	2, 4, 6, and 12–15 months
B. pertussis	Acellular purified	Children 2 months to <5 years of age	2, 4, 6, and 12–18 months
M. tuberculosis	Bacille Calmette-Guérin (BCG)	Not recommended in United States	Once in infancy

deficiency, or diseases associated with immunodeficiency or immunosuppressive therapy such as leukemia and lymphoma or those affecting transplant recipients.

Pneumococcal vaccines have proven to be effective in preventing invasive pneumococcal infections (proven bacteremia and/or isolation of the organism from normally sterile body fluids) in immunocompetent individuals. Their efficacy against noninvasive pneumococcal pneumonia and in immunocompromised individuals is more controversial.

Örtqvist et al reported the results of a randomized, double-blinded trial comparing pneumococcal vaccine and placebo in nonimmunocompromised patients 50 to 85 years of age who were being discharged from hospitals in Sweden with a diagnosis of CAP. A total of 693 patients were randomized: 340 received vaccine, 353 received placebo. In the vaccine group 63 patients developed recurrent pneumonia and in the control group 57 patients developed recurrent pneumonia (relative risk [RR] = 0.83; 95 percent confidence interval [CI] 0.58 to 1.2). Pneumococcal pneumonia was diagnosed in 16 and 19 of the patients in the placebo and vaccine groups, respectively (RR = 0.78; 95 percent CI 0.40 to 1.51). Thus, the pneumococcal vaccine did not appear to be protective against either pneumonia or pneumococcal pneumonia in this population.

Honkanen et al reported on a study in which patients 65 years of age and older living in Northern Finland were offered either a combination of influenza and pneumococcal vaccines (IPV, offered to those born in even years) or influenza vaccine (IV, offered to those born in odd years). Overall, 62 percent of the eligible populations decided to participate and there were 38,037 person-years of follow-up. There were 145 and 116 episodes of pneumonia in the IPV and IV groups, respectively (RR = 1.2; 95 percent CI 0.9 to 1.5). There were 52 and 40 episodes of pneumococcal pneumonia in the IPV and IV groups, respectively (RR = 1.2; 95 percent CI 0.8 to 1.9). There were 2 and 5 episodes of pneumococcal bacteremia in the IPV and IV groups, respectively (RR = 0.4; 95 percent CI 0.1 to 1.9). Thus, the pneumococcal vaccine appeared to offer incremental protection against bacteremic disease only.

Nichol et al reported on a retrospective cohort study (1993–1995) conducted among adults 65 years of age and older with a diagnosis of chronic lung disease who were enrolled in a health maintenance organization in Minnesota. Hospitalizations for pneumonia, influenza, and all deaths were assessed. Pneumococcal vaccination was associated with significantly lower risk of hospitalization for pneumonia (RR = 0.57; 95 percent CI 0.38 to 0.84) and for death (RR = 0.71; 95 percent CI 0.56 to 0.91). However, the authors noted that the patients who received pneumococcal vaccine were younger and had fewer co-morbid conditions than did the nonvaccinated cohort.

Jackson et al reported on a retrospective cohort study conducted between 1998 and 2001 among Group Health Cooperative member adults 65 years of age and older in Washington state. Pneumococcal bacteremia and CAP were the end points of the study. Receipt of pneumococcal vaccine was associated with a 44 percent reduction in the risk of pneumococcal bacteremia (RR = 0.56; 95 percent CI 0.33 to 0.93). However, receipt of the vaccine was not associated with a reduced risk of pneumonia (RR = 1.04; 95 percent CI 0.96 to 1.13).

French et al reported on the results of a trial of pneumococcal vaccine among untreated HIV-infected patients in Uganda. A total of 1392 HIV-infected patients were enrolled: 697 received the 23-valent pneumococcal vaccine; 695 received placebo. Invasive pneumococcal infection occurred in 15 and 7 patients in the vaccine and placebo groups, respectively (hazard ratio [HR] = 1.47; 95 percent CI 0.7 to 3.3). Pneumonia also was more frequent in the vaccine group (40 versus 21). Thus, pneumococcal vaccine offered no protection against invasive pneumococcal disease or pneumonia in this population of untreated HIV-infected patients.

Conaty et al conducted a review of cohort studies, case-control studies, and randomized clinical trials designed to study the efficacy of the pneumococcal polysaccharide vaccine in adult patients. Overall, these studies showed that the vaccine was effective against invasive pneumococcal diseases. The pooled efficacies of the randomized clinical trials, case-control studies, and observational studies reviewed were 0.62 (0.37 to 1.04), 0.45 (0.36 to 0.56), and 0.47 (0.41 to 0.54), respectively. Excluding studies done among young, high-incidence patients (e.g., South African gold miners), overall efficacy of the pneumococcal polysaccharide vaccine against all-cause pneumonia was less impressive. The efficacy of the vaccine in randomized, clinical trials was 0.97 (0.81 to 1.16), while its efficacy in the pooled cohort studies among the elderly was 0.68 (0.50 to 0.93).

Melegaro and Edmunds compared the published meta-analyses of pneumococcal polysaccharide vaccines in the elderly. These studies showed the vaccine to be effective against invasive disease in the general elderly populations (efficacy = 65 percent; 95 percent CI 49 to 92), far less effective in the high-risk elderly (efficacy = 20 percent; 95 percent CI −188 to −78), and generally ineffective against pneumonia (efficacy = 16 percent; 95 percent CI 50 to 53).

Fedson and Liss provided a critical analysis of the published results of trials and meta-analyses concerning pneumococcal polysaccharide vaccine efficacy and a counterpoint to some of their conclusions. These authors argued that many of the pneumococcal vaccine trials were underpowered and others used the wrong end points. For example, they contended that nonbacteremic pneumonia was a valid end point for studies because it could be diagnosed objectively by radiograph. However, they did not accept nonbacteremic pneumococcal pneumonia as a valid end point because recovery of pneumococcal isolates from sputum did not prove that this organism was present in the lung and causing the pneumonia seen on radiograph. Basically, they concluded (as did most authors) that pneumococcal vaccine is effective in preventing invasive complications of pneumococcal infection, but could make no firm conclusion about its efficacy against pneumonia. However, they contended that lack of proof of vaccine efficacy against pneumonia does not prove its lack of efficacy.

Data on efficacy of conjugate pneumococcal vaccines are less voluminous but point in the same general direction.

The seminal study on efficacy and safety of the protein conjugate vaccine was reported by Black et al. It was a randomized, double-blinded trial in which infants enrolled in the Kaiser-Permanente health system in Northern California were randomly assigned to receive the 7-valent conjugate-pneumococcal vaccine or meningococcal vaccine at 2, 4, 6, 12, and 15 months of age. Close to 38,000 infants were enrolled in the study and over 82 percent received 3 or more doses of the assigned vaccine. There were 40 cases of invasive disease caused by vaccine serotype *S. pneumoniae*. Thirty-nine of these were in the meningococcal vaccine recipients. The efficacy of the vaccine for fully vaccinated children was 97.4 percent (95 percent CI 82.7 to 99.9). The vaccine was highly effective against otitis media, reducing the number and severity of visits for this infection. The vaccine was well tolerated causing only slightly more local and systemic side effects than the meningococcal vaccine.

A conjugate pneumococcal vaccine also has been tested in developing countries. A trial conducted in The Gambia was reported by Cutts et al. In this trial, children 5 to 51 weeks of age were randomly assigned to receive 3 doses of a 9-valent conjugate pneumococcal vaccine or placebo. Over 8000 children were enrolled in each arm of the study. The primary end point of this study was radiologically confirmed pneumonia. Invasive pneumococcal disease, all-cause admissions, and death were secondary end points of this study. There were 333 children with radiologically confirmed pneumonia among the vaccine recipients and 513 among placebo recipients (vaccine efficacy [VE] = 37 percent; 95 percent CI 27 to 45). There were 9 and 38 cases of vaccine serotype-invasive pneumococcal infection among the vaccine and placebo recipients, respectively (VE = 77 percent; 95 percent CI 51 to 90). Compared to placebo the vaccine was 50 percent effective (95 percent CI 21 to 69) in reducing all invasive pneumococcal infection, 15 percent effective (95 percent CI 7 to 21) in reducing all-cause admissions, and 16 percent (95 percent CI 3 to 21) effective in reducing mortality in this patient population.

Use of the conjugate pneumococcal vaccine for children in the United States has yielded unanticipated benefits. Two publications have documented a declining rate of invasive pneumococcal disease that has occurred among older adults as well as children. Both of these publications used data from the Active Bacterial Core Surveillance (ABCS) Network. This network is situated in eight areas: San Francisco; the state of Connecticut; Atlanta; Baltimore; Minneapolis-St. Paul; Rochester, New York; Portland, Oregon; and Memphis-Nashville-Knoxville, Tennessee. The combined populations of these areas is approximately 19 million with approximately 5 million individuals who are 50 years of age or older.

In the first of these, Whitney et al reported on ABCS Network data during the first year (2001) following licensure of the conjugate vaccine compared to prior years. They found that there was a dramatic reduction in the rates of invasive pneumococcal infection in children under 2 years of age. They also found a small but significant reduction in invasive pneumococcal infections among adults.

The second report, by Lexau et al, provided follow-up data. In this study, the authors compared the rates of invasive pneumococcal disease in the ABCS Network populations during the pairs of years 2000–2001 and 2000–2003 following introduction of the vaccine compared to 1998–1999. They found that there was a 28 percent reduction in the rates of all serotype-invasive pneumococcal infections, a 55 percent reduction in the rates of the vaccine serotype invasive infections, and a slight increase in the rate of invasive disease caused by serotypes not in either the conjugate or pure polysaccharide vaccines in adults 50 years of age and older. A highly significant reduction in the rate of invasive pneumonia (pneumonia plus isolation of *S. pneumoniae* from blood or pleural culture) infections in the 50 years of age and older population was observed. However, not all older adults were benefited. The authors found that there was a significant increase in the rates of invasive disease among adults with HIV infection, diabetes mellitus, and immunosuppression such as Hodgkin's disease, leukemia, multiple myeloma, dialysis, nephritic syndrome, or transplantation recipients.

Appropriate use of the pneumococcal vaccine has become an indicator of quality of care in many large health care organizations in the United States including the Veterans Health Administration (VHA), the American Hospital Association, and the Joint Commission on Accreditation of Health Care Organizations. VHA was among the first to establish pneumococcal vaccination as a measure of quality of care and to measure vaccination rates by an external peer review of patient (EPRP) records program. Jha et al reported that the pneumococcal vaccination rate among VHA patient records reviewed in fiscal year (FY) 2000 was 81 percent compared to the rate of 27 percent in FY 1995 ($p < 0.001$), prior to the introduction of this measure.

In another study, Jha et al reported data on use of pneumococcal vaccine use in facilities that participated in the Hospital Quality Alliance Program (HQAP). Data were available from 3079 hospitals for 2004. They showed a lower rate of documented pneumococcal vaccine use than had the VHA study cited above. In 2004, less than 10 percent of the HQAP facilities had achieved a pneumococcal vaccination rate of 81 percent or more, the rate achieved by VHA facilities in 2000.

Finally, the National Health Interview Survey (NHIS) demonstrated that there are racial and ethnic disparities in receipt of pneumococcal vaccine. These NHIS data were collected in 2000 and 2001. They showed that both non-Hispanic blacks and Hispanics were significantly less likely to report receipt of pneumococcal vaccine than were non-Hispanic whites (odds ratio [OR] = 0.4; 95 percent CI 0.3 to 0.5 and OR = 0.4; 95 percent CI 0.3 to 0.5, respectively).

Pneumococcal vaccines are a remarkably safe and effective means of preventing invasive pneumococcal infections in children and adults. Their use is recommended for the very young, the elderly, and those at most risk from pneumococcal infections at all ages. Although it has not been proven that highly immunosuppressed patients respond to and are optimally protected by the vaccine, much broader use of these vaccines in the populations at risk should be encouraged.

Haemophilus influenzae, Type *b* Vaccine

H. influenzae is a common cause of pneumonia and bronchitis. Although many of the isolates from the respiratory tract are nontypeable, *H. influenzae,* type *b* (Hib) has been frequently associated with bacteremic pneumonia. For example, Farley et al found a total of 47 cases of invasive *H. influenzae* infection in patients 18 years of age or older in metropolitan Atlanta during the period from December 1, 1988 to May 31 1990 and calculated that the annual incidence was 1.7 cases per 100,000 population. Bacteremic pneumonia accounted for 70 percent of the cases and 44 percent of the 29 pneumonia-associated blood isolates that were serotyped were Hib. Twenty-two of the cases reported by Farley et al occurred in adults over 60 years of age (incidence 5.6 per 100,000 per year), and 21 of the 22 cases were associated with bacteremic pneumonia. Patients with HIV infection are another group at particularly high risk for bacteremic Hib infection.

Safe, immunogenic, protein-conjugate Hib vaccines (HibCV) exist. These have been licensed for use in the United States since 1987 and have proven to be remarkably effective in preventing invasive Hib infections. For example, the Centers for Disease Control (CDC) estimated that the rate of invasive Hib infections in U.S. children under 5 years of age was 100 per 100,000 prior to licensure of the vaccine in 1987, whereas in 2003 the rate of all serotype-invasive *H. influenzae* infections in this age group was 1.9 per 100,000 (376 reported cases), of which only 32 (9 percent) were serotyped to be Hib. Unfortunately, not all groups have benefited equally from wide use of the HibCV vaccines. The rate of invasive *H. influenzae* infections did not improve among the elderly (those who are 65 years of age and older). Further, American Indians and Native Alaskan children benefited less than other racial groups.

The HibCV program has virtually eliminated Hib meningitis, one of the most serious infections of early childhood, from the United States It also has dramatically reduced the number of Hib respiratory infections that occur. For example, Zhou et al estimated that HibCV prevents 1106 and 1567 cases per year of epiglottitis and pneumonia, respectively and prevents 663 deaths.

The ACIP recently added a footnote to its recommendations for adult immunization. This footnote pointed out that the HibCV are licensed for children 6 to 71 months of age and that, though data on their efficacy do not exist in older children and adults, the vaccines are safe and immunogenic in many high-risk populations (e.g., those with sickle cell disease, leukemia, and HIV infection). Administration of the vaccine to these patients is not contraindicated.

Pertussis Vaccine

Bordetella pertussis causes severe whooping cough in infants and young children. In recent years, however, clinical infections have been observed commonly in adolescents and young adults. For example, in the United States, a total of 11,647 *B. pertussis* infections were reported to the CDC in 2003, the highest number since 1964. Sixty-three percent of these infections occurred in persons who were 10 years of age and older. Currently, no pertussis vaccines are licensed in the United States for persons 7 years of age and older.

The typical features of *B. pertussis* infection in infants and young children are a persistent, paroxysmal cough followed by inspiratory gasps (whoops), vomiting, cyanosis, and apnea. Complications of *B. pertussis* infections (e.g., pneumonia, seizures, and encephalopathy) are most common in infants less than 1 year of age and are associated with inadequate vaccination. Death occurs in 0.4 percent of cases.

Recently, Lee et al reported on the morbidity and medical and societal costs of *B. pertussis* infections among adolescents and adults in Massachusetts. Two-thirds of the patients had severe, long-lasting cough with 31 percent of adolescents and 41 percent of adults reporting episodes of "whoops". Seventy-nine percent of adolescents and 81 percent of adults were still coughing at the time of interview, an average of 41 and 48 days, respectively, after onset of this symptom. Adolescents missed a mean of 5.5 days of school whereas working adults missed a mean of 9.8 days of work as a result of their pertussis infections. The medical costs of infection were approximately $275 per case (mean $242 for adolescents; $326 for adults). The nonmedical costs per case were $155 and $447 for adolescents and adults, respectively.

An acellular pertussis (aP) vaccine is available and is recommended for use in infants and young children in the United States. Acellular vaccines are composed of purified components of the bacteria that are thought to elicit protective immunity. They contain a combination of the filamentous hemagglutinin (FHA); detoxified pertussis toxin (PT); and pertactin, an outer-membrane protein. The aP vaccine is generally combined with diphtheria and tetanus toxoid vaccines and is given to children at 2, 4, 6, and 15 to 18 months of age with a final booster at 4 to 6 years of age or entry into kindergarten.

Pertussis vaccines can produce significant side effects. Local reactions include pain, tenderness, erythema, and induration at the inoculation site. Mild systemic reactions to pertussis vaccines include low-grade fever, drowsiness, fretfulness, and vomiting. Moderate to severe reactions include fever above 105°F, persistent inconsolable crying lasting at least 3 hours, and collapse (hypotonic-hyporesponsive episodes). Moderate to severe reactions are very uncommon with the acellular vaccine.

BCG Vaccine

Strains of the attenuated bovine tubercle bacillus, originally developed by Albert Calmette and Camille Guérin (bacille Calmette-Guérin, BCG), are among the most widely used and studied vaccines to prevent pulmonary infection. Worldwide, BCG has been in use since 1921, and over 3 billion individuals have been vaccinated. Despite this long history, use of the vaccine remains controversial, and it is not recommended for prevention of pulmonary tuberculosis (TB) in the United States.

Colditz et al reported on a meta-analysis of 15 prospective trials and 10 case-control studies of BCG. The efficacy of vaccine in preventing TB was 51 percent in the

prospective trials (RR = 0.49; 95 percent CI 0.34 to 0.70) for BCG recipients. The efficacy for preventing death was 71 percent (RR = 0.21; 95 percent CI 0.16 to 0.53). In case-control studies, the protective efficacy was 50 percent (RR = 0.50 (95 percent CI 0.39 to 0.64). Despite these data, use of the vaccine remains controversial.

One problem with BCG vaccine is that its observed efficacy varies greatly in different studies. Fine listed a number of possible reasons for the observed differences. These include: (1) differences in exposure of populations to nontuberculous mycobacteria (exposure to nontuberculous mycobacteria can affect the immune responses induced by BCG); (2) differences in the strains of BCG used (different strains elicit different immune responses); (3) differences in the age at which BCG was administered (BCG is most effective when given early in childhood and when protecting against primary infection); (4) differences in the time from vaccination to development of TB (protection can wane with time); and (5) differences in the nutritional status of the vaccine recipients (immune responses diminish as a result of malnourishment).

Recently, Aronson et al reported results of a 60-year follow-up study of the efficacy of BCG among American Indians and Alaskan Natives (subjects who have an unusually high risk of TB as well as other infectious diseases). This trial was originally conducted in Alaska, Arizona, North and South Dakota, and Wyoming between 1935 and 1938. It involved American Indian and Alaskan Native children and adults 1 month to 20 years of age who, prior to entry into the study, did not react to a second strength (250 TU) purified protein derivative (PPD) skin-test and who, upon entry, were given a single dose of BCG or saline placebo. The 60-year follow-up study showed that the overall incidence of TB was 66 and 138 per 100,000 person-years in the vaccine and placebo groups, respectively (efficacy 52 percent; 95 percent CI 27 to 69). Efficacy was observed for pulmonary and for extrapulmonary TB. Efficacy of BCG declined over time for men, but not for women.

BCG is *not* recommended for control of TB infection in the United States. Instead, a vigorous program of detection and treatment of latent and active TB is recommended for high-risk patients in high-risk settings (e.g., prisons, health care facilities) and for known contacts of patients (including infants and children) with active TB infection. However, research is recommended to develop an improved vaccine that would be effective in controlling latent TB infection.

VACCINES AGAINST VIRAL PULMONARY PATHOGENS

Although most viral respiratory infections are transient and benign, some can be associated with serious complications. Vaccines have been developed to prevent infections or limit the morbidity of some viral infections (Table 116-2). The most important of these are the vaccines against influenza, measles (rubeola), and chickenpox (varicella). An adenovirus vaccine was used exclusively in the military. However, it is no longer being manufactured and supplies have been exhausted.

Influenza Vaccine

Influenza viruses cause significant morbidity in all groups, but they are a particularly important cause of serious illness among aged and debilitated patients. For example, Thompson et al estimated that approximately 36,000 respiratory and circulatory deaths occur in the United States each year as a result of influenza virus infection. Over 90 percent of these occur in individuals 65 years of age and older. Further, the annual rates of influenza associated deaths in the United States increased steadily over the decade of the 1990s. This has increased the urgency for improving the influenza prevention and treatment programs.

Three distinct types of influenza virus exist: influenza A, influenza B, and influenza C. Influenza A viruses are

Table 116-2

Vaccines for Viral Pulmonary Pathogens

Pathogen	Vaccine	Targeted Population	Frequency
Influenza virus	Trivalent inactivated, whole or split	Persons ≥6 months of age	Annually
	Trivalent Live-attenuated	Healthy persons 5–49 years of age	Annually
Measles (rubeola)	Live-attenuated vaccine	All children Susceptible adolescents and adults	1st dose: 12–15 months 2nd dose: 4–6 years of age
Chickenpox (varicella)	Live-attenuated vaccine	All children Susceptible adolescents and adults	1st doses: 1–12 years of age 2nd doses: 6–8 weeks apart

classified into subtypes on the basis of two surface antigens: hemagglutinin (H0, H1, H2, H3, H4, H5, etc.) and neuraminidase (N1, N2, etc.). Immunity to these antigens, especially the hemagglutinin, reduces the chance and severity of infection. Influenza A and influenza B viruses undergo antigenic variation (drift and shift), although the latter has more stability. For the past two decades, two subtypes of influenza A and one of influenza B have circulated in the global community. However, an influenza A (H3N2) virus has been the predominant cause of morbidity and mortality.

Influenza virus infections can be prevented or controlled by annual vaccination. They also can be prevented or controlled by appropriate use of antiviral agents: amantadine or rimantadine for influenza A; oseltamivir and zanamivir for influenza A or influenza B. Two types of influenza vaccines exist: inactivated influenza vaccine and live-attenuated influenza vaccine (LAIV). Both are produced from egg-grown viruses that are highly purified. Inactivated virus vaccines are further divided into whole and split virus preparations. The latter are recommended for infants and children 6 months to 5 years of age because they are less likely to cause febrile reactions.

Every year, three influenza virus strains (usually two influenza A strains and one influenza B strain) are included in the vaccine preparations. For the past several years, the trivalent vaccine has consisted of an (H3N2), an (H1N1) influenza A, and an influenza B virus strain. These are chosen for the vaccine preparation on the basis of global monitoring by the World Health Organization (WHO) and anticipation that these viruses will circulate in the United States and other parts of the Northern Hemisphere during the late fall, winter, and early spring influenza season. For the 2006–2007 influenza season, the ACIP recommended vaccination for those at high risk of influenza and its complications as well as healthy adults over 50 years of age in October, November, and beyond throughout the influenza season.

Efficacy of the influenza vaccines has been difficult to assess because a number of agents can cause "flulike" symptoms and specific diagnostic tests (e.g., culture, serology) are rarely done in nonresearch, clinical situations. The ACIP estimated 70 to 90 percent efficacy of inactivated influenza vaccines in preventing illness in healthy adults over 65 years of age when the circulating viruses antigenically matched those used to prepare vaccine.

Bridges et al reported on a randomized, double-blind trial of inactivated influenza vaccine compared to placebo conducted among full-time, 18- to 64-year-old employees of the Ford Motor Company during the 1997–1998 and 1998–1999 influenza seasons. End points of this study were clinically defined influenza-like illnesses (ILI), days ill, associated physician visits, and time lost from work during the influenza season. During the 1997–1998 season, vaccine recipients reported more ILI, days ill, physician visits, and days lost from work than did placebo recipients. These differences were not significant. However, during the 1998–1999 season, vaccine recipients reported significantly fewer ILI, days ill, physician visits, and days lost from work than did the placebo recipients ($p = <0.001$ for each).

Demicheli et al reported results of a massive review and meta-analysis of the published literature on influenza control. Their analyses showed that parenteral vaccines had efficacies against virologically confirmed and clinical ILI cases of 68 percent (95 percent CI 49 to 79) and 24 percent (95 percent CI 15 to 32), respectively. They also reviewed data on LAIV, reporting efficacies of 48 percent (95 percent CI 24 to 64) and 13 percent (95 percent CI 5 to 13) against virologically confirmed and clinical ILI cases, respectively.

Influenza vaccination reduces the risk of hospitalization for cardiac disease and stroke as well as for respiratory disease among the elderly. For example, Nichol et al reported the results of a cohort study involving community-dwelling adults 65 years of age and older. They found that the risk of hospitalization for cardiac disease was reduced by 19 percent ($p = <0.001$) in vaccine recipients as compared to unvaccinated subjects. The risk of hospitalization for cerebrovascular disease was reduced by 16 percent ($p = 0.018$) in the 1998–1999 season and by 23 percent ($p = <0.001$) in the 1999–2000 season. The risk of death from all causes was reduced in vaccine recipients by 48 percent and 50 percent during the 1998–1999 and 1999–2000 seasons, respectively ($p = <0.001$).

Influenza vaccines are less effective in elderly, debilitated individuals. Therefore, the ACIP strongly recommends annual influenza vaccine administration to all health care workers (HCW). Studies have confirmed the benefits of this strategy in long-term care facilities. For example, Potter et al reported on a study in which patients and staff of geriatric, long-term care facilities were offered influenza vaccine. Facilities were divided into those where patients and HCW received vaccine, patient received vaccine but HCW did not, HCW received vaccine but patients did not, and facilities in which neither patients nor HCW received vaccine. Vaccination of HCW was associated in a reduction in mortality from 17 percent to 10 percent (OR = 0.56; 95 percent CI 0.40 to 0.80) and in ILI (OR = 0.57; 95 percent CI 0.34 to 0.94). Vaccination of patients was not associated with an effect on mortality (OR = 1.15; 95 percent CI 0.81 to 1.64). In another study, reported by Carman et al, the mortality of elderly patients in long-term care facilities was reduced from 22.4 percent to 13.6 percent (OR = 0.58; 95 percent CI 0.40 to 0.84) in facilities in which HCW were offered influenza vaccine.

The 2000 and 2001 NHIS data, referred to above, showed that non-Hispanic blacks were significantly less likely to report receipt of influenza vaccine than were non-Hispanic whites (OR = 0.7; 95 percent CI 0.6 to 0.8). However, there was no significant difference in the reported influenza vaccination rates for Hispanic and non-Hispanic whites (OR = 0.9; 95 percent CI 0.7 to 1.1).

Influenza vaccines are associated with relatively minor side effects. Local side effects of intramuscularly injected inactivated influenza vaccines, including soreness or swelling at the inoculation site, occur in 10 to 64 percent of patients, whereas systemic side effects (e.g., fever, malaise, and myalgia) are uncommon. Use of LAIV has been associated with runny nose or nasal congestion, headache, and low-grade fever. These were more often reported with the first dose of LAIV and were self-limited.

Occurrence of Guillain-Barré syndrome (GBS) following influenza vaccination has been of concern since an association between swine influenza vaccine use in 1976–1977 and GBS was first noted. As a result, the CDC established a Vaccine Adverse Event Reporting System (VAERS). During the 1993–1994 influenza vaccination season, an increase in the number of GBS cases reported to VAERS was noted. However, a careful study reported by Lasky et al showed that there was *not* an increase of vaccine-associated GBS during that period.

Two recent problems have refocused attention on control of influenza virus infections. The first is the shortage of influenza vaccine that occurred during the 2004–2005 season because of the problems of one vaccine manufacturer. As a result of that shortage, strategies to prioritize and stretch the use of available vaccine were developed. Two studies examined the immunogenicity of intradermal rather than the traditional intramuscular inoculation with influenza vaccine. These studies showed that a fraction of the conventional intramuscular dose elicited comparable seroconversion and presumed protective antibody titers when given intradermally. However, it was noted that reactions were more frequent following intradermal inoculations and that those over 60 years of age reacted less vigorously.

The second problem is the threat of avian influenza. WHO reported a total of 132 human cases of avian influenza A (H5N1) in Hong Kong, Vietnam, Thailand, Cambodia, Indonesia, and Fujian Province, China between 1997 and August 2005. Of these, 64 patients (48 percent) died. Most of the cases occurred in individuals who had exposure to infected poultry. However, there were clusters of infection within families. In addition, there were at least two incidents of apparent transmission of avian influenza from an infected 11-year-old girl to her 26-year-old mother and to a 32-year-old aunt with whom the child was living. The mother provided 16 to 18 hours and the aunt 12 to 13 hours of unprotected nursing care to the child. The child and her mother died from the infection, whereas the aunt survived.

The emergence of avian influenza as a human pathogen has raised concerns about the possibility of an influenza pandemic. A pandemic occurs when a highly contagious disease with novel antigens is introduced into a population with little immunity and spreads rapidly to cause worldwide disease. Influenza pandemics are known to have occurred in 1918, 1957, and 1968 when the H1N1, H2N2, and H3N2 influenza viruses were first introduced into the population, respectively. These prior pandemics were associated with approximately 40, 1, and 2 million deaths worldwide, respectively. The avian influenza (H5N1) has novel antigens for humans; there is little or no immunity to it. To date, avian influenza (H5N1) has not proven to be highly contagious either from fowl-to-humans or human-to-human. If, however, this virus acquires the genes that allow it to spread more efficiently, it could very well cause a pandemic associated with staggering morbidity and mortality.

At present there are no Food and Drug Administration (FDA)-approved, effective human vaccines against avian influenza (H5N1). The National Institute of Allergy and Infectious Disease (NIAID) has announced plans to test the immunogenicity of a candidate vaccine, but is unclear as to whether this will produce the desired antibody response, whether it will be approved without a clinical test of efficacy, or when it might be approved for use in humans.

Measles (Rubeola) Vaccine

Measles was a major cause of morbidity and mortality in the United States, and it remains an important pathogen in some other parts of the world. Before 1963, the year that a measles vaccine was introduced, approximately 400,000 cases of measles were reported annually in the United States, but as many at 3.5 million cases may have actually occurred. Prior to introduction of the vaccine, death occurred in 1 to 2 cases per 1000 measles cases in the United States. The risk of death was greater for infants, young children, and adults than it was for older children and adolescents. Death was usually associated with measles encephalitis or pneumonia. In 2003, there were only 56 cases of measles reported in the United States. Twenty-four of these were internationally imported cases, and an additional 19 were the result of exposure to internationally imported cases. In 2003, there were two measles-associated deaths in the United States.

Pneumonia is common in patients with measles. A study of 3220 U.S. Air Force recruits with measles showed measles pneumonia in 106 (3.3 percent) cases. Quiambao et al reported on 182 children with measles associated pneumonia who were admitted to the Research Institute for Tropical Medicine in Alabang, Philippines; 17 percent of these children died. Co-infection with bacteria (*Streptococcus pneumonia, Haemophilus influenzae, Staphylococcus aureus*) or other viruses was common and more likely to result in death.

Two doses of the live-attenuated measles virus vaccine are recommended for all children, adolescents, and adults without a true contraindication. These include severe allergic reaction after a previous dose or dose component, pregnancy, or severe immunodeficiency (congenital, hematologic malignancy, long-standing immunosuppression). A dose of the measles vaccine, generally combined with attenuated mumps and rubella vaccines (MMR) is recommended for children 12 to 15 months of age. A second dose should be given at 4 to 6 years of age prior to entry into kindergarten. Most colleges require documentation of two doses of measles vaccine before admission.

Measles vaccine can cause low-grade fever in 5 to 15 percent of recipients. This generally lasts 1 to 2 days. A transient rash may also occur.

Varicella Vaccine

The varicella-zoster virus (VZV) causes chickenpox in susceptible children and adults, and, as a result of latent infection in sensory ganglia, zoster in those who have had a previous case of chickenpox. Approximately 7 percent of healthy, young adults lack antibody to VZV.

Primary VZV was considered to be a relatively benign disease of childhood. However, it was associated with greater morbidity and mortality in adults. For example, Weber and Pellechia reported that 16 percent of military personnel with primary VZV infection had radiographic evidence of pneumonia. A number of factors increase the risk of developing VZV pneumonia including cigarette smoking, pregnancy, and prolonged use of nasal or inhaled steroids, immunodeficiency, malignancy, and transplantation. Meyer et al reviewed 2262 deaths that were ascribed to varicella during the 25-year period (1970–1994) prior to licensure of the vaccine in the United States. Adults had 25 times the risk and children under 1 year of age had 4 times the risk of dying compared to children 1 to 4 years of age with varicella. Pneumonia was the most common complication of the primary varicella infection in those who died.

Recently, Danovaro-Holliday et al reported on an outbreak of varicella involving 18 Mexican-born young adults residing in Alabama. Five of the cases were severe, requiring hospitalization. One patient developed pneumonia and another GBS. Fortunately, all of the patients survived. In an editorial commentary that accompanied this report, Gershon et al urged a more aggressive approach to identifying and vaccinating susceptible adults.

Live, attenuated varicella vaccine was approved for use in the United States in 1995. The number of varicella cases reported in the United States in 1984 and 2003 were 221,983 and 20,948, respectively.

Varicella vaccine is lyophilized and must be stored in a freezer at –15° to –20°C until use. It must be given within 30 minutes of thawing and reconstitution. Healthy children 12 months to 12 years of age should receive a single subcutaneous dose of the attenuated vaccine while adolescents and adults should receive 2 subcutaneous doses 4 to 8 weeks apart.

Approximately 15 percent of children inoculated with the attenuated varicella vaccine develop low-grade temperature elevations and 7 percent develop a transient, mild varicella-like rash.

Recently, a more potent version of the attenuated varicella vaccine was shown to be effective in preventing zoster infections in healthy adults over 65 years of age. However, it is not known whether this vaccine will be of any benefit in preventing the rare pulmonary infections that complicate zoster.

Adenovirus Vaccine

Adenoviruses cause respiratory infections in infants, children, adolescents, and young adults. They have been associated with pharyngitis, croup, bronchitis, and pneumonia. They are a particular problem in the military, where susceptible young men and women are brought together and where acute respiratory infections caused by adenoviruses types 4 and 7 are a leading cause of infirmary visits and hospitalization.

Inactivated vaccines, containing adenoviruses types 4 and 7 that were grown in monkey kidney tissue culture cells and then treated with formalin, were prepared and tested in military recruits in the 1950s and early 1960s. Randomized, controlled studies showed the inactivated vaccines to be more than 90 percent effective in reducing confirmed adenovirus infections.

Problems in production and contamination with simian viruses hampered further development of the inactivated adenovirus vaccine. Subsequently, Gutekunst et al tested a live, enteric, type 4 adenovirus vaccine in a placebo-controlled trial among marine recruits. The vaccine was 100 percent effective in preventing febrile respiratory disease in which adenovirus type 4 was recovered, 67 percent effective in preventing all febrile respiratory disease requiring hospitalization, and 77 percent effective in preventing all respiratory disease during the observation period.

For years, the enteric adenovirus vaccine was used by the military to protect recruits from adenovirus disease. Unfortunately, vaccine production was halted in 1995. The supply of adenovirus vaccine that remained was used by the military to vaccinate a limited number of recruits during 1996–1998 but was exhausted by 1999. By 1997, outbreaks of adenovirus infections had reappeared among military recruits. For example, Ryan et al reported an outbreak of 571 confirmed cases of adenovirus infection among recruits at a center in Great Lakes, Illinois that occurred in the fall of 1997. This outbreak was caused by adenovirus types 3 and 7. Similarly, Kolavic-Gray et al reported an outbreak of adenovirus type 4 infections that occurred in the fall of 1998 among U.S. Army recruits at Fort Jackson, South Carolina. This outbreak involved 678 recruits and caused 115 hospitalizations. In both of these outbreaks, respiratory symptoms were common.

CONCLUSIONS

Use of vaccines to prevent pulmonary infections has not been adequately emphasized in the past. Vaccines are a safe, effective, and relatively inexpensive means of preventing pulmonary infections that can be debilitating and, in some cases lethal. A number of vaccines are available and should be used in appropriate patients. These include the 23-valent polysaccharide and 7-valent conjugate pneumococcal vaccines, conjugate *H. influenzae*, type *b* vaccine, the acellular pertussis vaccine, the trivalent inactivated and live-attenuated influenza vaccines, and the live-attenuated measles and varicella vaccines.

A number of challenges to achieving a fully successful vaccination program exist. First, it is clear that there must be incentives for manufacturers to develop and maintain production of vaccines. A limited market for military recruits was an inadequate incentive for the manufacturer to sustain production of the adenovirus vaccine. Further, for many years, millions of doses of the inactivated trivalent influenza vaccines were unused. It is clear that manufacturers must have incentives to go through the costly process of preparing and maintaining supplies of vaccines. Subsidies may be necessary

to develop and sustain valuable vaccines with limited or unpredictable markets.

Second, there must be better incentives for health care providers to use or urge the use of existing vaccines. In 2006, Medicare will pay providers in New York City only $21.65 for administration of either the pneumococcal or trivalent influenza vaccines. This is less than the $23.08 that was paid for the same service in the same area in 2005. This cut in funding is not advisable. It is clear that there must be improvements in the financing of vaccination programs and/or development of alternate incentives (e.g., achievement of accreditation goals set by the Joint Commission on Accreditation of Healthcare Organizations, the American Hospital Association, and other organizations) to encourage provider participation in adult vaccination programs.

Finally, there must be better education of consumers and employers about the benefits of vaccination. Vaccination programs will be successful if there is demand for the vaccines. The most successful programs occur among our infants and children because parents demand and states or schools require evidence of vaccination. Consumers must be convinced that they need to be up-to-date with recommended vaccinations. Further, employers must be convinced that inexpensive vaccines can prevent illness and that healthy employees are more productive. Ultimately, patients are the beneficiaries of successful vaccination programs. Once this is recognized, they will demand the vaccines.

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Microbial Virulence Factors in Pulmonary Infections

Gregory Priebe • Gerald B. Pier

Beginning at birth, microbial organisms enter and leave the body, primarily on external or mucosal surfaces. Some of these predominantly commensal organisms become resident; others are transient; and still others establish latent foci in otherwise sterile spaces. Over a lifetime, a person is the reservoir for hundreds of strains of viruses, thousands of bacterial species, and a scattering of fungi and parasites. When these organisms violate their niche, invade, or produce toxic products, virulent interactions take place and occasionally lead to disease. Thus, organisms can cause disease without entering or adhering to tissues by releasing toxic products. However, many infections are preceded by attachment of organisms to surfaces, followed by their entry into cells or otherwise sterile spaces. These processes of invasion are complex and involve factors present in both the host and the organism. Most organisms are cleared by a variety of nonspecific and specific mechanisms, with nonspecific mechanisms generally falling under the heading of innate immunity and the specific under adaptive immunity. In some situations, however, organisms are able to propagate and produce clinical symptoms. A number of pathological conditions in the host predispose to entry and survival of microbes, ranging from breaks in mucosal surfaces to defects in the immune system. Organisms become parasites when they express the requisite *virulence determinants* to gain entry and overcome or evade host defenses.

An important step in establishing infection occurs when the potential pathogen encounters the immune system. There are numerous mechanisms whereby the immune system detects and tries to limit the extent of microbial challenge, including inflammation (acute and chronic), phagocytosis (neutrophils and macrophages), complement, and humoral and cellular immune responses. The immune system also maintains surveillance for organisms that invade phagocytes, propagate, and resist killing, and also for organisms that invade nonphagocytic cells. Means by which microbes can be controlled range from physical clearance mechanisms to phagocytosis (followed by oxidative or nonoxidative killing) to nutritional depletion (e.g., sequestration of iron, which is an essential nutrient for bacterial growth).

Microbes have evolved a variety of strategies to overcome host defenses, evade the immune system, scavenge for nutrients, and survive to spread to other hosts. These processes can lead to tissue damage and even death of the host. However, ultimate survival of the microbe requires eventual spread to a new host. A new "generation" of microbes is established (by clonal division) approximately once an hour, whereas a new generation of humans occurs about once every 20 years. Thus, the microbes have a clear genetic advantage in selecting properties that enhance virulence and survival. In response, the human immune system has developed to present a variety of defenses against a broad range of pathogenic mechanisms. Infections can occur at specific sites on surfaces or within the body or involve local, distal (metastatic), or systemic spread. Infection can occur without damaging cells,

through direct cellular damage by microorganisms or their toxins, or as a consequence of the immune response. When physiological disruption or cellular damage occurs, the host needs to recover and repair. In addition, the immune system attempts to recognize the pathogen and prevent reinfection. Pathogens have also evolved a series of mechanisms to avoid immune detection, including local interference with immune processes, antigenic variation, and avoidance of inducing an immune response.

Organisms are constantly evolving to meet the demands and opportunities of modern society. Just as the cities of the Middle Ages brought together humans and rats and caused outbreaks of bubonic plague, the use of antibiotics, chemotherapy, and various medical devices has led to a number of new pathogenic interactions between microbes and humans. A key to understanding the pathophysiology of infectious diseases and appreciating the complexity of both the immune system and the microbial world is knowledge of the facts and processes of each; this knowledge base is necessary for an understanding of the ideas presented above and the conceptual basis of immunity and infection as related to respiratory tract infections.

GENERAL MECHANISMS OF INFECTIOUS PROCESSES IN THE RESPIRATORY TRACT

The pathogenesis of acute and chronic microbial infections of the lungs entails complex interactions between the microorganisms and a variety of host defense mechanisms. The general steps and molecular factors involved in the pathogenesis of microbes causing lung infections are summarized in Table 117-1. Although the alveolar spaces are generally sterile, low levels of microorganisms are continually inhaled into the lungs. Inoculation of the lungs can occur from a variety of sources, including aspirated upper-airway secretion or bacteria in small aqueous droplets inhaled directly via the nose or mouth. Most commonly, inhaled organisms, either alone or in association with particles of mucus, gain access to the lower airways. They are generally either cleared by mucociliary flow or scavenged by phagocytes (see Chapter 111). Particulates greater than 10 μm in diameter are deposited in the upper airways. Particles of less than 5 μm that are not cleared in the upper airways can be deposited in alveoli. Most particulate matter is not infectious, and only spores or organisms that remain viable can cause infection. Thus, the pathogenesis of microbial infection will initially depend on a microbe's ability to enter the respiratory system and avoid clearance by mechanical and innate immune mechanisms.

As noted above, microorganisms can reach the lower airways from various sources. Organisms in ambient air can be inhaled as droplet nuclei—particularly in closed environments, where density is great and infected individuals can deposit organisms into the air. Perhaps the most important source of organisms causing pneumonia is the flora of the upper respiratory tract. A large ecosystem of microorganisms that includes both pathogenic and nonpathogenic bacteria and fungi normally resides in the upper airways. The quantity and species diversity of many of these organisms can be stable over long periods, but transient colonization

Table 117-1

Steps and Molecular Factors for Infectious Microorganisms to Cause Lung Disease

Step	Molecular Factors	Result
Attachment to or entry into the body	Pili, flagella, surface proteins, lipopolysaccharide (LPS), specific ligands for receptors on host cells or mucins	Establish organisms in a host
Multiplication	Iron-binding factors; quorum-sensing signals, biofilm matrix	Increase microbial numbers; activate other virulence systems; initiate clinical symptoms
Local or general spread into the lungs	Capsular polysaccharides, antiphagocytic factors, motility (pili and flagella), toxins	Evade defenses and the natural barriers to spread
Damage to lung tissue	Exotoxins (including type III secretion system), LPS, cytotoxins, immunosuppressive factors	Inflict basic pathology due to the infectious agent
Shedding (exit) from the body	None identified	Leave body at site and on a scale that ensures spread to a new host

with a variety of microbes also occurs with some frequency, and these changes are often correlated seasonally and/or with concomitant infections with respiratory viruses. For example, *Streptococcus pneumoniae* and *Neisseria meningitidis* are more frequently isolated from the nasopharynx or throat during the winter months. In addition, organisms that make up the normal microbial flora in other parts of the body can be transferred to the lung, where they can cause infection. In early onset group B streptococcal pneumonia and sepsis in neonates, the organisms are transferred during birth from the vaginal canal of the mother to the respiratory tract of the infant.

Organisms causing infections at other body sites can spread to the lungs. Although not common, hematogenous spread from the bloodstream to the lungs can occur. The existence of heavy colonization or infection in the upper airways also increases the potential for infection in the lungs by a variety of mechanisms, mostly by a simple dose effect, whereby a large burden of potentially pathogenic organisms overwhelms the clearance mechanism of the lungs. Another mechanism for pneumonic infection can result from infections that perturb the specific and nonspecific defenses, leading to respiratory infection as a sequela of another pathogenic process. The most common example of this process is bacterial infection secondary to influenza virus. In fact, the neuraminidase of influenza virus has been shown to play a synergistic role in pneumococcal pneumonia models by cleaving the sialic acid residues on host glycoconjugates, thereby leading to increased adherence of the bacterium. Finally, any process that disrupts the physiological and physical barriers between the upper and lower airways can lead to infection—for example, the placement of an endotracheal tube or changes in normal clearance mechanisms associated with cystic fibrosis.

Once a microorganism gains access to the lower respiratory tract, it must be able to attach to tissue factors, remain viable, and multiply. Usually organisms will either multiply locally, resisting local defenses, or spread to other body sites by traversing epithelial barriers that normally inhibit microbial spread. In order for extracellular organisms to multiply, they must scavenge for nutrients. Of particular note is the universal requirement for iron, which must be extracted from iron-binding molecules such as transferrin. Many bacteria produce iron-binding substances known as siderophores that have an affinity for iron of greater than 10^{18} M and bind to high-affinity receptors on the bacterial surface. Organisms must also avoid or resist opsonophagocytosis or be able to survive and multiply within phagocytes. Subsequent to microbial growth and resistance of host defenses, damage to the host tissues occurs. This process is aided by a variety of pathogenic factors and results in invasion of tissues often with destruction of cells. Secreted toxins can act locally and/or be systemically spread to cause clinical symptoms. Many gram-negative bacilli possess a type III secretion system which can function like a hypodermic needle to inject toxins directly into host cells. The potential for inflammation to cause tissue destruction can be a devastating consequence of microbial growth in normally sterile lung sites. Finally, although not necessary for the pathological process to take place, most organisms that successfully multiply will have mechanisms with which to leave the body and transmit disease, thereby propagating their species.

MOLECULAR FACTORS AND PROCESSES IN RESPIRATORY INFECTIONS

The study of pathogenic microorganisms has benefited greatly from the ability to identify microbial factors that are at work to elicit a particular pathological process. Often these factors by themselves are responsible for a particular aspect of the infectious process, whereas at other times these factors act in consort to promote microbial colonization, growth, infection, and ultimately host responses and disease.

The success of the microorganism in establishing infection (the presence of a microorganism in a tissue where it is not normally found) and causing disease (the signs and symptoms of clinical illness) is predicated on the organism's ability to elaborate specific molecular factors that allow it to progress from the colonization to the disease state. Factors that inhibit or neutralize the host's response to eliminate the organism are also critical for pathogenesis. The ability of specific microorganisms to produce virulence or pathogenic factors is highly variable and is doubtless a major reason for the differences in pathogenicity among closely related strains of bacteria. Initially, most microbes that establish themselves in the respiratory tract will bind to host tissues, often in a specific manner. Pathogens will produce specific molecules to promote this process. Some potentially pathogenic microorganisms, such as *S. pneumoniae* and *N. meningitidis,* can establish colonization in the nasopharynx or throat without causing harmful effects. Almost everyone is colonized by these potential pathogens many times during life. Viruses and obligate intracellular parasites, such as *Chlamydia,* usually must find their way to the lower respiratory tract and invade a specific cell in order to start growing. Bacterial pathogens, such as *Legionella pneumophila* and *Mycobacterium tuberculosis,* need to encounter alveolar macrophages where they are ingested but resist destruction within these cells.

In some cases, as long as a potential pathogen confines itself to a local site, no disease will ensue. At other times, growth at the local site causes frank disease; this is the mechanism of group A streptococcal pharyngitis and whooping cough caused by *Bordetella pertussis.* In general, the nasopharynx and throat readily tolerate the presence of a dynamic bacterial population, comprising mostly nonpathogenic strains along with potential pathogens that do not spread to other tissues.

Most of the initial host response to pathogens in normally sterile sites, indicative of infection, involves the basic inflammatory responses of innate immunity. The microbes generally initiate this response by activating complement, binding quasi-specific host molecules such as mannose-binding

lectin, and generating other tissue signals via cell-associated pattern-recognition molecules such as toll-like receptors that lead to an influx of inflammatory cells and serum factors into the site of infection. Inflammation leads to clinical symptoms in the form of a sore throat, sneezing, coughing, feeling of malaise, etc. Some particularly virulent microbes can produce much more serious disease rapidly as the organisms spread and cause inflammation diffusely throughout the respiratory tract. Failure to control microbial growth and sustained inflammation lead to pathological tissue destruction. The balance between the host inflammatory response and microbial growth is the key factor in the disease process. As is often the case with microbial infection, inflammation is a double-edged sword, critically important for resolution of infection but also responsible for tissue damage.

SPECIFIC VIRULENCE MECHANISMS OF MICROBIAL PATHOGENS

Much of our knowledge in the area of molecular mechanisms that microbial pathogens use to establish and cause respiratory infections is derived from studies of bacteria. In the case of viruses, clear factors, such as the neuraminidase and hemagglutinin proteins on the coat of the influenza virus, are needed to expose cellular receptors and promote viral binding, subsequent cellular invasion, viral replication, inflammation, and disease. All viruses causing respiratory infections must enter cells in some manner that includes binding of a specific viral factor to a specific host cellular receptor. Intracellular nonviral microbes such as *Chlamydia* are probably taken into cells nonspecifically by phagocytosis or endocytosis.

A fairly good understanding of the molecular basis for the pathogenesis of *B. pertussis* infection has been established. *B. pertussis* binds exclusively to the cilia on ciliated respiratory epithelium using at least two bacterial cell-surface factors, designated pertactin and filamentous hemagglutinin (FHA). A fraction of the organism's cell wall, the muramyl dipeptide, is then extensively produced and secreted, and this factor is toxic to the ciliated tracheal cells. These cells are extruded from the epithelial surface, perhaps in an attempt to clear the bacteria from the respiratory tract. Secretion of pertussis toxin also contributes to the pathology. Pertussis toxin is composed of two subunits, designated A and B; the B subunit binds to receptors on host cells, allowing the A subunit to enter the cell. The A subunit transfers the ADP-ribosyl part of NAD to a membrane-bound GTP-binding protein that normally inhibits the enzyme adenyl cyclase. This leads to increased synthesis of cyclic adenosine monophosphate (cAMP). One recently described role of pertussis toxin is to inhibit neutrophil recruitment, thereby delaying antibody-dependent clearance of the bacterium even in immune hosts.

Other extracellular pathogens that cause lung infections establish themselves in tissues by binding to either cellular receptors or factors in the mucus, notably mucin. Krivan and colleagues report that several bacterial pathogens that frequently cause pneumonia—including *Pseudomonas aeruginosa, Haemophilus influenzae, Staphylococcus aureus, Streptococcus pneumoniae, Klebsiella pneumoniae,* and some *Escherichia coli*—bind specifically to terminal or internal Ga1NAc-β(1-4)-Gal sequences lacking sialic acid residues commonly found on cellular glycolipids in the respiratory tract. *P. aeruginosa* itself has been prominently studied in regard to binding to respiratory mucins as a mechanism to establish and maintain infection in the lung. Nontypeable *H. influenzae* also appears to use pilus-mediated adherence to human respiratory mucins to establish chronic infections in the lung.

Intracellular respiratory bacterial pathogens usually are ingested by alveolar macrophages and must resist phagocytic killing in order to establish infection and cause disease. *M. tuberculosis* enters these cells in the lower and middle airways with high airflow, as it is an obligate aerobic organism. Bacterial ligands and cellular receptors involved in this process are not fully characterized, although dendritic cell-specific intercellular adhesion molecule-3 grabbing nonintegrin (DC-SIGN) on dendritic cells and macrophages appears to play a role. Following inhalation, most individuals will effectively clear or contain the tubercle bacilli, while in a minority the bacteria escape from the macrophage phagolysosome, or prevent its formation in the first place, leading to bacterial growth and host inflammation and resulting in lesions typical of tuberculosis. On the opposite side of the time spectrum from *M. tuberculosis*, inhaled spores of *Bacillus anthracis* are phagocytosed by alveolar macrophages but within 6 hours can germinate, escape from the phagosome, replicate within the cytoplasm, and escape from the macrophage to enter the lymphatics or bloodstream.

Respiratory pathogens elaborate additional virulence factors beyond those needed to establish infection in normally sterile tissues. Many respiratory bacterial pathogens are encapsulated—a critical factor in promoting bacterial resistance to phagocytic killing. Neutralization of this antiphagocytic property by specific antibody results in high-level host immunity. Successful vaccines against *S. pneumoniae, H. influenzae* type b, and certain serogroups of *N. meningitidis* have been developed by engendering capsule-specific immunity via immunization, and comparable vaccines against *P. aeruginosa, K. pneumoniae,* group B streptococcus, and *S. aureus* are in various stages of development and testing in humans. Many studies support a role for the M protein capsule-like antigen of group A streptococcus in preventing phagocytosis of this organism, although recent studies suggest that the nonimmunogenic hyaluronic acid capsule plays a more prominent role as an antiphagocytic factor for group A streptococci.

Regulation of the expression of virulence factors is tightly controlled by the pathogen via complex networks of two-component regulatory systems and other systems. In *P. aeruginosa*, quorum sensing (cell-density–dependent gene expression) via small organic molecules called acyl homoserine lactones has been shown to be important for virulence in

pneumonia models both by regulating expression of secreted toxins and by inducing inflammation. *S. aureus* strains control virulence through regulatory peptides involved in activating and suppressing the accessory gene regulator (*agr*) network, with similar systems found in other gram-positive pathogens as well. Interfering with these systems with appropriate inhibitors holds promise for future therapeutic interventions in bacterial pneumonia.

Many respiratory pathogens, particularly *P. aeruginosa* and *S. aureus*, elaborate some very potent toxins. *P. aeruginosa* secretes an elastase that can interfere with innate immunity in the lung by cleaving surfactant protein D, thereby abrogating its role in bacterial clearance. In addition to secreted toxins, protein effectors of the type III secretion system of *P. aeruginosa* can be directly injected into host cells, injuring the alveolar epithelium and subsequently allowing the release of proinflammatory cytokines such as tumor necrosis factor–α (TNF-α) into the circulation, resulting in septic shock. The recent emergence of strains of community-acquired methicillin-resistant *S. aureus* (MRSA) that secrete the Panton-Valentine leukocidin, a pore-forming toxin specific for white blood cells, has been associated with severe cases of necrotizing pneumonia. The gram-negative endotoxin, also called lipopolysaccharide (LPS), can cause serious damage to lung tissues, although the lung seems relatively resistant to the effects of inhaled endotoxin when compared with the systemic response to circulating LPS.

EXAMPLES OF THE MOLECULAR PATHOGENESIS OF ACUTE AND CHRONIC BACTERIAL RESPIRATORY INFECTIONS

Pneumococcal pneumonia is the prototypic acute bacterial respiratory infection. As important a pathogen as *S. pneumoniae* is in the respiratory tract, the understanding of how it causes pneumonia and sepsis is not extensive. The capsular polysaccharide is a critical virulence factor, but beyond this, the role of other bacterial products in pathogenesis is mostly unknown. The cell-wall bacterial phosphorylcholine of virulent *S. pneumoniae* has been shown to bind to the G protein–coupled platelet-activating factor (PAF) receptor following inflammatory activation of human cells. This leads to invasion of epithelial and endothelial cells, indicating a mechanism whereby *S. pneumoniae* could escape through the lung epithelium via the vascular endothelium into the circulation to cause sepsis. The fact that lung inflammation increases PAF receptor levels is likely another reason for the hypersusceptibility of people with viral upper respiratory infections to secondary infection with *S. pneumoniae.*

Chronic lung infections can be caused by a variety of bacterial pathogens, many of which occur in persons with underlying lung disease. Patients with chronic obstructive pulmonary disease are particularly susceptible to chronic infection with nontypeable *H. influenzae,* although beyond the propensity of the organism to bind to respiratory mucins, the molecular bases for infection and disease are mostly unclear. Interestingly, co-colonization experiments with *H. influenzae* and *S. pneumoniae* in mice have found that *H. influenzae* predominates due to *H. influenzae*-induced complement-dependent phagocytic killing of *S. pneumoniae.*

Among patients with cystic fibrosis (CF), 80 to 90 percent will become chronically infected with *P. aeruginosa.* This infection is currently the major factor limiting their life expectancy. A large research effort has focused on understanding how this pathogen infects the vast majority of patients with a genetic defect that does not appear related to chronic bacterial lung infection. In patients with CF, mutations are found in the CF transmembrane conductance regulator (CFTR) gene which codes for a large protein that regulates chloride ion secretions directly and also appears to affect the flow of other ions, such as sodium. Ninety percent of people carry at least one mutant CFTR allele that lacks the codon for the phenylalanine at position 508 (ΔF508 mutation), and about two-thirds of affected persons are homozygous for this mutation. The lack of phenylalanine at position 508 leads to an inability of the mature protein to get into the cell membrane.

The relationship of mutant CFTR and hypersusceptibility to chronic *P. aeruginosa* infection is undergoing intensive study. Pier and colleagues have proposed that clearance of *P. aeruginosa* from the lung following inhalation of bacteria is critically dependent on CFTR-controlled internalization of the bacterium by lung epithelial cells followed by rapid activation of innate immunity involving nuclear factor (NF)-κB nuclear translocation and production of inflammatory cytokines such as interleukin (IL)-6, IL-8, and CXCL1. The combined effects of epithelial cell internalization and shedding along with rapid activation of innate immunity that most likely brings in neutrophils to phagocytose and eliminate any other extracellular bacteria can lead to efficient microbial clearance. Resolution of this response via apoptosis has also been shown to be important in the CFTR-dependent response of the lung to *P. aeruginosa.* The CFTR protein has been identified as the actual cellular receptor for clearance of *P. aeruginosa* from the lung. In a neonatal mouse model of clearance of *P. aeruginosa* from the lungs after nasal inoculation of bacteria, it was found that blocking of CFTR-mediated epithelial cell ingestion of *P. aeruginosa* led to higher bacterial burdens in the lung. Similarly, in transgenic CF mice there is reduced epithelial cell uptake of *P. aeruginosa* and increased overall bacterial burdens in the lung. Of note, there appears to be little to no binding of bacteria to tracheal epithelial cells in infected CF mice whereas extensive binding, ingestion, and shedding of *P. aeruginosa* by epithelial cells can be seen in tracheas of infected wild-type mice. Thus, in vivo, *P. aeruginosa* binding to CF epithelial cells is not observed, a situation completely consistent with results from histopathological examination of lungs taken at transplant or autopsy from CF patients, where *P. aeruginosa* also is not seen binding to the epithelium but rather encased in mucous plugs within the airways. Overall, the initial establishment of *P. aeruginosa* infections in the lungs of CF patients can be directly attributable

to the lack of functional CFTR in cell membranes to bind to this microbe and initiate appropriate innate immune responses, which prevents efficient bacterial clearance from the lung.

The pathogenesis of chronic *P. aeruginosa* lung infections in CF patients is more extensive. After avoiding initial clearance, the bacteria adhere to mucins and become embedded in mucous plugs within the airways and eventually undergo a phenotypic conversion wherein they lose both their ability to produce the long O polysaccharide side chains that are usually on the LPS and acquire the ability to elaborate copious quantities of a bacterial exopolysaccharide called alginate. The hypermutable phenotype seen in *P. aeruginosa* strains from CF patients likely speeds this adaptation. Alginate is unable to provoke a protective antibody response in the host and encases the bacteria in microcolonies within a hypoxic microenvironment in the lung. Within this protective coating, phagocytes such as neutrophils are unable to ingest and kill the microorganisms. This leads to a vicious cycle of additional but ineffective inflammation and bacterial growth, the result of which is tissue destruction subsequent to the chronic inflammatory process. Alterations in the lipid A structure of the *P. aeruginosa* LPS in strains isolated from CF patients appear to confer resistance to antimicrobial peptides and a hyperinflammatory response. For most of the patient's life, *P. aeruginosa* infection appears to remain confined to endobronchial surfaces, which become plugged with mucus while the airway tissues are being destroyed, although recently reported histopathological results from lungs of CF patients who died in the 1970s, prior to more modern medical management with aggressive antibiotic therapy used in some countries, also showed extensive alveolar involvement. The finding of quorum-sensing signals in the CF lung suggests that the *P. aeruginosa* may exist as a biofilm (defined as a structured community of bacteria encased in a self-produced matrix), which likely contributes to the recalcitrance of this infection to antibiotics. Thus, the pathogenesis of chronic *P. aeruginosa* infection in CF involves at least two components: an initial phase of hypersusceptibility to infection that is predicated on an inability of CF patients to kill or clear inhaled *P. aeruginosa* cells and a subsequent phase directly related to the bacterium's ability to elaborate alginate, which allows the organism to resist host defenses while continuing to provoke inflammation that damages lung tissues.

From these two examples we garner some important insights into mechanisms whereby bacterial pathogens cause lung infections. Many of the principles apply to other types of pathogenic microbes that follow the basic scenario of entry, attachment, multiplication and survival, elicitation of inflammation, and ultimately tissue damage and compromise of respiratory function. Although each of these steps can often be characterized at a highly specific molecular level, usually using isolated factors such as toxins to elicit clinical symptoms of disease, the overall pathogenesis of disease requires that elaboration of molecular factors of pathogenesis be coordinated and that each step in the process occur under the proper circumstances and at the right time. Research in identifying and understanding the microbe's genetic and molecular factors that control and coordinate pathogenesis is in its infancy. Presumably, greater understanding of particular factors and the interactions among both the factors and host tissues will lead to development of better vaccines and other therapies that will minimize the occurrence of microbial infections in the lung.

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CHAPTER

Infections of the Upper Respiratory Tract

Marlene L. Durand

Upper respiratory tract infections are the most common infections and the most frequent reasons for office visits in the United States. Most upper respiratory infections are minor and self-limiting, but some (e.g., peritonsillar abscess, epiglottitis, invasive fungal sinusitis) may be life-threatening.

THE COMMON COLD

The common cold is a mild, self-limiting infection. Six major viral families are responsible: rhinovirus (30 to 40 percent of cases); influenza virus (25 to 30 percent); coronavirus (10 to 15 percent); adenovirus (5 to 10 percent); parainfluenza virus (5 percent); and respiratory syncytial virus (5 percent). Each virus has several serotypes; rhinovirus has 100. Adults have an average of two to four colds and children six to eight colds per year.

In the United States, the incidence of colds is seasonal, with most occurring fall through spring. Young children are the main reservoir of respiratory viruses, and adults with children have more colds than those without. Transmission probably occurs either by inhalation of infectious droplets or by hand-to-nose "self-inoculation" after touching infectious secretions. The pathogenesis of rhinovirus

infections is thought to include viral entry into the nose followed by infection of the epithelial cells of the upper airway. Symptoms (sneezing, nasal discharge and congestion, and a "scratchy" throat) develop 16 to 72 h after inoculation, and last for 1 to 2 weeks. The peak of rhinoviral excretion in nasal secretions coincides with the peak of clinical illness.

Complications of the common cold include bacterial superinfections of the upper respiratory tract, such as acute otitis media and acute sinusitis, and exacerbations of asthma. Recent studies have demonstrated that rhinoviruses may be present in the lower airways during the common cold, and are a major cause of asthma exacerbations in children and adults.

Treatment of the common cold is symptomatic, with nonsteroidal anti-inflammatory drugs (NSAIDs) and antihistamines providing some benefit. Development of a vaccine is unlikely given the number of viral pathogens and serotypes. Antiviral agents such as pleconaril have not provided sufficient benefit to outweigh risks or side effects. Herbal remedies, such as Echinacea, have shown no benefit. Careful handwashing and use of hand disinfectants may be the most effective preventive measures.

PHARYNGITIS

Over 6 million adults visit primary care physicians annually for sore throats, and three-fourths receive antibiotics. Most cases of acute pharyngitis occur as part of the common cold and are caused by viruses such as rhinovirus, coronavirus, and parainfluenza virus. These cases are mild, nonexudative, and self-limiting. Patients with primary human immunodeficiency virus (HIV) syndrome may also have a nonexudative pharyngitis. A severe, usually exudative pharyngitis occurs in about half of patients with either adenovirus infection or Epstein-Barr virus mononucleosis. The pharyngitis seen in herpangina, due to group A coxsackievirus, is characterized by a vesicular enanthem. Lesions (usually only two to six) begin as papules on the soft palate between the uvula and tonsils. These vesiculate, then ulcerate. Primary herpes simplex virus may cause a severe vesicular or ulcerative pharyngitis; when there is an overlying exudate, it may mimic streptococcal pharyngitis.

Group A streptococcus *(Streptococcus pyogenes)* is the most important bacterial cause of pharyngitis because of its suppurative (e.g., peritonsillar abscess) and nonsuppurative complications (e.g., rheumatic fever, acute poststreptococcal glomerulonephritis). It causes 15 to 30 percent of cases of pharyngitis in children and 5 to 10 percent in adults (likely higher in parents of school-age children). Symptoms and signs vary. Patients may have a severe exudative pharyngitis accompanied by fever, leukocytosis, and cervical lymphadenopathy, or they may have a mild pharyngitis that mimics that of the common cold. Some patients with mild disease have a viral pharyngitis but are colonized with group A streptococci. These patients must also be treated for presumed streptococcal disease. Features independently associated with group A streptococcal pharyngitis include tonsillar exudates, cervical lymphadenitis, lack of cough, and history of fever. Diagnosis of streptococcal pharyngitis is made by culture or by rapid antigen detection test (RADT). The latter is 95 percent specific but not as sensitive as culture. Therefore, a negative test requires culture confirmation in children and adolescents, while a positive test is sufficient for the diagnosis. In adults, practice guidelines suggest that a negative RADT may not require culture backup, as the incidence of streptococcal disease is lower than in the pediatric population and the risk of rheumatic fever extremely low. Treatment is with oral penicillin (or erythromycin in penicillin-allergic patients) for 10 days, or with a single intramuscular dose of benzathine penicillin. Cephalosporins are very effective in eradicating streptococci, and cefdinir and cefpodoxime have Food & Drug Administration (FDA) approval for 5-day treatment courses, as does the macrolide azithromycin.

Other bacteria may also cause pharyngitis. Group C and G streptococci may cause an exudative pharyngitis and may be endemic or related to foodborne outbreaks. *Arcanobacterium hemolyticum* may cause an exudative pharyngitis along with a maculopapular rash, and typically occurs in children and young adults. Diphtheria, caused by *Corynebacterium diphtheriae,* is rare in the United States. Sore throat is a common symptom (in 90 percent), and findings include mild pharyngeal injection and an overlying adherent gray membrane (especially over the tonsillar pillars) that bleeds if removal is attempted. *Yersinia enterocolitica* may cause an exudative pharyngitis; an associated enterocolitis is more common in children than in adults. *Neisseria gonorrhoeae* may cause a mild pharyngitis, although most cases are asymptomatic. *Neisseria meningitidis* has rarely been noted as a cause of pharyngitis, but it is often isolated from throat cultures because the meningococcal carrier state is common. Carriers are not treated except in epidemic situations or if they have had close contact with a case of invasive meningococcal disease. *Chlamydia pneumoniae* and *Mycoplasma pneumoniae* may cause a mild pharyngitis.

A peritonsillar abscess (quinsy) may follow untreated streptococcal pharyngitis or may be due primarily to mouth anaerobes. Patients have severe sore throat and trismus, and may speak with a "hot potato" voice. There is marked unilateral peritonsillar swelling and erythema, causing deviation of the uvula. The abscess should be aspirated or incised and drained by an otolaryngologist, and antibiotics active against streptococci and mouth anaerobes (e.g., ampicillin-sulbactam) should be given.

ORAL CAVITY INFECTIONS

The oral cavity extends from the lips to the circumvallate papillae of the tongue. Various streptococci (e.g., *S. mutans, S. mitis, S. salivarius*) and anaerobes (e.g., *Peptostreptococcus, Veillonella, Lactobacillus, Bacteroides, Prevotella*) heavily colonize this area, and are the main pathogens in dental and oral cavity infections. *S. mutans* is a major pathogen in dental

cavities. Gingivitis and periodontitis are associated with anaerobic gram-negative rods such as *Prevotella intermedia* and *Porphyromonas gingivalis.* Mouth anaerobes are the major cause of Vincent's angina (acute necrotizing ulcerative gingivitis, or trench mouth). Patients have gingival pain, halitosis, cervical adenopathy, and ulcerations of the interdental papillae. Treatment is with oral clindamycin or penicillin plus metronidazole.

Ludwig's angina is a rapidly spreading cellulitis of the sublingual and submandibular spaces. It usually begins in the floor of the mouth from an infected mandibular molar tooth. The sublingual area becomes edematous, pushing the tongue to the roof of the mouth. The infection can cause acute airway obstruction. Patients present with fever, difficulty swallowing, drooling, and prominent submandibular and sublingual swelling. They should be admitted for airway monitoring, as intubation or tracheostomy may be necessary. Intravenous antibiotics active against streptococci and anaerobes should be given. Surgical incision of the infected soft tissue compartment may be necessary. Noma, or cancrum oris, is a rare infection caused by mouth anaerobes, especially fusospirochetal organisms such as *Fusobacterium nucleatum.* It occurs mainly in malnourished children, and begins as a gingival ulcer that rapidly spreads as a necrotizing cellulitis of the lips and cheeks. Therapy includes intravenous penicillin, debridement, and correction of dehydration and malnutrition.

Primary herpes simplex infection may cause painful vesicles on the buccal mucosa as well as the lips and tongue, and should be treated with hydration and acyclovir. The most common fungal infection of the oral cavity is thrush, usually due to *Candida* species. It occurs most often in immunocompromised patients, but may occur in normal hosts after prolonged antibiotic therapy or in patients with asthma using inhaled steroids. Treatment is with topical (e.g., nystatin) or oral (e.g., fluconazole) antifungal agents.

LARYNGITIS

Laryngitis, or inflammation of the larynx, is characterized by hoarseness. Acute laryngitis is usually caused by the same viruses that cause the common cold, and treatment is symptomatic. Hoarseness may accompany infections with human metapneumovirus, a virus identified in 2001 and primarily associated with bronchiolitis in young children. Herpes simplex virus may cause acute laryngitis; ulcerations or vesicles are typically seen. Streptococcal pharyngitis may be associated with laryngitis and should be treated with penicillin. *Corynebacterium ulcerans* has been a rare cause of a membranous laryngopharyngitis that may mimic diphtheria. Some studies from Sweden have found *Moraxella catarrhalis* to be more prevalent in cultures of patients with laryngitis than in controls, but a review of randomized controlled trials found that antibiotics appeared to have no benefit in the treatment of laryngitis. Fungi such as *Candida* and *Cryptococcus* are rare causes of laryngitis.

Patients with chronic hoarseness often have gastroesophageal reflux disease, but must be examined for laryngeal malignancies. In rare instances, fungi or mycobacteria may cause chronic laryngitis. In chronic progressive disseminated histoplasmosis, ulcers may occur on the larynx, as well as on the tongue, buccal mucosa, and gingiva. Blastomycosis may also produce laryngeal ulcers. Tuberculosis (TB) may cause laryngeal lesions that mimic a laryngeal neoplasm. Patients typically present with hoarseness but often lack systemic symptoms to suggest TB. They may have negative sputum smears for acid-fast bacilli and a clear chest radiograph. In a retrospective study of 22 patients with laryngeal TB, 9 had clear lungs and only 7 had active pulmonary TB. The patients with concurrent pulmonary TB characteristically had multiple ulcerative lesions on their vocal cords, while those with clear lungs had nonspecific, polypoid, single laryngeal lesions.

CROUP

Croup, or acute laryngotracheobronchitis, is characterized by subglottic edema and occurs most often in children ages 3 months to 3 years old, with peak incidence in the second year of life. It is rare in children over age 6. Most cases occur in fall, winter, and spring; the most common cause, parainfluenza type 1, has caused biennial epidemics in the fall in the United States. Croup is characterized by fever, inspiratory stridor, and a "seal's bark" cough. In severe cases, there is both inspiratory and expiratory stridor. There is typically a fluctuating course, and there can be alternating clinical improvement and worsening within an hour. Croup usually follows the onset of upper respiratory tract infection symptoms by 1 to 2 days. The cause is nearly always viral, with parainfluenza virus types 1 through 3 accounting for the majority of cases; type 1 is the most common cause in the United States. Influenza virus, particularly type A, also causes croup and may be more severe. Respiratory syncytial virus causes between 1 and 11 percent of cases, and typically affects children under age 1. Adenovirus, rhinovirus, enterovirus, and *M. pneumoniae* are rare causes.

The diagnosis of croup is based primarily on clinical grounds. A diagnosis of the viral etiology may be made by one of the rapid viral antigen detection techniques (e.g., RT-PCR) on nasopharyngeal swabs. The most important differential diagnosis in the acute clinical setting is epiglottitis (see below). Children with epiglottitis usually lack the characteristic seal's bark cough of croup, appear more toxic, and their illness worsens more rapidly.

Treatment of croup consists of nebulized racemic epinephrine, corticosteroids, and humidified air, although the value of humidified air has been questioned. A recent study of high vs. low humidity vs. mist therapy for croup in an emergency department found no difference in outcome between the three groups at 30 and 60 minutes, nor in the percentage of patients requiring hospitalization. Nebulized racemic epinephrine has a well-established role in treating croup, producing signs of clinical improvement within 30 minutes and with a duration of action of about 2 hours. Children should be

monitored for rebound edema for several hours after initiation of therapy. Corticosteroids are also beneficial, with onset of action within 6 hours and duration of benefit 12 hours. Oral or intramuscular dexamethasone has shown benefit for moderate to severe croup, and a single dose of oral dexamethasone is beneficial for mild croup.

EPIGLOTTITIS

Acute epiglottitis (supraglottitis) is a medical emergency, as it can rapidly lead to airway obstruction. It begins as a cellulitis between the base of the tongue and the epiglottis, pushing the epiglottis posteriorly. It then involves the epiglottis itself, with rapid swelling and airway compromise. Epiglottitis has become a rare disease in children since the advent of vaccination against *Haemophilus influenzae* type b (Hib) in 1985, which decreased the incidence of all types of invasive Hib disease by over 99 percent. In the prevaccine era, the incidence of epiglottitis was highest in children ages 2 to 4. Disease in children is due to rare cases of Hib vaccine failure or to other organisms, including nontypeable *H. influenzae*. The incidence in adults has been increasing in the past 20 years, from 0.8 cases per 10,000 in 1986 to 3.1 in 2000. Blood cultures are usually negative in adults and cultures of the epiglottis difficult or dangerous to obtain, so the etiology is often unknown. Pathogens isolated from throat cultures in adults with supraglottitis include *H. influenzae*, *H. parainfluenzae, Streptococcus pneumoniae,* group A streptococcus, and *Staphylococcus aureus*. Viral epiglottitis is very rare and poorly substantiated.

In children, the onset of symptoms occurs rapidly, usually within 6 to 12 h, and patients appear toxic. Patients are febrile, irritable, complain of sore throat and dysphagia, prefer to sit leaning forward, and may be drooling. Inspiratory stridor may occur, but the barking cough seen in croup is absent. Adolescents and adults usually have a less fulminant presentation, often with 2 to 3 days of symptoms. Severe sore throat, odynophagia, and fever are the main presenting symptoms, each occurring in 90 percent of adults in a recent study; muffled voice was present in 70 percent. In adults, diagnosis is made by direct flexible fiberoptic nasolaryngoscopy, a procedure that takes just minutes to perform in the emergency room by an otolaryngologist. A swollen, erythematous epiglottis is seen. Children suspected of having epiglottitis should be transported, sitting up, to the operating room for direct endoscopic visualization of the epiglottis. An uncuffed endotracheal (or nasotracheal) tube should be immediately inserted (or, if necessary, a tracheostomy performed) if a "cherry red" edematous epiglottis is seen. Lateral neck radiographs, used in the past to demonstrate the "thumb sign" of an edematous epiglottis, are rarely used now as they may be falsely negative and may cause a critical delay in securing the airway.

All patients with epiglottitis should be monitored in an intensive care unit. Children with epiglottitis should be intubated for airway protection, while adults whose endoscopic examination reveals no impending airway compromise may be managed with close observation. Broad-spectrum intravenous antibiotics with activity against *H. influenzae*, such as ampicillin-sulbactam, should be given. If the patient with epiglottitis due to *H. influenzae* has household contacts that include an unvaccinated child under age 4, the patient and all members of the household should receive rifampin prophylaxis to eradicate carriage of the organism.

BACTERIAL TRACHEITIS

This rare disorder, sometimes called membranous croup, presents acutely like epiglottitis but primarily involves the subglottic region like croup. It may represent bacterial superinfection of a viral tracheitis. It usually affects children between 3 weeks and 13 years of age, and is uncommon in adults. Patients present with the acute onset of high fever, stridor, and dyspnea after a viral prodrome. They do not respond to racemic epinephrine or corticosteroids. On endoscopy, patients have a normal epiglottis but the subglottic trachea is covered with a thick exudate. Inspissated secretions may produce a pseudomembrane. Cultures of tracheal secretions yield *S. aureus* in half of the cases; other organisms include group A streptococcus, *S. pneumoniae*, and *H. influenzae*. Gram-negative bacilli have been rarely described. Most patients require immediate intubation; some require tracheostomy. Up to 60 percent will have concurrent pneumonia. Broad-spectrum intravenous antibiotics active against *S. aureus* and *H. influenzae* should be given, along with airway humidification and aggressive pulmonary toilet. Inspissated or copious secretions may cause airway obstruction even in patients with an artificial airway; several patients have died because of this complication.

LARYNGEAL PAPILLOMATOSIS

Recurrent respiratory papillomatosis (RRP) is a rare disease caused by human papillomavirus that involves the larynx, but also may involve the trachea and lungs. Human papillomavirus types 6 and 11 are the types usually responsible; type 11 tends to produce more aggressive disease and carry a higher risk (3 percent) for eventual malignant transformation. Patients typically present with hoarseness, but may present with airway obstruction. Disease tends to be more severe in children than in adults, with extensive involvement of the airway and multiple episodes of recurrent disease. Treatment is with endoscopically directed surgical excision of the papillomas. In some young patients, rapid regrowth of the papillomas requires surgical excision on a nearly monthly basis. Intralesional injection of cidofovir at the time of surgery has been helpful in prolonging the time to relapse in some patients. Adjuvant systemic therapies with reports of some success in reducing the frequency of recurrences include oral indole-3-carbinol, subcutaneous injections of interferon-α,

and intravenous cidofovir. There are few randomized controlled trials of these agents, however, in this rare disease.

SINUSITIS

The paranasal sinuses develop as outpouches of the nasal cavity. The maxillary and ethmoid sinuses are present at birth, the frontal sinus develops after age 2, and the sphenoid sinus develops after age 7. The sinuses are lined with respiratory epithelium that includes ciliated cells and mucus-producing goblet cells. The cilia normally move the mucous blanket toward the sinus ostia (and then to the nasopharynx) at a speed of up to 1 cm/min. Inflammation causes a marked decrease in the beat frequency of the cilia, as well as narrowing or obstruction of the sinus ostia due to mucosal edema. The resulting disruption of mucociliary transport results in sinusitis.

The most common cause of inflammation leading to acute sinusitis is a viral upper respiratory infection. Most adults with common colds have computed tomographic (CT) evidence of ostial obstruction and sinus abnormalities, although only about 0.5 percent of all colds are complicated by acute sinusitis. Viral infections increase the amount of mucus produced and may damage ciliated cells. Another predisposing factor for sinusitis is allergic rhinitis, which may cause ostial obstruction by mucosal edema or polyps. Dental infections, especially of the upper teeth that abut the maxillary sinus (second bicuspid, first and second molars), may cause some cases of maxillary sinusitis. Anatomic obstruction of the sinus ostia due to a deviated septum, tumor, granulomatous disease (e.g., Wegener's granulomatosis), or nasotracheal or nasogastric tubes may also lead to sinusitis. Barotrauma from deep-sea diving or airplane travel, chemical irritants, and mucus abnormalities (e.g., cystic fibrosis) are other risk factors for sinusitis.

Acute Community-Acquired Bacterial Sinusitis

Symptoms of acute bacterial sinusitis include purulent nasal or postnasal drainage, nasal congestion, and sinus pain or pressure. The location of this pain depends on the sinus affected. Patients usually complain of pain in their cheek or upper teeth in maxillary sinusitis, the sides of the bridge of the nose in ethmoid sinusitis, supraorbital or frontal pain in frontal sinusitis, and retro-orbital, frontal, occipital, or vertex pain in sphenoid sinusitis. Fever occurs in about half of adults with acute sinusitis.

The diagnosis of acute bacterial sinusitis is often difficult on the basis of history and physical examination alone. Identical symptoms may occur in patients with viral upper respiratory infections, although bacterial sinusitis should be suspected if the patient has had persistent symptoms for more than 7 days. The sensitivity and specificity of individual symptoms such as facial pain when bending forward, purulent rhinorrhea, and sinus tenderness are less than 70 percent, making these features of limited diagnostic usefulness. In evaluating a patient for sinusitis, the routine physical examination is usually not helpful. Nasal endoscopy is helpful as it usually shows purulent secretions emanating from the sinus ostia in acute sinusitis, but this procedure is performed mainly by otolaryngologists. Plain films of the sinus are helpful in diagnosing sinusitis only if there is complete sinus opacification, an air-fluid level, or mucosal thickening of at least 4 mm; sinusitis, however, may be present without these findings. Sinus CT is much more sensitive than routine radiographs, particularly for ethmoid and sphenoid disease, but not specific for acute bacterial sinusitis as viral sinusitis may also show similar changes.

The bacteriology of sinusitis has been well defined only for acute, community-acquired maxillary sinusitis. Sinus puncture studies of adults with this infection have revealed that over 50 percent of cases are due to *S. pneumoniae* or nontypeable *H. influenzae*. Other pathogens include other streptococci, anaerobes, *Moraxella catarrhalis*, and rarely *S. aureus*. Anaerobes are more common in adults and *M. catarrhalis* is more common in children. Studies of sinuses other than the maxillary sinus are hindered by the difficulty of obtaining culture material that is not contaminated by nasal flora.

Treatment should be empiric and target the bacterial pathogens noted above. Oral therapy (e.g., amoxicillin-clavulanate, cefuroxime, levofloxacin) for 10 days is sufficient except in severe disease or in patients who also have a complication of sinusitis (e.g., orbital sinusitis).

Nosocomial Bacterial Sinusitis

Nosocomial bacterial sinusitis is usually seen in patients in the intensive care unit, and typically considered in those with fever of unknown origin. The incidence is higher in patients with nasotracheal tubes. It is also higher in patients with nasogastric tubes vs. those without, 20 vs. 12 cases per 1000 patient-days in one study. A sinus CT scan showing sinus opacification or an air-fluid level suggests the diagnosis. Bedside nasal endoscopy performed by an otolaryngologist may be helpful in obtaining cultures, either by endoscopically directed cultures of purulent meatal secretions or by maxillary sinus (antral) puncture. Antral puncture may not be indicated in all intensive care unit patients suspected of having sinusitis, however. One study found that only 8 percent of antral punctures yielded positive cultures in patients with normal endoscopic examinations. The pathogens in nosocomial sinusitis are usually *S. aureus* and gram-negative bacilli, and often include antibiotic-resistant organisms. Empiric treatment should be directed against these organisms (e.g., intravenous vancomycin plus cefepime) until culture results are known.

Chronic Bacterial Sinusitis

Chronic sinusitis is characterized by symptoms that last for weeks to months. Patients complain of persistent dull pain, postnasal drainage, foul odor and taste, and fatigue. True fever is rare, although many patients complain of having temperatures around 99°F. Most patients have stable, low-grade symptoms punctuated by episodes of acute sinusitis. These

episodes may be signaled by a change to purulent secretions and increased sinus pressure. A sinus CT scan is indicated in patients with chronic sinusitis, both to define the extent of disease and to exclude other causes of their symptoms. Patients should be evaluated by an otolaryngologist to exclude conditions that may be causing obstruction, such as a deviated septum, nasal polyps, Wegener's disease, or cancers such as adenocystic carcinoma.

The bacteriology of chronic sinusitis is not well defined. Most patients with chronic disease will have sinus cultures positive for bacteria, but whether these are colonizers or pathogens is not always clear. Patients without sinus disease also have positive cultures when cultures are obtained intranasally. Sinus cultures cannot be obtained without contamination by nasal flora, and since *S. aureus* is a nasal colonizer in 30 percent of the normal population, recovery of this organism is particularly difficult to interpret in the patient with chronic sinusitis. Coagulase-negative staphylococci are not sinus pathogens and should not be treated. Recently, there has been interest in fungi as the major pathogens in chronic sinusitis via a local allergic mechanism, since careful cultures of nasal mucus yield fungi in most patients. However, the same study that demonstrated the prevalence of molds in nasal mucus in patients with chronic sinusitis also recovered them in cultures from all of the normal controls, so causality has not been demonstrated. Studies of topical or oral antifungal agents for chronic sinusitis have been small or have not shown benefit over placebo.

Complications of Bacterial Sinusitis

Orbital Cellulitis

The most common complication of bacterial sinusitis is preseptal cellulitis or deeper orbital infection, conditions usually grouped under the heading "orbital cellulitis" (Fig. 118-1). Most cases are secondary to ethmoid sinusitis, since the ethmoid is separated from the orbit by only a very thin plate of bone, the lamina papyracea. Preseptal cellulitis only involves the eyelids and surrounding skin anterior to the orbital septum, but not the structures of the orbit. The lids appear red and edematous, but vision is normal and there are no orbital findings. In patients with orbital cellulitis, subperiosteal abscess, or orbital abscess, the eyelids are also red and swollen, but examination of the eye reveals one or more orbital findings as well. These include proptosis, which may be only detectable by using a Hertel's exophthalmometer, limitation of extraocular movements, and decrease in vision. In subperiosteal and orbital abscess, the abscess is almost always located medially or superomedially in the orbit (reflecting the involvement of the adjacent ethmoid sinus), and the eye looks "down and out." Abscess cultures demonstrate that the major pathogens are *S. pneumoniae*, group A streptococcus, nontypeable *H. influenzae*, and *S. aureus*, and these are presumably also the major pathogens in sinus-related orbital cellulitis and preseptal cellulitis. Antibiotics should be directed against these pathogens. Blood cultures are usually negative in adults, but are positive in 4 to 8 percent of young children

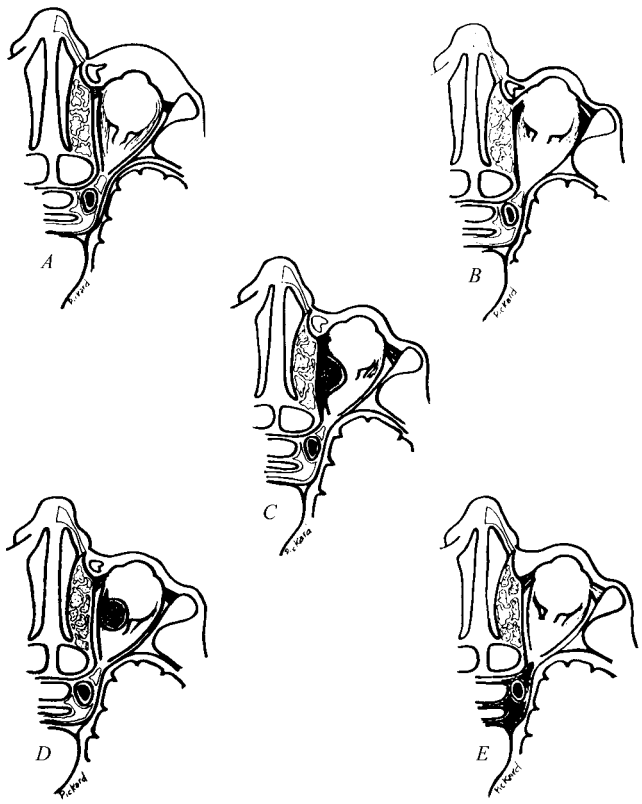

Figure 118-1 Orbital complications of sinusitis. *A.* Preseptal cellulitis. *B.* Orbital cellulitis. *C.* Subperiosteal abscess. *D.* Orbital abscess. *E.* Cavernous sinus thrombosis. *(From Chandler JR, Langenbrunner DJ, Stevens FR: The pathogenesis of orbital complications in acute sinusitis. Laryngoscope 1970; 80:1414–1428, with permission.)*

with preseptal cellulitis, in whom this condition may be secondary to bacteremic seeding by *S. pneumoniae*, other streptococci, or nontypeable *H. influenzae*. A CT scan should be performed on any patient with orbital findings, and an orbital or subperiosteal abscess usually requires emergency surgical drainage. Some authors also advocate a CT scan for children with apparent preseptal cellulitis, as some have a subclinical abscess.

"Pott's puffy tumor," or subperiosteal abscess of the frontal bone, is a complication of frontal sinusitis. Patients present with frontal pain and a tender, doughy swelling over the forehead. Treatment consists of 6 weeks of intravenous antibiotic therapy, and surgical drainage of the frontal sinus and subperiosteal abscess may be necessary. Intracranial complications of sinusitis usually result from frontal or sphenoid sinusitis. These include epidural abscess, subdural empyema, meningitis, cerebral abscess, and dural vein thrombophlebitis. Because of the proximity of the sphenoid sinus to the cavernous sinus, sphenoid sinusitis also may cause cavernous sinus thrombophlebitis.

Fungal Sinusitis

There are three forms of fungal sinusitis: allergic fungal sinusitis, sinus aspergilloma, and invasive fungal sinusitis.

Allergic fungal sinusitis (AFS) is characterized by the presence of "allergic mucin" in the involved sinuses and is thought to be due to a local hypersensitivity reaction to fungi. Mold spores are ubiquitous in the environment and in the nasal mucus, where they are trapped after being inhaled. Patients with AFS present with chronic sinusitis symptoms, and most have a history of nasal polyposis, aspirin allergy, and asthma. The CT typically shows inhomogeneous opacification of one or more sinuses, and there may be evidence of bony erosion of the sinus. Erosion is due to pressure necrosis, not fungal invasion. On magnetic resonance imaging (MRI), the affected sinus often appears black on T2 ("T2-weighted signal void"), a finding also seen in other types of fungal sinusitis. The diagnosis of AFS may be suspected at surgery because allergic mucin is tenacious, with the consistency of anchovy paste. It has histological features similar to that of mucin found in allergic bronchopulmonary aspergillosis, with many eosinophils and Charcot-Leyden crystals. Fungal hyphae are found in the mucus of half of the cases, but there is no evidence of tissue invasion. Only half of cases have positive fungal cultures, and these grow molds such as *Bipolaris, Curvularia, Alternaria,* and *Aspergillus.* Surgical removal of the inspissated mucus, along with intranasal steroids or short courses of oral steroids, seems to be effective. There is no proven role for antifungal agents.

Sinus aspergilloma is a noninvasive fungal disease that may cause symptoms of obstruction and chronic sinusitis. Usually only one sinus (most often maxillary) is affected, and symptoms are therefore unilateral. Surgical removal of the fungus ball is usually curative. Careful review of the pathological slides is required to verify that there is no tissue invasion.

Invasive fungal sinusitis carries a significant risk of mortality, in contrast to the other two benign forms of fungal disease. Estimates of mortality depend on the sinus affected and the immune state of the patient. In immunocompromised hosts, fungal disease presents acutely. Rhinocerebral mucormycosis is a life-threatening infection due to molds of the order Mucorales *(Rhizopus, Mucor, Absidia).* Approximately 70 percent of patients with mucormycosis have diabetes, while other risk factors include corticosteroid therapy or other immunosuppressant therapy, hematologic malignancies, and deferoxamine chelation therapy. Patients usually present with signs mimicking bacterial orbital cellulitis involving one eye, with swollen eyelids, proptosis, decreased extraocular movements, and decreased vision in that eye. In contrast with orbital cellulitis, eyelids may appear less red, unilateral frontal pain or temporal pain may be prominent, and there may be hypesthesia in the V_1 or V_2 distribution. If there are bilateral eye findings, involvement of the cavernous sinus should be suspected. Patients in whom the diagnosis is suspected should undergo immediate endoscopy by an otolaryngologist to look for a characteristic black eschar signifying infarcted intranasal or sinus mucosa. The eschar and adjacent tissue should be biopsied and examined for fungus on frozen section by a pathologist. On pathology, broad nonseptate hyphae are found invading tissue, often around blood vessels and nerves. In patients in whom the clinical suspicion for mucormycosis is high, the absence of a black eschar on clinical examination does not exclude the diagnosis, and biopsies of normal-appearing middle turbinate may yield the diagnosis. The absence of any evidence of sinusitis by CT scan also does not exclude the diagnosis. Treatment of mucormycosis requires a combination of aggressive surgical debridement and intravenous amphotericin or liposomal amphotericin therapy. Voriconazole is not active against mucormycosis. Posaconazole is a new agent that may be effective in patients who fail debridement and amphotericin therapy.

Aspergillus and other fungi (e.g., *Bipolaris, Curvularia, Exserohilum*) may also cause invasive fungal sinusitis. Immunocompromised patients, such as those who have received organ transplants, usually present acutely. Treatment is aggressive surgical debridement and systemic antifungal therapy. Normal hosts, in contrast, usually present subacutely, with weeks to months of symptoms. Fungi in the ethmoid and sphenoid sinuses may invade the orbital apex and cavernous sinus, affecting cranial nerves III, IV, V, and VI. Symptoms include headache, unilateral retroorbital pain, proptosis, ptosis, limitation of eye movement, decreased vision, and hypesthesia in the distribution of cranial nerve VI on the affected side. Symptoms of sinusitis are often absent. Diagnosis is suggested by the clinical findings and CT and MRI scans showing inflammation in the orbital apex or cavernous sinus. The diagnosis is made by demonstrating tissue-invasive fungi on pathology. Treatment is with appropriate systemic antifungal therapy (e.g., voriconazole for *Aspergillus*). Unlike immunocompromised patients with invasive fungal disease or patients with rapidly progressive mucormycosis, nonimmunocompromised patients may not require extensive surgical debridement as the disease is slowly progressive, allowing time for assessment of antifungal therapy.

EAR AND MASTOID INFECTIONS

Auricular Cellulitis and Perichondritis

In *auricular cellulitis*, the ear is usually red, edematous, hot, and mildly tender. The lobule is especially swollen and red. There may be a history of minor ear trauma from earrings, scratching, Q-tips, etc. Treatment is with warm compresses and antibiotics (e.g., nafcillin) directed against *S. aureus* and streptococci.

Perichondritis is an infection of the perichondrium of the ear that is often accompanied by infection of the cartilage of the pinna (chondritis). It may lead to ear deformity due to necrosis of the cartilage. Patients present with a swollen, hot, red, and exquisitely tender pinna; the lobule is usually spared. Usual causes include significant trauma to the ear (e.g., boxing) and burns. The most common pathogens are *Pseudomonas aeruginosa* and *S. aureus.* Intravenous antibiotics active against these organisms (e.g., ticarcillin-clavulanate or nafcillin plus ciprofloxacin) should be given for at least

4 weeks. This infection must be distinguished from relapsing polychondritis, a rheumatologic condition.

Otitis Externa

The external auditory canal is about 2.5 cm long. It is lined by a thin layer of skin, which covers cartilage in the lateral half of the canal and bone in the medial half. In the bony portion, the skin lacks a subcutaneous layer and is attached directly to the periosteum. This is an important feature in the pathogenesis of invasive otitis externa (see below). Glands secrete cerumen, which acidifies the canal and suppresses bacterial growth. Desquamated skin and retained moisture make the canal especially susceptible to *P. aeruginosa,* a hydrophilic organism.

Acute otitis externa, or swimmer's ear, occurs mostly in summer months and is often a result of exposure to water. It may be due to a decrease in canal acidity and the resulting bacterial overgrowth. The ear is pruritic and often extremely painful; the canal appears swollen and red. The usual pathogens are *P. aeruginosa, S. aureus,* and streptococci. Treatment consists of cleaning the ear (aural toilet) and topical antibiotic drops (e.g., ofloxacin 0.3 percent otic solution).

Herpes zoster oticus (Ramsay Hunt syndrome) is due to inflammation of the facial nerve by varicella-zoster virus. It is characterized by vesicles in the ear canal or concha, severe otalgia, loss of taste in the anterior two-thirds of the tongue, and ipsilateral facial nerve paralysis. Treatment is with an anti-herpes agent (acyclovir, valacyclovir, or famciclovir).

Invasive ("malignant") otitis externa (MOE) is a potentially life-threatening osteomyelitis of the temporal bone and skull base. First described in 1959, it occurs primarily in elderly diabetics and is nearly always caused by *P. aeruginosa.* The infection begins in the external canal, then invades the adjacent soft tissues, petrous apex of the temporal bone, and eventually the skull base. The typical patient is an older diabetic whose diabetes is in good control, who presents with unilateral hearing loss, ear pain, and drainage progressive over the previous weeks to months. The symptoms may have been misdiagnosed as chronic otitis media, a condition not characterized by otalgia. There is often a history of irrigation of the ear canal for wax removal a few days before the onset of ear pain. On examination, the ear canal is edematous, and there is granulation tissue in the inferior wall about halfway down the canal (the area overlying the bony-cartilaginous junction). Some patients also present with unilateral facial paralysis from involvement of cranial nerve VII; other cranial nerves (VI, IX, and X) may also be involved. Fever occurs in less than half of patients and the white blood cell count is usually normal. The sedimentation rate is almost always very elevated, however, typically in the 80 to 100 range. A CT and an MRI scan are essential for defining the extent of involvement. Bony involvement is best seen on CT, while soft-tissue changes are best seen on MRI. Cultures should be obtained of ear canal drainage or of superficial biopsies of canal granulation tissue; more extensive surgery is not usually indicated. Nearly all cases are due to *P. aeruginosa*, but cultures are important in determining antibiotic sensitivity and in excluding rare causes of invasive otitis (e.g., *S. aureus, Proteus, Aspergillus*). As soon as cultures are obtained, empiric treatment directed at *Pseudomonas* should be started. Usually two-drug therapy is given, such as intravenous ceftazidime plus ciprofloxacin (orally), and therapy is continued for at least 6 weeks. Aminoglycosides should be avoided due to the toxicities associated with prolonged therapy, especially in the elderly diabetics with hearing loss who typify the patient with MOE.

Acute Otitis Media

The middle ear is connected to the nasopharynx by the eustachian tube. Acute otitis media (AOM, Fig. 118-2), or infection of the middle ear, is thought to result from bacterial entry into the middle ear via the eustachian tube. It is often initiated by a viral upper respiratory infection, and is most common in fall through spring. The incidence of AOM decreases with age. More than two-thirds of children under age 3 have had at least one episode of otitis media, while the incidence in adults is only 0.25 percent. The most common symptoms are ear pain and decreased hearing. Children often have fever, but this is less common in adults. The tympanic membrane is usually red, opaque, and bulging. Spontaneous perforation of the tympanic membrane may occur, resulting in otorrhea and, frequently, decreased pain.

The bacteriology has been best defined in pediatric patients with AOM. The most common pathogens in nonneonates are *S. pneumoniae* (25 to 50 percent), *H. influenzae* (15 to 30 percent), and *M. catarrhalis* (3 to 20 percent). Most of the *H. influenzae* strains are nontypeable, but about 10 percent are type B and these cases may develop bacteremia or meningitis. Group B streptococci and enteric gram-negative bacilli are important in neonates. Viruses are recovered, sometimes along with bacteria, in 25 percent of pediatric cases. *H. influenzae* and *S. pneumoniae* are the most common isolates in adults.

Treatment of AOM is usually empiric and should be directed against *S. pneumoniae*, *H. influenzae*, and *M. catarrhalis.* Approximately 50 percent of *H. influenzae* strains and 100 percent of *M. catarrhalis* strains produce β-lactamase, and approximately 30 percent of *S. pneumoniae* are not susceptible to penicillin (15 percent are highly resistant) due to altered penicillin-binding protein. Amoxicillin should not be effective for any of these resistant organisms, yet approximately 20 percent of children with *S. pneumoniae*, 50 percent with *H. influenzae*, and 75 percent with *M. catarrhalis* will clear their AOM despite no or ineffective antibiotic therapy. Therefore, recent practice guidelines by the American Academy of Pediatrics recommend amoxicillin as first-line therapy for most children with AOM at doses of 80 to 90 mg/kg/day. Amoxicillin-clavulanate is recommended for children who present with severe disease, defined as fever of 39°C or higher and/or severe otalgia, or for amoxicillin-treatment failures as determined at 48 to 72 hours. For most children with non–type I allergy to penicillin, cephalosporins (cefdinir, cefpodoxime, cefuroxime) are recommended, and azithromycin or clarithromycin is recommended for those

with type I allergy. Ceftriaxone is recommended for children with severe disease and who are either penicillin-allergic with a non-Type 1 penicillin allergy or who have failed initial antibiotic therapy with amoxicillin-clavulanate. Clindamycin is recommended in patients who have failed therapy and have a type I allergy to penicillin.

Otitis Media with Effusion

Otitis media with effusion (OME), also called serous otitis, refers to the persistence of middle-ear fluid without other signs of infection. This condition may occur spontaneously as a result of eustachian tube dysfunction, or may occur as a result of AOM. Approximately 50 percent of children will have OME in the first year of life, and 90 percent before school age. Diagnosis is made by otoscopy. Many episodes resolve spontaneously, but 30 to 40 percent have recurrent OME and 5 to 10 percent have OME episodes that last at least 1 year. The American Academy of Pediatrics published practice guidelines in 2004 that state that antihistamines and decongestants are ineffective, and that antibiotics and corticosteroids have no long-term efficacy and thus are not recommended routinely for treating OME. These guidelines recommend hearing tests for children with persistent OME at 3 months; decisions regarding the need for tympanostomy tube placement may be determined by these test results. Children with OME at special risk for developmental delays (e.g., who also have blindness, autism, Down's syndrome) should have earlier hearing, speech, and language assessments.

Chronic Suppurative Otitis Media

Chronic suppurative otitis media (CSOM) is an inflammatory disease of the middle ear and mastoid characterized by tympanic membrane perforation, hearing loss, and persistent or recurrent otorrhea. It is associated with irreversible pathological changes of the mucosa of the middle ear and mastoid. There are two major subtypes of CSOM: CSOM with cholesteatoma and CSOM without cholesteatoma.

In CSOM with cholesteatoma, there is a perforation of the tympanic membrane, usually at the margin, which leads into a sac within the middle ear lined by skin. This sac constitutes a cholesteatoma, which contains desquamated keratin and may be superinfected with bacteria. Bacterial overgrowth results in purulent drainage via the perforation. An important feature of a cholesteatoma is its ability to enlarge by erosion of surrounding bone, which can result in serious intratemporal and intracranial complications.

In CSOM without cholesteatoma, there is a chronic central perforation of the tympanic membrane. Bacterial infection of the middle ear or mastoid can occur and leads to purulent drainage through the perforation ("active" chronic otitis media). Such drainage may be constant or episodic. The latter may be incited by an upper respiratory infection or by exposure of the ear canal to water.

The classic symptoms of both types of CSOM are painless otorrhea and hearing loss. Diagnosis is made with otoscopy. The appearance of the tympanic membrane varies with the type of CSOM (Fig. 118-2). Audiological assessment

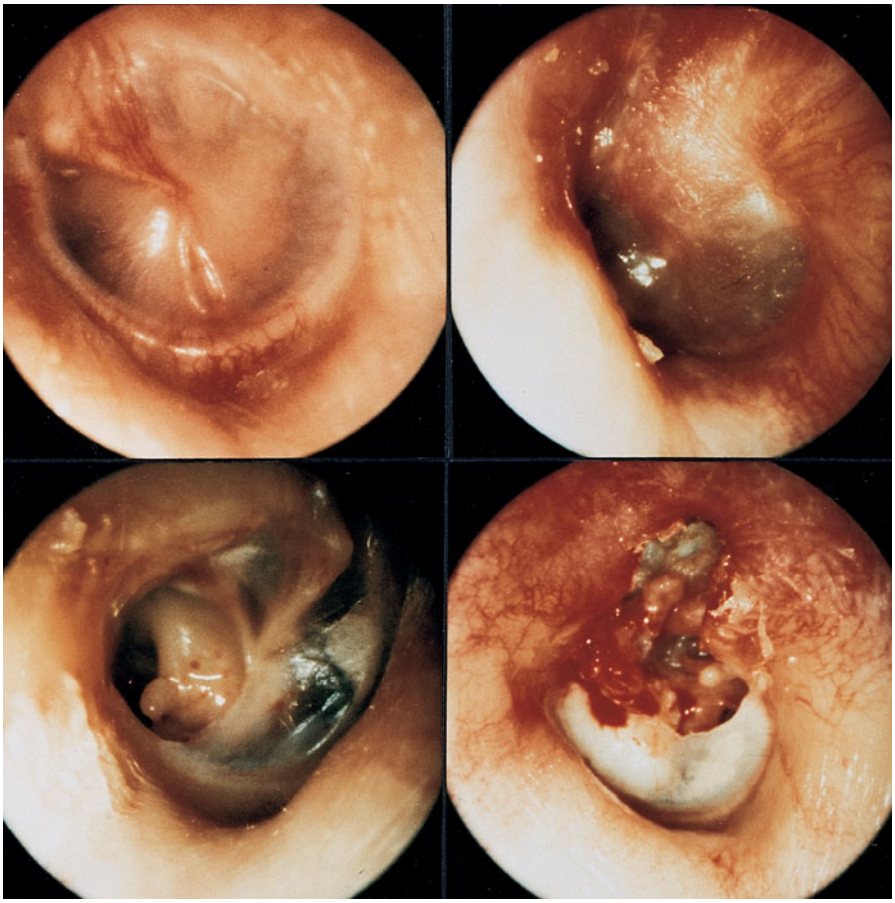

Figure 118-2 *Clockwise, from top left,* tympanic membranes: normal ear, resolving acute otitis media, chronic suppurative otitis media (CSOM) with cholesteatoma, CSOM without cholesteatoma. *(Courtesy of Steven D. Rauch, M.D.)*

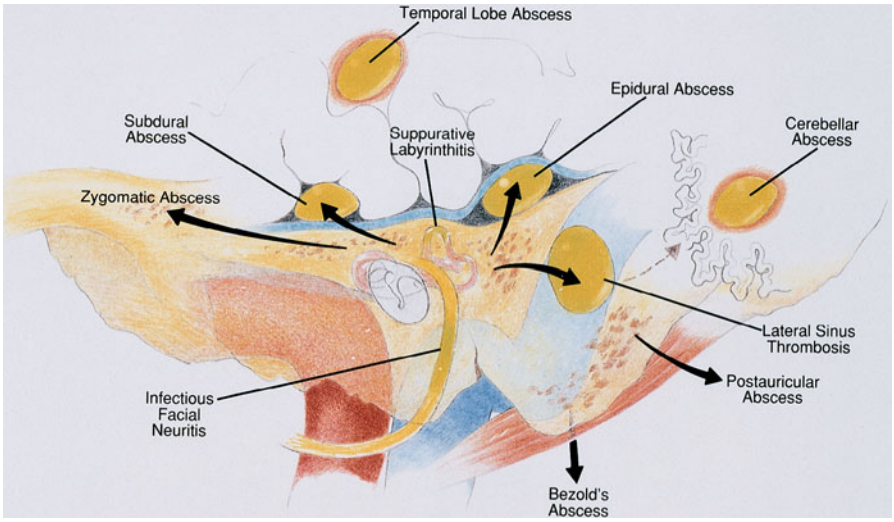

Figure 118-3 Complications of chronic otitis media. *(From Harris JP, Darrow DH: Surgery of the Ear and Temporal Bone. New York, Raven Press, 1993, with permission.)*

usually reveals a conductive type of hearing loss. Cultures of ears with CSOM in both adults and children often yield *S. aureus, Pseudomonas* and other gram-negative bacilli, and anaerobes. Most cases of CSOM with cholesteatoma require a mastoidectomy and tympanoplasty to remove the cholesteatoma and reconstruct the middle-ear sound transmission mechanism. Cases of "active" CSOM without cholesteatoma are treated with ear cleaning and topical antibiotic otic drops. Oral antibiotics are also sometimes used. The choice of antibiotics should be guided by culture results from the purulent middle-ear drainage, but most cases are treated empirically with a topical quinolone (e.g., ofloxacin 0.3 percent otic solution). Topical quinolones have proven to be nonototoxic and effective. Topical aminoglycoside therapy, commonly used in the past, is used infrequently now due to concern for ototoxicity. Surgery may be indicated in some cases of CSOM without cholesteatoma if medical therapy fails to control otorrhea or if surgery will improve hearing.

Acute Mastoiditis

The mastoid is the portion of the temporal bone posterior to the middle ear that contains a honeycomb of air cells lined by low, cuboidal epithelium. These air cells connect with the middle ear. Some degree of mastoid mucosal inflammation invariably accompanies episodes of AOM and is also present in many cases of CSOM. A CT scan of a patient with a middle-ear effusion or infection will often also show opacification of the mastoid air cells without destruction of the cells, and this usually represents a sterile effusion in the mastoid rather than acute mastoiditis. In contrast, acute mastoiditis is an acute bacterial infection of the mastoid. Untreated, this infection often results in breakdown of the bony partitions between the mastoid air cells and can extend beyond the mastoid compartment. Acute mastoiditis has become rare in the antibiotic era, and occurs primarily in children. It occurs with the first episode of AOM in 10 to 50 percent of children, but may also occur with an episode of recurrent AOM. Patients present with pain, tenderness, and swelling over the mastoid. The pinna is pushed out and forward when there is a subperiosteal abscess or cellulitis. A CT scan may demonstrate bony destruction or a mastoid abscess. Major pathogens include *Pseudomonas*, *S. pneumoniae*, group A streptococcus, and *H. influenzae*. *S. aureus* and enteric gram-negative bacilli are seen in a small percentage of cases. Treatment is with broad-spectrum intravenous antibiotics directed against these organisms; surgery is also necessary in many cases and may include myringotomy, drainage of subperiosteal abscess, and mastoidectomy.

Complications of Acute and Chronic Otitis Media

Otogenic complications are more likely to occur from chronic than from acute otitis media (Fig. 118-3). Extracranial complications include sensorineural hearing loss, labyrinthitis and the resulting vertigo, facial nerve palsy, and osteomyelitis of the petrous portion of the temporal bone. In mastoiditis, infection may track under the periosteum of the temporal bone and cause a subperiosteal abscess, or may break through the mastoid tip and cause an abscess in the neck deep to the sternocleidomastoid muscle (Bezold's abscess). Intracranial complications include epidural abscess, thrombophlebitis of the dural veins, meningitis, and temporal lobe abscess.

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Acute Bronchitis and Community-Acquired Pneumonia

Th omas J. Marrie

ACUTE BRONCHITIS

Acute bronchitis is an inflammation of the tracheobronchial tree, usually in association with a generalized respiratory infection. It occurs most commonly during the winter months and is associated with respiratory viruses, including rhinovirus, coronavirus, influenza viruses, and adenovirus. *Mycoplasma pneumoniae, Chlamydia pneumoniae,* and *Bordetella pertussis* may also cause bronchitis. Secondary invasion with bacteria such as *Haemophilus influenzae* and *Streptococcus pneumoniae* may also play a role in acute bronchitis.

Cough is the most prominent manifestation of acute bronchitis. Initially, the cough is nonproductive, but later mucoid sputum is produced. Still later in the course of the illness, purulent sputum is present. Many patients with acute bronchitis also have tracheitis. Symptoms of tracheal involvement include burning substernal pain associated with respiration and a very painful substernal sensation with coughing. Rhonchi and coarse crackles may be heard on examination of the chest; however, there are no signs of consolidation and the chest radiograph shows no opacity.

Most cases of acute bronchitis require measures directed only at relieving cough. For patients with fever or a predominant tracheitis component and purulent sputum, the sputum should be gram stained and cultured. If there is a predominant microorganism seen in the presence of more than 25 polymorphonuclear neutrophils and fewer than 10 squamous epithelial cells per low-power field, antibiotic therapy directed against *S. pneumoniae* and *H. influenzae* should be instituted. Most patients, however, do not require antibiotic therapy for acute bronchitis; it is a self-limited disease.

PNEUMONIA

Definition

Pneumonia is defined as inflammation and consolidation of lung tissue due to an infectious agent. Pneumonia that develops outside the hospital is considered community-acquired pneumonia (CAP). Pneumonia developing 72 hours or more after admission to hospital is nosocomial, or hospital

acquired. There is still some debate as to whether nursing home–acquired pneumonia should be considered community acquired or nosocomial pneumonia. For this reason, it is perhaps best to divide pneumonia into community acquired and institution acquired. (The latter includes hospitals, nursing homes, extended care facilities, psychiatric institutions, and rehabilitation facilities.) This chapter focuses on community-acquired pneumonia.

Epidemiology

Pneumonia is a common disease. The overall attack rate is about 12 cases per 1000 persons per year. In adults, the rate of admission to hospital for treatment of pneumonia is low from age 17 to 55 years, at which point it begins to increase. The attack rates are highest at the extremes of age. Pneumonia is the sixth leading cause of death in the United States. In a study recently carried out in Seattle, investigators found that the overall rate for CAP among those aged 65 to 69 years was 18.2 cases per 1000 person years compared with 52.3 cases per 1000 person years for those who were greater than or equal to 85 years. Just over 59 percent of episodes among seniors were treated on an outpatient basis and they estimated that there were approximately 915,900 cases of CAP among seniors annually in the United States. Data from the National Hospital Discharge Survey in the United States indicate that from 1990 to 2002 there were 21.4 million hospitalizations among those 65 years of age and over and infectious diseases accounted for 48 percent of these hospitalizations. Forty-six percent of the infectious diseases hospitalizations were due to lower respiratory tract infections and 48 percent of the infectious diseases deaths were due to these infections. In another study that also used the National Hospital Discharge Survey to examine pneumonia among those 65 years of age and older over the 15-year period 1988 to 2002, the investigators noted a 20 percent increase in pneumonia as a first or any listed diagnosis. They also observed that the in-hospital mortality rate was 1.5 times higher for pneumonia as a first listed diagnosis compared with the other most common causes of hospitalization.

The epidemiology of pneumonia has changed in recent years. This is due in part to changes in the population at risk and in part to the discovery of new microbial agents that cause pneumonia and changes in antimicrobial susceptibility of old microbial agents, such as *S. pneumoniae, H. influenzae,* and *Staphylococcus aureus.* Population changes include continued increase in the number and proportion of patients who are 65 years of age or older.

There has been a steady increase in the number of organ transplant recipients in the general population and in the number of patients with HIV infection. This has created a subset of patients with community-acquired pneumonia who may be infected not only with the traditional pathogens that cause pneumonia but also with opportunistic pathogens; furthermore, these patients may have severe or atypical presentations of this infection. Newer pathogens recognized as causing pneumonia include Hantavirus, SARS Co-V, human metapneumovirus, and *S. aureus* isolates carrying the Panton Valentine leucocidin genes, some strains of which are also methicillin resistant. *Pneumocystis jirovecii,* previously a rare cause of pneumonia in intentionally immunocompromised patients, is a common cause of pneumonia in HIV-infected patients with CD_4 counts of less than 200/μl.

In a study carried out in a Swedish town in which all persons 60 years of age and older were studied, independent risk factors for community-acquired pneumonia were: alcoholism, relative risk (RR) 9; asthma, RR 4.2; immunosuppression, RR 1.9; age greater than 70 years vs. age 60 to 69 years, RR 1.5.

Risk factors for specific etiologies of pneumonia may differ from those for pneumonia as a whole. Thus, dementia, seizures, congestive heart failure, cerebrovascular disease, and chronic obstructive lung disease were risk factors for pneumococcal pneumonia in one study. In other studies, cigarette smoking and asthma have been found to be independent risk factors for invasive pneumococcal disease. Among HIV-infected patients, the rate of pneumococcal pneumonia is 41.8 times higher than those in the same age group who are not HIV infected. However, with the advent of highly active antiretroviral therapy, the incidence of pneumococcal bacteremia among HIV infected persons has dropped from 24.1 episodes per 1000 patient years to 8.2 per 1000 patient years. Up until a recent study from the Centers for Disease Control, the effect of chronic illness on the incidence of invasive pneumococcal disease in adults was underappreciated. In this study, the overall incidence rates of invasive pneumococcal disease was 8.8/100,000 adults. For those with diabetes it was 51.4; 62.9 for adults with chronic lung disease; 93.7 for those with chronic heart disease; and 100.4 among those who abused alcohol. The rate was highest in adults with solid cancer, 300.4, and HIV/AIDS, 422.9.

Risk factors for Legionnaires' disease include male gender, tobacco smoking, diabetes, hematologic malignancy, cancer, end stage renal disease, and HIV infection. Risk factors for severe respiratory syncytial virus infection in elderly persons include the presence of underlying chronic pulmonary disease (odds ratio [OR] 3.97), functional disability (OR 1.67), and low serum neutralizing antibody titer (OR 5.89). The usual risk factors for aspiration pneumonia are altered level of consciousness and various neurological diseases that interfere with the swallowing mechanism. Recently, there has been an association between the use of gastric acid suppressive drugs and aspiration pneumonia. The incidence rates of pneumonia in non–acid-suppressive drug users and those who used these agents was 0.6 and 2.45 per 100 person years, respectively. The risk seemed to be highest among those using proton-pump inhibitors.

There is seasonal variation in the rate of pneumonia. Both attack rates and mortality rates are highest in the winter months. This is likely due to many factors, including more time spent indoors (crowding) and hence more opportunity for person-to-person spread of infectious agents. In a study carried out in Tennessee, the weekly frequency of invasive pneumococcal disease correlated with the weekly frequency of isolation of respiratory syncytial virus and influenza virus.

Antimicrobial resistance of the common bacterial pathogens is also a key component of the epidemiology of CAP. Penicillin-resistant *Staphylococcal pneumoniae* (PRSP) is now a fact of life in most North American communities. Many of the PRSP isolates are resistant to three or more antibiotic classes (multidrug resistance). In one study, 14 percent of bacteremic *S. pneumoniae* isolates were resistant to penicillin, 12 percent to ceftazidime, and 24 percent to trimethoprim-sulfamethoxazole. In a recent study, the investigators examined 1817 *S. pneumoniae* isolates collected from patients with community-acquired respiratory tract infections at 44 U.S. medical centers during the winter of 2002 to 2003. The overall rates of resistance were as follows: penicillin 34.2 percent; ceftriaxone 6.9 percent; erythromycin 29.5 percent; clindamycin 9.4 percent; tetracycline 16.2 percent; and trimethoprim-sulfamethoxazole 31.9 percent. There was no resistance to the following agents: vancomycin, linezolid, and telithromycin. Multidrug resistance was present in 22.2 percent of the isolates and 2.3 percent of the isolates had ciprofloxacin MICs of greater than or equal to 4 μg/ml. These investigators also made the observation that since 1994 to 1995, rates of resistance to beta lactams, macrolides, tetracyclines, and trimethoprim sulfamethoxazole have plateaued or begun to decrease. In contrast, fluroquinolone resistance is increasing. Fortunately, it is possible to predict who is likely to have pneumonia due to PRSP. Previous use of beta lactam antibiotics, alcoholism, noninvasive disease, age of less than 5 or greater than 65 years, and immunosuppression are risk factors for PRSP pneumonia.

Clinical Manifestations

Symptoms that are suggestive of pneumonia include fever, chills, pleuritic chest pain, and cough. The cough may be nonproductive (dry) or productive of mucoid or purulent sputum. It may be rusty in color and frankly bloody; in patients with a lung abscess (anaerobic infection), it may have a foul odor. The latter is suggestive of anaerobic infection.

Elderly patients complain of fewer symptoms than do younger patients. Indeed, those greater than 75 years of age with pneumonia had 3.3 fewer total symptoms than did patients aged 18 through 44 years with pneumonia.

For some time it was held that typical pneumonia (due to pyogenic organisms such as pneumococcus, staphylococcus, or *H. influenzae*) could be distinguished from that due to *Mycoplasma pneumoniae*, *Legionella* spp., and *Chlamydia pneumoniae*—so-called atypical pneumonia—on the basis of a distinct clinical presentation. Atypical pneumonia is said to be characterized by a more indolent illness than that of typical pneumonia, with a cough that is nonproductive or productive of mucoid sputum only. Careful studies have shown that one cannot reliably distinguish between typical versus atypical pneumonia on clinical grounds. However, this is not to say that a careful history and physical examination are not helpful in suggesting a cause of the pneumonia. Table 119-1 gives a partial list of clues to the cause of pneumonia that may be obtained from the history and physical examination.

Nonrespiratory symptoms such as headache, nausea, vomiting, abdominal pain, diarrhea, myalgia, and arthralgia are also common symptoms in patients with pneumonia. It is wise to remember that the elderly complain of fewer symptoms with pneumonia than do younger patients.

In some instances extrapulmonary signs and symptoms may dominate the clinical picture. Thus, *M. pneumoniae* pneumonia may be complicated by a variety of neurological manifestations including encephalitis, meningitis, and cranial nerve palsies. In addition a maculopapular skin rash is not uncommon. Occasionally, Stevens-Johnson syndrome develops. Patients with *Legionella* pneumonia may have glomerulonephritis or cerebellar ataxia. One should also remember that pyogenic bacteria that cause pneumonia *(S. aureus, S. pneumoniae)* can cause metastatic infections such as endocarditis, brain abscess, and meningitis. Indeed, all patients with pneumonia and *S. aureus* bacteremia should have a careful evaluation for endocarditis.

Physical Examination

Fever is usually present, but some patients may be hypothermic (a poor prognostic sign), and some (20 percent) are afebrile at the time of presentation with pneumonia. Crackles are heard on auscultation over the affected area of lung, and physical findings of consolidation (dullness to percussion, increased tactile, vocal fremitus, whispering pectoriliquy, and bronchial breath sounds) are present in about 20 percent of patients with pneumonia. A pleural friction rub is heard in about 10 percent of cases.

Radiographic Diagnosis

A clinical suspicion of pneumonia usually prompts a chest radiograph. An opacity on the chest radiograph is considered the gold standard for the diagnosis of pneumonia. However, this opacity may be due to infection, infarction, hemorrhage, edema fluid, malignancy, or inflammation caused by a variety of processes, such as vasculitis or adverse drug reactions. Several studies have shown that radiologists cannot differentiate bacterial from nonbacterial pneumonia on the basis of the radiograph. Representative chest radiographs of patients with pneumonia are shown in Figs. 119-1 to 119-4. For patients with pneumonia treated on an ambulatory basis, there is considerable disagreement (in up to 50 percent of cases) between the radiologist's reading of the chest radiograph regarding the presence of pneumonia compared with that of the attending physician. In about 20 percent of patients with symptoms compatible with pneumonia and a chest radiograph read as normal or no pneumonia by the radiologist, computed tomography of the chest will be compatible with pneumonia. It is noteworthy that when patients who are admitted to hospital with a clinical diagnosis of pneumonia (radiologist says no pneumonia) are compared with those with radiologist-confirmed pneumonia, there is no difference in mortality between the two groups. While the percentage of patients with positive blood cultures does not differ between the groups, the microorganisms isolated do; about

Table 119-1

Clues to the Etiology of Pneumonia from the History and Physical Exam

Feature	Organism
Environmental	
Exposure to contaminated air-conditioning cooling towers, recent travel associated with a stay in a hotel, exposure to a grocery store mist machine, visit or recent stay in a hospital with contaminated (by *L. pneumophila*) potable water	*Legionella pneumophila*
Pneumonia after windstorm in an endemic area	*Coccidioides immitis*
Outbreak of pneumonia in shelters for homeless men, jails, military training camps	*Streptococcus pneumoniae; Mycobacterium tuberculosis*
Exposure to contaminated bat caves, excavation in endemic areas	*Histoplasma capsulatum*
Animal contact	
Exposure to infected parturient cats, dog, cattle, sheep, or goats	*Coxiella burnetii*
Exposure to turkeys, chickens, ducks, or psittacine birds	*C. psittaci*
Travel history	
Travel to Thailand or other countries in Southeast Asia	*Burkholderia (Pseudomonas) pseudomallei (melioidosis)*
Pneumonia in immigrants from Asia, India, Africa	*M. tuberculosis*
Occupational history	
Pneumonia in a health care worker who works in a large city hospital with patients infected with HIV	*M. tuberculosis*
Host factors	
Diabetic ketoacidosis	*S. pneumoniae* *Staphylococcus aureus*
Alcoholism	*S. pneumoniae* *Klebsiella pneumoniae* *S. aureus*
Chronic obstructive lung disease	*S. pneumoniae* *Haemophilus influenzae* *Moraxella catarrhalis* *Pseudomonas aeruginosa* (in the subset of patients with advanced COPD)
Solid organ transplant recipient (pneumonia occurring >3 months after transplant)	*S. pneumoniae* *H. influenzae* *Legionella* spp. *Pneumocystis jiroveci* *Cytomegalovirus* *Strongyloides stercoralis*
Sickle cell disease	*S. pneumoniae*
HIV infection with	*P. jiroveci*
CD4 cell count <200/μl	*S. pneumoniae* *H. influenzae* *Cryptococcus neoformans* *M. tuberculosis* *Rhodococcus equi*

Table 119-1

(Continued)

Physical findings	
Periodontal disease and foul-smelling sputum	Anaerobes, may be mixed aerobic-anaerobic infection
Bullous myringitis	*Mycoplasma pneumoniae*
Absent gag reflex, altered level of consciousness, or a recent seizure	Polymicrobial (oral aerobic and anaerobic bacteria) can be macro- or microaspiration
Encephalitis	*M. pneumoniae* *C. burnetii* *L. pneumophila*
Cerebellar ataxia	*M. pneumoniae* *L. pneumophila*
Erythema multiforme	*M. pneumoniae*
Erythema nodosum	*C. pneumoniae* *M. tuberculosis*
Ecthyma gangrenosum	*P. aeruginosa* *Serratia marcescens*
Cutaneous nodules (abscesses) and CNS findings	*Nocardia* spp.

Source: From Marrie TJ. Commonly required Pneumonia. Clin Infect Dis *18:501–515. 1994.*

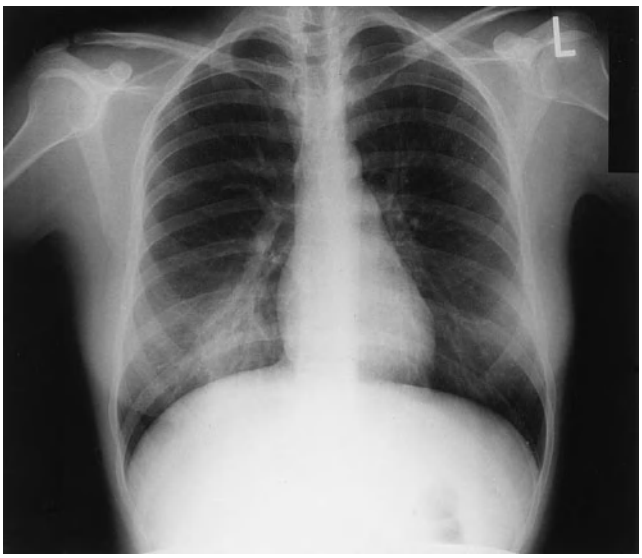

Figure 119-1 Right lower lobe pneumonia due to *Coxiella burnetfi* (Q fever). This young woman developed pneumonia after exposure to the products of conception of her infected pet cat.

60 percent of the isolates for those with definite pneumonia are *S. pneumoniae* compared with 31 percent for those with clinical pneumonia.

Etiologic Diagnosis

Pneumonia represents a difficult challenge for the clinician, since the etiology cannot be determined from the clinical presentation and data from microbiologic studies are not available for at least 48 hours. Even then, in the case of microorganisms isolated from the sputum, one cannot be sure that this is the organism causing the pneumonia, and not just a microorganism that had colonized the upper airway through which the sputum passed on its way to the specimen jar. For this reason, it is useful to categorize the etiology of pneumonia as definite or probable (Table 119-2).

The etiology of community-acquired pneumonia (CAP) as determined in prospective studies is given in Tables 119-3, 119-4, and 119-5. Table 119-4 shows data for patients with severe pneumonia requiring admission to intensive care units. Table 119-5 gives the etiologic data for bacterial pneumonia in patients with HIV infection. Early in the course of the HIV epidemic, *P. jiroveci* accounted for most cases of pneumonia. Now, with widespread use of prophylaxis to prevent *Pneumocystis* pneumonia, bacterial pneumonia is more common in HIV disease than previously seen (see Chapters 129 and 139). Indeed, the rates of pneumococcal pneumonia and *H. influenzae* pneumonia are 20 times higher among HIV-infected persons than in those of an age- and sex-matched population without HIV infection. In any young person with pneumococcal bacteremia, consider underlying HIV infection. However, one should not forget about *P. jiroveci* pneumonia, since many persons do not know they have HIV and this form of pneumonia is the presenting manifestation of HIV disease in these individuals. Likewise, one should never forget *Mycobacterium tuberculosis* as a cause of pneumonia, especially in the elderly.

Admission Decision

Once a diagnosis of pneumonia has been made, the next decision is whether or not to admit the patient to the hospital. Now, more than ever, there is considerable pressure to treat as many patients as possible at home. In order to do this, it is

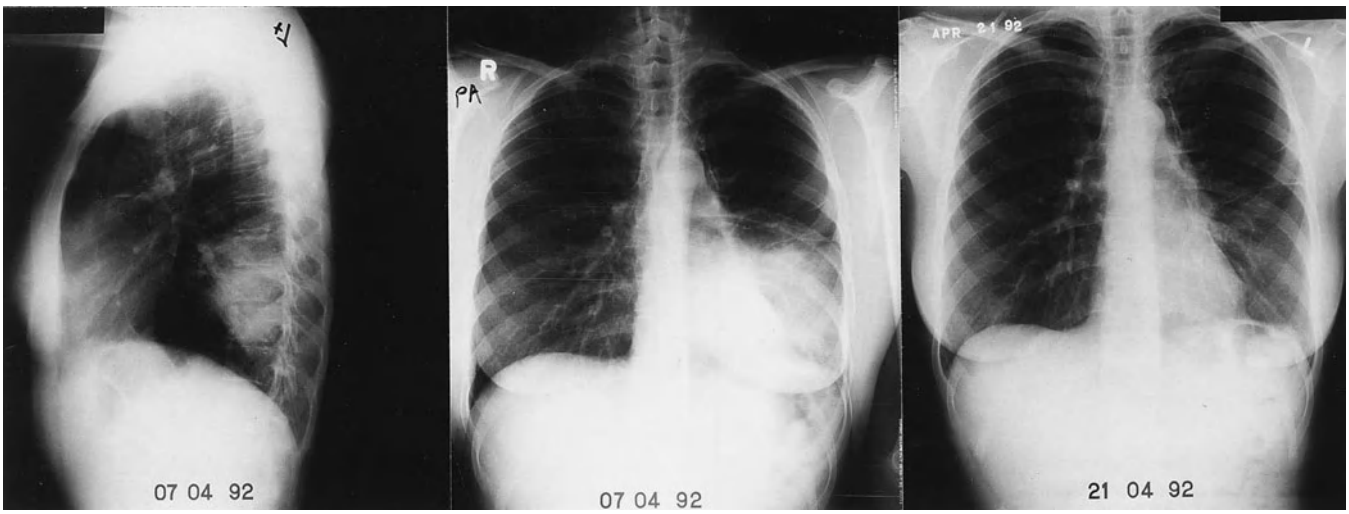

Figure 119-2 Serial chest radiographs of a 32-year-old nurse with *Chlamydia psittaci* pneumonia. She was severely ill with fever, chills, and headaches. She had severe fatigue for 8 months after this episode of pneumonia.

important to know the factors that are predictive of complicated course in pneumonia, some of which are given in Table 119-6. Several clinical rules that predict mortality have been developed that are often used to guide the admission decision. Two of these are the pneumonia severity index, often known as the PORT (patient outcomes research team) score (Tables 116–7 and 116–8) and the CURB-65 (confusion; urea; respiratory rate; blood pressure; age ≥65 years) rule (Table 116–9). The former, developed by Michael Fine and colleagues, assigns points to each of 20 different items that had been shown to be associated with mortality (see Table 119-7). This system allows categorization of patients with pneumonia into five strata, with increasing risk for mortality from risk class I to V. Mortality is less than 1 percent for patients in risk classes I to III, but increases to 9 percent in class IV and to 27 percent in class V (see Table 119-8). Patients in risk classes I and II can usually be treated at home; those in risk class III may require a period of observation in the emergency room before a decision is made about the optimal site of treatment. Patients with pneumonia generally prefer to be

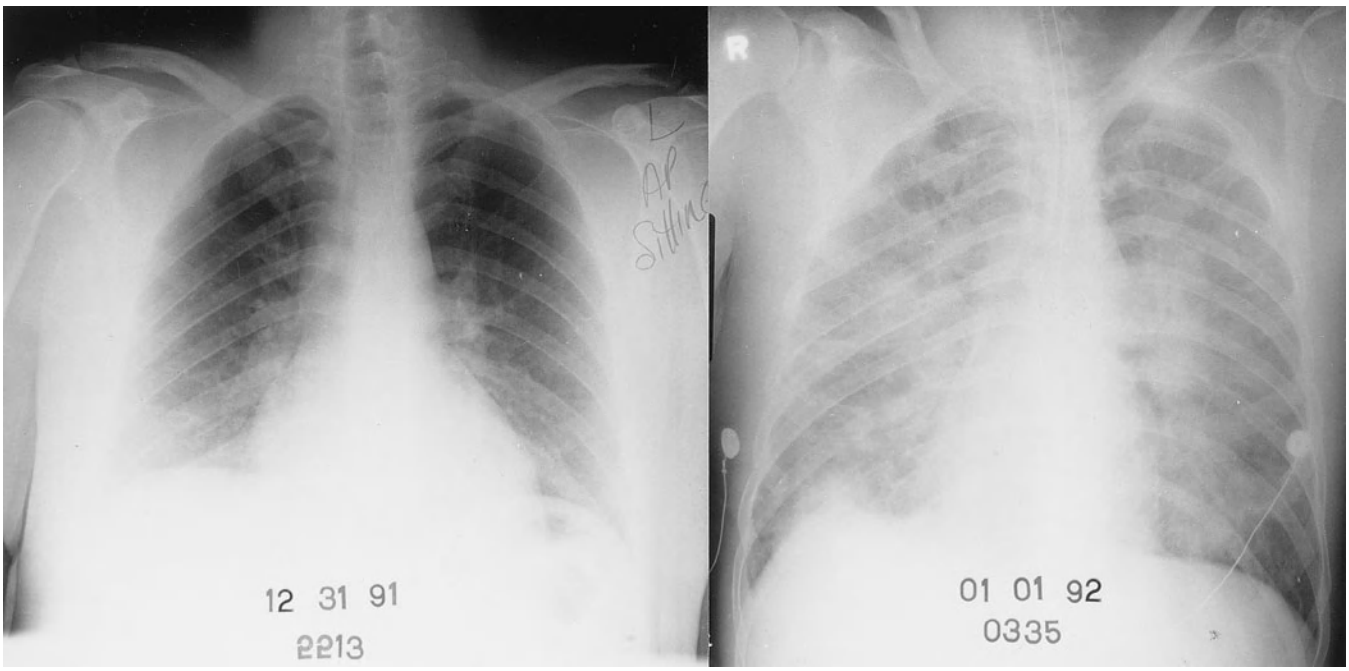

Figure 119-3 Chest radiographs showing rapidly progressive diffuse pulmonary opacities in a 22-year-old man with bacteremic *Streptococcus pneumoniae* pneumonia. This patient had had his spleen removed 6 years earlier. He rapidly developed septic shock and died about 8 hours after admission.

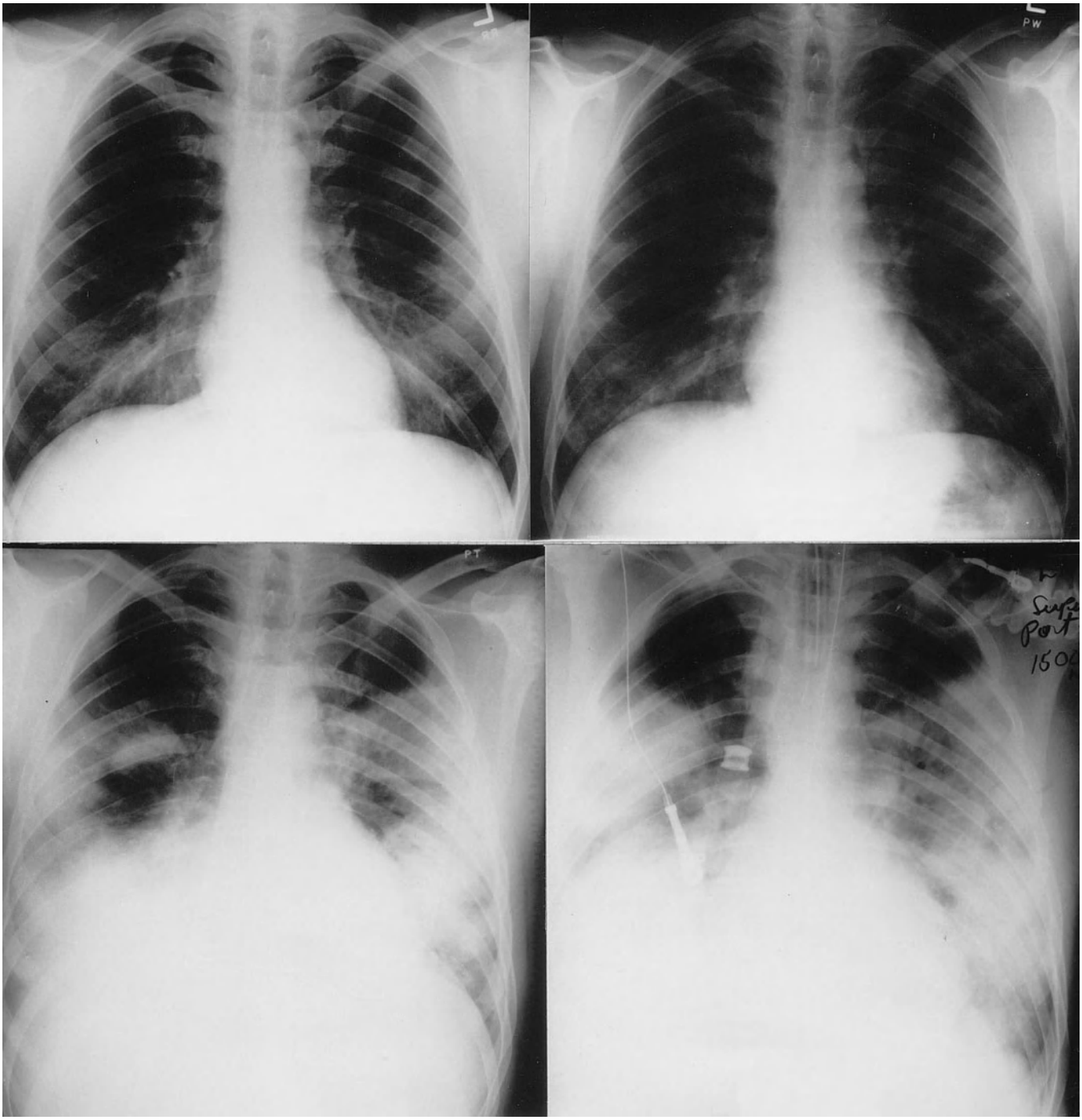

Figure 119-4 Serial chest radiographs of a 40-year-old man with pneumonia due to *Legionella pneumophila* serogroup 6.

treated at home if it can be done safely. As more experience has been gained with this predicition rule, not unexpectedly we have learned that the rule is only a guide. It does not factor social circumstances into the score and since the score is heavily age dependent, many young patients fall into the first three classes when it is readily apparent that they should be admitted.

In the CURB-65 rule the score can range from 0 (none of the elements present) to 5 (all of them present). For a score of 0 the mortality rate is 0.7 percent; 1 to 3.2 percent; 2 to 3 percent; 3 to 17 percent; 4 to 41.5 percent, and 5 to 57 percent (see Table 119-9).

However, the most important element in the admission decision is the physician's judgment. Prediction rules are no substitute for this. Functional status of your patient in the week prior to admission is also a powerful predictor of mortality. In one study, for those who were fully functional, the in-hospital mortality rate was 3.9 percent; for those

Table 119-2

Guidelines for Determining the Degree of Certainty of the Etiology of CAP

Definite
- Blood cultures positive for a pathogen
- Pleural fluid positive for a pathogen
- Presence of *Pneumocystis jiroveci* in induced sputum or in bronchoalveolar lavage luid
- A fourfold or greater rise in antibody titer to *Mycoplasma pneumoniae, Chlamydia pneumoniae, Coxiella burnetii*, or other pathogens for which serological testing is available.
- Isolation of *Legionella pneumophila* or a fourfold rise in antibody titer or positive urinary antigen test for *Legionella*
- Positive direct fluorescence antibody test for *Legionella* plus an antibody titer of ≥1:256 for *Legionella*
- Serum or urine positive for *Streptococcus pneumoniae* antigen
- Isolation of *Mycobacterium tuberculosis* from sputum
- Amplification of nucleic acid of *Legionella* species from a nasopharyngeal swab specimen

Probable
- Heavy or moderate growth of a predominant bacterial pathogen on sputum culture and a compatible Gram's stain
- Light growth of a pathogen in which sputum Gram's stain reveals a bacterium compatible with the culture results
- Amplification of nucleic acid of *Mycoplasma pneumoniae; C. pneumoniae;* influenza viruses A and B; parainfluenzae viruses 1,2,3; adenovirus, respiratory syncytial virus; human metapneumovirus from a nasopharyngeal swab specimen.
- Aspiration pneumonia as diagnosed on clinical grounds.

Source: Modified from Fang GD, Fine M, Odoff J, et al: New and emerging etiologies for community-acquired pneumonia with implications for therapy: A prospective multicenter study of 359 cases. Medicine *69:307–316, 1990.*

walking with assistance, it was 5.6 percent; for those who used a wheelchair, it was 20 percent; and for those who were bedridden, it was 25 percent.

Diagnostic Work-up

Patients who are well enough to be treated as outpatients need minimal diagnostic work-up. This should include a chest radiograph, complete white blood count, electrolytes, creatinine, and oxygen saturation by pulse oximetry. It is worth noting that there is controversy as to whether or not all patients who present in an office setting and are suspected of having pneumonia should have the described work-up. However, there is no doubt that those who present to a hospital emergency department and are suspected of having pneumonia should at the very least have the work-up outlined in the preceding. In addition, all individuals who have pleuritic chest pain and symptoms and signs suggestive of pneumonia should have a chest radiograph, and pulmonary thromboembolic disease should be considered. Pulmonary infarction can mimic pneumonia on occasion. Despite the opinion of some experts, a sputum specimen should be submitted for culture whenever possible. Blood cultures should be done on all ambulatory patients with fever (oral temperature greater than or equal to 38°C) and suspicion of pneumonia.

In patients who are ill enough to be admitted to the hospital, two sets of blood cultures should be performed. About 10 percent of patients with pneumonia have positive blood cultures. *Streptococcus pneumoniae* is the most common cause of bacteremic pneumonia, accounting for 60 percent of all cases. Despite the controversy about the utility of sputum gram's stain and culture, this is still a useful test. Take the time to obtain the specimen yourself. One of the chief reasons why this test has fallen into disrepute is that collecting the specimen is a task assigned to other members of a busy health care team. A sample collected hours after antimicrobial therapy has been initiated is useless.

All patients who present to the hospital with pneumonia should have their oxygenation status assessed. This can by done by pulse oximetry, and a blood gas analysis should be obtained if the oxygen saturation is less than or equal to 90 percent. Patients with chronic obstructive lung disease should have blood gases done because hypercarbia can not be detected by pulse oximetry.

Sputum Gram Stain and Culture

A sputum specimen should be cultured only if a smear of a representative portion shows more than 25 polymorphonuclear neutrophils and fewer than 10 squamous epithelial cells per low-power field. The gram stain on such a specimen is useful. If only one morphologic type of bacteria is seen in such a specimen, it is likely that this microorganism is causing the pneumonia. Indeed, in one study, when more than 10 gram-positive lancet-shaped diplococci were seen, the sputum was considered positive for pneumococci. This criterion was met in 62 percent of specimens that were culture positive for *S. pneumoniae*. The value of sputum culture in the diagnosis, management, and outcome of CAP remains a matter of controversy. The Infectious Diseases Society of America pneumonia guidelines recommend gram staining and culture of expectorated sputum for inpatients with CAP. The reasons for this recommendation are to permit optimal antibiotic selection directed to causative agent; limit injudicious antibiotic use in terms of cost, inducible resistance, and adverse drug reactions; allow for a rational basis for change from parenteral to oral therapy and any change in therapy necessitated by an adverse drug reaction; identify drug-resistant pathogens and monitor trends such as penicillin-resistant *Streptococcus pneumoniae*, beta lactamase–producing *Haemophilus influenzae*, or methicillin-resistant *Staphylococcus aureus*; and

Table 119-3

Etiology of Community-Acquired Pneumonia Requiring Hospitalization: North America

Reference	(Fang et al)	(Marrie et al)	(Bates et al)
No. of patients studied	359	719	151 (154 episodes)
No. (%) patients with sputum cultured	336 (94)	257 (36)	None*
Location	Pittsburgh, PA	Halifax, NS	Little Rock, Ark
Time period of study	Jul 1/86–Jun 30/87	Nov 1/81–Mar 18/87	1985
No. (%) with pneumonia of:			
Unknown cause	118 (32.9)	340 (47)	75 (48.7)
More than one cause (polymicrobial)	10 (2.8)	74 (10.3)	10 (6.4)
Streptococcus pneumoniae	39 (10.9)	61 (8.5)	9 (5.8)
Aspiration	12 (3.3)	52 (7.2)	Not stated
Mycoplasma pneumoniae	7 (2)	40 (5.6)	5 (3.2)
Influenza A virus	Not tested	40 (5.6)	7 (4.5)
Staphylococcus aureus	12 (3.3)	29 (4.0)	9 (5.8)
Haemophilus influenzae	39 (10.9)	27 (3.7)	2 (1.3)
Coxiella burnetii	Not tested	22 (3.1)	0
Influenza B virus	Not tested	17 (2.4)	0
Pneumocystis jiroveci	9 (2.5)	14 (1.9)	0
Legionella spp.	24 (6.7)	16 (2.2)	14 (9)
Mycobacterium tuberculosis	4 (1.1)	10 (1.4)	3 (1.9)
Chlamydophila pneumoniae	22 (6.1)	18/301 (6)†	12 (7.8)
Postobstructive	19 (5.3)	13 (1.8)	Excluded
S. epidermidis	0	0	4 (2.6)
Aspergillus spp.	0	0	1 (0.6)
Nocardia spp.	0	0	1 (0.6)
Francisella tularensis	Not tested	Not tested	5 (3.2)
Streptococcus spp.	10 (2.8)	19 (2.6)	4 (2.6)
Anaerobic bacteria	0	4 (0.6)	2 (1.3)
Other aerobic gram-negative bacteria	21 (5.9)	22 (3.1)	8 (5.2)

* *This study did not use information from sputum cultures in determining cause. Some patients had a variety of invasive diagnostic procedures.*

† *Only 301 patients had serum samples tested for antibodies to* Chlamydophila pneumoniae.

Sources: From Fang GD, Fine M, Orloff J, et al: New and emerging etiologies for community-acquired pneumonia with implications for therapy: A prospective multicenter study of 359 cases, Medicine *69:307–316, 1990; Marrie TJ, Durant H, Yates L: Community-acquired pneumonia requiring hospitalization: 5-year prospective study.* Rev Infect Dis *11:586–599, 1989; Bates JH, Campbell GD, Barren AL, et al: Microbial etiology of acute pneumonia in hospitalized patients.* Chest *101:1005–1112, 1992.*

prompt tracing of the contacts of those with *Neisseria meningitidis* pneumonia. On the other hand, the American Thoracic Society pneumonia guidelines recommend sputum culture only if a drug-resistant pathogen, or an organism not covered by usual empiric therapy, is suspected.

In patients with HIV infection, sputum production may be induced by inhalation of hypertonic saline, which irritates the tracheobronchial tree and produces bronchorrhea. This results in a specimen that is useful for examination for *P. jiroveci,* thereby obviating the need for bronchoscopy.

Patients who are ill enough to require admission to an intensive care unit for the treatment of their pneumonia should have an aggressive diagnostic work-up. This will usually include at least a bronchoscopy, with use of a protected brush to sample respiratory secretions and brochoalveolar lavage. If this is carried out before the initiation of antibiotic therapy, the diagnostic yield is up to 80 percent. When this procedure is performed after 72 hours or more of antibiotic therapy, however, the microbiologic yield is much lower, 18 percent.

Transthoracic needle aspiration can be used when the basal segment(s) of the lungs is (are) consolidated. A 20-gauge 3.5-inch needle is used to inject 2 to 3 ml of nonbacteriostatic saline into the lung. This is then aspirated and placed into a blood culture bottle. The diagnostic yield from this procedure ranges from 33 to 85 percent. This procedure is

Table 119-4

Etiology of CAP in Patients Requiring Admission to an ICU

Reference	(BTJ; PHLS)	(Torres et al)	(Pachon et al)	(Ortqvist et al)
No. studied	60	92	67	53
Mean age (yr)	54	53	56.8	52
No. (%) died	29 (48)	18 (20)	14 (21)	13 (25)
No. (%) with pneumonia due to (six most common causes listed):				
Unknown	25 (42)	44 (48)	45 (67)	25 (47)
Streptococcus pneumoniae	11 (18)	13 (14)	12 (17)	15 (28)
Haemophilus influenzae	7 (12)			
Legionella pneumophila	7 (12)	13 (14)	7 (10)	
Mycoplasma pneumoniae	4 (7)	6 (7)		3 (5)
Influenza virus	3 (5)			2 (4)
Staphylococcus aureus	2 (3)	1		2 (4)
Streptococcus spp.		3 (3)		
Chlamydophila psittaci				2 (4)
Other aerobic gram negative bacilli	2 (3)	5 (5)	8 (12)	

Sources: From British Thoracic Society Research Committee and the Public Health Laboratory Service: The aetiology, management, and outcome of severe community-acquired pneumonia on the intensive care unit. Respir Med *86:7–13, 1992; Torres A, Serra-Battles J, Ferrer A, et al: Severe community-acquired pneumonia: Epidemiology and prognostic factors.* Am Rev Respir Dis *144:312–318; 1991; Pachon J, Prados MD, Capote F, et al: Severe community-acquired pneumonia: Etiology, prognosis and treatment.* Am Rev Respir Dis *142:369–373, 1990; Ortqvist A, Sterner G, Nilsson JA: Severe community-acquired pneumonia: Factors influencing need of intensive care treatment and prognosis.* Scand J Infect Dis *17:377–386, 1985.*

Table 119-5

Etiology of Bacterial CAP in Patients with HIV Infection

Reference	(Burack et al)
Location of study	San Francisco, CA
Period of study	May 1990–April 1991
No. of pneumonia episodes	216
Cause of pneumonia (no., %)	
Haemophilus influenzae	4 (1.9)
Streptococcus pneumoniae	66 (30.6)
Moraxella catarrhalis	1 (0.5)
Other streptococcus	15 (6.9)
Cause unknown	54 (25)
Mixed infections	13 (6)
Haemophilus spp.	42 (19.4)
Klebsiella pneumoniae	4 (1.9)
Staphylococcus aureus	10 (4.6)
Pseudomonas aeruginosa	5 (2.3)
Serratia marcescens	1 (0.5)
Neisseria meningitidis	1 (0.5)

Sources: From Burack JH, Hahn JA, Saint-Maurice D, et al: Microbiology of community-acquired bacterial pneumonia in persons with and at risk for human immunodeficiency virus type 1 infection: Implications for rationale empiric antibiotic therapy. Arch Intern Med *154:2589–2596, 1994.*

contraindicated in those who are receiving mechanical ventilation. Occasionally, patients with CAP require an open lung biopsy. However, this is usually a last resort in a patient whose condition continues to deteriorate and there is no etiologic diagnosis despite the usual work-up, including bronchoscopy.

An acute-phase serum sample should be obtained from all patients who are admitted to hospital with CAP. If the patient responds promptly to antibiotic therapy, there is no need to obtain a convalescent sample. If the patient responds poorly to therapy, however, a convalescent sample should be obtained 3 to 6 weeks after the acute-phase sample. The diagnostic battery ordered depends on local epidemiologic conditions. In general, *M. pneumoniae, C. pneumoniae, Coxiella burnetti, Legionella pneumophila,* adenovirus, influenza A and B viruses, parainfluenza viruses 1, 2, and 3, and respiratory syncytial virus antibodies can be measured in most laboratories. Antibody titers to *S. pneumoniae* pneumolysin and detection of immune complexes to this antigen may be a tool for diagnosis of pneumococcal pneumonia in those who do not have sputum available for culture.

L. pneumophila serogroup 1 infection can be reliably diagnosed from detection of antigen in urine with a radioimmunoassay or an enzyme-linked immunosorbent assay. In the absence of an outbreak, *Legionella* spp. accounts for about 2 percent of cases of CAP. Thus, the dilemma is when to order this test. To some extent this depends on local epidemiology (in some hospitals the test is ordered for all patients sick enough to be admitted for treatment of CAP), but in general for patients with severe pneumonia this test probably should be done.

There is also a urinary antigen test for pneumococcal pneumonia. This test detects C polysaccharide, which is present in all serotypes of *S. pneumoniae.* It is reasonably sensitive and specific when bacteremic pneumococcal pneumonia is used as the gold standard. The question is, what is its usefulness in patients with negative blood cultures? There are false-positives in children with nasopharyngeal colonization with *S. pneumoniae.*

Multiplex polymerase chain reaction (PCR) is a tool that may be useful in the etiological diagnosis of CAP. Currently, from one specimen such as a nasopharyngeal swab or sputum, the following agents can be detected by multiplex PCR: *M. pneumoniae; C. pneumoniae; Legionella* spp.; influenza viruses A and B; parainfluenza 1,2,3 viruses; adenovirus; respiratory syncytial virus; human metapneumovirus; coronaviruses; and rhinoviruses. Using this technology, we have learned that viral pneumonia is more common in adults

Table 119-6

Risk Factors for a Complicated Course or Mortality in Patients with CAP

Age >65 years
Comorbid illnesses that are likely to be made worse by the pneumonia, especially chronic renal failure, ischemic heart disease, congestive heart failure, severe COPD, concurrent malignancy
Postsplenectomy state
Altered mental status
Alcoholism
Immunosuppressive therapy
Respiratory rate >30 breaths per minute
Diastolic blood pressure <60 mmHg; systolic blood pressure <90 mmHg
Hypothermia
Creatinine >150 mM/L or BUN >7 mM/L
Leukopenia <3000/μl or leucocytosis >30,000/μl
P_{O_2} < 60 mmHg or P_{O_2} >48 mmHg while breathing room air
Albumin <30 g/l
Hemoglobin <9 g/l
Pseudomonas aeruginosa or *Staphylococcus aureus* as the cause of the pneumonia
Bacteremic pneumonia
Multilobe involvement on chest radiograph
Rapid radiographic progression of the pneumonia defined as increase in the size of the pulmonary opacity of ≥50% within 36 h

Table 119-7

Community-Acquired Pneumonia Severity-of-Illness Scoring System: Assignment of Points*

Patient Characteristics	Number of Points
Demographic factors	
Age	
Men	Age in years
Women	Age in years minus 10
Nursing home resident	Age plus 10
Coexisting illnesses (definitions listed below)	
Neoplastic disease†	30
Liver disease‡	20
Congestive heart failure§	10
Cerebrovascular disease#	10
Renal disease¶	10
Physical examination findings	
Altered mental status**	20
Respiratory rate >30/min	20
Systolic blood pressure <90 mHg	20
Temperature <35°C (95°F) or >40°C (104°F)	15
Pulse rate >125/min	10
Laboratory and roentgenographic findings	
Arterial pH <7.35	30
Blood urea nitrogen >30 mg/dL (11 mmol/L)	20
Sodium <130 mmol/L	20
Glucose >250 mg/dL (14 mmol/L)	10
Hematocrit <30%	10
Partial pressure of arterial oxygen <60 mmHg	10
Pleural effusion	10

* *Based on Pneumonia Patient Outcomes Research Team (PORT) cohort study data.*
† *Any cancer (except basal or squamous cell carcinoma of the skin) active at presentation or within 1 year of presentation for CAP.*
‡ *Clinical or histologic cirrhosis or chronic active hepatitis.*
§ *Diagnosis documented by history or by findings on physical examination, chest film, echocardiogram, multiple gated acquisition scan, or left ventriculogram.*
# *Clinical diagnosis of stroke or transient ischemic attack, or stroke documented by MRI or CT.*
¶ *History of chronic renal disease or abnormal blood urea nitrogen and creatinine concentrations documented in this medical record.*
** *Disorientation as to person, place, or time that is not known to be chronic; stupor or coma.*

than was previously recognized. However, more study is necessary before we know the role of multiplex PCR in our diagnostic armamentarium.

Other Tests

C-reactive protein, serum procalcitonin, and neopterin have been used in an attempt to distinguish viral from bacterial infection. An ultrasensitive assay for procalcitonin looks promising in that at a level of less than or equal to 0.25 μg/L, antibiotic therapy has been successfully discontinued in

Table 119-8

30-Day Mortality Rate for Patients with Community-Acquired Pneumonia According to Risk Class in the Pneumonia Severity of Illness Scoring System

Risk class	Criteria	Outpatients Mortality	Inpatients Mortality
I	Age <50 years No existing illnesses or vital sign abnormalities	0	0.5%
II	<70 points	0.4%	0.9%
III	71–90 points	0	1.25%
IV	91–130 points	12.5%	9.0%
V	>131 points	NA	27.1%
	Mean mortality rate	0.6%	8.0%

Table 119-9

CURB-65 Rule Severity of Illness Scoring System for Community-Acquired Pneumonia

Confusion : new mental confusion
Urea >7 mM/L
Respiratory rate >30 breaths per minute
Blood pressure: Diastolic BP <60 mmHg or systolic blood pressure <90 mmHg
Age ≥65 years of age
Group 1: 0 or 1 of the above—mortality low—1.5%. Likely suitable for treatment at home.
Group 2: 2 of the above—mortality—9.2%. Hospitalization for treatment.
Group 3: 3 or more of the above—mortality—22%. Likely requires admission to ICU.

Source: From Lim WS, van der Eerden MM, Laing R, et al: Defining community-acquired pneumonia severity on presentation to hospital: An international derivation and validation study. Thorax 58:377–382, 2003.

patients with pneumonia. The inference is that patients with this level of procalcitonin have viral pneumonia.

TREATMENT

The initial therapeutic approach to pneumonia is empirical. Categorize the severity of the pneumonia as mild, moderate, or severe. It is then usually self-evident where the patient should be treated; at home, in the hospital, or in an intensive care unit. Table 119-10 outlines the guidelines for initial antimicrobial therapy for community-acquired pneumonia as proposed by the American Thoracic Society and the Infectious Diseases Society of America. A key concept in selecting empiric antibiotic therapy is to inquire about antibiotic therapy in the past 3 months and then select an agent that has not been used in that time period. If a macrolide has been used in this time period, then 35 percent of *S. pneumoniae* isolates are resistant to a macrolide compared with 7 percent if the patient did not have macrolide therapy in this time period. For penicillin or a cephalosporin, resistance increases from 5 to 9 percent in this setting. Thus, use a different class of antibiotic than the one the patient received in the past 3 months.

Since in everyday practice an etiologic diagnosis is frequently not made, antibiotic therapy has to be empirical. Osterheet et al. attempted to answer the question of whether combination therapy or monotherapy with a fluroquinolone (as recommended by the North American guidelines) is better than other therapy for the empiric treatment of CAP. They carried out a Medline search of studies published from January 1997 to April 2003. Only eight of the 135 articles fit their criteria for further analysis. In six of the eight studies, a significant reduction in all-cause mortality was found for patients treated with a combination of a beta lactam plus a macrolide or with monotherapy with a fluroquinolone. Three of these studies involved only patients with bacteremic pneumococcal pneumonia and in one study an effect was noted in one study year, 1993, but not in 1995 or 1997. Seven of the studies were retrospective and two involved administrative data bases. Clearly, a properly designed and conducted randomized clinical trial is necessary to answer this, the most fundamental question in the treatment of CAP.

Data from several retrospective studies suggest that combination therapy of bacteremic pneumococcal pneumonia with a macrolide and a beta lactam is better than single-agent therapy. Unfortunately, we do not have randomized control data to advise us. Recent data indicate that intravenous cefuroxime should not be used to treat bacteremic pneumococcal pneumonia, because the failure rate is higher than with other regimens.

In one study, treatment of patients hospitalized with CAP with moxifloxacin was associated with faster resolution of symptoms compared with patients who were treated with ceftriaxone plus erythromycin.

Table 119-10

Initial Empiric Antimicrobial Therapy for CAP

Outpatient
- Previously healthy
  - No recent antibiotic therapy: a macrolide, doxycycline telithromycin now known to cause hepatic necrosis.
  - Recent antibiotic therapy (within past 3 months). In general choose from a class of agents that the patient has not received within the past 3 months: a respiratory fluoroquinolone alone, an advanced macrolide (clarithromycin or azithromycin) plus high-dose amoxicillin, an advanced macrolide plus amoxicillin-clavulanate.
  - Co-morbidities such as congestive heart failure, chronic obstructive pulmonary disease, diabetes, or malignancy
  - No recent antibiotic therapy: an advanced macrolide or respiratory fluoroquinolone
  - Recent antibiotic therapy: Choose from a class of agents that the patient has not received within the past 3 months.
  - Suspected aspiration with infection: amoxicillin-calvulanate or clindamycin
  - Influenza with bacterial superinfection: a vancomycin or linezolid or respiratory fluoroquinolone

Inpatient
- Ward
  - No recent antibiotic therapy: a respiratory fluoroquinolone, or an advanced macrolide plus beta lactam, cefotaxime, ceftriaxone ampicillin ertapenem for selected patients.
  - Recent antibiotic therapy: An advanced macrolide plus a beta lactam, or respiratory fluoroquinolone alone. (The regimen selected depends on the nature of the recent antibiotic therapy. Choose from a class of agents that the patient has not received within the past 3 months.
- ICU
  - *Pseudomonas* infection is not an issue: a beta lactam plus an advanced macrolide or respiratory fluoroquinolone
  - *Pseudomonas* infection is not an issue but patient has a beta lactam allergy: a respiratory fluoroquinolone with or without clindamycin
  - *Pseudomonas* infection is an issue: an antipseudomonal agent plus ciprofloxacin or antispseudomonal agent plus aminoglycoside plus respiratory fluoroquinolone or macrolide
  - *Pseudomonas* infection is an issue and patient has a beta lactam allergy: aztreonam plus levofloxacin or aztreonam plus moxifloxacin or gatifloxacin with or without aminoglycoside
- Nursing home
  - Treatment in the nursing home: a respiratory fluoroquinolone or advanced macrolide plus amoxicillin-clavulanate
  - Hospitalized: same as ward or intensive care unit

Source: From Mandell LA, Bartlett JG, Dowell SF, et al: Update of practice guidelines for the management of community-acquired pneumonia in immunocompetent adults. Clin Infect Dis *37:1405–1433, 2003; Mandell LA, Marrie TJ, Grossman RF, et al: Canadian guidelines for the initial management of community acquired pneumonia: An evidence-based update by the Canadian Infectious Diseases Society and the Canadian Thoracic Society.* Clin Infect Dis *31:383–421, 2000; Niederman MS, Mandell LA, Anzueto A, et al: American Thoracic Society. Guidelines for the management of adults with community-acquired pneumonia. Diagnosis, assessment of severity, antimicrobial therapy, and prevention.* Am J Respir Crit Care Med. *163:1730–1754, 2001; Mandell LA, Wunderink RG, Aazueto A, et al. Infectious Diseases Society of America/American Thoracic Society Guidelines in the management of community-acquired pneumonia.* Clin Infect Dis *44:527–572, 2007.*

Once an etiologic diagnosis has been made, treatment should be changed to the cheapest, narrowest-spectrum agent effective against that microorganism. For example, if penicillin susceptible *S. pneumoniae* is determined to be the cause of the pneumonia, penicillin therapy is still the most appropriate treatment.

The response of patients to treatment depends on the severity of the pneumonia and the presence of co-morbidities that may be made worse by the pneumonia. Outpatients with mild to moderate pneumonia do very well. Mortality is rare (less than 1 percent), and only about 4 percent of patients fail therapy and require hospitalization. The issue of the most appropriate treatment for patients with pneumonia due to PRSP is unclear. We do know that pneumonia due to this microorganism can be treated successfully with high-dose intravenous penicillin. We also know that treatment with penicillin is not successful if there is concomitant pneumococcal meningitis. In this setting, vancomycin and ceftriaxone are recommended. If beta lactam antibiotics are used, the concentration of the antibiotic must exceed the MIC of *S. pneumoniae* 40 percent of the time for cure of pneumococcal pneumonia. In one study, high-dose amoxicillin was the most effective oral beta lactam antibiotic for the treatment of PRSP. Macrolide-resistant *S. pneumoniae* is also an issue in many communities. Because most cases of ambulatory pneumoniae are of unknown etiology and since there is less than 1 percent mortality among patients with pneumonia treated on an ambulatory basis, a worse outcome for

macrolide treated patients vs. other antibiotics may not be detected unless large RCTs are performed. Currently, about 2 percent of penicillin-susceptible *S. pneumoniae* isolates are resistant to macrolides, 12 percent of isolates intermediately resistant to penicillin are resistant to macrolides, while 25 percent of isolates that are highly resistant to macrolides are resistant to penicillin. Macrolide susceptibility of *S. pneumoniae* is defined as an MIC of up to 0.5 mg/L. The mean MICs for strains resistant because of an efflux mechanism is 10 mg/L; this accounts for 55 percent of the macrolide resistance in *S. pneumoniae*. Modification of the target (ribosomal) site accounts for 45 percent of the resistance and results in MICs of 64 mg/L. Thus, strains with resistance due to efflux mechanism may very well respond to treatment with a macrolide, whereas those due to target alteration will not. Resistance due to the efflux mechanism is more common in North America, while the reverse is true in Europe, i.e., most resistance is due to target alteration. Telithromycin, a new oral antibiotic, may be valuable for the ambulatory treatment of CAP in communities in which macrolide resistance is high. Telithromycin, a semisynthetic derivative of erythromycin, is the first of a new class of antibiotics, the ketolides. The α L-cladinose at position three is replaced by a keto group that prevents telithromycin from inducing MLS B resistance and results in improved activity against certain macrolide resistant bacteria. It is noteworthy that constitutively resistant *S. pneumoniae* is highly susceptible to telithromycin, but *S. pyogenes* and *S. aureus* expressing constitutive MLS B resistance are also resistant to telithromycin. Telithromycin is not affected by macrolide efflux mechanisms in bacterial cells. The dose is 800 mg OD for 5 to 10 days. Diarrhea, nausea, and vomiting are the major side effects followed by headache and dizziness. It has also been associated with elevations in hepatic transaminases and prolongation of the QT interval. It is a strong inhibitor of cytochrome P450 3A4 isoenzyme. Therefore, it is important to monitor for potential drug interactions with medications that prolong the QT interval or are metabolized by the CYP system. There is no need for adjustment in dosage for renal or hepatic failure.

The overall mortality for those admitted to hospital for treatment of pneumonia is 8 to 10 percent. In patients with nursing home–acquired pneumonia, it may approach 40 percent. For many of these patients, pneumonia is the final common pathway for a variety of chronic debilitating illnesses.

A recent concept in therapy of pneumonia requiring hospitalization is early switch to oral antibiotics. Patients who are stable by hospital day 3 (as evidenced by temperature of 37.5°C or less for 16 hours, white blood cell count returning toward normal, normal hemodynamics, no requirement for auxiliary oxygen, no complications of pneumonia such as empyema, and ability to take antibiotics by mouth) can be switched to antibiotics and discharged shortly thereafter. About one-third of patients qualify for this therapy. Prompt administration of antimicrobial therapy following a diagnosis of pneumonia intuitively makes sense. One study showed a lower mortality rate for elderly patients who received the first dose of antibiotics within 8 hours of presentation to an emergency department. In another large administrative data base study of over 18,000 patients among the 24.4 percent who were receiving antibiotics prior to presentation, antibiotic therapy within 4 hours of presentation was associated with a reduction in length of stay but not in mortality. Among the 75.6 percent of patients who were not receiving antibiotics prior to admission, there was both a reduction in LOS and mortality for those who received their first dose of antibiotic within 4 hours of presentation.

In a study of 399 patients with CAP treated on an ambulatory basis, symptoms had resolved within 14 days in 67 percent. The mean time to return to work in this population was 6 days compared with a median of 22 days for those who required hospitalization.

Some patients see their condition fail to improve or indeed worsen during therapy. Table 119-11 gives the factors that should be considered in this setting. One should not forget methicillin-resistant *S. aureus* (MRSA) as a cause of failure of initial treatment in patients with CAP. Also, in those who are admitted from nursing homes, consider extended spectrum beta lactamase (ESBL) producing enterobacteriaceae. Radiographic evidence of resolution of pneumonia lags behind clinical resolution and correlates with age and the presence of chronic obstructive pulmonary disease (COPD). In general, those who are under 50 years of age and have no COPD show radiographic resolution of pneumonia within 4 weeks. In contrast, resolution requires 12 or more weeks for those with pneumonia who are older than 50 years and have coexistent COPD or alcoholism. In about 2 percent of patients, pneumonia is the presenting manifestation of carcinoma of the lung (postobstructive pneumonia). It is important to demonstrate that the pneumonia has resolved radiographically for those who are at risk for carcinoma of the lung. In general, all tobacco smokers and those who are 50 years of age or older and have pneumonia should have a chest radiograph to determine whether or not the pneumonia has completely resolved. Table 119-11 gives an approach to the patient whose pneumonia is not responding to therapy.

ADJUNCTIVE THERAPY

In the PROWESS trial, drotrecogin alfa activated resulted in a 28 percent relative reduction in mortality among patients with severe CAP. Currently, patients with CAP and an APACHE II score of greater than 25 qualify for this drug, although the data suggest a beneficial effect beginning at an APACHE II score of 20. Tissue factor pathway inhibitor may also have a beneficial effect in severe pneumonia, and currently trials of this compound are underway.

Low-dose corticosteroid therapy is beneficial to those who are relatively adrenal insufficient (less than 9 μg/ml response in cortisol level to a dose of adrenocorticotrophic hormone). Hyperglycemia has been shown to be associated with higher mortality rates in patients who require hospitalization for community-acquired pneumonia, so it is likely that

Table 119-11

Considerations When Pneumonia Fails to Resolve or Worsens During Therapy

Reconsider the pneumonia diagnosis: Could this be pulmonary infarction, malignancy, vasculitis, drug reaction, or eosinophilic pneumonia?
Reconsider the etiologic diagnosis: Are you treating the appropriate microorganism(s)?
Remember that 10% of cases of community-acquired pneumonia are polymicrobial. Tuberculosis can mimic pyogenic pneumonia. Also consider unusual organisms such as *Actinomyces* or *Nocardia* species.
Are you dealing with a resistant microorganism? *Streptococcus pneumoniae* resistant to penicillin, erythromycin, and tetracycline is common in several European countries and the United States.
Has your patient developed nosocomial pneumonia? Such an event is common, particularly in patients who require endotracheal intubation and assisted ventilation. Is your hospital's potable water supply contaminated by *Legionella* spp.? If so, consider nosocomial Legionnaires' disease. Nosocomial legionnaires' disease should be a consideration anytime a patient with CAP is improving and develops nosocomial pneumonia.
Could this be postobstructive pneumonia (i.e., is endobronchial obstruction present)?
Have you considered empyema? Pus in the pleural space will continue to cause fever until it is drained.
Has metastatic infection occurred? Occasionally, patients who are bacteremic as a result of their pneumonia develop endocarditis, meningitis, septic arthritis, or a deep abscess such as splenic or renal abscess.
Always consider drug fever.

Sources: From Mandell LA, Bartlett JG, Dowell SF, et al: Update of practice guidelines for the management of community-acquired pneumonia in immunocompetent adults. Clin Infect Dis *37:1405–1433, 2003; Mandell LA, Marrie TJ, Grossman RF, et al: Canadian guidelines for the initial management of community acquired pneumonia: An evidence-based update by the Canadian Infectious Diseases Society and the Canadian Thoracic Society.* Clin Infect Dis *31:383–421, 2000, Niederman MS, Mandell LA, Anzueto A, et al: American Thoracic Society. Guidelines for the management of adults with community-acquired pneumonia. Diagnosis, assessment of severity, antimicrobial therapy, and prevention.* Am J Respir Crit Care Med *163:1730–1754, 2001.*

control of hyperglycemia will be beneficial to patients with pneumonia and elevated blood sugar.

Treatment of Pneumonia in the Nursing Home

In one study, if more than two of the following factors were present—respiratory rate greater than 30 per minute, temperature greater than 100.5°F, pulse rate greater than 90 beats per minute, and feeding dependence and mechanically altered diet—the failure rate of therapy of pneumonia in the nursing home was high. It is important to take patients' wishes into consideration in the decision to treat in the nursing home or transfer to the hospital. Treatment with ampicillin for nursing home–acquired pneumonia was associated with a significantly higher failure rate than was treatment with ceftriaxone. It seems that, given their antimicrobial spectrum and almost complete absorption following an oral dose, treatment of nursing home–acquired pneumonia with one of the "respiratory fluoroquinolones" is appropriate, although data from RCTs are still lacking for this group of patients.

PREVENTION

Influenza vaccination of the elderly results in reduction in the rate of hospitalization for pneumonia and influenza by 48 to 57 percent. The role of pneumococcal vaccine has not been as clearly defined as that of influenza vaccine; however, the Advisory Committee on Immunization Practice recommends pneumococcal vaccine for persons older than 65 years of age. A somewhat unexpected benefit of the use of a protein-polysaccharide conjugated pneumococcal vaccine during childhood has been the reduction of invasive pneumococcal disease in 20 to 39 year olds and among those equal to or greater than 65 years of age. Indeed, in the United States, the incidence of invasive pneumococcal disease among adults 50 years and older declined from 40.8 cases/100,000 prior to the introduction of the vaccine to 29.4 only 4 years later. The rate of death following an episode of invasive pneumococcal disease among adults aged 50 years or older decreased from 6.9 to 5.7/100,000. The authors estimated 6250 fewer cases and 550 fewer deaths per year among those 50 years of age and older in the United States compared with the years prior to introduction of the conjugate vaccine.

Prevention of aspiration in those at risk (post-stroke, advanced Parkinson's, and advanced Alzheimer's disease) is difficult. Head positioning, stimulation techniques, exercises to enhance the swallowing reflex, and eating pureed foods can all help to reduce the risk of aspiration. In addition, intensive oral care (cleaning teeth after every meal with an applicator of povidone iodine, and frequent dental care to control plaque) reduced the rate of pneumonia from 19 percent in the control group to 11 percent in the treatment group.

Of course, all those who are asplenic should be vaccinated with pneumococcal vaccine, *Hemophilus influenzae* B vaccine, and meningococcal vaccine. If possible, this should be done prior to splenectomy.

Patients with hypogammaglobulinemia should have periodic infusions of gammaglobulin in a regimen designed to keep the levels high enough to prevent infection.

QUALITY OF CARE MEASURES: PNEUMONIA

The following have been adopted as quality of care measures for patients with CAP requiring admission to the hospital: blood cultures prior to administration of antibiotics; measurement of oxygenation status; administration of antibiotics within 4 hours of presentation to the emergency department; ascertainment of influenza; and pneumococcal vaccination status and administration of these vaccines as necessary. In addition, for those who smoke tobacco products, at the very least information about cessation, and preferentially counseling regarding cessation of smoking.

A number of studies have examined the effect of using guidelines on patient care, and while the designs have differed, there is a strong suggestion that following guidelines has a "halo effect" in improving patient care and results in decreased mortality and, in some instances, reduced length of stay.

End-of-Life Decision Making

As indicated, many patients with CAP are elderly and many of these enter the hospital with advance directives. For all of these patients it is important to discuss life-sustaining measures such as assisted ventilation and admission to an intensive care unit should the need arise.

Specific Pathogens

Streptococcus pneumoniae

Streptococcus pneumoniae is still a common cause of pneumonia. Patients with bacteremic pneumococcal pneumonia are more likely to have diabetes mellitus, COPD, or alcoholism than those who have other causes of CAP. Capsular polysaccharide types 14, 4, 1, 6A/6B, 3, 8, 7F, 23F, and 18C are the most frequent causes of pneumococcal disease. Currently, 10 to 15 percent of *S. pneumoniae* isolates in the United States are intermediately or highly resistant to penicillin. These isolates are usually also resistant to erythromycin, tetracycline, and trimethoprim-sulfamethoxazole. Types 19A, 6A, 23, 19, 11, 6, 16, 9, and 14 are most frequently associated with penicillin resistance. The minimal inhibitory concentration (MIC) of penicillin for susceptible strains is under 0.06 μg/ml; isolates with MICs of 0.1 to 1 μg/ml are of intermediate resistance, and those with MICs of at least 2 μg/ml are highly resistant. These levels were established for central nervous system infections, for which trough concentrations of penicillin at 10 times MIC are necessary for cure. Generally, with intravenous antibiotics, high concentrations can be achieved in pulmonary tissue; therefore, even resistant strains of *S. pneumoniae* usually respond to treatment with high doses of penicillin or third-generation cephalosporin. If there is concomitant meningitis, however, both a third-generation cephalosporin and vancomycin should be given. A number of observation studies have indicated that the combination of a macrolide and beta lactam results in lower mortality rates for patients with bacteremic pneumococcal pneumonia compared with monotherapy or therapy with other combinations. Indeed, there is a suggestion that the combination of a beta lactam agent and fluoroquinolone results in higher mortality.

Staphylococcus aureus

Pneumonia due to this agent is usually of sudden onset, affects persons with co-morbid illnesses (except during influenza outbreaks, when healthy young adults may be infected), and is frequently complicated by cavitation (20 percent), pneumothorax (10 percent), jaundice (8 percent), empyema (5 percent), acute renal failure (5 percent), and pericarditis (2 percent).

MRSA is a rare cause of CAP. It does occur, however, and once established in a region, it can be a major problem. Vancomycin is used to treat MRSA, whereas cloxacillin or nafcillin is used to treat methicillin-susceptible strains. Surgical drainage is necessary for treatment of empyema. If multiple rounded opacities are seen in a patient with *S. aureus* pneumonia, suspect right-sided endocarditis. Toxic shock syndrome may complicate *S. aureus* pneumonia. Strains of *S. aureus* with the gene for Panton-Valentine leukocidin (PVL) have been described recently. PVL is an extracellular product of *S. aureus*. It is associated with primary skin infections such as furunculosis, and severe necrotizing pneumonia. In a recent report of eight cases of severe CAP caused by *S. aureus* strains carrying the PVL gene, six were fatal. The patients were all immunocompetent children or young adults. All had a preceding influenza-like syndrome before developing pneumonia, and the six deaths occurred shortly after diagnosis. Necropsy showed diffuse necrotizing hemorrhagic pneumonia. In another study, PVL-positive infections were more often marked by temperature greater than 39°C ($p = 0.01$), heart rate above 140 beats per min ($p = 0.02$), hemoptysis ($p = 0.005$), onset of pleural effusion during hospital stay ($p = 0.004$), and leucopenia ($p = 0.001$). The survival rate 48 hours after admission was 63 percent for the PVL-positive patients and 94 percent for PVL-negative individuals ($p = 0.007$). Histopathological examination of lungs at necropsy from three cases of necrotizing pneumonia associated with PVL-positive *S. aureus* showed extensive necrotic ulcerations of the tracheal and bronchial mucosa and massive hemorrhagic necrosis of interalveolar septa. Both methicillin-sensitive and methicillin-resistant strains have been described.

Haemophilus influenzae

This cause of pneumonia is more common in older patients with COPD. Both type B and non-B strains can cause pneumonia. About 30 percent of all *H. influenzae* isolates now produce beta lactamase and hence are resistant to ampicillin and amoxicillin. Between 7 and 14 percent of *H. influenzae*

isolates are resistant to trimethoprim-sulfamethoxazole. More than 90 percent of *H. influenzae* isolates are resistant to erythromycin; and 1 to 2 percent are resistant to tetracycline. Amoxycillin-clavulinic acid and a second- or third-generation cephalosporin reliably treat *H. influenzae* pneumonia.

Streptococcus pyogenes (group A streptococcus)

This agent is uncommon as a cause of pneumonia. One of its presentations is pneumonia accompanied by explosive pleuritis. Cases of group A streptococcal pneumonia may be accompanied by "toxic strep syndrome." Clindamycin, 600 mg given intravenously every 8 hours is superior to penicillin for the treatment of serious group A streptococcal infections. Of 2079 cases of invasive group A streptococcal (GAS) infection, 222 (11 percent) had pneumonia. The median age was 56 years. Underlying illness was present in 61 percent of cases. Most cases were community acquired (81 percent). The case fatality rate was 38 percent for GAS pneumonia, compared with 12 percent for the entire cohort with invasive GAS infection. In 2002, the largest outbreak of 127 cases of GAS pneumonia in the United States occurred among military recruits in San Diego. The epidemic continued despite prophylaxis with penicillin and required additional prophylaxis to end it.

Mycoplasma pneumoniae

This agent accounts for up to 30 percent of pneumonias treated on an outpatient basis. The extrapulmonary manifestations of *M. pneumoniae* are many and include cold agglutinin–induced hemolytic anemia, thrombocytopenia, encephalitis, cerebellar ataxia, Guillain-Barré syndrome, Stevens-Johnson syndrome, and myocarditis. This is primarily a disease of younger patients, but it accounts for 5 percent of all cases of pneumonia in persons 65 years of age or older. Macrolides (erythromycin, clarithromycin, and azithromycin) or tetracyclines are the treatment of choice.

Legionellaceae

This family, which includes 29 species and more than 49 serogroups (there are 15 serogroups of *L. pneumophila)*, causes two clinical syndromes: Legionnaires' disease and a self-limited flu-like illness (Pontiac fever). *L. pneumophila* serogroup 1, the microorganism responsible for the 1976 outbreak in Philadelphia that gave this disease its name, accounts for 70 to 90 percent of the cases of Legionnaires' disease. Legionnaires' disease can be community or hospital acquired, and it can occur in sporadic, endemic, and epidemic forms. Exposure to contaminated water (showers, cooling towers, or even ingestion of such water and subsequent microaspiration) is the prime mode of acquisition of this illness. Older age, male gender, immunosuppression (especially with corticosteroids), nosocomial acquisition, end-stage renal disease, and infection with *L. pneumophila* serogroup 5 are risk factors for death from this infection. On a molecular level, a mutation leading to a stop codon at position 392 resulted in a dysfunctional toll like receptor 5 protein unable to recognize flagellin. This was a risk factor for *Legionella pneumophila* infection.

There is now considerable evidence that quinolone antibiotics are superior to macrolides for the treatment of Legionnaires' disease. Azithromycin appears to be the macrolide of choice if this class of antibiotics is used. The disease may continue to progress for up to 4 days despite optimal therapy. Other options are doxycycline, 100 mg given twice intravenously in 24 hours and then 100 mg OD intravenously. Mild to moderately severe LD can be treated for 7 to 10 days while severe cases or LD in immunocompromised hosts should be treated for at least 21 days.

Hantavirus

In May 1993, reports of deaths due to severe pulmonary disease were received by the New Mexico Department of Health. Many of the affected persons were residents of the Navajo reservation located near the Four Corners area of New Mexico, Arizona, Colorado, and Utah. Within a few months a new Hantavirus (sin nombre, "no name" virus) had been isolated and shown to be responsible for this outbreak, which affected 17 persons. Hantavirus pulmonary syndrome (HPS) is characterized by a flu-like prodromal illness, followed by rapidly progressive noncardiogenic pulmonary edema. Fever, myalgia, cough or dyspnea, nausea or vomiting, and diarrhea are the most common symptoms. Hypotension, tachypnea, and tachycardia are the usual findings on physical examination. Leukocytosis (often with a severe left shift), thrombocytopenia (median lowest platelet count 64,500/mm^3), prolonged prothrombin and partial thromboplastin times, and elevated serum lactate dehydrogenase concentration are the most common laboratory findings. The mortality was high (88 percent) in the Four Corners outbreak. The initial chest radiograph showed infiltrates in 65 percent and no abnormality in 24 percent of patients. Subsequently, 16 patients (94 percent) had rapidly evolving bilateral diffuse infiltrates. In the few months after identification of this new Hantavirus, two more new Hantaviruses were identified in the United States and cases of HPS continue to be reported. The deer mouse, *Peromyscus maniculatus,* is the primary rodent reservoir for this virus.

Chlamydophila pneumoniae

This intracellular pathogen of humans is spread by aerosols. It causes sinusitis, pharyngitis, bronchitis, otitis media, and pneumonia. The last can be as a result of primary infection or as reactivation of latent infection. Primary infection affects mainly young adults and may be followed by reactive airway disease. Two weeks of treatment with doxycycline is adequate. Clarithromycin is very active in vitro against *C. pneumoniae,* but whether it is superior to doxycycline is not known.

The reactivation type of infection occurs in older adults, often as part of a polymicrobial infection. The rate of *C. pneumoniae* in this setting is unknown.

Diagnosis is by isolation of the organism from respiratory secretions or by serology. A greater than fourfold rise in IgM or IgG by microimmunofluorescence test or a single IgM titer of at least 1:16 or an IgG titer of at least 1:512 is considered diagnostic.

Severe Acute Respiratory Syndrome Coronavirus

In November 2002 an outbreak of severe acute respiratory syndrome (SARS) started in Guangdong Province in southern China and spread worldwide, affecting more than 8000 persons. SARS was due to a novel coronavirus that jumped the species barrier from civet cats to humans. Patients with typical SARS usually present 2 to 10 days following exposure with nonspecific symptoms including fever, myalgia, headache, malaise, and chills. Three to five days later, a nonproductive cough and dyspnea develop. Twenty percent of patients subsequently develop worsening respiratory distress requiring admission to an intensive care unit. Approximately 10 percent of all patients die from progressive respiratory distress or complications of their hospital admission, typically around the third week of symptomatic illness.

Approximately 75 percent of patients have unilateral or bilateral infiltrates on chest radiograph at the time of presentation. The majority of those without visible infiltrates have ground-glass opacities detectable on high resolution computer tomography at the time of presentation or progress to develop radiographic infiltrates. Generally, radiographic opacities peak between 8 and 10 days after onset of illness and then improve, correlating with the worsening and improvement of respiratory symptoms, but progressive radiographic deterioration may occur associated with a more protracted clinical course. There is no effective antiviral therapy. The management of severe cases is that of the management of severe respiratory failure. Attention to infection control measures designed to prevent spread of SARS is most important.

Human Metapneumovirus

Human metapneumovirus is a newly described member of the *Paramyxoviridae* family. Since its initial description in 2001, when it was isolated from nasopharyngeal aspirates of young children in the Netherlands, it has been described worldwide. Despite almost universal infection in early childhood, repeat infections do occur in adulthood, and it appears to account for about 2 to 3 percent of cases of pneumonia in adults. Unfortunately, there are no clinical or routine laboratory features that allow one to distinguish this type of pneumonia from bacterial pneumonia.

Mimivirus

A giant virus that stains gram-positive with gram stain has been found in amoebae. This virus is an uncommon but definite cause of some cases of community-acquired pneumonia.

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120

Acute Exacerbations of Chronic Obstructive Pulmonary Disease

Fernando J. Martinez • Jeffrey L. Curtis

DEFINITION

Although the topic remains controversial, a generally accepted definition of acute exacerbations of COPD (AE COPD) is "a sustained worsening of the patient's condition, from the stable state and beyond normal day-to-day variations, that is acute in onset and necessitates a change in regular medication in a patient with underlying COPD." It is important to exclude alternate causes of acute deterioration, including congestive heart failure, pneumothorax, and pulmonary emboli, among others. Two major approaches to defining an AE COPD have been advocated: symptom-based and event-based definitions. Symptom-based definitions are the most frequently used, with most modifying the criteria of Anthonisen et al. Although symptom-based definitions are the most relevant to patient care, some investigators have documented that a significant proportion of patients with an AE COPD may not report these symptoms to health care professionals. To circumvent difficulties with quantifying symptoms, event-based definitions have been utilized, particularly in clinical trials. This approach, which defines an AE COPD on the basis of health care utilization and therapy, may capture significantly fewer events. In fact, one group has compared symptom-based definition from daily diary cards to an event-based definition in a large, prospective study of an inhaled steroid/long-acting β-agonist; the correlation between the two definitions was quite weak. Accordingly, intensive investigation continues, seeking to develop optimal definitions both for clinical use and research studies.

The frequency and severity of exacerbations are quite variable among COPD patients. This variability may reflect the nature of data collection (prospective vs. retrospective), disease severity, medications administered, vaccinations, and smoking status. For example, investigators who identify AE COPDs through review of daily diary cards tend to identify more episodes per year. Studies that include patients with more severely impaired pulmonary function identify a greater number of yearly episodes.

IMPACT

Pulmonary Function

AE COPD episodes have been reported to result in measurable acute deteriorations in pulmonary function. Several groups have identified modest changes in pulmonary function, particularly in lung volumes, during the course of an AE COPD and its resolution. Importantly, persistent negative longitudinal effects of repeated AE COPDs have been reported by several groups; the additional decline in lung function averaged approximately 7 to 8 mL/year in FEV_1. As such, AE COPDs have measurable negative short- and long-term impacts on pulmonary function.

Health Care Utilization

AE COPDs are also major source of health care expenditure. Numerous groups have examined the economic impact of AE COPD on measures of health care utilization. In the United States in 1995, they were estimated to result in a total treatment cost of $1.2 billion in patients $\geq$ 65 years of age and $419 million in those < 65 years of age; these costs were predominantly for hospitalizations. A prospective Spanish study confirmed that patients who failed outpatient therapy, particularly those who required emergency department treatment and hospitalization, accounted for the majority of the total cost of care. Thus, patients with AE COPD, particularly those who require hospitalization, result in major health care expenditures.

Health Status

The negative effects of AE COPD are particularly evident on health-related quality of life (HRQoL). Cross-sectional studies have reported reduced HRQoL during AE COPD, while longitudinal studies have found that HRQoL improves from exacerbation to recovery. The greatest improvement in HRQoL after a single episode occurs during the first 4 weeks, although HRQL continues to improve over 26 weeks. A recurrence of AE COPD results in a markedly attenuated improvement.

ETIOLOGY

Viral Pathogens

Viral infections are increasingly recognized as causative in AE COPD. Rhinovirus infection of the bronchial epithelium induces the expression of numerous proinflammatory genes, including IL-8, Groα, and ENA-78. In fact, induction of NF-κB and other transcription factors has been clearly demonstrated with several viruses, including rhinovirus, respiratory syncytial virus (RSV), and influenza infection. In addition, rhinovirus and RSV infection of bronchial epithelial cell lines can be associated with the production of eotaxin, eotaxin-2, and CCL5. Experimental evidence has confirmed that rhinovirus infection can infect the lower airways. It is evident that viral infection could account for the inflammatory response previously described as typical of AE COPD.

Table 120-1

Viral Pathogens Implicated in Exacerbations of COPD

Rhinovirus
Coronavirus
Influenza A and B
Parainfluenza
Adenovirus
Respiratory syncytial virus
Human metapneumovirus

SOURCE: *Adapted from Martinez FJ, Han MLK, Flaherty K, et al: Role of infection and antimicrobial therapy in acute exacerbations of chronic obstructive pulmonary disease.* Expert Rev Anti Infect Ther *4:101–24, 2006.*

Clinical data implicating multiple viral pathogens in AE COPD are increasing (Table 120-1). Early studies, which relied on serologic studies or viral cultures of the upper airway, reported a relatively minor role for viral infection. More recent studies have utilized more sensitive techniques for virus identification, including polymerase chain reaction (PCR). Results have suggested that a much higher proportion of cases of AE COPD are related to viral infections (up to 60 percent in some series). As noted in Table 120-1, picornaviruses, respiratory syncytial virus (RSV), influenza and human metapneumoviruses have been identified most frequently. A prospective study of hospitalized patients with AE COPD found a viral pathogen in more than 48 percent of episodes (vs. 6.25 percent in the stable state), with a similar distribution of viral pathogens as previously noted; a clear relationship between viral infection and the inflammatory process was documented by this group (Fig. 120-1).

Bacterial Pathogens

The role of bacterial infection in individual AE COPD episodes remains controversial, in part due to the evolving diagnostic methods used to establish their etiologic role. These methods have included sputum culture, bronchoscopic sampling, molecular epidemiologic studies of bacterial pathogens, identification of an immune response, and recording a response to antimicrobial therapy.

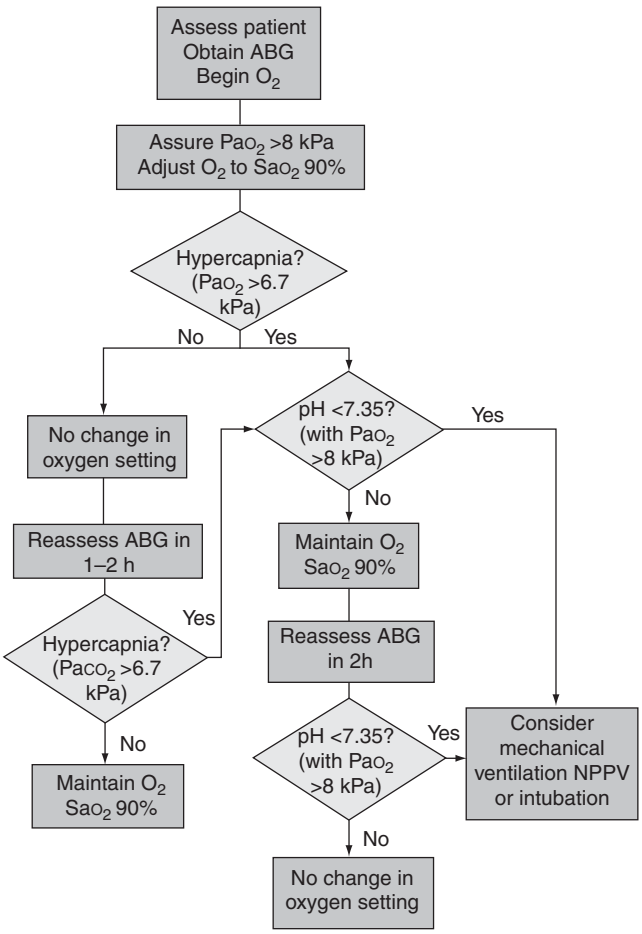

Figure 120-1 Proposed algorithm for the correction of hypoxemia in the acutely ill patient with AE COPD. ABG, arterial blood gas; NPPV, noninvasive positive pressure ventilation; O_2, oxygen; Pa_{O_2}, arterial oxygen tension; Pa_{CO_2}, arterial carbon dioxide tension; Sa_{O_2}, arterial oxygen saturation. *(From Celli BR, MacNee W, committee members: ATS/ERS Task Force. Standards for the diagnosis and treatment of patients with COPD: A summary of the ATS/ERS position paper.* Eur Respir J *23:932–946, 2004.)*

Sputum cultures have been the classic approach to identifying potentially pathogenic microorganisms (PPM) in AE COPD. Comprehensive reviews of comparative antimicrobial trials identified wide variable frequencies of PPM. The organisms most frequently isolated are non-typeable *Haemophilus influenzae* (NTHI), *Moraxella catarrhalis*, and *Streptococcus pneumoniae*. In general, greater airflow obstruction and prior use of antimicrobial agents identify COPD patients at higher risk for infection with *Pseudomonas* spp. or other enteric gram-negative rods.

Whether PPM are etiologic in AE COPD has been questioned, as early longitudinal studies showing that the frequency of bacterial isolation from sputum in a patient with AE COPD was no different from that of the stable state. Recent insights suggest that patients who have bacterial pathogens in the sputum during the stable phase have more frequent AE COPD and greater decline in lung function. These findings imply that the results of earlier studies were heavily influenced by case selection. Moreover, sputum cultures have important limitations, e.g., seriously underestimating colonization with NTHI in comparison to PCR-based detection. Although bronchoscopically collected samples have confirmed that PPM are found in many patients with COPD at a stable state, the burden of organisms increased during AE COPDs.

Recent longitudinal cohort studies that analyzed surface antigen diversity show that acquisition of a bacterial strain with which the patient had not been previously colonized more than doubled the risk of a clinical exacerbation. Interestingly, the identification of a new NTHI strain was not associated with a symptomatic exacerbation in the majority of patients. This finding is consistent with evidence that *H. influenzae* and *M. catarrhalis* strains associated with symptomatic exacerbations appear to differ inherently from strains not associated with such a clinical response, in that they are more likely to lead to neutrophil recruitment and IL-8 release. Further support for the importance of bacterial infection in the etiology of AE COPD comes from recent studies that confirmed a systemic immune response to homologous strains of *H. influenzae* and *M. catarrhalis* isolated simultaneously from sputum of patients during evaluation at time of stability and with symptomatic exacerbations. Demonstrating a systemic immune response has confirmed an interaction between bacterial and viral infections. It has been reported that almost half of exacerbations associated with a new NTHI strain are associated with evidence of acute viral infection. Overall, evidence of a viral infection was identified in 79 percent of patients with AE COPD. Taken together, these data strongly support a pathogenic role for bacterial pathogens in a large proportion of patients with AE COPD.

Which patients are more likely to experience AE COPD as a result of bacterial infection has been addressed by numerous investigators. Sputum purulence has been examined most critically in the clinical setting; patients with purulent sputum have been reported to be more likely to have polymorphonuclear cells and organisms in sputum. A multicenter study reported that increasing sputum purulence, as defined by a semiquantitative colorimetric scale, was associated with bacterial growth. Furthermore, deepening sputum color (yellowish to brownish) was associated with increased yield of gram-negatives and *P. aeruginosa/Enterobacteriaceae*. Importantly, the definition of color by patients and investigators was concordant in only 68 percent of cases without the aid of an objective color stick. A prospective study of 40 patients hospitalized for AE COPD provided sputum samples and underwent bronchoscopy with protected brush sampling (PSB). The concordance between sputum and PSB culture was high ($k = 0.85$, $p < 0.002$), while the presence of patient-reported sputum purulence was highly associated with positive PSB cultures (Fig. 120-2). The totality of these data suggests that new purulent sputum may identify a patient more likely to experience AE COPD related to bacterial infection.

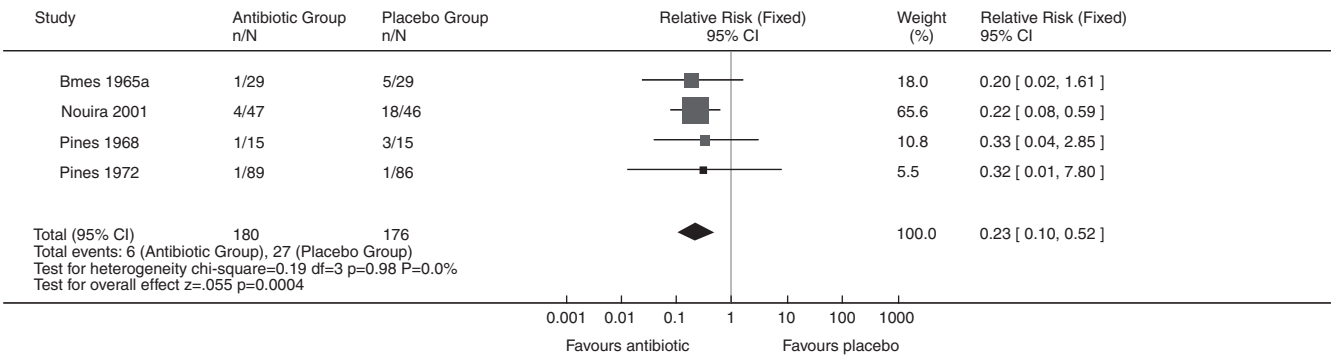

Figure 120-2 Comparison of effect of antibiotics versus placebo on short-term mortality during study intervention. *(From Ram FSF, Rodriguez-Roisin R, Granados-Navarrete A, et al: Antibiotics for exacerbations of chronic obstructive pulmonary disease (Review).* Cochrane Database Syst Rev *2006; Issue 3.)*

Environmental Exposures

Epidemiological studies and the inflammatory response provoked in patients with COPD by exposure to pollutants strongly support a role for environmental exposures in triggering AE COPD. Both particulate matter and nonparticulate gases have been implicated. For example, sulfur dioxide, ozone, black smoke, and nitrogen dioxide have been associated with an increased risk of admission to the hospital for COPD.

EVALUATION

Clinical

As noted, AE COPD is generally defined by a change in symptoms out of proportion to the usual daily variation, which may be considerable in a given patient. Given the central role of respiratory infection in AE COPD pathogenesis, in the absence of sputum purulence the diagnosis of AE COPD should be suspected and alternative diagnoses evaluated. Congestive heart failure, pneumothorax and pulmonary emboli are particularly important possibilities to exclude. In fact, pulmonary emboli have been identified in 25 percent of patients with COPD admitted with a severe exacerbation and no obvious evidence of infection. Previous thromboembolic disease and malignancy have been associated with pulmonary emboli in COPD patients. Similarly, the clinical history should be examined for risk factors for congestive heart failure.

Laboratory

Given this differential diagnosis, focused laboratory testing is of value in the assessment of a patient with a suspected AE COPD. Recent data have suggested a valuable role for the measurement of natriuretic peptides in differentiating congestive heart failure from non-cardiac disorders in patients with acute breathlessness, including patients with AE COPD. Numerous investigators have confirmed that this neurohormone is elevated in patients with left ventricular dysfunction and correlates with severity as well as prognosis in CHF.

Observational studies suggest that a chest radiograph (CXR) identifies abnormalities leading to changes in management in suspected AE COPD in 16 to 21 percent of cases. As such, an evidence-based review has suggested that CXR should be considered in AE COPD managed in the emergency room or hospital. Assessment of oxygenation, including arterial blood gas sampling in selected patients, adds valuable information in stratifying disease severity. Developing and validating cost-effective diagnostic algorithms is an important unmet research goal in AE COPD.

Table 120-2

Potential Therapeutic Options for an AE COPD Managed in the outpatient Setting

Patient education
Check inhalation technique and reinforce correct use
Consider use of spacer device
Bronchodilators
Short-acting β_2-agonists and/or ipratropium MDI with spacer or via handheld nebulizer as appropriate
Consider adding long acting bronchodilator
Corticosteroids
Prednisone 20–40 mg orally/day for 10–14 days
Consider use of an inhaled corticosteroid
Antibiotics
Can be considered in patients with altered sputum characteristics
Choice of agent should be based on local bacterial resistance pattern and host characteristics

SOURCE: *Adpted from Celli BR, MacNee W, and committee members: ATS/ERS Task Force. Standards for the diagnosis and treatment of patients with COPD: A summary of the ATS/ERS position paper.* Eur Respir J *23:932–946, 2004.*

Physiologic

Physiologic changes have been demonstrated during an AE COPD. A modest improvement in pulmonary function, particularly in lung volumes, has been reported over the first two weeks after therapy for an AE COPD started. On the other hand, several observational studies have concluded that spirometric assessment at the time of presentation is of limited value in the care of patients with AE COPD.

TREATMENT

Optimal therapy for AE COPD is multifactorial and depends, in part, on the site of therapy. Tables 120-2 and 120-3 enumerate suggested therapeutic options in patients with AE COPD treated as outpatients or in the hospital. The bases for these recommendations are discussed in individual sections.

Bronchodilators

Both inhaled β-agonists and anticholinergic agents have been documented to decrease airflow obstruction during AE COPD. Systematic reviews suggest that short-acting β-agonists and anticholinergic-inhaled bronchodilators have comparable effects on spirometry exceeding that of parenterally administered bronchodilators. Although the combination of an anticholinergic agent with a β-agonist has the potential for increased therapeutic benefit, studies combining agents from these classes have shown varied results, which, on average, do not seem to support the routine use of multiple agents for AE COPD. On the other hand, it is reasonable to add a second agent if a patient is experiencing suboptimal benefit on a single agent. The evidence for and against the utility of adding a methylxanthine to inhaled bronchodilators is also conflicting, although the high incidence of adverse reactions makes it difficult to recommend their routine use for AE COPD.

Steroids

The role for systemic corticosteroids in AE COPD is becoming better defined. A systematic review suggested that systemic steroid use results in physiologic improvement over the first 72 hours and reduced the odds of a treatment failure over the subsequent 30 days (OR 0.48, 95 percent CI 0.34 to 0.68), but with an increased risk of adverse drug reaction (OR 2.29, 95 percent CI 1.55 to 3.38). The largest study in hospitalized patients confirmed that parenteral steroid use

Table 120-3

Potential Therapeutic Options for an AE COPD Managed in the Inpatient Setting

Bronchodilators Short-acting β_2-agonists and/or ipratropium MDI with spacer or via handheld nebulizer as appropriate Consider adding long-acting bronchodilator
Supplemental oxygen
Corticosteroids Prednisone 20–40 mg orally/day for 10–14 days if tolerated If patient cannot tolerate oral steroids equivalent dose intravenously for 10–14 days Consider using inhaled corticosteroid
Antibiotics Can be considered in patients with altered sputum characteristics Choice of agent should be based on local bacterial resistance pattern and host characteristics

SOURCE: *Adapted from Celli BR, MacNee W, and committee members: ATS/ERS Task Force. Standards for the diagnosis and treatment of patients with COPD: A summary of the ATS/ERS position paper.* Eur Respir J *23:932–946, 2004; Global Initiative for Chronic Obstructive Lung Disease. Executive Summary: Global Strategy for the Diagnosis, Management, and Prevention of COPD.* http://www.goldcopd.org. *Accessed: July 24, 2006.*

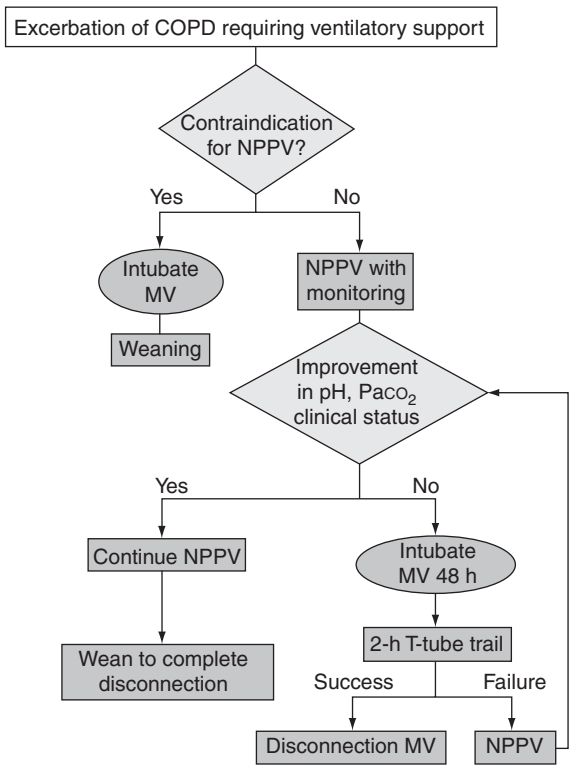

Figure 120-3 Proposed algorithm for the use of noninvasive positive pressure ventilation (NPPV) during an AE COPD. MV, mechanical ventilation; Pa_{CO_2}, arterial carbon dioxide tension. *(From Celli BR, MacNee W, committee members: ATS/ERS Task Force. Standards for the diagnosis and treatment of patients with COPD: A summary of the ATS/ERS position paper.* Eur Respir J *23:932–946, 2004.)*

(methylprednisolone 125 mg/day for 3 days followed by either a 15-day or 8-week taper) was associated with a faster improvement in FEV_1, a lower number of treatment failures, and a shorter length of hospital stay, although with greater side effects (particularly hyperglycemia). Subsequently, others confirmed these findings while using lower doses for shorter periods, including patients being discharged from the emergency department. Non-controlled studies have suggested that prednisone therapy hastened AECB recovery (by 2.63 days) while prolonging time to the next event. Thus, the modest but proven efficacy of systemic steroids in severe AE COPD implies that modulating the host immune response may benefit some patients. It remains unclear how one can best identify which patient is most likely to benefit from parenteral steroids.

Antimicrobial Agents

Given compelling data that bacterial infection is likely causative in approximately 50 percent of patients with AE COPD, it is not surprising that antimicrobial therapy has been intensively studied in this disease. Numerous placebo-controlled trials of antibiotics in AE COPDs have been published over the past several decades. Systematic reviews of these trials have suggested a treatment effect, including a potential survival benefit (Fig. 120-3). There has been significant heterogeneity in the results of the individual studies, with none designed in an optimal fashion. The majority of recent international guidelines interpreted these data to suggest that antimicrobial agents provide additional benefit in selected patients. Most recommend the use of antimicrobials in patients with an AECOPD who are more likely to have bacterial infection (Table 120-4), i.e., those experiencing a change in sputum characteristics or multiple symptoms as defined by Anthonisen et al. Serum procalcitonin has been shown by one group to define patients with AECOPD who have a higher likelihood of bacterial infection; additional, prospective investigation is required to better define this evolving technique.

The choice of antimicrobial agent remains contentious, although increasingly guidelines have taken the approach of stratifying patients according to the risk of treatment failure. One such schema is illustrated in Table 120-5. These stratification schemes have generally suggested features for a

Table 120-4

International Guideline Recommendations for the Use of Antimicrobial Therapy in an AE COPD

Guideline, Year	Recommendation
Canadian Thoracic Society, 2003	"The Panel proposes that antibiotics should only be considered for use in patients with *purulent exacerbations*."
Gold, 2004	"Antibiotics are only effective when patients with worsening dyspnea and cough also have *increased* sputum volume and *purulence*."
American Thoracic Society/ European Respiratory Society, 2004	"[Antibiotics] May be initiated in patients with *altered sputum characteristics*."
National Institute for Clinical Excellence, 2004	"Antibiotics should be used to treat exacerbations of COPD associated with a history of *more purulent sputum*."
European Respiratory Society, 2005	"[Hospitalized patients with COPD exacerbations should receive antibiotics if] I. Patients with all three of the followings symptoms: *increased* dyspnea, sputum volume and *sputum purulence* (a type I Anthonisen exacerbation). II. Patients with only two of the above three symptoms (a type II Anthonisen exacerbation) when *increased purulence of sputum* is one of the two cardinal symptoms. III. Patients with a severe exacerbation that requires invasive or noninvasive mechanical ventilation. IV. Antibiotics are generally not recommended in Anthonisen type II without purulence and type III patients (one or less of the above symptoms).

Table 120-5

Potential Antimicrobial Options for an AE COPD Based on Host and Pathogen Factors

Category	Likely Pathogens	Antimicrobial Treatment
Uncomplicated AECOPD Age < 65 years FEV_1 > 50% predicted < 4 exacerbations/year No comorbid conditions	*H. influenzae* *S. pneumoniae* *M. catarrhalis* *H. parainfluenzae* Viral *M. pneumoniae* *C. pneumoniae*	Macrolide* Ketolides† Doxycycline 2nd or 3rd generation cephalosporin Respiratory quinolone†
Complicated AECOPD Age > 65 years FEV_1 < 50% predicted ≥ 4 exacerbations/year Comorbid conditions	*H. influenzae* *S. pneumoniae* *M. catarrhalis* *H. parainfluenzae* Viral *M. pneumoniae* *C. pneumoniae* Gram-negative enteric bacilli	Respiratory quinolone† Amoxicillin/clavulanate
Complicated AECOPD at risk for *Pseudomonas aeruginosa* infection FEV_1 < 35% predicted Recurrent courses of antibiotics or steroids Bronchiectasis	*H. influenzae* *S. pneumoniae* *M. catarrhalis* *H. parainfluenzae* Viral *M. pneumoniae* *C. pneumoniae* Gram-negative enteric bacilli *Pseudomonas aeruginosa*	Fluoroquinolone with antipseudomonal activity‡

* *In active smokers* H. influenzae *infection is more prevalent—azithromycin and clarithromycin demonstrate improved in vitro activity.*
† *Levofloxacin, moxifloxacin, gatifloxacin, gemifloxacin, and telithromycin have activity against penicillin-resistant* S. pneumoniae.
‡ *Ciprofloxacin and levofloxacin have enhanced antipseudomonal activity.*
SOURCE: *Martinez FJ, Han MLK, Flaherty K, et al: Role of infection and antimicrobial therapy in acute exacerbations of chronic obstructive pulmonary disease.* Expert Rev Anti Infect Ther *4:101–124, 2006.*

high likelihood of infection with organisms that are not covered with standard antibiotic regimens (e.g., *P. aeruginosa*, drug-resistant bacteria) or host factors that predict treatment failure. The latter include worse lung function, increased frequency of exacerbation/office visits, ischemic heart disease and other comorbid conditions. The clinical implication of increasing antimicrobial resistance among common respiratory pathogens in patients with AECOPD remains unclear. COPD patients are at higher risk for infection with resistant organisms. In data collected prospectively, patients with complicated AE COPD appear to experience an inferior clinical response rate compared with those with uncomplicated AE COPD. The impact of utilizing different antimicrobial regimens based on different patient strata remains unproved. Hence, tailoring the initial antimicrobial regimen selection in individuals at increased risk for treatment failure (Table 120-5) is an attractive concept that requires prospective validation.

Mucolytics

An analysis of five randomized controlled trials concluded that pharmacological mucus clearance strategies did not shorten the course of treatment, but they may improve

symptoms. The agents evaluated in these trials included domiodol, bromhexine, ambroxol, S-carboxymethylcysteine, and potassium chloride.

Oxygen Therapy

Oxygen therapy has been described as a cornerstone of hospital treatment for COPD exacerbations. The benefits include decreasing pulmonary vasoconstriction, decreasing the right heart strain and possible ischemia, improving cardiac output, and subsequent oxygen delivery to the central nervous system and other vital organs. The concern regarding oxygen use is the relationship to hypercarbia and subsequent respiratory failure. A systematic review found that supplemental oxygen therapy increased Pa_{CO_2} in most patients, but most patients did not require subsequent mechanical ventilation. Patients with combined baseline hypercarbia and more severe hypoxemia had the highest risk of requiring mechanical ventilation following the administration of supplemental oxygen.

Oxygen should be administered for patients with AE COPD with a goal oxygen saturation of 90 to 92 percent (Pa_{O_2} 60 to 65 mmHg) under tightly controlled circumstances. Figure 120-3 illustrates an algorithmic approach to administering oxygen supplementation in a patient suffering from an AE COPD.

Mechanical Ventilation

Noninvasive positive-pressure ventilation (NPPV) has the potential of resting fatigued muscles and thus preventing the need for endotracheal intubation and mechanical ventilation. Decreased need for invasive mechanical ventilation and a potential survival advantage have been seen in several studies. Expert opinion supports administration of NPPV in an ICU or other similar closely monitored setting for optimal results. Criteria suggested to identify patients likely to benefit are enumerated in Table 120-6. A clinical practice guideline to the application and titration of this modality in AE COPD patient has been published. Patients who are intolerant of or do not benefit from NPPV should be considered for invasive mechanical ventilation (Table 120-7).

Table 120-6

Indications and Contraindications to the Use of Nasal Positive Pressure Ventilation in a Severe AE COPD

Criteria for consideration
Moderate to severe dyspnea with use of accessory muscles and paradoxical abdominal motion
Respiratory acidosis (pH $\leq$ 7.35) and hypercapni (Pa_{CO_2} > 45 mmHg)
Respiratory frequency > 25 breath/minute
Contraindications (relative/absolute)
Cardiac or respiratory arrest
Cardiovascular instability
Failure of nonrespiratory organs
Severe encephalopathy
Severe hemorrhage of upper digestive system
Uncooperative patient
Recent facial or gastrointestinal surgery
Craniofacial trauma, fixed nasopharyngeal abnormalities
Obstruction of the upper airway
High aspiration risk
Inability to cooperate or protect the airway
Extreme obesity
Burns

SOURCE: *Adapted from Global Initiative for Chronic Obstructive Lung Disease: Executive Summary: Global strategy for the diagnosis, management, and prevention of COPD.* http://www.goldcopd.org. *Accessed: July 24, 2006, Carrera M, Sala E, Cosio BG, et al: Hospital treatment of chronic obstructive pulmonary disease exacerbation: An evidence-based review.* Arch Bronchoneumol *41:220–229, 2005.*

Table 120-7

Indications and Contraindications to the Use of Invasive Mechanical Ventilation in a severe AE COPD

Absolute indications
Cardiac or respirtory arrest
Failure of noninvasive ventilation or contraindication to such
Persistent, life threatening hypoxemia (Pao_2 < 40 mmHg or Pao_2/FIo_2 < 200)
Worsening or severe respiratory acidosis (pH < 7.25 and hypercapnia—PaCO2 > 60 mm Hg)
Contraindications (relative/absolute)
Severe dyspnea with use of accessory muscles
Respiratory rate > 35 breaths/min
Somnolence, impaired mental status
Cardiovascular complications
Other complications (severe pneumonia, metabolic abnormalities, sepsis, pulmonary embolism, barotraumas, pleural effusion)

SOURCE: *Adapted from Global Intiative for Chronic Obstructive Lung Disease: Executive Summary: Global strategy for the diagnosis, management, and prevention of COPD.* http://www.goldcopd.org. *Accessed: July 24, 2006; Carrera M, Sala E, Cosio BG, et al: Hospital treatment of chronic obstructive pulmonary disease exacerbation: an evidence-based review.* Arch Bronchoneumol *41:220–229, 2005.*

Table 120-8

Indications for Hospitalization in Patients with an AE COPD

Presence of high-risk comorbid conditions
Indequate response of symptoms to outpatient or emergency department management
Marked increase in dyspnea
Inability to eat or sleep due to symptoms
Worsening hypoxemia
Worsening hypercapnia
Change in mental status
Inability of patient to care for herself or himself
Uncertain diagnosis
Inadequate home care

SOURCE: *Adapted from Celli BR, MacNee W, and committee members: ATS/ERS Task Force. Standards for the diagnosis and treatment of patients with COPD: A summary of the ATS/ERS position paper.* Eur Respir J *23:932–946, 2004.*

Hospitalization Decision

The decision to treat at home or in the hospital remains controversial with varying guidelines. General guidelines to aid in this decision are enumerated in Table 120-8.

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Pneumonia in Childhood

Mark S. Pasternack

Pneumonia and influenza are the seventh leading cause of childhood death in the United States. Although in this country the impact on overall childhood mortality is limited (0.4/100,000 children annually), the worldwide mortality due to acute respiratory tract infections in childhood may exceed 2 million deaths annually. In addition, the morbidity of lower-respiratory tract infections (LRTIs) is substantial. For example, the hospitalization rate for influenza among U.S. children under the age of 5 is comparable to that of adults over the age of 50.

LRTIs in children may be organized as a collection of distinct clinical syndromes based on the age of the child and the clinical setting. Pneumonia is a rather common problem for the practicing pediatrician, yet its management is frequently problematic because of a paucity of objective data. Historical information is often scant, especially when managing younger patients. The clinical and especially the radiologic features of pneumonia frequently are not closely correlated with particular etiologic agents, and it is often difficult or impossible to obtain sputum for microscopic analysis and culture. Rapid diagnostic methods detect only a fraction of the common viral causes of LRTI, and similarly blood cultures identify bacterial pneumonia in a small subset of children, and then only after significant delay. Occasionally, pneumonia in early childhood and syndromes of recurrent pneumonia may reflect a congenital or acquired anomaly or a genetic disorder associated with impaired host defense. Thus, the management of pneumonia in children often presents a greater challenge to the clinician than do similar illnesses in adults.

NEONATAL PNEUMONIA

Bacterial pneumonia in neonates generally follows acquisition of a pathogen during passage through the birth canal, and is a common focus of early onset neonatal sepsis. The incidence of neonatal bacterial infection is roughly 0.1 percent of all births, but is much greater in "high-risk" infants—infants delivered before the 36th week of gestation, after prolonged rupture of maternal membranes, maternal intrapartum fever, etc. At present group B streptococcus (*Streptococcus*

agalactiae, GBS), especially serogroup III, is the most common cause of neonatal sepsis, resulting in up to 60 percent of episodes; enteric gram-negative bacilli (predominantly *Escherichia coli*) are responsible for roughly 25 percent of episodes, greatly exceeding *Listeria monocytogenes*. The widespread adoption of universal third trimester maternal screening for GBS carriage and administration of intrapartum antibiotic therapy to GBS-positive mothers as well as to high-risk mothers at delivery has been successful in reducing significantly the incidence of all forms of invasive GBS disease over the past decade.

Early-onset GBS infection is commonly acquired intrapartum, with clinical evidence of sepsis appearing within the first few hours of life. In contrast, meconium aspiration is more common among term infants and is generally apparent in the delivery room. Respiratory distress, with grunting, flaring, and intercostal retractions, is the most commonly encountered sign of neonatal pneumonia. Thus, infants with GBS pneumonia cannot be readily distinguished clinically from those newborns with respiratory distress syndrome. The presence of fever or hypothermia, irritability, or hypotonia all point toward neonatal sepsis. The white blood cell count is frequently abnormal with either marked leukocytosis and an associated left shift with bands and earlier myeloid forms, or with leukopenia, but is not a reliable indicator of neonatal infection. Approximately half of the chest radiographs of infants with GBS pneumonia demonstrate symmetric ground-glass airspace infiltrates that are indistinguishable from the radiographic findings of hyaline membrane disease (Fig. 121-1). The remaining infants have asymmetric lobar or multilobar consolidations which are typical of bacterial pneumonia. The presence of a unilateral pleural effusion in a neonate with pulmonary infiltrates strongly suggests GBS pneumonia. Since the clinical features of GBS pneumonia overlap with those of respiratory distress syndrome, all infants with respiratory distress should undergo a "septic work-up" including blood, urine, and cerebrospinal fluid examination, followed by the empiric administration of ampicillin and gentamicin for 48 to 72 hours pending the results of the initial cultures. Infants requiring intubation and mechanical ventilation because of hypoxemia should also have endotracheally suctioned specimens sent for Gram's stain and culture. These infants must be monitored for the development of enlarging pleural effusions, which may require drainage to improve ventilatory function, and for the development of metastatic skeletal infections or meningitis. The duration of therapy is determined in part by the presence of bacteremia and metastatic infection, since meningitis will require 3 weeks of therapy, and skeletal infection will require even longer treatment.

Low-birth-weight infants with protracted stays in a neonatal intensive care unit (NICU) are at risk for the late development of nosocomial pneumonia, particularly those infants requiring prolonged intubation in the setting of severe prematurity and respiratory distress, or those with anatomic (e.g., tracheoesophageal fistula, duodenal atresia) or neurological defects resulting in aspiration. In such infants the spectrum of potential pathogens causing pneumonia is broad. In addition to the conventional neonatal pathogens, nosocomial flora may contain multiply resistant organisms, such as methicillin-resistant *Staphylococcus aureus* (MRSA), *Enterobacteriaceae (Klebsiella, Enterobacter, Serratia*), including extended spectrum β-lactamase producing organisms, or nonenteric gram-negative bacilli, such as *Pseudomonas aeruginosa* or *Acinetobacter*. Hence, potent broad-spectrum empiric antibiotic therapy such as vancomycin and gentamicin or amikacin, often with a broad-spectrum β-lactam agent such as cefepime or meropenem, should be given until a specific pathogen can be identified; antibiotic therapy can be modified at that time. The particular nosocomial

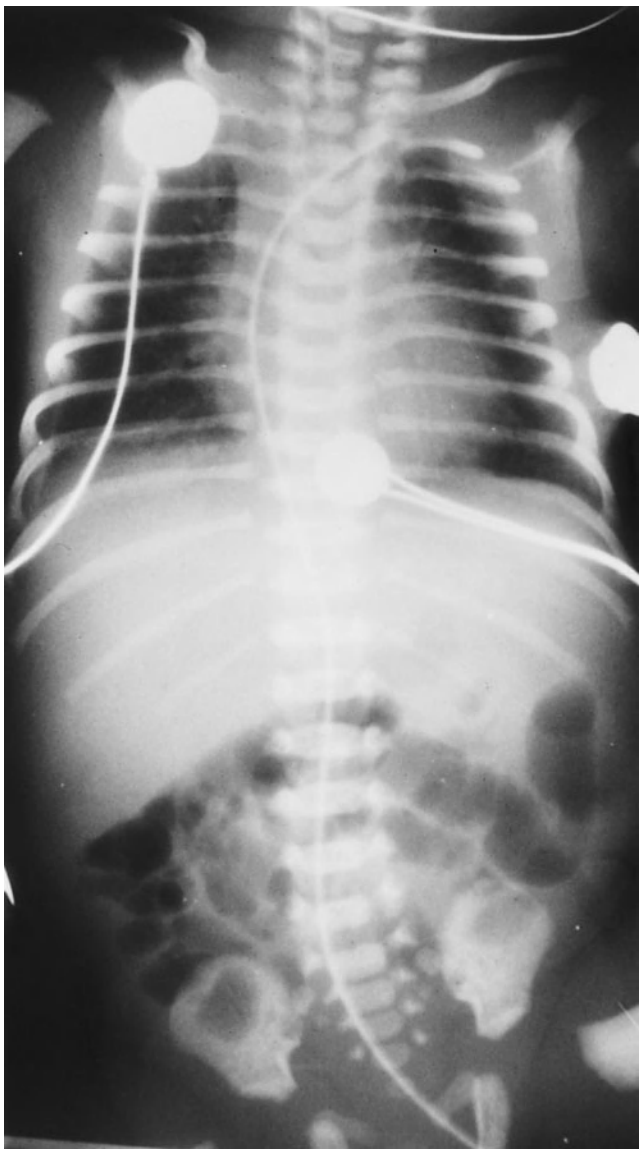


Figure 121-1 Early onset group B streptococcal pneumonia. There are hazy symmetric "ground-glass" infiltrates bilaterally obscuring the cardiac silhouette. Note the presence of a small right pleural effusion.

pathogens which pose the greatest risks to infants with nosocomial pneumonia reflect colonization patterns which may vary among different hospitals, and so the empiric antibiotic therapy used in this situation is frequently nursery-specific. Epidemics of nosocomial pneumonia often reflect breaches in standard precautions by physicians, nurses, or other direct care providers, and active surveillance for colonization of highly resistant pathogens as well as infections within NICUs, infant cohorting, and active hand disinfection programs are critical for controlling these outbreaks.

Congenital viral infections such as cytomegalovirus and rubella may occasionally be responsible for pneumonitis early in the neonatal period. Congenitally infected infants who have symptomatic tachypnea and/or hypoxemia in addition to the stigmata of congenital viral infection usually have extensive viral disease, with hepatosplenomegaly, microcephaly, and/or jaundice. Despite the radiologic findings of diffuse interstitial infiltrates, the clinical picture of systemic viral disease usually predominates, and frank respiratory failure is infrequent. In contrast, neonatal herpes simplex virus (HSV) infections are the consequence of intrapartum acquisition of virus through the birth canal of a (generally primarily) infected mother rather than a true congenital infection. Early onset herpetic infection can occur despite the absence of typical perinatal risk factors for bacterial sepsis. HSV pneumonitis in this setting is usually seen in early onset disseminated disease where the systemic features of fulminant herpetic infection with hepatitis, encephalitis, and myocarditis predominate. The prognosis in this setting is poor despite the availability of the nucleoside antiviral acyclovir. Rarely, hemorrhagic pneumonitis may be the sole manifestation of late-onset perinatal HSV infection. Similarly, early postnatal viral infections such as adenovirus may also result in fulminant respiratory failure in previously healthy full-term infants.

PNEUMONIA IN EARLY INFANCY

The bacterial pathogens responsible for neonatal pneumonia are rarely encountered after the first month of life, since most episodes of bacterial pneumonia accompany the early onset form of neonatal bacterial sepsis. By the second month of life, infants have an increasing risk of developing viral infection as well as chlamydial pneumonia (Fig. 121-2). Despite the broad range of potential pathogens, the lungs of young infants have a limited repertoire in response to illness. The combination of diminutive airways, compromised further by inflammatory mucosal edema and/or intraluminal secretions, results in characteristic airway obstruction. Infants may wheeze, and chest radiographs demonstrate hyperinflation and interstitial infiltrates, with or without atelectasis. Patchy asymmetric airspace disease may be present as well. Thus, the nonspecific chest radiographic findings are not helpful in narrowing the differential diagnosis, and clinical and epidemiological features guide management and therapy.

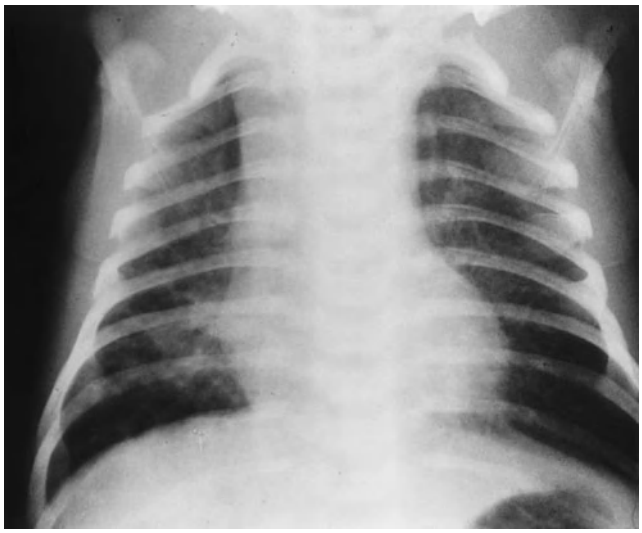


Figure 121-2 *Chlamydia trachomatis* pneumonitis. This 12-day-old infant had stereotypic findings of hyperinflation and asymmetric interstitial infiltrates.

Chlamydia trachomatis Pneumonia

Worldwide, *C. trachomatis* is the most common sexually transmitted pathogen. Vertically transmitted chlamydial pneumonia accounts for up to one-third of pneumonias in infants during the first 4 months of life. Infants generally acquire*C. trachomatis* during their passage through the birth canal from chronically (and usually asymptomatically) infected mothers, although horizontal infection in a nursery or at home due to inadequate handwashing is possible. The incidence of chlamydial infection is inversely proportional to the mother's age and directly proportional to the number of her sexual partners. *C. trachomatis* LRTI can develop despite ophthalmia prophylaxis with silver nitrate solution or tetracycline or erythromycin ointments. When infected secretions are aspirated intrapartum, symptomatic LRTI may develop during the first month of life. More commonly, the conjunctivae and/or upper-respiratory tract mucosa are infected initially, with subsequent spread of infection following aspiration of infected upper-respiratory secretions. The illness progresses insidiously, with the gradual development of cough and congestion over several days, with low-grade or no fever. Respiratory distress is generally only mild to moderate unless there is concomitant infection with a second pathogen (such as respiratory syncytial virus) or there is an underlying pulmonary process such as bronchopulmonary dysplasia. Chest auscultation generally reveals scattered rales, and the chest radiograph shows the nonspecific patchy pneumonitis and hyperinflation pattern described above. Infants often have mild leukocytosis, sometimes with modest eosinophilia. Hyperglobulinemia is common but nondiagnostic. Only half of infants with chlamydial pneumonitis have associated conjunctivitis. The laboratory diagnosis of chlamydial pneumonia may be confirmed by antigen detection in nasopharyngeal swab samples using monoclonal antibody or nucleic acid

detection methods, including polymerase chain reaction (PCR) technology. Systemic therapy with erythromycin (50 mg/kg/d divided q 6 h for 14 d) or azithromycin (20 mg/kg/d for 3 d) hastens resolution of symptoms. Infants with conjunctivitis should also receive topical therapy with erythromycin ophthalmic ointment or tetracycline solution.

Acute Viral Pneumonia

Most episodes of pneumonia in infants over 2 months of age present as acute febrile illnesses and are due to viral pathogens. Viral LRTIs may present primarily with clinical and radiologic features of bronchiolitis or with viral pneumonia and may be due to any of a variety of viral pathogens, requiring laboratory confirmation for definitive diagnosis. In addition to the traditionally recognized causes of viral pneumonia in infants and children (respiratory syncytial virus, parainfluenza viruses, influenza, and adenoviruses), which can be diagnosed by rapid antigen detection methods, molecular diagnostic approaches have identified important, newly recognized agents, such as human metapneumovirus and novel coronaviruses.

Respiratory syncytial virus and human metapneumovirus

Respiratory syncytial virus (RSV) is the most important cause of LRTI in infants, and is responsible for the majority of hospitalizations for bronchiolitis among young children. Interestingly this incidence has risen steadily over the past 25 years. Virtually all infections are symptomatic, although there is a clinical spectrum ranging from pure bronchiolitis, with wheezing, atelectasis, and hyperinflation as the dominant clinical features, to pneumonia, with true airspace disease. Most infants possess features of both processes. RSV circulates widely every winter, although in a given community the peak incidence may shift anywhere from early fall to early spring in a particular year. There are two major RSV serotypes, with considerable genotypic variation within these groups, and in a particular year, a single RSV serotype may predominate. However, the immune response following RSV infection in infants is not significantly protective against symptomatic lower-respiratory tract disease following exposures during subsequent winters regardless of the circulating serotype. The interplay between RSV and the adaptive immune response of infants and children is quite complex, and specific modulation by the RSV envelope G glycoprotein of CD8+ and CD4+ Th1 function may be responsible for the lack of protective immune responses and a propensity for prominent allergic symptoms (Th2 responses). RSV pneumonia is not common until the second month of life, and it is believed that among term infants, transplacentally acquired anti-RSV antibodies may be protective. As the titer of protective antibody wanes, infants are at risk for more severe illness.

RSV infection generally begins with a brief prodromal illness with low-grade fever and nasal congestion and/or rhinorrhea. Within a day or two, infants develop increased fever (101° to 103°F) and progressive respiratory distress, with tachypnea and intercostal retractions. Approximately 1 percent of infected infants develop respiratory distress requiring hospitalization.

Wheezing is prominent, and is believed to reflect mechanical obstruction of the airways due to inflammation, edema, and associated secretions, as well as true immunoglobulin E (IgE)-mediated allergic wheezing. The presence of rales reflects atelectasis and areas of pneumonitis. In very young infants, and in formerly premature infants, the initial presentation of RSV disease may be atypical, with little or no fever or wheezing, and with frequent but less specific episodes of apnea and bradycardia. High-risk infants (i.e., those with severe immunodeficiency states, primary congenital heart disease, particularly those with left to right shunts with pulmonary hypervascularity, pulmonary disease such as bronchopulmonary dysplasia, and low birth weight) are at particular risk for prolonged and life-threatening infection. In general, RSV infection in children infected with human immunodeficiency virus (HIV) is well-tolerated, although prolonged viral replication and shedding may persist, with attendant risks of nosocomial spread. The specific diagnosis of RSV infection can be confirmed in 85 to 90 percent of cases by rapid antigen detection techniques such as enzyme-linked immunosorbent assay (ELISA) or direct immunofluorescence of nasopharyngeal wash specimens. Specimens that are negative by rapid diagnostic methods can be cultured for RSV on Hep2 cells, with diagnostic syncytia appearing after 3 to 6 days. The treatment of RSV infection with the aerosolized nucleoside ribavirin is not often used at present due to concerns regarding efficacy, side effects, and potential teratogenicity risks for health care workers. Hospitalized infants with RSV pneumonia should be isolated (and cohorted if necessary) and placed under contact and respiratory precautions, since the virus can spread by large droplet, fomite, and aerosol. Long-term follow-up has suggested that recurrent wheezing and abnormalities in pulmonary function testing may be common in children after initial episodes of pneumonia and particularly after bronchiolitis, but whether this is a direct effect of RSV or other viral infection or whether subsequent chronic respiratory disease reflects an inherent underlying predisposition to asthma remains controversial. Passive immunoprophylaxis of high-risk infants against RSV infection has been shown to be safe and protective. The use of a high-titered polyclonal human RSV immune globulin (requiring IV administration) for the first two winters of life has been supplanted by palivizumab, a humanized murine monoclonal antibody to the F surface glycoprotein of RSV (administered intramuscularly); a second-generation monoclonal antibody with enhanced affinity and neutralization is under clinical development.

Human metapneumovirus (HMPV), a syncytium-forming negative-strand RNA virus, characterized in 2001, with significant genetic relatedness to RSV, is now established as the second human pathogen within the viral subfamily Pneumovirinae. It has clearly been associated with bronchiolitis and viral pneumonia in young children as well as in the elderly and immunocompromised. Like RSV, HMPV has two major genotypes, and generally causes significant

lower-respiratory tract disease in young children. It is estimated that HMPV is responsible for roughly 10 percent of LRTI infections requiring hospitalization in children, confirming that HMPV infections are an important public health issue. Dual RSV/HMPV infections may result in particularly severe illness, but data are limited. In contrast to RSV, rapid antigen-based diagnostic testing is not widely available for HMPV, and PCR-based methodologies are limited to research settings. Thus, most children with HMPV infection fall into the group of infants with typical bronchiolitis and/or viral pneumonia with negative studies. Potential therapeutic and immunoprophylactic strategies for HMPV are only beginning to be formulated.

Other Common Respiratory Viral Pathogens in Infancy

Parainfluenza viruses

The influenza viruses (of which there may be two type A strains and a type B strain circulating during a particular winter season) and the parainfluenza viruses (PIV, of which there are three major serotypes, 1, 2, and 3, and a less common serotype, PIV4), also are important causes of LRTIs in infants. Although PIV1 is commonly associated with croup (viral laryngotracheitis) among preschool-age children (especially in odd-numbered years), and PIV3 frequently mimics RSV and is more commonly associated with bronchiolitis and viral pneumonitis in the first year of life, all three serotypes may produce any syndrome of upper- and/or lower-respiratory tract infection. Thus, bronchiolitis and/or viral pneumonia in infants, mimicking RSV infection, may be caused by a parainfluenza virus or even influenza. Although parainfluenza viruses are ubiquitous and responsible for limited serious morbidity among most infants, fulminant disease leading to respiratory failure and death can rarely occur even in the absence of underlying immunodeficiency. Distinguishing among these distinct viral etiologies is of some use in the severely ill, since neuraminidase therapy may be considered for influenza. Aerosolized ribavirin has had only anecdotal usage in parainfluenza virus infection, and is probably even less active in these infections than in RSV disease; thus specific antiviral therapy for PIV is limited to the very rare infants with life-threatening infections. Children with primary or acquired immunodeficiency are at increased risk for developing progressive and ultimately fatal infections with these respiratory viral pathogens, and efforts to establish a prompt etiologic diagnosis by rapid diagnostic testing or viral culture is crucial in order to institute prompt antiviral therapy.

Influenza

Like RSV, influenza is a very important cause of lower-respiratory tract disease in infancy. The remarkable morbidity of influenza in children is demonstrated by the hospitalization rates (approximately 250/100,000) of young children with influenza, rates that are comparable to those of adults over the age of 50. Careful statistics of fatal influenza in children have been collected only recently, but in a single year (2003) at least 150 children in the United States died of influenza, and nearly half of these deaths occurred in previously healthy children. Universal immunization of children 6 to 59 months of age, as well as their family members and caregivers, is currently recommended to prevent influenza in children. Prompt diagnosis of influenza is critical if antiviral therapy is under consideration, since the efficacy of antivirals decreases when therapy is instituted after 48 hours of symptoms. When suspicion of influenza is high, the diagnosis may be confirmed by rapid antigen detection testing and the illness treated by the administration of amantadine (8 mg/kg/d divided q 12 h) or, for children over age 1 year, oseltamivir. Antiviral therapies have only moderate activity, shortening the duration of typical influenza illness by about 1 day; it is not clear if they are effective in treating high-risk patients or reducing the incidence of complications and/or severe disease. Unfortunately, there appears to be a significant secular trend toward amantadine resistance among influenza A isolates, so that oseltamivir is becoming the gold standard of anti-influenza therapy. Treatment decisions should incorporate the latest sensitivity data from the World Health Organization (WHO) and/or the Centers for Disease Control (CDC).

Concern has been increasing about H5N1 highly virulent avian influenza strains since the first recent human cases were reported in Hong Kong in 1997. Unlike conventional influenza A, the H5N1 isolates have been notable for remarkable lethality (mortality rate greater than 50 percent among more than 250 reported cases), with particular virulence among infected children. H5N1 disease has a more prolonged incubation period (2 to 8 days), and has been associated with prominent gastrointestinal prodromal symptoms, although multifocal pulmonary infiltrates and respiratory failure follow. Although human-to-human spread of H5N1 virus has been documented as the result of prolonged intimate contact between a mother and her sick child, to date there is little evidence of human adaptation of these strains. H5N1 isolates are resistant to M2 channel inhibitors, and have variable sensitivity to oseltamivir, but neuraminidase inhibitor therapy has been offered as the only therapeutic option.

Additional Respiratory Viral Pathogens

Adenoviruses are another important, but sporadic, cause of severe viral pneumonia in infants. The availability of rapid diagnostic tests is helpful from a diagnostic perspective, particularly since some infected children with prominent conjunctivitis and pharyngitis may be thought to have Kawasaki's disease, but no specific therapies are available. An important new strain of human coronavirus (HCoV NL-63, a type I coronavirus) was recently cloned from infants with bronchiolitis using molecular biologic approaches. Like HMPV, HCoV NL-63 is responsible for up to 10 percent of lower-respiratory tract illnesses (bronchiolitis and viral pneumonia) among hospitalized children whose conventional diagnostic studies are negative. The peak incidence of HCoV infection occurs among children under 2 years of age, similar to RSV

and HMPV. A nonspecific DNA primer amplification strategy has also identified a novel respiratory tract parvovirus, human bocavirus, which has been detected in respiratory specimens from children with acute respiratory tract infections. Bocavirus, like HMPV and HCoV NL-63, may be responsible for a significant fraction of LRTIs in hospitalized children.

Acquired cytomegalovirus pneumonia

Occasionally, infants in the first two months of life have an indolent syndrome of interstitial pneumonitis which mimics chlamydial pneumonia but actually represents cytomegalovirus (CMV) pneumonia. In contrast to infants with congenital CMV, in whom pulmonary disease is associated with severe congenital infection, otherwise healthy infants may develop mild-moderate respiratory distress as the result of peripartum or neonatal acquisition of CMV through breast milk or, in premature infants, through blood transfusion. A single culture for CMV obtained at the time of respiratory symptoms cannot readily distinguish between postnatal primary infection and asymptomatic shedding of congenitally acquired CMV. Otherwise uncomplicated postnatal CMV pneumonia does not serve as an indicator of significant underlying immunodeficiency. Extreme low-birth-weight infants with perinatally or postnatally acquired CMV may have more severe chronic lung disease than uninfected infants, but the role of ganciclovir therapy in this population has not been studied.

Additional Causes of Pneumonia in Infancy

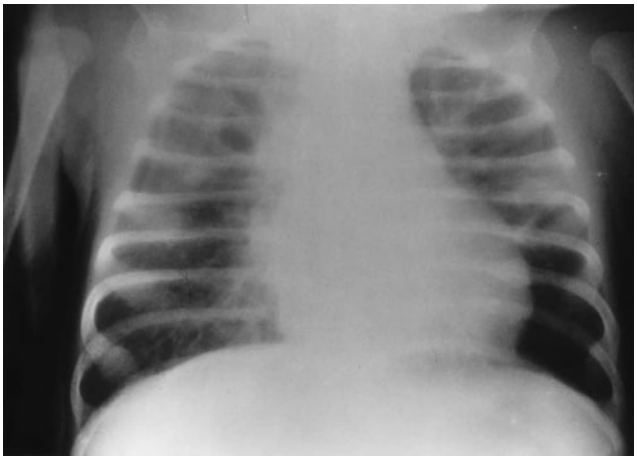
Conventional clinical diagnostic techniques for chlamydial and viral pathogens fail to identify a pathogen in up to half of all cases of pneumonia in infants. As noted above, a significant fraction of these infections may be due to viral agents, such as HMPV and HCoV NL-63, for which routine testing is not available. Additional microbiological and serological analyses have suggested that occasional infants may have neonatal pneumonia due to *Pneumocystis carinii* and *Ureaplasma urealyticum* in addition to the conventional pathogens described above. Pneumonitis associated with these pathogens was not readily distinguished from infections due to *C. trachomatis*. The short-term prognosis of these infections is presumably favorable, since diagnostic techniques to identify such infections are not employed in most centers, and infants with indolent pneumonia generally do well with supportive care.

PNEUMONIA AFTER THE FIRST 6 MONTHS OF LIFE

After the first 4 to 6 months of life, *C. trachomatis* pneumonia is no longer observed. Longitudinal studies of LRTIs in infants and children using conventional microbiological and serological techniques to determine the specific etiologies of pneumonia in infancy fail to identify a specific pathogen in roughly half of all episodes. Combined antigen detection testing, newer serological tests, and pneumolysin PCR testing identified approximately 80 percent of responsible agents, and multiplex PCR testing identified viral etiologies, due to the same viral pathogens that are responsible for viral pneumonia in early infancy, in approximately 90 percent of all episodes of pneumonia. Such intensive techniques commonly identify dual viral or mixed viral-bacterial infections. As noted above, recurrent symptomatic RSV disease in the second and third years of life is very common, and often results in clinically significant episodes of bronchiolitis and/or RSV pneumonia. Since the related parainfluenza and influenza agents represent at least six immunologically distinct pathogens that circulate in epidemic fashion each year, it is not surprising that infants remain at risk to develop significant viral pneumonia. The diagnostic and therapeutic challenges of managing community-acquired pneumonia in children were recently summarized by McIntosh.

Bacterial Pneumonia

Although far less common than viral pneumonia, bacterial pneumonia may be difficult to distinguish prospectively on clinical grounds from episodes of viral pneumonia. Both forms of pneumonia are common during the first two years of life after the neonatal period. Since the pathogenesis of bacterial pneumonia generally represents aspiration of pharyngeal pathogens, often in the setting of inflammatory edema and increased secretions triggered by an upper-respiratory tract infection, both processes may have similar initial prodromal findings associated with a low-grade fever. As the lower-respiratory process evolves, infants and toddlers will have similar features of significant fever, tachypnea, and possible respiratory distress with acral cyanosis and intercostal retractions regardless of etiology. A few physical findings are helpful: diffuse wheezing, when present, usually reflects bronchiolitis, making RSV or other viral pathogens (especially HMPV, parainfluenza viruses, and to a lesser extent, influenza viruses) the likely cause of infection. Similarly, markedly asymmetric breath sounds, with unilateral percussive dullness or a unilateral pleural friction rub, strongly suggest bacterial infection with spread of disease to the pleural space. Laboratory findings are also often nonspecifically abnormal, since the presence of moderate leukocytosis (e.g., to 15,000) and band forms may be seen in either type of pneumonitis. Extreme leukocytosis, with abundant early forms, usually suggests a bacterial process, often with bacteremia and/or spread of infection to the pleural space. Blood cultures should routinely be obtained in children with high fever, leukocytosis, or moderate respiratory distress, since such cultures may represent the only ready approach to recovering a bacterial pathogen. Chest radiographs are sensitive but surprisingly nonspecific in attempting to assess the etiology of pneumonia in children. Although focal consolidation is usually caused by bacterial infection, viral pneumonia may present with a dense focal infiltrate (Fig. 121-3). Conversely, bacterial infection may be associated with patchy segmental infiltrates or even interstitial changes, particularly in younger children. Radiologic



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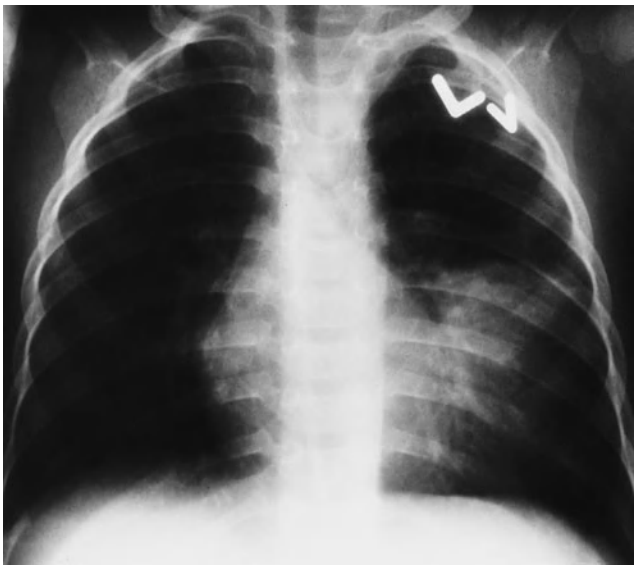

B

Figure 121-3 Viral pneumonia. *A.* This infant's chest radiograph is notable for hyperinflation and asymmetric interstitial infiltrates, representing a combination of atelectasis and pneumonitis. *B.* The presence of focal consolidation does not reliably distinguish between bacterial and viral infection in young children. This child did not respond to intravenous antibiotic therapy, and adenovirus was recovered in anasopharyngeal specimen.

investigation is helpful in assessing the extent of disease and the presence of intrathoracic complications, but has a more limited role in determining the etiology of pneumonia. Thus, the pediatrician must often initiate antimicrobial therapy for possible bacterial pneumonia based on inconclusive clinical and laboratory findings. In patients sufficiently ill to require hospitalization who have difficulty clearing respiratory secretions, nasotracheal suctioning should be considered both for pulmonary toilet as well as for diagnostic testing (Gram's stain and culture).

Even when these parameters point toward a bacterial process, identification of a specific pathogen remains problematic. Only the most severely ill infants and children have bacteremia accompanying pneumonia. Unless a bacterial pathogen is recovered from the blood or from a site of a secondary infection (pleural fluid, joint fluid, cerebrospinal fluid), the specific etiology cannot be readily determined. It is not generally possible to obtain expectorated sputum, and invasive attempts at culture at the time of nasotracheal suctioning or bronchoscopy may be unrewarding because of the incidental recovery of pharyngeal flora, or because prior antibiotic therapy suppresses the recovery of the true pathogen in the lung. In general, rapid bacterial antigen detection techniques have not been helpful in determining the etiology of pneumonia in children because of limited sensitivity. Recovery of the pathogen from a sterile site facilitates antimicrobial susceptibility testing, but most episodes require empiric therapy.

The microbiology of community-acquired pneumonia in infancy and early childhood reflects pharyngeal carriage of respiratory pathogens, and the spectrum of causative agents resembles that seen with otitis media. The dissemination of antibiotic resistant strains of *Streptococcus pneumoniae* and *S. aureus* in recent years has complicated empiric antibiotic therapy for childhood pneumonia. Although amoxicillin is inexpensive and well-tolerated, one can predict that conventional dose amoxicillin therapy will be efficacious in less than 85 percent of cases. Since failure of initial oral therapy may lead to hospitalization and greatly enhanced morbidity and expense, one should consider high-dose amoxicillin (approximately 100 mg/kg/d) to cover possible penicillin-insensitive *S. pneumoniae* isolates, or with more severe disease, an initial broad-spectrum oral agent, such as a second- or third-generation cephalosporin, to decrease the risk of primary antibiotic failure; macrolide resistance is generally high among pneumococci with reduced β-lactam susceptibility. Among hospitalized infants, the use of ceftriaxone has become increasingly popular since it is effective against β-lactamase–producing strains of *Haemophilus influenzae* and *Moraxella* and all but a small fraction of penicillin-resistant pneumococci. Nevertheless, it has limited efficacy against conventional *S. aureus* pneumonia and no activity against MRSA. The β-lactam/β-lactamase inhibitor combination agents such as ampicillin-sulbactam are also popular although more costly, and are ineffective against fully penicillin-resistant pneumococci as well as MRSA.

Pneumococcal Pneumonia

Pneumococci are the cause of most episodes of bacterial pneumonia in infants and children. The importance of polysaccharide-based serotype-specific opsonizing antibody, and the inability of children to mount anti-polysaccharide antibody responses in the first two years of life presumably explain why these encapsulated pathogens cause pneumonia so frequently. Pneumococci colonize the upper-respiratory tract, and spread contiguously to cause otitis media and sinusitis as well as pneumonia, or invade the bloodstream primarily from the pharynx or secondarily from the initial sites of invasive infection. Children with sickle cell disease or other

hemolytic anemias associated with splenic dysfunction are at particular risk of life-threatening infection. The adoption of a heptavalent polysaccharide-carrier protein conjugated pneumococcal polysaccharide vaccine in 2000 into routine infant immunization practice has had a striking impact in reducing invasive pneumococcal infections due to these prevalent serotypes, but the decline in pneumonia episodes among immunized children was a more modest 17 percent overall (although the decline was 32 percent in infants under 1 year of age).

Haemophilus influenzae Pneumonia

The routine use of conjugate *H. influenzae* type *b* (*Hib*) vaccine, the first polysaccharide-carrier protein conjugate vaccine, led to a marked diminution in pharyngeal carriage of *Hib* and a virtual disappearance of invasive *Hib* disease. Nevertheless, upper-respiratory carriage of nontypeable *H. influenzae* persists, and these strains continue to cause otitis, sinusitis, and pneumonia. The risk of bacteremia and metastatic infection is very low following nontypeable *H. influenzae* pneumonia, in contrast to the significant frequency of metastatic infections associated with *Hib* pneumonia. A significant fraction of these strains produce β-lactamase, requiring therapy with a second- or third-generation cephalosporin or a β-lactam/β-lactamase inhibitor combination. If an infant has proven invasive *Hib* disease, family contacts (as well as the index case) should receive eradicative therapy with rifampin.

Staphylococcal Pneumonia

S. aureus pneumonia is associated with necrotizing infection in infants, just as in older patients. Nasal carriage may lead to the aspiration of staphylococci, particularly in the setting of an acute viral upper-respiratory tract infection. Severe systemic toxicity, respiratory distress, and clinical and/or radiologic evidence of necrotizing pneumonitis are common. Chest radiographs characteristically demonstrate focal airspace disease, often with lobar consolidation, associated with cavitation or the development of smaller subpleural pneumatoceles. Pleural space involvement is also common, and frequently patients with *S. aureus* pneumonia present with dyspnea due to a giant pleural effusion. Depending on the duration of illness before evaluation, the pleural effusion may be small or large, and free-flowing or loculated. Later diagnosis is associated with larger and more viscid or even loculated pleural effusions. Pneumothorax or pyopneumothorax may develop, depending on the extent of subpleural necrotizing infection. These extensive abnormalities are not unique for staphylococcal pneumonia, and are occasionally encountered in the course of other bacterial infections in children, particularly in aspiration pneumonitis and, rarely, in pneumococcal disease. Traditionally, initial empiric antibiotic coverage with a second-generation cephalosporin such as cefuroxime or with ampicillin/sulbactam was reasonable. If staphylococcal disease was confirmed, antibiotic therapy with high doses of a semisynthetic penicillin (nafcillin, 200 mg/kg/d), or a first-generation or second-generation cephalosporin (cefazolin, 100 mg/kg/d or cefuroxime, 150 mg/kg/d, respectively) were administered. In patients who have immediate hypersensitivity to β-lactam agents, parenteral clindamycin (40 mg/kg/d) is far easier to administer than vancomycin (30 to 40 mg/kg/d). However, the current epidemic of methicillin-resistant staphylococcal infections (MRSA) has complicated empiric management considerably. Widespread MRSA disease is primarily due to the sudden appearance and rapid dissemination of MRSA infection among individuals who lack epidemiological risk factors for the acquisition of nosocomially spread MRSA. These community-acquired strains (CA-MRSA) are readily distinguished from nosocomial strains by greater susceptibility to other anti-staphylococcal agents such as macrolides, clindamycin, and trimethoprim-sulfamethoxazole, as well as by the presence of the Panton-Valentine leukocidin (PVL), a potent virulence factor in CA-MRSA strains. In many communities, MRSA is now responsible for a majority of serious skin and soft-tissue *S. aureus* infections, and vancomycin is necessary when treating likely staphylococcal disease, especially necrotizing pneumonia.

The management of pleural space infection varies widely among institutions due to variations in local expertise as well as the paucity of controlled clinical trial data to establish best practices. Thoracentesis has the potential of confirming the microbiologic diagnosis and establishing antimicrobial susceptibilities, reducing respiratory distress by enhancing lung expansion, and preventing the evolution of a thick, loculated empyema which may be the source of continuing respiratory distress and ongoing infection. Thoracentesis under sedation or anesthesia, particularly when guided by ultrasound or computed tomography (CT) scan, is a generally safe procedure even in infants and young children. When the fluid is thin, free-flowing, and not grossly purulent, the initial drainage procedure aimed at evacuating the pleural space is generally sufficient. If the initial fluid is turbid or viscous, thoracostomy drainage (pigtail catheter vs. larger bore surgical thoracostomy tube) should be instituted. The clinical course following closed drainage procedures is usually one of gradual improvement; fever for a week or more is common. Although generally safe, the efficacy of thrombolytic therapy as part of the management of pediatric empyemas remains controversial. Unfortunately, many infants are referred to a tertiary care center after the development of established empyemas, and remain persistently febrile with an increasing erythrocyte sedimentation rate despite placement of an initial chest tube. Sometimes persistent loculated infection may be identified by ultrasound or chest CT scan and evacuated by additional drainage procedures, but often these infants will require video-assisted thoracoscopy (VATS) with evacuation of the loculated pleural space infection and placement of additional thoracostomy tubes or open thoracotomy and decortication. In some centers early utilization of VATS as the primary drainage procedure has reduced the length of in-hospital stay.

Streptococcal Pneumonia

Pneumonia due to group A streptococcal infection is, like staphylococcal disease, commonly associated with the development of pleural effusions. In contrast to staphylococcal pneumonia, where empyema is a relatively late complication of destructive subpleural infection, group A streptococcal pneumonia elicits a prompt and marked increase in lymphatic drainage. When the rate of inflammatory edema generation exceeds the fixed capacity of pulmonary lymphatic vessels to drain this fluid, the excess lymphatic drainage accumulates as a pleural effusion. These collections occur very frequently with group A streptococcal pneumonia, and may be considered a part of the process rather than a complication. The effusions are generally free-flowing and often sterile parapneumonic collections early in the course of infection. These collections may become infected as group A streptococci are carried to the pleural space, and may become exudative in character, resulting in frank empyemas requiring surgical debridement. Once again, early intervention by percutaneous drainage may obviate the need for more extensive surgical procedures late in the course of the infection. In addition to concerns regarding the local complications of group A streptococcal pneumonia, one must be vigilant for the possible systemic sequelae following group A streptococcal infection. The expression of pyrogenic exotoxin A, particularly in M serotypes 1 and 3, has been associated with the development of streptococcal toxic shock syndrome, with scarlatiniform rash, shock, and multiple-organ system dysfunction.

Atypical Bacterial Pathogens

The atypical bacterial pathogens *Mycoplasma pneumoniae, Chlamydia pneumoniae*, and *Legionella pneumophila* are often considered together as "atypical" pathogens because of their inability to grow on routine bacterial culture media, the prominence of nonproductive cough, and their responsiveness to macrolide therapy.

Mycoplasma pneumoniae

The frequency of pneumonia due to the encapsulated bacterial pathogens such as pneumococci and *H. influenzae* decreases with increasing age, as do all invasive infections associated with these pathogens. Traditionally, young children with mycoplasma infection were thought to have mild or nonlocalizing infections, while school-age children developed "atypical pneumonia." The syndrome of *M. pneumonia* in school-age children, which is probably responsible for greater than 50 percent of all episodes of pneumonia in this age group, closely resembles symptomatic infection in adults who manifest an indolent influenzal illness, with fever, pharyngitis, myalgias, headache, and a progressive hacking nonproductive cough, or (in older children) a cough productive of mucoid or mucopurulent sputum. Although symptomatic atypical pneumonias were considered to be rare in young children, based on culture and complement-fixing antibody studies, more recent studies of pneumonia in young children, using reverse transcriptase-polymerase chain reaction (RT-PCR) or more sensitive serological assays, have demonstrated that roughly half of mycoplasmal and chlamydial infections develop in children under age 5, perhaps reflecting spread within day care centers. A variety of extrapulmonary features may be present, such as rash (including urticaria, maculopapular eruptions, erythema multiforme, and Stevens-Johnson syndrome), hemolytic anemia, bullous myringitis or meningoencephalitis, or rarely, hepatitis, perimyocarditis or arthritis. On occasion these features overshadow any mild pulmonary symptoms that a child may have, or occur in the absence of any respiratory tract complaints. Immunocompromised children and children with sickle cell disease may have more complicated illness, and *Mycoplasma* is a well-recognized cause of the acute chest syndrome. Indolent intrafamilial secondary spread of infection occurs regularly, with sequential illnesses occurring among siblings separated by intervals of 1 to 2 weeks. Physical examination is notable for fever and tachypnea, but there is often a paucity of adventitial sounds on chest auscultation. The radiologic features of *M. pneumoniae* may range from patchy asymmetric bibasilar infiltrates with plate-like atelectasis to dense focal airspace disease suggestive of bacterial pneumonia. Pleural effusions and hilar adenopathy may occur but are infrequently seen. Laboratory diagnosis of *M. pneumoniae* infection currently relies generally upon nucleic acid detection technology such as RT-PCR; serological confirmation of mycoplasmal infection requires paired acute and convalescent specimens. The development of cold agglutinins, immunoglobulin M (IgM) antibodies reactive with autologous erythrocytes, occurs in a minority of patients and is not truly specific for mycoplasmal disease. Thus, the diagnosis of *M. pneumoniae* is a presumptive one in children, especially in outpatients, and the most likely cause of pneumonia in school-age children. The differential diagnosis of atypical pneumonia includes adenoviral infection and *C. pneumoniae* infection. Both mycoplasmal and chlamydial infections respond to macrolide therapy, as do many pneumococcal infections; consequently, macrolides are routinely administered for the treatment of pneumonia in school-age children. In children who are intolerant of erythromycin, the newer macrolide agents, clarithromycin or azithromycin, may be given. Alternatively, tetracycline administration may be considered in children over the age of 8 years of age.

Chlamydia pneumoniae pneumonia

A second rather common cause of atypical pneumonia is attributed to the chlamydial species *C. pneumoniae. C. pneumoniae* infections have a broad spectrum of illness and range from asymptomatic seroconversion and mild isolated upper-respiratory tract syndromes (pharyngitis and/or sinusitis) to bronchitis and clinically significant episodes of pneumonia; it is thought to be responsible for over 10 percent of cases of community-acquired pneumonia in children over the age of 5 as well as in adults. Co-infection with *Mycoplasma* or *S. pneumoniae* or common viral pathogens often occur.

Pneumonia due to *C. pneumoniae* in young children, once thought to be rare, is now recognized more readily by sensitive serological or nucleic acid techniques. Pharyngitis is more common with this agent than with *M. pneumoniae*, although in individual patients, distinction between these two illnesses using clinical criteria is difficult and not really necessary, since both agents respond to macrolide or tetracycline therapy.

Legionnaires' disease

Seroepidemiological surveys of pediatric inpatients with pneumonia have documented a widely variable incidence (less than 2 to 52 percent) of *L. pneumofila* among children of all ages, presumably reflecting variation in environmental exposures. Although most children with *Legionella* infection are chronically ill due to a variety of underlying diseases, including hematologic malignancy and/or immunosuppression, no discrete pattern of underlying immunodeficiency has been specifically associated with the development of legionellosis. The clinical features of pediatric legionellosis mimic other bacterial processes, with fever, cough, and tachypnea, and are associated with unilateral or bilateral infiltrates, and cavitation or pleural effusion in a significant fraction of patients. Environmental exposures, particularly to contaminated sources of warm water, remain the dominant risk factor for *Legionella* infection. Nosocomial infections, including nosocomial pneumonia in premature infants in neonatal intensive care units, are an important problem. Although macrolide therapy is beneficial, an extremely high index of suspicion is required to pursue this diagnosis among pediatric patients. Rapid diagnostic options include urinary antigen testing for *L. pneumophila* serogroup 1 and direct fluorescent antibody staining or PCR testing of secretions. Culture of secretions on selective media and serological diagnosis (documenting either a high-titered acute specimen or a conventional rise or fall in paired serum samples) are also available. The presence of legionellosis among adults within a community due to an endemic source or an acute epidemic of legionellosis should alert pediatricians to the risk of *L. pneumofila* among children within the community.

TUBERCULOSIS

The prompt diagnosis and therapy of tuberculosis in children is particularly important since the development of life-threatening complications such as tuberculous meningitis or miliary tuberculosis (Fig. 121-4) can develop soon after the clinical onset of primary tuberculous pneumonia in infants and young children. The development of tuberculosis in a child reflects the presence of a contagious individual within the patient's circle of family, neighbors, or day care or school personnel. The pathogenesis of tuberculosis in young children is the same as for adults (i.e., one or a few *M. tuberculosis* bacilli are inhaled as small droplet aerosols and deposited within an alveolus, typically in a lower lobe). Unlike adults with primary tuberculous infection, in children the local and regional lymphatic barriers to mycobacterial dissemination are often less

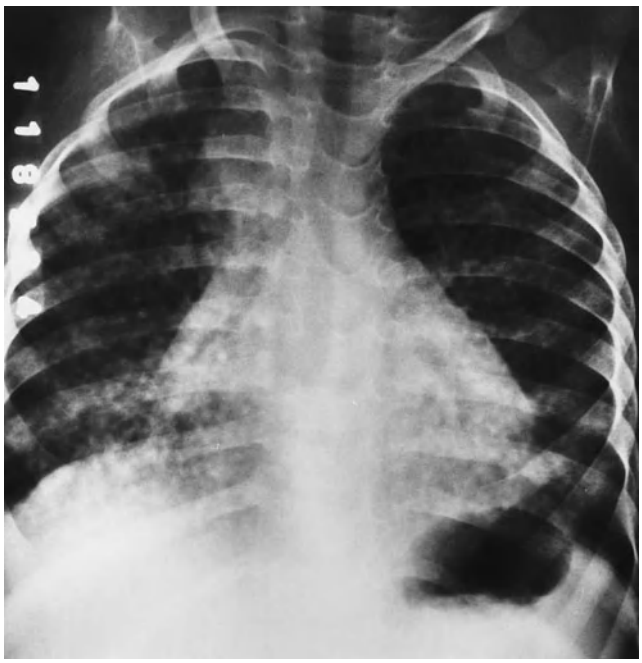

Figure 121-4 Miliary tuberculosis. The miliary pattern is quite prominent in this radiograph. Routine chest radiography may be normal in miliary tuberculosis.

effective, presumably because of subtle developmental deficiencies of T-lymphocyte activation and/or macrophage mycobactericidal activity. As a result, mycobacterial proliferation at the site of primary infection may result in local spread of organisms (producing primary tuberculous pneumonia (Fig. 121-5) as well as spread through the regional lymph nodes (with early bacillary dissemination to extrapulmonary foci of infection). Infants and children with primary tuberculous pneumonia are often only mildly ill, with persistent

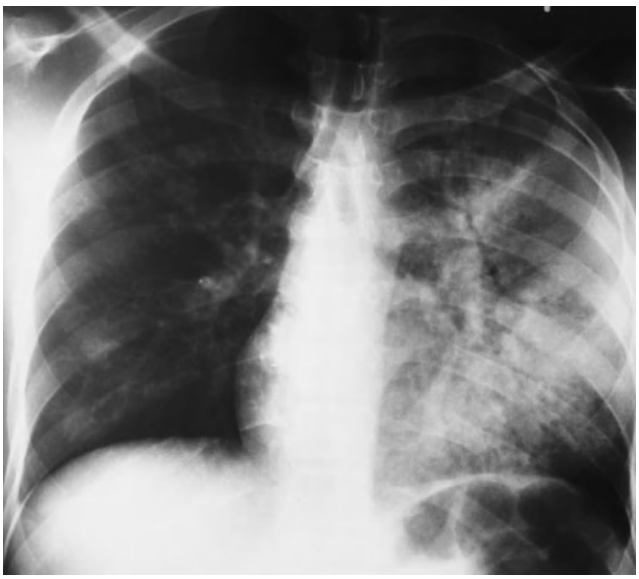

Figure 121-5 Acute tuberculous pneumonia. This 15-year-old Haitian boy had slowly progressive fatigue, cough, and low-grade fever for 1 month prior to evaluation.

cough in the setting of little or no fever despite (often repeated courses of) conventional oral antibiotic therapy. Chest radiographs demonstrating paratracheal or hilar adenopathy ipsilateral to an area of airspace consolidation strongly suggest possible mycobacterial infection. At times, atelectasis or lobar emphysema may be seen due to extrinsic compression of a bronchus by enlarged lymph nodes, and this may be accompanied by localized wheezing. The presence of pleural effusions or pulmonary cavitation is rare in children with primary tuberculosis. A positive tuberculin reaction usually develops within 4 to 6 weeks of initial infection, so that many children have a positive Mantoux test at the time they are evaluated for persistent respiratory symptoms. The presence of a compatible clinical illness with a positive Mantoux test provides presumptive evidence for *M. tuberculosis* infection. Since young children lack a productive cough, confirmation of the diagnosis can be achieved in roughly half of cases through the culture of gastric aspirates obtained by nasogastric suction each morning on three successive days, or by bronchoscopy (usually reserved for children where the differential diagnosis may be broader or where airway compromise mandates bronchoscopy to exclude the presence of an obstructing foreign body). It is highly desirable to obtain an *M. tuberculosis* isolate for each child in order to confirm the diagnosis and determine antibiotic susceptibility, although this information generally can be extrapolated safely from a newly diagnosed index case.

The therapy of tuberculosis in children utilizes the same principles used to treat adult tuberculosis, but unique challenges arise due to the lack of pediatric formulations and limited outcomes data. Initial combination chemotherapeutic regimens should include isoniazid, rifampin, and pyrazinamide. In communities where there is significant concern regarding drug-resistant tuberculosis, such as among immigrants and in children residing with adults who have failed conventional therapy for tuberculosis (including patients with HIV infection), ethambutol should be included as a fourth initial agent until a child's isolate has been studied for drug resistance. After a 2-month course of intensive (3- or 4-drug) therapy, in the absence of proven drug resistance, pyrazinamide and ethambutol may be stopped to complete a 6-month course of therapy. The incidence of isoniazid hepatotoxicity in children is considerably lower than in adult patients, but monitoring for hepatotoxicity in the setting of multidrug regimens is prudent. Although the ocular toxicities associated with ethambutol use cannot be elicited by history or color vision screening in young children, the incidence of this side effect is very low, particularly when ethambutol dosage is reduced to 15 mg/kg/d following an initial 4- to 6-week period of 25 mg/kg/d.

PNEUMONIA COMPLICATING CHILDHOOD VIRAL EXANTHEMS

Both varicella and measles may be complicated by the development of primary viral pneumonia as well as life-threatening bacterial superinfection. Pneumonia is a common complication requiring hospitalization among children with varicella (mean age 4 to 6 years) and measles (mean age 2 years), and occurs among normal as well as immunocompromised children.

Varicella

Varicella pneumonia generally develops a few days after the onset of the typical bullous eruption, but can occur before the onset of the rash. Symptoms of dyspnea, cough, and tachypnea are associated with an interstitial and fine nodular infiltrate, and may be severe, requiring intubation and mechanical ventilation. The prognosis generally is favorable if the child can be supported adequately during the acute phase of the illness. Symptomatic pneumonitis in this setting should lead to the prompt institution of parenteral acyclovir therapy (30 mg/kg/d divided q 8 h). Bacterial superinfection occurs in a large fraction of children with varicella pneumonia. This complication is associated with the development of typical focal consolidation and can be accompanied by the development of a pleural effusion or frank empyema. The common bacterial pathogens—*S. pneumoniae, S. pyogenes, S. aureus, H. influenzae*—are the usual etiologic agents, and require appropriate antibiotic coverage in addition to primary therapy with acyclovir. Although the risk of varicella pneumonia is extremely high in children receiving chemotherapy for hematologic malignancy, the risk of serious visceral complications is actually rather low in children with HIV infection. Neonates with peripartum exposure to maternal varicella are also at high risk of developing primary varicella pneumonia, and should be given zoster immune globulin at birth and parenteral acyclovir if they develop varicella.

Measles

The epidemiology of measles pneumonia and its complications closely resemble the features of varicella pneumonia, although most cases of measles pneumonia are seen in younger children. In contrast to the low incidence of varicella pneumonia in children, radiologic evidence of pulmonary involvement is more frequently seen in measles (2.7 to 36 percent), although some children have few symptoms, and some children develop a croup syndrome rather than pneumonitis. Primary measles pneumonia is associated with a diffuse interstitial infiltrate, and may also be associated with the development of secondary bacterial pneumonia. Fulminant respiratory failure may develop in association with diffuse interstitial pneumonia, diffuse airspace consolidation consistent with the adult respiratory distress syndrome, bacterial pneumonia, and/or spontaneous pneumothorax prior to intubation and mechanical ventilation. As with varicella pneumonia, typical community-acquired bacterial pathogens are generally responsible for bacterial pneumonia, and may be associated with bacteremia. The acute mortality of measles pneumonia requiring intensive care support approaches 50 percent, and pulmonary fibrosis and/or bronchiolitis obliterans may develop during after the acute phase of illness.

ASPIRATION PNEUMONIA

Aspiration commonly is observed among children with strong clinical risk factors for this complication, so that the diagnosis of aspiration pneumonia is usually rather straightforward. Infants with neonatal asphyxia and other causes of profound neurological impairment frequently have feeding difficulties and may aspirate oral feeds or saliva. In these infants, fundoplication and placement of a feeding gastrostomy tube may reduce the risk of aspiration of gastric contents but not of oral contents. However, aspiration pneumonia may occur in otherwise normal infants (Fig. 121-6). Aspiration during or shortly after feeding is most commonly due to gastroesophageal reflux and is far less commonly due to tracheoesophageal fistulae or vascular ring anomalies. Thus, the occurrence of aspiration pneumonia in infants mandates an appropriate diagnostic evaluation in addition to antibiotic therapy. Similarly, infants with recurrent pneumonia may be aspirating despite the absence of apparent feeding difficulty, and should undergo a structural evaluation in addition to the screening studies for occult immunodeficiency. Aspiration pneumonia is also a common complication of status epilepticus and of posttraumatic neurological injury, and may be seen as a complication of general anesthesia, particularly after emergency procedures. Older children may develop aspiration pneumonia as the result of alcohol or drug use or from primary neuromuscular disorders such as muscular dystrophy or myasthenia gravis, or generalized metabolic disease including the mitochondrial disorders. The radiologic features of aspiration pneumonia usually demonstrate the expected airspace consolidation in the dependent portions of the lung, recognizing that infants and children may be supine at the time of aspiration. Cavitation or pleural disease is infrequently seen at the time of initial evaluation, since the interval between the aspirational event and presentation with pneumonia is usually brief. A radiopaque foreign body is occasionally seen on chest radiograph and mandates prompt bronchoscopy.

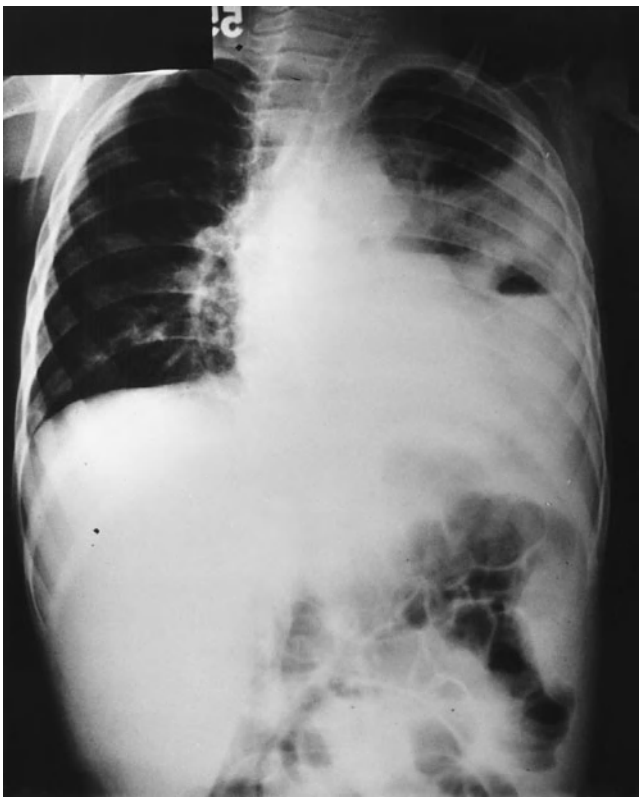

Figure 121-6 Aspiration pneumonia. This toddler presented with a loculated empyema (note multiple air-fluid levels) which grew mixed oropharyngeal flora in association with left lower-lobe pneumonitis.

The therapy of aspiration pneumonia depends on the child's age and overall clinical status. Neonates are usually given ampicillin and gentamicin to treat the conventional neonatal pathogens, since infants are not usually colonized by anaerobic bacteria until the eruption of primary dentition. Colonization of the normal oropharynx by ampicillin-resistant encapsulated pathogens such as *H. influenzae* or *Moraxella catarrhalis* or β-lactamase producing anaerobes offers a rationale for treating older infants and toddlers with a β-lactamase–resistant regimen such as ampicillin sulbactam or a combination of metronidazole together with ceftriaxone or cefuroxime. Chronically ill children have an increased risk of colonization by Enterobacteriaceae. In older children ampicillin-sulbactam or clindamycin (in β-lactam–allergic patients) may be considered for serious infections, and penicillin or ampicillin for milder episodes. A poor response to initial antibiotic therapy may be the result of inadequate antibiotic coverage or the presence of an obstructing endobronchial foreign body. Aspirated foreign bodies are particularly common in toddlers and preschool children who often place small objects in their mouths. Bronchoscopy is indicated in children who respond poorly to therapy or develop cavitation or empyema to exclude the presence of a foreign body as well as to obtain suitable endotracheal specimens for bacterial culture, and to improve bronchial drainage.

PNEUMOCYSTIS JIROVECI PNEUMONIA (PCP)

Symptomatic infections in children due to *P. jiroveci* generally occur in infants rendered immunodeficient by profound malnutrition, and in children of any age with significant compromise of cell-mediated immunity due to underlying disease or to immunosuppressive chemotherapy (Fig. 121-7). A more benign form of PCP in normal infants has also been reported. The infantile form of *P. jiroveci* is an indolent and generally afebrile process manifested by progressive tachypnea and poor feeding over a period of weeks. In contrast, older children typically present with an acute febrile illness with nonproductive cough and tachypnea disproportionate to the bland physical examination and often mild symmetric interstitial and fine alveolar infiltrate present on chest

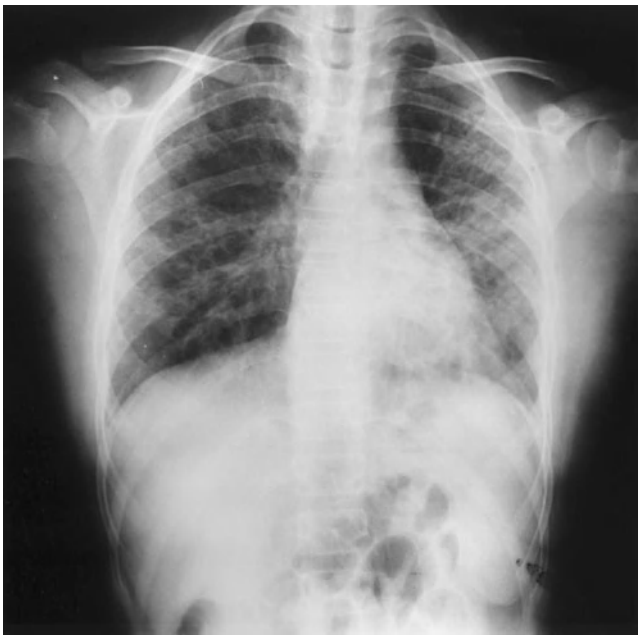

Figure 121-7 *Pneumocystis jiroveci* pneumonia in a teenager with acute leukemia. Depending on the extent of disease at the time of presentation, there may be predominance of interstitial or airspace disease. The radiographic findings are nonspecific, and may mimic viral pneumonitis and noninfectious causes of interstitial and alveolar lung disease such as drug hypersensitivity reactions.

radiograph. The course of *P. jiroveci* infection in HIV-infected children may be quite variable, and resemble either the indolent progressive course seen in malnourished infants or the more rapidly progressive illness seen in older children. The diagnosis of PCP can be made noninvasively in older children by microscopic examination of induced sputum, but in infants and young children bronchoscopy or lung biopsy is required. Trimethoprim-sulfamethoxazole therapy remains the mainstay of treatment, usually given at a dosage of 20 mg/kg/d of the trimethoprim component divided q 6 h for 2 to 3 weeks. Children intolerant to sulfonamide therapy are usually given intravenous pentamidine 4 mg/kg/d for 2 weeks. Short-term administration of methylprednisolone (1 mg/kg q 6 h for 7 d, followed by 7-day tapering course) has been associated with improved survival in HIV-infected patients. Long-term prophylaxis (with trimethoprim-sulfamethoxazole or one of several alternate regimens) is essential to reduce the risk of relapse.

RECURRENT PNEUMONIA

The occurrence of more than one episode of focal consolidative pneumonia, especially within a 1-year interval, raises concerns that a child may be experiencing recurrent pneumonia due to local or systemic risk factors. The radiologic distribution of these infiltrates directs the subsequent evaluation: recurrent pneumonia in a single lobe or lung suggests local risk factors, and recurrent infections distributed throughout the lungs suggest systemic causes of heightened susceptibility to infection.

Recurrent Focal Pneumonia

Recurrent pneumonia in a single lobe may be due to a variety of intraluminal lesions, particularly the presence of a foreign body, or to extraluminal compression due to enlargement of perihilar or regional lymph nodes due to granulomatous infection or malignancy (Fig. 121-8). In addition, a variety of pulmonary or bronchial lesions may be responsible for recurrent infection. Bronchial stenosis and bronchiectasis (especially involving the right middle lobe bronchus) are the most common bronchial abnormalities responsible for recurrent focal pneumonia. Congenital lesions such bronchogenic cysts and pulmonary sequestra may present as recurrent or nonresolving pneumonia. Since these structures lack normal communications with functional bronchi, pneumonitis which develops in these regions as a result of contiguous spread of infection from normal lung is slow to resolve and frequently fails conventional medical therapy. Aspiration should be considered in the setting of recurrent basilar pneumonia. Evaluation of children with recurrent focal pneumonia should begin with chest CT scanning and bronchoscopy to identify obstructing intraluminal lesions, intrinsic bronchial abnormalities such as bronchiectasis, extrinsic bronchial compression, or

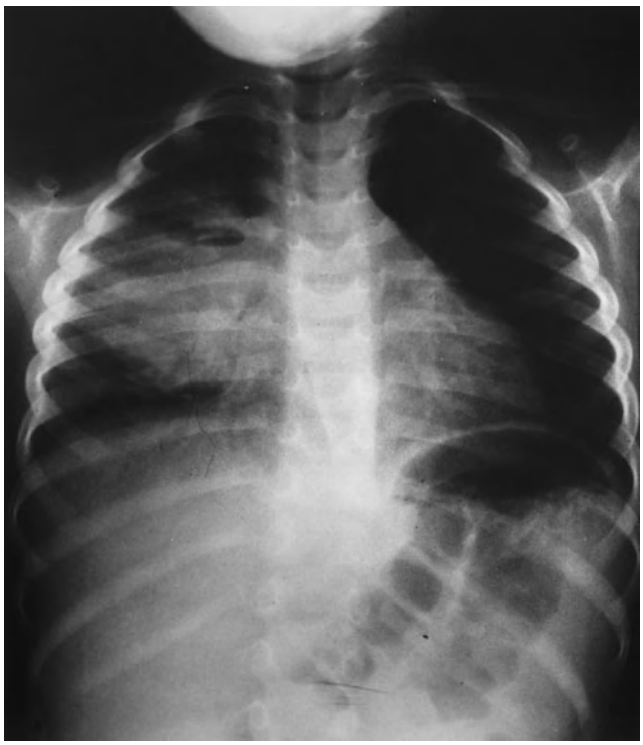

Figure 121-8 Recurrent pneumonia. This 5-year-old girl had three episodes of right lung consolidation, involving different lobes, shortly after immigrating to the United States from the Azores Islands. At bronchoscopy, cellophane tape was recovered from the right mainstem bronchus.

congenital malformations and serves as the primary modality for the removal of retained foreign material. When pulmonary sequestration is suspected, vascular imaging by conventional contrast or magnetic resonance angiography demonstrates the aberrant systemic vascular supply associated with these lesions.

Recurrent Pneumonia in Different Locations

Compromise of any of a variety of pulmonary or systemic host defense mechanisms may be associated with recurrent pneumonia, and in the setting of a such a generalized impairment, recurrent infections may occur anywhere in the lungs.

Defects in Pulmonary Defenses

Abnormalities in the bronchial mucociliary transport system are important considerations. Children with cystic fibrosis (CF) first may become symptomatic beyond the neonatal period with recurrent bronchopneumonia rather than with a picture of steatorrhea and failure to thrive, as is common in neonates. A large number of distinct CF genotypes have been identified, and some are associated with a later and milder onset of respiratory symptoms; in fact, on occasion the diagnosis of CF may not become apparent until adulthood. A family history of CF is often lacking among the families of children with CF. Initial episodes of pneumonia in these patients may be associated with conventional encapsulated bacterial pathogens or *S. aureus*; the development of chronic *P. aeruginosa* infection may be a relatively late event. The diagnosis should be explored with pilocarpine iontophoresis testing ("sweat test") at a center experienced in the diagnosis of CF, with genetic screening considered for borderline tests.

In contrast, congenital abnormalities of the ciliary system are very rare. Kartagener's syndrome of bronchiectasis, sinusitis, and dextrocardia is a subset of the group of immotile ciliary disorders. Such children often experience recurrent upper-respiratory tract infections such as sinusitis and suppurative otitis media in addition to recurrent pneumonia. Ciliary disease can be assessed by analysis of ciliary beat frequency from nasal mucosal specimens. The classic method of diagnosing immotile cilia based on ciliary morphology requires electron microscopic analysis of a bronchial biopsy. This procedure should be performed some weeks after recovery from an acute episode of pneumonia, since ultrastructural abnormalities may be seen after infection in the absence of a heritable ciliary defect. Tracheomalacia and tracheobronchomegaly (Mounier-Kuhn syndrome) also impair clearance of mucus and are associated with recurrent pneumonia.

Defects in Systemic Host Defenses

Humoral immunodeficiency

Humoral immunodeficiency states are the most common host defects associated with recurrent bacterial pneumonia. A variety of different antibody deficiency syndromes have been identified. Bruton's (X-linked) agammaglobulinemia is the most extreme example with a virtual absence of all circulating immunoglobulins. The hyper-IgM syndrome is due to the inability of T cells to activate B cell CD40 which is necessary to drive B-cell differentiation to produce normal quantities of IgG and IgA antibodies. In these children with profound hypogammaglobulinemia, recurrent pyogenic infections, including recurrent pneumonia, develop after transplacentally derived maternal antibody wanes following the first 6 months of life. Common variable hypogammaglobulinemia and transient hypogammaglobulinemia of infancy have moderate reductions in IgG and IgM levels, and may have little or no IgA. In contrast to these more dramatic conditions, IgG subclass deficiency states, particularly of IgG2 and IgG4, have been associated with recurrent respiratory tract infections. Rarely, patients with normal IgG subclass levels have an isolated inability to mount IgG responses to the conventional encapsulated bacterial pathogens; this can be assessed by obtaining pre- and post-immunization titers after administering a bacterial polysaccharide vaccine. Definitive therapy with intravenous immunoglobulin (IVIG) administration can be cumbersome, especially in young children where peripheral venous access is problematic, and where central venous catheters have a significant rate of catheter-associated bacteremia. It is reasonable to offer a trial of chronic oral suppressive antibiotic therapy with a β-lactamase–resistant agent in patients with mild or moderate disease, and to reserve IVIG therapy only to children who fail to improve on suppressive antibiotics. Complement deficiency states, particularly C3, C5, and properdin deficiencies are rare heritable causes of recurrent bacterial infections as well. These patients have an increased incidence of a variety of soft tissue and systemic infections in addition to recurrent pneumonia.

Granulocyte disorders

Quantitative and qualitative granulocyte abnormalities are rarely causes of recurrent pneumonia. Routine differential white cell counts will identify children with agranulocytosis; serial monitoring and bone marrow examinations will distinguish among cyclic neutropenia, immune neutropenia, and congenital agranulocytosis. In these children, pneumonia is often due to *S. aureus* or gram-negative bacilli, including *Pseudomonas*, or to fungal pathogens such as *Aspergillus*. If no response is seen to initial empiric therapy, bronchoscopy or lung biopsy may be necessary to guide further antibiotic therapy. A trial of granulocyte colony-stimulating factor (GCSF) is reasonable in this setting since the transient response in granulocyte number may hasten the resolution of the pneumonia. In contrast, children with chronic granulomatous disease (CGD) have a normal granulocyte number but impaired intracellular killing of bacteria. Like patients with complement deficiency, focal soft-tissue, skeletal, and lymph node infections may be seen in addition to recurrent pneumonia. The use of interferon-γ and long-term antibiotic suppressive therapy has greatly improved the long-term outlook for such patients. Defects in granulocyte function may result in invasive pneumonia due to fungi as well as bacterial pathogens. As

with neutropenic children, focal infiltrates which persist or progress (particularly with cavitation) despite reasonable initial empiric antibiotic therapy require vigorous investigation with chest CT scanning and biopsy.

Cell-mediated immunodeficiency

Defects in T-cell function are associated with primary immunodeficiency diseases such as severe combined immunodeficiency and DiGeorge syndrome, lymphoid malignancies such as acute lymphoblastic leukemia, therapy with immunosuppressive agents for the treatment of a variety of inflammatory diseases and organ transplantation, and HIV infection. The immunodeficient state triggered by acute systemic viral infection is transient and rarely associated with opportunistic pulmonary infection. Regardless of the initial mechanism of T-cell immunosuppression, these children are at risk of developing life-threatening pneumonia due particularly to common viral pathogens such as RSV, measles, and parainfluenza virus; fungal infections such as cryptococcosis or the endemic soil fungi; higher bacteria such as *Nocardia asteroides* and mycobacteria (both *M. tuberculosis* and atypical mycobacteria); and *P. jiroveci*. The radiologic features may point toward particular pathogens (e.g., focal infiltrates implicate fungal or bacterial pathogens, and diffuse infiltrates implicate viral pathogens or *P. jiroveci*) but the broad differential diagnosis, the possibility of polymicrobial infection and noninfectious processes such as drug hypersensitivity reactions, and the complexities of therapy mandate an invasive approach to diagnosis via bronchoscopy and/or open lung biopsy.

Human immunodeficiency virus

HIV infection in children results not only in a heightened susceptibility to infection by *P. jiroveci* and other pathogens classically associated with T-cell immunodeficiency states, but also in an increased susceptibility to bacterial infection, with an increased risk of bacterial pneumonia and bacteremia due to encapsulated pathogens such as *S. pneumoniae*. Tuberculosis is another important pathogen among HIV-infected children living in resource-limited environments. In addition, lymphoid interstitial pneumonia, an infiltrative process possibly associated with Epstein-Barr virus infection, may be responsible for pulmonary infiltrates and respiratory distress in these children. Unlike adult HIV-infected patients, the risk of *P. jiroveci* pneumonia in HIV-positive infants is not closely correlated with the CD4 count. Infants with vertically transmitted HIV have an increased risk of acquiring PCP regardless of CD4 count during the first year of life. All infants born of HIV-infected mothers should begin *P. jiroveci* prophylaxis at 4 weeks of life, and continue treatment until 1 year of life, or until follow-up PCR testing is negative for HIV transmission at 4 to 6 months of age. The need for continued prophylaxis thereafter among HIV-infected infants is based on the CD4 count. The syndrome of recurrent bacterial infections, including pneumonia, in these infants, has become less common since the widespread introduction of highly active antiretroviral therapy (HAART), and maintenance intravenous immunoglobulin (IVIG) therapy for HIV-infected infants is now rarely necessary. When HIV-infected children develop respiratory distress associated with diffuse interstitial and alveolar infiltrates, the broad differential diagnosis and the significant possibility of multiple concurrent processes warrants early consideration of an invasive biopsy process. Depending on the severity and tempo of illness, an empiric trial of therapy for PCP may be given, with lung biopsy reserved for those patients who fail to improve.

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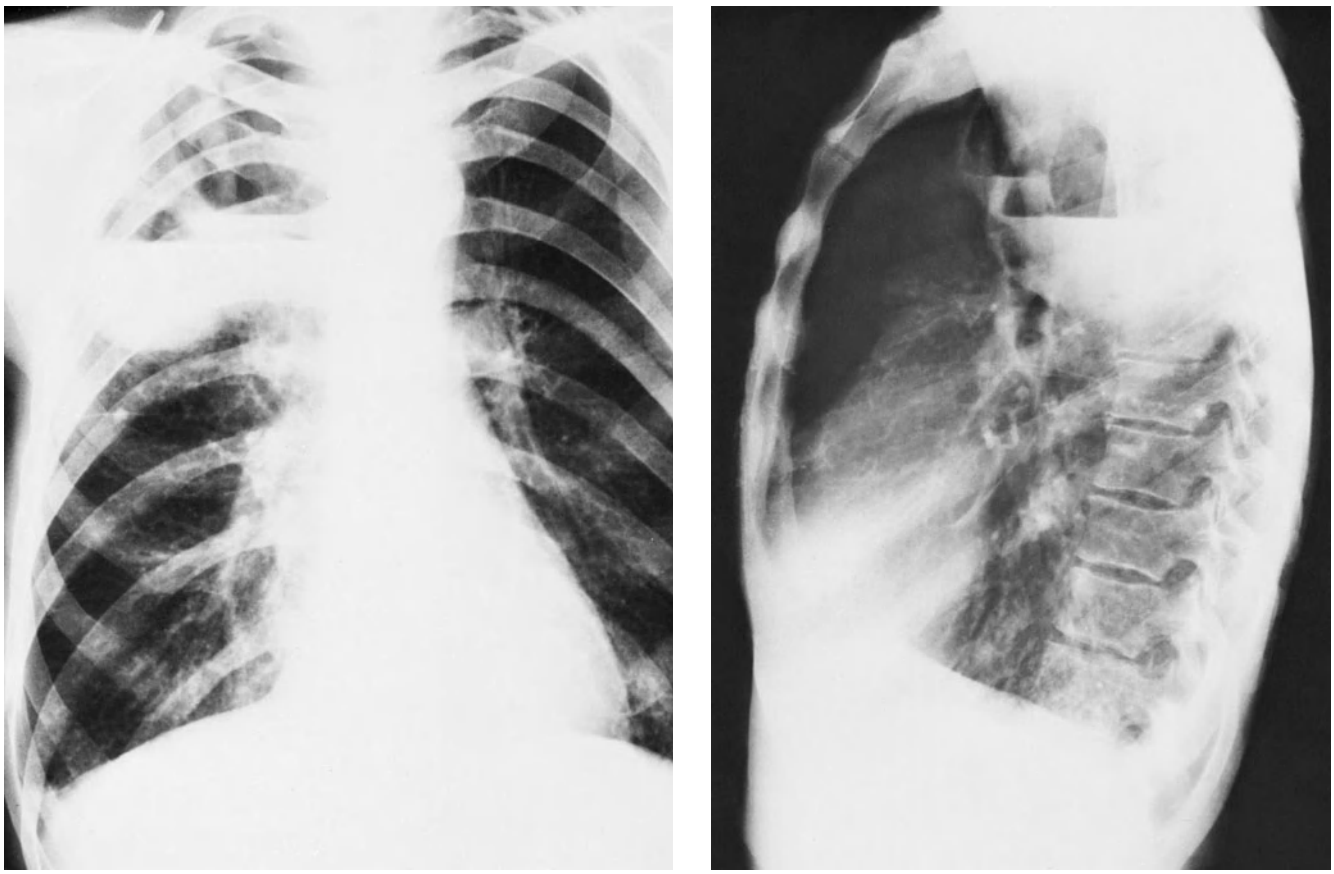
122

Aspiration, Empyema, Lung Abscesses, and Anaerobic Infections

Jay A. Fishman

Infection due to aspiration, lung abscesses, and empyema are important syndromes dominated, in part, by the unique role of anaerobic bacteria in the pathogenesis of each. *Aspiration pneumonia* refers to the pulmonary consequences that follow abnormal entry of fluid, particulate substances, or endogenous secretions from the upper airways or gastric contents into the lower airways. To develop aspiration pneumonia, there needs to be a compromise of the host defense mechanisms that normally protect the lower airways, including glottic closure, cough reflex, or other clearance mechanisms. The material aspirated must generate an inflammatory response or cause obstruction. The nature of the pneumonia that develops depends on the inoculum and the host response. Anaerobic bacteria are the most common pathogens in this setting, reflecting both pathogenic potential and importance in the normal flora of the upper airways. Risk factors for aspiration may be transient (anesthesia, intoxication) or persistent (e.g., neuromuscular disorders, achalasia) with the risk for recurrence depending on recognition and resolution of the inciting defect.

Empyema refers to a purulent collection in any body site, but is commonly used to indicate infection of the pleural space. Empyema is commonly associated with underlying pulmonary parenchymal infection, but may also be associated with blood-borne infection, thoracic surgery, trauma, abdominal infection, or neoplasm. *Lung abscesses* reflect infection with an unusual microbial burden (e.g., acute aspiration), a failure in microbial clearance mechanisms (e.g., bronchial obstruction), or both, with necrosis of pulmonary tissue and formation of cavities containing necrotic debris or fluid (Fig. 122-1). The formation of multiple smaller (less than 2 cm) abscesses in pulmonary tissue is occasionally referred to as *necrotizing pneumonia* or *lung gangrene*. Both lung abscess and necrotizing pneumonia are manifestations of the same pathologic processes, and the distinction is, therefore, arbitrary. Failure to recognize and treat either empyema or



A *B*

Figure 122-1 *A*. Anaerobic pneumonia with abscess formation in a 48-year-old alcoholic man. The abscesses are located in the posterior segment of right upper lobe, a dependent segment that is seen best on lateral view (*B*).

lung abscess is associated with a poor clinical outcome. In the pre-antibiotic era, lung abscess was associated with a mortality approaching 40 percent. However, controversy exists over the best approaches to both processes in terms of antimicrobial selection and physical drainage.

HISTORY

The clinical and bacteriologic features of anaerobic infections of the lung have been documented by extensive studies during two periods of investigation. The first was at the turn of the century, when anaerobic bacteria were initially reported as important causes of empyema. This early work continued through the late 1920s, when David Smith conducted classic studies on the pathogenesis of lung abscess. At that time, approximately one-third of patients with lung abscess died. Smith noted that the bacteria in the walls of the abscess at autopsy resembled the bacteria found in the gingival crevice, leading him to conclude that aspiration was the major mechanism in pathogenesis. He subsequently supported this hypothesis by inoculating the trachea of experimental animals with gingival crevice material to reproduce the sequence of events of pneumonitis, followed in 7 to 10 days by lung abscess formation. Bacteriologic studies of the inoculum showed that four bacterial species were critical, and all were anaerobic bacteria: a fusiform bacterium now recognized as *Fusobacterium nucleatum, Prevotella melaninogenica* (formerly *Bacteroides melaninogenicus*), Peptostreptococcus, and an anaerobic spirochete. This study is one of the first demonstrations of bacterial synergy; the demonstration of two or more bacterial species is required to produce a pathologic process that could not be reproduced by any single component of the inoculum.

In the first two or three decades of the antibiotic era, the role of anaerobic bacteria in this and other pathologic processes was largely ignored. Patients with lung abscesses often had putrid sputum and no identifiable pathogen; these infections were frequently referred to as *nonspecific lung abscess.* Although the microbial cause was unknown, it was well established that these patients almost invariably responded to penicillin treatment. The role of anaerobes in empyema was also largely ignored. Much of this neglect is ascribed to the paucity of laboratories capable of cultivating oxygen-sensitive bacteria. Studies of anaerobic bacteria were spawned by the ability to culture anaerobes in clinical laboratories with the introduction of GasPak jars, the description of the taxonomy

of these organisms, and the availability of new antimicrobial agents (clindamycin, metronidazole, cefoxitin) for therapy. The introduction and widespread use of transtracheal aspiration (TTA) in the late 1960s made it realistic to collect uncontaminated specimens from the lower airways that could be used for anaerobic cultures. TTAs are seldom performed at present, so anaerobic bacteria are rarely established as pulmonary pathogens. These organisms are often suspected on the basis of the etiologic route (oropharyngeal flora) of infection and their importance in patients with aspiration pneumonia, necrotizing pneumonia, lung abscess, and empyema.

MICROBIOLOGY OF ASPIRATION PNEUMONIA

The establishment of anaerobic bacteria in pulmonary infections requires specimens of respiratory secretions that are devoid of contamination from the upper airways. The usual procedures satisfying this criterion are TTA, transthoracic aspiration, open lung biopsy, thoracentesis, and most recently, bronchoscopy with quantitative cultures. In addition, there must be appropriate laboratory expertise for cultivation of anaerobic bacteria. The incidence of anaerobic lung infections reported in published studies from the antibiotic era that satisfy both requirements is summarized in Table 122-1.

Most published reports deal with the role of anaerobic bacteria in aspiration pneumonia or lung abscess, and these show recovery rates ranging from 62 to 100 percent. The usual specimens in these studies are TTA and transthoracic aspiration. One of the best studies is by Beerens and Tahon-Castel, who used transthoracic needle aspiration to characterize the flora in lung abscesses; this series showed recovery of anaerobic bacteria, usually in pure culture, in 22 of 26 cases (85 percent).

There have been few studies to identify the frequency of anaerobic bacteria in unselected cases of community-acquired pneumonia. One was by Ries and co-workers, who performed TTAs in patients hospitalized with a diagnosis of pneumonia and recovered anaerobic bacteria in 29 of 89 cases (33 percent). A more recent study by Pollock and colleagues, using fiberoptic bronchoscopy with a protected catheter and quantitative cultures, showed recovery of anaerobes in 16 of 74 patients (22 percent). These two reports suggest that anaerobic bacteria are actually relatively common pathogens among patients with community-acquired pneumonia and presumably account for a substantial proportion of cases that are now considered enigmatic. In nosocomial pneumonia, a study by Bartlett and colleagues utilized TTA in 159 consecutive patients and showed anaerobes in 56 (35 percent). Nevertheless, most of these patients also showed the concurrent presence of aerobic gram-negative bacilli or *Staphylococcus aureus,* with the clinical course determined largely by the aerobic pathogens.

Table 122-1

Incidence of Anaerobic Infection of the Lung

Number of Patients			
With Anaerobes	**Total**	**Percent**	**Reference**
Lung abscess			
53	57	93	Bartlett et al.
22	26	85	Beerens and Tahon-Castel
9	10	90	Brook and Finegold
37	41	90	Gudiol et al.
Aspiration pneumonia			
61	70	87	Bartlett et al.
17	17	100	Gonzales-C and Calia
29	47	62	Lorber and Swenson
69	74	93	Brook and Finegold
Empyema			
63	83	76	Bartlett et al.
23	45	51	Beerens and Tahon-Castel
28	72	39	Sullivan et al.
25	100	25	Mavroudis et al.
26	90	29	Grant and Finley
20	70	29	Lemmer et al.
Community-acquired pneumonia			
28	89	33	Ries et al.
16	74	22	Pollock et al.
Nosocomial pneumonia			
56	159	35	Bartlett et al.

MICROBIOLOGY OF EMPYEMA

In the pre-antibiotic era, up to 11 percent of cases of pneumococcal pneumonia were associated with empyema; 64 percent of all cases of empyema were associated with *Streptococcus pneumoniae.* β-Hemolytic streptococci (15 percent) and staphylococci (8 percent) were the other organisms most commonly isolated from empyema fluid. In the 1960s and 1970s, with new culture techniques, one study found *only* anaerobic bacteria in pleural empyema fluid in 35 percent of cases, and a *mixture* of aerobic and anaerobic bacteria in 41 percent in a series of 83 medical patients who had not received antibiotics or surgical intervention (Tables 122-2 and 122-3; Figs. 122-2, 122-3, and 122-4). With the introduction of the sulfa drugs and penicillins, the expansion of thoracic surgery, and the emergence of antibiotic resistance in the

Table 122-2

Bacteriology of Anaerobic Empyema: Predominant Flora

Organism	No. Isolates
Anaerobic iolates	
Fusobacterium nucleatum	19
Prevotella denticola-melaninogenica group	10
Prevotella oris	9
Prevotella intermedia-nigrescens group	8
Prevotella oralis	4
Prevotella buccae	3
Bacteroides fragilis	5
Other *B. fragilis* group	6
Unidentifiable *Bacteroides* spp.	4
Bacteroides gracilis	3
Campylobacter spp.	3
Peptostreptococcus micros	9
Peptostreptococcus anaerobius	5
Peptostreptococcus spp.	4
Peptostreptococcus magnus	3
Streptococcus intermedius	5
Eubacterium spp.	7
Lactobacillus spp.	7
Actinomyces spp.	4
Actinomyces odontolyticus	3
Propionibacterium acnes	4
Clostridium perfringens	3
Clostridium spp.	3
Aerobic Isolates	
α-Hemolytic streptococcus	21
Nonenterococcal group D streptococcus	4
Coagulase-negative staphylococci	4
Proteus spp.	3

SOURCE: *Based on data of Cien R, Jousimies-Somer H, Marina M, et al: A retrospective review of cases of anaerobic empyema and update of bacteriology.* Clin Infect Dis *20:S224–S229, 1995.*

staphylococci, the isolation of *S. pneumoniae* decreased and that of *S. aureus* and other nosocomial pathogens in empyema fluids increased. In more recent studies of empyema, the pneumococcus accounts for only 5 to 10 percent of cases, while anaerobes are found in 25 to 40 percent. The highest yield reported in recent years is a collaborative study at Cook County Hospital in Chicago and two VA hospitals in Los Angeles. Anaerobes were recovered in 63 of 83 cases (76 percent).

Anaerobic Bacteria in Empyema

The frequency of anaerobic infection of the lung and pleural space is a function of the colonization pattern of the individual patient, including the presence of hospital-acquired pathogens and the role of aspiration in many of these infections (Table 122-3). The most frequent isolates are the anaerobes *Prevotella, Fusobacterium nucleatum,* and *Peptostreptococcus* and the streptococci (Figs. 122-5 and 122-6). In early studies, the *Bacteroides fragilis* group was isolated from 15 to 20 percent of patients with anaerobic pleuropulmonary infections. However, later studies employing newer techniques and utilizing newer taxonomic criteria found *B. fragilis* group in only 6.8 percent of 46 patients with pleural empyema specimens. The *B. fragilis* group is important because of resistance to penicillin G (a property shared by a number of common anaerobes) and other antimicrobial agents. Subdiaphragmatic infection may extend to the lung or pleural space by way of lymphatics, directly through the diaphragm or defects in it, or by way of the bloodstream. Anaerobic pulmonary and pleural processes rarely extend to the chest wall unless associated with actinomycosis, tuberculosis, or tumor.

Non-anaerobic Infections

In immunologically normal adults, the aerobic organisms currently most often associated with empyema and lung abscesses are *S. aureus,* β-hemolytic streptococci, and various gram-negative aerobic or facultatively anaerobic bacilli, particularly *Pseudomonas aeruginosa, Escherichia coli, Klebsiella* species, and other nosocomial enteric gram-negative organisms—reflecting infections associated with pneumonia treated with antimicrobial agents to which the causative organism is resistant, with thoracic surgery or high-grade bacteremias. Mixed aerobic-anaerobic infections are often related to subdiaphragmatic processes. Increasingly, *Mycobacterium tuberculosis, Nocardia asteroides,* and fungi have been identified. In the immunocompromised host, the infecting organisms will more often be gram-negative bacteria (especially *Pseudomonas* and *Enterobacter*) or *Candida* or *Aspergillus* species, or will be due to reactivation of latent or subclinical infections due to *M. tuberculosis, Candida* species, or the less virulent streptococci. In all hosts, the colonization pattern of the individual will often predict the causative organisms, even if these are not easily isolated.

MICROBIOLOGY OF LUNG ABSCESS

In lung abscesses, anaerobes are recoverable from up to 89 percent of patients. In some patients, anaerobic organisms of presumably greater virulence (e.g., *Fusobacterium nucleatum* or *Peptostreptococcus* species) may be found as the sole infecting organism. In studies by Bartlett and coworkers, 46 percent of patients with lung abscesses had *only* anaerobes isolated in cultures, while an additional 43 percent had a *mixture* of anaerobes and aerobic bacteria. In addition to anaerobes, among the organisms often implicated in lung abscess formation or in necrotizing pneumonia are *S. aureus, Streptococcus pyogenes, Klebsiella pneumoniae,* and *P. aeruginosa.* Infrequently, other gram-negative bacilli, such as *E. coli* and *Haemophilus influenzae* type B, may cause pulmonary

Table 122-3

Correlation of Infecting Organism and Conditions Underlying Anaerobic Pleuropulmonary Infection

Bacteria	Aspiration	Tonsillitis, Tonsillectomy	Gingivitis, Dental Extraction, Pyorrhea	Bronchiectasis	Bronchogenic Carcinoma	Chest Trauma, Thoracotomy	Peritoneal Infection or Source in Bowel	Pelv Infect
Bacteroides fragilis group	11	1	0	3	1	3	16	1
Pigmented gram-negative anaerobic rods	13	0	7	2	0	0	2	0
Fusobacterium nucleatum	24	2	7	4	4	4	6	1
F. necrophorum	2	45	2	1	2	0	5	4
Peptostreptococcus	27	5	9	4	2	10	6	8
Microaerophilic streptococcus	17	0	5	0	4	0	5	1
Anaerobic, non–spore-forming, catalase-negative, gram-positive rods	6	1	0	1	2	1	3	0
Clostridium	6	3	1	0	0	15	7	

SOURCE: *Based on data of Finegold SM:* Anaerobic Bacteria in Human Disease. *New York, Academic, 1977.*

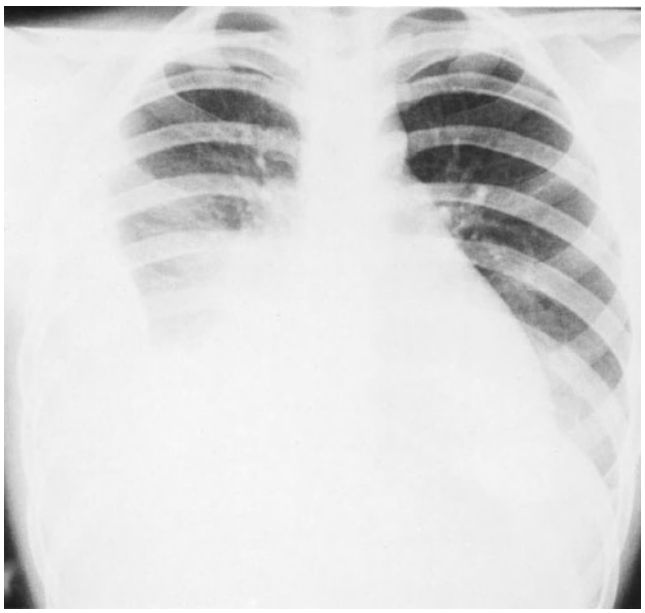


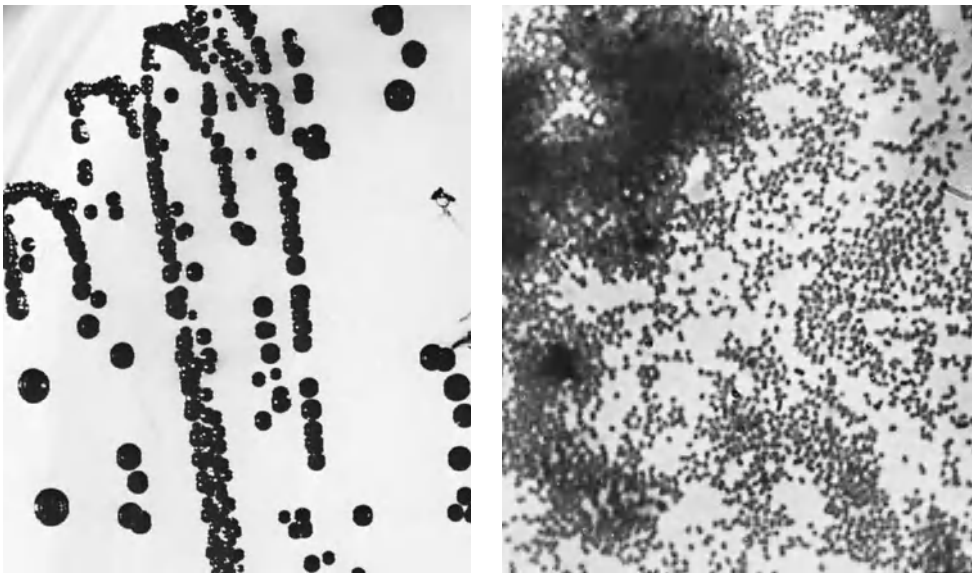
Figure 122-2 Large anaerobic empyema accompanying right middle-lobe pneumonia.

necrosis. Uncommon but important causes of cavitating pneumonia are *N. asteroides, Paragonimus westermani, Legionella* species, *Burkholderia pseudomallei,* and *B. mallei* (glanders), and tuberculosis. Certain fungal infections may cause cavitation in diabetic and immunocompromised hosts (e.g., the *Mucoraceae, Aspergillus* species). *Entamoeba histolytica* is an important, but uncommon, cause of lung abscess, almost always in the basilar portion of the right lower lobe.

Pathophysiology of Aspiration, Empyema, and Lung Abscess

The bacteria implicated in anaerobic lung infections represent the normal flora of the oral cavity—primarily the gingival crevice, where anaerobic bacteria are found in concentrations that approach the geometric limits with which bacteria occupy space: 10/g. Compromised consciousness or dysphagia predisposes most frequently to clinically significant aspiration. Common conditions associated with clinically significant aspiration include alcoholism, general anesthesia, seizure disorder, drug abuse, esophageal lesions, and neurologic deficits.

Numerous studies indicate that virtually all healthy persons aspirate, but that this is usually inconsequential. In one study, in which contrast material was placed in the mouths of sleeping patients, chest radiographs the following day showed contrast material in the lung in most of them, but there was no evidence of a disease process. Similarly, dye markers placed in the stomach of postoperative patients can be aspirated from the tracheobronchial tree at the time of surgery, indicating aspiration of gastric contents during general anesthesia in 7 to 16 percent. Scintigraphic methods have also been used to demonstrate frequent aspiration in patients with intubation of the airways or gastrointestinal tract. None of these studies have demonstrated any clinical consequences from this type of occult aspiration. The conclusion is that aspiration is relatively common, but usually resolves spontaneously. The decisive factor for the development of lung complications depends on the frequency, volume, and character of the material in the inoculum. The conditions cited in the preceding as causing clinically significant disease are associated with more frequent aspiration or aspiration of large volumes—factors that define the populations at greatest risk.



A *B*

Figure 122-3 *Prevotella melaninogenica. A.* Distinctive black colonies (on blood-containing medium); pigment is hematin. *B.* Microscopically, the organism is a coccobacillus.

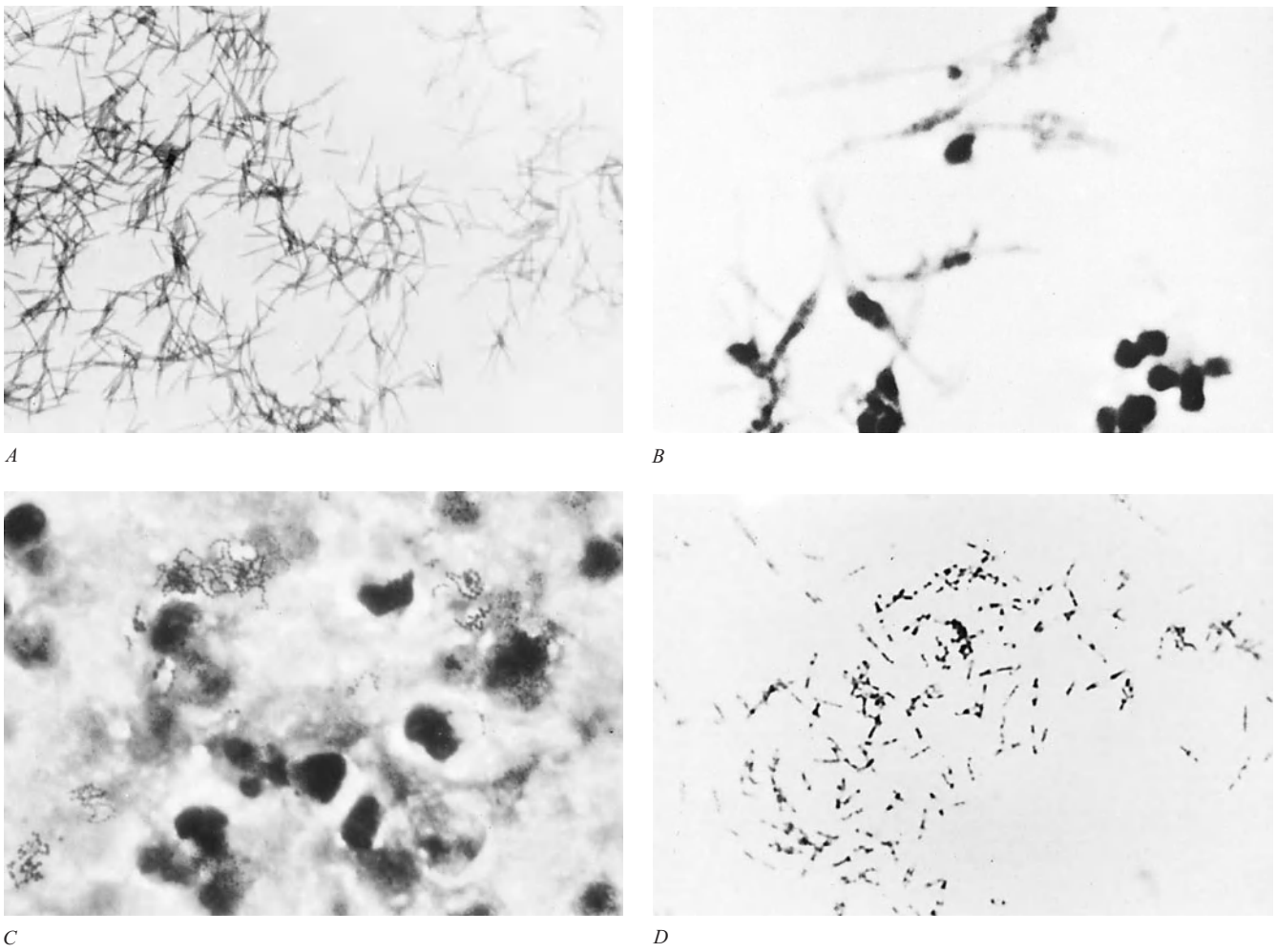
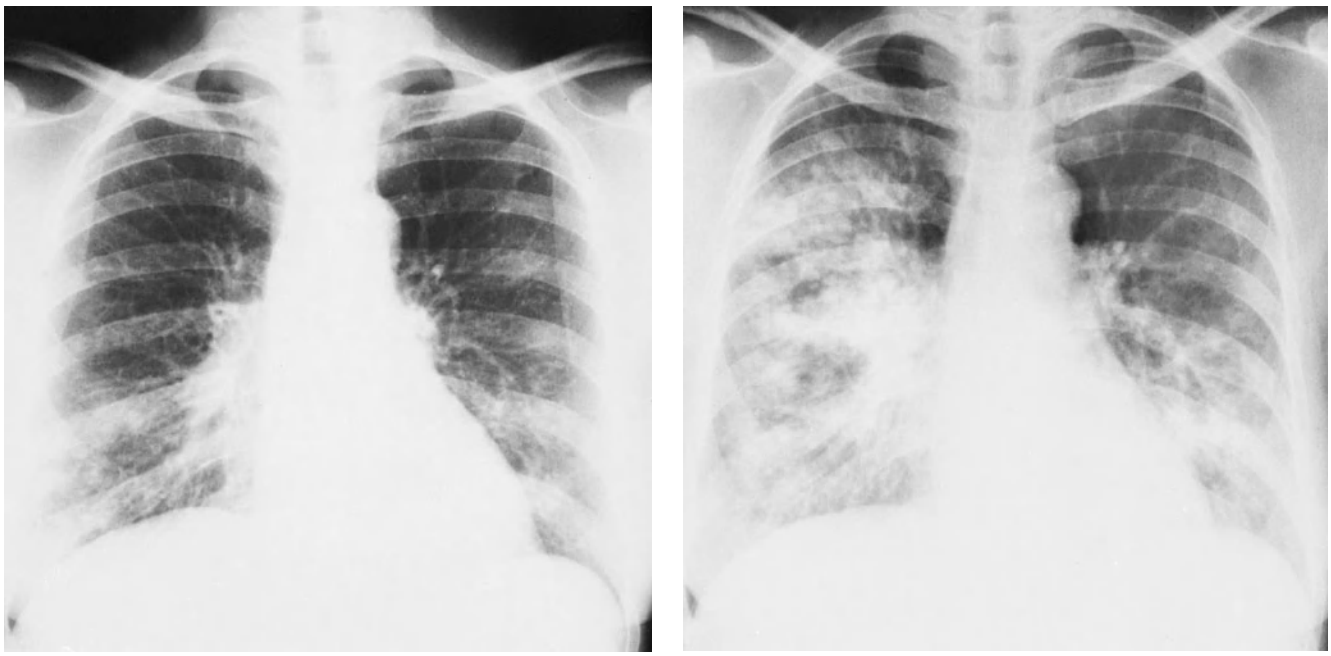


Figure 122-4 Bacteriology of empyema and lung abscess. *A. Fusobacterium nucleatum,* microscopic morphology. Organism is thin and delicate gram-negative bacillus with tapered ends (sometimes filamentous). *B.* Pleomorphic gram-negative bacillus with filaments containing swollen portions and with large round bodies. This appearance is seen with *F. necrophorum, F. mortiferum,* and *F. varium. C.* Pus showing microaerophilic streptococcus. *D.* Microscopic morphology of *Bacteroides fragilis.* Organism is an irregularly stained, gram-negative rod. Bipolar staining may be seen.

Additional conditions that appear to predispose to anaerobic infections include pulmonary infarction, obstruction due to carcinoma or a foreign body, and bronchiectasis. These conditions are associated with stasis or necrosis of tissue, which presumably accounts for the association with anaerobic infections.

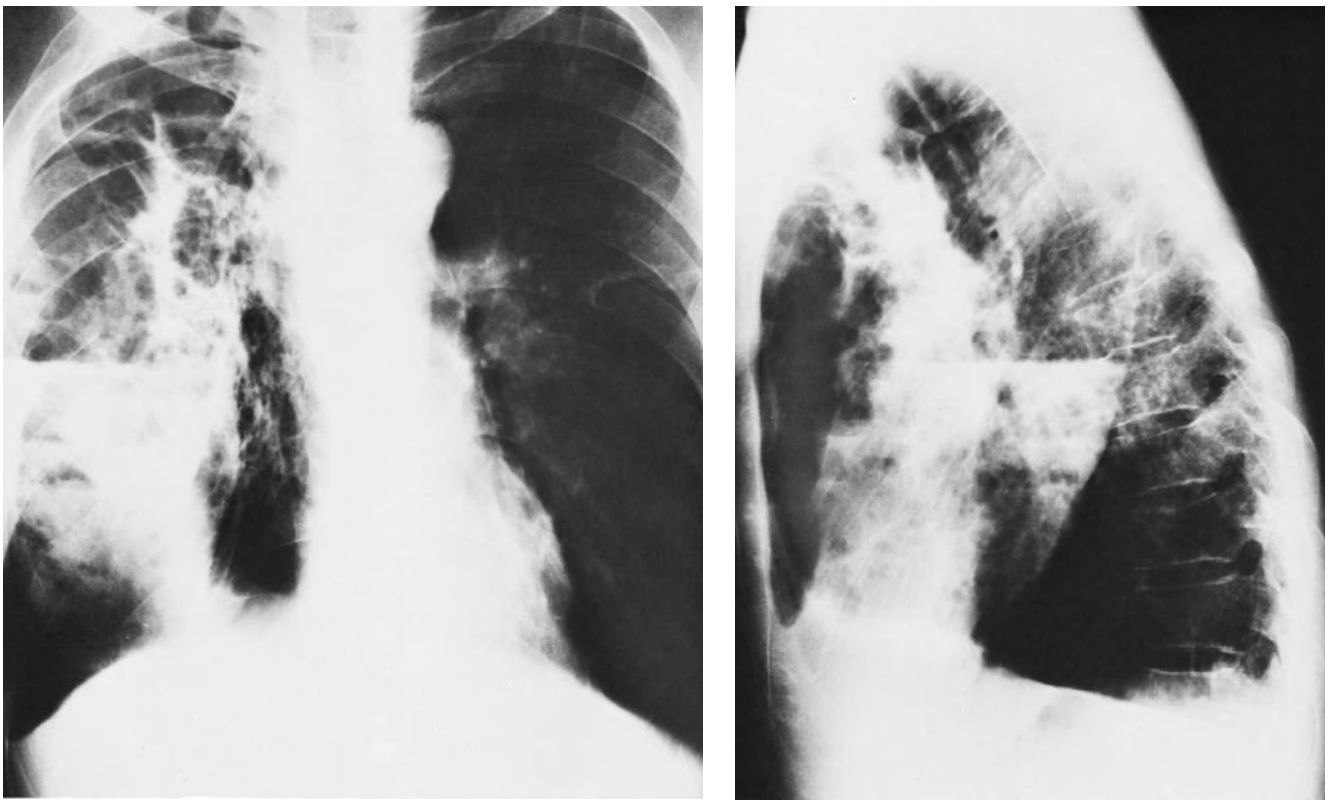
A somewhat unique feature of anaerobic lung infections is the penchant for necrosis of tissue, resulting in abscess formation or a bronchopleural fistula associated with empyema. Virulence factors of anaerobic bacteria presumed to account for this association include the capsular polysaccharide of anaerobic gram-negative bacilli. The most extensively studied is the polysaccharide of *Bacteroides fragilis,* but the same observations appear to apply to *P. melaninogenica* and probably other anaerobic gram-negative bacilli as well. The capsule consists of a family of polysaccharides composed of oligosaccharide repeating units with sugars containing positively charged free amino groups and negatively charged carboxyl or phosphorite groups. These positive and negative charges mediate the capacity to induce abscess formation in experimental animals. Another virulence factor possessed by most anaerobic bacteria is the production of short-chain fatty acids that inhibit phagocytic killing at low pH levels. Short-chain volatile fatty acids are metabolic products of anaerobic bacteria that are used to classify these organisms taxonomically, and they appear to be responsible for the putrid odor that is often a characteristic feature of infections by these organisms.

Because the most important predisposing condition for lung abscess is *aspiration*, lung abscesses are most often located in the posterior segment of the right upper lobe, less often in the left upper lobe, and the apical segments of the lower lobes (Fig. 122-1). Periodontal disease is highly associated with lung abscess formation; in edentulous people, lung abscesses are uncommon and may suggest the presence of an obstructing lesion of the bronchus, pulmonary embolus,



A *B*

Figure 122-5 Fulminating anaerobic pneumonia in a 44-year-old woman with onset of pneumonia 6 days before admission. *A*. Day of admission. Patchy consolidation in right lower lung field and behind the cardiac silhouette. *B*. One day after admission: Extensive patchy alveolar infiltrates bilaterally with areas of rarefaction on right suggestive of cavitation. The patient died 2 days later.



A *B*

Figure 122-6 "Gangrene" of the lung after aspiration, anteroposterior (*A*) and lateral (*B*) views. Extensive cavitation following necrotizing pneumonia in a 65-year-old man.

septic embolus, or unsuspected pathogen. Nosocomial aspiration often involves gram-negative bacteria, particularly organisms with hospital-acquired antibiotic resistance patterns.

Lung abscesses generally develop after inflammation produces tissue necrosis with cavitation. In the presence of pre-existing cavitary disease (emphysema or old tuberculous lesions), infection may proceed without frank necrosis. The abscess cavity may become lined with regenerated epithelium. Local obstruction may produce bronchiectasis or emphysema in the surrounding lung.

The classification of lung abscesses is based on the duration and likely cause of the process. *Acute abscesses* are less than 4 to 6 weeks old, whereas *chronic abscesses* are of greater duration. *Primary abscesses* are infections due to aspiration or to pneumonia in the normal host; *secondary abscess* is due to preexisting conditions (obstruction, spread from an extrapulmonary site, bronchiectasis, immune compromise). Abscesses with foul odors associated with anaerobic organisms are often called *putrid abscesses.*

Clinical Features of Aspiration and Anaerobic Lung Infections

Aspiration Pneumonia

Common clinical features of anaerobic pulmonary infections are summarized in Table 122-4, which categorizes the patients with respect to pneumonitis, lung abscess, or empyema. Features of anaerobic infections that are nearly unique are the association with conditions that predispose to aspiration and infection in the gingival crevice, putrid discharge, and a high frequency of suppurative complications in late stage-disease. Anaerobic lung infections may be acute, subacute, or chronic.

The first stage in the infection is pneumonitis. One review of 46 patients with anaerobic bacterial pneumonitis showed clinical features that were similar to those of pneumococcal pneumonia. The diagnosis was established by TTA, and the results in this group were compared with those in a second group of patients in whom TTAs yielded *S. pneumoniae.* The two groups were similar in terms of age, changes on the chest radiograph, peak temperature, and peripheral leukocyte count. Significant differences in the group with anaerobic infections were the lack of rigors, a somewhat longer duration of symptoms before presentation, and a more frequent association with predisposing conditions for aspiration. An important point to emphasize is that patients seen in this early stage of infection rarely have the features that are commonly associated with anaerobic lung infections, such as putrid sputum, tissue necrosis with abscess formation, and a chronic course. These infections presumably account for some and possibly many of the cases of community-acquired pneumonia in which no etiologic diagnosis is established despite extensive study; such cases account for 40 to 50 percent of cases in most series.

The initial stage of pneumonitis is often more subtle or neglected, so that patients may not seek medical attention until the infection has been present for weeks or even months. These cases are more analogous to tuberculosis than to most bacterial infections of the lung. As noted, many of these infections progress to suppurative complications, with presentation as lung abscess or empyema. Generally, 7 to 14 days is required for cavity formation.

Nearly all patients with anaerobic lung infections have the usual constitutional findings for patients with infection (Table 122-4). A review of 193 bacteriologically confirmed cases showed that the mean peak temperature for hospitalized

Table 122-4

Clinical Features of Anaerobic Pulmonary Infections*

	Lung Abscess (83 pts)	Empyema (51 pts)	Pneumonitis (only) (79 pts)	Total (193 (pts)
Age (median)	52 yr	49 yr	60 yr	51 yr
Peak temperature (mean, °F)	102.1	102.4	102.6	102.4
Peripheral leukocyte count (median/mm)	15,000	21,600	13,700	15,000
History of weight loss	36 (43%)	28 (55%)	3 (4%)	57 (30%)
Putrid discharge	41 (49%)	32 (63%)	4 (5%)	62 (32%)
Lethal outcome	3 (4%)	3 (6%)	3 (4%)	8 (4%)

** Based on retrospective chart review of 193 cases established by recovery of anaerobes as dominant flora in TTA, pleural fluid, or blood culture.*

SOURCE: *From Bartlett JG: Anaerobic bacterial infections of the lung.* Chest *91:901–909, 1987; Bartlett JG: Anaerobic bacterial infections of the lung and pleural space.* Clin Infect Dis *16:S248–S255, 1993; Marina M, Strong CA, Civen R, et al: Bacteriology of anaerobic pleuropulmonary infections: Preliminary report.* Clin Infect Dis *16:S256–S262, 1993.*

Table 122-5

Classification of Aspiration Pneumonia

Inoculum	Pulmonary Sequelae	Clinical Features	Therapy
Acid breathing	Chemical pneumonitis	Acute dyspnea, tachypnea; tachycardia; cyanosis, bronchospasm, fever Sputum: pink, frothy Radiographic: infiltrates in one or both lower lobes Hypoxemia	Positive-pressure Intravenous fluids Tracheal suction
Oropharyngeal bacteria	Bacterial infection	Usually insidious onset Cough, fever, purulent sputum Radiographic: infiltrate in dependent pulmonary segment or lobe ± caviation	Antibiotics
Inert fluids positive-breathing with isoproterenol	Mechanical obstruction Reflex airway closure	Acute dyspnea, cyanosis ± apnea Pulmonary edema	Tracheal suction Intermittent pressure oxygen and matter
Particulate	Mechanical obstruction	Dependent on level of obstruction, ranging from acute apnea and rapid death to irritating chronic cough ± recurrent superimposed infections particulate matter	Extraction of matter Antibiotics for infection

patients was 39.1°C, and all but five patients were febrile. The average peripheral leukocyte count was 15,000/ml^3. Patients who presented with the suppurative complications had a longer duration of symptoms before presentation; this was commonly associated with other evidence of chronic disease, including weight loss and anemia. Another common feature of patients with suppurative complications was putrid sputum or empyema fluid, which was noted in 40 to 60 percent. It should be emphasized that the putrid discharge in these cases is considered diagnostic of anaerobic infection, since aerobic bacteria are not capable of producing this characteristic odor either in vitro or in vivo. Thus, anaerobic bacteria may cause a diverse range of pulmonary infections, which may be acute, subacute, or chronic. The anaerobic etiology is rarely established or even suspected in patients with acute pneumonitis unless the appellation *aspiration pneumonia* is applied; in this case, anaerobes are the presumed pathogens in most community-acquired cases, and they may be contributing factors in many nosocomial infections. By contrast, anaerobic bacteria are readily recognized as probable pathogens in patients who have the late suppurative complications, such as lung abscess or empyema.

Other Aspiration Syndromes

Aspiration Pneumonia

Aspiration pneumonia refers to distinctive syndromes that are distinguished on the basis of the character of the inoculum, which dictates the pathogenesis of pulmonary complications, clinical presentation, and management strategies (Table 122-5). Aspiration pneumonia includes at least three different syndromes: chemical pneumonitis, bacterial infection, and airway obstruction.

Chemical Pneumonitis

Chemical pneumonitis refers to the aspiration of an inoculum that is inherently toxic to the lungs. Examples include acid, animal fats such as milk and mineral oil, and volatile hydrocarbons. These substances are toxic to the lower airways, and they initiate an inflammatory reaction. The prototypic example based on extensive study is gastric acid pneumonitis as classically described by Mendelson and often referred to as Mendelson's syndrome. This is a severe pneumonitis with fever and hypoxia and respiratory alkalosis, that generally either rapidly clears in 4 to 7 days in healthy hosts or may progress (e.g., with lung injury and superinfection) to pneumonia, lung abscess, or ARDS. Factors that contribute to hypoxemia are pulmonary edema, reduced surfactant activity, reflex airway closure, hyaline membrane formation, and alveolar hemorrhage. These patients' pulmonary function tests show decreased compliance, abnormal ventilation-perfusion, and reduced diffusing capacity. The pathophysiology of gastric acid pneumonitis has been studied in experimental animals with intratracheal instillation of graded acid inocula. This work shows that the pH must be 2.5 or less for the

inflammatory process to be initiated. There must also be a relatively large inoculum, usually 1 to 4 ml/kg. It is possible that smaller volumes initiate a less dramatic presentation or may go undetected. Support for this hypothesis is the observation of frequent bouts of pneumonitis and otherwise unexplained pulmonary fibrosis in patients with gastric reflux or esophageal disease.

The pathologic changes in acid pneumonia occur rapidly. Atelectasis occurs within seconds and is extensive by 3 min. There is also peribronchial hemorrhage, pulmonary edema, and bronchial epithelial cell degeneration. The alveolar spaces are filled with neutrophils by 4 h and hyaline membranes are seen within 48 h. Resolution begins by the third day and may be complete or may result in residual scarring of the pulmonary parenchyma.

Long-term follow-up studies in patients who have gastric acid pneumonia show either complete recovery or radiographic evidence of pulmonary fibrosis with abnormal gas exchange.

The diagnosis of acid pneumonia is usually presumed on the basis of clinical observations such as the abrupt onset of dyspnea in a patient who is aspiration prone and has radiographic evidence of infiltrates, usually in the lower lobes. Other characteristic clinical features are the rapid clearing of the infiltrates and progression to ARDS. Bronchoscopy demonstrates erythema of the bronchi, suggesting a "chemical burn." Confirmation of the acid inoculum is not possible because of rapid neutralization by pulmonary edema fluid and bronchial secretions within minutes after aspiration.

The treatment of gastric acid aspiration includes tracheal suction to clear fluids and particulate matter that may be aspirated concurrently. Supportive care consists primarily of ventilatory support with positive pressure ventilation, and intravenous fluids due to decreased intravascular volume with hypotension. Corticosteroids have not be useful. Antimicrobial agents are reserved for superinfection.

Mechanical Obstruction

Aspiration pneumonia may involve fluid or particulate material. In this form of aspiration pneumonia, the inoculum is not toxic to the lung but may cause obstruction or reflux airway closure. In most cases there is only transient, self-limited hypoxemia due to rapid clearance. Some patients develop pulmonary edema, with hypoxemia and reduced compliance apparently due to an intrinsic pulmonary reflex closure. Other patients suffer sequelae due to failure to clear relatively large volumes of the aspirate, as with near drowning victims and patients with profound neurologic deficits or in coma. The obvious critical intervention is tracheal suction.

Aspiration with mechanical obstruction may also be associated with solid particles. Foreign-body aspiration is most frequent in children 1 to 3 years of age. The most common objects in the lower airways are vegetable particles, inorganic materials, and teeth. The severity of the obstruction depends on the relative size of the material aspirated and the caliber of the lower airways. Large objects may cause obstruction at the level of the larynx or trachea, leading to sudden respiratory distress, cyanosis, and in some cases, aphonia. This is referred to as *café coronary syndrome* because it often involves meat aspiration during restaurant dining and may simulate an acute myocardial infarction. Aspiration of smaller particles may result in complete obstruction of more distant components of the tracheobronchial tree or partial obstruction. Chest radiographs often show atelectasis or obstructive emphysema. An important clue in some cases is unilateral wheezing. Bacterial infection is not important in the early stages of obstruction, but is a common feature when obstruction has been present for more than 1 week. The most common pathogens are anaerobic bacteria from the upper airways. These patients may respond well to antibiotics, but often have recurrent infections in the same pulmonary segment. The most important therapeutic intervention is removal of the foreign body, usually with bronchoscopy.

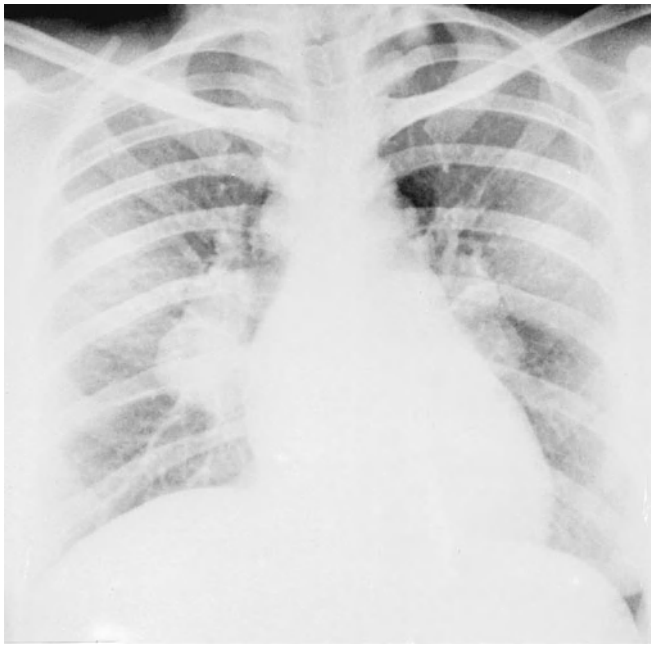
Empyema and Lung Abscess

The pathogenesis and presentation of both pleural empyema and lung abscesses are often indistinguishable. Shared presentations of empyema and lung abscess include the indolent development of symptoms, most often fever, sweats, cough, dyspnea, weight loss, and pleurisy; an association with conditions predisposing to aspirational events (altered consciousness, dysphagia, and gingivitis); and foul odors of sputum or breath associated with anaerobic bacteriology. Lung abscesses and empyemas often coexist. Both are generally associated with primary pneumonias.

The clinical presentation of empyema is determined by the underlying cause of infection. Empyema associated with aspiration pneumonia may develop over 1 to 3 weeks, usually with associated symptoms of pneumonia. The patient may have high fever and leukocytosis. Physical examination reveals dullness to percussion and decreased breath sounds on auscultation. These changes may be quite localized in the setting of loculated fluid. The empyema fluid is generally purulent by the time of detection, but pleural infection may be noted only after treatment for pneumonitis has failed to resolve fever or pleurisy. Empyema associated with thoracic surgery may be radiologically "hidden" in areas of the chest not drained by chest tubes or behind relatively benign pleural effusions. The patient may appear minimally toxic or severely ill, depending on the extent of the infection and organisms present. The presentation is modified by routine prophylactic antibiotic use, sedation, intubation, and antipyretics. Acute empyema may be seen in staphylococcal and streptococcal infections and following rupture of hepatic abscesses, especially those due to *E. histolytica.*

Lung Abscess

The clinical presentation of lung abscess may be coincident with the initial presentation of pneumonia or other underlying condition, or may occur later in the clinical course. Suspicion may be heightened by the presence of conditions predisposing to aspiration or anaerobic pneumonia: alcoholism or other causes of altered consciousness, anaesthesia, dysphagia



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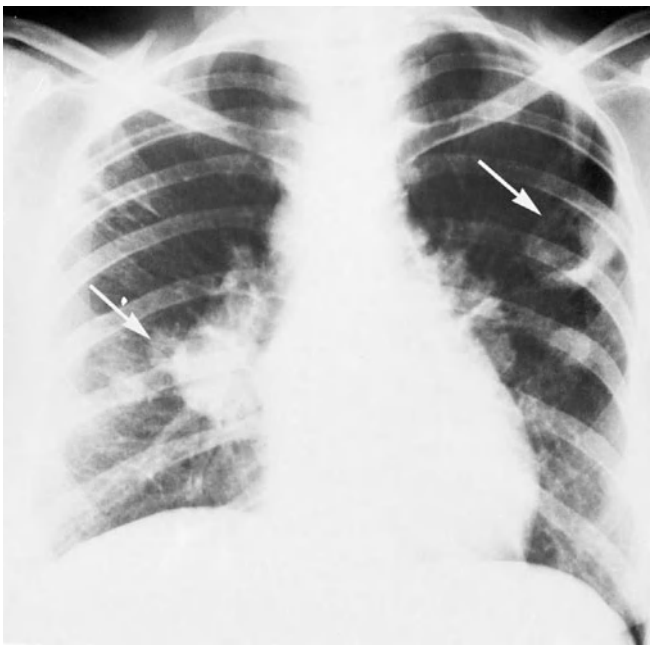

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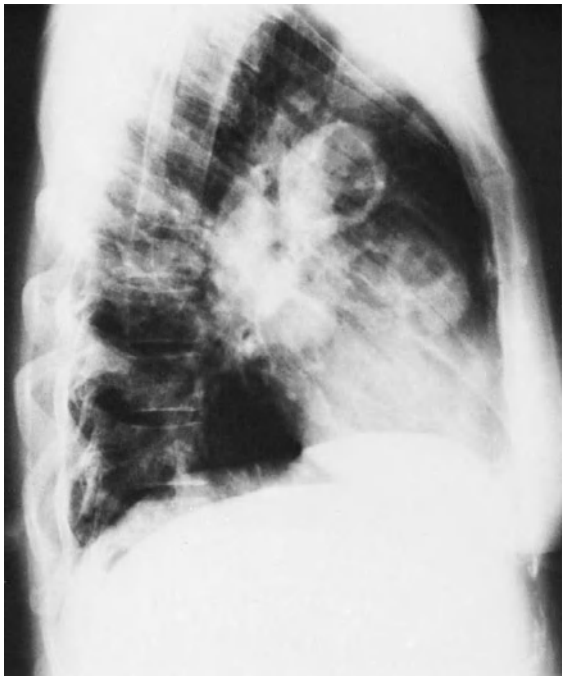

C

Figure 122-7 Septic emboli due to *Pseudomonas aeruginosa* in a 33-year-old woman with sarcoidosis and pyelonephritis following spontaneous abortion. The patient presented with headache, fever, backache, and purulent sputum. *Pseudomonas* grew from the sputum culture. *A*. Chest radiograph before present illness. Bilateral hilar adenopathy of sarcoidosis. *B*. Posteroanterior view of chest shows bilateral cavitary lesions (arrows). *C*. Lateral view. The lesions are more dramatically seen.

or pharyngeal dysfunction, gingivitis or pyorrhea, blunt or penetrating chest trauma or lung surgery, obstruction due to neoplasm, bronchiectasis, or pulmonary embolism. Bad breath or putrid sputum may be noted. However, the absence of a foul odor does not exclude the possibility of anaerobic infection, since certain anaerobes do not generate the end products of metabolism responsible for this type of odor, and communication may be lacking between the lesion and tracheobronchial tree. A change in sputum production, either increased or decreased, may be noted in patients with chronic bronchitis or bronchiectasis.

The patient with *primary lung abscess* gradually develops fever, cough, pleurisy, chest heaviness, shoulder pain, and malaise. Pneumonia may be present or suspected from history for a period of 1 to 3 weeks before the recognition of the lung abscess. By contrast, *secondary lung abscesses*—due, for example, to septic pulmonary emboli with infarction—can evolve over 48 to 72 h (Fig. 122-7). Clinically, the distinction between primary and secondary abscesses may be inapparent at the time of presentation, but is important in the proper management of the patient. Thus, the patient with staphylococcal or streptococcal endocarditis may present with pneumonia,

lung abscess, and empyema. The main clue to the presence of underlying endocarditis may be the development of new lung abscesses during the course of therapy. The patient with lung abscesses complicating subdiaphragmatic infection (amebic abscess of the liver or pancreatic phlegmon) may have abdominal signs in addition to acute pulmonary disease. Seizures due to brain abscesses are occasionally the presenting clinical manifestation of bacteremia due to lung abscesses.

RADIOLOGY AND DIAGNOSIS OF ANAEROBIC PLEUROPULMONARY INFECTIONS

Radiologic Diagnosis

Chest radiographs in patients with anaerobic lung infections show infiltrates, with or without cavitation, that most frequently involve dependent pulmonary segments. The favored locations are the superior segment of the lower lobes or posterior segments of the upper lobes; these are dependent in the recumbent position. The basilar segments of the lower lobes are favored in patients who aspirate in the upright position. The right lung is more frequently affected, owing to the more direct takeoff of the right mainstem bronchus.

With empyema, chest radiographs generally reveal fluid, most often in the costophrenic angles; free-flowing effusions layer on lateral decubitus radiographs. Loculations and pleural disease are often best defined by computed tomography of the chest, which should include the neck and diaphragms to rule out extrathoracic sites of infection. Spinal disease is better detected with magnetic resonance imaging (MRI). Before invasive diagnostic procedures, a careful history and physical examination may suggest a reason for the accumulation of pleural fluid. Non-infectious causes include bland pulmonary embolus, malignant effusion, benign postsurgical changes, pericardiotomy syndrome, collagen-vascular diseases (systemic lupus, rheumatoid arthritis), congestive heart disease, sympathetic effusion related to subdiaphragmatic disease (pancreatitis), leakage of ascites or peritoneal dialysis fluids, and hemorrhage (from venous access catheters or aortic tears). Infectious causes include extension of all classes of pulmonary infections from the lungs (parapneumonic), esophageal rupture, parapharyngeal space drainage, drainage or sympathetic effusion due to hepatic or subdiaphragmatic abscesses, septic metastasis, and direct infection via thoracic defects or chest tubes used for pleural drainage. Pyopneumothorax, in the absence of bronchopleural fistula, prior surgery, or prior thoracentesis, suggests the possibility of gas formation by bacteria implicated in the infection. Although nonspecific, pyo- pneumothorax suggests a component of anaerobic infection.

The classic radiographic appearance of a lung abscess is an irregularly shaped cavity with an air-fluid level inside. Because the presentation is often indolent, numerous chest radiographs may be needed to follow the evolution of pneumonia into *necrotizing pneumonia* and then into a pulmonary cavity (Figs. 122-5 and 122-6). Anaerobic infection is suggested by rapid pulmonary cavitation within a dense segmental consolidation; there may be rapidly enlarging nodular lesions, with or without cavitation. Although anaerobic pulmonary infections may be acute and fulminating, almost two-thirds of them have a subacute or chronic presentation. Natural progression of virulent infection, delays in appropriate therapy, or tissue infarction may allow the underlying infection to progress into *pulmonary gangrene* (Fig. 122-4). Seeding of infection or rupture of a lung abscess into the pleural space may cause empyema (Fig. 122-7). Up to one-third of lung abscesses may be accompanied by empyema. Solitary cavities are generally observed with primary lung infections, whereas many smaller collections may be found in metastatic infection. Chest tomography will define the size and location of abscesses, and may distinguish between related processes (empyema, infarction) better than conventional radiographs. The common organisms and conditions associated with lung abscesses are listed in Table 122-6.

Laboratory Diagnosis

Aspiration pneumonitis is a clinical diagnosis. It is generally assumed that there is an anaerobic component to pneumonia in patients with altered consciousness or after surgical procedures.

It is important to emphasize the utility of the Gram's stain in making the diagnosis of anaerobic lung infection. Often culture data are not available to document the presence of such organisms. However, most anaerobic gram-negative bacteria have unique morphologic features that make them relatively easy to identify or suspect on direct Gram's stain. Peptostreptococci appear like their aerobic counterparts. These are usually mixed infections involving multiple bacteria, and about half of the cases demonstrate mixtures of aerobic and anaerobic bacteria. Thus, the detection of polymicrobial flora or bacteria with the unique morphology of anaerobes on any specimen that is devoid of contamination by normal flora represents an important clue to the probable presence of anaerobic infection.

Determination of the microbiology of anaerobic infections of the lower airways requires a specimen devoid of contamination by the flora of the upper airways or quantitative cultures that distinguish pathogens from normal flora. Uncontaminated specimens that are considered valid for anaerobic culture include pleural fluid, transtracheal aspirates, transthoracic aspirates, and specimens obtained at thoracotomy. Quantitative cultures of specimens obtained at fiberoptic bronchoscopy, either by BAL or with the protected brush, may be used for this purpose also. Anaerobic bacteriology should not be used for bronchoscopic aspirates. It should be noted that quantitative culture of lower-airway secretions improves diagnostic accuracy with virtually any specimen that is subject to contamination, including expectorated sputum and tracheostomy aspirates. Most studies employing these techniques use them for detection of aerobic bacteria, and there are relatively few studies in which anaerobic cultures

Table 122-6

Organisms and Conditions Associated with the Radiographic Appearance of Lung Abscess

Infectious	Noninfectious and Predisposing Conditions
Bacteria Anaerobes; *Staphylococcus aureus*, Enterobacteriaceae, *Pseudomonas aeruginosa*, streptococci, *Legionella* spp., *Nocardia asteroides, Burkholdaria pseudomallei*	Anatomic Fluid-filled cysts, bland infarction Bronchiectasis Vasculitis
Mycobacteria (often multifocal) *M. tuberculosis, M. avium* complex, *M. kansasii*, other mycobacteria	Goodpasture's syndrome, Wegener's granulomatosis, periarteritis Obstruction (neoplasm, foreign body)
Fungi *Aspergillus* spp., Mucoraceae, *Histoplasma capsulatum, Pneumocystis carinii, Coccidioides immitis, Blastocystis hominis*	Pulmonary sequestration Pulmonary constusion Carcinoma
Parasites *Entamoeba histolytica, Paragonimus westermani, Strongyloides stercoralis* (post-obstructive)	
Empyema (with air-fluid level) Septic embolism (endocarditis)	

have been performed. It is important to emphasize the importance of obtaining specimens before inception of antibiotic treatment. Such specimens are not often obtained in clinical practice until the patient has developed complications of persistent infection (i.e., empyema or abscess). *Thus, the anaerobic component of infection should be considered in management even if an aerobic organism is isolated.*

It is essential that material obtained for culture be placed under anaerobic conditions promptly before transport to the laboratory. A sealed syringe provides the best container, with delivery of the specimen to the laboratory within 20 to 30 min for immediate plating. It is imperative that air bubbles be eliminated from the syringe and needle. Special anaerobic transport tubes are also available for brush or liquid specimens. It is important to obtain additional pulmonary specimens for culture and antibiotic susceptibility measurements from patients failing to respond to initial therapy (Fig. 122-8). Such data may demonstrate the presence of unrecognized or antibiotic-resistant organisms. Most of these infections are polymicrobial, and many of the organisms grow slowly in vitro. Thus, it often takes several days to separate, identify, and report results of anaerobic cultures. There is great variation in the availability and quality of in vitro susceptibility tests. These factors illustrate the need for empiric decisions regarding antibiotic selection.

Diagnosis of Empyema

The diagnosis of empyema is based on the characteristics of thoracic fluid. The urgency to diagnosis is due to the development of pleural scar and of loculated effusions in the presence of undrained pus. Thus, diagnostic thoracentesis should be attempted unless the nature of the pleural fluid is clear or the clinical risk to the patient is too great. Pleural fluid should be prepared for Gram's stain and cultures (routine, anaerobic, mycobacterial, and fungal), parasitologic examination when appropriate, fluid cell count and differential, cytology, pH, lactic dehydrogenase, and glucose measurements. Purulent fluid requires drainage. Empyema (defined in the preceding) is diagnosed on the basis of the neutrophilic predominance in fluids with more than 25,000 white blood cells per milliliter. Parapneumonic effusions will generally have lower white blood counts, negative Gram's stains and cultures, a pH over 7.3, and glucose over 50 percent of serum glucose levels. Parapneumonic fluids may become infected over time. Blood cultures and sputum cultures should be obtained as adjunctive guides to therapy.

DIAGNOSIS OF LUNG ABSCESS

Microbiologic specimens from patients with lung abscesses should be obtained, if possible, without contamination by oral flora, especially after nosocomial colonization. Thus, invasive procedures are preferred to routine sputum samples. In particular, the diagnosis of anaerobic infection is complicated by the prevalence of large numbers of anaerobes as normal flora in the mouth and upper respiratory tract (Fig. 122-9). However, there may also be significant

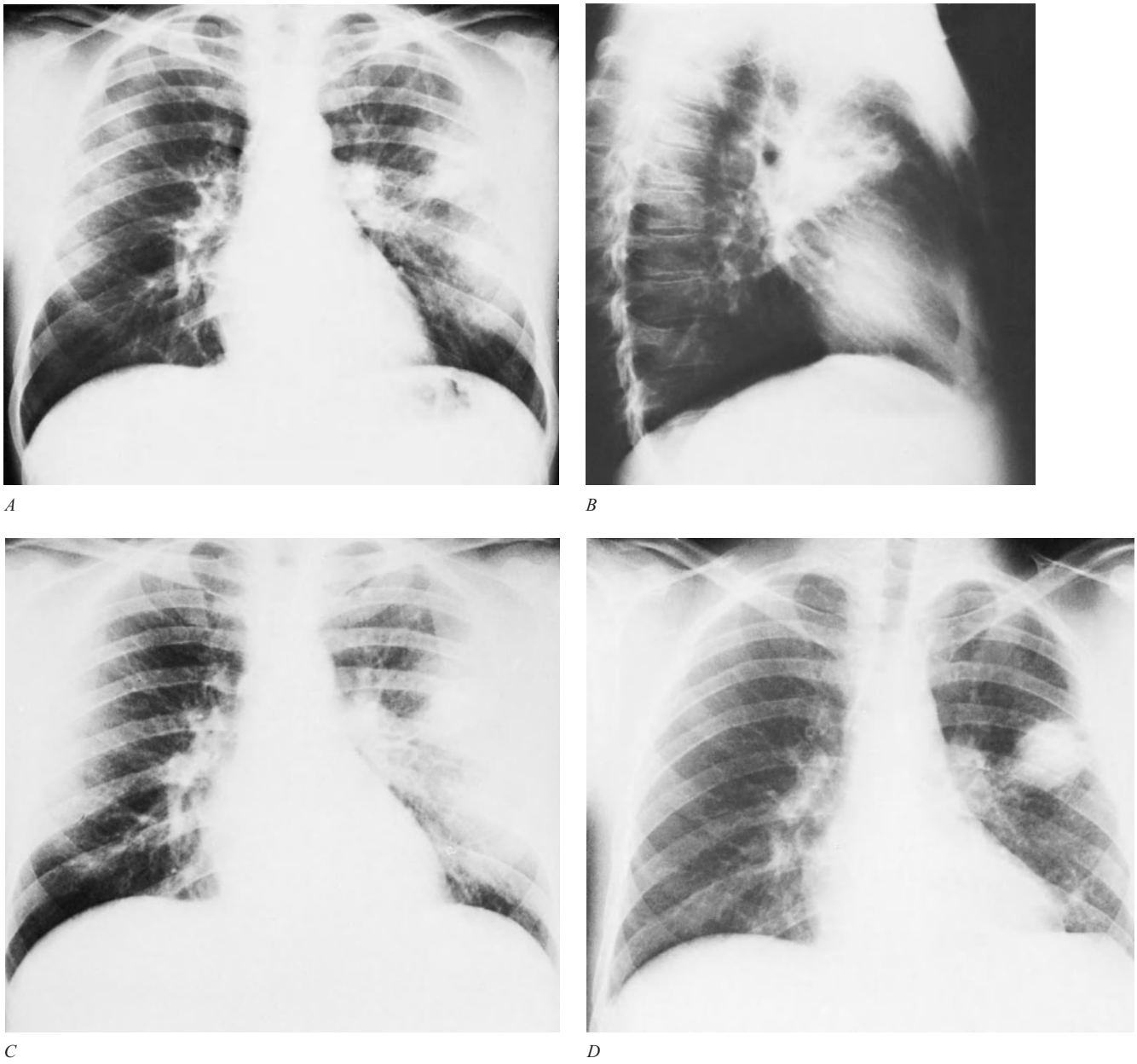

Figure 122-8 Failure of penicillin therapy for anaerobic lung abscess in a 29-year-old alcoholic man. *A*. Admission chest radiograph reveals a radiolucent area within a zone of consolidation in the left upper lung field. *B*. Lateral view demonstrates multiple cavities. The patient was treated for 5 days with penicillin (6 million units per day intravenously), followed by the same dosage orally for 10 days. *C*. Radiographic infiltrate persists but no cavity is visible. *D*. Six weeks after the cessation of penicillin therapy, the abscess has recurred in the same area. Marked pleural reaction is noted in the vicinity of the recurrent disease.

colonization with nosocomially acquired pathogens in hospitalized patients.

Blood cultures and sputum cultures should be obtained as adjunctive guides to therapy. When empyema or bacteremia complicates lung abscess, adequate specimens for microbiologic evaluation may be obtained from the blood or pleura. However, to obtain adequate specimens from the abscess, bronchoalveolar lavage, use of a protected double-lumen catheter, or percutaneous transthoracic aspiration under radiographic guidance is recommended. The specific procedure selected depends on the location of the infection and the expertise of the institution. Specimens collected through a fiberoptic bronchoscope, using bronchoalveolar lavage or a plugged double-lumen sampling catheter with a protected sampling brush, are preferred; these require the use of quantitative cultures. Growth at a dilution of 10 from a protected brush represents approximately 10 to 10 organisms per milliliter in the lower respiratory tract. Recovery of nonbacterial and anaerobic bacteria from these specimens has not been well standardized. Specimens obtained from blind, deep suctioning via an endotracheal tube may also be useful if cultured quantitatively and examined microscopically.

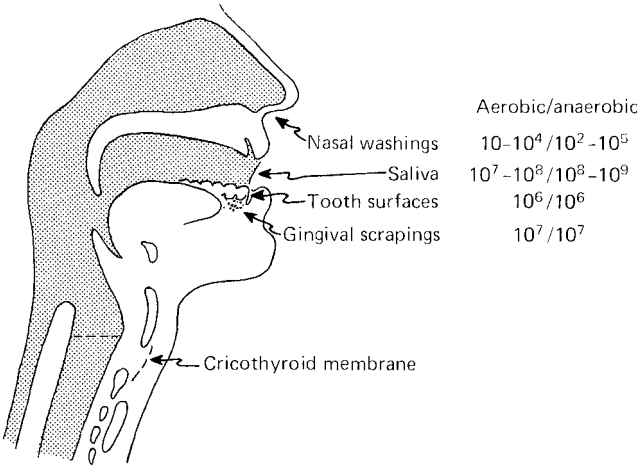

Figure 122-9 Sagittal section illustrating presence of large numbers of organisms, including anaerobes, as indigenous flora in upper respiratory tract. (Values given as number of aerobic/anaerobic organisms per milliliter.) *(Courtesy of P.D. Hoeprich.)*

Bacteriology

The bacteriologic findings in anaerobic lung infections from two large series are summarized in Table 122-7. Most of these infections involve multiple bacterial species, and approximately half of the patients have anaerobic bacteria combined with potentially pathogenic aerobic or facultative anaerobes. Analysis of community-acquired infections involving only anaerobes versus those that are mixtures of aerobic and anaerobic bacteria shows common clinical features with no difference in terms of the frequency of suspected aspiration, indolent presentation, or the frequency of putrid discharge. The implication is that a putrid lung abscess with *E. coli* in expectorated sputum or anaerobic bacteria plus *E. coli* in a TTA should usually be considered an anaerobic infection. Caution is advised in applying these conclusions to nosocomial pulmonary infections, since this is a setting in which the aerobic component of the infection is probably more important.

The major bacterial isolates in patients with anaerobic lung infections are Peptostreptococcus, *F. nucleatum,* and *P. melaninogenica.* Aerobic and microaerophilic streptococci are commonly present, and may be contributing factors in the pathogenic events. At least 15 to 25 percent of anaerobic bacteria responsible for lung infections are resistant to penicillin, generally because of penicillinase production. These susceptibility data are rarely available in individual cases unless specifically requested.

Table 122-7

Bacteriology of Anaerobic Lung Infections

	Bartlett	Marina et al.
Period reviewed	1968–1975	1976–1991
Patients	193	110
Total anaerobic isolates	461	404
Major isolates		
Gram-negative bacilli		
Bacteroides fragilis group	38*	18
Pigmented Prevotella†	76	63
Nonpigmented Prevotella	—	40
B. ureolyticus	—	23
Fusobacterium nucleatum	56	34
Bacteroides spp. (other)	37	138
Peptostreptococcus/ peptococcus‡	126	39
Gram-positive bacilli		
Clostridium spp.	18	12
Eubacterium spp.	18	22
Actinomyces	5	1
Lactobacillus	8	22
Propionibacteria	10	9

**Numbers indicate the total number of isolates. Some of the differences are due to taxonomic changes.*
†Pigmented Prevotella refers to organisms previously classified as B. melaninogenicus.
‡Most peptococci have been reclassified as Peptostreptococcus.

TREATMENT OF ASPIRATION PNEUMONIA AND ANAEROBIC LUNG INFECTIONS

Prevention

Treatment is focused on optimal antimicrobial therapy and drainage of any abscess or empyema (see below). The reversibility of underlying conditions predisposing to aspiration must be considered. It has recently been recognized, for example, that aspiration in lung transplant recipients is a major predisposing factor to graft injury and obliterative bronchiolitis. In the general patient population, nasogastric-feeding tubes, sedation, laying flat in bed while sleeping, reflux, and frequent choking are associated with aspiration, and should suggest strategies for remediation. Gastric surgery for obesity has also been associated with a high incidence of aspiration disease.

Methods to prevent aspiration have been most extensively studied in hospitalized patients, especially those who are aspiration prone. Most important is use of the semirecumbent or upright position. Additional factors that have variable degrees of success are tracheostomies, reduction of the stomach volume with suction or metoclopramide, feeding via gastrostomy tube, and neutralization of gastric acid with H_2 blockers or antacids. Many of these procedures may alter colonization patterns and predispose to more significant infections. Neutralization of gastric acid may increase colonization of the oropharynx and increase the risk of bacterial infection following aspiration of gastric contents. Tracheostomy is useful

Table 122-8

Antibiotic Treatment of Anaerobic Lung Infections: Results of Two Randomized Trials

		Number of Patients with				
Source	**Treatment**	**# Pts**	**Failure**	**Relapse**	**Fever**	**Putrid Sputum**
Levinson (1983)	Penicillin (6 mil units/d)	21	5 (29%)	3 (19%)	7.7	7.8
	Clindamycin (1.8 g/d)	17	0*	0	4.7*	4.1*
Gudiol (1990)	Penicillin (12 mil units/d)	18	7 (39%)	2 (11%)	7.2	7.3
	Clindamycin (2.4 g/d)	19	1 (5%)	0	6.4	3.9*

** Difference for treatment favoring clindamycin is statistically significant.*

in some patients with repeated aspiration, but inflation of the balloon may occlude the esophagus and promote aspiration of upper-airway contents. Patients who require nasogastric feedings are aspiration prone; percutaneous endoscopic gastroscopy is an attractive method to address this issue, but study results are quite variable. An alternative method sometimes favored is a feeding jejunostomy. The use of surgery with gastroesophageal reflux has given variable results.

Antimicrobial Therapy

It is essential, whenever possible, to obtain microbiologic samples from the lungs and blood in advance of antimicrobial therapy. As for all pneumonias, inappropriate initial therapy has an adverse impact on outcome. The initial choice of antimicrobial agents should be guided by the Gram's stain and the likely bacteriology of the infection, and then adjusted as culture data become available. The history and a review of old data may be useful in the selection of specific antibiotics. The standard drug historically for aspiration pneumonia and lung abscess involving anaerobic bacteria has been penicillin, usually given intravenously or with high-dose oral treatment. However, in the face of increasing penicillin resistance among *S. pneumoniae* and in 40 to 60 percent of strains of fusobacteria and *P. melaninogenica* as well as anaerobic gram-negative bacilli, alternatives should be considered for empiric therapy. In therapeutic trials in patients with lung abscess involving anaerobic bacteria (Table 122-8), clindamycin proved superior to penicillin in terms of response rates and time to defervescence. Alternative regimens that have been used successfully based on anecdotal experience include amoxicillin-clavulanate (Augmentin) and penicillin combined with metronidazole. Metronidazole should not be used as a single agent in patients with anaerobic lung infections, since there is a poor response in about 50 percent. The presumed explanation is the contributing role of aerobic and microaerophilic streptococci, which are resistant to this drug.

Many other antimicrobial agents are likely to be useful in anaerobic or mixed aerobic-anaerobic infections: combinations of a β-lactam with a β-lactamase inhibitor (ticarcillin-clavulanate, ampicillin-sulbactam, amoxicillin-clavulanate, piperacillin-tazobactam), chloramphenicol, imipenem or meropenem, and second-generation cephalosporins such as cefoxitin or cefotetan. Macrolides (erythromycin, clarithromycin, and azithromycin) offer good in vitro activity against most strains except fusobacteria. Tetracyclines show limited activity against many anaerobic bacteria in vitro; vancomycin is active only against gram-positive anaerobes. Oxacillin and nafcillin are much less active. Drugs that have virtually no activity against anaerobes include aminoglycosides, first-generation fluoroquinolones, aztreonam, and trimethoprim-sulfamethoxazole. Some of the newer fluoroquinolones (gatifloxacin, moxifloxacin) have broad coverage that includes anaerobes.

The appropriate duration of therapy is dependent on the clinical and radiographic response of the patient. Patients should be treated at least until fever, putrid sputum, and abscess fluid have resolved, and any fluid collection has resolved or stabilized over 2 to 3 weeks. A *minimum* of 2 to 3 weeks of antibiotics is recommended. Longer courses are often necessary. Relapse is common and may involve organisms resistant to initial antibiotic agents (Fig. 122-8).

Management of Empyema

The management of empyema includes antimicrobial treatment, identification and treatment of any anatomic processes, and drainage of the infected fluid. The approach to a specific patient is based on the clinical status of the patient as well as the microbiology of the infection. For example, patients with empyema following thoracic surgery and other hospitalized patients may have useful culture data available from chest tube drainage samples or sputum cultures to assist in the selection of antibiotics. The Gram's stain may indicate the predominant organism type. Mixed aerobic and anaerobic organisms may be the first suggestion of esophageal tear or parapharyngeal infection. Fastidious organisms (*S. pneumoniae*, anaerobes) may be seen on Gram's stain but not isolated in culture. Antibiotic susceptibility data should be used to guide therapy, especially in nosocomially acquired infection.

Local administration of antibiotics (e.g., inhaled, instilled) is unnecessary and may be irritating; intrapleural injection of antibiotics should be reserved for pleural ablation (pleurodesis), as may be achieved with erythromycin.

Drainage of empyema fluid is recommended but controversial. Ten to twenty percent of empyemas require external drainage or surgical intervention. Noninfected parapneumonic pleural fluids resolve with appropriate treatment of the underlying infections. *Drainage is required if infection or frank pus is present.* In the presence of pleural fluid and unexplained fever, leukocytosis, or bacteremia, or in the postoperative patient, thoracentesis should be performed routinely. Diagnostic thoracentesis may be performed with a needle adequate for removal of all but the most viscous material. Highly viscous or purulent fluids and fluids with acid pH require the insertion of a chest tube via thoracostomy or the thoracoscopic drainage of the fluid.

In the *early* or *exudative* phase of parapneumonic effusion, the fluid is thin and serous or serosanguineous. This may resolve during appropriate antibiotic therapy either without drainage or with multiple needle aspirations. If the pH is over 7.3, this method may be preferred. If the pH is less than 7.0, however, complete drainage should be performed, often requiring closed chest tube insertion. If the pH is between 7.0 and 7.3, failure to demonstrate improvement of infection or inflammation on multiple thoracenteses over 3 to 4 days should lead to consideration of formal drainage, especially if the primary process is adequately treated. Loculation of pleural fluid or failure to respond to antimicrobial therapy may require either multiple thoracenteses guided by ultrasound or chest tomographic evaluation (CT scans) or surgical intervention (see the following). Bloody fluid or persistent parapneumonic fluid should prompt cytologic evaluation and CT scans for lung masses or undrained mediastinal or retrocardiac collections.

Empyema diagnosed later in the course, persistently infected pleural fluid, viscous fluid, or fluids with acid pH may require large-bore tube drainage. This heavily proteinaceous fluid is characteristic of the *fibropurulent phase* of the evolving empyema. Indications for closed chest tube placement include bronchopleural fistula with empyema, loculated fluid unresponsive to thoracentesis and antibiotics, the presence of blood clots, and rapidly accumulating empyema not otherwise manageable. Under suction, and with removal of the gel-like material, pus, and clots, the lung expands and obliterates the empyema space. Failure to expand the underlying lung, persistence of drainage beyond 7 days, inability to achieve drainage assessed radiologically, fever without change in 2 to 3 days, or pus formation with persistent infection (as opposed to colonization of the chest tubes) necessitates a search for undrained foci of infection, failure to close a bronchopleural fistula or esophageal tear, undetected rupture of a lung abscess, or antibiotic failure. As the infection enters the *chronic phase,* open drainage with rib resection or pleurocutaneous fistula formation may be needed, with or without decortication, to achieve lung expansion and healing. Open drainage is obtained by making the pleura adherent to the chest wall during the insertion of chest tubes directly into the empyema cavities. Drainage achieved too late in the course of infection may result in the development of pleural scar and fibrous peel with restrictive pulmonary physiology. Decortication may be needed to achieve sterilization of the pleural space and restore lung expansion. Thoracoscopic drainage of empyema has been used with excellent results at a number of institutions, particularly in children. Often, thoracoscopic drainage of empyema is used as a temporizing maneuver (e.g., following acute rupture of a lung abscess into the pleural space). Patients achieving rapid re-expansion of the lungs may avoid open drainage procedures while achieving limited decortication and disruption of loculations. Alternatively, once a patient is stabilized and can better tolerate open drainage, or has demonstrated an inability to resolve the empyema without further drainage, surgical intervention may be needed. Early, aggressive treatment of empyema may reduce the duration of hospitalization and the risk of nosocomial superinfection.

TREATMENT OF LUNG ABSCESS

The treatment of lung abscess must be guided by the microbiology and knowledge of any underlying or associated conditions that may predispose to the development of severe pulmonary infection. A small abscess in an otherwise healthy person may respond to conservative management with antimicrobial therapy and chest physical therapy. A rapidly expanding pulmonary abscess in an immunocompromised host (e.g., due to one of the *Mucoraceae*) requires urgent lung resection in addition to antimicrobials. Intermediate to these approaches is the use of bronchoscopic or radiographically guided catheter drainage of any fluid and necrotic debris. In the absence of antibiotics, the mortality of lung abscess is approximately 33 percent. However, up to half of patients surviving a lung abscess acutely in the pre-antibiotic era had significant pulmonary complications, including recurrent infections and abscesses, pleural empyema and adhesions, chronic bronchitis, and bronchiectasis. The introduction of penicillin, orally or parenterally administered, resulted in resolution or collapse of the abscess in up to 90 percent of patients (although long courses of treatment were often needed). Therefore, these patients could avoid surgical resection.

The role of drainage or surgery is based on serial clinical assessments of the patient. Bronchoscopic drainage may be most useful in the relief of abscesses without air-fluid levels, which indicate the possibility of persistent connection with the bronchi. However, experience dictates *caution* with the bronchoscopic drainage of closed cavities; spillage of cavity contents into other lung segments may produce catastrophic pulmonary dysfunction. Further, there are few data to suggest that bronchoscopic drainage offers a significant advantage in terms of rapidity of recovery in the immunologically normal host. In patients with coexistent empyema and lung abscess, it is often useful to address drainage of the empyema first, stabilizing the patient, and then considering further procedures

for the lung abscess. In critically ill patients, or those with bronchial obstruction related to the abscess cavity, bronchoscopic drainage should be considered.

Bronchoscopy and chest CT have major roles in the evaluation of the patient failing therapy. Persistence of bacteremia or high-grade fevers after 72 h, or the absence of change in sputum production or character or in the radiographic images over 7 to 10 days suggests unappreciated anatomic or microbiologic problems. Obstruction or resistant organisms (including fungi, parasites, or mycobacteria) may be present. Multiple loculations may be present, or empyema, including drainage of the abscess into the pleural space, may develop. New sites of infection, including extrathoracic sites, may have developed in the bacteremic patient. Progression of pulmonary infiltrates may occur after the initiation of appropriate antibiotic therapy, reflecting the relatively poor activity of many antibiotics at the low pH levels of poorly ventilated and underperfused, infected lung tissues, as well as the delayed radiographic response to treatment.

Surgical resection of necrotic segments of lung is helpful if the response to antibiotics is poor, for large abscesses, or ventilation-perfusion scans suggest little residual lung function in a limited necrotic region. Infarcted lung or rapidly progressive infection may force surgical resection of the affected tissue. Surgery is also indicated if airway obstruction limits drainage. Such presentations are seen in the presence of tumor or a foreign body. In patients thought to be poor surgical risks, percutaneous drainage via catheters may be a useful temporizing measure. However, leakage of the abscess contents into the pleural space in such patients may be disastrous and must be avoided.

Mortality in patients with lung abscesses reflects the quality of the host's inflammatory response and overall condition. Patients with large abscesses (over 5–6 cm), progressive pulmonary necrosis, obstructing lesions, aerobic bacteria, immune compromise, old age, or systemic debility, and those with major delays in seeking medical attention have a significantly increased mortality.

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123

Mediastinitis

Mark E. Rupp • Mary L. Ricardo-Dukelow

MEDIASTINITIS

Mediastinitis can be conveniently organized into acute or chronic forms with etiologies, clinical presentations, and treatments that are strikingly different. Acute mediastinitis is a life-threatening infection that is increasingly recognized as a postoperative complication of cardiovascular surgery. Other less common causes of mediastinitis include esophageal perforation and contiguous spread from oropharyngeal foci. Regardless of the route of infection, a high-index of suspicion must be maintained for this clinical entity so that aggressive, potentially life-saving, measures can be promptly initiated.

Chronic mediastinitis, also known as sclerosing mediastinitis, fibrosing mediastinitis, or granulomatous mediastinitis, is a rare disorder that is most often due to *Histoplasma capsulatum.*

Anatomical Considerations

Detailed descriptions of mediastinal anatomy are available; a thorough review of this material is beyond the scope of this chapter. However, a few fundamental points will be emphasized. The mediastinum is the region within the thorax between the pleural sacs (Fig. 123-1). It extends from the diaphragm inferiorly to the superior aperture of the thorax. The 12 thoracic vertebral bodies border the mediastinum posteriorly and the sternum and costal cartilages make up the anterior boundary. The mediastinum is arbitrarily divided into four subdivisions: superior, posterior, anterior, and middle. Structures within the mediastinum include the heart and great vessels, the esophagus, the distal portion of the trachea and mainstem bronchi, vagus and phrenic nerves, the thymic remnant, and the thoracic duct. These structures are surrounded by adipose tissue, loose connective tissue, and lymph nodes. The mediastinum communicates with the structures of the head and neck via several fascial planes and potential spaces (Figs. 123-2 and 123-3). The three major routes by which infection spreads from the head and neck to the mediastinum are (1) the pretracheal space, (2) the long fascial planes of the posterior neck, and (3) the viscerovascular or lateral pharyngeal space. The long fascial planes of the posterior neck extend from the base of the skull to the diaphragm and are made up of the retropharyngeal or retrovisceral space, the prevertebral space, and the danger space. Pearse attempted to delineate the relative importance of each route in the pathogenesis of mediastinitis and found the retropharyngeal space to be involved in 71 percent of cases followed in frequency by the lateral pharyngeal space (21 percent) and the pretracheal space (8 percent). Knowledge of these fascial planes and anatomic relationships helps one to understand the pathogenesis and potential complications of mediastinitis.

ACUTE MEDIASTINITIS

Epidemiology and Pathogenesis

Primary infection of the mediastinum is a rare event. Essentially all cases of mediastinitis are secondary to the spread of infection from other sites or direct inoculation due to trauma

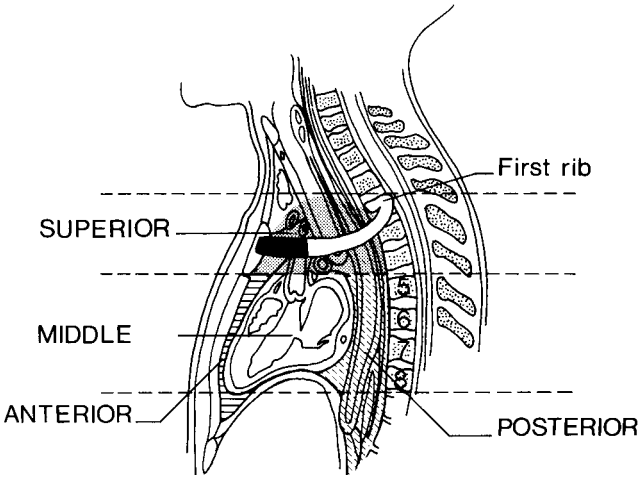


Figure 123-1 Anatomic boundaries and divisions of the mediastinum.

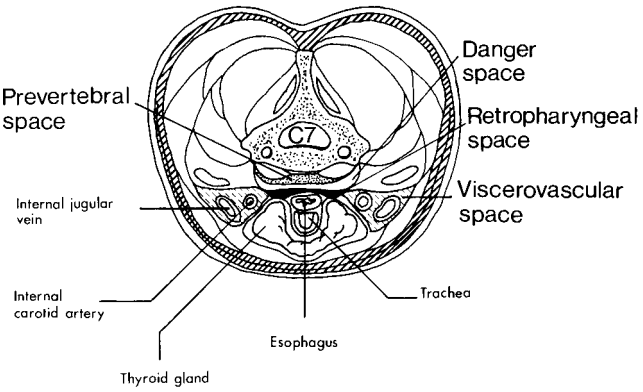


Figure 123-2 Cross-section of the neck at the level of the seventh cervical vertebrae demonstrating the potential spaces for spread of infection from the head and neck into the mediastinum.

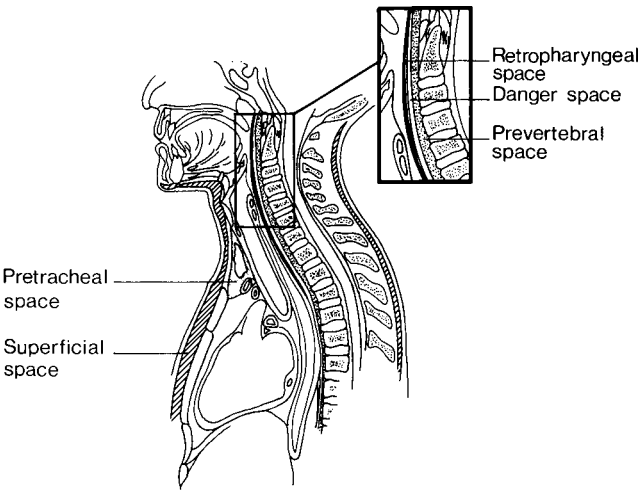


Figure 123-3 Sagittal section of the head and neck showing relationship of the fascial spaces to the mediastinum.

or surgery. The causes of mediastinitis are summarized in Table 123-1 and can be conveniently grouped into the following four categories: cardiothoracic surgery, esophageal perforation, head and neck infection, and infection originating at another site. The pathogenesis, clinical manifestations, and treatment vary with the underlying cause of mediastinitis. These aspects are summarized in Table 123-2.

Mediastinitis Secondary to Cardiothoracic Surgery

Cardiothoracic operations are among the most common surgical procedures performed in larger hospitals. Coronary artery bypass grafting and cardiac valve replacement accounted for 30 percent of the procedures reported between 1992 and 2004 to the Center for Disease Control's National Nosocomial Infection Surveillance System. Because of the large number of median sternotomies that are performed, mediastinitis has predominantly become a postsurgical infection. Numerous studies have documented the incidence of mediastinitis following cardiothoracic surgery and the risk factors for development of this serious complication. In 1984 Sarr et al reviewed the available literature and found the incidence of mediastinitis to range from 0.4 to 5 percent of patients undergoing median sternotomy. Since then studies documenting the experience in over 400,000 patients have been published, with incidence rates ranging from 0.66 to 2.4 percent. The largest study to date was derived from the Society of Thoracic Surgeons National Cardiac Database and involved analysis of over 330,000 coronary artery bypass graft cases performed during 2002 and 2003. Major infection occurred in 11,636 patients (3.51 percent), 25.1 percent of which was attributed to mediastinitis. The incidence of mediastinitis during outbreaks has been as high as 5 to 23.7 percent. Patients undergoing heart transplantation are at higher risk of developing mediastinitis, with frequencies of 2.5 to 7.5 percent. This risk of mediastinitis is further increased if a mechanical device, such as a left ventricular assist device or a total artificial heart, is used to support the patient awaiting a suitable donor heart. The frequency of mediastinitis in this circumstance ranges from 7.5 to 35.7 percent. Patients undergoing heart-lung transplantation appear to be at a roughly twofold greater risk of mediastinitis than those undergoing heart transplantation per se.

A number of factors have been identified as causes for an increase risk of mediastinitis. The studies examining these risk factors are primarily retrospective case-control studies; therefore, they are limited by the problems inherent in retrospective surveys. Risk factors can be divided into the following groups: preoperative, intraoperative, and postoperative (Table 123-3). Preoperative risk factors include diabetes mellitus, obesity, previous sternotomy, chronic obstructive pulmonary disease, cigarette smoking, low-cardiac output states, remote infection, history of endocarditis, method of hair removal, and prolonged preoperative hospitalization. Intraoperative and surgical risk factors include complexity of surgery, type of bone-saw used, type of sternal closure, use of internal mammary arteries in coronary artery bypass

Table 123-1

Causes of Acute Mediastinitis

Esophageal Perforation

Iatrogenic

Esophagogastroduodenoscopy, esophageal dilatation, esophageal variceal sclerotherapy, nasogastric tube, Sengstaken-Blakemore tube, endotracheal intubation, esophageal surgery, paraesophageal surgery

Swallowed Foreign Bodies

Bones, coins, can pull-tabs, drug-filled condoms, swords

Trauma

- Penetrating
  Gunshot wound, knife wound
- Blunt
  Steering wheel injury, seat-belt injury, cardiopulmonary resuscitation, whiplash injury, barotrauma

Spontaneous/Other

Emesis, cricoid pressure during anesthesia induction, heavy lifting, defecation, parturition, carcinoma

Head and Neck Infections

Odontogenic, Ludwig's angina, pharyngitis, tonsillitis, parotitis, epiglottitis

Infection Originating at Another Site

Pneumonia, pleural space infection/empyema, subphrenic abscess, pancreatitis, cellulitis/soft-tissue infection of the chest wall, osteomyelitis of sternum, clavicle, ribs, or vertebrae, hematogenous spread from distant foci

Cardio thoracic Surgery

Coronary artery bypass grafting, cardiac valve replacement, repair of congenital heart defect, heart transplantation, heart-lung transplantation, cardiac assist devices, other types of cardio thoracic surgery

grafting, use of bone wax, prolonged operative time, prolonged time on cardiopulmonary bypass, blood transfusions, indiscriminate use of electrocautery, and antibiotic prophylaxis. Postoperatively, patients at increased risk for mediastinitis require re-exploration to control bleeding, prolonged length of stay in the intensive care unit, mechanical ventilation for more than 24 to 48 hours, need for tracheostomy, use of cardiopulmonary resuscitation, and low cardiac-output states. However, agreement regarding these risk factors is not universal and their relative importance is undefined. For instance, even after three decades of surgical experience, it is unclear whether the use of internal mammary artery (IMA) grafts in coronary artery bypass surgery predisposes patients to mediastinitis. In 1972, based upon anatomical studies of sternal blood supply, Arnold suggested that the use of the IMA in coronary artery bypass procedures might lead to significant sternal ischemia and thus predispose patients to sternal osteomyelitis and mediastinitis. This suggestion has been supported by several laboratory and clinical studies. However, other investigators have not observed a significant increase in sternal wound infections in patients undergoing coronary artery bypass grafting when the IMA is used.

It is generally believed that the pathogenesis of postcardiac surgery mediastinitis is primarily due to the inoculation into the operative wound of organisms from the patient's endogenous bacterial flora or from the surgical field. Bacteria are able to propagate in the relatively protected avascular area of the surgical wound and cause infection. Therefore, a number of the putative risk factors are attractive intuitively, such as the duration of the surgery, the complexity of the surgery, and the need for re-exploration. In addition, outbreaks of mediastinitis have been linked epidemiologically to sources such as bacteria from a particular surgeon's hands or nares, lending support to the belief that intraoperative factors are important in the pathogenesis of mediastinitis. Following changes in the environment of the operating room, Ferrazzi et al observed a significant decrease in the incidence of gram-negative mediastinitis, without a significant change in the frequency of gram-positive infections. This observation supported the belief that many of these infections arise from gram-positive organisms resident on the patient's skin. Archer et al has demonstrated that patients are colonized by small numbers of antibiotic-resistant, coagulase-negative staphylococci which become the predominant species when subjected to the selective pressure of prophylactic antibiotics. In addition, various immunosuppressive effects of cardiopulmonary bypass have been elucidated that may contribute to the pathogenesis of mediastinitis after surgery.

The importance of postoperative factors has also been emphasized by outbreaks of mediastinitis which have been linked to environmental sources, including contaminated tap water and poor hand-washing technique in the postoperative care of cardiac surgery patients. However, Kaiser has warned persuasively against taking a "make-a-change-and-see-what-happens" approach to the analysis of risk factors related to the pathogenesis of postoperative infection. Controlled prospective studies are needed to improve the identification of factors that influence postcardiac surgery mediastinitis.

Table 123-2

Summary of Acute Mediastinitis

	Cardiovascular Surgery	Head and Neck Infection	Esophageal Perforation
Pathogenesis	Intraoperative wound contamination	Oral infection that extends to involve sublingual and submandibular spaces with spread through fascial planes of the neck into mediastinum	Inoculation of flora into mediastinum secondary to esophageal perforation
Clinical Presentation	Fever, chills, sternal instability, sternal wound drainage	Pain, fever, local signs and symptoms of infection	Pain, dysphagia, respiratory distress
Most Common Microbial Etiology	Gram-positive cocci: *saureus* (methicillin-sensitive or resistant), Coagulase-negative *Staphylococcus*, Streptococci, Gram-negative bacilli	Oral flora: Streptococcus *viridans*, peptococci, peptostreptococci, *Bacteroides sp, Fusobacterium*, Gram-negative bacilli	Similar to microbiology of head and neck infections
Risk Factors	Cardiac assist-device Low-cardiac output Prior heart surgery Length of surgery Co-morbid conditions Obesity Method of hair removal Prolonged preoperative hospitalization Poor hemostasis Hyperglycemia COPD Smoking	Conditions predisposing to dental infections or other head and neck infections: poor dentition, parotid stone, recurrent tonsillitis	Conditions predisposing to esophageal perforation: esophageal tumor, endoscopy, swallowed foreign body
Laboratory Testing and Findings	Leukocytosis Blood cultures (bacteremia observed in more than one-half of cases)	Leukocytosis Microbiologic cultures using anaerobic techniques	Leukocytosis Microbiologic cultures using anaerobic techniques
Radiologic Diagnosis	CT chest localized mediastinal fluid, pneumomediastinum	CT head and neck CT chest	Contrast esophagography, CT neck and chest
Surgical Treatment	Surgical debridement required Vacuum-assisted closure	Prompt surgical intervention when descending odontogenic or pharyngeal infection is observed	Prompt surgical intervention with drainage, debridement, and repair
Antibiotic Treatment	Initial broad-spectrum coverage, include vancomycin (or other anti-MRSA agent) if MRSA is likely; adjust antibiotics according to microbiologic data	Initial antibiotic coverage for oral flora including *Bacteroides sp*; pencillin G + metronidazole, clindamycin, or broad-spectrum β-lactam/β-lactamase inhibitor	Similar to antibiotic choice for head and neck infection

COPD, chronic obstructive pulmonary disease; CT, computed tomography; MRSA, methicillin-resistant S. aureus.

Table 123-3

Risk Factors for Mediastinitis

Preoperative	Preoperative New York Heart Association physiologic class ≥III Preoperative hyperglycemia Presence of one or more co-morbid conditions (pulmonary, hepatic, gastrointestinal, or malignant disease processes) Diabetes mellitus Obesity Previous sternotomy Chronic obstructive pulmonary disease (COPD) Cigarette smoking Remote infection History of endocarditis Method of hair removal Prolonged preoperative hospitalization
Intraoperative	Poor hemostasis at the time of closure Complexity of surgery Type of bone saw used Type of sternal closure Use of internal mammary arteries in coronary artery bypass grafting Use of bone wax Prolonged operative time Prolonged time on cardiopulmonary bypass Blood transfusion Indiscriminate use of electrocautery Inappropriate antibiotic prophylaxis Avoidance of staple use
Postoperative	Re-exploration to control bleeding Prolonged length of stay in the intensive care unit Mechanical ventilation >24–48 h Need for tracheostomy Use of cardiopulmonary resuscitation Low cardiac-output states Use of contaminated tap water to remove Betadine following cardiac surgery

Mediastinitis Secondary to Esophageal Perforation

Prior to the development of cardiac surgery, perforation of the esophagus was the leading cause of mediastinitis, followed by suppurative infections of the oropharynx. In 1724 Herman Boerhaave graphically described the first case of mediastinitis due to spontaneous rupture of the esophagus in a Dutch admiral who died 18.5 hours after self-induced emesis. Since then this entity has been known as Boerhaave's syndrome. Currently, esophageal perforation is most frequently due to iatrogenic etiologies. Flexible fiberoptic endoscopy of the upper-gastrointestinal tract is complicated by esophageal perforation in 0.074 to 0.4 percent of the procedures. The frequency of complication increases when sclerotherapy or dilatation procedures are performed. Swallowed foreign bodies, esophageal carcinoma, and nonsurgical trauma may also cause perforation of the esophagus and mediastinitis.

Depending on the site of the esophageal perforation, mediastinitis may result from migration into the mediastinum via the fascial planes of the neck or from direct spillage of esophageal contents into the posterior mediastinum. A necrotizing chemical mediastinitis ensues, followed by an aerobic and anaerobic bacterial mediastinitis. Often a synergistic necrotizing form of mediastinitis occurs. Spread of infection from the neck into the mediastinum is influenced by respiratory dynamics by which the negative intrathoracic pressure generated during respiration tends to force the infection into the mediastinum.

Mediastinitis Secondary to Head and Neck Infection or from Other Sites

Before antibiotics were widely available odontogenic and pharyngeal infections caused between 10 to 31 percent of cases of mediastinitis. Fortunately, these infections have currently become a rare cause of mediastinitis. The prototypic odontogenic infection leading to mediastinitis is Ludwig's angina which usually stems from an infection of the second or third mandibular molar to involve the sublingual and submandibular spaces. From these spaces, the infection can spread via the lateral pharyngeal space to involve the retropharyngeal space or carotid sheath and thus track into the mediastinum. During the antibiotic era approximately 3.5 percent of Ludwig's angina cases have been complicated by mediastinitis. Mediastinitis resulting from infections which involve the lateral pharyngeal space may originate from a number of sources including the teeth, parotid glands, tonsils, or, rarely, from otitis or mastoiditis. Infections of the retropharyngeal space generally arise from perforation of the esophagus or by extension from pharyngitis, epiglottitis, or tonsillitis. From the long fascial planes of the neck, these infections spread readily into the superior mediastinum, or, if the danger space is involved, the posterior mediastinum. The pretracheal space descends into the anterior mediastinum and most often is involved in mediastinitis, which complicates surgery of the thyroid or trachea. Rarely is mediastinitis due to spread from other sites. Instances have been described secondary to the following conditions: pneumonia, pleural space infection, osteomyelitis of the ribs, clavicle, sternum or vertebrae, subphrenic abscess, pancreatitis, cellulitis, and hematogenous seeding from distant foci.

Bacteriology

The bacteriology of mediastinitis complicating cardiovascular surgery is strikingly different from mediastinitis secondary to odontogenic or other head and neck infections (Table 123-4). Mediastinitis secondary to cardiothoracic

Table 123-4

Microbiology of Mediastinitis

Organisms Frequently Recovered in Mediastinitis Secondary to Infection of the Head and Neck or Esophageal Perforation

Anaerobic
- Gram-positive cocci
  - *Peptococcus* spp.
  - *Peptostreptococcus* spp.
- Gram-positive bacilli
  - *Actinomyces*
  - *Eubacterium*
  - *Lactobacillus*
- Gram-negative cocci
  - *Veillonella*
- Gram-negative bacilli
  - *Bacteroides* spp.
  - *Fusobacterium* spp.

Aerobic or Facultative
- Gram-positive cocci
  - *Streptococcal* spp.
  - *Staphylococci* spp.
- Gram-positive bacilli
  - *Corynebacterium*
- Gram-negative cocci
  - *Branhamella*
- Gram-negative bacilli
  - *Enterobacteriaceae*
  - *Pseudomonas* spp.
  - *E. corodans*
- Fungi
  - *C. albicans*

Organisms Frequently Recovered in Mediastinitis Secondary to Cardiothoracic Surgery

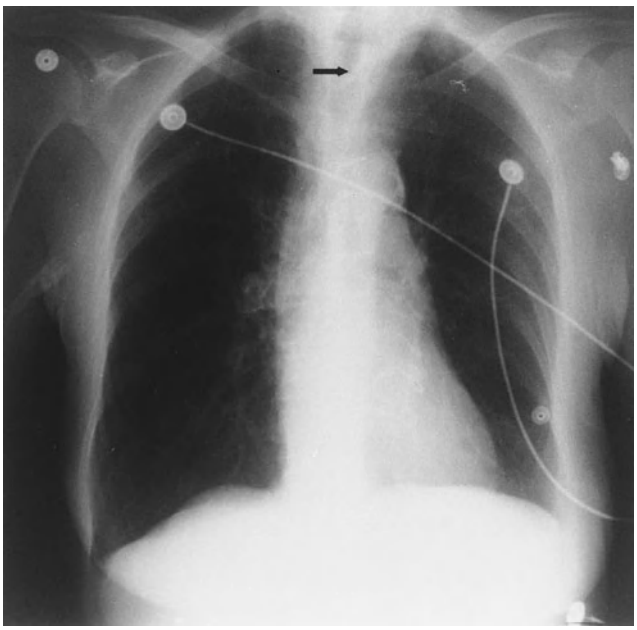
Organism	Range	Representative Rate
Gram-positive cocci		
S. aureus	7.1%–66.7%	25%
S. epidermidis	6%–45.5%	30%
Enterococcus spp.	8%–18.8%	10%
Streptococci spp.	0%–18.2%	2%
Gram-Negative Bacilli		
E. coli	0%–12.5%	5%
Enterobacter spp.	4%–21.4%	10%
Klebsiella spp.	0%–21.1%	3%
Proteus spp.	0%–7.1%	2%
Other		
Enterobacteriaceae	0%–20%	2%
Pseudomonas spp.	0%–54%	2%
Fungi		
C. albicans	0%–14.3%	<2%
Polymicrobial	0%–40%	10%
Other Occasionally Reported:		
Acinetobacter, Legionella spp. *B. fragilis, C. tropicalis, Nocardia* spp. *Kluyvera, M. fortuitum, M. chelonei, R. bronchialis*		

Other Unusual Causes of Mediastinitis:
Anthrax, brucellosis, actinomycoses, paragonimiasis

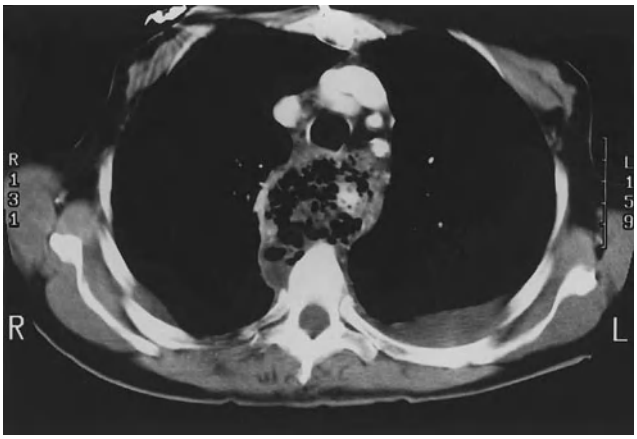
surgery is predominantly due to gram-positive cocci and less often by gram-negative bacilli. A recent review of 316 consecutive patients with mediastinitis that occurred in fewer than 30 days after sternotomy revealed the most common causative microorganisms to be methicillin-susceptible *Staphylococcus aureus* (45 percent), methicillin-resistant *S. aureus* (16 percent), gram-negative bacilli (17 percent), coagulase-negative staphylococci (13 percent), and streptococci (5 percent). A case-control study examined whether risk factors for specific pathogens could be identified. Multivariate analysis revealed that diabetes, female gender, and age greater than 70 years were associated with infection due to methicillin-resistant *S. aureus*, whereas obesity was the only independent risk factor associated with infection due to methicillin-susceptible *S. aureus*. The bacteriology of mediastinitis secondary to extension from head and neck sources is somewhat more complicated. The majority of these infections is polymicrobic. Often a synergistic infection made up of a number of oral anaerobes and gram-negative bacilli is evident. The most frequently isolated organisms include viridans streptococci, peptococci, peptostreptococci, *Bacteroides* spp., and *Fusobacterium*. The relative frequency with which these organisms are isolated is difficult to determine due to the difficulty of obtaining reliable anaerobic culture data.

Clinical Manifestations and Diagnosis

The clinical manifestations of mediastinitis also differ based on the underlying cause of disease. Patients who experience mediastinitis from extension of odontogenic or pharyngeal infections usually have obvious primary infections with significant pain, fever, and swelling of the affected site. Esophageal perforation may be clinically obvious or inapparent. Early in the course of mediastinitis, signs and symptoms may be subtle, but as the condition progresses, patients note increasing chest pain, respiratory distress, and dysphagia. Chest pain is often the most prominent symptom and may localize depending on the portion of the mediastinum involved. In anterior mediastinitis, pain is often located in the cervical or substernal region. Pain due to posterior mediastinitis may localize to the epigastric area with radiation to the interscapular region. Pleuritic chest pain may also be experienced due to pleural effusion, a relatively frequent complication. Retroperitoneal extension may be accompanied by acute abdominal signs and may prompt needless exploratory laparotomy. Examination may reveal fever, tachycardia, crepitus, and edema of the chest or neck. "Hamman's sign", a crunching rasping sound heard over the precordium synchronous with the cardiac rhythm, due to emphysema of the mediastinum, may be audible in up to 50 percent of patients with pneumomediastinum. The heart sounds may be distant and dull. In the later stages of mediastinitis, signs of bacteremia and sepsis may predominate. The early diagnosis of mediastinitis in the infant or neonate may be particularly challenging. A peculiar, interrupted, staccato type of inspiration has been described in a number of patients. The signs and symptoms of mediastinitis in older children are similar to those in adults.



A



B

Figure 123-4 *A*. Chest radiograph of elderly woman with esophageal perforation and mediastinitis. The patient had senile dementia and had unknowingly swallowed a portion of a broken glass jar resulting in esophageal perforation. The chest radiograph reveals a foreign body within the esophagus (arrow) and widening of the mediastinum. *B*. Computed tomography of the chest at the level of the sixth thoracic vertebrae demonstrating a large abscess within the posterior mediastinum and a left-sided pleural effusion. *(Radiographs courtesy of Dr. J. Gurney, University of Nebraska Medical Center.)*

Laboratory tests usually reveal a leukocytosis with a leftward shift evident on the differential blood count. Radiographically, plain films of the chest may reveal mediastinal widening, air-fluid levels, and subcutaneous or mediastinal emphysema. A lateral chest radiograph may be useful in demonstrating superior mediastinal gas not evident on upright films. In about 50 percent of instances of pneumomediastinum lateral views are required to establish the diagnosis. Examples of some of the radiographic manifestations of mediastinitis are shown in Figs. 123-4 and 123-5. Complications of mediastinitis, such as pleural effusion or

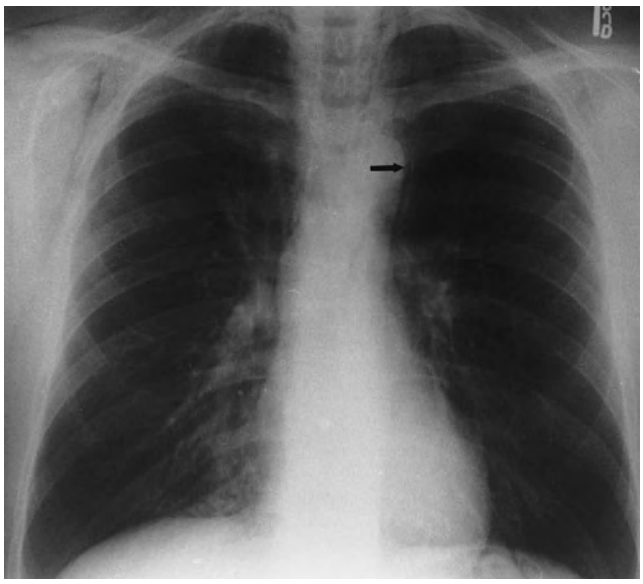


Figure 123-5 Chest radiograph demonstrating pneumomediastinum (arrow). *(Radiograph courtesy of Dr. J. Gurney, University of Nebraska Medical Center.)*

pneumoperitoneum, may also be evident on the chest radiograph. Esophageal perforation is best demonstrated by contrast esophagography which reveals extravasation of dye in 59 to 100 percent of cases. It is recommended that a water-soluble contrast agent be used initially to detect gross extravasation due to the inflammation and granuloma formation evoked by barium. If extravasation is not observed, barium should be used to detect subtle defects, since it provides better definition of the anatomy. Computed tomography (CT) is often helpful for patients in whom the diagnosis is not evident either clinically or on plain films. Technetium-labeled white blood cell scans are reported to be helpful in the diagnosis of mediastinitis in special circumstances when CT scan is not readily available. The role of magnetic resonance imaging (MRI) in the evaluation of mediastinitis is not well-established.

Postcardiothoracic surgery mediastinitis usually becomes evident clinically within the first 2 weeks following surgery. However, rare instances have been described that presented more than 1 year postoperatively. Infections due to gram-negative organisms generally present earlier. One study found that all cases of mediastinitis that presented more than 2 weeks postoperatively were due to gram-positive organisms.

The presentation of mediastinitis may be fulminant or subtle. Some patients may present with sepsis without localizing signs. Some patients may experience more than normal postoperative pain which may be pleuritic in nature. Dysphagia is a rare complaint. Fever and an abnormal appearance of the surgical wound, characterized by erythema, cellulitis, or purulent discharge, are the most frequent signs of mediastinitis. Sternal instability, dehiscence, or bubbles emanating from the sternal wound are less frequent. Occasionally emphysema of the chest wall occurs.

Post-sternotomy mediastinitis presenting as a deep neck abscess without abnormal findings on examinations of the chest has been reported. Laboratory tests usually show a

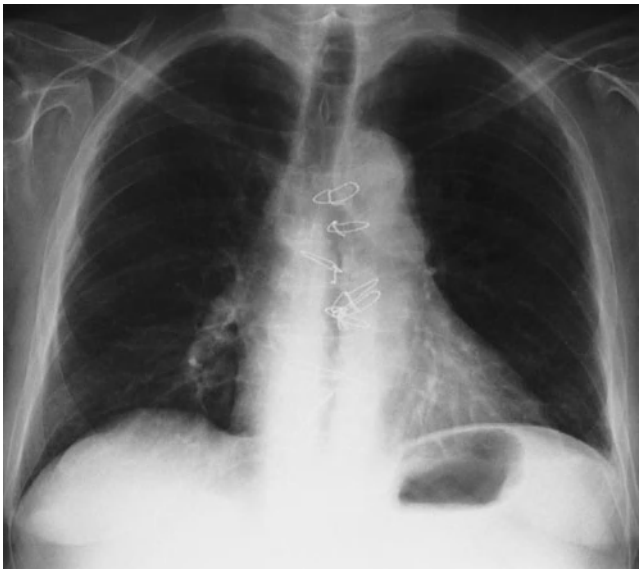


Figure 123-6 Chest radiograph of patient with mediastinitis following cardiac surgery. Dehiscence of median sternotomy is demonstrated by asymmetry of sternal wires. *(Radiograph courtesy of Dr. J. Gurney, University of Nebraska Medical Center.)*

moderate leukocytosis with a leftward shift of the white blood cell differential. Radiographically, mediastinal widening is a rare finding on plain chest films and routine radiographs are usually of very little use for the diagnosis of mediastinitis following cardiothoracic surgery (Fig. 123-6). CT scanning has proved to be helpful in many instances of postoperative mediastinitis, particularly in differentiating superficial wound infections from deeper retrosternal processes. However, normal postoperative collections of fluid and gas are at times difficult to differentiate from early signs of mediastinitis.

The diagnostic value of nuclear scans has been espoused by several investigators. Browdie et al evaluated the relative value of CT, indium-111 (^{111}In)–labeled leukocyte scanning, and epicardial pacer wire cultures in 24 patients undergoing evaluation for possible mediastinitis. They found that CT had a sensitivity of 67 percent and specificity of 71 percent, ^{111}In–labeled leukocyte scan was 83 percent sensitive and 100 percent specific; and epicardial pacer wire cultures were reported to be 100 percent sensitive and 92 percent specific. However, another investigator found that epicardial pacer wire cultures were associated with an unacceptably high false-positive rate. The role of MRI is not well-defined; it is contraindicated in instances in which ferromagnetic metals are used in sternal wires, artificial heart valves, cardiac pacemakers, or vascular clips. Several investigators have found that mediastinal needle aspiration is useful for the diagnosis of mediastinitis. This method, which has been reported to be positive in 65.8 percent of patients, appears to be particularly useful in diagnosing mediastinitis before it becomes more clinically obvious.

Treatment

Treatment that includes both medical and surgical techniques should be promptly initiated once the diagnosis of mediastinitis is made. In all cases aggressive supportive and nutritional therapy is required. Barrett is credited with documenting in 1946 the first successful treatment of mediastinitis due to esophageal perforation. Since then, most experts recommend aggressive surgical drainage, debridement, and repair in patients with mediastinitis secondary to esophageal perforation. However, based on experience with eight patients, Cameron et al identified a subset of patients that could be treated without surgical intervention. These patients will have a well-contained disruption of the esophagus, the abscess should drain back into the esophagus, minimal symptoms are present, and there should be minimal evidence of clinical toxicity. Shaffer et al expanded upon these recommendations based on the patients with esophageal perforation due to instrumentation detected before major mediastinal contamination. Santos et al have recommended transesophageal irrigation for patients in whom primary repair of the esophagus is not possible due to advanced local infection with extensive tissue necrosis.

As in patients with mediastinitis due to esophageal perforation, patients in whom the mediastinitis is secondary to descending odontogenic or pharyngeal infection require prompt surgical intervention. Because transcervical drainage is frequently inadequate, a transthoracic approach is generally necessary.

Although the importance of supportive therapy and surgical intervention cannot be overemphasized, administration of appropriate antibiotics is also an essential component of therapy. Empirical regimens are based upon the underlying etiology and should deal with the major pathogens listed in Table 123-4. Penicillin G has traditionally been the antibiotic of choice in the treatment of anaerobic infections that originate above the diaphragm and continues to exhibit excellent activity against most oral anaerobic bacteria. Unfortunately, oral *Bacteroides* spp. are increasingly resistant to penicillin G. Therefore, when infection with *Bacteroides* is suspected, treatment with metronidazole, clindamycin, or broad spectrum β-lactam/β-lactamase inhibitor antibiotics with activity against *Bacteroides* spp., as well as other oropharyngeal anaerobes, may be indicated. In addition, gram-negative enteric bacilli are often implicated in mediastinitis and should be taken into account in the initial empiric therapy. Antibiotic therapy should then be more specifically tailored to the infecting organisms when definitive culture results are available, but treatment directed against anaerobic oropharyngeal organisms should probably be continued due to the difficulty in obtaining reliable anaerobic cultures. Duration of therapy, which may range from weeks to months, is determined by the virulence of the bacteria, host factors, and the patient's response to therapy.

The treatment of postcardiac surgery mediastinitis generally requires aggressive surgical drainage and debridement. A small number of patients have been successfully treated via percutaneous catheter drainage. Two approaches have been used in the surgical management of postcardiac surgery mediastinitis—an open technique and a closed technique. The open technique involves debridement of infected tissue

and open packing of the wound with delayed closure. Disadvantages of this technique include respiratory insufficiency due to lack of mechanical support for the thorax, delayed healing and closure of the surgical wound, and hemorrhage from exposed vessels. The closed method involves debridement of affected tissues, closure of the sternum, and postoperative irrigation through drainage tubes within the mediastinum. Irrigants have included a variety of antimicrobial and antiseptic solutions, such as neomycin, gentamicin, bacitracin, polymyxin B, saline, and Dakin's solution. The use of irrigants has been associated with a variety of complications including emergence of resistant organisms, pericardial and tissue toxicity, and systemic absorption and toxicity. The most commonly employed irrigant is povidone-iodine. Use of povidone-iodine has been associated with iodine toxicity, renal failure, metabolic acidosis, and seizures. Therefore, this agent must be used with caution, and it has been recommended that serum iodide concentrations be measured to insure that toxic levels are not reached. Durandy et al reported a closed technique that successfully used Redon drainage devices in 11 patients who did not require postoperative irrigation. A number of investigators have reported the successful use of muscle flaps and omental grafts in many instances at the time of initial debridement to close mediastinal wounds, with or without postoperative irrigation. Fuchs et al suggest that vacuum-assisted closure (VAC) is a promising new method for the therapy of mediastinitis. A retrospective analysis of 68 cases that compared VAC to conventional therapy with open packing revealed earlier microbiologic cure, more rapid decline in C-reactive protein, shortened hospital stay, earlier rewiring, and higher survival in the VAC group.

The use of parenteral antibiotics has remained a cornerstone of therapy. Generally, empiric therapy should be directed at staphylococci and gram-negative aerobic bacilli until definitive culture results become available. As with mediastinitis secondary to infection of the head and neck, the duration of therapy is determined by multiple factors and may be quite prolonged.

Antibiotic Prophylaxis

Although cardiothoracic surgical procedures are categorized as clean procedures, and the risk of infection is low, the consequences of infection are devastating. Therefore, despite the lack of placebo-controlled studies documenting efficacy, antibiotic prophylaxis has become commonplace. Cefazolin has generally been regarded as the drug of choice for prophylaxis. The use of vancomycin or second-generation cephalosporins, such as cefamandole and cefuroxime, has also been considered. Studies regarding the relative efficacy of first- and second-generation cephalosporins are conflicting, and no agent has conclusively been shown to be superior to another. In a comparison between vancomycin, cefazolin, and cefamandole, Maki et al demonstrated a significant reduction in postoperative wound infection in patients receiving vancomycin prophylaxis. Vancomycin should be considered as a choice for prophylaxis in centers with a high frequency of infections due to methicillin-resistant staphylococci. The major disadvantages associated with the use of vancomycin are the long infusion time and the small number of patients who experience adverse events, such as hypotension and "red man syndrome". In addition, the emergence of vancomycin-resistant enterococci and staphylococci, due in part to the inappropriate overuse of vancomycin, must be considered as a long-term disadvantage to the use of vancomycin as a prophylactic agent.

Complications and Prognosis

Complications of mediastinitis include extension of the infection into a number of contiguous structures and spaces including the pericardial space, resulting in pericardial effusion and tamponade, the pleural space, and the peritoneum, resulting in peritonitis. A major complication of postcardiac surgery mediastinitis is sternal osteomyelitis. Prior to the development of modern surgery and antibiotics, mediastinitis, due primarily to esophageal perforation, was regarded as uniformly fatal. Unfortunately, since the time of Barrett's first successful surgical repair of the esophagus, morbidity and mortality have remained high, with many studies recording mortality rates of 30 to 50 percent. Survivors of mediastinitis usually have no permanent sequela. In examining the economic ramifications of mediastinitis, Loop et al found that the hospital charges for coronary artery bypass surgery patients who experience mediastinitis were 280 percent greater than patients with uncomplicated bypass surgery, and the median length of stay ranged from 38 to 51 days. The most important factor in determining outcome has been the length of time to diagnosis and initiation of definitive therapy. Other prognostic indicators have included blood urea nitrogen, white blood cell count, culture positivity, type of surgical repair, and cytomegalovirus shedding.

CHRONIC MEDIASTINITIS

Sclerosing, fibrosing, or *granulomatous mediastinitis* are terms for a chronic form of mediastinitis characterized by an invasive and compressive inflammatory infiltrate as summarized in Table 123-5. The first report of this entity, which may cause up to 10 percent of all primary mediastinal masses, reportedly dates to a description by Ulmont in 1855. Although the etiology of up to 83 percent of patients with sclerosing mediastinitis remains obscure, many experts believe that most instances are secondary to infection with *H. capsulatum.* With careful analysis, up to 73 percent of patients previously characterized as nonspecific granulomatous mediastinitis can be reclassified as secondary to *H. capsulatum* by re-staining the tissue with fungal stains and thorough review of the pathological sections. Other infectious etiologies that have been reported to cause this condition include tuberculosis, actinomycoses, nocardiosis, blastomycosis, coccidioidomycosis,

Table 123-5

Summary of Chronic Mediastinitis

Pathogenesis	Lungs provide portal of entry, indolent/progressive inflammatory infiltrate
Clinical Presentation	Usually asymptomatic Mediastinal mass Superior vena cava syndrome Pulmonary venous obstruction (cough, dyspnea, hemoptysis)
Most Common Microbial Etiology	*H. capsulatum*
Laboratory Diagnosis	Histopathology of tissue Granuloma, lymphohistiocytic aggregates, diffuse mononuclear infiltrates Fungal cultures, *Histoplasma* urinary antigen
Radiologic Diagnosis	Chest radiograph Mediastinal lymphadenopathy, bronchial narrowing, pulmonary artery narrowing, superior vena cava narrowing, infiltrate with or without calcification
Surgical Treatment	Early surgical intervention may prevent end-stage fibrosis, stent placement for pulmonary artery or venous compression, Palmaz stents for superior vena cava syndrome
Antimicrobial Treatment	Usually not indicated

aspergillosis, and infection with *Rhizopus* spp. Older literature often lists syphilis as a prominent cause of granulomatous mediastinitis. However, this was based upon seropositivity without other supporting evidence. Other conditions that closely mimic this entity include sarcoidosis, silicosis, lymphoma, mesothelioma, and mediastinal fibrosis associated with radiation therapy, idiopathic retroperitoneal fibrosis, Reidel's struma, or sclerosing cholangitis.

Approximately 40 percent of patients with sclerosing mediastinitis are asymptomatic and come to medical attention when a chest roentgenogram incidentally reveals a mediastinal mass. Symptomatic patients usually note symptoms related to invasion or obstruction of structures within or adjacent to the mediastinum. Sclerosing mediastinitis is the most common nonmalignant cause of superior vena cava syndrome and is responsible for up to 23 percent of cases. These patients generally present with plethora and edema of the face, neck and upper torso, neck vein distention, headache, and visual disturbances. Patients with obstruction of the pulmonary arteries often present with cough, dyspnea, and symptoms consistent with right-sided heart failure. Pulmonary infarction, although rare, has been reported to occur in patients with sclerosing mediastinitis. Pulmonary venous obstruction causes patients to experience cough, dyspnea, and hemoptysis. Patients with airway obstruction due to sclerosing mediastinitis usually present with wheezing, cough, hemoptysis, and recurrent episodes of bacterial bronchitis or pneumonia. Patients complaining of dysphagia may have esophageal obstruction due to posterior extension of the mediastinitis.

Sherrick et al reviewed the radiographic findings in 33 patients with sclerosing mediastinitis. The findings included bronchial narrowing (33 percent), pulmonary artery narrowing (18 percent), esophageal narrowing (9 percent), and superior vena cava narrowing (39 percent). Two distinctly different patterns of pulmonary infiltration were noted: localized with calcification (82 percent) and diffuse without calcification (18 percent). The authors believed that the localized pattern was most often secondary to histoplasmosis while the diffuse pattern was more likely to be due to a noninfectious etiology. Patients with sclerosing mediastinitis often have a mediastinal mass, most frequently located in the superior mediastinum at the level of the bifurcation of the trachea. CT frequently reveals calcification and delineates the extent of infiltration whereas MRI is superior for the assessment of vascular integrity. Ventilation-perfusion lung scans often reveal large perfusion defects due to obstruction of the pulmonary vessels.

The diagnosis of sclerosing mediastinitis requires pathological examination. The histological appearance is a

continuum which ranges from a predominantly granulomatous entity to an almost completely fibrosing process. The lesions include caseating granuloma, dense hyalinized collagenous tissue, and infiltrations of lymphocytes, plasma cells, and giant cells. Specific stains for fungi often reveal organisms consistent with *Histoplasma*, but cultures are usually negative.

The pathological features of this disease suggest a marked inflammatory reaction. Several different mechanisms have been proposed to explain the pathology of fibrosing mediastinitis. Some investigators believe that a caseous lymph node from primary infection with *Histoplasma* ruptures into the mediastinum evoking an intense inflammatory reaction. A second hypothesis invokes the development of a delayed hypersensitivity reaction due to the spread of soluble *Histoplasma* antigens into the mediastinum. Another explanation proposes that fibrosing mediastinitis represents an abnormality of collagen production and organization similar to idiopathic retroperitoneal fibrosis or Riedel's struma. Noguchi et al have implicated the eosinophil in the pathogenesis of fibrosing mediastinitis by demonstrating eosinophils or major basic protein in tissue specimens from five of seven patients with fibrosing mediastinitis.

No controlled trials of medical or surgical therapy have been conducted for the treatment of fibrosing mediastinitis. Although there is some anecdotal evidence of a beneficial effect of antifungal agents, most experts believe that there is little evidence of an active infection at the time of presentation and that antifungal agents are not indicated. Because the natural history of this disease is variable, with some patients progressing to compression of vital structures whereas others seem to have self-limited disease, it is difficult to make recommendations regarding the timing of surgical intervention. It has been suggested that early surgical intervention and removal of granulomatous tissue may prevent the development of subsequent end-stage fibrosis and involvement of vital structures. Clearly, patients experiencing obstruction or invasion of mediastinal structures require intervention, even though such surgery is often difficult and results are at times less than optimal. The superior vena cava syndrome, due to fibrosing mediastinitis, has been successfully alleviated through use of Palmaz stents. Therapy with corticosteroids does not appear to have a role in the treatment of fibrosing mediastinitis.

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Microbiology and Infection in Cystic Fibrosis

Scott H. Donaldson • Richard C. Boucher

Cystic fibrosis (CF) was first described as a unique disease entity in 1938. Patients typically presented with intestinal obstruction or malnutrition and died from overwhelming pneumonia within the first year of life. Postmortem studies revealed that CF was a multisystem disease characterized by mucous obstruction of pancreatic ducts, airways, and the gut early in life. Over the last 40 years, the median survival with CF has increased dramatically from 6 years in 1955 to 36 years in 2005. The improvement in CF outcomes has paralleled advances in antibiotic therapies, nutritional approaches, and the collection of clinical expertise into specialized treatment centers. These have been summarized by Voynow elsewhere in this volume. As CF patients survive longer, lung disease characterized by polymicrobial infection and progressive antimicrobial resistance have become prominent in patient management. Further, a multitude of pulmonary and non-respiratory complications are encountered. The pathogenesis and treatment of these issues are reviewed here.

DIAGNOSIS

The diagnosis of CF requires either detection of two disease-causing mutations in the CFTR gene, or a combination of a compatible phenotype with evidence for CFTR dysfunction. CFTR genotyping is usually restricted to the most common mutations in a given population, and is reviewed elsewhere. To date, more than 1500 individual CFTR mutations have been identified and are grouped into one of five classes based upon the effect that the mutation has on the resulting CFTR protein (Fig. 124-1).

PATHOGENESIS OF INFECTION

CFTR and Epithelial Transport

The CFTR gene encodes a cAMP-regulated chloride channel that appears to regulate other ion channels as well, including

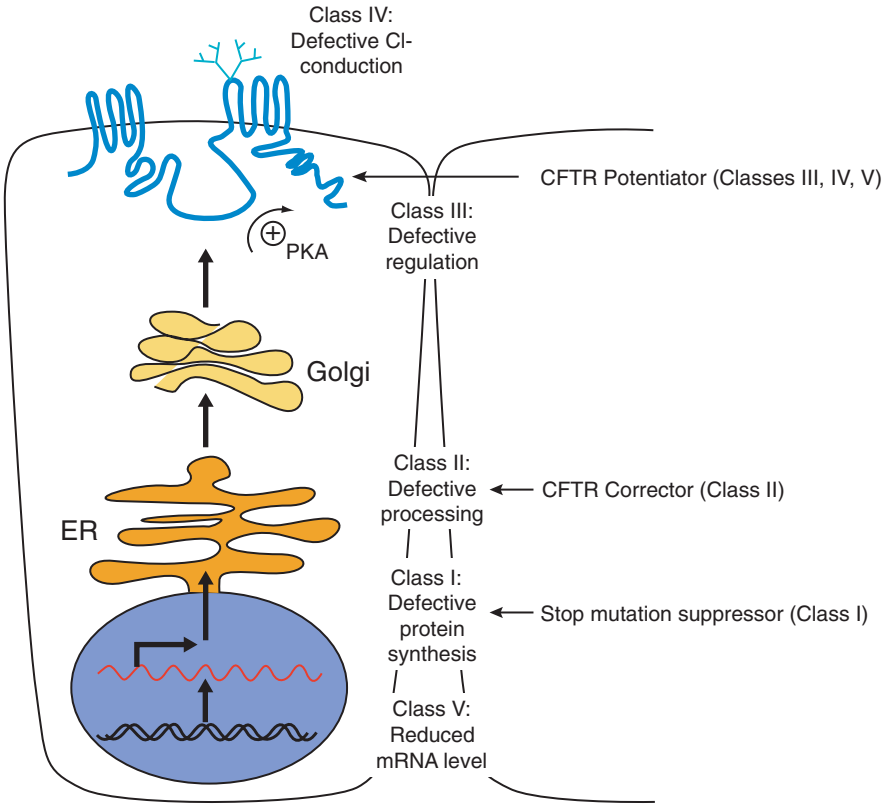

Figure 124-1 CFTR mutation classes. CFTR mutations are grouped into five classes, each characterized by a different problem in CFTR synthesis, maturation, regulation, or function as an ion channel. As shown, new therapies are being developed to target specific classes of CFTR mutations.

the epithelial sodium channel (ENaC) and calcium-activated chloride channel (CaCC). Therefore, CFTR plays a central role in the regulation of ion transport across airway epithelia. In CF, dysregulation of airway surface liquid (ASL) volume occurs as a consequence of ion transport dysfunction, which in turn impairs mucociliary clearance and, therefore, lung defense.

Airway Surface Liquid Regulation in Normal and CF Airways

Airway surfaces are coated with a thin layer of liquid, the ASL, which is composed of a periciliary layer (PCL) and a more viscous mucus layer. The mucus layer, which normally floats on top of the PCL, efficiently traps inhaled pathogens and particulates. The underlying PCL layer, in turn, provides a low viscosity environment in which cilia can beat freely and thereby propel the mucus layer toward the mouth. The PCL also acts as a lubricant layer that prevents adhesion of the mucus layer to cell surfaces. Therefore, proper regulation of ASL volume and the hydration of its component layers are critical to the maintenance of mucus clearance. Whereas an adequate PCL height is necessary to allow ciliary beating, adequate hydration of the mucus layer is a key determinant of its viscoelastic properties and transportability.

When considering the geometry and function of airways, it is clear that ASL volume must be regulated carefully. A gross excess of ASL volume would block small airway lumens, and thereby interfere with gas exchange, whereas even modest reductions in ASL volume may not be adequate to support mucus transport, as described. Therefore, the ability to add or subtract ASL volume is an important airway epithelial function that is carried out by active chloride secretion (in part via CFTR) and sodium absorption (via ENaC), respectively (Fig. 124-2 *A*). Normal airway epithelia blend these

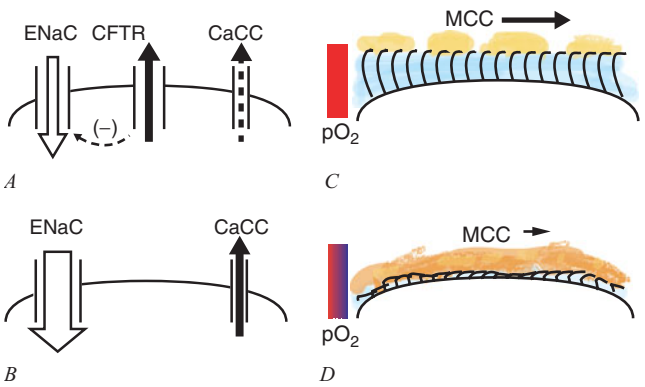

Figure 124-2 Relationship between ion transport and mucociliary clearance in normal and CF airways. *A*. In normal airway epithelia, CFTR and ENaC channels provide the pathways for coordinated chloride secretion and sodium absorption. The calcium-activated chloride channel (CaCC) is an important reserve pathway for additional chloride secretion. *B*. In CF, CFTR mediated chloride secretion is absent, as is the inhibitory effect this channel normally exerts over the ENaC. Preserved chloride secretion via CaCC partially compensates for the absence of CFTR. *C*. The normal airway epithelium maintains an adequate height of periciliary liquid, hydrates the overlying mucus layer, and thereby supports mucociliary clearance. *D*. In CF, the described ion transport abnormalities result in dehydration of the airway surface liquid components, impairs mucociliary clearance, and ultimately encourages the development of an anaerobic niche within airway-adherent mucus plaques.

activities in response to the local ASL environment, thereby maintaining an appropriate PCL height and adequate mucus hydration (Fig. 124-2*C*). In contrast, CF epithelia hyperabsorb liquid due to dysregulation of ENaC and have lost the capacity to secrete liquid via CFTR (Fig. 124-2*B*). As a result, the PCL layer becomes volume depleted and the mucus layer becomes concentrated and poorly transportable (Fig. 124-2*D*). These changes in the ASL compartment impair mucus clearance and predispose the patient to the development of chronic airway infections.

SECONDARY PATHOGENIC STEPS: MUCUS, PSEUDOMONAS, AND INFLAMMATION

As described, ASL dehydration produces progressive mucostasis and initiates a cascade of events that leads to clinically apparent CF lung disease. First, thickened mucus secretions eventually become adherent to airway surfaces with the loss of PCL volume, and begin to obstruct small airway lumens. Mucus plugs and plaques not only provide a protected environment in which bacteria can escape mechanical and immune-mediated clearance, but also create a unique environment that drastically alters bacterial gene expression. Paradoxically, the center of a mucus plug is in fact anaerobic (pO_2 less than 2 Torr) due to a combination of an increased diffusion distance for O_2 as well as increased oxygen consumption by CF epithelia (owing to heightened Na^+ transport). Within this environment, *P. aeruginosa* converts to an anaerobic mode of metabolism, increases alginate production, and ultimately establishes a biofilm structure. Organisms growing within the biofilm possess increased resistance to secondary host defense mechanisms (e.g., neutrophils and soluble antimicrobials), display vastly different antimicrobial sensitivity patterns, and are likely impossible to eradicate with antibiotic therapy. Ultimately, it is the persistent attempt but ongoing failure of neutrophils to clear this infection, accompanied by the release of proteases and other harmful substances, which destroys lung tissue and yields bronchiectasis.

Clinical Aspects

Optimal care for the diverse manifestations and complications of CF poses a significant clinical challenge (Fig. 124-3). This presentation focuses on management relevant to the risk for infection. An early, and perhaps primary, manifestation of CF lung disease is the development of airway obstruction with mucus driven by dehydration of airway surfaces, due to intrinsic ion transport abnormalities. With ASL volume depletion, mucus secretions become less transportable and ultimately adhere to airway surfaces, thus triggering further mucus accumulation and airway obstruction. Coupled with this accumulation is the development of a neutrophil-predominant inflammatory process with mucus hypersecretion in response to inflammatory mediators. The intensity of inflammation in relationship to the burden of

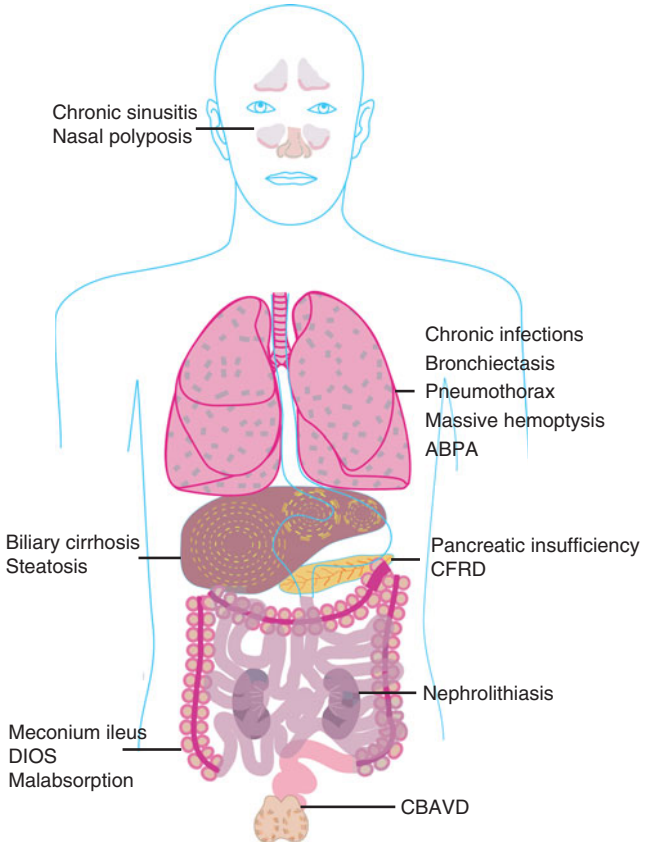

Figure 124-3 Multisystem manifestations of cystic fibrosis. Abnormal CFTR function in epithelial lined organs leads to a wide variety of manifestations in multiple organ systems.

identified pathogens is greater than in other childhood lung diseases and the tendency for the inflammatory process to persist after the apparent resolution of an acute infectious process is perhaps unique to CF. Interestingly, an animal model of CF lung disease, which exhibits ASL dehydration and mucus plugging, also develops chronic airway inflammation without readily identifiable bacterial infection. Current hypotheses to explain these findings include: (1) a low burden of typical bacteria avoids eradication in the dehydrated mucus environment of the CF lung and drives the inflammatory process in very early disease; (2) the presence of atypical, perhaps anaerobic, organisms are poorly identified with usual culture systems but dominate early disease and cause inflammation; and (3) intermittent events, including viral infections and/or gastric aspiration drive the inflammatory process early in life. Regardless, these observations point to the very early onset of lung disease, even in asymptomatic infants, and the need to develop and institute effective interventions in this population.

Over a relatively short period of time, the CF lung becomes chronically infected with typical pathogens. In childhood, *Haemophilus* influenzae and *Staphylococcus aureus* are often identified first, typically followed by the establishment of chronic *Pseudomonas aeruginosa* infection. *Pseudomonas* may take many morphologic forms, including rough, smooth, and small colony variants, but typically evolves to a mucoid

phenotype that signifies chronicity and the inability to eradicate this organism, even with aggressive antibiotic regimens. An increased emphasis on early detection and eradication has emerged, therefore, to delay the negative effects of chronic *Pseudomonas* infection. Other important pathogens that are encountered in CF include a variety of gram-negative bacteria, especially *Stenotrophomonas maltophilia, Achromobacter xylosoxidans,* and the *Burkholderia cepacia* complex (Bcc). The Bcc is currently subdivided into at least 9 genomovars, but genomovars II *(B. multivorans)* and III *(B. cenocepacia)* are most prevalent in CF. Bcc infection is associated with worse pulmonary outcomes, rapidly becomes antibiotic resistant, and certain strains carry the risk of rapid nosocomial spread to susceptible hosts (including other CF patients). Genomovar III is particularly problematic and is considered an absolute contraindication to lung transplantation at most centers because of the unacceptably high rate of early mortality due to sepsis. Mycobacterial pathogens are also encountered in CF, including *M. avium* complex and *M. abscessus.* MAC is the most prevalent mycobacterial pathogen in CF, but often does not cause discernible clinical disease, as opposed to the much more problematic infection with *M. abscessus.* Treatment of *M. abscessus* is often very prolonged (months), toxic, and often does not yield eradication. Viral infections, although probably not more frequent than in other populations, do appear to cause more morbidity and may be an important trigger of lung disease exacerbations. Fungi, particularly aspergillus species, are common colonizers but may cause allergic bronchopulmonary aspergillosis (ABPA).

Once the cycle of reduced mucus clearance, infection, and inflammation begins, progressive airway obstruction follows. This is manifested clinically by reductions in pulmonary function tests and radiographic changes. With spirometry, airflow rates reflecting the small airways (FEF_{25-75}) are affected first and most severely, followed thereafter by reductions in the FEV_1 and lesser changes in FVC. Routine spirometry, however, is often technically impossible in young children (less than 5 years) and is quite insensitive to the development of lung disease early in the course of disease. Chest radiographs may first show signs of hyperinflation followed by interstitial markings that reflect the development of bronchiectasis, but this technique is also a relatively insensitive tool for the detection of mild/early disease. More recently, thin-section CT scanning has been used to clinically characterize CF lung disease and has also been used as a clinical trial outcome measure. This technique, especially when combined with expiratory images to detect air trapping, often detects significant foci of disease prior to the ability to detect global airway obstruction with spirometry. Once CF lung disease becomes more advanced, all of these assessments of disease severity reflect the progressive development of bronchiectasis.

Exacerbations of CF lung disease are extremely important events in the life of a CF patient. These periodic illnesses often remove the patient from their usual work or school activities, are associated with significant reductions in quality of life, exact a large financial toll in terms of health care costs, and are associated with reduced survival. Exacerbations are typically acute to subacute events that are superimposed upon a previously stable clinical baseline. Patients usually report increased cough, sputum, fatigue, and weight loss during these episodes. Fever, leukocytosis, chest pain, and new infiltrates on chest radiographs are less consistent findings with exacerbations. The inciting events that trigger an exacerbation have not been clearly defined, although acute respiratory viral infection may be one important cause in addition to inadequate use of preventative therapies. Because significant disease progression can occur without many symptoms in patients with mild disease, lung function testing as a "screen" for exacerbations/progression are particularly important in this setting.

Other respiratory manifestations of CF lung disease, besides bronchiectasis, include massive hemoptysis and pneumothorax. In chronically inflamed, bronchiectatic CF airways the associated bronchial arteries often become massively dilated. In the setting of increased infection/inflammation, a dilated bronchial artery may erode through the overlying mucosa and bleed—under systemic arterial pressure—into the airway lumen. Minor to massive hemoptysis may ensue, at times requiring bronchial artery embolization in order to halt the bleeding. Massive hemoptysis is increasingly common in older patients, with an average annual incidence of 0.87 percent. Antibiotic therapy, correction of coagulation defects, and temporary cessation of unnecessary airway irritants (e.g., inhaled antibiotics) and chest physiotherapy are also mainstays of treatment for massive hemoptysis in CF.

Similarly, the incidence of pneumothorax also increases with the age of the patient. The annual incidence of this complication is 0.64 percent. In general, the management of pneumothorax in CF is not conceptually different than in other lung diseases. However, it should be recognized that, because of the inability of the lung to fully deflate in the setting of obstructive airways, even a small volume pneumothorax could in fact cause tension physiology. Also, because lung transplantation is often an eventual treatment consideration, persistent air leaks and recurrent pneumothoraces are preferentially dealt with via thoracoscopic approaches (bleb stapling and local pleurodesis) rather than with chemical or talc pleurodesis. These later approaches may significantly compromise the ability to excise the native lung at transplant.

ABPA complicates the clinical scenario of roughly 2 percent of CF patients. This syndrome, caused by allergic inflammation directed against colonizing fungi, may cause symptoms that mimic exacerbations of the underlying CF lung disease itself, and is therefore difficult to diagnose on clinical grounds. Laboratory tests, consequently, are quite useful. A total serum IgE level is often used as a screening test for the presence of ABPA and to track the level of disease activity. Classically, patients with active ABPA will have serum IgE levels greater than 1000 μg/L, although lesser elevations may also be observed in patients with active disease.

Immediate-type hypersensitivity reactions to an aspergillus skin test are sensitive but not specific for ABPA; therefore, a negative test can be used to rule out this entity. The demonstration of aspergillus-specific antibodies can be useful for the diagnosis of ABPA, as are the presence of sputum or blood eosinophilia. Of note, culture positivity for aspergillus may not always be demonstrated. Treatment is typically with systemic corticosteroids for fairly prolonged periods of time, although there is growing experience with the use of antifungal agents to limit the system exposure to corticosteroids.

Nasal and sinus disease are another troublesome respiratory manifestation of CF. Children in particular may experience recurrent nasal polyposis and require surgical removal of obstructing polyps. Sinus disease is nearly universal, either clinically or radiographically, and often requires chronic medical therapies (nasal steroids, antibiotics, nasal irrigation) as well as judicious use of surgery. It should be noted that the benefits of surgery for CF sinus disease are not well studied and often temporary. Overly aggressive surgical approaches may ultimately distort the underlying anatomy such that nasal/sinus mucus clearance mechanisms are disrupted and sinus symptoms recur and progress a short time after surgery.

Non-Respiratory Manifestations

Multiple epithelial lined organs outside of the lung are also affected by the absence of a functional CFTR protein (Fig. 124-3). Despite differences in the details of how CFTR normally functions in each of these organs, a general theme of altered luminal contents (e.g., altered ion composition, volume, or viscosity), causing reduced transit through the organ and obstruction, exists.

Pancreas, Gut, and Nutrition

The exocrine pancreas is affected in more than 90 percent of patients with CF. These issues are reviewed in detail elsewhere. Steatorrhea, malnutrition, and fat-soluble vitamin deficiencies (A, D, E, and K) are common and patients may also develop intestinal obstruction as the result of the bulky, poorly hydrated intestinal contents. This syndrome, termed distal intestinal obstruction syndrome (DIOS), occurs in roughly 20 percent of patients and increases in frequency with age. DIOS may present with abdominal pain, constipation, right lower quadrant mass, nausea, and vomiting. It is usually treated with relatively large volumes of iso-osmotic polyethylene glycol colonoscopy preparations by mouth or NG tube in the non-vomiting patient, or by enema treatments and bowel rest. A meglumine diatrizoate (Gastrografin) enema may be both diagnostic and therapeutic in severe cases. Meconium ileus, a similar syndrome that presents in the days after birth, is nearly diagnostic for the presence of CF and should prompt definitive diagnostic testing.

Endocrine functions of the pancreas, which do not rely on the presence of patent pancreatic ducts, are typically preserved much later into life than exocrine functions. Over time, however, progressive destruction of islet cells leads to insulin deficiency and the onset of CF-related diabetes (CFRD). The incidence of CFRD increases with age, with 15.6 percent of patients older than 13 years receiving insulin therapy. Given the insidious nature of CFRD and controversy over the need for insulin in patients without fasting hyperglycemia, this estimate of the problem is likely quite low. CFRD is a very important problem because it is associated with accelerated rate of lung function decline, worsened nutritional status, and poorer survival. For unclear reasons, females with CF appear to be particularly vulnerable to the adverse effects of CFRD, as its presence is associated with more pronounced effects on survival and lung function than in males. Therefore, screening for CFRD is recommended for all CF adults on an annual basis. Monitoring and treatment of hyperglycemia induced by acute illness (e.g., during exacerbations) is also recommended to avoid impairment of immune function and facilitate the return to normal nutritional status. Because CFRD represents an insulin-deficient state, insulin in the preferred therapy. Given the need to maintain an adequate nutritional status, calorie-restricted "diabetic diets" are not indicated. Rather, calorie-rich diets with adequate insulin coverage are prescribed. Interestingly, it appears that glycemic status can wax and wane in patients with CF over time, moving back and forth among normal glycemia, impaired glucose tolerance, and frank CFRD. Clearly, this CF manifestation warrants close, careful longitudinal assessments.

Hepatobiliary Disease

Steatosis and focal biliary cirrhosis are the most common pathological abnormalities of CF associated liver disease. Whereas severe malnutrition may contribute to fatty lesions in the liver, the absence of CFTR-mediated secretion by cells lining bile ducts is believed to cause the development of inspissated biliary secretions, which in turn leads to biliary cirrhosis. Portal hypertension and associated variceal bleeding occurs uncommonly, although roughly 2 percent of CF deaths are related to liver disease. Based on autopsy series, it appears that the prevalence of cirrhosis increases with age. Despite this observation, clinically apparent liver disease is usually diagnosed by the time patients reach adolescence and typically does not present de novo after age 20 years. Treatment of CF-associated liver disease with ursodeoxycholic acid can be considered. Although this treatment has the potential to prevent the development of cirrhotic lesions if started early in the course of disease, the unclear natural history and absence of factors that predict the development of clinically important disease makes this therapeutic decision somewhat difficult and controversial. Liver transplantation is an option for CF patients with end-stage liver disease and mild pulmonary dysfunction, and results are generally good. Liver failure may exceed pulmonary dysfunction requiring liver before lung transplantation.

Reproductive Tract and Other Manifestations

Males with cystic fibrosis have an approximately 99 percent chance of being infertile. Women with CF, in contrast,

have relatively intact intrinsic fertility. However, the presence of severe lung disease, CF-related diabetes, and significant malnutrition increase the risk of maternal morbidity and fetal intrauterine growth retardation. Other nonrespiratory manifestations include: (1) early and severe osteoporosis; (2) hypertrophic pulmonary osteoarthropathy; (3) cutaneous leukocytoclastic vasculitis; (4) calcium oxalate nephrolithiasis; (5) gallbladder abnormalities, including micro-gallbladder, stones and sludging; and (6) metabolic alkalosis and sweat loss syndromes in infants. A detailed review of these manifestations is beyond the scope of this chapter, but is presented elsewhere.

TREATMENT OF LUNG DISEASE

The strategies for treatment of CF lung disease are reviewed elsewhere. Available therapies include airway clearance maneuvers and exercise, inhaled mucoactive substances, bronchodilators, antibiotics, and anti-inflammatory agents. A cornerstone in the treatment of CF lung disease is the use of maneuvers and/or devices that facilitate the clearance of airway secretions. Because CF secretions are dehydrated and difficult to clear, additional efforts above and beyond cough must be applied on a regular basis to prevent their accumulation. Although indicated in almost all patients with CF, it remains controversial whether chest physiotherapy is appropriate for asymptomatic infants with normal lung function. Choices are often made based on an individual patient's perception of efficacy and preference for assisted vs. independent modalities. Chest percussion and vibration, with or without postural drainage, have long been the traditional airway clearance modalities, and are favored by many patients, especially when they are ill. Negative factors pertaining to this mode of therapy is the need for a caregiver to perform the treatment and the additional risk of inducing gastroesophageal reflux and aspiration when using head-down tilt positions in infants. Exercise is an additional treatment modality that may augment airway clearance, while providing other beneficial effects as well. Anecdotal experiences have long supported the usefulness of exercise in CF lung disease, but short-term studies only showed improved exercise tolerance rather than more substantial pulmonary benefits. One long-term, randomized controlled study of an in-home exercise program in CF, however, demonstrated that children with mild to moderate lung disease who were assigned to at least three times per week exercise sessions had slowed decline of lung function over a 3-year period; therefore, a program that combines exercise with other airway clearance maneuvers should be considered.

Medications that impact mucus clearance and benefit patients with CF include dornase alfa and hypertonic saline. Dornase alfa is an inhaled recombinant human DNAse enzyme that hydrolyzes free DNA molecules present in CF airway secretions. Because DNA is exceedingly viscous, the action of dornase alfa improves the cough-clearance of secretions and has been shown to improve lung function and reduce the frequency of exacerbations. The optimal time to initiate dornase alfa treatment is somewhat unclear. However, it has been shown that children (mean age 8.4 years) with mild lung disease (mean FEV_1 95 percent predicted) have sustained improvement in lung function and reduced disease exacerbations over 2 years of observation when treated with dornase alfa, and separately was shown to prevent an increase in markers of inflammation (IL-8, free elastase) as assessed by bronchoalveolar lavage at 18-month intervals.

Inhaled hypertonic saline draws water into the luminal compartment, thereby improving the hydration of the periciliary layer and of mucus secretions. Unlike dornase alfa, hypertonic saline has been shown to acutely stimulate mucociliary clearance, as measured via studies that use inhaled radiotracer particles, and to have sustained effects on mucus clearance rates (greater than 8 hours) in patients with CF as well. Unfortunately, there are no data that support the use of other mucolytics, including *N*-acetylcysteine, and their use cannot be recommended at this time. Bronchodilators, particularly beta-adrenergic agonists, are very commonly used in the setting of CF lung disease, although data supporting their efficacy are mixed.

ANTIBIOTICS

Antibiotics are a mainstay in the treatment of CF, and their use fulfills different purposes at different times. Oral azithromycin, although generally not active against the major colonizing organisms, has been shown to improve lung function and reduce exacerbations in CF patients with *Pseudomonas* infection when used chronically. The mechanism may be via anti-inflammatory actions. However, *Pseudomonas* growing under biofilm conditions has very different antimicrobial susceptibility patterns, and sensitivity to macrolides may actually occur under these conditions. Coexistent infection with mycobacteria is generally a contraindication to macrolide use and should be excluded prior to initiation of therapy.

Other oral antibiotics are also widely used in CF. Continuous use of anti-staphylococcal antibiotics was a common practice in the United States in patients who were infected with sensitive *S. aureus* species. This practice has fallen out of favor because of an absence of demonstrated benefit and an increased rate of *Pseudomonas* acquisition. Proponents of anti-staphylococcal treatment still exist, although this practice should be examined carefully, given the very real harm associated with an earlier acquisition of *Pseudomonas*.

Oral anti-pseudomonal agents are principally confined to the quinolone class of antibiotics. Quinolone use is associated with the rapid development of resistance and therefore should not be used chronically/prophylactically. Instead, inhaled antibiotics have become very important in the chronic management of CF. The inhaled route is attractive because

higher concentrations of drug reach the endobronchial site of infection via the inhaled route, so microbial resistance may be overcome. Also, inhaled tobramycin is associated with low blood levels and much less systemic toxicity than with the intravenous route. Six-month studies of inhaled tobramycin demonstrated improved lung function and fewer exacerbations when used in a cycling fashion (i.e., 1 month on, 1 month off). A small increase in *Pseudomonas* resistance was observed over these relatively short duration studies, but did not affect efficacy over this time period. However, it is unknown whether the same efficacy profile will be preserved with longer-term use of inhaled tobramycin, especially in the face of the progressive antimicrobial resistance that is likely to occur over time. Therefore, whether prophylactic use every other month is superior to less frequent dosing, or even intermittent use for minor changes in symptoms or lung function, is unknown.

Colistin has seen considerable use for CF, particularly in Europe. There are substantially fewer data to support the safety and efficacy of colistin use. Because this agent has excellent in vitro activity versus *Pseudomonas* and is infrequently used as an intravenous agent to treat exacerbations, use in maintenance therapy has theoretical advantages. There are also concerns over whether colistin is adequately converted to the active form in sputum by local hydrolases, difficulty with bronchospasm in some patients, and the need for somewhat complicated regimens to get the powdered drug into solution while avoiding problematic foaming during delivery.

A number of other antibiotics are either being formally developed for use via the inhaled route or have a history of being nebulized without adequate research into its delivery, safety, and efficacy. With adequate testing, additional inhaled antibiotic agents should prove to be useful in the treatment of CF.

ANTI-INFLAMMATORY AGENTS

Anti-inflammatory agents are an attractive option for the treatment of CF lung disease given the fact that persistent, neutrophil-predominant inflammation ultimately is the cause of airway destruction. Ibuprofen is currently the only available agent for chronic treatment with proven efficacy and safety in CF. In a long-term, prospective study ibuprofen slowed the rate of lung function decline, and the affect appeared to be greatest in younger patients with mild disease. Importantly, ibuprofen levels must be monitored during treatment, as therapy may be associated with gastrointestinal bleeding and renal dysfunction, whereas subtherapeutic levels are associated with a paradoxical increase in neutrophil migration, and super-therapeutic levels are more likely to yield toxicity (e.g., GI bleeding). Use of ibuprofen should be stopped during administration of other nephrotoxic agents, such as intravenous aminoglycosides. Inhaled steroids are of unproven benefit for the typical patient with CF.

ANTIMICROBIALS IN THE TREATMENT OF ACUTE EXACERBATIONS

The choice of antibiotics to treat an exacerbation should be made based upon the most recently available pretreatment sputum culture result. For mild exacerbations in a patient chronically colonized with *Pseudomonas,* an oral quinolone with antipseudomonal activity or inhaled tobramycin may be effective either as monotherapy or in combination. Combination therapy has the theoretical advantage of inducing less drug resistance, but this has not been well studied. For more severe exacerbations, selection of empiric intravenous antibiotics should be based on prior antimicrobial susceptibility data and, generally, two drugs from different classes should be selected. This may lessen emergence of bacterial resistance; true synergy for *Pseudomonas* has been documented only between aminoglycoside and β-lactam antimicrobial agents. It is unclear whether in vitro testing of *Pseudomonas* under log-phase growth conditions is clinically relevant given the role of biofilm in growth in vivo. In patients with CF, some drugs, particularly aminoglycosides, are renally cleared faster than normal individuals and levels should be followed to guide dosage adjustments. The treatment of other gram-negative infections (e.g., *B. cepacia* complex, *Stenotrophomonas maltophilia*, and *Achromobacter xylosoxidans*) is similarly based on susceptibility patterns. Coinfection with *S. aureus* or, increasingly, with non-tuberculous mycobacteria, may merit separate therapy.

CONCLUSIONS

A detailed understanding of the molecular events that underlie the pathogenesis CF lung disease is emerging. This knowledge is now guiding the development of new treatment strategies, using both existing and novel agents, to more effectively treat this disease. With the development of drugs that correct the earliest defects in CF, i.e., CFTR dysfunction and ASL dehydration, further increases in the already vastly improved survival with CF are predicted. It is likely, however, that improved survival will paradoxically increase the complexity of caring for adult patients with CF who continue to develop complications related to reaching older ages. Continued research, the identification of best available practices, and broader dissemination of expertise will certainly continue to drive improved outcomes in coming years.

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125

Bronchiectasis

Alan F. Barker • Sheela Y. Ahmed

Bronchiectasis (*broncos,* airways; *ectasia,* dilatation) is a morphological term used to describe abnormal irreversibly dilated and often thick-walled bronchi. This is an anatomic definition and is thought to have evolved from Laennec's original description in 1819 of ectatic bronchi in pathological specimens. Bronchiectasis represents the end stage of a variety of pathologic processes that cause destruction of the bronchial wall and its surrounding supporting tissues. The clinical manifestations include chronic cough and copious mucopurulent expectoration, often lasting months to years. Bronchiectasis shares many features with chronic bronchitis, including inflamed and easily collapsible airways, airflow obstruction on spirometry, and frequent exacerbations. The distinction between the two processes is a matter of degree and extent of the abnormality. Patel et al. from St. Bartholomew's Hospital in London evaluated the presence and extent of bronchiectatic changes in stable patients with moderate to severe chronic obstructive pulmonary disease (COPD). They showed that 50 percent of these patients had evidence of radiologic bronchiectasis, with high-resolution computed tomography (HRCT) changes seen most frequently in the lower lobes.

PREVALENCE

Bronchiectasis was a common disabling and fatal condition in the pre-antibiotic era. It remains an important cause of suppurative lung disease in the developing world. More recently, the declining incidence of this disease in the developed world has led to repeated suggestions that it be considered an orphan disease. The decline has been variously attributed to the advent of improved living conditions, frequent and early use of antibiotics, improved sanitation and nutrition, and introduction of childhood immunization, particularly against measles and pertussis. In the United States, the prevalence has recently been estimated to be 52 per 100,000. A slight female preponderance has been suggested in two large series of patients. Bronchiectasis has been reported to act more

virulently in women, but whether this represents an altered inflammatory-immune response, or there are environmental, genetic, and anatomic differences leading to this predisposition is not clear.

PATHOPHYSIOLOGY

The abnormal bronchial dilatation in bronchiectasis principally affects the medium-sized bronchi, but often extends to the more distal bronchi and bronchioles. On gross examination of surgically resected or autopsied lungs, the affected bronchi and bronchioles are so prominent as to be visible all the way to the pleural surface. These dilated and ectatic bronchi are commonly filled with purulent secretions. The affected bronchi show transmural inflammation, mucosal edema, cratering, ulceration, and neovascularization. The bronchial epithelium may show a polypoidal appearance due to underlying granuloma formation and mucosal prominence, ridging due to bronchial smooth muscle hypertrophy, and pitting due to the dilated bronchial mucous glands. Severe cases may show denudation of epithelial lining, with destruction of underlying elastic laminae, smooth muscle, and cartilage with fibrotic changes replacing these structures. Dilated and tortuous bronchial arteries may be seen secondary to the development of extensive bronchial-pulmonary anastomoses.

Microscopically, bronchiectasis is associated with loss of cilia, cuboidal and squamous metaplasia, hypertrophy of bronchial glands, and lymphoid hyperplasia. Intense infiltration of the bronchial wall with neutrophils, lymphocytes, and monocytes is seen. It has long been recognized that these changes are associated with chronic bacterial infection. The concept of the "vicious cycle" proposed by Peter Cole and colleagues from the Brompton Hospital has largely been accepted over the last three decades. While acute inflammation is an important host defense against bacterial infection, if it fails to clear the infection, it can result in lung damage. This theory proposed that chronic bacterial endobronchial infection and inflammation damage or destroy mucociliary defenses, leading to secretion stasis, which in turn propagates furthers bacterial infection, and increases airway inflammation and bronchial dilatation. Bacterial colonization and/or infection of the airways alone is not sufficient to produce true bronchiectasis. It seems likely that focal disturbances resulting in airway obstruction or impairment of drainage and/or systemic conditions, resulting in uncoordinated airway clearance or impaired immune response are required in addition to airway colonization and/or infection. The appearance of *Pseudomonas aeruginosa* in the respiratory tract of bronchiectasis patients on a chronic or recurring basis has been associated with worsening ciliary function and deleterious effects on host defenses, resulting in impaired health-related quality of life and worsened lung function. This may be due to the ability of this organism to release virulent exotoxins, form surrounding biofilms on tissue surfaces, and easily develop hypermutable *P. aeruginosa* strains resistant to antibiotics, all factors perpetuating and propagating bronchial damage.

Angrill et al., in a study looking at parameters of bronchial inflammation and colonization in clinically stable bronchiectasis, demonstrated findings suggesting that airway inflammation may occur even in the absence of bacterial colonization. They found a higher percentage of airway neutrophils and higher concentrations of IL-8 and IL-6 in the BAL fluid of patients with bronchiectasis and negative microbial cultures, than in nonsmoking controls who had no evidence of respiratory disease.

CLINICAL FEATURES

The classic clinical manifestations of bronchiectasis are daily cough and mucopurulent sputum production. Cough is invariably present and often may be the only symptom for years. Purulent, tenacious sputum production, frequently worse in the morning (having accumulated during recumbency in sleep) is present in most patients. Sputum production may be intermittent, being affected by recurrent infections, bronchial plugging, and antibiotic therapy. "Dry bronchiectasis" presenting as cough, minimal sputum expectoration, and/or hemoptysis is occasionally described. Hemoptysis may be seen in 40 to 70 percent of patients and may vary from blood streaks to large clots. Increasing cough, dyspnea, and volume of sputum production, fever, hemoptysis, and chest pain are hallmarks of acute exacerbations. Often patients give a history of recurrent chest infections, although single episodes of severe pneumonia, tuberculosis, or pertussis with secondary pneumonia may also result in bronchiectasis.

Most patients have abnormalities on physical examination. Chest auscultation usually reveals findings of early and mid-inspiratory crackles as well as diffuse rhonchi and prolonged expiration. Bronchial breath sounds may be heard in severe cases or patients with a complicating pneumonia. Digital clubbing and hypertrophic pulmonary osteoarthropathy, although common in the pre-antibiotic era, are rarely seen now. In severe advanced cases, there may be evidence of respiratory insufficiency and cor pulmonale.

CLASSIFICATION USING RADIOLOGY

Bronchiectasis may be classified by predisposing factors, pathological features, and radiographic appearance. Reid in 1950 described a correlation between pathological and bronchographic findings in bronchiectasis; since then, this has been the most widely used classification. There is considerable overlap and coexistence among the various forms of bronchiectasis. In c*ylindrical* bronchiectasis, the bronchi are regularly outlined (tubular), dilated in diameter, with straight

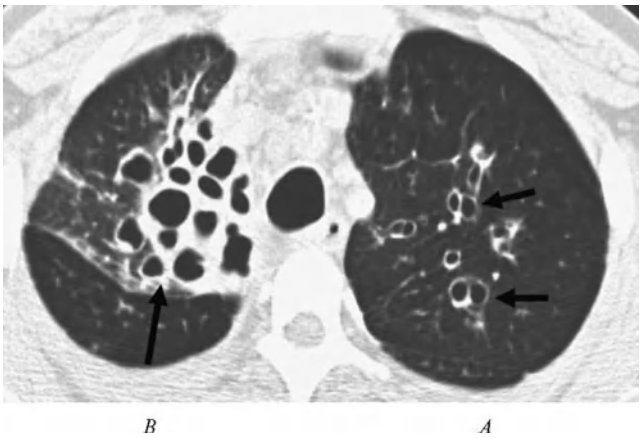

Figure 125-1 Chest computed tomography. *A.* (Left chest) *Cylindrical* bronchiectasis: Dilated and thickened airways. *B.* (Right chest) *Saccular* or cystic bronchiectasis: Very dilated airways clustered into saccules, cysts, or grapelike clusters.

walls, often coming to a straight abrupt end, instead of a tapering end, due to obstruction of the peripheral bronchial tree by secretions, casts, and inflammatory wall edema. *Varicose* bronchiectasis (illusion to varicose veins) is marked by the presence of irregular dilatations, outpouchings, and tortuosity of the airways. *Saccular* (cystic) bronchiectasis is characterized by the presence of cystic distortion of the distal airways that may be focal or more generalized, resulting in saccules that appear as a cluster of grapes (Figs. 125-1 and 125-2). Traction bronchiectasis, a term used to describe the dilated airways seen in diffuse pulmonary fibrosis secondary to fibrous tissue traction and elevated negative intrathoracic pressure, should be distinguished from usual bronchiectasis, because of the lack of intrinsic airway pathology and paucity of sputum expectoration. Congenital bronchial cysts (central and peripheral) are developmentally abnormal cystic bronchial structures, often filled with mucus and lined with respiratory epithelium. While usually lacking connection with the parent bronchus and distal alveoli, if infected they may communicate and mimic localized bronchiectasis. Intralobar bronchopulmonary sequestration too, may become infected and communicate with the bronchial tree, mimicking localized bronchiectasis.

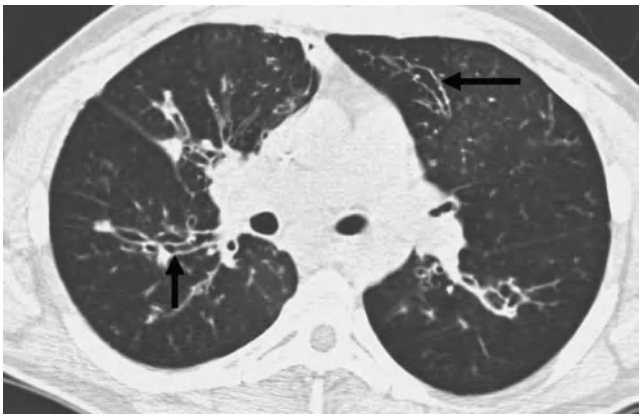

Figure 125-2 Chest computed tomography shows *varicose* bronchiectasis: dilated airways with irregular thickened mucosa.

PREDISPOSING OR ASSOCIATED FACTORS

Previously bronchial damage secondary to childhood respiratory tract infections such as pneumonia, pertussis, complicated measles, and tuberculosis were implicated as common causes of bronchiectasis. However, with the early use of antibiotics and childhood immunizations, the focus has shifted from postinfectious to intrinsic causes. Often regarded as a condition in which extensive investigation is unlikely to yield treatable causes, recent studies have shown results to the contrary. Thus, Pasteur et al. in a study of a northern European cohort of bronchiectasis patients with a low incidence of HIV and tuberculosis were able to identify a cause in 47 percent of cases. Postinfectious causes (29 percent) were still the largest group. Li et al. in a study of 136 patients were able to find an etiologic cause in 101 (74 percent) cases, and in 77 cases these diagnoses had implications for treatment and prognosis. The etiologic distribution in these studies is detailed in Table 125-1.

Infections

A number of pulmonary infections have been associated with the development of bronchiectasis. The association of

Table 125-1

Associated Factors or Etiology

Author, years studied	Li (1986–2002)	Pasteur (1995–1997)
Etiology or association	**Patients ($n = 136$)**	**Patients ($n = 150$)**
Immunodeficiency	46	12
Young syndrome	0	5
Aspiration	25	6
Primary ciliary dyskinesia	20	3
Childhood respiratory infection	5	44
Congenital structural malformation	5	1
ABPA	0	11
Rheumatoid arthritis	0	4
Cystic fibrosis	Excluded	4
Idiopathic	35	80
Ulcerative colitis	0	2

measles with bronchiectasis has been considered a complication secondary to the intense bronchial and peribronchial inflammation and epithelial proliferation. Complicating secondary infections with adenovirus, herpesvirus, and bacteria such as *Staphylococcus aureus, Klebsiella pneumoniae,* and *P. aeruginosa* possibly further contribute to the severity of a necrotizing bronchopneumonia.

Primary necrotizing bacterial pneumonias due to *S. aureus, K. pneumoniae*, and *P. aeruginosa* may result in bronchiectasis. *Streptococcus pneumoniae, H. influenzae,* and *Moraxella* infections typically do not cause bronchiectasis, but may be colonizers of bronchiectatic airways. Necrotizing anaerobic pneumonias secondary to aspiration or bronchial obstruction are often complicated by parenchymal destruction and bronchiectasis. Tuberculosis can result in bronchiectasis by several mechanisms. Bronchiectasis may be a consequence of tuberculous bronchitis, postobstructive bronchial damage secondary to post-tuberculous bronchial wall stenosis, and extraluminal bronchial obstruction by enlarged tuberculous lymph nodes.

The association of *Mycobacterium avium* complex (MAC) with bronchiectatic airways is well documented. While traditionally considered a secondary pathogen in an abnormal host or a colonizer in damaged lungs (bullous emphysema, cavitary lung disease) it is now recognized that MAC or other environmental mycobacteria infection can cause bronchiectasis in apparently normal hosts. CT scan of the chest in such cases is relatively specific, showing small irregular nodules in the middle lobe or lingula, but other parts of the lung may be affected. The phenotype for MAC-associated bronchiectasis seems to involve predominantly slender white women 50 to 70 years old without underlying lung disease or immune compromise. It is likely that a narrow angulated middle lobe bronchus and ineffectual coughing due to increased airway collapsibility explain this syndrome.

Bronchial Obstruction

Bronchial obstruction may result in the development of localized bronchiectasis. Various explanations have been advanced for this phenomenon. It has been suggested that following bronchial obstruction, airways proximal to the collapse are exposed to strong dilating forces caused by the difference in the atmospheric pressure in the bronchi and the negative pressure in the pleural space. Over time, these forces acting on weakened, inflamed airways may result in permanent and pathological airway dilatation. The presence of surrounding lung fibrosis, atelectasis, and loss of lung volume leading to regional increases in local retractile lung forces may also play a role. Animal experiments suggest that obstruction may facilitate the development of bronchiectasis by interfering with bronchial clearance and promoting bacterial infection, bronchial wall inflammation, and weakening.

Endobronchial adenomas, fibromas, chondromas, and lower respiratory tract papillomatosis causing partial airway obstruction and bronchiectasis have been described.

Localized bronchiectasis may also been seen in middle lobe syndrome, and is usually caused by intraluminal or extraluminal obstruction secondary to tumor, enlarged lymph nodes, or abnormalities of bronchial structure and branching.

Aspiration/Inhalation Airway Injury

Aspiration or inhalation of foreign matter, such as noxious fumes or particulates into the airways, may result in bronchiectasis. This may involve aspiration of oropharyngeal secretions containing microaerophilic and anaerobic bacteria, which may result in a necrotizing pneumonia. Refluxed material from the esophagus or stomach containing food particles, gastric, biliary, and pancreatic secretions, and gut microbes may enter and damage airways, especially if the aspiration events are large and repeated. Depressed sensorium (stroke, alcohol and drug use, seizure, postanesthetic), brain stem dysfunction (amyotrophic lateral sclerosis, multiple sclerosis, syringomyelia), defective laryngeal function (postsurgery, postirradiation), esophageal disorders (dysmotility, gastroesophageal reflux disease [GERD], achalasia, tracheoesophageal fistula), and gastric disorders (gastric outlet obstruction) influence the likelihood and frequency of aspiration. Bronchiectasis may present years after foreign body aspiration (aspiration is often unrecognized), though bronchiectasis has been seen to occur in animals as soon as 2 to 8 weeks after experimental foreign body introduction into the bronchial tree. GERD is the most common condition in this category contributing to the risk of bronchiectasis, and several studies are available documenting increased frequency of reflux in patients with bronchiectasis, asthma, and pulmonary fibrosis, all chronic pulmonary inflammatory conditions. The cause-effect conundrum of GERD in these conditions is still being debated. However, given the high rate of association of GERD with bronchiectasis and the fact that it is often treatable, GERD evaluation should be part of the bronchiectasis work-up.

Cystic Fibrosis

Cystic fibrosis (CF) and its variants are a common cause of bronchiectasis in the United States and other developed countries. This is a monogenic disorder that presents most commonly in childhood as a multisystem disease. However, 3 to 7 percent of patients with cystic fibrosis are diagnosed in adulthood, and due to improvements in therapy, 25 percent of childhood cases reach adulthood. This is an autosomal recessive condition resulting from a genetic defect located on chromosome 7 leading to a deficiency in the CF transmembrane regulator. However, more than 200 mutations in the CF gene have been identified and the specific manifestations, severity, and rapidity of progression of CF vary according to the genotype. Clues suggesting CF as a cause of bronchiectasis include upper lobe radiographic involvement and sputum cultures showing mucoid *P. aeruginosa*. Adults diagnosed with CF after the age of 20 are less likely than children to have homozygous cystic fibrosis transmembrane conductance regulator (CFTR)

mutation, pancreatic insufficiency (but not pancreatitis), and diabetes mellitus. The diagnosis of CF rests on a combination of clinical criteria accompanied by sweat chloride values above 60 mEq/L. However, normal sweat chloride values may be seen in patients with clinical manifestations of CF and genetically confirmed CF. Screening for other mutations in the CFTR gene may be necessary in these circumstances.

Young's Syndrome

Young's syndrome consists of a combination of obstructive azoospermia (with normal spermatogenesis) and chronic sinopulmonary infections (bronchiectasis and sinusitis). This syndrome is distinguished from ciliary dyskinesia by its lack of ultrastructural ciliary abnormalities. Young's syndrome is distinguished from CF by its lack of family history, absence of CF genetic mutations, the presence of normal sweat electrolytes, and normal pancreatic secretion. Typically, the pulmonary manifestations of Young's syndrome appear usually in childhood and become milder in adulthood, although severe progressive cases have also been reported. Diagnosis is usually made when affected individuals are evaluated for infertility.

Primary Ciliary Dyskinesia

Primary ciliary dyskinesia (PCD) is phenotypically and genetically a heterogeneous group of conditions. It has an autosomal-recessive inheritance pattern, although rarely other modes of inheritance, such as X-linked, are described. It is estimated to affect 1:20,000 to 1:60,000 people, with approximately 12,000 affected people in the United States. The disease phenotype is caused by defects of respiratory cilia, sperm tails, and cilia of the embryonic node.

Currently three genes (DNAI1, DNAH5, and DNAH11) that encode for dynein proteins (axonemal and cytoplasmic) have been linked to recessive PCD. It is hypothesized that given the small numbers of well-characterized affected families, the large size of the dynein genes, the different dynein proteins present in the axoneme, and the large number of regulatory and structural proteins necessary for ciliary function, dynein mutations may not be the only cause of primary ciliary dyskinesia. Since its initial description in 1933, Kartagener's syndrome (triad of situs inversus, bronchiectasis, and either nasal polyps or recurrent sinusitis) and the description by Afzelius in 1975 of the defects in the dynein arms underlying this condition, incomplete forms of this syndrome have increasingly been recognized. Thus, clinical findings may be varied in patients with PCD, including respiratory distress in neonates, recurrent respiratory tract infections, bronchiectasis, situs inversus, heterotaxia, infertility, and hydrocephalus, singly or in various combinations. In a study looking at 94 patients from 68 families, Noone et al. showed that cough was seen in 100 percent of patients, bronchiectasis (98 percent), sinusitis (47 percent), otitis media (92 percent), and situs inversus (46 percent).

Exhaled nitric oxide (NO) may be used as a screening test, with levels of NO being characteristically low. Ciliated epithelial cells obtained from the inferior or middle turbinate using a sterile cytology brush may be studied for ciliary beat pattern and frequency using digital high-speed video imaging, when the dyskinetic cilia are seen to lack the classical sideway recovery sweep. Abnormalities in ciliary beat have been correlated to ultrastructural defects, and normal ciliary motion essentially excludes PCD. Axonemal structure of respiratory cilia may be visualized by transmission electron microscopy and defects in dynein arms, peripheral and central tubules, radial spokes, and basal bodies may be seen. No structural abnormalities are found in 3 percent of cases of PCD, and diagnosis may be confirmed by establishing dysmotility. Several of these tests are only available in research centers.

Allergic Bronchopulmonary Aspergillosis

Allergic bronchopulmonary aspergillosis (ABPA) is a hypersensitivity lung disease caused by the ubiquitous fungus *Aspergillus fumigatus* and usually occurs as a complication of persistent asthma or cystic fibrosis. The excessive mucus production and impaired mucociliary clearance in these conditions allow the inhaled conidia of *Aspergillus* to persist and germinate, releasing exoproteases and other fungal products that further compromise clearance, breach epithelium, and activate immune responses. ABPA is characterized by a marked local and systemic eosinophilia, an elevated level of *Aspergillus fumigatus*–specific IgG and IgE antibodies, as well as a nonspecific elevation of total IgE. Clinically, ABPA manifests as recurring episodes of asthma, pulmonary infiltrates, and central bronchiectasis that may progress to fibrosis. Criteria have been established for the diagnosis of ABPA in the non-CF (Patterson criteria) as well as the CF population.

Inflammatory Disorders

Inflammatory and fibrotic processes affecting large and small airways may be seen in several rheumatic diseases and idiopathic inflammatory states. Significantly higher frequencies of bronchiectasis (20 to 35 percent) have been found in *rheumatoid arthritis* (RA) patients undergoing HRCT, both in symptomatic (30 percent) and asymptomatic (8 percent) patients, and was independent of smoking status. Bronchiectasis may precede or follow the development of rheumatoid arthritis, and the coexistence of both conditions is considered to portend a reduced survival. *Sjögren's syndrome* may also be complicated by bronchiectasis presumed to be secondary to the effects of inspissated bronchial secretions causing atelectasis and bronchial wall destruction. *Relapsing polychondritis* may be complicated by bronchiectasis in regions of recurring pneumonia as well as regions free of infection. It is not clear whether the chondritis itself or the recurrent infections predispose to bronchiectasis. While pulmonary involvement in *systemic lupus erythematosus* is diverse, bronchiectasis by

HRCT findings is less frequent than in patients with RA. *Idiopathic ulcerative colitis* has been reported to be associated with bronchiectasis. The pathogenesis remains unknown, although autoimmune and immune complex deposition theories have been proposed. This variant of bronchiectasis does not respond to colectomy and has been known to appear and progress after colectomy. Response to steroids is said to be dramatic. Bronchiectasis seen in sarcoidosis is usually traction bronchiectasis secondary to parenchymal and peribronchial fibrosis. Endobronchial sarcoid may result in localized bronchiectasis secondary to obstruction, atelectasis, and bronchial wall destruction.

Hypogammaglobulinemia

Recurrent sinopulmonary infections and bronchiectasis are clearly associated with hypogammaglobulinemia. Several forms of antibody deficiency have been linked with the development of bronchiectasis, including X-linked agammaglobulinemia, common variable immunodeficiency, IgA deficiency, and IgG subclass deficiency (usually IgG-G2 and IgG-G4). The issue of subclass deficiency (in the presence of normal or near-normal levels of total IgG) as a cause of bronchiectasis is controversial due to the wide range of values in normal individuals and the difficulties involved in accurately measuring these levels. A challenge with common humoral bacterial antigens, such as capsular polysaccharides of *H. influenzae* and *S. pneumoniae* followed by measurement of antibody titers 6 weeks later, may help establish the presence of such a deficiency. Early diagnosis of these conditions and replacement with intravenous immunoglobulin significantly reduces infections and prevents bronchiectasis, although the efficacy of this treatment in patients with selective IgM, IgA, and IgG subclass deficiency remains controversial. Standard doses in adults of 300 mg/kg by intravenous infusion every 4 weeks have been proved to reduce rates and severity of respiratory infections, but higher doses of 600 mg/kg appear more efficacious in reducing respiratory exacerbations and preserving pulmonary function in some patients.

DIAGNOSIS OF BRONCHIECTASIS

The diagnosis of bronchiectasis is based on history, clinical features, and radiologic demonstration of bronchiectatic airways. The diagnostic evaluation in these patients is largely aimed at identifying potentially treatable underlying causes of bronchiectasis. Thus, esophageal pH monitoring and ciliary analysis may be evaluated depending on the age of presentation; family history; other organ system involvement and level of clinical suspicion; total white blood cell count and differential for eosinophilia; immunoglobulin G, A, M, and E levels; serum α_1-antitrypsin levels; sputum cultures for bacteria, mycobacteria, and fungi; sweat chloride levels; skin prick tests or precipitins to *Aspergillus* spp.

Chest Radiograph

The chest x-ray may be abnormal and show the presence of increased pulmonary markings, ringlike structures, atelectasis, dilated and thickened airways (tram lines), and mucus plugging (finger-in-glove) appearance; however, the chest radiograph may be normal even in the presence of bronchiectasis.

High-Resolution Computed Tomography

The HRCT has been proved to be a reliable and noninvasive method for assessment of bronchiectasis. HRCT can accurately (sensitivity of 97 percent) diagnose bronchiectasis, localize and describe areas of parenchymal abnormality, and identify bronchiolar abnormalities and mucus plugging to the level of fifth- and sixth-order bronchi. It also can identify focal areas of air trapping as an indicator of small airway disease. It is indicated in the evaluation of bronchiectasis when surgical resection is contemplated, bronchiectasis is strongly suspected clinically and routine chest radiographs are normal, and other parenchymal abnormalities have to be better defined.

Airway dilatation can be detected by finding tram lines or end-on-ring appearance. A luminal diameter more than 1.5 times the adjacent vessel is indicative of bronchiectasis (Fig. 125-1). Bronchial wall thickening may also be seen. Evidence of small airway plugging with debris (tree-in-bud) may also be seen (Fig. 125-3).

Reports are available suggesting that the distribution and pattern of bronchiectasis may be sufficient to implicate a specific cause. Cartier et al. found that bilateral predominantly upper lobe bronchiectasis is seen most commonly in CF and allergic bronchopulmonary aspergillosis, a unilateral upper lobe predominance in tuberculosis and a lower lobe predominance in childhood viral infections.

Pulmonary Function

Pulmonary function is usually abnormal. The degree of impairment depends not only on the nature and extent of the

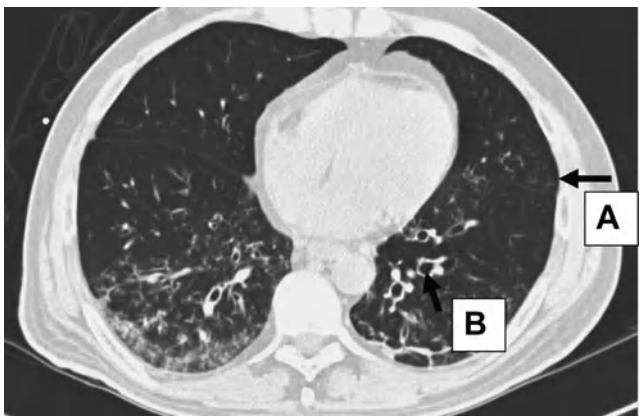

Figure 125-3 Chest computed tomography. *A.* Extensive peripheral branching opacities of tree-in-bud. *B.* Extensive peripheral branching dilated and thickened airways.

Table 125-2

Microbiology in Bronchiectasis

Author, Year Mean Age (Y)	Li, 2005 12	Nicotra, 1995 57	Pasteur, 2000 58	Angrill, 2001 53
	***n* = 136 (%)**	***n* = 123 (%)**	***n* = 150 (%)**	***n* = 42 (%)**
Microbiologic flora				
Hemophilus influenzae	53 (40)	37 (30)	52 (35)	11 (26)
Pseudomonas aeruginosa	15 (11)	38 (31)	46 (31)	4 (9)
Streptococcus pneumoniae	23 (18)	13 (11)	20 (13)	6 (14)
Staphylococcus aureus	5 (4)	9 (7)	NA	NA
Moraxella catarrhalis	3 (2)	3 (2)	30 (20)	2 (5)
Nocardia	0	4 (3)	NA	NA
Anaerobes	1 (1)	2 (1)	NA	NA
Mycobacteria	0	49 (40)	NA	NA
Aspergillus	1 (1)	6 (5)	3 (2)	1 (2)
Two or more organisms	21	60	NA	NA

morphologic abnormalities of bronchiectasis, but also on the presence or absence of associated chronic bronchitis, emphysema, and so on. Thus, patients with mild localized bronchiectasis and no chronic bronchitis may have normal lung function tests. Patients with diffuse involvement may show on spirometry a pattern of airways obstruction, with normal or reduced forced vital capacity (FVC), reduced forced expiratory volume in 1 s (FEV_1), and reduced FEV_1/FVC ratio. In some patients with accompanying atelectasis, parenchymal and pleural scarring, restrictive or mixed/obstructive and restrictive physiology may be seen with reduced FVC and normal FEV_1/FVC ratios. Lung volumes may help identify restriction, as the total lung capacity (TLC), functional residual capacity, and residual volume (RV) are reduced. With mainly obstruction, air trapping is evident with increased residual volume and increased RV/TLC.

BACTERIOLOGY

Patients with bronchiectasis are frequently found to be colonized by potentially pathogenic microorganisms. Thus even in stable conditions 60 to 80 percent of patients with bronchiectasis are known to be colonized. The most frequent microorganisms isolated are *H. influenzae* and *P. aeruginosa* and are often implicated as the cause of periodic exacerbations. Colonization with *P. aeruginosa,* in particular, has been associated with more severe impairment of lung function, more intense inflammatory response, and more extensive lung disease. Shah et al. showed an association between the isolation of *S. aureus* and the presence of ABPA or CF. Instances of airway colonization with other potential pathogens that may require specific treatment include *Nocardia asteroides, Aspergillus fumigatus,* and environmental *Mycobacterium* spp. Microbiologic flora isolated in three studies are shown in Table 125-2.

TREATMENT

The treatment of bronchiectasis is aimed at controlling infection, reducing inflammation, and improving bronchial hygiene, with surgical resection of affected areas being useful in selected patients. With few clinical trials for guidance, treatment often has to be tailored to the specific needs, tolerances, and preferences of individual patients.

Control of Infection

Since infection plays a major role in the causation and perpetuation of bronchiectasis, reducing the microbial load and

associated inflammatory mediators remains a cornerstone of therapy. Antibiotics are indicated to treat an acute exacerbation. However, they have been used variably to prevent recurrent infections by suppression and/or elimination of attendant flora. Antibiotics are directed at commonly isolated pathogens such as *H. influenzae, S. pneumoniae*, and *P. aeruginosa*. Oral fluoroquinolones are often used as initial antibiotic choices for treatment durations of 10 to 14 days. In the face of failure to respond to treatment or the occurrence of frequent exacerbations over short periods of time, sputum cultures and sensitivity tests should be done to help define antibiotic selection and/or aid in alternate diagnoses, e.g., atypical mycobacteria or fungae. Severe exacerbations due to *P. aeruginosa* require the intravenous administration of two antipseudomonal antibiotics and potential hospitalization.

The role of prophylactic/suppressive antibiotics remains controversial. Several approaches to the prescription of suppressive antibiotics exist, including daily antibiotics, antibiotics given for 1 to 2 weeks each month, as well as more prolonged courses lasting weeks to months.

The use of daily, twice weekly, and thrice weekly azithromycin as a biological response modifier in CF and diffuse panbronchiolitis has generated considerable interest about a role in the treatment of bronchiectasis. A pilot trial reported decreased frequency of exacerbations, reductions in sputum volume, and improvements in quality of life and pulmonary function and reductions in levels of C-reactive proteins. Macrolides have been shown to have several biologic effects not related to antibacterial effect. These include effects on nuclear transcription factors with down-regulation of proinflammatory cytokines, suppression of iNOS, reduced adhesion molecule expression, reduced neutrophil chemotaxis and degranulation, cytoprotection against phospholipids, improvement in mucus rheology, reduction in bronchial hyperreactivity, effects on *Pseudomonas* biofilm production, and quorum sensing function.

Administration of antibiotic aerosols (chiefly tobramycin 300 mg nebulized twice daily against *Pseudomonas*) is effective in CF. Pilot studies of non-CF bronchiectasis have demonstrated a reduction in *Pseudomonas* density and even eradication of *Pseudomonas* in some patients, although side effects were also noticed, including increased cough, wheezing, dyspnea, tinnitus, voice alteration, and tobramycin resistance. The effects of other aerosolized antibiotics, such as aztreonam, colistin, and gentamicin alone or in rotation with tobramycin need to be assessed for efficacy and side effects.

MAC-associated bronchiectasis should be considered in patients not responding to antibacterial therapy. The diagnosis requires three or more independent sputum cultures (or two positive cultures and one positive smear) and radiologic evidence of progressive infiltrates, multiple nodules, and cavitation on chest imaging. In this setting MAC should be treated per American Thoracic Society guidelines with a macrolide, rifampicin, and ethambutol for at least 12 months after culture negativity. Streptomycin should also be considered for the initial 8 weeks in patients with a substantial MAC burden, e.g., patients with persistent strongly positive sputum cultures and cavitary disease on radiology.

ABPA responds to oral prednisone in doses of 0.5 to 1 mg/kg per day. The addition of antifungal azoles (itraconazole 400 mg/day for 2 months; then 200 mg/day) may confer additional benefits in terms of reducing fungal burden, steroid dose, and exacerbations. Early and appropriate therapy for ABPA may prevent or delay permanent airway destruction. Because of its relapsing course, monitoring of clinical, radiographic, and serologic responses (IgE) is necessary.

Bronchial Hygiene

Airway mucus clearance is a problem in bronchiectasis. Chest percussion and postural drainage have been the traditional method of facilitating mucus clearance. The onerous and labor intensive nature of physical therapy procedures such as chest wall percussion and postural drainage, and potential issues of hypoxemia and chest discomfort may result in poor patient compliance and the search for alternative therapies. Autogenic drainage, mechanical vibration with ultrasonic devices, positive expiratory pressure, and Flutter valve use without the assistance of another caregiver have been shown to achieve good chest clearance provided the patient has motivation, breath control, and the neuromuscular function to perform. An intrapulmonary percussive ventilation device and vibratory vest help provide mucus clearance in patients unable to perform the other techniques mentioned in the preceding. Studies document increased sputum expectoration using all these methods, with no method being demonstrably more effective or preferred. Thus it is recommended that patients should choose their modality based on ability, motivation, preference, needs, and resources.

Mucus Clearance

Mucus hypersecretion is a prominent feature of chronic inflammatory airways disease and little is known about the effects of current therapies for airways disease, because of the difficulties in quantifying mucus hypersecretion in clinical studies, both at baseline and in response to treatment. Maintenance of hydration with oral and/or intravenous fluids is considered useful in preventing inspissated sputum retention. Humidification of inhaled air or oxygen as an adjunct to chest physical therapy has been shown to significantly increase the wet weight of sputum produced. The use of nebulized normal or hypertonic saline and acetylcysteine may be considered as important adjuncts to chest physical therapy, although bronchospasm may be associated with the use of these agents. A randomized multicenter study evaluating the efficacy of aerosolized DNAse in non-CF bronchiectasis did not find it efficacious in this group of patients. Rather it was associated with increased pulmonary exacerbation

rates, hospitalizations, antibiotic use, and a fall in FEV_1 and FVC.

Bronchodilators

Bronchodilators such as beta agonists, anticholinergics, or theophyllines are frequently used in patients with bronchiectasis, since these patients show signs of airway obstruction and hyperreactivity. There are few reports documenting efficacy in bronchiectasis.

Anti-inflammatory Therapy

Persistent endobronchial inflammation isknown to play a significant role in the pathogenesis of bronchiectasis, and anti-inflammatory therapy may be beneficial. The role of inhaled steroids (fluticasone) in bronchiectasis was evaluated by Tsang et al., who found reduced sputum volume and purulence and reduced rates of exacerbations.

Surgery

Bronchiectasis generally is a diffuse disease and surgical extirpation of affected areas is often not feasible. However, in selected cases surgical resection of the most severely affected segments, bleeding segments, or areas harboring resistant tuberculosis or atypical mycobacteria may confer significant benefits in terms of symptom control, reduction of tenacious sputum production, elimination of large-volume bronchial bleeding, reduction of acute infective episodes, and improved quality of life. The surgical approach varies according to the centers offering this treatment, with some preferring a video-assisted thoracoscopy approach, while others recommend the lateral thoracotomy approach. The complications associated with surgery include spread of infection, bleeding, prolonged air leak, and poor lung expansion following surgery.

Lung transplantation is now considered a viable option in advanced cases, when earlier the risks of persistence of infection in the face of prolonged immunosuppression seemed prohibitive. The outcomes of patients receiving lung transplantation in non-CF bronchiectasis were recently reported by Beirne et al. Overall 1-year survival was 68 percent, and overall 5-year survival was 62 percent. Survival was higher in patients receiving two lungs, as was the FEV_1 and FVC.

Miscellaneous

While not evaluated specifically for bronchiectasis, vaccinations against *S. pneumoniae* and influenza should be considered in these patients. Smoking cessation should be emphasized as a matter of routine. Patients with advanced bronchiectasis with evidence of exercise and/or nocturnal desaturation should be considered for oxygen supplementation to delay the onset of pulmonary hypertension and cor pulmonale and improve exercise tolerance. Pulmonary rehabilitation and inspiratory muscle training may be considered, as these modalities have been documented to improve exercise tolerance.

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CHAPTER

Pneumonia in Surgery and Trauma

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Pneumonia is the most common infectious complication in surgery and trauma patients, and importantly impacts on morbidity and mortality. Most postoperative and post-traumatic pneumonias and are acquired more than 48 hours after hospitalization and therefore are defined as nosocomial pneumonias. Nosocomial pneumonia is reviewed in detail in Chapter 130. Ventilator-associated pneumonia (VAP) is a subset of nosocomial pneumonia that occurs in critically ill surgery and trauma patients who are intubated and on mechanical ventilation. Although community-acquired pneumonia rarely occurs in surgery and trauma patients, the pathogens that are involved in pneumonia that occurs early after hospitalization may be the same as those that cause community-acquired pneumonia.

Several terms are currently used to describe various different nosocomial pneumonias. Hospital-acquired pneumonia (HAP) occurs 48 hours or more after admission to the hospital, and may or may not require treatment in the intensive care unit (ICU). Ventilator-associated pneumonia (VAP) occurs at least 48 to 72 hours after intubation. Health care–associated pneumonia (HCAP) occurs in patients who have had significant exposure to a health care facility, such as hospitalization within the 90 days prior to infection, residence in a nursing home or chronic care facility, recent treatment with intravenous antibiotics, or treatment in a hemodialysis unit.

Pneumonia is most often caused by gram-positive and -negative bacteria. Fungal and viral pneumonias are rare in surgery and trauma patients and generally occur in patients who are severely immunocompromised.

Numerous factors are involved in the development of pneumonia in surgery and trauma patients. Important host factors include age; pre-existing medical conditions; smoking; and pulmonary, nutritional, and immune status. Intubation

and mechanical ventilation increase the risk of pneumonia. Anesthesia increases the risk of developing pneumonia because there is the potential for aspiration during induction and intubation, particularly during emergency surgery and in patients with gastroesophageal reflux.

Making the diagnosis of pneumonia in surgery and trauma patients is fraught with difficulty because noninfectious pulmonary processes often have similar clinical and radiographic manifestations, and the respiratory tract may be colonized with bacteria that are not acting as pathogens. Generally, the combination of clinical findings (fever, cough, sputum production, and respiratory dysfunction) and laboratory and radiographic data are used to make the diagnosis of pneumonia. However, this strategy likely results in an overestimation of the rate of pneumonia.

Guidelines have been published for the management of nosocomial pneumonia. These guidelines are evidence based as much as possible and were generated based on extensive review of clinical studies, and on expert opinions in areas that have not yet been fully investigated. The guidelines are included in publications that provide exhaustive reviews of nosocomial pneumonia, including epidemiology, microbiology, diagnosis, and treatment.

Management of pneumonia in surgery and trauma patients falls into two basic categories: prevention and treatment. Preventive strategies are implemented to reduce the likelihood of developing pneumonia. Postinjury interventions are used to minimize the risk of aspiration, facilitate secretion clearance, decrease colonization of the respiratory tract, and facilitate opening of small airways and alveoli.

Treatment of established pneumonia includes antimicrobials and supportive therapies. Early appropriate treatment has been shown to be important in reducing mortality. Initial antimicrobial therapy is generally empiric and has broad coverage of gram-positive and -negative bacteria, and possibly anaerobes. Antifungal and antiviral therapies may be appropriate in some situations. Subsequently, the antimicrobial regimen should be tailored based on response to empiric therapy and culture results.

EPIDEMIOLOGY

Pneumonia is the most common cause of infection in surgery and trauma patients. The reported incidence and outcome of pneumonia following surgery and trauma depend on a variety of factors, including the diagnostic criteria for pneumonia, the surgical procedure or pattern and intensity of trauma, baseline host factors, and management strategies. Not surprisingly, critically ill patients with pneumonia have a particularly high mortality rate. However, for unclear reasons, nosocomial pneumonia has not been shown to be an independent risk factor for death.

The incidence of pneumonia following trauma has been reported to be as low as 4 percent, and as high as 87 percent. More recent studies suggest that the incidence in trauma patients is roughly 20 to 45 percent. The incidence of pneumonia is higher in patients cared for in the ICU. Head trauma patients are at highest risk of developing pneumonia. Several factors may contribute to the increased risk of pneumonia in head trauma patients. Intubation and mechanical ventilation, which are frequently required in patients with neurotrauma are known to increase the risk of pneumonia. In addition, altered levels of consciousness or impaired swallowing/airway reflexes due to localized neurological injuries may predispose patients to aspirate by impairing mechanisms involved in protecting the airway and clearing respiratory secretions. Trauma patients who develop pneumonia have a high mortality, although pneumonia is often not the direct cause of death. The mortality rate in trauma patients who develop pneumonia has been reported at approximately 44 percent versus 19 percent in trauma patients without pneumonia. The mortality rate is higher in patients who are infected with *Pseudomonas aeruginosa (P. aeruginosa)* or when there is associated bacteremia.

Pneumonia is currently the most commonly diagnosed postoperative infection, surpassing surgical wound, urinary tract, and bloodstream infections, which were more common than pneumonia in studies in the 1960s to 1980s. The postoperative nosocomial pneumonia rate has been reported in the approximately 1.5 to 20 percent. Pneumonia occurs more frequently in surgery patients with pre-existing lung disease and patients who undergo major upper abdominal or thoracic surgery. The mortality associated with postoperative pneumonia varies in different studies and has been reported at 20 to 50 percent. In one study, the mortality rate was reported at approximately 20 percent in surgery patients who develop pneumonia, and 2 percent in surgery patients without pneumonia.

RISK FACTORS

Numerous risk factors have been identified for the development of post-injury pneumonia (Table 126-1). Modifiable risk factors should be identified early so that preventive strategies can be implemented (Table 126-2). In some cases it may be appropriate to delay elective surgery to optimize the status of high-risk patients preoperatively.

Preinjury Risk Factors

Risk factors for development of postinjury pneumonia vary between surgery and trauma patients. Factors that have been shown to be associated with the development of pneumonia in trauma patients include: age greater than 55 years, low Glasgow coma score, head trauma, high injury severity score, blunt injury, shock, and emergency intubation. Pneumonia occurs most frequently in neurotrauma patients, perhaps due to aspiration resulting from a decreased ability to protect the airway, and increased need for emergency intubation.

Factors that have consistently been shown to increase the patient's risk of postoperative pneumonia include advanced age, pre-existing lung disease, a history of smoking,

Table 126-1

Factors that Increase the Risk for Nosocomial Pneumonia

Baseline Characteristics of Patient
- Age >55–60 years
- Preexisting lung disease
- History of smoking
- Obesity
- Poor nutritional status
- Immunocompromise
- High ASA* class

Operative Factors
- Emergency surgery
- Site/type of surgery: Highest with upper abdominal and thoracic surgery
- Anesthesia: General anesthesia

Trauma-Related Factors
- Aspiration during trauma
- Injuries to abdomen
- Injuries to chest
- Low Glasgow coma score

Post-Injury/Post-Operative Factors
- Prolonged intubation and mechanical ventilation
- Immobility
- Inadequate analgesia
- Enteral tubes and feeds
- Prior treatment with antibiotics
- Treatment with corticosteroids

*ASA = *American Society of Anesthesiologists.*

Table 126-2

Preventive Strategies

Preoperative and Intraoperative
- Optimize pulmonary status
  - Smoking cessation
  - Bronchodilators for COPD
  - Consider steroids for refractory wheezing in asthma patients
- Weight reduction
  - Decrease risk of aspiration during induction of anesthesia and intubation in patients with GE reflux, gastroparesis, full stomach
  - Metoclopramide to facilitate gastric emptying prior to induction
  - Consider rapid sequence induction of anesthesia and intubation with cricoid pressure throughout

Postoperative/Post-trauma
- Early ambulation
- Head of bed elevation
- Optimize analgesia
- Specialized beds: rotation and percussion
- Minimize antibiotics: limit duration of perioperative coverage if required
- Chest physiotherapy
- Oral antisepsis

obesity, poor baseline nutritional status, and immunocompromise. The baseline health status is clearly important. Additional factors that also have been reported to be associated with increased risk of postoperative pneumonia include weight loss over a 6-month period, long-term steroid use, recent significant alcohol use, and history of cerebrovascular accident or impaired sensorium. The American Society of Anesthesiologists physical status scale (ASA class) attempts to quantify patients' overall status preoperatively by assigning a score of 0 (no significant baseline medical problems) to 5 (moribund with little chance of survival). Studies suggest that the risk of postoperative complications is increased in patients with a higher ASA class.

Operative Risk Factors

The frequency of pneumonia is increased in patients undergoing emergency surgery. Various factors may contribute to pneumonia in patients undergoing emergency surgery. First, because time will not permit preoperative optimization, patients may be physiologically worse than patients who have been prepared for nonemergent surgery. Second, the nature of the process requiring emergency surgery is more likely to be associated with a worse overall physiological state. Third, patients undergoing emergency surgery often have a full stomach as they have not fasted preoperatively and may also have impaired gastrointestinal motility. This increases the risk of vomiting and aspiration during induction of anesthesia and endotracheal intubation.

The type of anesthetic may impact on postoperative pneumonia in patients who undergo nonemergent surgery. Studies suggest that the risk of pneumonia is higher in patients who undergo general anesthesia alone versus spinal or epidural anesthesia with or without general anesthesia. Patients undergoing upper abdominal, thoracic, neck, peripheral vascular, and neurosurgery have an increased likelihood of developing postoperative pneumonia. The risk of pneumonia is highest following upper abdominal and thoracic surgery. The risk of postoperative pneumonia is also increased in trauma patients who undergo craniotomy.

Trauma-Related Risk Factors

Pneumonia may result from aspiration at the time of or following trauma. Injuries to the chest or abdomen may predispose patients to respiratory infections because of inability to adequately clear secretions from the airways due to pain, and

inability to maintain adequate expansion of distal airways and alveoli, which is presumed to lead to atelectasis and collapse.

Postinjury Risk Factors

A variety of postoperative and post-traumatic causes may contribute to the development of pneumonia. Hospitalized patients have higher rates of colonization with gram-negative bacteria. The combination of increased oropharyngeal and gastric colonization, and decreased ability to clear secretions and fully expand small airways and alveoli probably contribute to the development of pneumonia. Normal host defenses that are designed to protect the airways from aspiration and facilitate clearance of microbes often are impaired. Factors that predispose include impaired immunity, the inability to protect the airway due to altered level of consciousness, inadequate cough and expansion of the lungs due to pain and splinting, and the presence of endotracheal tubes, which can provide a direct conduit for inoculation of microorganisms.

Immobility is an important factor in the development of pneumonia. Factors that contribute to immobility include inadequate pain control, weakness, alterations in level of consciousness, and the type of surgical procedure. Early ambulation and participation in efforts to mobilize secretions such as coughing or chest physiotherapy are important preventive measures. Adequate pain control to facilitate ambulation, coughing, and deep breathing decreases the likelihood of developing pneumonia in surgery and trauma patients. However, if narcotics are used in excess, they can depress the level of consciousness and impair the ability to protect the airway, and hence increase the risk of pneumonia.

The presence of devices such as endotracheal tubes and nasogastric tubes increase the risk for pneumonia. Intubation and mechanical ventilation has been reported to increase the risk three- to 21-fold, and the risk also increases with longer duration of intubation. The presence of nasogastric tubes and the use of enteral feeding also increase the risk. However, avoidance of enteral feeding is not encouraged since poor nutritional status and alternative options for nutrition (e.g., parenteral feeding) also increase the risk of infection. The supine position has also been shown to increase the risk of pneumonia in intubated and nonintubated patients perhaps due to increased tendency of gastric contents to regurgitate into the oropharynx. Many ICUs currently have protocols for routinely maintaining patients in a semirecumbent position, with the head elevated to 30 to 40 degrees, rather than in a fully supine position.

Gastric colonization with bacteria also may contribute to nosocomial pneumonia. In general, the stomach has an extremely low pH, which minimizes bacterial colonization of the stomach. The use of agents that alkalinize the stomach in order to prevent gastric stress ulcers increases gastric colonization with bacteria. Some reports suggest that ICU patients who are treated prophylactically for stress ulcer have a higher incidence of pneumonia. However, the populations under study may differ, and some studies suggest that trauma patients treated with H_2 receptor antagonists are not at an increased risk of developing pneumonia.

The in-hospital use of antimicrobial agents has been associated with an increased risk of nosocomial infections, including nosocomial pneumonia. Particularly in critically ill mechanically ventilated patients, the prolonged use of antimicrobial agents is thought to favor selection and subsequent colonization of the airways with multidrug-resistant pathogens. The use of broad-spectrum antibiotics has been shown to promote the occurrence of VAP from resistant strains of *P. aeruginosa*, *Acinetobacter* spp., and methicillin-resistant *staphylococcus aureus* (MRSA). A recent observational study of ICU patients identified the prolonged use of antibiotics and the use of quinolones as independent risk factors for the development of multidrug-resistant bacteria in tracheal aspirates, including MRSA, *P. aeruginosa*, *Acinetobacter* spp., and *Stenotrophomonas maltophilia*. In patients with acquired multidrug-resistant organisms, the infections were related to these organisms, longer duration of mechanical ventilation, and longer stay in the ICU are required.

Other factors that have been shown to be important include reintubation, tracheotomy, use of positive end-expiratory pressure, intense sedation, and the use of corticosteroids, muscle relaxants, barbiturates, and inotropic agents. However, many of these factors seem to reflect the poor overall status of the patient, and may not be directly responsible for causing pneumonia.

PATHOGENESIS

Environmental factors, the surgical procedure, the pattern and degree of traumatic injuries, and patient characteristics play a role in the development of pneumonia in trauma and surgery patients. Early pneumonia may result from gross aspiration at the time of the trauma, or during induction of general anesthesia. General factors that may contribute to the development of pneumonia include aspiration of colonized oropharyngeal secretions or inhalation of aerosolized matter, the inability of the patient to clear secretions, and impaired host immunity. Inadequate secretion mobilization may result from abnormal mucociliary function, inactivity, supine positioning, and inadequate cough due to weakness or splinting from pain.

Severe tissue injury causes generalized dysregulation of immunoinflammatory responses, which contributes to the development of infections in patients undergoing surgery or who have experienced trauma. It is currently believed that tissue injury activates a biphasic inflammatory response in which initial generalized hyperinflammation is followed by immunodepression. The generalized inflammation, or systemic inflammatory response syndrome (SIRS), leads to activation of the coagulation and complement cascades, and is believed to cause disturbances in microvascular blood flow, impaired use of oxygen, and to be responsible for the multiple organ dysfunction syndrome (MODS).

The anti-inflammatory response is characterized by increased levels of anti-inflammatory cytokines, decreased responsiveness of inflammatory cells to microbial toxins, and altered ratios of T-suppressor to T-helper cells. The immunodepression resulting from major trauma and surgery predisposes patients to the development of infectious complications, including pneumonia. Studies are currently underway to evaluate methods designed to restore proper balance to the immune system, so that there will be adequate defenses against infection without tipping the balance toward hyperinflammation (reviewed in Faist et al., 2004).

Numerous other factors also contribute to the development of pneumonia in particular situations. Prolonged intubation is known to increase the risk of VAP, probably through pooling and microaspiration of oropharyngeal secretions around the endotracheal tube cuff, and inoculation via devices such as suction catheters and bronchoscopes. Although there may be some advantage to the use of noninvasive ventilation in appropriately selected patients, studies do not support a strategy of noninvasive ventilation to avoid reintubation in patients who are failing extubation. In trauma patients with pulmonary contusions, lung lacerations, or pneumatoceles, the presence of blood or devitalized tissue provide conditions for bacterial growth leading to development of pulmonary infections.

MICROBIOLOGY

Pneumonia following surgery and trauma is most often caused by a mix of bacteria. Particular pathogens vary with the duration of hospitalization prior to the onset of infection, antecedent antibiotic treatment, and exposure to health care facilities. Early-onset pneumonia, which occurs within 4 days of hospitalization in patients who have not received antibiotics, is more likely to be caused by non–drug-resistant bacteria that had colonized the patient prior to admission. Pneumonia in the first week following trauma or surgery is most often caused by *Haemophilus influenzae*, *Staphylococcus aureus*, and *Streptococcus pneumoniae*.

Late-onset pneumonia, which occurs 5 or more days after admission, is more likely to be caused by multidrug-resistant bacteria. Common gram-negative bacterial pathogens include *Escherichia coli*, *Enterobacter* spp., *P. aeruginosa*, *Acinetobacter* spp., *Klebsiella pneumoniae*, and *Citrobacter* spp. *S. aureus* is the most common gram-positive pathogen in burn and surgical ICU patients. Methicillin-resistant *S. aureus* (MRSA) has increasingly become a problem in ICU patients. Recent studies suggest that more than 50 percent of *S. aureus* infections in the ICU are caused by MRSA. MRSA is also a common pathogen in head trauma patients. Anaerobic bacteria also have been cultured from respiratory secretions of patients with pneumonia, and may be important in the development of lung abscesses.

Fungi such as *Candida* spp. and *Aspergillus fumigatus* may cause pneumonia in patients who undergo organ transplantation, are neutropenic, or are otherwise severely immunocompromised. Although *Candida* spp. often colonize the respiratory tract of hospitalized patients, true *Candida* pneumonia is rare in immunocompetent patients.

CLINICAL FEATURES AND DIAGNOSIS

As mentioned, pneumonia in trauma and surgery patients is most often nosocomial, which is reviewed in detail in Chapter 130. Ventilator-associated pneumonia (VAP) is defined as pneumonia that occurs more than 48 hours after tracheal intubation. Since most clinical studies of nosocomial pneumonia have focused on VAP, our discussion of the diagnosis of pneumonia in surgery and trauma patients will focus on the entity of VAP.

Unlike community-acquired pneumonia, the diagnosis of VAP is difficult, and is still the subject of much debate. Clinically, the diagnosis of VAP includes three main components: a new or worsening consolidation on the chest radiograph, local (bronchial secretions) and systemic signs of infection, and microbiological evidence of respiratory infection. However, in trauma and surgical patients, systemic signs of inflammation can be virtually indistinguishable from infection (fever, leukocytosis, tachycardia, etc.). At one time, a dispute existed between those who favored a clinical versus a bacteriological diagnosis; it is now clear that a purely clinical diagnosis is no longer acceptable because of its low specificity in hospitalized, mechanically ventilated patients. Radiographic findings are notoriously nonspecific in critically ill patients and in those that have sustained chest trauma. Noninfectious infiltrates may be present in patients with pulmonary contusions, atelectasis or lobar collapse, or during episodes of congestive heart failure. Therefore, the clinical findings must be associated with definite microbiological evidence of deep seeded respiratory infection.

The current diagnostic debate in the literature is concerned with the type of bacteriological methodology that should be added to the clinical findings suggestive of nosocomial pneumonia. Although lung biopsy could be considered the gold standard diagnostic test, it is risky and impractical in most situations. The main available alternatives include: (1) blind tracheal aspiration of tracheobronchial secretions; (2) specimens of the distal airways by biopsy obtained using either broncho-alveolar lavage (BAL) or protected specimen brush (PSB), and (3) blindly collected specimens of the distal airways, or mini-BAL (Table 126-3). The major recommendations by experts concerning the use of these techniques have been published recently and can be summarized as follows:

1. Whenever possible, a sample of the distal airways should be obtained before starting or changing antimicrobial therapy. In principle, bronchoscopic techniques seem to be more reliable than blind techniques because they can direct the collection of

Table 126-3

Techniques Available to Sample Tracheobronchial Secretions to Diagnose Ventilator-Associated Pneumonia

	Advantages	Diagnostic Power	Disadvantages
Blind tracheal aspirate	Easy, safe, does not need a physician, rapid qualitative reading	High sensitivity (>90%), but high contamination rate—very low specificity	May lead to overuse of antimicrobial therapy
Bronchoscopic PSB	Lowest contamination from higher airways	Moderate sensitivity (90%), best specificity (≥90%)	24–48 hr wait for growth, technically difficult, expensive
Bronchoscopic BAL	Samples a large alveolar area, rapid qualitative reading	High sensitivity (>90%), moderate specificity because not protected	Time consuming, not ideal in unstable patients
Mini-BAL	Deeper than tracheal, protected, does not need a physician	Equivalent to BAL (small number of studies)	Blind, potential for inadequate sampling

specimens to the areas of the lung that the radiographs indicate are probably affected. However, this premise has not fully been confirmed by controlled studies. Non-protected specimens, such as those collected by simple bronchoscopy and BAL, can be contaminated by upper airway nonpathogens. The PSB yields the most specific results, but may decrease sensitivity somewhat because the specimen is limited in size and does not yield a result for 24 to 48 hours. Moreover, the PSB technique is somewhat cumbersome and expensive. BAL samples a larger area of the lung (including alveolar epithelium), and can be plated immediately.

2. Nonbronchoscopic sampling techniques of the distal airways (mini-BAL) are becoming popular because they are less labor intensive and can be safely and effectively performed by nonphysicians. Commercially available mini-BAL catheters enable protected collection of samples. The obvious concern with the use of these catheters is that they cannot be directed visually into the specific areas of the lung. However, a recent study has indicated that BAL specimens obtained using blindly inserted mini-BAL catheters and using bronchoscopy are equivalent.
3. Blind tracheal aspiration has the obvious advantage of being simple to implement and inexpensive. It has a high sensitivity for pneumonia, but low specificity. Consequently, blind tracheal aspiration tends to favor overuse of antibiotics, a known risk for nosocomial infection, including VAP. One situation in which tracheal aspirates may be almost equivalent in their specificity to the bronchoscopic techniques is during ongoing antimicrobial therapy, which tends to decrease the bacterial load in the airways.
4. Quantitative or semiquantitative cultures are suggested, as opposed to simple qualitative sampling.
5. Use of tracheal aspirates to guide therapy during the evolution of the process is not universally recommended, because of the lack of specificity of the technique, which will lead to unnecessary prolongation of therapy.

The distinction between aspiration pneumonitis and actual aspiration pneumonia can be difficult and is important in determining whether or not to initiate the use of antibiotics. Infectious and noninfectious pulmonary complications may result from aspiration during induction and tracheal intubation as well as at other times in the perioperative period. Aspiration pneumonitis, or Mendelson's syndrome, is a noninfectious chemical pneumonitis that results from aspiration of sterile gastric contents (reviewed in Marik PE, 2001). Aspiration pneumonia is an infectious process that results from aspiration of oropharyngeal or gastric secretions that contain bacteria. For both aspiration pneumonia and aspiration pneumonitis the chest radiograph may show an infiltrate in dependent portions of the lung, most often in the right lower lobe. Antibiotics are often begun in patients who have been witnessed to aspirate and are deemed to be at high risk of developing aspiration pneumonia; such patients include those who are immunocompromised or otherwise severely debilitated, are taking H_2 blockers or antacids, and/or have preexisting pulmonary disease. Antibiotics are often withheld in patients who have been witnessed to aspirate, but that do not have significant risk factors for developing pneumonia. In such patients, antibiotics are initiated only if there is failure of the pneumonitis to improve after 48 hours of observation.

Complications of pneumonia include acute lung injury/acute respiratory distress syndrome (ALI/ARDS),

empyema, lung abscess, and very rarely necrotizing (gangrenous) pneumonia.

PREVENTION

Preoperative/Intraoperative

Preoperative interventions, such as optimizing the pulmonary status, smoking cessation, and bolstering nutritional status may be indicated prior to elective surgery. Postoperative pulmonary complications have been shown to be decreased in COPD patients treated with bronchodilators preoperatively, and there is evidence that there are also fewer pulmonary complications in adequately treated asthma patients. In asthma patients with refractory wheezing, it may be appropriate to initiate corticosteroids prior to surgery and continue the steroids through the early postoperative period. Although smoking cessation has been shown to decrease the incidence of postoperative pulmonary complications, studies suggest that this decrease does not occur until more than 8 weeks following cessation.

Gastroesophageal reflux, gastroparesis, obesity, pregnancy, and emergency surgery increase the risk of aspiration during induction of general anesthesia and intubation. Measures to prevent reflux and aspiration should be considered preoperatively such as treating the patient with the promotility agent metoclopramide to facilitate gastric emptying. In addition, a rapid sequence induction with application of cricoid pressure should be considered in patients who are at high risk of vomiting and aspirating. The rapid sequence induction is generally accomplished by simultaneously providing the induction agent and muscle relaxant. In order to avoid distention of the stomach, the patient is then intubated without attempting to ventilate via a mask. Pressure is applied to cricoid cartilage on the anterior neck starting immediately before administration of induction agents throughout the entire induction and intubation to occlude the esophagus so that gastric contents do not reflux into the pharynx. This method of induction can be risky and have catastrophic consequences in patients who cannot be intubated and cannot be ventilated by mask. Thus, modifications may be appropriate depending on the patient's airway and pulmonary function/reserve.

A variety of interventions can be implemented following surgery or trauma to decrease the likelihood of developing pneumonia. The basic goals of these interventions are to: (1) prevent aspiration of colonized oropharyngeal or gastric secretions; (2) facilitate clearance of respiratory secretions; and (3) maintain adequate tidal volumes so that small airways and alveoli remain open to avoid atelectasis and collapse, which presumably provides good conditions for bacterial growth. Although the general principles of prevention are similar, the strategies used to prevent pneumonia vary based on the clinical status of the patient. For instance, nonintubated patients actively participate in prevention, whereas intubated patients play a more passive role. Other strategies include minimizing the duration of intubation, using specialized beds for percussion and oscillation to facilitate clearance of secretions, and oral decontamination with antiseptic.

1. **Early mobilization, including ambulation.** Patients who are not intubated and who are physically able to do so should begin to mobilize as soon as feasible after surgery and/or trauma. The measures include sitting at the edge of the bed or in a chair, and if possible, ambulating.
2. **Head of bed elevation.** Studies suggest that the frequency of pneumonia is decreased in patients who are maintained in a semirecumbent position, with the head of bed elevated at least 45 degrees, than in patients who are fully supine.
3. **Analgesia.** Adequate analgesia is required after surgery and trauma to allow patients to clear secretions through coughing and mobilization, and facilitate ventilation and prevent or correct atelectasis and collapse. A properly titrated analgesic should alleviate pain without sedating the patient. Excessive oversedation may lead to aspiration due to inability to protect the airway. Epidural analgesia may be of benefit in both surgery and trauma patients; a properly functioning epidural catheter should provide excellent analgesia without significantly affecting the sensorium.
4. **Rotational beds and percussion.** Specialized beds often are used to limit pooling of secretions and facilitate the clearance of secretions. Options include turning the patient, changing posture, and percussion.
5. **Chest physiotherapy (performed in both intubated and non-intubated patients).** It is believed to assist with mobilization of respiratory secretions and to prevent or facilitate expansion of atelectatic and collapsed areas of the lung.
6. **Oral antisepsis.** Oropharyngeal colonization has been shown to be an independent risk factor for the development of gram-negative pneumonia in ICU patients. Although oral antisepsis using chlorhexidine has been reported to decrease the rates of nosocomial respiratory infections in patients undergoing cardiac surgery, until now studies in ICU patients have not confirmed a decrease in pneumonia.

TREATMENT OF PNEUMONIA IN TRAUMA AND SURGERY PATIENTS

This section provides a general overview of the principles of treatment of pneumonia in surgery and trauma patients. A more comprehensive review of specific treatment protocols is discussed in Chapter 130. Early treatment with appropriate antibiotics significantly impacts on outcome, underscoring the importance of selecting particular antibiotics. Often

initial treatment must be empiric, without definitive culture data to guide therapy. Most empiric treatment is broad, covering gram-positive and -negative bacteria, and possibly anaerobes. When culture and sensitivity data become available, there should be a de-escalation of antibiotics. The final regimen should target individuals pathogens based on sensitivities to individual antibiotics and the regimen should be least likely to facilitate colonization and/or infection with more resistant bacteria.

The empirical choice of antibiotics in trauma and surgery patients is influenced by a number of factors, including the duration of hospitalization or exposure to health care facilities before the pneumonia, previous antibiotic treatment, prior culture results, the likely mechanism of the pneumonia (aspiration versus hematogenous spread versus invasion via a wound), and the presence of severe immunosuppression. The severity of illness may also factor into decisions about the choice of antibiotics and may prompt earlier empirical initiation of antibiotics. Empirical choices of antibiotics also must take into account the local flora and antibiotic resistance patterns that can vary considerably between different hospitals and communities. Much of the literature concerning treatment has focused on VAP, from which diagnostic and treatment strategies have been extrapolated and applied to the larger population of patients with hospital-acquired pneumonia.

Postoperative and trauma patients with pneumonia fall into two broad categories, which have important treatment implications. One category includes patients who develop pneumonia early during their hospitalization and have not had recent exposure to health care facilities. These patients are unlikely to be infected with multidrug-resistant pathogens; consequently they are not treated with empirical regimens that target resistant bacteria. The other group includes patients who develop HAP and VAP later during their hospitalization, and who therefore are likely to be colonized/infected with drug-resistant pathogens. These patients should receive broad-spectrum empirical therapy that targets multidrug-resistant bacteria. Empirical treatment with two agents against resistant gram-negative bacteria should be considered in patients who are severely ill and/or are likely to be infected with multidrug-resistant bacteria. Empirical treatment of pneumonia in patients who have recently received antibiotic should include an agent from a different antibiotic class.

Comprehensive guidelines for management of HAP, VAP, and HCAP and a comprehensive review of ventilator-associated pneumonia were recently compiled by a committee of experts from the ATS and IDSA. Important aspects of the guidelines include: (1) the early initiation of appropriate antibiotics; (2) tailoring empiric therapy to the likelihood of being infected with multidrug-resistant pathogens; (3) considering the use of combination antibiotic therapy for empiric or directed treatment of resistant gram-negative bacteria and for *P. aeruginosa*; (4) de-escalating therapy promptly when indicated by cultures of lower respiratory tract secretions and clinical response to therapy; (5) limiting the duration of therapy for "uncomplicated" pneumonia to 7 to 8 days to reduce the development of multidrug-resistant pathogens; and (6) considering using linezolid in lieu of vancomycin for treating MRSA VAP.

CONCLUSIONS

Pneumonia, a common problem following surgery or trauma, is associated with increased morbidity and mortality. Most instances of pneumonia in surgery and trauma patients are nosocomial because they occur more than 48 hours after admission to the hospital. However, pneumonia occurring early after surgery or trauma may be caused by the same pathogens that usually cause community-acquired pneumonia. Early pneumonia in patients who have not recently had significant exposure to a health care facility may be caused by non–drug-resistant microorganisms. Pneumonia that occurs later during hospitalization or in patients who have had significant exposure to health care facilities is more likely to be caused by antibiotic-resistant bacteria. This distinction has important implications when resorting to empirical antimicrobial therapy.

The diagnosis of pneumonia in patients who have experienced trauma or surgery can be difficult because the manifestations are non-specific. At present, the approach to the diagnosis is based on a combination of clinical, laboratory, and radiographic data. Sputum and blood cultures should be obtained before starting antibiotics to maximize the chance of identifying the pathogen. Initial treatment of pneumonia is usually empirical and uses broad-spectrum antibiotics that cover gram-positive and -negative aerobic and anaerobic bacteria. Subsequent antimicrobial therapy should be tailored to the pathogens identified in cultures of respiratory secretions or blood. Treatment with antiviral and/or antifungal agents may be appropriate in severely immunocompromised patients. When choosing antibiotics for the empirical treatment of pneumonia, it is important to take into account the local bacterial flora and patterns of antibiotic resistance.

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Pulmonary Infection in Immunocompromised Hosts

Jay A. Fishman

OVERVIEW

Prolonged survival of individuals with AIDS, after solid organ and bone marrow transplantation, with connective tissue diseases, primary immune deficiencies, and after intensive chemotherapeutic regimens for cancer, has greatly expanded the population of immunocompromised hosts. These patients are defined by their susceptibility to infection with organisms that have little native virulence for the normal host. The detection of underlying immune compromise has been facilitated by improvements in microbiologic techniques, particularly molecular assays, and advances in imaging. Survival has also been improved by the availability of new antimicrobial agents, including antifungal agents, macrolides, antivirals (ganciclovir, foscarnet, and oral agents),

hematopoietic growth factors, and highly active antiretroviral therapies (HAART) for HIV infection. The major challenges in these populations include systemic infections for which adequate therapies have not yet been developed (e.g., hepatitis C virus) and the progressive antimicrobial resistance of common pulmonary pathogens, including *Staphylococcus aureus*, Enterococcus, *Pseudomonas*, and *Stenotrophomonas* (formerly *Xanthomonas*) spp., and selection of novel strains of bacteria, including non-tuberculous mycobacteria and *Nocardia* spp. In addition, the incidence has increased of strains of streptococci (including pneumococci) resistant to antimicrobial agents used for routine prophylaxis (i.e., trimethoprim-sulfamethoxazole and quinolones). With the changing health care scene, medical care of immunocompromised individuals is increasingly managed outside of academic centers. Therefore, information about the clinical management of these patients has become increasingly important to the entire spectrum of medical practitioners.

GENERAL PRINCIPLES

Opportunistic Infection

Opportunistic infection is defined as an infection occurring in an individual as a result of a compromised immune function that would not be expected to occur or would cause disease of lesser intensity in the presence of normal immune function. Thus, immunocompromised individuals are subject to the common infections that are present in the community, but these infections are likely to be of greater frequency or severity than in the immunologically normal host. In addition, infection in these patients may be caused by organisms of low native virulence or that cause insignificant disease in the normal host, including such organisms as *Pneumocystis carinii (jiroveci)* or cytomegalovirus (CMV).

The risk of infection in any patient is determined by the interaction of two factors: the potential pathogens to which the individual is exposed (epidemiologic exposures), and a measure of the individual's susceptibility to infection, termed the "net state of immunosuppression" (Table 127-1). The occurrence of infection in an individual at a time when the immune status of the patient is thought to be nearly normal is evidence that either an excessive environmental exposure has occurred or that the immune status of the individual is depressed. Conversely, even minimal environmental exposures can cause invasive infection in an individual who is maximally immunosuppressed.

Epidemiologic Exposures

Epidemiologic exposures of importance to the immunocompromised patient can be divided into two general categories: those occurring within the community and those occurring within the hospital. Exposures within the community vary based on such factors as geography and socioeconomic status. Thus, opportunistic pathogens acquired in the community include the geographically restricted systemic mycoses (blastomycosis, coccidioidomycosis, and histoplasmosis), *Mycobacterium tuberculosis, Strongyloides stercoralis, Leishmania donovani, Pneumocystis carinii, Legionella* species, and community-acquired respiratory viral infections (e.g., influenza, respiratory syncytial virus, and parainfluenza). Common viral agents may include herpes simplex virus, cytomegalovirus, varicella zoster, and hepatitis B and C viruses. Due to the limited effectiveness of many vaccines in immunocompromised individuals, infections resulting from *Streptococcus pneumoniae* and *Haemophilus influenzae* are common.

Within the hospital, excessive environmental exposures can be divided into two general categories: domiciliary and non-domiciliary. Domiciliary exposures occur on the hospital unit where the patient is housed. When the air, food, equipment, or potable water supply is contaminated with pathogens such as *Aspergillus* species, *Legionella* species, or vancomycin-resistant enterococci, clustering of cases of infection in time and space are observed. As a result, an increased incidence of nosocomial pneumonia or catheter and wound infections may be seen. Non-domiciliary exposures occur when the patient is transported to contaminated operating rooms, radiology suites, or catheterization laboratories for procedures. Non-domiciliary outbreaks, although possibly more common, are more difficult to detect because of the lack of clustering on a particular hospital unit. The leading clue to the presence of a nosocomial hazard is the occurrence

Table 127-1

Factors in the Net State of Immune Suppression

Immunosuppressive therapy: dose, duration, temporal sequence
Underlying immune deficiency: autoimmune disease, functional immune deficits
Mucocutaneous barrier integrity: catheters, epithelial surfaces, devitalized tissue, fluid collections
Neutropenia, lymphopenia
Metabolic conditions Uremia Malnutrition Diabetes Alcoholism with cirrhosis
Viral infection: Cytomegalovirus Epstein-Barr Virus Hepatitis B and C Human immunodeficiency virus

of opportunistic infection in a patient whose net state of immunosuppression would not normally lead to such an event, or nosocomial infection with organisms not known to be present on the clinical unit on which the patient is housed.

Net State of Immunosuppression

The net state of immunosuppression (Table 127-1) is a concept that describes all of the host factors that determine infectious risk, including: the dose, duration, and temporal sequence in which immunosuppressive drugs are deployed; injuries to the primary mucocutaneous barrier to infection (e.g., indwelling catheters, gastrointestinal or bronchial anastomoses in organ transplant patients); neutropenia or lymphopenia; underlying immune deficiency; pulmonary aspiration injury; metabolic problems, including protein-calorie malnutrition, uremia, and, perhaps, hyperglycemia; the presence of devitalized tissues, and fluid collections (hematoma, effusions, ascites); and infection with immunomodulating viruses (cytomegalovirus or CMV, Epstein-Barr virus or EBV, hepatitis B or HBV, hepatitis C or HCV, and the human immunodeficiency viruses, HIV-1 and -2), which predispose to other opportunistic infections, and also to graft rejection and graft-vs-host disease. The sum of the congenital, metabolic, operative, and surgery-related factors is the patient's net state of immune suppression. Generally, more than one factor is present in each host; the identification of the relevant factors, and correction when possible, are central to the prevention and treatment of infection in these hosts.

For example, in the alcoholic patient with hepatitis C and cirrhosis who has undergone liver transplantation, the so-called net state of immune suppression includes immunosuppression needed to maintain graft function, immune deficits caused by cirrhosis and chronic illness; immunologic and inflammatory effects of infection by hepatitis C virus; exposure to, and colonization with, community-acquired and nosocomial organisms; and new infections (e.g., spontaneous peritonitis) that may occur during the prolonged waiting period for a compatible organ. When the organ for transplantation does become available, it may arrive contaminated by organisms acquired by the donor during hospitalization. This gravely ill patient is then subjected to a major surgical procedure. After surgery the lungs are apt to be compromised, recovery of function in the allograft is often slow, immunosuppressive drugs are initiated, biliary (T-tube), intravenous, and urinary catheters are placed, and major incisions need to heal. Drug toxicities at this stage are common, often resulting in neutropenia and hepatitis. Biliary function and anastomotic integrity are assessed by injecting contrast dye into ducts and tubes (e.g., T-tube cholangiogram) that are colonized by native and nosocomial organisms. The sum of the underlying, operative, and transplant-related factors is the *net state of immune suppression.* Thus, the spectrum of susceptibility to infection is a *continuum* from individual deficits (e.g., viral upper respiratory infection that paves the way for bacterial superinfection) to multiple simultaneous deficits (e.g., the transplant recipient).

Timetable of Infection

In the broad spectrum of immunocompromised hosts, the risks of infection may be *relatively stable* over time, as in the diabetic with vasculopathy and neuropathy who is prone to skin and soft tissue infections. The risks of infection may be *time limited,* as in the postsurgical patient without complications or in the autologous bone marrow transplantation recipient with effective engraftment. The risk of infection may be *cumulative and progressive,* as in the AIDS patient, in whom infection is a function of declining immunity (without therapy), falling CD4 lymphocyte counts, rising viral loads, and the effects of other persistent infections (CMV, *Cryptosporidium*) (Fig. 127-1). In these individuals the occurrence of new infections suggests the progression of immune compromise. The risks may also be *progressive but not cumulative.* Thus, the risks of infection in the recipient of allogeneic stem cell or solid organ *change predictably with time* as a function of the evolving condition of the patient. For example (Fig. 127-2), in the early phase after hematopoietic stem cell transplantation (HSCT), infection is often the result of nosocomial exposures during neutropenia. Subsequently, following marrow engraftment but in the absence of preformed cellular immunity, viral pneumonitis (CMV) and hepatic veno-occlusive disease may occur. Finally, during the development of, and treatment for, acute and chronic graft-vs-host disease, susceptibility to infection is a function of immune suppression and mucosal injuries (possibly from chemotherapy, radiation, or infections such as *C. difficile* colitis).

With standardized immunosuppressive and chemotherapeutic regimens, specific types of infections often occur in a predictable pattern (time line) as a reflection of the specific risk factors (surgery, immune suppression, acute and chronic rejection, re-emergence of underlying diseases, viral infections—see Figs. 127-1 and 127-2) present at each phase of the post-transplantation course. The patterns have been altered by the availability of a broader range of immunosuppressive and chemotherapeutic agents, the use of stem cells instead of marrow for transplantation, and antimicrobial prophylaxis. However, the general concepts and major determinants of infection remain the same—the exogenous immune suppression or chemotherapy and any additional immune suppression used to treat either graft rejection or graft-vs-host disease. Superimposed viral infections will enhance the risk of infection at any point along the time line.

Because each risk factor renders the patient susceptible to infection by new groups of pathogens, *infections occurring with the "wrong" pathogen or at the wrong time suggest an undiscovered immune deficit (fluid collection, neutropenia) or an unusual epidemiologic exposure.* the occurrence of specific infections can be prevented by the use of antimicrobial prophylaxis, vaccines, and behavioral modifications (e.g., no raw vegetables or digging in gardens without masks). This results in a shift to the right of the time line—infections generally observed later in the course of disease or therapy are observed at the appropriate time *in the absence of infections that tend to occur earlier* but have been prevented by a variety of preventive

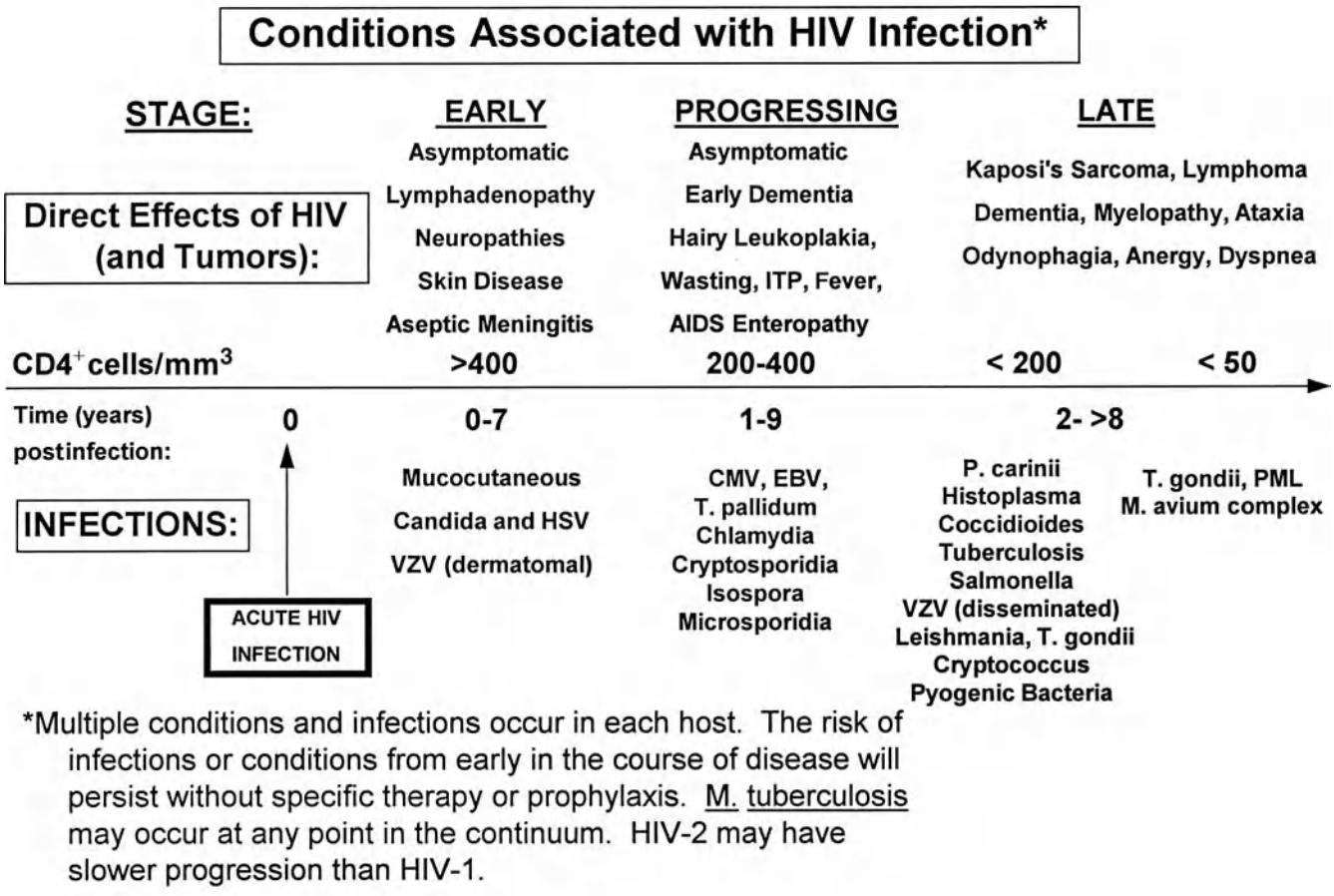


Figure 127-1 The progression of AIDS-associated conditions.

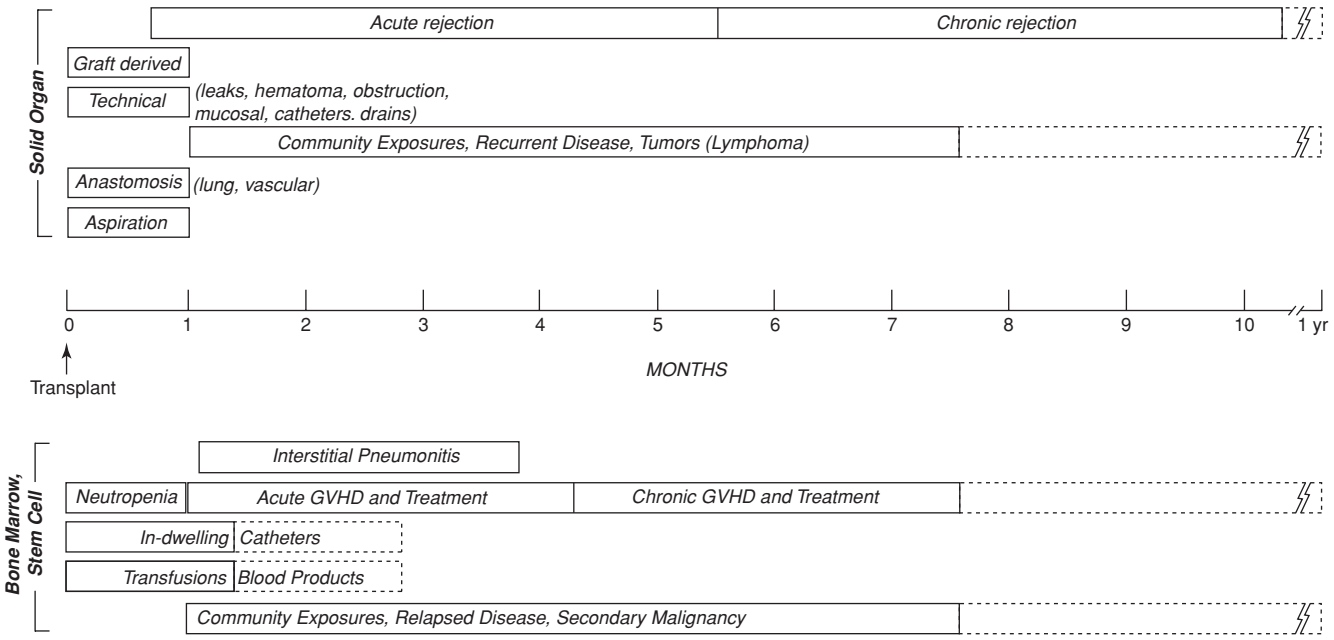


Figure 127-2 The timeline of conditions predisposing to infection in solid organ transplantation (above the timeline) and in bone marrow and stem cell transplantation (below the timeline). Patients will vary in individual susceptibility patterns.

measures. the timetables presented in Figs. 127-1 and 127-2 are useful in a number of regards:

1. Developing a differential diagnosis for infectious syndromes by time post-transplant: What type of infection is most likely at various times after transplantation.
2. Identification of excess epidemiologic hazards
   - Nosocomial: Aspergillus, MRSA, VRE: Clustered in time and space, by inpatient unit, procedures, or surgical suite
   - Community: Influenza, RSV, Legionella outbreaks
   - Individual: Unique exposures, travel, occupational hazards
3. Excessive immune suppression: Too many infections, too severe, or at the wrong time on time line suggests that a problem exists with immunosuppressive regimens used by a program.

MICROBIAL VIRULENCE AND INFECTION

The risk of infection in any individual patient depends not only on the sum of the immune deficits and the nature, duration, and intensity of the exposures to potential pathogens, but also on the *virulence* of the organism. Recent data suggest that the *specific host-pathogen interactions* are a critical factor in the development of infection. Such factors as the distribution of toll-like receptors, microbial production of biofilm, or antimicrobial resistance influence the pathogenesis of infection. Host cells may *enhance* the virulence of the invading organism by the *induction of genes in that organism* that contribute to bacterial persistence or invasion. Thus, resistance to phagocytosis is induced by target cells in *Yersinia* infections. Also, the survival of uropathogenic *E. coli* in urine and the growth of pili for attachment are induced by contact with the targeted uroepithelial cells. Another example of the host-pathogen interaction is the role of cytomegalovirus (CMV) in transplantation. CMV is the cause of common clinical syndromes that frequently occur in immunocompromised patients. Among these are pneumonitis, hepatitis, glomerulonephritis, gastritis, colitis, retinitis, and mononucleosis-like syndromes. CMV also induces an array of host responses (i.e., neutropenia, immune suppression, up-regulation of histocompatibility antigens and other cell surface antigens, TNFα secretion, graft rejection) that contribute to the host's susceptibility to infection (Table 127-2). Thus, the concept of immune status balanced against epidemiologic exposure may be incomplete: The immunoregulatory effects of some pathogens and the interaction of the organisms with the "correct" target cells of the host are best regarded as only part of the response to opportunistic infection.

Physical defects may also contribute to virulence. Foreign materials (vascular grafts, sutures, and eye or limb prostheses) may provide a nidus for infection by an organism that would not be capable of causing infection under normal conditions. Local immune defects coupled to physical factors may predispose to life-threatening infection. Thus, corticosteroid eye drops used for inflammation due to prosthetic lens implants may lead to eye infections with *Streptomyces, Bartonella, Sporothrix,* and *Fusarium* species. *Salmonella* infection in the organ transplant recipient "homes" to vascular anastomoses and may persist despite appropriate therapy, causing mycotic aneurysms.

Table 127-2

Effects of Viral Infection in the Immunocompromised Host

Direct causation of invasive viral infection
Immunomodulatory effects Systemic immune suppression—opportunistic infection Allograft injury Cellular effects—up-regulation of surface antigens and graft rejection
Oncogenesis and cellular proliferation Hepatitis B: hepatocellular carcinoma Epstein-Barr virus: B-cell lymphoproliferative disease (PTLD) Papillomavirus: squamous cell carcinoma, anogenital cancer HHV8 (KSHV): Kaposi's sarcoma, effusion lymphoma Cytomegalovirus: accelerated atherogenesis, bronchiolitis obliterans

PROTECTING THE PATIENT FROM INFECTION

Although the clinical care of the compromised host has improved, flaws in the armamentarium against infection have been highlighted by the emergence of bacteria and fungi that are resistant to common antimicrobial agents. For example, increasingly *Streptococcus pneumoniae* and *Neisseria gonorrhoeae* are detected that are resistant to penicillin, fluoroquinolones, and macrolides; enterococci are resistant to β-lactam antimicrobials, macrolides, vancomycin, teicoplanin, linezolid, quinupristin-dalfopristin, and aminoglycosides; *Pseudomonas* and enteric gram-negative bacteria are resistant to broad-spectrum β-lactam agents; and azole-resistant yeasts, all of which are routinely isolated both in the community and hospitalized patients. Moreover, decreases in the acquisition of infection by compromised hosts can only be accomplished by *complete* reverse precautions that entail the use of laminar airflow rooms and access to the patient only via glove-ports or the use of gowns, gloves, masks,

caps, and shoe covers. This practice reduces the incidence of hospital-acquired infection (as distinguished from spread of endogenous infection) by up to 50 percent, to the approximate rate of such infections in granulocytopenic patients.

However, the practice of *complete* reverse precautions is very costly and reduces patient contact by health care providers. Consequently, protection against both acquired and endogenous infections has fallen onto the broad use of prophylactic antimicrobials. Such oral agents as trimethoprim-sulfamethoxazole, quinolones, acyclovir (and related agents), and azole antifungal drugs now have widespread use in the management of both inpatients and outpatients. Oral decontamination regimens (i.e., nonabsorbable antimicrobials) have not been proved to prevent disease beyond limited periods of time, and are poorly tolerated because of taste, consistency, malabsorption of glucose and xylose bases, and cost. Moreover, the use of such prophylactic agents contributes to the emergence of antimicrobial-resistant organisms.

RECOGNITION OF NEW SYNDROMES

The identification of *new* infectious disease syndromes has often occurred in individuals with immune deficits. Thus, the cluster of cases of *Pneumocystis carinii* pneumonia in homosexual males was the first indicator of a new viral pathogen (HIV-1), and the role of *Cryptosporidium* as a common cause of diarrhea in both normal and compromised individuals was elucidated as a result of diarrheal disease in AIDS patients in the 1980s. Similarly, many uncommon bacteria (*Bartonella* species, *Rhodococcus equi*), viruses (Kaposi's-associated human herpesvirus 8, polyoma viruses), fungi *(Penicillium),* and parasites *(Microsporidia)* have been identified in immunocompromised patients. Thus, a continuing lookout for new pathogens or novel presentations of known pathogens is essential for the care of the immunocompromised patient. Often, infection in immunocompromised hosts presents without the expected signs and symptoms of infection. This lack of clinical manifestations may delay identification of the critically ill patient. In the outpatient setting, the practitioner must have a low threshold for performing tests (e.g., blood counts, cultures, radiographs) on patients with minimal complaints.

CONCOMITANT PROCESSES

Early and aggressive therapy of infection is required in the immunocompromised patient. Thus, most febrile or possibly infected patients are treated empirically while awaiting data that identify specific pathogens. The occurrence of multiple simultaneous infections or conditions often complicates and delays appropriate therapy (Fig. 127-3). For example, CMV infection may complicate the treatment of graft rejection or graft-vs-host disease and contribute to the pathogenesis of *Pneumocystis* or *Toxoplasma* pneumonia.

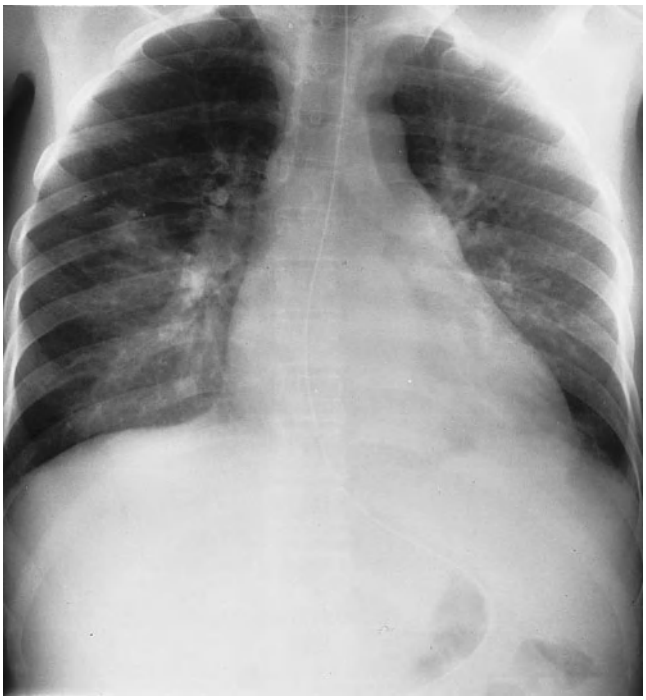


Figure 127-3 Chest radiograph of a 48-year-old heterosexual man with community-acquired pneumonia unresponsive to therapy. The patient was diagnosed as having AIDS on the basis of HIV seropositivity, CD4 lymphocyte count of 113 per milliliter, and *Pneumocystis carinii* and *Mycobacterium avium-intracellulare* complex pneumonia.

The radiologic appearance of pneumonia is altered by immune suppression (Fig. 127-4) (see also Chapter 114). Radiographic patterns may change during the care of the patient (e.g., cavitation of pulmonary nodules after the resolution of neutropenia). Noninfectious causes of pulmonary infiltrates may coexist with infection, and atypical patterns predominate. Drug toxicities (bleomycin, Cytoxan, sulfa drugs), leukoagglutinin reactions, radiation injury, pulmonary emboli, and lesions of metastatic cancer may coexist with opportunistic infection (Fig. 127-5). The typical evolution of pulmonary infection may be altered by the presence of underlying (e.g., interstitial) pulmonary disease as well as by diminished inflammatory responses. It is commonly necessary to repeat tests, to utilize computed tomography (CT), or invasive diagnostic modalities (biopsy) in the evaluation of the patient who is unresponsive to therapy. In the compromised host with fever and pneumonitis, chest radiographs may be difficult to interpret.

Complications of therapy may contribute to the development of new infections: Trimethoprim-sulfamethoxazole can cause pneumonitis, hepatitis, or Stevens-Johnson syndrome; ganciclovir can cause neutropenia; transfusion reactions can cause pulmonary infiltrates and hemolysis; cyclosporine can cause hemolytic-uremic syndrome; antimicrobials can contribute to thrush and *C. difficile* colitis.

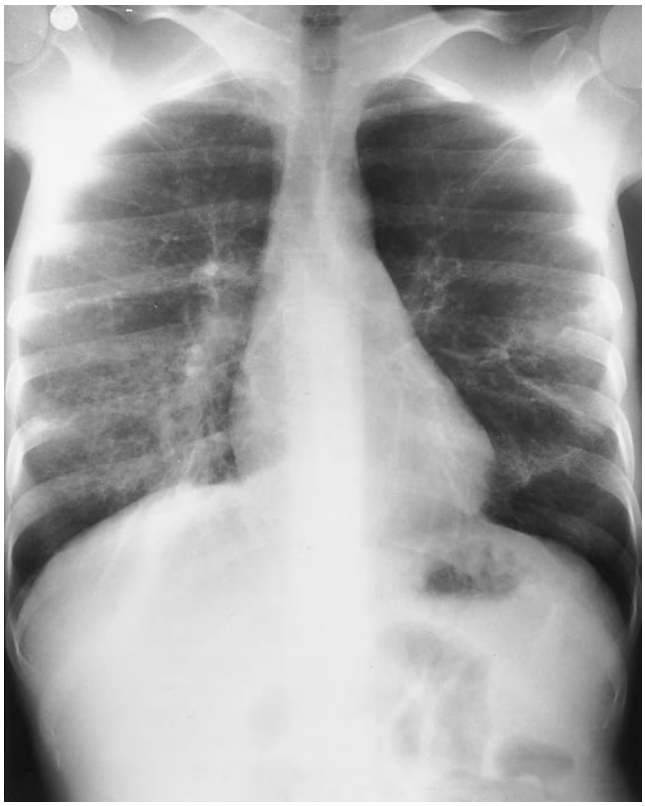


Figure 127-4 Chest radiograph of an AIDS patient with atypical cryptococcal pneumonia. Diffuse interstitial infiltrates may be observed in fungemic patients with primary or secondary pulmonary infection.

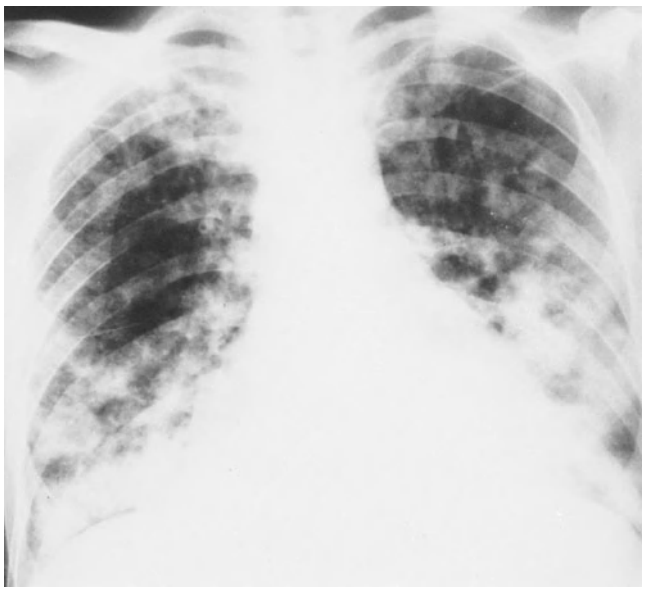


Figure 127-5 Chest radiograph of a 36-year-old homosexual man not known to be HIV-1 infected, with bilateral nodular infiltrates due to pulmonary Kaposi's sarcoma.

PATIENT MANAGEMENT

Antimicrobials alone may not suffice in the treatment of infection in the immunocompromised host. Improvement in host responses is often needed to clear ongoing infection. Infections may respond to a decrease in exogenous immune suppression, correction of neutropenia by growth factors, or treatment of simultaneous infections that predispose to superinfection (e.g., respiratory syncytial virus, CMV). Drainage of collections of infected fluid such as a hematoma or a lymphocele, or removal of drains or catheters enhances the treatment of infection. Identification of metastatic sites of infection (e.g., infections of the central nervous system due to *Nocardia* or *Cryptococcus* species) may facilitate management. Synergistic antimicrobial therapy must be used when available. Compromises often must be made. The loss of renal function due to antimicrobials used in the treatment of fungal infections significantly hinders patient management. However, progression of a fungal infection while on inadequate doses of amphotericin must be avoided.

Infection must be prevented in the susceptible host, since antimicrobials are often ineffective during acute infection. Whenever possible, vaccines should be given before immune suppression or splenectomy. During immune suppression, only killed or conjugate vaccines should be used. Repletion of immunoglobulin deficiencies (after BMT or solid organ transplantation) and the use of specific hyperimmune globulins (i.e., for exposure to varicella or for CMV) may help to prevent infection. Similarly, in patients susceptible to infection, the use of antimicrobials to prevent common infections is cost effective. The use of preemptive therapies based on tests that demonstrate the presence of infection (e.g., the administration of ganciclovir in patients with evidence of CMV infection by antigenemia assays or polymerase chain reaction studies) allows the interruption of infection before disease becomes manifest clinically. Similarly, routine surveillance cultures have been useful to detect specific pathogens in subgroups of patients (e.g., neutropenic patients with *Aspergillus* colonization) or in specific geographic regions.

The clinical *evaluation of the patient prior to immune suppression* may be very helpful in preventing disease. Patients with cystic fibrosis or chronic bacterial sinusitis may become colonized in the airways or sinuses with *Pseudomonas* or *Aspergillus*s pecies. These colonizing organisms may reactivate during immune suppression. Careful evaluation by radiography and invasive cultures may prevent major infection. Similarly, patients who are not immune to varicella zoster *may* benefit from vaccination. Patients seronegative for *Toxoplasma gondii* or CMV are at high risk of reactivation in the presence of an organ transplant from a seropositive donor. Similarly, seropositive patients with AIDS or before seronegative bone marrow transplantation are at high risk for reactivation disease due to *Leishmania,* CMV, or *Toxoplasma.* In endemic areas, transfusions and transplants may provide entry of *T. gondii, Trypanosoma cruzi* (Chagas' disease),

Leishmania species, *Acanthamoeba, Naegleria, Strongyloides stercoralis, Taenia* species, or *Echinococcus* species with exacerbation of infection by immune suppression. A careful clinical history and pretreatment of known infections or specific antimicrobial prophylaxis may prevent such complications of immune deficiency. Serologic tests are often useful in the stratification of risk for infection in the immunocompromised host.

GENERAL CONSIDERATIONS IN SPECIAL HOSTS

The spectrum of common infections varies with specific immune defects in each type of host (Table 127-3) and are considered subsequently.

HIV Infection and AIDS

The management of HIV infection has been dramatically altered for those individuals with access to antiretroviral therapies and is covered in detail by Fangman and Sax in Chapter 128. Anti-HIV therapy should be started before the immune system is irrevocably compromised. Most practitioners are treating all individuals with progressive HIV infection, and all HIV-infected individuals with CD4 counts below 200/mm^3. HAART has resulted in the recrudescence of immunity as manifested by rising CD4+ lymphocyte counts and diminished signs of opportunistic infection and cancer associated with severe T-cell deficits. Treatment of HIV infection with highly active antiretroviral therapy (HAART) with reversal of immune deficiency appears to eliminate the risk of *Pneumocystis* pneumonia (studied up to 2 years) in AIDS patients with and without prior *Pneumocystis* pneumonia. The risk of *Mycobacterium avium* complex, tuberculosis, and

Table 127-3

Infections Associated with Specific Immune Defects

Defect	Common Causes	Associated Infections
Granulocytopenia	Leukemia, cytotoxic chemotherapy, AIDS, drug toxicity, Felty syndrome	Enteric gnr, *Pseudomonas, S. aureus, S. epidermidis,* streptococci, *Aspergillus, Candida,* and other fungi, *S. aureus, Candida, streptococci*
Neutrophil Chemotaxis	Diabetes, alcoholism, uremia, Hodgkin's disease, trauma (burns) lazy leukocyte syndrome, CT disease	
Neutrophil killing	CGD, myeloperoxidase deficiency	*S. aureus, E. coli, Candida, Aspergllus, Torulopsis*
T-cell defects	AIDS, congenital lymphoma, sarcoidosis, viral infection, CT ds, organ transplants, steroids	Intracellular bacteria (*Legionella, Listeria,* mycobacteria), HSV, VZV, CMV, EBV, parasites (*Strongyloides, Toxoplasma*), fungi (*P. carinii, Candida, Cryptococcus*)
B-cell defects	Congenital/acquired agammaglobulinemia, burns, enteropathies, splenic dysfunction, myeloma, ALL surgery, sickle-cell anemia, cirrhosis	*S. pneumoniae, H. influenzae, Salmonella,* and *Campylobacter* spp., *Giardia lamblia*
Splenectomy		*S. pneumoniae, H. Influenzae, Salmonella* spp., *Capnocytophaga.*
Complement	Congenital/acquired defects	*S. aureus, Neisseria* spp., *H. influenzae, S. pneumoniae*
Anatomic	IV/Foley catheters, incisions, anastamotic leaks, mucosal ulceration, vascular insufficiency	Colonizing organisms, resistant nosocomial organisms

cytomegalovirus (CMV), has also decreased. Thus, prophylactic (both primary and secondary) and therapeutic regimens must be considered in light of the individual's immune status. Not all patients respond to HAART or maintain viral suppression during therapy. The specifics of antiviral therapy are not considered here.

One of the features of HAART is a syndrome of intensified inflammatory responses referred to as the immune reconstitution syndrome, which generally occurs within the first 3 months of starting effective antiretroviral therapy. This is thought to represent a hyperacute response to pathogens to which the HIV-infected individual has been exposed. It has been observed in *P. carinii* pneumonia, cytomegalovirus retinitis and vitreitis, disseminated *Mycobacterium avium* complex (MAC) as pneumonitis and lymphadenitis, cryptococcosis with meningitis and necrotizing lymphadenitis, and with acceleration of hepatitis C virus infection, including cryoglobulinemia and renal failure. Thus, effective antiviral therapy may result in more intense symptoms and unusual manifestations of some opportunistic infections while the overall incidence of new infections has declined.

HIV testing should be considered for all persons either in high-risk groups or with unusual infections. High-risk groups include intravenous drug users, sexually active homosexual or bisexual men, hemophiliacs or individuals requiring blood or clotting factors, persons with sexually transmitted diseases (especially syphilis), pregnant women, health care workers with exposure to body fluids or needle stick injury, and all patients with conditions commonly associated with AIDS (Table 127-4). Testing for HIV infection is generally divided into viral culture assays (uncommon now that molecular resistance tests are available), antibody tests, and specific, quantitative (molecular) viral tests, including molecular antiviral susceptibility testing. Most patients produce antibodies to HIV within 6 to 8 weeks, and almost 100 percent have detectable antibodies by 6 months after exposure. These tests are well standardized and easy to perform, but are troubled by false-positives (cross-reacting antibodies) and false-negatives (e.g., in the early period). Between 4 and 20 percent of Western blot tests are *indeterminate* because of seroconversion in progress, loss of antibody in advanced HIV disease, cross-reacting antibodies in pregnancy, blood transfusions, autoantibodies from collagen vascular disease, infection with HIV-2, recent influenza vaccination, or trial HIV vaccines. These subjects should be retested and inconclusive assays resolved with specific viral (molecular, p24 antigen, or culture) testing. *Specific viral tests* include the p24 antigen detection, molecular amplification by PCR, and culture-based assays. These are positive earlier than the antibody tests and therefore may be useful in primary infection before the development of antibody; they have high sensitivity (95–99 percent) and are often useful when the Western blot is indeterminate. Quantitative techniques are very useful in assessing the response to antiviral therapy and disease progression.

Measures of HIV viral RNA in plasma may not correlate with the CD4 lymphocyte count. The CD4 count provides a surrogate marker for the response to antiviral therapy and

Table 127-4

When to Suspect HIV Infection and AIDS

- History
  - High-risk behaviors or exposures
    - Unsafe or promiscuous sex
      - Sex with prostitutes
      - Sex with person at risk for HIV
    - Injection drug use
    - Blood or blood product transfusion between 1975 and 1985 (especially in high-prevalence areas)
    - Blood clotting concentrate transfusion before January 1985
  - Sexually transmitted disease
  - Tuberculosis, especially extrapulmonary
  - Racial and ethnic minority populations in high-prevalence areas of HIV disease
  - Homeless persons in high-prevalence areas of HIV disease
  - Individuals from high-prevalence areas for heterosexual transmission
- Symptoms and signs
  - Acute retroviral syndrome
  - Unexplained constitutional symptoms
    - Fatigue, malaise, fever, diarrhea, night sweats, anorexia, weight loss
  - Lymphatic
    - Persistent generalized lymphadenopathy
  - Dermatologic manifestations
    - Infectious
      - Severe herpes simplex (oral, anogenital), oral or genital candidiasis, staphylococcal skin infections, herpes zoster (especially recurrent), superficial dermatophytoses (tinea nail infection), molluscum contagiosum, warts, condyloma acuminata, oral hairy leukoplakia (EBV), necrotizing gingivitis or periodontitis
      - Kaposi's sarcoma, petechiae (ITP), seborrheic dermatitis, psoriasis (new or worsening), eosinophilic folliculitis, severe drug eruptions, aphthous ulcers, intraepithelial neoplasia
  - Neurologic conditions
    - Cranial neuropathy, Guilian-Barré syndrome, aspectic meningitis, peripheral neuropathy, myopathy, cognitive impairment
- Laboratory findings
  - Unexplained anemia, leukopenia, lymphocytopenia, atypical lymphocytosis, thrombocytopenia
  - CD4 lymphocytopenia
  - Polyclonal hyperglobulinemia
  - Elevated blood urea nitrogen or serum creatinine, proteinuria, hypoalbuminemia
  - Elevated lactate dehydrogenase
  - Hypocholesterolemia and hypertriglyceridemia

the risk of infection and death. At present, the best predictive value of testing is the combination of viral load with CD4 lymphocyte enumeration. Viral RNA levels in long-term nonprogressors are consistently under 10,000 copies per milliliter, whereas progression and immunologic deterioration are often associated with loads over 50,000 to 100,000 copies. Patients with viral loads of 10,000 to 50,000 are considered at intermediate risk. Viral load changes generally precede CD4 count changes. Immune alterations due to infection (e.g., cytomegalovirus) or immune modulation therapy (interferons) are not yet interpretable.

Immunization is a part of the routine management of AIDS. In general, HIV-infected persons are susceptible to the same community-acquired respiratory pathogens (with additions) as the normal host but with a greater severity of disease. Thus, patients should be vaccinated early in the course of disease when they are clinically stable. Live vaccines are generally contraindicated, but measles vaccine is generally well tolerated in children, and MMR is recommended for unvaccinated adults born after 1957 or vaccinated between 1963 and 1967. The efficacy of vaccination in this population is not clear; HIV viral loads may temporarily increase after vaccination. However, general practice suggests that pneumococcal, influenza (inactivated whole virus and split virus vaccines), *Haemophilus influenzae,* hepatitis B recombinant vaccine, and MMR be given as indicated.

Underlying lung disease is common in HIV-infected patients even before the development of opportunistic infection. Although FEV_1 and FVC are nearly normal, 11 to 13 percent of patients with CD4 lymphocyte counts below 200 per mm^3 or with a history of AIDS-associated extrapulmonary diseases (including thrush and varicella zoster infections) and weight loss have decreased D_{LCO} measurements. Intravenous drug users have a higher incidence of abnormal FVC, FEV_1, and D_{LCO} measurements (33.3 percent), consistent with patterns of cigarette smoking and racial distribution. Thus, susceptibility to pulmonary infection is further exacerbated in this population and the importance of vaccination increased.

Opportunistic Infections in AIDS

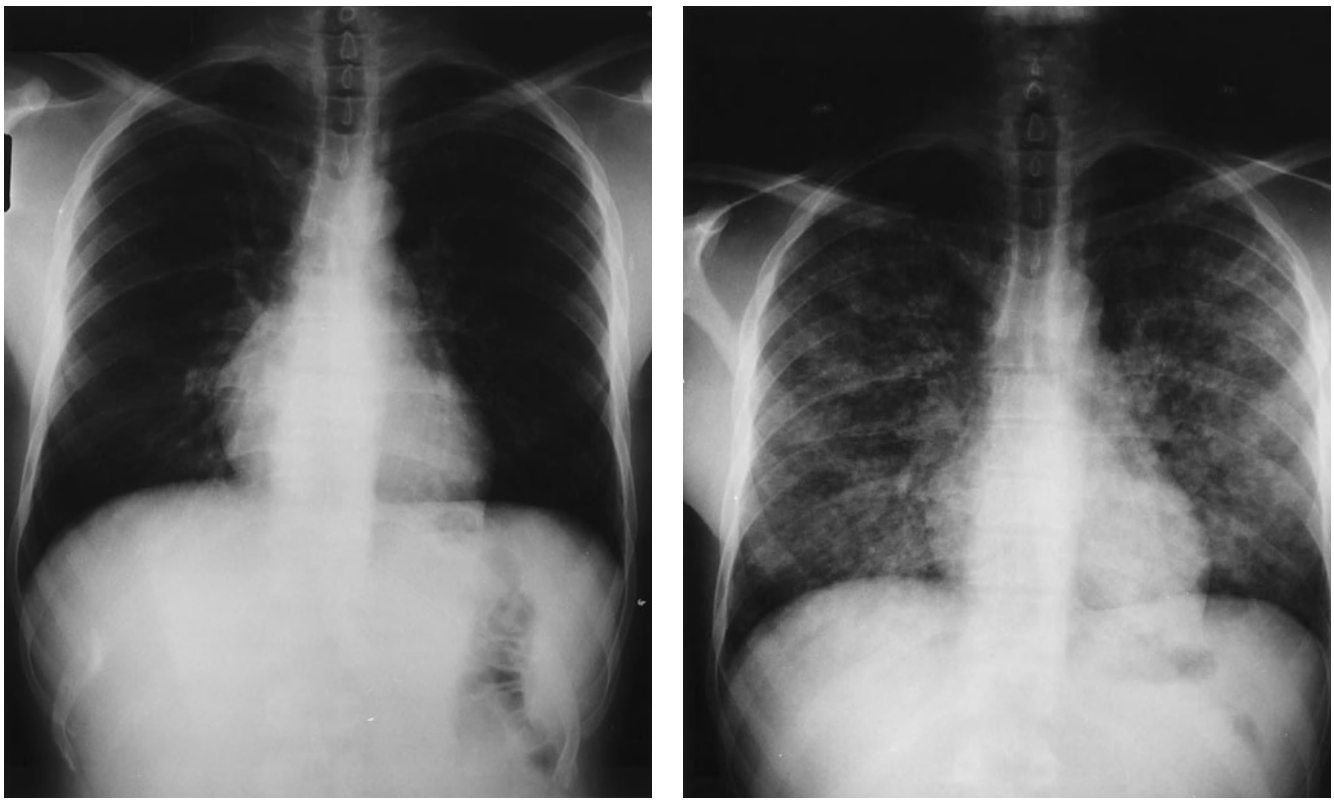
The problem of opportunistic infection in the *untreated or newly diagnosed AIDS patient* is unique because of the *progressive decline* in immune function when compared with the intermittent compromise seen after chemotherapy or the relatively stable immunosuppression used after solid organ transplantation. This progression appears to have been reversed by HAART, but such therapies are far from universally available. Specific opportunistic infections depend on the nature and duration of immune suppression as well as on the infectious exposures of the patient (Table 127-5). As a result of the progressive and cumulative risks, the incidence of opportunistic infections *increases* over time. A time line exists for the common infections and noninfectious manifestations seen in progressive AIDS, relating to the total CD4 lymphocyte count as a measure of susceptibility (Fig. 127-1). In an individual, the time line is also related to the patient's viral load, but an exact correlation does not exist. The specific pattern of opportunistic syndromes changes for individual patients, but it reflects the overall progressive immunological deterioration of untreated AIDS.

Many opportunistic pulmonary infections in AIDS patients were initially assumed to be reactivation of latent infection. However, some of these processes—including *P. carinii, T. gondii,* tuberculosis, and histoplasmosis—represent a mix of both new exposures and old disease. Similar observations have been made in terms of the drug susceptibility of mycobacterial isolates in recurrent disease (Fig. 127-6). The clinical manifestations of opportunistic infections in AIDS are

Table 127-5

Infectious Agents Commonly Associated with AIDS

Viral (with HIV-1, HIV-2)
Cytomegalovirus
Herpes simplex
Varicella zoster
Epstein-Barr virus
Parvovirus B19
HHV-6, HHV-8
HTLV-1, HTLV-2
Protozoan
Toxoplasma gondii
Cryptosporidium
Isospora belli
Microsporidium
Cyclospora
Fungal
Candida spp.
Cryptococcus neoformans
Histoplasma capsulatum
Blastomyces dermatidis
Aspergillus spp.
Petriellidium boydii
Coccidioides immitis
Penicillium spp.
Pneumocystis carinii
Sporothrix schenckii
Bacterial
Mycobacterium avium-intracellulare complex
M. tuberculosis
Legionella spp.
Nocardia asteroides
Encapsulated gram-positive bacteria
Salmonella spp.
Rhodococcus equi
Bartonella spp.
Campylobacter spp.



A *B*

Figure 127-6 Chest radiographs of a 39-year-old man with AIDS on zidovudine, ritonavir, and trimethoprim-sulfamethoxazole prophylaxis, and with a CD4 lymphocyte count of 89/ml. The patient presented to the outpatient clinic with low-grade fever, fatigue, and mild cough. *A.* Physical examination and chest radiograph were unremarkable. The patient was anergic on both PPD and control skin testing. Induced sputum examination was negative for bacteria, for *P. carinii,* and by mycobacterial stains. Blood cultures for mycobacteria were obtained. *B.* Ten days after initial presentation, the patient was admitted to the hospital with minimal dyspnea and cough; chest radiograph was remarkable for bilateral pulmonary reticulonodular infiltrates. Bronchoalveolar lavage samples were positive for mycobacteria. The organisms were subsequently identified from cultures of both blood and sputum as *M. tuberculosis,* resistant to both isoniazid and ethambutol. Induced sputum sample cultures remained negative for mycobacteria.

altered by prophylactic and therapeutic regimens, adverse drug reactions, and drug interactions. Toxicities of both prophylactic and therapeutic drug regimens (particularly rash, marrow suppression, and hepatic toxicities) are much more frequent in HIV-infected patients and are exacerbated by the simultaneous need for antiviral therapies.

Continued primary prophylaxis in AIDS patients who maintain CD4 lymphocyte counts above 200/mm^3 for over 3 to 6 months and with low or undetectable viral loads appears to be unnecessary, at least for *P. carinii* and mycobacterial infections. For other infections and secondary prophylaxis, the data are less clear. Up to 15 to 20 percent of AIDS patients have more than one opportunistic infection at one time. The spectrum of clinical diagnoses in pulmonary disease in AIDS includes bacterial infection (45.5 percent), *P. carinii* pneumonia (27 percent), Kaposi's sarcoma (7 percent), bronchitis (5 percent), *M. tuberculosis* (4.3 percent), other mycobacteria (4 percent), lymphoma (2.1 percent), and a variety of other processes. Common community-acquired upper respiratory infections, manageable on an ambulatory basis, constitute more than 50 percent of respiratory illnesses in HIV-infected persons. The incidence of fungal infections varies by geographic region, whereas the rate of demonstration of viral pulmonary infection is closely related to the diagnostic testing techniques used at each center and seasonal variation.

Approaches to the Diagnosis of Opportunistic Pulmonary Infections in AIDS

With the wide array of potential pathogens causing disease in HIV-infected patients, the frequency of atypical and multiple infections, and the urgency to diagnosis of infection in the immunocompromised host, a systematic approach to lung disease in these hosts is imperative. A few general rules are useful.

1. *Prophylaxis is generally effective.* When failure of prophylaxis occurs, it is usually due to noncompliance, malabsorption of drugs, emerging antimicrobial resistance, or coinfection or tumor that alters the local environment. For example, it is often impossible to eradicate *Candida* esophagitis unless erosive

esophageal herpes simplex virus infection is also treated. *Pneumocystis* is difficult to treat in the presence of CMV infection or bronchial obstruction.

2. *Specific therapies for individual infections have a high incidence of adverse reactions in the HIV-infected patient.* Thus, presumptive or empiric therapy without microbiologic confirmation, although often appropriate, has a greater risk in this population than the normal host.
3. *The utilization of newer diagnostic tests has improved the care of AIDS patients.* The interpretation of some tests is unclear, and the availability of some tests (urinary *Histoplasma* antigen or immunoperoxidase stains for *T. gondii*) is not universal. The *induced sputum examination* has been very useful in the early, noninvasive diagnosis of *Pneumocystis* infection, and for mycobacterial disease in the absence of spontaneous sputum production. The sensitivity of sputum induction for *Pneumocystis* infection approaches 90 percent, but the negative predictive value of the test is only 50 percent. The cost and sensitivity of this procedure cannot be justified for the routine diagnosis of bacterial infections, particularly in persons capable of producing sputum samples. The use of *more invasive tests,* such as bronchoscopy, with the obvious limitations of cost and risk to the patient, has the advantage of providing subglottic specimens and the potential for diagnosis of a broader range of pathogens. The interpretation of positive cultures for CMV or MAC may be uncertain without tissue histopathology for confirmation. In patients with a rapidly deteriorating clinical condition or a failure to respond to initial therapy, bronchoscopy with biopsy or needle aspiration may be preferable to bronchoalveolar lavage or sputum induction as an initial procedure. In general, noninvasive, nuclear isotope–based radiologic tests are rarely useful in the diagnostic evaluation of pulmonary disease in AIDS patients.
4. *The rate of progression of infection is often a clue to the type of disease.* Thus, community-acquired pneumonia develops rapidly (2–5 days), whereas the initial episode of *P. carinii* pneumonia generally evolves more slowly (over 7–12 days) in AIDS (as compared with other compromised hosts). Fungal infection and mycobacterial infection are generally preceded by systemic complaints. Pyogenic pulmonary infection is generally associated with sputum production, whereas the "atypical" infections may have little or no sputum despite cough and dyspnea.
5. *The radiographic pattern is often suggestive of the diagnosis (Table 127-6).* All "typical" patterns are altered by progressive immune deficits and coexisting or prior lung disease. *Diffuse infiltrates* (alveolar or interstitial) may be seen with a homogeneous distribution, as in *P. carinii, T. gondii,* CMV, mycobacterial species, *Histoplasma,* or *Coccidioides.* Drug toxicity may also cause pulmonary infiltrates. Inhomogeneity with these pathogens reflects altered pulmonary parenchyma from previous disease,

Table 127-6

Roentgenographic Findings in Opportunistic Pulmonary Diseases in AIDS

Diffuse Infiltrates	Cavitary Lesions	Hilar Adenopathy	Focal Infiltrates	Nodular Lesions	Pleural Effusions
Pneumocystis carinii	Tuberculosis	Tuberculosis	*Legionella* sp.	*C. neoformans*	Tuberculosis
Tuberculosis	Pyogenic bacteria	Lymphoma	Tuberculosis	*H. capsulatum*	Fungal
Toxoplasma gondii	Aspergillosis	Kaposi's sarcoma	*P. carinii*	Tuberculosis	Pyogenic
Histoplasma capsulatum	*Cryptococcus neoformans*	*Cryptococcus neoformans*	*Streptococcus pneumoniae*	*P. carinii*	Lymphoma, Kaposi's sarcoma
P. carinii and other agents	*P. carinii Rhodococcus equi*	HIV acute	Kaposi's sarcoma	Lymphoma	sarcoma
Lymphocytic interstitial pneumonitis	Septic emboli (addicts)	EBV acute	*Nocardia asteroides C. neoformans*	Septic emboli	

obstruction (e.g., with tumor, *Strongyloides stercoralis*), or upper-zone disease or pneumothorax in *Pneumocystis* pneumonia. Tumors may appear with interstitial radiographic patterns in HIV disease. Lymphoid interstitial pneumonitis is an interstitial process of unknown origin that is seen in AIDS patients. Diffuse interstitial infiltrates are often due to *P. carinii,* but not in patients receiving TMP-SMX prophylaxis and rarely without hypoxemia. Thus, the presence of a sepsis-like picture with a diffuse interstitial infiltrate in a patient receiving anti-*Pneumocystis* prophylaxis might suggest mycobacterial disease, *Legionella* infection, or *C. neoformans. Focal airspace disease* is most often seen with bacterial infections (pyogenic, mycobacteria, *Legionella* species), *Mycoplasma pneumoniae* (viral influenza, adenovirus, CMV), and mixed infections (e.g., CMV and *P. carinii*). Occasionally, primary cryptococcal pneumonia, *Aspergillus* infection, or obstructive disease presents with focal infiltrates. Each of these processes may evolve to frank *cavitation,* particularly infections due to pyogenic bacteria (*Staphylococcus, Klebsiella, S. pneumoniae*) or *M. tuberculosis.* Small cavities are seen with *P. carinii,* mycobacteria, and metastatic tumors. Large cavities are uncommon: *M. tuberculosis* or aspergilloma is most often present. *Nodular lesions* can be seen with any of the metastatic tumors or hematogenous infections. Endocarditis, KS, toxoplasmosis, tuberculosis, MAC, and *Cryptococcus* may all progress from nodules to small cavities. In particular, unusual bacterial pathogens (*Bartonella, Rhodococcus, Candida,* and *Salmonella*) have been observed as pulmonary nodules associated with right-sided endocarditis in AIDS patients. *Intrathoracic adenopathy* is common in AIDS patients, most often with infections earlier in the course of disease (CD4 count greater than 400/ml) and with tumors late in disease. Fungal infections (*Cryptococcus*, *Histoplasma,* and *Coccidioides*), CMV, and mycobacterial infections may also cause adenopathy. Adenopathy should prompt invasive diagnosis in the absence of a clear etiology in AIDS. *Pleural effusions* are common with tuberculosis, other pyogenic bacterial infections, and tumors.

6. *The CD4 lymphocyte count is a good indicator of susceptibility to specific infections, while the viral load is most closely associated with overall disease prognosis.* Unresolving community-acquired pneumonia due to *S. pneumoniae, H. influenzae, Mycoplasma,* or *Legionella* species may be the sentinel infection of HIV disease. As host immunity declines, other opportunistic infections occur. *M. tuberculosis,* an organism of high virulence, causes infections at *any* CD4 lymphocyte count but occurs increasingly as the CD4 lymphocyte count falls below 500/ml (Fig. 127-6). In contrast, less virulent organisms cause disease only with greater degrees of immune compromise.
7. *Chronic or recurrent sinus infection may provide a source of Pseudomonas or Aspergillus for pulmonary infection.*
8. *The spectrum of pulmonary disease varies by geographic region and by HIV transmission category.*
9. *Physical findings are often useful in establishing a differential for pulmonary disease in contrast, often, with other types of immunocompromised hosts.*

Infection in Cancer Patients

Immune Defects Due to Tumors and Chemotherapy

The incidence of infection in cancer patients is determined in part by the nature of the underlying neoplasm. Studies of infection in cancer have focused on patients with leukemia and lymphoma, due to severe and predictable immune deficiencies. In a series by Bodey and colleagues, fatal infections in acute leukemics were caused by bacteria in 66 percent, fungi in 33 percent, viruses in 0.2 percent, and protozoa (including *P. carinii*, now considered a fungus) in 0.1 percent (Fig. 127-7). In contrast, fatal infection in lymphoma patients (86 percent) and solid-tumor patients (94 percent) were more often bacterial. In studies of cryptococcal infection in cancer patients, the rate of cryptococcal infection in chronic lymphocytic leukemia was more than double that in Hodgkin's disease (24.3 versus 10.9 per thousand), and the rate in breast cancer was only 0.159 per thousand. Other tumors are also associated with specific infections. For example, lung cancer is associated with tuberculosis at a rate of 92 per 1000,

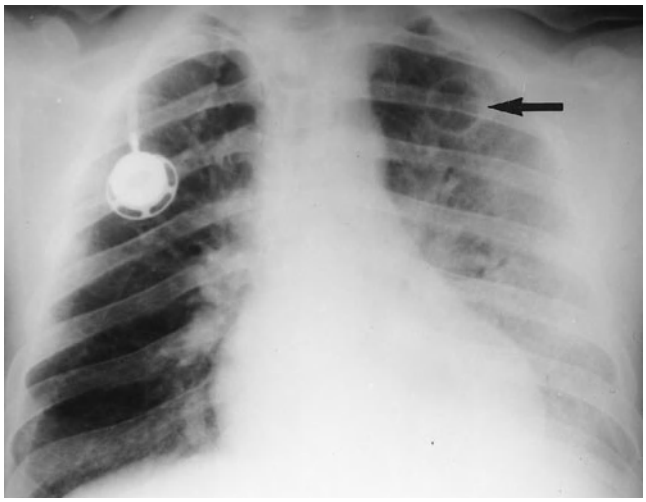


Figure 127-7 Lung abscess (arrow) in a febrile patient following intensive chemotherapy for relapsed acute myelogenous leukemia. Patient developed fever while granulocytopenic (less than 50 neutrophils/mm^3 for 8 days) without localizing symptoms and a clear chest radiograph. When the neutrophil count exceeded 200/mm^3, a lung abscess was detected in the left upper lobe. *Aspergillus fumigatus* was detected in fluid obtained from the abscess via CT-guided percutaneous needle aspiration. The infection responded well to amphotericin B treatment.

second only to the rate in patients with Hodgkin's disease (96 per 1000) due to cellular immune deficits. Without therapy, the degree of depression in cellular immunity (delayed-type hypersensitivity) is more prominent in lymphoma, whereas humoral immunity is impaired to a greater degree in diseases affecting B-lymphocyte function, such as multiple myeloma and chronic lymphocytic lymphoma. Thus, the lymphoma patient is particularly susceptible to intracellular organisms, including *Listeria monocytogenes*, *Mycobacterium tuberculosis*, viruses, and fungi, whereas the myeloma patient is more apt to develop pneumonia or bacteremia due to *Haemophilus influenzae*, *Streptococcus pneumoniae*, and a variety of other acute bacterial infections. Acute leukemia is associated with a depression in the number and function of circulating granulocytes and is associated with severe pyogenic bacterial infections. Patients with acute and relapsed leukemia have demonstrated impaired phagocytosis and killing of fungi and bacteria by these cells, which may appear morphologically normal. *These defects may persist well into periods of remission and may progress along with progression of the underlying disease.*

The impact of the various forms of chemotherapy on host defenses must be added to those caused by the underlying malignancy. Multiple immune functions are impaired by chemotherapy, including the phagocytosis and killing of bacteria by neutrophils (corticosteroids, carmustine, radiation); antibody production (methotrexate, cyclophosphamide, L-asparaginase, 6-mercaptopurine); uptake and processing of antigen by macrophages (corticosteroids, cyclophosphamide, dactinomycin); recognition of antigens by T and B lymphocytes (corticosteroids, cyclophosphamide); and antigen-driven lymphocyte proliferation (methotrexate, 5-fluorouracil, fludarabine, cytarabine, L-asparaginase, dactinomycin, 6-mercaptopurine, hydroxyurea). Predisposition to infection induced by chemotherapy may mask more subtle defects due to underlying disease; e.g., the effects of granulocytopenia due to intensive chemotherapy generally predominate over the effects of underlying lymphoma or myeloma.

Table 127-7

Causes of Neutropenia

Iatrogenic
Cancer chemotherapy
Drug toxities (TMP-SMX, chloramphenicol, gancicolovir, AZT)
Infection
Viral (cytomegalovirus, HIV, Epstein-Barr virus, hepatitis B)
Parasitic (*Leishmania*)
Bacteria (*Clostridium*)
Acute neutropenia of sepsis/endotoxemia (gram-negative sepsis)
Bone marrow failure of neonatal sepsis
Immune
Drug-induced autoimmunity (haptenic: penicillins, sulfa drugs)
Aplastic anemia (includes idiosyncratic reactions: phenothiazines, chloramohenicol)
Alloimmune neonatal neutropenia (maternal-fetal incompatibility)
Congenital autoimmune neutropenia
Primary autoimmune (systemic lupus erythematosus, Felty's syndrome, rheumatoid arthritis)
Transfusion induced
Antineutrophil antibody mediated
Cyclic neutropenia (CD57 lymphocyte expansion)
Hereditary
Infantile genetic agranulocytosis
Familial neutropenia
Cyclic neutropenia (autosomal dominant)
Old age

Neutropenia

The most common predisposing condition for infection in the cancer patient is granulocytopenia; it is often due to chemotherapy and occurs while awaiting engraftment of hematopoietic transplants. The *function* of inflammatory cells and other immune (e.g., mucosal) barriers is also of great importance and are much more difficult to assess. The risk of infection increases as granulocyte counts decrease. Thus, the risk of infection in the patient with neutropenia (under 1000 total granulocytes per mm^3) increases when granulocyte numbers fall further, to below $500/mm^3$; the risk is greatest when counts are lower than $100/mm^3$. The many causes of neutropenia differ qualitatively (Table 127-7). They include iatrogenic neutropenias (chemotherapy, drug toxicities), aplastic anemia and other immune neutropenias, the hereditary and acquired cyclic neutropenias, and malignancy-associated (especially acute leukemias) and infection-induced neutropenias. The rate of decline in white blood cell numbers and the duration of neutropenia influence the risk of infection. Thus, the patient with acute leukemia and rapidly falling neutrophil counts is at greater risk than the person in whom counts are falling slowly or are stable.

The Microbiology of Infection in Neutropenia and Cancer

Pulmonary infections in patients with functional or quantitative defects in neutrophils can reach the lungs via inhalation, microaspiration of colonizing organisms, and bacteremia after non-respiratory penetration and bacteremia (e.g., from vascular catheters or disrupted mucosal surfaces). Decisions about the management of these patients are often made empirically because of the urgency of therapy in

the immunocompromised host. Distinctions between pulmonary and extrapulmonary infections often become blurred in the attempt to treat most of the likely pathogens in a febrile neutropenic cancer patient. Often a specific, unsuspected pulmonary pathogen is detected on routine blood or urine culture or from a biopsy of an extrapulmonary infected site.

Common infections in the neutropenic host and cancer patient are most often the result of colonization with, and infection by, pyogenic bacteria, including *S. pneumoniae*, *Staphylococcus aureus*, the Enterobacteriaceae, *Pseudomonas aeruginosa*, *H. influenzae*, and *Stenotrophomonas* (formerly *Xanthomonas*) *maltophilia*. Common fungal pathogens include *Candida albicans*, *Aspergillus* species, *C. krusei*, *C. glabrata*, *Mucor*, *Absidia*, and *Rhizopus* species. The emergence of bacteria and fungi with antimicrobial resistance takes on special importance in the neutropenic host because therapy is generally empiric and is started before microbiologic data become available. The common "resistant" organisms include vancomycin-resistant *Enterococcus faecium* and *faecalis (now also resistant to linezolid, quinupristin-dalfopristin)*, methicillin-resistant *S. aureus*, inducible chromosomal and acquired plasmids encoding β-lactamase in gram-negative bacteria, and azole (i.e., fluconazole) resistance to *C. krusei* and *C. glabrata*. In individual patients, the spectrum of colonizing organisms also changes over time, especially with antimicrobial use (and abuse). Seeding from blood-borne infection (e.g., due to vascular access catheters or localized infection) occurs most often with the organisms described in the preceding; other organisms are *Candida* and *Aspergillus* and, occasionally, mycobacteria. Patients with solid lung tumors may develop obstructive pneumonia or pulmonary hemorrhage, followed by superinfection with the flora of the upper respiratory tract and oropharynx (Fig. 127-8).

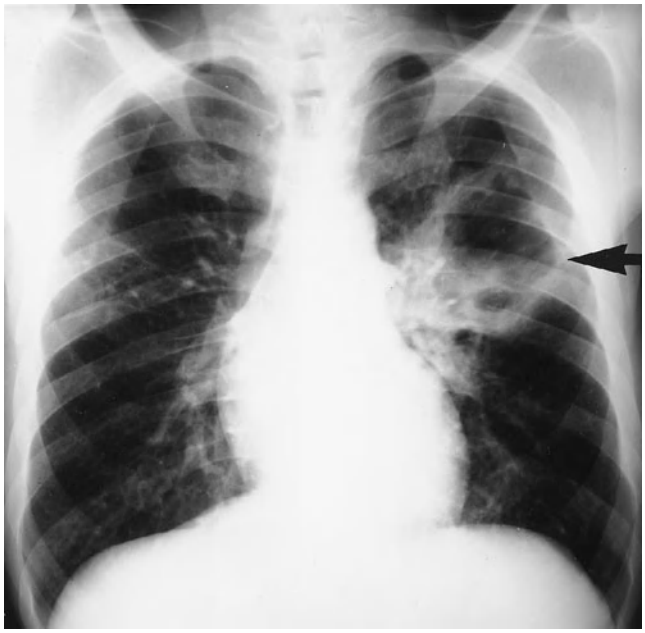
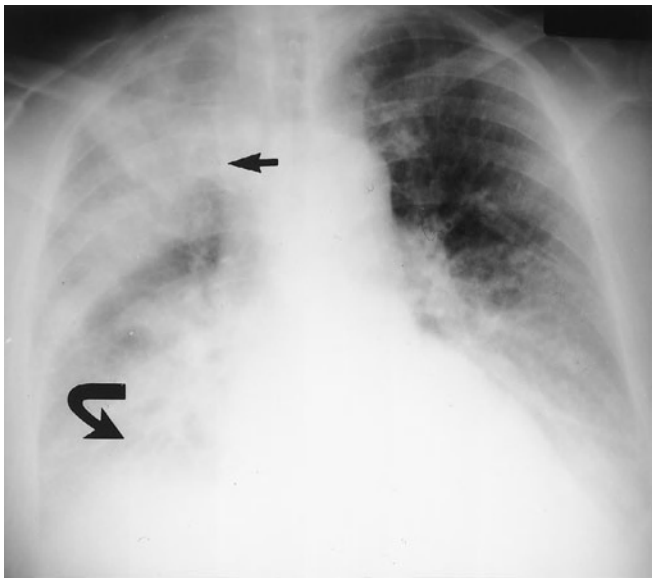


Figure 127-8 Postobstructive pneumonia and lung abscess (arrow) in a 45-year-old man with adenocarcinoma of the lung in the right hilum. The abscess was drained via a bronchoscopic approach. Cultures of the abscess fluid grew common oral bacterial flora, including *Prevotella melaninogenica* and *Bacteroides* species.

Fungi and Less Common Pathogens

Combined cellular and granulocytic deficiencies are often present after chemotherapy. As a result, in addition to the common pathogens described above, pathogens normally controlled by cellular immune mechanisms (especially intracellular pathogens) can be detected; among these are *M. tuberculosis*, *Brucella* species, the geographic fungi, *Cryptococcus neoformans*, *Strongyloides stercoralis*, *Salmonella*, and *Pneumocystis carinii*. Unusual pathogens have been identified in increasing numbers of cancer patients with neutropenia. The classic presentations of pneumonia, inflammation and perforation of the cecum (often with *Pseudomonas* and anaerobes), and "typhlitis" (often *Clostridium septicum*) may be the first signs of life-threatening infection in a neutropenic patient. Atypical presentations of infection may be from a portal of entry other than the gastrointestinal tract or the lungs. Thus, the first clinical signs of infection may be "spontaneous" or line-associated bacteremia (*Staphylococcus, enterococci*, gram-negative rods, *Bacillus*, *C. jeikeium*, *Candida* species, *Fusarium*), skin lesions (gram-negative sepsis, *Candida* species, *Nocardia asteroides*, *C. neoformans*, herpes simplex or varicella zoster), gingivitis (anaerobes), hepatic dysfunction (hepatosplenic candidiasis), or seizures (*Nocardia* or *Aspergillus* species in brain abscess associated with a slowly progressive pneumonia) (Fig. 127-9).

Because of the widespread use of antibacterial agents, mucosal injury, use of intravenous catheters and bone marrow transplantation, fungal infections have occurred with increasing frequency, most often in acute leukemia patients and following stem cell transplantation and graft-vs-host disease (Table 127-8). *C. glabrata* and *C. krusei* that may carry resistance to fluconazole may develop during antimicrobial treatment. Although Mucoraceae *(Rhizopus, Mucor, Absidia)*, like the *Aspergillus* species, may present with invasive disease of the sinuses and periorbital and frontal cortex in diabetics, they can also cause rapidly progressive hemorrhagic pneumonia with infarction and fungemia. Invasive disease of the sinuses and periorbital and frontal cortex is especially prevalent in neutropenic diabetics and in patients treated with deferoxamine, with prolonged corticosteroid therapy, or with broad-spectrum antimicrobials. The treatment of this invasive disease is *surgical débridement* in addition to antifungal therapy. In patients with neutropenia or acute leukemia, a group of "benign" dermatophytes—including *Trichosporon beigelii*, *Aureobasidium*, *Alternaria*, *Curvularia*, *Phialophora*, *Wangiella*, and *Cladosporium*—have been associated both with disease of the skin and with invasive infection of the lungs, the sinuses, and the central nervous system. Occasionally infections are caused by "atypical fungi" (e.g., *Saccharomyces cerevisiae*, *Pseudallescheria boydii*, *Cunninghamella bertholletiae*, *Drechslera*, *Fusarium* species, *Geotrichum candidum*, and *Penicillium* species). *Fusarium* causes infection of



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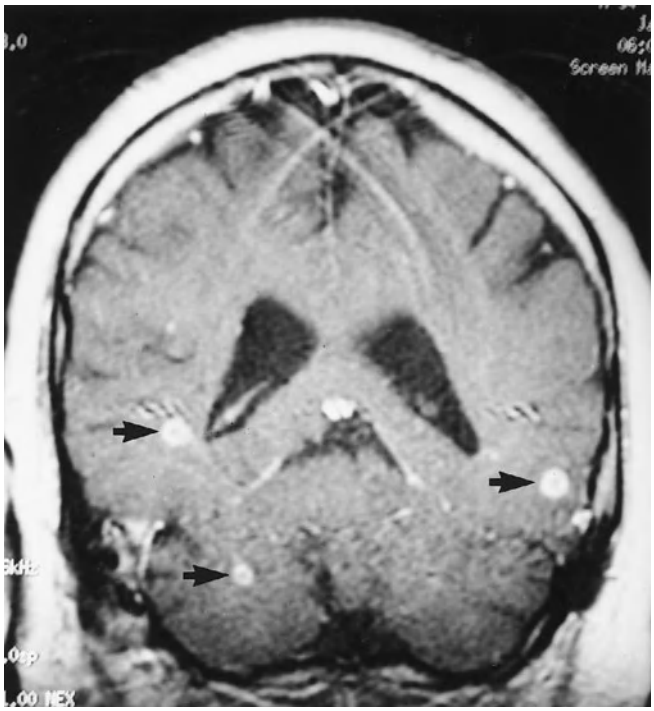


B

Figure 127-9 Multiple simultaneous infections in a 46-year-old man with Wegener's granulomatosis treated with cyclophosphamide and prednisone. The patient developed progressive pneumonia and neutropenia. Sputum cultures were unrevealing. *A*. Bronchoalveolar lavage revealed *Nocardia asteroides* (curved arrow) there was no clinical response to trimethoprim-sulfamethoxazole therapy. Bronchoscopic biopsy of a small abscess in the upper lobe (small arrow) revealed *Fusarium* species. *B*. Magnetic resonance imaging (MRI) of the brain revealed numerous small abscesses (arrows) diffusely distributed throughout the brain. These were initially thought to be consistent with infection due to *Toxoplasma gondii*. Brain biopsy revealed *Nocardia asteroides*.

the bloodstream and lungs that is indistinguishable from that due to *Aspergillus*, but with greater tendency to cutaneous involvement. The cardinal sign of *Pneumocystis* pneumonia is the presence of arterial hypoxemia out of proportion to physical or radiologic signs.

Viral Infections

Viral infection has become increasingly prevalent in cancer patients. This is a reflection of prolonged T-cell defects, use of depleting antilymphocyte antibodies, and improved molecular diagnostic assays. Herpes simplex virus (HSV) and varicella zoster virus (VZV) are frequently reactivated during periods of neutropenia or as a sign of the presence of new malignancies. Patients who are undergoing chemotherapy for Hodgkin's disease or who have received bone marrow transplants are at greater risk than other immunocompromised hosts (35–50 percent in the first year). Specific antiviral prophylaxis is effective in reducing the incidence and severity of these relapses. Most often, these viruses cause painful, but relatively benign, skin or mucosal (especially esophageal, gastrointestinal, and perianal) lesions. These lesions may progress in neutropenic patients and the skin rash may become more diffuse, with hemorrhagic or nonhemorrhagic lesions extending beyond dermatomal limits. Systemic dissemination to visceral organs occurs in 10 percent of patients with disseminated skin disease commonly involving the liver, lungs, brain, or gastrointestinal tract. Nasal, oropharyngeal, or esophageal HSV or VZV infections may spread directly to the lungs with the development of vesicular lesions in the trachea, or may cause viral pneumonitis in the parenchyma as a result of viremia secondary to cutaneous reactivation. Primary varicella pneumonia may accompany chickenpox in adults and in the compromised host. Pulmonary invasion occurs within the first 7 days of illness, with mortality approaching 18 percent. Chest radiographs reveal nodular or interstitial infiltrates in up to 16 percent of adults with chickenpox, whereas only 10 to 25 of these have clinical symptoms. Pulmonary invasion by HSV and VZV in the neutropenic host should be considered a life-threatening emergency.

In hematopoietic stem cell and bone marrow transplantation (BMT) recipients, CMV pneumonitis occurs in the CMV-seropositive recipient of CMV-seronegative cells. Because much of the lung injury is due to immune responses to CMV antigens, the full pneumonitis develops not during lymphopenia but, rather, with the engraftment of the marrow and with the re-emergence of immune function. Viral replication is not needed for CMV pneumonitis to occur. In the granulocytopenic host, pulmonary CMV infection may be fatal.

Table 127-8

Factors in the Development of Fungal Infections in Cancer Patients

Age/performance status
Prior chemotherapy or radiotherapy: dose and duration Steroids Purine analogues
Prior infections (specific isolates)
Recent antimicrobial use (resistance) Broad-spectrum antimicrobials Prophylactic agents
Functional immune status (cell number, activity)
Hematopoietic transplantation–related Delayed engraftment or function of marrow Graft-vs-host disease and treatment Degree of donor-recipient histocompatibility mismatch Insufficient dose of stem cells (CD34) Total T-cell number
Integrity of mucosal barriers (catheters, gastrointestinal)
Neutropenia (severity, duration > 2 weeks)
Hospital environment
Home environment—hobbies, travel
Nonhematopoietic organ failure (e.g., dialysis)
Other simultaneous infections (e.g., cytomegalovirus)

Parasitic Infection

The predominant parasitic infection enhanced by immune compromise is that due to *S. stercoralis*, a nematode that infects more than 100 million people worldwide, producing lifelong infection. *Strongyloides* is distinguished by its *ability to complete the replicative cycle within the human host.* Malnutrition is a major cofactor; neutropenia and corticosteroids are common coinducers of parasite replication. In the normal pattern of infection, the filariform larvae penetrate the skin, follow the veins to the lungs, and are then swallowed, entering the small intestine. The hyperinfection syndrome is the result of activation in the gastrointestinal tract by immune suppression, which causes penetration or transudation of worms across the wall, carrying gastrointestinal organisms with them. Peritonitis, bacteremia, and gram-negative, eosinophilic meningitis may result. Pneumonia may result from bacteremia or obstruction of small airways and pneumonitis; the pulmonary infection fails to resolve without therapy directed at eliminating the nematode.

In endemic regions, activation of *Toxoplasma gondii*, Chagas' disease *(T. cruzi)*, pulmonary or disseminated microsporidiosis or cryptosporidiosis (rare), leishmaniasis, and acute infection with *Acanthamoeba* and *Naegleria* species (primary amebic meningoencephalitis) must be considered in the differential of systemic and pulmonary infections. Splenectomized hosts are at special risk for intense infection due to babesiosis, malaria, and ehrlichiosis.

Clinical Approaches to Infection in the Cancer Patient

Clinical Signs of Infection

Clinical recognition of infection is often delayed in the neutropenic or cancer patient because the inflammatory response is diminished (decreased numbers or mobilization of granulocytes) and the usual signs of infection are absent. Thus, in neutropenic patients, pneumonia may not be associated with sputum production and radiologic changes. In the febrile neutropenic patient with leukemia, the source of obscure infection is often the perineal and perirectal areas; less common are infections of the urinary tract, skin (including venous lines and wounds), and the lungs. In nonhematopoietic cancer patients, however, pulmonary infections predominate. A site of origin for a febrile episode is undetermined in 20 to 50 percent of patients. Many sites of infection are detected only at autopsy, notably in patients with disseminated fungal or combined fungal and bacterial infections. Mortality in the febrile neutropenic population is 30 to 50 percent. Noninfectious causes of fever are common; among them are pulmonary thromboembolism, tumor, radiation pneumonitis, atelectasis with pulmonary edema, drug allergy or toxicity, and pulmonary hemorrhage. Often, the resolution of fever in response to a trial of antimicrobials is the only evidence of infection.

Initial Management of the Cancer Patient with Fever: Stratification of Risk

Each patient presenting with signs of infection must be evaluated in terms of the perceived risks of infection and noninfectious causes of fever and for the presence of neutropenia or other immune dysfunctions. Attempts to manage patients with greater efficiency and to shorten hospital stays have led to the development of *critical pathways*, which include standard patterns of evaluation and treatment for many patients, including those with cancer. Such uniform approaches are useful in establishing a *minimal standard* of care, but they do not address concerns about the pitfalls of failing to individualize therapy.

The safe application of critical pathways for the outpatient management of neutropenic patients necessitates careful stratification of these compromised patients by experienced clinicians in terms of their risk for infectious complications. *Any sign of infection* requires at least a brief hospitalization

(1–3 days), with careful evaluation. However, many experienced oncologists now manage some febrile neutropenic patients as outpatients. Any febrile neutropenic patient—or patient in whom absolute neutrophil count (ANC) is expected to fall below 1000/mm^3—with localizing signs (headache, altered mental status, rash, dyspnea, chest pain, pain over an indwelling catheter site, pulmonary infiltrates) should be considered for emergency admission. In particular, patients with leukemia or lymphoma, uncontrolled metastatic cancer, recent need for antimicrobials, or ANC under 100 (or expected to fall below 100) are generally considered higher-risk patients and are best managed as inpatients until clinically stable. Patients with a history of frank rigors or hypotension merit admission. Any febrile cancer patient needs an assessment of vital signs, oxygen saturation, complete blood count with differential, electrolytes and blood urea nitrogen and creatinine (for obstruction by tumor or acute drug toxicity), blood cultures (at least one peripheral and one from any indwelling catheter), urine sediment examination and culture, sputum Gram's-stain examination and culture, and chest radiograph. After a careful physical examination, the threshold for lumbar puncture and determination of serum or spinal cryptococcal antigen should be low. The patient's history and medical record should be reviewed, with attention to current drugs, recent chemotherapy (especially corticosteroids), recent microbiologic data, and antimicrobial use, allergies, and exposures.

Empiric Use of Antimicrobials in Fever and Neutropenia

After appropriate smears and cultures have been obtained, empiric antimicrobial therapy in the febrile neutropenic patient is essential. The specific antimicrobials selected for routine use in the febrile neutropenic patient remain controversial. Ultimately, this is because many combinations appear to work equally well, and there are few studies of various combinations in identical patient populations using the same entry and end point criteria. The antimicrobials selected must cover previously documented infections or surveillance culture data, physical findings, known hospital flora, and potential community exposures.

Initial therapy should assume that the organisms causing infection are likely to be resistant to current prophylactic or therapeutic antimicrobials. Many infections are loculated and require drainage (sinusitis, postobstructive pneumonitis) (Fig. 127-8). Patients thought to be at *low risk* for infection or other complications (nonleukemic, underlying cancer not progressing, no serious coexisting illness, no recent infections or courses of antimicrobials, expected ANC to remain above 100) may be *considered* for home management after 24 h (to await blood culture data), based on the clinical assessment. In these patients, empiric antimicrobials might include ticarcillin (or ticarcillin-clavulanate, piperacillin with or without tazobactam, ceftriaxone) plus gentamicin (or tobramycin or amikacin). Monotherapy with cefepime, ceftazidime, or carbapenems has also been found to be effective in medical centers that do not have nosocomial flora resistant to these agents. Optimal antimicrobial therapy should include synergistic therapy for *Pseudomonas* infection in medical centers in which this organism is prevalent or if the patient is profoundly neutropenic. The routine use of quinolones or aztreonam for initial therapy in high-risk patients has not been well studied and is not recommended, especially for patients receiving these agents for prophylaxis.

A decision regarding the use of coverage for gram-positive organisms, including MRSA or VRE (e.g., vancomycin) is made based on the possibility of catheter-associated infection and clinical judgment. Such patients might include those with skin wounds, decubitus ulcers, or indwelling vascular access catheters. Gram-positive bacterial infections generally progress more slowly than do gram-negative infections. Therefore, the *routine use* of vancomycin in these patients does not appear to be justified, because of the increased risk of vancomycin-resistant enterococci. Routine surveillance for VRE may be of assistance in adjusting the regimen if fever persists.

If an abdominal or anaerobic bacterial source is suspected, clindamycin or metronidazole can be added. Anaerobic infections other than those due to *Bacteroides fragilis* are uncommon as a source of major morbidity in these patients. Restrictions on the use of clindamycin have been instituted at many centers because of outbreaks of *C. difficile* colitis. Topical oral antifungal therapy (clotrimazole, nystatin) is commonly administered with broad-spectrum parenteral antimicrobials. Antimicrobials may be adjusted on the basis of microbiologic data or if the patient is afebrile for 7 to 10 days with the ANC over 500 and increasing.

Fever and Pulmonary Infiltrates

Pulmonary disease in the cancer patient is clinically challenging, owing to the large array of processes that may cause radiologic infiltrates (Table 127-9). Non-infectious causes of pulmonary infiltrates and fever (edema, cancer, radiation injury, drug toxicity, leukoagglutinin transfusion reaction, pulmonary embolus, hemorrhage, alveolar proteinosis) are common (up to 25 percent) and may closely mimic infection (discussed also in Approach to the Patient with Pulmonary Infections). Conversely, the absence of inflammatory cells or mobilization may mask signs of significant infection. In the patient undergoing chemotherapy or in the neutropenic host, cough, sputum, radiologic infiltrates or cavitation, and fever may all be absent. Infection may spread to the chest from contiguous structures (e.g., perforation of the esophagus due to *Aspergillus*) or may complicate anatomic changes (e.g., bronchial obstruction in lung cancer).

Radiologic Clues to Diagnosis

A number of clues are available to assist in the differential diagnosis of pulmonary infiltrates in cancer patients. For example, the clinical and radiographic appearance and progression of disease may suggest a diagnosis based on the time course and nature of the infiltrate (Table 127-9 and Chapter 114). In general, acute processes include both bacterial infections and

Table 127-9

Common Causes of Pneumonia in Cancer Patients Based on Radiographic Abnormalities and Disease Progression

Abnormality on Chest Radiograph	Common Cause by Rate of Disease Progression*	
	Acute (<24 h)	**Subacute-Chronic**
Consolidation	Bacteria (include *Legionella*) pulmonary embolus, hemorrhage, pulmonary edema	Fungi, *Nocardia*, tuberculosis (drug, virus [RSV], *P. carinii*, radiation)
Interstitial infiltrate	Pulmonary edema (include drug) Leukoagglutinin reaction (bacterial)	Viral, *Pneumocystis*, radiation, drug (fungi, *Nocardia*, tuberculosis, tumor)
Nodular infiltrate	Bacteria, edema (CMV, VZV)	Tumor, fungal, *Nocardia*, TB *Pneumocystis* (CMV)

** Common causes (and less common in parentheses) in the absence of specific epidemiologic exposures or past history.*

noninfectious injuries, such as pulmonary embolus or edema. Subacute processes include *P. carinii*, viral, *Mycoplasma*, or *Nocardia* or *Aspergillus* infections. More chronic processes include drug-induced, radiation-induced, mycobacterial, nocardial, or malignant invasion of the lungs.

In particular, bronchial obstruction by tumor or enlarged lymph nodes may cause atelectasis or postobstructive pneumonia. The underlying process may be suggested by pneumonia that fails to respond to antimicrobial therapy or recurs in the same location after successful treatment. Tumor masses, especially those due to lymphoma, may cavitate, giving the appearance of a lung abscess. Finally, it is important to bear in mind that a chronic process may be superinfected by an acute bacterial, viral, or drug-induced lung injury.

The clinical assessment coupled with the radiologic pattern of lung disease is usually the basis for forming a differential diagnosis for the patient with fever and pneumonitis. Computed tomography (CT scans) has greatly improved differentiation of some processes. For example, in patients with simultaneous processes affecting the lung (e.g., aspiration and tumor), CT scans may disclose distinctive patterns of parenchymal involvement (consolidation and infiltrative lesions with associated adenopathy) better than do conventional chest radiographs. Subtle interstitial infiltrates *(P. carinii)* or nodules *(Cryptococcus)* are better detected by CT scans than by conventional radiographs.

Noninfectious Pneumonitis

After a dose of radiation greater than 2000 rads, radiation injury is common. The injury may become evident either acutely or more than 6 months after the initial exposure. The acute form of radiation pneumonitis may present as a bronchitis or esophagitis with dry cough, fever, fatigue, hypoxemia, and dyspnea that develop over 6 to 12 weeks. The histologic picture reveals vascular damage, mononuclear infiltrates, and edema. The severity of lung injury due to radiation appears to correlate with the rapidity of the withdrawal of steroid therapy, but it may also reflect the emergence of the underlying inflammatory response. Radiation fibrosis usually occurs in 6 to 9 months, and pulmonary function may take up to 2 years to plateau.

Acute, drug-induced lung disease may reflect hypersensitivity to chemotherapeutic agents or sulfonamide agents. Methotrexate, bleomycin, and procarbazine can cause a syndrome of nonproductive cough, fever, dyspnea, and pleurisy with skin rash and blood eosinophilia. Chest radiographs demonstrate diffuse reticular infiltrates. Cytoxan may cause a syndrome of subacute pulmonary disease with interstitial inflammation and pulmonary fibrosis, with fever, dyspnea, fatigue, and cough. Drug toxicity for agents such as bleomycin, BCNU, and CCNU may be related to the cumulative dose (for bleomycin, over 450 mg) and patient age. Synergistic toxicity for the lung occurs between radiation and a variety of chemotherapeutic agents (e.g., bleomycin, mitomycin, and busulfan) and supplemental oxygen use. A variety of non-infectious processes may mimic infection. Alveolar proteinosis may be associated with hematologic malignancies or accompany infection due to *Nocardia* or, less often, *Cryptococcus*, *Aspergillus*, *M. tuberculosis*, and *Histoplasma*. Pulmonary infarction may mimic infections by causing hemoptysis, leukocytosis, pleuritic chest pain, and segmental pleural-based infiltrates on the chest radiograph.

Approach to Antimicrobial Therapy in Patients on Empiric Therapy

Empiric therapy must be individualized. In a patient receiving empiric therapy who becomes afebrile on antimicrobials by 72 h and with a neutrophil count above 500 per mm^3, the antimicrobials may be stopped after 7 days and the patient re-evaluated if no localizing source is found or untreated

pathogens detected. Patients who are clinically well and who become afebrile with neutrophil counts of 100 to 500 per mm^3 should be afebrile for 5 to 7 days before antimicrobials are stopped in order to re-evaluate sources of infection. If the patient is not clinically well (e.g., has mucositis, fewer than 100 neutrophils per mm^3, or unstable vital signs), the antimicrobials should be continued until the patient is stable and afebrile for 48 to 72 h.

Unless a specific source of infection is located and the pathogen(s) identified, patients with persistent fever and neutropenia should have antimicrobials broadened 48 to 72 h after the start of therapy. The options include: (1) addition of vancomycin (or other gram-positive agent if colonized with resistant organisms such as VRE); (2) addition of antianaerobic therapy for oral mucositis or gingivitis, abdominal pain, or perirectal tenderness; (3) expansion of gram-negative bacterial coverage (generally adding a second agent from a different class of antimicrobials); (4) consideration of antiviral therapy in patients with esophagitis or a history of HSV or VZV or at risk for CMV infection; and (5) addition of antifungal therapy. The toxicities of antifungal agents must be considered carefully in these patients, notably those with decreased renal function or systemic fungal infection. The use of amphotericin B products (lipid-associated) or deoxycholate form must be in full dose and patient must be well hydrated with attention must be paid to magnesium and potassium maintenance. Slowly advancing doses of this drug have been advocated without supporting data and entail the disadvantage of delay in achieving adequate therapy. Voriconazole (and other azoles) have significant interactions via the hepatic P450 metabolic system and the incipient has been associated with cardiac arrhythmias in renal dysfunction. The echinocandins have fewer drug interactions but are rarely the drug of choice for initial therapy of filamentous fungal infection. The Mucoraceae lack susceptibility to both voriconazole and echinocandins. Cryptococcus lacks susceptibility to echinocandins.

Special attention must be paid to any symptoms of pulmonary disease, the presence of new pulmonary infiltrates on chest radiographs, or the presence of sinus or CNS symptoms in patients with persistent fevers. New infiltrates should prompt examinations of sputum and procurement of specimens (open biopsy, thoracoscopic biopsy, or bronchoscopy, preferably with biopsies, or needle aspirates under tomographic guidance) for histologic and microbiologic evaluation.

BONE MARROW AND STEM CELL TRANSPLANTATION

Temporal Sequence of Pulmonary Disease Syndromes

The patterns of infection in hematopoietic transplantation have shifted due to earlier engraftment with hematopoietic stem cell transplantation (HSCT) compared with bone marrow transplantation (BMT) and the use of non-myeloablative transplantation (Fig. 127-2). The impact is apparent in the shorter duration of neutropenia in the initial phase, earlier engraftment—but has not decreased the incidence of graft-vs-host disease (GVHD) or the infections associated with immunosuppressive treatment of GVHD (Table 127-10). Specific pulmonary complications can be grouped according to the status of the individual patient: pre-engraftment neutropenia (1–4 weeks), engraftment (fever and cytokine release, renal dysfunction), early and late post-engraftment (up to approximately 26 weeks and 1 year), and late infections (based on the status of host immunity and epidemiology). Although this division is clinically useful, overlap occurs in the timing of specific complications, and the categorization of pulmonary complications is often arbitrary, since the cause of many respiratory abnormalities is uncertain. Inadequate tools are available to accurately assess the individual's immune function. T-cell depleted grafts and patients treated with T-cell depleting antibodies have less GVHD but more viral and fungal infections. Treatments including B-cell depletion have more bacterial infections due to encapsulated organisms. Prophylaxis served only to delay infection and to select resistant organisms unless immune function is restored. Killed organism vaccination is appropriate by one year post-transplant with use of live vaccines reserved until immune function has normalized, generally by two years post-transplantation.

In the early phase, neutropenia predominates with mucositis (and aspiration) being common, herpes simplex (in seropositive recipients), idiopathic pneumonia (respiratory viruses, cytomegalovirus [CMV], pulmonary edema), Aspergillus infection, and line-associated infections (Candida,

Table 127-10

Pulmonary Complications in BMT/HSCT

Pulmonary edema syndromes (engraftment syndrome)
Infectious pneumonia Bacterial Fungal Viral Protozoal
Idiopathic pneumonia
Oral mucositis
Pulmonary veno-occlusive disease
Bronchopneumonia
Idiopathic pneumonia
Viral pneumonia
Airflow obstruction (obliterative bronchiolitis)

Obstructive airflow among marrow recipients with chronic GVHD.

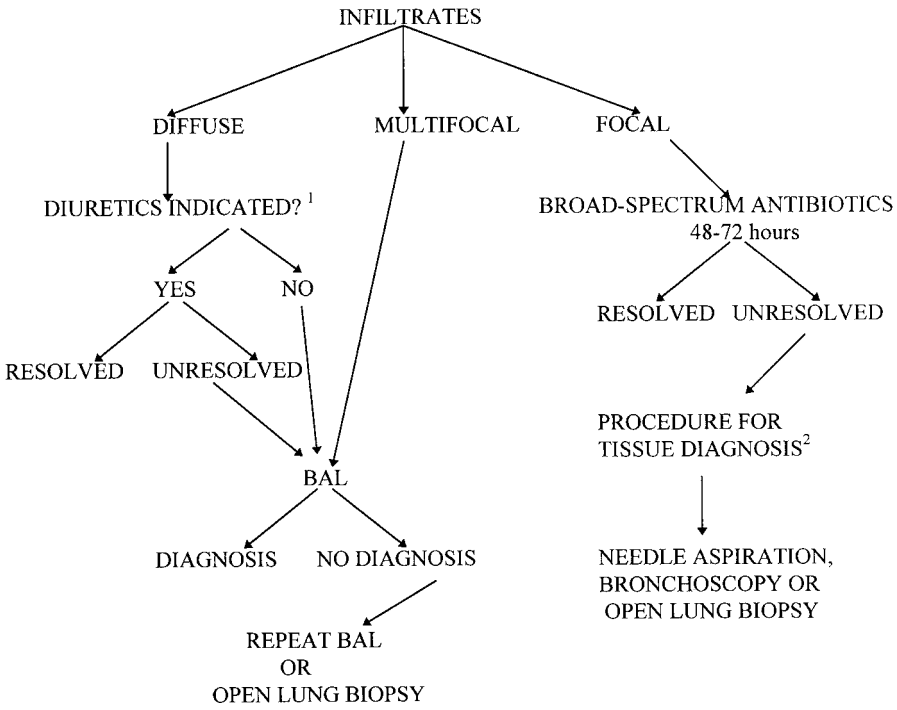
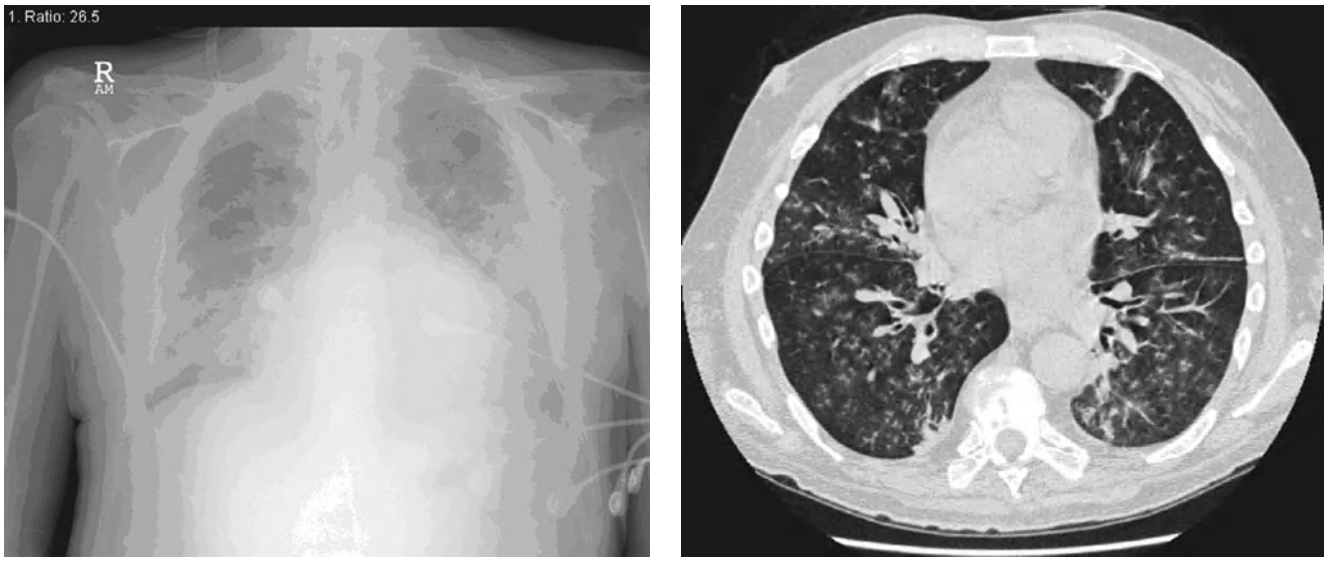


Figure 127-10 Diagnostic approach to pulmonary infiltrates after hematopoietic stem cell transplantation. 1. Diuretics often indicated in the first 30 days after transplantation. 2. Choice of procedure often influenced by results of CT scan of thorax.

gram-positive and -negative bacteria). Viral pathogens predominate after engraftment but before T-cell function normalizes—CMV, varicella zoster virus (VZV), adenovirus (and other respiratory viruses), but also *Pneumocystis carinii* (*jiroveci*, PCP), *Toxoplasma gondii* and moulds (Figs. 127-10 and 127-11). Routine prophylaxis (trimethoprim-sulfamethoxazole, antivirals) is generally effective in preventing such infections. Late and uncommon infections may occur at any time in the post-HSCT course notably in those with persistent immune deficits. Such individuals are at persistent risk for infections due to *Legionella, Nocardia, Mycoplasma*, Mycobacteria, *Strongyloides stercoralis*,



A *B*

Figure 127-11 Adenovirus pneumonia during week after marrow engraftment following allogeneic hematopoietic stem cell transplantation for acute myelogenous leukemia. *A*. Routine chest radiograph reveals diffuse pneumonia while *B*. CT scan demonstrates bronchiolitis. The patient failed to respond to cidofovir therapy but cleared infection after infusion of autologous stem cells.

Cryptosporidium species, Epstein-Barr virus (EBV, post-transplant lymphoproliferative disorder or PTLD), and in those with hypogammaglobulinemia, encapsulated organisms including *Streptococcus pneumoniae, Neisseria meningitis, and Haemophilus influenzae.*

The most important characteristic that separates patients receiving allografts from those receiving syngeneic or autologous marrow or stem cells is the occurrence of GVHD in the former group. Syngeneic and autograft recipients share early risk factors such as neutropenia with patients receiving allogeneic transplants, and are at risk of early pulmonary complications, such as bacterial or fungal pneumonia and non-infectious treatment-related pulmonary injury. Transplant recipients who have delayed engraftment or subsequent marrow failure are at continued risk of bacterial or fungal infection. Allogeneic marrow recipients with GVHD have continued abnormalities in immune function that increase the risk of opportunistic infections. Among patients with chronic GVHD, infection and pneumonia due to encapsulated organisms (e.g., *Streptococcus pneumoniae, Haemophilus influenzae,* and *Staphylococcus aureus*) appear related to deficiencies in specific antibody production, use of anti-CD20 antibodies, resistance to common antimicrobials used for prophylaxis, and possibly continued defects in macrophage and NK cell functions.

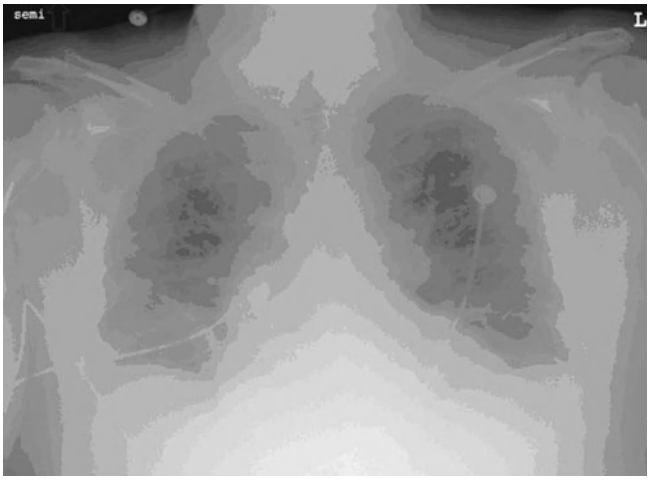
Common Clinical Presentations

Signs and symptoms of pulmonary disorders related to marrow and hematopoietic stem cell transplantation are often nonspecific (Fig. 127-12). Tachypnea is common, as are fever, cough, and rales. However, any or all of these may be absent at the time of presentation of pulmonary complications. Routine chest radiographs are obtained frequently during the first weeks of neutropenia and often provide the first indication of pulmonary impairment.

Diffuse Infiltrates

Diffuse infiltrates are common radiographic abnormalities noted in marrow recipients. However, these infiltrates are most often nonspecific. Infectious causes for diffuse infiltrates have been documented in fewer than 20 percent of marrow recipients undergoing open lung biopsy within 30 days after marrow transplantation. Within this early period, pulmonary edema syndromes predominate. The edema may be associated with cardiac decompensation or intravascular volume excess, or with acute respiratory distress syndrome (ARDS) and pulmonary capillary leak due to treatment-related toxicities or sepsis syndrome. Infections presenting with diffuse infiltrates within the first weeks after transplantation include respiratory viral causes, such as respiratory syncytial virus, while cytomegalovirus is uncommon (Fig. 127-11). Alveolar hemorrhage may contribute to the radiographic infiltrates in the presence of thrombocytopenia, regardless of the cause of the lung injury.

After marrow engraftment, infections are a major reason for diffuse radiographic abnormalities. Cytomegalovirus was common in the past, but it is now unusual in patients receiving appropriate prophylaxis. Diffuse pneumonia due to bacterial infections (occasionally disseminated nontuberculous mycobacterial disease, *Mycoplasma* or *Chlamydophila*) also is unusual; however, diffuse involvement with fungus may occur in as many as 20 percent of diffuse infiltrates and may be extremely difficult to detect.



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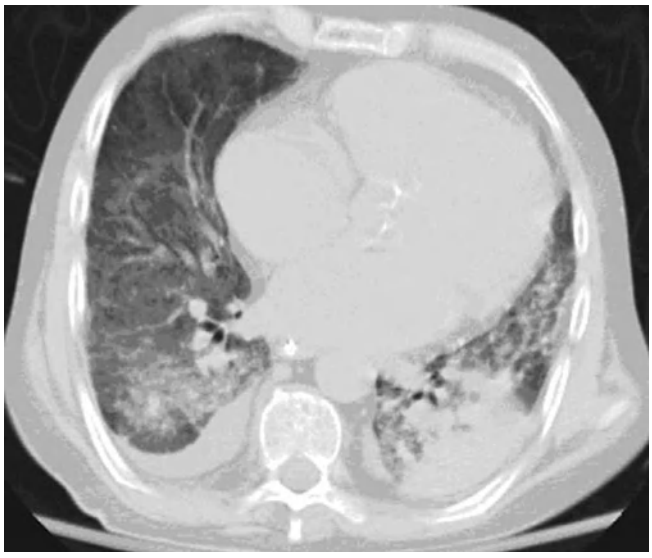


B

Figure 127-12 *A*. Diffuse process on plain radiograph of *Pneumocystis* pneumonia 8 weeks following hematopoietic stem cell transplantation for T-cell lymphoma. *B*. CT scan revealed pattern most consistent with aspiration pneumonia. Bronchoalveolar lavage revealed *Pneumocystis* and antimicrobial-resistant *Klebsiella pneumoniae*. Treatment of both processes resulted in resolution of infection.

Focal Lesions

Focal parenchymal infiltrates are frequently due to infection regardless of the time of presentation after transplant. Focal consolidations or masses are related to local fungal infection in 80 percent of marrow transplant recipients receiving broad-spectrum antimicrobials. Other causes are *Legionella* species, *Nocardia,* relapse of lymphoma in patients transplanted for that disorder, bronchiolitis obliterans with organizing pneumonia (BOOP), and, rarely, infarct due to thromboembolic disease.

Aspiration

Desquamation of the oropharyngeal mucosa is a frequent complication after intensive chemotherapy, and the stomatitis is often referred to as mucositis. It develops within the first week after radiotherapy and reaches its greatest severity after 10 to 14 days, and impaired mucociliary clearance is common. Recurrent aspiration of oropharyngeal contents is common among transplant recipients with oral mucositis due to sedation, poor cough reflex, and dysphagia. These patients may present with basilar infiltrates or consolidation.

Pleural Effusions

Pleural effusions are common in the first weeks after marrow transplantation and are rarely related to an identifiable infectious source. Pleural effusions may be associated with fluid retention of any cause, especially with ascites secondary to hepatic veno-occlusive disease (HVOD). HVOD may occur in as many as 60 percent of patients after total-body irradiation or in association with GVHD. Characteristics include weight gain within the first weeks after transplantation and elevation of the serum bilirubin, which usually precede the development of pleural effusions. The effusions are frequently bilateral. Bilateral pleural effusions in the presence of weight gain can be approached conservatively without diagnostic thoracentesis. Cautious diuresis coupled with treatment of GVHD often produces satisfactory results. Small effusions are common and may be associated with treatment-related pleuropericarditis or thromboembolic events, but a specific cause is seldom determined. A large unilateral or rapidly accumulating effusion in the presence of fever or ipsilateral chest pain may represent hemorrhage or infection and should be evaluated promptly by thoracentesis.

Non-Infectious Etiology

Non-infectious causes of lung injury after marrow and hematopoietic stem cell transplantation include a spectrum of syndromes: idiopathic pneumonia, alveolar hemorrhage, pulmonary edema, obliterative bronchiolitis, or BOOP. Idiopathic pneumonia is characterized as a syndrome of hypoxemia and radiographic nonlobar infiltrates in the absence of congestive heart failure and without evidence of an infectious origin. It is included as a form of "interstitial" pneumonia. The term *interstitial pneumonia* in marrow transplant recipients refers to the syndrome of diffuse inflammatory pulmonary disease presenting with fever and tachypnea. This term includes noninfectious causes, as well as infectious pneumonia due to viruses (CMV) or protozoa. To avoid the ambiguity of the term *interstitial* in relation to inflammatory disorders of the lung, it is preferable to classify the clinical conditions as *diffuse* pneumonia on the basis of the radiographic presentation. Most non-infectious causes of lung injury are attributed to treatment-related toxicities. Alkylating chemotherapy agents and ionizing irradiation are likely contributors; however, ARDS secondary to sepsis syndrome also may occur. While pneumonia is associated with the presence of GVHD, whether GVHD causes a direct lung injury is unproved. The role of unrecognized infections remains a concern.

Idiopathic Pneumonia Syndrome

The largest studies of idiopathic pneumonia after allogeneic marrow transplantation estimate the incidence at 12 to 17 percent. The spectrum of idiopathic lung injury is referred to as a syndrome (idiopathic pneumonia syndrome, or IPS) in recognition of the multiple causes and varied clinical presentation of this process (Table 127-11). The diagnosis of IPS is defined by a bronchoalveolar lavage (BAL) that does not reveal an infection in the presence of nonlobar radiographic infiltrates and physiological changes consistent with pneumonia. A common series of laboratory evaluations is presented in Table 127-12. Many clinicians use IPS only to describe noninfectious lung injury occurring within the first 3 to 4 months after transplantation.

Table 127-11

Criteria for Diagnosis of Idiopathic Pneumonia Syndrome

Evidence of widespread alveolar injury Multilobar infiltrates on chest radiograph or computed tomography Symptoms and signs of pneumonia Evidence of abnormal physiology
and Absence of active lower respiratory tract infection documented by Negative bronchoalveolar lavage
Lung biopsy or autopsy with examination of stains and cultures for bacteria, fungi, and viruses, including cytomegalovirus (CMV) centrifugation culture, cytology for viral inclusions and *Pneumocystis carinii*, and immunofluorescence monoclonal antibody staining for CMV, respiratory syncytial virus, influenza virus, parainfluenza virus, and adenovirus

Table 127-12

Routine Laboratory Evaluation of Bronchoalveolar Lavage Specimens in Marrow and Stem Cell Transplant Recipients

Pathology*
Wright-Giemsa stain
Papanicolaou stain
Silver stain
Modified Jimenez stain (or other suitable for detecting *Legionella*)
Fluorescent antibody stain for *Pneumocystis*
Microbiology
Stains
Gram's
Wet mount KOH or calcofluor white
Modified acid-fast
Fluorescent antibody stain for *Legionella*
Antigen/molecular
Mycoplasma PCR
Legionella urinary antigen
Cryptococcal serum antigen
Culture
Bacterial (aerobic), semi-or quantitative method
Fungal (consider epidemiology: Aspergillus, Histoplasma, Mucor—do not grind)
Legionella (chocolate yeast extract)
Mycobacterial culture
Nocardia/actinomyces
Virology
Fluorescent antibody stains†:
CMV
HSV
Adenovirus, RSV, parainfluenza, and influenza (direct fluorescent assay)
Culture or ELISA and/or molecular assay
CMV
HSV
Adenovirus
RSV, parainfluenza, and influenza viruses (in appropriate clinical setting)

** Fluorescent antibody stains may be supplemented or replaced by enzyme immunoassays (EIA) or molecular tests.*

† If available. Culture may be replaced with fluorescent antibody stains or EIA alone if culture facilities are unavailable.

The causes of diffuse idiopathic pneumonia are often multiple, and include treatment-related toxicities due to radiation or chemotherapeutic agents. However, sepsis-related pulmonary toxicity may account for a proportion of cases of diffuse idiopathic pneumonia with histology consistent with ARDS. Although GVHD is associated with an increased incidence of idiopathic lung injury, it is unclear whether this is a cell-mediated immune response to the lung or related to an increased incidence of sepsis in these immunosuppressed patients. Also, administration of large volumes of blood products during the transplantation procedure may lead to pulmonary vascular injury through leukoagglutination reactions. Other unusual causes of non-infectious diffuse pneumonia after marrow transplantation are leukemic infiltration due to relapse of primary malignancy, injection of malignant cells with reinfused autologous marrow, and fat embolization due to marrow infusion. Several cases of fat embolization have been associated with pulmonary hemorrhage and steroid administration.

The clinical presentation of IPS is nonspecific. Most patients develop a syndrome of fever, nonproductive cough, and tachypnea. Hypoxemia with hyperventilation is common. The onset is most often rapid, occurring over a few days. Occasionally, insidious onset similar to that of idiopathic pulmonary fibrosis is seen. Median onset is within the first 3 weeks of transplantation, but it may occur up to months later. The chest radiograph shows diffuse intra-alveolar and/or interstitial infiltrates. The presentation is not sufficiently distinct to be readily differentiated from that of pulmonary edema syndromes or diffuse infectious pneumonia. Marked tachypnea in the absence of radiographic infiltrates should raise the suspicion of obstructive airway disease or pulmonary veno-occlusive disease rather than idiopathic pneumonia.

IPS after marrow transplantation represents a histologic spectrum ranging from a primarily interstitial reaction with diffuse or focal widening of the alveolar septa and interstitial spaces with mononuclear inflammatory cells and edema to diffuse alveolar damage (DAD) with alveolar epithelial necrosis, intra-alveolar hyaline membranes, edema and hemorrhage, and type 2-cell hyperplasia. The predominantly interstitial presentation has been referred to as *idiopathic interstitial pneumonia,* whereas the pathology of diffuse alveolar damage is identical to that of ARDS. Variable degrees of alveolar hemorrhage may be seen with either of these presentations. By definition, all microbiologic and histologic evaluations for infectious agents (viral, protozoal, fungal, and bacterial) are negative in idiopathic pneumonia. The importance of a thorough microbiologic examination lies in the fact that these histologic presentations are similar to those of infectious pneumonia, especially cytomegalovirus pneumonia.

Mortality from idiopathic lung injury after marrow transplantation remains over 70 percent. The diagnosis of idiopathic lung injury rests largely on the results of BAL. Lung biopsy (transbronchial or open) appears to add little to the diagnostic sensitivity of BAL for infection in the presence of diffuse parenchymal infiltrates. At present, histopathology does not help to direct therapy in idiopathic lung injury after hematopoietic stem cell transplantation. Lung biopsy should be considered in cases with patchy or multifocal infiltrates because of the higher incidence of infection and concern for false-negative results from BAL. There are no

randomized studies of treatment of idiopathic lung injury after marrow transplantation. High-dose corticosteroids (ranging from 1 to 16 mg/kg per day of methylprednisolone) and other forms of intensive immune suppression are commonly used.

Pulmonary Hemorrhage

Robbins and colleagues described a potentially specific form of idiopathic pneumonia: diffuse alveolar hemorrhage (DAH). The syndrome consisted of progressive dyspnea, hypoxemia, cough, and a progressively bloodier return from BAL in autologous marrow recipients, usually within 2 weeks of transplant. The incidence of DAH was 20.5 percent and was associated with age over 40 years, high fever, transplantation for a solid tumor, severe mucositis, white blood cell recovery, and renal insufficiency. Thrombocytopenia was a common finding, and patients with (DAH) received more platelet transfusions than patients without DAH. It is unclear whether this hemorrhagic pneumonia represents a unique syndrome or represents severe lung injury in the presence of a bleeding diathesis.

Pulmonary Edema Syndromes

Biventricular failure after transplantation is often iatrogenic and associated with excessive fluid administration and an increase in total body weight. Radiographic evidence of pulmonary edema after marrow transplantation has been reported in up to 50 percent of patients, most occurring in the second week. Close attention to the total amount of sodium and fluids administered can lead to dramatic reduction in the incidence of pulmonary edema. Also, pulmonary edema may be associated with left ventricular decompensation related to cardiotoxic cytoreductive regimens, including anthracyclines in excess of 500 mg/m^2 and high-dose cyclophosphamide. Posttransplantation cardiac and pericardial toxicity occur in 4 to 10 percent of cases, usually associated with total-body irradiation and cyclophosphamide, often in the setting of prior anthracycline administration. The utility of cardiac imaging studies before transplantation to predict heart failure is limited.

The most frequent noncardiac association with pulmonary edema states is HVOD. The syndrome is often associated with interstitial pulmonary edema, the formation of pleural effusions, and renal failure. Noncardiac pulmonary edema also develops in association with acute GVHD and may be due, in part, to DAD and capillary leak. The presentation of pulmonary edema is nonspecific and usually occurs within 30 days after marrow infusion. Marrow recipients are often febrile and tachypneic at this time in the transplant course, and recipients of allogeneic marrow may display evidence suggestive of acute GVHD. Thus, the distinction between pulmonary edema and idiopathic pneumonia often cannot be made with certainty without pulmonary artery catheterization. However, recent increase in total body weight appears to correlate well with total-body fluid accumulation and should prompt a trial of diuretic therapy and a search for other signs of GVHD (GI, liver, skin) before consideration of invasive diagnostic procedures. Noninvasive assessment of cardiac function with ultrasonographic or radionuclide techniques is often warranted to guide treatment.

New-Onset Airflow Obstruction and Obliterative Bronchiolitis

About 10 percent of allogeneic marrow recipients with chronic GVHD are likely to develop airflow obstruction consistent with obliterative bronchiolitis. However, the reported incidence of obliterative bronchiolitis varies, in part, with the method used to identify the presence of the disease. Possibly because of decreased airway diameter. The onset of progressive airflow disease is related to the development of GVHD. Factors associated with the increased risk of GVHD, such as increasing age and HLA-nonidentical marrow grafts, are not independent risk factors for the development of obliterative bronchiolitis. The cause of obliterative bronchiolitis after marrow transplantation is unknown.

The main manifestation of new-onset airflow obstruction is the insidious onset of tachypnea, dyspnea on exertion, and dry, nonproductive cough. Fever is uncommon. Although the chest radiograph is commonly interpreted as normal, high-resolution chest CT often reveals parenchymal hypoattenuation and segmental bronchial dilatation. Auscultation of the chest may reveal scattered expiratory wheezing and occasionally diffuse inspiratory crackles, but results are sometimes normal. Arterial blood-gas analysis reveals moderate hypoxemia and, in the later stages, hypercarbia. Systemic evidence of GVHD is usually present. The major differential diagnoses of the gradual onset of nonspecific respiratory symptoms in the presence of a normal chest radiograph include pulmonary veno-occlusive disease and pulmonary embolism. Obliterative bronchiolitis is characterized by reduction in expiratory airflow on spirometry and increases in residual lung volumes not found in the other two diseases. Obstruction may be recognized incidentally as a result of coinfection due to respiratory viruses or *Pneumocystis*.

Patients with early onset of airflow obstruction after marrow transplantation tend to have a rapid decline in pulmonary function and a fatal outcome. These patients may not survive long enough to develop manifestations of chronic GVHD but usually display acute GVHD after BMT or HSCT. It is possible that infection plays a role in the development of the airflow obstruction in some of these patients. Marrow and stem cell recipients with later onset of airflow obstruction tend to have a more gradual decline in lung function. Airflow may stabilize in 50 percent of these patients.

There are no prospective trials of treatment for new-onset airflow obstruction. At present, the accepted approach to these patients is to aggressively control with immunomodulating agents the chronic GVHD that most often accompanies the airflow obstruction. Treatment usually consists of increased immunosuppression. Reversal of the airflow obstruction is uncommon. The usual goal of management

is stabilization of the obstruction. For this reason, prompt recognition and treatment for this progressive process are critical. Supportive measures include prophylaxis against *Pneumocystis carinii* pneumonia and *S. pneumoniae* infection, inhaled bronchodilators, supplemental immunoglobulin administration to maintain normal serum levels, and prompt treatment of intercurrent infections.

Pulmonary Veno-Occlusive Disease

Pulmonary veno-occlusive disease (PVOD) is a rare complication of treatment with chemotherapeutic regimens, and as a solitary pulmonary complication, PVOD is an uncommon but potentially catastrophic complication after transplantation. The primary histologic lesion of PVOD—obstruction of the pulmonary veins and venules by loose intimal fibrosis proliferation—may be difficult to detect with hematoxylin and eosin stains alone, and specific stains for elastic tissues, such as Verhoff–van Gieson stain, are required to demonstrate the fibrotic reaction in the veins. The typical presentation of PVOD is that of insidious dyspnea on exertion and resting tachypnea within 3 to 4 months after transplantation. Significant hypoxemia may occur along with hyperventilation. The chest radiograph is often unrevealing. On cardiac exam, there is evidence of pulmonary hypertension. Auscultation of the lungs is often normal, although scattered inspiratory crackles may be heard. Noninvasive examinations, echocardiography, perfusion-ventilation nucleotide scans, and electrocardiograms are nondiagnostic. Pulmonary function testing may be consistent with mild restrictive defect, but airflow obstruction, suggesting obliterative bronchiolitis, is absent. BAL has failed to demonstrate pathogens or inflammatory cells. The diagnostic procedure of choice is a pulmonary angiogram. Right heart catheterization reveals elevated pulmonary artery pressure, with normal pulmonary artery wedge pressures. Angiography excludes the presence of thrombi as a cause of the pulmonary hypertension. In most cases presenting after treatment for malignancy, the disease follows an insidious course, with progressive hypoxemia and dyspnea on exertion due to pulmonary hypertension. Some patients recover with high-dose corticosteroid therapy or other immunosuppressive therapy.

Infectious Etiologies

Cytomegalovirus and Viral Pneumonias

The incidence of cytomegalovirus (CMV) pneumonia has declined significantly in recent years with routine prophylaxis and monitoring. Most CMV infection occurring in seropositive patients is due to reactivation of latent infection. In the seropositive recipient of a seronegative allograft, pneumonitis may be severe. The risk of infection in seronegative patients with seronegative marrow or stem cell donors is attributable to blood product exposure, and this risk can be virtually eliminated by use of screened seronegative or filtered blood products.

Clinical Presentation

The clinical presentation of CMV pneumonia is not distinct from that of other entities associated with diffuse pneumonia. Patients with CMV pneumonia may have nonproductive cough, dyspnea, hypoxemia, or fever, with a median onset of 60 days after marrow transplant. Onset within the first 2 weeks is unusual. The period of risk of CMV pneumonia generally ends by approximately the fourth or fifth month after transplant, although later cases occur among patients with chronic GVHD or after autologous transplant. The chest radiograph generally shows bilateral infiltrates; in later stages, diffuse consolidation occurs. Unilateral, focal, and even nodular infiltrates have been seen in the early stages.

Treatment of proved CMV pneumonia remains disappointing despite the availability of effective antiviral agents, including ganciclovir, cidofovir, and foscarnet and CMV-specific immunoglobulins. Early therapy (any effect takes at least 5 days) should allow survival of up to 80 percent, but poor outcomes are common, notably in patients with respiratory failure at time of initial treatment. CMV pneumonia can be prevented in most cases with the prophylactic administration of ganciclovir or oral valganciclovir to seropositive recipients. Most seropositive patients who are at the highest risk of developing CMV pneumonia can be prospectively identified by CMV antigenemia or molecular assays on blood or sputum. Prospective use of these techniques after allogeneic transplantation permits preemptive treatment with ganciclovir, which appears to eliminate the incidence of CMV pneumonia. The side effects of the antiviral agents (neutropenia, thrombocytopenia, renal toxicity, neurotoxicity, magnesium wasting) may be limiting.

Other Viral Infections: RSV, Parainfluenza, Adenovirus, HSV, HHV-6

The respiratory viruses, particularly respiratory syncytial virus (RSV), influenza, parainfluenza (PIV), adenovirus (AV), picornaviruses, and human metapnuemovirus (hMPV), are increasingly recognized as significant pathogens in these populations. Nosocomial transmission from infected health care workers has been documented. Respiratory syncytial virus (RSV) is the most common respiratory viral pathogen in transplant recipients, but little progress has been made in managing RSV infections. Influenza annually causes increased morbidity and mortality in transplant recipients. M2 and neuraminidase inhibitors, alone or in combination, result in shorter duration of viral replication, decreased progression to lower tract disease, and reduced mortality. Parainfluenza (PIV) continues to be recognized as a significant pathogen that is a risk factor for the development of acute and chronic rejection. Therapeutic options remain limited for PIV infections. Adenovirus has recently been shown to cause asymptomatic viremia in association with respiratory infection that resolves without therapy. Approximately 20 percent of marrow transplant patients with adenovirus infection develop pneumonia (Fig. 127-11). Cidofovir appears to be the drug of choice in managing disseminated or

life-threatening adenoviral infections, but not all strains are susceptible. Rhinoviruses have recently been recognized to cause significant lower tract disease and increased mortality. Human metapneumovirus (hMPV) and coronaviruses, including severe acute respiratory syndrome (SARS)-associated coronavirus, have been recently discovered and are increasingly recognized as significant pathogens in immunocompromised hosts. Therapeutic options for both viruses are not yet clearly defined.

Pneumonia due to herpes simplex virus (HSV) or varicella zoster virus (VZV) occurs uncommonly. HSV pneumonia is generally due to contiguous spread of virus to the trachea or aspiration from the oropharynx, although it may be due to generalized infection with viremia. Pneumonia due to VZV occurs among patients with disseminated infection and viremia. Both situations have become exceedingly uncommon with the advent of acyclovir treatment and, in the case of HSV, acyclovir prophylaxis. Human herpesvirus 6, the cause of childhood roseola (exanthema subitum), has been detected in the lungs of some patients with idiopathic pneumonia. It is unclear whether this virus is a cause of pneumonia or merely latently reactivated, since virtually all adults are seropositive for the virus.

Fungal Infections

Fungal infections are reviewed in detail elsewhere. Major risk factors for invasive fungal infections are the level and duration of neutropenia, age of the patient, the presence of GVHD, total number of other infections, and immunosuppressive administration after BMT or HSCT (Table 127-8). The frequency of *Aspergillus* infections is similar in recipients of allogeneic and autologous transplants, but they occur during periods of neutropenia before engraftment among autologous marrow recipients and after engraftment and during GVHD among allogeneic recipients.

Nonbacterial Infections

Pneumocystis carinii pneumonia occurs in as many as 10 to 15 percent of HSCT recipients without the use of trimethoprim-sulfamethoxazole prophylaxis, although regional and center-to-center variations exist. Except for patients being treated for chronic GVHD (who remain at risk and who should continue to receive prophylaxis), the risk period for *P. carinii* pneumonia ends approximately 120 days after transplantation. Because it is highly effective, trimethoprim-sulfamethoxazole is the prophylactic regimen of choice. Other regimens have been discussed elsewhere. Patients with allergies to sulfa may undergo desensitization so that prophylaxis with trimethoprim-sulfamethoxazole can be administered.

Most infections with *Toxoplasma gondii* infection have had only central nervous system disease diagnosed and treated during life, while involvement of heart and lungs may be documented at postmortem. Chest radiographs show diffuse, patchy involvement. These patients have also had concomitant bacterial or viral infections. Most infections have been fatal.

Pulmonary Function Testing in Hematopoietic Stem Cell Transplantation

Pulmonary function testing (PFT) is a standard part of the pretransplant evaluation at many centers. The results form baseline data for comparison with later testing, and have been used as an indication to exclude a candidate for transplantation. Abnormalities in the measures of airflow, lung volume, and diffusing capacity have been associated with increased risk of pulmonary complications after transplantation. After accounting for other clinical characteristics associated with death after transplantation (age, relapsed malignancy, HLA-mismatched graft), restrictive lung defect (decreased total lung capacity), hypoxemia, and reduced diffusing capacity are associated with statistically increased risk of death, especially within the first few months after transplant. The risks associated with these PFT results are applicable to autologous as well as allogeneic marrow recipients, suggesting that they predict mortality due to treatment-related toxicities. Hypoxemia and reduced diffusing capacity were independently associated with death, each carrying risk.

PFT performed after marrow transplantation has consistently revealed reductions in lung volumes and diffusing capacities associated with total-body irradiation and intensive chemotherapy. PFT abnormalities have been reported to include declines in lung volume, gas diffusion, and airflow. Losses of lung volume are more pronounced among patients who survive pneumonia after transplant. The declines in lung volume may be at least partly reversible within 2 years after transplantation, whereas the low diffusing capacity reportedly persists for several years. Development of airflow obstruction has been seen in approximately 10 percent of allogeneic marrow recipients in the presence of chronic GVHD and most often is related to obliterative bronchiolitis. Such PFT results strongly suggest that lung parenchymal and vascular injury are common features of marrow transplant, even in the absence of recognized infection or idiopathic pneumonia.

SOLID ORGAN TRANSPLANTATION

Timetable of Infection

As immunosuppressive regimens have become standardized in recent years, it has become apparent that *different infectious processes occur at different points in the posttransplant course.* That is, although pneumonia can occur at any point in the posttransplant course, the etiology of pneumonia varies depending on the amount of time that has passed since transplantation (Fig. 127-2).

Infections in the First Month after Transplantation

In the first month after transplant, two major causes of pulmonary infection apply to all forms of organ transplantation. The first is the recurrence of pneumonia that was present prior to transplantation (in the lung allograft donor or in the recipient), but was incompletely treated, and which may be

exacerbated after transplant due to superinfection with nosocomially acquired gram-negative bacilli and fungal species. This is most commonly seen in patients with end-stage liver or cardiac disease who require critical care support prior to transplant. Second, infection due to aspiration of nosocomial flora is often the result of postoperative vomiting (because of gastric distention or metabolic dysfunction) or due to a technical problem with the endotracheal tube in the perioperative period. The risk of antimicrobial-resistant pneumonia increases with the duration of the pretransplant hospitalization as well as with the duration of posttransplant intubation or ventilatory restriction (following the transplant operation).

Donor-derived infection has been recognized in many recipients of lung transplants (mycobacteria, Aspergillus, colonizing gram-negative bacteria), occasionally with rapid progression after transplantation. It is essential to distinguish early lung allograft dysfunction from diffuse infection due to donor-derived viruses (HSV, VZV, CMV, respiratory viruses) or other pathogens (e.g., Mycoplasma). Extensive pulmonary injury before transplant places the patient at high risk for postoperative pneumonia that is poorly responsive to therapy. In the special case of the lung transplant patient who may require prolonged intubation, bacterial pneumonia and infection that threatens the bronchial anastomosis, particularly with *Aspergillus*, are special concerns. These patients require exquisite attention to the technical aspects of the transplant procedure, to the management of the endotracheal tube, and the maintenance of pulmonary toilet (including, on occasion, repeated therapeutic bronchoscopy).

Notable by their absence in the first posttransplant month are the opportunistic infections, despite the fact that the highest daily doses of immunosuppression are administered during this first month. This emphasizes that it is the *sustained exposure to immunosuppressive therapy,* the area under the curve, that is the major determinant of the net state of immunosuppression.

Infections 1 to 6 Months after Transplantation

In the period 1 to 6 months after transplant, the nature of pulmonary infection changes markedly. During this time period the immunomodulating viruses, particularly CMV, are of importance in terms of direct effects (invasive disease) and immunological or indirect effects (rejection, opportunistic infections). CMV can directly cause pneumonia itself; CMV may contribute to the incidence of graft rejection necessitating increased exogenous immune suppression and increasing the risk of opportunistic infection; or CMV (and the other immunomodulating viruses) are globally immunosuppressive and can enhance the likelihood of pulmonary infections due to *Pneumocystis carinii, Aspergillus* species, and *Nocardia asteroides* in the *absence* of an unusual epidemiologic exposure. Unlike the bone marrow transplant recipient, the risk of active CMV *disease* (as compared with viral secretion) in the solid organ transplant recipient is greatest in the CMV-seronegative recipient of an organ from a seropositive donor. Thus, CMV prevention and the utilization of diagnostic techniques for CMV viremia (e.g., antigenemia assays, polymerase chain reaction testing, shell vial cultures with early antigen detection) are important parts of the therapeutic program.

During this period, *in the absence of specific prophylaxis,* significant nonviral pulmonary infections are also common including those due to *P. carinii, Aspergillus* species, endemic fungi *(Histoplasma, Coccidioides)* and *Nocardia asteroides* (Figs. 127-13 and 127-14). There is important regional variation in the occurrence of each of these pathogens. At centers with high endemicity of these infections, low dose trimethoprim-sulfamethoxazole prophylaxis (which effectively eliminates *Pneumocystis* and nocardial infection) and epidemiologic protection against *Aspergillus* (as with a HEPA filtered air supply within the hospital) are effective, particularly in the context of effective CMV prevention.

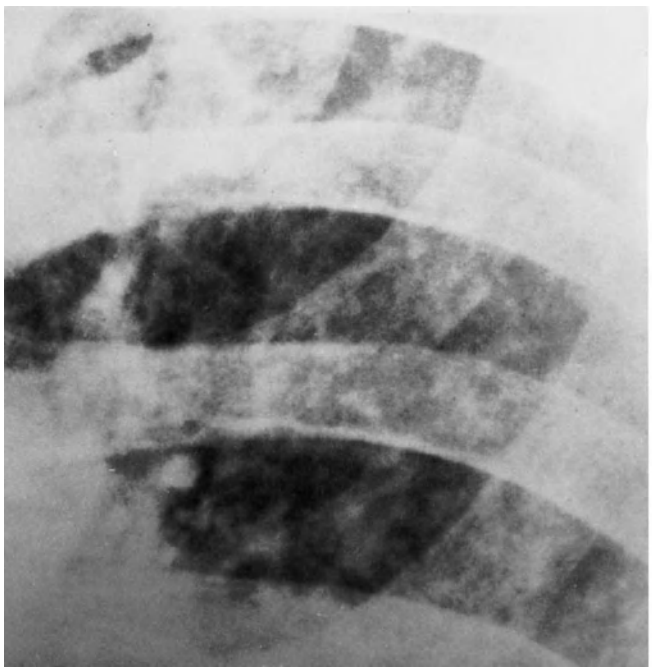
Infections beyond 6 Months after Transplantation

In the period more than 6 months after transplant, patients can be divided into two groups in terms of the forms of pulmonary infection that can develop. Most patients have a good result from their transplant and have good allograft function and receive relatively modest levels of maintenance immunosuppression. These patients are subject to community-acquired respiratory virus infection, particularly influenza and RSV, and pneumococcal pneumonia. The remaining patients have had a less positive outcome from their transplant; these individuals have less satisfactory graft function and require far more intensive acute and chronic immunosuppressive therapies to manage rejection. These patients, often termed "chronic ne'er do wells," are the subgroup of transplant patients at highest risk for pulmonary infection with such organisms as *Pneumocystis carinii, Cryptococcus neoformans, Nocardia asteroides,* and *Aspergillus* species (Fig. 127-15). For this subgroup of patients, prolonged trimethoprim-sulfamethoxazole prophylaxis, epidemiologic protection, and a consideration of fluconazole prophylaxis are indicated. Notable among the ne'er do well group is the liver transplant recipient with recurrent hepatitis C infection, the lung transplant with cystic fibrosis and resistant *Pseudomonas* or *Stenotrophomonas* infections, and the kidney transplant with chronic allograft dysfunction.

Radiologic Clues to the Diagnosis of Pneumonia in the Organ Transplant Patient

The presentation and evolution of the chest radiograph provide important clues to both the differential diagnosis of pulmonary infection in the transplant patient and the appropriate diagnostic workup that should be undertaken (Table 127-13). The following radiologic parameters are useful in developing clinical-radiologic-pathologic correlations:

1. Time of appearance, rate of progression, and time to resolution of pulmonary roentgenographic abnormalities in relation to clinical events.
2. Distribution of radiologic abnormalities. An abnormality confined to one anatomic area is considered



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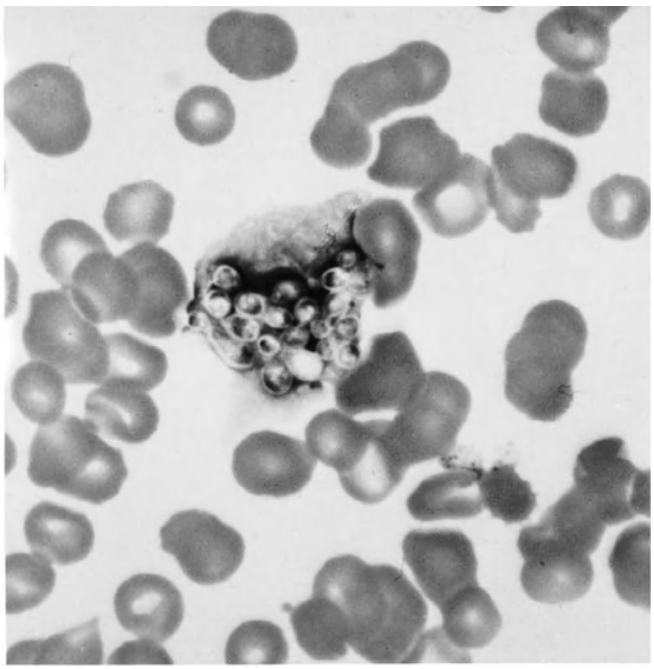


B

Figure 127-13 A 56-year-old man, lifelong resident of Kansas, presented 2½ years after a renal transplant with fever, nonproductive cough, and 3-month weight loss. The chest radiograph was diffusely abnormal. *A*. Close-up reveals extensive micronodular disease. *B*. Peripheral blood smear shows a macrophage laden with *Histoplasma capsulatum*. Treatment with liposomal amphotericin B resulted in clearing of the radiograph and cure of the infection.

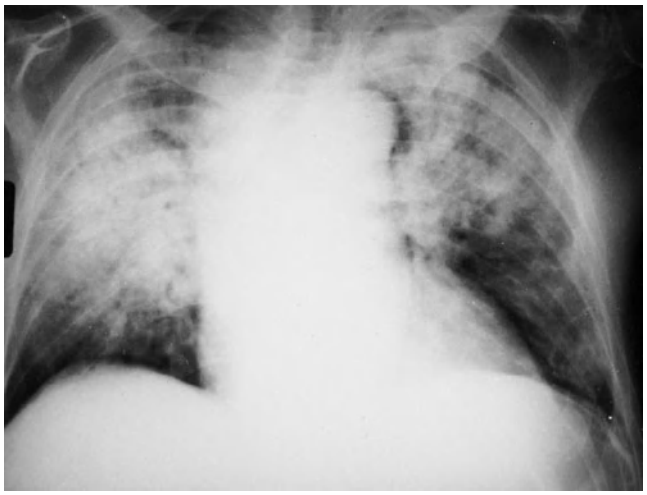
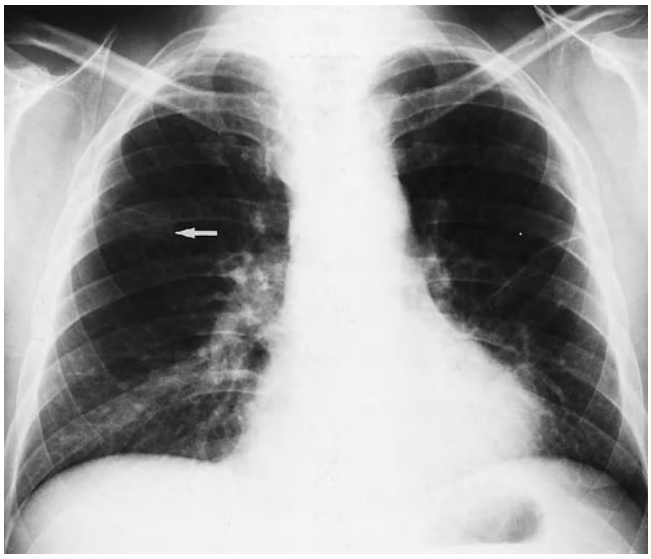


Figure 127-14 Invasive pulmonary aspergillosis after liver transplantation. A diffuse *Klebsiella* pneumonia was treated, with a good clinical response to therapy. After 2 days without fever, the patient became febrile with increasing shortness of breath although the chest radiograph remained unchanged. One day after this radiograph was taken, the patient died. Autopsy revealed two processes in the lungs: a diffuse gram-negative pneumonia and focal areas of invasive aspergillosis restricted to the right lower and middle lobes. This figure illustrates the difficulty in differentiating the focal areas of *Aspergillus* superinfection from the primary bacterial process.

focal, whereas widespread lesions are considered *diffuse*. Abnormalities that are present in more than one area, but are countable, are termed *multifocal*. As visualized particularly on computed tomographic scanning (CT), abnormalities may be located *centrally* or *peripherally* or both.

3. Which of three types of pulmonary infiltrate is present? The first type is a *consolidation*, in which there is substantial replacement of alveolar air by material of tissue density, typically with air bronchograms and a peripheral location of the abnormality. The second type is *peribronchovascular* (or *interstitial*), in which the infiltrate is predominantly oriented along the peribronchial or perivascular bundles. Finally, *nodular* lesions are space-occupying, nonanatomic lesions with well-defined, more or less rounded edges surrounded by aerated lung.
4. Other characteristics. These include pleural fluid, atelectasis, cavitation, lymphadenopathy, and cardiac enlargement. Pleural fluid is a clue to congestive heart failure and fluid overload when bilateral, and to necrotizing or granulomatous infection, especially when associated with lymphadenopathy or cavitation, when unilateral.

By combining this classification with information concerning the rate of progression of the illness (Table 127-13), a useful differential diagnosis is then generated. Thus, focal or multifocal consolidation of acute onset quite likely is



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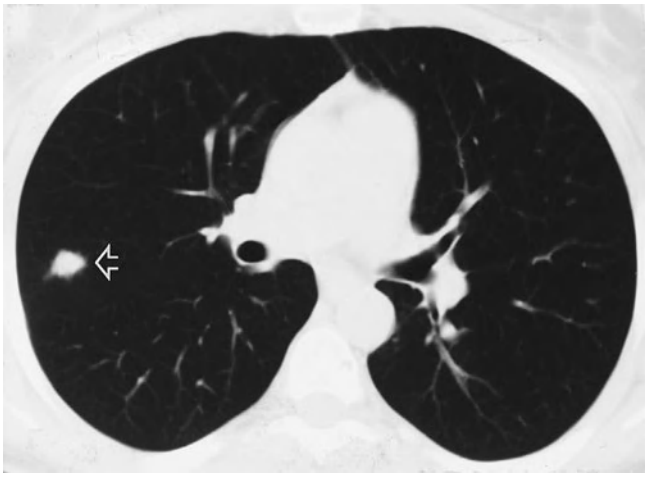

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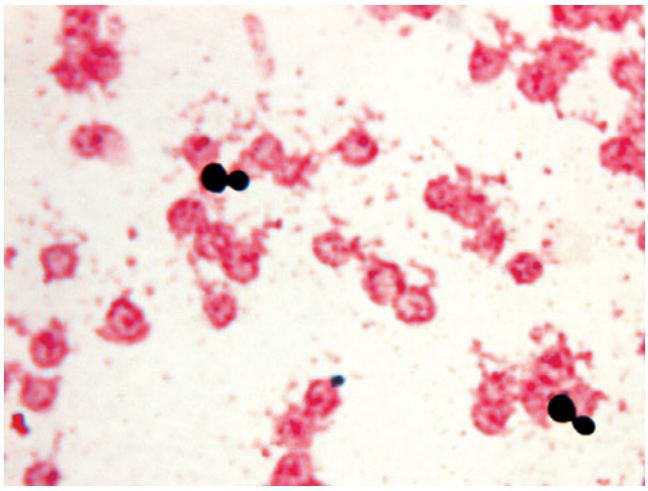


C

Figure 127-15 *Cryptococcus neoformans* in an asymptomatic renal transplant patient. The patient presented with minimal complaint of nonproductive cough of a few weeks' duration. *A*. The chest radiograph was essentially clear other than a shadow in the right midlung field (arrow). *B*. Chest tomography revealed a nodular lesion in the right midlung field (arrow). Percutaneous needle aspiration of this lesion yielded *Cryptococcus neoformans* on fungal culture. *C*. India ink stain of cerebrospinal fluid from same patient reveals narrow-based budding yeast forms consistent with *Cryptococcus neoformans*.

caused by bacterial infection. Similar multifocal lesions with subacute to chronic progression are more likely secondary to fungal, tuberculous, or nocardial infections. Large nodules are usually a sign of fungal or nocardial infection in this patient population, particularly if they are subacute to chronic in onset. Subacute disease with diffuse abnormalities, either of the peribronchovascular type or miliary micronodules, is usually caused by viruses (especially CMV) or *Pneumocystis carinii* (or, in the lung transplant patient, rejection). Additional clues can be found by examining the pulmonary lesion for the development of cavitation, with cavitation suggesting such necrotizing infections as those caused by fungi, *Nocardia,* and certain gram-negative bacilli (most commonly with *Klebsiella pneumoniae* and *Pseudomonas aeruginosa*). The depressed inflammatory response of the immunocompromised transplant patient may greatly modify or delay the appearance of a pulmonary lesion on radiograph, particularly if neutropenia is complicating the effects of the antirejection therapy. CT of the chest has revolutionized the evaluation of these immunocompromised patients, and CT is particularly useful when the chest radiograph is negative or when the radiologic findings are subtle or nonspecific (Fig. 127-15). An additional important application of CT in this patient population is defining the extent of the disease process. Particularly with opportunistic fungal and nocardial infection, precise knowledge of the extent of the infection at diagnosis, and the response of all sites to therapy, lead to the best therapeutic outcome, as therapy should be continued until all evidence of infection is eliminated, not just the primary site. CT findings are also quite useful in defining which invasive diagnostic procedure should be used to obtain diagnostic samples and in identifying the anatomic site at which sampling should be directed to optimize the diagnostic yield.

PRIMARY IMMUNE DEFECTS

Primary immune deficiencies are defined as alterations in the immune system that are congenital, as opposed to those

Table 127-13

Differential Diagnosis of Fever and Pulmonary Infiltrates in the Organ Transplant Recipient According to Roentgenographic Abnormality and the Rate of Progression of the Symptoms

Chest Radiographic Abnormality	Etiology According to the Rate of Progression of the Illness	
	Acute*	**Subacute-Chronic***
Consolidation	Bacterial (including Legionnaries' disease) Thromboembolic Hemorrhage (Pulmonary edema)	Fungal Nocardia Tuberculosis Viral (Drug-induced, radiation, *Pneumocystis* tumor)
Peribronchovascular	Pulmonary edema (Leukoagglutinin, reaction bacterial)	Viral *Pneumocystis* (Fungal, nocardial, tuberculous, tumor)
Nodular infiltrate†	(Bacterial, pulmonary edema)	Fungal Nocardial Tuberculous (*Pneumocystis*)

** An acute illness develops and requires medical attention in a matter of relatively few hours. A subacute-chronic process develops over several days to weeks. Note that unusual causes of a process are in parentheses.*

† A nodular infiltrate is defined as one or more large (> 1 cm^2 on chest radiography) focal defects with well-defined, more or less rounded edges, surrounded by aerated lung. Multiple tiny nodules of smaller size, as sometimes caused by such an agent as CMV or varicella-zoster virus, are not included here.

related to chemotherapy, autoimmune disease, organ transplant, or chronic systemic disease. Clinical problems that require evaluation of the immune system include chronic or recurrent bacterial or fungal infections of the skin, sinuses, and respiratory and digestive tracts and repeated infections with unusual viruses. Other suggestive signs and symptoms are persistent atypical rashes, chronic diarrhea, failure to thrive, paucity of lymphoid tissue, lymphadenopathy, chronic conjunctivitis, and unusual reactions to live virus vaccines. The evaluation of recurrent infections should analyze all compartments of the host defense system, including anatomic structures, mucociliary function, B- and T-cell activity, phagocytic cell function, and complement activity. Table 127-14 outlines both initial and confirmatory screening tests available to most clinicians.

Antibody (B-Cell) Deficiency

Antibody deficiency states are among the most common of the primary immunodeficiency diseases. Although the defect in immunoglobulin production can occur at any point in B-cell maturation/activation or secretion of antibody, or even in T- and B-cell interaction, the end result is a decrease in serum antibody levels or the inability to respond to antigens with specific antibody. Patients typically present with recurrent sinopulmonary infections caused by encapsulated bacteria such as *Streptococcus pneumoniae, Haemophilus influenzae* (both type b and non-typable), and *Staphylococcus aureus.* Diseases caused by mycoplasma, enteroviruses, and intestinal parasites also are seen occasionally. The incidence of autoimmune abnormalities and hematologic malignancies is also significant in patients with these defects. Treatment for most of these defects relies on the administration of gammaglobulin. Annual chest radiographs and pulmonary function tests are especially helpful, given that the lung disease in patients with hypogammaglobulinemia may be insidious in onset and progression.

X-Linked Agammaglobulinemia

X-linked agammaglobulinemia (XLA or Bruton's agammaglobulinemia) is a relatively common inborn error of immunity, occurring in 1 per 50,000 live births. A block in the normal maturation of immunoglobulin-producing B cells (block in VHDJH recombination) results in the absence or severe reduction of serum immunoglobulin, absence of circulating mature B cells, and absence of plasma cells in all lymphoid tissue. T-cell number and function are intact. Inheritance is sex-linked recessive, although a clinically indistinguishable syndrome with autosomal recessive inheritance has been observed in some patients. Recent studies have localized the defect to a protein tyrosine kinase gene (Bruton's tyrosine kinase, *btk*) on the proximal region (q21.3–q22) of the X chromosome. After maternal antibody is consumed (usually after the first 4–6 months of life), patients develop sinopulmonary infections, bacteremia, and meningitis with encapsulated gram-positive and -negative bacteria, such as *H. influenzae, S. pneumoniae, S. aureus, Pseudomonas aeruginosa,* and

Table 127-14

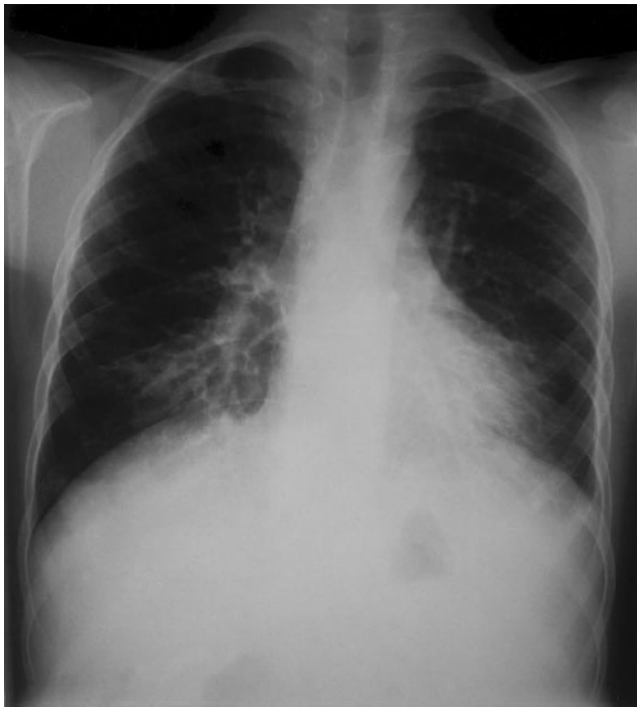
Immunologic Workup of Primary Immune Deficiencies

Suspected Abnormality	Screening Tests	Confirmatory Tests
Antibody deficiency	Serum IgM, IgG, IgA levels IgG antibody response to protein (diphtheria, tetanus, influenza) and polysaccharide (pneumococcus, *Hemophilus influenzae*) antigens Isohemagglutinin titers for IgM antibody response Serum IgG subclass levels	B-cell enumeration (total B [CD20] surface IgM-, IgG-, IgA-, IgD-bea B cells) In vitro immunoglobulin synthesis
Cell-mediated immunodeficiency	Total lymphocyte count Delayed hypersensitivity skin tests (diphtheria, Tetanus, *Candida*, PPD, SK/SD for T-cell function) Tests for HIV antibodies	Enumerate total T cells and T-cell subsets (CD3, CD4, CD8) Measure T-cell function with mitogenic, antigenic, and allogenei (mixed lymphocyte reaction) respo lymphokine production, cytotoxic Assays for Th and Ts activity Enzyme assay (ADA, PNP) for ADA PNP deficiency
Complement deficiency	CH_{50} or CH_{100} for classical pathway activity APH_{50} for alternative pathway activity Serum C2, C3, C4, C5, and factor B levels	Other specific component levels C1 esterase inhibition levels C1 esterase functional component
Phagocyte defects	NBT test for respiratory burst activity (defect in CGD) Serum IgE levels for HIE	Leukocyte adhesive protein analysis: (CD11a/CD18, CD11b/CD18, and CD11c/CD18) Adherence and aggregation Chemotaxis and random motility Phagocytosis Assays for respiratory burst activity (chemiluminescence, oxygen radiography production) Bacterial killing test Enzyme assay (MPO, glucose-6-phosphate dehydrogenase) for phagocyte enzyme defects Cytochrome *b* or cytosolic protein measurement for CGD

Mycoplasma pneumoniae. Respiratory disease due to *Pneumocystis carinii* or gastrointestinal infection with *Giardia lamblia* is also commonly observed. Although viral infections are not typical, enterovirus (polio and echo) and hepatitis viruses may cause severe or fatal disease. Autoimmune diseases, such as rheumatoid arthritis, occur in up to 20 percent of patients, whereas lymphomas and other lymphoreticular malignancies occur in approximately 5 percent of cases. IgG levels are very low (less than 100 mg/dl), and IgA and IgM are often undetectable.

Common Variable Immunodeficiency

Common variable immunodeficiency (CVI) is a common defect in general due to B-cell activation or differentiation defects, resulting in low serum levels of IgG and depressed levels of IgA or IgM. B cells may be normal, high, or low, and T-cell number and function, although usually normal at diagnosis, deteriorate with time. Although the disease is familial, it is not strictly X-linked or autosomally inherited. In some patients, the genomic defects of both CVI and isolated IgA deficiency appear to be localized to the major histocompatibility



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		Actual	Pred.	%Pred.
LUNG MECHANICS				
FVC	(L)	1.03	2.92	35
FEV1	(L)	0.97	2.56	38
FEV1/FVC	(%)	94	88	
FEF 25%	(L/sec)	7.10	4.82	147
FEF 50%	(L/sec)	2.98	3.51	85
FEF 75%	(L/sec)	0.80	1.89	43
FEF MAX	(L/sec)	7.34	6.46	114
FEF 25-75%	(L/sec)	2.29	2.95	78

B

Figure 127-16 *A*. PA chest radiograph of an adolescent boy with common variable immunodeficiency demonstrating marked bibasilar opacification, atelectasis, and infiltrative changes. Sputum culture grew only *H. influenzae* (non-typable). *B*. Pulmonary function tests from the same patient demonstrate significant restrictive, obstructive disease, supported by RV/TLC measurements. Marked improvement in radiographs and pulmonary function tests occurred with the use of continuous, rotating ciprofloxacin, Ceclor, and Biaxin, in conjunction with aggressive chest percussion via a percussor vest and inhaled DNAse.

complex region of chromosome 6.The disease is characterized by the development of recurrent sinopulmonary infections or chronic bronchiectasis in childhood or adulthood. Chest radiograph findings consistent with atelectasis, bronchiectasis, and/or interstitial markings, along with pulmonary function tests revealing mild to severe obstruction and restrictive disease, are seen in 60 to 80 percent of CVI patients (Fig. 127-16). A few patients with CVI present with infections with unusual organisms, such as *P. carinii*, mycobacteria, or fungi. Recurrent attacks of both herpes simplex and zoster are not uncommon.

Selective IgG Subclass Deficiencies

Patients with selective IgG subclass deficiencies have recurrent sinopulmonary infections associated with normal or decreased total concentrations of serum IgG, but with selective deficiencies of IgG subclass 1, 2, 3, or 4. Patients with IgG2 subclass deficiency can make antibody, but the spectrum of the response is decreased, resulting in recurrent infection. Recent studies suggest a critical role for IL-6 and IFN-γ in enhancing IgG subclass production. Titers to bacterial polysaccharide antigens are low even after immunization, since antibody responses to polysaccharides reside predominantly in the IgG2 subclass. Titers to protein antigens such as tetanus or diphtheria toxoids may be normal. IgG2 subclass deficiency may be associated with IgG4 subclass deficiency, IgA deficiency, Wiskott-Aldrich syndrome, and ataxia-telangiectasia. Persons with low or absent IgG2 or IgG4 appear to be particularly predisposed to recurrent or severe pneumonias and middle ear infections. Selective IgG3 deficiency is also associated with recurrent sinopulmonary infections, but the mechanism is not clear. These IgG3-deficient patients have normal responses to both common protein (Dt) and polysaccharide antigens; however, responses to influenza or rubella vaccine may be abnormal. Treatment is based on clinical findings of recurrent infections, rather than isolated laboratory abnormalities. It is important to document not only a low concentration of a subclass but also failure to make specific antibody when immunized, before immunoglobulin therapy is contemplated.

Selective IgA Deficiency

This most common of all the inborn defects of humoral immunity, occurring in 1 per 700 persons, accounts for more than 1 percent of recurrent infections in children. The defect is assumed to be a differentiation block affecting IgA-committed B cells. Typically, peripheral counts of patients with IgA deficiency show normal numbers of mature B lymphocytes, as well as normal numbers and proportions of CD4 and CD8 cells. Selective IgA deficiency has been defined as serum IgA less than 5 mg/dl in severe deficiency and greater than 5 mg/dl but less than 2 SD below the age normal mean in partial IgA deficiency. The diagnosis and treatment of IgA deficiency depend not only on the serum level of IgA but also on the history and results of related diagnostic studies, particularly the immune workup. In general, treatment relies on the administration of appropriate antimicrobials for acute infection or chronic suppressive therapy for chronic infection. When IgA deficiency is associated with IgG2 deficiency, IVIG depleted of IgA may be indicated.

Hyper-IgM Immunodeficiency

These patients have absent or markedly reduced IgA, IgE, and IgG levels, elevated levels of IgM, circulating mature B lymphocytes bearing IgM or IgD and plasma cells, as well as hyperplastic lymphoid tissue. Recurrent neutropenia, probably secondary to autoimmune phenomena, may coexist with the humoral defect. Because antibody protection for the

gastrointestinal and respiratory tracts is normally provided by IgA and IgG isotypes, patients with this syndrome are especially prone to respiratory and GI infections with pyogenic organisms. They are also predisposed to *P. carinii* pneumonia. As with other immunoglobulin deficiencies, patients with the hyper-IgM syndrome have very high rates of autoimmune (involving the formed elements of the blood) and lymphoproliferative disorders.

Complement Disorders

Disorders due to primary deficiencies of complement components are rare causes of pulmonary infections. Complement function can be assessed by determining the total hemolytic activity in serum (CH50), which measures the ability of serum to lyse antibody-coated sheep cells. A low to absent CH50 suggests a deficiency in a classic pathway complement component. Levels of specific complement components can then be determined.

Congenital absence of C3 or consumption of C3 due to deficiency of factor I (C3b inactivator) results in a clinical picture like that seen in deficiency of the critical antibody opsonins, including infections due to pyogenic bacteria including severe and recurrent pneumonias due to *S. pneumoniae, H. influenzae,* and Enterobacteriaceae.

The terminal complement components, C5–9, form the cytolytic membrane attack complex (MAC), and deficiency of any one of these will block MAC formation. C5–9 deficiencies predispose to disseminated infection with *N. meningococci* and *N. gonococci.*

C1 esterase inhibitor deficiency results in persistent consumption of C2 and C4 by the C1 esterases, resulting in release of vasoactive kinins and the development of nonpruritic angioedema. Although angioedema can occur in any tissue, including the GI tract, edema of the upper airway can be life threatening. Diagnosis is suggested by family history (autosomal dominant state), edema without pruritus, and chronically decreased C4 and C2 levels, especially during the 24 to 72 h of the episode. Patients with the familial form of the disease have low to absent C1 esterase inhibitor concentrations. Angioedema with later onset, without a familial pattern, may be due to the absence of the functional component of the inhibitor, which may be associated with malignancy. Treatment is with danazol or purified C1 inhibitor for acute attacks.

Cell-Mediated Immunity

Although the most characteristic infections in patients with cellular immune deficiency are those caused by opportunistic intracellular pathogens, including protozoa (*P. carinii* and *Toxoplasma gondii*), fungi (*Candida* and *Aspergillus* species), viruses (particularly those of the herpesvirus family), and some intracellular bacteria (including *Listeria* and *Mycobacteria* species), defects in humoral or phagocyte defense mechanisms can also be seen.

DIGEORGE'S SYNDROME

DiGeorge's syndrome (DGS) is a constellation of abnormalities resulting from dysmorphogenesis of the third and fourth pharyngeal pouches. Patients have hypoplasia or aplasia of the thymus and the parathyroid glands, complex cardiac malformations, esophageal atresia, bifid uvulas, cleft palate, short philtrums, mandibular hypoplasia, hypertelorism, and low-set notched ears. The severity of immunologic manifestations varies from severe forms with complete thymic aplasia, resembling severe combined immunodeficiency disease (SCID), to only latent hypoparathyroidism, which may also be seen in relatives of patients with DGS. Most patients have partial T-cell function, which may improve with age, presumably due to the adaptation of functional extrathymic sites for T-lymphocyte maturation. T-cell numbers are typically reduced, with reduced percentages of CD3 and CD4 cells, but CD8 cells may be normal or even elevated. Patients with more significant CD4 T-cell deficiency seem to have more frequent and severe infections requiring hospitalization. B-lymphocyte counts are usually normal; antibody production is also usually normal, but of poor biologic quality. Some patients may have low IgA or elevated serum IgE levels. Surviving infants often have the tendency to acquire parathyroid function, cell-mediated immunity, and functional T cells. Patients are prone to severe viral pneumonias, particularly those of the herpes and measles family. Pneumonias due to fungal and gram-negative bacilli and *P. carinii* also occur.

Severe Combined Immunodeficiency Disease

SCID is a syndrome of heterogeneous lymphocyte stem cell defects that affect both T- and B-cell function, resulting in profound hypogammaglobulinemia and absence of T-cell function. Laboratory analysis may reveal lymphopenia (10–20 percent) and normal or increased numbers of circulating B cells, but severely reduced IgG levels. In general, SCID syndrome patients present with a triad of mucocutaneous candidiasis, intractable diarrhea, and *P. carinii* pneumonia, evident shortly after birth or within 6 to 9 months of life and progressing to severe failure to thrive. Within a few days after birth, patients may also develop a morbilliform rash that is probably a manifestation of graft-vs-host disease (GVHD) from passively transferred maternal lymphocytes. Infections with a wide range of microbes occur in all forms of SCID, including viral pathogens, particularly herpesviruses (herpes, cytomegalovirus, and varicella), adenovirus, measles, influenza, and *Legionella.* Fatal giant-cell pneumonia has resulted from measles infection and live measles vaccination, and progressive vaccinia has occurred after smallpox vaccination.

Purine Nucleoside Phosphorylase

Absence of the enzyme purine nucleoside phosphorylase (PNP) is associated with marked cell-mediated immunodeficiency but intact humoral immunity. The gene encoding the enzyme is localized to chromosome 14q13.1. Patients are

prone to disseminated viral infections, *P. carinii* infection, mucocutaneous candidiasis, and chronic diarrhea. Neurologic disorders afflict more than 50 percent of patients, and more than a third of PNP patients develop autoimmune diseases.

Wiskott-Aldrich Syndrome

Wiskott-Aldrich syndrome (WAS) is caused by a defect localized to the short arm of the X chromosome (Xp11.22–11.3), resulting in severely impaired production of antibodies to polysaccharide antigens, as well as variable reductions of T-cell numbers and impaired mitogen responses that tend to worsen with age. Both T-cell numbers and function progressively decrease, and profound lymphopenia becomes apparent at approximately 6 years of age. Most patients have abnormalities of serum immunoglobulin levels, with low IgM and isohemagglutinin concentrations, a tendency toward elevated IgA and IgE levels, and normal or slightly depressed IgG levels. Males afflicted with this syndrome suffer from a triad of recurrent infections, thrombocytopenia, and a skin disease indistinguishable from atopic dermatitis. Typical infections include pyoderma or cellulitis associated with eczematoid eruptions, chronic otitis media with persistent otorrhea and/or mastoiditis, and chronic pneumonitis. Encapsulated pyogenic bacteria, such as *S. pneumoniae, H. influenzae,* herpesvirus, and *P. carinii,* are the most frequently identified pathogens.

Ataxia-Telangiectasia

This syndrome (AT) is characterized by profound deficiencies of cellular immunity (including lymphopenia, defects in cutaneous anergy, decreases in Th:Ts ratios, decreases in cytotoxic T cells, and an increase in immature T cells with increased γ/Δ TCR expression), impaired humoral responses (thymic hypoplasia associated with IgA deficiency, IgE deficiency, and IgG2 and IgG4 subclass deficiency), and a constellation of progressive cerebellar ataxia with degeneration of Purkinje cells. The defective genes of the two most common AT variants map to chromosome 11q22.3, which may result in a recombination defect that interferes with the rearrangement of T- and B-cell genes, an inability to repair damaged DNA, and a failure of normal organ maturation. Telangiectasias, particularly ocular and cutaneous, and a high incidence of malignancies, particularly non-Hodgkin's lymphoma, and breast cancer (in heterozygous female carries of the AT allele) are seen. AT is also associated with insulin-resistant diabetes mellitus, gonadal agenesis, premature aging, elevated levels of serum α_1-fetoprotein and carcinoembryonic antigen, and hypersensitivity of fibroblasts and lymphocytes to ionizing radiation, reflecting an inability to repair damaged DNA. Patients suffer from an increased incidence of bacterial and viral sinopulmonary infections, and many eventually develop chronic bronchiectasis. The most frequent pulmonary pathogens are *S. aureus* and other encapsulated bacteria. Concurrent IgG2 (50 percent), IgG4, and IgA deficiencies (70 percent) may be associated with the tendency toward recurrent infections of the respiratory tract. Approximately 80 percent of patients have depressed IgE levels.

Phagocytic Defects

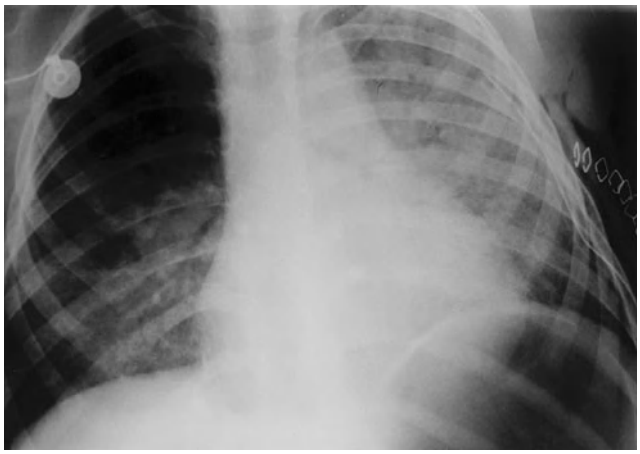
Disorders of Phagocyte Numbers

These disorders include cyclic neutropenia, Felty's syndrome, Kostmann's syndrome, Shwachman-Diamond syndrome, and autoimmune neutropenia. They are characterized by absolute PMN counts as low as 50 to 200/mm but typically lower than 1000/mm. Owing to the presence of a compensatory monocytosis, these disorders are associated with a low incidence of severe respiratory infections, although pneumonia is seen—as are furunculosis, subcutaneous abscess, and otitis media. Typical pathogens include *S. aureus, P. aeruginosa,* and enteric bacteria.

Defects of Phagocyte Function

Chronic Granulomatous Disease

CGD is caused by a defect in a membrane-associated nicotinamide adenine dinucleotide phosphate (NADPH) oxidase in phagocytic cells, resulting in the failure of phagocytic cells to produce superoxide, hydrogen peroxide, and other reduction products of oxygen that are necessary for killing certain microbial species. Diagnosis is made by the inability of neutrophils to reduce nitroblue tetrazolium (NBT) from yellow to blue-black formazan and by the inability of neutrophils to kill staphylococci or other catalase-positive microorganisms. Additional laboratory findings suggestive of CGD include leukocytosis, elevation of erythrocyte sedimentation rate, abnormal chest radiographs, and hypergammaglobulinemia. Onset is typically in infancy, childhood or, less commonly, early adolescence, with a male-to-female ratio of 6:1. All forms of CGD are characterized by abscess formation at sites of bacterial tissue invasion and in lymph nodes, liver, and lung. Patients present with severe recurrent lymphadenitis and infections of the skin, sinopulmonary, and GI tracts. Severe and recurrent pulmonary infections occur in almost all patients with CGD, including bronchopneumonia, empyema, lung abscess, and hilar adenopathy syndromes. Most young adult patients demonstrate chronic bilateral infiltrates, pulmonary fibrosis, or pulmonary calcifications associated with restrictive/obstructive disease. Aggregates of granulomas, leading to mechanical obstruction, may form as a response of activated macrophages to microbial persistence and chronic antigenic stimulation. *S. aureus* represents by far the most common cause of infections in CGD. Other catalase-positive and non–H_2O_2-producing organisms include *Escherichia coli, Klebsiella,* and *Enterobacter* species, *Serratia marcescens, Salmonella,* and *Pseudomonas* species. Pneumonias in CGD patients may be caused by *Mycobacterium tuberculosis,* atypical mycobacteria, and *P. carinii.* In specific geographic locations, such as the southeastern United States, *Chromobacterium violaceum* has been recognized as the cause of infection in several CGD patients. *Nocardia* infection, particularly of the respiratory system, is also relatively



A

		Actual	Pred.	%Pred.
LUNG MECHANICS				
FVC	(L)	0.75	1.05	72
FEV1	(L)	0.68	0.92	74
FEV1/FVC	(%)	91	87	
FEF 25%	(L/sec)	1.71	1.25	136
FEF 50%	(L/sec)	1.27	1.03	123
FEF 75%	(L/sec)	0.50	0.61	83
FEF MAX	(L/sec)	1.75	1.94	90
FEF 25-75%	(L/sec)	0.99		

B

Figure 127-17 *A.* PA chest radiograph of a child with CGD who originally presented as an infant with recurrent pneumonia in the right upper lobe diagnosed radiographically as cystic adenomatoid malformation. Subsequent histologic examination and culture revealed this to be nocardial pneumonia. This radiograph reveals recurrent diffuse nocardial pneumonia. *B.* Pulmonary function tests from the same patient showing mild restrictive disease, probably secondary to right upper lobectomy and recurrent airspace disease.

common, as are fungal infections (Figs. 127-17 and 127-18). Antimicrobials and interferon-γ have been useful in therapy.

Glucose-6-Phosphate Dehydrogenase Deficiency

This is a variant of CGD, in which G6PD levels are less than 1 percent, and results in an inability to generate oxygen by products and a slightly milder form of disease than that in patients with CGD.

Chediak-Higashi Syndrome

CHS is a rare autosomal recessive defect characterized by abnormal fusion of azurophilic lysosomes of neutrophils and cytoplasmic granules of monocytes and lymphocytes. This defect results in impaired microbicidal activity of phagocytes due to the presence of giant lysosomal granules, which have abnormal post-phagocytic phagolysosome fusion and degranulation. In addition, neutrophil counts tend to be low, secondary to their rapid turnover. Chemotactic defects and impaired natural killer cell activity have also been noted. Patients present with recurrent skin and upper and lower respiratory tract infections, including recurrent or chronic otitis media, sinusitis, and pharyngitis, in addition to lower respiratory tract infections, including bronchopneumonia. Segmental or lobar lung involvement can account for up to 30 percent of documented infections. Most infections are due to *S. aureus, H. influenzae,* group A streptococcus, and gram-negative enteric organisms *(Klebsiella, Proteus, Shigella, Pseudomonas). Aspergillus* and *Candida* represent less common etiologic agents. Respiratory failure can occur with extensive histiocytic infiltration of the lungs during an accelerated lymphoma-like proliferative phase marked by widespread tissue infiltrates of lymphoid and histiocytic cells, usually without malignant histologic characteristics. Anemia, hypersplenism, and platelet dysfunction, associated with the accelerated phase, and albinism or hypopigmentation, due to abnormal fusion of melanocyte pigment organelles, are also seen.

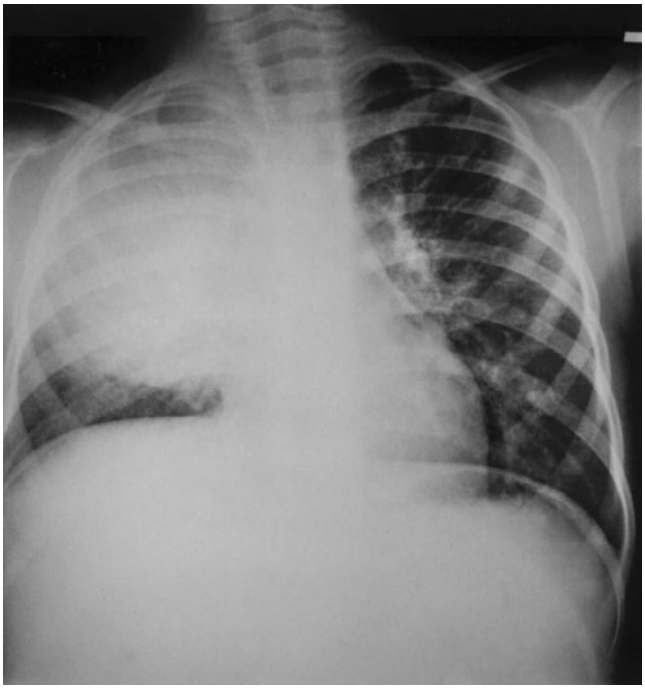


Figure 127-18 PA chest radiograph in a patient with CGD demonstrating nocardial abscess of right upper lobe, extending into the anterior chest wall.

Leukocyte Adhesion Deficiency

Patients with this autosomal recessive disease lack or have markedly reduced α_2 integrins, essential glycoprotein constituents of the CD11/CD18 receptor complex that mediates leukocyte adhesion. Recurrent necrotic and indolent infections of soft tissues, primarily in skin, mucous membranes, and the intestinal tract, are the clinical hallmarks of this disease. The recurrent infections reflect a profound impairment of leukocyte mobilization into extravascular inflammatory sites, despite peripheral blood granulocyte counts of 15,000 to 161,000/mm. A wide spectrum of gram-positive or -negative bacteria (*S. aureus* and gram-negative enteric bacteria) and

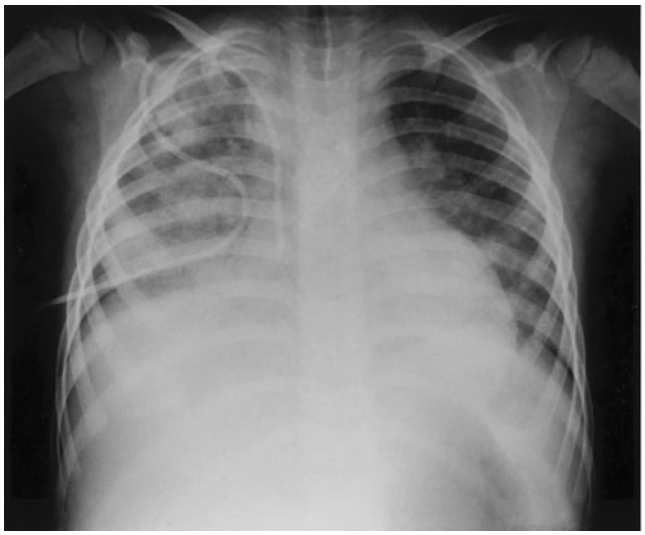


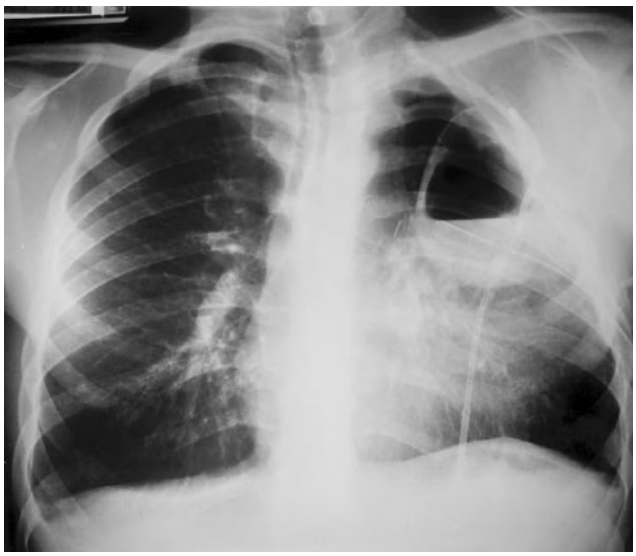
Figure 127-19 PA chest radiograph in a child with CD18 neutrophil receptor deficiency demonstrating extensive airspace disease due to probable candidal and pyogenic bacterial pneumonia.

fungal microorganisms (*Candida* and *Aspergillus*) infect LAD patients, similar to those with neutropenia syndromes (Fig. 127-19).

Hyperimmunoglobulin E Syndrome

Also known as the hyper-IgE (HIE) recurrent infection or Job's syndrome, this unusual disorder, which appears to be autosomal dominant with incomplete penetrance, is lacking an exact immunologic defect. Serum levels of polyclonal IgE are markedly elevated (above 2000 IU/ml), but immunoglobulins other than IgE are normal. Complete blood counts and differentials are mildly abnormal, with occasional borderline neutropenia. Most patients have mild to moderate eosinophilia, despite lacking a significant history of classic allergic diseases. All patients have chronically elevated erythrocyte sedimentation rates. Diagnosis of HIE can be established in patients (usually during infancy) with a history of staphylococcal infections of the skin and sinopulmonary tract, and IgE levels at least 10 times normal. Coarse facies, chronic eczematoid eruptions, cold cutaneous or subcutaneous abscesses, eosinophilia, and mucocutaneous candidiasis are also seen, as are recurrent bone fractures and osteopenia.

"Cold abscesses" are not seen in all HIE patients, but are rare in other immunodeficiency states. They can present in any part of the body as fluctuant masses, with little evidence of inflammation and often without fever. Drainage of these abscesses usually reveals large volumes of purulent material, which almost always grow *S. aureus.* Otitis externa and chronic otitis media, occasionally complicated by mastoiditis, are common in HIE patients. Recurrent bronchitis represents the most common pulmonary manifestation of HIE. Patients often suffer several days a month of productive cough, rarely associated with fever. Less commonly, pneumonia, with or without associated complications—including



A

		Actual	Pred.	%Pred.
LUNG MECHANICS				
FVC	(L)	3.14	3.90	81
FEV1	(L)	2.66	3.66	73
FEV1/FVC	(%)	85	94	
FEF 25%	(L/sec)	6.08	5.08	120
FEF 50%	(L/sec)	3.05	3.69	83
FEF 75%	(L/sec)	1.29	1.99	65
FEF MAX	(L/sec)	6.95	6.22	112
FEF 25-75%	(L/sec)	2.86	3.24	88

B

Figure 127-20 *A.* PA chest radiograph in a patient with Job's syndrome, after left upper lobectomy for bronchiectasis due to *Aspergillus fumigatus,* resulting in recurrent, severe hemoptysis. Chest radiograph shows residual bronchopleural fistula with loculated air collection in the left upper lobe, extensive airspace disease in the left lower lobe, and pleural thickening. *B.* Pulmonary function tests from the same patient showing mild restrictive and obstructive disease despite his extensive left-sided pulmonary disease.

bronchiectasis, lung abscess, empyema, pneumatocele formation, and bronchopleural fistula formation—may represent serious and potentially devastating features in HIE patients. *S. aureus* and *H. influenzae* are the most frequent causes of pneumonias in HIE, but fungal infections may complicate management (Fig. 127-20). Management relies on the use of narrow-spectrum antistaphylococcal prophylaxis, such as cloxacillin or dicloxacillin. Trimethoprim-sulfamethoxazole may also be employed as a prophylactic agent.

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128

Human Immunodeficiency Virus and Pulmonary Infections

John J.W. Fangman • Paul E. Sax

Combination antiretroviral therapy has resulted in dramatic reductions in morbidity and mortality attributable to human immunodeficiency virus (HIV) infection. However, respiratory complications remain a common cause of adverse outcomes in HIV-infected individuals. Pulmonary complaints are often the sentinel event that leads to the diagnosis of HIV infection in persons who are unaware of their HIV status. The list of pulmonary complications seen in persons with HIV is long and includes both infectious and noninfectious entities (Table 128-1). A structured approach to respiratory complaints in HIV-infected patients can result in a timely and cost-effective evaluation. This chapter outlines such an approach by reviewing the pathophysiology, epidemiology, and management of HIV infection. It then outlines an approach to the evaluation of respiratory complaints in patients with HIV and discusses common infectious and non-infectious pulmonary complications of HIV infection. The chapter concludes with an algorithm for the management of HIV-positive individuals who present with respiratory complaints.

PATHOPHYSIOLOGY

HIV Pathophysiology

Although a comprehensive review of the virology and immunology of HIV infection is beyond the scope of this chapter, a basic understanding of the biology of HIV is critical to the care of patients with HIV infection. HIV is the most important member of the Retroviridae family of single-stranded RNA viruses. HIV belongs to the genus lentivirus that contains two specific species, HIV-1 and HIV-2. HIV-2 is found primarily

Table 128-1

Causes of Pulmonary Disease Associated with HIV Infection

Most common	Bacterial *Streptococcus pneumoniae* *Haemophilus influenzae* No organism identified, but responsive to antibacterial therapy Mycobacterial *Mycobacteria tuberculosis** Fungal *Pneumocystis jiroveci*
Less common, but potentially clinically important in some settings	Bacterial *Pseudomonas aeruginosa* *Staphylococcus aureus (especially MRSA)* Enterobacteriaceae *Legionella* spp. *Nocardia* spp. *Rhodococcus equi* Mycobacterial *Mycobacterium kansasii* *Mycobacterium avium* complex Fungal *Cryptococcus neoformans* *Histoplasma capsulatum* *Coccidioides immitis* *Aspergillus* spp. *Blastomyces dermatitidis* *Pencillium marneffei* Viral Influenza Cytomegalovirus Herpes simplex virus Adenovirus Respiratory syncytial virus Parainfluenza virus Parasitic *Toxoplasma gondii* *Strongyloides stercoralis* *Microsporidia* spp. *Cryptosporidium parvum* Non-infectious Kaposi's sarcoma Non-Hodgkin's lymphoma Lung cancer Primary pulmonary hypertension Congestive heart failure Lymphocytic (or lymphoid) interstitial pneumonitis Emphysema Abacavir hypersensitivity

* *Frequency of* M. tuberculosis *infection is highly dependent on local rates of tuberculosis and the patient's exposure history.*
Processes are listed within categories in approximate order of frequency.

in patients who acquired their infection through contact with persons in West Africa and is far less common than HIV-1. Because the management of HIV-2 presents unique clinical challenges and is considerably less virulent than HIV-1 it is not covered in this chapter.

The HIV genome is composed of three structural genes *(gag, pol, env)* and a number of regulatory genes *(vif, vpr, tat, nef)*. The core of the HIV-1 virion is composed of two copies of single-stranded RNA that are packaged with the viral enzymes reverse transcriptase, protease, and integrase. This complex of RNA and viral proteins is encased in a conical nucleocapsid that is surrounded by a lipid bilayer envelope. The surface of the HIV-1 virion is studded with viral-derived gp41/gp120 glycoproteins as well as host-derived MHC class II molecules.

Although CD4-positive cells of macrophage lineage play an important role in HIV infection, the principal target of HIV-1 is the CD4-positive lymphocyte. Attachment of HIV-1 to target cells occurs when viral gp120 binds to the D1 domain of CD4 on the surface of lymphocytes. This interaction induces conformational changes in gp120 variable region that exposes a co-receptor binding domain in its V3 region. Based on the tropism of the infecting virus, this newly exposed binding site facilitates approximation of viral and targets cell membranes through interactions with either the CCR5 or CXCR4 co-receptor on the target cell. Further conformational changes in the gp120/gp41 complex lead to the insertion of gp41 into the target cell membrane, and that in turn brings the target cell and host lipid bilayers into close enough proximity that they fuse. After HIV-1 enters target cells, viral reverse transcriptase (RT) synthesizes a linear, double-stranded DNA copy (cDNA). The insertion of viral DNA into the chromosomal DNA of target cells is the hallmark of retroviral infection and is a prerequisite for transcription of the HIV-1 genome and translation of viral proteins. Using a variety of host and viral proteins, integrated proviral DNA is transcribed and mRNAs are subsequently translated into large polyproteins. Posttranslational modification of these polyproteins is catalyzed by HIV protease. Viral assembly occurs when *Gag* multimers complex with *Gag-Pol* polyproteins, viral RNA, *Vif, Vpr,* and several host proteins. These preassembled complexes are transported to specific lipid-rich regions of the host cell where budding occurs. Following budding, virions undergo protease-mediated structural modification, a process termed maturation.

Effective management of HIV infection depends on a working knowledge of several key features of this life cycle. Foremost among these is that fact that HIV replication requires incorporation of cDNA into the host's genetic material. Although nearly all infected CD4 cells are productively infected, a small minority (less than 1 percent) lie dormant after proviral DNA has been inserted into host DNA. Such latently infected CD4 cells are able to escape immune surveillance and are long lived. Because it is not currently possible to enhance the decay of the pool of latently infected CD4 cell, HIV infection can not be cured even with prolonged suppression of viral replication. Although cure of HIV infection remains an elusive goal, it is possible to control HIV replication.

Potent inhibitors of many steps in the life cycle of HIV have been developed, but their efficacy as monotherapy has been limited. The absolute requirement for combination antiretroviral therapy is due to two fundamental aspects of HIV replication: its rate of replication and the infidelity of HIV reverse transcriptase. Fundamental insights into the kinetics of HIV replication were derived through the application of PCR-based techniques to quantify viral replication in subjects receiving potent inhibitors of HIV protease. Using such techniques, investigators demonstrated that 1 to 10 billion viral particles were produced and cleared in the infected host each day. Further complicating management was the recognition that HIV's reverse transcriptase lacks a proofreading function and that on average an error occurs in every 1:1400 to 1:4000 base pairs transcribed. With limited exceptions, these insights led to a management strategy that uses multiple active agents with different mechanisms of action, often targeting different stages of the HIV replication cycle to control HIV infection.

PATHOPHYSIOLOGY OF HIV IN THE LUNG

When considering the impact of HIV infection on the lung, it is important to recognize that both systemic and lung-specific disturbances in immune function occur in HIV-infected individuals. The expression of altered pulmonary immunity is further affected by host-specific factors, viral determinants, and disease stage.

SYSTEMIC IMMUNODEFICIENCY

One of the hallmarks of HIV infection is the gradual decline in CD4-positive lymphocyte count that occurs during the course of the infection. Unlike other viral infections, HIV fails to produce a robust HIV-specific CD4 response. HIV preferentially infects activated CD4 cells, a fact that may blunt the expected clonal proliferation of HIV-specific CD4 expansion one expects with primary HIV infection. CD4-positive lymphocytes play a pivotal role in a variety of cell-mediated and humoral defenses, and the impact of HIV-induced CD4 dysfunction can be seen from early in the course of infection. Development of cytotoxic T-lymphocyte (CTL) response is also altered in HIV infection. The specificity and breadth of CTL response to HIV infection has been shown to inversely correlate with disease progression. Humoral immunity in HIV infection is limited as well. Although polyclonal elevations in immunoglobulin levels are quite common in HIV-infected individuals, the presence of neutralizing antibodies against HIV is very rare. This is due in part to the disproportionally high rate of mutations observed in regions of the gp41/gp120 surface proteins that are most accessible to immunologic recognition.

A variety of host factors have been identified that affect the infectivity and natural history of HIV infection. The identification of a 32-base pair deletion in the CCR5 gene (Δ32 mutation) in persons with repeated exposure to HIV-1 but no evidence of infection highlighted the importance of host-derived cofactors in HIV infection. Persons who are heterozygous for this mutation are able to be infected but have been shown to have a slower rate of progression to AIDS. HLA subtypes have also been shown to affect disease progression with HLA-B27 and HLA-B*5701 alleles generally correlating with slower rates of clinical progression. Virologic factors associated with alterations in the natural history of HIV infection are described as well. Since the 1980s, investigators have recognized that certain strains of HIV demonstrated trophism for macrophages, whereas others did not (so-called syncytia-inducing [SI] viruses). Isolation of SI viruses was less common, although the frequency increased in patients with advanced AIDS. The difference observed between these two strains in tissue culture was ultimately explained by a difference in tropism for chemokine receptors, which each type used to gain entry into target cells. Patients with SI viruses were shown to require the CXCR4 molecule to infect the target cell, and CXCR4 tropism was subsequently shown to be associated with more rapid progression to AIDS. Other examples of virologic factors that impact the natural history of HIV infection are less commonly observed. The most notable example of such uncommon viral variants is a cohort of patients with a common source exposure who experienced an exceptionally slow rate of progression to AIDS despite longstanding infection. Detailed analysis of their viral isolate revealed a deletion in the HIV regulatory gene *nef,* which is thought to explain the cause of their clinical stability despite longstanding HIV infection.

Neutrophil dysfunction is commonly seen in HIV-infected persons, especially in those with advanced immunosuppression. HIV infection itself can produce neutropenia, and is also commonly seen in association with medications used to treat HIV or an associated opportunistic infection such as AZT, trimethoprim/sulfamethoxazole or ganciclovir. Neutropenia has been associated with increased rates of serious bacterial infections and mortality in patients with focal infections such as pneumonia.

Although a variety of host and viral factors have been shown to alter the natural history of HIV infection, the immunologic defects associated with advanced AIDS are more stereotypical. Although HIV-specific CD4 response can be demonstrated in patients with advanced AIDS, the ability of such cells to undergo clonal expansion is limited. Advanced disease is correlated with loss of HIV-specific CTL, which in turn may be due to either impaired CD4 helper response or selection of escape mutants able to evade a previously generated CTL response. Alterations in coreceptor utilization is commonly seen in advanced HIV with a switch from CCR5-trophic virus to CXCR5 or mixed CCR5/CXCR4 strains.

LUNG-SPECIFIC IMMUNODEFICIENCY

Numerous studies support the principle that immune response to HIV infection may be different in tissue

compartments such as the gut or brain than that observed in the blood. A detailed understanding of the alterations in pulmonary immunity in HIV-infected persons allows a tailored approach to prophylaxis and treatment of pulmonary opportunistic infections. A comprehensive review of pulmonary immunology can be found elsewhere in this volume, but several features of lung immune function in patients with HIV deserve discussion. To date, most studies of the pathophysiology of HIV in the lung have focused on patients with advanced disease who were being evaluated for suspected pulmonary opportunistic infections. Investigators have tended to focus on alveolar macrophage function and other cell types that were accessible via bronchoalveolar lavage. Available data suggest that alveolar macrophages are an important reservoir for HIV in the lung. Studies have shown that alveolar macrophages obtained from uninfected donors can be infected by HIV-1 in vitro. The amount of HIV that can be obtained from alveolar macrophages is greater in patients with AIDS compared with those with less severe immunosuppression. Whether infection of pulmonary macrophages occurs predominantly in the lung or precursor cells in the bone marrow or peripheral blood is unknown. Arguing for differences in the biology of HIV infection in the lung are case reports demonstrating significant genotypic variation between isolates obtained from BAL and those obtained in peripheral blood mononuclear cells (PBMCs). Studies examining the impact of HIV infection on alveolar macrophage function show enhanced phagocytic activity against pathogens such as *Staphylococcus aureus* and *Cryptococcus neoformans,* but reduced activity against *Pneumocystis jiroveci.* Data on submucosal immune function in HIV infection are limited, as are studies looking at pulmonary immunology in those with less severe immunosuppression. Alveolar lymphocytes are increased in both early and advanced HIV infection. The impact of HIV infection on T-cell activity is less certain. Most investigators report normal to increased numbers of CD4+ lymphocytes in persons undergoing bronchoscopy for suspected opportunistic infection. CD4/CD8 ratios have been noted to be lower in such patients, a fact that may be explained by an influx of CD8 cells more than depletion of CD4-positive cells. Normal to increased numbers of CD8 cells do not necessarily confer enhanced cytotoxic T-cell response, however. Studies of CD8-positive lymphocytes obtained from patients with HIV have shown decreased cytotoxic activity compared with uninfected controls.

Humoral immunity is especially important in control of common bacterial pathogens. Although data on mucosal immunity are limited, studies of BAL fluid from patients with AIDS and respiratory complaints show increased levels of IgG, IgM, and IgA as well as increased numbers of B cells capable of secreting immunoglobulin. However, studies of asymptomatic patients with HIV infection demonstrated decreased levels of immunoglobulin compared with health controls, suggesting that impaired B-cell function may play a role in predisposition to opportunistic infection.

OVERVIEW OF HIV MANAGEMENT

HIV Natural History

Primary HIV infection is characterized by the presence of fever, lymphadenopathy, sore throat, mucocutaneous lesions, myalgia/arthralgia, diarrhea, headache, and weight loss. Symptoms typically last 1 to 2 weeks and can be quite severe. Primary infection is characterized by high levels of HIV viremia (usually greater than 300,000 copies/ml) and transient declines in CD4 count. Respiratory symptoms are uncommon during primary HIV infection, although case reports of typical opportunistic infections such as PCP have been described during this time. Following resolution of the acute illness, infected persons feel well. The average time between the acquisition of HIV and the development of AIDS is 7 to 10 years, although it may be as rapid as 2 to 3 years. Risk factors for more rapid progression include high viral load, rapid decline in CD4 count, advanced age, and injection drug use. Untreated, a variety of infectious, neurologic, and neoplastic complications may develop. Median survival is 3.7 years once a patient's CD4 count drops below 200 cell/mm^3, and 1.3 years after diagnosis of an AIDS-defining complication. Late-stage AIDS is characterized by profound CD4 cytopenia, high-level viremia, and often multiple concurrent opportunistic infections.

Combination Antiretroviral Therapy

The introduction of combination antiretroviral therapy in 1996 transformed the care of patients with HIV. Comprehensive guidelines are available on both antiretroviral therapy and the prevention and management of opportunistic infections. These guidelines are regularly updated: The most recent version can be found at http://www.aidsinfo.nih.gov. Optimal management of HIV infection requires early diagnosis. In the United States, about 25 percent of infected patients are unaware of their HIV status and 40 percent of newly diagnosed patients experience an AIDS-defining event in the following year. Risk associated with late diagnosis of HIV infection persists after treatment has been initiated. Even when asymptomatic at diagnosis, patients who present with advanced immunosuppression are more likely to develop complications related to their infection and therefore deserve particularly close monitoring. Patients with advanced age, active intravenous drug use, and marked CD4 depletion are less likely to regain a normal CD4 count, thus increasing their cumulative risk of opportunistic infection.

The decision to initiate antiretroviral therapy is based on clinical, immunologic, and virologic parameters as well as an assessment of an individual's readiness to adhere to antiretroviral therapy. The choice of a regimen depends on an assessment of co-morbid conditions such as liver disease, renal function, and cardiovascular risk factors and a review of the susceptibility of the dominant strain of virus the patient harbors (done through genotypic or phenotypic testing).

Treatment guidelines stress the importance of choosing a regimen that contains least three agents with preserved activity against HIV. A successful antiretroviral regimen is one that is well tolerated, convenient, and has a low incidence of short- and long-term complication while maintaining potent and durable suppression of HIV replication. With continuing advances in HIV drug development, the goal of antiretroviral therapy for all patients is to achieve an undetectable viral load in the blood using an ultrasensitive assay. Effective antiretroviral therapy should also result in restoration of at least partial cell-mediated immunity with successful treatment resulting in a rise of CD4-positive cells of 50 to 100 cells/mm^3 at the end of 1 year.

EPIDEMIOLOGY OF PULMONARY DISEASE IN HIV

HIV Epidemiology

According to 2005 data from the World Health Organization (WHO), 33.4 to 46 million people were estimated to be infected with HIV worldwide. In that year, approximately 4.1 million persons were newly infected with HIV and 2.8 million died, including an estimated 380,000 HIV-infected children. The HIV pandemic is global, but the vast majority of persons living with HIV infection reside in resource-limited settings. Although significant strides have been made in providing access to antiretroviral therapy to persons with HIV, most patients with HIV do not have access to comprehensive diagnostic, preventive, or treatment services. Lack of access to even basic preventive measures, such as immunizations and antimicrobial prophylaxis, has produced marked discrepancies is the epidemiology of HIV infection. Clinicians in the United States must also contend with disparities in access. Although men who have sex with men and injection drug users still make up the largest groups of people living with HIV in the United States, rates of heterosexual transmission are rising. New infections are increasingly occurring in women and ethnic minorities.

Epidemiology of Pulmonary Diseases in HIV

The spectrum of pulmonary disease seen in HIV-infected persons has changed since the identification of the first patients with HIV in 1981. Although *Pneumocystis jiroveci* remains a common pathogen, the introduction of prophylaxis and then combination antiretroviral therapy has dramatically reduced its frequency in patients receiving appropriate and timely care. Data from the era before combination antiretroviral therapy deserve review as they can inform the approach to patients who are entering care with newly diagnosed HIV infection, or in those who are poorly adherent to their prescribed antiretroviral therapy. The pulmonary complications of HIV infection study cohort followed 1100 HIV-infected patients from 1988 to 1994. The study also included 167 HIV-negative controls. Although the study preceded the availability of protease inhibitors and the widespread use of combination antiretroviral therapy, it provided the most accurate data regarding the incidence of specific pulmonary infections among HIV-infected individuals. Importantly, the study included the era, after which prophylaxis against *Pneumocystis jiroveci* pneumonia (PCP) became the standard of care. During the 5 years of follow-up in the study, acute bronchitis was the most common lower airway infection, occurring twice as commonly among those of HIV infection than in controls. By far the two most common AIDS-defining complications were bacterial pneumonia and PCP. These occurred with approximately equal frequency, with sequential follow-up showing higher rates of pneumonia with declining CD4 cell counts. Other specific causes of opportunistic infections occurred relatively infrequently, and included cases of cytomegalovirus, aspergillus, cryptococcus, and herpes simplex. The use of combination antiretroviral therapy has dramatically diminished the incidence of all of these complications, with some evidence of a greater decline in PCP than in bacterial pneumonia. For the former, this decline occurred independent of the frequency of use of PCP prophylaxis. Chronic administration of anti-*Pneumocystis* prophylaxis with trimethoprim sulfamethoxazole in particular, and *Mycobacterium avium* complex prophylaxis with macrolide antibiotics likely reduces the incidence of bacterial pneumonia. However, it has been shown that treatment with trimethoprim sulfamethoxazole increases the rate of colonization with resistant bacteria, especially pneumococci.

BASIC EVALUATION OF THE HIV-POSITIVE PATIENT WITH RESPIRATORY COMPLAINTS

The differential diagnosis of respiratory symptoms in a person with HIV is exceedingly broad and includes both infectious and noninfectious etiologies (Table 128-1). As noted, about 25 percent of infected patients in the Unites States are unaware of their HIV status, so the first step in managing such complaints is to consider the possibility of HIV infection in patients presenting with undiagnosed respiratory complaints. The diagnosis of HIV infection is made through identification of antibodies to HIV by enzyme-linked immunosorbent assay (ELISA) followed by confirmatory western blot of HIV-associated proteins. Whenever possible, such testing should use assays with rapid turnaround times (hours not days) so that preliminary results can be relayed to the patient during the initial encounter. Use of virologic assays such HIV viral load should be reserved for those with suspected acute HIV infection as the assay is subject to false-positive results and is not approved for the diagnosis of chronic HIV infection.

In patients with recognized HIV infection, optimal management of respiratory complaints starts with a careful review of presenting complaints, past medical history (including history of opportunistic infections), and current

medications. Rates of tuberculosis (TB) are higher in individuals with HIV infection. Because of the potential public health and infection control issues associated with HIV-TB co-infection, a decision on respiratory isolation should be made early in the course of the evaluation of most patients with HIV and respiratory complaints. The physical exam should ascertain the severity of the presenting complaints and should focus on identification of HIV-associated mucocutaneous, gastrointestinal, neurologic, and pulmonary diseases. Basic laboratory evaluation includes a CD4 cell count and percentage as well as complete blood count and comprehensive metabolic panel (including tests of renal and hepatic function). Quantification of peripheral viremia (viral load testing) can be helpful in discussions of prognosis and treatment in HIV infection, but is less useful in the evaluation of respiratory complaints. Coupled with a review of a patient's travel and exposure history, results of this basic evaluation helps structure microbiologic, imaging, and pathologic studies required to establish a definitive diagnosis.

Presenting Complaints

Although considerable overlap occurs in presenting complaints, the description offered by HIV-infected individuals often provides valuable clues to the origin of their respiratory complaints. Patients with bacterial pneumonia typically present much in the same way as those without HIV infection—with a relatively acute illness (measured in days) characterized by fever, chills, productive cough, and occasionally pleuritic chest pain. *Pneumocystis pneumonia,* by contrast, typically presents as a subacute to chronic illness of several weeks' duration, with the most prominent symptoms being fever and shortness of breath. Other helpful clues to PCP include chest tightness (specifically a sense that it is difficult to take a full breath) and a report that a typical day's activities (climbing stairs, conversing on the telephone) are now associated with dyspnea. The presence of constitutional symptoms, such as fever, night sweats, and weight loss, together with respiratory complaints suggest a systemic infectious process such as mycobacterial disease, fungal infection, or non-infectious conditions such as non-Hodgkin's lymphoma.

Past Medical History

One of the most fruitful approaches in the evaluation of pulmonary complaints in persons with HIV is to review their history of previous cardiopulmonary disease. It goes without saying that patients with a previous opportunistic infection such as PCP pneumonia are at higher risk of recurrence, especially if appropriate secondary prophylaxis and antiretroviral therapy are not taken. Although the pathophysiologic basis remains somewhat obscure, some patients with HIV appear to have more prominent B-cell dysfunction, and hence are at a much greater risk for the development of encapsulated bacterial infections, in particular those due to *Streptococcus pneumoniae* and *Haemophilus influenzae.* Such individuals frequently have a history of multiple prior visits or hospitalizations for bacterial pneumonia, as well as episodes of otitis media, bronchitis, and other bacterial respiratory infections. HIV-infected persons with active injection drug usage are more likely to develop invasive bacterial infections, including pneumonia, compared with HIV-positive individuals who acquired HIV from other routes. Even when CD4 cell counts are relatively high (greater than 500 cells/mm^3), HIV-infected patients are at substantially higher risk of bacterial pneumonia than non–HIV-infected controls. This relative risk increases as the CD4 cell declines.

Medication History

Faithful adherence to antiretroviral therapy is the most important intervention that alters the risk of opportunistic pulmonary complications in HIV infection. As discussed in the following, it is vital to review the specific medications used to treat HIV, as certain antiretrovirals may have direct effects on the lung and may alter the metabolism of coadministered agents. The differential diagnosis of respiratory complaints in HIV-positive patients is strongly influenced by the use of both primary and secondary prophylaxis has common opportunistic infections. Patients receiving trimethoprim sulfamethoxazole for *Pneumocystis* prophylaxis rarely suffer breakthroughs of PCP if they are compliant with therapy. By contrast, second-line prophylaxis such as atovaquone, dapsone, and aerosolized pentamidine are all associated with small but significant rates of treatment failure. Trimethoprim sulfamethoxazole has the added benefit of reducing the risk of all bacterial infections, including community pneumonia as well as less common HIV-associated opportunistic infections such as nocardia and toxoplasmosis. The effectiveness of prophylaxis has limitations and high rates of pneumococcal resistance to trimethoprim sulfamethoxazole and macrolides must be taken into consideration when selecting empiric therapy for patients with suspected bacterial pneumonia.

Physical Examination

A review of vital signs should identify patients with marked impairment of gas exchange or hemodynamic compromise. Pulse oximetry provides a non-invasive means of assessing gas exchange, although resting oxygenation saturation is not a sensitive test for mild hypoxemia. Signs of systemic inflammatory response syndrome (SIRS) are most commonly seen in patients with fulminant bacterial infections or rarely also with disseminated histoplasmosis, cryptococcosis, or other disseminated fungal infections. Alterations in mental status can be seen with overwhelming infections but should also prompt consideration of infections such as cryptococcus that produce both meningitis and respiratory complaints. Auscultation of the lung fields is commonly normal in diseases such as PCP but evidence of focal consolidation can be a clue to bacterial pneumonia. A careful cardiac examination may reveal the presence of both left- and right-sided heart failure.

Physical findings outside the chest can provide valuable clues to the etiology of pulmonary symptoms in patients

with HIV infection. Common opportunistic infections with prominent dermatologic findings include disseminated fungal infections (cryptococcus and blastomycosis in particular) and Kaposi's sarcoma. Funduscopic examination may suggest the presence of viral, fungal, or mycobacterial infection. The presence of hepatosplenomegaly or peripheral lymphadenopathy may be seen in disseminated mycobacterial disease, fungal disease, and non-Hodgkin's lymphoma.

Infection Control Issues

Because of the increased rates of tuberculosis in patients with HIV infection (see the following), it is essential that clinicians consider the possibility of TB when evaluating respiratory complaints in persons with HIV. As no clinical or radiographic presentation can entirely exclude TB, practitioners must have a high degree of suspicion and a low threshold to admit such cases to negative airflow rooms until TB has been ruled out or an alternative diagnosis has clearly been established. We admit patients with HIV and respiratory disease to negative airflow rooms if any of the following conditions is present: (1) any clinical presentation highly consistent with TB (cavitary lung disease, subacute course, weight loss); (2) prior residence in a highly TB endemic area; (3) other risk factors for TB exposure, such as contact with an active case, homelessness, or incarceration; (4) history of a positive tuberculin skin test without preventive therapy; (5) history of prior tuberculosis without documentation that appropriate treatment has been completed. Using these criteria minimizes, but does not eliminate, the chance that an HIV-infected person will be a potential source of a nosocomial exposure to tuberculosis. This topic is further reviewed elsewhere in this volume.

Basic Laboratory Evaluation

The laboratory approach to HIV-infected patients with respiratory complaints begins with several simple, commonly available non-invasive studies that are followed by increasingly intensive studies should these prove unrevealing (Table 128-2). These include a complete blood count with

Table 128-2

Diagnostic Tests Used in Patients with HIV Infection and Pulmonary Disease

Test	Comment
Indicated in all patients	
CBC with differential	If neutropenia is present, empiric therapy covering *Pseudomonas aeruginosa* is indicated
LDH	Elevated in most patients with PCP; non-specific
Blood cultures	Helpful for diagnosis of bacterial pneumonia, in particular that due to *Streptococcus pneumoniae*
Expectorated sputum	Often not available; gram stain and culture with low sensitivity and specificity, especially after antibiotics have been started
Induced sputum for PCP stain, AFB stain, and culture	Initial test of choice in most centers for *diagnosis* of *Pneumocystis jiroveci*, although sensitivity varies widely
Indicated for patients not responding to initial empiric therapy	
Fiberoptic bronchoscopy with broncheoalveolar lavage,+/− transbronchial biopsy	BAL highly sensitive for diagnosis of PCP; Kaposi's sarcoma often diagnosed by visualizing characteristic purple plaques, with no biopsy done due to risk of bleeding; biopsy often necessary to establish alternative diagnosis such as CMV, aspergillus, or lymphocytic interstitial pneumonitis
Video-assisted thoracoscopic biopsy	Useful in diagnosis of peripheral nodules, masses not reachable by bronchoscopic biopsy
Serum cryptococcal antigen	Nearly 100% sensitive for diagnosis of disseminated disease in patients with HIV; if positive, CSF examination is mandatory to exclude meningitis
Urinary histoplasmosis antigen	Indicated in patients residing in or from histoplasmosis-endemic areas, in particular if imaging demonstrates hilar adenopathy
High-resolution CT scan	May help identify abnormalities not evident on CXR; a normal test makes PCP highly unlikely
Gallium scan	Negative study rules out PCP; however, positive tests are non-specific, and other tests (high-resolution CT scan, sputum induction) provide more useful information with greater rapidity

differential (CBC), lactate dehydrogenase, two sets of blood cultures, and a sputum Gram stain and culture. Comprehensive metabolic profile should be obtained on most HIV-positive patients with respiratory complaints to rule out electrolytes disturbances as well as renal or liver disease. The CBC can provide important clues to the diagnosis of respiratory complaints in persons with HIV infection. Although anemia and thrombocytopenia are more common hematologic manifestations of HIV infection, neutropenia is not rare, particularly in patients with advanced AIDS. Neutropenia has been associated with increased risk of both bacterial pathogens (including *Pseudomonas*) and invasive fungi such as *aspergillus*. Pancytopenia is suggestive of disseminated infection, malignancy, or medication toxicity. Lactate dehydrogenase levels are generally elevated in patients with PCP, especially when the disease is severe enough to require hospitalization. A normal level suggests an alternative diagnosis, and conversely the level of elevation correlates with the severity of the disease. Since many conditions cause an increase in LDH, the test has a low specificity for PCP but is a helpful adjunctive diagnostic clue pending more definitive testing.

Clinical or Laboratory Stage of Immunosuppression

The vast majority of cases of *Pneumocystis jiroveci* pneumonia occur in individuals with CD4 cell counts less than 200 cells/mm^3. In cases in which the CD4 cell count is not immediately available, useful clinical correlates for advanced immunosuppression include the presence oral candidiasis or other clinical markers of advanced HIV disease such as weight loss. It should be emphasized that progressive immunosuppression increases the risk of all pulmonary infectious processes, including those that may occur with relatively preserved CD4 cell counts, such as bacterial pneumonia and tuberculosis.

Epidemiology

As noted, the most important epidemiologic consideration when evaluating HIV-positive persons with pulmonary complaints is to establish risk for tuberculosis. The incidence of tuberculosis as a complication of HIV infection varies markedly depending on local rates of TB and the patient's prior exposure history. In the United States, a high proportion of tuberculosis cases occur in persons who have emigrated from areas in which tuberculosis highly endemic; many of these areas (such as sub-Saharan Africa and parts of the Caribbean) also have high background rates of HIV infection. In addition, homelessness and incarceration both increase the risk of tuberculosis exposure and subsequent disease. A person's past residence or travel history may elicit potential exposure not only to tuberculosis, but also to endemic fungi such as histoplasmosis, coccidioidomycosis, and blastomycosis. A careful epidemiologic history can provide clues to a variety of HIV-associated pulmonary infections such as *Rhodococcus equi, Toxoplasma gondii, Strongyloides stercoralis, Cryptosporidium,* and *Microsporidia.*

Imaging

Chest Radiograph

All HIV-infected patients who present with respiratory complaints should receive posteroanterior and lateral radiographs of the chest. Although no x-ray findings are pathognomonic for a specific microbiologic diagnosis, certain radiographic patterns are observed more commonly with specific diagnoses (Table 128-3). Patients with bacterial pneumonia more likely have a focal infiltrate on chest radiograph compared with those with PCP, in whom diffuse interstitial infiltrates are much more common. Importantly, there are many exceptions to these generalizations, including the presence of a normal chest radiograph in up 10 percent of those with PCP or tuberculosis, and the occasional occurrence of diffuse interstitial infiltrates in persons with bacterial pneumonia (in particular secondary to *Haemophilus influenzae*). In fact, given the wide range of radiographic findings potentially due to PCP—including cavities, pneumatoceles, pleural effusions, nodules, and pneumothoraces—no radiographic appearance can entirely rule out the diagnosis of PCP in an otherwise susceptible HIV-infected host. Chest x-ray may also reveal mediastinal, pleural, and extrathoracic abnormalities, which should be aggressively pursued to obtain a definitive diagnosis.

Computed Tomography

Computed tomography (CT) has become an important tool in the evaluation of respiratory complaints in patients with HIV infection. The additive benefit of chest CT over plain films is discussed in detail elsewhere in this volume. Chest CT is more sensitive that plain film in detecting subtle interstitial changes and can provide more precise characterization of nodular lesions. Chest CT has a particular role to play in evaluating HIV-positive persons with respiratory complaints whose chest x-rays are normal. A normal chest CT has a high negative predictive value for opportunistic infections and HIV-associated malignancy. CT scan of the chest has also proved useful in directing invasive diagnostic studies such as bronchoscopy or transthoracic lung biopsy.

Nuclear Imaging

Radionucleotide imaging played a historically important role in the evaluation of HIV positive patients with respiratory complaints and a normal CXR. Although highly sensitive for PCP, radionucleotide studies (using gallium citrate, technetium, or thallium), are not specific for a particular pathogen, and this modality has been largely replaced by chest CT. The specificity of positron emission tomography (PET) imaging is likewise limited in diagnosing opportunistic

Table 128-3

Radiographic Appearance of Pulmonary Diseases in HIV Infection

Diffuse interstitial infiltrates
- *Pneumocystis jiroveci*
- *Mycobacterium tuberculosis,* (especially with CD4 < 200)
- *Histoplasma capsulatum*
- *Coccidioides imitis*
- *Cryptococcus neoformans*
- *Toxoplasma gondii*
- Cytomegalovirus
- Influenza
- Lymphocytic interstitial pneumonitis
- Abacavir hypersensitivity

Focal consolidation
- Pyogenic bacterial pnumonia due:
  - *Streptococcus pneumoniae*
  - *Haemophilus influenzae*
- *Mycobacterium tuberculosis*
- *Legionella* spp.
- *Rhodococcus equi*

Hilar adenopathy
- *Mycobacterium tuberculosis*
- *Histoplasma capsulatum*
- *Coccidiodes immitis*
- Non-Hodgkin's or Hodgkin's lymphoma
- *Mycobacterium avium* complex

Cavitary disease
- Pyogenic bacterial pneumonia:
  - *Pseudomonas aeruginosa*
  - *Staphylococcus aureus*
  - Enterobacteriaceae
- *Mycobacterium tuberculosis*
- *Cryptococcus neoformans*
- *Rhodococcus equi*
- *Histoplasma capsulatum*
- *Aspergillus* spp.
- *Nocardia* spp.
- *Mycobacterium avium* complex
- *Pneumocystis jiroveci*

Nodules or masses
- *Mycobacterium tuberculosis*
- *Cryptococcus neoformans*
- *Aspergillus* spp.
- *Histoplasma capsulatum*
- *Nocardia* spp.
- Non-Hodgkin's lymphoma
- Kaposi's sarcoma
- Lung cancer

Normal radiograph
- *Pneumocystis jiroveci*
- *Mycobacterium tuberculosis*

pulmonary infections in HIV-positive patients with respiratory complaints. As in patients without HIV infection, PET imaging has a role to play in staging patients with known or suspected thoracic malignancies.

Physiologic Testing

Arterial Blood Gas Analysis

Resting pulse oximetry is a useful, non-invasive tool for assessing gas exchange in HIV-positive individuals with respiratory complaints. The sensitivity of pulse oximetry for detecting milder disease can be improved if patients are monitored for desaturation below 90 percent while breathing room air during moderate exercise, a maneuver that has been used to screen for PCP in HIV-positive patients seen in outpatient settings. Measurement of arterial blood gases provides a more detailed picture of gas exchange. Although not commonly done, failure to demonstrate the normal decrease in alveolar-to-arterial oxygen gradient between rest and exercise is highly sensitive to PCP. Practically speaking, arterial blood gas analysis is performed most commonly in patients who present with severe respiratory distress or with a low oxygen saturation level on oximetry. Determining whether the Pa_{O_2} less than 70 mm Hg or A-a gradient greater than 35 mm Hg (see the following) has important therapeutic implications for potential use of adjunctive corticosteroids.

Pulmonary Function Testing

Pulmonary function testing (PFTs) can be useful in the evaluation HIV positive patients with idiopathic dyspnea and preserved CD4 counts, although their role in the evaluation of patients with AIDS is less clear. Measurement of the diffusing capacity for carbon monoxide (D_{LCO}) in HIV-positive patients with advanced disease is generally reserved for patients with normal CXR and undiagnosed respiratory complaints. Like radionucleotide imaging, an impaired D_{LCO} is common finding in patients with early or mild interstitial lung disease and may be the first objective sign that an opportunistic infection is present. Although typically not helpful in establishing a specific diagnosis, a D_{LCO} significantly below predicted levels should prompt further diagnostic testing.

Microbiologic Testing

Respiratory Secretions

Gram stain and culture of expectorated sputum is an important first step in the evaluation of HIV-positive patients with respiratory complaints. Empiric treatment decisions may be strongly influenced by the identification of a potential pathogen on Gram stain or AFB smear. The microbiologic evaluation of PCP and TB as well as the other less common opportunistic pathogens are reviewed in the following. If a definitive diagnosis has not been made with sputum Gram stain and culture, the decision to proceed with additional diagnostic tests, both non-invasive and invasive, depends on the patient's response to initial therapy. In practice, a prompt clinical response to empiric antibiotic therapy directed at the most common pathogens in HIV-related pneumonia (*Streptococcus pneumoniae* and *Haemophilus influenzae*) serves as indirect evidence that alternative processes have not been overlooked. For patients who have not improved clinically, and when the diagnosis is still unknown, expedited referral for fiberoptic bronchoscopy with bronchioalveolar lavage is indicated.

Peripheral Blood Cultures

The purpose of the blood cultures is to facilitate diagnosis of bacterial pneumonia, most notably due to *Streptococcus pneumoniae*, where rates of bacteremia in patients with HIV can approach 60 percent of cases. Given the low specificity of sputum gram stain, as well as the low sensitivity of sputum culture, a positive blood culture for a likely organism is often the only method of making a specific etiologic diagnosis in a patient with bacterial pneumonia. Fungal and mycobacterial cultures are occasionally useful in the diagnosis of disseminated histoplasmosis and MAC, as discussed in more detail in the following.

Tissue Diagnosis

For patients who have not improved clinically and in whom a diagnosis remains uncertain, tissue may be required to establish a definitive cause for respiratory complaints in the HIV-infected patient. Since BAL alone is highly sensitive for the diagnosis of PCP, and biopsy carries a risk of pneumothorax and pulmonary hemorrhage, many bronchoscopists prefer to perform a BAL alone initially, reserving biopsy for a repeat procedure if this is still indicated. The main indication to proceed with transbronchial biopsy is a high likelihood of an alternative diagnosis to PCP; this situation arises when a patient is taking trimethoprim sulfamethoxazole for PCP prophylaxis, has a relatively high CD4 cell count or atypical appearing CXR, or when a diagnosis requiring biopsy for identification is highly suspected. Examples of such conditions include CMV, aspergillus, lymphocytic interstitial pneumonitis, and malignancies other than Kaposi's sarcoma. Transbronchial needle aspiration should be reserved for the evaluation of mediastinal adenopathy, although the yield is variable. CT-guided biopsy is particularly useful when evaluation peripheral nodular lesions that are not amenable to transbronchial approach. Data on the diagnostic yield of CT-guided biopsy are limited but one study of patients with focal chest or mediastinal abnormalities on CT scan demonstrated a diagnosis in 84 percent using CT-guided biopsy. Open lung biopsy is the most invasive approach to obtaining a tissue diagnosis of respiratory complaints in HIV-positive patients and is generally reserved for patients with in whom transbronchial or CT-guided biopsy has failed to yield a diagnosis, although some clinicians favor this approach for HIV-positive individual with diffuse interstitial disease who have failed to respond to empiric therapy. Thoracotomy or, more commonly, video-assisted thoracic surgery (VATS) should be considered in such cases as it can yield valuable information in HIV-positive individuals with pulmonary complications. A study of open lung biopsy in HIV-positive patients with a non-diagnostic bronchoscopy, reported a definitive diagnosis in 13 of 18 patients (72 percent) who underwent open lung biopsy and similar study reported that open lung biopsy led to a change in therapy in 15 of 25 patients, eight of whom improved clinically and were discharged from the hospital. The authors outlined the following indications for open lung biopsy in HIV patients: (1) non-diagnostic bronchoscopy; (2) failed medical therapy after a diagnostic bronchoscopy; (3) failed empiric medical therapy after a nondiagnostic bronchoscopy; and (4) any of the preceding, in combination with a worsening chest radiograph. Even though no formal comparison of VATS and open lung biopsy has been made in HIV-infected patients, both procedures appear to be equivalent for obtaining diagnostic lung tissue. There may be less morbidity associated with VATS, as these patients generally require fewer days in hospital and less time with chest tube drainage. If the patient cannot tolerate single lung ventilation, which is necessary during VATS, or if the lesion can not be reached through a thoracoscope, then an open thoracotomy should be performed. In general, the choice of procedure is typically left to the surgeon.

Specific Pathogens

Bacterial Pneumonia

Bacterial respiratory infections are one of the most common causes of respiratory complaints in HIV-positive patients. In 1993, the classification system for HIV infection was revised to include recurrent pneumonia (with or without established microbiologic confirmation) as an AIDS-defining condition. Although HIV affects cell-mediated immunity most profoundly, abnormalities in antibody production and, in advanced AIDS, neutrophil function all contribute to the increased risk of bacterial pneumonia. The epidemiology of bacterial pneumonia is influenced by both epidemiologic and immunologic factors. Overall, the rate of bacterial pneumonia among patients with HIV is as much as 80-fold higher than in HIV-negative controls. Although this increased risk is seen throughout the course of HIV infection compared with HIV-negative controls, the relative risk increases as the CD4 count drops. In the era before combination antiretroviral therapy, studies documented 2.3, 6.8, and 10.8 episodes

of bacterial pneumonia per 100 patient years in patients with CD4 counts of greater than 500, 200 to 500, and less than 200 cells/mm^3, respectively. Bacterial pneumonia is more common in smokers with HIV than in nonsmokers. Injection drug use more than doubles the risk of bacterial lower respiratory track infections compared with those who acquired HIV through sexual exposure. HIV-infected injection drug users have much higher rates of *Staphylococcal* pneumonia, including necrotizing pneumonia complicating endocarditis. Interestingly, a previous diagnosis of PCP pneumonia appears to be an independent risk factor for bacterial respiratory infections. As with other opportunistic infections, use of potent combination therapy has resulted in decreased incidence of bacteria pneumonia (from 22.7 to 9.1 episodes/100 patient years in one study). Diagnosis of bacterial pneumonia is associated with increased risk of death in patients compared with HIV-positive patients who are matched for CD4 count. Mortality due to bacterial pneumonia is higher in HIV patients who have a CD4 cell count less than 100 cells/mm^3, radiographic progression of disease on therapy, and shock.

The microbiology of bacterial lower respiratory track infection is influenced by HIV disease stage as well. Since encapsulated bacteria (in particular *Streptococcus. pneumoniae*) are more intrinsically virulent than the opportunistic infections of advanced HIV disease, these infections may occur at any stage of HIV disease and hence be the sentinel opportunistic process in a person otherwise unaware that he or she has HIV infection. Neither the concomitant use of trimethoprim-sulfamethoxazole for PCP prophylaxis nor a history of having received immunization against *Streptococcus pneumoniae* are sufficiently protective against bacterial pneumonia to warrant a change in empiric therapy when considering this diagnosis. The most common identified pathogen in HIV-related bacterial pneumonia is *Streptococcus pneumoniae*, generally followed by *Haemophilus influenzae*. The presentation of these typical community acquired pathogens is similar to that observed in HIV-negative patients with pneumonia. Fever, productive cough, dyspnea, and chest pain are common. Although both typically present with a relatively acute illness and focal consolidation on CXR, *H. influenzae* may rarely cause a more subacute illness with diffuse interstitial infiltrates, suggestive of *Pneumocystis jiroveci* pneumonia.

Gram-negative bacilli and *Staphylococcus* aureus assume increasing importance as immunosuppression worsens, presumably due both to neutrophil dysfunction and selective pressure of other antimicrobials. *Pseudomonas aeruginosa* has been associated with neutropenia, prior treatment with cephalosporins, and CD4 cell counts less than 50 cells/mm^3. Like individuals with structural lung disease, pseudomonal respiratory infections in HIV-infected patients have a tendency to relapse and chronic colonization typically ensues, with relapse rates after therapy between 25 and 86 percent. Methicillin-resistant *Staphylococcus aureus* (MRSA) is increasingly common in may be acquired in health care setting or in the community. Although the epidemiologic picture is rapidly evolving, the impact of HIV infection on risk for

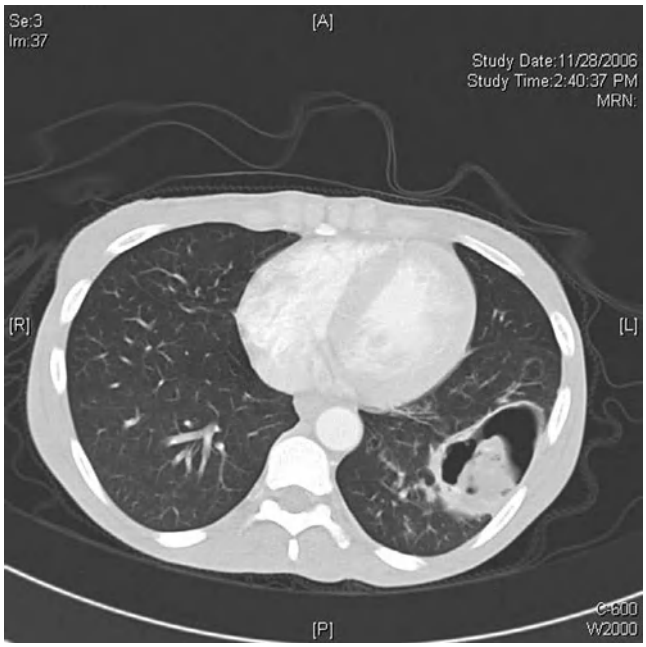

Figure 128-1 Cavitary pneumonia due to community-acquired methicillin-resistant *Staphylococcus aureus* in a 46-year-old man with AIDS, CD4+ cell count of 120. The patient was found to be bacteremic.

colonization and invasive disease with MRSA remains to be defined. Colonization with community-associated MRSA is more common in men who have sex with men (MSM) and injection drug users so the index of suspicion for MRSA infection should be high in HIV positive patients with these risk factors. MRSA pneumonia can be quite severe and commonly leads to cavitation (Fig. 128-1).

Compared with HIV-negative controls, atypical pathogens are a relatively uncommon cause of pneumonia in HIV-infected hosts, although important exceptions to this generalization exist. *Nocardia* species are an important cause of pulmonary disease in immunocompromised hosts, including those with HIV infection. The relative rarity of nocardiosis compared with other opportunistic processes may relate to the frequent use of trimethoprim-sulfamethoxazole for PCP prophylaxis, although this does not completely prevent nocardia infection from occurring. The disease is usually subacute to chronic, and limited to the lung, where cavitation may occur; therefore, it may present similarly to tuberculosis (Fig. 128-2). Dissemination with positive blood cultures is also possible, in particular in patients with advanced immunosuppression. *Rhodococcus equi* can cause both localized pulmonary and disseminated disease in HIV-infected hosts, who appear to be particularly susceptible to this pathogen. A gram-positive coccobacillus, *R equi* can be mistaken for routine oral flora on sputum smears. A potential clinical clue is that the organism appears weakly acid fast on sputum stains looking for tuberculosis. The typical presentation is one of a chronic pneumonia—with cough, sputum production, and sometime hemoptysis—with radiographs showing cavitary disease and often with associated pleural effusion; however,

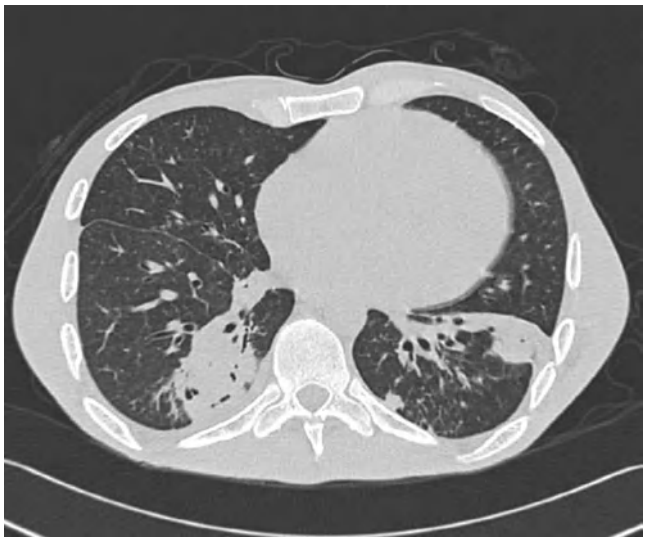

Figure 128-2 Pneumonia due to *Nocardia asteroids* in a 36-year-old man with AIDS, CD4+ cell count 30/mm^3. Infection resolved with prolonged therapy with imipenem.

diverse radiographic findings have been reported. Bacteremia commonly accompanies *Rhodococcus* pneumonia, and may be the most reliable way to make the diagnosis. As treatment requires prolonged therapy with multiple agents, persistence or recurrence of symptomatic infection is common unless the immune status can be improved with antiretroviral therapy. The frequency of *Legionella* pneumonia in HIV-positive patients who present with respiratory complaints has been difficult to define. Although early series seemed to suggest that these infections were relatively common, later studies have not supported the association. The epidemiology of *Legionella* infections shows significant variation and infections may be nosocomially acquired, facts that may alter the prevalence of such infections in both HIV-positive and -negative patients with respiratory complaints. TMP/SMX has activity against *Legionella* and hence TMP/SMX may partially protect HIV-positive patients if used for PCP prophylaxis.

The diagnosis of bacterial pneumonia in patients with HIV infection is similar to that of HIV-negative patients. Sputum should be collected for Gram stain and culture, preferably before administration of antibiotics. Susceptibility testing should be done on most clinical isolates giving rising rates of drug-resistant *Pneumococcus*, *Pseudomonas*, and MRSA. As bacteremia occurs in up to 60 percent of HIV-positive patients with pneumococcal pneumonia, two sets of blood cultures should also be collected. In patients with significant pleural effusions, consideration should be given to thoracentesis to rule out empyema. In patients in whom the diagnosis is unclear, supplemental testing such as a modified acid-fast stain (for *Nocardia* and *Rhodococcus*) or a urinary legionella antigen is appropriate.

Management of bacterial pneumonia is similar in both HIV-positive and -negative patients. Published guidelines for the treatment of community-acquired pneumonia are revised regularly and clinicians are encouraged to seek updated recommendations. Decisions on empiric therapy are based on the severity of the illness, presence of co-morbid disease and knowledge of local microbiology and resistance patterns. For patients with moderately severe disease, a third-generation cephalosporin along with either azithromycin or a respiratory fluoroquinolone such as levofloxacin or moxifloxacin is recommended. In HIV-positive patients with advanced disease, neutropenia or history of prior infection or colonization with *Pseudomonas* should receive an anti-pseudomonal cephalosporin such as cefepime or ceftazidime. Given the high rates of resistance in *Pseudomonas* infections, some experts advocate the addition of an aminoglycoside when this organism is isolated. Vancomycin or linezolid should be considered for HIV-positive patients who present with nosocomial pneumonia, rapidly progressive respiratory tract infection, or those with compatible clinical or Gram stain findings. Duration of therapy depends on the organism and response to treatment, but is generally similar to that of HIV-negative patients, typically 7 to 14 days.

Prevention of bacterial pneumonia should focus on restoration of immune function, observance of primary and secondary prophylaxis, and lifestyle modifications. Combination antiretroviral therapy should be considered for all patients with recurrent bacterial lower respiratory tract infections. In patients with severe neutropenia (less than 500 cells/mm^3), granulocyte colony stimulating factor (g-CSF) may reduce the risk of recurrent infection, whereas aggressive efforts are undertaken to identify and correct the cause(s) for neutropenia. Although not typically recommended for HIV-infected patients with recurrent bacterial respiratory track infections, TMP/SMX prophylaxis for PCP can reduce the rates of many bacterial pathogens as well. Pneumococcal vaccine is recommended for all HIV patients who have a CD4 cell count greater than 200 cells/mm^3, and the influenza vaccine should be given annually to all patients, regardless of CD4 cell count. Since most *Haemophilus influenza* infections in HIV patients are from non-typable strains, this vaccination is not recommended. Finally, given the strong links between bacterial respiratory infections and both tobacco abuse and intravenous drug use, HIV-infected patients with lower respiratory tract infections should be offered the full array of services to overcome these addictions.

Mycobacterial Infections

Detailed discussions of Mycobacterium tuberculosis and non-tuberculous mycobacteria can be found elsewhere in this volume, so we will limit our discussion to the distinct features of these infections in persons with HIV infection.

Mycobacterium Tuberculosis

Co-infection with HIV and TB accelerates the course of both infections. HIV viremia is higher in persons with active tuberculosis than those with similar CD4 counts as is HIV-related mortality. Whereas the lifetime risk of reactivation of latent tuberculosis infection (LTBI) is 5 to 10 percent in HIV-negative persons, it jumps to 7 to 10 percent annually in

HIV-positive persons. The likelihood that respiratory complaints in an HIV positive individual are due to tuberculosis is strongly influenced by environmental exposures, including current or past residence in TB endemic areas, and/or the presence of other known risk factors, such as homelessness or incarceration. Specifically, rates are high in immigrants from highly TB-endemic regions, such as sub-Saharan Africa, Latin America, Asia, and much of the Caribbean. The risk of co-infection with TB in patients with HIV in the United States is highest in the New York metropolitan area (including the cities of northern New Jersey), Florida, California, Chicago, the District of Columbia, Georgia, and Texas. Tuberculosis is seen at any stage of HIV infection. The frequency and clinical presentation of tuberculosis in HIV-infected patients depends on the degree of immunosuppression. In patients with relatively preserved higher CD4 cell counts (greater than 350 cells/mm^3), co-infection with TB tends to look like that seen in those without HIV (upper lobe predominance, cavitary disease and a low risk of extrapulmonary presentations). The presence of constitutional symptoms is variable in patients with higher CD4 counts but most HIV-positive patients with preserved CD4 count have fever, sweats, and weight loss. At more advanced stages of immunosuppression, HIV-positive patients with TB are more likely to have extrapulmonary disease accompanied by prominent constitutional symptoms (Fig. 128-3). In one series of 97 patients with HIV-TB co-infection, extrapulmonary disease was seen 30 of 43 patients with CD4 counts less than 100 cells/mm^3 versus 5 of 19 with a CD4 count greater than 300 cell/mm^3. Sites commonly involved with extrapulmonary TB in HIV-positive patients include the bloodstream, extrathoracic lymph nodes, bone marrow, genitourinary track, liver, and the central nervous system.

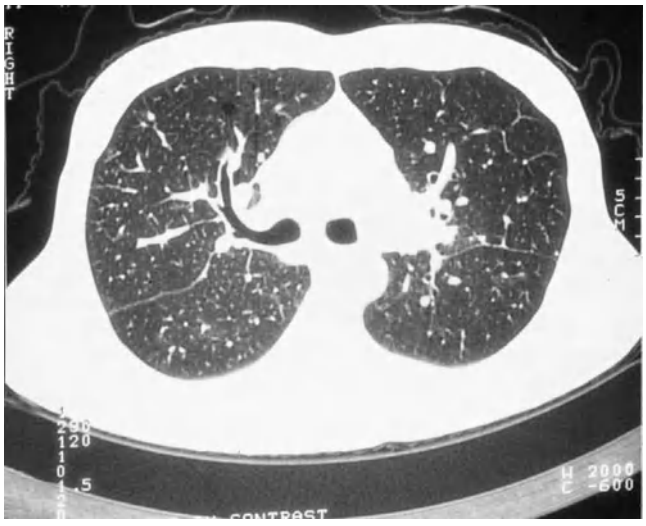

Figure 128-3 Disseminated tuberculosis with multiple small pulmonary nodules in a 40-year-old man with AIDS.

Non-Tuberculous Mycobacteria

Pulmonary symptoms due to non-tuberculous mycobacteria (NTB) are less common in HIV-positive than -negative patients. In the era before combination antiretroviral therapy, *Mycobacterium avium* complex (MAC) infection was a common opportunistic infection in persons with advanced AIDS (CD4 less than 50 cell/mm^3) and it still remains the most common NTB infection seen in patients with HIV. Clinical features of disseminated MAC include fever, anorexia, weight loss, hepatosplenomegaly, and anemia. Although the respiratory tract may serve as the portal of entry for MAC, it is rarely the primary cause of respiratory symptoms in patients with HIV. Recovery of MAC from respiratory secretions does not warrant treatment without compatible clinical and radiographic findings, although its presence may be a harbinger of disseminated disease. A discussion of the management of NTB mycobacterial infections can be found in Chapter 142 as well as the ATS guidelines for the diagnosis and treatment of non-tuberculous mycobacteria. Rates of disseminated MAC can be reduced by administering azithromycin 1200 mg by mouth once weekly to persons with CD4 counts less than 50 cells/mm^3; administration of effective antiretroviral therapy with improvement in the CD4 cell count virtually eliminates the risk of developing disseminated MAC.

Fungal Pathogens

Pneumocystis jiroveci

The initial case report of HIV infection in the June 5, 1981 issue of MMWR described five individuals without previously identified risk factors who were diagnosed with *Pneumocystis carinii* pneumonia (PCP). Pneumocystis infection is discussed in detail elsewhere in this volume. PCP in patients with HIV infection usually presents subacutely with progressive dyspnea, non-productive cough, and fever. Pleuritic chest pain or acute worsening of symptoms is an unusual manifestation of PCP in patients with HIV unless complicated by the development of a pneumothorax. Findings on physical exam are limited and nonspecific, and the lungs are generally clear on auscultation. Organism burden tends to be greater and neutrophil response diminished in HIV-associated PCP versus that seen in other immunocompromised groups, such as transplant recipients. Induced sputum is often the first diagnostic procedure, although a meta-analysis of studies in HIV-positive patients demonstrated a sensitivity of approximately 55 percent compared to the 95 percent sensitivity of BAL. Identification of cysts on appropriate stains is diagnostic of PCP, as there does not appear to be an asymptomatic carrier state. Persistence of organisms through and even after therapy is common, and does not reflect failure of therapy. Newer diagnostic techniques under investigation include polymerase chain reaction of saliva or sputum, as well as blood tests measuring levels of an S-adenosylmethionine, a metabolite used exclusively by *Pneumocystis jiroveci* and hence lowered in patients with active disease. Beta glucan, a component of the cyst wall of PCP, is also frequently elevated in patients with PCP, although the sensitivity and specificity of this test in various

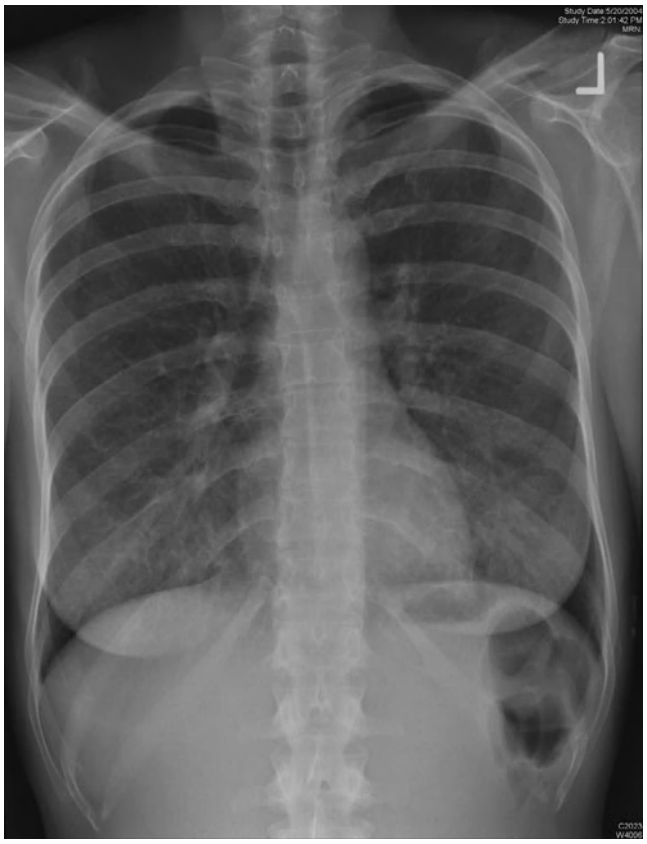

Figure 128-4 Bilateral interstitial pulmonary infiltrates in a 38-year-old woman (CD4+ cell count 60/mm^3) with *Pneumocystis jiroveci*. This was the initial AIDS-defining illness.

at-risk populations has not yet been defined. Chest imaging may be normal but more typically demonstrates bilateral diffuse interstitial abnormalities (Fig. 128-4). The treatment of PCP is discussed in detail elsewhere in this volume. Patients with PCP typically worsen after 2 to 3 days of therapy. In patients without known contraindications, treatment with trimethoprim-sulfamethoxazole (TMP-SMX) is the drug of choice for both intravenous and oral therapy. Because TMP-SMX has good bioavailability, patients can be treated with oral preparation unless concomitant gastrointestinal disease or the severity of the respiratory symptoms makes administration of oral medications difficult.

Cryptococcus neoformans

Cryptococcus neoformans is an encapsulated budding yeast that is found in soil throughout the world, typically in areas in which bird feces or decaying vegetable matter are found. Symptomatic cryptococcosis is most often seen in patients with HIV infection. Although exposure typically occurs through inhalation, the most common presentation of cryptococcosis in HIV-infected persons is meningitis, not pneumonia. Cryptococcal pneumonia typically presents with subacute and nonspecific symptoms such as fever, malaise, and cough; other associated pulmonary symptoms may include dyspnea, chest pain, and hemoptysis. Extrapulmonary symptoms depend on whether dissemination has occurred, most commonly to the central nervous system, in which basilar meningitis can lead to headache, cranial neuropathies, and in more severe cases, depressed consciousness. On occasion, physical exam reveals white papular lesions on the skin mimicking molluscum contagiosum. HIV-related cryptococcosis tends to occur in patients with CD4 counts of less than 100 cells/mm^3, although periodically symptomatic disease is diagnosed at slightly higher CD4 counts. Diagnosis of invasive *Cryptococcus neoformans* infection is patients with HIV is generally by cryptococcal antigen (CRAG) test, an assay that can be done on blood, cerebrospinal fluid (CSF), and respiratory samples (BAL specimen, pleural fluid). Treatment of HIV-positive patients with cryptococcal pneumonia depends on the severity of disease and the presence or absence of CNS disease. Patients with hypoxemia or other signs of extensive pulmonary disease or those with signs of CNS involvement should received induction therapy with amphotericin B and 5-flurocytosine until clear clinical improvement (at least 2 weeks in persons with CNS disease) followed by 8 weeks of fluconazole 400 mg daily. Although fluconazole or itraconazole could in theory be used to prevent cryptococcal disease in patients with AIDS, studies of primary prophylaxis have failed to demonstrate a survival benefit. HIV-positive persons with a history of cryptococcosis should be maintained on fluconazole 200 mg daily for secondary prophylaxis until their CD4 count rises to over 200 cells/mm^3 for at least 6 months.

Endemic Fungi

Histoplasmosis, coccidioidomycosis, blastomycosis, and penicilliosis are dimorphic fungi that are endemic to distinct regions but that may reactivate years after travel or residence in the area where exposure occurred. The endemic fungi rarely causes disease in patients with HIV until the patient is significantly immunosuppressed (CD4 less than 250 cells/mm^3). The use of combination antiretroviral therapy has reduced the incidence of all of these infections. Although the extent to which they produce respiratory symptoms in persons with HIV is variable, they all enter the host through the lungs before dissemination occurs to other sites. We will limit our discussions to the four most common endemic dimorphic fungi in the United States. Infection with Paracoccidioides brasiliensis should be considered in patients who present with the typical pulmonary and systemic complaints seen with the other HIV-related opportunistic endemic fugal infections in a person from Central or South America, although it is less common outside those regions in part due to the activity of TMP-SMX against this pathogen.

Histoplasma capsulatum

In patients with HIV infection, histoplasmosis most commonly presents with disseminated disease in an individual with a CD4 cell count less than 150 cells/mm^3. Signs of disseminated histoplasmosis include with fever, weight loss, adenopathy, diarrhea, and mucosal lesions. *Histoplasma*

capsulatum occasionally occurs in person with HIV and preserved CD4 counts (greater than 350 cells/mm^3) with clinical features similar to those of normal hosts (fever, headache, non-productive cough, chills, and chest pain). Cough and dyspnea are the most common pulmonary symptoms seen in patients with histoplasmosis and HIV infection. *Histoplasma capsulatum* can produce a sepsis syndrome as well with fever, hypotension, and multiorgan system failure. Disseminated histoplasmosis in a patient with AIDS may have normal chest radiographs, especially if he or she does not have respiratory complaints. Typical radiographic findings in those with pulmonary complaints include diffuse interstitial or reticulonodular infiltrates. The presence of hilar or mediastinal adenopathy may help distinguish histoplasmosis from *Pneumocystis jiroveci*, as the clinical presentation in susceptible hosts overlap significantly, although these are uncommon findings for *Pneumocystis*. The test of choice for diagnosing histoplasmosis is detection of polysaccharide antigen in urine or blood, where urine testing has been shown to be positive in up to 95 percent of patients with disseminated disease and AIDS. This test has supplanted antibody and skin testing, which are rarely indicated. Amphotericin is currently considered the drug of choice for severe or disseminated histoplasmosis in HIV-positive patients and should be continued for 3 to 10 days until clear clinical improvement has occurred before patients are switched to itraconazole to complete a total of 3 months of therapy. Published guidelines suggest that patients with HIV infection be maintained on suppressive doses of itraconazole indefinitely. Discontinuation of secondary prophylaxis has not been studied sufficiently to comment on CD4 level at which it is safe to stop itraconazole in patients who have responded to antiretrovirals. The treatment of pulmonary histoplasmosis is persons with preserved CD4 counts (greater than 500 cell/mm^3) is controversial, as this is often a self-limited process. Antifungal therapy is not recommended for primary prophylaxis of patients with HIV infection and depressed CD4 counts, although such individuals should be advised to minimize exposure to soil.

Coccidioides immitis

Coccidioides immitis is endemic to the southwestern United States, Northern Mexico, and parts of South and Central America, where it is found in soil. Sporadic cases seen in areas outside of these regions are thought to represent reactivation of latent infection in persons who acquired *Coccidioides immitis* while traveling in endemic regions. Coccidiomycosis often presents with pulmonary complaints that may look like PCP. Symptomatic disease typically occurs in individuals with advanced immunosuppression (CD4 cell counts less than 250 cells/mm^3). Coccidiomycosis in patients with preserved CD4 counts is often confused with typical community-acquired pneumonia. As with histoplasmosis, pulmonary findings are often accompanied by clinical evidence of dissemination, including involvement of the skin, lymph nodes, bone, liver, and meninges. Radiographic abnormalities on chest radiograph are diverse, and may include reticulonodular disease, alveolar infiltrates, nodules, adenopathy, cavities, and pleural effusions. The presence of hilar adenopathy, eosinophilia, or lack of response to conventional antibiotics should prompt consideration of pulmonary coccidiomycosis in patients from endemic areas. Isolation of the organism in respiratory secretions—usually through bronchoscopy—is generally required to make the diagnosis. Culture of respiratory secretions in patients with active pulmonary disease is quite sensitive and often yields results in 3 to 5 days. A positive isolator blood culture confirms the presence of disseminated disease. Although serologic testing should be pursued, the sensitivity of these tests is probably lower in patients with HIV (about 70 percent sensitive). *Coccidioides immitis* serology has a more established role to play in monitoring response to therapy. Skin testing with coccidial antigen has no useful role diagnostically. Treatment guidelines list amphotericin B as the drug of choice for patients with isolated pulmonary disease or disseminated coccidiomycosis without meningeal involvement in patients with HIV infection. Treatment should be continued until clear clinical improvement has been demonstrated, at which time patients may be switched over to itraconazole or fluconazole. HIV-positive persons with meningeal involvement should be treated with high-dose fluconazole, which has demonstrated success rates of approximately 80 percent and, as with HIV-negative patients, therapy should be continued indefinitely. Coccidiomycosis has high rates of recurrence in patients with HIV, so suppressive therapy with either fluconazole or itraconazole should be administered. There are inadequate data to guide decisions on discontinuation of secondary prophylaxis in patients who have experienced CD4 recovery in the setting of effective antiretroviral therapy but, as noted, meningeal disease should be treated with lifelong therapy. There are no formal guidelines for primary prevention of *Coccidioides immitis* infection in patients with HIV. Preliminary studies suggest that preemptive therapy with itraconazole or fluconazole may be considered in patients with positive serology, although the potential benefits of this approach have not been established.

Blastomyces dermatitidis: Like *Histoplasma capsulatum*, *Blastomyces dermatitidis* is dimorphic fungi endemic to the Mississippi, Ohio, and St. Lawrence River valleys, although they are less common outside of the United States. Of the endemic fungi, *Blastomyces dermatitidis* is the least likely to act as an opportunistic pathogen in patients with HIV. In normal hosts, blastomycosis most commonly involves the lung and skin, although nearly every organ of the body may be involved including the CNS. HIV-associated blastomycosis tends to occur in patients with CD4 counts less than 200 cells/mm^3 and is more likely to be disseminated. Unlike some of the other endemic fungi, most HIV-positive patients with blastomycosis have pulmonary complaints, even if their infection is disseminated. A case series of blastomycosis in 15 HIV patients, 12 had evidence of pulmonary involvement and 5 also had disseminated disease at the time of diagnosis. The predominant symptoms at presentation were

fever, weight loss, and cough. Diagnosis of blastomycosis is most definitively made by fungal culture of respiratory secretions or tissue samples. A variety of serologic tests are available for *Blastomyces dermatitidis* but the utility of these assays have not been validated in HIV-positive patients. Antigen assays hold promise for diagnosing blastomycosis with reported sensitivities in normal hosts of 80 percent for disseminated disease and over 95 percent for patients with isolated pulmonary disease. Amphotericin is the drug of choice for severe or disseminated histoplasmosis, although there are no specific guidelines for the treatment of *Blastomyces dermatitidis* in HIV-positive patients. Treatment guidelines for HIV-negative patients suggest treating with amphotericin until the patient has received a total of 1.5 to 2.5 g. CNS or bone involvement may require longer courses. At the completion of this induction phase, patients should be switched over to itraconazole chronically. Discontinuation of secondary prophylaxis has not been studied and there are no data on primary prophylaxis in patients with AIDS. Importantly, such recommendations for use of prolonged courses of amphotericin and lifelong suppressive therapy precede the widespread use of azoles and the remarkable recovery of the immune system that occurs with antiretroviral therapy. As such, there are certain clinical cases where shorter courses of amphotericin and discontinuation of chronic suppressive therapy may be appropriate.

Penicillium marneffei

Penicillium marneffei is a dimorphic fungus that is endemic to Southeast Asia. It is isolated most commonly in the soil, especially in areas in which bamboo rats are found. Although direct inoculation through skin can occur, it is thought that inhalation is the main route of exposure. *Penicillium marneffei* has emerged as one of the leading opportunistic infections in persons with HIV in Southeast Asia, ranking behind only cryptococcosis and tuberculosis in some studies. *Penicillium marneffei* is generally seen in patients with advanced AIDS (CD4 less than 50 cell/mm^3), where it commonly presents with extrapulmonary symptoms (fevers, weight loss, sweats, hepatosplenomegaly, and hematologic abnormalities). It also commonly produces cutaneous findings, particularly umbilical papules that may be confused with either cryptococcosis or molluscum contagiosum. Respiratory symptoms are common though they are much more commonly associated with systemic disease, then isolated pneumonia. Chest radiographs most demonstrate interstitial changes though nodules, cavitation and pleural disease have all been reported previously. Serologic testing is of limited utility in penicilliosis and microbiologic diagnosis requires isolation of the organism from blood, skin, bone marrow, or lymph nodes. Treatment of *Penicillium marneffei* in patients with HIV infection depends on the severity of infection. In patients with disseminated infection, amphotericin B should be used to control the infection. Patients who have demonstrated clear clinical improvement can be switched to twice-daily itraconazole to complete a 3-month treatment course. Relapse is common in HIV-positive patients with *Penicillium marneffei*, so secondary prophylaxis with daily itraconazole should be maintained until patients have achieved a CD4 count of greater than 200 cells/mm^3 for at least 6 months. Fluconazole does not have activity against *Penicillium marneffei*. Primary prophylaxis with itraconazole for *Penicillium marneffei* has been shown to reduce the incidence of *Penicillium marneffei,* although it did not confer a survival advantage. HIV-positive persons traveling to endemic areas should be told to avoid concentrated exposure to dusts and soil while traveling.

Aspergillosis

Invasive pulmonary aspergillosis in patients with HIV infection occurs almost exclusively in those with advanced immunosuppression (CD4 cell count less than 50 cells/mm^3). Aspergillus species are found worldwide in soil, especially around decaying vegetable matter. Patients with AIDS who are diagnosed with invasive disease often have other risk factors for aspergillosis, such as receipt of corticosteroids or neutropenia. Although a number of species of *Aspergillus* have been reported in HIV infection, *Aspergillus fumigatus*, and to a lesser extent *Aspergillus niger* are the most common causes of invasive aspergillosis. Respiratory tract disease is the most common manifestation of aspergillosis and both tracheitis and invasive pneumonitis may develop. In the former, fever, cough, dyspnea, and wheezing are common symptoms: The diagnosis is established when endoscopic examination reveals an exudative pseudomembrane adherent to the tracheal wall. In invasive pneumonitis, fever and cough may be accompanied by pleuritic pain and hemoptysis. Radiographic abnormalities in both of these forms overlap, and can show diffuse infiltrates, cavities, and focal wedge-shaped abnormalities reflecting pulmonary infarction. Despite the predilection for the organism to invade blood vessel walls and disseminate, focal CNS disease due to aspergillus in AIDS patients appears to arise more commonly from contiguous spread from the sinuses, orbits, and ears. A definitive diagnosis of invasive aspergillosis requires identification of the fungus on a biopsy specimen in a patient with the appropriate clinical syndrome. Not uncommonly, a presumptive diagnosis of pulmonary disease is made when *Aspergillus* spp. are cultured from respiratory secretions in a patient fever, cough, infiltrates, and severe immunosuppression. The diagnosis is especially likely when concomitant risk factors (e.g., corticosteroid exposure or neutropenia) are present. It is important to note, however, that aspergillus is a common colonizer of diseased airways, so definitive diagnosis requires documentation of tissue invasion. Outside of isolated case reports, the utility of noninvasive tests such as the serum galactomannan or PCR-based techniques have not been studied in patients with HIV. Data on the management of invasive aspergillosis in HIV-positive patients are limited. Published guidelines list voriconazole as the agent of choice for invasive aspergillosis, although potential drug-drug interactions in patients receiving antiretroviral medications should be closely monitored. Amphotericin products and echinocandins remain potential

alternatives. There are no formal recommendations for length of treatment or prophylaxis (secondary or primary), although every effort should be made to provide effective antiretroviral therapy, to correct neutropenia by discontinuing offending agents or by using stimulatory cytokines, and to eliminate exogenous immunosuppression by discontinuing corticosteroids.

Viral Pneumonia

Although patients with HIV infection are at risk for viral pneumonia, the magnitude of risk is hard to estimate. As with immunocompetent patients, a definitive viral etiology for respiratory complaints is less commonly established than with other respiratory pathogens. Although many respiratory viruses produce disease in patients with HIV, only cytomegalovirus is an AIDS-defining opportunistic infection. Furthermore, not all viruses identified in respiratory secretions produce lower respiratory infections. For example, identification of herpes simplex virus from cultures of BAL fluid generally reflects disease in the upper airway or oropharynx, not the lungs. For this reason, HIV-positive patients with HIV infection and respiratory complaints may require an aggressive evaluation, including histopathology, to definitively establish a viral pathogen as the sole cause of a lower respiratory tract infection.

Cytomegalovirus

Cytomegalovirus (CMV) is a complex DNA virus belonging to the β-group of the family Herpesviridae. Like other herpes virus infections, CMV establishes latency in a variety of cell types, including polymorphonuclear cells, T lymphocytes, and salivary gland cells. Serologic evidence of CMV infection is common in patients with HIV infection, with rates of seropositivity over 95 percent reported in HIV-positive men who have sex with men. Asymptomatic persons with CMV infection excrete the virus in saliva, respiratory secretions, urine, and semen. Clinically significant HIV-related CMV infection is associated with severe immunosuppression (CD4 less than 50 cells/mm^3). CMV-associated syndromes most commonly seen in patients with AIDS are retinitis and enteritis (colitis or esophagitis). A variety of CMV-related neurologic complications have been described, including polyradiculitis, ventriculitis, and mononeuritis multiplex. As noted, the exact frequency of lower respiratory tract infection with CMV is difficult to establish. As is the case with herpes simplex virus, isolation of CMV from BAL specimens is relatively common. In most studies, patients with positive BAL cultures for CMV have evidence of a more likely alternative diagnosis (especially PCP or bacterial pneumonia), and may improve without specific therapy directed at CMV. Nonetheless, in a patient with advanced HIV disease (CD4 cell count less than 50 cells/mm^3), interstitial infiltrates on chest radiograph, and no alternative organism isolated, CMV pneumonitis may be the sole responsible pathogen. Because symptomatic reactivation of CMV in advanced AIDS often occurs in more than one location, patients being considered for treatment for CMV pneumonitis should be screened for GI symptoms and undergo a dilated retinal exam to rule out co-incident retinitis. When disease is limited to the chest, definitive diagnosis requires demonstration of cytopathic change on histopathology (usually obtained via transbronchial biopsy or VATS). In such cases, cultures are confirmatory rather than diagnostic. In the rare case of primary CMV infection, detection IgM antibody may be helpful, especially when IgG antibodies are negative. Unfortunately, CMV antigenemia assays or amplification-based techniques are neither specific nor sensitive enough to diagnose or exclude end-organ disease due to CMV, as viral replication occurs in asymptomatic persons as well. The agents of choice for the treatment of established CMV pneumonitis is oral valganciclovir, with the IV formulation a suitable alternative in those who cannot take oral therapy. For refractory disease, foscarnet would be an appropriate alternative, although its use is associated with high rates of renal dysfunction and other metabolic abnormalities. The duration of therapy for CMV pneumonitis is unknown, but is typically 2 to 3 weeks. For those who have started with intravenous therapy and improve, patients can be switched to oral valganciclovir. Unlike CMV retinitis, there is no standard secondary prophylaxis for CMV pneumonitis. However, as with other opportunistic infections, the antiretroviral therapy with restoration of the CD4 cell count plays a critical role in preventing recurrences. A study evaluating a strategy of preemptive valganciclovir in patient with AIDS and asymptomatic evidence of reactivation of CMV by PCR assay did not find benefit to this approach. Patients with HIV infection who are CMV IgG negative and require blood product support should followed standard guidelines for minimizing the risk of transfusion-related CMV infection.

Other Respiratory Viruses

Available data on the frequency and natural history of other respiratory viral infections are limited. Because of the availability of both rapid and reliable diagnostic techniques and antiviral agents with documented efficacy, influenza is the most important viral pathogen to consider when evaluating an HIV-positive patient with respiratory track symptoms. During influenza season, HIV-infected patients who present with a compatible clinic picture (an acute febrile illness associated with cough, myalgias, sore throat, and rigors), should be tested for influenza via either antigen or PCR-based techniques. Although data are limited, it appears that patients with HIV are at no greater risk for severe infection or secondary complications than HIV-negative controls. Chest radiographs are typically unrevealing, suggesting that, as with HIV-negative patients, primary influenza pneumonia is unusual. Data on the potential benefits of neuraminidase inhibitors in patients with HIV are limited, although it is reasonable to consider administering either oseltamivir or zanamivir to patients with documented influenza, especially when the onset of the symptoms are acute, immunosuppression is severe, or presentation is severe. Influenza is a preventable infection and all patients with HIV infection should be encouraged

to get annual vaccination. Although declines in CD4 count and rises in HIV viral load may be seen after influenza vaccination, these adverse laboratory events are generally transient and have not been shown to be associated with adverse clinical events. HIV-positive patients with significant exposure to persons with HIV may benefit from prophylaxis as well.

As with other immunosuppressed populations, pneumonitis in HIV patients has been reported due to herpes simplex virus, as well as adenovirus, respiratory syncytial virus, and parainfluenza virus type 3. These are rare causes of pneumonia in HIV-infected patients, but should be considered when clinicians cannot identify an alternative diagnosis. As discussed, identification of herpes simplex virus in respiratory secretions usually indicates evidence of reactivation in the aerodigestive tract rather than primary pneumonitis, although pulmonary or tracheal infection may rarely occur, especially in the context of endotracheal or nasogastric intubation.

Parasitic Pneumonia

Parasitic diseases do not commonly cause of respiratory tract symptoms in patients with HIV. Of the parasitic diseases seen with increased frequency in patient with HIV infection, *Toxoplasma gondii*, *Strongyloides stercoralis*, cryptosporidium, and microsporidia, all may produce pulmonary symptoms. Although parasitic diseases typically produce more prominent extrapulmonary symptoms, each of these pathogens may produce respiratory complaints, sometimes even overshadowing symptoms associated with the primary target of the infection. Of the parasitic disease that can produce respiratory complaints, *Toxoplasma gondii* is probably the most common pathogen to do so. Pulmonary toxoplasmosis is a cause of pneumonia in patients with HIV, and is most commonly seen in patients with markedly depressed immune function (CD4 less than 50 cells/mm^3). The clinical presentation of pulmonary toxoplasmosis is similar to that of PCP, but unlike PCP it may be accompanied by a sepsis-like syndrome with hypotension. Radiographic abnormalities are diverse, consisting most commonly of interstitial infiltrates, but also potentially nodules, effusions, or mass lesions. As with PCP, an elevated LDH is a commonly reported laboratory finding. Diagnosis may be established by identification of toxoplasma tachyzoites on Giemsa stain of BAL fluid or tissue obtained on biopsy. Treatment of pulmonary toxoplasmosis in patients with HIV infection is similar to that recommended for patients with CNS disease. Pyrimethamine plus sulfadiazine is the first-line treatment, although clindamycin may be substituted if the patient cannot tolerate sulfadiazine. The course of therapy is generally 6 weeks, and patients should receive secondary prophylaxis until their CD4 count is greater than 200 cell/mm^3 for over 6 months. Prophylaxis with double strength TMP/SMX once daily in HIV-positive patients with CD4 counts less than 100 cell/mm^3 has been shown to reduce the risk of CNS toxoplasmosis, and likely also prevents pulmonary disease. Patients who are IgG negative for *Toxoplasma gondii* should be counseled to avoid undercooked meat (in particular lamb, pork, and beef), and wash hands thoroughly after contact with cat litter. Despite its association with defects in cell-mediated immunity, disseminated infection to the lung of *Strongyloides stercoralis* is surprisingly rare in HIV-infected individuals, even in areas highly endemic for both HIV and strongyloides. Indeed, many patients with HIV who experience strongyloides superinfection syndrome have other classic risk factors, including receipt of corticosteroids, severe wasting, or HTLV-I co-infection. Despite its rarity, clinicians should consider the diagnosis of strongyloidiasis in an HIV-infected patient who presents with pneumonitis, or gram-negative sepsis with associated meningitis. Identification of strongyloides larvae on a centrifuged BAL specimen is diagnostic; eosinophilia is variably present, and its absence does not exclude the diagnosis. When strongyloides is identified in the lung, disseminated disease has occurred by definition; treatment should be with extended courses of ivermectin plus albendazole. Although predominantly involving the gastrointestinal tract, both cryptosporidiosis and microsporidiosis can rarely be found in the lung and lead to pulmonary disease. Diagnosis is through direct visualization of the organism on respiratory secretions or histopathology, using appropriate stains—modified acid-fast for cryptosporidiosis—and the modified trichrome stain for microsporidiosis. As antimicrobial treatment for these conditions is suboptimal, improving immune function with antiretroviral therapy is the preferred strategy.

Noninfectious Pulmonary Complications of HIV

Although opportunistic infections must be excluded when a patient with HIV infection presents with respiratory complaints, the differential diagnosis includes a number of noninfectious pulmonary complications as well. HIV-related malignancies such as Kaposi's sarcoma (KS) and non-Hodgkin's lymphoma (NHL) may involve the lung, and patients with HIV appear to have both increased rates of lung cancer and more aggressive disease compared with uninfected controls. In addition to these malignancies, HIV infection is associated with increased risk of pulmonary hypertension. Although interstitial lung disease is most often due to opportunistic infection, lymphocytic interstitial pneumonitis (LIP) may cause these findings, especially in children. Pulmonary diseases such as chronic obstructive pulmonary disease (COPD) and thromboembolic disease are reported with increased frequency in HIV-positive persons as well.

Kaposi's Sarcoma

Like PCP, KS was one of initial complications noted in the first descriptions of HIV infection. KS is associated with human herpes virus type 8 (HHV8) infection. Endothelial cells latently infected with HHV8 are activated by HIV, which in turn drive the angiogenesis characteristic of this vascular malignancy. KS may develop in patients with preserved CD4 counts, although the pulmonary involvement is most commonly seen in advanced disease (CD4 less than

100 cells/mm^3). In the United States, KS is most commonly seen in men who have sex with men. Rates are also high in some areas of sub-Saharan Africa, where HHV8 is endemic. The prevalence of KS has dropped dramatically since the introduction of combination antiretroviral therapy. Patients with pulmonary KS usually have evidence of cutaneous and/or mucosal disease. In one series, only 16 percent had disease limited to the lungs. Pulmonary KS may be asymptomatic even in patients with extensive abnormalities on chest radiograph. Radiographic finding of pulmonary KS are variable and can include nodular infiltrates with or without pulmonary effusions. Lesions tend to show peribronchovascular distribution. Diagnosis is generally made through direct visualization of characteristic purplish plaques on bronchoscopy. As these lesions are highly vascular and quite typical, biopsy is often deferred to avoid the risk of hemorrhage. Chemotherapy is indicated for symptomatic pulmonary disease. However, as with cutaneous KS, potent antiretroviral therapy can induce significant improvement in pulmonary KS, as well as sustained remissions. In some cases, antiretroviral therapy can even obviate the need for chemotherapy. As discussed in the following, antiretroviral therapy also has been rarely associated with inflammatory worsening of KS as a form of the immune reconstitution syndrome.

Non-Hodgkin's Lymphoma

The risk of developing non-Hodgkin's lymphoma (NHL) is 200 to 600 times greater in persons with HIV compared with those who are uninfected. Non-Hodgkin's lymphoma tends to be more aggressive in patients with HIV, and such patients tend to present more commonly with stage IV and extranodal disease. HIV-associated NHL can occur at any stage of the infection, but rates rise dramatically when the CD4 count falls below 100 cells/mm^3. The prevalence of NHL in HIV-infected persons has dropped significantly since the introduction of combination antiretroviral therapy. Most HIV-related NHL demonstrates high-grade histologic features (diffuse large cell or Burkitt-like) and many of these are Epstein Barr virus (EBV)–related. Primary effusion lymphoma (also called body cavity lymphoma) is a distinct type of HIV-associated NHL that presents with unexplained effusions of the pleura, pericardium, or peritoneum without associated mass lesion. Although evidence of EBV infection is often found in such lymphomas, HHV-8 infection appears to be the most important cofactor in the pathogenesis of HIV-associated NHL. The chest-specific radiographic findings of HIV-associated are diverse, and may consist of nodules, masses, and pleural effusions. Non-specific findings that suggest lymphoma are elevations in LDH and a positive gallium scan corresponding to the area of abnormality on chest imaging. Although the diagnosis can sometimes be established through BAL with cytology, transbronchial biopsy, or thoracentesis, these procedures have a low yield and VATS is often required. Management of HIV-related NHL depends on the specific histological features and organ involvement. In the era before combination antiretroviral therapy, prognosis for patients with HIV and NHL was generally poor, especially with low baseline CD4 cell counts. More recent data suggest that restoration of immune function with antiretroviral therapy along with chemotherapy improves survival.

Lung Cancer

Although the role of HIV infection in the pathogenesis of other malignancies is unproved, evidence is accumulating that HIV-positive patients are at increased risk of developing lung cancer. Furthermore, although rates of KS and NHL have declined, rates of lung cancer in HIV-positive persons are rising. Lung cancer is the most frequently diagnosed non-AIDS–related malignancy, with reported rates of three- to eightfold higher than those without identified infection. HIV-associated lung cancers appear to be more common in blacks than whites. Although the proportion of small cell and non–small cell lung cancers appear to be comparable with that seen in the general population in some studies, others report increased rates of adenocarcinomas in patients with HIV. The prognosis for persons with HIV-related lung cancer is worse, as these malignancies tend to present at a younger age and with more advanced disease. HIV-related immunologic decline does not appear to be a major factor in the higher death rate from lung cancer seen in patients with HIV. While CD4 count at the time of diagnosis of lung cancer may be depressed, it is more commonly preserved. Data from ALIVE cohort at Johns Hopkins demonstrated increased lung cancer death rates in HIV-positive injection drug users (IDVs) compared to HIV negative IDUs. The diagnostic approach to patients with suspected lung cancer is the same regardless of HIV status. In a subset of the John Hopkins cohort who received their HIV care in the system prior to diagnosis of lung cancer, 60 percent had had a chest radiograph in the year preceding diagnosis and several of these had either normal or non-specific findings that were attributed to an undiagnosed infectious complication. Whether more aggressive screening for lung cancer will prove effective in improving outcomes is yet to be determined, but it is important to maintain a high index of suspicion for lung cancer when evaluating HIV-positive patients with preserved CD4 counts and unexplained respiratory symptoms or radiographic abnormalities.

Pulmonary Hypertension

HIV infection is a risk factor for the development of pulmonary hypertension. Attempts to identify HIV in endothelium from the pulmonary vasculature have been unsuccessful. The most common hypothesis for the association of HIV and pulmonary HTN is an alteration in pulmonary cytokine profile that increases expression of vasoactive substances such as endothelin-1. HIV-related pulmonary hypertension (HRPH) is a diagnosis of exclusion and can only be made after other secondary causes of pulmonary hypertension have been excluded. HRPH can occur at all stages of HIV disease, with variable CD4 cell counts and HIV RNA levels at the time of presentation. In some series, women represent a disproportionate number of the cases. Like all patients with pulmonary

hypertension, the most common symptom of HRPH is exertional dyspnea, although cough, fatigue, and chest pain may also be present. The key to the diagnosis is recognizing that the symptoms are not related to a primary pulmonary infectious process. Physical exam signs consistent with right ventricular hypertrophy or failure are helpful, but often not present initially. An echocardiogram will show evidence of right atrial hypertrophy and elevated pulmonary pressures; this is then confirmed with right heart catheterization. Management of pulmonary hypertension is as for HIV-negative hosts, with prostaglandin agonists (epoprostenol), diuretics, and anticoagulation. Sildenafil may also have a role, but it is associated with potential drug-drug interactions in patients receiving with protease inhibitors. Unfortunately, reports have not shown a consistent beneficial response of this condition to antiretroviral therapy.

Lymphocytic Interstitial Pneumonitis

Although lymphocytic interstitial pneumonitis (LIP) is seen more commonly in HIV-infected children, adults may rarely develop this complication as well. LIP is characterized by polyclonal inflammatory lymphoid proliferation of bronchus-associated lymphoid tissue (BALT). In children, LIP has been associated with EBV infection and some experts suggest that LIP in adults is a lung-specific immune response to HIV itself. HIV-positive patients with LIP tend to present with gradual onset of cough, shortness of breath, and constitutional symptoms. Diffuse reticulonodular or interstitial infiltrates are seen on chest imaging, making differentiation from PCP difficult (Fig. 128-5). LIP in patients with can be confused with other HIV non-infectious causes of interstitial lung disease. Diffuse infiltrative lymphocytosis syndrome (DILS) is a multisystem disorder characterized by oligoclonal expansion of CD8+ T lymphocytes that can produce interstitial infiltrates similar to that seen in LIP. In addition to the pulmonary symptoms, DILS can involve produce parotitis, hepatitis, neuropathies, and myositis. However, compared with patients who develop HIV-related opportunistic infections, those with LIP usually have a relatively preserved or even normal CD4 cell count. Whereas the diagnosis of LIP in children may be made on clinical grounds after extensive evaluation for infectious complications of HIV, diagnosis of LIP in adults almost always requires transbronchial or video-assisted thorascopic biopsy to definitively establish the diagnosis. Several case reports have demonstrated that antiretroviral therapy may lead to substantial improvement in LIP. For unresponsive cases, corticosteroids may be effective.

Chronic Obstructive Pulmonary Disease

There is evidence that patients with HIV are at greater risk for the development of emphysema than HIV-negative subjects. Investigators have postulated that the higher proportion of CD8+ T lymphocytes seen in BAL fluid from patients with HIV compared with uninfected controls may help explain this difference. It is unknown whether effective antiretroviral therapy offsets the increased susceptibility to this condition. As cigarette smoking is highly prevalent in many clinical centers among HIV patients, this is an area of prevention often overlooked among providers.

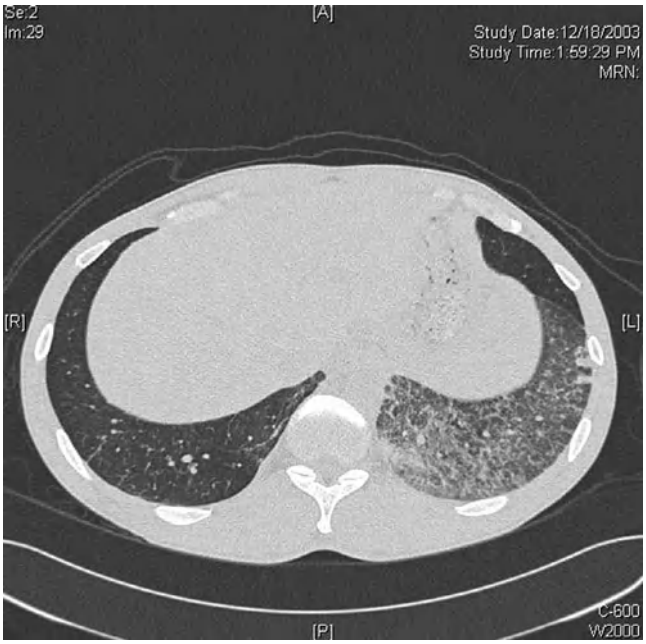

Figure 128-5 A 39-year-old man with HIV infection, CD4+ cell count 260/mm^3, presented with fever and cough. Ground-glass opacities were identified in the left lower lobe. Bronchoalveolar lavage was negative for all pathogens, but transbronchial biopsy demonstrated findings consistent with lymphocytic interstitial pneumonia. Antiretroviral therapy produced significant clinical improvement.

Thromboembolic Disease

Patients with HIV infection are at two- to tenfold increased risk of thromboembolic disease compared with healthy controls. The increased risk attributable to HIV (vs. the complications with which HIV is associated) is uncertain, although alterations in cytokine profiles in patients with untreated HIV infection have been proposed as a mechanism to explain such increased risk. Until large, well-controlled studies establishing the relative risk for thromboembolic complications have been completed, recommendations on the prevention and treatment of DVT and PE must follow those for patients who HIV status is unknown.

Special Considerations

Practitioners should be aware of several important clinical scenarios that require special consideration when managing HIV-positive patients with respiratory complaints. Despite the unquestionable benefits of antiretroviral therapy, combination antiretroviral therapy may rarely be associated with significant and even life-threatening toxicities. The nucleoside reverse transcriptase inhibitor (NRTI) abacavir may produce systemic reaction that can be fatal if not promptly recognized. In addition to toxicity produced by the medications directly, antiretroviral agents have may alter the pharmacokinetics of compounds with which they are co-administered.

Successful control of HIV replication (as evidenced by complete suppression of HIV in peripheral blood and rise in CD4 count) is not without the potential for respiratory complications, as restoration of immune function may itself produce a paradoxical worsening of symptoms, a syndrome called immune reconstitution inflammatory syndrome (IRIS). Finally, all practitioners should be aware of CDC guidelines for the management of occupational exposure to HIV infection to minimize nosocomial spread of this uncurable infection.

Abacavir-Hypersensitivity Syndrome

Abacavir is a nucleoside reverse transcriptase inhibitor that causes a systemic hypersensitivity reaction (HSR) in approximately 5 percent of individuals receiving the drug. Abacavir HSR is more common in whites, and is most strongly associated with HLA-B*5701 haplotype. Symptoms of the abacavir HSR usually appear in the first 6 weeks of treatment and include fever, rash, malaise, GI upset, myalgia, and arthralgias. Cough and dyspnea also may occur and may mimic bronchitis or pneumonia. It is critical that clinicians evaluating patients who have recently been started on abacavir who present with fever and respiratory symptoms consider abacavir hypersensitivity in the differential diagnosis, as continued abacavir treatment in the face of this reaction can be fatal. Symptoms generally resolve slowly after cessation of the drug. Abacavir should never be resumed in such circumstances, as re-challenge can lead to an immediate and life-threatening recurrence of the hypersensitivity reaction. As abacavir hypersensitivity can mimic other processes, in particular influenza, helpful clinical clues that make hypersensitivity more likely are worsening of symptoms after each dose, the presence of GI symptoms, and rash. Management of abacavir HSR requires prompt discontinuation of the drug and supportive care. Screening for the HLA-B*5701 haplotype has been introduced in some clinical centers, and markedly reduces the risk of this complication.

HIV Pharmacology

Protease inhibitors and non-nucleoside reverse transcriptase inhibitors are both substrates for and interact with the cytochrome P450 enzymes. In general, the protease inhibitors are potent inhibitors of CYP3A4, whereas the NNRTIs efavirenz and nevirapine are inducers. The inhibitory property of the PIs is used therapeutically when the ritonavir is administered at low doses to boost the levels of other agents. A detailed review of potential drug-drug interactions is beyond the scope of this chapter, but it is critical that physicians recognize the potential for drug-drug interactions when prescribing new agents to patients receiving combination antiretroviral therapy.

Immune Reconstitution Inflammatory Syndrome

Immune reconstitution inflammatory syndrome (IRIS) arises when patients develop paradoxical worsening after initiating combination antiretroviral therapy due to the development of an inflammatory response to a pathogen that may or may not have been evident before treatment for HIV infection was initiated. Patients with IRIS generally have initiated antiretroviral therapy when severely immunosuppressed (CD4 count typically less than 50 cell/mm^3), and demonstrate a particularly robust CD4 cell count recovery compared with those who do not develop IRIS. However, cases may occur even with relatively high baseline CD4 cell counts or, similarly before a substantial increase in the absolute CD4 cell count occurs. IRIS typically develops in the first several months after starting antiretroviral therapy, although it occasionally develops later than this. Symptoms of IRIS depend on the organ system involved. The most commonly described form involves inflammatory lymphadenitis, occurring in any of the visceral, thoracic, or peripheral lymphatic chains. IRIS was first described in response to unrecognized *Mycobacterium avium* infection, although the list of potential pulmonary pathogens that have produced IRIS includes tuberculosis, cryptococcus, PCP, histoplasmosis, aspergillus, CMV, Kaposi's sarcoma, and strongyloides. IRIS is a diagnosis of exclusion and coincident opportunistic infections, malignancies, and drug toxicities must all be ruled out. Management of IRIS should include anti-infective or anti-neoplastic therapy directed at the primary etiology; given the advanced state of immunosuppression typically encountered in patients with IRIS, every effort should be made to continue the antiretroviral therapy. Palliation of severe inflammatory symptoms (such as high fevers or expanding mass lesions) often can be achieved with corticosteroids. The dose and duration of such therapy are not well established, but may involve pharmacologic doses of prednisone for weeks or even months.

Occupational Exposure to HIV

It is estimated to approximately 400,000 occupational exposures to the HIV virus occur every year in the United States. Risk of transmission depends on the route of exposure and inoculum (HIV viral load). Risk of transmission from percutaneous exposure is estimated at 0.3 percent and that via mucous membrane exposure of 0.006 percent. After thoroughly rinsing the exposure area(s), health care workers with potential exposure to HIV should report immediately to their employee health department or the site designated by their facility for a formal evaluation. Animal studies of postexposure prophylaxis (PEP) have demonstrated efficacy of postexposure prophylaxis if administered within 24 hours of exposure and continued for 28 days. Retrospective analysis suggests that HIV PEP may reduce the risk of acquiring HIV by 79 percent. Decisions about the specific antiretroviral regimen that should be offered to health care workers depend on what is known of the exposure, likelihood of HIV infection in the source patient, and medical co-morbidities of the exposed health care worker. Whenever possible, the source patient should undergo rapid testing for HIV and other blood-borne infections to help guide PEP decisions. In addition to providing PEP for potential HIV exposure, exposed health care workers should be considered for post-exposure prophylaxis

against hepatitis B (if not immune) and should be educated about the signs and symptoms of acute hepatitis C so that this infection may be rapidly treated if they did develop.

EMPIRIC THERAPY AND THE HIV-POSITIVE PATIENT WITH PULMONARY COMPLAINTS

HIV-positive patients who present with respiratory complaints often require empiric therapy pending definitive diagnosis. We have outlined an approach to such decisions in Figs. 128-6 and 128-7. Patients presenting acutely with fever, productive cough, and focal infiltrates should be treated presumptively for community acquired bacterial pathogens pending further testing. Those presenting with subacute complaints and focal infiltrates should be placed in negative pressure isolation while being evaluated for TB, fungal pneumonia, and non-infectious causes. HIV-positive persons with a CD4 count of less than or equal to 200 cells/mm^3 who present with fever, progressive dyspnea, and diffuse interstitial infiltrates on CXR are likely suffering from PCP. When such individuals are at low risk for TB, have not been taking PCP prophylaxis, and are not suffering from severe impairment of gas exchange, it is reasonable to begin treatment for PCP while waiting for the results of induced sputum testing. Because of the high pre-test probability of PCP, HIV-infected persons with a depressed CD4 count and normal CXR should be treated empirically if they demonstrate impaired gas exchange. In patients at lower risk for PCP (CD4 count greater than 200 cells/mm, undetectable HIV viral load, or adherence to PCP prophylaxis) or those with more severe illness, empiric therapy for PCP may also be considered, but further testing should be aggressively pursued so that alternative etiologies for a patient's respiratory complaints can be evaluated. The extent of additional evaluation depends on the patient's degree of immunosuppression and the tempo of their illness. Patients with a CD4 count of less than or equal to 50 cells/mm^3 who present with progressive hypoxemia despite appropriate empiric treatment for PCP would likely benefit from early bronchoscopy with bronchoalveolar lavage. By contrast, individuals with preserved CD4 counts and chronic respiratory complaints may benefit first from pulmonary function testing or echocardiography to evaluate non-infectious causes of respiratory difficulties. In patients who remain undiagnosed, bronchoscopy with transbronchial biopsy, video-assisted thoracoscopic surgery (VATS), and/or open lung biopsy are often needed to make a definitive diagnosis.

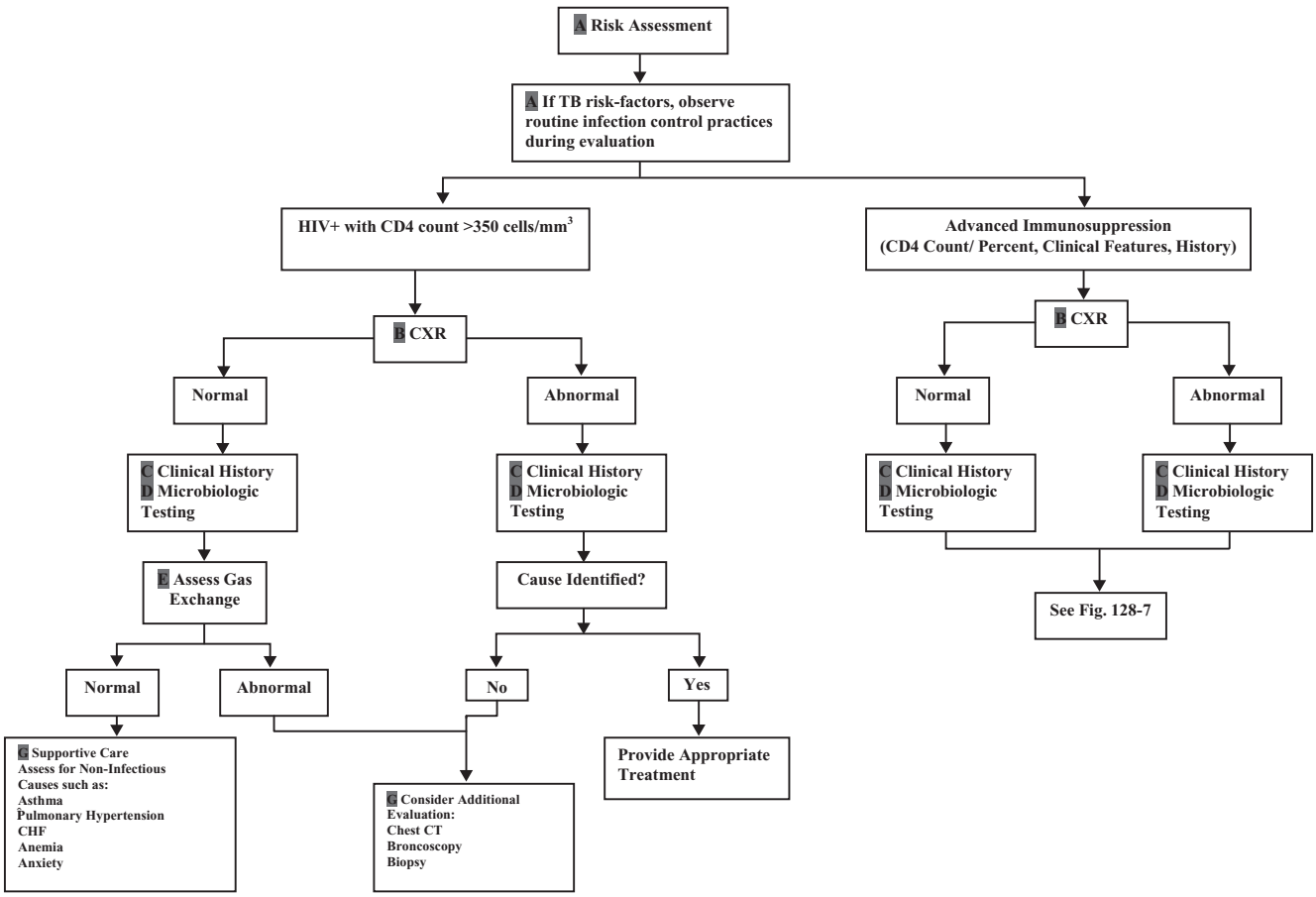

Figure 128-6 The evaluation of the newly diagnosed HIV-positive individual with subacute respiratory complaints.

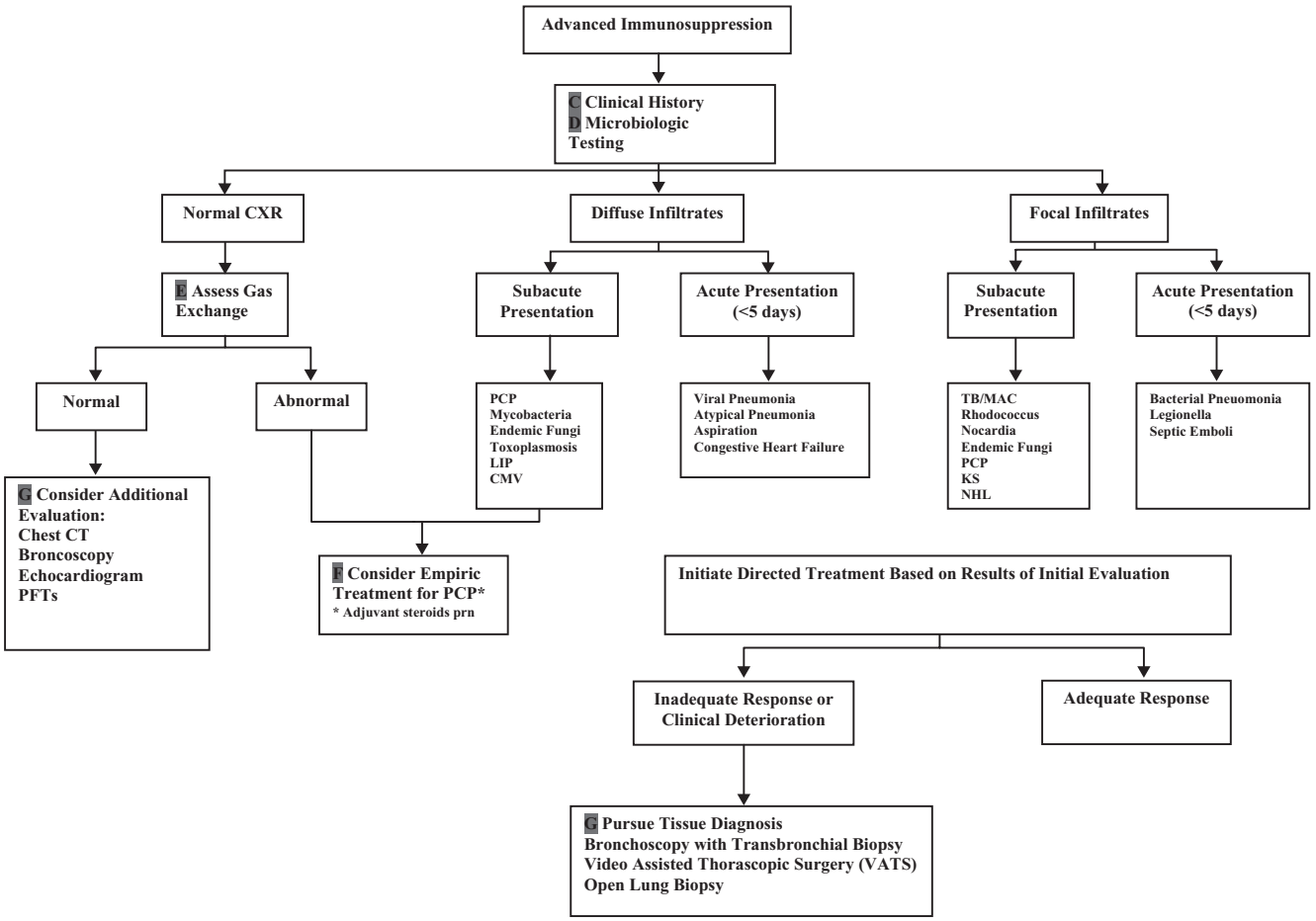

Figure 128-7 The evaluation of the newly diagnosed HIV-positive individual with acute respiratory complaints.

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CHAPTER

Pneumonia Caused by Gram-Positive Bacteria

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STREPTOCOCCUS PNEUMONIAE

Microbiology

Streptococcus pneumoniae is a gram-positive, catalase- and cytochrome-negative, facultative anaerobic organism that measures 0.5 to 1.25 μm in diameter. Alpha-hemolytic circular colonies are observed when the organism is incubated aerobically on blood agar. Both unencapsulated and encapsulated strains exist in vivo; virulent strains are usually encapsulated. Ninety serotypes of encapsulated strains have been identified to date. In adults, approximately 90 percent of bacteremic infections are caused by 23 of the capsular serotypes.

Pathogenesis

The organism periodically colonizes the human nasopharynx in most persons. Disruption of normal respiratory tract epithelial cells such as by antecedent viral infection predisposes to infection. In pneumococcal pneumonia, bacteria gain access to the lower respiratory tract by microaspiration. The organism is usually cleared from the

healthy respiratory tract by a combination of mechanical means and phagocytosis. In the early stages of infection phagocytosis is dependent on complement to stimulate cytokines and attract polymorphonuclear leukocytes. Capsule, however, inhibits opsonin-mediated phagocytosis by polymorphonuclear leukocytes. Without anticapsular antibodies, phagocytic cells have a limited ability to ingest and kill the organism. In addition, glycopeptide components of the pneumococcal cell wall provoke an intense inflammatory reaction. Damaged and congested alveoli provide a serous fluid-filled environment suitable for bacterial proliferation. Once the infection is established, alveoli become congested with white cells, erythrocytes, and debris but remain intact in this typically non-necrotizing infection. If host defense mechanisms cannot contain the infection, the organism may migrate through the lymphatic channels to the systemic circulation. Infection may occur in the pleural or pericardial space by direct extension. Metastatic infection can occur in the joints, bones, peritoneum, heart valves, and meninges through hematogenous dissemination.

Recovery from established infection is dependent on type-specific capsular antibodies that normally appear after 5 to 10 days of infection. Subsequent infection with the same serotype is rare in the absence of immunoglobulin dysfunction.

Epidemiology

Streptococcus pneumoniae is an obligate parasite of humans. The pneumococcus may cause up to one-half of all cases of community-acquired pneumonia in western countries. Pneumococcal pneumonia is not a reportable disease in the United States, so exact precise data concerning frequency are unavailable. However, data from the Active Bacterial Core Surveillance program estimate an overall incidence of pneumococcal bacteremia of 14 cases per 100,000 and an incidence of 42 per 100,000 population over age 65 (http://www.cdc.goc/ncidod/dbmd/abcs/survreports/ spneu03.pdf). Because bacteremia occurs in considerably less than one-half of the patients with pneumococcal pneumonia, these numbers represent an underestimate of the true incidence of pneumococcal pneumonia in the United States.

Certain ethic groups and co-morbid conditions are associated with higher rates of infection. For example, for unknown reasons, native Americans, native Alaskans, and African Americans are more susceptible to infection than is the white population. Although the following is not exhaustive, other risk factors include diseases associated with altered immunity (agammaglobulinemia, dysgammaglobulinemia, common variable immunodeficiency, complement deficiencies, acquired or anatomic asplenia, HIV/AIDS, glucocorticoid use, renal insufficiency, cirrhosis, diabetes mellitus, chronic lymphocytic leukemia), decrease in mechanical defense mechanisms (as caused by cigarette smoking, viral upper respiratory tract infection including influenza, chronic obstructive pulmonary disease, congestive heart failure with pulmonary edema), close interpersonal contact (prisons, day care, military, homeless shelters, refugee camps), generalized deconditioning, and others. The incidence of pneumococcal pneumonia in patients co-infected with HIV is higher than in healthy control subjects.

The incidence of invasive pneumococcal disease has decreased since the introduction of the heptavalent pneumococcal conjugate vaccine. Widespread use of the vaccine in children has been associated with a decrease in invasive disease in the elderly, perhaps by reducing the circulating pool of selected pneumococcal serotypes in the general population.

Clinical Manifestations

Pneumococcal pneumonia is often preceded by a viral respiratory tract infection manifested by coryza, nonproductive cough, and low-grade fever. Classically, bacterial infection is heralded by sudden onset with shaking chills, fever, cough productive of rusty sputum, and pleuritic chest pain. Nausea, vomiting, and diarrhea may be present and the patient often appears to be anxious. Herpes labialis may be present. Consolidation occurs during the next 24 to 48 hours and is suggested by increased vocal fremitus and tubular breath sounds over the affected area. Inspiratory crackles may be heard if the patient is able to move sufficient air through the affected airways. In untreated disease, fever typically lasts for 5 to 10 days. This period is then followed by a "crisis" marked by defervescence and the formation of anticapsule antibodies. However, elderly individuals may present with a more insidious course associated with confusion, low-grade fever, fatigue, and/or hypoxemia. Elderly, asplenic, and otherwise immunocompromised individuals may progress rapidly to septic shock without classic antecedent signs and symptoms. In the majority of patients, institution of appropriate antimicrobial therapy in a timely manner results in measurable clinical improvement and defervescence over several days.

Involvement of the pleural space may follow pulmonary infection. Empyema is suggested by splinting of the affected side, dullness to percussion at the lung base, absent vocal fremitus, and persistent fever despite appropriate antimicrobial therapy. Obtundation or neck stiffness suggests meningitis.

While *S. pneumoniae* is the most common bacterial cause of community-acquired pneumonia, the differential diagnosis of this infection is broad and includes both infectious and noninfectious etiologies. Infectious causes include "atypical" pneumonias caused by *Legionella pneumophila, Mycoplasma pneumoniae*, and*Chlamydia pneumoniae* as well as other bacteria including, *Haemophilus influenzae, Moraxella catarrhalis,* and *Staphylococcus aureus.* Anaerobic bacterial infection is associated with aspiration and poor dental hygiene. Viral and fungal etiologies of pneumonia may be suspected when there is an appropriate geographic and exposure history along with characteristic clinical manifestations. Mycobacterial infections that can present with consolidation and a similar clinical course include *Mycobacterium tuberculosis* and *Mycobacterium kansasii.* Noninfectious causes of

disease that can occasionally mimic pneumococcal pneumonia include lung cancer, foreign body aspiration or granuloma formation, pulmonary infarction, vasculitis, graft-vs-host disease, atelectasis, and congestive heart failure.

Diagnosis

Blood cultures are positive in approximately one-fourth of patients with pneumococcal pneumonia. A positive blood culture for *S. pneumoniae* in a patient with clinical and radiological evidence of pneumonia establishes the etiology. In most patients, etiological diagnosis of bacterial pneumonia is dependent on culture and gram stain of sputum. The positive predictive value of a sputum gram stain demonstrating a preponderance of polymorphonuclear cells, a paucity of squamous epithelial cells, and numerous gram-positive diplococci is quite good for the diagnosis of *S. pneumoniae* pneumonia (Fig. 129-1). For maximum yield, sputum culture must be obtained prior to antibiotic therapy and must be plated promptly after collection. Fewer organisms are recovered after a delay of only hours when compared to immediate plating of sputum at the bedside. Centralization of microbiology facilities as a cost-containment strategy requires transport and delay of clinical specimens and may affect recovery rates of fastidious bacteria. When incubated aerobically on blood agar, *S. pneumoniae* appears as alpha-hemolytic colonies. A zone of inhibition around an ethylhydrocupreine hydrochloride (Optochin) disk differentiates approximately 98 percent of *S. pneumoniae* from other viridans streptococci (Fig. 129-1). Identification of bacteria in sputum by molecular methods, such as PCR, is under investigation.

The pneumococcal urinary antigen test is useful in supplementing blood culture and gram stain and culture of sputum in adults. The assay is an immunochromatographic membrane test that detects pneumococcal cell wall polysaccharide which is common to all serotypes. Nasopharyngeal colonization in children gives a false-positive result so that the assay is more useful in adults, with a sensitivity of approximately 50 to 70 percent and a specificity of approximately 90 percent in comparison to standard methods. Advantages of the assay are the rapid results, use of a readily obtainable sample (urine), and its relatively high specificity in adults.

Antibiotic Resistance

A major consideration in the treatment of pneumococcal pneumonia is the increasing worldwide incidence of resistance to antibiotics. *S. pneumoniae* remained sensitive to penicillin for decades after the introduction of the drug, but resistance was detected in the late 1960s. β-lactam resistance is caused by altered penicillin binding proteins that possess lower affinity for β-lactam antibiotics. Genes that encode these altered proteins are often mosaics of native pneumococcal DNA and DNA acquired from viridans streptococci. Approximately 15 percent of strains in the United States are intermediately resistant to penicillin (minimum inhibitory concentration 0.1 to 1.0 μg/ml) while an additional 18 percent are fully resistant (minimum inhibitory concentration greater than 2.0 μg/ml). These concentration limits may not reflect accurate breakpoints for amoxicillin in pulmonary tissue (where much higher levels can be achieved), but instead

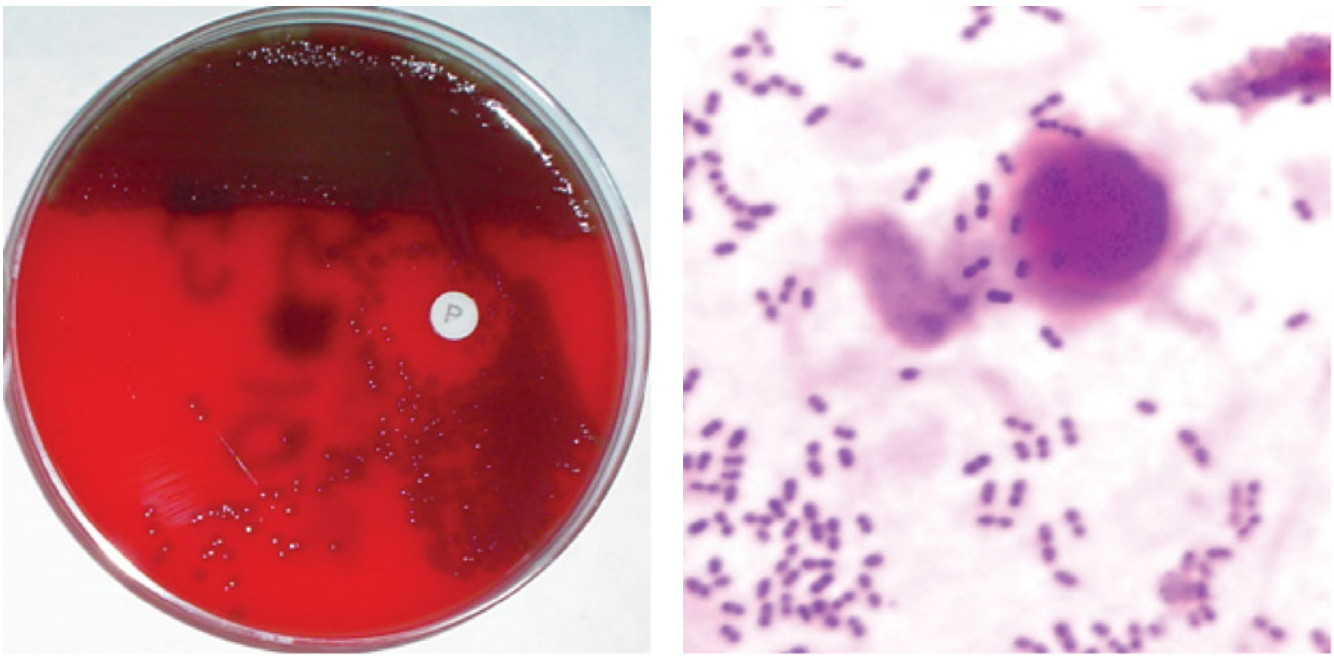

Figure 129-1 *Left*. Sputum cultured on blood agar and incubated overnight (5 percent CO_2, 37°C). *Streptococcus pneumoniae* growth is inhibited by Optochin (white disc). Therefore, its presence can be distinguished from the other Optochin-resistant alpha-hemolytic colonies also present in this sample. *Right*. Gram stain of the sputum sample demonstrating numerous gram-positive diplococci.

indicate appropriate cutoff levels for blood and meningeal infection. Approximately one-fourth of strains in the United States are resistant to the macrolide antibiotics including erythromycin, azithromycin, and clarithromycin. The majority of resistant strains seen in the United States possess macrolide efflux capacities encoded by the *mef*A gene. In Europe and South Africa, resistance is more often due to altered ribosomal targets encoded in the *erm*B gene. Strains that possess the latter mechanism usually possess high level resistance and often lack sensitivity to the lincosamides (clindamycin) and streptogramin (quinupristin). A disconcerting epidemiologic study of more than 31,000 strains of *S. pneumoniae* revealed an increasing number of organisms that possess both *mef* and*erm* encoded resistance mechanisms. Resistance to tetracycline and sulfa drugs occurs in approximately 16 and 32 percent of strains, respectively.

The organism is more predictably sensitive to other classes of antimicrobials. In most areas, resistance to the respiratory fluoroquinolones (e.g., levofloxacin, moxifloxacin, gatifloxacin) is low. However, higher rates of resistance occur in regions where usage is heavy. Vancomycin, linezolid, and telithromycin offer reliable activity. Rare tolerance to vancomycin has been reported. The glycyclines (tigecycline), a new class of antimicrobials related to minocycline, appear to be effective against resistant strains of pneumococci. Daptomycin should be avoided in pulmonary infections due to inability to achieve sufficient drug levels in the pulmonary parenchyma.

Treatment

Successful treatment necessitates appropriate antimicrobial therapy as well as the rapid institution of required supportive measures including oxygen, mechanical ventilation, and drainage of significant effusions. The overall mortality for bacteremic pneumococcal infection is 15 to 20 percent with a higher rate in the elderly (http://www.cdc.goc/ncidod/dbmd/abcs/survreports/spneu03.pdf).

Antibiotic therapy is generally started empirically when the patient is initially seen. Whenever possible, gram stain and culture of sputum, as well as blood culture, should be obtained prior to the initiation of antimicrobial therapy. Choice of empirical therapy may be influenced by local patterns of resistance of the organisms. It is important to inquire about recent antibiotic use and recent hospital admissions. Recent use of penicillin, trimethoprim-sulfamethoxazole, or a macrolide is associated with increased risk of resistance to all three agents. Although still rare in the United States, fluoroquinolone resistance is associated with previous use of a fluoroquinolone, current residence in a nursing home and nosocomial acquisition of the pneumonia. Commonly employed regimens for initial therapy include a third-generation cephalosporin/macrolide combination or monotherapy with a respiratory fluoroquinolone. Vancomycin should be considered as an alternative or as an additional agent in persons with severe illness or in those potentially infected with a multidrug resistant strain. Combination therapy with two effective agents may decrease mortality in severely ill patients with bacteremic disease.

After results of culture and antimicrobial susceptibility testing become available, antimicrobial therapy can often be specifically tailored. Therapy should be continued at least 5 days after defervescence and longer if bacteremia is proved or suspected. Persistent fever or deteriorating clinical status should prompt investigation for empyema or metastatic infection. Significant pleural effusion should be drained. Repeat chest imaging should be considered several weeks after resolution of disease to search for malignancy or anatomic obstructions in the pulmonary tree.

Prevention

Smoking cessation, influenza vaccination, and correction of reversible underlying immunosuppressive conditions are paramount preventive measures. Additional preventive measures should include immunization with the 23-valent polysaccharide vaccine in adults. Introduced in the year 2000, children are now routinely immunized with the heptavalent protein-conjugated vaccine that is effective against 82 percent of the most common bacteremic strains in the United States. Widespread use of the conjugate vaccine in children appears to have an indirect benefit in older adults, perhaps by reducing the circulating pool of selected pneumococcal serotypes in the general population.

The original polysaccharide vaccine was developed in the 1940s but was soon discontinued after penicillin use became widespread and effective. The 23-valent capsular polysaccharide vaccine was reintroduced in the 1970s and has been the subject of much investigation. Overall, analysis of multiple randomized controlled trials and objective studies suggest a modest benefit in preventing pneumococcal disease in adults. The vaccine is now recommended for certain populations by the Immunization Practices Advisory Committee, including all persons 65 years of age and older. Persons younger than 65 years of age with alcoholism, functional or anatomic asplenia, diabetes mellitus, chronic renal insufficiency, hepatic cirrhosis, chronic pulmonary disease, and a cerebrospinal fluid leak should be immunized. Immunosuppressed persons including those with multiple myeloma, lymphoma, HIV infection, an organ transplant or an indication for chronic glucocorticoid therapy should also be immunized. Persons 65 years of age and older who were immunized before 65 years of age should be offered a second dose if at least 5 years have passed since the original immunization. Persons undergoing elective splenectomy should be immunized several weeks in advance of surgery if possible.

STAPHYLOCOCCUS AUREUS

Microbiology

Of the many species within the *Staphylococcus* genus, *Staphylococcus aureus* is an especially virulent pathogen for humans.

It causes a wide range of infections ranging from relatively mild folliculitis and furunculosis to life-threatening cellulitis, pneumonia, bacteremia, and infective endocarditis. *S. aureus* is an aerobic, non-motile gram-positive coccus that is most often visualized as a small cluster of organisms on gram stain. The bacterium grows readily on a variety of laboratory media. Colonies are circular, smooth, and honey colored when cultured on blood agar and are often surrounded by a zone of β-hemolysis on blood agar. The organism elaborates multiple virulence factors. Coagulase, one such virulence enzyme, is the basis for laboratory differentiation from other "coagulase-negative" species of staphylococci such as *S. epidermidis.*

Epidemiology

The incidence of *S. aureus* infection has been increasing at a rapid rate. *S. aureus* transiently colonizes approximately 60 percent of the general population, persistently colonizes about 20 percent, and never colonizes 20 percent. The anterior nares are the most common site of colonization. Other sites of colonization include damaged skin, vagina, axillae, perineum, and pharynx. Higher rates are observed in patients with insulin-dependent diabetes mellitus, HIV infection, renal disease requiring hemodialysis, and those who use drugs administered by injection. These sites of colonization are often the source of invasive infections.

Risk factors for developing *S. aureus* pneumonia include nasal colonization, antecedent influenza infection, endotracheal intubation, tricuspid-valve infective endocarditis with septic emboli, structural diseases of the lung, certain immune defects, such as chronic granulomatous disease, and recent thoracic surgery. *S. aureus* is an uncommon cause of community-acquired pneumonia but causes 15 to 35 percent of nosocomial pneumonia. The incidence in any given population or facility depends on patient demographics and diagnostic methods. *S. aureus* is a common cause of severe ventilator-associated pneumonia. In addition, a recent increase in the incidence of community-acquired *S. aureus* infection, including pneumonia, has been observed in children and adults.

Pathogenesis

Lower respiratory tract infections with *S. aureus* most commonly originate from either aspiration of colonizing bacteria or hematogenous dissemination from an endovascular focus of infection. Local edema, hemorrhage, and necrosis are common sequelae of pulmonary infection. Pneumatoceles, or thin air-filled cavities, may occur in children. Thick-walled abscesses may be noted in adults.

Virulence factors, including serine proteases, hyaluronidases, thermonucleases, and lipases, facilitate the infection. The Panton-Valentine leukocidin (PVL) toxin, a virulence factor that is present in some strains of methicillin-resistant *S. aureus* (MRSA), is cytolytic to polymorphonuclear cells, macrophages, and monocytes and is associated with pulmonary infection by MRSA, including severe community-acquired disease.

Clinical Manifestations

Recognition of *S. aureus* pneumonia requires a high index of suspicion because the disease may resemble pneumonia caused by other bacterial pathogens. Once believed to be solely a severe and lethal infection, recent studies demonstrate a broad range of disease, including subtle manifestations. This recognition of the range of clinical manifestations of *S. aureus* pneumonia parallels a shift in patient demographics as well as a better understanding of the pathogenesis of the disease. Increasing numbers of patients requiring mechanical ventilation as well as an increasing population of nursing home residents have probably contributed to this appreciation of the range of clinical manifestations of *S. aureus* pneumonia. In children less than 1 year old, infection is commonly related to an antecedent influenza or measles infection. Fever, tachypnea, grunting, and productive cough are frequently observed. Diminished breath sounds and localized rales are heard over the involved area. Pleural effusion, empyema, pneumothorax, and pneumatocele formation may occur.

S. aureus remains an uncommon cause of community acquired pneumonia in adults who are otherwise healthy. When this does occur, it is usually preceded by influenza infection or tricuspid-valve infective endocarditis. More often, *S. aureus* pneumonia is hospital acquired and frequently associated with mechanical ventilation. Progression of the disease is highly dependent on both host susceptibility as well as bacterial virulence. Complications include purulent pericarditis, pulmonary necrosis with abscess formation, bronchopleural fistula with empyema formation, and endovascular infection from secondary bacteremia.

Diagnosis

In the proper clinical setting, pneumonia caused by *S. aureus* is strongly suggested by a gram stain of sputum demonstrating a large number of inflammatory cells and gram-positive cocci in clusters and a positive sputum culture. Antibiotic susceptibility testing is an essential diagnostic test. MRSA accounts for over one-half of hospital-acquired isolates of *S. aureus* in many hospitals and has more recently been recognized as a cause of community acquired disease. Because of the high frequency of upper airway consolidation in the general population, a positive sputum culture, however, does not establish an etiological diagnosis of *S. aureus* pneumonia. Clinical acumen is essential. Isolation of the organism from a source that is normally sterile, such as blood or pleural fluid, establishes the diagnosis. Approximately 20 percent of *S. aureus* pneumonia is associated with concurrent bacteremia. Bloodstream infection should prompt consideration of primary endovascular infection even in the presence of pneumonia since pulmonary disease may be hematogenously acquired. False negative sputum cultures are unusual given the hearty nature of the organism. Therefore, the absence of the *S. aureus* in a sputum

sample in a patient who is not receiving antibiotics argues against the diagnosis of *S. aureus* pneumonia.

Fever, cough productive of purulent and blood-tinged sputum, and hypoxemia are common. Imaging studies may reveal single or multiple patchy areas of bronchopneumonia with or without pleural effusion. Lobar consolidation is rare. Abscesses and/or pneumatoceles may be observed in advanced disease.

Antibiotic Resistance

Most isolates of *S. aureus* express β-lactamase, which mediates resistance to penicillin. Antistaphylococcal penicillin derivatives including methicillin, nafcillin, and oxacillin are active against β-lactamase–producing *S. aureus* isolates. An increasing proportion of isolates have acquired resistance to these agents. These methicillin-resistant *S. aureus* (MRSA) possess the *mec*A gene that encodes penicillin binding protein 2a, which has decreased affinity for all currently available β-lactam antibiotics, thereby causing MRSA to be resistant. MRSA comprise over half of *S. aureus* isolates in many hospitals in the United States. Hospital isolates of MRSA are often resistant to multiple antibiotics, including fluoroquinolones, trimethoprim-sulfamethoxazole, erythromycin, and clindamycin. Vancomycin is active against most isolates of MRSA. More recently, intermediate-resistant and resistant strains to vancomycin have been identified. Although strains with reduced susceptibility to vancomycin are rare, isolates of *S. aureus* should be monitored carefully for the development of resistance. The newer agents linezolid, dalfopristin/quinupristin, daptomycin, and tigecycline have activity against MRSA.

More recently, an increasing proportion of community-acquired *S. aureus* isolates have proved to be MRSA, including those causing pneumonia. These isolates were originally thought to be hospital strains that had spread to the community. However, in contrast to hospital-acquired MRSA that are clonal and resistant to multiple antibiotics, community-acquired MRSA are more polyclonal, susceptible to multiple antibiotics other than methicillin and are associated with severe pneumonia in otherwise healthy people. Community acquired MRSA are often susceptible to fluoroquinolones, trimethoprim/sulfamethoxazole, and clindamycin.

Treatment

The antistaphylococcal penicillin derivatives oxacillin and nafcillin are bactericidal against methicillin-sensitive *S. aureus* and are the treatment of choice when the organism is sensitive to these agents. If initial empirical therapy is started with vancomycin and the organism is eventually identified as MRSA, treatment should be changed to an antistaphylococcal penicillin derivative because superior efficacy is achieved compared to therapy with vancomycin.

When *S. aureus* is suspected as a cause of nosocomial pneumonia, therapy should be initiated with vancomycin until the results of susceptibility testing becomes available. The choice of empirical antimicrobial therapy for suspected community-acquired *S. aureus* pneumonia is more difficult. Risk factors that increase the likelihood of MRSA include nasal colonization by MRSA, recent hospital admission, and local epidemiological considerations. If such risk factors are present, then consideration should be given to empiric administration of vancomycin as initial therapy. In both hospital and outpatient settings, the results of antimicrobial susceptibility should be used to tailor treatment.

Recent retrospective data suggest that the efficacy of linezolid may be superior to that of vancomycin for the treatment of ventilator-associated pneumonia caused by MRSA. It is hypothesized that high and predicable levels of the agent in the pulmonary parenchyma may facilitate cure. Definitive recommendations will require prospective trials. If vancomycin is the chosen therapy, monitoring serum levels of vancomycin is important, especially in the setting of fluctuating renal function or fluid homeostasis.

Other agents with activity against *S. aureus* that may be considered in particular clinical settings include trimethoprim-sulfamethoxazole, doxycycline, clindamycin, quinupristin-dalfopristin, and tigecycline. Rifampin and an aminoglycoside may be considered as adjunctive therapy in some instances. Two to four weeks is often an appropriate length of therapy for *S. aureus* pneumonia in the absence of endovascular infection, metastatic infection or other complicating factors, which may require longer therapy. A careful evaluation for the presence of endocarditis should be undertaken in all patients who are bacteremic.

RHODOCOCCUS EQUI

Rhodococcus equi, formerly *Corynebacterium equi,* is a pleomorphic gram-positive coccobacillus that is isolated from a variety of land and water animals and is present in soil worldwide. The first reported case of *R. equi* human infection was in 1967. The incidence and recognition of *R. equi* infection in humans subsequently increased coincident with the emergence of HIV infection and advances in organ transplantation and cancer treatment. However, overall, *R. equi* is an unusual infection in humans.

The primary manifestation of *R. equi* infection is pneumonia. Two-thirds of reported cases of *R. equi* pneumonia are in patients with advanced HIV infection. Most patients have CD4 counts less than 100 cells/mm^3. *R. equi* pneumonia is also seen in other immunocompromised hosts, particularly in the setting of defective cell-mediated immunity. Case reports have documented the occurrence of *R. equi* infection in immunocompetent hosts but this is rare.

Patients with *R. equi* pneumonia typically present with a subacute onset of symptoms including fever, cough, and fatigue. Pleuritic chest pain is also common. Chest radiography reveals nodules, cavities, or infiltrates; cavitary lesions are the most common pattern in HIV infection. The differential diagnosis of cavitary lesions in the setting of advanced HIV infection should include tuberculosis, *Nocardia,* and *R. equi.*

A diagnosis is established by isolating the organism from blood, sputum, or samples obtained by bronchoscopy.

Blood cultures are positive in approximately half of HIV-infected people and one-third of organ transplant recipients. *R. equi* grows well on routine laboratory media but may be overlooked or discarded as commensal diphtheroids, so laboratory personnel should be alerted if *R. equi* is suspected.

R. equi pneumonia is associated with considerable mortality and infections have a propensity for recurrence. Standard treatment regimens have not yet been developed. Most isolates of *R. equi* are susceptible in vitro to vancomycin, erythromycin, fluoroquinolones, rifampin, imipenem, and linezolid. The organism is often resistant to penicillins, which are not recommended for therapy. A rational approach to therapy in immunocompromised hosts and those with serious infections includes intravenous treatment with two or three drugs, for 2 to 3 weeks, followed by at least two oral agents for 2 to 6 months. Patients with HIV infection may benefit from continued oral suppressive therapy until immune reconstitution occurs.

STREPTOCOCCUS PYOGENES (GROUP A STREPTOCOCCUS)

Overall, group A streptococcus is an uncommon cause of pneumonia in adults. However, in surveillance studies, pneumonia is recognized as the source in 10 to 20 percent of cases of invasive group A streptococcal infections. The organism is transmitted in households and in healthcare institutions and has a predilection for causing pneumonia in clusters and in people residing in crowded living conditions, such as a large recent outbreak in a military training facility. The very young and the elderly and those with underlying medical conditions are at increased risk.

Group A streptococcus causes a severe pneumonia, which typically has an abrupt onset with fever, chills, and productive cough. Pleural effusion and empyema occur in up to one-third of cases. A patchy bronchopneumonia picture is seen on the chest radiograph. Bacteremia occurs in 15 to 20 percent of patients. Treatment consists of a penicillin and drainage of empyema when present. While the mortality is low in the absence of significant underlying disease, substantial mortality is seen in elderly patients and those with co-morbid conditions. In view of the increased risk of serious infection in contacts, consideration should be given to prophylaxis of those in close contact with patients with group A streptococcal pneumonia.

Other streptococci, including Lancefield groups B, F, and G, are rare causes of pneumonia in adults. Most such patients have underlying conditions, most notably diabetes mellitus, alcoholism, or neurological disorders.

OTHER GRAM-POSITIVE PATHOGENS

Corynebacterium pseudodiphtheriticum is a rare cause of pneumonia in patients with advanced HIV infection and other immunocompromised hosts. *C. diphtheriticum* is part of the normal flora so diagnosis of this infection requires blood or tissue culture documentation.

Bacillus species, particularly *B. cereus,* are rare causes of pneumonia. These infections occur almost exclusively in profoundly immunocompromised patients and in this setting are associated with substantial mortality. Because *Bacillus* species colonize the normal upper respiratory tract, the diagnosis of these rare infections must be established by cultures of blood or pulmonary tissue.

Inhalation anthrax is caused by inhalation of spores of *B. anthracis.* While spores enter through the respiratory tract, inhalation anthrax does not cause pneumonia per se. The organisms are phagocytosed by alveolar macrophages and are transported to mediastinal lymph nodes where multiplication and systemic dissemination occur.

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130

Nosocomial Pneumonia

Jay A. Fishman

Nosocomial pneumonia has been defined as an infection of the lung parenchyma that was neither present nor incubating at the time of hospital admission. Health care–associated and nosocomial pneumonias are the second leading cause of hospital-acquired infections and are increasing in proportion to the use of assisted ventilation and with prolonged care of critically ill patients. It has been estimated that there are up to 200,000 nosocomial respiratory tract infections per year in the United States or between 5 and 15 cases per 1000 hospital admissions depending on the case definition and study population. Nosocomial pneumonia results in an average of 5.9 extra hospital days at a cost of $5683 in 1992 dollars. Patients with ventilator-associated pneumonia are subject to prolonged intensive care unit (ICU) stays by over ~6 days and hospital costs increases of over $10,000 per episode. The incidence of ventilator-associated pneumonia (VAP) is 6- to 20-fold greater than in nonventilated patients. Overall, nosocomial pneumonia results in an estimated 7087 deaths and contributes to 22,983 deaths per year in the United States. Of note, while the microbiology of these infections has not changed substantially, increasing resistance to multiple antimicrobial agents is now a common feature of these infections that has substantially altered therapy. In the absence of new classes of antimicrobial agents, preventative strategies must be considered including noninvasive ventilation, drainage of subglottic secretions, and gastrostomy. Initial empiric antimicrobial therapy of nosocomial pneumonia should be based on knowledge of the individual's colonization history and local antimicrobial resistance patterns. Newer guidelines developed by a joint committee of the American Thoracic Society (ATS) and the Infectious Diseases Society of America (IDSA), emphasize microbiologic data and de-escalation of broad spectrum antimicrobial agents when possible with reduced duration of antimicrobial therapy (7 to 8 days). Clinicians need to adapt the treatment recommendations and preventive strategies to their own institutions, as the routes of infection and agents causing pneumonia vary considerably among health care facilities.

Included in this discussion are hospital acquired (HAP), ventilator-associated (VAP), and "health care–associated" pneumonias (HCAP), as a great proportion of patients in the acute care setting may be admitted from other chronic care facilities or with recent hospitalizations. The important distinction that must be made is the level of risk for multi-drug resistant (MDR) pathogens, which determines the need for initial, empiric, therapy with broad-spectrum antimicrobial agents. In general, HCAP is included in the spectrum of HAP and VAP, and patients with HCAP need therapy

for MDR pathogens. Antimicrobial agents quickly affect the ability to culture susceptible organisms from pulmonary secretions. Thus, a lower respiratory tract specimen for gram stain and culture needs to be collected from all patients before antibiotic therapy, but collection of cultures should not delay the initiation of therapy in critically ill patients. This practice assists the clinician in avoiding inadequately treated HAP, VAP, or HCAP; failure to initiate appropriate and adequate therapy promptly is associated with increased mortality. In general, the approach to nosocomial pneumonia should include:

- Suspicion that the patient is at risk for nosocomial pneumonia
- Early chest radiography and sputum gram stain and cultures
- Empiric therapy in the patient with pneumonia, initially with antimicrobial coverage broad enough for the likely pathogens given the individual patient's risk factors for colonization with antimicrobial resistant pathogens
- Use host to define the urgency and duration of empiric therapy
- Adjustment of therapy based on microbiologic data (days 3 to 5)
- Switch to oral therapy or discontinue antibiotics with clinical improvement or absence of documented infection
- *If no response, reassess, consider invasive diagnosis*

PATHOGENESIS

The pathogenesis of nosocomial pneumonia has been extensively reviewed. Bacteria may invade the lower respiratory tract by three major routes: aspiration of oropharyngeal flora, inhalation of infected aerosols, and less frequently, hematogenous spread from a remote focus of infection (Fig. 130-1).

The major cause of nosocomial pneumonia is believed to be colonization of the oropharynx and gastrointestinal tract by pathogenic microorganisms, followed by aspiration of these pathogens, and the development of pneumonia in the setting of impaired host defenses. Aspiration of oropharyngeal secretions has been noted in approximately 45 percent of normal subjects during sleep. In normal subjects, however, the volumes of aspirate are small and the aspirated flora are generally nonpathogenic. Several factors that are common in hospitalized patients are associated with an increased frequency or volume of aspiration: altered consciousness, abnormal swallowing, depressed gag reflexes, delayed gastric emptying, and decreased gastrointestinal motility. Oropharyngeal colonization with aerobic gram-negative bacilli is favored by coma, hypotension, acidosis, azotemia, alcoholism, diabetes mellitus, leukocytosis, leukopenia, pulmonary disease, use of nasogastric or endotracheal tubes, and antibiotic use. Thus, hospitalized patients, especially those in intensive care units, have an increased frequency of oropharyngeal colonization by more pathogenic aerobic gram-negative bacilli and are often at increased risk for aspirating this more pathogenic flora.

The importance of oropharyngeal colonization in nosocomial pneumonia was elegantly demonstrated by Johanson and colleagues, who showed that pneumonia occurred in 23 percent of patients colonized with aerobic gram-negative bacilli but only 3 percent of noncolonized patients. More recently, the stomach has been postulated as an important reservoir of organisms capable of causing nosocomial pneumonia. Normally, the stomach is rendered sterile by hydrochloric acid; however, elevations of gastric pH from normal levels to levels at or above 4 allow microorganisms to multiply to high concentrations. Elevated gastric pH may occur in patients with advanced age, achlorhydria, ileus, or upper gastrointestinal disease, and in patients receiving enteral feeding, antacids, or histamine$_2$ (H_2) antagonists.

Intubation for respiratory support is the most important risk factor for subsequent nosocomial pneumonia. Nasotracheal or orotracheal intubation predisposes patients to bacterial colonization and nosocomial pneumonia by a variety of pathophysiological alterations: (1) sinusitis and trauma to the nasopharynx (nasotracheal tube); (2) impaired swallowing of secretion; (3) acting as a reservoir for bacterial proliferation; (4) increased bacterial adherence and colonization of airways; (5) ischemia secondary to cuff pressure; (6) impaired ciliary clearance and cough; (7) leakage of secretions around the cuff; and (8) suctioning often required to remove secretions. Contaminated respiratory care equipment may lead to nosocomial pneumonia by two routes. First, respiratory care equipment may serve as a reservoir for microorganisms, especially gram-negative bacilli. Fluid-containing devices such as nebulizers and humidifiers may become heavily contaminated by bacteria capable of multiplying in water. Pathogens may then be spread to the patient by hospital personnel or aerosolization into room air. Second, contaminated equipment may lead to direct airway inoculation of microorganisms if it is directly linked to the ventilatory system or if contaminated medications are instilled by aerosolization. The role of contaminated respiratory equipment as a source or reservoir for nosocomial pneumonia has recently been reviewed.

Hospital personnel and the hospital environment also play an important role in nosocomial pneumonia. Cross-transmission between patients may occur when the hands of medical personnel become transiently colonized with pathogenic organisms. Such pathogens may be acquired from direct patient care or from contact with contaminated equipment or hospital surfaces. For this reason, it is crucial that health care providers carefully wash their hands before and after each patient contact. Patients may acquire respiratory infections—including influenza, respiratory syncytial virus, pertussis, group A streptococcus, diphtheria, and *M. tuberculosis*—transmitted by the droplet or airborne routes from infected health care personnel, other patients, or visitors.

The hospital environment may also serve as a reservoir for *Aspergillus, Zygomycetes,* and *Legionella.* Nosocomial

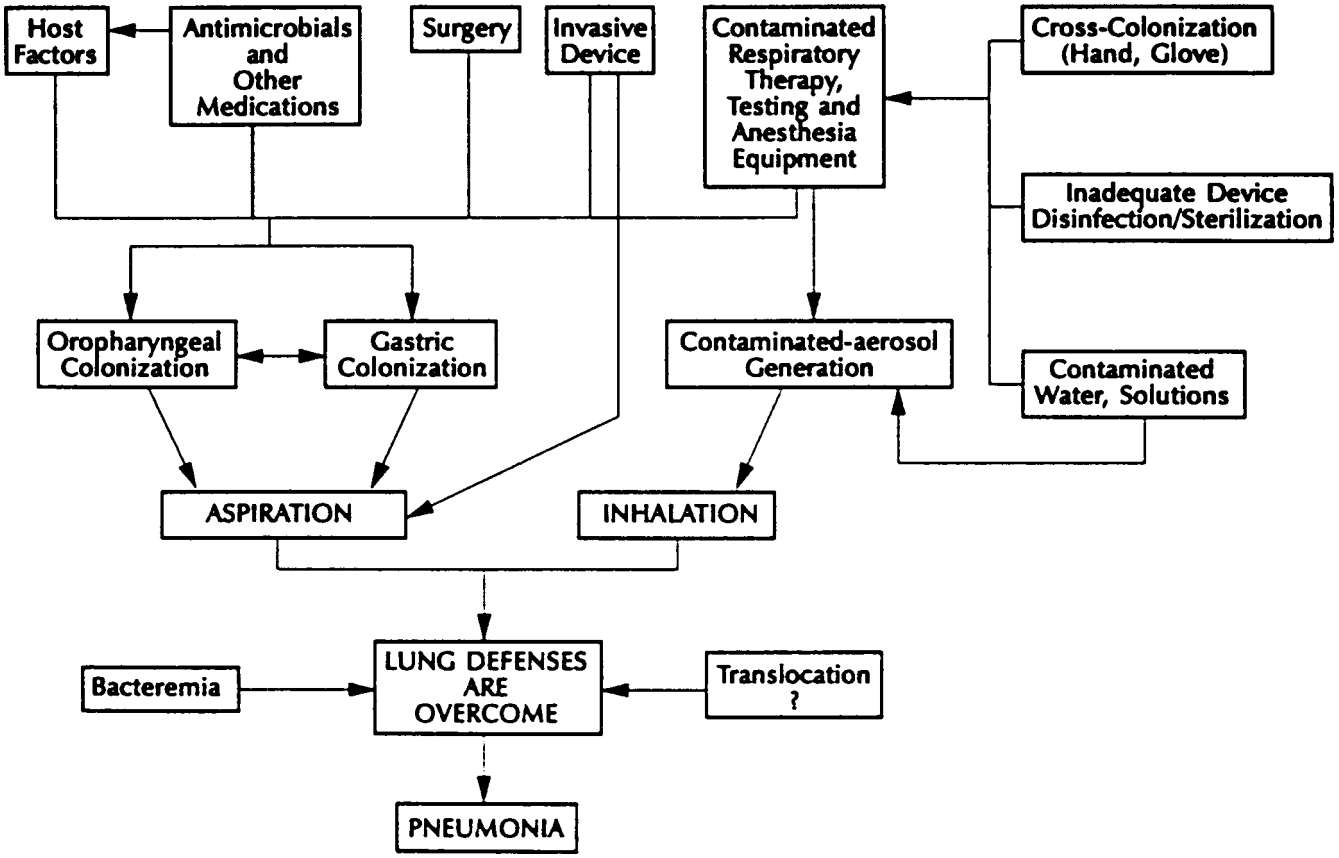

Figure 130-1 Pathogenesis of nosocomial bacterial pneumonia. *(Based on data from Tablan OC, Anderson LJ, Arden NH, et al, and the Hospital Infection Control Practices Advisory Committee: Guideline for prevention of nosocomial pneumonia.* Infect Control Hosp Epidemiol *15:587–627, 1994.)*

pneumonia may result when these pathogens are inhaled, especially if the patient is immunocompromised. The recovery of *Aspergillus* or *Zygomycetes* within hospitals has been variable, but commonly at least small numbers can be isolated from the air, accumulated dust, and environmental surfaces. More than 25 outbreaks of nosocomial fungal pneumonia have been reported. Sources of airborne fungi in hospitals have been reported to include: (1) dust associated with hospital renovations; (2) outside construction, with an inadequate or malfunctioning hospital ventilation system; (3) contaminated cellulose fireproofing material; (4) contamination of the hospital air supply by pigeon droppings, helicopter flights from a roof helipad, or contaminated air filters and air-conditioning coils; and (5) an inadequate filtration system, coupled with location of the outside air intake vent near a refuse container.

Nosocomial acquisition of *Legionella pneumophila* and *L. bozemanii* have been linked to contamination of hospital water supplies, and the association has been strengthened by use of molecular epidemiologic typing methods (e.g., DNA fingerprinting by pulsed field gel electrophoresis) and clinical and environmental strains. *Legionella* can be isolated from more than 50 percent of the potable water supplies and more than 10 percent of the distilled water supplies in hospitals. The subjects of *Legionella* in hospitals and disinfection of water distribution systems for *Legionella* have been reviewed.

INCIDENCE

The incidence of nosocomial pneumonia varies among hospitals for a variety of reasons, including the sensitivity and specificity of the surveillance definition, the vigor with which the diagnosis is sought, and the frequency of intrinsic (e.g., patient age) and hospitalization-specific (e.g., intubation) factors among patients that alter their risk for nosocomial pneumonia. The most representative data regarding the incidence of nosocomial pneumonia have been provided by the National Nosocomial Infections Surveillance (NNIS) system, a Centers for Disease Control and Prevention (CDC) surveillance system of more than 150 hospitals. In 1984, the overall incidence of nosocomial pneumonia was 6.0 per 1000 discharged patients. The incidence varied by hospital type, being 4.2 in nonteaching hospitals, 5.4 in small teaching hospitals, and 7.7 in large teaching hospitals.

The incidence of ventilator-associated pneumonia has ranged from 11 to 54 cases per 100 patients, depending on the population studied (Table 130-1). Intubation and mechanical

Table 130-1

Incidence and Mortality of Ventilator-Associated Pneumonia in Recent Studies

Reference	Year	Study Years	Patient Population	Diagnostic Criteria	Ratio*	Rate†	Case Fatality Ratio
Craven et al.	1986	1983–1984	MSICU, MV > 48 h	Clinical	21	~21	55
Rashkin and Davis	1986	1983–1984	MICU, TI > 72h	Clinical	11	—	—
Ruiz-Santana et al.	1987	—	MSICU, any MV	Clinical	31	~30	—
Daschner et al.	1987	—	MSICU	Clinical	31 (any MV) 43 (MV > 24 h)	— —	— —
Daschner et al.	1988	1983–?	MSICU, any MV	Clinical	48	—	—
Fagon et al.	1989	1981–1985	MSICU, MV >72 h	PSB	9	~10	71
Jiminez et al.	1989	1986	MSICU, MV >48 h	Clinical & PSB	27	~16	28
Klein et al.	1989	1984–1987	PICU, any MV	Clinical	8	15, 21	—
Langer et al.	1989	1983–1984	MSICU, MV >24 h	Clinical	23	~35	44
Reusser et al.	1989	1984–1986	NSICU, MV >48 h, TI >96 h	Clinical	38	—	13
Deppe et al.	1990	1986–1987	MSICU, TI >48 h	Clinical	27	—	—
Jacobs et al.	1990	—	MSICU, EF, MV >72 h	Clinical	54	—	—
Torres et al.	1990	1987–1988	MSICU, MV >48 h	Clinical & PSB	24	—	23
Dreyfuss et al.	1991	—	MSICU, MV >96 h	PSB	30	—	23
Rello et al.	1991	1988–1989	MSICU, MV >48 h	Clinical & PSB	22	—	21
Kollef	1993	1992–1993	MICU/SICU/CTICU, MV >24 h	Clinical	16	—	37
CDC	1995	1990–1995	CCU	Clinical	—	9.8	—
	1995	1990–1995	MICU	Clinical	—	9.6	—
	1995	1990–1995	MSICU	Clinical	—	12.7	—
	1995	1990–1995	NSICU	Clinical	—	20.7	—
	1995	1990–1995	PICU	Clinical	—	6.0	—
	1995	1990–1995	SICU	Clinical	—	15.4	—
	1995	1990–1995	BICU	Clinical	—	22.2	—
	1995	1990–1995	RICU	Clinical	—	6.3	—
	1995	1990–1995	TICU	Clinical	—	16.6	—
	1995	1992–1995	Neonates, ≤1000 g	Clinical	—	4.8	—
	1995	1992–1995	Neonates, 1001–1500 g	Clinical	—	4.6	—
	1995	1992–1995	Neonates, 1501–2500 g	Clinical	—	3.9	—
	1995	1992–1995	Neonates, > 2500 g	Clinical	—	3.0	—

** Ratio: Number of cases per 100 patients.*

† Rate: Number of cases per 1000 ventilator days.

Note: Abbreviation: BICU = burn intensive care unit; CCU = coronary care unit; CTICU = cardiothoracic intensive care unit; EF = emergency floor; MICU = medical intnsive care unit; MSICU = medical/surgical intensive care unit; MV = mechanical ventilation; NSICU = neurosurgical intensive care unit; PICU = pediatric intensive care unit; PSB = protected specimen brush; RICU = respiratory intensive care unit; SICU = surgical intensive care unit; TI = tracheal intubation; TICU = trauma intensive care unit.

ventilation represent the most important risk factor for nosocomial pneumonia, with a 6- to 21-fold increased risk. For this reason, the CDC and other investigators now report the incidence of nosocomial pneumonia as cases per 1000 days of mechanical ventilation. This serves to adjust the rates to take into account the presence and duration of mechanical ventilation. Ventilator-associated pneumonia rates (cases per 1000 ventilator days) reported by the NNIS system vary by hospital, type of ICU, and for neonatal intensive care units, patient birth weight. Rates among ICUs ranged from 6.0 in the pediatric ICU to 22.2 in the burn ICU. Rates reported from individual hospitals exhibit considerable variation; for medical-surgical ICUs, the lowest 10 percent of reporting hospitals had a rate of 3.8, while the upper 10 percent had a rate of 20.0.

Several investigators have described the actuarial risk of pneumonia as a function of the duration of mechanical ventilation. Langer and associates showed that the rate of pneumonia was constant through the first 8 to 10 days of respiratory assistance and then decreased. While the rate of nosocomial pneumonia per day decreases, the cumulative incidence increases, so by day 30 of mechanical ventilation, an episode of nosocomial pneumonia will have developed in more than 60 percent of patients. Fagon and co-workers reported the actuarial risk of pneumonia during mechanical ventilation as 6.5 percent at 10 days, 19 percent at 20 days, and 28 percent at 30 days. Ruiz-Santana and colleagues reported actuarial risks for pneumonia as 8.5 percent at day 3, 21.1 percent at day 7, 32.4 percent at day 14, and 45.6 percent for ventilation after 14 days. In a systematic review of 38 prospective cohort and nonrandomized studies including approx 48 000 mechanically ventilated patients, the incidence of ventilator-associated pneumonia varied from 10 to 20 percent with twice the mortality of similar patients without VAP.

RISK FACTORS FOR NOSOCOMIAL PNEUMONIA

Many risk factors have been demonstrated to be associated with nosocomial pneumonia (Table 130-2). In general, these factors can be divided into several broad categories: (1) intrinsic host factors such as age, underlying medical disorders such as pulmonary disease, and nutritional status; (2) hospital factors such as abdominal or thoracic operations, antibiotic use, immunosuppression, and treatment in an ICU; (3) equipment and device use, especially intubation with mechanical ventilation; and (4) factors that increase the risk of aspiration such as depressed consciousness.

Intrinsic Factors

The incidence of nosocomial pneumonia is increased at the extremes of life. However, a case control study by Hanson and colleagues, using regression analysis, demonstrated that age was not an independent risk factor for nosocomial pneumonia. Rather, the increased incidence of pneumonia in the elderly was a function of an increased frequency of both intrinsic and hospital risk factors, such as poor nutrition, neuromuscular disease, and endotracheal intubation.

Intrinsic risk factors reported in the literature have included chronic lung disease, poor nutrition, thoracic surgery patients, and immunosuppression. Ventilator-associated pneumonia is common in patients with chronic obstructive pulmonary disease (COPD), reflecting poor pulmonary mechanics and clearance and increased colonization with antimicrobial-resistant pathogens after multiple courses of antibiotics for tracheobronchitis. In this population, *P. aeruginosa* is common (up to one-third) and initial antimicrobial therapy is often inadequate. After major noncardiac thoracic surgery, nosocomial infection is common and carries a high mortality. Pneumonia often masks empyema at the surgical site and CT scans may be needed to diagnose this complication. Lung resection is a special risk group, often with underlying lung disease, obstruction or malignancy, often with pre-existing bronchial colonization. *Haemophilus influenzae* and *Streptococcus pneumoniae* are commonly isolated (suggesting aspiration).

Nosocomial pneumonia outside the ICU or mechanical ventilation population has not been well studied, but often reflects severe community-acquired infection (*Streptococcus pneumoniae* and *Legionella* species) co-existing with nosocomial pathogens.

Hospital Factors

Management in an ICU has been reported as an important risk factor for the development of nosocomial pneumonia. The incidence (number per 100 patients) in various intensive care patients is as follows: ICUs, all patients, 0.5 to 31.5 (median 9.5); intensive care patients, no ventilation, 0.4 to 6.9; adult medical and surgical intensive care patients, mechanical ventilation, 8 to 54 (median 24); and pediatric intensive care patients, mechanical ventilation, 1.5 to 8.

Other important hospital factors reported in the literature are intracranial pressure monitor, chest and abdominal surgery, large-volume gastric aspiration, reintubation, tracheostomy, prior antibiotic use, organ failure, and use of H_2-blocker therapy.

Many studies have documented that the administration of antacids and H_2 blockers—used to prevent stress bleeding in critically ill, intensive care patients—has been associated with gastric bacterial overgrowth. Several studies and three meta-analyses have demonstrated a lower rate of pneumonia in patients treated with sucralfate, a cytoprotective agent, than in those treated with antacids or H_2 blockers. In their review, Craven and Steger note that most current data using a clinical diagnosis of ventilator-associated pneumonia suggest that sucralfate provides similar protection against stress bleeding but poses a lower risk of nosocomial

Table 130-2

Risk Factors for Nosocomial Pneumonia

- Ventilator-associated pneumonia
  - Independent risk factors
    - Age >60 years
    - COPD/PEEP/pulmonary disease
    - Coma/impaired consciousness
    - Therapeutic interventions
    - Intracranial pressure monitoring
    - Organ failure
    - Large volume gastric aspiration
    - Prior antibiotics
    - H_2 blocker +/− antacids
    - Gastric colonization and pH
    - Season: fall, winter
    - Ventilator circuit changes 24 vs. 48 h
    - Reintubation
    - Mechanical ventilation ≥2 days
    - Tracheostomy
    - Supine head position
- Ventilated and Nonventilated patients
  - Independent risk factors
    - Age >60 years
    - APACHE II >16
    - Trauma/head injury
    - Impaired airway reflexes
    - Coma
    - Bronchoscopy
    - Nasogastric tube
    - Endotracheal intubation
    - Upper abdominal/thoracic surgery
    - Low serum albumin
    - Neuromuscular disease
- Ventilator and nonventilated patients
  - Univariate risk factors for pneumonia
    - Age >60 years
    - Male sex
    - Smoking
    - Underling disease, rapidly fatal vs nonfatal/ultimately fatal
    - Simplified acute physiological score >9
    - ASA class IV
    - Inspired O_2 >0.50
    - Prior care facility
    - Alcohol intake
    - Renal failure/dialysis
    - Intra-aortic balloon pump
    - Chronic obstructive pulmonary disease
    - Chemical paralysis
    - Airway instrumentation
    - Aspiration before intubation
    - Mechanical ventilation >2 days
    - No prior surgery
    - H_2 blockers or antacids vs. sucralfate
    - Coma
    - Head trauma
    - Cascade humidifier vs. heat moisture exchanger
    - Tracheostomy
    - Continuous enteral feeding
    - Prior antibiotics
    - Nosocomial maxillary sinusitis
    - Type of intensive care unit
    - Repeat intensive care unit admission
    - APACHE II score
    - Emergency surgery
    - Nasotracheal tube
    - Nasogastric tube
    - Subglottic secretions

Interventions were markers of severe underlying disease and included dopamine, dobutamine ≥5 μg/min, barbiturate therapy for increased intracranial pressur and continuous intravenous antiarrhythmic or artihypertensive therapy.
Note: Abbreviation: APACHE = acute physiological score and chronic health evaluation; ASA = American Society of Anesthesiology; COPD = chronic obstructive pulmonary disease; PEEP = positive end-expiratory pressure.
Source: Adapted from Craven DE, Steger KA: Nosocomial pneumonia in mechanically ventilated adult patients: Epidemiology and prevention in 1996. Semin Respir Infect *11:32–53, 1996.*

pneumonia. For this reason, they recommend that if stress bleeding prophylaxis is prescribed and there is no contraindication, the risk–benefit ratio for reducing ventilator-associated pneumonia appears to favor the use of sucralfate over antacid or H_2 blockers for patients who require a gastric tube.

The use of a nasogastric tube is increasingly recognized as a risk factor for nosocomial pneumonia. Nasogastric tubes may increase the risk of nosocomial sinusitis, oropharyngeal colonization, reflux, and bacterial migration.

RISKS ASSOCIATED WITH RESPIRATORY DEVICES

Intubation with mechanical ventilation is the single most important risk factor for the development of nosocomial pneumonia. For this reason, intubation should be used only when medically necessary, and strict adherence to equipment maintenance is critical. Infected biofilm in the endotracheal tube, with subsequent embolization to distal airways, may be

important in the pathogenesis of VAP. Aspiration of oropharyngeal pathogens, or leakage of secretions containing bacteria around the endotracheal tube cuff, are major routes of bacterial entry into the lower respiratory tract and also suggest the advantage of subglottic suctioning for prevention.

Fluid-containing respiratory devices are the major environment-associated reservoirs for nosocomial pneumonia. However, most or all phases of respiratory support have been linked to nosocomial respiratory infections or suggested as potential environmental reservoirs. These include mechanical ventilation bags, ventilators, aerosolized medications, bronchoscopy, suction catheters, and respiratory support personnel. Evidence suggests that alterations in infection control practices during the 1960s decreased the number of cases of nosocomial pneumonia from environmental sources.

Flexible bronchoscopy has proved to be an invaluable diagnostic and therapeutic procedure. In general, the incidence of postprocedure fever or pneumonia has been reported to be less than 1 percent. However, the use of contaminated bronchoscopes has led to both pseudoepidemics and clinical infection. Pseudoepidemics with clusters of positive cultures of bronchoscopic washings have been linked to the use of contaminated bronchoscopes, contaminated tubing or suction devices, cocaine for topical use, and green dye added to the topical anesthetic. Microorganisms isolated in these cases included *Trichosporon cutaneum* and *Penicillium* species, *Pseudomonas aeruginosa, P. fluorescens-putida, Bacillus* species, *Mycobacterium* species, and *Rhodotorula rubra.* Cross-transmission of respiratory pathogens has led to clinical infections with *M. tuberculosis, P. aeruginosa,* and *Serratia marcescens.* Factors leading to the use of contaminated bronchoscopes have included post-disinfection rinsing in tap water and disinfection with an iodophor, cetrimide-chlorhexidine, and 70 percent alcohol. Failure to sterilize damaged bronchoscopes or bronchoscope suction valves contaminated by *Mycobacteria* has been noted with both ethylene oxide and immersion in 2 percent glutaraldehyde for 30 minutes. Prevention of nosocomial infection related to contaminated bronchoscopes requires adherence to guidelines that delineate proper techniques of cleaning and disinfection of bronchoscopes.

MORTALITY

Nosocomial pneumonia is an important cause of mortality in hospitalized patients. Nosocomial pneumonia has been reported to contribute to 60 percent of all infection-related hospital deaths. Daschner and colleagues reviewed 1000 autopsy reports and noted that pneumonia was associated with 7.5 percent of deaths and was the most common nosocomial infection contributing to death. Intensive care patients with nosocomial pneumonia have a two- to tenfold increased risk of mortality compared to patients without pneumonia. Independent risk factors for mortality in nonventilated patients include infection with *P. aeruginosa,* bilateral infiltrates on chest radiography, and respiratory failure.

Table 130-3

Risk Factors for Mortality in Patients with Nosocomial Pneumonia

Aerobic gram-negative bacilli as pathogen(s), especially *P. aeruginosa*
Severity of underlying illness
Inappropriate antibiotic therapy
Advanced age
Shock
Bilateral infiltrates
Prior antibiotic therapy
Neoplastic disease
Duration of prior hospitalization
Supine head position in patients receiving mechanical ventilation

Source: Adapted from George DL: Epidemiology of nosocomial pneumonia in intensive care patients. Clin Chest Med *16:29–44, 1995.*

The crude mortality for ventilator-associated nosocomial pneumonia has ranged from 13 to 70 percent, but most investigators have reported rates in the range of 20 to 40 percent. Many risk factors have been associated with mortality in ventilated patients (Table 130-3). Several studies using a matched cohort design have evaluated the attributable mortality from nosocomial pneumonia. In these studies, in which patients were matched by demographic factors and comorbidity, the attributable mortality was reported to be 13.7, 33.3, 27.1, and 35.8 percent, respectively.

ETIOLOGIC AGENTS

The common etiologic agents of nosocomial pneumonia reported from the NNIS hospitals from 1990 to 1992 were *Staphylococcus aureus* (20 percent), *P. aeruginosa* (16 percent), *Enterobacter* species (11 percent), *Klebsiella pneumoniae* (7 percent), *Candida albicans* (5 percent), *Haemophilus influenzae* (4 percent), *Escherichia coli* (5 percent), *Acinetobacter* species (4 percent), and *S. marcescens* (3 percent) (Table 130-4). Only *Acinetobacter* spp. were found to significantly increase over the period of study, from 4 to 7 percent. As a group, aerobic enteric gram-negative bacilli accounted

Table 130-4

Common Pathogens Currently Associated with Nosocomial Pneumonia

Pathogen	Frequency (%)	Source of Organism
Early-onset bacterial pneumonia		
S. pneumoniae	5–20	Endogenous; other patients
H. influenzae	<5–15	Respiratory droplet
Late-onset bacterial pneumonia	≥20–60	
Aerobic gram-negative bacilli		Endogenous; other patients, environment, enteral feeding; health-care workers; equipment, devices
P. aeruginosa		
Enterobacter spp.		
Acinetobacter spp.		
K. pneumoniae		
S. marcescens		
E. coli		
Gram-positive cocci		
S. aureus	20–40	Endogenous; health-care workers; environment
Early- and late-onset pneumonia		
Anaerobic bacteria	0–35	Endogenous
Legionella spp.	0–10	Potable water; showers, faucets; cooling towers
M. tuberculosis	<1	Endogenous; other patients, staff
Viruses		
Influenza A and B	<1	Other patients, staff
Respiratory syncytial virus	<1	Other patients, staff; fomites
Fungi/protozoa		
Aspergillus spp.	<1	Air; construction
Candida spp.	<1	Endogenous; other patients, staff
P. carinii	<1	Endogenous; other patients (?)

Crude rates of pneumonia may vary by hospital, patient population, and method of diagnosis.
Source: Adapted from Craven DE, Steger KA: Epidemiology of nosocomial pneumonia: New perspectives on an old disease. Chest *108(Suppl): 1S–16S, 1995.*

for approximately one-third of all pathogens responsible for pneumonia. In ventilated patients, gram-negative bacilli have accounted for 58 to 83 percent of infections, gram-positive cocci for 14 to 38 percent, and anaerobes for only 1 to 3 percent. Polymicrobial infections were common, being noted in 26 to 53 percent of cases (median 40 percent). The importance of viral diseases such as cytomegalovirus, influenza, and respiratory syncytial virus is unknown, but they have clearly been under-ascertained and underreported.

The relevance of the NNIS data is called into question by reports that document the inability of clinical criteria to accurately identify cases of nosocomial pneumonia and the failure of expectorated sputum or tracheal aspirates to reliably identify pathogens in the distal areas of the lung (Table 130-5). Combining reports in which the diagnosis of pneumonia was made by an invasive procedure and more specific microbiologic criteria were used, the etiologic agents of pneumonia were *P. aeruginosa* (16 percent), *S. aureus* (20 percent), *Acinetobacter* species (14 percent), *H. influenzae* (10 percent), *S. pneumoniae* (4 percent), and other streptococci (4 percent). Enteric gram-negative bacilli (*E. coli, Enterobacter, Proteus, Serratia, Klebsiella,* and *Citrobacter*) accounted for only 13 percent of isolates. Thus, generalizing from the NNIS data would overestimate the importance of enteric gram-negative bacilli and underestimate the importance of *Acinetobacter* species as causes of pneumonia in ventilated patients. One must stress that the specific etiologic agents isolated in an individual institution may vary from these summary statistics depending on many factors, including patient demographics, patterns of antimicrobial use, environmental reservoirs for pathogens such as *Legionella* and *Aspergillus,* and the mix of host defects in the patient population.

In the United States, while the list of common pathogens has not much changed, there has been a significant increase in cephalosporin-resistance, production of extended spectrum beta-lactamase (ESBL), and multidrug-resistance

Table 130-5

Microorganisms Isolated from Respiratory Tract Specimens Obtained by Various Representative Methods from Adult Patients with a Diagnosis of Nosocomial Pneumonia

	Emori, 1993	**Barlett, 1986**	**Fagon, 1989**	**Torres, 1990**
Hospital type	NNIS	Veterans	General	General
Patients studied				
Ventilated or nonventilated	Mixed	Mixed	Ventilated	Ventilated
Number	N/A	159	49	78
Number of episodes of pneumonia	N/A	159	52	78
Specimen culture	Sputum, tracheal aspirate	Transtracheal aspirate, blood, pleural fluid	Protected specimen brush	Protected specimen brush, lung aspirate, pleural fluid, blood
Culture results				
No organisms isolated	N/A	0	0	54%*
Polymicrobial N/A	54%*	40%*	13%*	
Number of isolates	8891	314	111	N/A
Aerobic bacteria				
Gram-negative bacilli	59%†	46%‡	75%‡	16%§
Pseudomonas aeruginosa	16%†	9%‡	31%‡	5%§
Enterobacter spp.	11%	4%	2%	0%
Klebsiella spp.	9	23	4	0
Escherichia coli	4	14	8	0
Serratia spp.	3	0	0	1
Proteus spp.	2	11	15	1
Citrobacter spp.	1	0	2	0
Acinetobacter calcoaceticus	4	0	15	9
Others	5	0	10	0
Hemophilus influenzae	5	17%‡	10%‡	0%§
Legionella spp.	N/A	N/A	2%‡	2%§
Gram-positive cocci	26%†	56%‡	52%%‡	4%§
Staphylococus aureus	20%†	25%‡	33%‡	2%§
Streptococus spp.	2	31	21	2
Others	4	0	8	0
Anaerobes	0	35%‡	2%‡	0
Peptostreptococcus	N/A	14%‡	N/A	0
Fusobacterium spp.	N/A	10	N/A	0
Peptococcus spp.	N/A	9	N/A	0
Bacteroides melaningenicus	N/A	9	N/A	0
B. fragilis	0	8	N/A	0
Fungi	7%†	N/A	0	1%§
Aspergillus spp.	N/A	N/A	0	1%§
Candida spp.	6%‡	N/A	0	0
Viruses	1	N/A	N/A	N/A

* *Percent episodes.*
† *Percent isolates.*
‡ *Percent episodes (percentages not additive owing to polymicrobial origin in some episodes).*
§ *Percent patients with pure cultures.*
Note: N/A = Not applicable: not tested or reported; NNIS = National Nosocomial Infection Surveillance System;
Source: Adapted from Tablan OC, Anderson LJ, Arden NH, et al, and the Hospital Infection Control Practices Advisory Committee: Guideline for prevention of nosocomial pneumonia. Infect Control Hosp Epidemiol *15:587–627, 1994.*

in *Pseudomonas, Xanthomonas, Klebsiella* and *Acinetobacter* species. Of note, the role of methicillin-resistant *Staphylococcus aureus* (MRSA) has increased both in nosocomial and community-acquired infections, with a major impact on the related mortality. Nosocomial bacteremic *Staphylococcus aureus* pneumonia (NBSAP) occurs late in the hospital stay, generally in patients with prolonged mechanical ventilation and after previous antimicrobial therapy. When recognized and treated appropriately, the mortality and length of stay were not different between individuals with MSSA and MRSA-pneumonia. Mortality of nosocomial staphylococcal pneumonia is closely related to APACHE II score and early, appropriate therapy. The role of common organisms (*Streptococcus pneumoniae, Mycoplasma pneumoniae, Chlamydia pneumoniae*) in ventilator-associated pneumonia is difficult to assess given the high sensitivity of molecular diagnostic tools and the frequency of these organisms in the general population. *Candida* species are commonly isolated in respiratory specimens but are rarely, if ever, associated with invasive infection in the absence of underlying lung pathology (endocarditis with embolization, infarction, or surgery).

Enterobacteriaceae

Microbiology and Epidemiology

Enteric gram-negative bacilli are an important cause of nosocomial pneumonia. In certain patients, such as those in chronic care facilities, immunocompromised patients, or those with underlying lung disease, they are also an important cause of community-acquired pneumonia. Of the enteric pathogens, the most common agents in pneumonia are *Klebsiella, E. coli, Enterobacter, Acinetobacter, Proteus,* and *Serratia.* All these pathogens grow readily on blood or MacConkey's agar. These bacteria are normal flora of the gastrointestinal tract. As previously noted, hospitalization and other host factors (e.g., alcoholism) favor colonization of the oral cavity.

Clinical Features and Diagnosis

The enteric bacteria are opportunistic pathogens that cause pneumonia in the setting of impaired host defenses. All may produce a destructive pneumonia. Characteristically, patients with pneumonia due to enteric pathogens have fever, chills, cough with production of sputum, shortness of breath, and pleuritic pain. The clinical features are not specific enough to distinguish among the many enteric bacteria capable of causing pneumonia. In some patients—including immunosuppressed persons, the elderly, and patients with hematogenously spread pneumonia—the signs and symptoms of pneumonia may be reduced or absent. Blood cultures have been reported to be positive in 10 to 50 percent of patients, depending on the etiologic agent and the patient population. The radiographic findings do not allow microbiologic diagnosis, although they may be suggestive. As previously noted, the presence of a bulging fissure suggests pneumonia with *K. pneumoniae.* Gram-negative pneumonia is suggested by early necrosis and abscess formation, although it may also be seen with *S. pneumoniae, S. aureus,* and *Legionella.*

Treatment and Prevention

The most active agents against gram-negative enteric pathogens are the third- and fourth-generation cephalospo- rins (cefotaxime, ceftriaxone, ceftazidime, cefepime), a penicillin combined with a β-lactamase inhibitor (piperacillin-tazobactam), carbapenems (imipenem, meropenem), monobactams (aztreonam), and fluoroquinolones. Aminoglycosides are active but are rarely used as primary therapy as penetration into infected lung tissue is often inadequate. Some strains of *Klebsiella, Enterobacter, Acinetobacter,* and *Serratia* may be resistant to multiple antibiotics. Definitive therapy should be guided by in vitro susceptibility results and clinical response. Special hosts (cystic fibrosis, immunocompromised) may have invasive infection due to organisms of lesser virulence or dual infection (non-tuberculous mycobacteria or viral with gram-negative infection).

Pseudomonas Aeruginosa

Microbiology and Epidemiology

The family Pseudomonadineae contains more than 150 species. However, the most important member of this family is *P. aeruginosa. P. aeruginosa* is an obligate, motile, rod-shaped (0.5 to 0.8 by 1.5 to 3.0 μm) gram-negative bacillus with a single flagellum. It may produce a variety of pigments, including pyocyanin (a pigment produced by approximately 50 percent of clinical strains), which causes colonies to appear blue or green. *P. aeruginosa* is capable of utilizing more than 30 organic compounds for growth. It grows optimally at 37°C.

P. aeruginosa can be isolated from soil, water, plants, and animals. Its minimal nutritional requirements allow it to reproduce in many ecologic niches in the hospital. Reservoirs discovered during outbreaks have included many moist devices and surfaces found in hospitals, including endoscopes, endoscope washers, disinfectants, food mixers, and enteral foods. *P. aeruginosa* may also be part of the normal flora of humans. *P. aeruginosa* is primarily a nosocomial pathogen and is the most common gram-negative bacillus causing hospital-acquired pneumonia. Within the hospital, *P. aeruginosa* acts as opportunistic pathogen. Particularly vulnerable are patients with skin or mucous membrane disruption, intravenous catheters, urinary tract catheters, neutropenia, immunosuppressive medication, cystic fibrosis, and diabetes mellitus.

The pathogenesis of *P. aeruginosa* infections is very complex and includes many virulence factors. Key factors include the pili or fimbriae, which mediate adherence to respiratory epithelial cells; the mucoid capsule, which aids in anchoring the organism to its environment; cell-associated factors, which protect the organism from host phagocytes and complement; and extracellular enzymes and toxins, which promote penetration and impair host defenses.

Clinical Features and Diagnosis

P. aeruginosa causes respiratory infection almost exclusively in patients with impaired respiratory host defenses. Only

occasionally does *P. aeruginosa* cause community-acquired pneumonia, and then usually in patients cared for in extended care facilities or with chronic lung disease or other serious underlying illness. *P. aeruginosa* and *S. aureus* are the most important pathogens in patients with cystic fibrosis. Pneumonia due to *P. aeruginosa* is usually a fulminant infection and is characterized by fever, rigors, severe dyspnea, cough productive of sputum, cyanosis, and systemic shock. The chest radiograph commonly reveals diffuse bilateral bronchopulmonary pneumonia with distinctive nodular infiltrates and small areas of radiolucency. Although pleural effusions are common, empyema is rare.

Bacteremic pneumonia may occur in severely neutropenic patients. Patients with bacteremic pneumonia characteristically have ill-defined hemorrhagic, nodular areas that are frequently subpleural. Central necrosis of these areas may occur.

Treatment and Prevention

P. aeruginosa is typically treated with an aminoglycoside plus an antipseudomonal penicillin (piperacillin), cephalosporin (ceftazidime, cefepime), carbapenem (imipenem, meropenem), or monobactam (aztreonam). The fluoroquinolones are also active, but synergy with aminoglycosides has not been demonstrated. Despite therapy, the mortality from hospital-acquired pseudomonal pneumonia is approximately 70 percent. Unfortunately, there are no specific measures to prevent nosocomial pseudomonal infections available at the present time.

DIAGNOSIS

It is difficult to accurately diagnose nosocomial pneumonia. Clinicians have traditionally relied on the presence of clinical findings (i.e., fever, cough, the development of purulent sputum, and evidence of consolidation on physical examination), radiographic evidence of new or progressing pulmonary infiltrate, and laboratory findings (gram's stain of sputum and cultures of sputum, blood, tracheal aspirate, and pleural fluid). Many studies have demonstrated that clinical criteria with appropriate cultures of tracheal specimens may be sensitive for bacterial pathogens but are highly nonspecific, especially in intubated patients on mechanical ventilation. Blood cultures have been reported to yield the etiologic pathogen in approximately 10 to 20 percent of patients with nosocomial pneumonia. Among patients with severe nosocomial pneumonia, however, an additional source of infection has been present in up to 50 percent of those with positive blood cultures.

Several techniques are available for diagnosing nosocomial pneumonia or providing specimens for culture, including quantitative cultures of bronchoalveolar lavage (BAL) and quantitative culture of protected specimen brushing (PSB) or from plugged telescoping catheters (PTC). The reported sensitivity and specificity of these methods have ranged from 70 to 100 percent and 60 to 100 percent, respectively. In the absence of a "gold standard," however, the sensitivity and specificity of these measures cannot be definitely determined. False-positive results using PSB have been attributed to prior antibiotic therapy or bacterial colonization of the lower airway. False-negative results may also occur in significant numbers. Invasive procedures used to diagnose pneumonia may lead to clinical complications, including hypoxemia, bleeding, and arrhythmia. The clinician must also be cautious regarding interpretation of quantitative culture data. Cutoffs for "positive cultures" are somewhat arbitrary and cannot take into account patient-specific factors. Thus, bronchoscopy with quantitative cultures *may miss early forms of nosocomial pneumonia* based on exclusion criteria for the concentration of organisms/ml: i.e., Protected Specimen Brush (PSB) = 10^3; Bronchoalveolar Lavage (BAL) = 10^4; Endotracheal Aspirates (EA) = 10^5. Thus, in multiple series, when PSB contain a concentration of organisms between $10^2$and 10^3 (i.e., below the cutoff), repeat cultures (BAL) revealed over 10^4 within 72 hours in up to one-third.

Diagnostic strategies recommended in the literature for the diagnosis of nosocomial pneumonia range from a clinical approach to routine use of invasive techniques to obtain lower respiratory cultures. Controversy exists as to which invasive approach is most effective. For this reason, a definitive algorithm cannot be provided for the diagnosis of nosocomial pneumonia. However, the following approach to nosocomial pneumonia is suggested (Table 130-6). Patients with suspected nosocomial pneumonia should undergo a careful history and physical examination to define the severity of pneumonia. An arterial blood gas or pulse oximetry should be performed both to aid in defining the severity of infection and determine the need for supplemental oxygen. Mechanical ventilation should be considered for patients with hypoxia not correctable by supplemental oxygenation, hypercapnia, or inability to protect their airway. If the patient is suspected to have a communicable disease transmitted by the droplet or airborne route (e.g., respiratory syncytial virus, tuberculosis, influenza), appropriate respiratory precautions (droplet precautions or airborne precautions; see below) should be instituted. All patients should undergo chest radiography and two sets of blood cultures. The chest radiograph will aid in identifying the presence of pneumonia, the extent and location of infiltrates, and the presence of a pleural effusion. The radiographic appearance may provide clues to the cause of the respiratory failure. Other laboratory studies (complete blood count, electrolytes, liver function tests, tests of renal function, etc.) may be useful in patient management.

When a pleural effusion is present, consideration should be given to obtaining a diagnostic thoracentesis, especially if the patient is toxic or a large effusion (greater than 10 mm on a lateral decubitus film) is present. The pleural fluid should be sent for complete blood cell count and differential, protein, glucose, LDH, pH, gram's stain, and aerobic and anaerobic bacterial cultures. Consideration should also be given to fungal and mycobacterial stains and appropriate fungal and mycobacterial cultures.

Table 130-6

Evaluation of Patients with Suspected Nosocomial Pneumonia

Routine evaluation
- History
  - Recent exposure to possible pulmonary infectious agents (e.g., influenza, tuberculosis)
  - Travel
  - Occupational exposures
  - Animal exposure
  - Immunocompromising conditions (e.g., steroids, risk factors for HIV)
- Physical evaluation
- Chest radiograph
- Measure of oxygen saturation (arterial blood gas or pulse oximetry)
- Obtain expectorated sputum in nonventilated patients and a tracheal aspirate in patients who have been intubated or have a tracheostomy. Send the specimen for gram stain and bacterial cultures.
- Consider additional diagnostic tests, depending on the clinical findings and epidemiologic circumstances: viral culture, direct antigen testing for respiratory syncytial virus, *Legionella* DFA and culture, smear and culture for *Mycobacteria*, smear and culture for fungi, stain for *P. carinii*

Evaluation to exclude extrapulmonary sources of infections
- Routine evaluation
  - Blood cultures from two different sites
  - Urine analysis and culture
  - Examination of wounds, if present
- Additional tests directed by history, physical examination, and laboratory findings
- Consider removal of central and arterial vascular catheters, with semiquantitative culture of the subcutaneous portion and tip of the catheter in patients with positive blood cultures and/or evidence of sepsis
- Consider lumbar puncture following head CT or MRI in patients at high risk (e.g., after neurosurgery) or with unexplained change in mental status
- Consider radiographic imaging of the abdomen (CT or MRI) in patients with rigid abdomen, ileus, or localized or diffuse tenderness or at high risk for abdominal sepsis (i.e., after abdominal surgery, with pancreatitis, gastrointestinal bleeding, or carcinoma, or receiving high-dose corticosteroids)
- Consider abdominal ultrasound in patients with right quadrant tenderness or abnormal liver function tests, or who are too unstable for transfer to CT
- Obtain stools for *C. difficile* toxin assay in patients with more than two watery stools per day. If fever persists with a discernible cause, consider CT scan of sinuses to exclude sinusitiss, with aspiration of the maxillary sinus in patients with air-fluid levels or opacification, and/or consider nucleotide scan (gallium 67 scintigraphy,tagged white cell scan)

Additional pulmonary evaluation
- If pleural effusion is suspected, obtain decubitus films, ultrasound, or CT. If pleural effusion is present, consider diagnostic thorocentesis
- Consider need to exclude thromboembolic disease: impedance plethysmography or Doppler ultrasound evaluation of the lower extremities; ventilation-perfusion scan of the lung; pulmonary arteriogram
- Consider need for invasive diagnosis in patients with rapidly progressive pneumonia, severe pneumonia in intubated patients on mechanical ventilation, immunocompromised patients, and patients who have failed to respond to empiric therapy or have progressed on empiric therapy: bronchoscopy with protected specimen brush and bronchoalveolar lavage or protected bronchoalveolar lavage

Evaluation to rule out atelectasis
- Inhalation of bronchodilators every 2 h for 4 treatments, then every 4 h
- Percussion or vibration over the area of the chest with new densities on chest radiography
- Repeat chest radiograph in 48 h
- Consider Other Sources of Fever
  - Incorrect antibiotic administration: incorrect dose, route, frequency
  - Drug fever
  - Noninfectious source of fever and pulmonary infiltrate (e.g., aspiration, hemorrhage)
  - Foreign body
  - Superinfection
  - Overgrowth
  - Development of drug-resistant pathogen

Source: Adapted from Meduri GU: Diagnosis and differential diagnosis of ventilator-associated pneumonia. Clin Chest Med *16:61–91, 1995.*

In nonintubated patients, expectorated sputum should be obtained for gram's stain and bacterial culture. Epidemiologic or clinical findings should be reviewed, and consideration should be given to obtaining appropriate stains and cultures for viruses, fungi, mycobacteria, *Legionella,* and *P. carinii.* It is important, however, to remember that expectorated sputum is neither sensitive nor specific for the diagnosis of nosocomial pneumonia. Its major value is to identify the antibiotic susceptibilities of the organisms present and thereby aid in the proper choice of therapy.

In intubated patients, a tracheal aspirate should be obtained. The gram's stain may reveal a predominant pathogen. The culture has been shown to have both poor sensitivity and specificity in identifying the etiologic agents of nosocomial pneumonia. Cultures obtained by tracheal aspiration may be of most use in excluding certain potential pathogens (e.g., methicillin-resistant *S. aureus*) and providing information about the antimicrobial susceptibility spectrum of isolated pathogens. Studies of postintubation tracheal aspiration show this to be a reliable alternative to other techniques with the advantage of low cost and speed (recalling that specimens must be obtained prior to antimicrobial therapy whenever possible).

Consideration should be given to performing an invasive procedure to better assess the diagnosis of pneumonia and potential pathogens in the following circumstances: an immunocompromised patient with a broad range of potential pathogens (e.g., heart or lung transplant patient), a critically ill patient with severe hospital-acquired pneumonia (see below), and a patient whose condition does not improve with empiric antimicrobial therapy.

Clinicians should always consider other potential causes of fever and pulmonary infiltrate in the hospitalized patient—including atelectasis, acute radiation pneumonitis, large-volume gastric aspiration, pulmonary embolus with infarction, lung contusion (in trauma patients), pulmonary hemorrhage, and acute respiratory distress syndrome with diffuse alveolar damage.

THERAPY

General Considerations

Despite the development of broad-spectrum antibiotic agents, nosocomial pneumonia continues to carry an unacceptably high mortality. The ATS/IDSA recommendations should be considered general guidelines, for the following reasons: (1) new antibiotics continue to be approved for the treatment of nosocomial pneumonia (e.g., cefepime, linezolid); (2) the spectrum of pathogens causing nosocomial pneumonia varies among hospitals (e.g., frequency of *Legionella*, *Acinetobacter* spp.); (3) the antimicrobial susceptibility spectrum of nosocomial pathogens varies among hospitals (e.g., frequency of MRSA); and (4) the role of invasive techniques to diagnose nosocomial pneumonia remains incompletely defined.

Initial empiric therapy of presumed nosocomial pneumonia may be guided by an assessment of disease severity, the presence of risk factors for specific organisms, and time of onset of nosocomial pneumonia (Fig. 130-2; Tables 130-7, 130-8, and 130-9). An empiric therapy regimen should include agents that are from a different antibiotic class than the

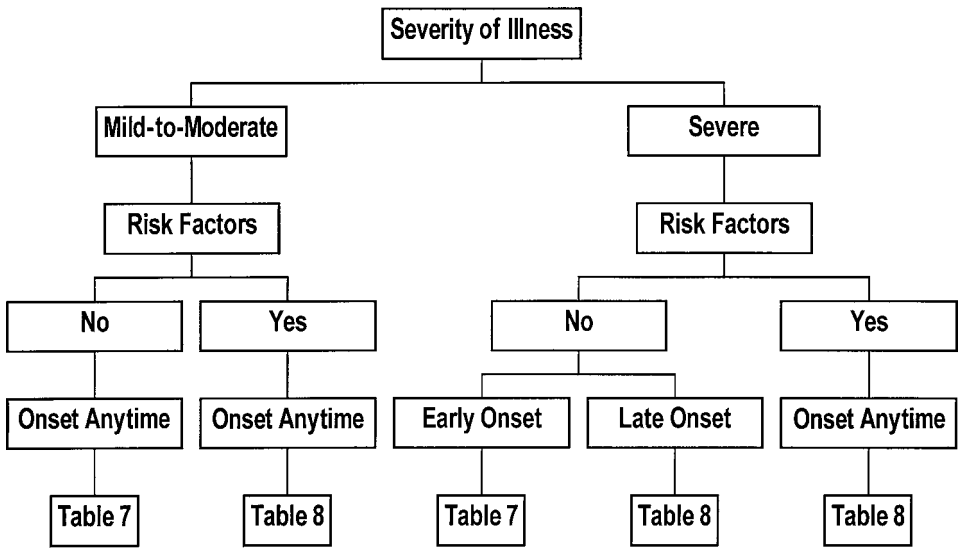

Figure 130-2 Algorithm for classifying patients with nosocomial pneumonia. Specific drugs and doses, recommended in Tables 130-7, 130-8, and 130-9, are adapted from the American Thoracic Society Consensus Statement and represent the views of the authors. Doses provided are for an adult of average weight and normal renal and hepatic function. Doses may need to be adjusted depending on the patient's weight, age, renal function, hepatic function, use of interacting agents, and other factors. Physicians should be thoroughly familiar with the guidelines in individual drug manufacturers' inserts regarding dosing, drug interaction, contraindications, precautions, and administration.

Table 130-7

Patients with Mild to Moderate Nosocomial Pneumonia, No Unusual Risk Factors, Onset Anytime, or Patients with Severe Nosocomial Pneumonia with Early Onset*†

Core Organisms	Core Antibiotics
Enteric gram-negative bacilli	Piperacillin-tazobactam 3.375 g IV q 4 h *or*
(non-*Pseudomonas*)	Piperacillin-tazobactam‡ 4.5 g IV q 6 h *or*
Enterobacter spp.	Cefotaxime 1–2 gm IV q 8 h *or*
Escherichia coli	Ceftriaxone 1 g IV q 12 h *or*
Klebsiella spp.	if allergic to penicillins/ cephalosporins
Proteus spp.	Clindamycin *or*
Serratia marcescens	vancomycin plus Ciprofloxacin IV *or*
	aztreonam
Hemophilus influenzae Methicillin-sensitive *S. aureus* *Streptococcus pneumoniae*	

* *Excludes patients with immunosuppression.*
† *Early-onset pneumonia, ≤4 days after hospitalization.*
‡ *Not an FDA-approved indication or dose.*
Source: Adapted from the American Thoracic Society, Infectious Diseases Society of America. Guidelines for the management of adults with hospital-acquired, ventilator-associated and healthcare-associated pneumonia. Am J Respir Crit Care Med *171:388–416, 2005.*

Table 130-8

Patients with Mild to Moderate Nosocomial Pneumonia with Risk Factor, Onset Anytime*

Core Organisms Plus	Core Antibiotics Plus
Anaerobes	Clindamycin 600 mg IV Q 8 h *or*
(recent abdominal surgery, witnessed aspiration)	Piperacillin-tazobactam 3.375 g IV q 6 h (alone)
Staphylococccus aureus	+/− Vancomyycin (until methicillin-resistant *S. aureus* is excluded) *or*
(coma, head trauma, diabetes mellitus, renal failure)	Linezolid
Leggionella spp.	Fluoroquinolone *or* Macrolide
P. aeruginosa (prolonged ICU stay, steroids, antibiotics, structural lung disease)	Treat as severe nosocomial pneumonia (Table 130-6)

* *Excludes patients with immunosuppression.*
Source: Adapted from the American Thoracic Society, Infectious Diseases Society of America. Guidelines for the management of adults with hospital-acquired, ventilator-associated and healthcare-associated pneumonia. Am J Respir Crit Care Med *171:388–416; 2005.*

patient has recently received. Antimicrobial therapy should always be prescribed with adequate doses (e.g., loading doses where appropriate) to optimize efficacy. The choice of a specific agent will depend on several factors. The first is the spectrum of antimicrobial susceptibility of respiratory pathogens causing nosocomial pneumonia at one's health care facility. It is important for all health care facilities to periodically review the pathogens causing nosocomial pneumonia and their susceptibility patterns and disseminate this information to clinicians. Second, a history of allergic reactions to antimicrobials should be obtained from all patients. Because of the possibility of cross reactivity between β-lactam antibiotics, the use of a cephalosporin in a penicillin-allergic patient should be considered only if the benefit exceeds the risk. Third, antimicrobial therapy should be chosen to minimize drug interactions. Fourth, in patients with renal or hepatic dysfunction, specific drugs may be chosen to minimize the need for dose adjustment. Fifth, potential drug toxicities may provide relative contraindications to use in specific patients (e.g., avoidance of aminoglycosides in patients with neuromuscular disorders or avoidance of aminoglycosides in patients predisposed to renal dysfunction). Sixth, intrinsic patient factors—including age, pregnancy, and breast-feeding—may limit the choice of antibiotics. Finally, if several equally efficacious and safe choices exist, the least costly regimen should be instituted.

The mechanism of bacterial action may be relevant in antibiotic selection and dosing. In general, bactericidal rather than bacteristatic antibiotics are preferred. β-Lactam antibiotics (penicillins, cephalosporins, carbapenems, and monobactams) and vancomycin are bactericidal in a time-dependent fashion. Quinolones and aminoglycosides, which are bactericidal in a concentration-dependent fashion, exhibit killing more rapidly at high concentrations. In general, bactericidal antibiotics exhibit a prolonged postantibiotic

Table 130-9

Patients with Severe Nosocomial Pneumonia with Risk Factors, Onset, or Patients with Severe Nosocomial Pneumonia, Late Onset*†

Core Organisms Plus:	Therapy
P. aeruginosa	Aminoglycoside (gentamicin, tobramycin, amikacin)‡
	or
Acinetobacter spp.	Fluoroquinolone *plus* one of the following:
Consider methicillin-resistant *S. aureus*	Piperacillin-tazobactam 3.375 g IV q 4 h
	or
	Piperacillin-tazobactam§ 4.5 g IV q 6 h
	or
	Imipenem 500 mg IV q 6 h
	or
	Meropenem§ 1.0 g IV q 8 h
	or
	Ceftazidime 2.0 g IV q 8 h
	or
	Cefepime 1–2 g IV q 8 h
	or
	+/− Vancomycin 1 g IV q 12 h
	or
	Linezolid 600 mg IV/PO q 12 h

**Excludes patients with immunosuppression.*
†Late-onset pneumonia, ≥5 days after hospitalization.
‡Consider single daily dosing.
§ ot an FDA-approved indication or dose.
¶Not an FDA-approved drug.
Source: Adapted from the American Thoracic Society, Infectious Diseases Society of America. Guidelines for the management of adult with hospital-acquired, ventilator-associated and healthcare-associated pneumonia. Am J Respir Crit Care Med *171:388–416; 2005.*

effect in which bacterial replication is suppressed for a period after antibiotic levels have fallen below inhibitory concentrations. These pharmacologic features may lead to specific dosing recommendations such as the use of single daily dosing of aminoglycosides.

A controversial area in the treatment of respiratory infections is the importance of antibiotic penetration into lung tissue. It remains unclear whether concentrations in bronchial secretions or in epithelial lining fluid are relevant for predicting efficacy in patients with pneumonia. Also controversial is the role, if any, of inhaled antibiotics in seriously ill patients with nosocomial pneumonia.

Lower respiratory tract cultures are the key to knowing whether, in an immunologically normal host, antimicrobial therapy can be modified or stopped. De-escalation of antibiotics should be considered once microbiologic data are available and based on the patient's clinical response. Negative results can be used to stop antibiotic therapy in a patient who had cultures obtained in the absence of an antibiotic change since cultures were obtained and for at least 72 hours.

Specific Regimens

Initial empiric therapy for nosocomial pneumonia may be guided by severity, presence or absence of risk factors for specific pathogens, and length of hospital stay before the development of nosocomial pneumonia (Tables 130-7, 130-8, and 130-9). Guidelines have been developed for the management of antimicrobial agents; however the concepts remain the same. In the absence of specific risk factors for colonization with multi-drug resistant pathogens, the most common pathogens of early-onset nosocomial pneumonia are *S. pneumoniae, H. influenzae,* enteric gram-negative bacilli (*E. coli, Enterobacter* species, *Klebsiella* species, *Proteus* species, *S. marcescens*), and *S. aureus.* For these patients, a non-pseudomonal third-generation cephalosporin or β-lactam–β-lactamase inhibitor combination are generally used. Inducible β-lactamase may cause resistance to cephalosporins to emerge during therapy. Increasing resistance to fluoroquinolones (e.g., in MRSA or *Pseudomonas*) has made this class less useful as sole agents for this indication although recommended by ATS guidelines. The initial use of vancomycin must be considered in patents with gram-positive organisms on gram-stained sputum smear given the risk for MRSA and for penicillin-resistant pneumococcus. This should be modified according to local hospital epidemiology. Linezolid is an alternative to vancomycin, but advantages for VAP due to methicillin-resistant *S. aureus* need to be confirmed in trials larger than those currently available.

In the presence of certain risk factors and in later-onset infections, broader coverage may be warranted. Anaerobic bacteria are frequently isolated from the respiratory tract of patients with witnessed gastric aspiration, recent thoracoabdominal surgery, or the presence of an obstructing foreign body in the airway. The significance of these anaerobes is unclear, however, since the aerobic bacteria are generally more pathogenic. Nevertheless, patients with witnessed gastric aspiration should be treated with a broad-spectrum agent with anaerobic coverage (e.g., piperacillin-tazobactam, imipenem, meropenem) or have a specific anaerobic agent added (e.g., clindamycin).

Prolonged hospitalization, prior antibiotic therapy, and mechanical ventilation in an ICU increase the likelihood of infection with more resistant bacteria, including methicillin-resistant *S. aureus, P. aeruginosa, Enterobacter* species, and *Acinetobacter* species. In such patients, initial empiric therapy should be broad. Although few studies have evaluated severe nosocomial pneumonia, it is reasonable to initiate very broad empiric antibiotic coverage (i.e., including vancomycin, an anti–gram-negative agent, and macrolide) in such patients to treat methicillin-resistant *S. aureus* and *Legionella* species. In such patients, double or combination treatment for

gram-negative bacteria other than *P. aeruginosa* has not been proved to be superior to monotherapy. True synergy has been demonstrated only for the combination of β-lactam antimicrobials and aminoglycosides. Other combinations for gram-negative infection should be used only as part of initial empiric therapy until microbial susceptibility data are available.

Immunocompromised Patients

The preceding guidelines were not designed to provide recommendations for the treatment of patients with immunocompromising conditions such as HIV infection, organ transplantation, neutropenia, hematologic malignancies, or high-dose steroid use. The presentation and etiology of respiratory infection in immunocompromised patients depend on several factors: (1) the nature of specific host defense abnormalities; (2) the duration of immunosuppressing conditions; (3) the presence or absence of latent infections (e.g., cytomegalovirus); and (4) epidemiologic exposures. The patient's overall susceptibility to infection will reflect the net sum of all factors that alter host defenses, including underlying medical conditions, immunosuppressive therapy, and hospital-related interventions (e.g., indwelling lines). This subject is reviewed elsewhere.

PREVENTION

General Preventive Interventions

Prevention of nosocomial pneumonia begins with strict adherence to standard infection control guidelines (Table 130-10). Among the most important infection control guidelines are proper hand cleaning, isolation precautions, and proper disinfection, and sterilization of equipment. Patients with potentially communicable diseases should be rapidly evaluated and placed on appropriate isolation precautions. "Standard precautions" synthesize the major features of universal precautions (blood and body fluid precautions) and body substance isolation and apply them to all patients receiving care in hospitals, regardless of their diagnosis or presumed infection status. Standard precautions apply to blood; all body fluids, secretions, and excretions except sweat, regardless of whether or not they contain visible blood; non-intact skin; and mucous membranes. Standard precautions are designed to reduce the risk of transmission of microorganisms from both recognized and unrecognized sources of infection in hospitals. Standard precautions include handwashing before and after patient contact, whether or not gloves are worn; wearing gloves when touching blood, body fluids, secretions or excretions, and contaminated items; wearing a mask and eye protection or a face shield during procedures and patient care activities that are likely to generate splashes or sprays of blood, body fluids, secretions, or excretions (e.g., bronchoscopy, arterial line placement); and wearing a gown during procedures and patient-care activities that are likely to generate splashes or sprays of blood, body fluids, secretions, or excretions.

Airborne precautions are used for patients with a communicable disease transmitted by the airborne route, such as tuberculosis, varicella-zoster virus infections (with the exception of dermatomal zoster in the non-immunocompromised host), and measles. Patients with these diseases should be placed in rooms with the following air-handling characteristics: private room, room at negative pressure with respect to the corridor, air directly exhausted to the outside or

Table 130-10

General Methods to Reduce the Frequency of Nosocomial Pneumonia in Mechanically Ventilated Patients

General methods
Aggressive treatment of patient's underlying disease
Review need and avoid antacids + histamine2 blockers for stress ulcer prophylaxis
Keep patient elevated at ≥30°
Review nutrition regimen and tube feeding procedures
Extubate and remove nasogastric tube as clinically indicated
Controlled use of antibiotics
Respiratory care equipment
Discriminate between equipment with nebulizers and humidifiers
≥48-h circuit changes (tubing and humidifier) for mechanical ventilators with humidifiers; no changes for circuits with heat-moisture exchangers
Proper removal of tubing condensatte and education of staff to prevent washing contaminated condensate into the patient's trachea
No transfer of equipment or devices between patients
Review use and care of in-line medication nebulizers
Infection control
Surrveillance in the ICU
Education and awareness programs on nosocomial infection
Handwashingg and/or barrier precautions
Review technique for suctioning patients; type of catheter used
Review method of condensate hisposal
Use effective methods of disinfection of devices and equipment
Consider selective decontamination of the digestive tract with oral nonabsorbable antibiotics to prevent nosocomial infections

Source: Adapted from Craven DE, Steger KA: Nosocomial pneumonia in the intubated patient: New copncepts on pathogenesis and prevention. Infect Dis Clin North Am *3:843–866, 1989.*

monitored high-efficiency filtration before the air is circulated to other areas of the hospital, and 6 to 12 air exchanges per hour. Personnel caring for patients with known or suspected tuberculosis should don an N-95 respirator before entering into the room. Droplet precautions are used for patients with diseases transmitted by the droplet route, such as pertussis, meningococcal pneumonia, pharyngeal diphtheria, rubella, measles, *H. influenzae* epiglottitis, mycoplasmal pneumonia, and group A streptococcal infections (in infants and young children). Droplet precautions consist of private room and limiting patient transport. Personnel should don a surgical mask when working within 3 feet of the patient. Contact precautions are used for patients infected or colonized by direct contact, transient colonization of the hands of caregivers, or contamination of an inanimate object such as a medical instrument. Diseases requiring contact precautions include varicella-zoster infection, *C. difficile* infection, rotavirus, shigellosis, herpes simplex, methicillin-resistant *S. aureus,* and infection by multi-drug–resistant pathogens.

Many reports attest to the ability of contaminated bronchoscopes to transmit pathogens leading to outbreaks or pseudo-outbreaks. For this reason, all endoscopic equipment should be rigorously cleaned immediately after use and then appropriately disinfected or sterilized.

Selective Decontamination with Antibiotics

In recent years, many studies have tried to determine whether selective decontamination of the digestive tract (SDD) is associated with a decreased incidence of nosocomial pneumonia. The SDD regimens have usually included a combination of nonabsorbable local antibiotics (e.g., an aminoglycoside, polymyxin B, and amphotericin) and intravenously administered drugs (e.g., cefotaxime, trimethoprim, or a quinolone). The local antibiotics have been applied as a paste in the oropharynx, and often also provided orally or through the nasogastric tube.

Craven and Steger summarized all trials employing SDD to prevent lower respiratory tract infection. They noted that despite several favorable reports, two large double-blind, placebo-controlled trials were unable to demonstrate that SDD was beneficial. Concerns have been expressed that the use of SDD may lead to the emergence of antibiotic-resistant pathogens and the lack of effect on the duration of mechanical ventilation or hospital stay and cost-effectiveness. For these reasons, many experts and the CDC do not support the routine use of SDD for all medical and surgical intensive care patients. Additional data will be needed regarding the benefits of SDD in special patient populations, such as those with trauma.

Gram-Negative Pneumonia

Gram-negative pneumonias may be divided into several groups: community-acquired pathogens *(H. influenzae, Klebsiella, Bordetella pertussis),* hospital-acquired pathogens (enteric gram-negative rods, especially *E. coli, Enterobacter, Proteus,* and *Serratia*), and zoonotic pathogens (*Francisella tularensis, Yersinia pestis,* and *P. multocida*). The separation of gram-negative pathogens into community- and hospital-acquired groups is only relative, as any of these pathogens may cause pneumonia in either setting. The community-acquired pneumonias are discussed elsewhere in this text.

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131

Aspergillus, Candida, and Other Opportunistic Mold Infections of the Lung

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PULMONARY ASPERGILLOSIS

Aspergillus is a ubiquitous saprophytic mold with worldwide distribution that plays an essential role in recycling carbon and nitrogen. This fungus has a simple biological cycle characterized by a high sporulating capacity, which results in the release of conidia at high concentrations (1 to 100 conidia/m^3) into the atmosphere. *Aspergillus* conidia have a diameter small enough (2 to 3 μm) to reach the lung alveoli. However, despite the fact that humans constantly inhale *Aspergillus* conidia, such conidia are effectively eliminated in immunocompetent individuals.

Epidemiology

Infections by *Aspergillus* species cause a wide spectrum of illnesses in humans depending on the immune status of the host. Hence, in normal hosts, isolation of *Aspergillus* spp. in respiratory secretions generally reflects colonization, not infection. In atopic individuals, the fungus triggers immune phenomena, including allergic rhinitis, asthma, hypersensitivity pneumonitis, and allergic bronchopulmonary aspergillosis (ABPA). In patients with preexisting cavitary pulmonary lesions, saprophytic growth of *Aspergillus* spp. leads to aspergillomas. Finally, in immunocompromised individuals, some *Aspergillus* conidia germinate into the lung to form hyphae, the invasive form of the fungus, which causes a severe, frequently fatal angioinvasive infection called invasive pulmonary aspergillosis (IPA). The degree of fungal invasion, response to antifungal therapy, and outcome of invasive aspergillosis (IA) depend on the type and severity of immunosuppression. In fact, there is a continuum between the colonization seen with aspergilloma and tissue invasion with *Aspergillus*. Thus, in patients with subtle or no immune defects, chronic forms of *Aspergillus* infections in the lung, which are characterized by a benign clinical course over the years with the development of progressive

Table 131-1

Spectrum of Pulmonary Aspergillosis

Clinical Manifestation	Immune Status	Underlying Lung Architecture	Degree of Tissue Invasion
Simple colonization	Normal	Chronic obstructive airway disease	None
Hypersensitivity reactions			
Allergic bronchial asthma	↑*	Normal	None
ABPA	↑	Excess airrway mucus	None
Bronchocentric granulomatosis	↑	Excess airway mucus	None
Extrinsic allergic alveolitis	↑	Normal	None
Saprophytic growth			
Aspergilloma	Normal	Preexisting cavity	None
Invasivve infection			
IBA†	↓	Lung transplantation	++
Bronchial stump aspergillosis	Normal	Pneumonectomy	+
CPA‡	↓§	Chronic obstructive airway disease	+
IPA#	↓↓↓¶	Normal	+++

* ↑ *Hyperactive humoral response.*

† *Includes tracheobronchitis, pseudomembranous tracheobronchitis, and ulcerative tracheobronchitis. These latter two forms typically manifest as anastomotic infections in lung transplant recipients.*

‡ *Includes the following forms: CNPA, CCPA, and CFPA.* Aspergillus *hyphae occasionally invade the lung parenchyma in CNPA. Significant overlap exists among these entities.*

§(↓) *Supressed immune response.*

May have features of invasive disease surrounding the cavity. It occurs in two settings with distinct histopathologies and immunopathogenesis: angioinvasive IPA in profoundly neutropenic patients and nonangioinavasive IPA in immunocompromised nonneutropenic individuals, including those receiving corticosteroid-based treatment, recipients of HSCTs with severe graft-versus-host disease (GVHD), patients with AIDS, recipients of solid organ transplants, and patients with chronic granulomatous disease (CGD). Mixed forms and significant overlap exist.

¶ ↓↓↓ *Severely depressed immune response, neutropenia.*

cavitary lesions, systemic symptoms, and minimal or no evidence of parenchymal invasion, have occasionally been described. A less acute form of IA, frequently called subacute IPA, has been described in patients with acquired immunodeficiency syndrome (AIDS) and chronic granulomatous disease (CGD), whereas rapidly progressive IPA has been encountered in severely immunocompromised hosts. The spectrum of pulmonary aspergillosis is described in Table 131-1.

There is no doubt that since it was first described in the 1940s, IA has emerged as the major problem of modern mycology. Currently, IA is a leading cause of death in severely immunocompromised individuals, with mortality rates approaching 70 to 90 percent in patients with leukemia and recipients of hematopoietic stem cell transplants (HSCTs). At the same time, over the past decade, we have witnessed a significant expansion in the antifungal armamentarium with the introduction of agents with anti-*Aspergillus* activity. In addition, new promising nonculture-based diagnostic methods are being developed, and considerable progress has been made in understanding the epidemiology and immunopathogenesis of IA. As a result, a significant portion of this chapter is devoted to IPA, which currently accounts for more than 90 percent of invasive *Aspergillus* infections.

Mycology and Host Defenses

Of the nearly 200 *Aspergillus* spp., around 20 have been encountered as pathogenic in humans. *Aspergillus fumigatus* is the most frequently identified of these species; however, other species, such as *Aspergillus flavus*, *Aspergillus niger*, *Aspergillus terreus*, and *Aspergillus nidulans*, have recently emerged as important pathogens in immunocompromised individuals. Notably, *A. fumigatus* is virtually always the cause of allergic pulmonary disease. *Aspergillus* spp. are rapidly growing, hardy molds identified by the appearance of the colony and microscopic examination of the spore-bearing structures. Microscopically, *Aspergillus* spp. are characterized by the production of uniform 4- to 6 μm–wide hyphae with

parallel walls and distinct septa. Dichotomous branching of hyphae occurs at 45-degree angles. A wide range of microscopic appearances may be observed in clinical specimens. Other filamentous fungi, such as *Fusarium* spp. and *Pseudallescheria boydii*, share the same histopathological features with *Aspergillus* spp.

Sputum specimens obtained from patients and examined by direct mounting or KOH and ink may reveal the typical 45-degree branching hyphal fragments of aspergilli, which are often associated with eosinophils and Charcot-Leyden crystals in patients with ABPA. Stained tissue sections reveal regular hyaline septate hyphae that are best observed with the use of periodic acid-Schiff (PAS) and Gomori's methenamine silver (GMS) stain. Fungus ball specimens obtained from cavities connected to open bronchi have hyphae that often appear to be lifeless and stain poorly. Also, although seldom seen, the fruiting heads and conidia may appear to be well formed.

Host Immune Responses

Despite significant improvements, the immunologic mechanisms of host resistance to *Aspergillus* spp. are not completely understood. Protection of the normal host against *Aspergillus* infection is mediated by a highly coordinated response that involves both innate and adaptive immunity.

Innate immunity consists of three main effector cells: (1) regional dendritic cells that orchestrate innate and adaptive immune responses and antigen presentation; (2) pulmonary alveolar macrophages that ingest and kill the inhaled conidia, primarily by nonoxidative mechanisms; and (3) circulating polymorphonuclear and mononuclear cells that mediate hyphal damage, mainly by oxidative killing. Not surprisingly, quantitative and qualitative defects in phagocytic cell function associated with prolonged and profound neutropenia and corticosteroid-induced dysfunction of macrophages and monocytes have long been recognized as the major risk factors for IA.

Humoral factors also participate in the initial events of host response to *Aspergillus* infection. Resting conidia, germinating conidia, and hyphae are all potent activators of both the alternative and classical components of the complement cascade, promoting opsonization and chemotaxis. In addition, C-type lectins, including mannose-binding lectins, surfactant protein A (SP-A), and surfactant protein D (SP-D), which are present in alveolar fluid, enhance chemotaxis, binding, phagocytosis, and oxidative killing of conidia. C-type lectins also appear to be able to agglutinate, immobilize, and inactivate conidia. Importantly, alteration of SP-D and certain polymorphisms in mannose-binding lectins were recently shown to be associated with an increased risk of chronic pulmonary aspergillosis (CPA).

Aspergillus antigens induce activation and maturation of dendritic cells, which play an instrumental role in linking innate and adaptive immune responses against fungi. Following exposure to *Aspergillus*, dendritic cells migrate to the spleen and drain lymph nodes and induce local and peripheral T-helper (Th) cell reactivity to the fungus. Ingestion of *Aspergillus* conidia and hyphae proceeds through distinct phagocytic mechanisms, and elicited immune responses differ depending on the morphotype encountered.

The development of specific Th responses is an essential determinant of the host's susceptibility or resistance to *Aspergillus* infection. Th CD4+ cells are the major effector cells responsible for cell-mediated immune responses against pathogens. Upon stimulation by exogenous antigens, Th cells differentiate into Th1 or Th2 cells, which are morphologically indistinguishable but differ in the pattern of cytokines they produce. Th1 cytokines induce a predominantly cell-mediated inflammatory response, whereas Th2 cytokines facilitate antibody production.

Th1 cytokines include tumor necrosis factor-alpha (TNF-α), interferon-γ, interleukin (IL)-12, and IL-15 and have been shown to confer protection against *Aspergillus* infection in animal models. These cytokines augment superoxide production and enhance the antifungal activity of polymorphonuclear and mononuclear phagocytes against *Aspergillus* spp. In a murine model of IPA, exposure of immunocompetent animals to a sublethal inoculum of *Aspergillus* conidia has been shown to lead to the development of resistance to subsequent systemic infection. The protective Th1 response was characterized by the presence of antigen-specific CD4+ T cells that produced interferon-γ and IL-2. Notably, adoptive transfer of *Aspergillus*-specific CD4+ splenic T cells from these animals conferred protection in naïve animals challenged with the *Aspergillus* conidia. Similarly, dendritic cells pulsed with *Aspergillus* conidia or transfected with conidial RNA can induce Th1-cell priming. Upon adoptive transfer, such cells were protective against IA in mice that underwent allogeneic hematopoietic stem cell transplantation. Thus, dendritic cells may be employed as one of the vaccine strategies against IA.

In comparison, Th2 responses, which are characterized by IL-4 and IL-10 production, have been associated with disease progression, and neutralization of them has been associated with resistance to infection in animal models. Th2 cytokines impair fungicidal activity and hyphal damage mediated by mononuclear cells, resulting in increased susceptibility to acute *Aspergillus* challenge. However, later in the course of *Aspergillus* infection, high-level production of IL-10 may be beneficial by contributing to resolution of the inflammatory response. Recent evidence suggests that IL-10 produced by cells of the innate immune system is responsible for preventing activation of the protective innate effector phagocytic cells, which accounts for fungal latency and persistence.

Cell surface and secreted pattern recognition receptors mediate the development of Th responses. Specifically, signal transduction mediated by toll-like receptors (TLRs) has been shown to play a key role in immunity against aspergillosis. Of the 10 human TLRs identified thus far, TLR2 and TLR4 are involved in the regulation of cytokines that are important to the

pathogenesis of *A. fumigatus*. In a previous study, *Aspergillus* conidia stimulated both TLR2 and TLR4 to induce a Th1 cytokine response, whereas germination of hyphae led to the loss of TLR4-mediated signals; however, TLR2-dependent mechanisms remained intact, induced IL-10 secretion, and ultimately led to a predominant Th2 response. Thus, switching from a proinflammatory to an anti-inflammatory cytokine profile during germination of *Aspergillus* hyphae may represent an escape mechanism by which the fungus evades the host defense.

Another recently identified secreted pattern recognition receptor, the pentraxin PTX3, has been shown to bind to a range of microbial products, including *Aspergillus* conidia, and to confer resistance to the fungus. In addition, PTX3-deficient mice were susceptible to IPA because of impaired recognition of aspergilli by alveolar macrophages and dendritic cells and inappropriate induction of a Th2 response.

Aspergillus Virulence Factors

Uncertainty remains regarding the attributes that mediate *Aspergillus* pathogenicity. Several putative virulence factors in *A. fumigatus* have been identified, including various proteolytic enzymes (elastases, collagenases, trypsin), phospholipases, ribotoxin, hemolysin, gliotoxin, and many other enzymes and toxins. The mycotoxin gliotoxin in particular has received significant attention and been studied extensively. Gliotoxin exhibits immunomodulatory properties, as it has been shown to inhibit the phagocytosis of macrophages, promote apoptosis of macrophages, and block B- and T-cell activation. In addition, some have postulated that the production of catalases, superoxide dismutases, and mannitol by *Aspergillus* may protect the fungus from oxidative damage induced by phagocytic cells. Moreover, the melanin pigment and rigid protein coat layer composed of rodlet fascicles on the *Aspergillus* conidial surface may also confer resistance to phagocytosis. However, molecular studies have yet to identify a single target that meets the Koch's postulates for virulence in IA. On the other hand, recent evidence from comparative genomic analysis across filamentous fungi suggests that *A. fumigatus* virulence results from the immunosuppression or possibly genetic susceptibility of the host rather than from specific, unique fungal determinants. Hence, *A. fumigatus* appears to be a saprotrophic fungus that only becomes pathogenic for very simple biological reasons: It is present in high concentrations in the atmosphere, it grows faster than any other airborne fungi at 40°C, and it can overcome the defense of the host not because of specific virulence mechanisms, but because of the failure of host immune responses. Taken together, these data suggest that approaches targeted at augmenting cellular immunity, such as neutralization of Th2 cytokines, enhancement of Th1 responses, and dendritic cell vaccine–based vaccination, warrant future investigation as therapeutic modalities for invasive *Aspergillus* infections.

Clinical Manifestations

Hypersensitive Reactions

Hypersensitivity lung diseases that result from exposure to *A. fumigatus* allergens include allergic asthma, ABPA, and hypersensitivity pneumonitis. In atopic individuals, inhalation of *Aspergillus* spores triggers an IgE-mediated allergic inflammatory response in the bronchial mucosa, leading to excessive mucus production, bronchial obstruction, and asthma. Similarly, ABPA develops following sensitization to *A. fumigatus* allergens in a unique subset of atopic individuals and patients with cystic fibrosis (CF), who are genetically susceptible for ABPA. The immune response to *Aspergillus* antigens in both patients with allergic asthma and those with ABPA is characterized by a robust Th2 CD4+ response.

In nonatopic individuals, persistent airway colonization and, more rarely, a type of hypersensitivity pneumonitis called *extrinsic allergic alveolitis* can occur as a result of massive or repeated inhalation of *Aspergillus* conidia. Hypersensitivity pneumonitis in these patients manifests with dyspnea because of pulmonary constriction and an influenza-like syndrome with fever, malaise, and fatigue. However, in contrast with other allergic diseases caused by *A. fumigatus*, hypersensitive pneumonitis is characterized by extensive infiltration of neutrophils in the acute phase as a result of a Th1 CD4+ response. Early recognition of these syndromes is important for early initiation of appropriate treatment to prevent progression to permanent lung damage. Table 131-2 summarizes the hypersensitivity syndromes that result from exposure to *Aspergillus*.

Simple Colonization

Although there is no uniform definition of colonization, it should be considered in cases of isolation of *Aspergillus* spp. from cultures of the respiratory tract in patients without concomitant evidence of invasive or allergic disease. Patients with structural lung diseases such as chronic obstructive pulmonary disease (COPD) are at increased risk for persistent *Aspergillus* colonization. Tissue invasion by aspergilli is not a feature of saprophytic colonization, although pulmonary aspergillosis with subsequent dysfunction of host defenses may develop. In fact, *Aspergillus* colonization has been shown to be a marker for the development of IA in immunocompromised individuals, particularly lung and bone marrow transplant recipients, and may precede invasion for up to 3 mo. Quantitative real-time polymerase chain reaction (PCR) holds promise as a tool for distinguishing *Aspergillus* colonization from invasive infection.

Allergic Bronchial Asthma

Asthmatic patients may become sensitized to *Aspergillus* conidia as a consequence of thick bronchial secretions that trap fungal spores. These spores seldom germinate in the bronchial airways. Allergic bronchial asthma develops in patients who are atopic and is perpetuated by inhalation of *Aspergillus*

Table 131-2

Hypersensitive Reactions to *Aspergillus*

	Asthma	ABPA	Extrinsic Allergic Alveolitis
Pathology	Hypertrophied mucus glands	Colonization of airways, viscid mucoid impaction, tissue eosinophilia	Lymphocytic infiltration of interstitium, noncaseating granuloma
Radiographic features			
Early	Normal, hyperinflation	Migratory peripheral infiltrates, atelectasis, bronchiectasis	Diffuse alveolar-interstitial infiltrates
Late	Normal, hyperinflation	Fibrosis	Reticulonodular interstitial opacities
Skin test reactions to *Aspergillus* antigens			
Immediate	Positive	Positive	Positive
Delayed	Negative	Positive	Positive
Peripheral eosinophilia	Negative*	Positive	Negative
IgG *Aspergillus* precipitins	Positive (up to 25%)	Positive	Positive
Serum IgE levels	Normal or mildly elevated	Marked elevation	Normal

** Occasionally positive.*

antigens, which typically cause acute bronchospasm. The presence of transient infiltrates has been described during the immediate reaction but is not frequent. As is typical in asthma of other etiologies, eosinophils and serum IgE antibody are increased. Immediate skin reactions to *Aspergillus* antigens are positive, but specific precipitating antibodies (IgG) are usually negative. Avoidance of exposure to *Aspergillus* spores can diminish the frequency and severity of bronchospasm in this group of patients.

ABPA

Immunopathogenesis-Risk Factors

It has been recently proposed that ABPA develops in genetically susceptible patients with asthma or CF because of increased activity of *A. fumigatus*–specific Th2 CD4+ cells. Hence, in addition to a history of atopy, predisposing factors for ABPA include immunogenetic human leukocyte antigen (HLA)–distinct phenotypes (e.g., HLA-DR 2– and HLA-DR 5–specific alleles), mutations in the CF transmembrane conductance regulator (CFTR) gene, polymorphisms of the collagen region of the surfactant protein A2, and/or other collectins (e.g., mannose-binding lectins). In addition, particular physicochemical characteristics of respiratory secretions and a history of environmental exposure may play a role in ABPA pathogenesis.

In patients with ABPA, inhaled *A. fumigatus* conidia are able to colonize, persist, and germinate, leading to growth of hyphae in mucus plugs, which are often seen in expectorated sputum. During this process, *A. fumigatus* releases a panel of proteases and other toxins that are capable of further compromising mucociliary clearance, breaching the airway epithelial barrier, and activating the immune system in the lung.

IgE molecules on the surface of mast cells initially recognize *A. fumigatus* antigens. Binding of these antigens with IgE causes mast cell degranulation, releasing mediators that cause vasodilatation and vascular leakage so that serum components, including anti-*Aspergillus* IgG, enter the bronchi and combine with *Aspergillus* antigens to form IgG-containing immune complexes. These complexes activate the complement cascade leading to inflammation and pulmonary damage. Importantly, investigators have identified specific *Aspergillus* antigens capable of inducing IgE and IgG responses in patients with ABPA but not in control patients who did not have ABPA, implying that an aberrant host response occurs in patients with ABPA.

The key element in the immunopathogenesis of ABPA appears to be an abnormal T-lymphocyte cellular immune

response to *A. fumigatus* conidia. Hence, *A. fumigatus* allergens released by mycelia are processed by antigen-presenting cells bearing HLA-DR 2 or HLA-DR 5 and presented to T cells within the bronchoalveolar lymphoid tissue. The T-cell response to *Aspergillus* allergens is then shifted toward a Th2 CD4+ cell response with synthesis and secretion of the cytokines IL-4, IL-5, and IL-13. In addition, production of chemotactic cytokines (chemokines) by inflammatory cells, including monocyte chemoattractant protein-1 (MCP-1/CCL2), eotaxin (CCL11), IL-8, and macrophage inflammatory protein-1α (MIP-1α/CCL3) appears to promote the Th2 cell response. In addition, T cells, B cells, natural killer cells, and eosinophils may be hyper-responsive to IL-4. This leads to a positive-feedback amplification loop of Th2 CD4+ cells, synthesis of IL-4, and polyclonal activation of CD23+ CD86+ B cells.

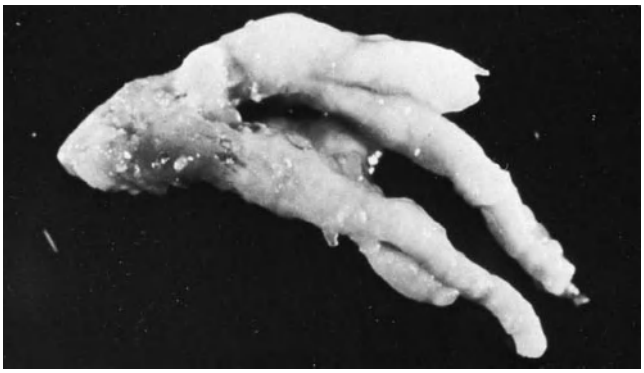


Figure 131-1 Mucus plug expectorated by a patient with ABPA. Of note is the tapering, cylindrical shape with branching characteristic of the parent bronchi. *(Courtesy of Frederic Askin, Chapel Hfl l, NC.)*

Clinical Features

ABPA is a hypersensitivity disease of the lung that is virtually almost always related to *A. fumigatus* (discussed in detail in Chapter 49). Some key points are highlighted here. Seven to 14 percent of patients with poorly controlled asthma and 7 to 9 percent of those with CF meet the diagnostic criteria for ABPA. In fact, nearly all patients with ABPA have a history of chronic asthma. Patients rarely present without symptoms or physical findings despite having radiographically detected abnormalities. Clinically, ABPA manifests with episodic wheezing, malaise, low-grade fever, cough, sputum containing brown flecks and plugs, chest pain, pulmonary infiltrates, and sputum and blood eosinophilia. Patients may have a history of recurrent pneumonia and frequent use of antibiotic therapy. Mucus plugs form in the proximal bronchi and can progress to mucoid impaction, resulting in atelectasis with transient pulmonary infiltrates. Mucus plugs often yield aspergilli in culture (Figs. 131-1 and 131-2). As ABPA progresses, central bronchiectasis becomes a dominant feature of the disease and may result in chronic bronchorrhea and occasionally hemoptysis, development of clubbing, and fixed, characteristic radiographic abnormalities. In patients with CF in particular, ABPA often manifests with hemoptysis and may be complicated by pneumothorax.

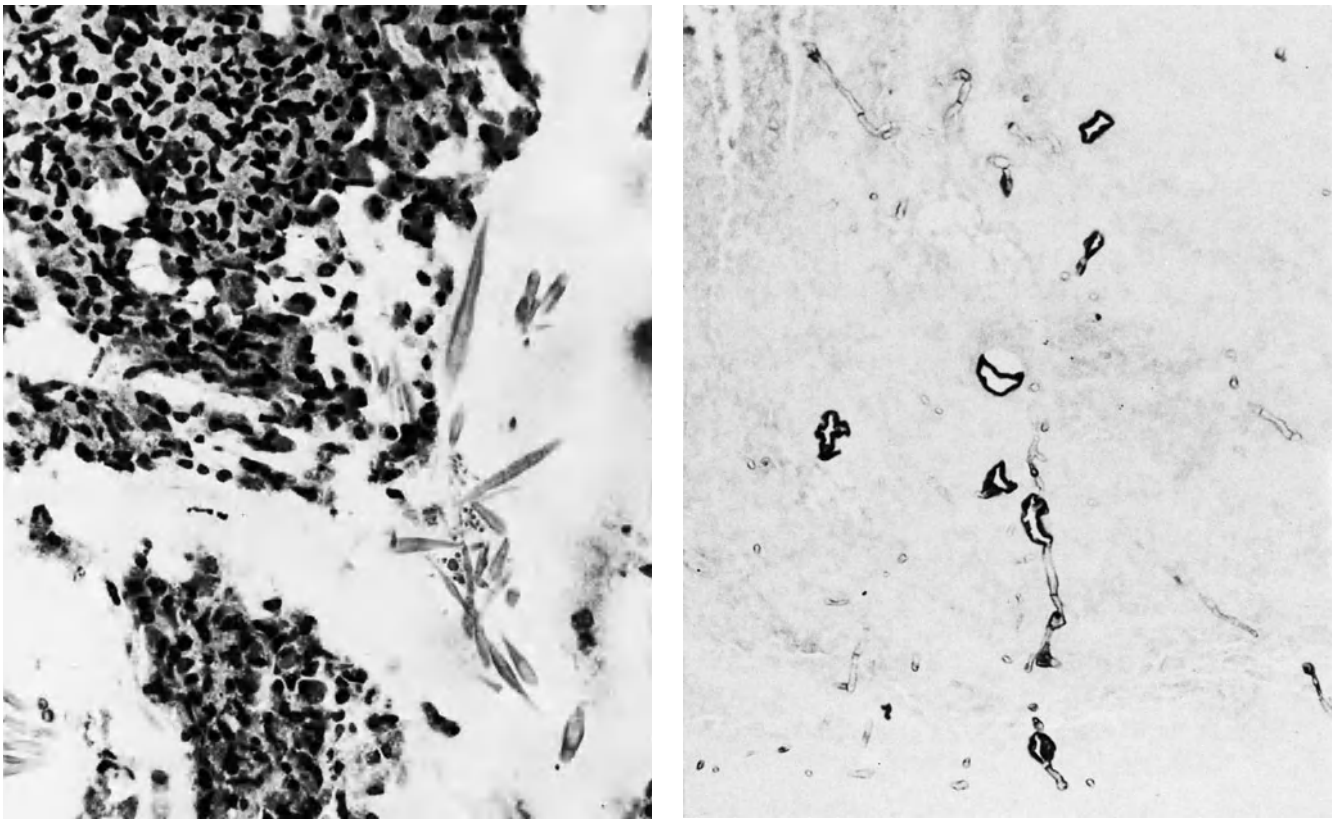
Radiographic Findings

The radiographic features of ABPA have an essential role in diagnosis, as they may distinguish ABPA from simple chronic asthma. Pulmonary infiltrates in patients with ABPA are initially transient, but they ultimately progress to permanent radiographic changes. In many instances, the ring sign indicative of bronchial wall thickening, "parallel" shadows or "tram lines" suggestive of bronchiectasis, and branching "finger-in-glove" opacification of the dilated bronchi because of mucoid impaction are seen on regular chest radiographs of patients with ABPA (Fig. 131-3). Such ABPA lesions are either focal or bilateral and tend to occur more frequently in the upper lobes. Late radiographic findings in patients with ABPA include cavitation, local emphysema, contracted upper lobes, and honeycomb fibrosis. However, the presence of proximal bronchiectasis (Figs. 131-3 and 131-4), which is characterized by normal filling of bronchi distal to the saccular bronchial lesion, is considered a hallmark for diagnosis of ABPA.

Chest computed tomography (CT) has been a significant aid in diagnosing ABPA because it is more sensitive than regular chest radiography; however, there are no pathognomonic CT findings for this entity. Besides central bronchiectasis, CT findings highly suggestive of ABPA include the presence of varicose or cystic bronchiectasis of segmental and subsegmental bronchi (90 percent in ABPA versus 30 percent in simple asthma), mucoid impaction of the segmental and subsegmental airway (67 percent in ABPA versus 4 percent in simple asthma), and small airway abnormalities such as centrilobular nodules and tree-in-bud opacities (93 percent in ABPA versus 28 percent in simple asthma). In patients with CF especially, CT diagnosis of ABPA is particularly challenging, as there is a significant overlap in the radiographic features of both entities. In fact, the presence of high-attenuation mucus plugs because of dystrophic calcification is the only CT finding that favors the diagnosis of ABPA in patients with CF.

Diagnosis

The "classic" patient with ABPA fulfills the criteria listed in Table 131-3. It has been suggested that the minimal essential criteria for diagnosis of ABPA include the presence of: (1) asthma; (2) immediate cutaneous reactivity to *Aspergillus* antigens; (3) elevated total serum IgE levels (greater than 1000 U/ml); (4) elevated serum IgE and IgG levels to *A. fumigatus;* and (5) central bronchiectasis. However, asymptomatic pulmonary involvement occurs in patients with ABPA and may lead to diagnostic uncertainty, delayed diagnosis, and irrevocable structural lung damage. Furthermore, corticosteroid-based therapy for asthma may mask the signs of ABPA, allowing a progressive decline in pulmonary function. Because the above criteria may not apply in such cases, some have proposed that serologic evidence (all three



A *B*

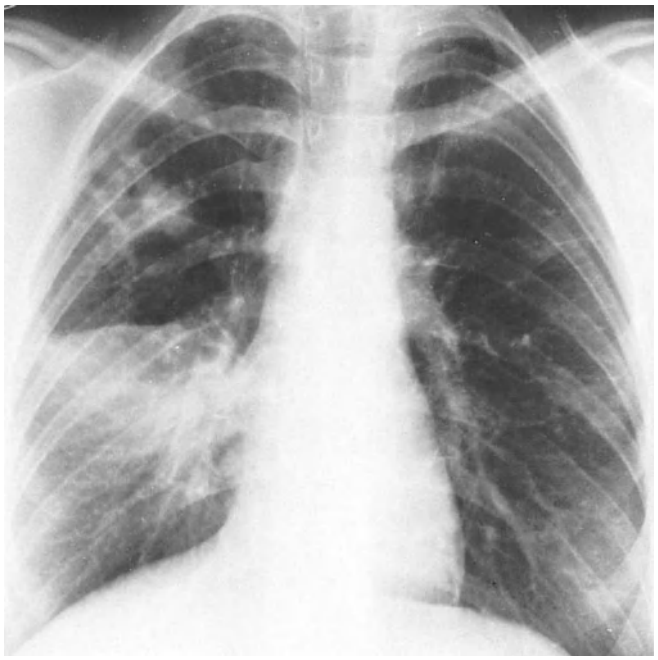
Figure 131-2 High-magnification photomicrograph of inspissated mucus in mucoid impaction of the bronchus. *A.* Groups of Charcot-Leyden crystals adjacent to clusters of necrotic eosinophils. H&E stain, ×520. *B. Aspergillus* hyphae. Of note is the transition from regular, thin septate hyphae to dilated, often folded degenerating forms. H&E stain, ×354. *(Courtesy of S. Albelda and G. H. Talbot.)*

serologic tests listed in Table 131-3 and immediate skin reactivity test to *Aspergillus* antigens need to be positive) without the presence of bronchiectasis may be sufficient to support early diagnosis of ABPA. In addition, the diagnostic criteria for ABPA in patients with CF were recently modified, because there are overlapping features between these entities. The new criteria consist of: (1) clinical and/or pulmonary function deterioration from baseline status; (2) positive immediate cutaneous reaction to *A. fumigatus* antigens or elevated serum IgE *A. fumigatus* antibody level; (3) elevated total IgE level greater than 1000 U/ml; (4) elevated serum IgG *A. fumigatus* antibody level or positive *A. fumigatus* precipitins; and (5) abnormal chest imaging findings or a change in baseline abnormalities.

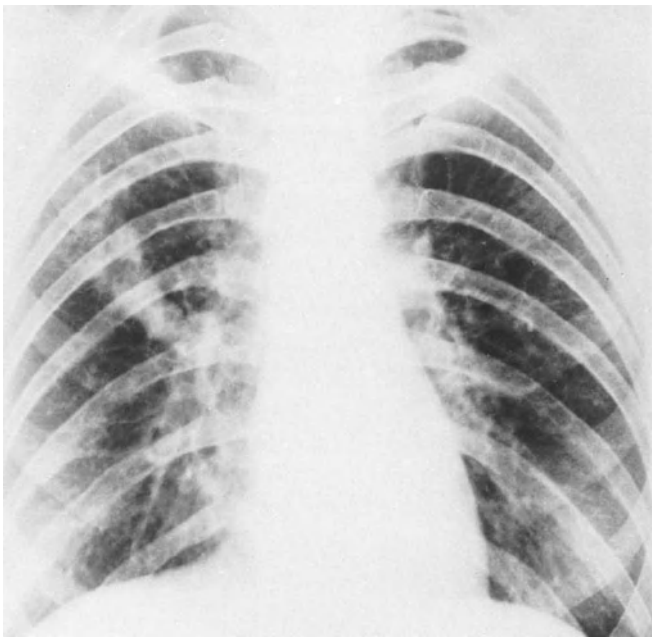
Important clinical clues that should alert clinicians to the possibility of ABPA include refractory asthma or asthma with any of the following features: bronchiectasis, radiographic infiltrates, prominent eosinophilia, and expectorated brown plugs that may contain eosinophils or hyphae in 50 percent of cases (see Fig. 131-2). In addition, in patients with CF, prominent wheezing is considered to be suggestive of ABPA. Rarely, ABPA may be caused by non-*fumigatus* aspergilli or other fungi; in such cases, the serologic tests will be negative.

Because no single clinical or immunologic feature is diagnostic for ABPA, this disease remains underdiagnosed. Until recently, serologic diagnosis of ABPA was based on *Aspergillus* crude extracts, which are cumbersome, lack reproducibility, and frequently crossreact with other antigens. However, recent studies indicate that standardized recombinant *A. fumigatus* allergens have the potential to substantially increase the specificity and sensitivity of diagnosis of *A. fumigatus*–related diseases, including ABPA. Several recombinant *A. fumigatus* allergens, including Aspf1, Aspf2, Aspf3, Aspf4, Aspf6, and Aspf16, show high specificity for the detection of sensitization to *A. fumigatus* and for diagnosis of ABPA and appear to be superior to crude *Aspergillus* allergen extracts. However, because the sensitivity of each recombinant *A. fumigatus* allergen is suboptimal, use of a panel of recombinant allergens is required to increase the sensitivity of diagnosis of ABPA. Further standardization and development of commercially available immunoassays containing a combination of these allergens holds promise for improving the diagnosis of ABPA.

Because patients with CF are at high risk for ABPA, initiation of annual screening at high school age for ABPA with monitoring of serum total IgE levels has been recommended in patients with IgE levels greater than 500 U/ml. Likewise,



A



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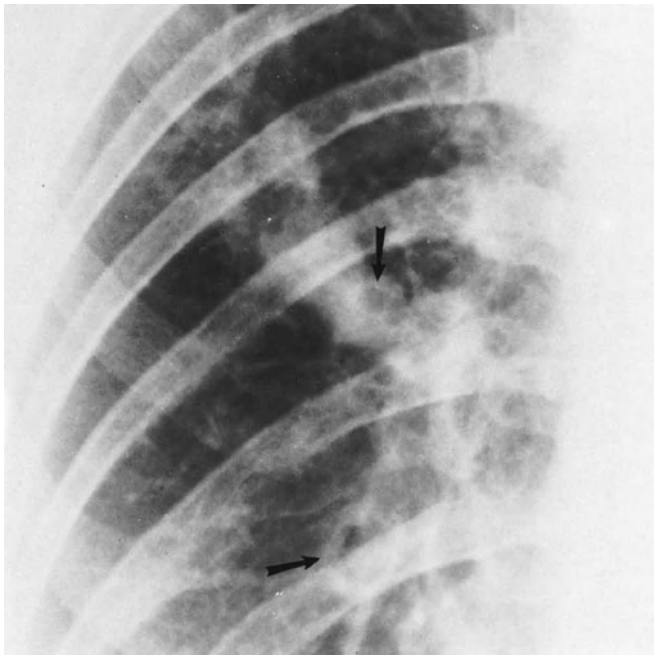


C

Figure 131-3 A 23-year-old woman with documented ABPA. *A*. Chest radiograph showing mucoid impaction in the right upper lobe and alveolar consolidation in the right middle lobe. *B*. Eight months later, the alveolar consolidation has resolved, and the appearance of the mucoid impaction in the right upper lobe has changed. *C*. Close-up of the right lung in (*B*) showing the "gloved finger" appearance of mucoid impaction as well as ring shadows (arrows) characteristic of bronchiectasis. *(Courtesy of S. Albelda and G. H. Talbot.)*

because treatment with corticosteroids has a significant impact on disease progression, screening CT has been advocated for asthmatics with a skin-prick hypersensitivity test positive for *A. fumigatus* to identify ABPA at an early stage.

Histopathology

Because the diagnosis of ABPA is based on clinical and laboratory criteria, use of lung biopsy to confirm the diagnosis is usually not required. The presentations of the hypersensitivity syndrome associated with fungi are discussed in detail in Chapter 49. Some of the histopathological presentations associated with ABPA overlap those of invasive *Aspergillus* infection. Thus, eosinophilic infiltrates may be present in patients with invasive *Aspergillus* infection as well as in those with other allergic lung entities, such as Loeffler's syndrome, tropical eosinophilic pneumonia, and chronic eosinophilic pneumonia (see Chapter 72). Mucoid impaction associated with ABPA or other fungi may predispose patients to superinfection (see Figs. 131-1 and 131-2). Necrotizing granulomata in association with the presence of *Aspergillus* spp. in asthmatic patients may be observed and is considered part of the ABPA syndrome. The histopathological distinction between

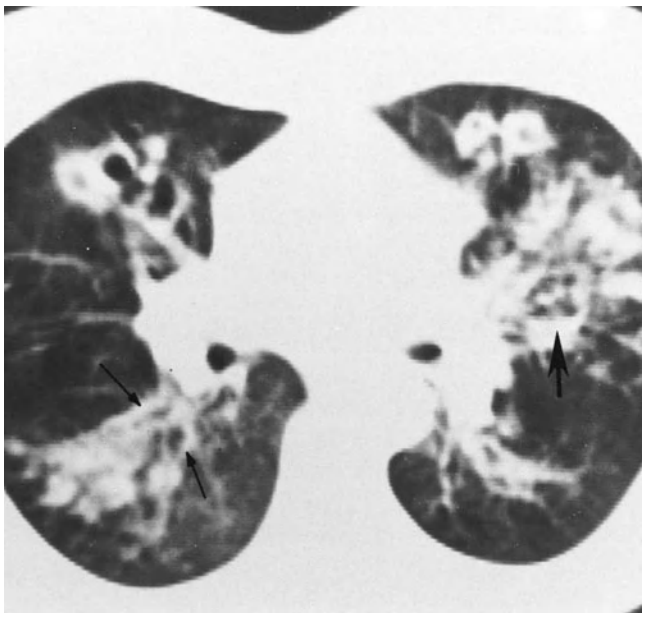


Figure 131-4 Proximal saccular bronchiectasis characteristic of ABPA. The CT scan reveals multiple rounded, dilated bronchi (small arrows). Note the air-fluid level (large arrow). *(Courtesy of S. Albelda and G. H. Talbot.)*

ABPA, with fungal elements restricted to the airways, and semi-invasive or fully IA may be obscured by tissue necrosis or poor granuloma formation. These presentations are discussed further below and in Chapter 49.

Table 131-3

Criteria for the Diagnosis of ABPA

Primary
Episodic bronchial obstruction (asthma)
Peripheral blood eosinophilia (>1000/mm^3)
Immediate type skin reactivity to *Aspergillus* antigens*
Precipitating serum antibodies (precipitins) against Aspergillus antigens*
Elevated serum IgE concentrations (>1000 ng/ml)*
Elevated serum IgE and/or IgG antibodies specific to *A. fumigatus**
History of pulmonary infiltrates (transient or fixed) on chest radiographs or CT scans
Central bronchiectasis on chest CT scans
Secondary
A. fumigatus in sputum (by repeated culture or microscopic examination)
History of expectoration of brown plugs or flecks
Arthus reactivity (late skin reactivityy) to *Aspergillus* antigen

Adapted with permission from Rosenberg M, Patterson R, Mintzer R, et al: Clinical and immunologic criteria for the diagnosis of allergic bronchopulmonary aspergillosis Ann Intern Med *86: 405–414, 1977.*
** Test must be positive for serologic diagnosis in asymptomatic patients.*

Treatment

ABPA may progress through five stages based on clinical, serologic, and radiographic findings, which are summarized in Table 131-4. It is important to note that the first four stages are potentially reversible without long-term sequelae; only the last stage, which is characterized by fibrosis and bronchiectasis, is irreversible. The goals of therapy for ABPA are to treat acute exacerbations of disease and prevent the development of fibrosis and bronchiectasis. Therefore, early diagnosis of ABPA before permanent lung damage occurs is critical. Therapeutic modalities for ABPA include oral corticosteroids, metered-dose inhaler medications, and antifungal agents.

Use of oral corticosteroids remains the cornerstone of treatment of ABPA. These agents suppress the inflammatory response provoked by *Aspergillus* infection rather than eradicate the fungus. Recommended corticosteroid doses for acute exacerbations of ABPA are 0.5 to 1.0 mg/kg of prednisone equivalent daily for 1 to 2 weeks followed by 0.5 mg/kg every other day for 6 to 12 weeks. The physician should then attempt to taper the patient's corticosteroid dosage. However, some patients cannot be successfully weaned of corticosteroids and require a daily maintenance dose of at least 7.5 mg.

Increasing, use of itraconazole, an azole antifungal with activity against *Aspergillus* spp., has been employed as adjunctive fungal antigen-reducing therapy for ABPA, especially in patients with frequent relapses or corticosteroid dependence. A recent randomized controlled study reported that oral administration of itraconazole (200 mg twice daily) was beneficial in terms of significant improvement of symptoms, pulmonary function, chest radiographic findings, and serum IgE levels in asthmatic patients with ABPA; uncontrolled studies suggested a similar benefit in patients with CF and ABPA. However, use of itraconazole requires determination of drug levels to ensure adequate absorption and poses significant issues with long-term tolerability and drug-drug interactions. Voriconazole is a newer triazole that has shown improved fungicidal activity against *Aspergillus* spp. and better bioavailability when compared with itraconazole. However, there are no data available on the role of voriconazole in the treatment of ABPA. In addition, voriconazole is also associated with significant drug-drug interactions.

Use of inhaled corticosteroids may help control the symptoms of asthma but does not prevent episodes of eosinophilic infiltration and mucus impaction and is generally thought to have no influence on progressive lung damage. Inhaled bronchodilators such as β agonists, anticholinergics, and leukotriene antagonists may be used to treat asthma-related symptoms. Inhaled antifungal agents such as nystatin and amphotericin B deoxycholate (AMB-D) may offer temporary suppression of colonization, but their penetration into plugged bronchi is limited, and recolonization rapidly occurs once therapy ends. Meticulous bronchial toilet is important for clearance of *A. fumigatus* from the airway. Also, physical therapy with postural drainage is an important adjunctive

Table 131-4

Staging System for ABPA

Stage	Symptoms	Radiographic Features	Laboratory Features	Management
I. Acute	Fever, productive cough, wheezing	Pulmonary infiltrates, mucoid impaction	Blood eosinophilia, elevated serum IgE level, positive skin test	Corticosteroids to achieve remission
II. Remission	Asymptomatic	Normal	Decrease in IgE and blood eosinophilia	Careful follow-up
III. Exacerbation	All or some of acute-stage symptoms	All or some of acute-stage findings	At least a doubling of IgE in asymptomatic patients and an increase in IgE in symptomatic patients	Retreat with steroids to induce remission
IV. Corticosteroid dependent	Syymptomatic steroid-requiring asthma	Variabble	Usually continued elevation of IgE	Long-term steroids to control asthmatic symptoms and keep IgE levels at baseline
V. Fibrotic	Severe dyspnea, fibrotic lung disease, as well as bronchospasm	Pulmonary fibrosis	Restrictive plus reversible and irreversible obstructive function tests; may have continued increased IgE	Long-term corticosteroid use

Adapted with permission from Mendelson EB, Fisher MR, Mintzer RA, et al: Roentgenographic and clinical staging of allergic bronchopulmonary aspergillosis. Chest *87:334–339, 1985; and Patterson R, Greenberger PA, Radin RD, et al: Allergic bronchopulmonary aspergillosis: Staging as an aid to management.* Ann Intern Med *96:286–291, 1982.*

treatment. Increased hydration, use of expectorants, and in selected patients, bronchial lavage may aid in viscid mucus clearance. Avoidance of environmental reservoirs of *Aspergillus* spp. such as compost heaps, grain silos, and decayed organic matter may help prevent exacerbation of ABPA. In patients with CF ABPA differentiating between a bacterial exacerbation of CF and an ABPA flare is important, because initiation of corticosteroids may have detrimental effects in patients with bacterial infection; a serologic assessment is essential as part of this evaluation.

Immunotherapy with injection of conventional allergens has not been shown to be of value for ABPA. However, newer immunomodulatory approaches, including immune modulation toward a Th1 response by using *A. fumigatus* synthetic peptides, DNA-based vaccines, and immunostimulatory molecules such as cytosine polyguanine oligonucleotides, are being explored in animal models with promising results.

Monitoring of treatment efficacy and toxicity is imperative. Long-term follow-up of patients with ABPA has shown that increasing serum levels of IgE are often a harbinger of a clinical flare of the disease and that the levels decline with a clinical response to corticosteroids. Thus, a prudent course of action is to determine baseline serum IgE levels when ABPA has been controlled by corticosteroid-based therapy and then monitor serum IgE levels regularly (every 1 to 2 months). Total serum IgE levels usually should decrease by at least one-third within 6 weeks from the initiation of corticosteroid-based treatment; infiltrates should be resolved after 1 to 2 months, and the results of pulmonary function tests should improve. Although serum IgE levels seldom return to normal, reinstitution of corticosteroids should be considered even in asymptomatic patients if the serum IgE level is double that of the baseline value. In patients with symptomatic ABPA, chest radiographs should be obtained every 3 months during the first year of follow-up and yearly thereafter; pulmonary function tests also should also be performed yearly. However, no one has identified certain prognostic indicators for progression or regression of ABPA, and whether treatment of asymptomatic flares alters the natural history of the disease remains controversial.

Bronchocentric Granulomatosis

Bronchocentric granulomatosis is a rare hypersensitivity syndrome that is characterized histologically by replacement of

bronchial mucosa with necrotizing granulomatous tissue. Also, eosinophilic infiltration of bronchioles and fibrosis are prominent, whereas there is no evidence of *Aspergillus* invasion. *Aspergillus* hyphae have been demonstrated within the lesions in approximately one-half of the cases of bronchocentric granulomatosis. This syndrome is associated with asthma in one-half of the patients described and likely represents a severe manifestation of ABPA revealed as a localized pathological reaction rather than the more generalized pulmonary pathology evident in patients with ABPA. Patients typically present with chronic symptoms, such as malaise, cough, low-grade fever, dyspnea, dull chest pain, and hemoptysis associated with a focal lesion on chest radiographs, often in an upper lobe. Occasionally, radiographic findings of multiple nodular masses simulate metastatic carcinoma. Diagnosis of bronchocentric granulomatosis is made based on biopsy or often retrospectively after removal of the lesion, which is curative. Some patients may need corticosteroid-based therapy for ABPA, especially those with multifocal lesions.

Extrinsic Allergic Alveolitis

Heavy or repeated exposure to *Aspergillus* conidia and mycelia may result in a hypersensitivity reaction affecting the alveoli in nonatopic individuals known as *extrinsic allergic alveolitis.* Malt workers, distillers, brewers, and others exposed to moldy straw or grain have suffered attacks consisting of cough, dyspnea, fever, chills, myalgia, and malaise 4 to 8 h after exposure to *Aspergillus* antigens. Repeated exposure may lead to malt worker's lung or farmer's lung or to the development of granulomatous disease or interstitial fibrosis. The immunopathogenesis of extrinsic allergic alveolitis involves cell-mediated immunity (type IV response) and immune complex deposition (type III response) and likely involves an intricate interaction between these immune mechanisms.

Radiographic changes in the acute syndrome include diffuse alveolar-interstitial infiltrates that may resolve with removal of the inciting antigen. Patients with chronic extrinsic allergic alveolitis may have a fine reticulonodular interstitial infiltrate that may progress to pulmonary fibrosis with honeycombing. Serum IgG antibodies (precipitins) against *Aspergillus* antigens are present in patients with extrinsic allergic alveolitis; however, the serum IgE level is typically normal. Skin tests usually demonstrate an Arthus reaction at 4 to 8 h and occasionally may be preceded by an immediate wheal and flare reaction and followed by a delayed reaction (36 to 48 h afterward). Removal or avoidance of the source of antigen exposure is crucial in the management of extrinsic allergic alveolitis, as spontaneous recovery often ensues once exposure has ended. Administration of corticosteroids is helpful in aiding the resolution of acute symptoms and reduces the likelihood of structural damage. However, corticosteroids are not helpful once fibrosis has developed.

Aspergilloma

Saprophytic colonization of a parenchymal lung cavity by *Aspergillus* is referred to as *aspergilloma*,*mycetoma*, or a *fungus ball.* A fungus ball consists of both dead and living mycelial elements, fibrin, mucus, amorphous debris, inflammatory cells, and degenerating blood and epithelial elements. The mycelial mass may lie free within the cavity or be attached to the cavity wall by granulation tissue. Spontaneous shrinkage or disappearance of aspergilloma has been reported in 7 to 10 percent of cases and is often associated with bacterial superinfection of the cavity. Aspergillomas only rarely increase in size. Most aspergillomas are caused by *A. fumigatus*, but some, especially in patients with diabetes mellitus, are caused by *A. niger*, in which case oxalic acid crystals may be seen in the sputum.

Pathophysiology

The pathogenesis of aspergilloma usually involves colonization and proliferation of the fungus in a preexisting pulmonary cavity (secondary aspergilloma). The cause of a preexisting cavity is most commonly prior cavitary tuberculosis; aspergilloma has been reported in 11 to 17 percent of patients with post-tuberculosis cavities. However, an aspergilloma may complicate a wide spectrum of cavitating pulmonary diseases, such as sarcoidosis, histoplasmosis, blastomycosis, AIDS pneumonia (especially in cases of atypical *Pneumocystis jiroveci* pneumonia), and/or lung abscess, pulmonary or bronchial cysts, bronchiectasis, pulmonary fibrosis, asbestosis, adenocarcinoma, ankylosing spondylitis, rheumatoid nodules, cyanotic heart disease, and pulmonary infarction.

Primary aspergilloma, which arises within the bronchial tree with proliferation of *Aspergillus* leading to a pulmonary cavity, is far less common. The clinical conditions leading to the initiation of a cavitary process and formation of a fungus ball include IPA, chronic necrotizing pulmonary aspergillosis (CNPA), and ABPA. IPA may lead to primary aspergilloma during bone marrow recovery, as the host is able to mount an inflammatory response and ward off the fungus. Pneumothorax may be a severe complication of pulmonary mycetoma that is reported as a rare occurrence in patients with hematological malignancies. ABPA may cause bronchiectasis in the chronic phase of the disease and result in aspergilloma secondary to growth of a fungus distal to a plugged bronchus. In fact, aspergillomas have been found in 7 percent of patients with ABPA in one study. Thus, aspergilloma may provide a stimulus for the perpetuation of ABPA.

Clinical Features and Diagnosis

Hemoptysis is the typical manifestation of aspergilloma, as it is seen in 50 to 90 percent of patients. Hemoptysis is typically infrequent and mild but is occasionally massive or even fatal. The presence of any other symptoms, including dyspnea, fever, malaise, and weight loss, in patients with aspergilloma should be attributed to the underlying cavitary pulmonary disease or bacterial superinfection or suggest the presence of an overlapping IPA syndrome such as CNPA. The diagnosis is usually made based on clinical and chest radiographic features

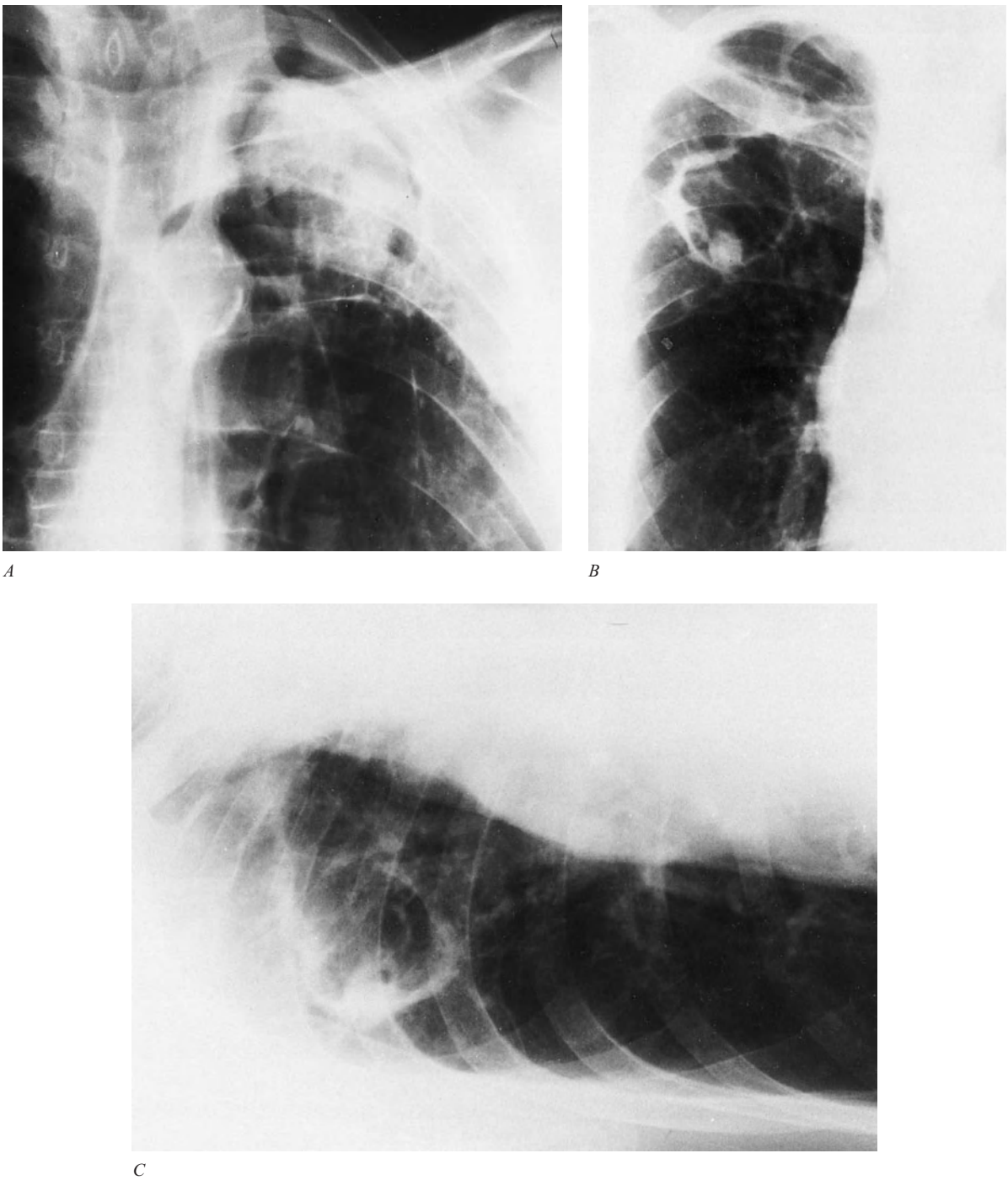


Figure 131-5 Radiographic appearances of pulmonary aspergillomas. *A*. A 51-year-old man with a history of tuberculosis showing the classic crescent-shaped patch of air (Monod's sign) as well as marked pleural thickening. *B*. A 49-year-old man with ankylosing spondylitis in whom an aspergilloma developed inside a thin-walled cavity. *C*. Decubitus film of the patient in (*B*) showing a fungus ball that moved when the patient changed position. *(Courtesy of S. Albelda and G. H. Talbot.)*

coupled with serologic evidence of precipitating antibodies to *Aspergillus* spp.

Chest radiographs reveal a solid round mass within a cavity (3 to 5 cm in diameter) partially surrounded by a radiolucent crescent (Monod's sign; Fig. 131-5). Movement of the fungus ball within the cavity may be appreciated when comparing upright and decubitus images. A solitary lesion in the upper lung fields is the most common radiographic feature of aspergilloma, as preexisting tuberculosis cavities are the most common predisposing condition. However, aspergillomas can be bilateral and multiple. In many cases, chest CT may be helpful in further delineating the radiographic

features of an aspergilloma that are not apparent on chest radiographs. On CT scans, globules of gas are often seen within the interstices of the hyphal mass. CT angiography may also provide useful information for patients with hemoptysis by identifying hypertrophic bronchial arteries that often supply the cystic wall of aspergillomas.

Although sputum cultures are positive for *Aspergillus* in more than one-half of all patients with aspergilloma, it is not a sensitive and specific diagnostic marker. Precipitating antibodies to *Aspergillus* antigens are present in the sera of more than 95 percent of patients with aspergilloma; however, some patients receiving corticosteroids may be seronegative. Eosinophilia, IgE, and skin-test reactivity may be seen in individuals who are allergic to the fungus, but these are not consistent findings. The main challenge for the clinician is to differentiate aspergilloma from other lung conditions, including lung cancer, cavitating Wegener's granulomatosis, a blood clot in a preexisting cavity, a disintegrating hydatid cyst, and a pulmonary abscess, all of which often share radiographic features with aspergilloma. Therefore, a positive precipitin reaction for *Aspergillus* is particularly helpful in establishing the diagnosis of aspergilloma. Clinical judgment and a low threshold for performing a lung biopsy in atypical cases are required.

Predictors of poor prognosis for aspergilloma include a progressive increase in the size and/or number of aspergillomas, severe underlying lung disease with a poor underlying lung reserve, immunosuppressive therapy, AIDS, sarcoidosis, a rising *Aspergillus*-specific IgG titer, and repetitive episodes of severe hemoptysis.

Treatment

There is no consensus on the treatment of aspergilloma because of a lack of controlled studies. Because life-threatening hemoptysis occurs only in a minority of patients, subjecting all patients with aspergilloma to surgical therapy, which is often associated with significant morbidity and mortality, seems to be inappropriate. Management options for aspergilloma currently include systemic or local administration of antifungal agents, surgical resection, and conservative management with careful follow-up without specific medical or surgical intervention. Often, the best course of action for asymptomatic patients with aspergilloma is carefully repeated clinical evaluation with periodic chest radiographs without surgical intervention. Therapeutic considerations must include the individual patient's health status with attention to the potential risks of each treatment.

The definitive treatment of aspergilloma is surgical resection. However, in many patients, surgery is contraindicated because of severe underlying pulmonary dysfunction, whereas the operation per se is associated with significant mortality and serious postoperative complications such as hemorrhage, bronchopleural fistula, bacterial superinfection, and empyema. Therefore, it has been suggested that surgical resection of aspergilloma should be restricted to patients with severe, life-threatening hemoptysis and preserved pulmonary function. Surgical resection should also be considered for patients with poor prognostic features (e.g., chronic immunosuppression, sarcoidosis, and increasing *Aspergillus*-specific IgG titers). Extrapleural resection has been reported to improve outcome. For patients who are unfit for surgical resection, an alternative approach is cavernostomy, which is performed under local anesthesia; however, cavernostomy is also associated with mortality and mediocre results. This procedure should be considered as a last resort.

Intracavitary instillation of an antifungal agent is a promising alternative treatment in patients with severe pulmonary dysfunction who are poor candidates for surgery. CT-guided percutaneous instillation of AMB-D has been shown to be effective for aspergilloma in several cases of massive hemoptysis, with resolution of hemoptysis within 5 d. The response to percutaneous injection of AMB-D is sustained with no recurrences for several months, improvement or even resolution of radiographic abnormalities, and reduction of serum *Aspergillus* antibody titers. Endobronchial instillation of ketoconazole via fiberoptic bronchoscopy has also been successful. Overall, topical therapy with antifungal agents is ideal for patients with a solitary aspergilloma who have severe hemoptysis and contraindications to surgical resection.

Bronchial arterial embolization (BAE) has been extensively used in the management of hemoptysis in patients with aspergilloma. However, this approach has proved to be only temporarily effective, and recurrence of hemoptysis usually occurs because of the presence of collateral vessels in the involved area. Hence, BAE seems to be appropriate only as a "bridge" procedure in patients with massive hemoptysis until surgical resection of the aspergilloma can be performed. Also, radiation therapy has been shown to be effective for aspergilloma, even in patients with massive hemoptysis. This modality has been recommended for cases of recurrence of life-threatening hemoptysis after BAE.

Itraconazole is an orally administered antifungal agent with activity against *A. fumigatus* and high tissue penetration into the lung. The use of itraconazole for aspergilloma has been reported in several noncontrolled studies. Data from these studies showed that the use of itraconazole at doses ranging from 200 to 400 mg/d for 6 to 18 mo resulted in radiographic and symptomatic improvement in almost two-thirds of the patients and may have a place for the treatment of aspergilloma. Serum itraconazole levels were not measured in most of these studies, but a recent study of treatment of pulmonary aspergilloma with itraconazole (100 to 200 mg/d) demonstrated sufficient itraconazole levels within the aspergilloma cavities. The major limitation of itraconazole is that it works slowly; thus, use of it would not be prudent in cases of life-threatening hemoptysis. In addition, recurrence of aspergilloma often follows discontinuation of itraconazole treatment, whereas acquisition of secondary resistance of *A. fumigatus* isolates to itraconazole has been described in patients with aspergilloma following prolonged treatment.

Invasive Bronchial Aspergillosis

The term invasive bronchial aspergillosis (IBA) refers to infection involving the large airways. Further subclassification of IBA based on the bronchoscopic appearance has been proposed, including tracheobronchitis, pseudomembranous tracheobronchitis, and ulcerative tracheobronchitis. In fact, these entities represent a continuous spectrum of this infection.

Aspergillus tracheobronchitis is the least invasive form of IBA and is characterized by the presence of a superficial tracheobronchial inflammation, intact mucosa with no evidence of ulcers, and pseudomembranes or other abnormalities; *Aspergillus* spp. are identified in mucus exudates. In contrast, pseudomembranous tracheobronchitis is characterized by significant necrosis of bronchial epithelium and formation of pseudomembranous plaques, which are white, gray, or black in color. These lesions may progress and result in extensive invasion of the large airways; however, in the majority of patients, the depth of invasion does not extend beyond the bronchial cartilage. Finally, ulcerative tracheobronchitis is the most aggressive form of IBA and manifests with endobronchial plaques, nodules, or areas of ulceration and necrosis; additionally, the infection may extend to the adjacent pulmonary parenchyma and pulmonary vasculature. Late sequelae of ulcerative tracheobronchitis include the formation of excessive granulomatous tissue with resulting bronchial stenosis.

The pseudomembranous form of IBA is typically seen in lung transplant recipients. In fact, IBA is the most common infection within 3 months following lung transplantation, whereas IPA tends to occur much later in this patient population. Occasionally, pseudomembranous tracheobronchitis is found in various clinical settings, including HSCT, hematological malignancies, metastatic renal cell carcinoma, postinfluenza, COPD, AIDS, and even in immunocompetent individuals. Patients may be initially asymptomatic or have symptoms attributed to the underlying illness with negative chest radiographs. However, as the infection progresses, symptoms become more pronounced, including characteristic stridor, resulting in respiratory failure and, ultimately, death.

The ulcerative form of IBA occurs almost exclusively at the site of bronchial anastomosis in lung transplant recipients. Bronchoscopically, the appearance is that of severe tracheobronchitis with multiple ulcers at the site of anastomosis. The symptoms are similar to those of pseudomembranous IBA. Complications include acute IPA, severe bronchial stenosis, anastomotic dehiscence, and bronchial necrosis with bronchoarterial anastomotic fistula. Rarely, ulcerative IBA develops in patients with AIDS or solid tumors. Diagnosis of all forms of IBA requires a high index of suspicion and is established only by bronchoscopic examination.

Bronchial stump aspergillosis is an unusual complication of lung resection. The period from pneumonectomy to the onset of infection usually ranges from 6 to 12 months, although one case was noted after 3 years. Patients may present with a productive cough and hemoptysis, sputum that may be putrid, and occasionally, expectoration of fungal material or suture thread. Chest radiographs are usually unchanged when compared with those taken at baseline. The cause is secondary *Aspergillus* infection of silk suture material used to close the bronchus after pulmonary resection. Local inflammation, compromised tissue viability, and the high capillarity of silk thread favor the establishment of *Aspergillus* infection. Substitution of nylon monofilament for silk sutures at surgery has virtually eliminated this infectious complication.

All of the forms of IBA, including bronchial stump anastomosis, require prompt treatment with systemic antifungals for IA (discussed in detail below). Data from controlled studies of the treatment of IBA are lacking, however. A common although unproven practice is to combine systemic antifungal therapy, such as intravenous AMB-D or voriconazole, with aerosolized AMB-D. Notably, most reported failures occurred during interruption of the treatment. Finally, surgical resection and stent placement may be necessary in conjunction with antifungal therapy if dehiscence of the anastomosis occurs because of tracheobronchial aspergillosis.

CPA

Chronic forms of *Aspergillus* infection of the lung have long been recognized. CPA occurs in patients with chronic cavitary lung disease and is characterized by an indolent clinical course over months to years, constitutional symptoms, serum precipitins to *A. fumigatus*, elevated acute phase markers of inflammation, and an immune status that ranges from normal to mild immunosuppression. Locally invasive (semi-invasive) *Aspergillus* infection may be evident histopathologically. However, both angioinvasion and dissemination are absent. A variety of terms have been used for CPA, including pulmonary aspergillosis with cavitation, complex aspergilloma, chronic granulomatous aspergillosis, semi-invasive pulmonary aspergillosis, and CNPA.

In an attempt to better define CPA, a subclassification of this entity based on clinical and radiographic findings was recently proposed, introducing the terms CNPA, chronic cavitary pulmonary aspergillosis (CCPA), and chronic fibrotic pulmonary aspergillosis (CFPA). CNPA comprises a syndrome of slowly progressive cavitary lung disease, chronic respiratory symptoms, and the presence of precipitating antibodies to *Aspergillus*. Some cases of CNPA have invasion of the lung parenchyma by *Aspergillus* spp. However, in most of the described cases, there is no tissue invasion despite the presence of extensive and progressive tissue damage. CCPA refers to cases in which there is formation and expansion of multiple cavities over time, whereas CFPA refers to cases in which cavity formation is followed by a pronounced fibrotic reaction. In addition, it has been recommended that any case with proven hyphal invasion of tissue should be classified as CNPA.

Defects in mucociliary clearance associated with structural lung disease appear to be a critical factor in the pathogenesis of CPA. Prior mycobacterial lung infection, emphysema, bullae, asthma, sarcoidosis, pneumoconiosis, lung cancer, thoracic surgery, upper lobe fibrosis complicating ankylosing spondylitis, and a history of *Legionella* infection have been described as predisposing conditions for CPA. In addition, subtle but essential defects in innate immunity may play a role in the pathogenesis of CPA. Hence, defects in mannose-binding lectins, alterations in surfactant protein D, certain polymorphisms in transforming growth factor-β, and systemic illnesses associated with a degree of immunosuppression, such as corticosteroid-based therapy, diabetes mellitus, AIDS, and alcohol abuse, have all been associated with CPA. However, the precise pathophysiological mechanism of new cavity formation remains uncertain.

CPA tends to affect middle-aged individuals who are not relatively immunocompetent and more male than female individuals. It has an indolent progressive course that lasts for years. Chronic productive cough and weight loss with mild hemoptysis, dyspnea, and fatigue are the usual presenting symptoms. Pleural fibrosis and *Aspergillus* empyema appear to complicate some cases of CPA.

Although the diagnosis of CPA may be suspected with a single chest radiograph, sequential chest radiographs are typically required to confirm the progressive nature of CPA lesions. CT is particularly useful in defining the precise pattern and extent of the disease. Typical radiographic findings include the presence of one or more cavities, which may or may not contain fungus balls, often located in the upper lobes. New cavity formation and expansion of preexisting cavities are also characteristic of CPA. Pericavitary infiltrates and adjacent pleural thickening are frequently observed and appear to correlate with the overall disease activity. With appropriate treatment, these radiographic abnormalities may regress, leaving residual thin-walled empty cavities.

The combination of characteristic clinical and radiological findings and either the presence of *Aspergillus*-positive precipitins or the isolation of *Aspergillus* spp. from respiratory samples is highly indicative of CPA. Although the demonstration of precipitating antibodies to *Aspergillus* is the cornerstone and a prerequisite for the diagnosis of CPA, these antibodies may be negative, especially in case of infection with non-*fumigatus Aspergillus* spp. Histopathology demonstrates chronic inflammation and fibrosis, sometimes with granulomatous features with or without hyphae. The absence of hyphae does not exclude the diagnosis of CPA because of the paucity of high fungal burden in patients with CPA.

Differentiating CPA from other serious lung conditions that require specific therapy, such as cancer and chronic cavitary mycobacterial and endemic fungal infections, as well as other inflammatory lung conditions is a major challenge. In fact, there is a strong association between CPA and atypical mycobacterial infections. In these cases, imaging is not helpful, so biopsy and comprehensive microbiological studies must be used to exclude the co-existence of CPA with such entities. In addition, CPA differs from simple aspergilloma because of the presence of constitutional symptoms, the development of persistent pericystic lung nodules or pleural thickening, consolidations or ground-glass opacities, and the development and/or progression of cavities. Finally, one should always consider the possibility of a pyogenic infection in a cavity that may require drainage and appropriate antibacterial treatment.

CPA requires prolonged treatment with systemic antifungal agents. In the literature, most patients with CPA have received treatment with oral itraconazole, whereas AMB-D has been successfully used in refractory cases. In a recent series of 18 patients, use of itraconazole resulted in improvement or stabilization of disease in 71 percent of the cases. Use of voriconazole has been associated with favorable responses in anecdotal reports and should be considered as another treatment option. Although the reported response to AMB-D (81 percent) appears to be slightly better than that to itraconazole, administration of it requires long hospitalization periods and is associated with considerable toxicity. Anecdotal reports of improved outcome as a result of adjunctive immunomodulating treatment with interferon-γ have also been reported.

Surgery plays a limited role in the treatment of CPA because of the poor overall lung function in many patients. Major postoperative complications, such as respiratory failure, bronchopleural fistulae, pleural extension of aspergillosis, and even dissemination of *Aspergillus* can occur. Thus, surgery should be reserved for selected patients with reasonable respiratory reserves for whom there are no other treatment options. For example, surgery may be appropriate for patients with severe hemoptysis if embolization fails.

Although systemic antifungal therapy for CPA seems to be beneficial, assessment of response to it is difficult to gauge because the activity of the disease may fluctuate over time. Weight gain and improved energy levels are the earliest and most reliable indicators of response. Inflammatory markers also improve albeit more slowly, and they usually remain elevated even during long-term therapy. Relapse months or years after discontinuation of treatment is frequently reported.

IPA

Epidemiology

Aspergillus has emerged as one of the most common causes of infectious death in severely immunocompromised patients, with mortality rates approaching 70 to 90 percent in patients with leukemia and recipients of HSCTs. Recent surveillance studies demonstrated a three- to fourfold increase in the frequency of *Aspergillus* infections at major cancer centers over the past two decades. In fact, IA has actually surpassed invasive candidiasis as the most common fungal infection found upon autopsy at several institutions, and approximately 15 to 20 percent of patients with leukemia die of fungal pneumonia caused by *Aspergillus* spp. Similarly, in allogeneic HSCT recipients, 15 to 30 percent of deaths are caused by refractory

fungal infections, mainly caused by *Aspergillus* spp., and most of these infections occur late in the postengraftment period in the setting of graft-versus-host disease (GVHD).

The reasons for the dramatic increase in *Aspergillus* infections are not completely understood, but they probably reflect improvements in the prevention or pre-emptive treatment of bacterial infections and other opportunistic pathogens, especially *Candida* and cytomegalovirus (CMV), broadening of the spectrum and intensity of immunosuppressive agents with profound and prolonged effects on T-cell function (e.g., purine nucleoside analogues, anti–T-cell immunoglobulin, monoclonal antibodies), and the growing number of allogeneic HSCT recipients who are at increased risk for GVHD.

In particular, changes in HSCT practices over the past decade have greatly impacted the epidemiology of IA. Autologous HSCT is associated with a low risk of IA because of shortened periods of pre-engraftment neutropenia and a lack of GVHD. On the other hand, IA has a bimodal distribution in allogeneic HSCTs, with patients at risk before and after bone marrow engraftment. The increasing use of peripheral blood stem cells, growth factors, and nonmyeloablative conditioning regimens (minitransplants) in allogeneic HSCT has shortened the duration of pre-engraftment neutropenia (0 to 30 days after engraftment) and the incidence of IA. In contrast, late (40 to 80 days after engraftment) and very late (80+ days after engraftment) IA has increased. This trend is associated with increased use of matched unrelated-donor allogeneic transplants and with interrelated risk factors, such as lymphopenia, chronic GVHD, corticosteroid-based therapy, and/or CMV infection. In fact, among HSCT recipients, IA now predominantly occurs in nonneutropenic patients late after engraftment, in whom GVHD and its management with increasingly intense immunosuppression have emerged as major risk factors.

In addition to the "classic" groups of patients at risk for IA, such as those with prolonged, profound neutropenia because of a hematological malignancy (5 to 25 percent risk) or aplastic anemia; recipients of allogeneic HSCTs (5 to 30 percent risk), or lung transplants (17 to 26 percent risk); those with AIDS, severe combined immunodeficiency, or CGD (25 to 40 percent lifetime risk); burn patients; and patients receiving chronic corticosteroids, IA has been increasingly described in new groups of patients. Hence, patients with systemic lupus erythematosus, patients with multiple myeloma who receive high-dose steroids, and premature neonates are prone to the development of severe IA. Furthermore, several cases of IA have been reported lately in patients with Crohn's disease or rheumatoid arthritis who received treatment with antitumor necrosis factor inhibitors (e.g., infliximab). Even the use of high-potency inhaled steroids may predispose some apparently normal hosts to IPA in rare instances.

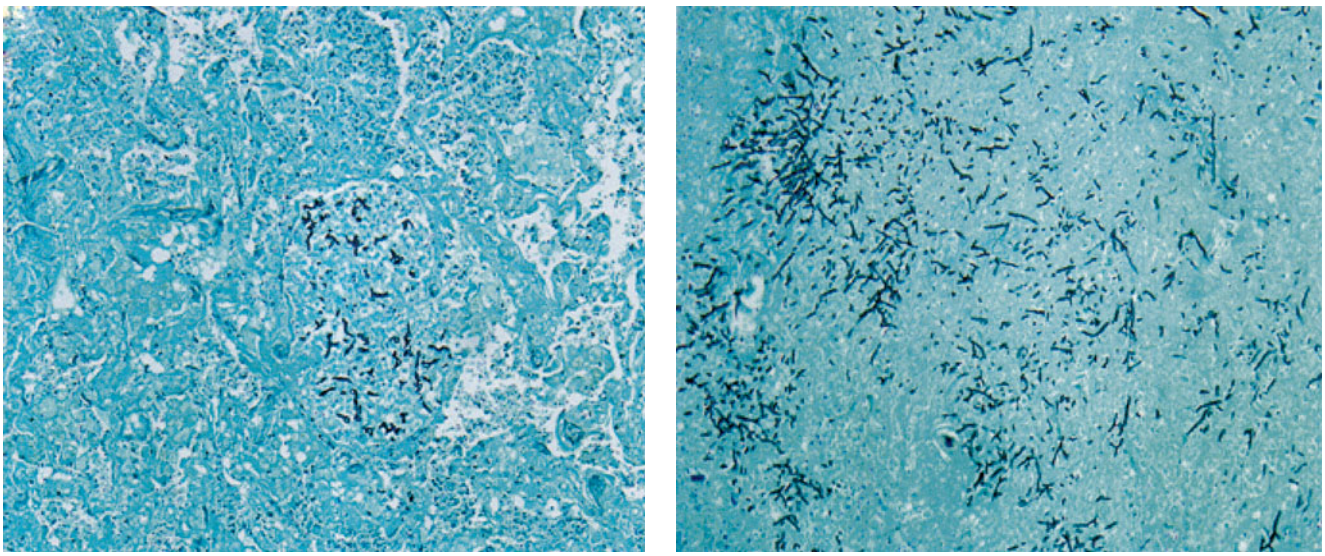
An alarming trend in the epidemiology of IA is the increasing frequency of infections caused by those less susceptible to antifungal such as *Aspergillus* spp. other than *Aspergillus fumigatus*, such as *A. terreus and A. flavus*. This phenomenon may be at least partially a reflection of antifungal selection pressure determined by extensive empirical and prophylactic use of antifungal agents in high-risk patients. Alternatively, because non*fumigatus* aspergilli cause nosocomial infections more frequently than *A. fumigatus* does, an epidemiological niche for these species may also account for their predominance in some institutions. These data are worrisome given that these species are inherently resistant to AMB.

A substantial number of nosocomial clusters of IA have been reported over the past three decades. There have been a large number of clusters associated with hospital construction and defects in air-handling equipment. Air and environmental surfaces have been the focus of most investigations. Recently, water has been implicated as an additional source of nosocomial transmission of *Aspergillus* spp., although this has not been confirmed in other studies.

Pathogenetic Mechanisms

Because *Aspergillus* is a saprophytic mold that colonizes in the respiratory tract of immunocompromised patients, the pathogenesis of infection depends on the host's underlying immunosuppression. In the immunocompromised host, IPA typically occurs following inhalation of *Aspergillus* conidia, although hematogenous dissemination from a cutaneous or gastrointestinal source is seen occasionally. Damage to respiratory epithelium because of radiation therapy, chemotherapy, GVHD, or infection may facilitate attachment of *Aspergillus* conidia to the respiratory epithelial surface. In the normal host, germinating conidia that escape phagocytosis by macrophages and hyphal forms are destroyed by recruited polymorphonuclear neutrophils (PMNs) and monocytes. However, these successive lines of cellular defense are most commonly impaired by corticosteroids (pulmonary macrophages) and cytotoxic chemotherapy (neutropenia), placing the host at risk for invasive infection by *Aspergillus* spp.

Once *Aspergillus* has invaded the respiratory tract, control of the infection is highly dependent on successful selection and clonal expansion of Th lymphocytes to direct professional effector cells with activity against *Aspergillus* hyphae. Lymphopenia and local/global dysregulation of the host adaptive Th1/Th2 polarization has been shown to play a key role in the subacute progression of IA in cases in which neutropenia is not an underlying risk factor. Hence, in the late postengraftment period, allogeneic HSCT recipients have a low interferon-γ/IL-10 ratio, which is suggestive of a Th2 response that potentially accounts for their susceptibility to IA. In comparison, healthy individuals mount a predominantly Th1-type cellular response to *Aspergillus* infection. In humans, iatrogenic suppression of protective Th1 responses is common, particularly in the setting of chronic GVHD (an excessive Th1 response of allograft T lymphocytes) treated with high-dose corticosteroids and/or other immunosuppressive regimens. Importantly, *Aspergillus*-mediated suppression of host Th1 responses by production of gliotoxin is also plausible. Similarly, recent preclinical data indicate that herpes virus reactivation and bacterial co-infection in the lungs



A *B*

Figure 131-6 The characteristic pattern of *Aspergillus* invasion in tissue obtained from (*A*) an HSCT recipient with IPA and severe GVHD, and (*B*) a patient with acute leukemia and severe neutropenia in whom IPA developed. Extensive inflammation, less *Aspergillus* burden and absence of angioinvasion was observed in the patient with GVHD. In comparison, the histopathology of IPA in the patient with severe neutropenia was characteristic for scant infiltration by phagocytic cells, extensive coagulative tissue necrosis caused by angioinvasion, and a high fungal burden. Gomori's methenamine silver stain, ×100. *(Courtesy of M. Luna.)*

induce profound dysregulation of immune responses, facilitating the development of IPA. For example, CMV infection can result in dysfunction of dendritic cells and phagocytes, which may predispose patients to IA.

Once germination of conidia occurs, *Aspergillus* hyphae rapidly invade pulmonary arterioles and lung parenchyma, leading to ischemic necrosis. Hematogenous dissemination with thrombosis, hemorrhagic infarction, and invasion of distant organs may result from invasion of arterioles by *Aspergillus* hyphae and is found in approximately one-third of patients with IPA at autopsy. Thus, IA can present with a clinical picture similar to that of other thrombotic and embolic diseases, such as pulmonary embolism, cerebral vascular accidents, Budd-Chiari syndrome, and renal papillary necrosis. In addition, IA can spread to contiguous structures, across the diaphragm to the stomach, or from the lung to the heart or superior vena cava.

Importantly, it has been recently demonstrated that IPA has different pathophysiological mechanisms depending on the type of immunosuppression. Thus, a low *Aspergillus* tissue burden, extensive inflammatory injury, absence of angioinvasion, and localized infection have been observed in corticosteroid-immunosuppressed mice, whereas minimal inflammation, extensive angioinvasive *Aspergillus* growth, and disseminated infection are characteristic of IPA in cyclophosphamide-treated neutropenic mice. In corticosteroid-treated mice, host immune effector cells appear to have limited activity against *Aspergillus* hyphae but cause extensive alveolar damage and exudative bronchiolitis, which appears to be more important than the *Aspergillus*-induced injury itself. This non-angioinvasive form of IPA has been increasingly recognized in a wide range of non-neutropenic hosts, including those who received corticosteroids, recipients of solid organ transplants and allogeneic HSCTs with GVHD, patients with AIDS, and patients with CGD (Fig. 131-6). Similar to the animal models of IPA, histopathology in those nonneutropenic patients is characterized by extensive pyogranulomatous inflammatory reactions, inflammatory necrosis, and extensive cavitation.

Clinical Features

Symptoms of IPA begin with fever (unless the patient is receiving corticosteroids), which may be followed by a mild nonproductive cough suggestive of bronchitis. Pleuritic chest pain and progression to pneumonia occur within 1 to 2 days. Cavitation tends to occur in patients if immunosuppression is decreased, such as in leukemic patients during recovery of bone marrow function or when steroid-based therapy is reduced significantly, and on occasion gives rise to massive hemoptysis (Figs. 131-7 and 131-8). Pleuritic pain and slight hemoptysis may suggest pulmonary infarction. Patients also may expectorate necrotic tissue filled with hyphae. Cough, sputum production, and pleural effusion are either absent or minimal. IA must be strongly considered when dealing with susceptible patients in whom treatment with broad-spectrum antibiotics fails.

Extrapulmonary sites may be involved, including the highly vascular organs such as the kidneys, liver, spleen, and central nervous system. Invasive disease of the nose and paranasal sinuses occurs in immunocompromised patients, and contiguous invasive spread into the orbit or into the

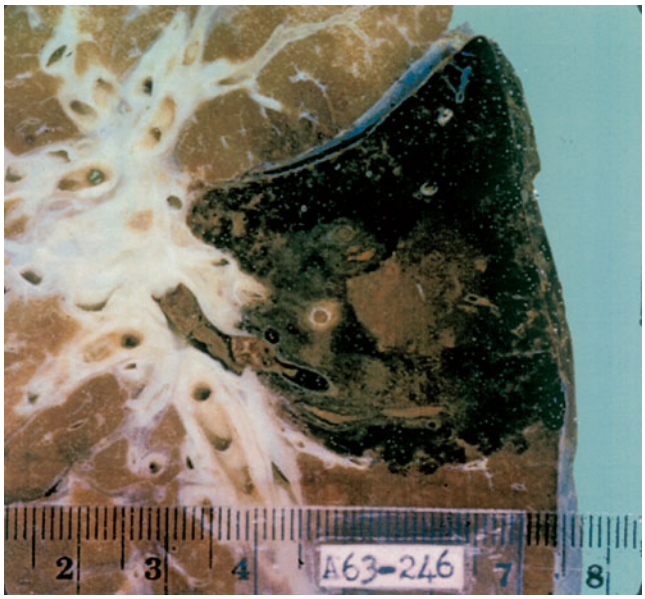


Figure 131-7 A 62-year-old man with acute leukemia in whom IPA developed. The gross appearance of the fungal lesion shows a central necrotic area surrounded by a lining of hemorrhagic infarction. *(Courtesy of G. P. Bodey.)*

cranial vault can result in a syndrome similar to rhinocerebral mucormycosis.

Diagnosis

Substantial delay in establishing an early diagnosis remains a major impediment to the successful treatment of IPA. Chest radiographs are not sensitive in detecting early forms of bronchopulmonary IPA, and up to 10 percent of patients with proven IPA have "normal" chest radiographs within a week of death. High-resolution CT scans of the chest may reveal small wedge-shaped subpleural lesions or nodules typically surrounded by intermediate attenuation. This halo sign correlates with hemorrhage and edema surrounding an infarct caused by thrombosis and is highly suggestive of acute IPA, especially in neutropenic patients with leukemia. However, the halo sign has been documented in 33 to 60 percent of patients and is transient. In fact, to be useful for the diagnosis of IA, CT must be performed within 5 days of the onset of infection, because more than 75 percent of initial halo signs disappear within a week. With neutrophil recovery, these lesions coalesce and cavitate, forming the "air crescent" sign, a classic sign of late filamentous invasive infection. However, the air crescent sign does not appear until the third week of the infection, and its appearance may be too delayed to be helpful in the diagnosis of IA. Importantly, even with effective antifungal therapy, lesions frequently increase in size until neutrophil recovery.

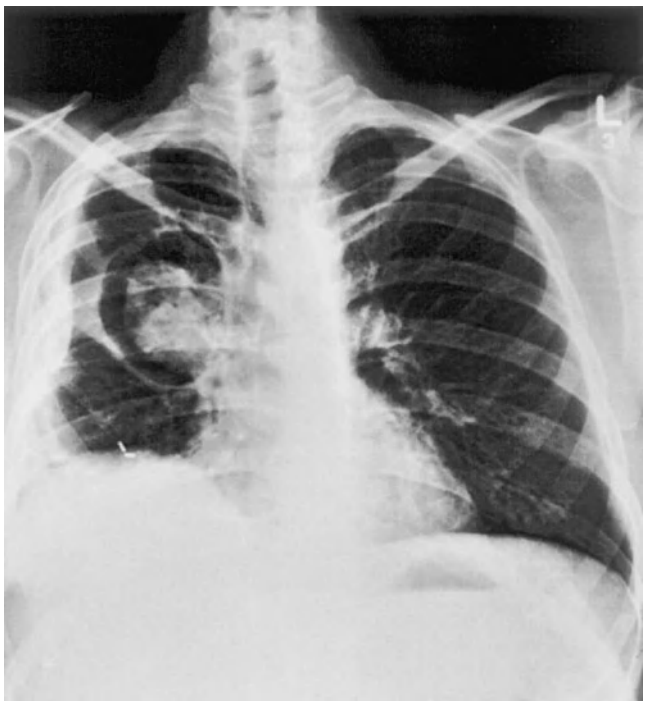


Figure 131-8 The characteristic radiographic features of IPA following neutrophil recovery illustrated in a patient with acute leukemia. A lesion has cavitated, creating the air crescent sign. *(Courtesy of G. P. Bodey.)*

Persistently febrile neutropenic patients with leukemia would benefit from the use of early high-resolution chest CT to identify early signs of IPA. In a recent study of febrile neutropenic patients, early and routine CT scanning coupled with early intensive antifungal-based treatment and surgery resulted in increased survival rates when compared with therapy initiated at the first sign of a pulmonary fungal infection. CT also plays a critical role in determining the feasibility of various diagnostic procedures (bronchoalveolar lavage [BAL], percutaneous needle biopsy, and open lung biopsy) in patients with IPA.

Respiratory cultures of *Aspergillus* from expectorated sputum, bronchial washings, or BAL specimens have low sensitivity (less than 30 percent) for diagnosing IA but a high positive predictive value (greater than 60 percent) in heavily immunocompromised patients. Blood cultures have little diagnostic value for IA but may reflect true disease cases of *A. terreus* infection. Ultimately, open lung biopsy may be required for a definitive diagnosis of IPA and may not be feasible until late in the course of infection or recovery of pancytopenia.

In recent years, efforts have been directed toward identifying nonculture-based markers for rapid, reliable diagnosis of IA. Those based on the detection of anti–*Aspergillus* antibodies have very poor sensitivity for IA, especially in patients receiving immunosuppressive agents. Instead, tests based on identifying circulating fungal antigens or metabolites are promising. To date, the two approaches that have demonstrated the greatest promise in early clinical studies are detection of antigens and measurement of *Aspergillus* nucleic acids by using PCR.

Galactomannan is a polysaccharide cell wall component of *Aspergillus* spp. that is released into the circulation during fungal growth in tissues and can be detected in the serum of patients with IA. A sandwich enzyme-linked immunosorbent assay (ELISA) capable of detecting galactomannan at concentrations as low as 0.5 ng/ml has been

developed recently. Studies evaluating the role of galactomannan assay in the diagnosis of IA have been predominantly conducted with profoundly neutropenic patients undergoing chemotherapy for cancer or recipients of HSCTs. These studies have documented sensitivity rates ranging from 67 to 100 percent and specificity rates ranging from 86 to 99 percent in these patients. When serially monitored, the galactomannan assay preceded the diagnosis of IA by an average of 6 to 14 days. However, in a recent study that evaluated the value of the galactomannan assay in the detection of early IA, the appearance of major lesions (halo sign, air crescent sign, and cavitation) on high-resolution CT scans almost coincided or even preceded the detection of the galactomannan antigen in serum. Furthermore, uncertainties remain regarding the performance of this assay in other settings, such as breakthrough IA to mold-active antifungal prophylaxis, pediatric populations, and solid organ transplant recipients. Other factors, such as the pretest probability of infection, the patient's immune status (neutropenia versus GVHD), antifungal therapy, antibacterials, and diet may affect both the performance and interpretation of the galactomannan assay. Hence, sensitivity rates as low as 30 percent have been reported in non-neutropenic HSCT recipients receiving mold-active antifungal prophylaxis and lung transplant recipients. In addition, false-positive results have been described in patients receiving β-lactam antibiotics, particularly piperacillin-tazobactam, as well as in those ingesting certain cereals, pastas, nutritional supplements, and soy sauce produced with fermentation products of *Aspergillus oryzae*, a fungus commonly used in food production. Finally, although the detection of galactomannan in other fluids, particularly BAL, appears to be highly sensitive, specificity might be an issue.

A colorimetric assay for the detection of 1,3-β-D-glucan, an integral cell-wall component in a number of pathogenic yeasts and filamentous fungi, recently became commercially available. The sensitivity and specificity rates for this test in limited studies thus far have ranged from 67 to 100 percent and from 84 to 100 percent, respectively. False-positive test results have been reported in patients with cirrhosis, those undergoing hemodialysis, receiving chemotherapy with particular agents, and patients following abdominal surgery. Furthermore, the 1,3-β-D-glucan assay has been reported to be less sensitive and reproducible and become positive later in the course of IA when compared with galactomannan antigen assay.

PCR detection of *Aspergillus* nucleic acids is a promising method for early detection of IA. The sensitivity of PCR is excellent, but its specificity for invasive infections can be problematic, and false-positive results are common. Multiple unresolved issues accompany the use of PCR for diagnosis of IA, including the sample type (serum, BAL fluid), amplification strategy (nested versus conventional PCR), protocol (real-time quantitative versus conventional PCR), and primer selection (*Aspergillus*-specific or pan-mold, pan-fungal primers). There have been no good studies examining how PCR performs in comparison with galactomannan detection for the early diagnosis of IA. However, it has been shown that PCR is inferior to serum galactomannan assay in animal models and in some but not all human studies. Like galactomannan antigen testing, PCR is likely to become an adjunct diagnostic method with standard microbiological, histological, and radiographic methods of diagnosing IA.

Treatment of IPA

Although the arsenal of agents with anti-*Aspergillus* activity has expanded over the past decade, the mortality rate in patients with IPA remains unacceptably high. Several strategies have been applied in an attempt to improve the outcome of IA. These include the use of investigational antifungals, increasing the dose intensity of antifungals, use of new delivery systems to improve the therapeutic index of currently available antifungals, combination antifungal therapy, surgical excision of sequestered large necrotic lesions, and use of immunomodulating agents. There has not been a systemic evaluation of the merit of each of these strategies in the treatment of refractory IA, however. This is not surprising in view of the complexity of IA and the paucity of organized, prospective controlled clinical studies of this opportunistic mycosis. Furthermore, difficulties with the early diagnosis of IA and methodological problems related to a lack of uniform criteria for treatment response complicate the evaluation of these strategies.

The principles of management of IPA are listed in Tables 131-5 and 131-6. Until recently, AMB-D was the only drug available for the treatment of aspergillosis, and no prospective evaluations of this drug had been attempted. A major obstacle to evaluating the merit of antifungal therapy for IPA was the difficulty in establishing the diagnosis; hence, most patients received empirical treatment. The recent introduction of uniform diagnostic criteria for proven, probable, and possible IA by the European Organization for Research and Treatment of Cancer (EORTC)/Mycoses Study Group (MSG) consortium has been a major advance. These criteria are practical, validated, standardized, and reproducible and consist of host-risk, microbiological, clinical/radiological, PCR, and/or galactomannan antigen criteria. However, the clinical applicability of the EORTC/MSG criteria was questioned in a recent study in which more than 60 percent of autopsy-proven cases of IA in patients with hematological malignancies were not identified antemortem according to the EORTC/MSG criteria.

Recently, the broad-spectrum triazole voriconazole was introduced for therapy for aspergillosis. It is available in both intravenous and oral preparations and is much better tolerated than AMB-D. In a large prospective randomized trial comparing voriconazole with AMB-D in patients with definite or probable aspergillosis, the response rate was 53 and 32 percent, respectively, and the survival rate at 12 weeks was 71 and 58 percent, respectively. Improved response was seen irrespective of the underlying condition, site of infection, and presence or absence of neutropenia. Patients in whom initial therapy failed received other medications; this occurred more

Table 131-5

Therapeutic Options for Invasive Fungal Infections

Regimen	Advantages	Disadvantages
AMB-D	Broad-spectrum activity, lack of frequent resistance, fungicidal activity, lower cost	Acute chronic toxic effects, minimally effective in patients with neutropenia and with chronic disseminated candidiasis, intravenous preparations only
Lipid formulations of AMB	Broad-spectrum activity, reduced nephrotoxicity, increased doses can be administered	Only prospective randomized trial, showed no advantage in efficacyy over AMB-D despite higher doses, more expensive, intravenous preparations only
Fluconazole	Oral and intravenous preparation, as effective as AMB in randomized trials of non-neutropenic individuals, minimal toxicity, more effective for chronic disseminated candidiasis, little experience in neutropenic patients but appears to be as effective as AMB	Variable activity against *C. glabrata* and *Candida dubliniensis*, inactive against *C. krusei*, some drug-drug interactions, inactive against molds
Itraconazole	Broad spectrum of activity, lower cost, oral and intravenous preparations	Drug-drug interactions and poor absorption (capsules) are common causes of clinical resistance, marked interpatient variability in serum levels
Voriconazole	Oral and intravenous preparations; broad-spectrum activity, including fluconazole-resistant species (e.g., *C. kursei)*; fungicidal against *Aspergillus*	Drug-drug interactions, more expensive than fluconazole, inactive against *Zygomycetes*, cross-resistance with fluconazole?
Echinocandins (caspofungin, micafungin)	Fungicidal activity against most *Candida* spp., minimal toxicity, lack of cross-resistace with azoles, as active as AMB and fluconazole in randomized trials	No oral preparation, poor central nervous system penetration, narrow spectrum of activity *(Candida, Aspergillus)*, limited experience in neutropenic patients
Flucytosine	Synergistic with AMB and fluconazole, combination of flucytosine and AMB may be superior to AMB alone for chronic disseminated candidiasis and *C. tropicalis* infection	No preparation, causes myelosuppression, often requires monitoring of serum concentrations, emergence of resistance if used alone

frequently among the AMB-D population primarily because of the drug's toxicity. The improved survival observed in this comparative study makes voriconazole the preferred drug for first-line therapy for IA. However, in view of the extensive and prolonged use of voriconazole, either prophylactically, empirically, or therapeutically for IA, it is unclear whether resistance would occur, thereby devitalizing this drug.

Use of lipid formulations of AMB is an attractive alternative to AMB-D because of reduced nephrotoxicity. Because many patients with aspergillosis have to undergo prolonged therapy, nephrotoxicity is a very frequent side effect of AMB-D that requires dosage modification. Many physicians believe that responses are more likely to occur with maximum tolerated doses and recommend initiating therapy with daily doses of AMB-D of 1.25 to 1.50 mg/kg, which inevitably lead to nephrotoxic effects. The standard daily dose of lipid formulations of AMB-D is 5 mg/kg, although the most appropriate dose has yet to be determined. Uncontrolled studies have shown efficacy rates for lipid formulations of AMB ranging from 40 to 60 percent in patients with aspergillosis whose

Table 131-6

Drug Dosages for Serious Invasive Fungal Infections of the Lung

Drug	Loading Dose	Daily Dose	Route
AMB-D	—	1.0–1.5 mg/kg	IV only
Lipid AMB	—	3–5 mg/kg	IV only
Fluconazole	800 mg	400–800 mg	IV, PO
IV itraconazole	200 mg bid × 2 d	200 mg	IV
Itraconazole sol	200 mg bid × 2 d	200 mg	PO
Itraconazole caps	200 mg bid × 3 d	200 mg bid	PO
IV voriconazole	6mg/kg q 12 h	4 g/kg q 12 h	IV
Voriconazole tab	—	200 mg q 12 h (($\geq$40/kg) 100 mg q 12 h ($<$40/kg)	PO
Caspofungin	70 mg	50–70 mg	IV

bid = twice a day; caps = capsule; p = day; h = hours; IV = intravenous; PO = oral; q = every; sol = solution; tab = tablet; tid = three times a day.

disease was refractory to AMB-D or could not tolerate it. Although no comparative trials between the lipid formulations of AMB have been conducted thus far, they appear to be equally efficacious, although both their toxic effects and costs differ. Whether the efficacy of AMB in the treatment of IA is improved by these formulations remains debatable. Moreover, the substantially higher acquisition costs of the lipid formulations of AMB has forced many hospitals to restrict first-line use of these agents to patients who are at highest risk for clinically significant nephrotoxic effects. An even more controversial issue is whether there are clinically meaningful differences between the various lipid formulations of AMB. Most of the available data have been derived from indirect comparisons and suggest that all lipid formulations of AMB, when given at the standard dosage of 5 mg/kg, appear to have comparable efficacy. However, the lipid formulations of AMB clearly differ with respect to the rate and extent of drug delivery to the respiratory tract. Specifically, use of lipid complex AMB results in substantially higher concentrations of the drug in lung tissue when compared with liposomal AMB and thus might theoretically achieve more rapid and complete *Aspergillus* killing. Liposomal AMB, which is the most expensive agent, also seems to be the least toxic, even though some of the toxic reactions that occur with the other formulations may be insignificant or preventable. Hence, the overall cost-effectiveness of these formulations remains undefined.

Itraconazole was the first azole introduced for the treatment of aspergillosis. All of the reported studies with this drug have been open trials. In a review of 269 cases reported in the literature, the complete and partial response rate was 63 percent, but it varied from 39 to 80 percent in the different series. Partial responses generally referred to cases in which the infections were controlled but residual lesions persisted. The role of neutrophil recovery in the response of neutropenic patients is unclear in these presentations. Initially, only an oral capsule preparation was available, and it was not consistently well absorbed from the gastrointestinal tract. Recently, an intravenous preparation and a well-absorbed oral solution of itraconazole have become available. Unfortunately, the oral solution is not well tolerated by some patients. A small multicentered trial of the intravenous preparation demonstrated that adequate serum concentrations of itraconazole were achieved, the drug was well tolerated, and about one-half of the patients had a response.

Caspofungin is one of a new class of antifungal agents (echinocandins) that inhibit the synthesis of 1,3-β-D-glucan an essential component of the cell wall of many fungi. It is available only in an intravenous preparation. In a noncomparative trial of 90 patients with definite or probable aspergillosis in whom other therapies had failed, a complete or partial response occurred in 45 percent of the patients. Responses were observed in 50 percent of the patients with pulmonary infection but in only 26 percent of patients with neutropenia. Finally, terbinafine, a squalene epoxidase inhibitor, has been shown to be efficacious against *Aspergillus* spp., and its use in combination with azoles has been shown to result in synergy in vitro.

Combination Treatment

The lack of an effective treatment modality for aspergillosis has made the concept of combination therapy theoretically appealing. To date, no clinical studies have convincingly determined whether antifungal combinations are more beneficial than monotherapy for aspergillosis. For instance, the sequence of administration of itraconazole in combination with AMB has produced a spectrum of responses ranging from synergy to antagonism. With the recent introduction of echinocandins, which have a different mechanism of action than other antifungals, determining whether use of new combinations (e.g., azoles plus echinocandins, AMB plus echinocandins, terbinafine plus azoles, AMB plus azoles, and echinocandins) given either concomitantly or sequentially would result in additive or synergistic effects is important. Recently, separate retrospective studies suggested that a combination of caspofungin and a lipid formulation of AMB may be more effective as primary therapy than the single agents alone. However, when this combination is used in salvage therapy for IA, less benefit is seen. A retrospective analysis of 47 AMB-refractory IA cases in HSCT recipients showed that salvage therapy with the combination of voriconazole and caspofungin was associated with better survival rates compared with voriconazole alone. Performance of well-conducted randomized clinical trials comparing voriconazole, the preferred drug for the treatment of IA, with a combination of voriconazole and an echinocandin (either as a primary or salvage therapeutic strategy) is an important direction in this complex area.

Surgery

The role of adjunctive surgery in the management of IPA also has not been demonstrated conclusively. Pulmonary infarcts and tissue sequestration are common causes of antifungal therapy failure and fatal hemorrhage in patients with IPA. Resection of infected pulmonary tissue is beneficial for some patients. Residual cavitary lesions, especially when containing fungus balls, after successful antifungal therapy may cause late exsanguinating hemorrhage or reactivation of infection during subsequent myelosuppressive chemotherapy. Removal of these lesions, if surgically feasible, should be considered and may provide survival benefit. Surgical intervention may be a life-saving procedure for patients with IPA who experience acute pulmonary hemorrhage, when preformed early in the disease process. It is less evident whether early removal of well-circumscribed lesions close to pulmonary arteries is beneficial. Likewise, the value of late debulking of a pulmonary mass if the patient has multiple fungal lesions that cannot be completely resected is uncertain. Recent uncontrolled data suggest that resection of the lobe most adversely affected by IA is beneficial in treating pulmonary lesions that worsen despite the use of intense antifungal therapy.

Immune Augmentation Treatment

Because host immunodeficiency is the critical determinant of the outcome of IA, a large number of studies, mostly preclinical ones, over the past two decades have focused on measures designed to augment cellular immune defenses against invasive mold infections. The available preclinical data suggest that quantitative and qualitative deficiencies in host cellular immune responses can be corrected with adjunctive cytokine therapy, such as the use of myeloid growth factors (e.g., granulocyte colony-stimulating factor [G-CSF], granulocyte-macrophage colony-stimulating factor [GM-CSF]), interferon-γ, or a combination of these cytokines plus infusion of host effector cells [e.g., interferon-γ plus granulocyte transfusions]). Granulocyte transfusion therapy has become more feasible since the introduction of G-CSF/corticosteroid mobilization into the donor leukocyte collection process. Currently, there are no data from randomized clinical trials examining the efficacy of granulocyte transfusions for IA or other serious infections during neutropenia. Future studies in this area will likely examine the use of vaccinations and/or cellular transfer with or without adjunctive cytokines to boost adaptive Th1 immunity in immunosuppressed hosts. Clearly, this is a challenging area of investigation. Carefully designed clinical trials will be required to verify promising results in animal models and other preclinical observations.

Prophylaxis in High-Risk Patients

Specialized air-handling systems such as high-efficiency particulate air (HEPA) filtration with or without laminar airflow ventilation have proved to be effective at excluding *Aspergillus* spores. However, HEPA filters have not been shown to prevent *Aspergillus* infections during building renovation and may not prevent outbreaks of these infections related to building demolition or renovation. More recently, hospital water systems have been implicated as potential sources of high-level spore bursts of pathogenic fungi. During bathroom activities such as showering and toilet flushing, patients may create aerosolized mists of fungal spores that increase the risk of IA. In addition, researchers recently reported an association between molds (*Aspergillus* and *Fusarium* spp.) cultured on hospital sinks and water sources and invasive mold infections in patients with leukemia. As a result, some have recommended cleaning of patient showers and bathroom areas with a phenolic cleaning solution prior to use by severely immunocompromised patients. Although these preliminary data are intriguing, establishing a causal link between nosocomial exposure to *Aspergillus* spores and subsequent development of IA remains difficult and requires the demonstration of genetic relatedness of environmental *Aspergillus* strains and clinical isolates. In fact, one of the largest molecular epidemiological studies of IA suggested that any *Aspergillus* strain could be pathogenic in the appropriate host background and that isolates causing invasive disease are not necessarily nosocomially derived.

Fluconazole is inactive against *Aspergillus* spp. In addition, prophylactic trials of itraconazole have had controversial results. These differences may relate to the poor oral bioavailability of itraconazole. A recent meta-analysis suggested that intravenous and oral solutions but not oral capsules

of itraconazole were effective in preventing yeast and mold infections in neutropenic patients. Intravenous AMB-D is not appropriate for prophylaxis because of its nephrotoxicity. Also, low doses of liposomal AMB have failed to demonstrate any prophylactic efficacy in HSCT recipients. Inhalation of AMB-D is poorly tolerated (causing cough, bronchospasm, and nausea), and the overall benefit of it is not obvious; however, aerosolized lipid complex AMB is tolerated much better and results in higher tissue concentrations when compared with aerosolized AMB-D.

The new oral, extended-spectrum triazoles such as voriconazole and posaconazole have a satisfactory pharmacokinetic profile and documented efficacy in the treatment of infections, which may make them suitable for prophylaxis in HSCT recipients and neutropenic patients. Recently, antifungal prophylaxis with the echinocandin micafungin in HSCT recipients was shown to reduce the incidence of IA; however, the fact that echinocandins are parenteral drugs limits their ability for use as extended antifungal prophylaxis during the postengraftment period, when IA is most likely to occur.

Secondary Prophylaxis

Patients with a history of IA are at high risk of reactivation of the infection if they undergo further intensive chemotherapy or HSCT. Patients receiving prophylaxis have fewer relapses than those who do not. To date, no optimal drug or dose can be recommended for secondary prophylaxis in the absence of comparative clinical trials; voriconazole, itraconazole, and lipid formulations of AMB seem to be the most appropriate agents.

PULMONARY CANDIDIASIS

Candida, a commensal fungus of mucosal surfaces, is the predominant fungal pathogen in humans. The spectrum of *Candida*-induced illnesses is broad, ranging from mild, chronic mucocutaneous infections to life-threatening acute invasive infections involving potentially any organ. Pulmonary candidiasis is an infrequent form of invasive *Candida* infection that occurs in cases of aspiration pneumonia in immunocompromised patients who have heavy colonization of *Candida* spp. in the oral cavity (primary *Candida* pneumonia) or as part of disseminated candidiasis.

Candida pneumonia is a challenging infection because of a lack of established, reliable clinical criteria for making the diagnosis. Hence, *Candida* is frequently an asymptomatic colonizer, particularly among debilitated individuals who are receiving antibacterials. Thus, cultures of sputum and/or BAL that are positive for *Candida* in a patient with a pulmonary infiltrate do not establish the diagnosis of *Candida* pneumonia. A recent autopsy study of patients with cancer demonstrated that whereas many patients with pneumonia had *Candida* spp. cultured from sputum and BAL specimens, the specificity (57 to 60 percent) and positive predictive value (29 to 42 percent) of cultures of both types of specimens were low. Similarly, quantitative cultures of transbronchial lung biopsy samples in critically ill, mechanically ventilated patients have been of no predictive value for *Candida* pneumonia. Therefore, only histopathological demonstration of yeast cells or pseudohyphae in lung tissue is confirmatory of *Candida* pneumonia, which is often impossible in many patients.

Epidemiology

The true incidence of *Candida* pneumonia is unknown, and most of the data on this infection are extrapolated from autopsy series. The fact that only 55 patients with unequivocal evidence of primary *Candida* pneumonia had been reported in the literature up to 1993 emphasizes the rarity of this infection. Two of the larger autopsy surveys in patients with cancer reported a prevalence of primary *Candida* pneumonia ranging from 0.2 to 0.4 percent. In another autopsy study that included a general population of patients, primary *Candida* pneumonia comprised 17 percent of all *Candida* infections, with an overall prevalence of 0.3 percent. On the other hand, primary *Candida* pneumonia has been a relatively frequent finding in autopsy studies of high-risk patients, such as premature neonates (1 percent) and critically ill, mechanically ventilated patients (8 percent).

In contrast with primary *Candida* pneumonia, secondary lung involvement by *Candida* spp. is a common finding at autopsy, occurring in 42 to 81 percent of cases of disseminated candidiasis. However, the clinical significance of *Candida* pneumonia identified at autopsy, especially in cases of hematogenous dissemination, has been questioned. For example, a recent study demonstrated that almost one-half of such *Candida* infections were incidental autopsy findings without clinical significance.

Although large surveillance studies to capture the prevalence of *Candida* pneumonia are lacking, *Candida* was the third most common fungal pathogen after *Aspergillus* and *Cryptococcus* in a series of 140 patients with biopsy-proven invasive fungal pneumonia. Interestingly, an increasing number of patients with primary *Candida* pneumonia were reported during the last years of the study. However, whether these latter cases represented a true increase in the incidence of *Candida* pneumonia or simply reflected a bias because of improved diagnosis is not certain.

Mycology

Similar to the other forms of invasive candidiasis, *Candida albicans* is the predominant species in patients with primary *Candida* pneumonia, accounting for 40 to 70 percent of all reported cases. Until the early 1990s, *Candida tropicalis* and *Candida parapsilosis* were the most common non-*albicans Candida* spp. in patients with primary *Candida* pneumonia. However, the widespread use of broad-spectrum azole antifungals over the past decade has led to the emergence of less susceptible, non-*albicans Candida* spp., such as *Candida glabrata* and *Candida krusei*, as important causes of

Candida pneumonia. Hence, *C. glabrata* is currently considered the second most common *Candida* spp. in cases of primary *Candida* pneumonia in immunocompromised individuals. In cases of secondary *Candida* pneumonia caused by hematogenous dissemination, the distribution of the species appears to follow that in bloodstream candidiasis, with *C. albicans* being the predominant species followed by *C. glabrata*, *C. tropicalis*, *C. krusei*, and *C. parapsilosis*.

Pathogenesis

Most of the data on the pathogenesis of *Candida* pneumonia have been gained from analysis of histopathological findings at autopsy and studies of animal models of aspiration-induced pneumonia. *Candida* pneumonia develops only rarely in normal hosts, and most of the reported cases of this infection occurred in heavily colonized immunocompromised individuals. A constellation of factors suggests that primary *Candida* pneumonia has a distinct pathophysiology when compared with other forms of invasive candidiasis and develops under a particular clinical scenario. Specifically, the very high percentage of intrabronchial and intra-alveolar fungal involvement without significant vascular invasion, the frequent finding of aspirated material at autopsy, and the concomitant presence of candidal esophagitis at autopsy in most of the patients with primary *Candida* pneumonia demonstrate that the mechanism of entry of *Candida* is aspiration of oropharyngeal contents. In addition, several studies indicated that the typical risk factors for invasive candidiasis, such as chemotherapy-induced neutropenia, prolonged corticosteroid use, immunosuppressive agent use, prior antibiotic use, hyperalimentation, diabetes mellitus, and the presence of vascular devices were not significantly associated with the development of *Candida* pneumonia. In contrast, alteration of mental status (with or without subsequent aspiration) was the most important contributing factor in the majority of these patients. Thus, individuals prone to aspiration who experience heavy colonization of *Candida* spp., such as those with head and neck cancer receiving chemoradiation, premature neonates, and critically ill, mechanically ventilated patients, comprise the population at highest risk for primary *Candida* pneumonia.

However, a distinct type of overwhelming secondary *Candida* pneumonia caused by hematogenous dissemination has been described occasionally in profoundly neutropenic patients with cancer. The histopathological characteristics of *Candida* lesions mandate pulmonary seeding from systemic bloodstream infections. Specifically, autopsy examination of these patients found evidence of pneumonia with scant inflammation and pools of *Candida* yeast cells and pseudohyphae present in large portions of the involved lung sections in a pattern that closely resembled *Candida* growth in culture medium. Furthermore, in contrast with primary *Candida* pneumonia, destruction of lung parenchyma is subtle, whereas hemorrhage and angioinvasion by pseudohyphae are prominent. Although speculating that typical risk factors for disseminated candidiasis may apply in cases of secondary *Candida* pneumonia is reasonable, the majority of cases of clinically significant infection have been described in profoundly neutropenic patients with leukemia.

Innate immunity is the dominant protective mechanism against all forms of invasive candidiasis, including primary *Candida* pneumonia. Notably, studies in murine models of aspiration-induced *Candida* pneumonia revealed that immunocompetent animals were remarkably resistant to intrathecal inoculation of *Candida*, whereas they succumbed to infection after intravenous injection of a much lower inoculum. These studies revealed that resident pulmonary macrophages largely account for resistance against *Candida* infection, with a remarkable ability to engulf and kill yeast cells. In addition, neutrophils are recruited to the lung within a few hours after initial challenge and have a predominant role in clearing *Candida* infection from the lungs within hours after inoculation. Neutropenic mice are highly susceptible to *Candida* pneumonia. In contrast, although use of corticosteroids somewhat delays the clearance of *Candida* cells by phagocytic cells, it does not significantly increase the susceptibility of mice to infection. On the other hand, genetically engineered mice deficient in myeloperoxidase and/or other components of respiratory burst are extremely susceptible to *Candida* pneumonia, indicating the importance of mechanisms of oxidative killing of phagocytic cells. Although the role of humoral immunity has not been explored extensively, production of IgA and IgG1 has been shown to be important for protection against *Candid*a pneumonia in mice. In contrast with cases of disseminated candidiasis, in which a Th1 cellular response appears to be critical for outcome, a combination of Th1 and Th2 anti-*Candida* responses associated with synthesis of IL-4 and IL-5 is required for optimal immunity in cases of *Candida* pneumonia. Intriguingly, in patients with CF, colonization of respiratory epithelia with *Pseudomonas* species appears to play a protective role against the development of *Candida* pneumonia through production of toxins with potent anti-*Candida* activity.

Clinical Manifestations

The clinical manifestations of primary *Candida* pneumonia are nonspecific and mainly include persistent fever and tachypnea. Chest pain, cough, and sputum production occur occasionally. Also, physical examination and routine laboratory studies are nonspecific. Chest radiographs may demonstrate a local or diffuse infiltrate involving one or both lungs, which is most often associated with infection acquired by the endobronchial route. A miliary-nodular pattern is most often associated with hematogenous seeding of the lung in cases of disseminated candidiasis and often appears late in the clinical course of the disease (Fig. 131-9).

Extrapulmonary manifestations such as skin lesions, myositis, and endophthalmitis may be the first signs of *Candida* fungemia. Multiple organ involvement prior to or concurrent with pulmonary findings, particularly kidney and myocardial failure, may indicate hematogenous seeding that warrants investigation.

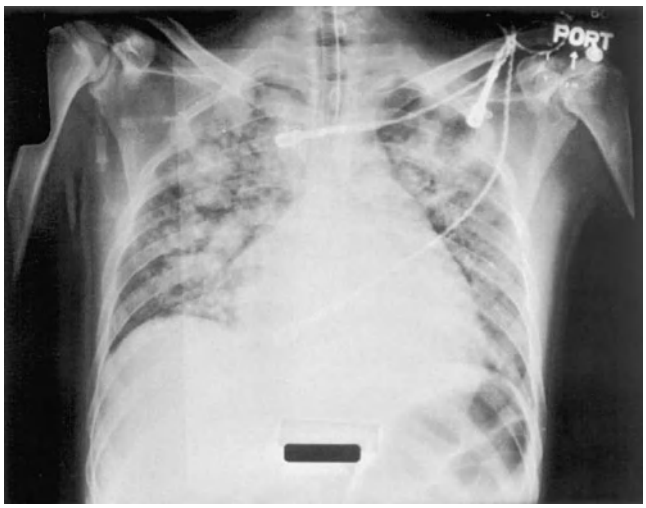


Figure 131-9 The radiographic features of *Candida* pneumonia in a patient with acute leukemia and severe neutropenia in whom disseminated candidiasis developed. Diffuse bilateral infiltrates along with the characteristic macronodular lesions are shown. *(Courtesy of G. P. Bodey.)*

Lung transplant recipients are prone to early (within 2 weeks after transplantation) and fulminant *Candida* pneumonia. This association is probably caused by occult aspiration of *Candida* colonizing the donor lung followed by invasive pulmonary *Candida* infection after transplantation, when immunosuppression is most intense.

Asthma related to an IgE-mediated allergy to *C. albicans* or allergic bronchopulmonary candidiasis develops occasionally. Allergic bronchopulmonary candidiasis should be considered in patients with ABPA with serologic and skin tests negative for *Aspergillus.* In addition, cases of chronic eosinophilic pneumonia with peripheral eosinophilia and selective sensitization to *C. albicans* occur rarely in the absence of asthma. Early diagnosis and corticosteroid-based therapy may prevent late fibrosis in those patients.

Diagnosis

Diagnosis of pulmonary candidiasis is challenging and depends on evidence of tissue invasion. Isolation of yeast from sputum does not prove invasive yeast infection of the respiratory tract because of contamination by commensals from the oropharynx. *Candida* is present in the oropharynx of approximately 20 to 40 percent of all patients, especially those with chronic lung disease and those receiving chronic antibacterial treatment.

Bronchial washings and BAL specimens provide a more representative picture of the respiratory pathology compared with sputum. However, they can still be contaminated with mouth flora. At least in a selected group of patients with acute leukemia and severe neutropenia, if other organisms are absent and abundant *Candida* yeast cells and pseudohyphae are detected in the cytologic examination of BAL specimens, clinical suspicion of *Candida* pneumonia should be high. On the other hand, cultures from lung specimens negative for *Candida* spp. have a high negative predictive value and virtually exclude *Candida* pneumonia.

Histopathological demonstration of tissue invasion by *Candida* spp. in open lung biopsy or fine-needle aspiration is definitive, although such biopsies are difficult to perform in pancytopenic patients with pneumonia. Transbronchial biopsy revealing tissue invasion by *Candida* spp. is also diagnostic.

Isolation of *Candida* from the blood may be helpful in diagnosis of disseminated candidiasis; however, the organism may not be isolated even from multiple blood culture specimens in up to 40 percent of patients with widespread infection demonstrated at autopsy. The use of lysis centrifugation, the BacT-Alert system that monitors CO_2 production, and the high-volume BACTEC system with infrared detection has improved the yield of *Candida*-positive blood cultures. A variety of methodologies have been developed to detect circulating *Candida* antigens and metabolites, including PCR, but none of them have been entirely satisfactory for routine adaptation to the clinical microbiology laboratory.

In cases of disseminated candidiasis, characteristic eye lesions suggestive of *Candida* infection may develop; hence, a careful ophthalmological examination should be performed when this infection is suspected. In addition, typical skin lesions, generalized or localized to the extremities, have been described in up to 10 percent of patients with hematogenous candidiasis. Some of these patients also have associated myositis, particularly in cases of *C. tropicalis* infection. *Candida* spp. can be identified in the dermis and cultured from about one-half of all biopsy samples. Finally, CT scans of the abdomen may suggest invasive hepatosplenic candidiasis in compromised hosts with an unrevealing microbiological evaluation.

Treatment

An unknown number of patients with primary *Candida* pneumonia may have had a response to empirical antifungal therapy but have gone unrecognized because of the difficulty in establishing the diagnosis of this infection. Primary *Candida* pneumonia is considered a life-threatening infection, with mortality rates approaching 70 percent in severely immunocompromised patients. Therefore, rapid clinical diagnosis and prompt initiation of systemic antifungal therapy are important upon suspicion of the infection in the appropriate setting.

Given the rarity of primary *Candida* pneumonia, there are no controlled studies of the treatment of it. Most patients with primary *Candida* pneumonia have received AMB-D (0.7 to 1.0 mg/kg per day) for a minimum of 2 weeks after all signs and symptoms of infection disappeared and until bone marrow recovery in those with neutropenia. In cases of secondary *Candida* pneumonia associated with hematogenously disseminated infection, therapy directed at disseminated candidiasis rather than at *Candida* pneumonia is indicated. However, over the past decade, several new antifungal agents, including fluconazole and the newer triazoles, lipid

formulations of AMB, and the echinocandins, have become available for treatment of invasive candidiasis, showing comparable efficacy and significantly less toxicity when compared with AMB-D in several prospective randomized trials. Nevertheless, most of the new antifungal agents have been studied in non-neutropenic patients with candidemia, and uncertainty remains as to how these drugs apply in immunocompromised neutropenic patients with *Candida* pneumonia.

With all of the limitations of the aforementioned studies, and given the fact that fluconazole has been used extensively for prophylaxis in many institutions, initiation of therapy for *Candida* pneumonia with AMB-D plus fluconazole with subsequent discontinuation of AMB-D use may be a reasonable approach in such cases. Also, using higher doses of fluconazole (800 mg/day), at least initially, may be appropriate in neutropenic patients.

Voriconazole has been recently found to be equally effective and significantly less toxic when compared with AMB-D and exhibits significant activity against fluconazole-resistant non-*albicans Candida* spp. However, there are concerns about cross-resistance with fluconazole, particularly against *C. glabrata* species.

Although lipid formulations of AMB are less nephrotoxic, there is no convincing evidence that they are more effective than AMB-D. Because most patients with candidiasis do not require prolonged therapy, use of these more expensive preparations is usually not justified.

The breakthrough in the treatment of invasive candidiasis has been the introduction of the echinocandins. Caspofungin, the first discovered agent in this class, has shown broad-spectrum fungicidal activity against *Candida* spp., including azole-resistant non–*albicans Candida* spp. In fact, because of its potency and minimal toxicity, caspofungin is displacing AMB-D as the drug of choice for candidemia in seriously ill and unstable patients. Recent studies demonstrated that the activity of caspofungin is superior to that of AMB-D and fluconazole in cases of candidemia. The accumulating experience with the treatment of other invasive pulmonary mycoses with caspofungin holds promise for the use of this agent in the treatment of *Candida* pneumonia.

PULMONARY ZYGOMYCOSIS (MUCORMYCOSIS)

Zygomycosis, or mucormycosis, is a life-threatening angioinvasive infection caused by fungi of the class *Zygomycetes*, order *Mucorales*. Fungi in the other order of Zygomycetes class, the *Entomophthorales*, rarely cause chronic subcutaneous infections, which predominantly afflict immunocompetent hosts in subtropical countries. *Zygomycetes* species have emerged as important opportunistic pathogens over the past decade, particularly in patients with hematological malignancies and recipients of HSCTs. Unlike *Aspergillus* and other opportunistic fungi, *Zygomycetes* spp. tend to cause infections in a wide range of hosts with qualitative and/or quantitative defects in phagocytic cells and occasionally in immunocompetent individuals.

Fungi of the order *Mucorales* are distributed into six families, all of which can cause serious invasive infections (Table 131-7). Species of the family *Mucoraceae* are isolated more frequently from patients with zygomycosis than are species of any other family. Among the *Mucoraceae*, *Rhizopus oryzae (Rhizopus arrhizus)* causes the vast majority (greater than 70 percent) of *Zygomycetes* infections. Other less frequently encountered species of the *Mucoraceae* family include

Table 131-7

Classification of Fungi in the Class *Zygomycetes*, Order *Mucorales**

1. *Mucoraceae*
   - a. *Absidia*
     - i. *A. corymbifera*†
   - b. *Apophysomyces*
     - i. *A. elegans*†
   - c. *Mucor*†
     - i. *M. circinelloides*
     - ii. *M. hiemalis*
     - iii. *M. racemosus*
     - iv. *M. ramosissimus*
     - v. *M. rouxianus*
   - d. *Rhizomucor*
     - i. *R. pusillus*†
   - e. *Rhizopus*
     - i. *R. arrhizus*†
     - ii. *R. azygosporus*
     - iii. *R. microsporus var. rhizopodiformis*†
     - iv. *R. microsporus var. oliogosporus*
     - v. *R. microsporus var. microsporus*
     - vi. *R. schipperae*
     - vii. *R. stolinfer*
2. *Cunninghamellaceae*
   - a. *Cunninghamella*
     - i. *C. bertholletiae*†
3. *Mortierellaceae*
   - a. *Mortierella*
     - i. *M. wolfii*
4. *Saksenaeaceae*
   - a. *Saksenaea*
     - i. *S. vasiformis*
5. *Syncephalastraceae*
   - a. *Syncephalastrum*
     - i. *S. racemosum*
6. *Thamnidaceae*
   - a. *Cokeromyces*
     - i. *C. recurvatus*

* *Based on the classification outlined by Ribes et al.*
† *These species are the more common etiological agents associated with zygomycosis in humans.*

Rhizopus microsporus, *Absidia corymbifera*, *Apophysomyces elegans*, *Mucor* spp., and *Rhizomucor pusillus*. *Cunninghamella berthollethiae* is an increasingly reported cause of zygomycosis and appears to be the most virulent *Zygomycetes* species in humans. All of these organisms are indistinguishable by histopathology. Various terms have been used in the past to indicate infections caused by *Zygomycetes*, such as mucormycosis, phycomycosis, and simply mucor. However, the more accurate term zygomycosis is used throughout this chapter to indicate opportunistic mold infections in humans caused by *Zygomycetes*, because this is the taxonomically correct description.

Epidemiology/Risk Factors

The *Zygomycetes* are saprophytic fungi ubiquitous in soil and decaying organic material. *Mucorales* species that are pathogenic in humans grow rapidly on any carbohydrate substrate and produce abundant sporangiospores. Spores produced by the fungi become airborne, and inhalation of *Zygomycetes* conidia into the respiratory tract occurs daily. Even though these fungi grow in many ecological niches, the rarity of zygomycosis reflects the low virulence potential of *Zygomycetes* in immunocompetent hosts.

The overall estimated incidence of zygomycosis is 1.7 cases per 1 million people annually. However, over the past decade, zygomycosis has emerged as the second most common opportunistic mycosis after IA in severely immunocompromised patients; this increase in the incidence of zygomycosis has been largely attributed to changes in HSCT practices, leading to increasing rates of chronic GVHD requiring steroid therapy and the broad use of relatively narrower spectrum, mold-active antifungals, including voriconazole and caspofungin, as prophylaxis or preemptive therapy in this patient population. In autopsy series, the prevalence of zygomycosis has ranged from 2 to 8 percent in patients with leukemia and recipients of allogeneic HSCT. For reasons that remain unclear, the incidence of *Zygomycetes* infections, particularly of *Cunninghamella, Absidia,* and *Apophysomyces* spp., is higher in male (65 percent) than female patients. A seasonal variation in *Zygomycetes* infections was implied in some studies, with the majority of infections occurring from August to November.

Zygomycetes cause acute angioinvasive infections in patients with a variety of immunosuppressive conditions, including poorly controlled diabetes mellitus (especially with diabetic ketoacidosis), neutropenia, malignancies, burns, chronic renal failure, and iron overload; recipients of transplants; and patients receiving chronic immunosuppressive therapies or deferoxamine-based therapy.

Disease Manifestations

The most common manifestation of zygomycosis is sinusitis, including rhinocerebral infection (39 percent), pneumonia (24 percent), disseminated infection (23 percent), soft tissue infection (19 percent), and gastrointestinal infection (7 percent). Of note, the different forms of zygomycosis tend to occur in patients with specific host immune defects. For example, patients with diabetic ketoacidosis are prone to the development of the rhinocerebral form of zygomycosis, but much more rarely suffer from pulmonary or disseminated infection. In contrast, patients with hematological malignancies and/or recipients of allogeneic HSCTs more commonly have pulmonary zygomycosis. The predominance of pulmonary infection in patients with malignancies may be a result of chemotherapy-related defects in innate pulmonary host defenses associated with neutropenia and/or chemotherapy-induced mucociliary dysfunction. Profound neutropenia, prolonged treatment with high doses of corticosteroids, GVHD, diabetes mellitus, malnutrition, and CMV reactivation are the main risk factors for zygomycosis in these patients. Administration of antithymocyte globulin or tumor necrosis factor inhibitors for the treatment of acute GVHD may pose additional risk for zygomycosis. Importantly, antifungal prophylaxis with agents that have anti–*Aspergillus* activity, such as voriconazole and caspofungin, was recently independently associated with the development of zygomycosis in severely immunocompromised patients.

Patients with renal failure receiving the iron (and aluminum)–chelating agent deferoxamine have an increased risk of pulmonary and disseminated zygomycosis. Although rare, there have been a number of reports of pulmonary zygomycosis in patients with AIDS. It is important to emphasize that dissemination may occur from one of the primary sites of *Zygomycetes* infection, mainly in patients with profound immunosuppression. In addition, nosocomial transmission of zygomycosis has been reported as a result of the use of iatrogenic interventions such as intravenous catheters, bandages, and even tongue depressors.

Mycology

Zygomycetes are molds characterized by growth of hyphae in the environment and in tissue. They grow rapidly—within 2 to 5 days on most culture media—as fluffy gray or brownish colonies, with many of the species demonstrating aggressive vertical growth toward the lid of the Petri dish; these species are referred to as "lid lifters." As the *Zygomycetes* colony matures, the mycelium may darken and exhibit a black pepperlike effect as large numbers of sporangia are formed. Cycloheximide inhibits the growth of these fungi, and media that contain this compound, such as Mycosel and mycobiotic agar, should not be used. All pathologic species grow well at 37°C.

Microscopic examination for the presence and location of rhizoids and apophyses and to determine the morphology of the columellae differentiates the genera. Isolating and speciating the organism is important for selection of treatment. However, morphological identification of *Zygomycetes* species is often imprecise.

Pathogenesis

Host factors influence each particular zygomycosis syndrome. The pathogenesis of pulmonary zygomycosis begins with

the inhalation of spores into the respiratory tract; however, hematogenous or lymphatic spread from other sites to the lungs occasionally occurs. Infection may remain localized in the lung or disseminate hematogenously.

Both mononuclear and polymorphonuclear phagocytes of the normal host kill *Zygomycetes* spores by generating oxidative metabolites and the cationic peptides defensins. Polymorphonuclear phagocytes are the major immune effector cells responsible for inhibiting hyphal growth of *Zygomycetes*, and neutropenic patients as well as patients with qualitative defects in immune effector cell function are at increased risk of zygomycosis. In addition, both hyperglycemia and acidosis are known to impair chemotaxis and the killing activity of phagocytic cells against *Zygomycetes* by impairing oxidative and nonoxidative mechanisms. Likewise, corticosteroid-based treatment impairs the ability of macrophages to prevent germination of the spores in vitro and in vivo. However, the exact mechanisms by which ketoacidosis, diabetes, and steroids impair the function of phagocytes remain unknown. Also, little is known about the interaction of *Zygomycetes* spp. with specific receptors of phagocytic and/or endothelial cells (e.g., TLR receptors).

Besides immunocompromised individuals, patients with iron overload states, including those undergoing chelation therapy with deferoxamine are uniquely at increased risk for zygomycosis. Deferoxamine abolishes the fungistatic effect of serum and increases in vitro fungal growth by acting as a siderophore for *Zygomycetes* spp. Similarly, there is evidence suggesting that the increased susceptibility to zygomycosis of patients with acidosis, including diabetic acidosis, is likely caused by increased availability of serum iron.

A hallmark of zygomycosis is extensive angioinvasion with resultant vessel thrombosis and tissue necrosis (Fig. 131-10). Interaction of *Zygomycetes* spores with endothelial cells appears to play a critical role in angioinvasion. Importantly, researchers recently showed that heat-killed germinating *Zygomycetes* spores are still able to induce endothelial cell damage in vitro and to kill mice in vivo; the molecular mechanisms of these interactions have not been elucidated yet.

Clinical Manifestations

The clinical manifestations of pulmonary zygomycosis are similar to those of IPA. In fact, these two entities are almost indistinguishable clinically. Timely diagnosis of pulmonary zygomycosis is challenging because symptoms are subtle and nonspecific even at the late stages of infection. Patients with pulmonary zygomycosis present with fever refractory to broad-spectrum antibiotics, cough that is typically nonproductive, severe or subtle pleuritic chest pain, and rapidly progressive dyspnea. Also, pleural friction may be heard upon auscultation. Angioinvasion results in necrosis of tissue parenchyma, which may ultimately lead to cavitation and/or hemoptysis. Fatal hemoptysis as a result of fungal invasion of a major blood vessel has been reported occasionally.

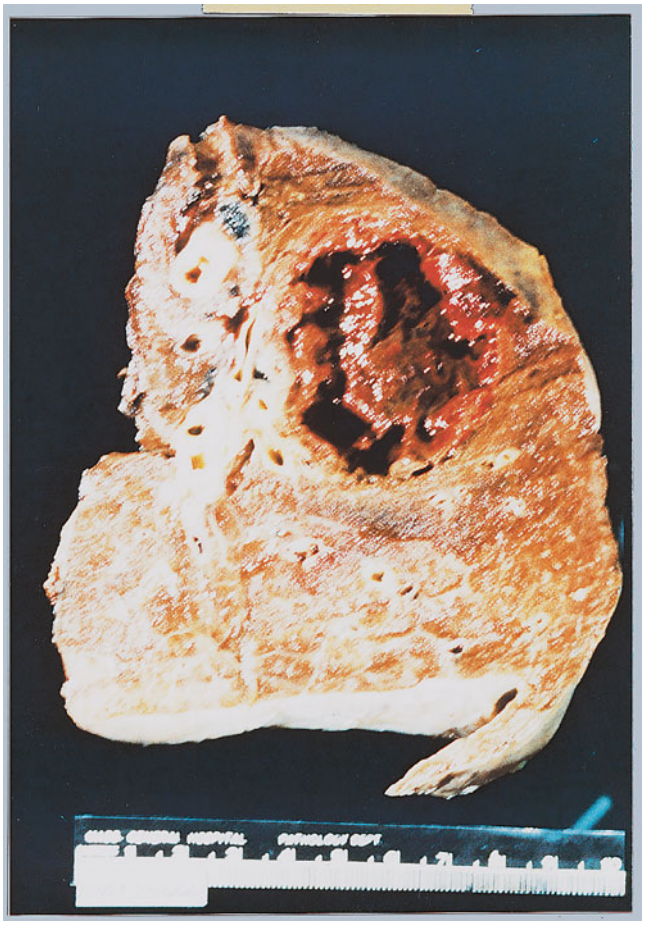


Figure 131-10 Pulmonary mucormycosis in a 63-year-old diabetic kidney transplant recipient with a rapidly expanding pulmonary mass. *(Courtesy of Jay A. Fishman, Massachusetts General Hospital.)*

In patients with a hematological malignancy, clues essential to distinguishing pulmonary zygomycosis from IPA are the presence of concomitant sinusitis and a history of antifungal prophylaxis with *Aspergillus*-active agents such as voriconazole and echinocandins.

A multitude of patterns may be present in a regular chest radiograph for a patient with pulmonary zygomycosis, including in descending order of frequency: lobar consolidation or nonspecific infiltrates, cavities, masses, and nodules. Wedge-shaped infarcts of the lung may also be seen, particularly following thrombosis of the pulmonary vessels caused by fungal angioinvasion. Previous studies found that pulmonary lesions in patients with zygomycosis have a predilection for the upper pulmonary lobes in 55 to 84 percent of all reported cases.

As with IPA, high-resolution chest CT is the best method of determining the extent of pulmonary zygomycosis and may demonstrate evidence of infection before it is seen on chest radiographs. The halo and air-crescent signs are encountered in zygomycosis at the same low frequency as in IPA. Importantly, the presence of the air-crescent sign has been

associated with an increased risk of massive hemoptysis. We recently found that the presence of multiple nodules and, to a lesser degree, pleural effusions on CT scans favors a diagnosis of pulmonary zygomycosis over pulmonary aspergillosis in high-risk patients with cancer.

Hematogenous dissemination to the contralateral lung and other organs occurs frequently when pulmonary zygomycosis is not treated promptly. Patients with untreated pulmonary zygomycosis usually die from of disseminated disease before respiratory failure occurs. The notable exception is the rare patient with massive hemoptysis. The overall mortality rate for pulmonary zygomycosis ranges from 50 to 70 percent but is greater than 95 percent when it is part of a disseminated infection.

Some atypical presentations of pulmonary zygomycosis include chronic infection with constitutional symptoms that last for several months in relatively immunocompetent hosts, multiple mycotic pulmonary artery aneurysms and pseudoaneurysms, bronchial obstruction, asymptomatic solitary nodules, or even normal chest radiographs. Of interest, patients with diabetes mellitus have an apparent predilection for the development of endobronchial lesions, accounting for more than 80 percent of reported cases in the literature. Furthermore, pulmonary zygomycosis tends to present with a less fulminant, subacute (greater than 4 weeks) clinical course in these patients. However, endobronchial lesions occasionally lead to obstruction of major airways or erosion of major pulmonary blood vessels and fatal hemoptysis.

Similar to *Aspergillus* spp., *Zygomycetes* spp. rarely produces an asymptomatic mycetoma within a preexisting lung cavity. Allergic *Rhizomucor* sinusitis has been also reported in immunocompetent individuals. In addition, hypersensitivity pneumonitis caused by *Rhizopus* has been described in farm workers as well as in Scandinavian sawmill workers (so-called wood trimmer's disease).

Diagnosis

Little improvement has been made over the past few decades in the diagnosis of zygomycosis, which relies on conventional culture methods. Timely diagnosis of zygomycosis requires a high index of suspicion and largely depends on histopathological demonstration of tissue invasion by the characteristic hyphae or by isolation of *Zygomycetes* spp. in cultures of sterile tissue.

To provide histopathological evidence of invasive zygomycosis, bronchoscopy with transbronchial biopsy, percutaneous needle biopsy of the lung, or open lung biopsy must be employed. Touch slides prepared from the biopsy specimen with potassium hydroxide may reveal fungal hyphae. Hematoxylin and eosin (H&E)–stained tissue sections will show the typical hyphae in infected tissue. These fungi stain poorly with the periodic acid-Schiff (PAS) and gram stains but stain very well with the Grocott-Gomori methenamine-silver and calcofluor white stains. The use of lectin-binding stains on histological preparations has been reported for the confirmation of the diagnosis of zygomycosis, but these stains are not widely available.

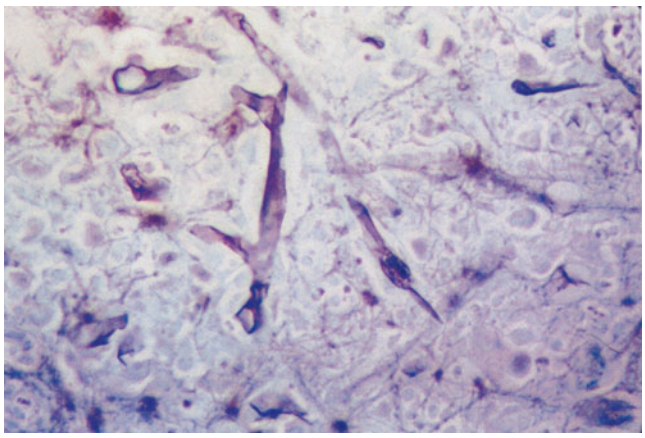


Figure 131-11 Histopathological features of *Zygomycetes* hyphae in a profoundly neutropenic patient with leukemia in whom pulmonary zygomycosis developed. Of note are the characteristic broad nonseptate or rarely septate hyphae with branches at right angles. H&E stain, ×400. *(Courtesy of G. P. Bodey.)*

In tissue specimens *Zygomycetes* appear as broad (10 to 20 μm in diameter) nonseptate hyphae with branches occurring at right angles. Rarely, occasional septae can be visualized. During the handling of infected tissues, hyphae may collapse and fold, giving the characteristic ribbon appearance (Fig. 131-11). Grinding of tissue for culturing is not recommended. Differentiation of *Aspergillus*,*Fusarium*, and *Pseudallescheria* subspecies from *Zygomycetes* hyphae in tissue involves visualizing thinner, more regularly shaped fungal elements with more frequent acute angle branching and the presence of septae in the former group. Tissue histology of *Zygomycetes* infection has revealed a neutrophil infiltrate (in non-neutropenic hosts), necrosis, and invasion of blood vessels with thrombosis in more than 94 percent of the cases. Inflammatory vasculitis involving arteries and veins, and in chronic cases mononuclear cell infiltration with occasional giant cells is observed in chronic cases.

However, in the majority of patients with pulmonary zygomycosis, establishment of a definite diagnosis with biopsy is hampered by the presence of comorbidities, such as thrombocytopenia. Furthermore, routine laboratory cultures, even if performed from specimens with abundant *Zygomycetes* hyphal growth, have a yield of less than 50 percent, and many specimens, including blood, sputum, gastric fluid, and nose swabs, are difficult to culture and often have no diagnostic value. Sputum cultures are not reliable indicators of infection, because some *Zygomycetes* spp. often colonize the respiratory tract. In addition, nonculture-based diagnostic methods such as fungal antigen detection and molecular diagnosis with the use of PCR remains investigational, and no assays with sufficient sensitivity or specificity have been identified. The fact that more than one-half of zygomycosis cases are diagnosed at autopsy indicates the importance of maintaining a high index of clinical suspicion and a low threshold for performing

diagnostic biopsy and repetitive imaging studies in high-risk patients.

Treatment

General Principles

Successful treatment of zygomycosis largely depends on timely diagnosis, reversal of the underlying predisposing factors (when possible), and early and ideally broad surgical débridement of infected tissue in conjunction with systemic antifungal therapy. Early diagnosis is critical to the outcome of patients with zygomycosis because small focal lesions can often be surgically excised before the infection progresses to involve critical structures or disseminates to other organs. Time is of the essence in the treatment of zygomycosis given the fact that the infection has the ability to rapidly spread and disseminate even in relatively asymptomatic patients. For example, studies have shown that making therapeutic decisions based on examination of frozen tissue sections instead of waiting for fixed and stained histopathology is correlated with better outcome in patients with zygomycosis. In addition, rapid correction of underlying conditions such as appropriate control of hyperglycemia and/or correction of diabetic ketoacidosis, tapering of corticosteroids and immunosuppressive drugs, and discontinuation of deferoxamine treatment is critical to outcome. Notably, there have been rare cases in which a patient with cavitary pulmonary zygomycosis recovered from the infection without undergoing antifungal treatment after correction of diabetic ketoacidosis.

Antifungal Treatment

There have been no prospective studies for the primary treatment of pulmonary zygomycosis. Most evidence of the activity of existing antifungal agents comes from small case series, anecdotal case reports, and in vivo studies in animal models of zygomycosis. Therefore, the optimal therapy is uncertain. Currently, the recommended antifungal therapy for zygomycosis includes AMB-D at the highest tolerated dosage, usually 1.0 to 1.5 mg/kg per day. The nephrotoxic effects and acute infusional toxic effects of high-dose conventional AMB frequently preclude long-term high-dose therapy. As a result, the liposomal preparations of AMB present an attractive alternative for treating zygomycosis. Lipid formulations have been used to treat zygomycosis, although no comparative studies have been performed thus far. Outcomes with the use of the lipid formulations of AMB appear to be similar to those historically reported for conventional AMB-based therapy, albeit with fewer adverse effects. In the largest reported case series of zygomycosis, 64 patients received a lipid complex of AMB for refractory disease or intolerance of conventional AMB. The overall response rate (improvement in or cure of infection) was 50 percent, and there were no significant toxic effects, even in patients with preexisting renal disease. Numerous case reports of liposomal AMB used for zygomycosis also indicate favorable responses, including those to the use of particularly high doses of liposomal AMB (10 to 15 mg/kg per day) or prolonged therapy to achieve a cure in some cases. Drainage and AMB instillation into refractory abscesses and cavities was also reported to be successful in a limited number of patients. Successful treatment of pulmonary zygomycosis with an aerosolized lipid complex of AMB (50 mg/day via a Respirgard II nebulizer) and combination antifungal treatment with terbinafine or rifampicin and AMB has been described in single case reports.

Most azoles, including fluconazole and voriconazole, have no meaningful activity against *Zygomycetes* spp. However, posaconazole (200 mg given four times a day), an orally available broad-spectrum investigational triazole, appears to possess potent activity against fungi of this class. In a recently reported open-label salvage trial, the overall success rate of posaconazole (800 mg) was 70 percent in 24 patients. The drug was well tolerated with only minimal gastrointestinal side effects. Similarly, a recent retrospective review of posaconazole-based salvage therapy in 91 patients who had refractory zygomycosis indicated an overall success rate of 61 percent, including a success rate of 65 percent in the group of patients with pulmonary zygomycosis. Furthermore, an additional 21 percent of subjects had stable disease after 12 weeks of treatment. These encouraging preliminary data suggest that use of posaconazole represents an unmet need in the treatment of zygomycosis. For patients requiring further immunosuppression following treatment of zygomycosis, secondary chemoprophylaxis is often desired. Posaconazole seems to be a favorable option for patients who need continuous long-term antifungal therapy because they remain at high risk for relapse of infection. Determining whether posaconazole alone or in combination with a lipid formulation of AMB is preferable will require further studies.

Caspofungin lacks significant activity against *Zygomycetes* in vitro, and clinical experience with caspofungin in the treatment of zygomycosis is extremely limited. Nevertheless, in case reports and a study with a model of disseminated zygomycosis in diabetic mice, echinocandins appear to have some role, especially in combination with a polyene, in serious cases of zygomycosis. Given the fact that several cases of breakthrough zygomycosis to echinocandins have been reported, further studies on the role of echinocandins in treatment of zygomycosis are needed.

Surgical Treatment

Because zygomycosis is a highly angioinvasive infection with resulting extensive thrombosis and tissue necrosis, antifungal agents often display poor penetration at the site of infection. Therefore, even if the causative *Zygomycetes* strain is susceptible to the antifungal agent in vitro, the agent may be ineffective in vivo. Surgical débridement of infected tissue should be performed on an urgent basis. In patients with pulmonary zygomycosis, surgical treatment in conjunction with antifungal therapy has been shown to significantly improve survival when compared with antifungal therapy alone. Hence, a comprehensive review of cases of pulmonary zygomycosis showed that the mortality rate in patients who received antifungal

agents alone was 55 percent versus 27 percent in patients who received antifungal agents and surgery. Removal of as much of the infected or devitalized tissue as possible while the infection is localized has the greatest benefit. Lobectomy is often required, and pneumonectomy may be necessary for proximal or extensive involvement. Also, repeated procedures may be needed. The benefit of pulmonary resection diminishes as dissemination occurs.

Other Adjunctive Therapies

A recent review of 28 cases of zygomycosis suggested that treatment with hyperbaric oxygen (HBO) may be a beneficial adjunct to the standard surgical and medical antifungal therapy for zygomycosis, particularly in patients with diabetes mellitus who have rhinocerebral disease. The increased oxygen pressure achieved with treatment with HBO appears to improve the ability of neutrophils to kill organisms. Furthermore, by correcting lactic acidosis, treatment with HBO promotes the oxidative action of AMB. Additionally, high oxygen pressure inhibits fungal growth in vitro and improves the rate of wound healing by elevating tissue oxygen levels and releasing growth factors. However, data on treatment with HBO of pulmonary zygomycosis are scarce, and its role in this setting remains uncertain.

The role of adjunctive cytokine therapy for zygomycosis has not been studied in detail. Cytokines that activate phagocytic activity, such as interferon-γ and GM-CSF, increase the killing efficacy of phagocytic cells against *Zygomycetes* spp. in vitro. Case reports have indicated a favorable outcome in patients with rhinocerebral zygomycosis following the addition of interferon-γ and GM-CSF to the treatment regimen. Further studies of cytokines that activate host phagocyte function are warranted for this infection.

The central role of iron metabolism in the pathogenesis of zygomycosis supports the hypothesis of using effective iron chelators as adjunctive antifungal therapy. In contrast with deferoxamine, other iron chelators do not allow the organism to take up iron, thereby inhibiting its growth in vitro in the presence of iron. Furthermore, whereas administration of deferoxamine in a previous study significantly worsened disseminated *R. oryzae* infection in an animal model of zygomycosis, treatment with an iron chelator significantly increased the median survival rate in the animals.

OTHER EMERGING OPPORTUNISTIC MOLDS

Over the past decade, and with the ever-expanding spectrum of immunocompromised patients, we have witnessed the emergence of less common but medically important opportunistic fungal pathogens, including septate filamentous fungi such as hyalohyphomycetes (e.g., *Fusarium*, *Scedosporium*, and *Trichoderma* spp.), dematiaceous fungi (e.g., *Phaeohyphomycetes*), endemic dimorphic pathogens (e.g., *Penicillium marneffei*), and rare pathogenic yeasts (e.g., *Trichosporon* spp.). The diagnosis of invasive fungal pneumonia caused by septate filamentous fungi is particularly challenging because of the similarity of the manifestations and histopathological features of these mycoses with those of IA. Given the fact that most of these infections have a poor outcome because of broad-spectrum resistance to conventional antifungal agents, timely diagnosis is critical for outcome. Therefore, pulmonary infections caused by hyalohyphomycetes, including *Fusarium* and *Scedosporium* spp., are discussed below.

Pulmonary Fusariosis

Fusarium spp. are ubiquitous filamentous fungi found in soil, water, and decaying material. Although *Fusarium* is a well-known plant pathogen, only a few of the 50 different species have been reported to be pathogenic in humans, including *Fusarium solani*, *Fusarium oxysporum*, *Fusarium moniliforme*, *Fusarium verticilloides*, *Fusarium dimerum*, and *Fusarium proliferatum*. Of these species, *F. solani* is the most virulent, causing one-half of all cases of invasive fusariosis reported in humans. Since the description of the first case of disseminated fusariosis in a child with acute leukemia in 1973, invasive fusariosis has emerged in several tertiary care cancer centers as the second most common invasive mold infection in profoundly immunocompromised patients after IA.

There seems to be a distinct seasonal peak and geographic distribution of invasive fusariosis. Hence, the vast majority of the cases have been reported in the United States during the rainy summer season, when the dispersion of fusarial conidia in the air is most pronounced. More than 90 percent of human invasive fusariosis cases occur in neutropenic patients with hematological malignancies, especially those with acute leukemia. Another risk factor for invasive fusariosis is GVHD treated with high doses of corticosteroids during the postengraftment period in HSCT recipients.

The skin and respiratory tract are the primary portals of entry for *Fusarium* infection. Inhalation of *Fusarium* conidia through the lung and paranasal sinuses by a severely immunocompromised host may lead to sinopulmonary infection characterized by angioinvasion, extensive tissue necrosis, and secondary dissemination. In addition, disruption of skin integrity because of local trauma or placement of a central venous catheter or in the setting of onychomycosis with associated cellulitis appears to be a relatively common portal of entry for disseminated *Fusarium* infection that involves the lung in immunocompromised hosts. The ability of *Fusarium* spp. to undergo adventitious sporulation with formation of microconidia in vivo facilitates dissemination and may account for the high rates of positive blood cultures and associated skin lesions in cases of fusariosis. Neutrophils probably play the most critical role in the control of human *Fusarium* infections. Several studies have demonstrated that the prognosis for patients with fusariosis is clearly associated with prompt recovery of neutrophil counts. In fact,

the mortality rate in patients with fusariosis in the setting of profound, prolonged neutropenia is essentially 100 percent, even with aggressive antifungal treatment, compared with a rate of approximately 30 percent in the setting of neutrophil recovery.

Fusariosis in immunocompromised patients manifests in four major patterns: refractory fever of unknown origin, sinopulmonary infection or pneumonia, disseminated infection, and a variety of focal single-organ infections. Pneumonia occurs in more than 80 percent of patients with invasive fusariosis. Sinopulmonary fusariosis is most often clinically and radiographically indistinguishable from the much more common IA and other invasive mold infections. Sinus involvement is also frequent, as it has been observed in up to 80 percent of cases in some reports. One of the diagnostic challenges in immunocompromised patients with fungal pneumonia is differentiating among IA, invasive fusariosis, and zygomycosis. Hence, recovery of *Fusarium* spp. from cultures of appropriate specimens is essential for a definite diagnosis.

The histopathological picture of *Fusarium* is identical to that of *Aspergillus* and other hyalohyphomycetes (e.g., *Scedosporium* spp.) and may lead to misidentification. Even so, there are subtle differences in the histopathological features of *Aspergillus* and *Fusarium* spp. that can facilitate differentiation between the two species based on the histopathology itself, including the presence of *Fusarium* chlamydospores in tissue (Table 131-8).

Because hyalohyphomycetes (*Aspergillus* versus *Fusarium* versus *Scedosporium* spp.) have different levels of susceptibility to antifungals, the ability to differentiate among these molds before culture results are available by using molecular identification methods could have significant implications on therapeutic decision making. In situ hybridization directed against ribosomal 18S RNA sequences was recently shown to rapidly and accurately distinguish *Fusarium*, *Aspergillus*, and *Scedosporium* spp. from histopathological specimens. However, further standardization of these promising molecular methods is needed. Thus, tissue cultures remain the gold standard for differentiation among these fungi.

Despite the clinical similarities between pulmonary fusariosis and IPA, there are some characteristics that favor the diagnosis of invasive fusariosis (see Table 131-8). First, *Fusarium* spp. are usually recovered from blood specimens in the setting of disseminated disease. The reported rate of positive blood cultures in patients with disseminated fusariosis ranges from 50 to 70 percent, and fungemia may be the only manifestation of infection. In fact, *Fusarium* spp. are the most common molds associated with true fungemia in HSCT recipients. This feature contrasts with disseminated IA and zygomycosis cases, in which these molds are rarely (less than 5 percent) isolated from blood specimens, with the notable exception of *A. terreus*.

Another distinctive feature of invasive fusariosis is the high incidence (50 to 70 percent) of skin lesions in patients with disseminated disease. This contrasts with the low incidence of skin lesions in patients with disseminated aspergillosis (less than 10 percent). In fact, skin lesions are frequently the sole diagnostic material for invasive fusariosis. Several patterns of skin lesions can be seen: subcutaneous nodules, purpura, red or gray macules and/or papules with or without progressive central necrosis, flaccid pustules, vesicles, and hemorrhagic bullae. The most characteristic skin lesions encountered in cases of disseminated fusariosis are "ecthyma gangrenosum-like" lesions, which are red or gray macules with central ulceration or black eschar. *Fusarium* skin lesions are often tender, especially subcutaneous nodules, and can involve any skin site, although they appear predominantly in the extremities. Most patients have lesions at different stages of evolution. Accompanying myalgia is also common, reflecting concomitant muscle involvement.

Fusarium is one of the fungi most resistant to the arsenal of modern antifungal agents, and breakthrough infections to AMB or triazoles are common. In particular, *F. solani* is the most resistant species within the genus. The mainstay in the treatment of fusariosis has traditionally been AMB-D. However, the in vitro susceptibility of *Fusarium* spp. to AMB-D is mediocre at best. Whether the in vitro susceptibility of *Fusarium* spp. alone can predict outcome is unclear, because other factors (e.g., neutrophil recovery) are probably the most critical determinants of the prognosis for fusariosis. There have been reports of improved outcome of fusariosis with the use of high-dose lipid formulations of AMB. Hence, the mortality rate in patients who received high doses of a lipid complex of AMB (greater than 5 mg/kg per day) was significantly lower (less than 30 percent) than that observed in patients who received conventional AMB-D doses (greater than 75 percent) in a previous study.

Among the antifungal triazoles, fluconazole and itraconazole are not active against *Fusarium* spp. However, the newer broad-spectrum triazoles voriconazole and posaconazole have variable in vitro activity against *Fusarium* spp. and show promise in the management of fusariosis. In a recent study, administration of voriconazole resulted in a favorable response in five (45 percent) of 11 patients with fusariosis refractory to or intolerant of standard therapy. Posaconazole, an investigational broad-spectrum triazole, is also active against *Fusarium* spp. both in vitro and in animal models. In a recent case series including patients with fusariosis refractory to or intolerant of standard treatment modalities, salvage treatment with posaconazole had a response rate of 50 percent. Given that AMB and the newer triazoles voriconazole and posaconazole are the most active agents against *Fusarium* spp., a strategy combining a lipid formulation of AMB with one of these triazoles is reasonable and should be explored further.

Because the neutrophil count seems to be the most crucial prognostic determinant in fusariosis cases, a potentially beneficial adjuvant therapeutic strategy is to transfuse granulocytes obtained from G-CSF– and GM-CSF–stimulated donors. Granulocyte transfusion has been suggested to result in more favorable response rates (33 to 50 percent) in profoundly neutropenic patients by shortening the duration of neutropenia.

Table 131-8

Differentiating Features among the Major Opportunistic Mold Infections of the Lung

Incidence	*Aspergillus* causes the vast majority of cases of fungal pneumonia, followed by *Zygomycetes*
Predisposing factors	*Zygomycetes* spp. are associated with the presence of diabetes mellitus, malnutrition, iron overload states, and voriconazole prophylaxis
Clinical features	Skin lesions are more common in disseminated fusariosis (50%–70%) than in disseminated IA (<10%) and disseminated zygomycosis (<10%)
	Skin lesions in fusariosis are different from those in IA and zygomycosis (*Aspergillus* and *Zygomycetes* skin lesions are fewer, less widespread, have a larger diameter, and present with a black eschar with a thinner erythematous halo)
	Fungemia is more common in fusariosis (60%–70%) than in IA (<5%) and zygomycosis (virtually absent)
	Fungemia also often occurs earlier in fusariosis than in IA (shortly before death or after death)
	The *Zygomycetes* and *Fusarium* spp. are highly resistant to antifungal agents and develop as breakthrough infections to antifungals with anti-*Aspergillus* activity
Histopathological features	Broad-based nonseptate or pauciseptate ribbon-like hyphae are pathognomonic for *Zygomycetes*
	The presence of chlamydosporia in histopathology is pathognomonic for *Fusarium* spp.
CT features	On CT scans, multiple nodules, and pleural effusions favor the diagnosis of pulmonary zygomycosis versus IPA
	Pulmonary zygomycosis has a predilection for the upper lung lobes
Serology	Positive galactomannan antigen is virtually diagnostic for IPA

Pulmonary Scedosporiosis

The genus *Scedosporium* comprises a group of filamentous fungi found ubiquitously in the environment. The two major human pathogenic species are *Scedosporium apiospermum*—the asexual state of *Pseudallescheria boydii*—and *Scedosporium prolificans*. Both of these species histologically resemble *Aspergillus* spp., with hyphae that are septate and branching at acute angles. Although *Scedosporium* infections can occasionally occur in immunocompetent individuals, the overall incidence has increased over the past decade because of improved diagnostic modalities and the expanding population of immunocompromised individuals. These fungi can cause fatal angioinvasive infections in immunocompromised hosts that manifest with sinopulmonary, central nervous system, osteoarticular, ocular, endovascular, and lymphocutaneous involvement. Disseminated infection is associated with high (greater than 75 percent) mortality rates. *Scedosporium* spp. are known to be remarkably resistant to most conventional antifungals, such as AMB; however, treatment with newer triazoles, such as voriconazole, appears to be more efficacious.

Spores of *Scedosporium* spp. enter the respiratory tract by inhalation and the skin by direct inoculation to areas of trauma. Germination of conidia results in hyphal invasion in tissue with the potential to disseminate hematogenously to distant anatomic sites. Similar to *Fusarium* spp., dissemination may be facilitated by the ability of *Scedosporium* spp. to undergo adventitious sporulation in vivo. In general, strains of *S. prolificans* are more virulent than strains

of *S. apiospermum*. *S. prolificans* produces melanin, which may be an important virulence factor contributing to in vivo protection against host defense mechanisms.

Patients with AIDS, congenital or acquired immunodeficiency, or hematological malignancies as well as recipients of stem cell and solid organ transplants and those receiving antineoplastic or immunosuppressive medications are especially susceptible to these filamentous molds. In these immunocompromised individuals, sinopulmonary disease with lymphatic and/or hematogenous dissemination to various organs most often occurs.

The spectrum of pulmonary scedosporiosis largely mimics aspergillosis, ranging from respiratory tract colonization to allergic bronchopulmonary hypersensitivity to saprophytic fungus ball formation in preexisting pulmonary cavities and finally to invasive pulmonary or disseminated scedosporiosis. Invasive disease without preexisting lung tissue damage caused by *S. apiospermum* can occur only in immunocompromised hosts during or immediately after periods of prolonged neutropenia, and fever is the most common clinical presentation. Onset of infection may also be manifested by pulmonary symptoms, maculopapular skin lesions that later may become necrotic, myalgia, and central nervous system and other organ involvement. On rare occasions, pulmonary infections that spread to involve the central nervous system are reported in immunocompetent individuals after massive inoculation with *S. apiospermum* by aspiration of polluted water. Fungemia is diagnosed in more than two-thirds of patients with disseminated *S. prolificans* and *S. apiospermum* infection. The radiographic appearance of pulmonary infections caused by *S. apiospermum* and *S. prolificans* is essentially indistinguishable from that of IPA. Because no radiographic findings are truly pathognomonic for *Scedosporium* infections, diagnosis relies on prompt histopathological and microbiological evaluation.

Histopathological features of *Scedosporium* spp. in tissue sections can be confused with those of other fungi that have acute-angle–branching septate hyphae. The melanin-specific Fontana-Masson stain may be used to confirm the presence of dematiaceous hyphae of *S. prolificans* in tissue. Nevertheless, definitive diagnosis requires fungal culture and is crucial for antifungal susceptibility testing.

In general, *S. prolificans* is resistant to all clinically available antifungal agents, whereas *S. apiospermum* is susceptible to miconazole, voriconazole, and posaconazole. Both species are inherently resistant to the polyenes, including AMB. Data from clinical studies are limited. In a multicenter study of voriconazole administered as salvage therapy for scedosporiosis, the overall response rate of voriconazole for scedosporiosis outcomes of voriconazole therapy for *S. apiospermum* (33 percent) was better than that for *S. prolificans* (25 percent).

Severe *S. prolificans* infections have been successfully treated with a combination of voriconazole and terbinafine. In combination with azoles, terbinafine, an allylamine that blocks squalene epoxidase in the ergosterol synthesis pathway, has demonstrated synergistic interactions in vitro against clinical isolates of *S. prolificans*. Limited experience in patients with disseminated *S. prolificans* suggests that the combination of voriconazole and terbinafine is a legitimate treatment option.

Surgical débridement in cases of pulmonary scedosporiosis should be considered, especially for abscess drainage as well as for localized infections. In general, neutrophil recovery has been associated with an improved prognosis. Interferon-γ and GM-CSF have been shown to enhance neutrophil oxidative mechanisms of killing against *S. prolificans* hyphae. Although clinical data are scarce, in view of the dismal prognosis for patients with *Scedosporium* infections, immunomodulating therapy, including G-CSF, GM-CSF, interferon-γ, and primed white blood cell transfusions, should be considered as an adjunct treatment modality for these infections.

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132

Cryptococcosis and the Endemic Mycoses

L. Joseph Wheat • Mitchell Goldman • Kenneth Knox

Histoplasmosis and blastomycosis mostly afflict those living in the Mississippi and Ohio river valleys while coccidioidomycosis occurs primarily in the southwestern US desert (Fig. 132-1). Histoplasmosis and coccidioidomycosis also are endemic in parts of Mexico and Central and South America. Infection with *Cryptococcus neoformans* var. *gatti* is endemic to parts of British Columbia and Australia while *C. neoformans* var. *neoformans* exhibits no geographical predilection.

These organisms are found in the soil, and infection occurs following inhalation of the infectious forms of these fungi when sites containing the organism are disturbed. In some endemic areas over one-half of residents have acquired these mycoses early in life. In healthy individuals the infections are usually asymptomatic or clinically self-limited. In others, especially if the patient is immunosuppressed, the course is progressive and fatal without treatment. While these mycoses are less often seen in patients with acquired immunodeficiency syndrome (AIDS) who have access to effective antiretroviral therapy, they are occurring more frequently in those with other immunosuppressive conditions, and continue to be pathogenic for individuals without underlying disease.

In a study evaluating hospitalized patients with histoplasmosis, blastomycosis, or coccidioidomycosis in 2002, mortality was 5 percent in children and 7 percent in adults; only 13 percent were immunosuppressed; and the hospital costs exceeded $250 million, providing an estimate of the impact of the endemic mycoses in the United States. Advances in diagnosis and treatment provide opportunities to improve the outcome of these mycoses.

CRYPTOCOCCAL INFECTIONS

Cryptococcosis is caused by infection with the encapsulated fungus *Cryptococcus neoformans,* an organism with a worldwide distribution. Inhalation of *C. neoformans* initiates the infection in the lung with hematogenous dissemination most often involving the meninges. Although pulmonary infection

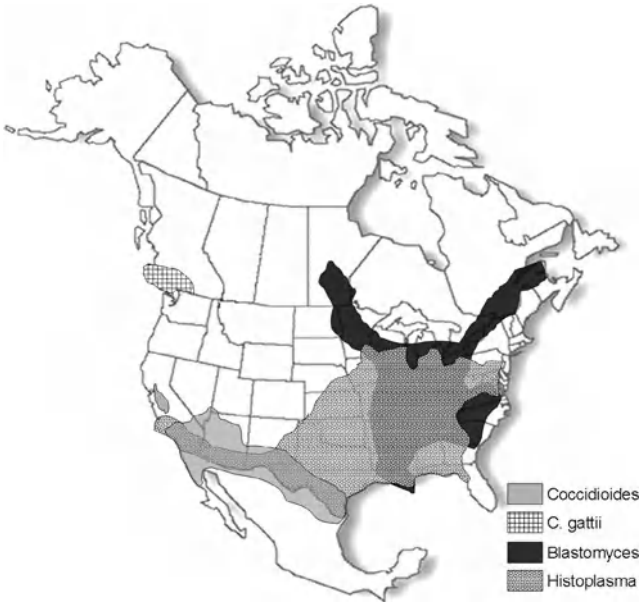


Figure 132-1 Geographical distribution of endemic mycoses in the Americas. The area of histoplasmin skin test reactivity in the southwestern US represents cross-reactivity caused by coccidioidomycosis, not endemic histoplasmosis.

may be discovered in the presence or absence of disseminated infection, meningoencephalitis remains the most commonly diagnosed form of cryptococcal infection. The spectrum of disease ranges from asymptomatic pulmonary infection in the immunocompetent host to diffuse pulmonary disease associated with respiratory failure and widespread disseminated disease in the immunocompromised host. The incidence of cryptococcosis in patients with AIDS in the United States has declined since the introduction of potent antiretroviral therapy; most cases now occur in those with limited access to care.

Mycology

C. neoformans is a yeast that is characterized by its thick polysaccharide capsule. The yeast measures 4 to 6 μm in diameter but the capsule thickness varies from 1 to more than 30 μm. Organisms are smaller and less well encapsulated in the environment, explaining their ability to reach the terminal airways following inhalation. *C. neoformans* grows readily in fungal media, allowing isolation in less than 48 hours and identification by biochemical tests or DNA probes. Four serotypes of *C. neoformans* have been described—A, B, C, and D.

Epidemiology

Serotypes A and D predominate in North America and Europe and grow best in composted bird droppings or rotted vegetation. Serotypes B and C are classified as *C. neoformans* var. *gatti* and are more common in tropical and subtropical regions in association with eucalyptus trees rather than avian excreta. Recently outbreaks of infection caused by *C. neoformans* var. *gatti* have been reported in British Columbia (Fig. 132-1). Otherwise outbreaks or clusters of cases are rare in cryptococcosis, and in most cases a history of exposure to birds or dust is lacking. Person-to-person transmission does not occur if cryptococcosis has been transmitted through organ transplantation; cutaneous infection has occurred after direct inoculation.

Patient populations at increased risk for progressive cryptococcosis include those with T-cell–mediated immune defects caused by AIDS, lymphoreticular malignancy (particularly Hodgkin's disease), or immunosuppressive medications, including tumor necrosis factor (TNF) inhibitors. The disease also appears to be more frequent in diabetics. *C. neoformans* var. *gatti* infection occurs mostly in immunocompetent hosts.

Pathogenesis

Cryptococcosis is acquired by inhaling aerosols containing the yeast but rarely by direct inoculation. Progressive disease often follows exposure in patients with impaired cellular immunity. In tissue, a mixed macrophage, lymphocyte, and plasma-cell response is seen, but inflammation may be minimal in immunodeficient subjects. Granulomas are uncommonly found in the nervous system and may be seen in other tissues.

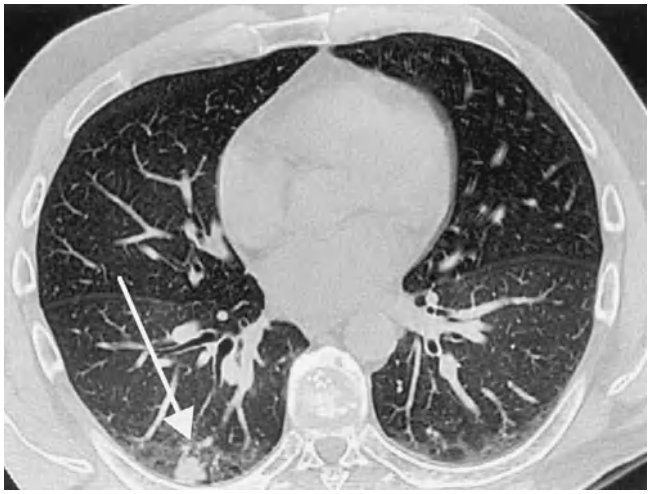
Macrophages, natural killer cells, and T lymphocytes play the key roles in cellular defense against *C. neoformans*. Inflammatory cytokines (interleukin [IL]-2, IL-12, interferon-γ) and macrophage colony-stimulating factor enhance the antifungal activity of these cellular mechanisms. Humoral immunity complements cellular mechanisms in defense against *C. neoformans*.

Clinical Findings

Cryptococcal infection results in asymptomatic or self-limited pulmonary disease in most healthy individuals. While symptomatic isolated pulmonary cryptococcosis may be diagnosed, meningoencephalitis is the most commonly recognized manifestation of cryptococcosis and the most common cause of death. Hematogenous dissemination to almost any tissue occurs in fewer than 25 percent of cases.

Pulmonary

Isolated pulmonary infection is not uncommon, and saprophytic colonization has been observed. Pulmonary cryptococcosis often is asymptomatic, discovered when chest radiographs are done for other reasons. Concurrent disseminated disease occurs in about 15 percent of cases. In symptomatic cases, common complaints include dry cough, dull chest discomfort, and low-grade fever. Less commonly night sweats, fatigue, weight loss, or hemoptysis may occur. Nodular infiltrates are typical of pulmonary cryptococcosis in the normal host (Fig. 132-2). Pulmonary cryptococcosis in



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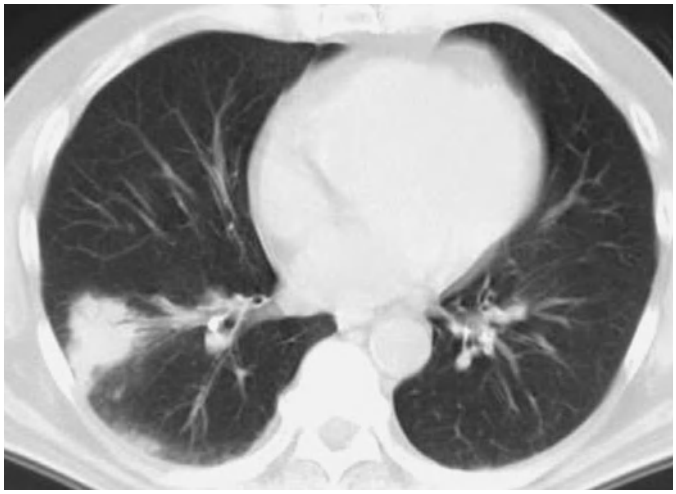

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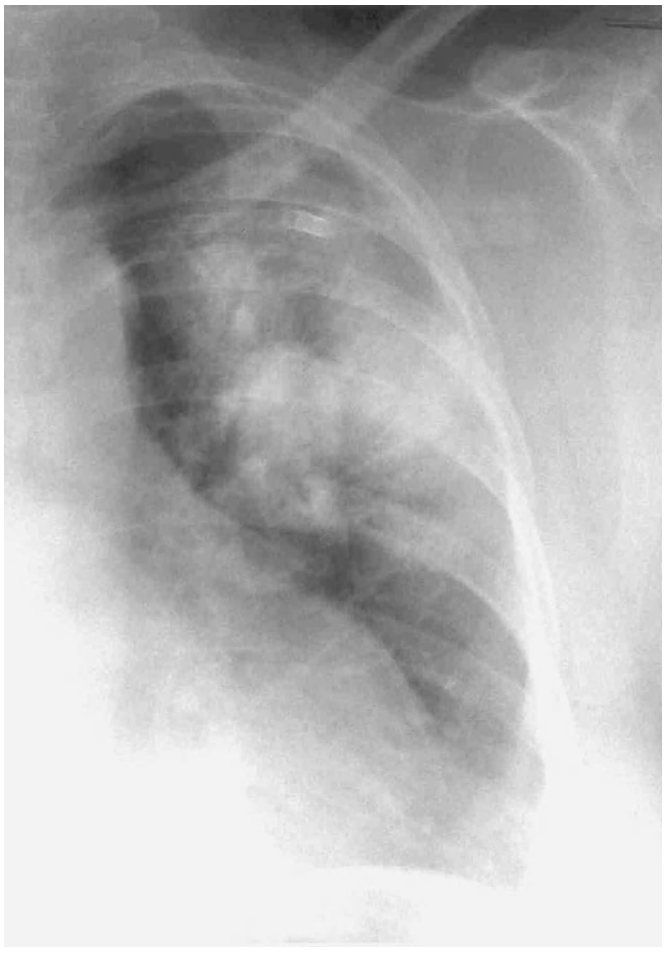

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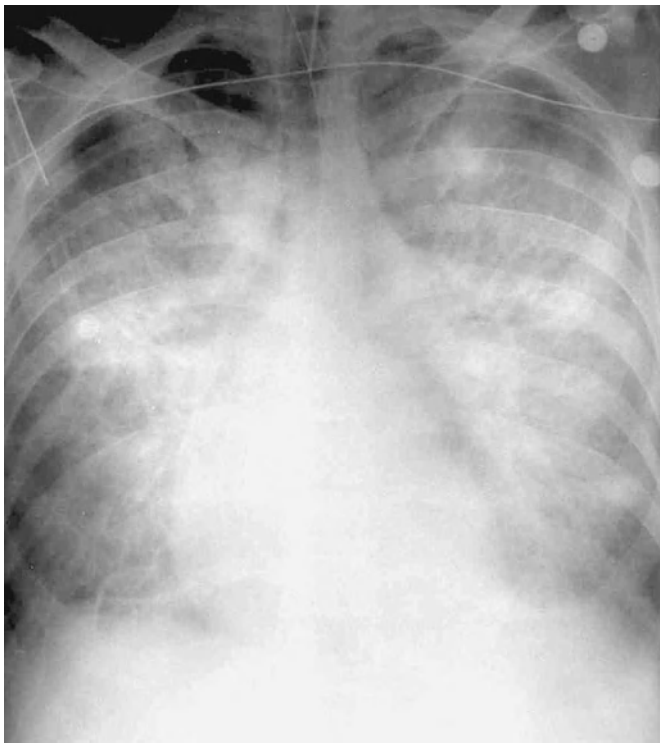

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Figure 132-2 Chest radiograph findings of cryptococcosis. *A*. Peripheral nodule. *B*. Masslike lesion. *C*. Computed tomography of mass lesion. *D*. Chest radiograph showing diffuse infiltrate.

nonimmunosuppressed patients usually resolve without therapy. Occasionally pulmonary cryptococcosis progresses slowly or may be accompanied by meningoencephalitis or dissemination to other organs after improvement of the pulmonary process.

In contrast to nonimmunocompromised patients, most immunocompromised patients exhibit fever and cough. Diffuse interstitial infiltrates or widespread alveolar consolidation causing respiratory failure is common in severely immunodeficient hosts. Radiographs in patients with less profound cell-mediated immune defects usually show nodular or patchy alveolar infiltrates (Fig. 132-2). Mortality is high in immunosuppressed patients with diffuse pulmonary involvement. Mass lesions are not uncommon and may

resemble malignancy. Cavitation is uncommon and mediastinal adenopathy, pleural effusion, and calcification are rare. A halo sign, usually attributed to aspergillosis, may be observed in cryptococcosis. Empyema, pleural disease suggesting a Pancoast's tumor, and pneumothorax have been reported. As immunosuppressed patients with pulmonary cryptococcosis often have meningoencephalitis, a lumbar puncture is recommended in these patients even in the absence of signs or symptoms of central nervous system (CNS) infection.

Meningoencephalitis

Meningoencephalitis is the most common manifestation of cryptococcosis. A gradual onset is typical, but a more rapid presentation may be seen in patients with severe immunodeficiency. Symptoms include fever, headache, nausea, and vomiting, while less than one-third of patients exhibit meningismus, altered mentation, or focal neurological abnormalities. Elevated intracranial pressure is common and may cause brain-stem herniation. Focal brain lesions occur in about 10 percent of cases, alone or in combination with meningoencephalitis.

Other Sites of Dissemination

Extraneural involvement may be seen in patients with meningoencephalitis or pulmonary cryptococcosis. Hepatosplenomegaly and bone marrow suppression are seen most commonly while lesions involving the skin, eyes, bones, or joints occur in about 5 percent. Other sites of dissemination include the heart, pericardium, muscle, gastrointestinal tract, peritoneum, thyroid, larynx, breast, placenta, urinary tract, prostate, and organ of Corti.

Immune Reconstitution Syndrome

Up to 30 percent of patients with AIDS and a recently diagnosed cryptococcal infection may exhibit an immune reconstitution inflammatory syndrome (IRIS) following initiation of highly active antiretroviral therapy (HAART). Similar findings have been reported following organ transplantation. Clinical findings have included worsening of meningitis with development of intracranial hypertension, hypercalcemia, intrathoracic lymphadenopathy, cavitation of pulmonary lesions, and soft-tissue abscess. These findings represent sterile inflammation resulting from an enhanced inflammatory response made possible by immune reconstitution, and while such changes may resolve spontaneously at times, the inflammatory changes within the CNS have led to death. This has resulted in the suggestion of some researchers that HAART should be withheld for individuals recently diagnosed with cryptococcal meningitis, at least until control of the infection is assured.

Diagnosis

Pneumonia

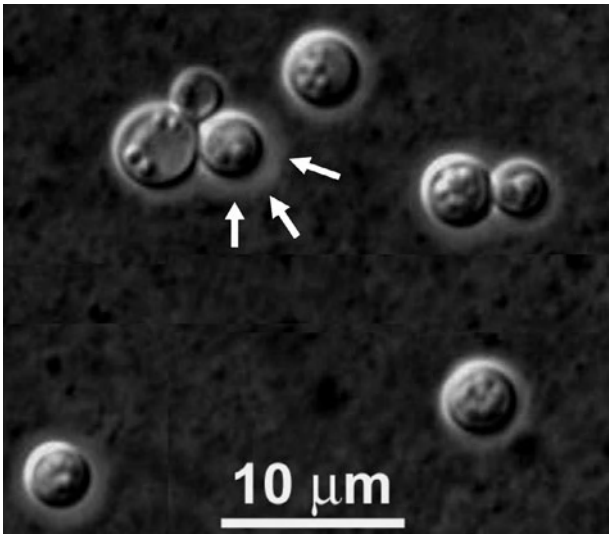
The diagnosis is usually made by cytology of histopathology of respiratory secretions or lung tissue, and confirmed by culture (Table 132-1). Once a diagnosis of pulmonary cryptococcosis is made, an evaluation for extrapulmonary dissemination should be initiated. A serum cryptococcal antigen test should be performed along with fungal blood culture. Cerebrospinal fluid (CSF) examination is recommended if the patient has any symptoms of meningitis or brain involvement, or is immunosuppressed. The Infectious Diseases Society of America (IDSA) guidelines indicate that a lumbar puncture should be performed in all patients with pulmonary

Table 132-1

Diagnostic Studies in Cryptococcosis

	Pulmonary, Nondisseminated		
	Nonimmunocompromised	**Immunocompromised**	**Meningitis**
India Ink		55% (Meyohas et al, 2005)	50%
Histopathology	5% (Nadrous et al, 2003)	66% (Chechani Kamholz, 1990)	NA
Antigen, serum	5% (Nadrous et al, 2003)	89% (Chechani Kamholz, 1990)	90%
Antigen, BAL		86% (Meyohas et al, 2005)	NA
Antigen, CSF	NA	NA	95%
Culture	72% (Nadrous et al, 2003)	100% (Chechani & Kamholz, 1990); 92% (Meyohas et al, 2005)	90%

BAL = bronchoalveolar lavage; CSF = cerebrospinal fluid; NA = not applicable.



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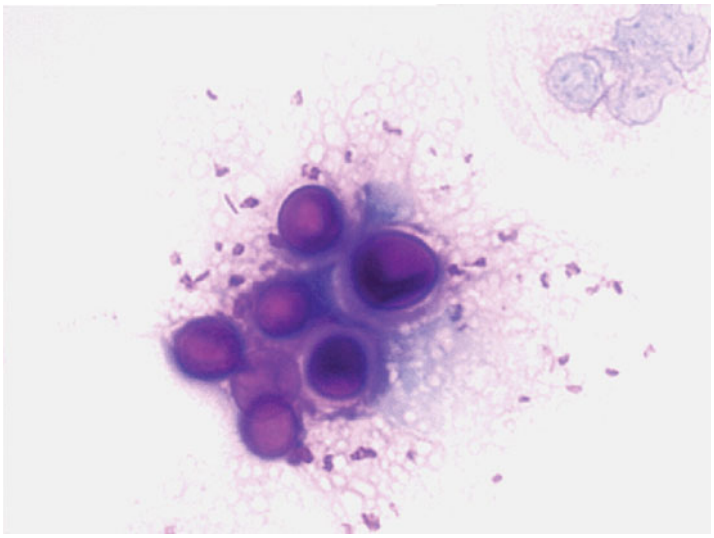

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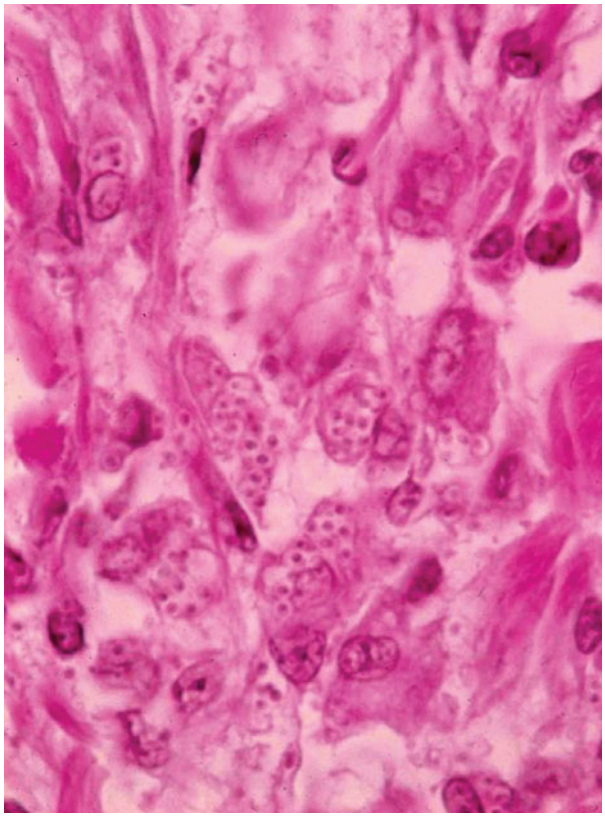

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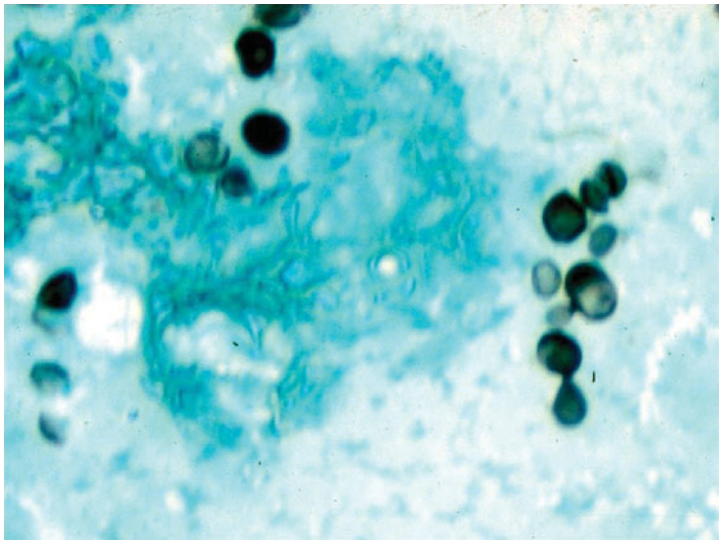

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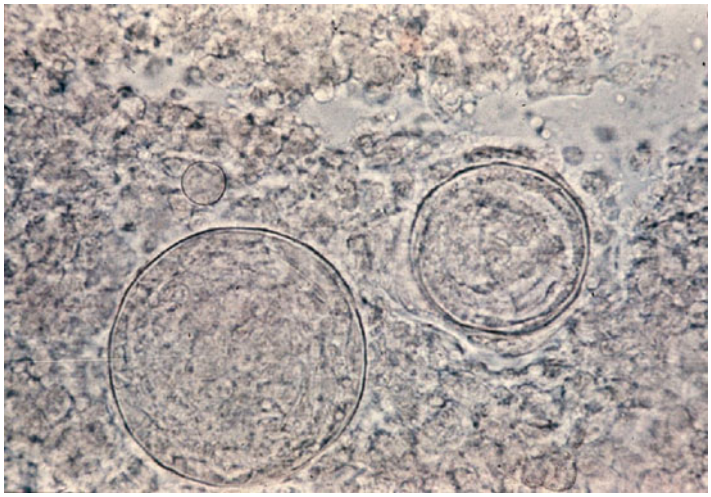
Figure 132-3 Fungal histopathology. *A*. India ink wet mount *C. neoformans*. *B*. Periodic acid–Schiff (PAS) stain of *C. neoformans*. *C*. Hematoxylin and eosin (H&E) stain *H. capsulatum*. *D*. Gomori methenamine silver stain of *H. capsulatum* yeast. *E*. Potassium hydroxide (KOH) wet mount showing *C. immitis* spherule. *F*. H&E stain *C. immitis* spherule in the tissue. *G*. KOH wet mount showing *B. dermatitidis* yeast. *H*. Papanicolaou stain showing *B. dermatitidis* yeast.

disease without exception, including those who are asymptomatic. However, data supporting such an approach are lacking, and not all experts agree that lumbar puncture is needed in those without clinical findings suggesting the presence of CNS involvement.

Histopathology and Cytology

C. neoformans can be recognized in tissue as a globose or oval to lemon–shaped yeast with a polysaccharide capsule (Fig. 132-3). Cryptococci are readily identified by the Gomori methenamine silver (GMS) and periodic acid–Schiff (PAS) stains. More specific stains for *C. neoformans* include the Mayer's mucicarmine stain, which stains the fungal capsule and the Masson-Fontana melanin stain, which may detect capsule-deficient cryptococci. Direct microscopic examination of bronchoalveolar lavage (BAL) fluid sediment stained with India ink can identify the organism. The sensitivity of histopathology in patients with AIDS is about 67 percent.



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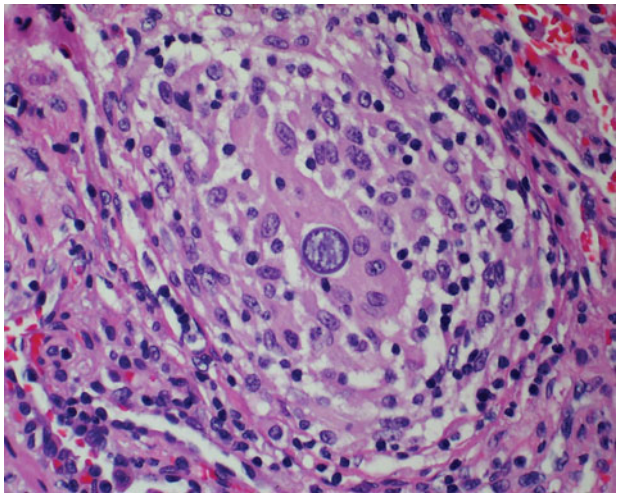

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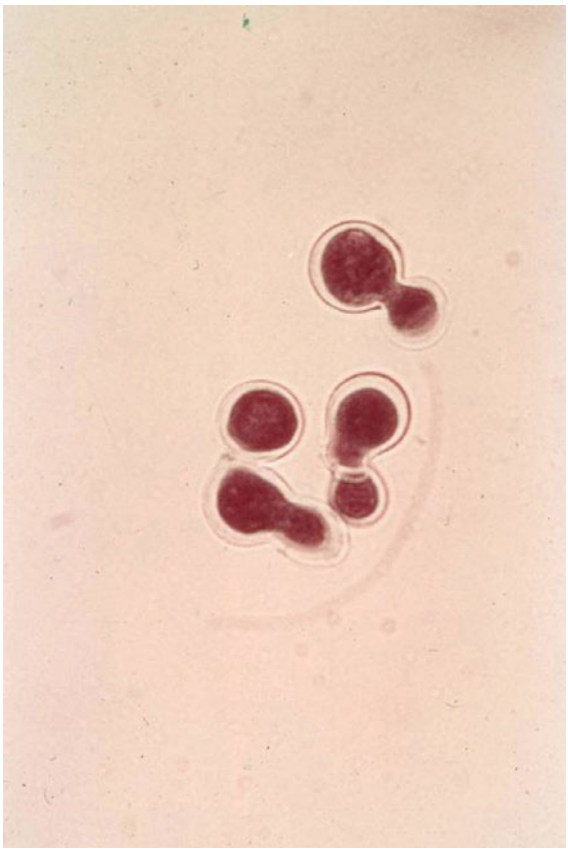

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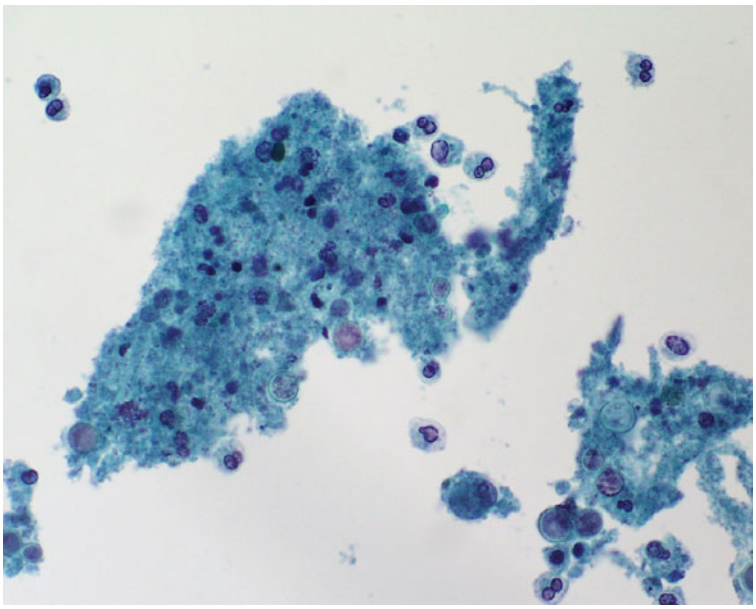


H

Figure 132-3 (*continued*)

In the nonimmunocompromised host, fungal stains of respiratory specimens are rarely positive (approximately 5 percent) despite isolation of the fungus in over two-thirds of cases.

Antigen Detection

In patients with cryptococcal pneumonia, the serum cryptococcal antigen is usually not detected unless extrapulmonary dissemination has occurred, the pneumonia is extensive, or the patient is immunosuppressed. A negative serum cryptococcal test should not be used to exclude the diagnosis of cryptococcal pneumonia. In patients with AIDS with pulmonary cryptococcosis the serum cryptococcal antigen is positive in most cases. Cryptococcal antigen also may be detected in BAL and pleural fluid.

Culture

C. neoformans often can be isolated from sputum in patients with cryptococcal pneumonia. However, isolation from sputum may represent mere colonization. In patients unable to

produce sputum, bronchoscopy may be useful. Cultures of BAL or lung tissue yield the organism in 50 to 90 percent of cases while fungal stains are positive less often. Needle aspiration of focal lesions also may be useful. Thoracentesis may yield the organism in patients with pleural involvement. Blood cultures may be positive in immunocompromised hosts.

Meningoencephalitis

The diagnosis of meningitis can be made initially by India ink stain or detection of antigen in CSF and confirmed by isolation of the organism from fungal cultures. Antigen also can be detected in serum, providing a clue to the diagnosis before lumbar puncture is performed. Cultures also may be positive from extrapulmonary sites in up to two-thirds of patients.

Treatment

Treatment is indicated in patients with symptomatic pulmonary infections, especially if they are immunocompromised and in all patients with meningoencephalitis or disseminated infection (Table 132-2). The rationale and supporting evidence for these recommendations are discussed in an IDSA guideline document. Patients with a diagnosis of cryptococcosis at any site should be provided close follow-up for at least 1 year as the majority of relapses occur during this time period.

Table 132-2

Treatment Recommendations for Cryptococcosis

Pulmonary disease only	
Mild-moderate severity	Fluconazole 200–400 mg/d for 6–12 months
Severe or immunocompromised	Same as CNS disease
Central nervous system (CNS disease)	
Induction/consolidation	Amphotericin B 0.7–1.0 mg/kg/d plus flucytosine 100 mg/kg/d for 2 weeks then fluconazole 400 mg/d for 10 weeks
Maintenance/suppressive	Fluconazole 200–400 mg/d
AIDS	12 months and CD4 count >150 cells/ml
Other immunosuppression	6–12 months

Source: Data from Sang MS, Graybill RJ, Larsen RA, et al. Practice guidelines for the management of cryptococcal disease. Clin Infect Dis *30:710–718, 2000.*

Indications for Treatment

Pneumonia

For asymptomatic patients without extrapulmonary disease, antifungal therapy may be withheld for up to a month if patients can be followed closely. Increasing size or numbers of lesions would be indications for treatment. For symptomatic patients, those who are immunocompromised, and patients showing progression during observation, treatment is advised.

Meningoencephalitis

Treatment is indicated in all cases.

Extrapulmonary Dissemination, without Meningoencephalitis

Treatment is indicated in all cases.

Selection of Antifungal Agent

Pneumonia

For nonimmunosuppressed patients, fluconazole 200 to 400 mg/d for 3 to 6 months is recommended, and itraconazole 200 to 400 mg/d is an alternative. In more severe cases amphotericin B and flucytosine should be given as recommended for meningitis (see below). Treatment guidelines for meningitis should be followed in immunosuppressed patients.

Meningitis

Amphotericin B 0.7 to 1.0 mg/kg/d and 5-flucytosine 100 mg/kg/d should be given for 2 weeks (induction) followed by fluconazole 400 mg/d for 10 weeks (consolidation). 5-flucytosine accelerates sterilization of the CSF and reduces the risk for relapse. Lipid preparations of amphotericin B are less toxic than the standard formulation and are recommended in patients with renal impairment or those who are thought to be at increased risk for amphotericin B nephrotoxicity. Fluconazole alone is not recommended as induction therapy. Itraconazole 200 mg twice daily is an alternative in patients unable to take fluconazole for consolidation therapy. Aggressive management of elevated intracranial pressure through removal of large volumes (about 25 ml) of CSF is essential to achieve the highest survival. Addition of interferon-γ led to clinical improvement in two patients with CD4 lymphopenia unresponsive to amphotericin B.

In patients with AIDS or other immunosuppressive conditions, so-called maintenance or suppressive treatment with fluconazole 200 mg/d is recommended. Itraconazole is inferior to fluconazole for chronic maintenance therapy and is not advised. If itraconazole is used, 200 mg twice daily is recommended. Amphotericin B 1 mg/kg one to three times weekly is another alternative maintenance regimen.

With HAART, two small prospective studies and one larger retrospective study suggested that maintenance therapy can be safely stopped in selected patients. Criteria for withdrawal of maintenance therapy include treatment with fluconazole for at least 1 year and HAART for at least 6 months, a CD4 count of more than 150 cells/ml, and a viral load of

less than 50 copies/ml. Patients require careful monitoring for relapse and continued response to HAART. Resumption of antifungal therapy is recommended if the CD4 count falls below 100 cells/ml. Monitoring serum cryptococcal antigen may be useful, as rising would support resumption of antifungal therapy.

For immunosuppressed patients without AIDS, a 6- to 12-month course of fluconazole is recommended. As in patients with AIDS, careful follow-up is required after antifungal therapy is stopped. In some patients who relapse following such a course of therapy, lifelong maintenance therapy may be appropriate.

Disseminated/Extrapulmonary, without Meningoencephalitis

Trials have not been performed evaluating treatment of non-CNS extrapulmonary disease, and recommendations are based upon experience of the IDSA guideline committee. Recommendations outlined above for pneumonia should be followed in nonimmunosuppressed patients and for meningitis in those who are immunosuppressed.

Role of Fluconazole Resistance

Resistance may be a cause for fluconazole failure. The minimum inhibitory concentration (MIC) of fluconazole required to inhibit greater than 90 percent of strains of *C. neoformans* was 8 μg/ml, which is the breakpoint for defining resistance. In another recent report, nearly one-half of isolates from Spain were resistant to fluconazole. Relapse or treatment failure has been reported in cases with MICs of 25 μg/ml or more.

Newer Antifungal Agents

Alternatives to itraconazole and fluconazole are needed for patients who fail or do not tolerate those agents. Voriconazole and ravuconazole are slightly more active in vitro than posaconazole, with MIC_{90s} of 0.12 to 0.25 μg/ml. Voriconazole penetrates CSF, but not as well as fluconazole. Furthermore, strains with high-level resistance to fluconazole may be cross-resistant to voriconazole. Posaconazole was effective in a murine model of cryptococcal meningitis, but has not been studied in humans, while voriconazole has not been studied in either. There are, however, a few case reports supporting their potential effectiveness. Neither would appear to offer advantages over fluconazole, however. The echinocandins are not active in vitro, have not been studied in animal models, and are not recommended in patients.

Prevention

Although fluconazole and itraconazole reduced the incidence of cryptococcosis in patients with AIDS, prophylaxis is not recommended, largely because of the low attack rate. Other reasons include unlikely cost-effectiveness, limited impact on survival, and potential to induce fluconazole resistance among other fungi. One study reported a survival benefit, however, supporting prophylaxis for populations at unusually high risk.

HISTOPLASMOSIS

Histoplasmosis is the most common endemic mycosis and a major cause of morbidity in patients who live in endemic areas. Progressive disseminated histoplasmosis is an important complication of AIDS and, more recently, of treatment with tumor necrosis factor-α (TNF-α) inhibitors. Understanding of the clinical syndromes and untreated course of the infections is essential in the diagnosis and management of patients with histoplasmosis. Improved laboratory tests have made it possible to rapidly diagnose the more severe cases. Expanded treatment options are available using newer triazole antifungal agents and liposomal formulations of amphotericin B.

Mycology

Histoplasma capsulatum grows as a mold in the soil and converts to a yeast in the tissues (Fig. 132-3). Microconidia measuring 2 to 4 μm in diameter are the infectious particle in the mold-phase of the organism. *H. capsulatum* also grows as a mold on fungal media in the laboratory. Definitive identification of a mold as *H. capsulatum* is made by DNA probe or exoantigen detection. At temperatures above 35°C, *H. capsulatum* grows as a yeast, which is the pathogenic form found in the tissues. The yeast measures about 2 to 5 μm and exhibits narrow-based budding.

Epidemiology

H. capsulatum is endemic in areas of North and South America (see Fig. 132-1) but can be found throughout the world. Bird and bat excrement enhance growth of the organism by accelerating sporulation. Cases outside the endemic region may have been acquired by exposure during travel or prior residence in the endemic area, or exposure to microfoci containing the organism within the nonendemic area. In the endemic areas over 50 percent of individuals exhibit histoplasmin skin test positivity as evidence of past histoplasmosis, and over 500,000 new cases occur annually.

Pathogenesis

Infection develops when conidia are inhaled and germinate into yeast. In many cases primary infection is asymptomatic and goes undiagnosed. Clinical illness most often follows exogenous infection or reinfection. With development of cell-mediated immunity during the first month following initial infection, interferon-γ and IL-12 arm macrophages to kill the fungus and halt progression of the disease. TNF-α also is very important for immune defense against *H. capsulatum*. These defense mechanisms are sufficient to control the infection in immunocompetent individuals, explaining the subclinical or self-limited course characteristic of acute histoplasmosis.

Reactivation of latent infection may account for some cases occurring in individuals with past histoplasmosis who become immunocompromised. Studies showing a low

incidence (less than 0.5 percent) of histoplasmosis following organ transplantation, in patients with AIDS, or following treatment with TNF inhibitors, however, suggest reactivation is rare.

Clinical Manifestations

Heavy exposure can cause severe illness even in healthy subjects. Low-level exposure is more common, however, and usually causes asymptomatic infection or clinically self-limited infection. The common self-limited presentations include acute and subacute pulmonary histoplasmosis, pericarditis, and rheumatological syndromes.

Asymptomatic Infection

In endemic areas, over one-half of residents exhibit histoplasmin skin test reactivity by age 20. In most of these cases, infection was presumed to have been asymptomatic. Most asymptomatic cases are identified as an incidental finding on chest radiographs or computed tomography (CT) scans performed for other reasons. The most common findings are enlarged mediastinal or hilar lymph nodes or pulmonary nodules. The main significance of such findings is the need to differentiate them from malignancy or tuberculosis. Asymptomatic infection also may be identified by demonstration of seropositivity during evaluation of another condition.

Pulmonary Syndromes

Acute Pulmonary Histoplasmosis

Following heavy exposure, patients present with diffuse pulmonary involvement often causing respiratory insufficiency. Chest radiographs usually show diffuse interstitial, reticulonodular infiltrates, nodular, or patchy air-space disease, but a miliary pattern suggestive of hematogenous dissemination may be seen (Fig. 132-4). Initial radiographs may appear normal, evolving to show infiltrates over the next few weeks. Mediastinal adenopathy is common. Evidence for extrapulmonary dissemination is present in less than 25 percent of cases. While patients may recover without therapy, recovery may be slow, respiratory failure may develop, and some infections may be fatal.

Subacute Pulmonary Histoplasmosis

More commonly, the inoculum is small and the presentation is subacute. Patients present with fever, cough, and chest pain. Chest radiographs show mediastinal lymphadenopathy with patchy infiltrates. Most patients recover in a few weeks but some experience persistent fatigue.

Chronic Pulmonary Histoplasmosis

Chronic pulmonary histoplasmosis occurs in patients with underlying lung disease and is characterized by persistent or recurrent pulmonary symptoms, progressive lung infiltrates, fibrosis, and cavitation. Upper lobe infiltrates and cavities are characteristic, resembling the findings in tuberculosis. Progression is manifested by cavity enlargement, formation of new cavities, spread to other areas of the lungs, and bronchopleural fistula. Bacterial pneumonia, *Aspergillus* superinfection, and malignancy also must be considered in evaluation of new masses or infiltrates.

Nodules

Nodules need to be differentiated from malignancy. Calcification suggests histoplasmosis, but does not exclude malignancy. Conversely, absence of calcification, does not exclude histoplasmosis. Positive positron emission tomography (PET) scan, assumed to support malignancy, is common in histoplasmosis. Rarely nodules may cavitate, but cavitation of nodules does not represent chronic pulmonary histoplasmosis and does not require therapy. Nodules also may rarely enlarge up to 2 mm/y, but enlargement is not caused by progressive infection and is not a basis for treatment. Calcification occurs in the necrotic central and surrounding fibrous tissue. An approach to the evaluation of pulmonary nodules has been reviewed.

Broncholithiasis

Lymph nodes and pulmonary granuloma calcify and may erode into adjacent bronchi causing hemoptysis or obstruction. Patients may expectorate rocklike particles of tissue and experience recurrent and severe hemoptysis, bronchial obstruction, or tracheoesophageal fistula.

Relationship to Sarcoidosis

Sarcoidosis and histoplasmosis share several clinical and radiographic findings. Angiotensin-converting enzyme (ACE), sedimentation rate, C-reactive protein, and immunoglobulin elevation occur in both conditions. Noncaseating granulomas are seen with each, and caseation, which is more typical of histoplasmosis, also occurs in sarcoidosis. Histoplasmosis is one of the most common infections that must be excluded before sarcoidosis is diagnosed to prevent mistakes in patient management, most notably administration of immunosuppressive therapy to patients with active histoplasmosis.

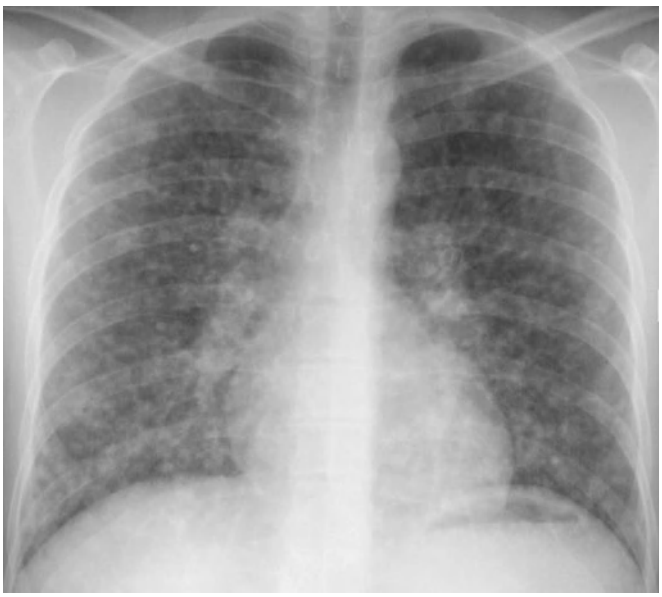
Mediastinal Syndromes

Mediastinal Adenitis

Mediastinal lymph node involvement is present in most cases of acute and subacute pulmonary histoplasmosis. Although usually asymptomatic, chest pain is the most common manifestation. Rarely, the airways, esophagus, or superior vena cava (SVC) may be impinged, causing obstructive symptoms. Airway obstruction is more likely in children because the airways are less rigid.

Mediastinal Granuloma

Histopathology shows a necrotic central core, often containing yeast, surrounding caseating and noncaseating granuloma, fibrous tissue, and a thin-walled (less than 5 mm) capsule. The fibrosis is less exuberant than in fibrosing mediastinitis, and does not invade adjacent structures. Symptoms



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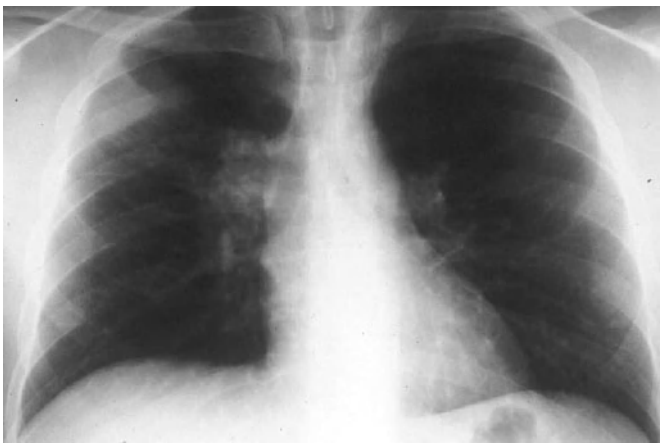

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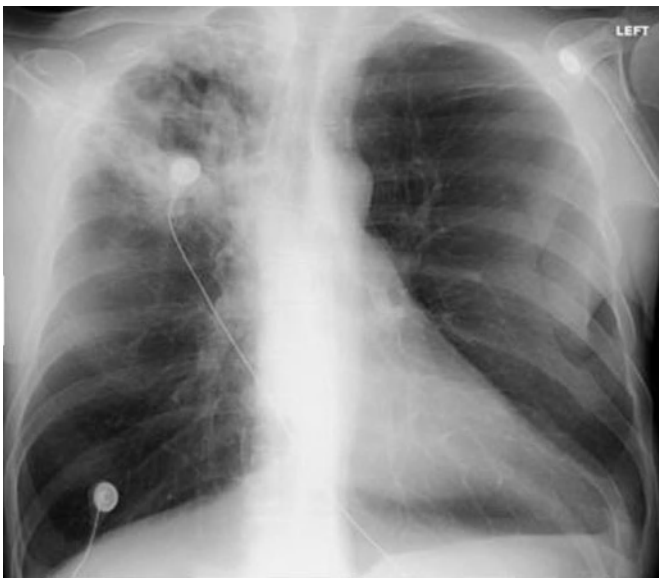

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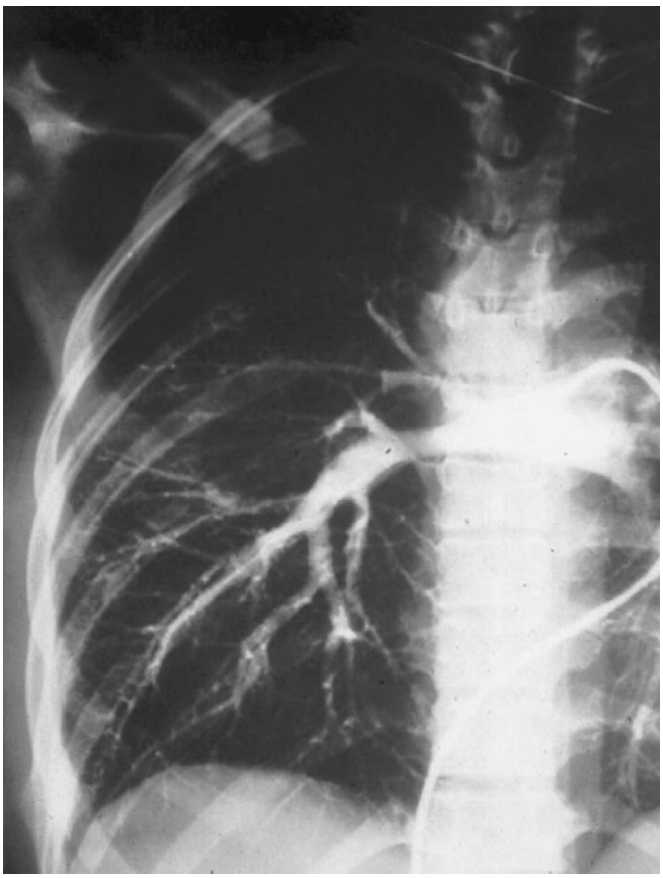

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Figure 132-4 *A*. Chest radiograph of acute diffuse histoplasmosis after large inoculum exposure. *B*. Computed tomography of subacute histoplasmosis with mediastinal adenopathy. *C*. Chest radiograph of cavitary histoplasmosis. *D*. Pulmonary arteriogram showing obstruction of pulmonary artery to right upper lung caused by fibrosing mediastinitis.

are usually caused by compression of the SVC, esophagus, or airways, and in some cases the nodes liquefy and drain into adjacent structures. Disruption of the capsule, either spontaneous or caused by surgery, may create fistula to the airways, pericardium, skin, or esophagus. Esophageal involvement may result in diverticulum formation.

Mediastinal Fibrosis

Mediastinal fibrosis represents an exuberant scarring reaction to mediastinal histoplasmosis. The SVC is most commonly involved, but the fibrosis also may occlude airways, pulmonary arteries or veins, or esophagus, and invade the thoracic duct, recurrent laryngeal nerve, or atrium in rare

cases. Chest radiographs show subcarinal or superior mediastinal widening, while CT scans reveal fibrotic restriction and invasion of mediastinal structures and calcification of the lymph nodes. Recurrent and often serious hemoptysis results from lung or airway damage and vascular compromise. Respiratory failure ensues in one-third of cases.

Other Inflammatory Syndromes

Rheumatological Syndromes

Patients with subacute histoplasmosis may experience arthritis or arthralgia accompanied by erythema nodosum, a manifestation often misdiagnosed as sarcoidosis. Chest radiographs usually show mediastinal lymphadenopathy and focal pulmonary infiltrates, but may be normal. These findings represent a systemic inflammatory response rather than disseminated infection, and are managed by anti-inflammatory treatment, not antifungal therapy. The illness may recur when treatment is stopped.

Pericarditis

Pericarditis is another inflammatory complication of primary histoplasmosis, occurring in less than 10 percent of cases. Findings include chest pain, pericardial friction rub, and occasionally signs of pericardial tamponade. Chest radiographs usually show mediastinal lymphadenopathy and increase in the cardiac silhouette, while CT scan and echocardiogram may show pericardial effusion. These patients respond to anti-inflammatory treatment but may require drainage of the pericardial fluid for management of tamponade. Late constriction is rare.

Progressive Disseminated Histoplasmosis

Progressive disseminated histoplasmosis (PDH) occurs in about 1 in 2000 cases, usually in patients who are immunosuppressed or at the extremes of age. Treatment with TNF-α inhibitors is a common predisposing condition. PDH develops during the first few months of infliximab therapy, and later following etanercept, but vigilance for PDH should be maintained throughout the course of immunosuppression.

Fever and weight loss are the most common findings in PDH. Examination reveals hepatomegaly or splenomegaly in about one-half of cases and lymphadenopathy in one-third. A syndrome resembling sepsis may be seen in cases with severe immunosuppression, in whom corticosteroids are given for presumed inflammatory or autoimmune disease, or in which diagnosis is delayed. Meningitis or focal brain lesions occur in about 10 percent of cases. Other common sites of dissemination include the oral mucosa, gastrointestinal tract, skin, and adrenal glands in 5 to 10 percent of cases. Chest roentgenograms are abnormal in 70 percent of patients, usually showing diffuse interstitial or reticulonodular infiltrates, and less often a miliary pattern.

In patients with AIDS and PDH in which HAART is initiated, an immune reconstitution syndrome has been reported. Manifestations have included worsening of hepatic enzymes, hepatic abscesses, lymphadenitis, arthritis, uveitis, and intestinal obstruction.

Diagnosis

Diagnostic modalities were recently reviewed, and are summarized in Table 132-3. Histopathology, cytology, and antigen detection are most useful for rapid diagnosis in patients with acute pulmonary and progressive disseminated histoplasmosis, cases that require therapy. A serological test for antibodies forms the basis for diagnosis in subacute manifestations in most cases. Serology or culture of respiratory secretions usually provides the basis for diagnosis of chronic pulmonary histoplasmosis. To achieve a high sensitivity for diagnosis by culture, multiple specimens must be obtained,

Table 132-3

Diagnostic Studies in Histoplasmosis

Test	Acute Pulmonary	Subacute Pulmonary	Chronic Pulmonary	Mediastinal Granuloma or Fibrosis	Progressive Disseminated
Antigen	75	25	<25	<25	90
Fungal stain	20	<25	40	25–50	50
Culture	40[154]	<25	75	<25	85
Serology	25–75	95	100	70	75

Note: In acute pulmonary histoplasmosis, the sensitivity of antibody detection ranges from about <25% during the first 2 weeks of illness to 75% by the sixth week.
Source: Data derived from Williams B, Fojtasek M, Connolly-Stringfield P, et al: Diagnosis of histoplasmosis by antigen detection during an outbreak in Indianapolis, Ind. Arch Pathol Lab Med *118:1205–1208, 1994.*

often requiring invasive procedures. Culture results may not be available for up to 1 month, limiting their use for diagnosis of severe disease.

Antigen Detection

Detection of antigen in the body fluids offers a valuable approach to rapid diagnosis in patients with PDH and acute pulmonary histoplasmosis, providing results within 24 to 48 hours. Antigen is found in urine of over 90 percent of patients with PDH and 80 percent with acute diffuse pulmonary disease. Sensitivity is improved using a new second-generation antigen assay, developed to prevent false-positive results in organ transplant patients treated with human anti-rabbit antibodies. Antigen detection in urine is less sensitive in subacute pulmonary and chronic pulmonary histoplasmosis. Detection of antigen in BAL fluid may improve the sensitivity for diagnosis of these pulmonary syndromes. Antigen may be found in CSF in 50 percent of patients with *Histoplasma* meningitis. Positive results caused by cross-reacting antigens occur in patients with African histoplasmosis, blastomycosis, paracoccidioidomycosis, and *Penicillium marneffei* infection. Antigen levels decline during treatment and increase with relapse, providing a tool for monitoring therapy.

Histopathology

Fungal staining permits rapid diagnosis but has a lower sensitivity than antigen detection. The highest yield is from bone marrow. Fungal stain of BAL is positive in 70 percent of cases of diffuse pulmonary histoplasmosis in patients with AIDS with PDH. The sensitivity of fungal stain of sputum or BAL in patients with other types of pulmonary histoplasmosis has not been reported but appears to be low. Yeast may be seen in peripheral blood smears in patients with severe PDH. *Pneumocystis carinii, Candida glabrata, Blastomyces dermatitidis, Toxoplasma gondii,* and *P. marneffei* may be misidentified as *H. capsulatum.*

Serological Tests

Antibodies to *H. capsulatum* measured by immunodiffusion or complement fixation develop in most patients. Antibodies first appear 4 to 8 weeks following exposure and persist for several years. Also, the antibody response is greater in patients with heavy exposure and/or more severe clinical disease. Patients with asymptomatic or mild infection, and those who are immunocompromised, may not mount an antibody response. In a study of dogs with naturally acquired chronic disseminated histoplasmosis, immunosuppression with corticosteroids, azathioprine, and cyclophosphamide precipitously reduced antibody levels in animals that were seropositive before immunosuppression.

Serology is most useful in patients with subacute manifestations of histoplasmosis (pulmonary, rheumatological, pericarditis, mediastinal syndromes) and chronic pulmonary infection, positive in 90 percent of such cases. Sensitivity is higher while specificity is lower using complement fixation rather than immunodiffusion methods. Complement fixation titers greater than or equal to 1:32 are more suggestive of active infection but titers of 1:8 to 1:16 should not be disregarded. Cross-reactions occur in patients with other fungal diseases. Also, antibodies persisting following prior histoplasmosis may cause confusion in patients with other lung diseases.

Fungal Cultures

Cultures provide the strongest proof for histoplasmosis but are limited by low sensitivity in self-limited infections and delayed growth (2 to 4 weeks). Cultures are most useful in patients with chronic pulmonary histoplasmosis and PDH. Sputum production is rare in patients with acute pulmonary histoplasmosis, but organisms can be cultured from BAL or other bronchoscopy specimens in some cases. In chronic pulmonary histoplasmosis patients commonly expectorate sputum, and organisms can be found in sputum or bronchoscopy specimens in 60 to 85 percent of cases. Multiple specimens must be cultured to achieve the highest yield. In PDH, the highest yield is from bone marrow or blood, positive in over 75 percent of cases, and in BAL of patients with pulmonary infiltrates. Cultures are usually negative in pulmonary nodules and mediastinal nodes representing subacute or old healed lesions despite demonstration of yeast by histopathology.

Polymerase Chain Reaction

Several laboratories report diagnosis of histoplasmosis by polymerase chain reaction (PCR) on tissues or body fluids. PCR was positive on only 8 percent of urine specimens with elevated *Histoplasma* antigen. PCR is less sensitive than fungal stain for examination of tissue specimens. Currently PCR does not appear to be useful for diagnosis of histoplasmosis.

Histoplasmin Skin Test

Skin tests are not useful diagnostically because of high-background rates of skin test positivity (50 to 80 percent) in endemic areas, false-positive results in patients with other fungal diseases, and false-negative results in PDH. Furthermore, skin tests boost antibody levels, compromising interpretation of serological tests. Skin test reagents are no longer available in the United States. In vitro interferon-γ production upon exposure of mononuclear cells to *Histoplasma* antigen, however, is a surrogate for skin test reactivity.

Exclusion of Histoplasmosis in Workup of Patients with Suspected Sarcoidosis

Considering the similarity between the two conditions, and the risk for progression of histoplasmosis during immunosuppression for presumed sarcoidosis, active histoplasmosis must be excluded before immunosuppressant therapy is initiated. Fungal cultures of BAL, transbronchial lung biopsy, blood, and other sites of suspected involvement should be performed. BAL and urine should be tested for *Histoplasma* antigen, and serum should be tested for anti-*Histoplasma* antibodies. If mediastinal node or lung biopsy is performed, fungal histopathology and culture should be ordered. Biopsy of

other extrapulmonary tissues, when performed, also should be examined for *Histoplasma* by histopathology and culture. Demonstration of yeast by histopathology or elevated levels of *Histoplasma* antigen provide strong evidence for histoplasmosis, and would support delay in immunosuppressive therapy until active histoplasmosis could be excluded. Elevated anti-*Histoplasma* antibodies also should raise concern about active infection, but they may persist several years after the initial infection, and would not exclude a diagnosis of sarcoidosis. If immunosuppressive therapy was initiated in patients with laboratory findings suggestive of histoplasmosis, the patient should be followed closely for evidence of progression of histoplasmosis. Also, if patients with suspected sarcoidosis initially respond to immunosuppressive treatment but later relapse, testing for histoplasmosis should be repeated, as immunosuppression may have accelerated the progression of pulmonary or disseminated histoplasmosis.

Treatment

Most infections are asymptomatic or clinically self-limited, requiring no therapy. Furthermore, treatment has only been studied in PDH and chronic pulmonary histoplasmosis, precluding assessment of effectiveness in the other syndromes. While treatment in cases of acute pulmonary histoplasmosis appears to be effective, patients usually recover without therapy, and studies showing that therapy hastens the response or reduces morbidity have not been conducted. Furthermore, the subacute pulmonary, inflammatory, and mediastinal syndromes are unlikely to be influenced by antifungal treatment as the fungal burden is usually low and the manifestations may not be caused by the residual organisms but rather by the inflammatory response or mass effects of the enlarged nodes.

Indications for Treatment

Acute Pulmonary Histoplasmosis

Patients with symptomatic acute pulmonary histoplasmosis appear to benefit from antifungal therapy (Table 132-4). Adjunctive therapy with corticosteroids may hasten recovery in such patients. Amphotericin B 0.7 to 1.0 mg/kg/d would be preferred as initial therapy in patients who are more severely ill. Itraconazole, 200 mg once or twice daily, is recommended in patients with milder illnesses, and following response to amphotericin B. A 6- to 12-week course is recommended in the absence of PDH, which should be excluded. In cases with PDH, 6 to 12 months of therapy is recommended.

Subacute Pulmonary Histoplasmosis

Patients with subacute pulmonary histoplasmosis usually recover without treatment, and there have been no studies to determine if treatment alters the course or prevents complications. Nevertheless, treatment is reasonable in patients who show no improvement of symptoms after a month of observation. Oral therapy with itraconazole would be appropriate, 200 mg once daily for 6 to 12 weeks.

Table 132-4

Indications for Treatment of Histoplasmosis

Definite
Acute pulmonary, symptomatic
Chronic pulmonary/cavitary progressive
Disseminated
Uncertain
Subacute pulmonary, persistent >1 month
Mediastinal syndrome, persistent >1 month
Inflammatory syndrome, on corticosteroids

Chronic Pulmonary Histoplasmosis

Treatment improves survival, reduces symptoms, promotes radiographic healing, and eradicates *H. capsulatum* from the sputum. Most patients with chronic pulmonary histoplasmosis can be managed without hospitalization and respond well to treatment with itraconazole 200 mg once or twice daily for 12 to 24 months. Amphotericin B 0.7 to 1.0 mg/kg/d is recommended for initial therapy in patients with more severe respiratory insufficiency to achieve a more rapid response.

Mediastinal Adenitis and Granuloma

Patients with obstructive symptoms or fistula caused by mediastinal granuloma should be treated, but whether treatment alters the outcome remains unknown. Itraconazole, 200 mg daily for 6 to 12 weeks, is recommended, after which imaging studies should be repeated to assess response. If the enlarged nodes show reduction in size, therapy might be continued for a total of 3 to 6 months. Surgery should be considered if symptoms persist and are sufficiently bothersome. Antifungal treatment or resection of enlarged mediastinal lymph nodes to prevent fibrosing mediastinitis is not indicated since progression of enlarged mediastinal nodes to fibrosing mediastinitis has not been documented.

Mediastinal Fibrosis

Antifungal treatment is not thought to improve the outcome of mediastinal fibrosis, but therapy with itraconazole, 200 mg daily for 6 to 12 weeks, is commonly tried on at least one occasion and is not unreasonable considering the seriousness of this complication. Occasionally patients benefit from placement of stents in pulmonary vessels or the SVC. Stenting of the airways is not recommended because of the risk for growth of inflammatory tissue causing obstruction of the stent. Surgery is associated with a high mortality and limited efficacy, and should be discouraged. In patients with no other options, care should be taken to select a surgeon experienced with this rare manifestation of histoplasmosis.

Broncholithiasis

Surgical therapy is required for patients with significant hemoptysis or recurrent pneumonia and for repair of fistulae. Antifungal therapy would not be expected to reduce the symptoms since active infection is uncommon in such cases.

Inflammatory Syndromes

Rheumatological syndromes and pericarditis are noninfectious, inflammatory manifestations and respond to anti-inflammatory therapy. Antifungal therapy is not indicated unless the bone, joint, or pericardium are sites of disseminated infection, or if corticosteroids are used for treatment of the inflammatory syndrome.

Disseminated

Treatment is indicated in all patients with PDH. The mortality of untreated disseminated histoplasmosis is 80 percent but can be reduced to less than 25 percent with therapy. Amphotericin B 0.7 to 1.0 mg/kg/d, liposomal amphotericin B 3 mg/kg/d, and itraconazole 200 mg once or twice daily are highly effective. A total duration of 12 to 24 months is recommended in most cases. Among the new antifungal agents, posaconazole appears to be most effective in treating histoplasmosis.

Selection of Antifungal Agents

Amphotericin B may act more rapidly than other antifungal agents. Amphotericin B is recommended for severe cases and women who are pregnant. In patients with AIDS who also have PDH, liposomal amphotericin B (AmBisome) is more effective than standard amphotericin B, with more rapid resolution of fever, higher overall response, better survival, and lower toxicity. Liposomal amphotericin B, 3 to 5 mg/kg/d, is preferred for patients with severe or moderately severe PDH. Treatment can be changed to itraconazole after the patient improves, usually in 3 to 14 days.

Itraconazole is highly effective in most mild to moderately severe cases of PDH and in chronic pulmonary histoplasmosis. Itraconazole capsules require an acidic gastric environment for solubilization and should be given with food or cola. Medications that reduce gastric acidity should be avoided. Itraconazole solution is a good alternative in patients who require gastric acid suppression or who have low blood levels while taking the capsule.

Itraconazole blood levels should be measured after 5 to 7 days of therapy with a sample obtained just before a dose to assure that levels are detectable at trough, and if levels exceed 10 μg/ml by bioassay or 6 μg/ml (combined itraconazole and hydroxy-itraconazole) by high pressure liquid chromatography (HPLC), dosage may be reduced. For those with levels below 1 μg/ml, the oral solution provides better absorption and increases the blood concentration.

Hepatic enzyme inducers reduce itraconazole concentrations and should be avoided. Itraconazole also inhibits intestinal and hepatic cytochrome P450 3A4, causing accumulation of several drugs and increasing their toxicity. As the list of contraindicated medications continues to evolve, physicians should review the drug interactions before starting itraconazole and when new medications are added to the regimen. Furthermore, itraconazole is eliminated by hepatic metabolism and may be ineffective in patients receiving medications that induce cytochrome P450 enzymes. Itraconazole also may cause congestive heart failure and should be avoided in patients with heart disease unless the benefit outweighs the risk. If itraconazole is used in patients with cardiac disease, careful follow-up for development of heart failure is essential, and if heart failure develops, itraconazole should be stopped.

Fluconazole is less active in vitro than itraconazole in histoplasmosis. In patients with AIDS and PDH treated with 800 mg/d of fluconazole for 12 weeks followed by 400 mg/d indefinitely, failure occurred in up to one-half of patients within 6 months. Isolates from patients who failed fluconazole exhibited at least a fourfold reduction in susceptibility to fluconazole in over two-thirds of cases.

Newer Antifungal Agents

Posaconazole and voriconazole are active against *H. capsulatum*, and posaconazole was effective in an experimental model of histoplasmosis. However, voriconazole MICs are higher than itraconazole and posaconazole, and fluconazole treatment induced an increase in MIC to voriconazole (submitted for publication). A few patients have been treated with voriconazole, with inconsistent results, while posaconazole was highly effective, and appears to be the preferred alternative to itraconazole. Echinocandins are not active in vitro or effective in murine models and have not been studied in patients with histoplasmosis.

Maintenance Therapy

Lifelong maintenance therapy was the standard of care in patients with AIDS complicated by PDH before the advent of HAART. With HAART, maintenance therapy can be discontinued in patients who have received at least 1 year of itraconazole, antigen levels less than 4 units in urine and serum, and a CD4 count greater than 150 cells/ml. As with cryptococcosis, patients must be carefully monitored for relapse and continued response to HAART. Resumption of antifungal therapy is recommended if the CD4 count falls below 100 cells/ml or if antigen levels in urine or serum increase, providing evidence of relapse.

Prevention

Patients at high risk for dissemination should avoid activities that expose them to *H. capsulatum*, such as caving or remodeling old buildings inhabited by bats or birds. Hand washing reduces the risk for acute histoplasmosis among persons exposed while crawling in a bat-inhabited cave, while use of loose-fitting paper masks does not. A placebo-controlled study using itraconazole, 200 mg daily, in persons with AIDS demonstrated reduction in the incidence of histoplasmosis. However, since the introduction of HAART, the incidence of

these infections has declined, and is too low to justify prophylaxis. Prophylaxis may be reasonable in areas where the combined incidence of systemic fungal infections exceeds 10 cases/100 patient-years.

COCCIDIOIDOMYCOSIS

Coccidioidomycosis is the most serious of the endemic mycoses, often failing therapy. Furthermore, large outbreaks in Arizona and southern California, increasing population in the southwestern states, and travel have placed large numbers of persons at risk. *Coccidioides immitis* is listed as a "Select Agent" of bioterrorism, complicating its use in the clinical and research laboratory.

Mycology

Coccidioidomycosis is caused by the pathogenic fungus, *Coccidioides,* which includes two species, *C. immitis* and *Coccidioides posadasii.* Except for different geographical locations (*immitis* in California and *posadasii* in Arizona), the laboratory properties, virulence factors, pathogenesis, clinical findings, diagnostic approach, and treatment are the same, hence, *C. immitis* will be used to refer to both species in this section.

C. immitis is highly virulent, causing infection upon exposure to only a few conidia and severe disease with larger inoculum. *C. immitis* has been designated as a select agent by the Centers for Disease Control, requiring that it be destroyed upon identification in the laboratory except at facilities approved for handling select agents. *C. immitis* grows as a mold with septate hyphae in the soil and on culture media and as an endosporulating spherule in the tissues of patients. Its arrow-shaped arthroconidia are 2.5 to 4 × 3 to 6 μm in size and are the infectious particles found in soil.

C. immitis converts to an endosporulating spherule at 37° to 40°C. Spherules measure 30 to 60 μm in diameter and contain numerous 2 to 5 μm endospores (see Fig. 132-3). Growth on fungal media occurs rapidly (less than 5 days) and identification may be possible by the 10th day.

Epidemiology

Coccidioidomycosis occurs in a spotty distribution in the southwestern US, northern Mexico, and Central America (see Fig. 132-1). Growth is enhanced by bat and rodent droppings. Climates in the endemic areas are characterized by hot summers, mild winters, and arid conditions. Exposure is heaviest in the late summer and fall when the soil is dry and conditions are windy, especially following rainy winters. In the United States 100,000 new cases occur annually.

Cases often are identified in construction or agricultural workers and archaeologists or students doing projects in the desert, conditions associated with exposure to soil, but winds carry the spores for miles exposing persons with no direct contact with contaminated soil. Cases often are identified outside the endemic area in travelers or past residents of the endemic area, often years after exposure. Coccidioidomycosis also is a threat to laboratory personnel working with the organism outside of biosafety cabinets.

Coccidioidomycosis is a serious opportunistic infection in immunosuppressed patients, including those with AIDS, bone marrow transplantation recipients, and organ transplantation recipients, those who are receiving immunosuppressive treatment, including TNF-α inhibitors, and those with other immunodeficiency conditions.

Pathogenesis and Pathology

Infection occurs following inhalation of arthroconidia of the mycelial phase of the fungus or reactivation of latent infection during immunosuppression. Reactivation is less common than new infection as a cause for infection in immunocompromised individuals. Person-to-person transmission does not occur and exposure by direct inoculation is rare. Transmission by transplantation of an infected allograft has been reported and causes rapidly progressive disease in the recipient.

In the lungs, the arthroconidia enlarge to form thick-walled spherules, which contain multiple endospores. Spherules rupture releasing endospores, which spread locally and disseminate hematogenously. Cellular immunity and neutrophils both are involved in host defense in coccidioidomycosis. Patients with deficient cellular immunity experience severe progressive forms of coccidioidomycosis.

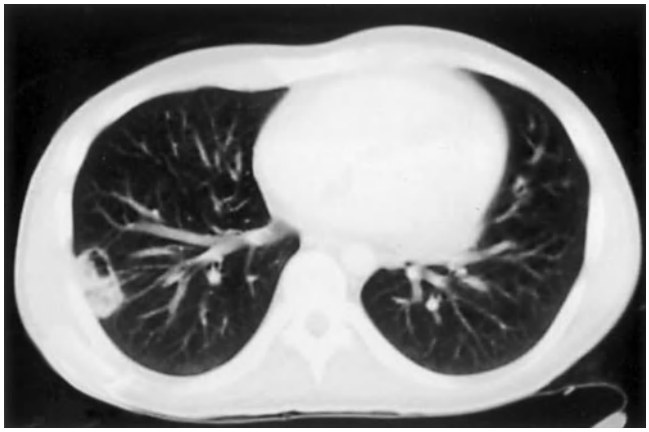
C. immitis produces several mixed pyogranulomatous reactions in the tissues. but, unlike *H. capsulatum*, it is an extracellular pathogen. The neutrophil response and caseous necrosis may lead to development of large abscesses, which often require surgical drainage. Abscesses also may spontaneously rupture or produce fistulas. Tissue and blood eosinophilia often are prominent. Inflammation is less pronounced in patients with AIDS. Fibrosis may be prominent in the lungs or meninges, and as in histoplasmosis, healed lesions frequently calcify.

Clinical Findings

Coccidioidomycosis is asymptomatic in over one-half of cases, and in the remainder symptoms appear 1 to 4 weeks following exposure. In symptomatic cases, a pulmonary illness is most common. While most immunocompetent patients recover without treatment, in some outbreaks over one-fourth of patients experienced severe disease requiring hospitalization, nearly 5 percent developed disseminated disease, and 2 percent died. Disseminated disease is more common in those with underlying immunosuppression.

Primary Pulmonary Infection

Symptoms develop within a few weeks following exposure, depending on the intensity of the inoculum and the immunity of the patient. Low inoculum exposure in the



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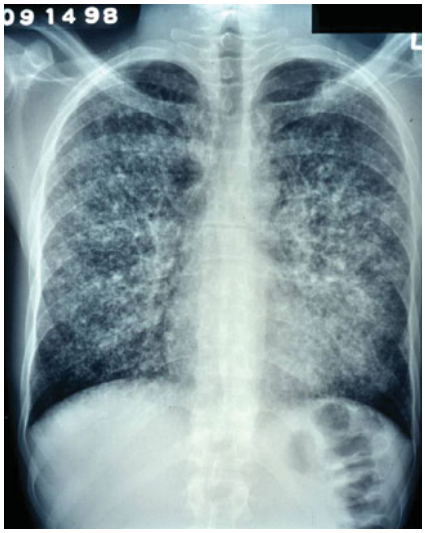

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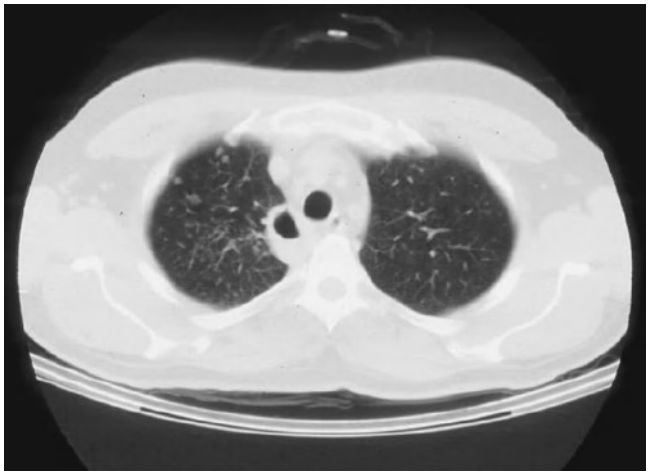

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Figure 132-5 *A*. Chest computed tomography (CT) of cavitary peripheral nodule in acute coccidioidomycosis. *B*. Chest radiograph of diffuse infiltrates in disseminated coccidioidomycosis. *C*. CT of nodular masslike infiltrate that has cavitated.

nonimmunocompromised host usually results in a localized pneumonia, which is often misdiagnosed as community-acquired bacterial pneumonia. In an outbreak following an earthquake, over 80 percent of cases were misdiagnosed as community-acquired pneumonia.

Localized Pneumonia

Symptoms include pleuritic or dull chest pain, nonproductive cough, fever, and malaise. Headache also is common. Macular rash, erythema nodosum, and erythema multiforme are common. A constellation of fever, arthralgia, and erythema nodosum is referred to as "desert rheumatism." Infection is more severe in older persons, those with diabetes, and smokers. Chest radiographs show patchy infiltrates, often with mediastinal adenopathy. Pulmonary nodules occur in about 20 percent of cases and thin-walled cavities in 10 percent, which are usually asymptomatic and clear without therapy (Fig. 132-5). Rarely cavities rupture into the pleural space causing pyopneumothorax, bronchopleural fistula, or empyema. Less commonly pericardial effusions also may be seen.

Diffuse Pneumonia

Diffuse pneumonia may follow large inoculum exposure in the nonimmunocompromised host, and often causes respiratory failure. A miliary pattern, representing hematogenous or lymphangitic dissemination throughout the lungs, although rare, portends a high mortality, and likelihood of extrapulmonary dissemination. Patients with diffuse or miliary infiltrates may develop septic shock, which also carries a poor prognosis.

Chronic Progressive Fibrocavitary Pneumonia

Chronic fibrocavitary infection similar to histoplasmosis and tuberculosis may be seen in coccidioidomycosis. This manifestation is seen in patients with underlying lung disease and tends to progress without treatment, as in histoplasmosis.

Disseminated Disease

Progressive disseminated disease occurs in less than 0.5 percent of cases overall but it is reported in nearly one-half of cases occurring in patients with underlying

immunosuppression. Disseminated disease is often first recognized years following exposure. Risk factors for disseminated disease include nonwhite race, extremes of age, and pregnancy.

Pulmonary involvement is common. Chest radiographs usually show diffuse reticulonodular or miliary infiltrates, but focal pulmonary lesions, nodules, cavities, adenopathy, and pleural effusions also may be seen (see Fig. 132-2).

The extrapulmonary sites commonly involved are skin, bone, joints and meninges, and a shock syndrome associated with respiratory failure has been described. Bone involvement was more common in African Americans while skin and CNS disease occurred more often in Filipinos. Less frequently involved extrapulmonary sites include lymph nodes, liver, peritoneum, kidneys, epididymis, prostate, testes, retina, ears, larynx, heart, thyroid, adrenal, and pituitary glands, esophagus, and pancreas.

Meningitis occurs in up to one-fourth of patients with disseminated coccidioidomycosis, usually presenting within the first month of infection. Patients complain of headache, nausea, vomiting and confusion, and CSF shows lymphocytic pleocytosis. Meningitis carries a poor prognosis and tendency to relapse, despite long-term maintenance therapy. Abscesses may develop in the brain or spinal cord.

Diagnosis

A battery of tests including fungal stain, culture, and serology are useful for diagnosis of coccidioidomycosis (Table 132-5). The sensitivity of these methods is affected by the extent of exposure, immune status of the patient, and the type of infection.

Antigen Detection

Antigen-detection assays for *C. immitis* have been described, but have not been refined for clinical use. Research is ongoing to develop a clinically useful antigen-detection assay for rapid diagnosis of coccidioidomycosis.

Cytology or Histopathology

The sensitivity for examination of sputum is low but may be improved by bronchoscopy, if lesions in the lung or airways can be biopsied, or with BAL. Cytology was positive in 35 percent of culture-positive bronchoscopy specimens for patients with pneumonia, more so with diffuse (46 percent) versus focal (26 percent) infiltrates. In a study of severe diffuse pneumonia in patients with AIDS, Papanicolaou smear was positive in 9 or 14 BAL specimens, compared to KOH wet mount in only 3, calcofluor white stain in 2, and culture in 12. Histopathology is positive on needle-biopsy specimens from lung nodules in about one-half of cases. The sensitivity in extrapulmonary lesions has not been reported but presumably is high, except for meningitis.

Serology

Serological tests are positive in 90 percent of clinically recognized cases, and the magnitude of response correlates with the extent of the infection. Serology is usually negative in asymptomatic cases and often negative in those with mild illness, including thin-walled cavities and nodules. Some report reduced sensitivity in the immunosuppressed host. In patients with AIDS and severe pneumonia, however, serology was positive in only 7 of 13 in one report. In another study of patients with diffuse pneumonia, serology was positive in about two-thirds of cases. Sensitivity may be increased by concentrating the specimen first. Detection of antibody in CSF is invaluable for diagnosis of meningitis. The test proved positive in over 80 percent of cases, while cultures were positive in less than one-third.

The immunoglobulin M (IgM) response can be measured by tube precipitation (TP) or agar gel diffusion (IDTP) and is positive in 50 percent of acute cases during the first week and over 90 percent by the end of the first month of the illness, fading over the next 6 months. However, in an outbreak in

Table 132-5

Diagnostic Studies in Coccidioidomycosis

Test	Acute Pneumonia, Focal	Acute Pneumonia, Diffuse	Nodule or Cavity	Chronic Fibrocavitary	Disseminated (Crum et al, 2004)
Papanicolaou smear or histopathology	<25%	64% (Sarosi et al, 2001)	50% (Forseth et al, 1986)	35% (Sarosi et al, 1970)	>75%
Culture	<10% (Rosenstein et al, 2001)	86% (Sarosi et al, 2001)	10% (Forseth et al, 1986)	95% (Sarosi et al, 1970)	39% (Rosenstein et al, 2001)
Serology	90% (Pappagianis, 2001)	54% (Sarosi et al, 2001)	<50% (Smith & Saito, 1957)	95% (Sarosi et al, 1970)	95% Rosenstein et al, 2001)

Kern County, California, the IDTP test was positive in only 23 percent of patients with mild pneumonia, 39 percent with severe pneumonia, and 21 percent with disseminated disease.

The immunoglobulin G (IgG) response measured by complement fixation (CF) or immunodiffusion (IDCF) follows the IgM and peaks during the fourth month of illness, and then slowly fades. In the Kern County outbreak, CF was positive in 94 percent of patients with mild pneumonia, 91 percent with severe pneumonia, and 94 percent with disseminated disease. CF titers correlate with the extent and severity of infection, and titers greater than or equal to 1:32 suggest dissemination. While CF titers greater than or equal to 1:32 are more common in disseminated versus pulmonary coccidioidomycosis, titers were less than or equal to 1:16 in nearly 25 percent of disseminated cases in a recent report. CF titers greater than 1:32 are also common in patients with chronic pulmonary coccidioidomycosis.

IgM and IgG antibodies also can be measured by enzyme immunoassay (EIA). IgM results were positive in 72 percent of patients with mild pneumonia, 65 percent with severe pneumonia, and 67 percent with disseminated disease in Kern County. However EIA results do not correlate well with CF titers and specificity in fungal controls has not been fully examined. If the EIA test is used, positive results should be verified by immunodiffusion (ID) and/or CF.

Antibody titers decline with treatment, assisting in monitoring therapy and identifying relapse. Serial testing is also indicated in patients who are not receiving therapy, as rising titers suggest progressive infection and support evaluation to exclude dissemination.

Culture

Although few data are available, cultures of respiratory specimens are thought to be infrequently positive in patients with acute pneumonia. The sensitivity of culture for diagnosis of the other pulmonary syndromes also is uncertain because culture positivity was a basis for inclusion in the published studies. Interestingly, cultures were positive in less than 10 percent of needle-biopsy specimens in which spherules were seen by histopathology. Cultures of skin or bone lesions were positive in more than 95 percent of cases of disseminated coccidioidomycosis, while blood, urine, and CSF cultures are positive infrequently, except in renal transplant patients. However, among all disseminated cases, culture was positive in only 39 percent in one study, and the diagnosis was based on serology in the remainder.

C. immitis poses a risk in the laboratory, and must be handled in a biosafety cabinet using biosafety level 3 precautions. Furthermore, as a select agent of bioterrorism, cultures must be destroyed upon identification in laboratories that are not approved for handling them.

Polymerase Chain Reaction

Polymerase chain reaction (PCR) methods have been described but have not yet been studied sufficiently to recommend them for routine use. Their sensitivity, specificity, and accuracy compared to standard methods are unknown.

Coccidioidin or Spherulin Skin Test

Skin test reagents are no longer commercially available. Production of interferon-γ by peripheral blood mononuclear cells upon incubation with *Coccidioides* antigen provides similar information, however, but is not commercially available.

Treatment

Guidelines for treatment have recently been updated. Most infections are asymptomatic or self-limited pulmonary infections, and require no treatment in the absence of immunosuppression. Before withholding treatment, however, patients must be evaluated carefully for the extent of disease and evidence for extrapulmonary dissemination, and in some cases bone scan to identify skeletal lesions and lumbar puncture to assess CNS symptoms may be indicated. In patients in which treatment is withheld, radiographic and clinical follow-up at 3- to 6-month intervals for 2 years is recommended to identify evidence for progressive infection.

Indications for Treatment

Acute Uncomplicated Pneumonia

Some physicians recommend treatment to prevent long-term complications, but most recommend observation without therapy (Table 132-6). Circumstances warranting treatment include immunosuppression, other chronic diseases or conditions affecting recovery from the acute infection, such as diabetes, pregnancy, age greater than 55 years, African American or Filipino descent, and severity of illness. Indicators of severe illness include weight loss greater than 10 percent, intense night sweats for more than 3 weeks, infiltrates involving more than one-half of one lung or portions of both lungs,

Table 132-6

Indications for Treatment of Coccidioidomycosis

Acute pneumonia if special circumstances*
Diffuse pneumonia–bilateral reticulonodular or miliary infiltrates
Cavity, symptomatic
Cavity, ruptured, causing pyopneumothorax
Chronic progressive fibrocavitary pneumonia
Disseminated

** Special circumstances include underlying immunosuppression, other chronic disease affecting outcome (e.g., diabetes, heart, or lung disease), age >55 years, pregnancy, Filipino or African ancestry, severe manifestations, infiltrates > one-half of one lung or portions of both lungs, complement fixing antibody titer ≥ 1:32, inability to work, symptoms > 2 months.*

prominent or persistent hilar adenopathy, inability to work, and symptoms persisting for more than 2 months.

Persistent Cavities or Nodules

Five to ten percent of patients with acute pulmonary coccidioidomycosis will develop nodules or cavities, which often are asymptomatic, and require no therapy. Symptoms may include pain, hemoptysis, and those associated with bacterial superinfection. Antifungal therapy is appropriate in patients with persistent symptoms for more than 2 months, in conjunction with antibacterial antibiotics if super infection is suspected. Treatment also is recommended in those with lesions contiguous with the pleura, or exhibiting progressive enlargement. Excision should be considered if the cavity does not decrease in diameter in response to therapy, or persists after 2 years of observation. For cavities that rupture into the pleural space, optimal therapy requires surgical closure by lobectomy and decortication, and antifungal therapy. In patients who are too ill to undergo extensive surgery, chest tube drainage may be appropriate.

Chronic Progressive Fibrocavitary Disease

Antifungal treatment is recommended in patients with chronic progressive fibrocavitary disease.

Extrapulmonary or Disseminated

Treatment is indicated in all patients with disseminated coccidioidomycosis. More controversial is the role of antifungal therapy in the immunosuppressed host with serological, radiographic, or clinical evidence of prior coccidioidomycosis. Death from coccidioidomycosis was reduced by antifungal therapy used as secondary prophylaxis in solid organ transplant patients with a history of symptomatic coccidioidomycosis up to 5 years before transplantation, supporting a recommendation for preventive treatment.

Selection of Antifungal Agents

Amphotericin B 0.7 to 1.0 mg/kg/d is indicated in severe cases, immunosuppressed patients with diffuse pneumonia, and during pregnancy. The lipid formulations are recommended in patients who cannot take the standard formulation because of underlying renal disease or amphotericin-induced nephrotoxicity.

Itraconazole and fluconazole are effective in milder cases. In patients with bone disease, outcome was better with itraconazole. Recommended dosages for fluconazole and itraconazole are 400 mg/d for nonmeningeal disease. Drug interactions and inadequate drug exposure occur more often with itraconazole than fluconazole.

Treatment for meningitis is less effective than for other forms of coccidioidomycosis. Fluconazole 400 to 1000 mg per day is recommended because of its excellent penetration into CSF in conjunction with amphotericin B intravenously in more severe cases. Toxicities may be greater using doses above 400 mg daily, however. Some physicians also administer amphotericin B intrathecally.

Newer Antifungal Agents

The newer triazoles exhibit in vitro and in vivo activity against *C. immitis* and there are a few reports of successful treatment with posaconazole and voriconazole, including cases with meningitis. Despite poor in vitro activity, caspofungin demonstrated efficacy in animal studies; but its effectiveness in patients has been inconsistent, discouraging its use.

Duration of Therapy

In patients with acute pulmonary coccidioidomycosis, a short course of therapy (e.g., 2 to 4 months) may be sufficient. Patients should be re-evaluated before treatment is stopped to identify evidence for chronic infection or extrapulmonary dissemination, in which case treatment should be continued for 12 to 18 months. Treatment should be continued indefinitely for patients with meningitis or those with severe underlying immunodeficiency states. Relapse has been reported in a patient with AIDS with a CD4 count greater than 300 cells/ml who discontinued fluconazole.

Adjunctive Surgical Therapy

Surgical debridement or resection of infected tissue often is necessary as an adjunct to antifungal therapy. Chronic foci of pulmonary necrosis or cavitation may require resection to prevent progression or relapse. Soft-tissue, joint, or bony abscesses may require drainage or debridement.

Prevention

Patients with diseases that impair cellular immunity probably should avoid activities involving dust or soil, areas experiencing active outbreaks, and the desert during dry and windy periods. Antifungal prophylaxis for high-risk patients is not recommended. Some, however, would recommend screening for coccidioidomycosis by chest radiograph and serology before initiating TNF-α inhibitor therapy, and treatment of those with positive results. Efforts to develop a vaccine have been unsuccessful to date.

BLASTOMYCOSIS

Blastomycosis is the least common of the endemic mycoses. Although recognized in immunocompromised individuals, in whom manifestations are more severe, it is less common than histoplasmosis or coccidioidomycosis in this setting. Unfortunately, the diagnosis is often overlooked until late in the course of the disease, when the patient is severely ill and the prognosis is poor.

Mycology

Blastomyces dermatitidis is a thermally dimorphic fungus producing mycelia with 2 to 10 μm dumbbell-shaped conidia at 25°C and doubly retractile, broad-based budding yeasts varying in size from 8 to 30 μm at 37°C (see Fig. 132-3). Isolation

of *B. dermatitidis* in the mycelial form from cultures may require several weeks. Definitive identification is made using DNA probes or exoantigen tests.

Epidemiology

B. dermatitidis is found in microfoci near water that is enriched with animal excreta, and its endemic distribution overlaps that of histoplasmosis (see Fig. 132-2). The organism has been isolated from soil in areas inhabited by farm animals and from beaver lodges or dams. Decaying organic matter enhances its growth in the environment. Several common source outbreaks have been reported, usually associated with outdoor activities such as hunting, camping, or canoeing in wooded or swampy environments.

Pathogenesis and Pathology

Pulmonary disease follows inhalation of conidia and often is accompanied by hematogenous dissemination. Neutrophils are first recruited to sites of infection, followed by lymphocytes. Cellular immunity plays a lesser role in defense in blastomycosis than in histoplasmosis, but disease is more severe in immunosuppressed individuals.

Pathologically, blastomycosis is characterized by granuloma formation with central microabscesses, so-called pyogranulomas, but not by caseation as seen in histoplasmosis or tuberculosis. Histological changes in the skin may resemble those of squamous-cell carcinoma or keratoacanthoma. Calcification is uncommon.

Clinical Manifestation

Following exposure, the incubation period ranges from 2 to 10 weeks, but usually is less than 1 month, although diagnosis is often delayed. In up to one-half of cases the infection is asymptomatic, and in symptomatic cases pneumonia is most common. The importance of consideration of blastomycosis in the differential diagnosis of community-acquired pneumonia was dramatically illustrated by the recent report of fatal outcome in several children.

Pneumonia

Patients exhibit fever, cough, dyspnea, chest pain, and often expectorate purulent sputum. Fibrocavitary disease, as seen in histoplasmosis and coccidioidomycosis, is uncommon in blastomycosis, occurring in only 6 percent of cases. Radiographic findings included nodules, focal infiltrates or consolidation, lung masses, and diffuse infiltrates (Fig. 132-6). Areas of consolidation may resemble cancer, leading to lung resection. Mediastinal lymphadenopathy and calcification are uncommon. The radiographic findings in patients with acute blastomycosis and those with chronic disease are similar, except that cavities and consolidation are more common in patients with chronic and diffuse infiltrates in acute infection.

Acute Respiratory Distress Syndrome

Although acute respiratory distress syndrome (ARDS) may be the presenting manifestation of blastomycosis, in most patients it follows a chronic illness. Patients may have underlying diseases or be otherwise healthy, and about one-half exhibit extrapulmonary dissemination. Pathology is characterized by dense consolidation, microabscesses, hyaline membranes, and alveoli packed with yeast forms. Mortality is high, with death occurring in less than a week following presentation in most cases.

Disseminated Blastomycosis

Dissemination is rare in acute pulmonary blastomycosis but common in those who are undiagnosed and manifest chronic illness. Skin lesions are the most common manifestations, followed by bone, genitourinary, and CNS involvement. Other sites include the sinuses, ears, eyes, thyroid gland, heart, pericardium, pancreas, spleen, liver, and adrenal glands.

Immunocompromised Host

Blastomycosis is more aggressive in this group, with a mortality of nearly 30 percent. CNS involvement or ARDS was reported in 5 to 10 percent of cases. Except perhaps for increased mortality and a tendency to relapse, the clinical findings are similar to that in nonimmunocompromised individuals.

Diagnosis

Fungal stain, cytology, or antigen detection provides the first evidence for the diagnosis in most cases (Table 132-7). Culture, although usually positive, does not permit early diagnosis because growth may be slow. Serology using recombinant antigens promises to be useful in blastomycosis.

Antigen Detection

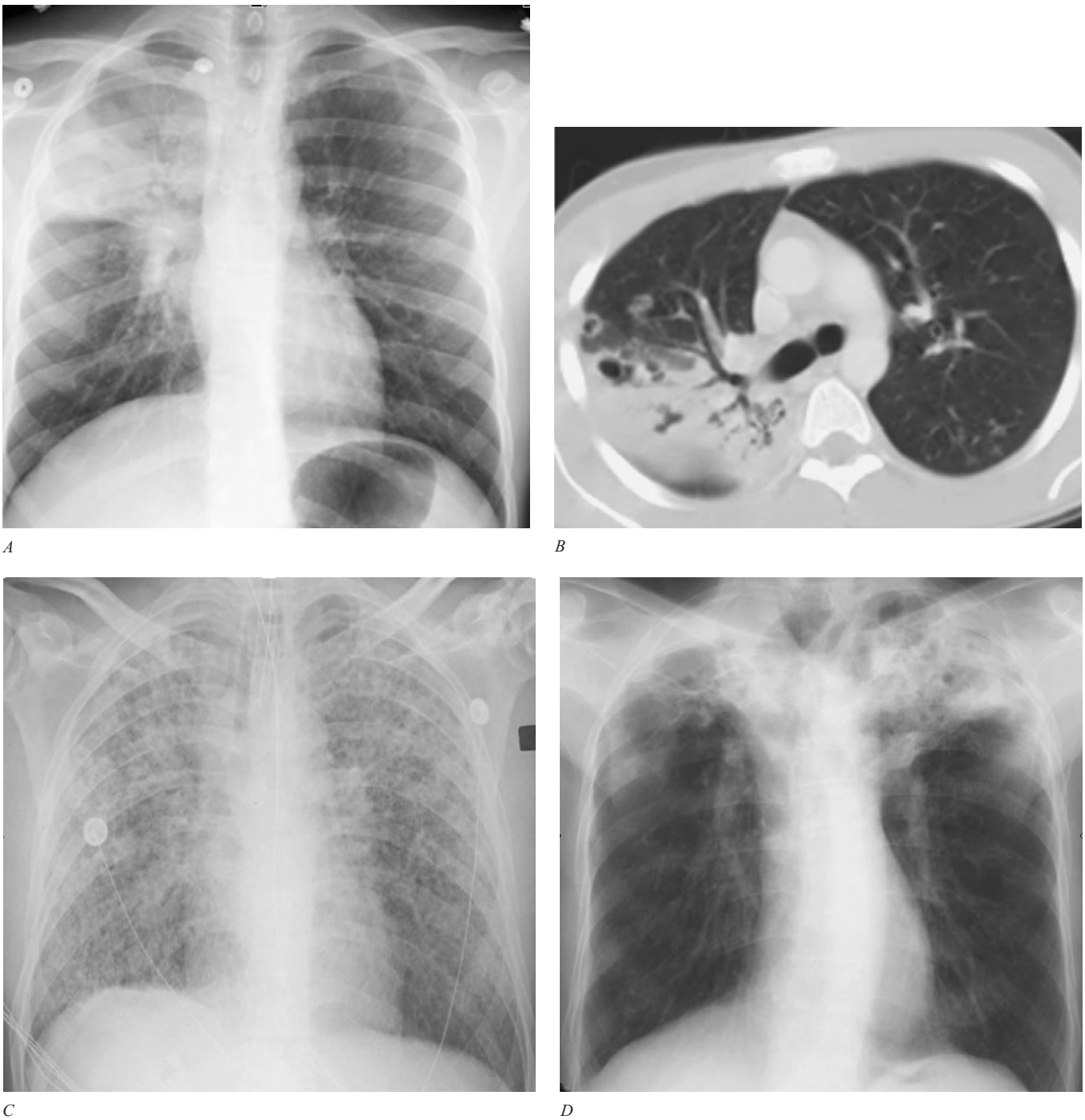
Antigen can be detected in the urine and/or serum of 92 percent of patients with disseminated or pulmonary blastomycosis. Antigen also can be detected in BAL specimens from patients with pulmonary blastomycosis and CSF of those with CNS involvement. Antigen declines with treatment and rebounds with relapse, guiding treatment decisions.

KOH, Cytology, or Histopathology

Cytology and KOH exhibit variable sensitivity in different laboratories. The sensitivity is similar in pulmonary and extrapulmonary specimens, ranging from below 50 percent to over 90 percent. Bronchoscopy may improve the sensitivity in pulmonary cases with negative results on sputum specimens. The organism also may be identified by GMS or PAS stain in most cases.

Mycology

Definitive diagnosis requires isolation of the organism by culture and identification by exoantigen testing or nucleic acid



A

B

C

D

Figure 132-6 *A*. Chest radiograph of infiltrate resembling bacterial pneumonia in acute blastomycosis. *B*. Computed tomography scan showing lobar infiltrate. *C*. Chest radiograph of diffuse infiltrates associated with acute respiratory distress syndrome. *D*. Chest radiograph of cavitary blastomycosis.

hybridization. Cultures are positive in two-thirds to three-fourths of cases, but rarely provide the basis for initial diagnosis because of slow growth.

Serology

Serology using recombinant antigens may assist in diagnosis of blastomycosis. While older methods using crude antigens are neither sensitive nor specific, an immunoassay using recombinant WI-1/Bad1 protein is more accurate. An EIA using Bad1 protein is under investigation.

Polymerase Chain Reaction

PCR methods have been described but have not yet been studied sufficiently to recommend them for clinical use.

Table 132-7

Diagnostic Studies in Blastomycosis

Test	Sensitivity %	Author
Antigen	93	Durkin et al, 2004
Cytology	50–93	Patel et al, 1999; Martynowicz & Prakash, 2002; Lemos et al, 2000
KOH	29–83	Patel et al, 1999; Martynowicz & Prakash, 2002; Lemos et al, 2000
Histopathology	85	Lemos et al, 2000
Culture	66–75	Martynowicz & Prakash, 2002; Lemos et al, 2000
Serology	<50	Martynowicz & Prakash, 2002; Klein et al, 1987

Treatment

Treatment is indicated in most symptomatic patients, according to published guidelines and recent reviews.

Indications for Treatment

Treatment is indicated in all patients with diffuse pneumonia, disseminated disease, underlying immunosuppression, or persistent symptoms more than a month following acute infection (Table 132-8). In some cases of acute pneumonia, the course is self-limited and resolves without treatment. Some authorities recommend treatment for all cases, but if observation is under consideration, the following conditions should be met: mild illness and absence of immunosuppression or extrapulmonary dissemination. Furthermore, such patients should be followed carefully for several years for evidence of progression or dissemination.

Whether pregnancy alters the course of infection in the mother is unknown, but there is risk for transplacental transmission to the fetus. Treatment of the mother may reduce the risk for transmission to the fetus. Amphotericin B is recommended as the triazoles are contraindicated because of embryo toxicity and teratogenicity.

Table 132-8

Indications for Treatment of Blastomycosis

Acute pneumonia, moderately severe or severe
Acute pneumonia, mild if not improving after 1 month observation
Disseminated infection
Immunocompromised host

Selection of Antifungal Agent

Amphotericin B 0.7 to 1.0 mg/kg/d is recommended for initial therapy in severe cases and itraconazole for others. In patients who improve with amphotericin B, treatment could be changed to itraconazole 200 to 400 mg daily. Fluconazole is less effective than itraconazole and should be reserved for those unable to take itraconazole.

Newer Antifungal Agents

Voriconazole and posaconazole are active against *B. dermatitidis* and effective in a murine model of blastomycosis. Neither has been studied in humans, but there are a few reports of successful therapy with voriconazole. The echinocandins showed variable activity in vitro but have not been studied in animal models or humans, and are not recommended.

Duration of Therapy

Treatment should be continued for at least 6 months, until clinical and laboratory findings have normalized including antigen levels in urine and serum, and radiographic abnormalities have resolved or at least stabilized to represent residual healed lesions. Some experts recommend chronic maintenance treatment for patients with AIDS or other underlying immunosuppressive conditions. Experience in AIDS is insufficient to assess the safety of discontinuation of maintenance. If maintenance therapy is stopped, the patient should be followed clinically for relapse, and antigen levels should be monitored. Treatment should be resumed if CD4 counts decline below 100 cell/mm or antigen levels rise.

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Pneumocystis Pneumonia

Jay A. Fishman

Despite significant advances in our understanding of the treatment and pathophysiology of *Pneumocystis* infection, *Pneumocystis carinii* remains an important pathogen in the immunocompromised host. Since the original association of this organism with epidemics of interstitial plasma cell pneumonitis of young, malnourished children, *P. carinii* has been identified as a cause of pneumonia in a broad range of immunocompromised hosts. The incidence of *Pneumocystis* pneumonia has decreased with appropriate deployment of antimicrobial prophylaxis in appropriate hosts and with the advent of highly effective antiretroviral therapy (HAART) in HIV-infected individuals. PCP remains an important syndrome in HIV-infection in the developing world, with high mortality and often in association with tuberculosis. *Pneumocystis* pneumonia (PCP) has also remained an important syndrome as the survival of immunocompromised individuals has increased after organ and hematopoietic stem cell and bone marrow transplantation, and with the broader use of immunosuppressive therapies in connective tissue and other immune disorders. The proposed change in nomenclature, renaming of *Pneumocystis carinii* as *Pneumocystis jiroveci,* reflects the increase in knowledge about the organisms responsible for this syndrome in different host species and has generated significant controversy among scientists, clinicians, and journal editors. Advocates and detractors alike agree that *Pneumocystis* pneumonia or PCP should be used to describe disease caused by this organism in humans. For this discussion, and in the absence of a clear consensus, the term *P. carinii* is retained for both the human and non-human forms of the organism.

HISTORY AND BACKGROUND

The cyst form of *P. carinii* was described in 1909 (Chagas) and 1910 (Carini) as a part of the life cycle of the trypanosome. It was described in 1912 (Delanoe and Delanoe) as a unique organism infecting the lungs of rats. *P. carinii* was not described in humans until 1942 (van der Meer and Brug), and was not associated with human disease until 1952 (Vanek and Jirovec), when it was found in association with "plasma cell interstitial pneumonitis" in malnourished children and neonates. Small epidemics of plasma cell interstitial pneumonitis had been noted in children in orphanages in Europe in the 1930s. In the 1950s, studies of the immune system led

to the recognition of congenital immune deficiencies and the development of immunosuppressive therapies. At that time, *P. carinii* was recognized in patients receiving corticosteroids and chemotherapeutic drugs, and in immunosuppressed rats receiving corticosteroids. The first case of *PCP* was reported in the United States in 1956.

The increasing incidence of PCP led to epidemiologic and therapeutic studies of the disease by the Centers for Disease Control (CDC) in 1970 and in 1974, based on the provision of the sole therapeutic agent available at that time (pentamidine methanesulfonate) by the CDC. Clusters of *P. carinii* have been reported at a variety of clinical oncology and transplant centers. However, the development of pyrimethamine and sulfadoxine and of trimethoprim (TMP) and sulfamethoxazole (SMX) for the treatment and prevention of *Pneumocystis* infection greatly reduced the occurrence and the morbidity of the infection. These agents are now generally used in a fixed combination (TMP-SMX, cotrimoxazole). *P. carinii* became the first disease-defining illness associated with AIDS in the 1980s, causing over one-fourth of community-acquired pneumonias in HIV-infected persons and more than 200,000 cases of *PCP* occurring since 1979 seen without the use of antibiotic prophylaxis and antiretroviral therapy in the HIV-infected population. Fortunately, as with other AIDS-defining illnesses, effective HAART for HIV-infection has resulted in the dramatic reductions in the incidence of PCP in regions in which such therapies are available. PCP remains a frequent complicating infection in areas without access to HAART, including mycobacterial and endemic fungal pneumonias.

STRUCTURE AND LIFE CYCLE

In humans and animals, three forms of the organism have been identified: trophozoite, cyst, and sporozoite (or intracystic bodies) (Fig. 133-1). The trophozoite, 2 to 5 μ in diameter, is either round or sickle-shaped and contains a nucleus, mitochondria, and vacuoles; it also includes pseudopodia and filopodia, used in limited motility. The cyst usually measures between 3 and 6 μ in diameter. Its cell wall consists of three layers, and its cytoplasm contains eight small pleomorphic intracystic (oval) bodies (sporozoites). Two other cystic forms have been described, but these are probably intermediates including empty or developing cysts (Fig. 133-1). Many small surface projections (tubular expansions) form a branching network over the surfaces of the cysts and the trophozoites. The role of these projections is unknown.

In the alveolus, *Pneumocystis* are covered with a variety of glycoproteins derived from both the organism and the environment. Specific and nonspecific immunoglobulins, albumin, surfactant proteins, laminin, fibronectin, and other serum and lung proteins coat the surface. The organism itself produces a relatively limited array of surface glycoproteins that share antigenic epitopes; these are 110 to 120, 55 to 60, 40 to 50, and 20 to 27 kd in molecular weight. These, and some minor components, are found on both animal- and human-derived organisms. *P. carinii* from different species share antigenic epitopes in addition to carrying unique epitopes. Of note is that most adult patients with *Pneumocystis* pneumonia carry antibodies to the major epitopes of the

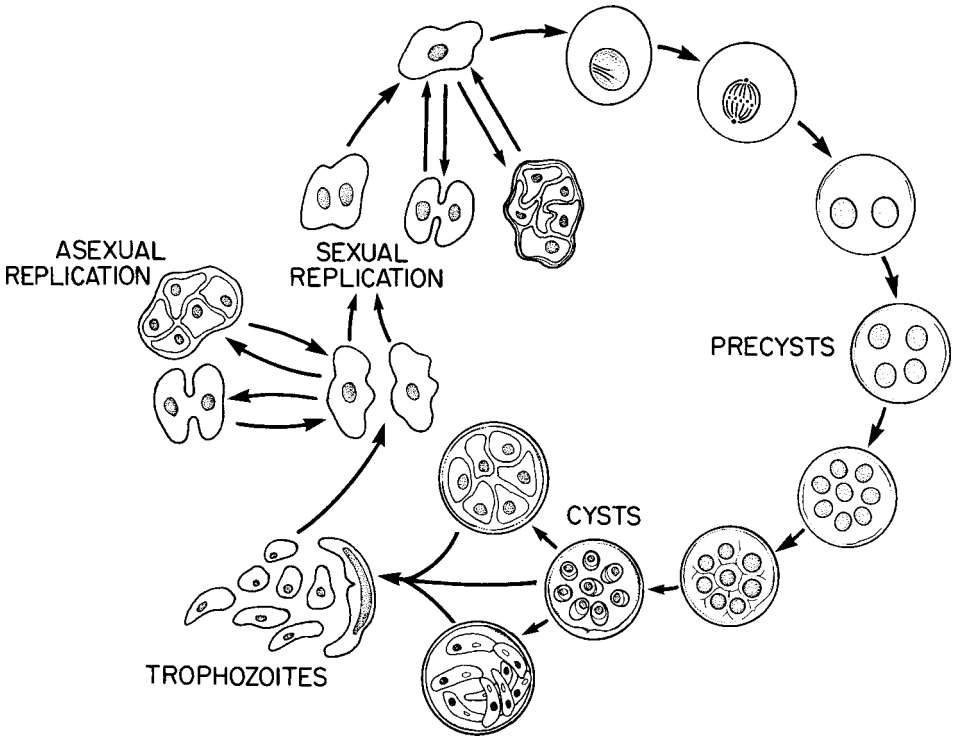


Figure 133-1 The life cycle of *Pneumocystis carinii.*

organism. The cell wall contains cholesterol but no ergosterol and does not appear to synthesize sterols de novo; this accounts for the lack of susceptibility to many of the antifungal antibiotics. The presence of chitin in the cell wall is controversial. The surface of *P. carinii* is carbohydrate rich with glucose, mannose, and β-1,3-glucan, which may play a role in phagocytosis of the organism by macrophages. The surface also contains carbohydrate-binding moieties, which may play a role in attachment to epithelial or surfactant layers.

The life cycle of *Pneumocystis* is poorly understood (Fig. 133-1). Many of the studies of the life cycle have used organisms derived from infected animals and passaged on a feeder cell layer of epithelial or fibroblastoid cells in tissue culture. Continuous growth has not been achieved in this system, and the human-derived organism has not been grown consistently in vitro. Success with axenic or cell-free cultivation of *P. carinii* has been limited. It is now believed that the sporozoites (daughter forms) emerge from the cyst to develop into trophozoites; some of the trophozoites mature to form cysts and then repeat the cycle. This sequence is far from settled, however, and both sexual and asexual intermediate stages have been postulated. It is likely that some differences exist in *Pneumocystis* growth in different hosts and with different immune defects.

Research on *Pneumocystis* has been hampered by the difficulties encountered in propagating the organism in vitro. Studies have been performed on organisms derived from immunosuppressed rodents, which spontaneously develop PCP. Hughes and coworkers have used this model to demonstrate the aerosol transmission of *P. carinii.* Cell culture techniques are not useful diagnostically, because of the difficulty in culturing the organism from infected human tissues. *Pneumocystis* is occasionally grown as a contaminant in viral cultures of bronchial lavage fluid on a variety of feeder cell lines.

TAXONOMY AND MOLECULAR BIOLOGY

Phylogenetic data support the identification of *P. carinii* with the fungi (*Rhizopoda, Myxomycetes, Zygomycota, Schizosaccharomyces, Neurospora, Candida,* and the red yeasts in various studies), based on conserved mRNA sequences. The presence of separate genes encoding the thymidylate synthase and dihydrofolate reductase of *P. carinii,* the presence of a cyst wall rich in β-glucan that stains with periodic acid–Schiff and silver stains, the poorly developed mitochondria, the absence of typical protozoan intracellular organelles, and the airborne spread of infection all support this taxonomic position. The neutral lipid fraction of *P. carinii* includes a variety of phytosterols shared by plants and fungi, including *Physarum* species. However, the appearance of the organism with a thick-walled cyst with internal sporozoites and ameboid trophozoites, the absence of ergosterol, susceptibility to antibiotics used in the treatment of protozoan infections (pentamidine, atovaquone, sulfamethoxazole), and the existence of antigenic variation in the major surface glycoprotein (gp120, gpA, MSG) lend credence to identification with the protozoa.

Based on these observations, it was likely that a new phylogenetic category is needed within the *Ascomycota* for *Pneumocystis.* Difficulty in ascribing *Pneumocystis* to one or another family may be further complicated by the apparent exchange of membrane lipids and perhaps glycoproteins between *P. carinii* and host cells. This may allow the adaptation of *P. carinii* to the host environment, decrease the effectiveness of the immune response, and enhance survival by decreasing the membrane synthetic demands of the organism. Unique cell wall components (glucans, phytosterols) and synthetic pathways (e.g., topoisomerases) may participate in the pathogenesis of infection due to *P. carinii* and may provide targets for the development of new antibiotics.

The existence of different strains of *Pneumocystis* has been demonstrated using pulsed-field gel electrophoresis to establish chromosomal patterns. It appears that infections are often clonal, although multiple strains may coexist in the infected person. Characteristic chromosome patterns have not yet been associated with specific virulence or host characteristics. Characteristic shifts in the telomeric ends of the chromosomes suggest that genetic exchange is ongoing between chromosomes, as occurs in the mechanism of antigenic variation by movement of genetic cassettes noted in the subtelomeric region of the trypanosomes.

P. carinii expresses both unique and some common antigens in different host species. Surface antigens have been characterized at the glycoprotein and molecular levels. The major surface glycoprotein (MSG) represents the main humoral immunogen in the rat model, although other antigens (gp45–55) may have importance in human infection. Several MSG types (up to three) have been observed simultaneously in single infected humans and animals with monoclonal antibody staining and genetic characterization. Because some antigens are shared between glycoproteins of differing sizes and between species, it is unclear whether a single organism can express more than one MSG or switch MSG expression during the life cycle. The MSG appears to represent a large family of related genes (more than 30), many of which are located in tandem repeated arrays in the subtelomeric regions and may contribute to the generation of the variety of antigenic types.

Data from a number of laboratories, including our own, suggest that each genomic copy of an MSG includes an upstream highly conserved expression site and a unique segment downstream that encodes the differing antigenic characteristics of each clone. The organization of the joining region between the conserved and variant segments contains alternating conserved and variant segments, whose function remains to be determined. It is not yet clear whether the conserved intron-exon structure represents a splicing system related to that of the African trypanosomal variant surface glycoprotein, which allows the serial expression of a variety of antigenic types. No evidence for active switching of genotypes has been developed to date (e.g., under selective immune pressure).

However, the presence of splicing is suggested by the absence of genomic intergenic regions in the mRNA transcripts encoding cloned MSGs.

EPIDEMIOLOGY OF INFECTION DUE TO *PNEUMOCYSTIS*

Over the past 50 years, *PCP* has been transformed from a medical curiosity into an important respiratory infection that affects four categories of immunocompromised host: (1) *congenital,* caused by inborn immune defects in antibody-synthesizing capacity and/or in the cellular mechanisms responsible for delayed hypersensitivity; (2) *induced,* by immunosuppressive therapy, especially corticosteroids in the treatment of hematopoietic malignancies; (3) *acquired,* occurring as an identifying opportunistic pathogen in HIV infection or with exogenous immune suppression; and (4) *nutritionally deficient with epidemic infection,* seen primarily in neonates and infants.

P. carinii causes pneumonia in persons with a wide variety of underlying immune deficiencies (Table 133-1). Studies performed in immunosuppressed animals and clinical experience indicate that T-cell immune defects predominate in individuals with *P. carinii* infection. Passive transfer of immune T lymphocytes is protective against *PCP* in mice, whereas transfer of immune globulin alone is only partly protective.

The relative risk of infection with *Pneumocystis* is predictable in most hosts in which this infection occurs. For example, the risk of *Pneumocystis* pneumonia is greatest in the first 6 months after transplantation, after 3 to 6 months of oral corticosteroid therapy, and during periods of increased immune suppression, for example, during the use of bolus corticosteroids or antilymphocyte therapies for graft rejection (Table 133-2). Disease occurring outside the hosts or timeframe predicted on the basis of the predicted degree of immune suppression should suggest an excess epidemiologic hazard or immune deficiency. PCP has also complicated the syndrome of rapamycin lung an idiosyncratic syndrome of diffuse pulmonary infiltrates in solid organ transplant recipients receiving sirolimus-based immune suppression. In AIDS, risk for PCP increases with the progressive fall of the CD4-positive lymphocyte counts to below 200 per cubic centimeter or to less than 20 percent of the total lymphocyte pool. The correlation with T-lymphocyte numbers is such that the rate of infection nearly doubles with a drop in CD4-positive lymphocyte counts from between 100 and 200 to below 100/cm^2. The presence of thrush has also been shown to be an independent predictor of risk for PCP in patients with HIV as a previous bout of PCP. Rarely, PCP occurs at CD4 counts greater than 200 cells/mm and prophylaxis should be offered to such patients starting around the level at which PCP occurred. The occurrence of PCP infection in persons not

Table 133-1

Conditions Associated with *Pneumocystis* Pneumonia

Acquired immunodeficiency syndrome (AIDS) (without HAART)
Chemotherapy (especially corticosteroids)
Radiation therapy
Organ transplantation
Prematurity
Malnutrition (protein and calorie)
Malignancies (especially hematopoietic)
Congenital immune deficiency diseases (cellular and/or humoral)
Collagen vascular disease
Hematologic disorders
Cushing's syndrome
Nephrotic syndrome

Table 133-2

Reported Attack Rates for PCP by Underlying Condition in Patients Not Receiving Prophylaxis

Underlying Disorder	Attack Rate (%)
Acute lymphoblastic leukemia	6.5–42.9
Severe combined immunodeficiency syndrome	27–42
Rhabdomyosarcoma	4–25
Wegener's granulomatosis	3.5–12
Hodgkin's disease	1.3
Collagen vascular disease	<2
Primary or metastatic central nervous system tumor	1.3–1.7

in these categories should suggest exposure to infected persons, other immunosuppressive effects (e.g., coinfection with cytomegalovirus, lymphoma, neutropenia), or in the HIV-infected person, a rapid progression of viral infection with the accompanying decline in systemic immune function. The spectrum of patients developing PCP has changed with the advent of highly active antiretroviral therapy (HAART) for HIV infection and the routine use of prophylaxis for most patients with hematological malignancies or after organ transplantation. In most HIV-negative, immunocompromised patients, the risk of disease is of the order of 5 to 15 percent. The major risk factors for PCP are reflected in a retrospective study of 116 HIV-negative patients with PCP of which 30.2 percent had hematologic malignancies, 25 percent were organ transplant recipients, 22.4 percent had inflammatory disorders, 12.9 percent had solid tumors, and 9.5 percent had other conditions. Corticosteroids use was reported in 90.5 percent of these patients. The median daily dose was 30 mg of prednisone; however, 25 percent of the patients had received as little as 16 mg/day of prednisone. The median duration of corticosteroid therapy before the diagnosis of PCP was 12 weeks. However, 25 percent of the patients developed PCP after 8 weeks or less of corticosteroid use.

In children, epidemiologic studies suggest that PCP may occur as a result of concomitant viral infections and were prominent among infants who die unexpectedly in the community. Beard et al. demonstrated that different strains of *Pneumocystis* appeared to be present in specimens obtained from infants compared with those from HIV-infected adults, suggesting that different strains were circulating among immunocompetent infants and in HIV-infected adults.

The natural reservoir of infection remains unknown. Aerosol transmission of infection has been demonstrated in animal models, and clusters of infections have developed in clinical settings—for instance, between HIV infected persons and renal transplant recipients. *P. carinii* DNA has been detected by polymerase chain reaction (PCR) in the air of hospital rooms, bronchoscopy suites, and clinics used by infected subjects. The frequency of infection varies both by institution and geography. For example, it appears that the incidence of *Pneumocystis* in AIDS patients is much lower in Africa than in the United States. However, this may reflect limited diagnostic capabilities and the morbidity associated with the endemic level of tuberculosis and diarrheal pathogens in Africa, rather than a reduced epidemiologic exposure. The use of PCR technology suggests that carriage of *P. carinii* in African AIDS patients is, in fact, common.

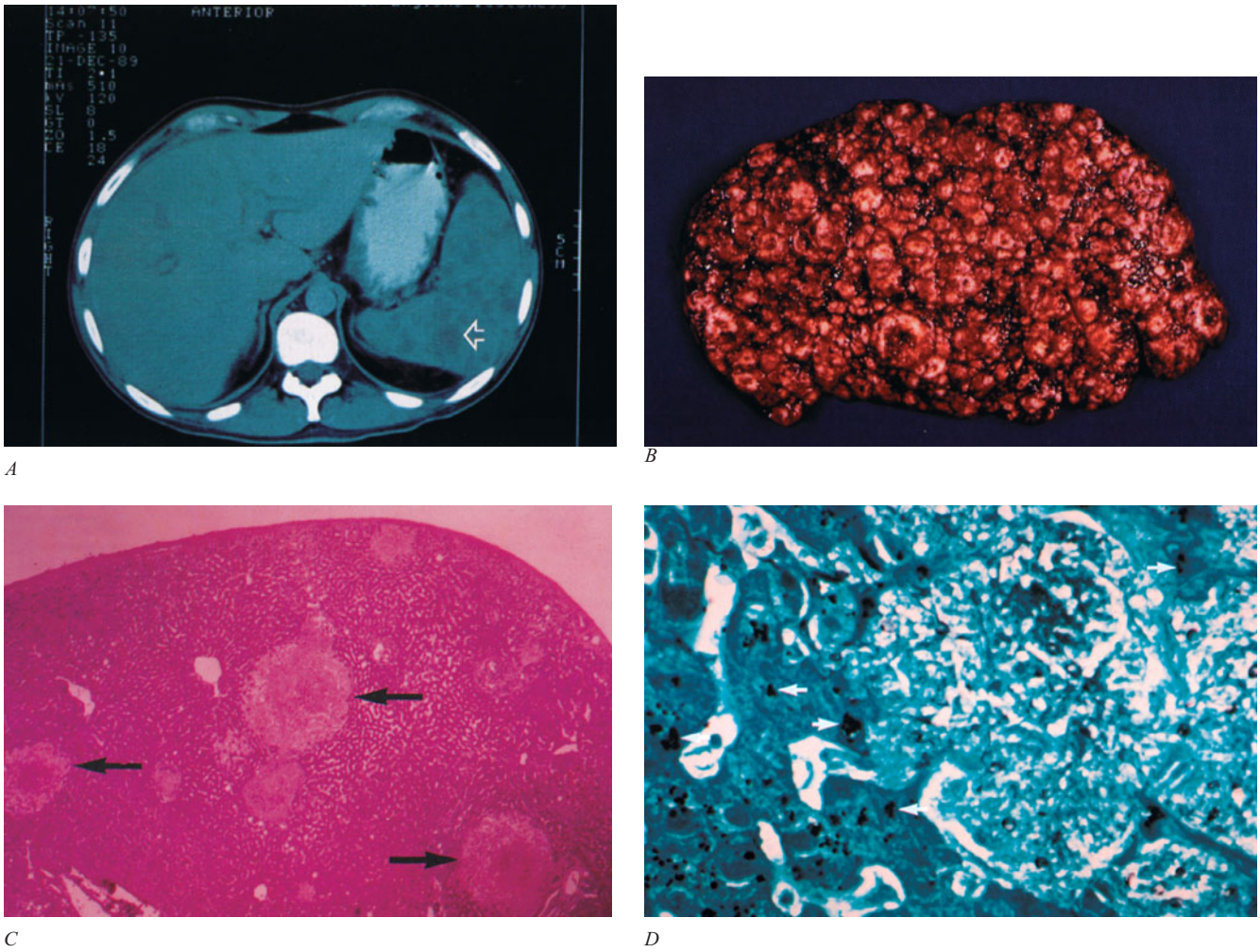
The prevalence of infection with *P. carinii* in patients with AIDS prompted a large effort to develop diagnostic serologic tests that might be applied to the general population. Serologic testing has reinforced the view that subclinical infection is common and that a reactivation of latent infection is often a factor in the pathogenesis of *PCP*. However, in studies of rats cured of *Pneumocystis* pneumonia by trimethoprim-sulfamethoxazole (TMP-SMX), immunosuppression alone does not result in recurrent infection if the animals are maintained in a sterile environment. Recent molecular studies in animals and humans using a variety of genetic probes, including probes for *P. carinii,* ribosomal mRNA internal transcribed spacer regions have suggested that *both reinfection and the reactivation of latent infection are significant factors in the incidence of disease.*

Most people have serologic evidence of exposure by age 4. The rate of identification of organisms in autopsy studies is less than 8 percent. An autopsy series from patients with malignant lymphoma or leukemia demonstrated a 5 percent incidence of identification of pulmonary *P. carinii,* compared with a less than 0.5 percent incidence in immunologically normal subjects. Thus, while the isolation of patients infected or potentially infected with *P. carinii* from immunologically normal patients (who are likely to be seropositive for *Pneumocystis* antigens) is not essential, uninfected, immunocompromised patients should not be exposed to persons with active PCP.

A clear correlation with circulating viral loads in AIDS is not established. Historically, the rate of *Pneumocystis* pneumonia in AIDS was halved by the use of zidovudine for the duration of the effective antiviral effect of this agent. More pronounced effects have been observed in individuals who regain immune function for more than 6 months under HAART therapies; such patients should be able to avoid primary prophylaxis. The rate of infection appears to double in homosexual males with AIDS when compared with intravenous drug users. In the absence of effective prophylaxis or HAART, more than 80 percent of AIDS patients are expected to develop *Pneumocystis* pneumonia.

Corticosteroid use, neutropenia, and lung transplantation are also major predisposing factors in the development of infection. However, in most non-AIDS patients, the risk of disease is around 5 to 15 percent, depending on the nature and duration of the immune suppression. In the solid organ transplant recipient, chronic immune suppression that includes corticosteroids is most often associated with *Pneumocystosis* (Fig. 133-2). Bolus corticosteroids and cyclosporine may also contribute to the risk for *Pneumocystis* pneumonia. Active infection due to cytomegalovirus (CMV) may also enhance the growth of *Pneumocystis* in any affected population (Figs. 133-3*D* and 133-5*B*). Whether CMV directly stimulates the proliferation of *Pneumocystis,* acts systemically as an immunosuppressive agent, or is simply a fellow traveler in the immunocompromised host remains to be settled. The clinical association of CMV with *P. carinii* may reflect similarities in the susceptible hosts or subtle shifts in the alveolar microenvironment.

Clinically symptomatic infection may emerge during the weaning of immunosuppressive agents or as a part of the immune reconstitution syndrome seen with HAART in AIDS. This is consistent with the limited inflammatory response generated by the organism in the susceptible host. Patients with *PCP* generally have both antibodies and T lymphocytes directed at the organism at the time of presentation. Thus, the assumption has been made that such immunities are not protective, the correlates of protection (the target antigens) have



A *B*

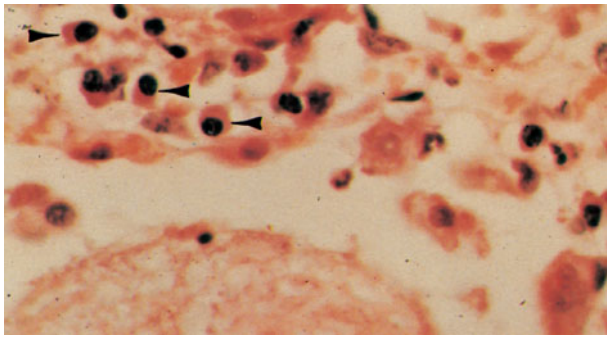
C *D*

Figure 133-2 Extrapulmonary pneumocystosis in a patient with AIDS on aerosolized pentamidine prophylaxis presented as a splenic mass lesion with abdominal pain. The computerized body tomographic (CBT) scan reveals a mass lesion (*A*), seen after splenectomy on gross pathology *(B,C)* and on microscopic examination (silver stain, *D*). *(Courtesy of Dr. J. Davis Allen, Jr., New England Deaconess Hospital.)*

not yet been identified, antigenic variation has "switched" the antigens expressed on the surface of the organisms, or protection rests with the cellular immune control of alveolar macrophage function. In the presence of *P. carinii*, cytokine production and phagocytosis by alveolar macrophages are abnormal. Surfactant proteins A and D, members of the collectin family, are increased during *Pneumocystis* pneumonia in patient and animal models, while surfactant lipids are reduced. These changes may contribute to diminished uptake of organisms by resident macrophages.

CLINICAL PRESENTATION

The hallmark of infection due to *P. carinii* is the presence of marked hypoxemia, dyspnea, and cough out of proportion to physical or radiologic findings. In the transplant recipient or the person undergoing corticosteroid therapy, *Pneumocystis* pneumonia is generally acute to subacute in development and often masked by other processes, including allograft rejection or infection. In the AIDS patient with first episode of infection, the evolution is more gradual (often 2 to 5 weeks) and constitutional symptoms and weight loss are prominent. Subsequent infections may evolve more rapidly. In the cancer patient receiving chemotherapy or in the organ or bone marrow transplant recipient, the use of corticosteroids, prior lung infection, abnormal pulmonary lymphatics (after heart, lung, or liver transplantation), and neutropenia may contribute to the absence of radiologically apparent disease. The rate of development of clinical infection is exacerbated by the presence of preexisting lung disease or other infections (e.g., CMV, *Legionella*, mycobacteria) (Fig. 133-2) or allograft rejection (in lung transplantation recipients). In the organ transplant recipient, *Pneumocystis* pneumonia occurs approximately 2 to 4 months after the initiation of immune suppression or during periods of increased immune suppression (pulsed steroids, antilymphocyte therapies, CMV infection). The incidence of infection varies between institutions and with the prophylactic regimens employed. In some series of patients



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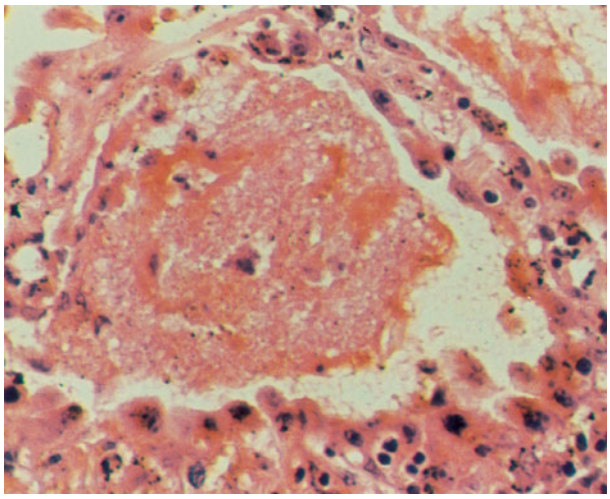

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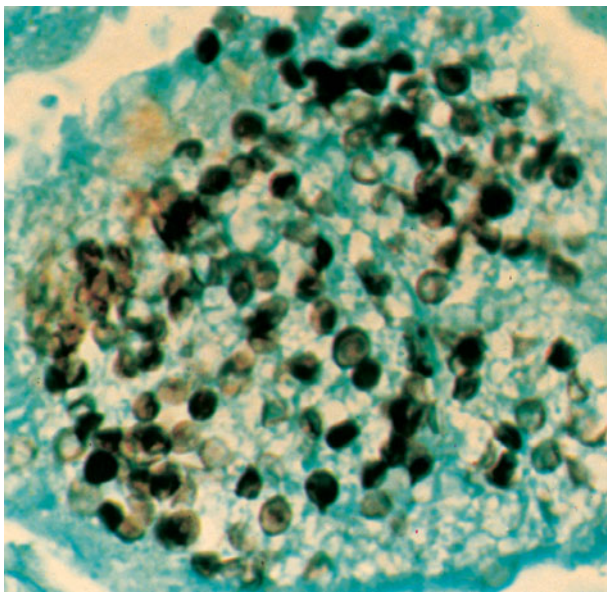

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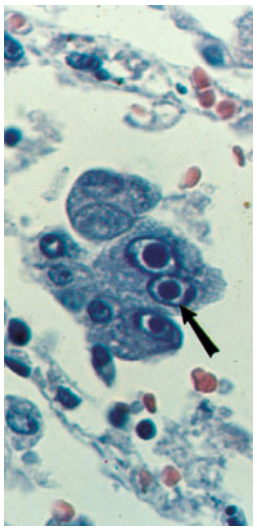

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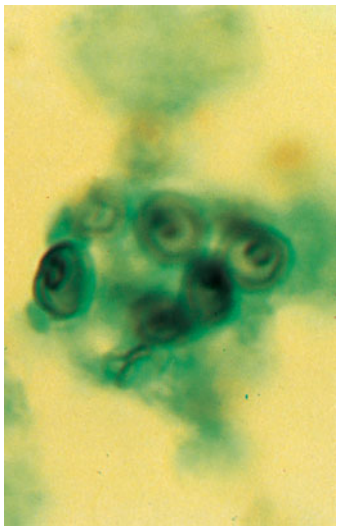

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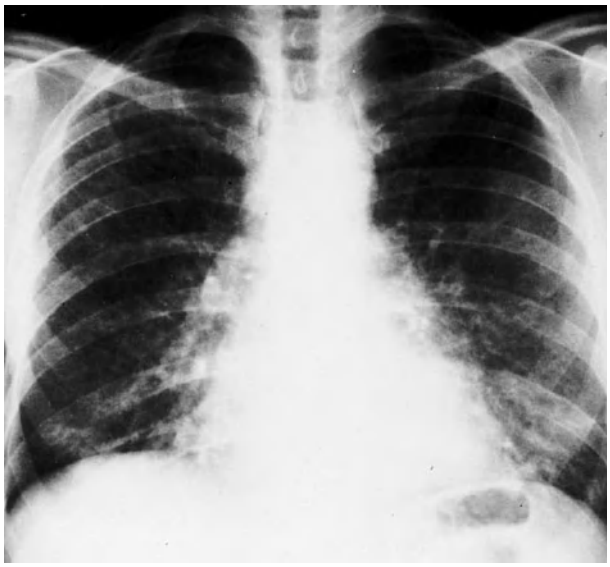


F

Figure 133-3 *Pneumocystis carinii* pneumonia: *A*. Lung of a malnourished infant showing an intra-alveolar foamy exudate and plasma cells (arrowheads) in the interstitium (H&E stain, × 620). *B*. Typical alveolar exudative pattern from the lung of an adult with *Pneumocystis* pneumonia after therapy with corticosteroids. Swelling of the alveolar epithelial cells and interstitial edema are seen. Inflammatory response in interstitium is minimal (H&E stain, × 500). *C*. *Pneumocystis* in the form of thick-walled cysts within the foamy exudate (displayed by Gomori's methenamine-silver nitrate stain and brilliant green counterstain, × 1250). *D*. Cytomegalovirus inclusion bodies in alveolar macrophages in a patient with *Pneumocystis* pneumonia (H&E stain, × 720). *E*. *Pneumocystis* cysts in cytologic preparation of induced sputum from an AIDS patient (silver stain, × 1250). *F*. *Pneumocystis* pneumonitis. Typical chest radiograph showing bilateral, diffuse interstitial infiltrates extending from hilar area.

receiving lung transplants the rate of asymptomatic isolation of *P. carinii* approaches two-thirds of the total. Of these, up to half are expected to develop symptomatic disease without treatment.

In AIDS patients without HAART, the presentation of *Pneumocystis* pneumonia is often complicated by a variety of factors. Prophylaxis with aerosolized pentamidine or other antibiotics may delay or alter the presentation of disease. As in most immunocompromised hosts, coinfection may accelerate the progression of disease or alter the radiographic pattern; in particular, CMV, *Histoplasma capsulatum, Legionella* spp., and mycobacterial species may contribute to the constitutional symptoms, hypoxemia, and the locality of pulmonary lesions.

Acute exposure to *Pneumocystis* is rarely documented; in animal models, inoculation of *P. carinii* induces a neutrophilic infiltrate that is rapidly (2 to 3 days) replaced with lymphocytes and macrophages. Similarly, in transplant recipients and despite therapy with cyclosporine, *Pneumocystis* induces lymphocyte- and neutrophil-predominant infiltration into the lungs acutely, followed by macrophage infiltration and clearance of organisms. This contrasts with the macrophage- and neutrophil-predominant infiltrates seen in AIDS patients with acute disease. The lymphocytes are primarily T lymphocytes with normal CD4/8 ratios. *Coinfection with CMV and other pathogens will be detected in more than half of* Pneumocystis-*infected patients.* The nature of the immune suppression determines the types of other opportunistic pathogens that coinfect the compromised host. Thus, fungal coinfection has increased as cyclosporine has replaced high-dose corticosteroids in transplant recipients. The expected mortality due to *Pneumocystis* pneumonia is increased in patients taking cyclosporine when compared with other immunocompromised hosts.

EXTRAPULMONARY PNEUMOCYSTOSIS

Pneumocystis was known to cause extrapulmonary disease in the pre-AIDS era, but metastatic infection to significant degrees has been observed only in patients with untreated AIDS. Few cases of systemic infection due to *P. carinii* have been observed in patients receiving systemic prophylaxis with TMP-SMX, while the diagnosis is occasionally not considered in patients using pentamidine prophylaxis. Pulmonary disease may be minimal or absent in such patients. In our hands, blood samples from up to half of the patients with *Pneumocystis* pneumonia have PCR evidence of circulating DNA from this organism. In addition to the liver and spleen, sites of extrapulmonary disease have included eye, ear, lymph nodes, thymus, skin, mastoids, ascites, GI tract and omentum, pleura, kidney, bone marrow, pancreas, and adrenal glands, and it has been reported as a cause of thromboembolic disease. Vasculitis has been reported due to *P. carinii* as a cause of ischemic necrosis of digits.

The presentation of extrapulmonary infection is generally a mass lesion with accompanying fever, sweats, and malaise. Visual loss may accompany retinal lesions, hepatitis with liver impairment, and ascites and GI tract obstruction with peritoneal and omental lesions. By computed tomographic (CT) scan, many nonenhancing, low-attenuation masses, often with necrosis and/or hemorrhage, may be seen in the liver or spleen (Fig. 133-2). Calcification may occur at the edge of such necrotic lesions during the acute infection, often in the hepatic or renal parenchyma. Histopathology will demonstrate granulomas with giant cells, calcification, or cavities. Distant sites may also contain the same frothy hyaline material seen in the alveoli in pulmonary disease (Fig. 133-3). *P. carinii* will be seen adherent to the blood vessel walls, with myointimal inflammation and thrombosis.

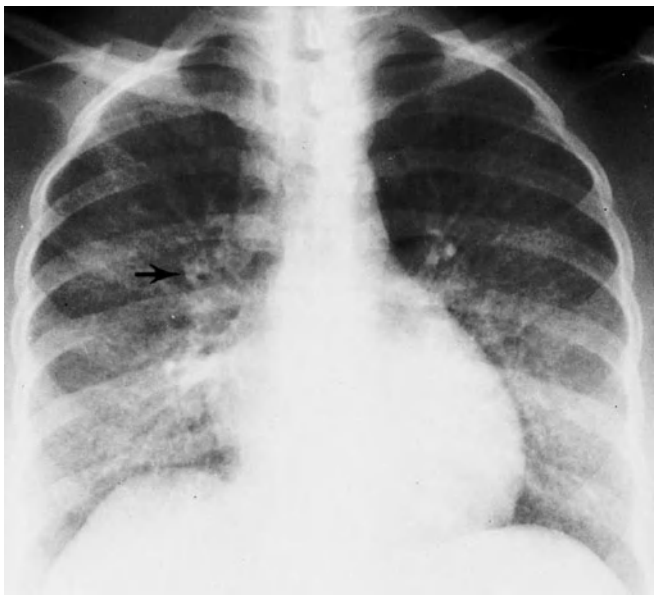
Dual infections may occur with any organism, including mycobacteria, *Histoplasma, Legionella,* fungi, or common bacteria. Unless superinfection has occurred or splenic rupture or other life-threatening condition is imminent, systemic treatment of multiple small abscesses due to *Pneumocystis* infection should be adequate without surgical intervention.

RADIOGRAPHY

The Chest Radiograph

The chest radiograph plays a central role in the diagnosis of *PCP* (Figs. 133-4 and 133-5). However, no radiographic pattern is pathognomonic for *Pneumocystis* infection, any more than for the other atypical pneumonias—interstitial processes on chest radiograph that present with hypoxemia and fever, but without sputum production. The radiographic pattern depends on the patient's underlying or accompanying disease, state of immunosuppression, and duration of infection. Sometimes the chest radiograph is normal despite overt pulmonary disease. More often, the early stage of *PCP* is manifested by fine, bilateral, perihilar, diffuse infiltrates that progress to an interstitial alveolar butterfly pattern; from the hilar region, the infiltrates spread to the apices or bases. Despite therapy, this pattern is often succeeded in 3 to 5 days by progressive consolidation, the appearance of air bronchograms, and complete opacification of the lung fields.

As in many of the atypical pneumonias, unusual courses and patterns are seen: nodules, unilateral infiltrates, or even lobar consolidations (Figs. 133-4 and 133-5). Small pleural effusions also occur. Distortions in pattern are commonly produced by prior radiation, drug-induced pulmonary injury, or concurrent infection with other organisms. The patient with recurrent disease may develop chronic interstitial markings, small cysts, or honeycombing on chest radiograph. The distribution of cysts in pneumocystosis, when present at all, is more often diffuse, while peripheral or apical bullae are often seen without infection in intravenous drug abusers. Rarely, cavitary disease is seen in the absence of other pathogens;



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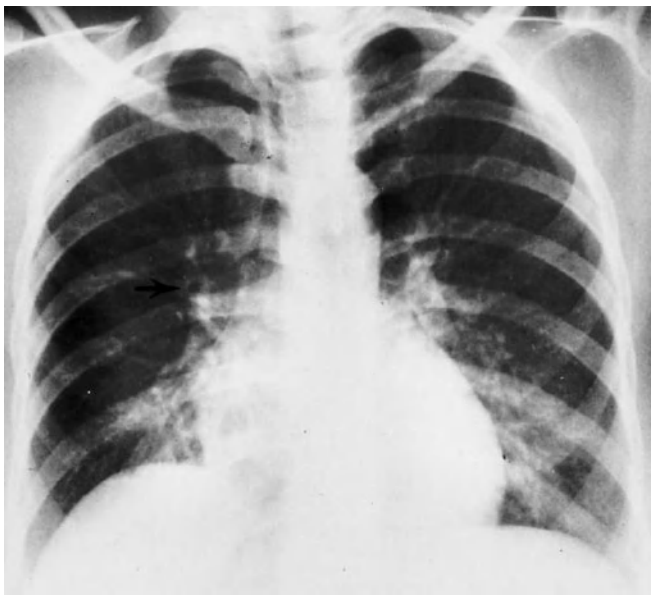

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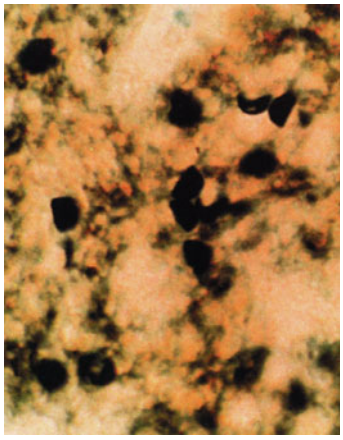

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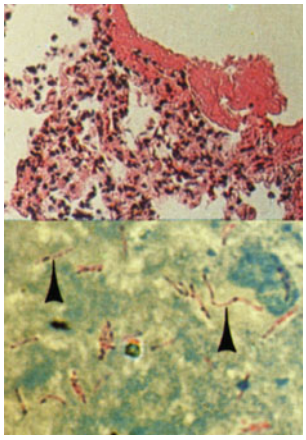


D

Figure 133-4 Atypical pattern of *Pneumocystis* with *Mycobacterium avium-intracellulare* in a Haitian woman with AIDS. *A*. Diffuse pulmonary infiltrates before treatment of *Pneumocystis* infection. Arrow indicates small abscess cavity. *B*. After treatment for *Pneumocystis,* many small cavities persist (arrow). *C*. Transbronchial lung biopsy of initial infiltrate reveals *Pneumocystis* cysts (silver stain, × 760). *D*. Open lung biopsy after therapy for *P. carinii* included areas of pneumonitis atypical for *Pneumocystis* (upper), which contain *M. avium-intracellulare* (arrowheads, lower) (Kinyoun acid-fast stain, × 950.)

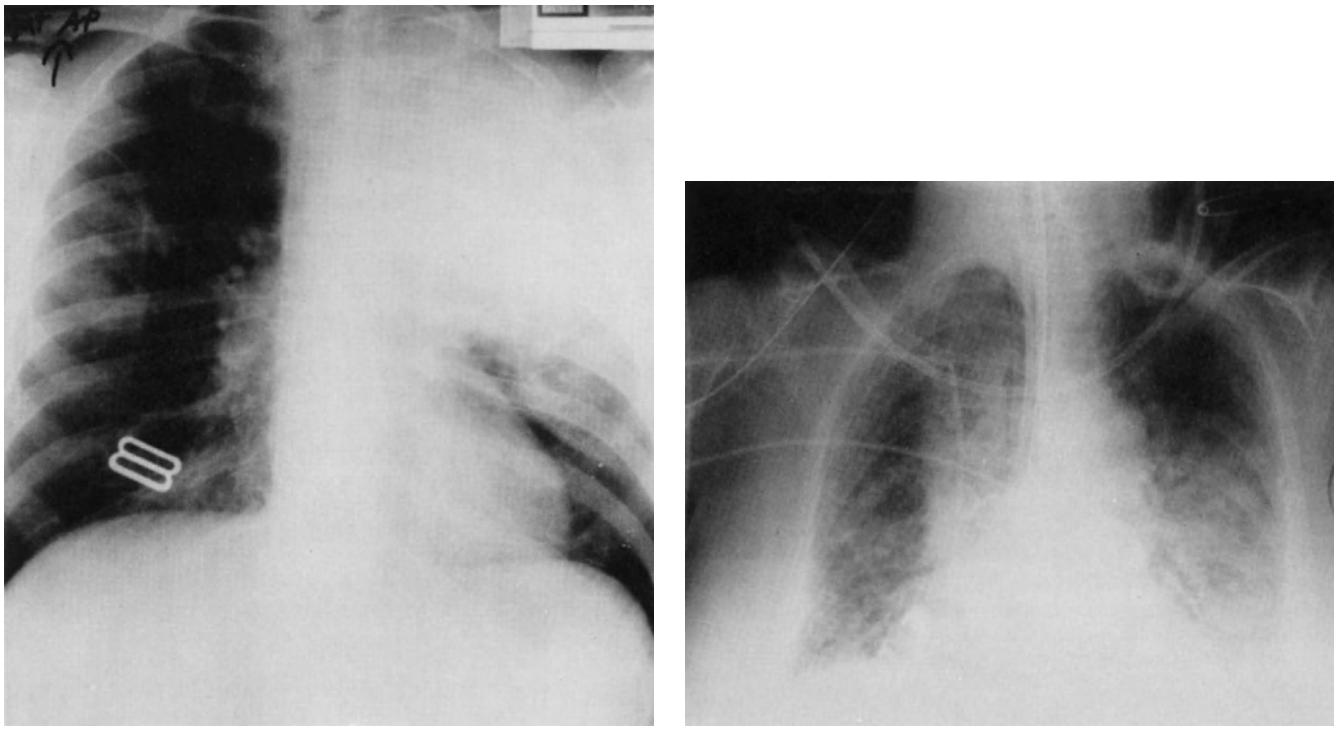
however, *P. carinii* can superinfect fungal or mycobacterial cavities.

The use of aerosolized pentamidine for the therapy and prophylaxis of *Pneumocystis* pneumonia in AIDS created some new problems in the diagnosis and treatment of pneumocystosis (Fig. 133-5). The disease may present largely or solely in the upper lobes on chest radiograph. Similar disease may be seen without pentamidine use, suggesting a predilection of infection for the upper lobes. Cystic changes are more common in patients undergoing prophylaxis who develop *Pneumocystis* pneumonia. The development of spontaneous pneumothoraces may indicate the recurrence of *P. carinii* in the upper lobes despite ongoing prophylactic therapy. Pneumothorax may also complicate the management of intubated patients with *Pneumocystis* pneumonia; active pneumonia or fibrosis in the upper lobes is usually implicated. Undiagnosed, this complication is responsible for a 50 percent mortality rate. Dense consolidation of tissues may suggest dual infection, often with a bacterial agent.

In lung transplant patients, rejection and infection often produce abnormal chest radiographs. In the first month, rejection of the transplanted lung will cause radiographic changes in up to 75 percent of patients. These changes include nodular and interstitial infiltrates in the perihilar area and the lower lobes, which may progress to consolidation. These changes may also occur with infection, of which CMV is the most common. CMV may be indistinguishable from organ rejection without biopsy. After the first month, rejection less often yields radiographic changes (about 25 percent), and the radiographic findings of infection are similar to those of other immunocompromised hosts.

Inflammation Imaging

Nuclear medicine scans are generally nonspecific and add little to the diagnosis of pulmonary pneumocystosis. However, a normal scan will generally exclude diffuse pulmonary infection due to *Pneumocystis*. Gallium citrate, technetium,



A *B*

Figure 133-5 Atypical pneumocystosis. *A*. Upper-lobe pneumonia in an AIDS patient on prophylactic aerosolized pentamidine therapy for a history of *Pneumocystis* pneumonia. The patient had both *P. carinii* and *Legionella pneumophila* infections. *B*. Persistent pulmonary infiltrates in a patient undergoing chemotherapy for non-Hodgkin's lymphoma. Despite 21 days of therapy for *P. carinii,* oxygenation and pulmonary infiltrates failed to improve. An open lung biopsy revealed cytomegalovirus pneumonitis (which responded to therapy with ganciclovir) and drug-induced interstitial fibrosis.

indium-immunoglobulin, white blood cell, and diethylenetriamine penta-acetate (DTPA) scans are abnormal in more than 90 percent of patients with *Pneumocystis* infection. These may be most useful in following the resolution of infection. Gallium scintigraphy can be entirely normal for patients with opportunistic pneumonia with or without AIDS. Conversely, AIDS patients may have abnormal gallium scans in the absence of other infection. Gallium scans often become abnormal before the radiographic appearance of pulmonary disease. Lymph node uptake alone may indicate the condition formerly referred to as AIDS-related complex (ARC), due to HIV infection. Diffuse pulmonary uptake may indicate occult infection in the asymptomatic patient, which would allow early intervention for therapy or prophylaxis. The cost of routine gallium scanning for AIDS patients probably outweighs utility when compared with the judicious use of antiviral or anti-*Pneumocystis* antibiotics based on CD4 cell counts, viral load measurements, or other clinical data. The pattern of lymphoid interstitial pneumonitis (LIP) in children with AIDS is indistinguishable from that of *Pneumocystis* pneumonia.

Some centers make a presumptive diagnosis of *PCP* in the patient with AIDS when a decrease in diffusing capacity (Dlco) is coupled with an abnormal chest radiograph and gallium scan. The clearance of radiolabeled inhaled DTPA is also increased in *PCP* (as in other pulmonary infections). Although these tests are usually abnormal in *PCP*, they lack specificity.

Imaging with radiolabeled (indium) human immunoglobulin (IgG) has proved to be a useful adjunct to the diagnosis and treatment of *Pneumocystis* pneumonia, for two reasons. First, the IgG scan is more sensitive to inflammatory changes than is the gallium scan. This allows the detection of superimposed focal pulmonary processes due to other pathogens in addition to the diffuse pattern seen in *P. carinii*. This sensitivity also allows the IgG scan to be used to follow the resolution of infection in response to therapy, which has not been possible with gallium. Second, the IgG scan has been useful in detecting unsuspected extrapulmonary foci of infection; this may be important in the management of AIDS patients with disseminated *P. carinii* or other processes. The IgG scan is not useful in the neutropenic patient or the uremic patient with dysfunctional neutrophils.

Other Diagnostic Techniques

The chest CT scan will detect interstitial and micronodular disease not visible on routine chest radiographs. Further, the CT and magnetic resonance imaging (MRI) scans

and ultrasound imaging are better suited to the definition of pneumocystomas occurring outside the lung (discussed above; see Fig. 133-2).

LABORATORY FINDINGS

A number of nonspecific indicators of pulmonary processes have been used in the presumptive diagnosis of *Pneumocystis* pneumonia. In general, the patient will have a PO_2 less than 60 mmHg and a respiratory alkalosis. The serum lactic dehydrogenase (LDH) enzyme will be elevated in most cases of *Pneumocystis* pneumonia (over 300 IU/ml), with high levels (over 600 to 700 IU/ml) carrying a poor prognosis in the setting of histologically confirmed infection. Lymphoma, other diffuse pneumonias, and LIP may also raise the LDH level. Respiratory distress and respiratory failure requiring intubation carry a poor prognosis. The marked hypoxemia of *Pneumocystis* pneumonia is accompanied by a PaO_2– PaO_2 gradient rise; gradients over 30 mmHg at the start of therapy are associated with a high mortality (and are an indication for the use of adjunctive corticosteroid therapy). Both LDH and the arterial oxygenation gradient will return to normal with successful therapy. Another nonspecific indicator of lung injury in *PCP* is the angiotensin-converting enzyme (ACE) level (also elevated by smoking and sarcoidosis, among other causes). While pulmonary function testing may reveal abnormalities in oxygen exchange and compliance in *Pneumocystis* pneumonia, they are not useful diagnostically. Arterial blood gas measurements are helpful in the management of patients with regard to decisions about intubation and the use of corticosteroids as an adjunct to initial antibiotic therapy (see Therapy, below). Corticosteroids are of greatest use in nonintubated patients with PaO_2 of less than 75 mmHg and greater than 35 mmHg on room air, or a hypoxemia ratio (PaO_2/FiO_2) of less than 350 and greater than 75.

SPUTUM EXAMINATION AND HISTOLOGIC DIAGNOSIS

The diagnosis of *PCP* depends on the identification of characteristic organisms on examination of pulmonary specimens (Table 133-3). The methods used in making the diagnosis have been changed by the use of the induced sputum

Table 133-3

Diagnostic Techniques for *P. carinii*

Technique	Yield	Complications	Comments*
Routine sputum	Poor	Rare	Cultures needed
Induced sputum	30–75%	Rare	First choice; excellent in AIDS
Transtracheal aspiration	Fair (with experience)	Common: bleeding, subcutaneous air	Rarely worthwhile
Gallium scan	Nonspecific	Injection site of infected patients	Positive in >95%
Bronchoalveolar lavage (BAL)	>50% (>95% in AIDS)	Bleeding, aspiration fever, bronchospasm	Wedges terminal BAL with immunofluorescence
BAL/brushing	As for BAL alone	As for BAL	Not useful for *P. carinii*
BAL/transbronchial biopsy	>90% (all patients)	See BAL; pneumothorax	Impression smears; cultures/ pathology
Open lung biopsy	>95% (all patients)	Anesthesia, air leakage, altered respiration, wound infection	"Gold standard" noninfectious/ infectious processes; large sample
Needle aspirate	≤60%	Pneumothorax, bleeding	Best in localized disease

* *All sample should be cultured and stained for bacteria (including mycobacteria), fungi, and viruses, and examined for protozoa. Optimal procedures will depend on the locally available expertise.*

examination and bronchoscopic alveolar lavage (BAL) without biopsy, and by immunofluorescent staining using monoclonal antibodies to *P. carinii*. As a result, the morbidity associated with diagnostic procedures has been reduced and the diagnosis of simultaneous pathogens by these methods is decreased.

The initial step in the diagnosis of *PCP* is the realization that the patient is at risk for opportunistic infection. The first procedure should be a routine sputum examination for bacterial, mycobacterial, and fungal stains and cultures. Subsequently, the choice of diagnostic test depends on the status of the patient (ability to cooperate with sputum induction), the distribution of pulmonary disease, and the urgency of diagnosis. Given a single procedure, a more invasive test may be preferred. The diagnostic test of choice is the induced sputum examination, coupled with direct immunofluorescent staining for *P. carinii* and for mycobacterial smears and cultures. Some bacteria and fungi may not survive the hypertonic saline used for induction, and the yields for these pathogens do not exceed those of routine sputum samples. Induced sputum may be collected after 20 to 30 minutes of exposure to aerosolized hypertonic saline or water, or after oral hydration.

Before the availability of immunofluorescent antibody staining techniques, smears were prepared from the mucoid, nonpurulent portion of the specimen and stained with Giemsa or Diff-Quik stain (for intracystic bodies or sporozoites and trophozoites; see Fig. 133-6) or with toluidine blue O or silver, which stains the cyst wall. Because cysts represent only 5 to 10 percent of the organism burden, many laboratories prefer the Giemsa to the more complex silver stain, but Giemsa-stained smears are more difficult to read. In experienced hands, these stains should detect *P. carinii* in up to 85 percent of AIDS patients and in up to 60 percent of other immunocompromised patients. Proper induction and smearing techniques are critical to success.

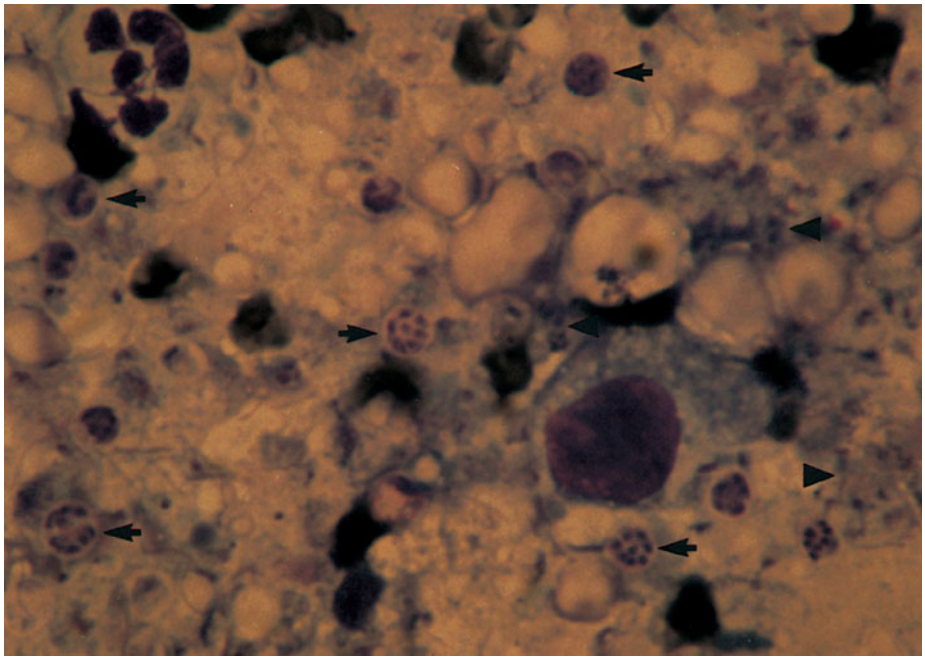
The staining method of choice for sputum as BAL specimens is direct immunofluorescent staining with monoclonal antibodies (Fig. 133-6). This method is costly, but significant cost savings may be achieved in terms of specimen preparation and examination time. Rapid staining with immunofluorescent monoclonal antibodies directed against surface antigens of *P. carinii* has a high degree of specificity and a sensitivity for screening of sputum smears. This technique may detect 10 to 15 percent of *Pneumocystis* infections beyond the standard histologic stains (Fig. 133-2). Some of the commercially available antibodies produce high backgrounds and some nonspecific staining; each laboratory must optimize the fluorescent staining technique. Smears may be improved through use of mucolytic agent (Mucomyst, dithiothreitol) just before preparation.

As with PCR testing, the heightened sensitivity of immunofluorescent staining, coupled with the use of either induced sputum or bronchoscopic lavage samples, may detect "infections" that are not of clinical significance. The meaning of a few organisms on smear in a patient with fever and cough may not be clear. Owing to the broad antibacterial spectrum of TMP-SMX, response to therapy is only a partial confirmation of the existence of *PCP*. AIDS patients often have residual (dead) organisms in their sputum for many weeks after successful treatment. However, organisms found in the non–AIDS-immunosuppressed patient should suggest disease meriting therapy. Insignificant "colonization" of the respiratory tract before therapy has not been demonstrated; significant numbers of organisms have not been found by BAL in asymptomatic AIDS patients. Of note is that a negative smear does not indicate the absence of *P. carinii*. With use of ribosomal sequence–derived primers on pulmonary specimens, the PCR has more than 98 percent specificity and sensitivity, compared with 78 percent sensitivity for immunofluorescence on the same samples. Serologic tests are useful only for epidemiologic studies.

The *histopathology* of *Pneumocystis*-infected lung is usually distinctive enough to be diagnostic even when organisms cannot be identified. In the adult, the disease appears to be predominantly alveolar. The airspaces are filled with a foamy eosinophilic exudate and appear honeycombed. The intra-alveolar exudate consists of organisms, large amounts of surface glycoprotein, proteinaceous exudate from the lungs, and debris of macrophages and inflammatory cells. At the same time, the alveolar interstitium is infiltrated by polymorphonuclear leukocytes and lymphocytes (Fig. 133-3). Patchiness in the distribution of disease within the lungs is common. In contrast to the adult disease, *Pneumocystis* pneumonia in malnourished infants has a major interstitial component: The interstitium is filled with fluid, plasma cells, and lymphocytes; these formed elements seem to overflow into the airspaces, which are also filled with a frothy eosinophilic exudate. In both forms, the organisms usually appear intermingled with alveolar macrophages in the alveolar exudate (Fig. 133-3). By light microscopy, trophozoites predominate numerically (in more than 90 percent of the organisms), but cysts are more readily identified.

The earliest indication of disease is the presence of organisms adjacent to the epithelial layer. Cysts or clumps of trophozoites may be seen, with a minimal inflammatory infiltrate. As the number of organisms increases, epithelial injury occurs. The mechanism of alveolar epithelial cell injury is uncertain. The organism preferentially adheres to and injures the surface of type I alveolar epithelial cells, while the adjacent type II cells undergo hyperplasia. Desquamation of alveolar epithelial cells occurs early in the course of disease; denuded basement membrane is occasionally seen. Epithelial injury is followed by mononuclear cell infiltration in the interstitium. Organisms may be seen within vacuolated alveolar macrophages, as well as free in the proteinaceous and cellular debris that fills the airspace (Fig. 133-3).

In AIDS, the interstitial inflammation is less marked than in other adult forms of *Pneumocystis* pneumonia, and greater numbers of both cysts and trophozoites are seen in the alveoli. While HIV-infected alveolar macrophages appear to bind organisms normally, internalization of *P. carinii* may be impaired and clearance of organisms delayed. Many dead macrophages are found in BAL samples from HIV- and



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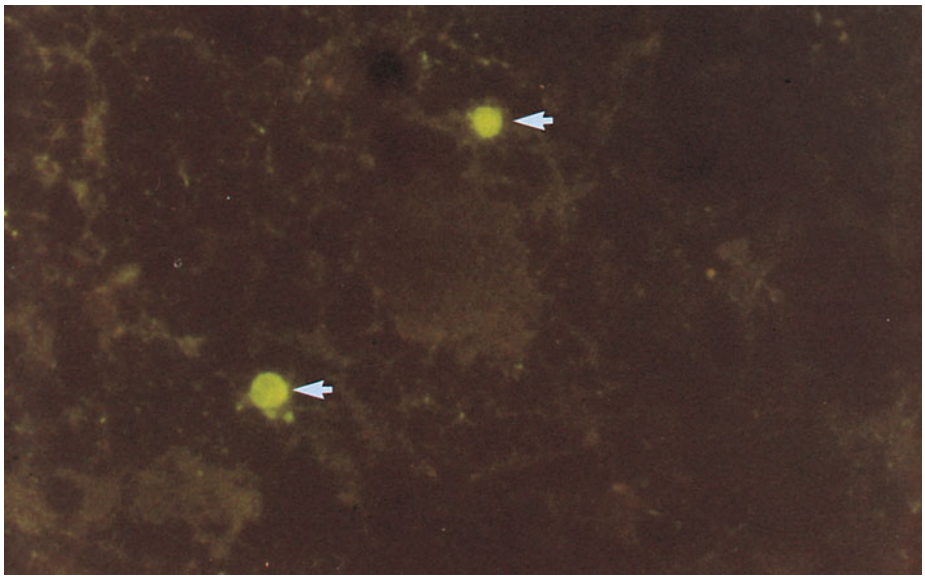

B

Figure 133-6 Rapid staining of sputum and biopsy specimens for *P. carinii: A.* Impression smear (touch preparation) from the cut surface of a human lung biopsy stained with Diff-Quik stain reveals the nuclei of clumped trophozoites (arrowheads) and of the sporozoites within cysts (arrows). *B.* Human *P. carinii* cysts in an induced sputum specimen that has been stained with fluoresceinated monoclonal antibodies raised to the 116-kd surface antigen of human *P. carinii.*

Pneumocystis-infected lungs. In children with AIDS, the appearance is similar to that of adult AIDS, with the addition of some degree of plasma cell infiltration of the interstitium. Although hyaline membranes may line alveoli, they are not diagnostic of infection with *Pneumocystis,* since oxygen toxicity, alveolar proteinosis, or ARDS can evoke similar changes. These may coexist with *Pneumocystis* infection. In pediatric AIDS, lymphocytic interstitial pneumonitis, without evidence of an infectious origin, and bacterial pneumonia may mimic or coexist with *PCP.*

The *Pneumocystis* cyst wall is displayed by a variety of staining techniques. Of these, the Gomori methenamine silver nitrate method (which stains organisms brown or black) is most reliable, even though it is susceptible to artifacts and does not stain intracellular bodies (Fig. 133-3). Sporozoites and trophozoites are stained by polychrome stains,

particularly the Giemsa stain. The Giemsa, Wright, toluidine blue O, and Grocott's rapid silver stain techniques are most useful in dealing with lung imprints, BAL fluid, and pulmonary aspirates. Rapid polychrome staining (Diff-Quik) and a rapid silver staining technique have proved useful in screening smears (Fig. 133-6). When a silver stain is used, a counter stain such as Gram, Wright, Giemsa, hematoxylin, or trichrome may be required to identify intracystic bodies and to distinguish cysts from red blood cells and yeasts. Up to 97 percent of the organisms are trophozoites. Thus, silver stain substantially underestimates the organism burden.

Even when chest radiography indicates that *PCP* has cleared, interstitial fibrosis is likely to be found at rebiopsy or autopsy. Unfortunately, the contribution of *Pneumocystis* to the residual fibrosis is often obscured by the tendency of superimposed infection, therapeutic agents, or intervening radiation therapy to elicit inflammatory responses in the interstitium. Subsequent infections are likely to present with more rapid progression to hypoxemia due to persistent restrictive lung disease. In AIDS patients, pulmonary interstitial fibrosis has been observed in up to 27 percent of autopsy and biopsy series, and emphysematous changes are also common. These changes do not appear to be associated with prior *Pneumocystis* infection. A pathogenic role for chronic or recurrent viral (HIV, CMV) infections or immunologic injury has been postulated.

The demonstration of CMV by culture is not helpful in regard to the presence of CMV *disease.* Coinfection due to CMV and *P. carinii* is common, however, and may necessitate treatment for both entities. Nucleic acid diagnostics (hybridization and/or PCR) are used routinely at some centers; the interpretation of positive results remains uncertain because of the high degree of sensitivity of the test. PCR may be best used to determine the risk of *Pneumocystis* infection in patients who might otherwise not receive prophylaxis. Preliminary data support the hypothesis that systemic dissemination is common during infection in AIDS patients (up to 50 percent have *Pneumocystis* DNA in the blood), but it is generally well controlled by resident phagocytes.

INVASIVE DIAGNOSIS OF PNEUMOCYSTOSIS

In the immunocompromised patient with significant pulmonary disease, the inability to make a diagnosis of infection on examination of the induced sputum, or the failure to respond to appropriate therapy, should lead to a more invasive diagnostic procedure: BAL (with biopsies if possible), radiologically guided needle aspiration (for accessible cystic or mass lesions), or open lung biopsy. The choice of the specific test depends on the clinical condition of the patient and the expertise available at the institution (Table 133-3).

Invasive procedures for the diagnosis of *PCP* fall into several categories: tracheal aspiration, fiberoptic bronchoscopy, transthoracic aspiration, and open lung biopsy. Attempts to avoid the use of invasive procedures by resorting to empiric therapy run a great risk of inappropriate medications and undesirable side effects, as well as delaying effective therapy. Pulmonary specimens obtained by invasive approaches should be processed for bacterial (including mycobacteria, *Nocardia, Actinomyces,* and *Legionella*), fungal, and viral evaluation in addition to making slides for rapid staining with fluorescent antibodies, toluidine blue O, silver, Diff-Quik, Giemsa, or Wright stain. Early diagnosis can be made and therapy initiated on the basis of such smears, especially in AIDS.

Tracheal Aspiration

The yield from this procedure is generally low, and the hazards, particularly in inexperienced hands, are high. In intubated patients, respiratory secretions should be carefully smeared on slides, stained, and examined. If the physician or the microbiology technician has had little experience with *Pneumocystis* smears, and direct immunofluorescence techniques are not available, fiberoptic bronchoscopy or open lung biopsy is indicated for the immunocompromised patient with pulmonary disease, followed by methenamine silver staining of the tissue sections.

Fiberoptic Bronchoscopy

The importance of knowing the success rate of the institution as a basis for selecting the optimal invasive technique is illustrated by published reports of diagnostic yields from fiberoptic bronchoscopy. In proven instances of *PCP* in non–AIDS-immunocompromised hosts, the reported yields range from 5 to 95 percent. As a rule, institutions with a large experience with *PCP* are very successful in identifying the organism. Indeed, when bronchial lavage and transbronchial lung biopsies are part of the diagnostic procedure, the success rate exceeds 90 percent. The yield has been even higher in AIDS, and lavage alone (i.e., without biopsy), coupled with immunofluorescent staining of the specimens, will be successful in up to 95 percent of cases. In these patients, lavage specimens must be gathered from a wedged bronchoscope with at least 50 ml of physiological saline for alveolar washings. Lavage should be performed from the upper lobes if diffuse disease is present. The diagnostic yield in HIV-infected persons with pulmonary symptoms is more than 60 percent: 18 percent with *P. carinii* and another pathogen, 16 percent with *P. carinii* alone, and 25 percent with other infectious causes, including *Histoplasma, Cryptococcus,* mycobacteria, and other bacteria. Trophozoites predominate in bronchial washings, so Giemsa or Diff-Quik staining should be performed routinely to back up other staining methods. In general, lung biopsy is not essential for the diagnosis of *PCP* in AIDS patients. Patients suspected of harboring multiple pathogens may still benefit from any of the more invasive procedures. Although bleeding from the biopsy site is common (in up to 25 percent of

patients), it is rarely life threatening if the coagulation indices are normal.

Percutaneous Needle Aspiration

High success rates in finding *P. carinii* have also been reported in patients with *PCP* (up to 60 percent), particularly when aspiration of localized radiologic infiltrates is performed under fluoroscopic guidance. Needle aspiration is also advantageous when a focal process (e.g., abscess) is peripherally located in the lung parenchyma. Pneumothoraces occur in up to one-third of patients as a result of the procedure. In approximately 20 percent of pneumothoraces, insertion of a chest tube will be necessary.

Lung Biopsy

Thoracotomy followed by open lung biopsy or VATS (video-assisted thoracoscopic biopsy) affords the most unequivocal avenue for diagnosis. Although the patient may be quite ill by the time this step is taken, in the hands of skilled surgeons these procedures are safe, even for the intubated patient and provide histologic information that may allow the separation of significant infection of the lower respiratory tract from colonization of the upper respiratory tract by a variety of respiratory pathogens. This information may be critical to therapeutic decision making, as in the use of antiviral agents in the treatment of CMV infection. Thoracoscopic biopsies can often be performed as minimally invasive procedures.

Often, accurate diagnosis in the non-AIDS patient may require invasive procedures despite the excellent yields of sputum induction and immunofluorescence (Table 133-3). One element in the choice of procedure depends on the clinical state of the patient: patients who have an uncorrectable coagulopathy are poor candidates for either bronchoscopy with biopsy or open lung biopsy. Patients with atypical presentations or unique epidemiologic exposures have a higher incidence of dual processes or non-*Pneumocystis* infections. Institutions unfamiliar with the proper technique for sampling or handling specimens for the diagnosis of *Pneumocystis* infection should probably use open lung biopsies, which are likely to be more rewarding. Because disease caused by *PCP* may progress rapidly, the likelihood of success in treatment is greatest at the outset. Therefore, invasive procedures to disclose the organism and any secondary infections should be undertaken early in the course of the disease.

The demonstration of *Pneumocystis* organisms is necessary for diagnosis in the transplant recipient. No more than 15 to 25 percent of pulmonary infiltrates are caused by *P. carinii* in the non-AIDS patient, although regional and underlying disease-specific variations exist. Empiric therapy is more reasonable in the AIDS patient not receiving prophylaxis, as *PCP* occurs in up to 90 percent of such persons; however, dual infections remain common. Empiric therapy in the transplant recipient may delay specific treatment for other opportunistic pathogens and subject the patient to avoidable toxicities of TMP-SMX or pentamidine. Demonstration of infection due to *P. carinii* should lead to successful treatment, barring superinfection or ARDS.

PROPHYLAXIS AND PROPHYLACTIC STRATEGIES

In the pre-AIDS era, the prevention of *PCP* was associated with time-limited antibiotic use in the setting of prolonged neutropenia due to cancer chemotherapy. Because many of the chemotherapeutic regimens included corticosteroids, the incidence of *Pneumocystis* pneumonia was predictably high. Prophylactic TMP-SMX was pioneered by Walter Hughes and his colleagues at the St. Jude's Children's Research Hospital for use in children with hematopoietic malignancies and severe combined immunodeficiency (SCID) syndrome. This combination agent became the standard for prophylaxis in the AIDS era as well. In pre-HAART AIDS, such prophylaxis was lifelong rather than time-limited. In general, prophylaxis can be stopped in patients with undetectable viral loads for at least 6 to 12 months and CD4 counts that surpass 200 for that period. Without HAART, more than 60 percent of those cured of *PCP* in AIDS will suffer a recurrence within 1 year. The increased incidence (50 to 60 percent) of side effects due to TMP-SMX in AIDS when compared with patients without AIDS (10 to 20 percent) has led to the development of alternative regimens for prophylaxis against *P. carinii.* Among non-AIDS patients, routine prophylaxis should be reserved for centers or patient groups that are known to have a fixed high incidence of disease (i.e., about 3 to 5 percent of susceptible hosts), or for persons with recurrent *Pneumocystis* disease.

The use of appropriate prophylaxis should prevent *Pneumocystis* pneumonia. In AIDS patients and in transplant recipients, the failure to utilize appropriate prophylaxis is generally a reflection of the toxicities associated with the necessary medications or a failure in compliance due to the large number of medications these patients may be expected to consume. Prophylaxis should be maintained in the stable transplant patient for at least 6 months after surgery. In lung transplantation and in stem cell transplant recipients with significant graft-vs.-host disease or overall poor recovery, prophylaxis is for at least a year and generally for the duration of treatment. It should be noted that in transplant centers without a fixed, high incidence of *Pneumocystis* pneumonia, prophylaxis may be reserved for patients in whom chronic, high-level immune suppression, especially with corticosteroids, is needed to maintain graft function. If immune suppression cannot be reduced after a course of treatment for *Pneumocystis* pneumonia, prophylaxis should be maintained indefinitely. In Europe, where immunosuppressive regimens are often less intense, such reductions may not be feasible. Prophylaxis should be reinstituted with increases in immune suppression, including those resulting from pulse steroids or antilymphocyte therapies in transplantation, CMV infection

in AIDS or transplantation, treatment of graft-vs.-host disease following bone marrow transplantation, new-onset neutropenia, or similar conditions.

In untreated HIV infection, adults and adolescents with CD4 counts of fewer than 200 cells/mm^2 (or 15 to 20 percent of the total lymphocyte number), unexplained fever for more than 2 weeks, a history of oropharyngeal candidiasis, or rapid progression of disease, as measured by rising viral titers or falling CD4 counts, should receive prophylaxis. Prophylaxis in HIV-infected children is recommended for CD4 counts of fewer than 1500 cells/mm^2 for less than 11 months, fewer than 1000 cells/mm^2 between 1 and 5 years, or fewer than 500 cells/mm^2 after age 5, and in any child in whom the CD4 percentage falls to less than 24 percent. The greatest risk for children may be at 3 to 6 months of age, making the identification of the HIV-infected infant critical to survival.

Prophylaxis is needed against many opportunistic infections in AIDS and other compromised patients. Very few HIV-infected persons are capable of completing a long-term (36 months) course of any particular agent. The median time to switch of therapies that have begun with either TMP-SMX or dapsone is approximately 2.5 years, with approximately 20 percent of patients requiring several (two or more) changes in prophylactic regimen. Thus, over time, more patients receive less adequate therapies. Prophylaxis has a significant impact on survival, quality of life, and hospitalization frequency. Benefits (about 9 to 12 months' survival) are less marked outside North America, where the incidence of *Pneumocystis* pneumonia is lower.

Resistance of *P. carinii* to antibiotics has been proposed based on clinical failures while receiving prophylaxis. Resistance *may* develop in association with mutations in the dihydropteroate synthase gene of *P. carinii*. Predictably, the use of prophylaxis both for *P. carinii* and for yeasts and the resultant improved survival of HIV-infected persons have increased the relative frequency of other causes of pulmonary disease in transplant recipients, including both infections (e.g., CMV, azole-resistant fungi, mycobacteria) and noninfectious processes.

Trimethoprim-sulfamethoxazole (TMP-SMX, cotrimoxazole) is the agent of choice for the prevention of *Pneumocystis* infection in any patient who can tolerate this fixed-combination agent. At a dose of one single-strength tablet per day (80 mg TMP and 160 mg SMX), a wide variety of opportunistic infections are prevented, including *P. carinii, Toxoplasma gondii, Listeria monocytogenes, Nocardia asteroides, Isospora belli,* and susceptible bacteria, including pneumococci, *Haemophilus influenzae,* community-acquired staphylococci, and some enteric gram-negative rods. While the protection against *T. gondii* is incomplete in AIDS patients (80 to 90 percent effective) at this dosage (generally a double-strength tablet a day might be used in seropositive persons without a history of *T. gondii* infection), breakthrough infection has not been seen in transplant recipients or in cancer patients. Studies of low- and high-dose regimens for prophylaxis (single- or double-strength TMP-SMX) in HIV-positive subjects suggest no advantage to the higher dose (no disease in either group when compliant) and earlier occurrence of toxicity in the high-dose group.

Drug toxicity is commonly observed even with low-dose regimens, especially in the form of mild bone marrow suppression. Such bone marrow toxicity is notable in combination with other marrow suppressive agents (e.g., azathioprine, ganciclovir, Cytoxan, allopurinol), malnutrition, or infection (HIV, mycobacteria, or cytomegalovirus). For *Pneumocystis* prevention, it is equally effective, given the slow replication of the organism, to administer the antibiotics on 3 days a week. Toxicity has been related to serum levels of the sulfa component in AIDS. Some patients will not tolerate any dose of sulfa drugs, owing to significant rash (occasional Stevens-Johnson syndrome), hepatitis (particularly in liver allograft patients), eosinophilic nephritis, or neutropenia. Generally, significant toxicities evolve within the first month of therapy. Hyperkalemia may be observed in the setting of normal renal function as a result of trimethoprim interfering with the secretion of potassium in the renal distal tubule. This is reversible and more common during therapy than with prophylaxis. In general, neutropenia should not be treated with folate, which has been associated with treatment failures. Both oral and intravenous desensitization regimens will allow the use of TMP-SMX in many patients otherwise intolerant of the combination. Reintroduction of TMP-SMX at reduced dose is often tolerated in AIDS patients not severely intolerant of this agent. This is generally preferable to the use of any alternative agent. Non-AIDS immunocompromised patients appear to be less able to tolerate desensitization.

Alternative regimens are available for the patient intolerant of TMP-SMX. The use of prophylaxis with aerosolized pentamidine isethionate (300 mg every 3 to 4 weeks) was pioneered in AIDS patients and is well tolerated in organ transplant recipients. Pentamidine aerosol prophylaxis is generally effective after the second or third dose administered by experienced personnel with a nebulizer, producing droplets in the range of 1 to 3 μ. The Fisons nebulizer has also been used with an alternative schedule of five 60-mg doses over 2 weeks, followed by 60 mg every 2 weeks. Because the distribution of drug may not reach the upper lobes, or because the growth of *Pneumocystis* may be favored in the upper lobes, adjusting patient positioning during inhalation may be useful.

Breakthrough infection has been observed in some patients receiving aerosolized and intravenous pentamidine prophylaxis (particularly in the upper lobes). These breakthroughs are in patients receiving primary prophylaxis after transplantation or in AIDS patients who have not yet received two or more doses of antibiotic (i.e., in the first 8 to 10 weeks), in CMV-infected persons, or in secondary prophylaxis after incomplete clearance of infections. In single-lung transplant recipients, prophylactic failures have been observed in the residual (native) lung despite successful protection of the allograft. When breakthrough occurs, diagnosis by noninvasive means is often complicated by reduced organism numbers; biopsy may be required. The use of *intravenous* pentamidine (300 mg every 3 to 4 weeks) for prophylaxis has been

successful, with the single exception of disease occurring in transplant patients coinfected with CMV or receiving antilymphocyte globulins for graft rejection, or in AIDS patients with rapidly progressive disease and/or infected with CMV.

Cough and bronchospasm are the common side effects of aerosolized pentamidine therapy; they are generally reversible with bronchodilator therapy. Less often, pneumothorax and hypoglycemia or hyperglycemia are noted. Transient, mild hypoglycemia or nausea is more common after intravenous administration than with the aerosolized method. The use of pentamidine prophylaxis requires the simultaneous administration of a second antibiotic (e.g., quinolone) for antibacterial prophylaxis in transplant recipients—which is not required in patients receiving TMP-SMX.

In general, alternative prophylactic agents have been preferred to pentamidine. In AIDS patients, dapsone (diaminodiphenylsulfone), with or without trimethoprim or pyrimethamine, is in wide use in a variety of combinations. In general, neutropenia (especially in the G6PD-deficient host), hepatitis, and rash are limiting for each of these regimens, and they offer no benefit over low-dose TMP-SMX. Because of a long half-life, dapsone may be administered in doses of 50 to 100 mg per day to 100 mg per week. Breakthrough infection has been observed in AIDS patients at 50 mg per day, but toxicity begins to be limiting at 100 mg a day. Therefore, pyrimethamine is administered weekly (25 or 50 mg) to supplement dapsone in a dose of 50 mg a day. It should be noted that significant excess mortality (almost twofold) occurred in AIDS patients receiving 50 mg a day of dapsone alone in a comparison trial with aerosolized pentamidine for secondary prophylaxis. Trials of dapsone at doses of 100 mg two or three times per week show equivalence to pentamidine therapy; doses of 100 mg per day are equivalent to TMP-SMX therapy. Trimethoprim may replace pyrimethamine in this regimen (100 to 200 mg per day) in patients with creatinine clearances over 15 ml per min. The incidence of intolerance to dapsone—65 to 70 percent—is roughly equivalent to that for TMP-SMX. Up to half of the patients who discontinue prophylactic therapy with either of these agents will be able to tolerate the other drug. This strategy is not recommended for any person with severe allergic reactions, including desquamation to sulfa drugs, persistent bone marrow suppression, G6PD deficiency, or severe hepatitis. Toxicities observed with dapsone are long-lived and may limit utility, especially in liver transplantation recipients. Dapsone alone does not protect against toxoplasmosis—necessitating dual therapy for prophylaxis.

Fansidar (weekly) has been used successfully to prevent pneumocystosis. Atovaquone (formerly BW566c80) has been approved by the FDA for the treatment of mild to moderate *P. carinii* infections and may be equally useful for prophylaxis because it is well tolerated, undergoes enterohepatic circulation without metabolism, and has a long half-life. The drug has been reformulated as a liquid to improve bioavailability. Large-scale toxicity studies have not been performed in the non–HIV-infected host. In AIDS patients receiving 750 mg orally (three tablets) three times a day, some breakthrough infections have been observed. Rash, nausea, and elevated liver transaminases were occasionally documented. Experience suggests that the bioavailability in AIDS patients is one-half to one-third that in other compromised hosts. Prophylactic doses of reformulated liquid drug in the range of 1000 to 1500 mg a day exceed the MIC in serum for *P. carinii* in transplant recipients, but higher doses (1500 to 2250 mg a day) may be needed in AIDS patients. The incidence of side effects is quite low in either population. Some patients complain about the flavor and color of atovaquone liquid (which stains clothes), but many find it preferable to aerosolized pentamidine. In small numbers of transplant recipients, interactions of atovaquone with cyclosporine and other toxicities have been insignificant; prospective randomized comparative studies are under way.

Patients receiving prophylaxis for toxoplasmosis (sulfadiazine, triple sulfa, clindamycin/primaquine, atovaquone) generally have also been protected against *P. carinii.* Transplantation recipients receiving quinolone for postoperative prophylaxis will be at the same risk for *Pneumocystis* pneumonia as the general transplant population.

TREATMENT OF *PNEUMOCYSTIS* PNEUMONIA

The incidence of *Pneumocystis* infection in AIDS patients has led to the development of a number of newer options for the treatment of this infection in all susceptible hosts (Table 133-4). Treatment should be initiated as soon as the suspicion of *Pneumocystis* infection is entertained. The short-term use of treatment (48 hours) will not impair the diagnosis of infection if, for example, bronchoscopic or laboratory support services are unavailable. It is likely to be more useful clinically to obtain specimens for *P. carinii,* mycobacteria, *Legionella,* fungi, and routine cultures when these can be properly handled by the clinical laboratory. Further, because the pneumonia can be rapidly progressive, early therapy is essential. Treatment of *Pneumocystis* should be successful if a 14- to 21-day course of therapy is tolerated.

The incidence of adverse reactions to antibiotics, necessitating switching of agents, is increased in the organ and marrow transplant recipient, as it is in AIDS patients. In general, side effects in transplantation are related to synergistic drug toxicities. For example, the bone marrow suppression seen in infection with CMV and treatment of this infection with ganciclovir may be further exacerbated with TMP-SMX. Generally, elevations in liver function tests in the liver transplant recipient or depression in the leukocyte count in the marrow recipient due to therapy with TMP-SMX is of concern in the transplant recipient but may be tolerable in other hosts. Nephrotoxicity is common in transplant recipients (both renal and extrarenal) receiving therapy with TMP-SMX, even with adjustment of dosing for renal dysfunction. Thus, while the incidence of intolerance by transplant recipients to one or another agent is somewhat less than the 50 percent seen

Table 133-4

Treatment of *P. carinii**

Agent(s)(route)†	Dose	Options†
Trimethoprim and sulfamethoxazole (TMP-SMX) (IV/PO)	15 mg/kg/day TMP (to 20) 75 mg/kg/day SMX (to 100)	Treat through rash: reduce TMP or SMX by one-half; desensitize; first choice
Pentamidine isethionate (IV)	4 mg/kg/day 300 mg/day max.	Lower dose (2–3 mg/kg) after loading; IM not advised
Dapsone (PO) with TMP (PO/IV)	100 mg/day 15–20 mg/kg/day (900 mg)	Methemoglobinemia, G6PD; *may* be tolerated in sulfadizaine allergy
Clindamycin (IV/PO) diarrhea and primaquine	450–600 mg q6h 15–30 mg base qd	Methemoglobinemia, (pyrimethamine for primaquine)
Trimetrexate (IV) with folinic acid (Not available)	30–45 mg/m/day 80–100 mg/m day	Leukopenia, anemia, thrombocytopenia; relapse common
Pyrimethamine (PO) with sulfadiazine (PO)	Load 50 mg bid × 2d, then 25–50 mg qd Load 75 mg/kg, then 100 mg/kg/day	Not studied fully in clinical trials
Piritrexim (IV) with folinic acid	Max. 4 gm in two doses; up to 8 g	
Atovaquone (PO) suspension	750 mg (PO) tid to 1500 bid	Variable absorbance, improved with fatty food; rash, GI intolerance

*Adjunctive therapies *(see text): Corticosteroids (high dose with rapid tapering), possibly γ-interferon, granulocyte-macrophage colony–stimulating factor.*
†*Based on clinical judgment of physician; some agents are not FDA approved for this indication.*

in AIDS patients, significant toxicity remains a common feature of therapy. As was noted, resistance to antibiotics has not yet been demonstrated by *P. carinii*. Thus, changing antibiotics *other than for toxicity* does not appear to be indicated. While there are patients who appear to do better on one agent than another, it is much more common to recognize a second process (infection, tumor, allergy, ARDS) as complicating *Pneumocystis* pneumonia than a resistant infection. The chest radiograph is a less reliable indicator of failure than is oxygenation. Adding pentamidine to TMP-SMX offers no advantage over simply switching agents. Indeed, animal experiments suggest the possibility of antagonism between these agents when used in combination. As a rule, patients who need to be switched from co-trimoxazole to pantamide, or vice versa, do not fare as well as those who can be treated for 14 to 21 days with either agent alone. The success rate with either pentamidine or TMP-SMX for initial treatment is around 60 to 80 percent. Adjunctive therapies (see below) may also be more useful than switching agents.

The proper duration of therapy has not been studied but is generally 14 to 21 days in all patients. Residual organisms persist after treatment for a number of months (up to 3), but the role of these organisms in recrudescent or persistent infection is not clear. Following treatment with TMP-SMX, most residual organisms are dead; relapse in the non–AIDS-immunocompromised patient should not be expected *as long as immunosuppression can be reduced* (notably, with steroid therapy).

Trimethoprim-sulfamethoxazole is the agent of choice for the treatment of *Pneumocystis* pneumonia and extrapulmonary disease in all hosts. This combination antibiotic has the advantage of excellent tissue penetration, the most rapid clinical response of anti-*Pneumocystis* agents (3 to 4 days), and bioavailability from oral therapy comparable with that of parenteral administration. Survival without intubation and mechanical ventilation appears to be greater with TMP-SMX than with pentamidine (by up to 20 percent). The incidence of some of the side effects is related to serum concentrations and is also greater than with other agents. In part, this is a reflection of the use of dosage schedules derived for children in adults and in the setting of abnormal renal function. The proper dosing in adults has not been completely studied. Therapy is initiated at 15 to 20 mg/kg per day of the TMP component (100 to 150 mg/kg per day of SMX), divided into three or four doses. Therapy should be initiated intravenously if there is uncertainty about GI function or marked hypoxemia. Peak levels are obtained about 2 h after oral dosing and should approach the range of 100 to 150 μg/ml of SMX (5 to 15 μg/ml TMP). Levels of over 200 μg/ml of SMX are associated with a higher incidence of side effects, especially bone

marrow suppression. After a clinical response is observed, the dosing can be reduced to 10 to 15 mg/kg per day, in divided doses.

Therapy can be continued (with adjustments) despite mild side effects (rash, transaminase elevations, neutropenia) tolerable to the patient and physician. Dose reduction will often eliminate toxicity in AIDS patients. Desensitization to TMP-SMX may be used in the patient with mild intolerance. With renal dysfunction, dosing must be reduced; daily dosing is sufficient (3 to 5 mg/kg per day) for a glomerular filtration rate of 10 to 50 ml/min. Renal impairment developing in a patient taking TMP-SMX should prompt a search for urinary eosinophils and an assessment of the need for further therapy with this agent. Nephrotoxicity occurs frequently in the renal transplant recipient on full-dose therapy; this toxicity is both idiosyncratic and dose related. Nephrotoxicity often occurs without demonstrable urinary eosinophils, perhaps as a reflection of the use of corticosteroids for immune suppression. In these patients, interstitial eosinophils may be found on renal biopsy. The transplanted liver is particularly susceptible to TMP-SMX toxicity (eosinophilic infiltrates, hepatocyte necrosis, bilirubinemia) and may be confused with, or complicate treatment for, early rejection or systemic infection. The side effects of TMP-SMX are generally those of sulfa allergy: rash (including Stevens-Johnson syndrome), transaminase elevation, neutropenia, thrombocytopenia, erythema multiforme exudativum, and nephrotoxicity. The bone marrow suppression is marked in patients with underlying hematologic disorders; folinic acid supplementation is rarely useful and should be avoided in patients with acute leukemia.

Dapsone (100 mg orally per day), in place of SMX and in combination with oral TMP (15 mg/kg per day), is an effective alternative therapeutic regimen. Many AIDS patients intolerant of sulfamethoxazole will tolerate dapsone, which is metabolized by the liver (half-life at least 30 hour). However, the long half-life and side-effect profile in the non-AIDS patient (hemolysis in G6PD deficiency, rash, hepatitis) may be particularly disadvantageous in the transplant recipient. Manifestations of sulfa and TMP toxicity may be masked by corticosteroids. Similarly, side effects of azathioprine (hepatitis, macrocytic anemia, neutropenia, hepatic veno-occlusive disease) may be accentuated by TMP-SMX. In AIDS, the toxic side effects of TMP-SMX are generally those of the sulfonamide; however, trimethoprim allergy is not uncommon, and allergies to the "carriers" in the various preparations of TMP-SMX (dyes, coatings, filler) have also been reported. Both components of TMP-SMX interfere with folate metabolism. Leukopenia, thrombocytopenia, and anemia caused by co-trimoxazole are generally relieved by folinic acid, whereas drug rash, fever, azotemia, and increased blood levels of transaminases will reverse only when therapy is stopped. Folinic acid should not be used in patients with acute leukemia.

Pentamidine isethionate is the first alternative agent for the treatment of *Pneumocystis* pneumonia. Pentamidine isethionate was first administered intramuscularly during an epidemic of the infantile form of the disease. It decreased mortality from 50 to 3.5 percent of those affected. Subsequently, less dramatic effects were obtained with this agent in older children and adults: survival rates of 25 to 85 percent have been reported following its use. Pentamidine is now judged to be about 70 percent effective. Pentamidine isethionate may be administered either intravenously or intramuscularly, although only the intravenous route is currently recommended. Complications with early therapy occurred in up to 50 percent of patients, notably sterile abscesses at the site of intramuscular injection. Intravenous pentamidine isethionate is given by slow (1- to 2-h) infusion in 5 percent glucose solution as a single dose of 4 mg/kg per day. Evidence exists that lower doses (3 mg/kg per day) are equally effective. Pentamidine achieves therapeutic levels in the lungs slowly (in 5 to 7 days), owing to high levels of extrapulmonary tissue binding. Slow accumulation of pentamidine in pulmonary tissue may account for the delayed onset of activity when compared with TMP-SMX. However, increased serum levels and a long serum half-life and gradual accumulation in the lungs may play a role in the continued therapeutic effect after the cessation of therapy. Because this agent has a long serum half-life (6.4 hour) and delayed excretion due to extensive tissue binding (more than 240 hour), pentamidine tends to accumulate during therapy. The reduction of symptoms by pentamidine may be due, in part, to suppression of the secretion of tumor necrosis factor by alveolar macrophages as well as to treatment of infection. Pentamidine has largely been supplanted by TMP-SMX for therapy of *Pneumocystis* infection in the non-AIDS patient. But pentamidine continues to be used for infection in patients with adverse reactions to trimethoprim or to sulfonamides.

Idiosyncratic side effects include transient hypoglycemia, pancreatitis, diabetes (after prolonged therapy, with or without prior pancreatitis), pancytopenia, hypotension, and renal dysfunction. These side effects are exacerbated by intravenous administration and in the presence of decreased renal function. Pentamidine should be avoided in pancreas transplant recipients, owing to the potential for islet cell necrosis. New diamidine compounds under development may have significantly superior therapeutic and side-effect profiles when compared to the parent molecule.

Alternative regimens have been developed as a reflection of toxicities observed in AIDS patients treated with either TMP-SMX or pentamidine. Atovaquone (750 mg orally three times a day) has been approved by the FDA for the treatment of mild to moderately severe *Pneumocystis* pneumonia. Atovaquone is a hydroxynaphthoquinone and inhibitor of electron transport with a prolonged serum half-life (at least 70 hours). Absorption is enhanced by fatty foods and decreased by diarrhea and in AIDS patients. Bioavailability has been improved by reformulation as a liquid form. Comparative trials between atovaquone (tablets) and TMP-SMX suggest that TMP-SMX is the preferred agent in patients who tolerate this therapy. Up to 7 percent of HIV-infected patients develop limiting toxicity on atovaquone (compared to 20 percent for TMP-SMX); however, significantly more patients failed therapy owing to lack of response in the atovaquone group than

in the TMP-SMX group. When pentamidine was compared with atovaquone for therapy of mild to moderate infection, lack of response was observed in 29 percent of atovaquone patients and 19 percent of pentamidine patients. However, atovaquone was better tolerated. Like TMP-SMX, atovaquone may clear *P. carinii* from the lungs in patients who complete a course of therapy better than other alternative agents, reducing the rate of relapsed infection.

Trimetrexate (NeuTrexin, US Bioscience, 45 mg/m per day) is no longer being manufactured. Trimetrexate is a dihydrofolate reductase inhibitor and is lipid soluble, with a serum half-life up to 34 hours. It will produce severe neutropenia in the absence of folinic acid supplementation (80 mg/m per day) which should be continued for 3 to 5 days after cessation of trimetrexate. Side effects include fever, rash, leukopenia, and transaminase elevation. Infection relapse in AIDS patients has been somewhat more frequent than with other therapies. Piritrexim is pharmacologically similar to trimetrexate but has been most useful in combination with a sulfonamide.

The combination of clindamycin (600 to 900 mg intravenously every 6 to 8 hours) and primaquine (15 to 30 mg base per day orally) is effective in mild to moderate infection, with the main side effect being *Clostridium difficile* colitis. Pyrimethamine (50 to 100 mg a day by mouth after 100- to 200-mg load) and sulfadiazine or trisulfapyrimidines (4 to 8 g a day) are also effective, but require folinic acid (10 mg a day) supplementation. Pyrimethamine will decrease the renal clearance of creatinine without attaining the glomerular filtration rate. The newer macrolides (azithromycin, clarithromycin) have little efficacy alone but appear to enhance the efficacy of sulfamethoxazole. However, this combination provides little benefit over TMP-SMX. The utility of DFMO (α-difluoromethylornithine) has not been established. The presence of the target enzyme in *P. carinii* (ornithine decarboxylase) suggests that efficacy is possible, but it binds the drug less well than the host enzyme. Newer agents under study include the echinocandins (glucan synthase inhibitors), which block formation of cysts, the 8-aminoquinolines, the dicationic substituted bis-benzimidazole (pentamidine derivatives), isoprinosine, bilobalide (a sesquiterpene from *Gingko biloba* leaves), quinghaosu albendazole, proguanil, terbinafine, guanyl hydrazones, and some nonquinolone topoisomerase inhibitors.

Adjunctive therapies to the treatment of *Pneumocystis* pneumonia include corticosteroids and, potentially, colony-stimulating factors. Delayed response to therapy or the inability to reduce immune suppressive therapy may allow progressive disease despite appropriate therapy for *Pneumocystis* pneumonia. Given the risks of nosocomial superinfection associated with intubation for assisted ventilation, the use of adjunctive corticosteroids was developed to prevent the early deterioration of AIDS patients with documented *Pneumocystis* pneumonia. The use of corticosteroids (prednisone, 40 to 60 mg three or four times a day, orally or intravenously) in the first 72 hour after admission may reduce pulmonary inflammation to a degree sufficient to avoid intubation. When studied in AIDS patients, the use of corticosteroids in patients with a PaO_2 of 35 to 72 mmHg or with a hypoxemia ratio of 75 to 350 was of significant benefit in terms of preventing deterioration in oxygenation in the first 7 days of therapy, mortality, and the avoidance of intubation (50 percent reduction). After such therapy, the exercise tolerance and survival of patients were also improved. Steroid tapering is necessary to avert relapse of pulmonary inflammation. Patients experience an increase in oral thrush and herpes simplex after 2 to 3 weeks of therapy and tapering. The impact of corticosteroids in the non–AIDS-compromised host and in AIDS patients failing initial therapy appears to be similar. However, the utility of additional steroids in the transplant or cancer patient has not been subjected to a controlled clinical trial.

Cytokines, including γ-interferon, have been shown to reduce the amount of *Pneumocystis* found in animal models of disease without greatly increasing the inflammatory response. The colony-stimulating factors (CSF), including those for the monocyte/macrophage (M-CSF), granulocytes (G-CSF), and granulocyte/macrophage (GM-CSF) lineages, have come into use to supplement immunity in the immunocompromised host. G-CSF has been used successfully in many of our neutropenic cancer and organ transplant recipients without adversely affecting the transplanted organs. GM-CSF has been used with systemic antifungal therapy in patients with acute fungal infections with some success. Preliminary data suggest that M-CSF and GM-CSF may be useful in enhancing the clearance of *P. carinii* by resident alveolar macrophages. Some investigators have endorsed the use of aerosolized pentamidine in addition to standard anti-*Pneumocystis* therapy. Some theoretical advantage may accrue to local administration.

The response to therapy is generally excellent in patients who receive a diagnosis before respiratory failure. The ability to reduce immune suppression or to supplement the immune response (see above) also improves the rapidity of clearance of infection. The failure to observe clinical improvement by days 4 to 5 (TMP-SMX) or 5 to 7 (pentamidine) should suggest the presence of another process: fibrosis, ARDS, dual infection (especially CMV), abscess, bronchial obstruction, drug allergy, and carcinoma. Bronchoscopic lavage and biopsy for microbiology and pathology, or chest tomography (CT scan), may be revealing in these patients.

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Viral Infections of the Lung and Respiratory Tract

John Treanor

GENERAL PRINCIPLES

Viral infections of the upper and lower airways have a major impact on health. Acute respiratory illnesses, largely caused by viruses, are the most common illness experience for otherwise healthy adults and children. The National Health Interview Survey suggests that such illnesses are experienced at a rate of 85.6 illnesses per 100 persons per year, and account for 54 percent of all acute conditions exclusive of injuries. A total of 44 percent of these illnesses require medical attention, and result in 287 days of restricted activity, 94.4 days lost from work, and 182 days lost from school per 100 persons per year. Estimates from family-based surveillance suggest that

approximately one-fourth of these illnesses result in consultation with a physician. Illness rates for all acute respiratory conditions are highest in young children; children below the age of 9 are estimated to experience between five and nine respiratory illnesses per year, whereas adults experience between three and five such illnesses.

Mortality due to acute viral respiratory infection in otherwise healthy individuals in economically developed countries is relatively rare, with the exception of epidemic influenza. However, acute respiratory infection is a major cause of childhood mortality in developing countries, and it is estimated that 4.5 million children under 5 years of age die annually from acute respiratory infection. Viruses are identified in about 3 to 40 percent of cases of respiratory disease in this setting, and are estimated to play a contributing role in approximately 20 to 30 percent of deaths. In addition, new and emerging respiratory viruses such as the coronavirus associated with severe acute respiratory syndrome (SARS) and potentially pandemic avian influenza A viruses, pose a continuing threat.

Epidemiology

Many of the viruses associated with acute respiratory disease display a significant seasonal variation in incidence. Although the exact seasonal arrival of each virus in the community cannot be predicted with precision, certain generalizations are useful diagnostically and in planning control strategies. For example, influenza and respiratory syncytial virus epidemics both occur predominantly in the winter months, with a peak prevalence in January to March in the northern hemisphere. Parainfluenza virus type 3 (PIV-3) infections show a predominance in the spring, whereas types 1 and 2 (PIV-1 and PIV-2) cause outbreaks in the fall to early winter. Rhinoviruses may be isolated throughout the year, with increases in frequency in the spring and fall. The peak prevalence of enteroviral isolations is in late summer and early fall, whereas adenoviruses are isolated at roughly equal rates throughout the year. The herpes viruses also do not show significant seasonal variation in incidence, except for varicella, which occurs throughout the year, but more commonly in late winter and early spring.

The reasons for these seasonal changes are not entirely clear. One mechanism may involve seasonal effects on virus transmissibility either because of more favorable environmental conditions for virus survival or behavioral changes that increase transmission, such as indoor crowding. Heretofore unknown effects of season on host susceptibility or response to infection could also play a role.

Characteristics of the Viruses

Classification

Viruses of importance in the respiratory tract include both those considered to be principal respiratory viruses, whose replication is generally restricted to the respiratory tract, and others in which respiratory involvement is part of a generalized infection. Virus classification depends in part on the type and configuration of the nucleic acid in the viral genome, the characteristics of the viral structural proteins, and the presence or absence of a lipid-containing envelope surrounding the virus particle (Table 134-1). The number of distinct antigenic types in each of the virus families varies. For example, the adenovirus and rhinovirus groups are composed of large numbers of antigenically (serotypically) distinct immunotypes, but other groups, such as paramyxovirus and coronavirus, are composed of only a limited number of immunotypes. As a general rule, it appears that immunity is longer lasting, and reinfection with the same virus type less common, in groups with many immunotypes than in those with only a few. The degree of antigenic stability of the virus is another important factor in determining frequency of reinfection. This characteristic is particularly important for influenza type A virus, which periodically undergoes both minor and major changes in its surface antigens.

Transmission

The routes by which the different respiratory viruses spread from person to person are still not established with certainty. Rhinovirus and respiratory syncytial virus spread, at least in part, by direct hand contact with contaminated skin and environmental surfaces. This is followed by self-inoculation of infectious virus onto the nasal mucosa or conjunctiva. Others, including influenza, measles, and varicella-zoster viruses, spread at times in small-particle aerosols. Many viruses may spread by means of large-particle aerosols over short distances (1 meter). The relative importance of the various transmission routes under natural conditions for each virus is unknown.

A number of respiratory viruses have been documented to cause outbreaks of infection in closed populations. In hospitals, nurseries, day care centers, and homes for the elderly, secondary spread to staff members and other patients may occur. Such outbreaks have been observed for viruses that appear to be spread by small-particle aerosols, including measles and varicella-zoster virus, and for those spread by direct contact with infectious secretions, such as respiratory syncytial virus, rhinoviruses and coronaviruses, where there is frequent close contact between patients and staff.

Pathogenesis of Infection

The initial sites of infection and pathogenesis differ for the various virus groups. Some, such as rhinovirus, are associated mainly with upper respiratory tract involvement. Others, such as influenza, commonly invade the lower airways and sometimes pulmonary parenchyma in addition to causing upper airway disease. The viruses also differ in the amount of damage produced in the cells lining the respiratory tract. Extensive damage to the respiratory epithelium is a characteristic feature of influenza virus infection, but biopsy studies show little evidence of nasal epithelial damage in persons with rhinovirus colds. Instead, colds are related both to virus damage to the respiratory tract and to the host responses to

Table 134-1

Common Respiratory Viruses

Virus	Family	Genome	Seasonality	Diseases	Vaccine	Antivirals
Influenza virus	Orthomixoviridae	ss RNA (−)	Yes (winter)	Influenza, croup, bronchitis, pneumonia	Yes	Yes (oseltamivir, zanamivir)
Respiratory syncytial virus (RSV)	Respiroviridae	ss RNA (−)	Yes (winter)	Bronchiolitis, pneumonia	No	Yes (ribavirin)
Metapneumovirus (hMPV)	Respiroviridae	ss RNA (−)	Yes (winter)	Bronchiolitis, pneumonia	No	No
Parainfluenza virus (PIV)	Paramyxoviridae	ss RNA (−)	Yes (winter)	Croup (PIV1), pneumonia (PIV3)	No	No
Measles	Paramyxoviridae	ss RNA (−)	No	Croup, pneumonia	Yes	No
Rhinovirus	Picornaviridae	ss RNA (+)	Yes (spring, rail)	Common cold	No	No
Coronavirus (CoV)	Coronaviridae	ss RNA (+)	No	Common cold (OC43), pneumonia (HuCoV-SARS)	No	Yes (interferon alpha?)
Sin nombre virus	Bunyaviridae	ss RNA (+/−)	No	Pneumonia	No	No
Adenovirus	Adenoviridae	ds DNA	No	Croup, pneumonia	Yes	No
Herpes simplex virus	Herpesviridae	ds DNA	No	Pneumonia	No	Yes (acyclovir, famciclovir)
Varicella zoster virus	Herpesviridae	ds DNA	No	Pneumonia	Yes	Yes (acyclovir, famciclovir)
Cytomegalovirus	Herpesviridae	ds DNA	No	Pharyngitis, pneumonia	No	Yes (ganciclovir cidofovir)
Epstein-Barr virus	Herpesviridae	ds DNA	No	Pharyngitis	No	No
Bocavirus	Parvoviridae	ss DNA (+/−)	No	Bronchiolitis, colds	No	No

infection, including immunologic events, release of mediators of inflammation, and neurogenic reflexes.

An additional important feature of respiratory virus infections is their effect on the resident bacterial flora of the upper airways. Respiratory virus infections have been found to alter bacterial colonization patterns, increase bacterial adhesion to respiratory epithelium, and reduce mucociliary clearance and phagocytosis. These impairments of host defenses by virus allow colonization by pathogenic bacteria and invasion of normally sterile areas, such as the paranasal sinuses, middle ear, and lower respiratory tract, resulting in secondary infection.

A summary of the specific viral etiologies most commonly associated with syndromes of upper respiratory

Table 134-2

Virus-Associated Respiratory Tract Infections

Clinical Syndrome	Associated Viruses
Common cold	Rhinovirus, other picornaviruses, RSV, PIV, coronavirus, adenovirus
Pharyngitis	Rhinovirus, influenza, EBV, CMV, HSV, HIV
Tracheobronchitis	Influenza, adenovirus, rhinovirus
Croup	PIV1, PIV2, influenza, adenovirus, measles
Bronchiolitis	RSV, hMPV, HuCoV-NL63, bocavirus
Pneumonia: Adults	Influenza, adenovirus, RSV, PIV, measles, VZV, sin nombre virus, HuCoV-SARS
Children	RSV, PIV, influenza, measles, adenovirus, rhinovirus, CMV
Immunocompromised	CMV, HSV, VZV, adenovirus, RNA viruses

tract infection is given in Table 134-2. The following sections briefly summarize the important points of viral respiratory tract infections.

THE COMMON COLD

Clinical Features

The term "cold" really does not constitute a single entity, but rather a group of similar illnesses of differing cause. However, all colds include symptoms of rhinitis with variable degrees of pharyngitis. Predominant associated symptoms include nasal stuffiness, sneezing, runny nose, and sore throat. Patients often report chills, but fever is not a typical feature of uncomplicated colds. Cough and hoarseness are variably present and may be more frequent in the elderly but, other lower respiratory tract signs and symptoms are not typical of colds and should raise suspicion of other entities.

Physical findings are nonspecific and most commonly include nasal discharge and pharyngeal inflammation. More severe disease, with higher fever, may be seen in children. Although colds are generally self-limited, symptoms may last for a surprisingly long period of time, with a median duration of illness of approximately 9 to 10 days in adults. Recognized complications of colds include secondary bacterial infections of the paranasal sinuses and middle ear, and exacerbations of asthma, chronic bronchitis, and emphysema. Colds are frequently associated with involvement of the middle ear, likely due to eustachian tube dysfunction. Colds are associated with symptomatic otitis media in approximately 2 percent of cases in adults, and in a higher proportion in young children.

Colds are also associated with detectable abnormalities of the paranasal sinuses, which may or may not be evident clinically. Mucosal thickening and/or sinus exudates have been observed in as many as 77 percent of subjects with acute colds. These abnormalities are transient and usually not associated with symptoms, although they may persist 21 days or longer. However, clinically manifest acute sinusitis is seen in a small (0.5–5 percent) proportion of individuals with naturally occurring colds.

Clinical colds in atopic individuals may be more severe or more likely to result in wheezing than in normal individuals, and rhinoviruses have been identified as major causes of asthma exacerbations in children and adults. The mechanism of this increased susceptibility is unclear, but may be related to an altered immune response to infection. Rhinovirus colds may increase asthma by augmenting airway allergic responses such as histamine release and eosinophil influx after antigen challenge. Rhinoviruses have also been identified as important causes of exacerbations of chronic obstructive pulmonary disease (COPD).

Viral Etiologies and Differential Diagnosis

Epidemiologic studies have established that the great majority of common colds are associated with infection with the human rhinoviruses or other picornaviruses. Other agents frequently associated with common colds include coronaviruses OC43 and 229E, and, in adults, parainfluenza and respiratory syncytial virus, with a variety of other agents implicated occasionally. The clinical characteristics of illness due to each of these viruses are similar, and a specific viral etiology generally can not be deduced on clinical grounds alone. Epidemiologic studies have indicated that on an annual basis, any one antigenic type of virus is responsible for less than 1 percent of all colds.

The differential diagnosis of individuals presenting with typical signs and symptoms is not extensive. However, in the presence of additional signs or symptoms that are not part of this clinical description, such as high persistent fever, signs of respiratory distress, or lower respiratory tract disease, alternative diagnoses should be sought. Allergic causes should be considered in individuals who present with recurrent symptoms restricted to the upper respiratory tract.

Pathogenesis

Studies of the pathogenesis of the common cold have largely focused on rhinoviruses, the most commonly implicated

viral etiology. Transmission of most of the viruses responsible for the common cold is by direct contact, with inoculation of virus into the upper respiratory tract. In situ hybridization studies of nasal biopsy specimens from rhinovirus-infected subjects demonstrate that infection is largely confined to relatively small numbers of ciliated nasal mucosal epithelial cells, although occasional nonciliated cells are also infected. Sloughing of these epithelial cells is seen in naturally occurring colds, but the epithelial lining remains intact, with structurally normal cell borders. Infection is associated with significant increases in the numbers of polymorphonuclear leukocytes in nasal mucosa and secretions, probably due to elaboration of IL-8 by infected cells. Although rhinoviruses are not able to grow efficiently at body temperature, virus can be detected within cells of the lower airway even in uncomplicated colds in healthy subjects.

In general, the number of infected cells appears to be quite limited, even in fairly symptomatic individuals, and there is no clear correlation between the level of virus replication or the number of cells infected, and the level of symptomatology. These results have suggested that virus-induced cellular injury is not the direct cause of symptoms in rhinovirus colds, but rather that inflammatory mediators play an important role. Analysis of the nature of the mucosal exudate during rhinovirus colds suggests that the nasal secretions during the initial response to rhinovirus infection are predominantly the result of increased vascular permeability, as demonstrated by elevated levels of plasma proteins in nasal secretions, whereas later glandular secretions (lactoferrin, lysozyme, and secretory IgA) predominate. Similar observations have been made in allergic rhinitis. However, in contrast to the situation in allergic rhinitis, histamine does not appear to play a role in the induction of symptoms in colds, as nasal histamine levels do not increase, and therapy with selective H1 antihistamine is not effective. Nasal secretion kinin levels do correlate with symptoms in natural and experimental colds, and intranasal administration of bradykinin mimics the induction of signs and symptoms in the common cold, including increased nasal vascular permeability, rhinitis, and sore throat.

Diagnostic Tests

Rapid diagnostic tests have been developed for many of the viruses associated with the common cold. By using specific primers, most of the responsible viruses can be detected in nasal secretions by reverse-transcriptase-polymerase chain reaction (RT-PCR), or other nucleic acid–based tests. Since there is no specific therapy and the clinical characteristics of colds due to different viruses are similar, use of techniques for specific viral diagnosis in the common cold is generally limited to the research setting.

Treatment and Prevention

The recommended treatment for colds is to use individual remedies to treat specific symptoms. Symptoms of sneezing and rhinorrhea can be alleviated with nonselective sedating antihistamines such as brompheniramine, chlorpheniramine, or clemastine fumarate. The effect is probably due to the anticholinergic properties of these drugs but treatment with selective H1 inhibitors is not effective. Studies of pseudoephedrine have demonstrated measurable improvements in nasal air flow consistent with a decongestant effect. In previously healthy children and adults, there is no danger from the routine use of cough suppressants, although they should be used cautiously in patients with serious underlying COPD. Cough syrups containing expectorants are of unproved value in common colds, although guaifenesin may reduce the cough reflex.

Symptomatic therapy with systemic anticholinergic drugs or anticholinergic-sympathomimetic combinations has not been shown to confer any benefit, non to be associated with significant side effects. In addition, the use of the decongestant phenylpropanolamine is associated with an increased risk of hemorrhagic stroke, and this drug has been removed from over-the-counter cold remedies.

Topical application of vasoconstrictors such as phenylephrine or ephedrine provides relief of nasal obstruction, but may be associated with a rebound of symptoms upon discontinuation if used for more than a few days. Thus, nasal sprays containing decongestants should be used for no more than 3 days. Topical application of ipratropium, a quaternary anticholinergic agent that is minimally absorbed across biologic membranes, reduces rhinorrhea significantly in naturally occurring colds. This agent probably exerts its major effect on the parasympathetic regulation of mucous and seromucous glands.

There has been considerable interest in the development of antiviral agents for the common cold. Several problems confront the successful development of such an antiviral agent. Because of the numerous etiologic agents, the ideal drug would require a wide spectrum of activity. In addition, many drugs that appear to have excellent in vitro activity have failed in clinical trials, apparently because they did not reach sufficient levels within the nasal mucosa where virus replication occurs. Finally, because symptoms in colds are not clearly related to the level of virus replication, a successful treatment strategy may also require use of drugs to antagonize the effects of the inflammatory mediators described herein.

LARYNGITIS AND PHARYNGITIS

Clinical Features

Pharyngitis is a common complaint of both adults and children, and is one of the more common reasons for seeking outpatient medical care. In general, this syndrome refers to individuals who present with the primary complaint of sore throat, and should probably be reserved for those individuals who manifest some objective evidence of pharyngeal inflammation as well. The clinical manifestations of pharyngitis are dominated by the specific causative agent. However, generally

the syndrome can be divided into those cases in which nasal symptoms accompany pharyngitis, which are predominantly viral in nature, and those cases without nasal symptoms, which have a somewhat more diverse spectrum of etiologic considerations, including both group A and nongroup A streptococci, chlamydia (strain TWAR), mycoplasma, and other agents.

Viral Etiologies and Differential Diagnosis

Rhinovirus colds are frequently accompanied by pharyngitis, although objective signs of pharyngeal inflammation are uncommon. Adenovirus infections are frequently associated with pharyngitis, and a specific syndrome of pharyngoconjunctival fever, consisting of fever, pharyngitis, and bilateral conjunctivitis is associated with adenovirus types 3 and 7. A variety of enteroviral serotypes are associated with febrile pharyngitis. Herpangina is a specific Coxsackie virus-induced pharyngitis in which small (1- to 2-mm) vesicular lesions of the soft palate rupture to become small white ulcers. Pharyngitis is a typical component of acute influenza in which individuals experience the sudden onset of systemic symptoms of fever, myalgias, and malaise accompanied by upper respiratory signs and symptoms, including pharyngitis. Primary oral infection with herpes simplex virus may present with pharyngitis, typically with vesicles and shallow ulcers of the palate, and cervical lymphadenopathy.

Pharyngitis may be the presenting or predominating symptom in more generalized viral infections. Pharyngitis is a significant complaint in approximately one-half of cases of the acute mononucleosis syndrome due to Epstein-Barr virus. Pharyngitis in this syndrome is generally exudative and is accompanied by cervical and generalized lymphadenopathy, as well as fever, hepatosplenomegaly, and other systemic symptoms. The heterophile antibody test is typically positive in the second week of illness. Cytomegalovirus can cause an identical syndrome that is monospot negative. Cytomegalovirus may be associated with pharyngitis more commonly in children than in adults. An acute mononucleosis-like syndrome with pharyngitis may also be the presenting manifestation of primary HIV infection. Viruses in the hemorrhagic fever group produce an acute pharyngitis that occurs early in the disease, before skin lesions appear. Also, exudative pharyngitis is a common clinical manifestation in Lassa fever.

The differential diagnosis of acute pharyngitis generally centers upon the differentiation of streptococcal from viral etiologies. Features suggestive of streptococcal pharyngitis include tonsillar swelling, moderate to severe tenderness on palpation, enlargement of lymph nodes, presence of scarlatiniform rash, and absence of coryza. The presence of nasal symptoms or of conjunctivitis favors a viral etiology, and as described, some viral syndromes may present with distinguishing characteristics that help in their identification. Generally, acute pharyngitis in children less than 3 years of age is predominantly viral in origin. The presence of exudate is suggestive of bacterial etiology, but exudates may also be seen with adenovirus or EBV.

Pathogenesis

As described, pharyngitis in the common cold is probably the result of chemical mediators of inflammation, which are potent stimulators of pain nerve endings. Potentially similar mechanisms may account for pharyngitis in other viral syndromes as well. Direct viral damage and other host inflammatory responses may also contribute. Pharyngitis occurs most often as part of the common cold syndrome and thus is usually associated with the same viruses that cause colds. In some cases, pharyngeal symptoms predominate to a degree that overshadows other complaints. The kinins are potent stimulators of pain nerve endings, and high levels of bradykinin and lysyl bradykinin are present in nasal secretions of patients with rhinovirus colds. Intranasal application of bradykinin promotes sore throat and nasal symptoms in volunteers, supporting a role for these agents in the pathogenesis of cold symptoms.

Diagnostic Tests

Identification of viral causes of pharyngitis is generally possible through isolation in cell culture, but is seldom attempted in clinical practice. Rapid antigen detection tests are available for respiratory syncytial virus and influenza A virus.

Rapid diagnostic tests are widely available for the office identification of group A streptococci, and are indicated in most cases in which the etiology is uncertain. When highly sensitive tests are used, backup cultures are generally not necessary. Routine studies for other bacterial and nonbacterial pathogens are usually not obtained. When guideline recommendations for the selective use of throat cultures are used with antibiotic treatment based only on positive rapid test or throat culture, results can reduce unnecessary use of antibiotics for treatment of pharyngitis.

Treatment and Prevention

The treatment of most cases of viral pharyngitis is symptomatic, as noted in the section on common colds. Patients suspected of having influenzal pharyngitis who are seen within the first 2 days of illness can be treated with antiviral therapy (see the discussion on influenza virus). In immunosuppressed patients with chronic herpetic pharyngitis or normal hosts with primary gingivostomatitis, acyclovir therapy is recommended (see the discussion on herpes simplex virus).

Treatment of group A streptococcal infections with antimicrobial agents is generally initiated to prevent rheumatologic complications of this infection, and because treatment of acute streptococcal pharyngitis is associated with more rapid resolution of symptoms, although the absolute benefits are rather modest.

TRACHEOBRONCHITIS (CROUP)

Clinical Features

Croup, or viral laryngotracheobronchitis, is a clinically distinct illness that predominantly affects children under the age of 3. The illness typically begins with upper respiratory tract symptoms of rhinorrhea and sore throat, often with a mild cough. After 2 or 3 days, the cough deepens and develops a characteristic brassy, barking quality, which is similar to a seal's bark. Fever between 38 and 40°C is common, although those with croup due to respiratory syncytial virus may have normal temperatures. The child may appear apprehensive and most comfortable sitting forward in bed. The respiratory rate is elevated, but usually not over 50; this contrasts with bronchiolitis, in which more severe tachypnea is often seen. Chest wall retractions, particularly in the supraclavicular and suprasternal areas, may be observed. Children with this finding on presentation have a higher risk of hospitalization or of requiring ventilatory support.

The characteristic physical finding of croup is inspiratory stridor. Inspiration is prolonged, and in very severe cases, some degree of expiratory obstruction may also be seen. Rales, rhonchi, and wheezing, which reflect the characteristic involvement of the lower respiratory tract, may be heard on physical examination. A fluctuating course is typical for viral croup, and the child may appear to worsen or improve within an hour. The typical duration of croup is 3 to 4 days.

Hypoxemia occurs in 80 percent of children with croup severe enough to require hospitalization. The degree of hypoxia is generally difficult to ascertain clinically, but pulse oximetry provides a reliable and noninvasive means to monitor the state of oxygenation. Children who develop respiratory insufficiency as a result of increasing fatigue also may have elevations in Pa_{CO_2}.

Children with croup characteristically exhibit subglottic narrowing of the tracheal air shadow on PA films of the neck, the so-called "steeple" sign). This finding may be useful in differentiating croup from epiglottitis. However, radiographs are limited in accuracy, and when the diagnosis is uncertain, radiologic and pharyngeal examination should be avoided because of the risk of cardiorespiratory arrest in acute epiglottitis. Emergency assessment by an otolaryngologist or an anesthesiologist is indicated in this situation. Chest x-rays may reveal parenchymal infiltrates which are part of the characteristic involvement of the lower respiratory tract in this syndrome.

Viral Etiologies and Differential Diagnosis

Parainfluenza viruses type 1 and 2 are the most common viruses responsible for croup, accounting for about 75 percent of cases, and the seasonal incidence of croup reflects the seasonal variations in parainfluenza virus incidence. Less common causes of croup include respiratory syncytial virus, influenza A or B viruses, measles, rhinoviruses, and adenoviruses as well as *Mycoplasma pneumoniae*. Parainfluenza virus type 2, influenza A viruses and measles are associated with more severe disease, but generally, the clinical presentation of the croup syndrome due to individual agents is similar. Specific viral diagnosis can be made by viral culture, but is not routinely performed, since the clinical syndrome is sufficient for diagnosis, and management generally does not depend on identification of the specific agent.

The majority of cases of inspiratory stridor in children are caused by viral croup. However, it is critical to distinguish these syndromes from other, potentially more serious causes of airway obstruction such as bacterial epiglottitis and tracheitis early in clinical management. Epiglottitis is an acute cellulitis of the epiglottis and surrounding structures. Patients present with acute respiratory distress and drooling, but the barking cough of croup is absent. Since the introduction of effective vaccines for the major bacterial cause or epiglottitis, *Haemophilus influenzae* type b (Hib), the incidence of epiglottitis in children has also declined considerably. In adults, and rarely in children, epiglottitis may be caused by a variety of other bacterial agents such as *Haemophilus parainfluenzae* or alpha hemolytic streptococci, which may spread from a contiguous focus of infection. Bacterial tracheitis is a relatively rare syndrome that mimics croup. Abundant purulent sputum is often present. Bacterial tracheitis is usually caused by *Staphylococcus aureus* or Hib; other bacteria such as *Streptococcus pneumoniae* have also been associated with this syndrome. Other infectious causes of stridor, including peritonsillar or retropharyngeal abscess, or diphtheria, should be considered. Evidence of noninfectious causes of stridor such as trauma or aspiration of a foreign body, should also be sought in the history and physical examination.

Pathogenesis

The severity of clinical symptoms in parainfluenza virus croup appears to be directly related to the level of virus replication. The viral infection in croup produces inflammation both in the upper respiratory tract, and in the lung parenchyma. The classic signs of croup, including the barking cough and inspiratory stridor, arise mostly from inflammation occurring in the larynx and trachea. Inflammatory changes are seen by histology in the epithelial mucosa and submucosa of the larynx and trachea. The cellular infiltrate includes histiocytes, lymphocytes, plasma cells, and polymorphonuclear leukocytes. The inflammation and obstruction are greatest at the subglottic level, which is the least distensible part of the airway because it is encircled by the cricoid cartilage. Consequently, localized inflammation and edema lead to obstruction to airflow. The impeded flow of air through this narrowed area produces the classic high-pitched vibration. Obstruction is greater during inspiration because it occurs in the extrathoracic portion of the airway, and is enhanced in small children because the walls of the airways in these individuals are relatively compliant. Obstruction of airflow results in an initial decline in tidal volume, which is compensated by an increase

in respiratory rate to maintain adequate alveolar ventilation. However, if the obstruction increases, the work of breathing may increase until the child tires, and as the respiratory rate declines, the child develops hypercarbia and respiratory failure.

Involvement of the lower respiratory tract with resulting hypoxia is integral to the pathophysiology of croup. Inflammatory changes are noted throughout the respiratory tract, including the linings of the bronchi, bronchioles, and even the alveoli. Although some degree of hypoxia can be explained on the basis of hypercarbia, the major pathophysiologic mechanism is ventilation-perfusion mismatching.

Pulmonary edema may complicate severe croup and upper airway obstruction. The onset of pulmonary edema often is immediately following intubation. Pulmonary edema in these cases does not appear to be due to pulmonary artery hypertension, but to local hypoxia, and increased alveolar-capillary transmural pressure.

In addition to these anatomic pathophysiologic events, immunologic mechanisms may also play a role in some manifestations or in determining the severity of disease. Virus-specific IgE responses appear earlier and are of greater magnitude in patients with parainfluenza virus-associated croup than in age-matched controls with simple upper respiratory illness. Histamine is also detectable in upper respiratory tract secretions in this condition. There also appears to be a relationship between croup and subsequent reactive airways disease and/or heightened responsiveness to bronchodilators, particularly in children with recurrent croup.

Diagnostic Tests

Parainfluenza viruses and other viruses associated with croup can be isolated in cell culture, but specific viral diagnosis is generally not indicated in the management of croup.

Treatment and Prevention

Because the majority of hospitalized children are hypoxic, oxygen is the mainstay of treatment for severe disease, and should be given to all hypoxemic patients. Use of helium as the carrying gas, rather than air, may decrease the work of breathing. However, this approach requires use of 70 percent helium to be effective and limits the amount of oxygen which can be delivered. Humidified air, or mist therapy is commonly used, and has several potential roles. Desiccation of the inflamed epithelial surfaces is decreased, and the viscosity of the exudate is reduced. However, the value of mist therapy has not been proven, and it should be recognized that water from the standard home-use vaporizer cannot reach the lower respiratory tract because of the large particle size. In addition, removal of the child from the parents and placement in a mist tent can be more distressing to the child than beneficial.

Administration of nebulized racemic epinephrine generally gives rapid, symptomatic relief in croup. It is believed that alpha-adrenergic stimulation by this drug causes mucosal vasoconstriction, leading to decreased subglottic edema. Several randomized trials have demonstrated a rapid beneficial effect on airway obstruction. The onset of action is rapid, often within minutes, but the duration of relief is also limited, lasting 2 hours or less. Therefore, treated subjects should be observed closely for clinical deterioration. Although symptomatic relief is considerable, use of epinephrine is not associated with improvements in oxygenation, probably because the defect in oxygen is associated with ventilation perfusion mismatching due to lower respiratory tract involvement. In addition, tachycardia may occur. Thus, inhaled epinephrine is generally reserved for children who fail to respond to more conservative management, although some centers use it routinely.

Steroids have been shown to confer significant benefits in the management of mild, moderate, and severe croup, including more rapid improvement in symptoms, reduced length of hospital stay, and reduced rates of intubation. Administration of intramuscular, oral, or nebulized steroids appears to be equally effective. Administration of single-dose steroid therapy in this setting has not been associated with significant side effects, and should probably be used in any patient with illness significant enough to require an emergency room or clinic visit.

Antiviral agents effective against some of the viruses responsible for croup are available, but have not been tested for efficacy in this situation. However, the potential benefit of the use of antiviral agents in the typical self-limited course of croup would likely be limited. Since croup is a viral illness, antibiotic therapy is of no benefit.

Effective prevention of croup will largely depend on development of vaccines for the individual viral agents responsible for this syndrome. Vaccines are currently available for both measles and influenza. There are currently no vaccines available for parainfluenza virus, although a live vaccine for type 3 is in clinical development.

TRACHEOBRONCHITIS

Clinical Features

In addition to causing croup and bronchiolitis, viral infection of the trachea and bronchi may cause tracheitis or tracheobronchitis. The diagnosis of acute bronchitis is usually applied to cases of acute respiratory disease with severe and prolonged cough that continues after other signs and symptoms of the acute infection have subsided. Cough occurs during the first week of illness in 30 percent of rhinovirus colds in young adults and in 80 percent or more of cases of influenza A virus infection, in which it is often prolonged. Adenovirus infections characteristically involve the tracheobronchial tree, with resultant bronchitis that in military populations is part of the syndrome of acute respiratory disease. Tracheitis is characterized by tracheal tenderness, which can be elicited by gentle pressure on the anterior trachea just below the cricoid cartilage. Substernal discomfort on inhalation,

and nonproductive paroxysmal cough are noted. Paroxysmal nonproductive cough is also characteristic of tracheobronchitis, and is usually much more severe at night. Later in the course of illness, small amounts of clear or whitish sputum may be produced. Accompanying symptoms may include fever, headache, myalgias, malaise, and anorexia. After several days of coughing, chest wall or abdominal discomfort that is muscular in nature may be noted. Physical findings are generally nonspecific; examination of the chest may reveal no adventitious sounds, but more commonly diffuse rhonchi and occasional wheezing. Physical signs such as egophony, pleural friction rubs, or areas of dullness to percussion, are not present.

Pathogenesis

The mechanisms of cough production in viral infection are not well understood but may include direct damage to the respiratory mucosa, release of inflammatory substances in response to the infection, increased production and/or decreased clearance of respiratory secretions, and stimulation of airway irritant receptors. Intranasal application of several prostaglandins also produces cough in uninfected volunteers. Infection may also enhance airway reactivity, leading to increased sensitivity to cold air and pollutants such as smoke.

Viral Etiologies and Differential Diagnosis

Tracheobronchitis is most typically caused by influenza A or B virus. In adults other common respiratory viruses such as parainfluenza virus or respiratory syncytial virus may present with prolonged cough. Herpes simplex has been associated with necrotizing tracheobronchitis in nonimmunocompromised hosts. This syndrome is often accompanied by refractory bronchospasm.

The differential diagnosis of acute bronchitis includes nonviral infections and noninfectious etiologies such as cough-variant asthma. *Mycoplasma pneumoniae* and *Chlamydia pneumoniae* infections cause prolonged cough. *Bordetella pertussis* infection should also be considered in the differential diagnosis. In otherwise healthy persons, workup of acute cough should be directed toward determining the presence of pneumonia.

Diagnostic Tests

Influenza viruses can be isolated in cell culture, as can many of the other viruses associated with bronchitis. In addition, rapid antigen tests or nucleic acid tests are available for some of these viruses. Specific viral diagnosis is generally not necessary for appropriate management of bronchitis.

Treatment and Prevention

Treatment in adults is best effected by prescribing rest, aspirin for headache and fever, cold water vapor inhalation; and a cough syrup such as guaifenesin with dextromethorphan. For children, a cough suppressant may be helpful. In the absence of signs of pneumonia, treatment of prolonged cough with antibacterial agents is of no benefit.

BRONCHIOLITIS

Clinical Features

Bronchiolitis is a fairly characteristic syndrome whose presenting symptoms are dominated by the major pathophysiologic defect, obstruction to expiratory air flow. The onset of lower respiratory symptoms is usually preceded by rhinitis, often with nasal congestion and discharge. More severe symptoms characteristically occur 2 to 3 days later, but in some cases are concurrent with the onset of upper respiratory symptoms. In many instances, there may be a history of exposure to an adult or sibling with a cold or other minor respiratory illness, or history of exposure to other cases of bronchiolitis in the day care setting.

The hallmark of disease is wheezing, which can be quite marked, with flaring of the nostrils and use of accessory muscles of respiration. Cough may or may not be prominent initially, and when cough is present, it may be paroxysmal in nature. Slight cyanosis is often observed, but the presence or absence of cyanosis is not a reliable indicator of the degree of oxygenation or of the severity of disease. Physical findings are generally confined to the chest, with development of rales, which are usually musical in the beginning, and then become moister. Hyperresonance of the chest may be observed, and the liver may be displaced downward. The respiratory rate is elevated, with rates of from 50 to 80 breaths per min. Fever is frequently present at the beginning of the illness, but may no longer be present at the time lower respiratory tract involvement develops. Among hospitalized infants, one-third or more are afebrile, but have marked lower respiratory tract disease. Thus, the presence or absence of fever does not indicate the severity of the child's illness. Mild conjunctivitis is noted in about one-third of cases, with pharyngitis of varied severity in about one-half, and otitis media in 5 to 10 percent. The hospital course is variable, but most infants show improvement in 3 to 4 days.

Radiologic findings are generally nonspecific, with reported findings including air trapping, consolidation, and collapse. Air trapping is particularly indicative of RS bronchiolitis and may be the only radiologic finding. However, there is no correlation between the chest x-ray findings and the clinical course. Chest x-rays should be obtained to rule out alveolar filling defects suggestive of bacterial pneumonia and in those infants with severe disease, sudden deterioration, or underlying disorders. Results of routine laboratory tests are generally unremarkable. The peripheral white blood cell count is usually not elevated. Electrolyte disturbances, most notably, hyponatremia, may be seen with severe disease, particularly if excessive amounts of hypotonic fluid are administered. Acute disease may be associated with elevations in pulmonary artery pressure, but echocardiographic studies

are usually unremarkable in infants with structurally normal hearts.

Bronchiolitis is a disease predominantly of infancy, and the peak age incidence is between 2 and 6 months of age, with over 80 percent of cases occurring in the first year of life. The risk of hospitalization and severe bronchiolitis is particularly high in infants with congenital heart disease, chronic lung disease, or immunodeficiency. In addition, infants born prematurely, and those who are less than 6 weeks of age at the time of presentation are also at increased risk of hospitalization. More severe disease has also been documented in children with a family history of asthma, and those exposed to cigarette smoke in the family setting.

Viral Etiologies and Differential Diagnosis

Respiratory syncytial virus (RSV) causes the majority of cases of bronchiolitis and during the RSV epidemic season, essentially all cases are due to this virus. Overall, RSV is recovered from about three-fourths of all infants admitted to the hospital with bronchiolitis. Several other respiratory viruses are associated with bronchiolitis, including parainfluenza viruses, influenza virus, mumps, and rhinoviruses. The epidemiology and pathophysiology of parainfluenza bronchiolitis is similar to that of RSV, and particularly severe disease may be associated with parainfluenza virus type 3. Adenoviruses types 3, 7, and 21 are relatively uncommon causes, but may be associated with more severe disease, including the development of bronchiolitis obliterans. Rhinoviruses represent a small but significant proportion of cases of bronchiolitis, and may mimic RSV infection in infants with bronchopulmonary dysplasia. Rhinoviruses and *Mycoplasma pneumoniae* become more important causes of infection-induced wheezing as children become older. Surveys of bronchiolitis in various parts of the world have suggested a similar pattern of viral etiologies.

Recently, it has been recognized that a significant number of cases are associated with the newly discovered human meta pneumovirus (hMPV). hMPV appears to be responsible for a spectrum of acute respiratory illnesses ranging from very mild or asymptomatic infection to severe bronchiolitis and pneumonitis. The clinical picture most closely resembles that of RSV, and bronchiolitis is the major manifestation in children. Clinical features include wheezing and hypoxia. There are no clinical features that can distinguish between disease caused by hMPV and RSV, although generally those due to RSV may be more severe. Novel human coronaviruses, such as NL-63, have also been associated with lower respiratory tract disease in infants. An additional recently described human parvovirus, the human Boca virus, has been found in as many as 20 percent of cases of acute wheezing in young children. This virus is often detected in the presence of other viruses, and the exact role it plays in this syndrome has not been determined completely.

The differential diagnosis of diseases characterized by expiratory airflow obstruction in infants is relatively small. Pertussis can occasionally be confused with bronchiolitis; however, more frequent vomiting and more paroxysmal cough would be clues to the diagnosis. Anatomic defects such as vascular rings can cause obstruction of the airway. Foreign bodies should be considered strongly, especially in young infants. Gastroesophageal reflux is an additional consideration. The major differential diagnostic consideration is asthma, which is uncommon under the age of 1 year.

Pathogenesis

The pathophysiology of infectious bronchiolitis has been described most completely in the case of infection with RSV. The average incubation period is 4 to 5 days, with a range of 2 to 8 days. Virus replication is limited to the respiratory tract mucosa, which may be involved through its entire length. Involvement of the lower respiratory tract probably occurs by cell-to-cell spread through the respiratory epithelium or aspiration of upper respiratory secretions. Pathologic findings in RSV bronchiolitis include necrosis of bronchiolar epithelium, loss of ciliated epithelial cells, and marked peribronchiolar mononuclear inflammation. Virus-induced cytopathology and associated submucosal edema leads to obstruction of smaller bronchioles, particularly in infants, with distal collapse or air-trapping.

Viral infection of epithelial cells of the bronchioles leads to destruction and necrosis of the ciliated epithelium. Lymphocytes can be seen in increased numbers in the peribronchial tissues. The submucosa becomes edematous, and there is increased production of mucus. Ultimately, dense plugs of alveolar debris and strands of fibrin form within small bronchi and bronchioles, which may partially or completely obstruct airflow. The pathogenic basis for respiratory difficulty in bronchiolitis is related to obstruction of these small airways. Hypoxemia is the major abnormality of gas exchange, with ventilation-perfusion imbalance the major cause of the hypoxemia. In addition to hypoxia, hypercarbia and respiratory acidosis have been observed in some severely ill infants.

Infants are particularly susceptible to the consequences of viral infection for several reasons. The peripheral airways are disproportionately narrow in the early years of life. In addition, collateral channels of ventilation, such as the pores of Kohn, are deficient both in number and size in the infant lung. Finally, the airways of infants are intrinsically more reactive to bronchospastic stimuli than are the airways of older children.

The possibility that immune responses are involved in the pathogenesis of RS bronchiolitis has received considerable attention. The presence of preexisting infection-induced antibody does not appear to play a role in enhancing the severity of disease because maternal antibody, or passively transferred antibody is protective. It has also been postulated that cellular immune responses may be involved in the pathogenesis, since infants infected with RSV who have clinical bronchiolitis have higher levels of cell-mediated immunity to RSV than those with uncomplicated upper respiratory tract disease. Immediate hypersensitivity type reactions have also been postulated to play a role in the pathogenesis of wheezing in bronchiolitis. Production of virus-specific IgE

and subsequent release of mediators of bronchoconstriction have been documented with RSV and PIV bronchiolitis. Leukotriene C4, a potent stimulant of airway smooth muscle constriction and mucus secretion, is also released into the airway in acute bronchiolitis. Elevated levels of histamine and prostaglandin $F_2\alpha$ metabolite have been found during acute bronchiolitis and increased levels of eosinophilic cationic protein in nasopharyngeal secretions, suggesting that release of chemical mediators of inflammation in response to viral antigens is one factor contributing to the development of severe bronchiolitis.

The innate immune response also plays an important role in the pathogenesis of RSV disease in infants, and it has been recognized that single nucleotide polymorphisms in several genes that control the inflammatory response have an important impact on the severity of RSV disease. Examples include polymorphisms in the genes for IL-4, IL-8, and IL-13, and in TLR-4 and the CCR5 receptor, among others.

Following recovery from acute bronchiolitis, some children experience continued episodes of wheezing, especially during viral upper respiratory infections. Estimates are that from 5 to 50 percent of children diagnosed as having bronchiolitis in infancy go on to develop recurrent episodes of wheezing. Generally wheezing episodes wane in frequency over the next several years. After clinical bronchiolitis, some individuals also may demonstrate increased bronchial responsiveness to histamine or cold challenge, which generally decreases over time. The mechanism by which RSV or other viral infection might lead to increased episodes of wheezing is unclear. Some individuals develop elevated levels of viral specific IgE, which may play a role in triggering bronchospasm upon reexposure. In some studies, persistent wheezing correlates with a family history of asthma, and with higher levels of IgE.

Diagnostic Tests

Rapid viral diagnosis can be made by identification of viral antigens in nasopharyngeal secretions. Both immune-based assays, such as immunofluorescence or enzyme-linked immunosorbent assay (ELISA), and nucleic acid-based techniques, such as hybridization or polymerase chain reaction (PCR), have been developed. Immune-based techniques are generally preferable for routine diagnostic purposes, and several kits are commercially available. The sensitivity of such techniques is dependent on the quality of the nasopharyngeal specimen, with nasopharyngeal aspirates superior to brushings or swabs. Commercially available immunofluorescence or ELISA antigen detection has a sensitivity of about 75 to 90 percent relative to culture for specimens collected from children, who shed large quantities of virus. The sensitivity of such tests in adults, who shed lower quantities of virus, is much lower (generally less than 20 percent). In transplant patients with suspected RSV pneumonia, samples of the lower respiratory tract by bronchoalveolar lavage are more sensitive than throat swabs for detection of RSV antigens.

Respiratory syncytial virus grows well in several human cell lines, in which it causes formation of characteristic syncytia. Because the virus is thermolabile, freezing of clinical specimens should be avoided. Bedside inoculation of monolayers or transport of specimens on wet ice to the laboratory helps assure maximal isolation rates. Virus can be detected as early as 2 days and usually within 7 days on primary isolation from specimens collected from children.

Treatment and Prevention

Recommendations regarding the treatment and prophylaxis of bronchiolitis have been summarized recently. Correction of hypoxemia is the most important aspect of managing RSV lower respiratory tract disease. Oxygenation should be monitored by pulse oximetry, and oxygen administered to infants whose oxygen saturation consistently falls below 90 percent. Since bronchiolitis is a viral disease which is infrequently complicated by bacterial superinfection, routine treatment with antibiotics is not warranted. Because of the dehydrating effect of tachypnea and reduced oral intake in some hospitalized infants, parenteral rehydration is often needed, but care must be taken to avoid inducing hyponatremia. Fluid intake and electrolyte concentrations should be carefully monitored in all infants with severe bronchiolitis, as hyponatremia and syndrome of inappropriate secretion of antidiuretic hormone (SIADH) may occur.

Data concerning the potential benefits of bronchodilator therapy are somewhat conflicting. Generally, bronchodilators produce modest short-term improvements in clinical scores, but do not improve oxygenation, rates of hospitalization, or duration of hospital stay. In addition, bronchodilating drugs may contribute to increased restlessness and cardiovascular stress. Because some children do respond to these drugs, a reasonable strategy is a short trial of nebulized bronchodilator with continued therapy only in selected children who respond.

The majority of studies of systemic corticosteroids have also failed to demonstrate a beneficial effect in acute bronchiolitis, and oral corticosteroids do not appear to have a beneficial effect in terms of long-term outcomes, either. Steroids may also be associated with evidence for delayed viral clearance. Although a recent meta-analysis suggested that systemic steroids have a small but statistically significant effect in decreasing length of stay, the clinical significance is minimal; therefore, corticosteroids should not be used routinely.

Antiviral therapy is available for some of the viruses responsible for bronchiolitis. The use of such therapy for the most common etiology, RSV, remains controversial. Ribavirin (1-β-D-ribofuranosyl-1,2,3-triazole-3-carboxamide) is a broad spectrum antiviral agent with antiviral activity against RSV in a variety of cell culture systems and animal models. It does not achieve suitable levels in respiratory secretions when administered systemically, so that therapy of bronchiolitis has used aerosolized drug. Although initial randomized placebo-controlled trials of ribavirin small particle aerosol showed benefit in treatment of bronchiolitis, subsequent experience with use of the drug in clinical practice did not confirm this clinical benefit. These findings, and the

expense of this drug, suggest that ribavirin should be considered only in selected infants and young children with severe illness or at high risk for serious RSV disease.

Bronchiolitis due to RSV can be prevented by passive transfer of antibody against this agent. A humanized neutralizing monoclonal antibody to the RSV F protein, palivizumab (Synagis) has significant protective efficacy in a population of infants with prematurity or bronchopulmonary dysplasia, as well as in children with hemodynamically significant congenital heart disease. Current recommendations for the use of passive antibody prophylaxis are to consider use in infants and children less than 2 years of age with chronic lung disease or congenital heart disease, and in infants born at 32 weeks of gestation or earlier (who would be expected to receive little placental transfer of maternal antibody). Palivizumab may be considered for infants born between 32 and 35 weeks who have at least two additional risk factors, such as exposure to second-hand smoke or attendance at day care. Palivizumab is not effective for therapy of RSV disease.

Interruption of nosocomial transmission may be facilitated by thorough handwashing, decontamination of surfaces and inanimate objects, and isolation or cohorting of infected infants. Use of disposable eye-nose goggles by pediatric staff reduces the risk of nosocomial RSV infection in both staff and patients. Regular use of gowns, gloves, and possibly masks by hospital staff caring for infected children may also reduce the risk of nosocomial RSV spread. Protective isolation of high-risk infants or deferring their elective admission has been recommended during institutional outbreaks of RSV.

Vaccines are available to prevent bronchiolitis due to influenza virus and mumps, but there is no vaccine currently available for prevention of bronchiolitis due to RSV. There are multiple significant hurdles to the development of such a vaccine, including the very young age at which the disease presents, the suppressive effect of maternal antibody on vaccine responses, and the potential for enhanced disease in vaccine recipients. However, several promising live vaccine candidates are in clinical development, and it has been demonstrated that it is possible to prevent RSV lower respiratory tract disease with such a vaccine.

INFLUENZA

Clinical Features

The onset of influenza is typically abrupt, and the illness is characterized by the predominance of systemic symptoms, including fever, prostration, myalgias, and malaise. Respiratory symptoms may be relatively minimal, particularly early in the course, and include nasal complaints, sore throat, hoarseness, and nonproductive cough. Because of the involvement of tracheal epithelium in infection, complaints of burning throat and substernal pain may be seen. Among healthy adults, the best clinical predictors of influenza virus positivity are the presence of cough and fever in patients presenting during epidemics.

Other than fever, there are usually few findings on physical exam. Affected individuals may exhibit rhinitis, pharyngitis, conjunctival injection, and tracheal tenderness. The chest is usually clear in uncomplicated cases. Most acute symptoms resolve in 3 to 5 days, but complete recovery may take weeks. The clinical features of influenza A and B virus infection are similar.

Influenza is an important cause of acute febrile illness in children during epidemics. Generally symptoms of influenza are similar to those in adults, although children may have higher fever with febrile seizures. As described, influenza may be associated with otitis media or croup in children. Pneumonia represents the most severe complication of influenza virus infection in both normal and compromised hosts. Primary influenza viral pneumonia is characterized by rapid progression of dyspnea, cough and cyanosis, and development of respiratory distress syndrome acute (ARDS). Chest roentgenographs reveal bilateral interstitial infiltrates, sputum production is scanty, and gram stain reveals few organisms. Secondary bacterial pneumonia may present 1 to 2 weeks after apparent recovery from an acute influenza episode with recurrence of fever, and signs and symptoms of typical lobar pneumonia.

Recently, human infections with avian influenza viruses have been described, and infections with H5N1 viruses have been particularly alarming. The available data regarding the signs and symptoms of H5N1 infection is mostly from hospitalized patients. The frequency of subclinical and mild forms of infection is currently unknown. Most patients present with the nonspecific complaints of a fever greater than or equal to 38°C along with cough and shortness of breath. In many patients, there is a progression of symptoms leading to respiratory failure requiring ventilation and other supportive measures. Atypical symptoms such as nausea, vomiting, encephalopathy, bleeding gums and nose have been reported. Watery diarrhea may be present prior to the onset of respiratory symptoms. The majority of patients have an abnormal chest x-ray with diffuse and multifocal or patchy infiltration, but pleural effusions are rare.

Epidemiology

After any given strain has caused widespread infection within a population, the presence of high levels of antibody in the population against that strain provides selective pressure that favors the emergence of viruses with amino acid changes in key antibody binding epitopes of the HA and NA. These antigenically variant viruses become the predominant strains in subsequent influenza epidemics, a process referred to as antigenic drift. As new strains emerge, they tend to replace previous strains so that in any given season there is usually one predominant influenza A H1N1, A H3N2, or influenza B strain.

Occasionally, influenza A viruses emerge with more radical antigenic changes in the HA and/or NA, a process referred to as antigenic shift. Antigenic shift is defined by the presence of a new HA or NA subtype, and only occurs in influenza A viruses. Antigenic shift has been noted three times

in the twentieth century. In 1918, H1N1 viruses emerged and replaced previous H3N2 viruses, in 1957 H2N2 viruses replaced H1N1 viruses, and in 1968 H3N2 viruses replaced the H2N2 viruses. Because there is little or no population immunity to the new viruses, antigenic shift typically results in rapid spread and high attack rates, resulting in worldwide epidemics, or pandemics. Thus, influenza epidemiology is characterized by two patterns: reliable yearly epidemics of greater or lesser severity depending on the degree of antigenic drift (seasonal influenza) and rare cataclysmic events with high mortality and morbidity resulting from antigenic shift (pandemic influenza).

Influenza is typically associated with seasonal epidemics of greater or lesser severity, which occur during the winter months in temperate climates in both the northern and southern hemispheres. Outbreaks in the northern hemisphere are usually noted between the months of November and March or April, and typically last for from 4 to 6 weeks in any given community. The reasons for the seasonal behavior of influenza are not known but have been the subject of much interest. Some suggested mechanisms have included the seasonal effects of heat and humidity on the viability of virus in the environment, behavioral patterns that facilitate transmission, such as attendance at schools, or sunlight effects on baseline immune function.

Seasonal influenza epidemics are regularly associated with excess morbidity and mortality, and both influenza A and B can be associated with severe illness. During interpandemic years, influenza is characterized by a "U-shaped" epidemic curve, in which attack rates and medically attended illness rates are generally highest in infants and young children, whereas mortality is generally highest in the elderly. Excess morbidity and mortality are particularly high in those with underlying medical conditions, including chronic cardiovascular or pulmonary disease, chronic metabolic disease including diabetes mellitus, renal dysfunction, hemoglobinopathies, or immunodeficiency, including HIV. Women in the second and third trimesters of pregnancy also have increased rates of cardiopulmonary hospitalizations during influenza epidemics. For this reason, these groups are targeted for special efforts toward prevention and therapy.

Young children are generally more susceptible to influenza infection than are adults, and shed higher levels of virus for longer periods. Influenza is a significant cause of medically attended illness in children, and is the most common cause of physician visits for febrile illness in children during influenza epidemics. Healthy children younger than 1 year of age are hospitalized for influenza at rates comparable to those of older children and adults with chronic high-risk conditions and are special targets of prevention measures.

Pathogenesis

The mechanisms responsible for transmission of influenza viruses from person to person have never been completely defined, and it is likely that both large particles (i.e., droplet) and small particles (aerosol) released from the airway during coughing and sneezing play a role. Once virus is deposited on the respiratory tract epithelium, it can attach to and penetrate columnar epithelial cells if not prevented from doing so by specific secretory antibody (IgA), by nonspecific mucoproteins to which virus may attach, or by the mechanical action of the mucociliary apparatus. The duration of the incubation period to the onset of illness and virus shedding varies from 18 to 72 h depending in part on the inoculum dose. Viral shedding in the respiratory tract is first detected just before the onset of illness (within 24 h), rapidly rises to a peak and remains elevated for 24 to 48 h, and then rapidly decreases to low titers. Usually influenza virus is no longer detectable after 5 to 10 days of virus shedding. Both the duration as well as the level of virus shedding is typically longer in young children than in adults. In general, the course of the clinical illness correlates temporally with the pattern of virus shedding, and severity is correlated with the quantities of virus shed.

Bronchoscopy of individuals with typical, uncomplicated acute influenza has revealed diffuse inflammation of the larynx, trachea, and bronchi, with mucosal injection and edema. Histologic findings on autopsy of more severe cases show extensive necrotizing tracheobronchitis, with ulceration and sloughing of the bronchial mucosa, extensive hemorrhage, hyaline membrane formation, and a paucity of polymorphonuclear cell infiltration. Abnormalities of pulmonary function are frequently demonstrated in otherwise healthy, nonasthmatic young adults with uncomplicated (nonpneumonic) acute influenza. Demonstrated defects include diminished forced flow rates, increased total pulmonary resistance, and decreased density-dependent forced flow rates consistent with generalized increased resistance in airways less than 2 mm in diameter, as well as increased responses to bronchoprovocation. In addition, abnormalities of carbon monoxide diffusing capacity and increases in the alveolar-arterial oxygen gradient have been seen. Of note, pulmonary function defects can persist for weeks after clinical recovery.

Aberrant cytokine responses have also been implicated in the pathogenesis of influenza, particularly in recent human cases of H5N1 disease. In vitro, the levels of TNF-α and other proinflammatory cytokines are higher in cells infected with the H5N1 virus when compared to cells infected with H3N2 and H1N1 viruses. Autopsy findings in humans have revealed changes of a reactive hemophagocytic syndrome, ARDS and multi-organ failure, findings typically associated with production of high levels of cytokines like TNF-α and interferons.

Viral Etiologies and Differential Diagnosis

The influenza viruses are classified into three distinct types: influenza A, influenza B, and influenza C viruses. Both influenza A and B viruses can cause the typical syndrome of influenza, and both are responsible for seasonal epidemics associated with increased morbidity and mortality. However, influenza A viruses differ from influenza B viruses by having a significant animal reservoir (birds) and by the development of numerous antigenic subtypes, which may be responsible

for pandemics. Influenza C viruses cause relatively minor respiratory disease, mostly in children.

The typical nomenclature for influenza viruses include the type (A, B, or C), the geographic origin of the specific viral strain, and strain number, and the year of isolation. In addition, the viral subtype, based on the hemagglutinin (H) and neuraminidase (N) are also given. Thus, the current influenza A virus of the H3N2 subtype is referred to as influenza A/Wisconsin/03/06 (H3N2). Since influenza B viruses, influenza A (H1N1) viruses, and influenza A (H3N2) viruses may all cause disease in any given year, the influenza vaccine contains recent examples of all three strains.

Diagnostic Tests

Viral culture is highly sensitive and specific, and also has the advantage that after isolation the virus is available for further characterization. However, it may take several days for the culture to become positive; the results are not available during the time when decisions regarding management and therapy of an individual case must be made. Thus, there has been considerable interest in the development of rapid, point-of-care tests for influenza diagnosis.

The most widely used tests are based on immunologic detection of viral antigen in respiratory secretions. In these tests, a sample of respiratory secretions is treated with a mucolytic agent and then tested, on a filter paper, in an optical device, or with a dipstick in which reaction with specific antibody results in a color change. All of the tests are designed to detect both influenza A and B, but only some of the tests differentiate between the two. Some of the tests that are minimally complex may be eligible for waivers that allow them to be used in the office setting. In general, sensitivities in adults and elderly patients tend to be lower than reported in young children, who tend to shed much larger quantities of virus in nasal secretions and therefore have much higher concentrations of antigen in their samples. Although all types of respiratory samples can be used in such tests, the sensitivity appears to be better with nasopharyngeal swabs and aspirates than with throat swabs or gargles.

Treatment and Prevention

Vaccines for Influenza

Two types of vaccines, inactivated and live, are currently available for prevention of influenza (Table 134-3). Inactivated influenza vaccines are designed to induce primarily serum antibody to the hemagglutinin and neuraminidase. The viruses selected to be contained in the vaccine are grown in embryonated hen's eggs, and the virions are chemically inactivated, and then chromatographically purified. Because influenza A (H1N1), A (H3N2), and influenza B viruses are all circulating in human populations, current formulations of influenza vaccine are trivalent; that is, they contain one example of H1N1, H3N2, and B viruses thought to be the most likely to cause disease in the upcoming influenza season. Live attenuated influenza vaccines have as their primary goal the induction of mucosal antibody in the respiratory tract, which appears to play a critical role in prevention of influenza infection. The vaccine is a so-called "cold-adapted" vaccine, generated by genetic reassortment between circulating wild-type strains and cold-adapted, attenuated master donor viruses. These vaccines are also generated in embryonated hen's eggs and are administered nasally as a trivalent formulation.

Influenza vaccine can be used in any individual who wishes to reduce his or her risk of developing influenza. Efforts at vaccination are generally targeted at two groups of individuals: persons who, for reasons of age or medical conditions, are at increased risk for developing complications, hospitalization, or death due to influenza, and contacts who may transmit infection to these high-risk individuals. Currently, high-risk groups are considered to be those 5 years of age or under, and those 50 years of age or older, as well as individuals with chronic heart or lung conditions, immunosuppressive diseases including HIV, persons with diabetes and other endocrine disorders, pregnant women, and others. Persons who may transmit to high-risk persons include family members, out of family caregivers, and especially health care

Table 134-3

Features of Influenza Vaccines

	TIV	CAIV
Produced in	Eggs	Eggs
Administration	Intramuscular infection	Intranasal spray
Immune response	Serum antibody	Mucosal immunity
Formulation	Inactivated	Live, attenuated
Storage	4C	4C
Side effects	Sore arm at injection site In some years, increased risk of Guillain-Barré syndrome	Runny nose Increase in wheezing in children <1 yr
Indications	Any person >6 mo	Healthy persons >1–49 yrs
Efficacy		
Children	++	++++
Healthy adults	++++	++++
Elderly	+++	+

Table 134-4

Antivirals Active Against Influenza

Drug	Dosage in Adults	Dosage in Children	Comments
Oseltamavir	75 mg PO bid for 5 d	≤15 kg: 30 mg twice daily >15–23 kg: 45 mg twice daily >23 kg: 60 mg twice daily >40 kg: 75 mg twice daily	Controlled trials available in adults, elderly, and children Approximately 1–2 d earlier resolution of symptoms, reduced otitis in children Other effects demonstrated include earlier return to work, decreased diagnosis of bronchitis Meta-analysis shows reduced hospitalization rates Well tolerated, main adverse event is nausea
Zanamavir	10 mg via inhalation bid for 5 d	≥7 y: 10 mg via inhalation twice daily <7 y: not recommended	Similar safety and efficacy profile as oseltamivir, without nausea Reports of exacerbations of reactive airways disease
Amantadine	<65 y: 100 mg twice daily for 5 d >65 y: 100 mg once daily	1–9 y: 5 mg/kg/d, not to exceed 150 mg/d in two divided doses 10–12 y: 100 mg twice daily	High levels of resistance in current influenza A viruses
Rimantadine	100 mg twice daily for 5 d >65 y: 100 mg once daily	≤12 y: not recommended	High levels of resistance in current influenza A viruses Not approved for use in children

workers. However, it is important to note that the recommended groups continue to expand, and as the supply of vaccine increases, it is likely that a universal recommendation for all individuals to receive yearly vaccination will eventually be made.

Antiviral Therapy

Two classes of antiviral agents have been developed with efficacy against influenza A in humans (Table 134-4). The adamantina (amantadine and rimantadine) are referred to as the M2-inhibitors, because their mechanism of action is the result of inhibition of the viral M2 protein, an ion channel involved in viral uncoating. M2 inhibitors are only active against influenza A viruses, because influenza B viruses do not contain an M2 protein. Although the M2 inhibitors are highly effective drugs for the prophylaxis and therapy of influenza A, resistant viruses are generated quite readily in treated individuals, and can be transmitted to, and cause disease in contacts. Currently, the great majority of influenza A (H3N2) viruses worldwide, as well as most Clade 1 H5N1 viruses, are completely resistant to M2 inhibitors. Therefore, M2 inhibitors are no longer recommended for use as antiviral agents against influenza.

A second class of agent is referred to as the neuraminidase inhibitors, because they are potent and selective inhibitors of the neuraminidase enzymes of both influenza A and B viruses. In cell culture, inhibition of neuraminidase function is predominantly manifested as inhibition of cell-to-cell spread of virus. The results of clinical trials of the two licensed drugs, oseltamivir and zanamivir, have been very similar, and although no head to head trials have been performed, their clinical efficacies appear equivalent. Both drugs also have an excellent safety profile. Since licensure, there has been considerably greater use of oseltamivir than zanamivir, reflecting the relative ease of administration of the oral tablet compared to oral inhalation mode of delivery.

As a general principle, it is clear that early initiation of therapy is critical to the effectiveness of antiviral therapy of acute influenza. This general observation is consistent with the typical pattern of viral shedding in an immunologically primed individual in which the peak of virus shedding is in the first few days of illness, and is rapidly controlled by the immune system. Therapy initiated beyond 48 h of symptoms does not appear to be useful in immunocompetent adults and children, and the greatest benefit is seen when therapy is begun within 12 or 24 h after the onset of symptoms. Relatively little controlled data are available related to the use of

antivirals in immunocompromised individuals with influenza or in primary influenza infections, and it is unclear whether these same constraints would apply in these situations.

Antiviral Prophylaxis

Although not a substitute for vaccination, antiviral drugs can be used for prevention as well as treatment. Generally, two strategies for antiviral prophylaxis have been evaluated. Seasonal prophylaxis refers to the strategy of administration of drug throughout the entire period of potential influenza exposure, i.e., the influenza season, typically 6 to 8 w in any given community. The second strategy administers prophylaxis for a relatively shorter period of time to a person who has close contact with an index case known or suspected to have influenza. Examples of this strategy include administering prophylaxis to family members of a person with influenza, and administering prophylaxis to patients who may be exposed during a nosocomial outbreak at a health care institution such as a nursing home or hospital.

VIRAL PNEUMONIA

Clinical Features

As described, viral infections of the lower respiratory tract represent a wide spectrum of clinical entities including croup and bronchiolitis, tracheobronchitis, and reactive airways changes. The development of pneumonia is defined by inflammation of the lung parenchyma, often associated with visible changes on chest x-ray or abnormalities of other radiologic studies such as gallium scanning and accompanied by the development of abnormalities of alveolar gas exchange. Although there can be considerable variety to the presentation of this syndrome depending on the age and immunologic competence of the host and the specific viral pathogen, there are certain general features that are described in the following.

Viral pneumonia in adults is usually associated with nonproductive cough, although production of frothy, pink-tinged sputum is seen in some severely ill individuals. Cyanosis and hypoxemia are prominent features of severe primary viral pneumonia. Physical findings are often nonspecific. The patient may appear acutely ill, conjunctivitis and rhinitis may be noted, and the trachea may be somewhat tender if accompanied by viral tracheitis. There is an increased respiratory rate, and diffuse rales and wheezes. A variety of chest x-ray patterns have been described, including lobar infiltrates, but most typically primary viral pneumonia presents with diffuse, bilateral interstitial infiltrates. However, there are really no x-ray patterns that reliably differentiate between bacterial and viral pneumonia. The sputum is relatively scant, generally shows few polymorphonuclear leukocytes, and gram stain reveals minimal numbers of bacteria.

The basic presentation of viral pneumonia in children is similar. The clinical presentation varies considerably with the specific causative agent, but typically includes fever and lower respiratory tract signs and symptoms, such as difficulty breathing, nonproductive cough, and physical findings of wheezing or increased breath sounds. Young infants may present with apneic episodes with minimal fever. The clinical presentation may be dominated by the associated croup or bronchiolitis, which are frequently present.

Underlying cardiopulmonary diseases, such as valvular heart disease or COPD, are well recognized risk factors for viral pneumonia in adults and children. Pregnancy, particularly in the second and the third trimester, has been recognized as a risk factor for cardiopulmonary hospitalizations associated with influenza epidemics.

Bacterial superinfection is a common complication of viral lower respiratory tract infection, particularly in adults. The classic presentation is that of a typical episode of viral illness with more or less complete recovery, followed 2 to 14 d later by a recurrence of fever and development of cough and dyspnea. CXR reveals lobar infiltrates, and the clinical course is typical of bacterial pneumonia. In addition, combined bacterial and viral pneumonia, with clinical features of each, are common in adults and with certain viruses in children. Bacterial superinfection of viral pneumonia can occur with many bacteria, but the most common bacteria responsible for bacterial pneumonia complicating influenza is *Streptococcus pneumoniae*. There are also increases in the relative frequency of staphylococci and *Haemophilus influenzae*.

Viral Etiologies and Differential Diagnosis

Evaluation of the specific cause of acute pneumonia, and in particular, attribution of pneumonia to a particular viral etiology, is complicated by difficulty in obtaining appropriate samples for culture, in isolating or detecting certain pathogens, and the frequent asymptomatic shedding of some viruses, such as herpes viruses or adenoviruses. Serologic diagnosis essentially establishes a temporal, but not causal, relationship between viral infection and a clinical syndrome, which may be misleading during times of high prevalence of a particular viral agent. With these qualifications in mind, it is reasonable to make several broad generalizations regarding the role of viruses in acute pneumonia. The impact of viral pneumonia and the spectrum of associated viral agents is highly dependent on the age group and immune status of the host. Viruses are clearly important and frequent causes of pneumonia in young children. The role of viruses becomes less apparent in older children, and in healthy adults, pure viral pneumonia is rare, and is predominantly due to influenza. Elderly adults may experience more significant lower respiratory tract signs and symptoms following infection with agents which normally cause upper respiratory tract illness in younger adults, but generally have similar rates of viral pneumonia as do healthy young adults. Finally, viral pneumonia is an important cause of morbidity and mortality in individuals with compromised immune systems, with a broader spectrum of viral agents than seen in immunologically intact individuals.

Immunologically Intact Adults

Influenza

The majority of cases of viral pneumonia in immunocompetent adults are probably due to or associated with influenza viruses, which typically cause disease during the winter months in temperate climates. In addition, lower respiratory tract involvement with severe viral pneumonia is a characteristic feature of human infection with avian influenza A (H5N1) viruses. The features of influenza are described in the preceding. In addition, multiple other viral pathogens are associated with a similar syndrome of viral pneumonia in otherwise healthy adults, and are described in the following.

Respiratory Syncytial Virus

Respiratory syncytial virus frequently causes detectably altered airway reactivity in adults, and on occasion, lower respiratory tract involvement becomes clinically manifest as pneumonia in otherwise healthy adults. RSV is being increasingly recognized as a cause of significant lower respiratory tract disease in the elderly. It has been estimated that 2 to 4 percent of pneumonia deaths among the elderly in the United States may be due to RSV.

Parainfluenza Virus

The parainfluenza viruses are most typically associated with viral pneumonia in children, particularly serotype3 (PIV3). However, occasionally these viruses may be associated with pneumonia in adults. Frequent contact with small children is probably a risk factor. Parainfluenza viruses have occasionally been reported as causes of pneumonia in adults and in the elderly.

Adenovirus

Adenovirus was first recognized as a cause of viral pneumonia in military recruits and has since been recognized as a rare cause of pneumonia in civilian adults and children. Outbreaks in institutionalized populations occur. The clinical characteristics of adenovirus pneumonia are similar to those of other pneumonias, so that it is difficult to make an accurate etiologic diagnosis on the basis of clinical features. In fatal cases there has been extensive pulmonary damage, with death occurring 2 to 3 weeks into the illness. Intravascular coagulopathy has also been a late feature of some cases, and a septic shock picture has been described. Bacterial superinfection, particularly with *N. meningitidis*, may occur. Since 1996, a specific variant of adenovirus type 7 (Ad7d2) has been responsible for several civilian outbreaks and a large military outbreak. The appearance of new Ad 7 genotypes may herald a shift in the predominant strains with greater disease impact.

Measles

Measles can be complicated by clinically severe pneumonitis in a small percentage of healthy adults, and bacterial superinfection is common.

Varicella Zoster Virus

Viral pneumonia is the major complication of varicella zoster virus (VZV) in normal adults, in whom it occurs with an estimated 25-fold higher frequency than in children. Smoking is a significant risk factor. Pneumonia associated with varicella is usually apparent 1 to 6 d after the onset of rash. Symptoms include cough, dyspnea, pleuritic chest pain, and hemoptysis. Physical findings other than fever and tachypnea are often modest. The intensity of the rash does not necessarily correlate with the severity of pneumonia. The characteristic radiographic pattern is that of diffuse nodular (1–10 mm) infiltrates, which may resolve with miliary calcific densities. Hilar adenopathy, pleural effusions, and peribronchial infiltrates are frequently present. Pulmonary infarction may complicate the clinical picture. Pulmonary function studies have found normal spirometric values but decreased carbon monoxide diffusing capacity, which may persist for months. One prospective radiologic study of military recruits with varicella found abnormalities in approximately one in six patients, but only one-fourth of those with radiographic changes had cough, and none experienced severe disease.

Emerging Viruses

In addition to these viruses, which have a widespread distribution and cause sporadic cases of viral influenza, two novel emerging pathogens have caused severe outbreaks of respiratory disease in previously healthy adults.

Hantavirus Pulmonary Syndrome

Clinical features of the Hantavirus pulmonary syndrome (HPS) include onset of severe pulmonary dysfunction after a 2- to 3-d prodrome of nonspecific influenza-like symptoms of fever, myalgias, cough, gastrointestinal symptoms, and headache. Laboratory abnormalities included leukocytosis, increased hematocrit due to hemoconcentration, and thrombocytopenia with coagulopathy. However, clinical bleeding is unusual, in contrast to other systemic Hantavirus syndromes. Moderately elevated levels of serum lactate dehydrogenase and aspartate aminotransferase are typically seen. A variety of radiographic abnormalities have been described. Radiographic findings that may help to distinguish HPS from ARDS include early, prominent interstitial edema, and nonperipheral distribution of initial airspace disease.

Presentation of HPS begins with a prodrome of fever, chills, and myalgias, occasionally accompanied by abdominal discomfort and gastrointestinal symptoms, and generalized malaise. Upper respiratory symptoms are usually absent. After a variable period of several days, the patient presents with mild, nonproductive cough and progressive dyspnea resulting from leakage of high-protein edema fluid into the alveoli. On physical exam patients are febrile, with tachypnea and tachycardia with mild hypotension. Examination of the chest may reveal rales but is otherwise unremarkable.

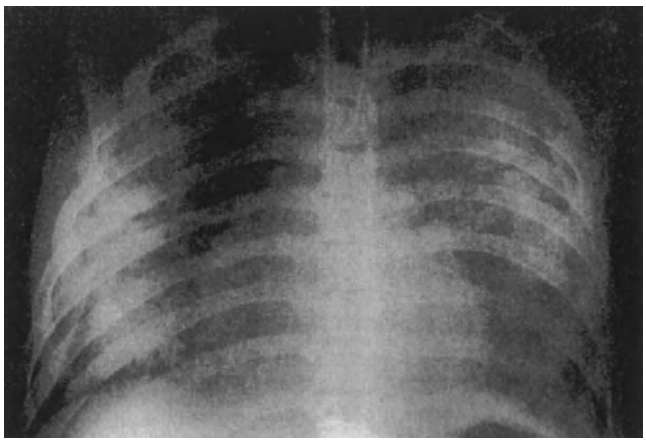

Figure 134-1 Chest radiograph showing diffuse interstitial and alveolar infiltrates in a patient with Hantavirus infection. *(From Duchin et al.,: Hantavirus pulmonary syndrome.* N Engl J Med *330: 949–955, 1994. with permission.)*

Laboratory studies generally reveal hemoconcentration, mild thrombocytopenia, and mildly elevated lung function tests (LFTs). The triad of thrombocytopenia, left shift with circulating myeloblasts, and circulating immunoblasts, is highly suggestive of HPS. Multivariate analysis has identified dizziness, nausea, and the absence of cough as clinical symptoms predictive of HPS, as well as thrombocytopenia, elevated hematocrit, and decreased serum bicarbonate as features which help distinguish HPS from other causes of acute respiratory distress such as pneumococcal pneumonia and influenza. Mild renal abnormalities may be detected, but unlike hemorrhagic fever with renal syndrome (HFRS), do not progress to renal failure.

Chest radiograph typically shows both interstitial and alveolar infiltrates and resemble noncardiogenic pulmonary edema (Fig. 134-1). Pleural effusions are present in most cases. Early in the course of HPS these effusions are transudative, while later they develop higher fluid protein content and in severe cases have the protein characteristics of plasma. Cardiopulmonary manifestations in severe cases include a shock state with low cardiac index, low stroke volume index, and high systemic vascular resistance. Typically, the pulmonary artery wedge pressure is normal or low. Progression is associated with worsening cardiac dysfunction and development of lactic acidosis. The case-fatality rate averages approximately 30 to 40 percent. In those patients who survive, recovery is usually complete, but some patients have manifested long-term pulmonary dysfunction. The syndrome in children and adolescents is similar to that in adults.

Severe Acute Respiratory Syndrome

Epidemics of SARS initially in southern China and subsequently in multiple locations in Asia and elsewhere in the early spring of 2003 were associated with the emergence of a novel coronavirus, referred to as the Human SARS Coronavirus (HuCoV-SARS). After an intense epidemic associated with 8096 cases and 774 deaths, the disease disappeared, largely due to aggressive infection control practices.

Extensive sequence data strongly suggests that HuCoV-SARS was introduced into human populations from an animal species, likely the palm civet or a related animal. Subsequent transmission took place largely in the health care setting. Transmission appeared to be by droplet spread and required close contact. Virus shedding was at its peak at the time that illness was most severe, which may account for the preponderance of transmission occurring in the hospital setting. Generally, the reproductive number in the absence of infection control measures was estimated to be about 3, i.e., each case transmitting to an estimated three additional individuals. In addition, a poorly explained phenomenon in which certain individuals appear to be responsible for an extraordinarily large number of transmissions, or so-called "super spreaders" was described.

Generally, SARS has a nonspecific presentation that is difficult to distinguish on clinical grounds from other forms of viral acute respiratory illness, particularly influenza. The most common symptoms on presentation are fever, chills and/or rigors, and myalgias. Cough and dyspnea are the predominant respiratory symptoms but may not be present initially. Upper respiratory symptoms, such as rhinorrhea or sore throat are infrequent. In addition, about one-third of patients have diarrhea at some point in the clinical course. Respiratory disease is progressive and becomes more severe over 4 to 7 d, leading to significant hypoxemia. About 20 percent of patients require respiratory support. The overall case fatality rate is about 10 percent, but is much higher in older adults.

Laboratory abnormalities on presentation include elevations in lactate dehydrogenase, transaminases, and creatine kinase, and hematologic abnormalities, particularly lymphopenia, as well as thrombocytopenia. The lymphopenia includes depletion of both CD4 and CD8 cells.

Radiologic abnormalities have included unilateral or bilateral ground-glass opacities or focal unilateral or bilateral areas of consolidation. In hospitalized patients the abnormalities tend to progress to bilateral airspace consolidation. In most patients, peripheral involvement is seen, often involving the lower lung zones. However, the initial chest radiographs have been normal in about 10 percent of cases. Thin-section chest CT is more sensitive at detecting radiologic abnormalities in SARS. Common findings include ground-glass opacification, and interlobular septal and intralobular interstitial thickening. Pulmonary fibrosis may develop after recovery from the acute illness.

Features associated with a higher risk of intubation and death include older age, and the presence of comorbid conditions, particularly diabetes. However, even relatively healthy young health care workers may have very severe disease. Clinical features predictive of a worse outcome have included the presence of bilateral disease at presentation and the peak level of lactate dehydrogenase.

For reasons that are unclear, children have been reported to have milder disease than adults. SARS in children has a similar presentation to that in adults, including fever, cough, and alveolar infiltrates. However, younger children

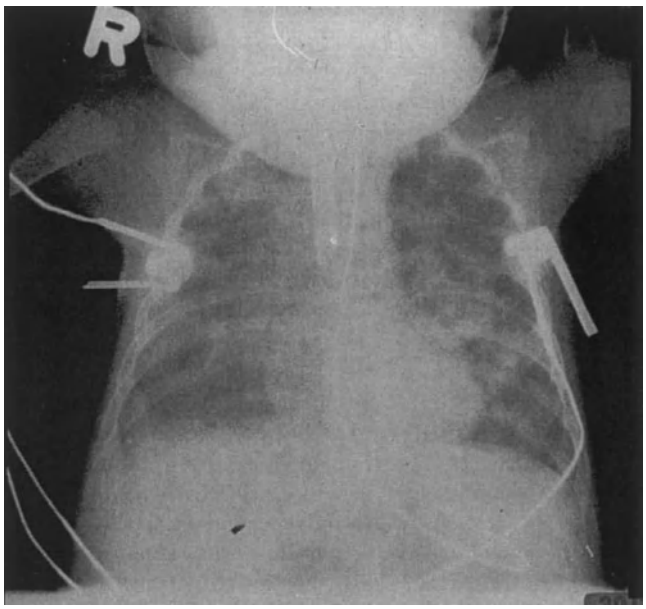

Figure 134-2 Premature infant at 3 months of age with respiratory syncytial virus pneumonia. *(Courtesy of Dr. Janet Englund, Baylor College of Medicine.)*

generally do not require oxygen therapy, and have a relatively benign clinical course.

Children

Respiratory Syncytial Virus

In most series, RSV has been associated with the largest proportion of viral pneumonia in young children, particularly if accompanied by bronchiolitis. It should be noted in this regard that bronchiolitis and pneumonia represent a spectrum of lower respiratory tract involvement with RSV, frequently coexist, and are not clearly distinguishable. The most typical finding is diffuse interstitial pneumonitis (Fig. 134-2). Lobar or segmental consolidation are evident by CXR in about one-fourth of children with RSV lower respiratory tract disease.

Parainfluenza Virus

The parainfluenza viruses are second only to RS virus as causes of pneumonia in this age group. As described, lower respiratory tract involvement is integral to the pathophysiology of croup, but pneumonia with pulmonary infiltrates is most commonly associated with parainfluenza virus type 3.

Influenza Virus

Influenza A and B viruses are both significant causes of pneumonia in children, especially during periods of epidemic prevalence. In infants and children, the most frequent manifestation of influenza pneumonia is an interstitial pneumonitis similar in appearance and course to those of the other predominant viral agents of pneumonia in this age group, except that a secondary bacterial pneumonia may occur more frequently than with RS or parainfluenza viruses.

Adenovirus

Adenoviruses are frequently isolated from children with respiratory disease and are implicated in about 10 percent of childhood pneumonias. However, the true impact of adenoviruses as causes of pneumonia in this age group is difficult to assess because of the long and intermittent asymptomatic respiratory shedding of these viruses in children. Hilar adenopathy on CXR is somewhat more common with this form of pneumonia than other types.

Measles

Pneumonia is the most frequent serious complication of measles. The prodrome of typical measles lasts 2 to 8 d and is characterized by fever, malaise, anorexia, cough, coryza, and conjunctivitis. Koplik's spots, which are erythematous macular lesions with central white-yellow or gray puncta, appear on the buccal or labial mucous membranes toward the end of the prodromal period. The maculopapular, erythematous eruption begins about the face and neck and progresses to involve the upper body, trunk, and extremities. The rash typically disappears after 5 to 6 d in the order in which it appeared. Defervescence and symptom improvement occur several days after the appearance of the rash, although persistent cough is common. Leukopenia is common during the prodromal and early exanthematous stages of measles. Pronounced leukopenia (less than 2000 cells/mm^3) is associated with a poor prognosis. The development of neutrophilic leukocytosis suggests the possibility of bacterial superinfection or other complications.

Cytomegalovirus

Respiratory distress is part of the clinical picture in infants with congenital cytomegalovirus (CMV) disease. Older infants and children may exhibit prolonged respiratory disease with bronchitis or pneumonia associated with CMV carriage.

Rhinovirus

Rhinoviruses have also been associated with a significant proportion of community acquired pneumonias in children, despite the relative inability to grow efficiently at body temperature. Other viruses that may occasionally cause viral pneumonia in children include enteroviruses, rubella virus, and herpes simplex virus.

Immunocompromised Individuals

Individuals with diminished host immunity may develop severe, life-threatening pulmonary infections with the entire spectrum of RNA and DNA viruses, including both viruses that are typical causes of lower respiratory tract disease in normal hosts, and other, more opportunistic viral pathogens. DNA viruses have received the most recognition in this regard.

Cytomegalovirus

CMV is a frequent, severe pneumonitis in immunosuppressed individuals, particularly transplant recipients, or individuals infected with the human immunodeficiency virus (HIV).

The highest risk in the transplant population is 1 to 3 mo posttransplantation, with the peak incidence at 8 w posttransplant. Diffuse interstitial pneumonitis is the most frequent presentation, but multiple other CXR presentations have been reported, including nodular infiltrates resembling nocardia. Multiple associated findings are present in severe infection, and reflect the disseminated nature of the infection; the presence of neutropenia, abnormalities of liver function tests, and mucosal ulcerations may be clinical clues to the diagnosis.

Characteristically, patients with CMV pneumonia have sustained fever, nonproductive cough, and dyspnea. Rales and tachypnea are often present, and marked hypoxemia is an indicator of life-threatening infection. Pneumonitis may be accompanied by mild neutropenia, thrombocytopenia, and elevated liver enzymes, which may be helpful in differential diagnosis. Chest radiographic changes are usually bilateral, with diffuse or focal haziness involving the mid and lower lung fields. Both miliary and interstitial radiographic patterns have been described. Often the perihilar distribution of the infiltrate is suggestive of pulmonary edema. Common CT scan findings include small nodules, consolidation, and ground-glass attenuation.

Herpes Simplex Virus

HSV infection of the lower airway may occur either as the result of direct extension of infection from the tracheobronchial tree to the lung or as the result of hematogenous dissemination of virus from mucocutaneous lesions of the upper airway or genitourinary tract. Dyspnea, cough, and hypoxemia are usually seen, but the clinical features of the pneumonia do not permit an etiologic diagnosis to be made antemortem. Focal or multifocal infiltrates were seen on chest roentgenograms of patients with the pattern of direct extension, whereas diffuse bilateral infiltrates were found in patients with pneumonia due to presumed hematogenous dissemination of virus. CT scan findings include multifocal segmental and subsegmental ground-glass opacities, but are not distinctive. In one study, more than one-half of the patients had concomitant pulmonary infection with other microorganisms, including bacterial, candidal, and *Aspergillus* species, and cytomegalovirus. Histologic evidence of herpetic esophagitis was present in 10 of 16 patients with herpes pneumonia in whom esophageal examination was performed.

Herpes simplex virus infection of the lower airway has also been found in association with ARDS. The relationship of HSV infection to ARDS is unclear, but the presence of HSV in the lower respiratory tract was associated with the need for prolonged respiratory support and an increased late mortality. Isolation of HSV from lower respiratory tract secretions has also been common in mechanically ventilated patients and may be associated with a poor outcome.

Varicella Zoster Virus

VZV is an important problem in individuals with hematologic malignancies and others with iatrogenic immunosuppression, with the greatest risk seen in organ transplantation. Prolonged fever and/or recurrent crops of lesions are predictors of visceral dissemination, and pneumonia is generally seen in this setting. Pulmonary manifestations may include pleuritic chest pain due to vesicular lesions of the pleura, and, as is also true in normal hosts, the CXR may demonstrate nodular lesions.

Adenoviruses

Adenoviruses are significant causes of morbidity and mortality in immunocompromised patients, particularly after transplantation. In contrast to infection in normal hosts, infection in immunocompromised subjects tends to be disseminated, with isolation of virus from multiple body sites including lung, liver, gastrointestinal tract, and urine. In addition, the spectrum of serotypes includes both those found in immunocompetent individuals as well a markedly increased frequency of isolation of higher-numbered serotypes found rarely in immunologically normal subjects.

RNA Viruses

RNA viruses have also received increasing recognition as potential causes of significant morbidity and mortality in this population. RSV has been well recognized as a cause of pneumonia in recipients of bone marrow and solid organ transplantation. Nosocomial transmission of RSV in this setting has been well documented, and may be the source of many infections in this susceptible population. The illness typically begins with nondescript upper respiratory symptoms that progress over several days to severe, life-threatening lower respiratory tract involvement. Mortality rates of 50 percent or higher are typical, particularly if disease occurs in the preengraftment period. Parainfluenza viruses have also been reported as an infrequent lower respiratory tract pathogen in both solid organ and bone marrow transplantation. PIV-3 has been most commonly serotype isolated, but all four serotypes have been implicated. Influenza may also cause severe disease in transplant recipients, but most subjects have survived. Rhinovirus infections in this population are also common, but tend to be associated less frequently with lower respiratory tract disease. However, chronic rhinovirus infection, with graft rejection, has been described in lung transplant recipients.

Measles giant cell pneumonia is a severe, usually fatal form of pneumonia associated with measles infection in immunosuppressed individuals. Most cases have occurred in those with hematological or other malignancies, or individuals with AIDS. Recent outbreaks of measles worldwide, coupled with the increasing incidence of HIV infection, has increased the frequency and impact of measles giant cell pneumonia. Giant cell pneumonia also occurs in significantly malnourished individuals. Multinuclear giant cells with intranuclear inclusions are seen, and may be demonstrable in fluid obtained by bronchoalveolar lavage. An important feature of measles pneumonia in immunocompromised hosts is that many patients present without rash or other typical manifestations of measles, and a high index of

suspicion must be maintained. It has been speculated that such hosts may not mount the cellular immune responses involved in the pathogenesis of rash in immunologically intact individuals. In hospitalized patients, mortality rates are approximately 70 percent in oncology patients and 40 percent in HIV-infected patients.

Pathogenesis

The pathogenesis of viral infections of the lower respiratory tract can conveniently be considered in terms of infections initiated in and primarily confined to the respiratory tract, or so-called primary viral pneumonia, such as with influenza or RSV; processes in which infection is initiated in the respiratory tract with subsequent systemic manifestations, such as in measles or varicella, and processes in which respiratory tract involvement is secondary to a systemic infection, such as with CMV. Each of these situations may lead to what is recognized clinically as a viral pneumonia. In this discussion, the general features of primary viral pneumonia are discussed using influenza as a model, and pathogenesis of other forms of viral pneumonia are discussed briefly in comparison.

In primary influenza viral pneumonia, virus infection reaches the lung either by contiguous spread from the upper respiratory tract, or inhalation of small particle aerosols. Infection initially occurs in ciliated respiratory mucosal epithelial cells of the trachea, bronchi, and lower respiratory tract, and leads to widespread destruction of these cells. The trachea and bronchi contain bloody fluid, and the mucosa is hyperemic. Tracheitis, bronchitis and bronchiolitis are seen, with loss of normal ciliated epithelial cells. Submucosal hyperemia, focal hemorrhage, edema, and cellular infiltrate are present. The alveolar spaces contain varying numbers of neutrophils and mononuclear cells admixed with fibrin and edema fluid. The alveolar capillaries may be markedly hyperemic with intra-alveolar hemorrhage. Acellular, hyaline membranes line many of the alveolar ducts and alveoli.

The pathologic changes in the lower respiratory tract in children with viral pneumonia due to RSV and parainfluenza virus are nonspecific and include epithelial necrosis with bronchiolar mucus plugging and widespread inflammation and necrosis of lung parenchyma, and severe lesions of the bronchial and bronchiolar mucosa as well. In fatal cases of RSV pneumonia in children, hemorrhagic pneumonia with peribronchial mononuclear infiltration and cytoplasmic inclusion bodies in epithelial cells are seen.

Bacterial superinfection is a well-recognized complication of viral pneumonia and accounts for a large proportion of the morbidity and mortality of viral lower respiratory tract disease, especially in adults. Consequently, the spectrum of disease and pathophysiology of bacterial superinfection has been studied intensively, and a number of factors identified in viral respiratory disease which could play a role in increasing the risk of bacterial infection. The disruption of the normal epithelial cell barrier to infection, and loss of mucociliary clearance undoubtedly contribute to the enhancement of bacterial pathogenesis. The physiologic consequences of these alterations have been demonstrated as markedly decreased mucociliary clearance of labeled particles in human subjects with acute, naturally acquired influenza. In addition, increased adherence of bacteria to virus-infected epithelial cells has been demonstrated. Polymorphonuclear leukocytes and mononuclear cells are susceptible to abortive infection by some respiratory viruses with resulting decreased function that may also contribute to enhanced bacterial infection. Finally, bacteria themselves may enhance the replication of some viruses such as influenza viruses by the release of proteases that cleave the viral hemagglutinin.

The Hantavirus pulmonary syndrome represents an additional example of a viral infection that involves the lung as part of a systemic infection. The pathogenesis of HPS involves extensive infection of endothelial cells throughout the body, which is particularly intensive within the endothelial cells of the lung. Abundant viral antigen and nucleic acid can be detected within these cells. Microscopic examination of the lung reveals mild to moderate interstitial pneumonitis with variable degrees of congestion, edema, and mononuclear cell infiltration. The cellular infiltrate is composed of a mixture of small and large mononuclear cells, which consist predominantly of T lymphocytes, and macrophage/monocyte cells. The picture is one of immune mediated capillary leak and not of cell necrosis or inflammatory pneumonitis. High levels of cytokines have been detected in the blood and likely mediate the endothelial damage.

Cytomegalovirus pneumonia is a problem predominantly in individuals with compromised immune systems, particularly after transplantation, and also represents a systemic infection that involves the lung secondarily. There are several features of this disease in the transplant setting that suggest that both host and viral factors interact in pathogenesis. CMV pathogenicity is enhanced in transplant recipients and frequently occurs at the site of the transplanted organ. The risk of CMV pneumonitis is highest in individuals at the highest risk for graft-versus-host disease. Finally, treatment with antivirals alone is ineffective, while treatment with antivirals and immune globulin, which serve to mitigate the graft-versus-host component, is effective.

The pathogenesis of CMV pneumonia is partly related to viral replication but also is thought to have an immunopathologic basis. The development of CMV pneumonitis reflects a complex interaction between viral infection and graft-versus-host disease, particularly in marrow transplant recipients. Two patterns of histopathology have been described in the lung tissue of bone marrow transplant patients with serious pneumonia. One is a miliary pattern, with multiple focal lesions showing extensive cytomegaly with localized necrobiosis, alveolar hemorrhage, fibrin deposition, and neutrophilic response. The other is of interstitial character, with alveolar-cell hyperplasia, interstitial edema, lymphoid infiltration, and diffusely distributed cytomegalic cells.

Diagnostic Tests

Epidemiologic or clinical features of the presentation of viral pneumonia, such as the time of year, history of exposures,

or, in some situations, presence of systemic signs or symptoms, such as rash, may be very useful in establishing the potential viral etiologies in specific cases of viral pneumonia. However, the clinical presentation is rarely distinctive enough to allow a specific viral diagnosis to be made on clinical grounds alone. Specific diagnosis generally depends on isolation of viral agents from appropriate respiratory specimens. Many of these viruses can be isolated from nasopharyngeal swab or wash specimens, or from lower respiratory tract secretions. Rapid antigen detection tests are available for detection of RSV and influenza A virus in respiratory secretions. Definitive attribution of pneumonia to viruses that are typically shed asymptomatically in the upper respiratory tract, such as herpes simplex virus, is more difficult and requires detection of virus in the lower respiratory tract, usually in association with pathologic evidence of invasive disease.

Differentiation between viral and bacterial forms of pneumonia on clinical grounds can be difficult in children, and radiologic criteria do not always distinguish these entities well and mixed viral and bacterial pneumonia may be present. However, in normal infants and children with RS or parainfluenza virus pneumonia, bacteria do not appear to play an important role, and routine addition of antibacterial agents is not useful. The exception to this observation is in developing countries, where mixed viral and bacterial pneumonias in children are frequent and severe.

Treatment and Prevention

Therapy of viral pneumonia is dependent on the severity of disease, the age and immune status of the host, and the specific causative viral agent. General supportive measures, particularly the management of hypoxia, are critically important, and some patients have required high frequency ventilation or extracorporeal membrane oxygenation. Since mixed viral-bacterial infections or bacterial superinfections are common, antibacterial agents may be required, for example, in patients with lobar pneumonia or productive sputum.

Antiviral therapy is generally indicated for severe disease and in immunocompromised hosts, and should be guided by the results of diagnostic tests. As described above, the neuraminidase inhibitors zanamivir and oseltamivir have mostly been studied in uncomplicated influenza in healthy adults, but it seems reasonable to use antiviral agents if the patient is still virus positive at the time of presentation. Because of widespread resistance, use of the drugs amantadine or rimantadine is no longer recommended.

The only option available for the other RNA viruses is ribavirin, but there is little evidence of efficacy of this agent for any viral pneumonia. In immunocompromised hosts, treatment of established RSV pneumonia has not been successful. One approach that appears promising is treatment with ribavirin, possibly in combination with immunoglobulin, early in the illness when predominantly URI symptoms are present. Controlled trials in parainfluenza virus infection are not available, although anecdotal reports suggest potential efficacy. Limited controlled trials have suggested that aerosolized ribavirin may reduce the severity of symptoms in children with measles, and some immunocompromised patients with measles pneumonia have done well following treatment with aerosolized or intravenous forms of the drug. Intravenous ribavirin is effective in the treatment of several human Hanta-virus diseases, including Lassa fever and HFRS, but was not effective in a controlled trial of therapy of hantavirus pulmonary syndrome.

Antiviral agents with proven clinical usefulness for human coronavirus infection are currently unavailable. However, the severity of the SARS coronavirus epidemic has led to an extraordinary effort to discover and develop effective antivirals, and it is likely that multiple agents will be reported in the near future. The most promising to date appears to be the type I interferons (alpha and beta), which are highly active in cell culture. Treatment with parenteral interferon at doses used typically to treat hepatitis C virus infection appeared to lead to clinical improvement in a small series of patients in the Toronto epidemic.

Acyclovir is active in vitro against herpes simplex virus types 1 and 2; it is approximately ten-fold less active against VZV and does not have clinically useful activity against cytomegalovirus or Epstein-Barr virus. Although controlled clinical trials of this drug in herpes simplex pneumonia have not been conducted, the drug has proven clinical efficacy in other herpesvirus infections and would be indicated in any serious HSV lower respiratory tract infection. Acyclovir is also effective in the therapy of varicella, and intravenous acyclovir has been effective when initiated early in the course of varicella pneumonia. The related drugs famciclovir and penciclovir are similar to acyclovir in their spectrum of activity against herpes viruses. Viruses resistant to the activity of these drugs have been isolated from treated patients, and may be susceptible to the antiherpes drug phosphonoformic acid (foscarnet).

Once CMV pneumonitis is established, particularly in allogeneic bone marrow transplant patients, it is very difficult to treat. Ganciclovir is highly active against CMV in vitro but monotherapy is not effective in pneumonitis in BMT recipients. The combination of ganciclovir therapy and intravenous CMV immune globulin can reduce mortality from approximately 90 to 50 percent or lower in these patients. The effect of the immune globulin in this situation may be mostly to ameliorate graft-versus-host disease. Whether combination therapy is required in solid organ transplant recipients with CMV pneumonia is uncertain. Cidofovir and foscarnet are other antiviral drugs with activity against CMV. Both have been used to successfully treat CMV retinitis, but their effectiveness for treating CMV pneumonia has not been established. All of the available CMV antivirals have serious side effects that limit their usefulness.

Guidelines for reducing the risk of CMV disease in stem cell transplant recipients have recently been published. Transplant candidates should be screened for evidence of CMV immunity, and CMV-seronegative recipients of allogeneic stem cell transplants from CMV-seronegative donors should receive only leukocyte-reduced or CMV-seronegative RBCs and/or leukocyte-reduced platelets. In mismatched

solid organ transplant recipients (donor+/recipient–), post-transplant prophylaxis with oral ganciclovir or its prodrug valganciclovir significantly reduces the risk of CMV disease, although late-onset disease still occurs. Another strategy is preemptive therapy with ganciclovir or another anti-CMV agent when screening detects infection, but before disease develops. This strategy requires the use of sensitive and specific laboratory tests for diagnosis.

Antiviral treatment of proven value for adenovirus infection is not available. Both the broad spectrum antiviral agents ganciclovir and cidofovir are active in vitro, and an increasing number of reports indicate that intravenous ganciclovir may be useful in seriously ill patients, although at the expense of significant renal toxicity. Cidofovir has also been used for preemptive therapy in high-risk immunocompromised patients.

Various forms of intravenous immunoglobulin have also been evaluated in viral pneumonia. As mentioned, IVIG is important in the treatment of CMV pneumonia in bone marrow transplant recipients; the effect is unrelated to the titer of CMV neutralizing antibody contained in the preparation, and may act through modulation of the immune response. Intravenous immunoglobulin is effective for the prevention of measles after exposure of susceptible individuals, and may be useful in the treatment of measles pneumonia, especially when combined with ribavirin. As described above, a humanized, neutralizing monoclonal antibody directed against the F protein of RSV (palivizumab) is highly effective for the prevention of severe RS disease in at-risk infants, but is not effective for therapy of established disease.

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Protozoan Infections of the Thorax

Louise C. Ivers • Edward T. Ryan

AMEBIASIS

Entamoeba histolytica

Entamoeba histolytica is a protozoan infection of humans that is found worldwide and is globally responsible for up to 100,000 deaths annually. It is endemic in most temperate and tropical areas of the world, particularly in areas with poor socioeconomic development and limited sanitation. Serological evidence of prior or current infection with *E. histolytica* is present in 5 to 50 percent of individuals in impoverished populations. *E. histolytica* is infectious in its cyst form. Transmission usually occurs as a result of contamination of food or water, but may also occur by means of oral-anal contact. Infection is common in developing countries. In Europe and the United States, infection is most commonly seen in individuals who have lived in endemic areas of the world. Institutionalized individuals are also at increased risk of infection. Sexually active men who have sex with men are also at increased risk of infection, although recent studies suggest that this group is not necessarily at increased risk of invasive disease. There does not appear to be an increased risk of invasive disease in persons with HIV infection.

A morphologically identical, but non-pathogenic protozoan, *Entamoeba dispar*, also infects the human gastrointestinal tract. It has recently been distinguished from *E. histolytica* by antigenic, genetic, and immunologic methods. Infection is 10 times more prevalent with *E. dispar* than with *E. histolytica*; however, the former does not cause invasive disease. In the United States, infection with *E. histolytica* or *E. dispar* is estimated at 4 percent. Many older epidemiological studies relied on microscopic diagnosis alone, and inadvertently incorporated both pathogenic and nonpathogenic species in estimates of prevalence of infection.

E. histolytica has a simple life cycle involving an infectious cyst and an ameboid trophozoite phase. Cysts may survive in the external environment for several weeks to months, especially in damp conditions and temperatures between −5°C and 40°C. After ingestion by humans, cysts excyst in the small intestine, each forming eight daughter trophozoites. These motile trophozoites can adhere to the intestinal wall; it is in this form that they may invade the mucosa, causing symptomatic invasive disease. In the colon, trophozoites encyst to complete the life cycle and are excreted. Trophozoites do not survive outside the human host.

Clinical Manifestations

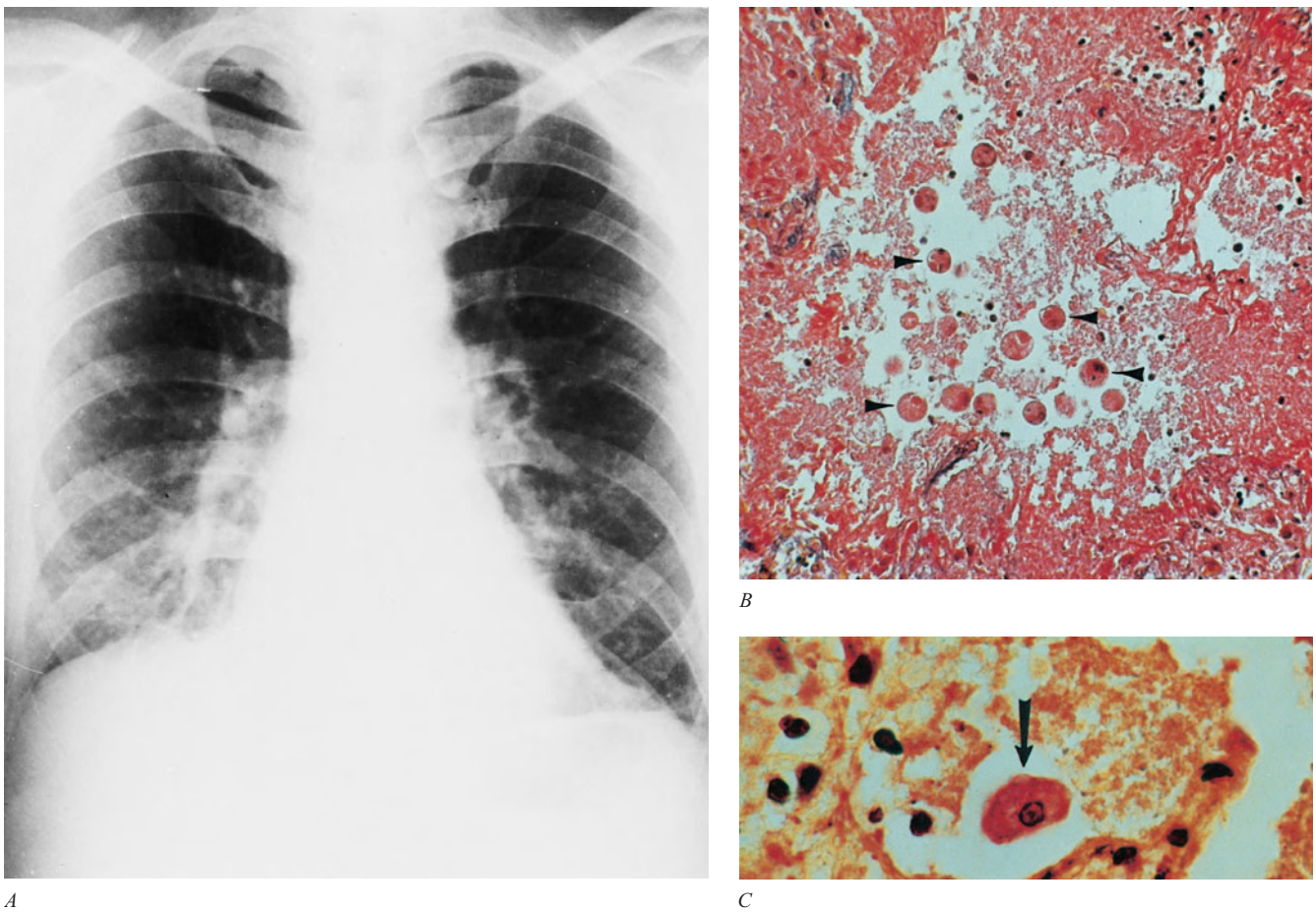
The incubation period for intestinal amebiasis is usually 1 to 4 weeks, but ranges from a few days to months. Infection with *E. histolytica* is asymptomatic in up to 90 percent of cases, but may cause a range of gastrointestinal symptoms from mild diarrhea to severe colitis with bloody diarrhea. Symptoms result from penetration of the trophozoites through the mucosal barrier with invasion of the colon wall. In the absence of frank blood, stool is usually positive for occult blood. Fever is present in less than half of cases. Fecal leukocytosis is usually less marked than in bacterial colitis. Rarely, progression of invasive intestinal disease may lead to severe colitis and bowel perforation. On occasion, granulation tissue formation surrounding a localized area of invasive disease may form an inflammatory mass (an "ameboma") and manifest as a tender abdominal mass.

Extraintestinal disease most commonly occurs in the liver, and manifests as a liver abscess. In this instance, trophozoites migrate to the liver via the portal veins, and infection results in inflammation, necrosis, and ultimately an abscess. Eighty percent of amoebic hepatic abscesses are solitary, and 80 percent occur in the right lobe of the liver. Extraintestinal disease may present years after residence in an endemic area and should be considered in all patients with an appropriate travel history and suggestive symptoms. Liver abscesses occur more frequently in men than women, and usually in the age range of 18 to 50 years.

Thoracic manifestations of *E. histolytica* infection are rare; they have been reported in 2 to 3 percent of cases of invasive amebiasis. They can be considered chiefly as either pleuropulmonary or pericardial. A case of *E. histolytica* osteomyelitis of the rib has been reported, as has a case of pulmonary amebiasis presenting as superior vena cava syndrome.

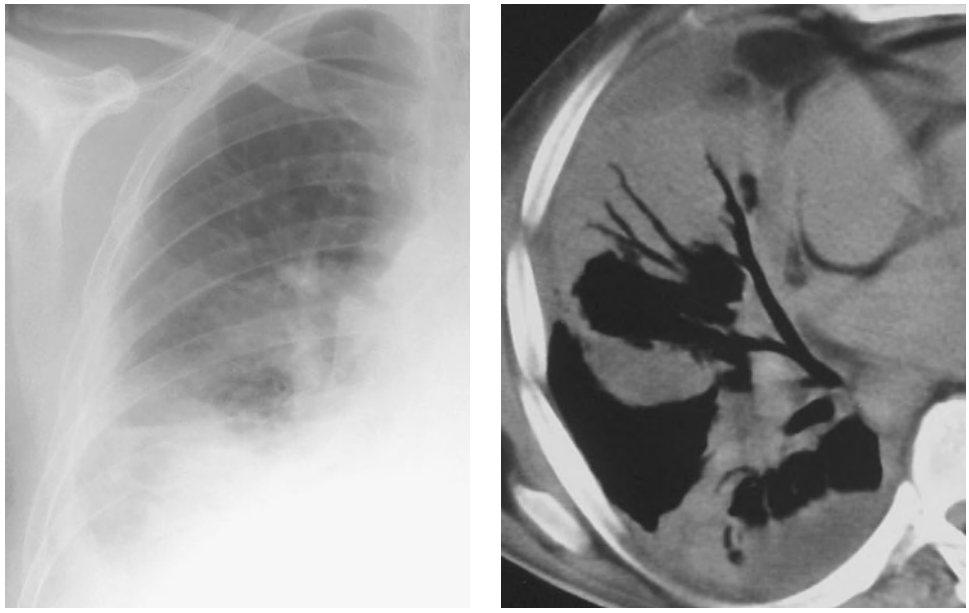
Pleuropulmonary Disease

Amoebic pulmonary disease may occur by a number of mechanisms. It most often occurs as the result of a concomitant liver abscess. The abscess may result in a sympathetic pleural effusion that does not require specific therapy. A liver abscess may alternatively rupture through the diaphragm into the pleural space, causing respiratory distress, empyema, and subsequent parenchymal lung abscesses (Figs. 135-1, 135-2, 135-3). Pulmonary parenchymal disease in the form of lung



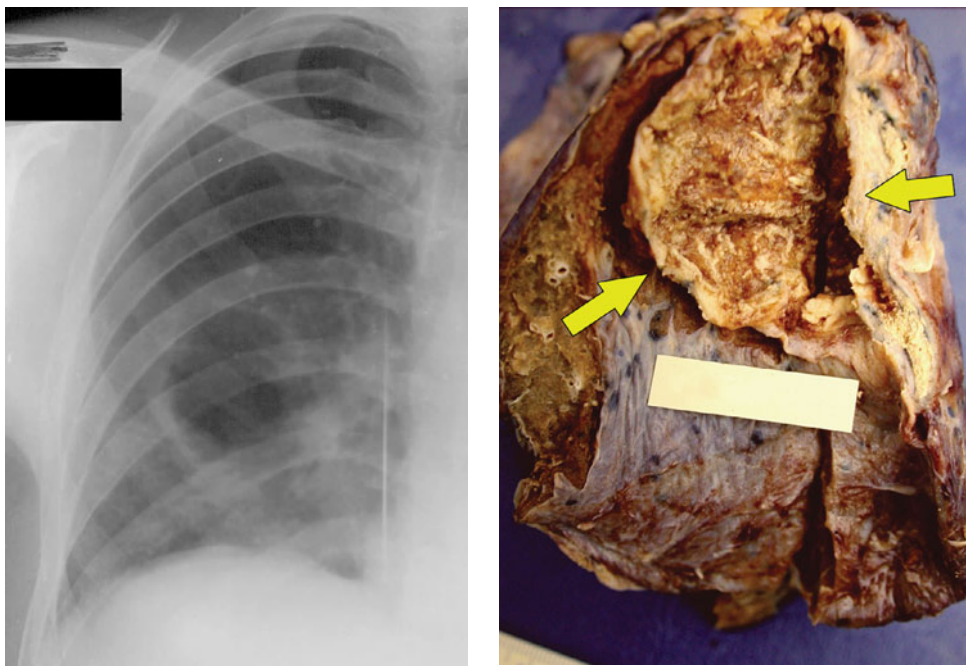
A *B* *C*

Figure 135-1 Entamoeba histolytica involving the right lung after rupture of a hepatic abscess through the right hemidiaphragm. *A*. Chest radiograph shows elevated right hemidiaphragm, right lower lobe infiltrate, and effusion. (*Courtesy of Armed Forces Institute of Pathology.*) *B*. Alveolar spaces are filled with ameba (arrowheads). (Iron hematoxylin stain, ×300; courtesy of Dr. Y. Gutierrez.) *C*. Trophozoite (arrow) and necrotic debris.



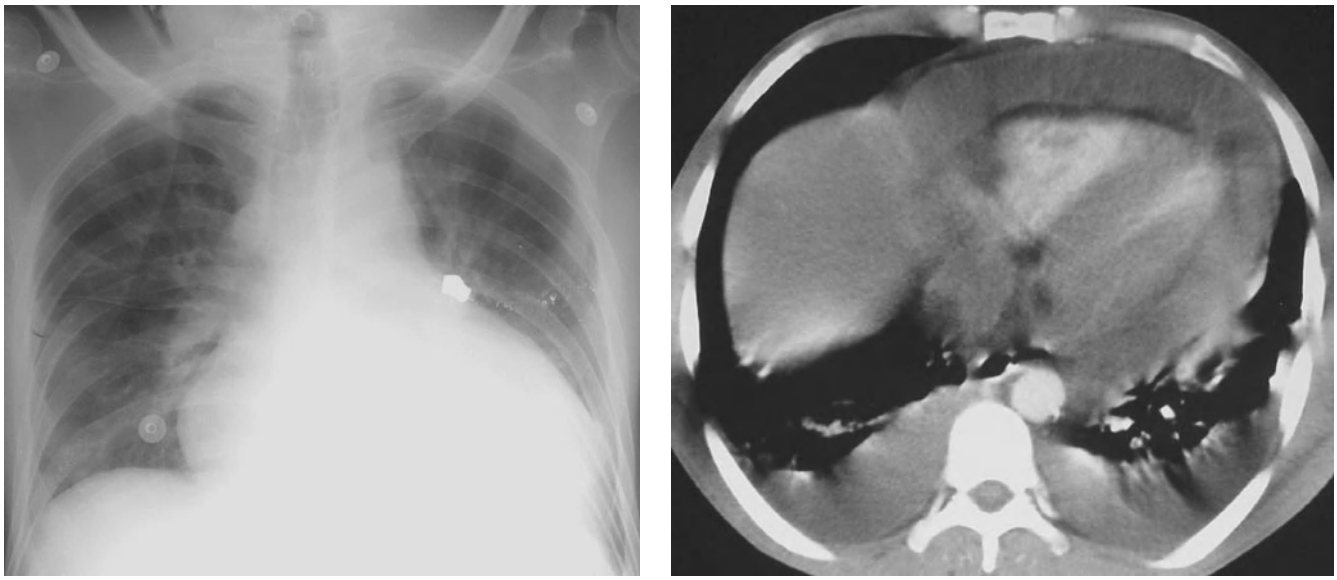
A *B*

Figure 135-2 Right-sided amoebic pleural empyema and pneumonia in a 43-year-old man with an abscess of the right hepatic lobe. *A.* Initial chest radiograph shows pleural effusion and right-sided basal consolidation. *B.* Chest CT scan helps confirm pleural involvement and right-sided basal alveolar infiltrates. Trophozoites of *E. histolytica* were obtained at bronchoalveolar lavage. (*Reproduced with permission from Martinez S, et al.: Thoracic manifestations of tropical infections: A pictorial review*. RadioGraphics *25:135–155, 2005.*)



A *B*

Figure 135-3 Right-sided amoebic pneumonia in a 35-year-old man with a hepatic abscess. *A.* Chest radiograph shows elevation of the right hemidiaphragm and right-sided basal consolidation with cavitation. *B.* Photograph of the gross specimen demonstrates an irregular cavitary lesion (arrows). Anchovy sauce content and trophozoites of *E. histolytica* (not shown) were found on the lesion wall. (*Reproduced with permission from Martinez S, et al.: Thoracic manifestations of tropical infections: A pictorial review*. RadioGraphics *25:135–155, 2005.*)



A *B*

Figure 135-4 Amoebic pericardial tamponade in a 27-year-old man with an abscess of the left hepatic lobe. The patient presented with pulsus paradoxus, fever, and chills. *A.* Chest radiograph shows enlargement of the cardiac silhouette. *B.* Chest CT scan shows extensive pericardial effusion that resulted from rupture of a left hepatic lobe abscess (not shown) into the pericardial space. (*Reproduced with permission from Martinez S, et al.: Thoracic manifestations of tropical infections: A pictorial review.* RadioGraphics *25:135–155, 2005.*)

abscesses and consolidation less often occurs in the absence of hepatic disease, but may occur if there has been hematogenous spread of trophozoites to the lung.

Most patients with extraintestinal amebiasis have not had symptomatic intestinal disease, so the absence of preceding gastrointestinal symptoms does not exclude the diagnosis. Patients with liver abscess often present with insidious onset of fever, right upper quadrant pain, and hepatic tenderness on palpation. Pleuritis, respiratory symptoms such as cough, dyspnea, and/or physical examination consistent with pleural effusion further suggest involvement of the pleuropulmonary system. Sputum production may range from scant to copious, and sputum may contain purulent material, particularly if a hepatobronchial fistula has developed. Classically, the purulent material of amoebic abscess is reddish "anchovy paste." Jaundice is uncommon. Leukocytosis may be present, but eosinophilia is not a feature of the disease.

Pericardial Disease

Pericardial disease can result from either sterile inflammation of the pericardium as a result of a contiguous liver abscess in the left lobe of the liver, or may be a purulent infection as a result of rupture of a hepatic amoebic abscess into the pericardial space (Fig. 135-4). Chest pain, pericardial friction rub, and symptoms and signs of pericarditis may be presenting features. Presentation may be acute and severe, with symptoms and signs of pericardial tamponade.

Diagnosis of Pleuropulmonary and Pericardial Disease

Stool microscopy may reveal the presence of *E. histolytica* trophozoites or cysts, but microscopy is neither a sensitive nor a specific method for diagnosis of amebiasis. Microscopy is unable to distinguish *E. histolytica* from non-pathogenic *E. dispar*, and extraintestinal disease is associated with presence of the pathogen in stool in only a minority of cases. Stool may be concentrated and stained with iodine to evaluate for the presence of cysts. Trophozoites are best seen on a fresh smear with iron hematoxylin and trichome stain. Microscopy of abscess fluid occasionally may reveal presence of trophozoites. Diagnosis of extraintestinal disease is best made by a combination of microscopic examination of samples, antigen detection, and serology tests.

Antigen Detection

Antigen detection methods are increasingly commercially available to detect *E. histolytica.* These tests are able to distinguish *E. dispar* from *E. histolytica.* Stool antigen tests are over 95 percent sensitive and specific for the diagnosis of intestinal disease. Antigen detection assays are also highly sensitive and specific when applied to abscess fluid.

Serology

Most patients infected with *E. histolytica*, but not *E. dispar*, develop a serum antibody response. Amoebic serology is positive in over 90 percent of patients with extraintestinal disease. Serological analysis may be negative in early infection. The presence of IgG antibodies does not always indicate active disease; IgG may persist for many years after active infection.

Treatment

Metronidazole or tinidazole is effective in the treatment of individuals with intestinal and extraintestinal amebiasis. To

prevent a relapse, a luminal agent such as iodoquinol or paromomycin also should be administered. Sympathetic pleural effusions do not need specific therapy, other than treatment of the underlying liver abscess. Amoebic empyema and amoebic pericarditis are best treated with aspiration or percutaneous drainage, in combination with administration of antiamoebic microbial therapy.

FREE-LIVING AMOEBA: *ACANTHAMOEBA*

Free-living amoeba are rarely associated with human infection; however, when infection does occur, disease tends to be progressive and difficult to treat.

Acanthamebiasis

Acanthamoeba species are ubiquitous, and have been isolated from a wide variety of locations, including the nasal passages of healthy adults, water sources, soil, and contact lens fluid. Infection in humans usually manifests as either keratitis or systemic disease. Systemic disease usually involves the central nervous system, manifesting as granulomatous amoebic encephalitis. Amoebic infection of skin also has been reported.

Clinical Features

Acanthamoeba sp. keratitis is usually a disease of healthy individuals, often contact lens wearers. Infection is thought to result from direct deposition of amoeba into the eye. In contrast, systemic disease results from hematogenous dissemination of amoeba, which are thought to first enter the human host via the respiratory tract or skin. Systemic disease is primarily a disease of immunocompromised or debilitated persons, including individuals with the acquired immunodeficiency syndrome (AIDS), and those who have undergone bone marrow transplantation, organ transplantation, or are otherwise immunosuppressed. Pulmonary nodular infiltrates and pneumonitis have been reported in cases of systemic disease.

Diagnosis

Diagnosis of systemic acanthamebiasis is usually made late in the clinical course, and unfortunately, very often at autopsy. Evaluation of cerebrospinal fluid from individuals with granulomatous amoebic meningoencephalitis may disclose hypoglycorrhachia and elevated protein, but amoeba are not usually seen. Evaluation of biopsies of lesions of skin or brain usually provides the definitive diagnosis. *Acanthamoeba* spp. can be identified on histopathology, and may be cultured on nutrient agar overlaid with *E. coli*. Radiographic imaging of the central nervous system is often helpful.

Treatment

No single drug is effective against systemic *Acanthamoeba* spp. infection. Combinations of treatment with amphotericin B, azithromycin, fluconazole, 5-fluorocytosine, pentamidine, and sulfadiazine have been attempted, with success in some cases and failure in other cases that used similar regimens. Most individuals with systemic amebiasis do not survive, irrelevant of therapy. Individuals with acanthamebic keratitis are usually treated topically and may require corneal grafting.

SYSTEMIC COCCIDIOSIS

Toxoplasmosis

Toxoplasmosis is caused by *Toxoplasma gondii*. Asymptomatic disease is common. Symptomatic disease usually occurs in persons with suppressed cell-mediated immunity and infants born with congenital infection.

Epidemiology and Life Cycle

Understanding the life cycle of *T. gondii* is important in the understanding the disease process. The parasite is found worldwide. It has both sexual and asexual stages, the latter being the pathogenic stage in humans and other animals. Cats are the definitive host, and in the feline, oocysts develop after an intestinal intraepithelial sexual cycle. Oocysts are then passed in cat feces, and after 2 to 3 days become infectious. They may persist in soil. If ingested by humans or other animals (sheep, pigs, rodents, or cats), oocysts produce rapidly dividing tachyzoites. Tachyzoites invade varying cell types, and result in cell death and tissue necrosis. Eventually the host immune response curtails this process, and tachyzoites give rise to slowly dividing bradyzoites, which encyst and persist indefinitely in host tissues. Bradyzoites are infectious if ingested, giving rise to tachyzoites in the new host. Bradyzoites may also revert to tachyzoites if a host becomes immunocompromised, leading to "reactivation" of disease. Humans and other animals may be infected, not only by ingestion of oocysts, but also by ingestion of tissue cysts, such as following the consumption of undercooked infected meat. Toxoplasma infection may also be acquired by transplacental passage of tachyzoites, resulting in congenital infection, or by organ transplantation.

Serologic studies demonstrate a wide geographic variation in prevalence of infection between 10 and 90 percent. In the United States, rates range from 3 percent in Denver, Colorado, to 17 percent in Massachusetts, and 30 percent in Birmingham, Alabama.

Clinical Features

Infection may be primary or due to reactivation. After ingestion of infectious oocysts or tissue cysts, tachyzoites disseminate and invade organs, replicating intracellularly. Acute infection may result in tachyzoites being found in all organs, especially muscle, lymphatic tissue, and the central nervous system. Primary infection may be subclinical or asymptomatic. If symptomatic, the most common manifestations of acute disease include fever, painless lymphadenopathy, and a mononucleosis-like syndrome. More rarely pneumonitis, myocarditis, and myositis may occur.

Congenital infection is usually the result of primary infection in the mother, with transplacental passage of tachyzoites resulting in infection of the fetus. Infected infants may be symptomatic at birth, or may have hepatosplenomegaly, pneumonitis, myocarditis, rash, or jaundice. Congenitally infected children may be asymptomatic initially, but may subsequently develop central nervous system or ocular manifestations.

Reactivation disease occurs in persons who are immunocompromised, particularly those with deficiency in cell-mediated immunity. Patients with HIV infection and CD4 cell counts less than 100 cells/mm^3 are at particular risk of life-threatening disease, and although primary infection may occur in these individuals, reactivation disease is most common. Reactivation disease may be prevented in those at particular risk with the prophylactic use of trimethoprim-sulfamethoxazole. Necrotizing central nervous system disease is the most common manifestation of reactivation toxoplasmosis in AIDS patients. Affected individuals usually present with altered mental status, fever, headache, and clinical findings suggestive of focal CNS disease, and neuro-imaging often reveals multifocal, ring-enhancing lesions.

Pulmonary-Thoracic Disease

Pulmonary involvement in toxoplasmosis is common, and is usually reported in patients with AIDS or in individuals who have undergone bone marrow or solid organ transplantation (Fig. 135-5). Cases may also occur, albeit less frequently, in individuals without evidence of immunosuppression. Shortness of breath and cough are the most common presenting symptom, of pulmonary involvement during toxoplasmosis. In one review, immunocompetent patients with toxoplasmic pneumonitis were more likely than immunocompromised individuals to have evidence of hepatosplenomegaly at presentation, but clinical findings were otherwise similar. Bilateral interstitial pulmonary infiltrates are most often evident in radiography; however, a variety of other findings, from discrete pulmonary opacities to cavitary disease, also have been described. Severe disease or the acute respiratory distress syndrome (ARDS) may develop. *T. gondii* organisms can invade myocytes, and during acute or reactivation disease, myocarditis may occur and may be severe.

Diagnosis

In primary toxoplasmosis, the differential diagnosis is broad, but IgM-specific antibodies will usually be present. During reactivation of toxoplasmosis, IgM and IgG anti-toxoplasma antibodies are usually present in serum. Absence of anti-toxoplasma IgG antibodies makes the diagnosis of reactivation toxoplasmosis unlikely, but the presence of the antibody itself does not differentiate between latent and active disease.

Biopsy can confirm the diagnosis. Polymerase chain reaction (PCR) analysis of tissue samples or cerebrospinal fluid is sensitive, and PCR analysis of amniotic fluid is particularly helpful in the antenatal diagnosis of congenital infection. PCR has been used to detect toxoplasma in sputum specimens, but the sensitivity of this method for diagnosing pulmonary toxoplasmosis has not yet been determined. In pulmonary disease, microscopic or molecular analysis of bronchoalveolar lavage fluid or open lung biopsy may be required for confirmation of the diagnosis.

Treatment

Except in the case of pregnant women or individuals with severe or persistent symptoms, primary toxoplasmosis in immunocompetent individuals usually does not require treatment. Reactivation disease in immunocompromised individuals is usually treated for the duration of the period of immunosuppression, as therapy does not fully eradicate the parasite. Standard therapy is pyrimethamine and a sulfonamide, usually sulfadiazine. Leucovorin is added to overcome the bone marrow suppressive effects of pyrimethamine. Clindamycin may be used as an alternative in those intolerant of sulfonamides. After acute disease has been controlled, secondary suppressive therapy should be continued for the duration of immunosuppression to prevent relapse. Unfortunately, mortality in immunocompromised patients with toxoplasma pneumonia diagnosed antemortem has been as high as 40 percent.

INTESTINAL COCCIDIOSIS

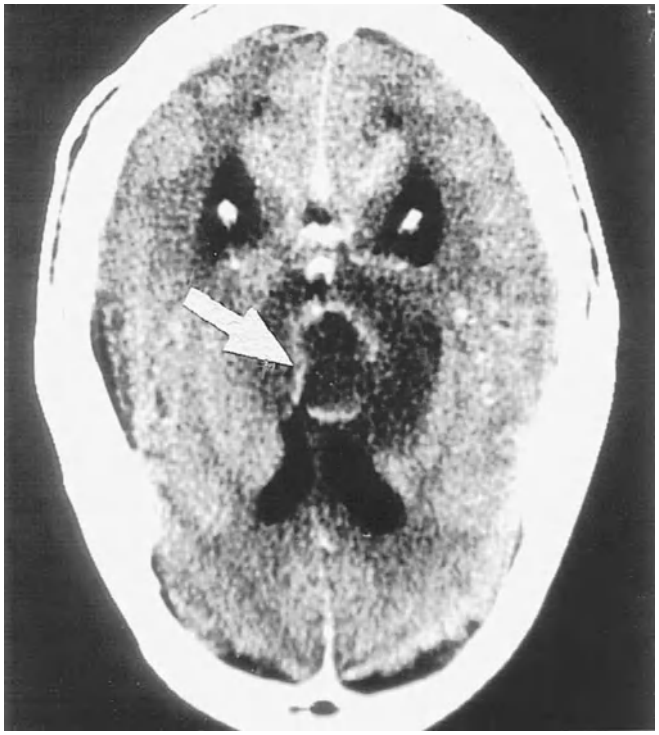
Cryptosporidiosis

Cryptosporidium parvum is an intracellular protozoan that mainly causes intestinal pathology (Fig. 135-6). Disease may occur in immunocompetent hosts, but is more common and severe in immunocompromised individuals, particularly in patients with AIDS, in whom cryptosporidiosis may result in severe and persistent diarrhea. The organism also causes infection in a variety of animals, and fecal contamination of water or food is a common source of infection in humans, although person-to-person transmission also occurs.

The life cycle of *Cryptosporidium parvum* begins when the infectious oocyst is ingested. These organisms, which are 4 to 5 μm in diameter, may remain viable in the environment for months. After ingestion, they excyst in the small intestine, and release four motile sporozoites, which invade epithelial cells of the intestinal wall. Asexual maturation then results in merozoites being released back into the intestinal lumen. These merozoites either result in re-invasion of epithelial cells, or undergo maturation to become oocysts. The oocysts may then be excreted, or may excyst while still in the lumen to "auto-infect" the host.

Clinical Features

Cryptosporidial infection may be asymptomatic, or may be associated with a range of illness from mild diarrhea to severe gastroenteritis. Invasion of the intestinal epithelium results in secretory diarrhea. The biliary tree may be infected, causing cholangitis, and hepatitis and pancreatitis also have been



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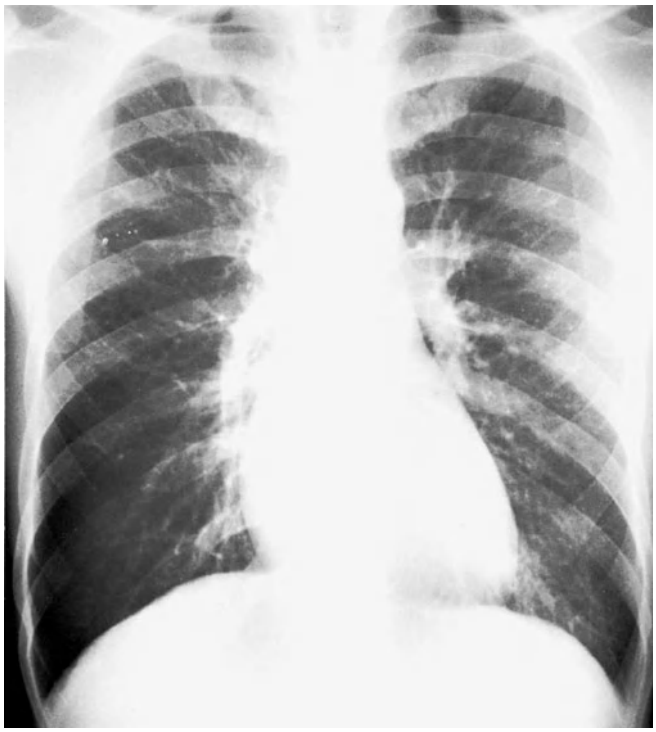

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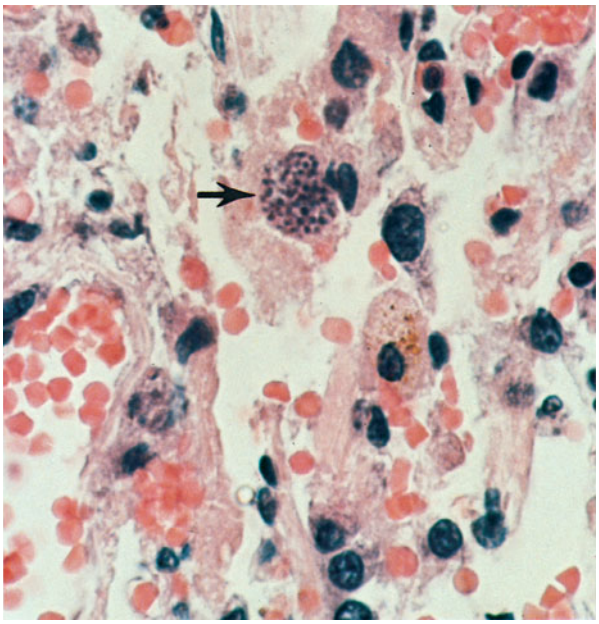

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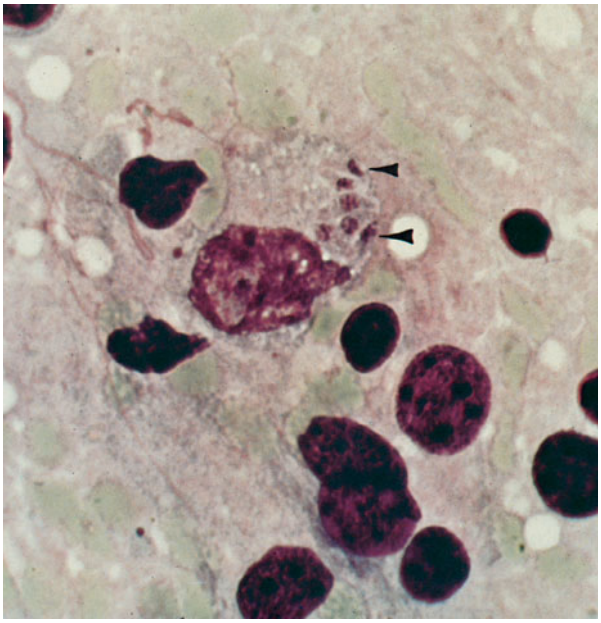


D

Figure 135-5 *Toxoplasma gondii* in brain and lung of a patient with AIDS. *A.* Brain CT scan shows Toxoplasma abscess as a contrast-enhancing lesion (arrow). *B.* Chest radiography. Diffuse bilateral infiltrates and hilar adenopathy. *C.* Lung biopsy show, Toxoplasma forms (hematoxylin & eosin stain, ×100). *D.* Impression smear of brain biopsy shows five intracellular tachyzoite (trophozoite) forms (arrowheads; Giemsa stain ×1500). (*C* and *D* are courtesy of Dr. Y. Gutierrez.)

described. Infection may be associated with systemic symptoms such as malaise, nausea, and abdominal cramps. In some patients, diarrhea is voluminous and has been described as "cholera-like." In patients with a normal immune system, cryptosporidial diarrhea usually resolves within 2 weeks. In immunocompromised individuals, especially those with HIV infection and CD4 cell counts less than 100 cells/mm^3, symptoms often continue until the immune status of the individual is restored. In such individuals, cryptodoridiosis may result in a severe wasting syndrome.

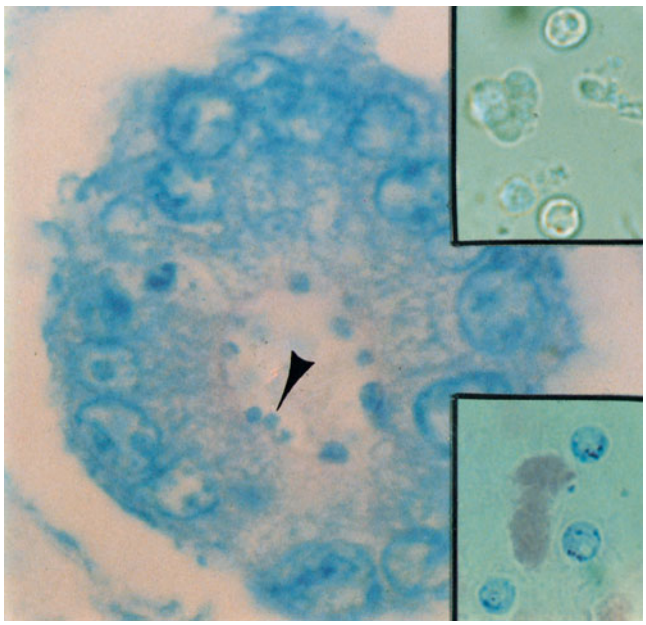


Figure 135-6 *Cryptosporidium parvum* infecting an intestinal crypt (arrowhead). Parasites line the apical surface of the epithelial cells and are covered by host membranes. *Insets*: Oocysts isolated from feces. *Upper* = organisms isolated after a Sheather's sugar flotation, ×1360. *Lower* = Giemsa-Jenner stain, ×1360. (*Courtesy of J.A. Fishman, Massachusetts General Hospital.*)

Pulmonary Cryptosporidiosis

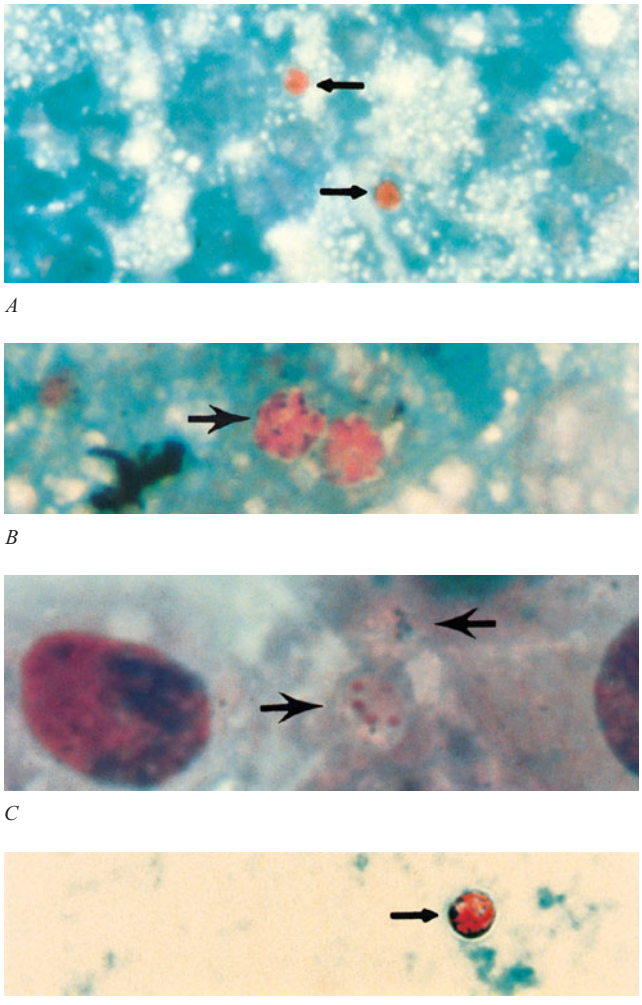
Respiratory infection with *C. parvum* is rare, but has been reported, usually in patients with AIDS (Fig. 135-7). Pulmonary involvement, as with other extraintestinal manifestations of cryptosporidiosis, usually occurs in the setting of intestinal disease. At least one case of pulmonary infection, however, has been reported with no apparent evidence of intestinal infection. Pulmonary involvement may appear as an interstitial infiltrative process or as areas of focal consolidation. Some authors suggest that the prevalence of pulmonary cryptosporidiosis is underestimated, and one study reported a prevalence of 17 percent in HIV positive patients with respiratory symptoms.

Diagnosis

Cryptosporidium may not be cultured in vitro, and diagnosis of cryptosporidiosis relies largely on demonstration of pathological findings in tracheal or bronchial tissues, and visualization of cryptosporidial cysts by microscopy. The cysts may be best seen by acid-fast staining of specimens. Oocysts have been detected in bronchoalveolar lavage, open lung biopsy, and sputum specimens.

Treatment

Nitazoxanide decreases diarrhea in immunocompetent individuals with intestinal cryptosporidiosis. However, reliable efficacy has not been demonstrated in individuals with disseminated cryptosporidial disease, or those who are immunocompromised. Thus, in most individuals, treatment is predominantly supportive while attempts are made to restore immune function; in AIDS patients, this is chiefly through the use of antiretroviral therapy. In addition to nitazoxanide, other agents have been administered to individuals with cryptosporidiosis, although efficacy has not been demonstrated. Administered agents have included paromomycin, trimethoprim-sulfamethoxazole, and metronidazole. Anecdotally, azithromycin has been successfully combined with paromomycin in the therapy of pulmonary infection.



A

B

C

D

Figure 135-7 Pulmonary cryptosporidiosis. *A.* Touch preparation from a lung biopsy of a patient with AIDS. Arrows show organisms stained with a modified acid-fast stain (modified cold Kinyoun, MCK), which stains the organisms red (×880). *B.* Same preparation and stain as *A* showing internal red-black dense granules characteristic of the organism. *C.* Same preparation as *A* showing similar morphology using a rapid Giemsa hemacolor stain. *D.* Sputum stained with MCK technique reveals organisms. (*A through D courtesy of Dr. P. Ma.*)

CYCLOSPORIASIS

Cyclospora cayetanensis is a protozoan organism, usually associated with diarrheal illness in humans. It is ubiquitous,

and transmitted usually as a result of contamination of food or water. The protozoan is usually detected as an approximately 10-μ organism on acid-fast stains of specimens. Infection usually responds to trimethoprim-sulfamethoxazole. A single case report of possible pulmonary cyclosporiasis has been reported. A 60-year-old Brazilian man with a history of treated tuberculosis was found to have *C. cayetanensis* organisms in sputum specimens examined for evaluation of respiratory distress and pulmonary infiltrates. No other organisms were detected, and the patient's symptoms resolved following administration of trimethoprim-sulfamethoxazole (and treatment of concomitant intestinal parasitosis).

MALARIA

Malaria in humans is the result of infection by one of four species of plasmodia: *P. falciparum, P. vivax, P. ovale,* and *P. malariae.* Human malaria is endemic in parts of sub-Saharan Africa, India, Southeast Asia, the Caribbean, and Central and South America. Over 1 million deaths annually are attributed to malaria, usually among pregnant women and children under the age of 5 years who live in endemic areas. The majority of malaria-related fatalities are a result of infection with *P. falciparum.*

Malaria is acquired by the bite of an infective female *Anopheles* sp. mosquito. In non-endemic areas, malaria cases are found largely in travelers who have returned from malaria endemic areas, but the parasite also may be transmitted by contaminated blood products, in utero from mother to child, and by organ transplantation. Malaria infection in persons co-infected with HIV is associated with increased HIV viral load, and increased symptoms in the setting of parasitemia.

Life Cycle

When bitten by an infective mosquito, malarial sporozoites enter the host and travel to the liver, where they invade hepatocytes and divide, forming tissue schizonts in an asymptomatic stage. These schizonts then rupture, releasing thousands of daughter merozoites into the bloodstream. These merozoites invade erythrocytes, and develop to form mature ring forms and ultimately erythrocytic schizonts. A small percentage of merozoites develop into sexual forms called gametocytes. Gametocytes do not cause symptoms, but when another mosquito bites an infected human host, the gametocytes are ingested by the feeding mosquito, permitting the malarial life cycle to continue. *P. falciparum* may infect red blood cells of all ages, resulting in the potential for very high levels of parasitemia.

Infection with *P. vivax* and *P. ovale* may result in a dormant liver phase in which parasites remain in the liver in the form of hypnozoites, potentially causing relapse many months after first infection. *P. falciparum* and *P. malariae* do not have such a dormant stage, and do not cause late relapsing disease.

Pathogenesis

Malaria related morbidity and mortality occurs predominantly in children and pregnant women. Most individuals who live in endemic areas develop partial immunity to symptomatic disease as they age. This immunity does not prevent infection, but reduces the frequency of symptoms and severity of disease despite ongoing parasitemia. Infection with any of the four human-specific species of malaria causes hemolysis, resulting in anemia that may be severe.

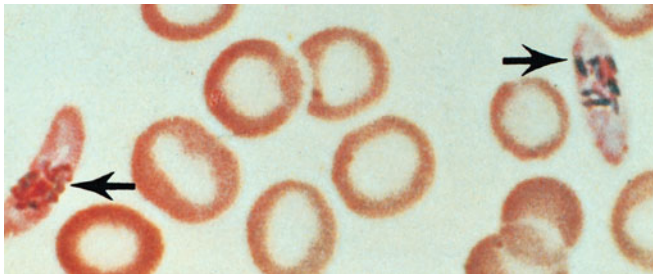
Certain genetic traits associated with hemoglobin structure or erythrocyte surface antigens are associated with decreased infection rates or decreased symptomatic disease. For example, absence of the Duffy antigen on the surface of erythrocytes protects against *P. vivax* infection, and sickle cell trait is protective against severe *P. falciparum* infection. *P. falciparum* also causes the formation of "sticky knobs" on the surface of infected erythrocytes. These knobs are comprised of host cell and parasite antigens, and mediate binding of infected erythrocytes to endothelial surfaces. This binding results in sequestration of infected erythrocytes, and may result in "sludging" of blood flow. This sequestration and sludging contributes to micro-vascular obstruction that can result in organ dysfunction.

Clinical Features

Patients with malaria typically present with fever and a constellation of other nonspecific symptoms such as headache, chills, and myalgias. Vomiting, nausea, diarrhea and cough also may be present. Anemia, thrombocytopenia, and hepatosplenomegaly may be present. Sequestration of infected erythrocytes in the brain may cause cerebral malaria. Individuals with cerebral malaria may present with altered mental status, seizures, focal neurologic findings, or coma. Even with treatment in modern intensive care units, mortality during cerebral malaria is high. Other organ-specific complications of infection are also largely related to microvascular sequestration of parasitized red blood cells in specific tissues, and may manifest as placental, renal, or pulmonary dysfunction (Fig. 135-8).

Pulmonary Features

Pulmonary symptoms such as cough and increased respiratory rate are common during malaria. In African children, malaria frequently presents with symptoms and signs suggestive of pneumonia. Metabolic acidosis is an important cause of respiratory distress in these children, but pneumonitis as a result of sequestered parasitized red blood cells is also responsible. In more severe disease, noncardiogenic pulmonary edema may develop. Initial acute lung injury may progress to acute respiratory distress syndrome (ARDS) (Fig. 135-9). Tachypnea and dyspnea, followed by hypoxemia and respiratory failure may develop. Studies have confirmed the development of impaired alveolar-capillary membrane function in patients with severe malaria. Lung injury in severe disease is postulated to be not only the result of pulmonary



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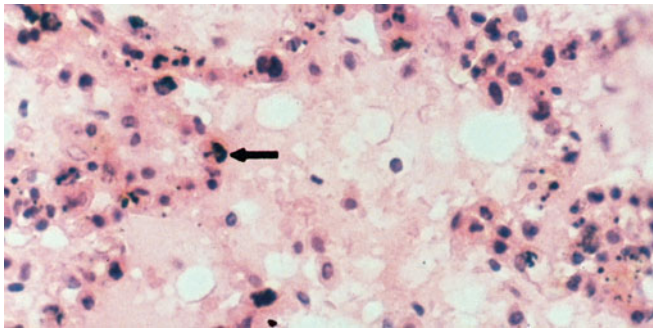

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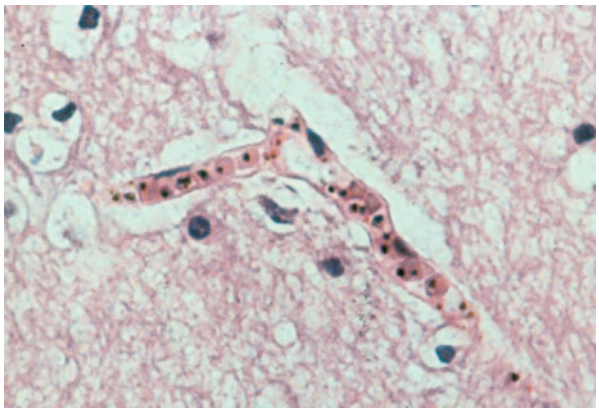

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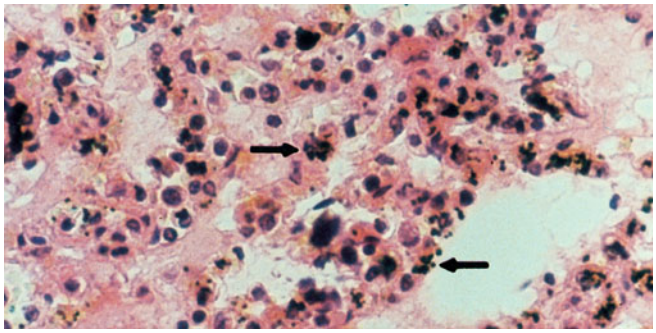

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Figure 135-8 *Plasmodium falciparum*. *A.* Banana-shaped gametocytes on peripheral blood smear (arrows). This form is only seen with falciparum malaria (Wright stain, ×1375). *B.* Cerebral vessels obstructed by parasitized red blood cells with surrounding edema (hematoxylin and eosin stain, ×1375). *C.* Acute pulmonary edema due to pulmonary venular occlusion (organism at arrow; hematoxylin and eosin). *D.* Deposition of malarial pigment (arrows) in vicinity of occluded pulmonary vessels.

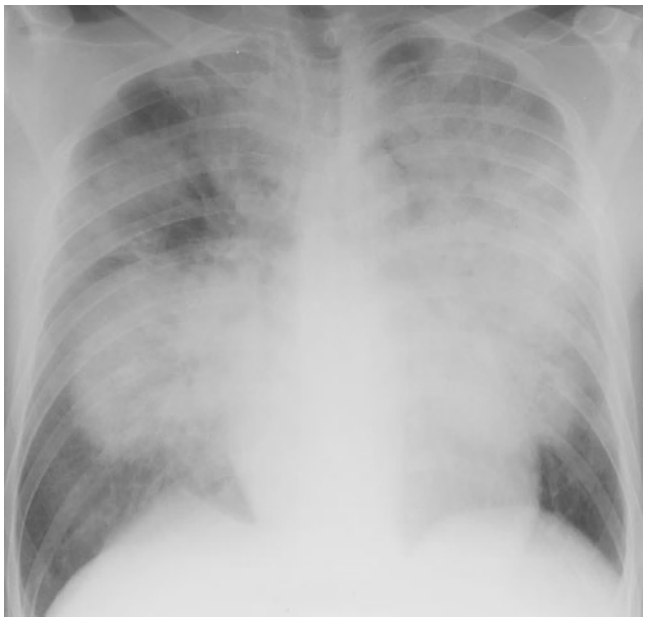


Figure 135-9 ARDS in a 31-year-old man with *P. falciparum* malaria. Chest radiograph demonstrates patchy bilateral areas of increased opacity. *P. falciparum* trophozoites were found in a thick blood smear. (*Reproduced with permission from Martinez S, et al.: Thoracic manifestations of tropical infections: A pictorial review*. RadioGraphics *25:135–155, 2005.*)

microvascular sequestration, but also a consequence of the inflammatory response to infection.

In a recent study of uncomplicated symptomatic malaria, altered pulmonary physiology, including increased airflow obstruction, decreased gas transfer, impaired ventilation, and increased pulmonary phagocytic activity were found in both *P. vivax* and *P. falciparum*-associated infections, but were worse in cases of *P. falciparum* malaria. ARDS has also been reported in cases of malaria caused by *P. vivax*, and one case of pulmonary edema has been reported complicating a case of *P. ovale* malaria; however, significant pulmonary morbidity is largely confined to infection by *P. falciparum*, and usually occurs in the context of multisystem involvement. The principal differential diagnosis for pulmonary disease in malaria infection is metabolic acidosis and bacterial pneumonia.

Diagnosis

The diagnosis of malaria should be considered in any symptomatic patient who has had exposure to the parasite in a malaria endemic area. Rare cases of transmission by blood products, organ transplantation, or congenital infection also have occurred. Individuals with malaria caused by *P. falciparum* usually develop symptoms within 3 months of the mosquito bite, and usually within 1 month. Since *P. vivax*

and *P. ovale* have potentially dormant liver phases, individuals infected with these parasites may not develop symptoms for many months after exposure (usually within 1 year of the mosquito bite).

Malaria is usually diagnosed through microscopic examination of blood smears. A thick smear examined by an experienced microscopist is highly sensitive for detecting infection. Review of a thin smear provides further detail to allow identification of the infecting species. Antigen detection assays identifying falciparum-specific histidine rich protein 2 (HRP-2), or parasite lactate dehydrogenase (pLDH, which is present in all four species), are also commercially available.

Treatment

Appropriate treatment of individuals with malaria depends on the infecting species, severity of disease, age and pregnancy status, and the ability of the patient to take drugs by mouth. Non-falciparum malaria is generally susceptible to chloroquine phosphate, although to date, resistance has been reported in parts of Indonesia, Papua New Guinea, India, Myanmar, and Brazil. Non-severe cases of chloroquine-resistant falciparum malaria can be treated with oral atovaquone-proguanil or mefloquine, or quinine sulfate in combination with either doxycycline or clindamycin. Severe cases of falciparum malaria should be treated parenterally with quinine dihydrochloride, quinidine gluconate, or artesunate. Therapy with artemisinin-based combinations of drugs is increasingly being recommended, particularly in endemic areas; however, artemisinin derivatives are not commercially available in many countries, including the United States.

Individuals with malaria caused by *P. vivax* or *P. ovale* also should be treated with primaquine to treat the hypnozoite form of disease. Primaquine should not be administered to individuals deficient in glucose-6-phosphate dehydrogenase or pregnant women. Pulmonary manifestations and other organ-specific complications of severe infection are treated supportively. Mechanical ventilation may be required. Early institution of renal replacement therapy may prevent subsequent development of ARDS in severe malaria. Exchange transfusion has been recommended for patients with severe falciparum-associated disease with parasitemia levels over 5 percent, although data on efficacy are controversial.

BABESIOSIS

Babesiosis is a tick-borne infection usually caused by *Babesia microti* in the United States, and *Babesia divergens* in Europe. In the United States, the disease has been reported from Minnesota, Maryland, Virginia, California, Washington State, Georgia, Wisconsin, and Indiana; however, most cases occur in the Northeastern states. Transmission also may occur as the result of infected blood transfusions.

Babesia parasites invade, multiply within, and lyse red blood cells. In immunocompetent hosts, disease is most commonly asymptomatic or relatively mild, and characterized by fever, flulike illness, myalgias, and nausea. More severe manifestations may include thrombocytopenia, hemolytic anemia, jaundice, meningismus, non-cardiogenic pulmonary edema, disseminated intravascular coagulation, hypotension, and shock. Severe disease is most common among the elderly or individuals with compromised immunity. Asplenic individuals are at particular risk of severe disease, and individuals infected with HIV are at particular risk of persistent disease. Pulmonary disease in babesiosis occurs in association with multisystem disease, and usually presents as ARDS or non-cardiogenic pulmonary edema.

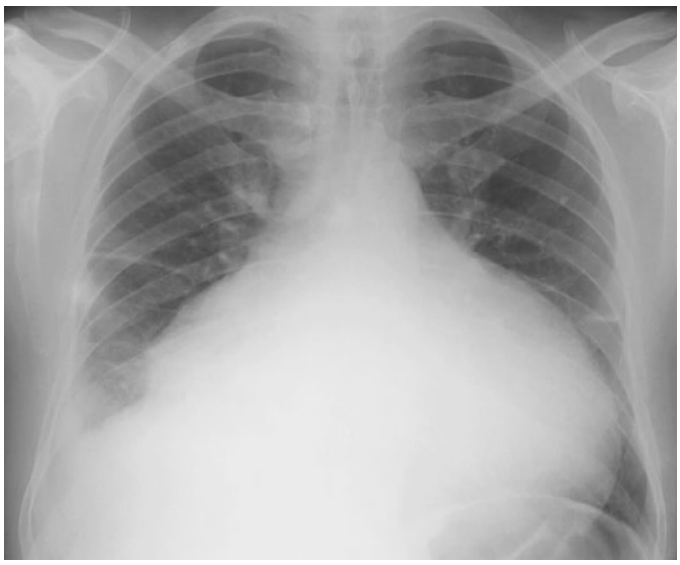
The diagnosis of babesiosis should be considered in any patient with appropriate exposure history who presents with fever or a sepsis syndrome. Diagnosis is usually confirmed by microscopic examination of peripheral blood. Atovaquone, azithromycin, quinine and clindamycin all have anti-Babesia activity; combination therapy is usually administered.

TRYPANOSOMIASIS

American Trypanosomiasis (Chagas' Disease)

Chagas' disease is caused by infection with *Trypanosoma cruzi*, a protozoan parasite transmitted to humans most often via the feces of an infected reduviid bug. The disease is endemic in certain South and Central American countries. Clinical manifestations may occur acutely after initial infection. More commonly, clinical manifestations may not become evident until years or decades after initial infection. When acute symptoms do occur, they may include fever, peripheral edema, hepatosplenomegaly, and myocarditis. Chronic sequelae may occur in up to one-third of infected individuals, and usually involves the heart, esophagus, or large bowel (Fig. 135-10).

Cardiac disease usually manifests clinically as congestive-dilatory cardiomyopathy. Chronic dilatation of the esophagus or colon resulting from denervation of the gut may result in Chagasic mega-esophagus or mega-colon. Acute myocarditis may result in pulmonary edema. Pulmonary involvement during Chagas' disease is usually secondary to cardiac or intestinal disease, and may include pulmonary edema secondary to congestive heart failure, pulmonary hypertension secondary to right-sided dilatory cardiomyopathy, or aspiration pneumonia secondary to vomiting and regurgitation associated with mega-esophagus or mega-colon. Recurrent aspiration and pneumonitis may lead to lung abscesses, fibrosis, scarring, and bronchiectasis. The debilitation of chronic Chagas' disease may lead to cachexia, and may be associated with a higher rate of tuberculosis. In an autopsy review of 69 adult cases of Chagasic mega-esophagus in Brazil, 35 percent of patients had pneumonia, and 22 percent had pulmonary tuberculosis—rates that were higher than in a cohort of patients in the same study who had Chagasic cardiac disease, but no mega-esophagus.



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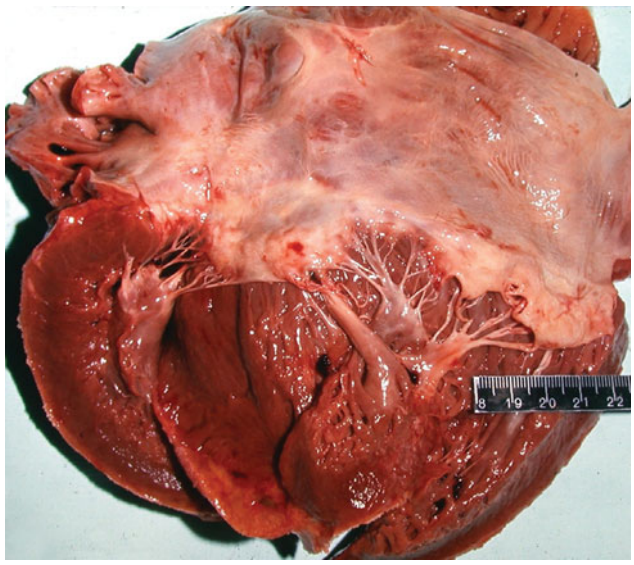

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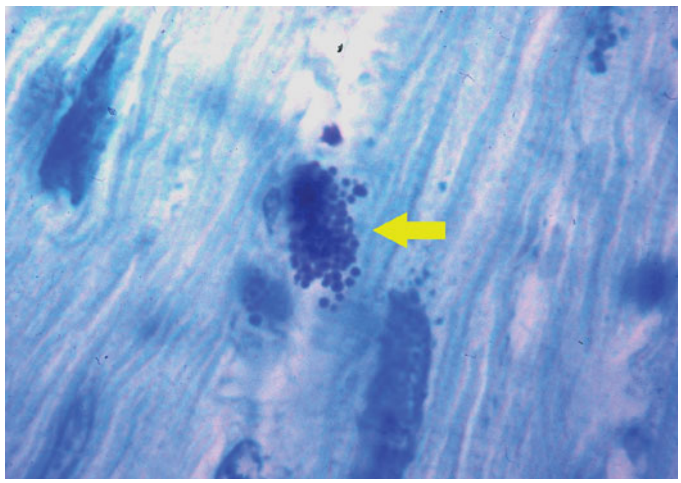

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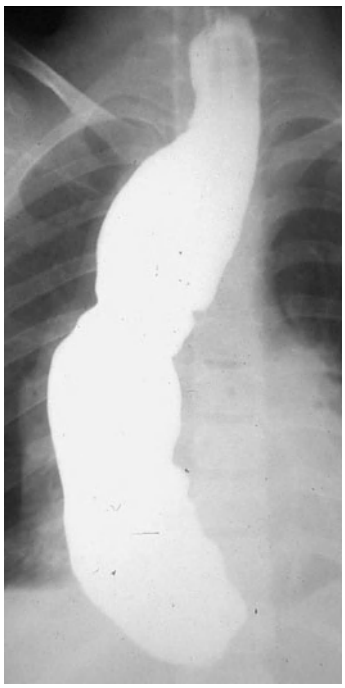

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Figure 135-10 Chronic Chagas' disease in a 39-year-old man with chronic dilated cardiomyopathy. *A.* Chest radiograph shows global cardiomegaly with pulmonary congestion. *B.* Photograph of the gross specimen demonstrates dilatation of the cardiac chambers with thickening of the ventricular myocardium. Scale is in centimeters. *C.* Low-power photomicrograph (original manifestation, ×10; Giemsa stain) shows *T. cruzi* amastigotes within a myofiber (arrow). D. Chagasic achalasia in a 13-year-old girl with Chagas' disease. Barium esophagogram shows diffuse and severe dilatation of the esophagus. Histologic analysis demonstrated *T. cruzi* amastigotes within the esophageal wall. (*Reproduced with permission from Martinez S, et al.: Thoracic manifestations of tropical infections: A pictorial review*. RadioGraphics *25:135–155, 2005.*)

Congenital Chagas' disease has been associated with pneumonitis; and in an autopsy review of 10 congenital cases, pathologic finding have included diffuse pulmonary interstitial edema and endothelial swelling in lung tissues.

Diagnosis in acute Chagas' disease may be made by detecting parasites on blood smear. Culture of parasites from specimens is possible using specialized media, although the usefulness of this method is limited because culture may take several weeks. In chronic disease, parasites are not usually visualized. Diagnosis is usually based on serologic analysis, suggestive radiology, and, more rarely, pathological examination of tissues. Treatment in acute disease and in patients

with immunosuppression is warranted, and nifurtimox and benznidazole are the mainstays of therapy. The utility of treating individuals with established, chronic disease with antiparasitic agents is currently unclear.

African Trypanosomiasis (African Sleeping Sickness)

Trypanosoma brucei gambiense and *Trypanosoma brucei rhodesiense* are the causative agents of African trypanosomiasis (African sleeping sickness). African sleeping sickness is usually transmitted by the bite of an infective tse tse fly. East African trypanosomiasis is caused by *T.b. rhodesiense*. Individuals with East African trypanosomiasis are often acutely ill with fever, lymphadenopathy, headache, and myalgia. Disease may be fulminant, and individuals may develop disseminated intravascular coagulopathy, ARDs, hypotension, and shock. The most common pulmonary manifestations during acute disease is non-cardiogenic pulmonary edema and ARDS. West African trypanosomiasis is caused by *T.b. gambiense*. Individuals with West African trypanosomiasis usually do not develop severe disease during the acute stage. Rather, months or years after initial infection, infected individuals present with mental status changes, personality changes, recurrent fever, lymphadenopathy, weight loss, and disorders of circadian rhythm. The most common pulmonary manifestation during late stage disease is pneumonitis second to recurrent aspirations associated with inanition and altered mentation. Direct pulmonary involvement is not common in West African trypanosomiasis. A single case report describes an African child who presented with severe respiratory symptoms, and was later found to have African trypanosomiasis.

LEISHMANIASIS

Leishmaniasis is caused by an intracellular protozoa parasite in the Leishmania genus. The Leishmania parasites are widely distributed, and are usually transmitted through the bite of an infective sand fly. Infection of humans may be asymptomatic, or may involve the skin (cutaneous leishmaniasis), the mouth or nose (mucocutaneous leishmaniasis), or be systemic (visceral leishmaniasis). Human infection is most common in South and Central Asia, the Middle East, the Mediterranean, Balkans, North Africa, sub-Saharan Africa, and Central and South America. Specific organisms are often responsible for specific clinical syndromes, although overlap occurs. Disease is often considered as "New World" or "Old World," based on geographic location. The parasite exists as an intracellular organism (amastigote) in host macrophages, and as an extracellular promastigotes in the sandfly gut—being inoculated into the host's skin during the bite of the fly.

Clinical Features

Cutaneous syndromes may range from localized disease, usually on exposed areas of skin, to widespread cutaneous involvement. In localized disease, painless ulcers develop and most often resolve spontaneously over months. Classically, "Old World" cutaneous leishmaniasis is caused by *L. major, L. tropica, L. aethiopica,* or *L. infantum*; ' "New World" cutaneous disease is usually caused by *L braziliensis* or *L. mexicana*-complex organisms. Some New World species are associated with development of mucocutaneous disease months to years after resolution of the initial skin lesions. Severe destruction and disfiguration of the face with resultant aspiration pneumonitis may occur.

Visceral leishmaniasis is usually caused by *L. donovani, L. infantum,* or *L. chagasi*. Individuals with visceral leishmaniasis usually present with fever, hepatosplenomegaly, weight loss, pancytopenia, and hypergammaglobulinemia. Lymphadenopathy is commonly present. Gastrointestinal symptoms are common in advanced disease, and individuals with untreated visceral leishmaniasis develop a wasting syndrome. Pneumonia and tuberculosis may be the cause of death.

Pulmonary Disease

Pulmonary involvement from leishmaniasis in immunocompetent hosts is rare, but interstitial pneumonitis has been reported. However, immunosuppressed patients, particularly those with HIV infection, are at increased risk of atypical disease. In areas surrounding the Mediterranean, where seroprevalence for *L. infantum* in young adults may be as high as 30 percent, an increase in the incidence of HIV infection has caused an increase in the number of advanced cases of visceral leishmaniasis; a result either of new infections or reactivation of old infections. Patients with leishmaniasis and HIV infection may present with cough, dyspnea, hemoptysis, granulomatous mediastinal lymphadenopathy, solitary pulmonary nodules, or pleural effusions.

Treatment of leishmaniasis depends on type of disease (cutaneous vs. mucocutaneous vs. visceral), infecting species, parasite resistance patterns, severity of disease, and status of the host. Therapeutic options include amphotericin B, liposomal preparation of amphotericin, pentavalent antimony (sodium antimonylgluconate or N-methylglucamine antimonate), pentamidine, and miltefosine.

CILIATE INFECTIONS

Balantidium coli

Balantidium coli is the only ciliated protozoa that infects humans. Infection of humans usually occurs in individuals with contact with pigs, and human disease usually manifests as an infectious colitis very similar to amebiasis. Rare cases of pulmonary infection have been reported in humans: in a leukemic patient who presented with pulmonary lesions, in a 71-year-old woman with anal cancer and pneumonia, and a patient with chronic colitis and an intrapulmonary mass. Diagnosis is usually made through histological examination of

tissue samples. Treatment with tetracycline, metromedozole, or iodoquinol is usually effective.

FLAGELLATES

Trichomonas sp.

Trichomonads are flagellated protozoa. Pulmonary disease has been attributed most commonly to *Trichomonas tenax*, an organism that is most often considered a commensal in the human oropharynx, especially in individuals with poor oral hygiene. In one study of symptomatic patients, prevalence of *T. tenax* by PCR among 100 immunocompromised and 100 patients with chronic pulmonary disease was 10 percent. Diagnosis is most often made by examination of a wet mount of sputum or bronchoalveolar lavage specimen. Chronic purulent, necrotic pulmonary disease has been described, often thought to be a result of aspiration. Affected individuals have responded to metronidazole therapy.

Giardia Lamblia

Giardia lamblia is a pathogenic intestinal flagellate of humans. In humans, it usually causes chronic diarrhea and malabsorption. There is one case report of uncertain significance of recovery of *G. lamblia* trophozoites from bronchoalveolar lavage fluid.

MICROSPORIDIOSIS

Microsporidia is the name given to a group of spore-forming obligate intracellular organisms from the phylum *Microsporidia*. These organisms have been variously considered with the protozoa and fungi. Over 1200 microsporidia species occur worldwide, but the most common human pathogens are *Enterocytozoon, Encephalitozoon, Nosema, Pleistophora*, and *Septata* spp.

The microsporidia spore is the infective form of the organism, and when ingested or inhaled, it extends a polar tubule that infects the host cell. Within the host cell, replication occurs and more spores are formed. When spores sufficiently fill the cell, the cell membrane ruptures and spores are released; they may then proceed to infect nearby cells, or be passed into the environment in stool, urine, or respiratory secretions.

Most clinical cases of microsporidiosis in humans occur in immunocompromised hosts. In immunocompetent patients, infection with *Enterocytozoon bieneusi* can be asymptomatic or may cause acute and very rarely chronic diarrhea. In patients with HIV infection, symptomatic microsporidiosis tends to occur in advanced disease, such as when CD4 cell counts are less than 100 cells/mm^3. *Enterocytozoon bieneusi* and some species of Enterocephalitozoon (*E. hellem, E. cuniculi,* and *E. intestinalis*) have come to be recognized as major causes of diarrheal enteritis and disseminated infection in patients with AIDS. Disseminated disease caused by *Trachipleistophora* also has been described. Microsporidial species have been associated with disseminated disease including biliary tract disease, sinusitis, myositis, respiratory infection, and keratoconjunctivitis.

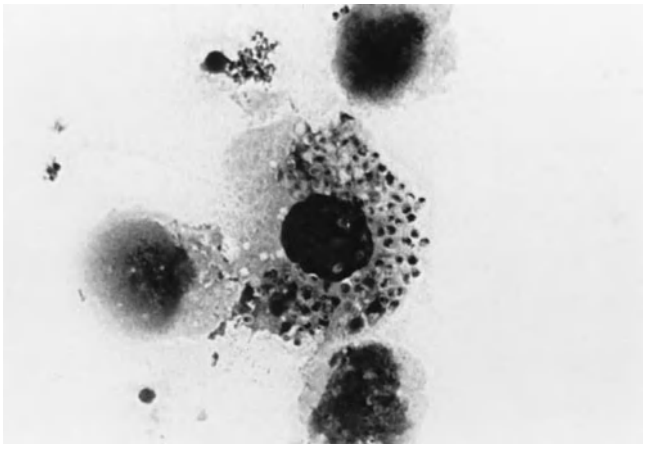

Figure 135-11 Pulmonary microsporidiosis. Tiny organisms (~1μm) within a pulmonary macrophage obtained via bronchoalveolar lavage (Giemsa-Wright stain, ×1000). (Courtesy of Dr. C. Wanke.)

Pulmonary Disease

Microsporidial disease with specific pulmonary involvement has been described in cases of patients with HIV infection, and in individuals who have undergone bone marrow or organ transplantation (Fig. 135-11). Pulmonary disease usually occurs in the setting of concomitant intestinal infection. In one retrospective review of 42 patients with HIV and microsporidial infection, 24 percent had respiratory symptoms, and four of six patients who had specimens examined had sputum or bronchoalveolar lavage positive for microsporidia.

Diagnosis

Diagnosis of microsporidiosis is based on identification of organisms in specimens of tissue or stool. Modified trichome staining allows detection of organisms on light microscopy, but electron microscopy is currently the definitive diagnostic method. Tissue culture, serologic assays, and PCR testing are used in research settings, but are not yet commercially available.

Treatment

Albendazole has activity against *Encephalitozoon* species, but is only partly effective against *E. bieneusi.* In immunocompromised individuals, treatment is directed at enhancing the immune status of the patient, i.e. antiretroviral therapy in patients with HIV infection, and decreased immunosuppression in transplant recipients. Duration of albendazole therapy depends on the severity of illness. *E. bieneusi* infections may be refractory to treatment.

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Helminthic Diseases of the Lungs

Jay A. Fishman

Parasitic helminths are a distinct group of infectious agents that are among the most prevalent causes of morbidity and mortality in humans worldwide. Billions of people harbor parasitic worms. People with helminthic infections of the lungs often seek medical advice because of one or more common chest complaints—cough, pain, or breathlessness. They may also have unexplained laboratory abnormalities, including eosinophilia or pulmonary nodules. They often pose a diagnostic challenge, particularly in areas where helminthic infections are not endemic. Other, more common causes of chest complaints have to be excluded, a history of residence in certain geographic locations or of dietary or other exposures has to be elicited, and the proper procedures for making the diagnosis of helminthiasis selected.

The helminths that parasitize humans include the nematodes (roundworms) and platyhelminths (flatworms), with the flatworms divided into the cestodes (tapeworms, segmented worms) and trematodes (schistosomes and other flukes). The biology of each of these groups is distinct. Ectoparasites are uncommonly associated with lung disease (e.g., leeches or Annelida or segmented worms) and are not discussed here.

In humans, worms produce a variety of pulmonary parenchymal and vascular diseases (Table 136-1). Because several stages in the life cycle of the parasite are found in humans, and pulmonary lesions occur at a particular phase of the life cycle, familiarity with the biologic behavior of the organisms is essential for proper diagnosis and treatment.

BIOLOGY AND IMMUNOLOGY

Biology of Helminths

Worms are multicellular organisms that vary considerably in size, from a few millimeters to several meters. They are covered by a tegument cuticle that protects them from the environment. Reproductive organs, both sexual and hermaphroditic, take up a large portion of the body. They are among the most developed and elaborate of human parasites. Their parasitic capabilities are such that they often parasitize more than one host and survive different hostile environments. Despite their relatively large size, the infective stages of worms invade human tissues by ingestion, penetration of skin, or the bite of insect vectors. Furthermore, parasitic helminths have developed a myriad of mechanisms by which they can evade the protective mechanisms of the host.

The life cycle of the helminths includes an egg form, larval stages, and an adult form. Human infection is by ingestion of the eggs or larvae, penetration of the skin by larvae, or insect

Table 136-1

Pulmonary Parenchymal and Vascular Diseases Produced by Worms

Major Pulmonary Presentation	Infection	Causative Organism	Infective Stage	Pathogenic Stage
Loeffler-like syndrome	Ascariasis	*Ascaris lumbricoides*	Embryonated eggs in soil	Migrating larvae
	Hookworms	*Ancylostoma duodenale*, *Necator americanus*	Larvae in soil Larvae in soil	Migrating larvae
	Strongyloidiasis rhabditiform	*Strongyloides stercoralis*	Larvae in soil	Migrating larvae
	Hyperinfection with filariform	*S. stercoralis* *S. stercoralis*	Larvae in bowel	Migrating larvae
Pulmonary eosinophilia	Lymphatic filariasis	*Wuchereria bancrofti*, *Brugia malayi*	Larvae in mosquito	Microfilariae
Eosinophilia, cough	Visceral larva migrans	*Toxocara cani*, *T. catis*	Egg ingestion	Larvae
Space-occupying lesions	Echinococcosis	*Echinococcus granulosus*	Eggs in soil	Hydatid cysts
	Paragonimiasis	*Paragonimus westermani*	Metacercariae	Adult worms
	Schistosomiasis	*Schistosoma mansoni*, *S. japonicum*, *S. haematobium*	Cercariae in fresh water	Eggs

transmission of larvae. Humans may be the only host, an accidental host, an intermediate host (asexual reproduction), or a definitive host (with sexual reproduction in humans). A basic biologic generalization about helminthic infections is that the worms, as a rule, cannot multiply within the mammalian host. This phenomenon is important to the understanding of the dynamics of helminthic infection and the relationship between the intensity of a particular worm load within the host and its pathologic consequences. However, there are exceptions to this rule. For example, *Strongyloides stercoralis* and *Echinococcus granulosus* can increase their numbers within a host even though the host is not exposed to additional infective forms. This ability of *S. stercoralis* to autoinfect the same subject and cause a hyperinfection syndrome is of considerable clinical significance, especially in immunosuppressed patients, which may be fatal. A different example is that of echinococcosis, in which dissemination is usually a consequence of leakage or rupture of a hydatid cyst—thereby releasing its contents, which seed sites elsewhere and initiate similar lesions.

Another biologic characteristic of worm infections, particularly those migrating in host tissues such as the lungs, is the association with eosinophilia in the peripheral blood and tissue. When eosinophilia is marked, this association provides a clinically useful sign of a migratory worm infection. The prominent peripheral blood eosinophilia of tissue migratory worm infections contrasts with no eosinophilia in persons in whom the worm infection is confined to the gut lumen or in whom the infection is due to other agents (e.g., viruses or bacteria). The mechanism and specificity of this eosinophilic response depend on the integrity of the *cellular* immune response of the host: Sensitized T lymphocytes produce mediators that induce differentiation in the bone marrow or progenitor cells into mature eosinophils; this is done either directly or via other cell products from mononuclear phagocytes. Eosinophilia does not occur in athymic nude mice infected with *Trichinella spiralis* or *Schistosoma mansoni.* Similarly, eosinophilia often does not feature prominently when strongyloidiasis occurs in immunosuppressed persons. Eosinophil production appears to be affected by interleukin 3 (IL-3), GM-CSF, and IL-5. Only IL-5, however, is specific for the maturation of eosinophils and basophils. The cytokine interact with eosinophils through a cell surface–specific receptor. It induces a state of metabolic as well as functional activation of eosinophils. In contrast, the specific helminthic antigens responsible for initiating this response are unknown. It should be noted that corticosteroids may lyse eosinophils and complicate diagnosis.

Investigations have suggested that the increased eosinophil level that occurs in experimental animals or

humans with helminthiasis is related to their biologic role as an integral component of host defenses. In vitro, eosinophils along with antibodies or complement kill the larval forms of several helminths. The killing of parasites is accompanied by a respiratory burst in these cells and evacuation of the contents of their granules onto the surface of the helminth. In vivo, depletion of eosinophils in experimental animals leads to loss of their acquired resistance to infection from several helminths, such as *T. spiralis* and *S. mansoni.* Both oxidative and non-oxidative products of eosinophil granules have been implicated in target killing.

Host-Parasite Relationship in Pulmonary Helminthiases

Human disease caused by pulmonary helminthiases results from various factors. Most classes of helminths can reside in human lungs during one or more of their parasitic stages, including nematodes, trematodes, and cestodes. The stage of the life cycle that causes human pulmonary disease also varies—e.g., larvae of nematodes, eggs of schistosomes, and adult worms in paragonimiasis, and cestodes. The multiplicity and complex structure of these etiologic agents lead to a heterogeneous set of responses, both immunologic and nonimmunologic. Moreover, disease may result from the mechanical presence of worms (space-occupying lesions) and the associated inflammatory responses or as a byproduct of the host immune responses, or both. For example, in echinococcosis, hydatid cysts displace lung tissues, but in pulmonary schistosomiasis, the vascular obstructive lesions are predominantly the outcome of the delayed-hypersensitivity granulomatous response of the host. Therefore, the understanding of the host-parasite relationship in pulmonary helminthiasis is based on an appreciation of the heterogeneity of etiologic agents and corresponding host responses.

An additional and biologically relevant factor concerning helminthic infections and their role in the etiology of human disease is the intensity of infection. Since most worms that infect humans cannot increase their population without additional exposure to the infective stages, the worm load largely determines the degree of pathologic sequelae. For example, the number of schistosome eggs reaching the pulmonary circulation is an essential determinant of the severity of the induced disease. Although the number of eggs reaching the lungs may be influenced by several factors, the most important determinant is the number of adult worms in the infected person.

The immune responses of the host often feature prominently in shaping the pathologic consequences of helminthic infection of the lungs. In experimental animals, the degree of tissue injury and host responsiveness to several helminthiases has been shown to be regulated by modulatory antibody, cellular, and cytokine responses.

Whether humans acquire resistance to helminthic infection and resistance can be induced have not been settled. Resistance against several helminths occurs in experimental animals after primary infection, and can be induced by defined antigens.

APPROACH TO THE PATIENT WITH HELMINTHIC INFECTION OF THE LUNGS

As indicated, the major symptoms and signs of pulmonary disease are common to most etiologic agents, non-infectious as well as infectious. Although in general helminth infections are particularly common in temperate and hot areas of the world, some are transmitted in the United States and other colder and developed areas. A history that the patient has lived overseas or in certain parts of the United States is helpful in alerting the examiner to the possibility of a helminthic infection. The geographic distribution of the major helminthic infections is roughly known. Also, some infections, such as those with *E. granulosus,* are common in sheep-raising countries and in certain sheep-raising areas in the United States. Knowledge of the immunologic status of the patient is valuable in suggesting helminthic infection—e.g., the hyperinfection syndrome caused by *S. stercoralis.*

Eosinophilia in peripheral blood, sputum, or pulmonary tissue is a helpful clue in directing the diagnostic workup. Although increased eosinophil counts do occur in several other pulmonary diseases, the close association with helminthic infections necessitates appropriate diagnostic procedures to determine whether a worm is implicated. Definitive diagnosis of helminthic infections of the lungs requires isolation and identification of diagnostic stages in the life cycle of the parasite that routine examination of appropriate specimens may miss. Therefore, the appropriate laboratory personnel should be alerted to the possibility of a worm infection so that proper samples can be obtained and preserved for special examinations. Serologic testing for helminthiasis is particularly useful in nonendemic areas. It should always be considered an adjunct and important diagnostic procedure.

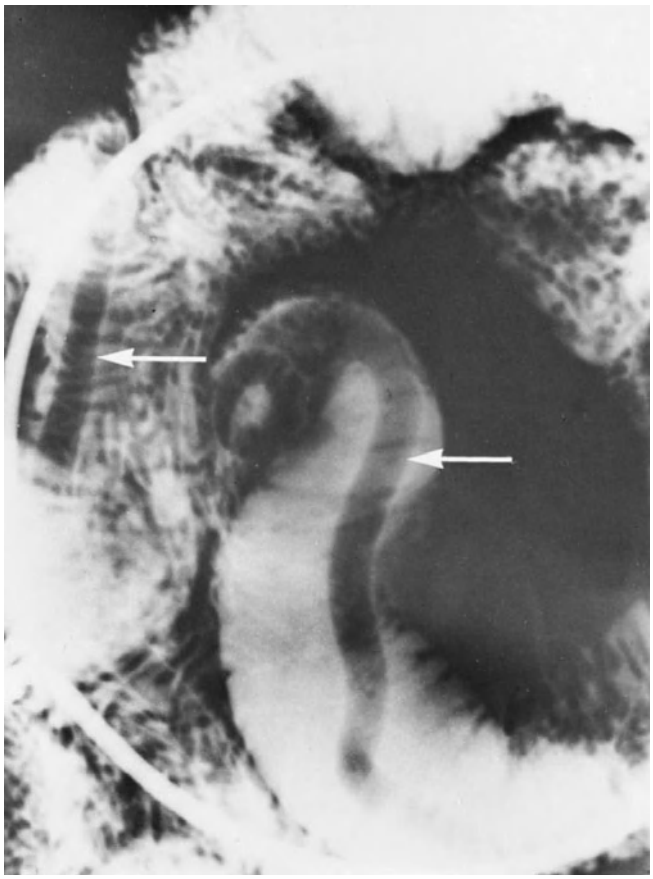
DISEASES DUE TO NEMATODES (ROUNDWORMS)

Ascariasis, Hookworms, and Strongyloidiasis

Human infections with *Ascaris lumbricoides,* the hookworms *Ancylostoma duodenale* and *Necator americanus,* and *S. stercoralis* are among the most prevalent helminthiases worldwide. Transmission also occurs in the southeastern United States.

Etiology

Human ascariasis (Fig. 136-1) results from ingestion of embryonated *A. lumbricoides* eggs that are contained in feces-contaminated soil. Ingestion of contaminated vegetables and fruits that have not been properly washed is the most frequent transmission vehicle. *Ascaris* eggs hatch in the gastrointestinal



A

B

Figure 136-1 Nematodes. *A.* Ascariasis. Barium in the small intestine outlines two *Ascaris* worms (arrows). *(From Shaba JK: Protozoan and metazoan infections, in Fishman AP (ed). Pulmonary Diseases and Disorders. New York, McGraw-Hill, 1980, pp 1182–1201). B. Strongyloides stercoralis.* Rhabditiform larvae. *(Courtesy of Dr. Stanley H. Abadie.)*

tract, producing larvae that penetrate the gut wall and migrate via venous blood and the right side of the heart to the lungs. Hookworms (*A. duodenale* and *N. americanus*) and *S. stercoralis* infect humans when infective larvae, found in soil, penetrate intact skin. Larvae of hookworms or of *S. stercoralis* travel via the bloodstream to the lungs (Table 136-1). The parasite larvae migrate via pulmonary capillaries into alveolar spaces. They then ascend toward the trachea to be swallowed en route to their final habitat in the small intestine. Although larvae are sometimes found in the sputum of infected persons, more often the eggs (*A. lumbricoides, A. duodenale,* and *N. americanus*) or the larvae *(S. stercoralis)* are found in stools. Passage to the outside environment, where the stool forms develop into stages infective for humans, completes their life cycle.

Pathogenesis and Pathology

In nematode infections, the most prominent pulmonary pathologic changes occur in persons with ascariasis or with the hyperinfection syndrome of strongyloidiasis. *Ascaris* pneumonia may occur in 1 to 2 weeks after infection. Portions of larvae are seen in the pulmonary parenchyma, surrounded by patchy infiltrate of neutrophils and eosinophils. The alveoli contain a serous exudate; the production of bronchial mucus is increased. Later, migrating larvae are destroyed within aggregates of eosinophils. The nature of the inflammatory process in *Ascaris* pneumonia suggests hypersensitivity. The intensity of the reaction depends on the number of parasite larvae and previous sensitization. In areas in which transmission of *Ascaris* eggs occurs seasonally, pulmonary reactions are usually more in evidence during these periods.

In *immunocompetent* subjects, pulmonary disease caused by hookworms or *S. stercoralis* is unremarkable. It should be recalled that infection with *Strongyloides* is lifelong and that reactivation with suppression of cell-mediated immunity can occur decades after initial exposure. As a result, life-threatening infection with *S. stercoralis* seems to relate to the premature development of filariform larvae in immunocompromised persons and invade across the gut wall or perianal skin, carrying intestinal bacteria into the peritoneum and bloodstream. Tissue migration occurs through most body organs, including the lungs. Gram-negative meningitis and sepsis are components of this syndrome. Initially, the pulmonary lesions resemble those of *Ascaris* pneumonia. In some patients, bronchopneumonia and lung abscesses develop. The lungs of fatal cases show intra-alveolar hemorrhages and inflammatory changes.

Clinical Features

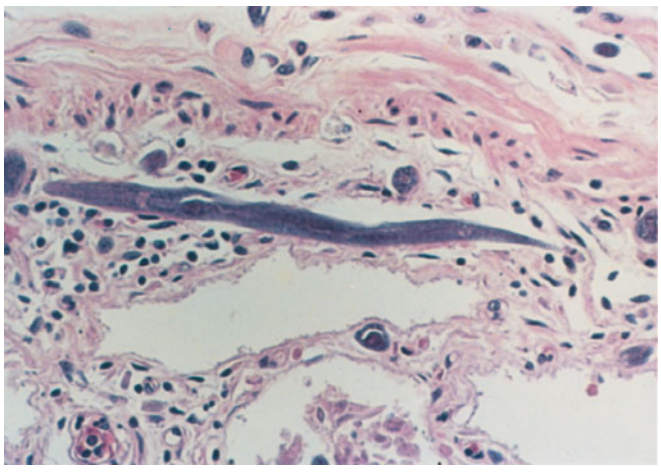
The major clinical manifestations caused by infection of the lungs with the larval forms of intestinal nematodes resemble those of Loeffler's syndrome; these manifestations occur typically in patients with seasonal or *Ascaris* pneumonia. The symptoms include persistent, irritating, and nonproductive cough, substernal pain, and in the severely ill, hemoptysis and dyspnea. Eosinophilia is the most consistent laboratory finding. Radiographic signs—e.g., patchy or miliary infiltrate—are sometimes seen.

The onset of the Loeffler-like syndrome caused by intestinal nematodes usually occurs 2 to 3 weeks after infection, coincident with larval migration from the pulmonary circulation to the alveoli. This coincidence was illustrated by the occurrence of the syndrome in a group of students exposed to eggs of the pig roundworm *(A. suum)*. Typical symptoms occurred 10 to 15 days later; some of the students developed marked respiratory failure. In locations in which transmission of ascariasis is cyclic because of environmental factors, pneumonitis occurs seasonally. Mild symptoms are occasionally encountered in persons with hookworm infection or in immunocompetent subjects who have strongyloidiasis.

The most clinically significant pulmonary syndrome induced by intestinal nematodes is caused by hyperinfection with *S. stercoralis* (Fig. 136-2). As a rule, the syndrome occurs in patients with compromised cell-mediated immunity, although it is occasionally encountered in normal persons. Immunosuppression is usually caused by neoplastic diseases, such as Hodgkin's, other lymphomas and leukemias, or nonmalignant conditions that are being treated with corticosteroids—e.g., organ transplantation. The sequence of events in immunosuppressed patients indicates that a change has occurred in the reproductive cycle of the parasite: In non-immunosuppressed subjects, the rhabditiform larvae have to go to the outside world to transform into the infective filariform organisms; in immunosuppressed patients, the change to infective larvae occurs within the host. The organisms penetrate the intestinal mucosa—resulting in massive invasion of almost every organ, including the lungs. The major clinical features include asthma, pulmonary opacities and cavitation, consolidation, and diffuse focal infiltrates. Usually, widespread dissemination of the nematode is accompanied by secondary infection caused by gram-negative organisms carried along with *S. stercoralis*. Eosinophilia is often absent in patients with the *S. stercoralis* hyperinfection syndrome, due to either defective cell-mediated immunity or the use of corticosteroids in many patients. The *S. stercoralis* hyperinfection syndrome is often fatal: mortality occurs in up to 77 percent of people with such infections.

Management

Diagnosis of infection with intestinal nematodes that causes a Loeffler-like syndrome can be difficult. Only occasionally is the search for parasite larvae in sputum rewarding. Indeed, not infrequently, definitive diagnosis is delayed for weeks, until the adult worms mature in the small intestine. At this stage, fecal examination discloses the characteristic eggs of hookworms or *Ascaris* or the larvae of *S. stercoralis*. The management of patients with the pulmonary manifestations of these parasitic worms is non-specific and symptomatic. Reduction of exposure in areas in which transmission of ascariasis is seasonal decreases the prevalence and severity of clinical presentations. Specific antihelminthic therapy is ineffective during



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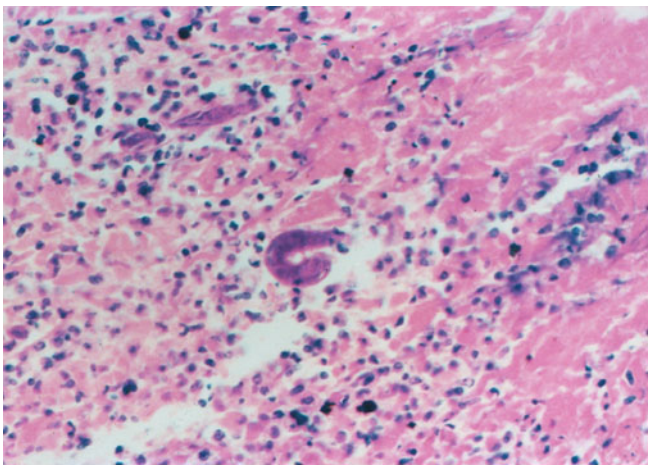


B

Figure 136-2 Strongyloidiasis. *A*. 55-year-old man with chronic lymphocytic leukemia who presented with abdominal discomfort and weight loss. The patient developed progressive pulmonary congestion and edema with dyspnea, fever to 103°F, and progressive hypotension before death. Blood cultures revealed *Escherichia coli*. Histologic section of colon at autopsy shows adult *S. stercoralis* in wall. *B*. A 24-year-old man with AIDS who developed diarrhea, weight loss, and, finally, shock with *E. coli* bacteremia and strongyloidiasis. The larval form is shown in the jejunum. *(Courtesy of Dr. Jay A. Fishman.)*

Table 136-2

Therapies of Pulmonary Diseases Produced by Worms

Organisms	Common Therapies	Comments
Ascaris lumbricoides	Albendazole, mebendazole, pyrantel, ivermectin, piperazine	Infection may persist for 1–2 years
Ancylostoma duodenale		Infection for ~ 1 year
Necator americanus	Albendazole, mebendazole, levamisole, pyrantel	Infection may persist for 3–5 years
Strongyloides stercoralis	Ivermectin, albendazole, thiabendazole	Hyperinfection with *S. stercoralis* with meningitis or sepsis requires therapy for gram negative or mixed infection; infection may be latent for >30 years (lifetime)
Wuchereria bancrofti, Brugia malayi	None satisfactory; diethylcarbazine or ivermectin reduce worm burden but no effect on clinical course	Prevention by mosquito control; possible addition of albendazole to other therapies
Echinococcus granulosus	Albendazole, mebendazole	Space-occupying lesion may require surgical resection in toto; may risk dissemination without cysticidal therapy (hypertonic saline, 0.5% cetrimide, 70%–95% ethanol, iodine); PAIR procedure—percutaneous aspiration and cysticidal therapy
Paragonimus westermani	Praziquantel (bithionol not always available)	
Schistosoma mansoni, S. japonicum, S. haematobium	Praziquantel (oxamniquine for *S. mansoni* and metriphonate for *S. hematobium* not always available)	
Toxocara cania, T. catis	None proved (albendazole, thiabendazole, mebendazole, diethylcarbazine, others)	Anti-inflammatories for cough; corticosteroids for symptoms or with therapy

the pulmonary stage but can cure the infection once the parasites reach maturity in the small intestine.

Albendazole 400 mg po once or mebendazole 100 mg per day for 2 to 3 days (or 500 mg po once) are the drugs of choice for treating ascariasis and hookworms (Table 136-2). Ivermectin 200 μg/kg per day for 2 days or albendazole 400 mg po daily for 2 days (7 days for hyperinfection syndrome) are recommended for strongyloidiasis. In patients suspected of having the hyperinfection syndrome, early diagnosis, modification of the immunosuppressive therapy, and prompt anti-*Strongyloides* chemotherapy and antibacterial therapies are important elements in averting a fatal outcome. Thus, a high degree of suspicion that strongyloidosis is present is needed in dealing with pulmonary disease associated with bacteremia in immunosuppressed patients. Most instances of strongyloidiasis in these patients are diagnosed at autopsy or shortly before death. Aggressive efforts at demonstrating *S. stercoralis* larvae entail repeated examination of stools and duodenal aspirates. Sputum and bronchial washings are examined for parasite larvae. Serology may be of help. In these patients, therapy is started as early as possible and continued for at least 7 to 10 days. Serologically positive individuals for *Strongyloides* should be treated in advance of immune suppression for organ transplantation or cancer therapy, generally with empiric ivermectin.

Pulmonary Filariasis (Tropical Pulmonary Eosinophilia)

Persons living in areas endemic for *Wuchereria bancrofti* and *Brugia malayi* may present with an acute or chronic lung disease, usually referred to as *tropical pulmonary eosinophilia.*

This is still a poorly defined clinical entity. Its main features are a history of residence in filaria-endemic areas, particularly India, chronic nocturnal paroxysmal cough, marked eosinophilia, positive serologic evidence, and a therapeutic response to the administration of diethylcarbamazine.

Etiology

Human infection with the tissue nematodes *W. bancrofti* or *B. malayi* can cause several amicrofilaremic syndromes, including tropical pulmonary eosinophilia. Infection is transmitted by the bite of several species of mosquitoes, thereby introducing the infective third-stage larvae. These organisms undergo ill-defined maturational stages, culminating in the development of adult male and female worms that are usually situated in lymphatic vessels and lymph nodes. Mature worms deposit microfilariae that appear in peripheral circulation, often at maximum numbers at specific times of the day. However, some filariae show no periodicity with respect to the appearance of their microfilariae in peripheral blood. Microfilariae are taken up by mosquitoes during their bites, thereby completing the life cycle of the parasite.

The life span of adult filariae is not known. Nonetheless, serologic or histopathologic evidence of infection can be obtained in the syndrome known collectively as *amicrofilaremic states,* even though larvae cannot be found in the blood. For example, in tropical pulmonary eosinophilia, high concentrations of antifilarial IgG and IgE in serum have been demonstrated despite invariably negative blood examinations for parasites. Also, despite the negative blood examinations, microfilariae have been found in lung and lymph node biopsies, confirming the filarial origin of this syndrome.

Pathogenesis and Pathology

Patients with pulmonary filariasis *(tropical pulmonary eosinophilia)* show evidence of humoral hyperreactivity manifested as increased serum levels of total IgE and antifilarial IgG and IgE. The possibility has been raised that these antibodies play a causal role in producing the pulmonary symptoms by inducing clearance of microfilariae and acute IgE-mediated responses, which are manifested clinically as asthma and eosinophilic pulmonary infiltrates. Histopathologically, the earliest lesions are histiocytic infiltrates in the interstitium and alveolar spaces. In established cases, the cell infiltrate consists predominantly of eosinophils, lymphocytes, and histiocytes, and it assumes a nodular configuration.

Clinical Features

Young males are predominantly afflicted with tropical pulmonary eosinophilia. The syndrome is characterized by episodes of dry night cough, low-grade fever, and general fatigue. Examination of the chest may reveal coarse rales and rhonchi, along with wheezing. In many patients, pulmonary function tests disclose a restrictive pattern in which vital and total lung capacity and residual volumes are all decreased. Some patients with chronic disease have perfusion impairment. Radiographically, the syndrome may be associated with reticulonodular opacities and increased bronchovascular markings. The sera of these patients usually demonstrate high IgE levels and specific antibodies to the parasite. Eosinophil counts in peripheral blood generally exceed $3000/mm^3$.

Management

Diagnosis is based on the typical clinical, radiographic, functional, and immunologic findings in the setting of an appropriate epidemiology history—i.e., previous residence in a filaria-endemic area. A favorable response to doxycycline 100 mg po bid for 8 weeks has been documented, possibly by reducing bacteria available for nutrition. This agent appears active against both adult worms and filarial. Diethylcarbamazine therapy 6 mg per kg po once appears to be as effective as prolonged therapies (14 days) as an alternative. Recurrences of tropical pulmonary eosinophilia are rare. If they do occur, a second course of antihelminthic chemotherapy is indicated.

Dirofilariasis

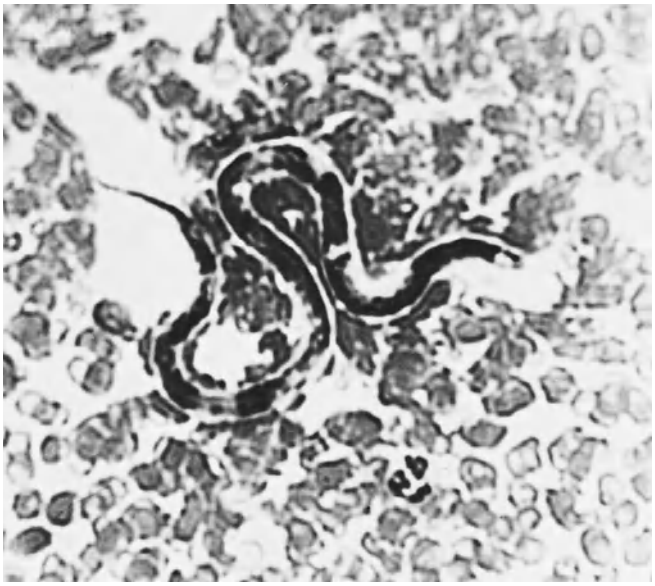
Another filarial parasite, *Dirofilaria immitis* (dog heartworm), may accidentally be transmitted to humans by the bites of the mosquito intermediate vector (Fig. 136-3). Several cases of dirofilariasis have been reported in the United States. In most, the infection was discovered as a coin lesion on the chest radiograph after a worm lodges in the pulmonary arteries. In some, cough, chest pain, hemoptysis, and eosinophilia were manifested. Definitive diagnosis is usually obtained from microscopic examination of excised lesions.

Toxocariasis (Visceral Larva Migrans)

Toxocariasis is due to human infection with animal parasites (dog or cat ascarids). It is most commonly encountered in children. The invading parasite larvae migrate in human tissues, but cannot mature to adult worms. *Toxocara canis* and *T. cati* are the two recognized etiologic agents of human visceral larva migrans. They both are widely distributed, in both developing and developed countries.

Etiology

The eggs of *T. canis* and *T. cati* are passed in the stools of dogs and cats, respectively. Transmission to humans occurs by ingestion of embryonated eggs in the soil or contamination of food. Larvae hatch in the small intestine, penetrate the gut wall, migrate to the liver, and are then carried via systemic veins to the systemic arterial circulation for distribution throughout the body. Larval migration through the host tissues and the associated inflammatory responses are considered responsible for the manifestations of disease. Most of these manifestations relate to liver pathology, eosinophilia, and pulmonary invasion. The concentrations in serum of total and specific immunoglobulins are also increased.



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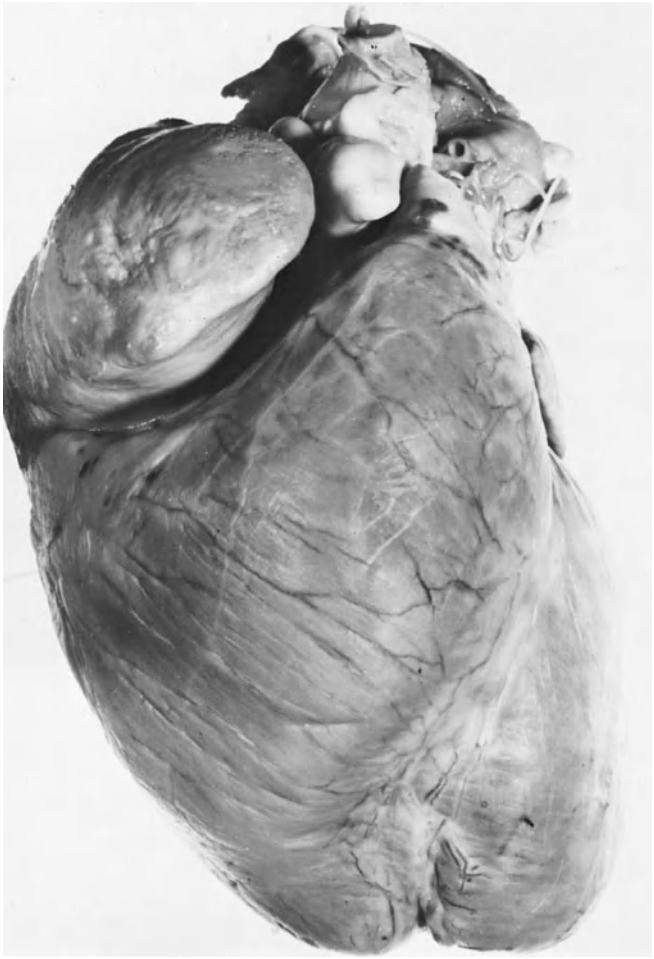


B

Figure 136-3 Pulmonary dirofilariasis in the dog. *A*. Microfilaria *(Dirofilaria immitis)* in blood. *B*. Right ventricular hypertrophy due to dirofilariasis. *C*. Heartworms filling the right atrium and protruding through the pulmonary valve. *(Courtesy of Dr. David H. Knight; from Shaba JK: Protozoan and metazoan infections, in Fishman AP (ed). Pulmonary Diseases and Disorders. New York, McGraw-Hill, 1980, pp 1182–1201.)*

Pathogenesis and Pathology

It is not clear whether tissue injury results from the invasion of different organs by the parasite larvae or from death and encapsulation of some organisms by an eosinophilic response of the host. The most commonly affected organ is the liver, in which granulomas surround parasite larvae. Similar lesions can be induced in experimental animals (Fig. 136-4). In the few fatal cases of toxocariasis, autopsy revealed that the major pathologic lesions were in the central nervous system.

Clinical Features

Toxocariasis is generally a disease of children 1 to 4 years of age, although it may be seen uncommonly in older individuals. It is particularly common in those with a history of pica. The two main presenting features relate to the chest and abdomen. Pulmonary complaints, such as cough and wheezing, and pulmonary infiltrates occur in more than one-third of symptomatic children. Peripheral eosinophilia is usually marked and may persist for years. In one study of serologically

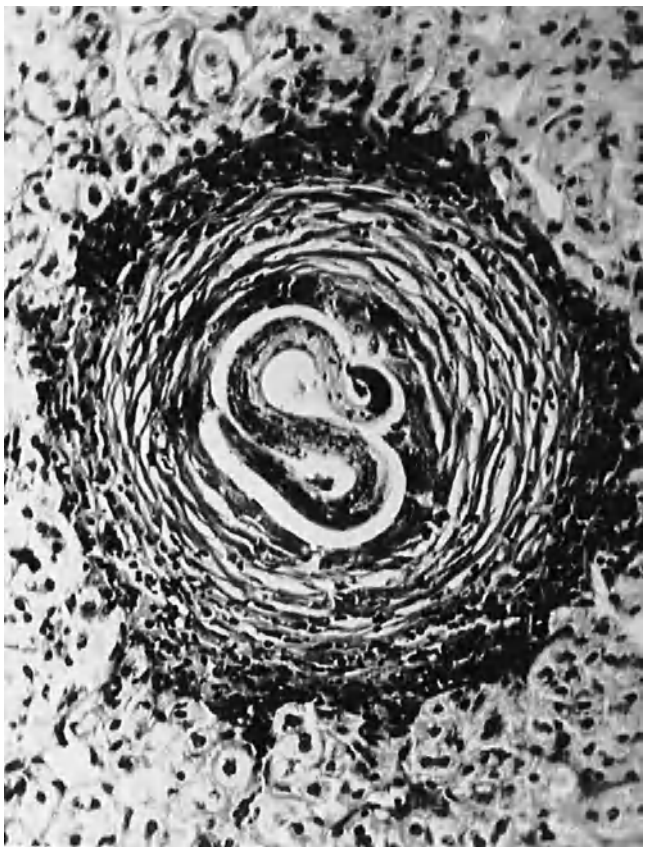


Figure 136-4 *Toxocara canis.* Granulomatous response to larvae in the liver. *(Courtesy of the American Society of Pathologists.)*

proven toxocariasis, hepatomegaly was present in 25 percent of patients.

Management

Toxocariasis is a cosmopolitan infection of children. Diagnosis is suspected because of the clinical presentation and serologic evidence of anti-*Toxocara* antibodies. Since the disease is usually benign and self-limiting and since the efficacy of most anti-helminthics against *Toxocara* infection is doubtful, no specific therapy is recommended. Corticosteroids may be necessary to limit the inflammatory response in patients with extensive disease of the lungs or central nervous system.

Rare Nematode Infections

In severe human *T. spiralis* infection, pneumonitis is accompanied by eosinophilia. The pulmonary syndrome follows the intestinal phase of infection and is usually associated with other allergic manifestations of trichinosis, including periorbital edema, muscle swelling, and weakness.

Anisakiasis in humans results from infection with the larval form of a nematode of marine mammals. The disease has been reported in Japan and Western Europe. Although it is usually manifested as an intestinal eosinophilic disorder, it has also been implicated as the probable cause of cough, eosinophilia, and pleural effusion.

DISEASES DUE TO CESTODES (SEGMENTED WORMS)

Echinococcosis

Human infection with the larval stage of the canine tapeworm *Echinococcus granulosus* is one of the most important helminthic pulmonary diseases. *E. granulosus* is worldwide in distribution; it occurs most commonly in sheep- and cattle-raising areas, particularly in Australia, South America, the Mediterranean, and some parts of Africa. The infection has also been reported in the United States.

Etiology

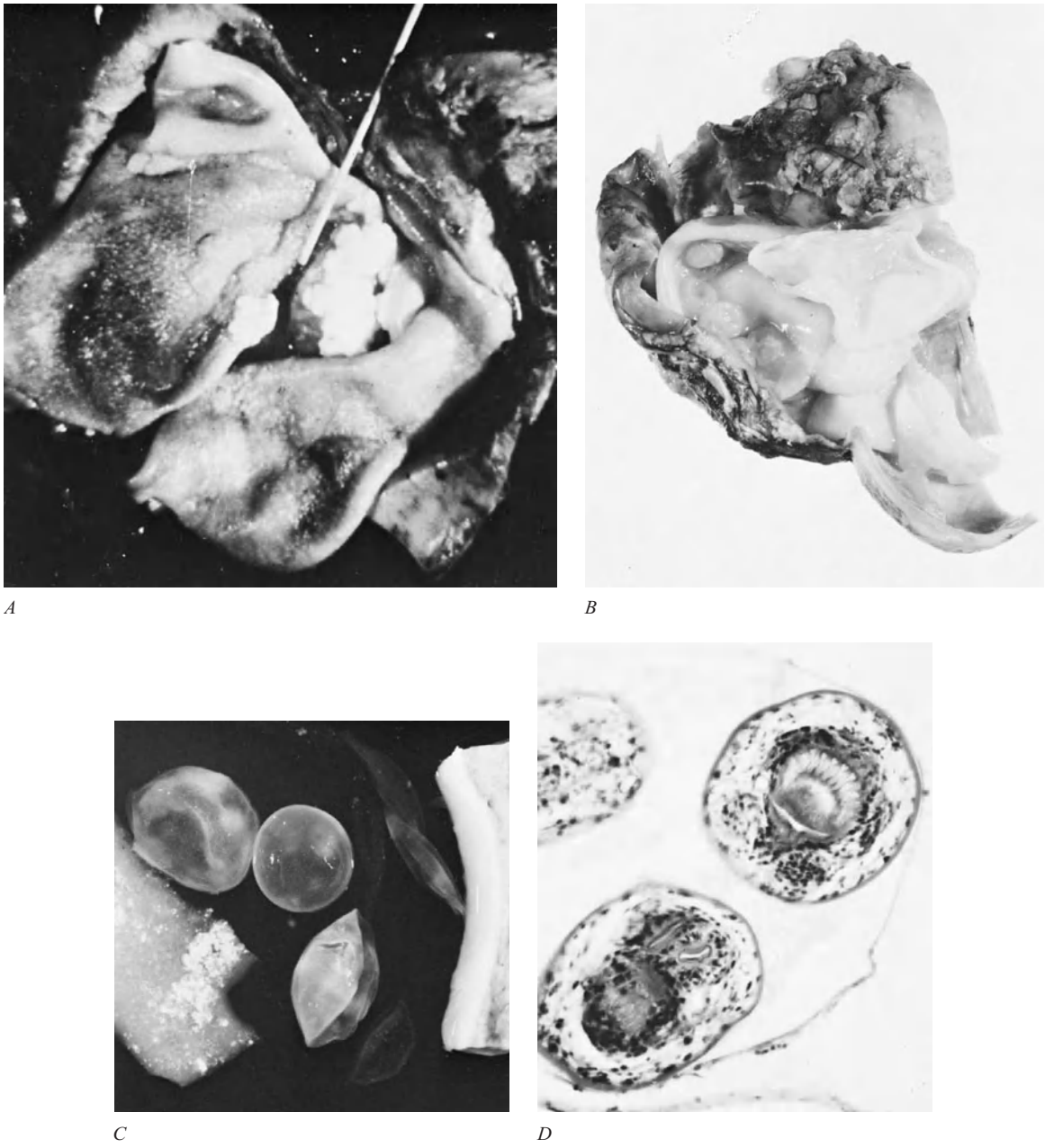
Adult *E. granulosus* worms are found in the intestines of dogs and wolves. They release eggs from their gravid segments that are passed in the feces. Humans acquire the infection by ingesting the eggs; embryos are then released and migrate to the liver, where most cysts in humans are found. Embryos may also migrate to the lungs or other tissues. Once the parasite has lodged in human tissues, it may develop in a space-occupying hydatid cyst. The inner lining of these cysts is a germinal layer capable of producing daughter cysts that may seed other organs upon spontaneous rupture or surgical manipulation of the original cyst (Fig. 136-5).

Pathogenesis and Pathology

Hydatid cysts are more frequently found in the lungs of children than of adults. In most instances, the slowly enlarging, space-occupying lesion is well tolerated. Cysts in the lungs are usually discovered early in the course of the disease because radiographic examinations of the chest are now so common. Pulmonary cysts are usually solitary, in 72 percent of cases affecting one lobe. The classic unilocular hydatid cyst is usually fertile: Cyst contents can seed other sites and start new cysts. The cyst is surrounded early in the course of infection by a granulomatous reaction on the part of the host; later, the inflammatory reaction is succeeded by fibrosis. Rupture of a fertile hydatid cyst may occur through a bronchus, leading to expectoration of scoleces in the sputum. Rupture into the mediastinum or pleural cavity can lead to secondary implantations. The fluid content of a hydatid cyst is believed to be immunogenic, and leakage of the cyst may evoke an anaphylactic response. Although eosinophilia has been reported to accompany hydatid disease of the lung, its frequency is not known.

Clinical Features

Hydatid cysts are usually asymptomatic; approximately half of the clinically diagnosed cysts are in the lungs. Most patients with pulmonary hydatid disease are children. In about three-fourths of patients, the cysts are in one lobe. Approximately half of the patients present with cough; smaller fractions present with dyspnea or chest pain. On chest radiography,



A *B*

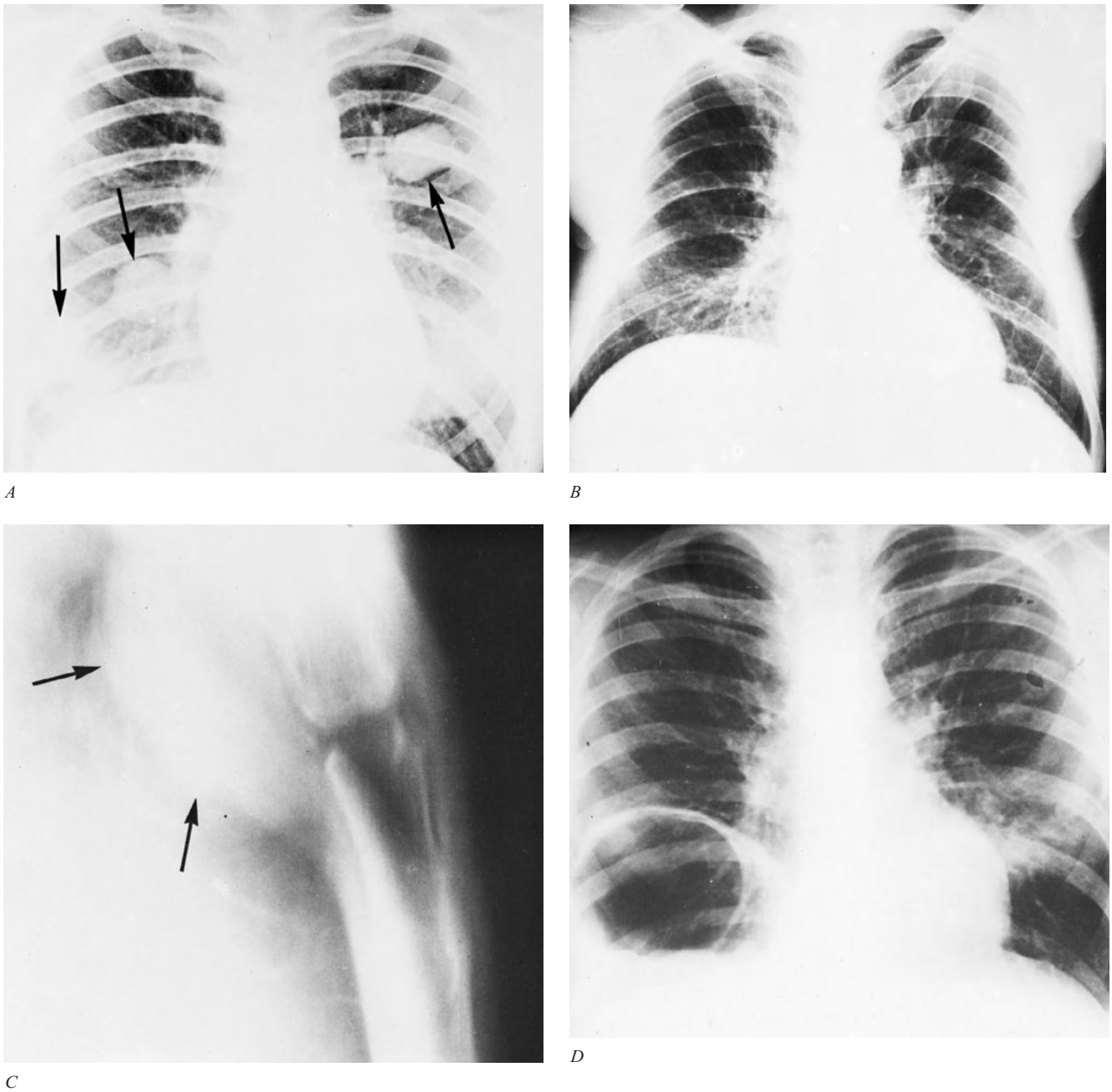
C *D*

Figure 136-5 Echinococcosis. *A*. Hydatid cyst in the lung. The glistening membrane constitutes the wall of the cyst. *B*. Hydatid cysts in mesentery. Note similarity to appearance in the lung. *C*. Fragment of liver on the right is lined with *Echinococcus* membrane. Brood capsules are on the left. *D*. Three scoleces of *E. granulosus*. The upper right scolex shows the hooklets of the organism. *(A, courtesy of Dr. Stanley H. Abadie; B to D, courtesy of Dr. Daniel H. Connor, Armed Forces Institute of Pathology.)*

the lesions vary in diameter from 1 to 20 cm; sometimes the cyst is surrounded by an area of pneumonitis or atelectasis. Less often, a fluid level, "water lily sign" (Fig. 136-6), or calcification is seen. Other diagnostic procedures—e.g., serology and computed tomography—may be useful in improving characterization of the lesions.

Management

In most instances, diagnosis of the hydatid nature of a pulmonary cyst depends on immunologic procedures. Surgery is the treatment of choice for hydatid disease of the lungs. The Barrett procedure is currently recommended for small- or moderate-size cysts; the open method, in which the parasite cyst is removed but the cavity is left draining to the pleural space, is preferred for large cysts. More extensive procedures, such as lobectomy and segmental resection, may not be necessary for most pulmonary hydatid cysts. The use of the PAIR procedure with percutaneous aspiration, injection of cysticidal agent (hypertonic saline or absolute alcohol, although other agents have been used), and re-aspiration is common with radiographic guidance. This has proven successful in many cases. This is coupled with albendazole starting before



A

B

C

D

Figure 136-6 Echinococcus. *A*. Multiple pulmonary cysts (arrows). *(Courtesy of Dr. Carl Heitz.) B*. Another patient with echinococcus cyst behind the sternum. The retrosternal mass is difficult to discern on the posteroanterior radiograph. *C*. Lateral view. Mass (cyst) is seen (arrows). *D*. Hydatid cyst, right lower lobe. *(Courtesy of Dr. Philip Lerner.)*

and continuing after drainage for 28 days (400 mg po bid for a greater than 60-kg individual; 15 mg/kg divided into two doses for those a less than 60-kg individual).

DISEASES DUE TO TREMATODES (FLAT WORMS)

Schistosomiasis

Schistosomal infections of humans represent one of the major endemic helminthiases in Southeast Asia, the Middle East, Africa, the Caribbean, and South America. Five species represent the most common and clinically significant infections: *Schistosoma haematobium, S. mansoni, S. japonicum, S. mekongi,* and *S. intercalatum.*

Etiology

The schistosomes are blood flukes; in humans, they inhabit the venous system around the urinary bladder or the small and large intestines. Human infection is initiated by penetration of intact skin by the free-living cercariae that are shed by specific freshwater snails. The cercariae change within a

few hours into schistosomula, which migrate from the subcutaneous tissues to the lungs and then the liver, where they mature into adult worms. Fecund adult parasites then migrate to their final habitat: the veins around the ureters and urinary bladder *(S. haematobium)* and the mesenteric veins (all other species). Adult worms deposit eggs that are intended to pass through the lumen of ureters or gut to the outside environment to complete the life cycle of the parasite. However, some of these ova may be trapped in the host tissues. Other ova may be carried by the venous circulation to the heart and then lungs. In *S. haematobium* infection, schistosome eggs reach the pulmonary circulation via the inferior vena cava. Eggs of the other species reach the systemic circulation after the development of portal hypertension and portosystemic anastomosis.

Pathogenesis and Pathology

Schistosome eggs reach the pulmonary circulation by routes that depend on the species of the parasite, their final habitat, and the stage of infection. Because *S. haematobium* worms parasitize the vesical plexus, which connects directly with the inferior vena cava, egg seeding to the lungs may occur at any phase of infection. By contrast, the anatomic location of adult worms of the other species in the mesenteric veins does not allow parasite ova to travel through the portal to the hepatic, and subsequently systemic, circulations. Eggs of these species are believed to reach the lungs only in the late stages of infection, after portal hypertension develops and anastomotic channels open between the portal and systemic circulations.

Upon reaching the pulmonary circulation, schistosome eggs usually gather in small arterioles, where they induce the formation of delayed-hypersensitivity granulomas, made up of eosinophils, lymphocytes, and macrophages (Fig. 136-7). In addition, deposition of fibrous tissue causes narrowing, thickening, and occlusion of pulmonary arterioles. In an autopsy study of 32 cases of *S. mansoni* cor pulmonale, two characteristic histopathologic lesions were identified: (1) focal changes related directly to the presence of schistosome eggs; these were located either within the alveolar tissue or within the pulmonary arteries or arterioles; and (2) plexiform or angiomatoid lesions consisting of several thin-walled and dilated vessels. The most prominent vascular lesions were associated with the focal changes surrounding mature schistosome eggs in the lumen of pulmonary arteries or arterioles. These were accompanied by fibrin deposition and remarkable proliferation of endothelial cells. Fibrosis surrounds most focal lesions. Because of the curtailment of the pulmonary vasculature and the decreased distensibility caused by the perivascular fibrosis, pulmonary hypertension and cor pulmonale ensue. Pulmonary function is predominantly restrictive and is accompanied by a decrease in the diffusing capacity.

Clinical Features

It is not clear whether schistosome infection during its early phases in humans is associated with appreciable pulmonary disease. Migration of schistosomula through human lungs is not known to cause detectable symptoms or signs. By contrast, after the onset of oviposition, some ova may reach the lungs, particularly in *S. haematobium* infection. Furthermore, chronic infection with the other schistosome species may be associated with sufficient deposition of eggs in the lungs to cause the development of cor pulmonale. The clinical features and radiographic findings in schistosomal pulmonary hypertension and cor pulmonale are not distinctive. The prevalence of the pulmonary hypertensive syndrome in schistosome-infected patients is not known. In Egypt, 7.5 percent of patients hospitalized with schistosomal hepatomegaly had cor pulmonale; in Brazil, 23 percent of similar patients had pulmonary hypertension (i.e., pulmonary arterial blood pressure higher than 20 mmHg).

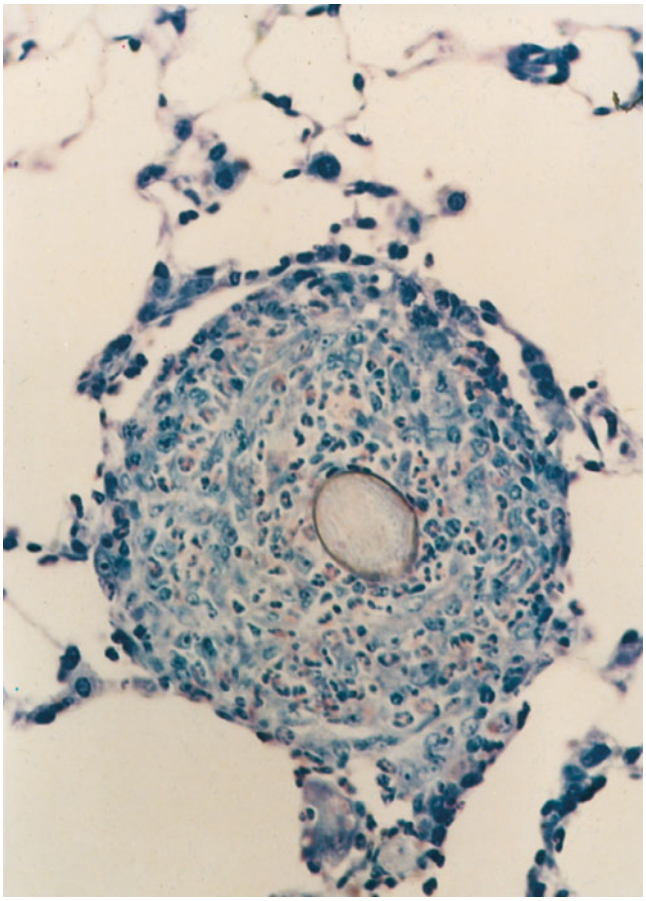


Figure 136-7 Schistosomal granuloma. *(Courtesy of Dr. Jay A. Fishman.)*

Management

Diagnosis of pulmonary disease due to schistosomiasis may be achieved by finding the parasite eggs in urine or stools of persons with suggestive clinical manifestations. However, pulmonary disease may occur several years after infection, and finding parasite ova may be difficult. Under these circumstances, demonstrating the characteristic pathologic

changes and ova in tissues or positive serology may settle the diagnosis.

Active schistosome infections are treated with praziquantel, which kills adult worms and stops further destruction of tissue by ova deposition. The drug is administered as 20 mg/kg body weight bid for 1 day (two doses) for *S. mansoni* and *S. haematobium* infection and three times a day (three total doses) for *S. japonicum* infection. However, reversal of pathologic lesions in the lungs after antischistosomal chemotherapy has not been documented.

Paragonimiasis

Human infection with species of the lung fluke *Paragonimus* is prevalent in the Far East, Africa, and South and Central America. Infection is maintained in endemic areas through contamination of water sources, with feces or sputum of infected individuals resulting in infection of the intermediate snail and crustacean hosts. Symptomatic paragonimiasis is initially characterized by cough and bloody sputum that may lead to bronchiectasis or lung abscesses.

Etiology

Human infection with *Paragonimus* is acquired from eating raw or pickled crustacea (freshwater crayfish and crabs) that harbor the infective parasite stage (metacercariae). These forms excyst in the duodenum, penetrate the intestinal wall, and migrate via the diaphragm and pleural cavity to the lungs, where they mature into adult worms (12 × 6 × 5 mm). Adult *Paragonimus* worms are hermaphroditic; they produce golden-brown eggs, which are coughed up and voided through either sputum or feces. The life cycle of the parasite outside the human host goes through a specific snail intermediate host; metacercariae then encyst on freshwater crustacea.

Pathogenesis and Pathology

The primary site of infection in humans is the lungs. The worm is also found in the brain in 25 percent of patients and less often in many other tissues. During invasion of the lungs by the maturing adult worms, parasite tunnels in the pulmonary parenchyma can usually be demonstrated, particularly in peripheral areas. The tunnels and parasites are surrounded by a granulocytic reaction made of eosinophils and neutrophils. Charcot-Leyden crystals are often seen. In patients with encysted worms, the parasites are enclosed with cystic lesions that may communicate with each other or with a bronchus. Death of the worms usually leads to collapse of the cyst, disintegration of the parasite, and fibrosis or calcification. The surrounding pulmonary tissue may show evidence of atelectasis, bronchiectasis, or compensatory emphysema. In some patients, secondary infection and lung abscess develop in the cystic lesions surrounding adult parasites. The radiographic changes correspond roughly to the three stages of parasite development within the lungs: (1) on arrival in the lungs, maturing worms are associated with the development of radiographic opacities; (2) these are succeeded by nodules that correspond to the parasite cysts; (3) fibrosis or calcification ensues.

Clinical Features

The incubation period between infection and the development of maturing adults in the lungs is 2 to 20 days. Few specific symptoms have been described during this stage. In persons with established infection, the worm load seems to determine the extent of clinical features. Light infection is invariably asymptomatic. In moderate to heavy worm loads, complaint of cough and respiratory discomfort (particularly upon rising in the morning) and rusty, blood-tinged sputum containing parasite eggs, necrotic material, and Charcot-Leyden crystals are common. Frank hemoptysis, sometimes severe, also occurs in patients with pulmonary paragonimiasis.

The chest radiograph is normal in 10 to 20 percent of infected persons. Radiographic signs in the others include infiltrate, cavitation, fibrosis, and pulmonary thickening. The characteristic ring shadow with a crescent corona occurs in some infected persons.

Management

The diagnosis of paragonimiasis is made from detection of the characteristic eggs in the sputum or stools of infected persons. Serologic testing may be helpful in egg-negative cases. The drug of choice for treating paragonimiasis is praziquantel. It is administered orally, 25 mg/kg three times per day for 2 days, or bithionol 30 to 50 mg/kg po alternate days for five doses. Chemotherapy usually leads to cessation of egg passage in sputum and stools, some clearing of the chest radiograph in almost two-thirds of treated patients, and a decrease in serum IgG antibodies against the parasite.

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137

Zoonotic and Other Unusual Bacterial Pneumonias

Arnold N. Weinberg • Camille Nelson Kotton

Many different microorganisms can infect the lungs. Routes of spread are few, clinical presentations overlap, radiologic changes are often nonspecific, and pathophysiological mechanisms are limited. Making a clinical diagnosis of pneumonia is relatively easy; defining the causative agent can be difficult. The search for the specific agent is driven by a number of compelling issues, including the desire to use a specific therapy for a specific pathogen; the potential for progressive respiratory impairment when the wrong antibiotic is used; and epidemiological concerns in the family, the hospital community, and the general public for isolation and containment. An even more critical public health issue has emerged following the "mail room" anthrax attack in 2001 and concern for the aerosol use of anthrax spores and other zoonotic pathogens by terrorists.

In the three decades that have passed since the epidemic of acute respiratory disease erupted among delegates to the American Legion Convention in Philadelphia, physicians, microbiologists, and epidemiologists have become better prepared for the diagnostic challenges of patients with unusual pneumonias. The greater awareness of investigators and clinicians of the variety of infectious agents capable of causing respiratory disease is illustrated by the increased frequency of the *clinical* diagnosis of Q fever (due to *Coxiella brunetti*) in addition to retrospective serologic diagnoses. *Chlamydia pneumoniae,* the former "TWAR" agent, has been identified in military and school epidemics and as an important cause of pneumonia in isolated cases. The rapid identification of a Hantavirus in 1993 as the cause of a newly recognized respiratory syndrome is an example of the multidisciplinary approach toward recognition of emerging infectious diseases. The sudden appearance of severe acute respiratory syndrome (SARS) during the winter of 2002–2003 is a recent example of the emergence of a new respiratory disease. The response of the world community led to the rapid identification of a novel coronavirus as the causal agent of SARS and effective global efforts to understand the disease and contain its spread.

These infectious agents and diseases are covered in detail elsewhere in the text. They appear as part of the differential diagnosis in obscure pneumonia, and illustrate the range of pathogens associated with animals and their environments and acute respiratory disease in individuals and groups. The examples presented above include a number of viruses while the agents to be discussed in detail in this chapter are all bacterial pathogens and most are closely associated

with animals or animal products. Zoonotic infections may reflect an initiating event and then person-to-person spread, as exemplified by the SARS coronavirus. The avian influenza virus (H_5N_1) is another zoonotic microorganism that has spread to individuals within close contact with domestic chickens; fortunately, the jump to humans has led to very rare human-to-human spread. The potential for pandemic influenza as well as SARS are subjects dealt with in other chapters in this textbook.

A number of microorganisms, including many of the zoonotic bacteria discussed in this chapter, are recognized by the Centers for Disease Control and Prevention (CDC) and the National Institute of Allergy and Infectious Diseases (NIAID) as Category A Priority Pathogens. The global community has been developing rapid diagnostic technology and countermeasures to protect and treat people in the event of a bioterror attack. The "mail room" anthrax epidemic of September 2001 illustrated the potential for widespread inhalation disease, public panic, diagnostic and therapeutic challenges, significant costs in human life and infrastructure stability, and the expense involved in decontamination. Physicians need to become familiar with the typical and atypical spectrum of disease caused by these pathogens, including the impact and variable expression of a large inoculum aerosol release in a crowded urban area or building.

The general features of epidemiological and clinical data that should be helpful in evaluating typical and atypical features of disease in spontaneous and terrorist related events are described in Table 137-1. This discussion of *unusual bacterial pneumonias* focuses on a limited number of microorganisms and not on an exhaustive list of possible causative agents. The unique properties of these bacteria exemplify how bacteriology, ecology, epidemiology, and pathogenesis serve as helpful clues to earlier etiologic diagnosis and, therefore, specific therapy (Table 137-2).

Table 137-1

An Overview of Zoonotic and Other Unusual Pneumonias

Environmental Niche	Microorganism	Disease	Epidemiologic Associations	Distribution
Live animal contact or via arthropod	*Pasteurella multocida*	Tularemia	Contact with animals, birds, or arthropods	North America, Europe, Asia
	Yersinia pestis	Pasteurellosis	Feline and dog contact; chronic lung disease	Worldwide
	Francisella tularensis	*Rhodococcus* pneumonia	Airborne droplets; contact with soil contaminated with horse, cow, or swine excrement	Worldwide
	Rhodococcus equi	Plague	Contact with rodents, fleas; contact with plague pneumonia case	Worldwide, including Asia, southwest U.S.
Soil, stagnant water, and inert animal products	*Bacillus anthracis*	Inhalation anthrax or wool-sorter's disease	Industrial; use of animal products in hobbies	Worldwide in warmer regions
	Brucella species	Brucellosis	Ingestion or contact with infected animal products	Worldwide
	Burkholderia pseudomallei	Melioidosis	Direct penetrating contact with soil, water	Latitude 20°N to 20°S, especially rural Asia
	Yersinia enterocolitica	Yersiniosis	Ingestion of contaminated foods, water; cirrhosis	Worldwide
Obligate human commensal	*Neisseria meningitidis*	Meningococcal pneumonia	Airborne droplets, human to human; postviral, nosocomial	Humans worldwide
	Moraxella catarrhalis	*Moraxella* pneumonia	Aspiration, especially individuals with underlying lung disease	Humans worldwide

Table 137-2

Diagnostic Studies and Treatment Recommendations in Zoonotic Pneumonias

Disease	Gram's Stain Morphology	Culture Methods	Identifying Tests	Therapy Total Dose/Number of Doses Per Day*
Anthrax	Large gram-positive bacillus (rarely seen)	BAP, blood cultures	FA	CIP 800 mg/2 or D(200 mg/2) + CL (2.7 g/3) + RI (600mg/2) If PCN susceptible, PCN (24 mu/6)
Brucellosis	Small gram-negative coccobacillus (rarely seen)	Media enriched with serum, CO_2 + O_2	Rise in AA, Prozone	TMP-SMX (480 mg + 2.4 mg/3) + SM (1 g/2) D (200 mg/2) + RI (600 mg/1)
Melioidosis	Bipolar staining gram-negative bacillus	BAP, MAC	Morphology, FA, AA	TMP-SMX (640 mg + 3.2 g/4) and ceftazidime (6–9 g/3) or CL (4–6 g/4) + D (200 mg/2)
Pasteurellosis	Small bipolar staining gram-negative bacillus	BAP, CO_2	Inhibited by MAC, biochem. tests	PCN or A (6 mu or 8 g/4) or cefotaxime (6–8 g/4) or CL (3 g/4)
Plague	Enteric bipolar staining gram-negative bacillus	BAP, MAC, enteric media, blood cultures	Biochem. tests, FA, AA	SM (2 g/2) and D (200 mg/2) or CL (4–6 g/4)
Rhodococcus	Gram-positive coccobacilli (slightly acid-fast positive)	BAP	Biochem. tests	E (2 g/4) or CLA (1 g/2) or AZ (500 mg) and CIP (1.5 g/2) and RI (600 mg)
Tularemia	Small gram-negative coccobacillus	Enriched media with cysteine, serum	FA, AA, rarely cultured	SM or gentamicin (2 g/2 or 4.5 mg/kg/3) or CL (3–4 g/4) or D (200 mg/2)
Yersiniosis	Enteric gram-negative bacillus	BAP, MAC, enteric media, blood cultures	Biochem. tests, motility 25°C	A (8 g/4) or 2d or 3d gen. cephalosp. (4–6 g/4) or CL (3 g/4)

** Expressed as million units (mu), grams (g), or milligrams (mg) divided by number of doses in 24 h.*
NOTE: BAP = blood agar; MAC = MacConkey agar; FA = fluorescent antibody; AA = agglutinin antibody. Antibiotics include A = ampicillin; AZ = azithromycin; CIP = ciprofloxacin; CL = chloramphenicol; CLA = clarithromycin; D = doxycycline; E = erythromycin; PCN = penicillin; RI = rifampin; SM = streptomycin; TMP-SMX = trimethoprim-sulfamethoxazole.

ZOONOTIC BACTERIAL PNEUMONIAS

Pasteurella multocida

Pasteurella multocida is a common commensal of the oral cavity of most felines and many dogs and a frequent respiratory pathogen in animals and birds. The respiratory tract is the second most common site of *Pasteurella* infection following skin and supporting tissues. Respiratory infections are probably underreported and include tracheobronchitis, pneumonia, lung abscess, and empyema. Elderly people with structural lung diseases such as emphysema, bronchiectasis, or malignancy are at higher risk for pulmonary infection. Immunocompromised patients, including those with AIDS, may be prone to spontaneous infection without close contact or traumatic dog or cat exposures.

Bacteriology

P. multocida is a small gram-negative bipolar-staining coccobacillary organism that resembles *Haemophilus* spp. and

may form pairs and chains. Rapid growth on blood agar and inhibition by MacConkey medium separate this microorganism from other common components of the respiratory flora, including *Haemophilus* spp. Numerous virulence factors in *P. multocida* have been identified. These include the capsule in serogroups A and B (which interferes with phagocytosis), a toxin in strains causing atrophic rhinitis in pigs, lipopolysaccharide endotoxin, several iron acquisition proteins (e.g., TonB, ExbD, and ExbB), and the putative filamentous hemagglutinins PfhB1 and PfhB2.

Ecology and Epidemiology

In cats and other felines, the organism resides periodontally in the anterior regions of the mouth. Isolates from dogs are characteristically from the posterior pharynx. Many birds and domestic and wild animals worldwide harbor this organism as a commensal in oral or gastrointestinal areas. *P. multocida* is occasionally found in the secretions of persons with chronic lung disease, especially those with bronchiectasis and domestic animal contacts. Human-to-human transmission has been documented from mother to newborn infant, resulting in neonatal pneumonia. The organism can survive in soil and water for more than 3 weeks and in animal carcasses for approximately 2 months. In about half the cases of respiratory disease, no clue to airborne spread exists, but there are usually cats in the local environment.

Pathogenesis and Pathophysiology

Pathogenic strains have a polysaccharide capsule that inhibits phagocytosis, and they contain endotoxin in the cell envelope. Exotoxins and other pathogenicity-promoting factors have not been specifically identified (see Bacteriology). Almost all patients who develop respiratory infections have underlying chronic pulmonary disease. Aspiration probably initiates active infection. Necrosis and lung abscess, empyema, septicemia, and transbronchial spread to other lung segments have been described.

Clinical and Radiologic Features

The clinical features of *P. multocida* respiratory disease include worsening of the patient's baseline pulmonary function—especially when high fever, tenacious secretions, and pleural effusions develop. Radiologic changes include lobar, multilobar, or diffuse patchy infiltrates, usually sparing the upper lobes, superimposed on underlying chronic lung disease (Fig. 137-1). Effusions, including empyema, have been noted in approximately 20 percent of cases. Bacteremia has been reported in up to 55 percent of patients with pneumonia and endocarditis has occasionally complicated bloodstream invasion.

Diagnostic Features

Diagnosis depends on isolation of the organism from sputum, pleural fluid, or blood. Usually the pathogen can be identified with the routine methods of the diagnostic laboratory. The bipolar gram-negative staining bacilli resemble *Brucella*

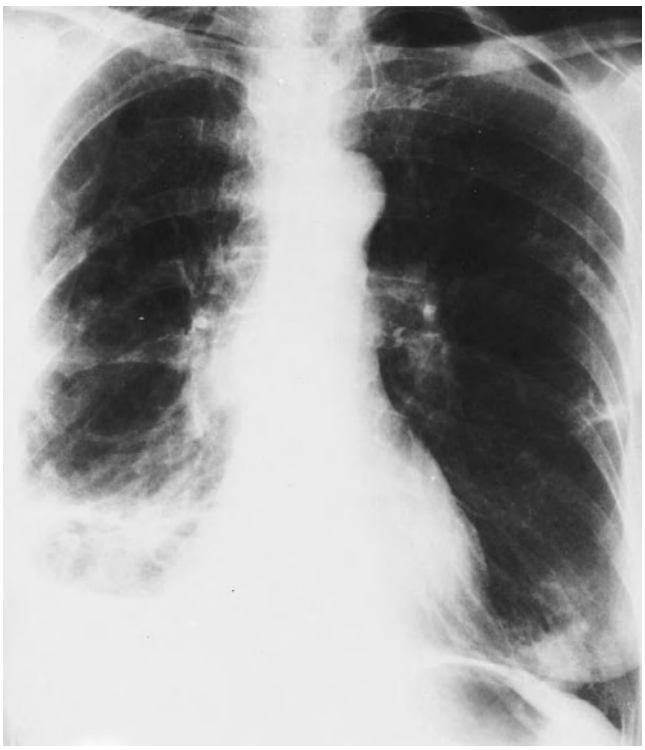

Figure 137-1 Bilateral pneumonia due to *Pasteurella multocida* in a 69-year-old woman suffering from chronic obstructive pulmonary disease and a prior right lower lobectomy for carcinoma. Infiltrates disappeared with penicillin therapy.

spp., *Yersinia pestis, Francisella tularensis, Burkholderia* (formerly *Pseudomonas*) *pseudomallei,* and *Haemophilus* spp., but the clinical history of exposure to cats and/or dogs and bacteriologic characteristics can rapidly clarify the identification.

Treatment

Most strains are exquisitely susceptible to penicillin or ampicillin. The third-generation cephalosporins, cefotaxime and ceftriaxone, are as active as penicillin and more potent than earlier-generation relatives. Oral preparations of cephalosporins and penicillins are not recommended for treating pneumonias caused by *P. multocida* due to reduced bioavailability. The newer fluoroquinolones, including moxifloxacin, trovafloxacin, levofloxacin, and gatifloxacin, are very active in vitro against *P. multocida* and other *Pasteurella* spp., although there is limited published experience in humans. Tetracycline and chloramphenicol are effective alternatives when a history of allergic reactions precludes use of a β-lactam agent. (See Table 137-2 for further details.)

Yersinia pestis

This organism left an indelible mark on humanity long before its late–nineteenth-century isolation and characterization. The cause of three major pandemics from the sixth through the nineteenth centuries, pulmonary disease in a few victims led to aerosol spread to countless others, resulting in acute primary pneumonia and the "black death" of

epidemic plague. During the period from 1932 through the end of World War II (1945) the Japanese biological warfare program included the use of aerosol drops of *Y. pestis* as well as infected flea disseminations in occupied China and at the infamous experimental Unit 731. The effectiveness of the flea drops remains in question to this day but the aerosol disposal definitely led to clinical pneumonic plague. A contemporary global scare emanated from India's Maharashtra state in 1994, with reports of suspected pneumonic and bubonic plague. No exported cases were documented during rigorous quarantine and airplane surveillance measures, and no travelers to India became ill with a plague syndrome. In the United States, fewer than 20 cases of plague are reported yearly, of which one in five has lung involvement. Early recognition and specific therapy, combined with isolation procedures and appropriately directed prophylaxis of contacts, should help maintain the record of no human-to-human transmission in the United States since the 1920s. When plague is diagnosed outside an endemic area, bioterrorism should be considered. When *Yersinia* pneumonia occurred in a couple that recently became ill in New York City, the event was originally investigated as a potential bioterrorism event until their travel from an endemic area of plague was discovered. Although the bacteria are difficult to process, handle, and disperse in an aerosol form, person-to-person airborne spread is very efficient and laboratory accidents have occurred.

Bacteriology

Y. pestis is a bipolar-staining, gram-negative bacillus closely related to *Escherichia coli* and other *Enterobacteriaceae*. It grows well on blood or MacConkey agar and is identified definitively with differential biochemical tests, agglutination reactions, and direct fluorescent antibody staining. Concerns for laboratory safety have lead to routine of Biosafety Laboratory level 2 (BSL-2) procedures as well as better communication between clinicians and microbiology laboratory personnel.

Ecology and Epidemiology

In the United States, *Y. pestis* is endemic in rock squirrels, prairie dogs, rabbits, rats, and other small ground animals primarily in the Southwest. Spread among animals occurs via several species of rodent fleas, especially *Xenopsylla cheopis*. Domestic animals that wander outdoors, like cats, can become infected by direct contact with sick rodents or via rodent flea bites. In addition, cats and dogs can inadvertently carry fleas into the home. Occasionally rodent die-offs, called epizootics, occur, and many dead animals can be found with viable organisms in carcasses and in the soil surrounding ground dwellings.

In the United States, spread to humans occurs when an infected flea feeds on a susceptible person. Living or working in proximity to local enzootic "hot spots" places certain groups (such as Native Americans, geologists, hikers, veterinarians, and pet owners) at risk. Bubonic and cutaneous plague are usually acquired on exposed areas by contact with infected fleas, but aerosols from ill animals or carcasses can lead to primary pneumonia, pharyngitis, or conjunctivitis. Several cases of cat-to-human aerosol spread have been associated with respiratory infection or submandibular abscesses in pets. A great concern of physicians caring for patients with respiratory infection is the potential for rapid airborne dissemination, especially during coughing and face-to-face contacts.

Pathogenesis and Pathophysiology

After the organism gains access to human tissues at 37°C, massive multiplication occurs. The polysaccharide capsule imparts virulence properties that include resisting phagocytosis and persistence of bacteria within nonsensitized monocytes. Virulence factors include a potent endotoxin and V and W antigens of the cell envelope, which influence intracellular survival. Recent work with a mouse model has demonstrated a biphasic illness with an initial anti-inflammatory phase that rapidly progresses to a highly pro-inflammatory state by 48 hours and death by 3 days. Microarray analysis demonstrates a change in the expression of about 10 percent of the bacterium's genes after it infects a host.

Bacteremic spread usually follows initial multiplication in regional nodes (buboes) or at the local fleabite site (chancriforme lesion). Secondary pneumonia involving the well-perfused basilar segments can follow. When a person with plague pneumonia coughs, there may be aerosol spread to persons nearby, resulting in primary pneumonia and rapidly developing adult respiratory distress syndrome (ARDS).

Clinical and Radiologic Features

Clinical presentations include subclinical cases (positive serology without evidence of disease); a chancriform skin lesion (pestis minor abortive bubonic plague); pharyngitis; bubonic plague; septicemic plague; pneumonic plague; and meningitis. The clinical presentation of pneumonia depends on the mechanism of spread. In contemporary experience in the United States, cases have all been secondary to bubonic plague, primary septicemia without an overt skin lesion, or inhalation of droplets from an infected pet cat. The onset of respiratory disease follows after days to a week of a febrile illness, and is ushered in by the gradual onset of cough, dyspnea, and increasing toxicity. Pink to hemorrhagic frothy sputum, pleurisy, and increasing respiratory distress are additional symptoms. The unique feature in most cases of pneumonia is the epidemiological association with classic bubonic plague; i.e., in a person in or from an endemic area or who has had contact with a pet cat ill with respiratory symptoms or a facial abscess. From histories of primary inhalation pneumonia described previously, exposure to an index case may be followed by the rapid development of a fulminating respiratory illness, with dyspnea, cyanosis, and thin, watery sputum that rapidly becomes hemorrhagic. The clinical picture is not unlike that of overwhelming pneumococcal pneumonia, with marked toxicity and mental torpor associated with progressive cyanosis.

The radiologic features of secondary pneumonia include basal segment nodular to hazy airspace infiltrates, hilar and mediastinal node hypertrophy, and occasionally pleural effusions. In primary pneumonia, infiltrates may be minimal during the first 24 hours, followed by progressive airspace disease resembling ARDS or pulmonary edema.

Diagnosis and Differential Diagnosis

The presence of characteristic bipolar-staining gram-negative bacilli in sputum suggests the diagnosis when epidemiological clues are present. Cultures of blood, sputum, and lymph node aspirates often yield positive results. Direct fluorescent antibody staining can provide immediate etiologic confirmation. A passive hemagglutination test can be performed as a confirmatory study on acute and convalescent sera at selected reference laboratories such as CDC. Other acute respiratory infections caused by microorganisms that appear as gram-negative bacilli with bipolar staining must be considered, including *Francisella tularensis* and *P. multocida.* Rapid assays for diagnosis of plague are under active development, especially given the interest in its potential as a bioterror agent.

Treatment and Prevention

The combination of streptomycin and tetracycline has been the treatment of choice for serious plague infections. Gentamicin can be substituted for streptomycin if intravenous therapy is necessary or streptomycin is not available. Doxycycline and fluoroquinolones such as ciprofloxacin may also be effective in treating pneumonia; chloramphenicol is another option. (See Table 137-2 for further details.) Multi–drug resistant plague has been reported and clinicians should be aware of local trends as well as the potential for terrorist-instigated modifications in antibiotic susceptibility.

Persons suspected of having plague pneumonia should be rapidly isolated, and strict contact, respiratory, and conjunctival precautions instituted. Anyone exposed face to face with a coughing patient, including health care workers, should be given preventive tetracycline or ciprofloxacin (trimethoprim-sulfamethoxazole is used in pregnant women and children). Isolation procedures are continued until productive cough is no longer present or sputum cultures are negative for *Y. pestis.*

A vaccine is available for laboratory workers and others with frequent exposure to the microorganisms or hyperendemic areas, although it does not appear to protect against pneumonic plague. Careful surveillance of ground rodent populations, posting warnings in endemic regions, watching for die-offs that indicate epizootic spread, and spraying for local flea control may also be effective preventive measures along with public education.

Francisella tularensis

Tularemia is a common animal disease in the United States as well as many other regions of the temperate globe. The causative agent, *F. tularensis,* is ubiquitous, distributed among many species of wild and domestic animals and birds. Bloodsucking arthropods, especially ticks and deerflies, serve an important role in transmission to humans. As with plague, the major clinical manifestations include skin lesions and swollen or draining regional lymph nodes. Pulmonary impairment occurs secondary to bacteremia or as primary inhalation pneumonia. Approximately 150 human cases are reported in the United States yearly, but this is probably an underestimate. In the summer of 2000, an outbreak of pneumonic tularemia occurred on Martha's Vineyard, Massachusetts, and 11 of 15 patients were diagnosed as primary pneumonic tularemia; lawn mowing and brush cutting were found to be risk factors for infection. In addition to primary inhalation pneumonia, pulmonary invasion is seen following bacteremia in 10 to 15 percent of ulceroglandular cases and in more than 50 percent of patients with the typhoidal syndrome. An epidemic of tularemic pharyngitis from ingestion of contaminated well water and food occurred in war-torn Western Kosovo primarily among young children originally suspected of having group A Streptococcal pharyngitis. No secondary pneumonias were reported.

Bacteriology

F. tularensis is a fragile-appearing gram-negative coccobacillary organism that is quite fastidious and grows poorly on artificial media unless fortified with serum and cysteine (or sulfhydryl compounds). The potential for laboratory-acquired inhalation or ingestion-associated disease is great. Most routine laboratories will not attempt to culture the organism, leaving this to special reference centers. Identification is on the basis of morphologic and biochemical determinants, but direct fluorescent staining or agglutination reactions with specific antisera are also useful.

Ecology and Epidemiology

The organism is associated with more than 100 species of wild and domestic animals and birds, including aquatic mammals, but most clinical cases arise from contact with rabbits, squirrels, or arthropods. Of great concern is the recent fad for exotic pets; and tularemia in prairie dogs has led to spread in holding pens and to human transmission. In cold weather the organism can persist in water and mud environments for weeks to months. Bloodsucking arthropods, especially ticks and deerflies, act as reservoirs capable of harboring the pathogen for long periods and are responsible for dissemination among wildlife species as well as infecting people. Domestic cats represent a potentially increasing problem.

Less than half of human cases are acquired from contact with infected animals during hunting, trapping, and other outdoor pursuits, especially during colder months. In southern areas, or in the summer season in northern latitudes, gardening and lawn mowing without animal contact are becoming important methods of dissemination. Bloodsucking arthropods, constitute a significant and increasing mode of spread, especially in warmer seasons. Ingestion of contaminated food or water, animal bites, conjunctival contact, and

aerosol dissemination are also important mechanisms for acquiring the pathogen. In recent years, cases secondary to arthropods have been more frequent than those associated with direct animal contact, although domestic cat bites and airborne spread appear to be increasing. Human-to-human transmission is rare, in contrast to the significant theoretical potential for spread of pneumonic plague. If *F. tularensis* were to be used by terrorists, aerosol release would most likely be the mode of spread, with respiratory as well as other locations (skin, conjunctival, pharynx) occurring in the exposed population. Those criminally processing this organism would be at great risk for laboratory infection.

Pathogenesis and Pathophysiology

F. tularensis contains a number of protein and polysaccharide antigens in the cell envelope as well as an endotoxin component that is similar to endotoxins of other gram-negative microorganisms. Very little is known about other mechanisms of pathogenesis. The organism is capable of remaining viable in reticuloendothelial cells of nonimmune subjects and in macrophages that have not been activated by recent exposure to intracellular pathogens. As few as 10 to 50 organisms can initiate disease following cutaneous penetration or by inhalation, but a significant number are required when the challenge is through ingestion of contaminated water or foods. Local growth usually is followed by regional node suppuration and occasionally bacteremic dissemination to many organs, including the lungs. Rhabdomyolysis may accompany bacteremia and pneumonia. Ingestion may result in pharyngeal infection, involvement of the gastrointestinal tract, or subclinical disease followed by a typhoidal syndrome. Primary pneumonia follows inhalation of organisms, resulting in numerous areas of inflammation, necrosis, a tendency to granuloma formation, hilar and mediastinal adenopathy, and pleural inflammation and effusion.

Clinical and Radiologic Features

In appropriate epidemiological settings, respiratory disease is heralded by the onset of a nonproductive cough, usually in a febrile patient ill with the ulceroglandular form of tularemia. In the absence of a local chancriform lesion or tender swollen lymph node (bubo), the disease may be dominated by constitutional symptoms, with high fever, severe headache, prominent myalgias, and shaking chills (typhoidal tularemia). Pneumonia following an inhalation exposure results in cough, dyspnea, and occasionally pleurisy. Respiratory disease can be subtle, and the diagnosis may be apparent only if a chest radiograph is done. Pleural effusions may be serosanguineous or frankly bloody, an uncommon finding with other pulmonary infections except anthrax.

Radiologic changes include evidence of parenchymal and pleural disease, which is often out of proportion to the findings on examination. Diffuse areas of bronchopneumonia occur, with hilar node enlargement and occasionally mediastinal widening, similar to radiologic appearance of anthrax. Unilateral or bilateral pleural effusions are often noted

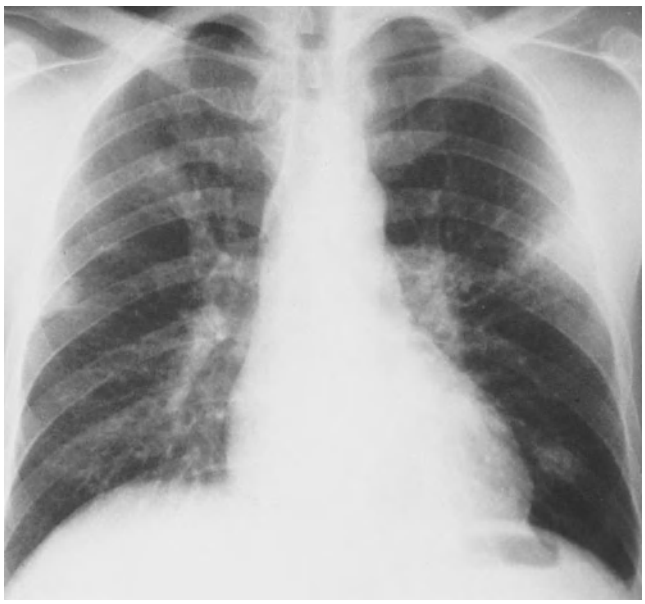

Figure 137-2 Patchy nodular and bronchopneumonia, hilar adenopathy, and left pleural effusion due to *Francisella tularensis* in a 38-year-old veterinarian exposed to a cat dying with a respiratory infection. All the findings resolved with tetracycline therapy.

(Fig. 137-2). Central oval infiltrates, described as characteristic in early reports, are seldom observed today. Lobar airspace disease, a miliary pattern, and lung abscess are unusual additional patterns that have been described.

Diagnosis and Differential Diagnosis

Any febrile patient with animal, arthropod, or landscaping exposure in an endemic region, especially presenting with a chancriforme skin lesion and/or a tender lymph node should be evaluated for tularemia. Cough, when present, is usually nonproductive, and blood cultures are seldom positive. Characteristic organisms are rarely seen in pleural fluid or aspirates of suppurating nodes. Direct fluorescent antibody staining of exudates can confirm the diagnosis, but this method is not widely available. Serologic testing remains the method of choice for confirming a diagnosis. ELISA and microagglutination methods may be more sensitive than tube agglutination testing. A single convalescent titer of 1:160 or greater is considered highly suspect for active disease, but a fourfold rise in titer between acute and convalescent (1 to 5 weeks) sera is more reliable, since antibodies can persist for many years after infection. Polymerase chain reaction and other molecular biological techniques have successfully diagnosed tularemia in human specimens. An elevated blood level of creatine phosphokinase may be a clue that tularemia-induced rhabdomyolysis is a response to the acute infection, especially in highly endemic areas. Skin testing can be helpful in diagnosis, but the antigen is currently not commercially available.

Perplexing diseases that are also associated with outdoor and animal exposures, such as psittacosis and Q fever, may be confused with tularemia. Legionnaires' disease and mycoplasmal pneumonia can present with similar clinical courses, without diagnostic sputum. Plague, tuberculosis,

and systemic fungal infections produce a spectrum of acute to chronic respiratory manifestations that can mimic pulmonary tularemia.

Treatment and Prevention

Streptomycin was the first effective antibiotic for treating all forms of tularemia, and it remains the agent of choice. Gentamicin appears to be equally potent and has the advantage of a broader spectrum of activity if one is initiating treatment when the etiologic diagnosis is less secure. Additionally, it can be given intravenously, and blood levels can be monitored. *Tobramycin, however, appears to be unreliable and therefore should not be substituted for other aminoglycosides.* Recent experience confirms that results of therapy are optimal when an aminoglycoside is chosen early in the clinical illness. Tetracycline/doxycycline, ciprofloxacin, and chloramphenicol may be useful alternatives when an aminoglycoside is contraindicated. Relapse rates are higher with the bacteriostatic tetracycline/doxycycline and chloramphenicol, especially when given for less than 2 weeks. β-Lactam antibiotics are not effective. The prognosis is excellent with appropriate antimicrobial therapy. (See Table 137-2 for further details.)

Cautious practices are required when one is dealing with animals and their carcasses. Using gloves, cooking wild animal meat thoroughly, and wearing protective clothing and repellants to avoid bloodsucking arthropods are helpful measures. An attenuated live vaccine strain (LVS) has been available for over 50 years, although it is not fully licensed (in part due to a lack of knowledge regarding the basis of attenuation), and does not offer a high level of protection against respiratory challenge. With the increase in concern in bioterrorism, numerous groups are working to develop an improved vaccine.

Rhodococcus equi

Rhodococcus equi, formerly known as *Corynebacterium equi,* was first isolated in 1923 by Magnussen when it was identified as a cause of suppurative pneumonia in foals. It was later shown to be a frequent pathogen in horses, cattle, and swine. First described as a pathogen in humans in 1967, the majority of recognized cases in recent years have been in immunocompromised patients, especially individuals receiving corticosteroids, those infected with the human immunodeficiency virus, or those who have undergone solid organ transplantation.

Bacteriology and Pathogenesis

Rhodococcus is a pleomorphic gram-positive bacillus in the order *Actinomycetales.* It grows well aerobically on most media, at 37°C, as mucoid pale-pink or salmon-pink colonies that are usually observed by 48 hours of incubation. *R. equi* has a high cell wall mycolic acid content and is acid-fast, similar to *Nocardia* spp. and *Mycobacteriaceae.* Some strains ferment glucose, but the majority will not ferment carbohydrates. Most produce catalase and hydrogen sulfide. β-Lactamase is present in some strains.

R. equi is a facultative intracellular pathogen that survives within macrophages. Prevention of phagosome–lysosome fusion is a major pathogenic mechanism. Humoral response as well as cell-mediated immunity has been demonstrated in animals, but it is unclear how much of a protective role each plays. In equine models, administration of antibody decreases the severity of pneumonia in foals challenged with aerosol inoculation. Protection was not seen in a murine model when the animals were infected intravenously. In murine models, depletion of both CD4+ and CD8+ T cells impairs the ability to clear the infection, although the CD8+ cells appear to play a more significant role.

Epidemiology

The majority of reported cases occurring in humans without HIV infection have been in patients who had significant contact either with livestock or soil and environments that were heavily contaminated with livestock waste. In contrast, HIV-related *Rhodococcus* disease appears to occur in patients who do not have any particular environmental exposure history—implying a wider distribution of the organism. There is no known geographic endemicity.

Pathogenesis and Pathophysiology

R. equi usually is inhaled, although soft-tissue infections after cutaneous inoculation can occur. As an intracellular pathogen it causes disease primarily in patients with impaired cell-mediated immunity and defects in phagocytic processing of organisms. Diseased tissues usually show a necrotizing

Table 137-3

Diagnosing *Rhodococcus equi* Respiratory Infection

History of exposure to horses, cattle, or their environment
Immunocompromised host: malignancy, steroids, HIV
Cavitary or nodular infiltrates on radiograph
Gram-positive pleomorphic bacilli
Modified acid fast
Pale-pink or salmon-pink mucoid colonies
Grows rapidly, aerobically on most media
Differential diagnosis includes, *Nocardia* species, mycobacteria

granulomatous reaction, with histiocytes and macrophages frequently containing bacteria. In contrast to lesions associated with *Mycobacterium tuberculosis* and systemic fungi, there is also a prominent infiltration of neutrophils in the affected areas, a characteristic shared with other *Actinomyces* spp.

Clinical and Radiologic Features

Patients frequently complain of indolent symptoms, such as fever, nonproductive cough, and mild dyspnea. Typically there is a paucity of findings on physical examination of the chest, but signs of consolidation and pleural friction rubs may be present. Patients with HIV infection generally present in a manner similar to patients without HIV infection, although pleuritic chest pain may be more common. In HIV-infected patients, *R. equi* disease tends to occur after there has been significant deterioration in their immune systems, with CD4 lymphocyte counts less than 200 cells/mm^3. It is often found associated with other pulmonary infections. Extrapulmonary dissemination occurs in HIV-infected and non–HIV-infected patients, but there appears to be a significantly greater rate of recovery of the organism from blood cultures in HIV patients. The central nervous system is a recognized site of metastatic infection, as it is for *Nocardia* spp.

The most common radiographic abnormalities are lobar infiltrates, which usually evolve into nodular or cavitating lesions within weeks or months. There is no predilection for involvement of any particular lobe. Pleural effusions are common, occurring in up to 40 percent of HIV patients with pulmonary *R. equi* infection. Significant hilar adenopathy is unusual.

Diagnosis and Differential Diagnosis

R. equi can readily be cultured from sputum, bronchial lavage, pleural fluid, or other infected tissue and often from blood. Since the organisms stain as pleomorphic gram-positive bacilli, grow readily on most media, and are usually catalase producers, they can be mistaken for "diphtheroid" or "Coryneform" contaminants unless further testing is done. Therefore it is important for the clinician to alert the microbiology laboratory staff if the possibility of *R. equi* is entertained. *R. equi* is slightly acid fast with modified Ziehl-Neelsen stain.

Rhodococci share many microbiologic features with *Mycobacteria* and *Nocardia,* and this may account for similarities in the subacute to chronic evolution of the disease. The high mycolic acid content of their cell walls results in their acid-fast staining properties and may also play a role in their similar clinical and pathological manifestations. *Nocardia* spp., *M. tuberculosis,* and nontuberculous mycobacteria also should be considered when acid-fast organisms are found in clinical specimens, especially in immunocompromised patients with nodular or cavitary pneumonia (Table 137-3).

Other considerations in the differential diagnosis of nodular or cavitating pulmonary lesions include malignancy, fungal infection such as *Cryptococcus neoformans,* anaerobic lung abscess, and necrotizing pneumonia caused by facultative bacteria such as *Staphylococcus aureus* or *Klebsiella pneumoniae.*

Treatment

Antibiotic therapy alone is usually adequate to achieve cure. As with mycobacterial infections, multidrug regimens and therapy of 2 to 6 months' duration may be needed, especially in immunocompromised patients. Erythromycin, rifampin, ciprofloxacin, and other fluoroquinolones, chloramphenicol, sulfonamides, and aminoglycosides are active against most isolates. *R. equi* is an intracellular pathogen that is capable of multiplying in phagocytes. Therefore, antibiotics that are capable of achieving high intracellular levels, such as rifampin or fluoroquinolones, but especially erythromycin and the expanded-spectrum macrolides, clarithromycin or azithromycin, are preferred. (See Table 137-2 for further details.) In some patients, surgical resection of a nodular or cavitating lesion may be necessary to achieve cure.

ENVIRONMENTAL AND ANIMAL PRODUCT PNEUMONIAS

This section focuses on four diseases that are spread to humans predominantly from contact with contaminated soil, water, foods, or animal structural elements. Epidemiological and ecologic characteristics are essential to understanding how humans become infected. The diagnosis usually depends on a careful history. Once alerted, the clinician can request studies that may reveal the cause of these often-obscure diseases. It should be apparent that this distinction—an association with environmental contamination and animal products—is somewhat arbitrary. For example, anthrax bacilli can spread directly from animals to humans, and *R. equi* contamination of soil could place it in this group rather than in the group infected via direct animal exposure.

Anthrax

Inhalation anthrax was a common enough disease in the nineteenth and early twentieth centuries to be referred to variously as Bradford's disease, after the English town, and woolsorter's disease for the epidemiological association with the sheep industry. Fortunately, inhalation anthrax has become a rare spontaneously acquired disease. An epidemic of anthrax following an accidental release at a bioweapons facility occurred in the area of Sverdlovsk (now renamed Ekaterinburg) in the former USSR in 1979, resulting in 42 deaths due to inhalational anthrax. In 2001 there were 18 confirmed cases of inhalational and cutaneous anthrax and an additional four suspected cases of cutaneous anthrax in the United States; of the 22 cases, $\geq$20 were definitively related to mail contaminated with the same strain of *B. anthracis.* The potential zoonotic as well as terrorist-induced exposure of susceptible

persons to *Bacillus anthracis* spores argues for including this devastating, often lethal, disease in this chapter.

Bacteriology

B. anthracis is a large (red blood cell diameter), square-ended bacillus that stains gram-positive and has a tendency to form chains. Growth on sheep blood agar results in dull, sticky, irregularly shaped colonies within 24 hours. The organism possesses a polyglutamic acid capsule, produces a complex potent trivalent exotoxin, and, under adverse conditions, forms highly refractile, centrally located spores that are very resistant to temperature and moisture extremes.

Ecology and Epidemiology

Anthrax is primarily a disease of herbivores. The resistant spores are present after animals dying of the disease contaminate the soil. Anthrax "hot spots" are found, for example, in milder regions in the United States, such as Oklahoma, Texas, and California. The optimal conditions for germination of spores and multiplication of bacilli include alkaline soils containing adequate calcium and low areas that are wet for prolonged periods, termed *incubator areas,* with thick vegetation that produces heat with decay. Periods of extreme drought after a rainy season favor spore formation. Animals grazing in these areas can inhale or ingest spores or pick them up on their fur. The cycle is completed when an animal develops the disease and dies, returning organisms to the soil, where they eventually sporulate under adverse conditions.

Inhalation anthrax rarely occurs from contact with live infected animals, and there is no human-to-human transmission. The animal hide industry, exposure to bone meal fertilizer, and use of imported goat skins and raw wool in home crafts can lead to inhalation of spores and clinical disease in susceptible persons. The unvaccinated individual who occasionally enters a goat wool or hide processing plant to do needed repairs is at greatest risk for an inhalation or contact exposure.

Pathogenesis and Pathophysiology

Inhalation results in activation of bronchial clearing mechanisms and entrapment of spores in hilar and mediastinal nodes, where reversion to vegetative bacilli can occur. The polyglutamic acid capsule is antiphagocytic, and the extracellular microorganisms produce a protein exotoxin that leads acutely to profound local edema, accompanied by hemorrhage in the mediastinal and hilar areas, with compromise of airflow. Recent studies have clarified the mechanisms involved in the pathogenesis of this tripartite toxin, which consists of a protective antigen, an edema factor and a lethal factor. The protective antigen fragment of the toxin serves as the binding domain, essential for cell penetration by both the edema factor and the lethal portions of the molecule. Edema factor is a potent adenylate cyclase; activation within mammalian cells stimulates production of cAMP, and the resultant flux of sodium, potassium, and water leads to abundant local edema. When this process takes place in hilar and mediastinal nodes and surrounding tissues, profound airway obstruction ensues, with pooling of secretions and if the patient survives, secondary bacterial pneumonia. Lethal factor is a potent protease that acts primarily in macrophages, activating intracellular mitogen-activated protein kinase kinase (MAPKK), leading to production of proinflammatory cytokines and reactive oxygen intermediates. The pathogen rarely invades lung tissue, as death from asphyxia occurs rapidly, usually associated with pleural effusions (secondary to lymphatic obstruction) and hemorrhagic septicemic lesions in many organs, including the central nervous system. Typical thoracic pathological findings include hemorrhagic mediastinitis with hemorrhagic mediastinal lymphadenopathy. In a large inoculum exposure, as occurred in the 2001 "mail room" criminal outbreak, patients developed disease within the pulmonary parenchyma and the gastrointestinal tract.

Clinical and Radiologic Features

In spontaneously occurring disease, the onset is insidious, usually resembling a nonspecific febrile influenza–like illness. Malaise and muscle aches, mild headache, coryza, pharyngitis, and chest pains have been described as early symptoms. Cough, if present, is usually mild and nonproductive, and fever is low grade. At this stage, it is hardly possible for the physician to entertain a presumptive or possible diagnosis of anthrax unless a history of industrial or craft-related exposure to imported animal hair or hides or to animal products such as bone meal is obtained. A number of the nonspecific features described above may be relevant. Watery nasal discharge can be indicative of nasal or paranasal sinus involvement. Cough may represent hilar and mediastinal node swelling, and careful auscultation may reveal prolonged expiration wheezes or evidence of a pleural effusion. Chest pain may be the first clue that hilar and mediastinal inflammation is present.

Within hours to a few days, the mild complaints abruptly worsen and acute airway obstructive features dominate the clinical picture. Any activity precipitates severe dyspnea, stridor, and wheezing. Impairment of the nervous system (hemorrhagic meningitis) and hypoxemia result in decreasing levels of consciousness. Edema of the pharynx, neck, and anterior chest may develop. Chest pain, fever, and cyanosis are progressive changes. Worsening airway obstruction can lead to intercostal space retraction, and pleural effusions are noted on examination. Death usually occurs within hours to a day once acute respiratory symptoms are present.

Inhalation anthrax is primarily a mediastinitis, and the radiologic features mostly reflect the pathological findings. Widening of the mediastinum or prominence of hilar nodes is the earliest radiologic finding, sometimes accompanied by pleural effusion. In advanced cases, the mediastinal shadow is greater than 9 cm in width and sharply demarcated from surrounding lung tissue because of absence of airspace consolidation. There may be perihilar and peribronchial streaking associated with edema and hemorrhage. In the 2001 exposure to a significant spore burden some patients had a biphasic

illness with early upper respiratory and gastrointestinal symptoms, followed by respiratory distress days later.

Diagnostic Features

A physician alerted to the possibility of inhalation anthrax has few laboratory studies to rely on. Nasal secretions and sputum rarely reveal the characteristic bulky gram-positive bacilli. Half of the reported cases of inhalation disease are complicated by meningitis, and hemorrhagic cerebrospinal fluid with observable organisms can confirm the diagnosis. There are no available data on examination of buffy-coat smears, and therapy must be instituted before blood culture results become available. Microscopic examination of pleural fluid may reveal the characteristic organisms. The most commonly recognized form of anthrax, the cutaneous chancriform necrotic lesion, does not usually accompany inhalation cases in naturally occurring disease.

Differential diagnosis includes other causes of acute mediastinitis, such as esophageal perforation. Tuberculosis, histoplasmosis, and tularemia rarely produce acute respiratory failure as part of hilar and mediastinal node involvement. Hantavirus pulmonary syndrome is associated with similar central pulmonary changes, including edema, but should be separable from anthrax by epidemiological data, the presence of air space disease and absence of mediastinal involvement. Lymphoproliferative diseases, like nodular sclerosing Hodgkin's disease, evolve at a slower pace. Chest wall and neck edema, associated with acute breathing difficulties, can accompany diphtheria or *Streptococcus pyogenes* pneumonia, with bilateral pleural effusions an early manifestation of streptococcal pneumonia. Acute epiglottitis, caused by *Haemophilus influenzae,* was an occasional disease of preteen children prior to vaccine development and can mimic some of the manifestations of inhalation anthrax. A large epiglottis seen by direct examination or a lateral radiograph or computed tomographic scan of the neck in a person not immunized for *H. influenzae* type B can alert the physician to this possibility.

Treatment and Prophylaxis

Combination therapy is currently recommended based upon the "mail room" epidemic of 2001. Regimens with ciprofloxacin or doxycycline, plus clindamycin (to block toxin production) and rifampin (which penetrate CSF and intracellular sites) are favored. Monotherapy with penicillin should not be used in inhalation disease since the strain in the 2001 "mail room" outbreak, as well as multiple historical strains, produce an inducible β-lactamase. There is concern that the bacteria could be weaponized and highly antibiotic resistant. Treatment is recommended for 60 days to avoid activation of persistent spore forms. (See Table 137-2 for specific recommendations.) Corticosteroids should be considered for treatment of significant mediastinal edema or meningitis and early thoracentesis appears to be beneficial. Unfortunately, the airway obstructive manifestations are not reversible once acute respiratory manifestations have progressed. Assisted ventilation and use of diuretics are all reasonable support efforts, but they are generally not successful due to the continued effects of tissue bound toxin. Historically, before 2001 mortality in inhalation anthrax approached 100 percent of cases, compared with the rarity of death from cutaneous disease. In the 2001 experience mortality was 45 percent (5 of 13 respiratory cases) and knowledge gained from that experience may prove helpful in future cases.

In the animal hide industry, vaccination is the cornerstone of preventing anthrax. Plant workers and others in contact with potentially infected animal products should be immunized with the currently available vaccine. Numerous new vaccines are under development, many based upon the protective antigen segment of the toxin. Animal products imported from endemic regions of the world (e.g., Africa, the Near East and the Indian subcontinent) are steam sterilized, and there is modern ventilation in the workplace. At-risk subjects, then, are people who service these plants, such as ventilation specialists and other transients who are unlikely to be vaccinated. Bone meal is another vehicle for carrying inert spores. It should be treated by heat sterilization before packaging for use by commercial and home gardeners. Those who import yarn from endemic areas are at special risk unless the rules for commercial hide sterilization are also imposed on casual animal hair imports. A recent case of inhalation anthrax in a drum maker who carried goatskins into the United States emphasizes the need for appropriate education and importation controls.

Brucella spp.

In the approximately 200 cases of brucellosis that are reported yearly in the United States, acute respiratory manifestations are usually insignificant. Lung involvement is an uncommon presentation of brucellosis. Brucellosis is often a prolonged and perplexing illness however, and in chronic cases pleurisy, hilar adenopathy, and nodular lung lesions can be encountered. Exposure to animals or animal foods, or residence in an endemic region is usually present when sought.

Bacteriology

Brucellae are small coccobacillary, gram-negative, nonmotile, aerobic, nonencapsulated organisms that are now classified with the alpha-Proteobacteria, closely related to *Rochalimaea* and *Bartonella* spp. Carbon dioxide is essential for growth of *Brucella abortus,* and all four pathogenic species require growth medium enriched with vitamins and serum. With the aid of a battery of biochemical, metabolic, and immunologic criteria, *Brucellae* pathogenic for humans can be classified as *B. abortus, B. suis, B. melitensis,* and *B. canis.* In general, the species designation corresponds to the animal usually colonized or diseased.

Ecology and Epidemiology

Brucellae spp. are distributed worldwide. Infection and disease occur primarily in domestic animals in geographic

regions such as the Mediterranean littoral (*B. melitensis*), worldwide except areas of Europe and Japan (*B. abortus*), the midwestern United States (*B. suis*), and North and Latin America (*B. canis*). Spread from one region to another occurs with live animal movements or when infected animal products are commercially or privately shipped. Rigorous control measures such as herd inspections and vaccination procedures have dramatically reduced enzootic and epizootic disease in many regions.

The epidemiology of brucellosis is intimately related to the association of susceptible persons with infected animals and animal products. Abattoir workers (especially slaughterers) and others in the meat-processing industry, farmers, dairy workers, veterinarians, and bacteriology laboratory technicians account for most cases in the United States, with a general preponderance of male patients. An eightfold increase in incidence in California, Texas, and the other borderlands between the United States and Mexico has been noted when compared with the national rate. Also at risk are military personnel and travelers to endemic regions who eat local foods and people who consume imported goat cheese, sausage, and other unpasteurized edibles from endemic areas. The organisms are usually acquired by ingestion, through skin abrasions and lacerations, or via conjunctival inoculation. Evidence indicates that aerosol spread can be a route in abattoir workers. No human-to-human transmission has been reported.

Pathogenesis and Pathophysiology

Organisms invade the local reticuloendothelial system and lymph nodes, followed by bacteremic spread to many organs during the following weeks. There is increasing evidence that the aerosol route may be especially efficient as a portal of entry. The distribution of nodular lesions in lung tissue is primarily in basal segments, however, which argues for bacteremia rather than primarily an inhalation mechanism for most cases of pulmonary disease.

A race between bacterial growth and the development of cell-mediated immunity ensues, primarily in lymph nodes and the reticuloendothelial system. As with tuberculosis, the end result is often containment within granulomas that eventually become fibrotic or calcify. Species and strain differences account for the wide variety of tissue reactions encountered, including granulomas, necrosis, and abscess formation. Smooth variants appear to be more virulent than rough forms, and many contain polysaccharide polymers in their superficial envelope that, like true capsules, inhibit phagocytosis and intracellular destruction. Lipopolysaccharide endotoxin is present in the cell envelope and may be responsible for profound metabolic and cardiovascular effects initially and as organisms are killed during therapy. *Brucella* spp. are able to survive within nonstimulated macrophages and can destroy these cells while escaping host antibodies and physician-directed antibiotic therapy. As macrophages become activated, they develop the capacity to rapidly kill phagocytosed *Brucella* organisms. The development of host immunity appears to be primarily cell mediated, just as in *M. tuberculosis* disease. Impairment of cell-mediated immunity can lead to reactivation of latent *Brucella* or greater susceptibility and severity of a primary infection.

Clinical and Radiologic Features

The clinical expression of brucellosis is dominated by nonspecific flu-like constitutional manifestations, including fever and headache. Nonproductive cough has been described in 10 to 33 percent of cases, but other indicators of respiratory involvement are rarely or poorly described. In one review of 59 cases, dyspnea and pleuritic chest pain were present in 10 percent of the patients. Hoarseness, bronchitis, and, rarely, mucopurulent, purulent, or hemorrhagic sputum have been noted. Only one patient with verified pulmonary invasion was described in a review of 160 acute and subacute cases of brucellosis reported in 1974. In a recent review of 37 patients with *Brucella* respiratory disease, 32 percent had typical lobar pneumonia, 41 percent had an interstitial pattern on chest x-ray, and a honeycomb pattern was seen in 11 percent, with pleural effusion(s) in the same number. Extrapulmonary disease was found in 76 percent of patients, with 22 percent having greater than one extrapulmonary complication. Direct comparison of the clinical manifestations of *B. abortus* with *B. melitensis* reveal that the latter presents more acutely as fevers of unknown origin with statistically significant higher rates of abdominal tenderness, hepatomegaly, splenomegaly, thrombocytopenia, pancytopenia, and hepatic dysfunction. Unilateral hilar adenopathy and granulomas occur occasionally.

Diagnostic Features

During the acute illness or in relapse, blood cultures may be positive—especially if kept for a minimum of 14 days. In the presence of an infiltrate or pleural effusion, material for gram stain and culture should be obtained, even though the yield from these studies is small. A positive culture may be obtained from a lymph node or pulmonary granuloma biopsy. In most cases the diagnosis is made from a fourfold rise or a single value of at least 1:160 in the agglutination titer. Occasionally "inhibitory" or blocking antibodies are present in the serum, and a positive titer is discovered only if the serum is further diluted (so-called prozone phenomenon). The standard tube agglutination test utilizes *B. abortus* as the antigen and will detect antibodies to *B. suis* and *B. melitensis,* but not to *B. canis.* Diagnostic confusion and numerous alternative diagnoses are the rule in cases of brucellosis. Acute disease can be confused with miliary tuberculosis, endocarditis, tularemia, disseminated histoplasmosis, and lymphoproliferative diseases. Subacute and chronic cases must be differentiated from subacute bacterial endocarditis, tuberculosis, histoplasmosis, other systemic fungal infections and sarcoidosis.

Treatment and Prevention

The combination of doxycycline with rifampin for 4 to 6 weeks is one of the most effective and easiest oral antibiotic

regimens. Doxycycline combined with streptomycin or gentamicin, or trimethoprim-sulfamethoxazole are also effective alternative regimens. Fluoroquinolones are active in vitro, but they are associated with an unacceptably high relapse rate as monotherapy (see Table 137-2).

Preventive measures for cattle have been successful utilizing vaccination programs and destruction of diseased animals. Quarantine and inspection activities have diminished the risk of importing infected animals into the United States, and this reduction of disease in cattle has resulted in a decline in human cases. The program for *B. suis* eradication has been ineffective, and human cases of *B. suis* now outnumber those due to *B. abortus.* The efficacy of human vaccines is marginal. Education programs for workers in abattoirs have been aimed at protecting and preventing skin lacerations and eye contamination.

Burkholderia (pseudomonas) pseudomallei

Melioidosis is primarily an acute necrotizing or, in the later stage, a chronic fibronodular cavitating process indistinguishable from tuberculosis. It is a disease of tropical latitudes, and most cases have been seen in Southeast Asia, associated with rural settings. A number of cases were noted in survivors of the 2004 tsunami. Infection with *Burkholderia pseudomallei* has been seen in the United States almost exclusively after a latent period of months to years in military personnel returning from regions such as Vietnam and in refugees from endemic areas, although case reports from areas such as the Caribbean, Africa, the Middle East, and Brazil have also been reported.

Bacteriology

The organism is an aerobic, bipolar-staining gram-negative bacillus that is motile and lacks a well-defined capsule. Similar to the pseudomonads, *B. pseudomallei* grows well on minimal as well as enriched media, including blood and MacConkey agar, used in most routine laboratories. Typical colonies are distinctive in appearance, rough or wrinkled, and cream to orange in color; they may resemble a flower with folds radiating from a central core. Colonies have the typical musty, fruity odor of the pseudomonads but lack pyocyanin and other pigments that characteristically color the surrounding medium. Identification rests on a battery of biochemical reactions, and confirmation is based on agglutination or fluorescent antibody studies.

Ecology and Epidemiology

B. pseudomallei occupies an environmental niche that includes moist soils, rice paddies, and other stagnant water in tropical and subtropical regions, approximately subtended by latitude 20 degrees north to 20 degrees south. Evidence of subclinical and clinical disease occurs in wild and domestic animal populations, as well as in humans living permanently or transiently in rural endemic areas, especially in southeast Asia and northeast Australia. As many as 10 to 30 percent of native populations have evidence of prior infection based on serologic data. Approximately 1 to 2 percent of healthy American military personnel who served in Southeast Asia have antibodies, and almost 9 percent of soldiers wounded in Vietnam have titers for *B. pseudomallei.* A significant number of the approximately 3 million U.S. soldiers who fought in the region constitute a reservoir of latent disease that, like tuberculosis, can become active even decades later, far removed from an endemic area. Refugees from Southeast Asia represent another important group of carriers.

Transmission is mainly by direct contact with contaminated soil or water through minor abrasions or major wounds. Ingestion and inhalation are probably less frequent modes of spread, but common source outbreaks occur in animals and humans. Animal-to-human disease is very rare, with only three cases reported from Australia, and human-to-human spread has also been exceptional, associated with breastfeeding, urinary catheter contamination, or between siblings with cystic fibrosis. In endemic regions, lack of previous exposure and debilitating circumstances, including malnutrition and uncontrolled diabetes, may increase susceptibility to infection and disease. In a survey of 524 patients with melioidosis in northeast Thailand, coinfection with HIV was detected in only 8 of 524 adults (1.5 percent); clinical presentation and acute outcome were similar in HIV-positive and -negative patients. Melioidosis in a diabetic renal transplant patient has been reported from India, although it is not clear if solid organ transplant alters the risk for melioidosis.

Pathogenesis and Pathophysiology

The presence of potent endotoxin and the absence of an antiphagocytic capsule have been noted. Acute infections are associated with necrotic lesions containing polymorphonuclear neutrophils (PMNs) in lung and other tissues. Chronic infections, especially in the respiratory tract, resemble tuberculosis with granuloma formation, Langhans or foreign-body giant cells, central caseating necrosis, and occasionally a PMN response in the necrotic area. Activation of latent infection after a period of months to even decades occurs. This "awakening" can be in the wake of influenza and other acute infections, acute stress (trauma, thermal burn, surgery, etc.), and immunosuppressing illnesses or therapies, but spontaneous activation also occurs. The location of dormant microorganisms and the specific molecular events that stimulate recurrent disease are unknown but remain an area of active investigation.

An antecedent local infection in an area of broken skin can be followed by acute septicemia in nonimmune subjects. Initial pulmonary lesions occur predominantly in the better-vascularized basal segments consistent with bacteremic spread to the lungs. Eventually other areas of the lungs and other tissues are affected. Subacute and chronic disease may result from a subclinical primary focus, often localized in an apical segment, resembling tuberculosis in location

and propensity for granuloma formation and cavitation. Subpleural invasion can result in empyema or sympathetic sterile effusions.

Clinical and Radiologic Features

Primary melioidosis occurs within a few days to 3 weeks of exposure, usually in persons present in or recently from an endemic area. Military personnel with outdoor injuries constitute a potential group for delayed active disease. Although the acute phase of melioidosis is the most common manifestation in endemic areas, it is very rarely seen in the United States. The portal of entry may be present as a small necrotic skin lesion in an area of known trauma, with accompanying cellulitis or lymphangitis. In addition to marked toxicity and high fevers, the respiratory complaints include cough, dyspnea, pleuritic pain, and purulent sputum. Bibasilar rales may be heard, but objective physical findings are often minimal in the face of severe toxicity.

Milder types of subacute and chronic pneumonia are often seen. In addition to fever, productive cough, and pleuritic pain, many patients experience marked weight loss and a clinical picture resembling tuberculosis or fungal disease. Secondary skin manifestations are rarely seen unless bacteremia ensues. Physical changes are often subtle but can include localized rales, a pleural friction rub, signs of an effusion, and manifestations of disease localized to soft tissues, lymph nodes, bones, or joints.

Radiologic findings reflect the stage of disease present. In acute fulminant infections, airspace disease can be absent or miliary to larger nodular densities seen in basal segments. In subacute and chronic cases, fibronodular or cavitary apical lesions are found, similar to reactivation tuberculosis.

Diagnostic Features

Melioidosis should be seriously entertained in any febrile patient with a history of residence in a major endemic region such as Southeast Asia or northeast Australia. If sputum is available, the gram-negative bipolar staining bacilli may be seen, and the organisms can be readily cultured and identified in the routine laboratory. Blood and urine cultures are frequently positive in acute cases. In more indolent infections, biopsy may be necessary. Molecular biology techniques such as polymerase chain reaction are being developed for diagnostic use. Serologic studies can be helpful in active and recrudescent disease, especially in patients residing in nonendemic areas. A specific IgM immunofluorescence test is often positive in recent infections and recrudescent disease. Complement fixation and indirect hemagglutination tests are available and require testing of paired sera over several weeks to confirm active disease.

Differential Diagnosis

In patients from Southeast Asia, acute fulminating infections with pneumonia may be due to traditional bacteria and viruses, but may also be caused by infection with *Y. pestis* (plague) and *F. tularensis* (tularemia) (see above). Chronic forms of melioidosis resemble tuberculosis and fungal infections such as histoplasmosis and blastomycosis. Occupation, travel, and history of respiratory illness should help to clarify the cause. Confirmation usually requires appropriate cultures and sometimes biopsy or serologic data.

Treatment and Prevention

Recommendations for therapy of acute septicemic melioidosis must be couched in cautious statements. During the Vietnam War, mortality greater than 50 percent occurred, even with use of three-drug regimens in massive doses. In subacute and chronic pneumonias and recrudescent disease cure rates approach 100 percent. Treatment must be prolonged and surgical intervention for drainage or removal of cavitary lesions is sometimes necessary to prevent relapse.

Imipenem/meropenem or the third-generation cephalosporin ceftazidime in high doses are considered first-line therapy. Once a good clinical response is seen, oral therapy may be initiated. Combination therapy for several months results in a lower relapse rate; regimens are varied and include such agents as doxycycline, chloramphenicol, trimethoprim-sulfamethoxazole, azithromycin, and ciprofloxacin. Amoxicillin-clavulanic acid may be used in children. A study of clinical isolates from Thailand demonstrated an 81 percent trimethoprim-sulfamethoxazole resistance rate among 200 isolates tested. With the exception of kanamycin, other aminoglycosides are ineffective.

No prophylactic antimicrobial studies are available, nor has a vaccine been developed. People traveling, living, or working in endemic regions should be advised of this soil- and water-dwelling organism. Care and caution should be used to avoid traumatic injuries, and any wounds contaminated with soil or stagnant water should be assiduously cleaned.

Yersinia enterocolitica

Most infections caused by *Y. enterocolitica* are gastrointestinal, resulting in a self-limited gastroenteritis or appendicitis-mimicking mesenteric and terminal ileum adenitis. Septicemias and involvement of the lungs and other viscera are extremely rare, usually occurring in persons suffering from cirrhosis or who are immunocompromised.

Yersinieae belong to the family *Enterobacteriaceae. Y. enterocolitica* is a gram-negative, facultative bacillus that resembles many other enteric microbes. Identification procedures include the ability to grow and exhibit motility at room temperature plus a battery of biochemical and serologic tests. Although occasionally overlooked in stool because it is confused with many other members of the fecal flora, the organism is readily identified in blood and respiratory specimens. Most strains are non-lactose or slow lactose fermenters, causing confusion with *Y. pestis, Salmonella, Shigella,* and several other members of the Enterobacteriaceae family. Cold enrichment techniques and highly selective media, extensively used to identify this organism in feces, are not

necessary in other specimens. Various serotypes and biotypes, with distribution in geographically distinct regions, have been described.

Y. enterocolitica has been isolated from a variety of rodents and other wild species, and from cats, dogs, and other domestic animals. There is little evidence for direct transmission or for spread among people other than by the fecal–oral route. Most cases occur singly, but epidemics involving families and hundreds of people have been described. Disease is initiated by ingestion of contaminated milk or other food. Most cases of respiratory disease have been reported in immunocompromised hosts, alcoholics, and cirrhotics.

Direct aspiration may be the mechanism for initiation of pulmonary disease, following an initial pharyngitis focus. Bacteremia can complicate pharyngeal disease, although the most likely mechanism entails ulceration of Peyer's patches in the terminal ileum, mesenteric adenitis, and portal bacteremia. Systemic shunting to the lungs can follow, especially in cirrhotics, the group that most frequently develops septicemia. Strains virulent for animals and causing human disease have plasmid-mediated V and W envelope antigens, temperature-sensitive calcium dependency (as with *Y. pestis*), a factor that enhances cell penetration, and endotoxin. An enterotoxin, similar to stable toxin of *E. coli,* is also produced, but an extra-gastrointestinal role has not been established for this protein. The development of immune complex manifestations such as erythema nodosum and nonsuppurative polyarthritis may contribute to pathogenicity and same as clues to etiology.

In the past three decades, approximately 15 cases of pneumonia have been described in the literature. Respiratory infections occur in association with an acute febrile septicemic illness or as a primary respiratory process, with cough, dyspnea, and signs of consolidation. The history is usually vague for gastrointestinal symptoms, animal exposure, or unusual food intake. There may be signs of increasing hepatic failure with ascites or peritonitis in patients with underlying cirrhosis. Radiologic findings include nodular basilar densities consistent with septicemic spread, dependent segment infiltrates suggesting an aspiration mechanism, occasionally with cavitation, and fluffy widespread densities consistent with septic emboli. Immunocompromised patients may be especially prone to severe necrotizing pulmonary infections.

The diagnosis often depends on information obtained from blood or sputum cultures. Enteric gram-negative bacilli can be seen in sputum. Pharyngeal cultures should be done if signs of local inflammation are present. Suppurating nodes and peritoneal or joint fluids are other sources of material that may contribute to the diagnosis.

Cases of respiratory infection have responded well to a variety of antibiotics, including ampicillin or second-generation cephalosporins. Third-generation cephalosporins, chloramphenicol, aminoglycosides, fluoroquinolones and trimethoprim-sulfamethoxazole may also be effective. Treatment should be based on antibiotic susceptibility testing. Underlying diseases influence the outcome, but when pneumonia is the major problem, prognosis is excellent. Treatment is usually continued for a total of 3 to 6 weeks. (See Table 137-2 for further details.)

Preventive measures include avoiding rodent or domestic animal contamination of food and water supplies. Opportunities for susceptible individuals to come in contact with this zoonotic microorganism may be increasing as well, as healthy and immunocompromised people turn to oraganically grown foods and mountain streams for improved health but with potential contamination with pathogens from animal droppings.

PNEUMONIAS CAUSED BY OBLIGATE HUMAN COMMENSALS

Most bacterial pneumonias are caused by encapsulated obligate human commensals that are easy to isolate, such as *Streptococcus pneumoniae.* Among the less common causes of pneumonia due to human commensals, *Neisseria meningitidis* (the meningococcus) and *Moraxella* (formerly *Branhamella*) *catarrhalis* stand out as pathogens or opportunists that may escape bacteriologic identification and therefore present problems in diagnosis and therapy.

Neisseria meningitides (Fig. 137-3)

During the influenza viral pandemic of 1918–1919, *N. meningitidis* was an important respiratory pathogen. Afterward, few references to the meningococcus appeared in the medical literature on bacterial pneumonias, as reports of meningococcal disease focused on its role in causing meningitis and septicemia. With the advent of improved bacteriologic techniques, an increasing number of cases of *N. meningitidis* pneumonia have been diagnosed.

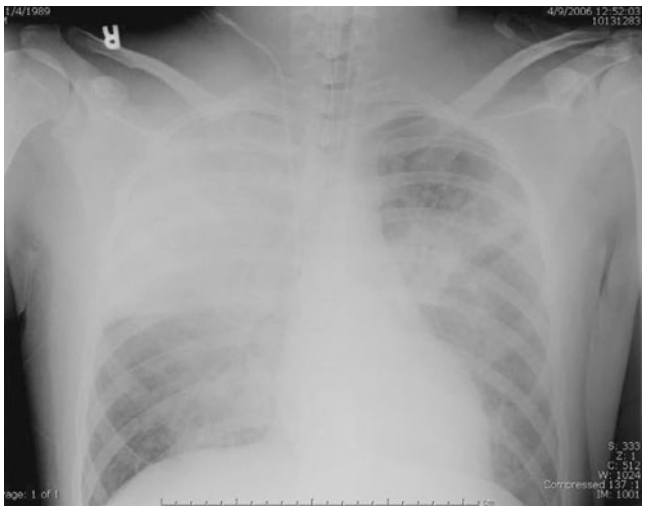

Figure 137-3 Patchy bronchopneumonia, predominantly in the right upper lobe, in 16-year-old boy with *Neisseria meningitidis* pneumonia and bacteremia. *(Image courtesy of Holly Rawizza, MD.)*

Bacteriology and Immunology

Neisseria are oxygen-requiring, gram-negative cocci recognized by their characteristic pairing as kidney-shaped diplococci. They are fastidious, succumbing rapidly to the external environment and extremes of temperature or humidity. Although *Neisseria* can grow on blood agar, optimal conditions include enriched media, such as chocolate agar, and incubation in an atmosphere of 6 percent CO_2 at 35 to 37°C with 50 percent humidity. *N. meningitidis* is distinguishable from other *Neisseria* spp. that are residents of the oral-respiratory region by sugar fermentation reactions and serologic identification, which depends on specific capsular polysaccharides. Isolation and identification of *N. meningitidis* in sputum are facilitated by the use of a selective medium, such as modified Thayer-Martin agar (MTM), which contains antibiotics that suppress more rapidly growing microorganisms. The presence of *Neisseria*-like diplococci in a Gram's stain of sputum should provide the impetus to culture the specimen on MTM media as well as on less selective media, such as blood and chocolate agar (Fig. 137-4).

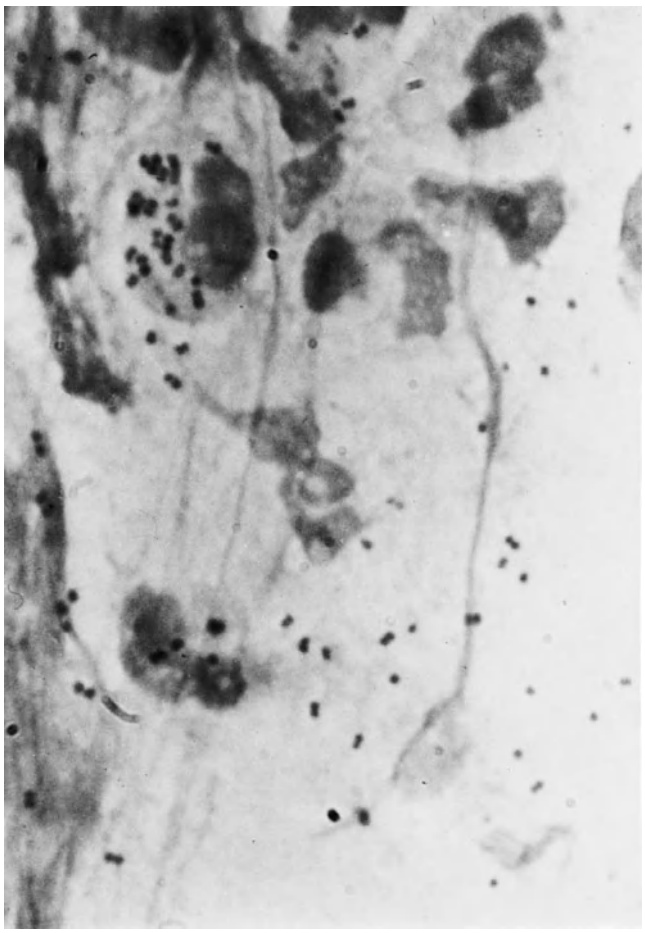

Figure 137-4 Gram stain of expectorated sputum from a patient with proven *Moraxella* pneumonia. In this black-and-white photomicrograph, the distinguishing features include the presence of morphologic kidney-shaped diplococci (gram-negative) associated with polymorphonuclear neutrophils. This appearance suggests *Neisseria* or *Moraxella* infection.

N. meningitidis is a typical gram-negative organism containing a potent lipopolysaccharide endotoxin in the outer membrane layer of the cell envelope. Exterior to this layer is a polysaccharide capsule, by which *N. meningitidis* can be separated into at least 13 chemically defined serogroups. Groups A, B, C, Y, and W-135 are currently the most important clinically. The less frequently observed serogroup Y meningococci accounted for 44 percent of isolates in one series of 58 cases of meningococcal pneumonia.

Immunity to meningococci is complex. Bactericidal antibody, present in the newborn, disappears by approximately 6 months of age. During childhood and adolescence, overt disease and subclinical encounters with various capsular strains of *N. meningitidis,* as well as with nonpathogenic *Neisseria* spp., lead to stimulation of bacterial antibody. Immune lysis of organisms is facilitated by the terminal complement components C5 through C8. Congenital absence of one or more of these terminal complement components has been associated with recurrent acute meningococcal disease. Antibodies to certain outer membrane proteins and a variety of envelope antigens of *E. coli* and other commensals cross-react with antigens from *N. meningitides* and may import nonspecific immunity. Persons lacking bactericidal or capsular antibody to a specific serogroup are susceptible to colonization and disease caused by that serogroup. With increasing age, acquisition of protective antibodies is associated with less likelihood of developing clinical disease.

Epidemiology

Nasopharyngeal carriage of various serogroups of meningococci occurs in approximately 5 to 25 percent of subjects. Convening and crowding large numbers of young persons from widely separated geographic areas, as occurs in the military, in boarding schools and universities can result in significant and rapid spread of an individual serogroup from a few asymptomatic carriers to many susceptible individuals. A case of meningococcal disease in a family is often associated with an increased prevalence of meningococcal isolation from relatives with symptoms of upper respiratory infection. In the prior experience military carrier rates could rapidly approach 100 percent, followed by many cases of meningitis if prophylactic antibiotics and other prevention measures were not undertaken. Today, protective immunization has markedly altered this concern.

Respiratory disease due to meningococci was recognized early in the twentieth century, especially during the influenza pandemic of 1918–1919. In the mid-1970s, outbreaks of serogroup Y meningococcal pneumonia occurred in military installations. Over the past 25 years, isolated respiratory disease, primarily due to serogroups Y and W-135, has been detected in civilian populations and nosocomially in persons in contact with an index case. Spread is probably by aerosol droplets during close contact, since drying rapidly kills meningococci. People ill with influenza or adenoviral respiratory infections appear to be more susceptible—as occurs with other respiratory pathogens, including *S. pneumoniae* and *Staphylococcus aureus.*

Pathogenesis and Pathophysiology

Initiation of infection begins when an encapsulated strain colonizes the nasopharynx of a person lacking immunity to that serogroup. Attachment to mucosal cells is facilitated by filamentous pili and outer membrane proteins such as Opa and Opc, and perhaps by the action of bacterial IgA1 protease. The capsule helps evade complement fixation and subsequent phagocytosis. Lipopolysaccharide (endotoxin) stimulates release of inflammatory mediators, including TNF-α, IL-1β, IL-6, and IL-8, and thus has a crucial role in the pathogenesis of meningococcal septic shock. The lower respiratory tract is invaded by aspiration or inhalation of droplet particles. A preceding viral infection can stimulate excessive airway secretions, damage surface epithelial structures, and interfere with clearance of microorganisms. Meningitis, petechial eruptions diffuse intravascular coagulation, and ARDS seldom accompany pneumonia, supporting a postulated aspiration mechanism. Bronchopneumonia, lobar extension, and necrosis and abscess formation are seen. Modern pathological correlations are lacking, since there are no animal models of meningococcal pneumonia and histopathological material is essentially nonexistent due to favorable outcome of this primary respiratory infection.

Clinical and Radiologic Features

The clinical presentation of meningococcal pneumonia resembles that of pneumococcal infection (Table 137-4). Productive cough, pleuritic pain, chills, and fever are associated with physical changes of rales with consolidation. Unlike pneumococcal disease, pleural rubs, and hemoptysis are unusual. Suspicion of meningococcal disease is enhanced if many cases of bacterial pneumonia erupt in closed populations such as military or school groups or among hospital patients. The spectrum of respiratory disease includes pharyngitis, common in outbreaks, and purulent tracheobronchitis. Invasive meningococcal respiratory disease carries a mortality rate of 5 to 10 percent.

Table 137-4

Diagnosing Meningococcal Pneumonia

Antecedent viral respiratory infection
Multiple community or hospital respiratory cases
Purulent or frothy sputum
Kidney-shaped gram-negative diplococci on smear (Fig. 137-4)
Culture sputum on modified Thayer-Martin medium
Incubation with CO_2 enrichment

Radiologic features are nonspecific and include patchy bronchopneumonia and lobar airspace infiltrates. The air space disease is usually located in the right lung (56 percent, the majority with findings in the right lower lobe) or left lung (24 percent). Bilateral involvement occurs in 20 percent of cases and an effusion is noted in about 13 percent of cases. Occasionally, as occurs in pneumococcal pneumonia the radiologic appearance resembles diffuse pulmonary edema or an antecedent viral infection.

Diagnostic Features

Diagnosis depends on isolation of predominantly *N. meningitidis* from a carefully collected sputum specimen that has characteristic gram-negative diplococci and PMNs on the stained smear (Fig. 137-4). Attention to these criteria is essential, since pathogenic and nonpathogenic *Neisseria* and *Moraxella* spp. are part of the normal respiratory flora. Invasive procedures such as bronchoscopy are not necessary if valid sputum is available, and the gram stain appearance prompts culturing the specimen on MTM media. Alternative methods of identification include the capsular swelling technique (to rule out pneumococcal infection), latex bead coagglutination, and fluorescent antibody staining. Recent purification of all of the major group-specific capsular polysaccharides should lead to expansion of these rapid diagnostic methods. Blood cultures were positive in a significant number of recent cases.

Differential Diagnosis

Respiratory infections due to other causes, especially when there are clusters of cases, must be considered in the differential diagnosis. Viral agents such as influenza A or B or adenoviruses can cause acute respiratory infections affecting a number of people, especially under institutional or crowded circumstances. A viral diagnosis is usually confirmed by the epidemiological and clinical circumstances; a nonspecific sputum examination, positive laboratory test, absent or interstitial infiltrates radiologically, and paired serologic titers.

Mycoplasmal pneumonia is frequently biphasic, with upper respiratory inflammation and headache prominent early symptoms and, occasionally, bullous tympanitis producing severe ear pain. The sputum is often purulent, with a mixture of PMNs and mononuclear cells, but no dominant microorganism is observed with gram stain. Diagnosis is usually confirmed by a cold agglutinin titer of 1:32 or greater, a rising titer of complement-fixing antibody, or PCR of sputum. When many cases occur in a family or closed community, they usually erupt sporadically over many weeks rather than days to a week. Other atypical pneumonias to consider include *Legionellae*, *Chlamydia psittaci,* and *Chlamydia pneumoniae.*

Acute bacterial pneumonias often follow in the wake of viral respiratory infections. *S. pneumonia* and *S. aureus* infections are differentiated with microscopic examination, culture of sputum, and the results of blood cultures. In hospitals, especially among immunocompromised patients or patients

attached to respirators, a variety of gram-negative microorganisms can produce pneumonia. *H. influenzae* infections can usually be suspected, but *M. catarrhalis* resembles *Neisseria* morphologically and may not respond to penicillin treatment (see below).

Acute respiratory failure secondary to small-vessel endothelial cell damage or ARDS can complicate Rocky Mountain spotted fever. A petechial or morbilliform eruption is usually seen on the extremities. With meningococcal respiratory disease, a rash is rarely seen and the seasonal appearance and tick exposure help to separate the two diseases. Any large cluster of respiratory cases must also raise the specter of a terrorist-mediated pathogenic exposure.

Treatment and Prevention

Although penicillin was first-line therapy until 1991, the majority of patients since then have received cephalosporins. Low-dose penicillin is effective for most cases of susceptible *N. meningitides* pneumonia, although those complicated by cavitation or empyema should be treated with a minimum of 6 million units daily. Patients allergic to β-lactams can be given chloramphenicol. In contrast to meningitis or meningococcemia, respiratory infections appear to respond uniformly well to treatment.

Meningococci spread via droplet aerosols, so isolation of suspected cases is essential, especially during the first 24 hours of treatment. Chemoprophylaxis and immunoprophylaxis are effective in epidemics of meningitis, but no data are available for respiratory disease protection. Penicillin, the drug of choice for treating active disease, does not reliably eradicate the carrier state or protect intimately exposed contacts. Rifampin is an effective prophylactic agent probably due to its transport into oral and respiratory tract secretions in high concentrations. Fluoroquinolones such as ciprofloxacin are also effective. Minocycline diffuses into upper respiratory secretions in high concentrations and is a useful alternative to rifampin.

Immunoprophylaxis has been safe and effective when given systematically to large at-risk groups in military installations, schools, day care centers, or defined communities. Both a polysaccharide as well as a protein conjugate quadrivalent vaccine is commercially available, containing serogroups A, C, Y, and W-135. Vaccines for serogroup B are in development or available presently in other countries. There are no contemporary data for efficacy of the vaccine for respiratory infections. Immunizing persons with influenza viral vaccines should eliminate some cases of secondary bacterial infections, including those caused by *N. meningitidis.*

Moraxella (Branhamella) catarrhalis

Formerly considered a nonpathogenic respiratory commensal, *M. catarrhalis* has aroused renewed interest as an opportunist and primary pathogen. Resemblance to *Neisseria* on gram stain encourages its inclusion in this section.

Bacteriology

Moraxella are gram-negative cocci that pair as kidney-shaped diplococci; hence, they cannot be distinguished morphologically from *Neisseria.* The organisms grow well on nonselective media such as sheep blood agar and enriched chocolate agar, especially when supplemented with added CO_2. Growth of *Moraxella* is variable on selective media such as MTM—in contrast to pathogenic *Neisseria,* which thrive on that medium. They fail to utilize a variety of sugars. These and other biochemical tests help to distinguish them from *Neisseria.* Many clinical isolates produce β-lactamase and, therefore, are resistant to penicillin.

Epidemiology

A member of the resident microflora of the nasopharynx and pharynx, *M. catarrhalis* can also colonize the mucosa of the genital tract. Among persons with chronic lung disease it can be found, along with other bacteria, in respiratory secretions. The extent of colonization of mucous surfaces in healthy or diseased subjects is not known. There is no evidence for human-to-human transmission, although infections in the hospital occur and are probably related to nosocomial spread and the selective pressures from the various antimicrobials used. In normal children and adults, otitis media, sinusitis, and laryngotracheobronchitis probably result from direct invasion from colonized mucosal surfaces. This view is supported by the finding of mixed infections with other commensals, such as *H. influenzae* and mouth anaerobes.

Pathogenesis and Pathophysiology

In contrast to pathogenic *Neisseria, Moraxella* lack antiphagocytic capsules and IgA proteases. They have outer-envelope lipopolysaccharide endotoxin, characteristic of all gram-negative microbes. Neutrophils as well as humoral immunity have been reported as significant factors in natural host defense of this member of the normal flora.

The mechanism of initiation of respiratory disease appears to be primarily related to underlying obstruction and chronic inflammation. Aspiration of nasopharyngeal secretions, stimulated by an acute viral upper respiratory infection, is the most common predisposing pathophysiological event. Contributing immunocompromising conditions—such as steroid therapy, malignancy, hypogammaglobulinemia, and neutropenia—are present in a large number of patients. Paranasal sinus and ear infections occur predominantly in children, probably because of compromised drainage ducts in anatomically crowded areas. Rarely, *Moraxella* produce primary invasive diseases outside the respiratory tract, including meningitis, endocarditis, septic arthritis, and, in immunocompromised patients, septicemia.

Clinical and Radiologic Features

Most people who develop respiratory infections are adults with chronic lung disease associated with smoking, industrial exposures, or bronchitis and bronchiectasis. Purulent bronchitis or bronchopneumonia can follow an intercurrent viral

infection. Respiratory distress, if present, may be related to the acute process, with bronchospasm and fever superimposed on the chronic underlying disease. Signs of consolidation or pleural fluid may be present, along with persistent obstructive changes. Evidence has been accumulating that normal adults may develop primary laryngitis and children a nonproductive cough as other manifestations of clinical respiratory tract disease, but primary pneumonia is very uncommon at any age in subjects with healthy lungs.

The underlying chronic lung disease influences the radiologic appearance. No acute changes may be observed, but usually increased markings are seen superimposed on the findings of obstructive lung disease and fibrosis. Patchy consolidation is often noted. Lobar infiltrates, cavitation, and pleural effusions are distinctly unusual findings and suggest mixed infections or other complications of the underlying disease.

Diagnostic Features

The unique challenge in cases of *M. catarrhalis* respiratory infections is identifying this organism when gram-negative kidney-shaped diplococci associated with a PMN exudate are noted and suggest a meningococcal infection (Fig. 137-4). Diagnosis depends on careful examination of an adequate expectorated sputum sample and culturing the specimen on nonselective blood and enriched chocolate agar as well as on selective MTM. The use of several media assures that these fastidious organisms will be identified in a crowd of other commensals. Serologic methods are not available to help verify a pathogenic role for *Moraxella* in mixed infections (Table 137-5).

Differential Diagnosis

The major diagnostic confusion results from the presence in sputum of *Neisseria* spp. and other potential pathogens, such as *S. pneumoniae* and *H. influenzae*. In patients with chronic lung disease, mixed infections make it impossible to ascribe pathogenicity to a single organism. Coccobacillary microorganisms, or gram-negative bacilli that demonstrate bipolar staining (e.g., *Brucella, Pasteurella*) can also be confused with *M. catarrhalis*.

Table 137-5

Diagnosing *Moraxella* Pneumonia

Underlying chronic lung disease
History of aspiration
Kidney-shaped gram-negative diplococci on smear (Fig. 137-4)
Growth on sheep blood and enriched chocolate media
No growth on selective modified Thayer-Martin medium

Treatment

As the pathogenic role for *M. catarrhalis* was recognized, it became apparent that many isolates produced β-lactamase and were resistant to penicillin and ampicillin. Numerous treatment failures with penicillins have been described, often with dramatic improvement once an alternative antibiotic was administered. Therefore, therapy should be initiated with either a second- or third-generation cephalosporin such as cefuroxime, or trimethoprim-sulfamethoxazole. Alternatives include the expanded-spectrum macrolides clarithromycin or azithromycin, amoxicillin–clavulanic acid (Augmentin), or a fluoroquinolone until β-lactamase activity is determined. In vitro testing may appear to deceptively demonstrate susceptibility to penicillin, amoxicillin-clavulanic acid, or first-generation cephalosporins if β-lactamase production is at a low level. Clinical failures may occur if these drugs are used. Supportive therapy with adequate hydration, bronchodilators, and other measures directed at treating the underlying respiratory disease is essential for a successful outcome.

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138
CHAPTER

The Epidemiology, Prevention, and Control of Tuberculosis in the United States

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Tuberculosis is a contagious disease that progresses from a systemic infection caused by bacteria of the *Mycobacterium tuberculosis* complex. Most commonly, *M. tuberculosis* is spread from person to person by airborne transmission of droplet nuclei. Despite a relatively low transmission rate compared with other contagious diseases and the existence of effective chemotherapy for five decades, tuberculosis remains a major global public health problem. Approximately one-third of the world's population is infected with tuberculosis. Each year there are 9 million new cases and nearly 2 million deaths attributed to this disease. The continuing spread of human immunodeficiency virus (HIV) infection has dramatically altered tuberculosis epidemiology and is driving much of the global tuberculosis epidemic, especially in Africa and Asia. Another million deaths attributed to HIV infection also have tuberculosis as a contributing cause of death. The current epidemic has been accompanied by a rise in multidrug-resistant (MDR, defined as resistance to at least isoniazid and rifampin) tuberculosis cases, highlighting the impact of failure to adequately invest in public health programs in many parts of the globe.

In the 1980s, factors, such as HIV infection, MDR, increased immigration from high-incidence countries, and deteriorating public health infrastructure eroded the capacity

to control tuberculosis in the United States. The resulting unprecedented resurgence (for an industrialized country) translated into an estimated excess of 52,000 cases by 1992. Several outbreaks of drug-resistant tuberculosis greatly strained the existing public health infrastructure, created public concern, and brought significant attention to the national tuberculosis epidemic. A decision to address the problem and a comprehensive strengthening of tuberculosis control activities, including the allocation of large, sustained increases in tuberculosis-specific federal, state, and local support, are credited with reversing the rising tuberculosis case rate. Since that time, the United States has experienced a steady decline in tuberculosis cases and case rates, although the decline in cases has primarily been limited to U.S.-born persons. The number of cases among foreign-born persons has not changed substantially. As a consequence, recent surveillance data suggest the overall number of tuberculosis cases in the United States may be starting to plateau. Thus, without control of the global tuberculosis epidemic, the goal of elimination of tuberculosis in the United States is likely to remain elusive in the near future.

SURVEILLANCE

Tuberculosis is a reportable disease in all U.S. health jurisdictions. The Centers for Disease Control and Prevention (CDC) began collecting aggregate tuberculosis surveillance data from reporting jurisdictions in 1953. Since 1985, individual tuberculosis case reports, without identifying information, have been relayed to CDC from 60 reporting areas (50 states, the District of Columbia, New York City, Puerto Rico, and seven other jurisdictions in the Pacific and Caribbean). For surveillance purposes, a case of tuberculosis must meet either laboratory criteria or the clinical case definition (Table 138-1). The laboratory criteria for case confirmation are: (1) isolation of *M. tuberculosis* from a clinical specimen; (2) demonstration of *M. tuberculosis* from a clinical specimen by nucleic acid amplification test; or (3) demonstration of acid-fast bacilli (AFB) in a clinical specimen when a culture has not been or cannot be obtained. A clinical case is defined by satisfying all of the following four criteria: (1) a positive tuberculin skin test; (2) symptoms and signs consistent with tuberculosis, such as worsening or improving chest radiograph or clinical evidence of disease; (3) treatment with two or more antituberculosis drugs; and (4) a completed diagnostic evaluation.

EPIDEMIOLOGY

Overall Incidence and Trends

From 1953, when CDC began systematic national tuberculosis surveillance, until 1985, reported cases decreased at about 5 percent per year from 84,304 (case rate 52.6*) to 22,201 (case rate 9.3). This steady decline was interrupted, however, by a resurgence of tuberculosis beginning in 1985 and peaking in 1992 (Fig. 138-1) during which time the number of reported cases increased to 26,673 (case rate 10.5). This increase was concentrated in young (predominantly aged 25 to 44 years), urban (especially New York, New Jersey, and California), racial and ethnic minority populations. Tuberculosis was also found to be prevalent among the homeless, injection and non-injection drug users, and inmates of correctional facilities. In many of these groups, the rise in tuberculosis was linked to high rates of HIV infection. A second epidemiologic trend emerged with increased immigration to the United States of persons from countries in which tuberculosis is prevalent (especially Latin America, South and

*All case rates are per 100,000 population.

Table 138-1

CDC Tuberculosis Case Definition for Public Health Surveillance*

Clinical description

A chronic bacterial infection caused by *Mycobacterium tuberculosis*, characterized pathologically by the formation of granulomas. The most common site of infection is the lung, but other organs may be involved.

Clinical case definition

A case that meets all of the following criteria:
- A positive tuberculin skin test result
- Other signs and symptoms compatible with tuberculosis, such as an abnormal, unstable (i.e., worsening or improving) chest radiograph, or clinical evidence of current disease
- Treatment with two or more antituberculosis medications
- A completed diagnostic evaluation

Laboratory criteria for diagnosis

- Isolation of *M. tuberculosis* from a clinical specimen,† or
- Demonstration of *M. tuberculosis* from a clinical specimen by nucleic acid amplification test,‡
- Demonstration of acid-fast bacilli in a clinical specimen when a culture has not been or cannot be obtained

Case classification

Confirmed: a case that meets the clinical case definition or is laboratory confirmed

** CDC: Case definitions for infectious conditions under public health surveillance. MMWR 46(RR-10):40, 1997.*
† Use of rapid identification techniques for M. tuberculosis (e.g., DNA probes and mycolic acid high-pressure liquid chromatography performed on a culture from a clinical specimen) are acceptable under this criterion.
‡ Nucleic acid amplification (NAA) tests must be accompanied by culture for mycobacteria species. However, for surveillance purposes, CDC will accept results obtained from NAA tests approved by the Food and Drug Administration (FDA) and used according to the approved product labeling on the package insert.

Figure 138-1 Reported tuberculosis cases in the United States, 1982–2004. (Adapted from Centers for Disease Control and Prevention: *Reported Tuberculosis in the United States, 2004*. Atlanta, GA, U.S. Department of Health and Human Services, CDC, 2005.)

Southeast Asia, Africa, and Eastern Europe). Because of extensive national, state, and local control efforts, the annual incidence of tuberculosis has been on the decline again since 1992, falling 46 percent between 1992 and 2004 (Fig. 138-1). During 2004, 14,517 (case rate 4.9) tuberculosis cases were reported to CDC, the lowest annual incidence. Despite this welcome decline, the associations of this disease with conditions such as HIV infection, homelessness, injection drug use, and foreign birth remain. Of perhaps even greater concern, the decreases in reported cases from 2002 to 2003 (1.4 percent) and 2003 to 2004 (2.3 percent) represent the smallest and third smallest yearly declines, respectively, since 1992.

Age, Race, and Ethnicity

In older adults, tuberculosis usually results from activation of infection acquired some time in the past. There is an intervening period of latency lasting years or decades between initial infection and activation of disease, which has also been called post-primary tuberculosis.[†] In contrast, tuberculosis in infants and young children is due to progression of recent infection and termed primary tuberculosis. Primary tuberculosis may develop in more than 40 percent of untreated infected children less than 1 year of age. As tuberculosis incidence declines, there is less transmission to uninfected persons, especially children and younger adults. Consequently, it is not surprising that as tuberculosis incidence decreased in the United States, the median age of persons with tuberculosis increased, rising to 49 years in 1985. With cases increasing starting in 1985, the median age of persons with tuberculosis fell to 43 years, and there were more cases of tuberculosis in younger persons, especially among racial and ethnic minorities. With the number of tuberculosis cases declining again in recent years, the case rate in children (defined as under 15 years of age) has decreased sharply (from 2.9 1993 to 1.6 in 2004). Case rates in adults have also fallen by 25 to 50 percent, depending on the age group (adults aged 15 to 24 years from 5.0 to 3.8, 25 to 44 years from 11.5 to 5.9, 45 to 64 years from 12.4 to 5.9, and 65 years and older from 17.7 to 7.8).

Along with many other conditions, tuberculosis reflects a health disparity in the United States because it disproportionately affects racial and ethnic minorities. Differences in case rates between white and nonwhite populations have been associated with socioeconomic status (tuberculosis is essentially a disease of the poor) and country of birth. When tuberculosis was decreasing prior to 1985, the rate of decline was less for nonwhite persons than for white persons. During the period of resurgence from 1985 through 1992, tuberculosis cases in minorities rose while those in whites continued to decrease. Cases among non-Hispanic blacks and Hispanics increased 26.8 and 74.5 percent, respectively. As total cases declined again after 1992, minority tuberculosis cases also decreased. In 2004, Asian and Pacific Islanders had the highest TB rate, 27.2, which was down from 44.1 in 1993. Rates declined about 50 percent over the past decade in other racial/ethnic minority groups: among non-Hispanic blacks from 28.5 in 1993 to 11.3 in 2004, among Hispanics from 19.9 to 10.1, and among American Indians and Alaska Natives from 14.0 to 7.3. In 2004, for the first time, Hispanics (29 percent) exceeded blacks (28 percent) as the racial/ethnic group with the largest percentage of cases.

Country of Birth

Over the past decade, one of the most notable trends in tuberculosis epidemiology in the United States is the increase in the proportion of cases that has occurred in persons born outside the United States (Fig. 138-2). In 1993, 69 percent of reported cases were among U.S.-born persons (case rate 7.4), whereas 29 percent were in foreign-born persons (case rate 33.6). In comparison, by 2004, 54 percent of reported cases occurred among foreign-born persons, and the respective case

[†]The term "reactivation" has also been used; historically, in the pre-chemotherapeutic era, this term referred to patients who developed tuberculosis, experienced self-cure, and then subsequently progressed to disease for a second time (in the absence of exogenous reinfection). Although this term has been applied in the post-chemotherapeutic era to patients who are latently infected and then progress to disease, this usage may be seen as inaccurate because patients have only experienced one episode of disease, and have not "reactivated."

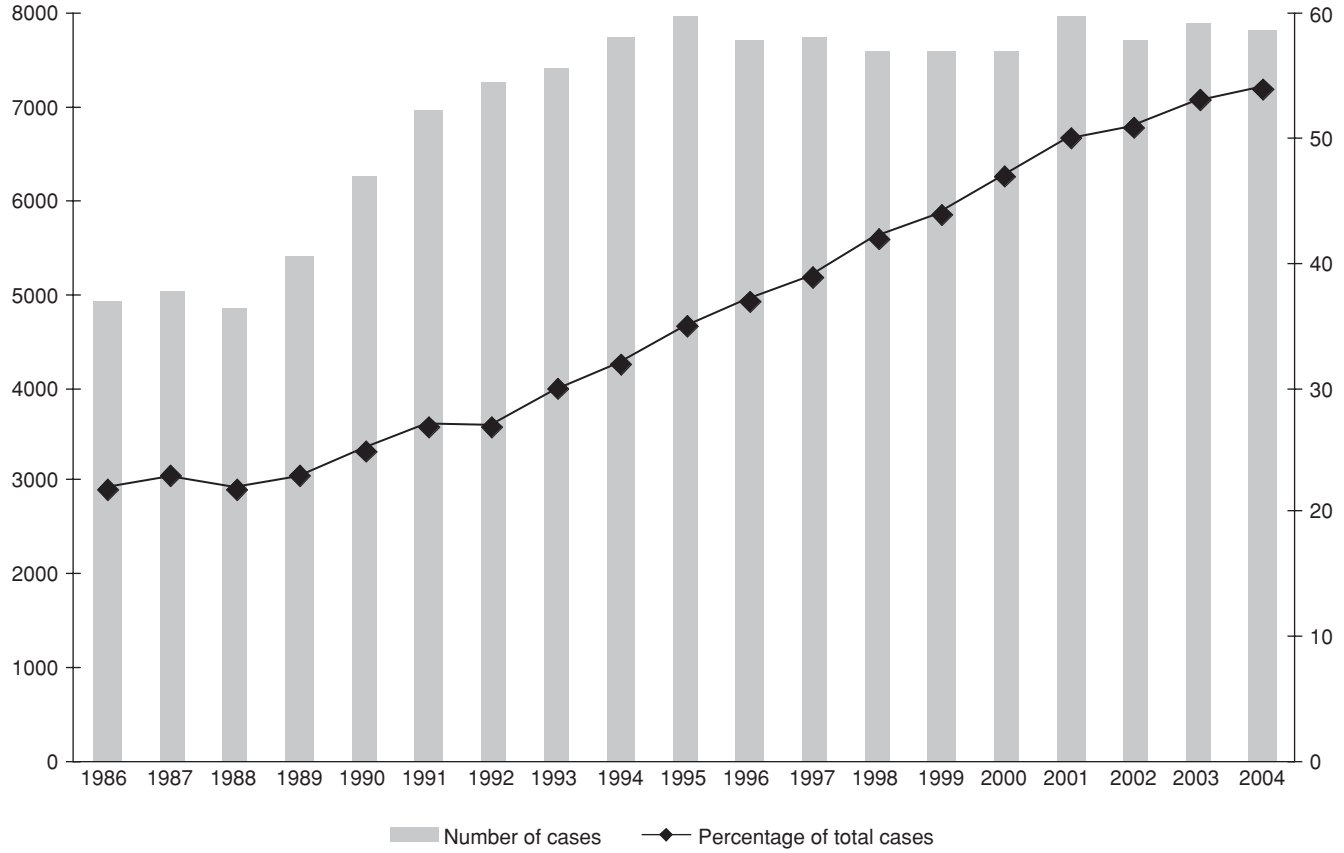

Figure 138-2 Trends in tuberculosis cases in foreign-born persons, United States, 1986–2004. (Centers for Disease Control and Prevention: *Reported Tuberculosis in the United States, 2004*. Atlanta, GA, U.S. Department of Health and Human Services, CDC, 2005.)

rates were 2.6 for U.S.-born persons and 22.8 for foreign-born persons. The number of states reporting more than 50 percent TB cases among foreign-born persons increased from five in 1993 to 22 in 2004. Of these 22 states, six (California, Hawaii, Massachusetts, Minnesota, Nebraska, and New Hampshire) had more than 70 percent of their cases among foreign-born persons. In 2004, the top five countries of origin of foreign-born persons with tuberculosis (by percentage of cases) were Mexico (25 percent), the Philippines (11 percent), Vietnam (8 percent), India (7 percent), and China (5 percent). Although these national trends are informative, local epidemiological profiles vary and should be developed by state and county health departments to respond to local public health needs.

Anatomic Site of Disease

The lung is the most common disease site for persons reported with tuberculosis (about 80 percent of cases), and pulmonary tuberculosis poses the greatest public health concern because of its contagiousness. In 2004, 71.2 percent of reported cases involved the lung only and 8.3 percent involved the lung and an extrapulmonary site. For extrapulmonary tuberculosis, the most common types were lymphatic (43.8 percent), pleural (19.0 percent), bone and joint (11.2 percent), meningeal (5.8 percent), peritoneal (5.5 percent), and genitourinary (3.8 percent). Two severe forms of disease, meningeal and miliary tuberculosis, are more common in children and comprise approximately 20 percent of cases reported in newborns to 4 year olds.

HIV Infection

Beginning in the 1980s, untreated HIV infection came to be recognized as the greatest risk factor for progression from latent tuberculosis infection (LTBI) to tuberculosis disease. In the absence of antiretroviral therapy, seven to ten percent of HIV-infected persons with LTBI will progress to tuberculosis disease *per year*; this is comparable to the *lifetime* risk of progression of five to ten percent in otherwise healthy people. Because of the high likelihood of progression from infection to disease, which often occurs rapidly, numerous outbreaks among HIV-infected persons have been reported, including outbreaks of MDR tuberculosis. Chest radiograph findings in HIV-infected tuberculosis patients, especially in those with CD4+ T-lymphocyte counts below 200/μl, are frequently atypical: Cavities are less common, whereas hilar adenopathy and lack of pulmonary infiltrates are seen more frequently than in immunocompetent patients. Extrapulmonary tuberculosis is more common in HIV-infected patients, occurring in as many as 40 to 60 percent of patients in some studies.

Incomplete reporting has limited the analysis of national tuberculosis surveillance data by HIV status. Reporting

of HIV status has improved slowly since 1993, the year such information was first included on tuberculosis case reports submitted to the CDC. In 2004, 64 percent of tuberculosis case reports for persons aged 25 to 44 years (highest risk age group) included information about HIV status. Thirty-four states, New York City, and the District of Columbia reported this information for at least 75 percent of cases among persons in this age group. Of these states and cities that also reported HIV results on at least 10 cases, the percentage of tuberculosis cases aged 25 to 44 years with HIV co-infection varied from 3.7 to 41.9 percent (Nevada and District of Columbia, respectively). To help estimate the proportion of reported tuberculosis cases with HIV co-infection, state health departments have compared tuberculosis and acquired immunodeficiency syndrome (AIDS) registries. Using registry matched data to supplement HIV test results reported on the individual tuberculosis case report, minimum estimates of the proportion with HIV co-infection ranged from 15 percent in 1993 to 1994 to 10 percent in 1998 to 1999 for persons of all ages reported with tuberculosis and from 29 percent in 1993 to 1994 to 19 percent in 1998 to 1999 for persons aged 25 to 44.

Homelessness, Incarceration, and Substance Abuse

Other conditions associated with poverty are also risk factors for tuberculosis. Prominent among these are homelessness, incarceration, and substance abuse. In 2004, 5.8 percent of cases were reported as being homeless within the past 12 months of diagnosis, whereas 3.4 percent were residing in a correctional facility at the time of diagnosis. In addition, injection drug use, non-injection drug use and excess alcohol use were reported in 1.8, 7.4, and 14.2 percent, respectively, of tuberculosis cases reported in 2004. In tuberculosis patients, these conditions frequently overlap with HIV infection.

Drug Resistance

In individual mycobacteria, drug resistance begins with spontaneous genetic mutations that confer resistance to specific drugs. Even though the rate of spontaneous mutations is low (on the order of one mutation per 10^{10} organisms to one mutation per 10^6 organisms), patients with advanced tuberculosis disease have a very large burden of organisms (one cavity may have 10^9 organisms). Therefore, thousands of mutants resistant to an individual drug may be present. With prolonged exposure to a single drug, the subpopulation of organisms resistant to that drug will be selected, expand, and become dominant. This phenomenon is termed acquired drug resistance. Consequently, from a bacteriological perspective, tuberculosis disease must be treated with at least two drugs to which the organism is susceptible. Drug-resistant tuberculosis may also be transmitted directly from a contagious patient to another person. Persons who contract drug-resistant tuberculosis in this manner have what is called primary or initial drug resistance.

Resistance to isoniazid is fairly common in the United States, ranging from 7.0 to 8.4 percent in the years 1993 to 2004. Isoniazid resistance is more frequent in foreign-born tuberculosis cases than U.S.-born tuberculosis cases (10.4 versus 4.5 percent in 2004) and more frequent in cases with a previous history of tuberculosis (in 2004, 11.4 percent versus 7.8 percent in those without previous tuberculosis).

MDR tuberculosis is defined as tuberculosis caused by an organism resistant to at least isoniazid and rifampin. MDR tuberculosis is difficult to treat and generally requires a minimum of 18 to 24 months of therapy with second-line medications (generally less effective, more toxic, and more costly); surgery is also indicated in some patients. The greatest risk factor for the presence of MDR-tuberculosis is a history of prior treatment for tuberculosis. Patients with tuberculosis from U.S. communities or foreign countries with high MDR tuberculosis rates are also at increased risk.

Since 1993 (when the case report was expanded to include drug-susceptibility results) the proportion of patients with primary MDR tuberculosis decreased from 2.5 percent to 0.9 to 1.2 percent each year during 1998 to 2004. The number of overall primary MDR tuberculosis cases in 2004 was 101, and only 27 of those cases were in U.S.-born persons. Decreases in the percentage of cases with primary MDR tuberculosis have been documented in both the U.S. born and foreign born, although the decline in the U.S. born is more pronounced. Since 1999, the percentage of U.S.-born persons with MDR tuberculosis has remained at approximately 0.6 percent. However, of the total number of reported primary MDR tuberculosis cases, the proportion occurring in foreign-born persons increased from 26 percent (105 of 410) in 1993 to 73 percent (74 of 101) in 2004.

TRANSMISSION

Determining Factors

M. tuberculosis is transmitted from person to person via the airborne route. Infection may occur after an uninfected person inhales respiratory droplets containing *M. tuberculosis*, most commonly produced when a patient with pulmonary tuberculosis coughs. As water evaporates, residual particles, known as droplet nuclei, remain suspended in the air. When inhaled, these particles are small enough (1 to 5 μm in size) to evade upper airway defenses and settle in the alveoli of the lung, causing infection in susceptible hosts.

Several factors determine the probability of tuberculosis transmission: (1) infectiousness of the source patient—a positive sputum smear for acid fast bacilli or a cavity on chest radiograph being strongly associated with infectiousness; (2) host susceptibility of the contact; (3) duration of exposure of the contact to the source patient; and (4) the environment in which the exposure takes place—a small, poorly ventilated space providing the highest risk. Even among household contacts of active tuberculosis patients, the risk of infection is surprisingly low; the United States Public Health Service (USPHS) reported an approximate 30 percent incidence of infection in household contacts. In addition, animal and human studies have demonstrated that *M. tuberculosis*

transmission may dramatically decrease within days to weeks of instituting effective treatment.

Medical procedures that generate aerosols of respiratory secretions, such as sputum induction and bronchoscopy, entail significant risk for *M. tuberculosis* transmission unless proper precautions are taken. In addition, transmission has occurred with aerosol generation in association with irrigation of draining wounds and performance of autopsies.

Molecular Epidemiology

Over the past decade, genotyping of *M. tuberculosis* strains has become an increasingly valuable tool in tuberculosis control. Molecular epidemiology has helped to identify unsuspected transmission, determine likely locations of transmission, and measure the extent of transmission. Often traditional contact investigations focus on persons in the household and workplace. Numerous reports describe tuberculosis cases linked through genotyping of *M. tuberculosis* isolates, where detection of transmission was initially missed by conventional contact investigation because the setting was non-traditional. Frequently this type of transmission occurs among members of a "social network" that is centered around a specific activity, including illicit drug use, excess alcohol use, or gambling, or location, such as a homeless shelter, adult entertainment club, or HIV residential care facility. When genotyping detects previously unrecognized transmission in a non-conventional setting, public health interventions to contain and subsequently end the outbreak can be redirected to focus on the social network or location associated with transmission.

PREVENTION AND CONTROL

Prevention and Control Strategies

There are three ordered priority strategies for tuberculosis prevention and control in the United States: (1) identifying and treating persons who have tuberculosis disease; (2) contact investigation—finding persons exposed to infectious tuberculosis patients, evaluating them for *M. tuberculosis* infection and disease, and providing subsequent treatment, if appropriate; and (3) targeted testing—screening populations at high risk for LTBI and progression to tuberculosis disease to detect infected persons and provide treatment to prevent progression to disease.

The first priority of tuberculosis control in the United States is detection and treatment of patients with tuberculosis disease. Diagnosing and reporting a patient with suspected or confirmed tuberculosis triggers several interventions that interrupt transmission. These include placing the patient in respiratory isolation if contagious, starting the patient on tuberculosis treatment, and conducting a contact investigation. Health departments seek to be notified of persons with suspected or confirmed tuberculosis as early as possible and use active and passive methods of case finding to achieve this goal. Details of the diagnosis and treatment of tuberculosis disease are discussed in Chapter 140.

Investigation of contacts of persons with infectious tuberculosis is an essential function of tuberculosis control in the United States and has been identified as the second priority. Among close contacts, approximately 1 to 2 percent will have tuberculosis disease and 31 to 36 percent will have LTBI. Approximately 3 to 5 percent of contacts with newly acquired LTBI will develop tuberculosis within 2 years of infection. Therefore, contact investigations are an effective method for active case finding and identifying persons with LTBI who are also at a high risk of developing tuberculosis disease. State and local public health agencies are responsible for ensuring that contact investigations are conducted effectively and that all exposed contacts are identified, evaluated for tuberculosis infection and disease, and appropriately treated. Consequently, 90 percent of contact investigations in the United States are performed by public health departments.

The third priority for tuberculosis control in the United States is targeted tuberculin testing and treatment of persons with LTBI. The number of persons in the United States with LTBI is estimated at 9.5 to 14.7 million. To continue progress toward the elimination of tuberculosis in the United States, public health programs must devise effective strategies to address the challenge of preventing tuberculosis in this population of infected persons. Guidelines on targeted testing and treatment of LTBI have been published and revised. Those guidelines include recommendations for diagnosis and treatment of LTBI, as well as recommendations for identifying persons and groups to target for testing.

Although prevention and control of tuberculosis in the United States is primarily the responsibility of state and local tuberculosis control programs, rarely are these activities implemented solely by the health department. Patients with tuberculosis disease are usually diagnosed and often treated by private providers. Contacts to infectious cases may also be evaluated and treated by their private physicians or other community providers. Private providers, as well as non-health department community or governmental entities, also screen and treat individuals at high risk for LTBI. However, the health department is responsible for coordination and oversight of these activities to ensure that objectives related to tuberculosis prevention and control are achieved.

Diagnosing Tuberculosis Infection

The Tuberculin Skin Test

The tuberculin skin test (TST) is a major tool for investigating tuberculosis infection. It can be used diagnostically in the individual patient and epidemiologically in the general population. The recommended method for the TST, the Mantoux method, is performed by the intradermal injection of a standardized, stabilized dose of 5 tuberculin units of purified protein derivative (PPD). The extent of induration is measured 48 to 72 hours later. Multiple puncture techniques (e.g., tine test or Heaf test) are not recommended. The interpretation of the TST is based on an individual's epidemiological risk factors

Table 138-2

Criteria for a Positive Tuberculin Skin Test by Risk Group*

Reaction 5 mm of Induration	Reaction 10 mm of Induration	Reaction 15 mm of Induration
Human immunodeficiency virus (HIV)–positive persons	Recent immigrants (i.e., within the last 5 y) from high-prevalence countries	Persons with no risk factors for tuberculosis
Recent contacts of tuberculosis patients	Injection drug users	
Fibrotic changes on chest radiograph consistent with prior tuberculosis	Residents and employees‡ of the following high-risk congregate settings: prisons and jails, nursing homes and other long-term facilities for the elderly, hospitals and other health care facilities, residential facilities for patients with HIV, and homeless shelters	
Patients with organ transplants and other immunosuppressed patients (receiving the equivalent of 15 mg/d of prednisone for 1 mo or more), including those receiving TNF-α antagonists†	Mycobacteriology laboratory personnel	
	Persons with the following clinical conditions that place them at high risk: silicosis, diabetes mellitus, chronic renal failure, some hematologic disorders (e.g., leukemias and lymphomas), other specific malignancies (e.g., carcinoma of the head or neck and lung), weight loss of 10% of ideal body weight, gastrectomy, and jejunoileal bypass	
	Children younger than 4 y of age or infants, children, and adolescents exposed to adults at high risk	

** Modified from American Thoracic Society and Centers for Disease Control and Prevention: Targeted tuberculin testing and treatment of latent tuberculosis infection. MMWR 49(RR-6): 1, 2000.*

† Risk of TB in patients treated with corticosteroids increases with higher dose and longer duration.

‡ For persons who are otherwise at low risk and are tested at the start of employment, a reaction of 15 mm induration is considered positive.

for tuberculosis infection. The 2000 American Thoracic Society (ATS)/CDC guidelines for interpretation of TST results are as follows (Table 138-2): (1) 5 mm induration is considered a positive result for (a) individuals with HIV infection or other comparable immunosuppression (equivalent to receiving 15 mg or greater of prednisone for one month or more), including patients receiving tumor necrosis alpha [TNF-α] antagonists, (b) close contacts to an active tuberculosis case, or (c) patients with a chest radiograph suggestive of prior tuberculosis (e.g., fibronodular) disease (also termed inactive disease)); (2) 10 mm induration is considered a positive result for (a) recent immigrants (within the last 5 years) from high-incidence countries, (b) injection drug users, (c) residents and employees of high-risk congregate facilities such as nursing homes, homeless shelters, or prisons, (e) mycobacterial laboratory personnel, (f) persons with underlying medical conditions such as diabetes, silicosis, end-stage renal disease, certain malignancies, and low body weight (loss of at least 10 percent of ideal body weight), or (g) children younger than 4 years of age and infants, children, or adolescents exposed to adults at high risk; and (3) 15 mm induration is considered a positive result for all others.

In general, a positive TST result is considered to indicate the presence of infection with *M. tuberculosis*. A targeted testing strategy prioritizes those at highest risk for progression to tuberculosis disease if infected and those, who if

they get disease, will experience greater morbidity and mortality. Consequently, testing should be reserved for persons at high risk for LTBI or at high risk to progress to disease based on their epidemiological profile. In the United States it is recommended that persons with positive results receive treatment for LTBI to prevent progression to disease. Thus, an intent to test for LTBI (based on a proper assessment of risk) should indicate an intent to treat (assuming exclusion of medical contraindications to drug therapy) for LTBI when found.

In a number of situations, the TST is neither sensitive nor specific for *M. tuberculosis* infection. A positive TST result is a manifestation of type IV delayed hypersensitivity. Certain biologic conditions, such as viral illnesses, including HIV infection, vaccination, malignancies and other debilitating illness (including advanced tuberculosis disease), and certain medications (e.g., TNF-α antagonists, corticosteroids, and other immunosuppressive drugs), will suppress the type IV response and T-lymphocyte function. In addition, proper application of the TST requires careful attention to technique and interpretation. TST should be performed by well-trained, experienced operators. False-positive test findings can occur for a number of reasons, including cross-reactions caused by non-tuberculous (atypical) mycobacterial infection and bacille Calmette-Guérin (BCG) vaccination.

Interferon-Gamma Release Assays

The QuantiFERON-TB Gold (QFT-G, Cellestis Ltd., Carnegie, Victoria, Australia) test is a blood assay for *M. tuberculosis* (BAMT). This in vitro test detects the release of interferon-gamma (IFN-γ) from lymphocytes of sensitized persons when their blood is incubated with peptide mixtures simulating two *M. tuberculosis* proteins called ESAT-6 and CFP-10. QFT-G has been approved by the U.S. Food and Drug Administration (FDA) for use as an in vitro aid in diagnosing *M. tuberculosis* infection, including both LTBI and tuberculosis disease. It replaces an earlier version of the test, QuantiFERON-TB (QFT), which used PPD and was indicated solely for the diagnosis of LTBI. Current data indicate that ESAT-6 and CFP-10 are secreted by all *M. tuberculosis* and pathogenic *M. bovis* strains, but are absent from all BCG vaccine strains. These proteins are also absent from commonly encountered non-tuberculous mycobacteria, with the exception of *M. kansasii*, *M. szulgai*, and *M. marinum*. Thus, QFT-G offers the possibility of detecting *M. tuberculosis* infection with greater specificity than has been possible previously with tests that used tuberculin PPD as the tuberculosis antigen.

Although the performance of QFT-G has not been sufficiently evaluated in select populations of interest (e.g., the HIV infected), available data indicate that QFT-G is as sensitive as TST for detection of tuberculosis disease and more specific than TST for detection of LTBI. CDC guidelines for QFT-G recommend that QFT-G can be used in place of TST in all circumstances in which TST is currently used. This includes initial and periodic screening of individuals at risk for *M. tuberculosis* infection and screening of exposed persons in contact investigations.

The performance of QFT-G, in particular its sensitivity and its rate of indeterminate results, has not been determined in persons who, because of impaired immune function, are at increased risk for infection progressing to disease. Conditions or treatments known or suspected to decrease responsiveness to the TST (see the tuberculin skin test above) also might decrease production of IFN-γ in the QFT-G assay. Consequently, as with a negative TST result, negative QFT-G results alone might not be sufficient to exclude *M. tuberculosis* infection in these persons. In addition, only limited data document the performance of QFT-G in children aged less than 17 years; a subset of this population, children younger than 5 years old, is also at high risk for rapid progression from infection to disease, including meningitis and miliary tuberculosis. With TST or BAMT, persons who have a negative test result can still have LTBI. Those who have a negative result, but who are likely to have LTBI and are at greater risk for severe illness or poor outcomes if TB disease occurs, such as persons with HIV infection, should be considered for LTBI treatment and close monitoring for disease.

QFT-G represents one type of IGRA. The other type of assay, called Elispot, enumerates individual lymphocytes producing IFN-γ after peripheral blood mononuclear cells are incubated with similar antigens. Although a commercial Elispot test for the diagnosis of tuberculosis infection exists (T-SPOT, Oxford Immunotech, Oxford, UK), it has not been reviewed or approved by the FDA for use in the United States.

BCG Vaccination

Two methods have been used for tuberculosis prevention: BCG vaccination and isoniazid therapy for LTBI. BCG is a live, attenuated bacterial vaccine that has been evaluated extensively. In 1974 BCG was incorporated into the WHO's Expanded Program of Immunization and BCG is thought to be one of the most commonly administered vaccines in the world. The World Health Organization recommends administering BCG once at birth in endemic countries. There has been some concern about vaccinating congenitally HIV-infected infants, and symptomatic infants with AIDS should not be vaccinated. In immunocompetent persons, however, except for occasional local reactions, BCG's toxicity is minimal.

In controlled trials, the efficacy of BCG vaccination as measured by case reduction has varied from 0 percent to greater than 80 percent. In most trials, the incidence of miliary and meningeal tuberculosis in children has been greatly reduced. There are many hypotheses for variations in the efficacy of case reduction. These include flaws in study design, differences in vaccine potency based on the BCG strain used, heterogeneity in virulence of *M. tuberculosis* strains encountered in various geographic regions, differences in nutritional status and host (genetic) susceptibility of the population vaccinated, and geographic variability in environmental mycobacterial strains that may mask vaccine effect. In a

recent study, the vaccine's protective effect against tuberculosis disease has been shown to be persistent, up to 60 years in duration.

The vaccine generally converts an individual's TST result to positive, at least in the short term; however, the TST response has been somewhat variable with different vaccines and in different individuals and it correlates poorly with vaccine effectiveness. BCG may therefore limit the diagnostic value of the TST in certain circumstances. BCG has not been used in the United States because the original studies did not demonstrate efficacy and its use is not justified because of the low incidence of tuberculosis. BCG has been most useful in areas of the world where the case rate and new infection rate remain high.

Treatment of LTBI

The principal preventive tool in the United States has been treatment of LTBI with isoniazid. In the 1950s, when isoniazid became available as an inexpensive, bactericidal, and relatively nontoxic drug for the treatment of tuberculosis disease, controlled trials were instituted to determine its efficacy for the treatment of LTBI. In more than 70,000 patients, the USPHS and others consistently demonstrated a 60 to 70 percent case reduction rate attributable to isoniazid therapy. Follow-up for as long as 15 years confirmed the long-term protection isoniazid provides against progression to disease.

Concern regarding toxicity, especially hepatotoxicity, and the need for adherence to a prolonged course of therapy have limited isoniazid therapy's effectiveness as a public health intervention. Older studies revealed that isoniazid-associated liver injury occurred in almost 1 percent of patients, and deaths secondary to isoniazid-induced liver injury were reported. More recently, however, public health clinics in Seattle and San Diego reported incidences of hepatotoxicity of 0.1 and 0.3 percent, respectively, among over 14,000 patients treated. There were no deaths reported and only one hospitalization. Despite the low incidence of liver injury, completion rates for 6 months of therapy were below 65 percent in both reports.

The preferred isoniazid regimen is 9 months of daily therapy for all groups of patients, including those with HIV infection, those with a chest radiograph suggestive of prior tuberculosis disease (inactive tuberculosis), and children. Six months of treatment is considered an acceptable alternative for immunocompetent adults without evidence of prior tuberculosis on chest radiograph, but this shorter duration is felt to be less effective based on existing data (Table 138-3). Clinical monitoring, on a monthly basis at minimum, is recommended for all patient receiving isoniazid. Routine transaminase monitoring should be reserved for individuals at particular risk for hepatotoxicity including those who are pregnant or in the immediate postpartum period (first 3 months) or those with HIV infection, a history of liver disease, a history of excess alcohol use, or other risks for liver disease.

Initial studies done in HIV-infected patients suggested that the combination of daily rifampin and pyrazinamide for 2 months (called 2RZ) was equally efficacious and safe for the treatment of LTBI when compared with 6 or 12 months of isoniazid. Subsequently, as this regimen came in to general use, multiple hospitalizations and deaths resulting from hepatoxicity were reported. A follow-up study determined that the rate of severe toxicity, defined as hospitalization or death, due to the combination of rifampin and pyrazinamide for 2 months was on the order of 1 per 1000. ATS and CDC now recommend that the combination of rifampin and pyrazinamide should generally not be offered to persons with LTBI.

Table 138-3

Drug Regimens for Treatment of Latent Tuberculosis Infection (LTBI)*

Drugs	Months of Duration	Interval	Minimum Doses	Rating (Evidence)†	
				HIV−‡	HIV+
Isoniazid	9	Daily	270	A (II)	A (II)
		Twice weekly	76	B (II)	B (II)
Isoniazid	6	Daily	180	B (I)	C (I)
		Twice weekly	52	B (II)	C (I)
Rifampin	4	Daily	120	B (II)	B (III)

** The combination of rifampin and pyrazinamide had been recommended for the treatment of latent tuberculosis infection in the publication Targeted Tuberculin Testing and Treatment of Latent Tuberculosis Infection (*MMWR *49(RR-6):1, 2000.), but this regimen is generally not recommended for use based on subsequent reports of severe hepatotoxicity (Update: adverse event data and revised American Thoracic Society/CDC recommendations against the use of rifampin and pyrazinamide for treatment of latent tuberculosis infection—United States, 2003. MMWR 52:735, 2003).*

† Ratings are based on modification of US Public Health Service rating system as described in Targeted Tuberculin Testing and Treatment of Latent Tuberculosis Infection (MMWR 49(RR-6): 1, 2000.). A = preferred, should generally be offered; B = alternative, acceptable to offer; C = offer when preferred or alternative regimens cannot be given; I = at least one randomized trial with clinical end points; II = clinical trials that either are not randomized or were conducted in other populations; III = expert opinion.

‡ HIV− = human immunodeficiency virus negative; HIV + = human immunodeficiency virus infected.

For contacts exposed to isoniazid-resistant, rifampin-susceptible tuberculosis patients, rifampin (4 months duration) can be used. It is important to note that rifampin and a closely related medication, rifabutin, interact with protease inhibitors and non-nucleoside reverse transcriptase inhibitors that are used to treat HIV. Consultation with an expert familiar with both HIV infection and tuberculosis treatment is recommended in this situation.

For MDR tuberculosis exposures, the selection of medication should be based on the drug susceptibility test results of the source patient and the likelihood of disease progression. If the source isolate is susceptible, some experts have recommended the use of pyrazinamide and ethambutol or pyrazinamide in combination with a fluoroquinolone. Subsequent reports have described toxicity and poor tolerance of these recommended regimens. If the exposed contact cannot tolerate a combination of medications, treatment with a fluoroquinolone alone may be considered. Data on the efficacy of these regimens are not available, however.

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The Microbiology, Virulence, and Immunology of Mycobacteria

Jennifer A. Philips • Eric J. Rubin

Tuberculosis (TB) remains a leading killer, in part because it is still a diagnostic and treatment challenge. Although molecular details underlying bacterial pathogenesis and host response are emerging, the picture remains incomplete. Newer culturing systems and molecular techniques have the potential to improve the speed and certainty with which a diagnosis can be made, but they have not yet replaced conventional tuberculin skin testing, smear, culture, or antibiotic sensitivity testing, all of which remain imperfect diagnostic tools. Furthermore, development of a much-needed vaccine is still a formidable task. Thus, for the clinician in low- prevalence areas, TB often presents a challenge both diagnostically and therapeutically, while the vast burden of disease exists in settings where resources are lacking and access to emerging technology is limited.

TUBERCULOUS AND NONTUBERCULOUS MYCOBACTERIA

The genus *Mycobacterium* contains a large number of species which span the spectrum from pathogen to commensal. The group of closely related species that constitute the *Mycobacterium tuberculosis* complex (*M. tuberculosis, M. bovis*, *M. africanum*, *M. microti*, and *M. canetti*) is composed of obligate pathogens. Nontuberculous mycobacteria (NTM) can be distinguished based upon their pigment production, growth rates, and biochemical properties (Table 150-1). Clinically, species identification helps to determine the likelihood that an organism is a true pathogen. For example, rapidly growing mycobacteria (e.g., *M. chelonae*) are associated with acute infections such as abscesses, more slowly growing organisms (e.g., *M. kansasii*) generally cause lung disease, and other commensals (e.g., *M. gordonae*) rarely cause disease but can contaminate clinical specimens. Infection with NTM, in particular members of the *M. avium* complex (MAC), is associated with immune-compromised states. For example, MAC often causes systemic infection in the setting of profound defects in cell-mediated immunity as seen in advanced acquired immunodeficiency virus (AIDS). In contrast to *M. tuberculosis*, there is little evidence of person-to-person spread of NTM, and instead, NTM are likely acquired from environmental sources. For example, rapidly growing mycobacteria have been associated with nosocomial transmission via infected instruments or solutions. Because NTM have different antibiotic susceptibility than *M. tuberculosis*, the identification of the organism helps

Table 139-1

Classification of the Nontuberculous Mycobacteria Recovered from Humans

Clinical Disease	Common Etiologic Species	Features of the Common Species		Unusual Etiologic Species
		Geography	Morphologic Features*	
Pulmonary disease	1. *M. avium* complex	Worldwide	Usually not pigmented; slow growth (> 7 d)	1. *M. simiae* 2. *M. szulgai*
	2. *M. kansasii*	USA, coal mining regions, Europe	Pigmented; often large and beaded on acid-fast stain	3. *M. fortuitum* 4. *M. celatum*
	3. *M. abscessus*	Worldwide but mostly USA	Rapid growth (<7 d); not pigmented	5. *M. asiaticum* 6. *M. shimodii*
	4. *M. xenopi*	Europe, Canada	Slow growth, pigmented	7. *M. haemophilum*
	5. *M. malmoense*	UK, northern Europe	Slow growth, not pigmented	8. *M. smegmatis*
Lymphadenitis	1. *M. avium* complex	Worldwide	Usually not pigmented	1. *M. fortuitum*
	2. *M. scrofulaceum*	Worldwide	Pigmented	2. *M. chelonae*
	3. *M. malmoense*	UK, northern Europe (especially Scandinavia)	Slow growth	3. *M. abscessus* 4. *M. kansasii* 5. *M. haemophilum*
Cutaneous disease	1. *M. marinum*	Worldwide	Photochromogen; requires low temperatures (28–30° C) for isolation	1. *M. avium* complex 2. *M. kansasii* 3. *M. nonchromogenicum*
	2. *M. fortuitum* 3. *M. chelonae* 4. *M. abscessus*	Worldwide, mostly USA	Rapid growth, not pigmented	4. *M. smegmatis* 5. *M. haemophilum*
	5. *M. ulcerans*	Australia, tropics, Africa, SE Asia	Grows slowly, pigmented	
Disseminated disease	1. *M. avium* complex	Worldwide	Isolates from patients with AIDS unusually pigmented (80%)	1. *M. abscessus* 2. *M. xenopi* 3. *M. malmoense*
	2. *M. kansasii*	USA	Photochromogen	4. *M. genavense*
	3. *M. chelonae*	USA	Not pigmented	5. *M. simiae*
	4. *M. haemophilum*	USA, Australia	Not pigmented; requires hemin, often low temperatures, and CO_2 to grow	6. *M. conspicuum* 7. *M. marinum* 8. *M. fortuitum*

** Photochromogen: isolate is buff-colored in the dark turns yellow with brief exposure to light.*

Source: American Thoracic Society Statement: Diagnosis and treatment of disease caused by nontuberculous mycobacteria. Am J Respir Crit Care Med 156:S1–S25, 1997.

guide antibiotic choices while awaiting drug susceptibility testing.

In addition to species distinctions, there are also differences among *M. tuberculosis* strains. Strains can be differentiated by methods that rely on highly variable genomic sequences or the distribution of mobile genetic elements (insertion sequences). Some strains, such as the W/Beijing strain, appear to be spreading more widely, suggesting that they have characteristics mediating increased transmission.

HOST DETERMINANTS OF DISEASE

The most striking feature of TB is the ability of disease to remain latent for as long as decades. While approximately 95 percent of patients infected with *M. tuberculosis* do not develop acute disease upon infection, most (perhaps all) patients are unable to eradicate infection even in the presence of a normal immune system. Because organisms are inaccessible during the latency period, our understanding of this state is

necessarily limited, but it is clear that the immune response is intimately involved in maintaining latency. For example, patients with human immunodeficiency virus (HIV) and other compromised states are highly susceptible to both primary infection and reactivation of latent TB.

While the determinants of the immune response remain poorly understood, the macrophage is unquestionably important in controlling infection, although ultimately inadequate at eradicating it. The initial interaction between bacteria and macrophages likely occurs through innate "pattern recognition receptors" such as Toll-like receptors, DC-SIGN, complement receptors, and mannose receptors. Bacteria are taken up into the macrophage phagosome, a compartment that ordinarily becomes acidified and fuses with lysosomes. However, the phagosome containing mycobacteria do not acquire the proton pump required for acidification, and the internalized bacteria are not exposed to mature lysosomal enzymes. Therefore, mycobacteria persist and grow within this specialized structure, an environment that may limit antigen presentation and protect them against immune-mediated killing mechanisms.

Additional effectors play an important role in controlling infection. Animal models of TB have shown that both CD4+ and CD8+ Tcells are required for protection against disease, an observation borne out clinically in patients who lack adequate T-cell function. At least in part, T cells function to activate infected macrophages, making them more potently bactericidal. Several cytokines that mediate the interaction between T cells and macrophage are important. Chief among these is interferon-γ (IFN-γ). Mice lacking this signaling molecule die rapidly of *M. tuberculosis* infection, while children who lack the IFN-γ receptor develop serious infections with mycobacteria that rarely cause disease in normal hosts. Similarly, defects in interleukin (IL)-12, its receptor, or the downstream intracellular signaling mediator STAT1 lead to abnormal susceptibility to mycobacterial infection. Tumor necrosis factor-α (TNF-α) is also crucial in host immunity as patients who receive infliximab are uniquely susceptible to reactivation of TB. Other TNF-α inhibitors may also increase risk but appear to do so to a lesser degree. These cytokines result in the production of nitric oxide and the induction of apoptosis in infected macrophages, both of which help control mycobacterial growth. However, additional pathways and effectors are also likely to play a role.

It remains unclear how the immune system recognizes mycobacteria. Although several potent T-cell antigens and immunogenic mycobacterial lipids have been described, none are individually protective in model systems. Therefore, we currently lack good markers of a protective immune response, and, likewise, have a limited understanding of the determinants that define host susceptibility. Aside from the rare genetic diseases described above, several common allelic variants may influence the risk of developing active infection. For example, genes involved in antigen presentation or modulating macrophage function may have some effect in human populations. Likewise, genetic studies in mice suggest that Ipr1 and LRG-47 are strong modulators of disease, but this is yet to be confirmed in human studies. Currently none of these markers appear to have strong enough predictive power to be clinically useful.

BACTERIAL DETERMINANTS OF DISEASE

Mycobacteria are quite distantly related to most other pathogens. Members of this genus have an unusual lipid-rich cell wall that seems vital for bacterial survival. These bacteria synthesize distinctive long chain fatty acids (mycolic acids). The presence of these and other associated lipids has important implications for disease and its treatment. The cell wall represents a barrier to diffusion and is likely responsible for the observation that few routinely used antibiotics have significant activity against mycobacteria. In addition, cell wall lipids play an integral role in interaction with the host. For example, a complex lipid (phthiocerol dimycoserate) is required for bacterial growth in the lungs of mice. Likewise, modification of mycolic acids and production of specific glycopeptolipids modulate mycobacterial virulence, although the molecular mechanisms by which these lipids exert their effects are unknown.

Lipids, of course, are not the only determinants of mycobacterial virulence. In fact, sequencing of the complete mycobacterial genome has provided an entire catalogue of potential virulence factors. Unfortunately, as with all complete genomes to date, the function of many of the potential genes is unknown and thus their contribution to virulence mechanisms remains obscure. The genome sequence has, however, served as a starting point for many experimental investigations. For example, it has provided a direct genomic comparison between the avirulent vaccine strain, bacille Calmette-Guérin (BCG), and *M. tuberculosis*. Although there is considerable sequence identity between these strains, several genomic regions are deleted in *M. bovis*-BCG. Among these is a region that encodes two secreted proteins (ESAT-6 and CFP-10) and several associated proteins that appear required for their secretion. Deletion of this region in an otherwise wild type strain results in marked attenuation. At this point, several other bacterial factors have been identified that may play an important role in pathogenesis, but details regarding how they function to coordinate bacterial survival remains poorly understood.

DIAGNOSIS OF TUBERCULOSIS

Indirect Methods

Infection with *M. tuberculosis* can be detected by direct or indirect methods. Indirect methods rely on measuring host responses to infection and, at least as currently implemented, cannot distinguish between active and latent infection. Direct

methods, which are insensitive, are only useful to detect active infection.

There is no gold standard to detect latent infection. Evidence of infection can be obtained by detecting a delayed type hypersensitivity response to protein derivative (PPD). However, PPD is a crude mix of *M. tuberculosis* antigens that can also elicit responses due to prior vaccination with *M. bovis*-BCG or exposure to NTM, thus limiting its specificity. Unfortunately, the test also cannot rule out active infection, as only 75 to 90 percent of patients with active TB are positive, and the sensitivity drops in patients with underlying immunosuppression.

Newer diagnostic tests, such as QuantiFeron-TB Gold or T Spot-TB, measure release of IFN-γ from sensitized lymphocytes *in vitro*. These tests have enhanced specificity because they selectively detect responses to CFP-10 and ESAT-6, antigens secreted by *M. tuberculosis* that are not present in BCG, hence diminishing false positives due to prior BCG vaccination. In addition, most NTM do not have antigens that generate cross-reactivity, with the possible exceptions of *M. kansasii*, *M. szulgai*, and *M. marinum*, perhaps making the test more specific in low-prevalence areas as well. Both tests are promising in their ability to discriminate latent TB infection from prior BCG vaccination and may also be more sensitive in detecting active TB. Therefore, in countries with adequate resources, QuantiFeron-TB Gold or T Spot-TB may ultimately replace skin testing in the diagnosis of latent TB infection while also serving as an adjunct in the diagnosis of active TB.

Direct Microscopic Examination

Direct examination of specimens by means of an acid-fast stain such as Ziehl-Neelsen or Kinyoun provides supportive evidence of mycobacterial disease weeks before the culture and identification may be available. In addition, the presence of sufficient numbers of bacteria to be seen on direct smear correlates with infectivity. The term *acid fast* refers to the fact that dilute acids fail to remove basic dyes such as carbolfuchsin from the mycobacterial cell wall, owing to its lipid-rich complex structure. Although microscopic examination is rapid, simple, and economical, it is relatively insensitive, requiring more than 10,000 bacilli per milliliter to detect acid-fast bacilli (AFB). The sensitivity can be improved with a fluorescent (auramine) stain and sputum concentration. Nonetheless, smear still has a low sensitivity, failing to detect up to 30 percent of pulmonary TB when compared to culture.

Conventional Culture Techniques

Although culture remains the gold standard, it is also imperfect. It is generally able to detect 100 bacilli/ml of sputum, but results take weeks and approximately 20 percent of clinically suspected pulmonary *M. tuberculosis* infections remain culture-negative. The false-negative rate is likely to be even higher in extrapulmonary disease, though lack of a gold standard makes this difficult to estimate. Growth on solid media (such as Lowenstein-Jensen or Middlebrook agar) takes 3 to 6 weeks. Broth detection systems are designed to detect early changes in the media due to growth of bacteria, such as consumption of oxygen, reduction of tetrazolium salts, production of carbon dioxide, or changes in pressure. These systems can provide a more rapid turnaround time, often becoming positive after 1 to 2 weeks.

Since solid and liquid media will support growth of most NTM as well, once an isolate is recovered further testing is required for species identification. Molecular approaches have significantly speeded this process. For example, AccuProbe (Gen-Probe) is able to make species identification within a day by hybridizing a single-stranded, chemiluminescent DNA probe to ribosomal RNA, which differs between species. Commercially available probes can identify *M. tuberculosis* complex, *M. avium* complex, *M. gordonae*, and *M. kansasii*.

Certain NTM exhibit specific growth characteristics that aid in their identification. For example, specimens obtained from skin and soft-tissue infections are incubated at 28 to 32°C, in addition to the standard temperature of 35 to 37°C, because common soft-tissue pathogen, such as *M. ulcerans*, *M. marinum*, and *M. chelonae*, may only grow at lower temperatures. If an AFB culture becomes positive in several days, the species is invariably a rapid grower, which is most commonly *M. fortuitum*, *M. abscesses*, or *M. chelonae*.

Techniques for the Rapid Diagnosis of Tuberculosis

Nucleic acid amplification (NAA) tests have improved the identification of *M. tuberculosis*, but have not obviated the need for smears or cultures. These tests detect mycobacterial nucleic acids directly from clinical respiratory specimens and can be processed within several hours. In other words, NAA tests can quickly determine whether the AFB seen on smear is a member of the *M. tuberculosis* complex prior to culture. Unfortunately, these tests have been relatively insensitive on smear negative samples, so that, currently, the main advantage afforded by NAA testing is enhanced diagnostic certainty and the ability to confirm *M. tuberculosis* infection weeks before cultures are available.

Given the low sensitivity of smear, it would be advantageous to be able to detect *M. tuberculosis* in smear-negative samples as well. Modified direct amplification tests with enhanced sensitivity may be able to do this. An alternative approach involves detecting the presence of mycobacteria in sputum samples by infecting them with mycobacteriophages. The number of phages produced reflects the number of mycobacteria in the original specimen. Phage technology, commercially available as FAST Plaque TB, used in combination with smears, may confirm the presence of *M. tuberculosis* in 80 to 90 percent of culture-positive specimens, although it has also been reported to have variable results. Although NAA and phage technology have the potential to improve detection of mycobacteria in smears, neither can replace conventional smear and culture, which provide information on infectivity, response to therapy, and antibiotic susceptibility.

DRUG SUSCEPTIBILITY TESTING

Drug susceptibility testing has become increasingly important with the emergence of multidrug-resistant TB (MDR-TB), in which isolates exhibit resistance to at least isoniazid and rifampin, two of the first-line antimycobacterials. Unfortunately, conventional drug susceptibility testing takes months, as the bacteria have to grow initially in culture and then be subjected to subculturing in the presence of antibiotics. This period can be reduced by the liquid medium–based methods, but these are also costly and require sophisticated equipment and trained personnel. Therefore, more rapid methods to detect antibiotic susceptibility, particularly those that could be employed in resource-limited settings, are needed.

A number of molecular strategies have been developed that are designed to detect mutations that are commonly associated with antibiotic resistance. In the case of rifampin, approximately 95 percent of all resistant strains contain mutations within the core region of the *rpoB* gene, so detecting the common mutations can identify most resistant isolates. Moreover, since rifampin resistance is often a marker of other drug resistance, this allows a rapid method to detect suspected MDR cases. A variety of molecular strategies are feasible, but a limitation of this approach is that only the most common mutations are sought, so there is a failure to detect rare or unknown mutations, making conventional phenotypic testing a necessary adjunct. Nonetheless, in the future such genotypic tests may be helpful in providing rapid antibiotic sensitivity information in cases where MDR-TB is suspected. Unfortunately, most MDR cases occur in parts of the world least able to afford such tests.

There are several emerging strategies to rapidly determine drug susceptibility that are more amenable to implementation in resource-poor settings. In all cases, the goal is to detect viable bacteria in the presence of antibiotics by some means other than growth. This can be achieved by assessing a change in the color of the medium due to bacterial metabolism as indicated by colorimetric redox indicators. Alternatively, phage technology can determine the presence of viable bacteria based upon their ability to support infection by mycobacteriophages. These are potentially affordable assays that do not require highly skilled personnel or expensive reagents. Although the experience with these tests remains limited, phage-based assays appear sensitive and specific for detecting rifampin resistance in low-resource reference laboratories.

PREVENTION

The widely used vaccine, BCG, is an attenuated strain of *M. bovis* that was derived fortuitously during serial passage in the laboratory. Although the vaccine may have some efficacy in preventing severe disease in children (particularly tuberculous meningitis), it does little if anything to diminish pulmonary disease in adults. Development of an improved vaccine, however, remains a formidable challenge. First, the vaccine needs to generate long-lived protective immunity, but the determinants of such immunity are poorly understood. In fact, infection with *M. tuberculosis* itself may fail to generate protective immunity, as at least some individuals are susceptible to reinfection. Similarly, in mice treated for an episode of TB, immunity is inadequate to prevent subsequent reinfection and disease. Thus, there is reason to think that a vaccine will have to do a better job in eliciting immunity than natural infection. Ideally, a vaccine should also generate protective immunity in patients co-infected with HIV and must be safe in populations of immunocompromised individuals. In addition, as the vaccine will be used in areas with a high rate of existing latent TB infection, it should not generate an overly exuberant inflammatory response that could worsen underlying disease.

Several features of BCG may explain why it is a suboptimal vaccine against *M. tuberculosis*: it is derived from a different species, has numerous changes from the parent strain, and fails to make certain T-cell antigens. Hence, one strategy has been to genetically engineer a new attenuated strain from *M. tuberculosis*, while attempting to maintain its antigenicity. Directed mutations have been made that render the strain defective for growth in the absence of certain nutrients, such as leucine, which make it attenuated for growth in animals. The hope is that this will prove more effective than the "overly attenuated" BCG. Alternatively, it may be possible to improve BCG, for example, by restoring secretion of known antigens such ESAT-6. The complication of this approach is that, at least for ESAT-6, this is also a virulence factor, so immunity may be improved but potentially at the cost of safety.

There are reasons to think that *M. tuberculosis* has active mechanisms that undermine the establishment of adequate immunity, for instance by blunting cytokine signaling and inhibiting antigen presentation. Thus, an alternative approach has been to deliver immunodominant antigens, for instance a fusion of ESAT-6 and Ag85B, using a DNA delivery system such as adenovirus, either as a priming vaccine or to boost immunity from prior BCG vaccination. It might also be possible to improve the visibility of antigens present in BCG to the host immune system. Because the bacteria are generally sequestered in the phagosomal compartment and do not induce significant amounts of apoptosis of host cells, there may be relatively poor presentation of antigens via major histocompatibility complex (MHC) class I. A clever strategy has been to modify BCG such that it lyses the phagosomal membrane and generates enhanced cellular apoptosis. This appears to generate a more robust protective immune response without compromising safety. Although our improved molecular understanding has provided several avenues to explore for improved vaccines, the logistical barriers are still substantial. In particular, since we lack good markers of protection and only a fraction of infected people develop active disease over decades, efficacy studies will require following large numbers of patients for many years.

TREATMENT

Current treatment guidelines for TB require multiple antibiotics for a minimum of 6 months. The standard regimen of INH, rifampin, pyrazinamide, and ethambutol is long and complex, often complicated by side effects or drug interactions, resulting in a substantial rate of treatment failure. These drugs each function by distinct mechanisms—INH inhibits mycolic acid synthesis in the cell wall, rifampin inhibits RNA synthesis, while pyrazinamide targets the cell membrane. All of the drugs are most active against replicating bacteria. With the exception of rifampin, they have limited activity against non-growing bacilli which makes them ineffective at eliminating dormant bacteria.

Despite the limitation of current therapy, no medication with a new mechanism of action has been brought to market for TB therapy in over 40 years. However, a number of antibiotics, developed against other bacteria, have activity against *M. tuberculosis*, and there is a concerted effort to identify novel therapeutics, some of which are entering clinical trials. Among already available antibiotics, fluoroquinolones, in particular moxifloxacin and gatifloxacin, have potent anti-TB activity. The bactericidal and sterilizing activity of moxifloxacin suggest that it may have a role as a first-line drug with the potential to shorten treatment. However, given the widespread use of fluoroquinolones for other infections, there is concern that emerging antibiotic resistance may limit their use. Linezolid also has antituberculous activity and has been used in combination therapy for the treatment of MDR-TB, although the poor tolerability with prolonged use limits its utility in this context.

There are two strategies for identifying new drugs. The first involves the identification of potential drug targets—for example, molecules that are essential for bacterial growth. If the activity of these molecules can be assayed *in vitro*, then it is possible to screen for small molecules that inhibit the activity. The advantage of this approach is that the drug target is known, greatly aiding modifications of lead compounds. The limitation, however, is that although the compound may inhibit the desired activity *in vitro*, it does not guarantee that it will be able to cross the microbial cell wall or bypass bacterial defenses such as degradative enzymes or efflux pumps. Moreover, it is impossible to identify pro-drugs, which require activation by the bacterial cell.

The alternative approach involves identifying compounds that inhibit microbial growth. This straightforward approach identifies molecules with antimicrobial activity, but in the past, it has been difficult to subsequently determine the drug target. The ability to make structure-based modifications, which is usually necessary to improve activity and minimize toxicity, is then limited. However, a promising new anti-TB agent was identified using this strategy, and the putative target was quickly found by use of modern genomics. In this case, a library of diarylquinolone compounds was screened, identifying a bactericidal agent (R207910) with broad activity against mycobacterial species. Whole genome sequencing of resistant isolates quickly established the molecular lesion responsible for resistance, thus identifying the putative target. This drug appears to be effective in animals and well tolerated in humans.

Other drugs reported to be in development include PA-824, a nitroimidazopyran that inhibits protein and cell wall lipid synthesis. It exhibits activity against both replicating and static *M. tuberculosis*, and has sterilizing effects similar to the combination of INH and rifampin. A compound from Otsuka Pharmaceutical Group and LL-3858 of Lupin Laboratories are also under investigation, although there is little publicly available information. Although the clinical efficacy and safety of newer agents awaits further trials, the identification of novel drugs highlights the promise of functional genomics, structure-based drug design, and combinatorial chemistry for improved TB therapeutics.

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Clinical Presentation and Treatment of Tuberculosis

Mary Elizabeth Kreider • Milton D. Rossman

Tuberculosis is a disease that has afflicted humankind throughout recorded history. Spinal lesions that are highly suggestive of tuberculosis have been observed in a skeleton recovered from a grave near Heidelberg that dates from 5000 B.C.; a skeleton excavated from the Arene Candide Cave in Liguria, Italy that dates from 4000 B.C.; and similarly ancient graves in Denmark and the Jordan Valley. Mycobacterium tuberculosis DNA has been recovered from a pre-Columbian mummy from Peru. The earliest records that are consistent with tuberculosis are Egyptian wall paintings that depict typical hunchback deformities and correlate with the findings of spinal tuberculosis in mummies. Hippocrates not only described the condition, but also named it "phthisis," which means to melt or waste away. Aristotle noted its contagious nature, but it was not until Koch discovered the tubercle bacillus in 1882 that the etiologic agent was identified. Today tuberculosis describes an infection in humans that is caused by either *Mycobacterium tuberculosis* or *Mycobacterium bovis*. Infections caused by other mycobacteria should be referred to as diseases caused by each specific mycobacterium. Despite the discovery of the cause of tuberculosis and the development of effective chemotherapy in the 1950s, tuberculosis continues to be a major pulmonary pathogen and is a leading cause of infectious death in adults worldwide.

The pathogenesis of tuberculosis is reviewed in detail elsewhere in this volume and is only briefly summarized here. The lung is the site of entry in the overwhelming majority of cases of tuberculosis. After inhalation, the tubercle bacillus sets up a localized infection in the periphery of the lung where it is deposited. The first stage of infection typically results in few or no clinical signs or symptoms. In 4 to 6 weeks the host immune system develops a hypersensitivity response to the bacillus and at this time mild fever and malaise may develop, and occasionally other hypersensitivity manifestations are noted.

In the preponderance of patients, the process is contained by local and systemic defenses and no further evidence of disease develops. The subpleural location of the initial infection occasionally leads to a rupture into the pleural space leading to tuberculous pleurisy with effusion. Commonly, the infection can also spread locally to hilar lymph nodes, and from there to other areas of the body. This hematogenous dissemination results in both the pulmonary and extrapulmonary foci that are responsible for the major clinical manifestations of tuberculosis. On chest radiographs this spread is manifested by enlargement of the lymph nodes, with later calcification of both the lymph nodes and parenchymal lesion (the Ghon's complex). Progressive (or reactivation) tuberculosis usually develops after a variable period of dormancy and arises from the sites of hematogenous distribution.

Accordingly, the first infection with tuberculosis frequently is clinically silent or unrecognized. In the majority of patients, the disease remains latent either indefinitely or for many years, and when a breakdown occurs it may be secondary to a decrease in immunity (e.g., the development of cancer, immunosuppressive therapy, etc.).

CLINICAL PRESENTATION

Pulmonary Tuberculosis

The lung is the most commonly affected organ in tuberculosis. In the 2004 CDC surveillance reports, 79.5 percent of the newly diagnosed cases of tuberculosis had lung involvement. Similar rates of pulmonary involvement are found in both immunocompetent and immunocompromised hosts, such as those with human immunodeficiency virus (HIV) infection. Studies from the 1980s to the 1990s suggested that the rates of pulmonary involvement in HIV were 70 to 92 percent. However, these individuals are also more likely to have extrapulmonary disease.

Symptoms and Signs

Given the wide spectrum of lung involvement seen in tuberculosis, ranging from skin positivity with clear x-rays to far advanced disease, a wide range of signs and symptoms can also be seen. Frequently there are minimal symptoms that are fairly non-specific until the disease is far advanced, and these may be attributed to other causes. Symptoms are often divided into two categories: constitutional and pulmonary. The most frequently reported symptoms in studies of active pulmonary tuberculosis include cough (23 to 47 percent), fever (18 to 79 percent), weight loss (7 to 24 percent), and hemoptysis (8 to 9 percent). The frequency of these symptoms differs according to whether the patient has primary tuberculosis or reactivation tuberculosis, with lower frequencies of all symptoms in the primary tuberculosis groups. A classic fever pattern has been described, with a fever that develops in the late afternoon and may not be accompanied by pronounced symptoms. With defervescence (typically at night) sweating occurs—the classic "night sweats." As the infection progresses and the caseation necrosis and liquefaction occur, patients can develop a productive cough often associated with mild hemoptysis. Chest pain may be localized and pleuritic. Shortness of breath typically is due to extensive parenchymal lung disease and is therefore a late manifestation of the infection.

Laboratory Examination

Routine laboratory examinations are rarely helpful in establishing or suggesting the diagnosis. A mild normochromic normocytic anemia may be present in chronic tuberculosis. The WBC count is often normal, and counts over 20,000/μL may suggest another infectious process; however, a leukemoid reaction occasionally may occur in miliary tuberculosis. Other nonspecific tests that may be elevated in active tuberculosis include the sedimentation rate, α_2-globulins, and γ-globulin. On rare occasions, the serum sodium may be depressed owing to inappropriate secretion of antidiuretic hormone. This only occurs in advanced pulmonary tuberculosis.

Radiography

Primary

The most common radiographic appearance of primary tuberculosis is a normal radiograph. Primary tuberculosis parenchymal involvement can happen in any segment of the lung. In the primary infection there is only a slight predilection for the upper lobes. The airspace consolidation (Fig. 140-1) appears as a uniform density with ill-defined

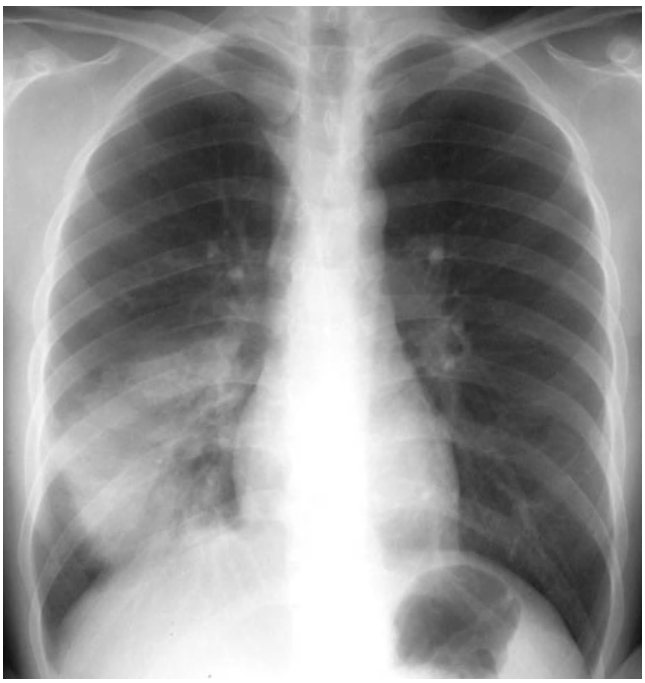
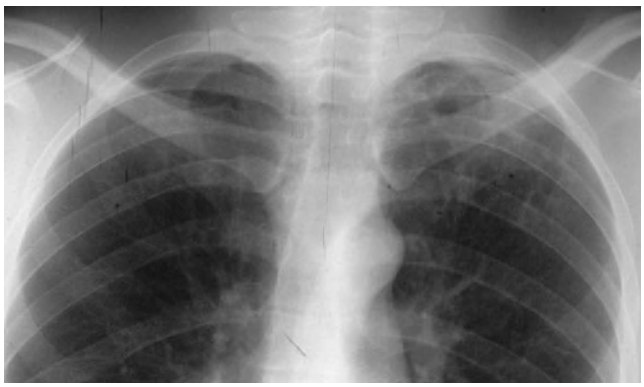


Figure 140-1 Primary tuberculosis: A 31-year-old woman from Taiwan with mild cough and fever. There is an infiltrate in the right lower lobe. PPD was positive. Primary TB must be considered in the differential of this radiograph. *(Courtesy of Wallace Miller, Jr., M.D.)*

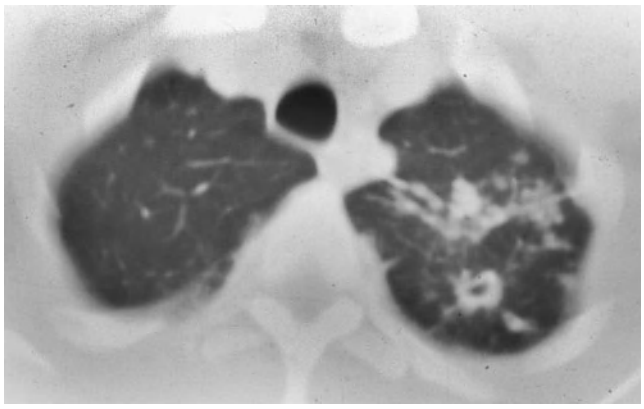
borders, and cavitation is rare except in malnourished or other immunocompromised patients. Typically these infiltrates are small and subpleural in location. Hilar or paratracheal lymph node enlargement is a characteristic finding in primary tuberculosis. However, it is most commonly seen in children. Usually, the adenopathy is unilateral. In contrast to lymphadenopathy, infiltrates are seen more commonly in adults with primary TB. Miliary involvement (seen as multiple small nodules) at the onset of disease is seen in less than 3 percent of cases, most commonly in children under 2 to 3 years of age, but can also be seen in adults. Finally, an isolated pleural effusion of mild-to-moderate degree may be the only manifestation of primary tuberculosis.

Reactivation Tuberculosis

Although reactivation tuberculosis may involve any lung segment, the characteristic distribution usually suggests the disease. In 95 percent of localized pulmonary tuberculosis, the lesions are present in the apical or posterior segment of the upper lobes (Fig. 140-2) or the superior segment of the lower lobes. The typical parenchymal pattern of reactivation tuberculosis is of an airspace consolidation in a patchy or confluent nature. Frequently there are increased linear densities to the ipsilateral hilum. As the lesions become more chronic, they become more sharply circumscribed and irregular in contour. Lymph node enlargement is rarely seen. Cavitation can occur in up to 40 percent of cases. These cavities typically have moderately thickened walls, but fewer than 10 percent of cases have air-fluid levels. Cavities are associated with endobronchial spread of the disease. Fibrosis leads to volume loss in the involved lung. The combination of patchy pneumonitis, fibrosis, and calcification is suggestive of chronic granulomatous disease, often tuberculosis.



A



B

Figure 140-2 Reactivation tuberculosis: A 31-year-old man with persistent right chest pain. *A*. View of the lung apices demonstrates an indistinct pulmonary opacity in the left apex. *B*. Computed tomographic images demonstrate small nodules and a cavitary lesion. Sputum cultures were positive for *M. tuberculosis*. *(Courtesy of Wallace Miller, Jr. M.D.)*

Chest Computed Tomography

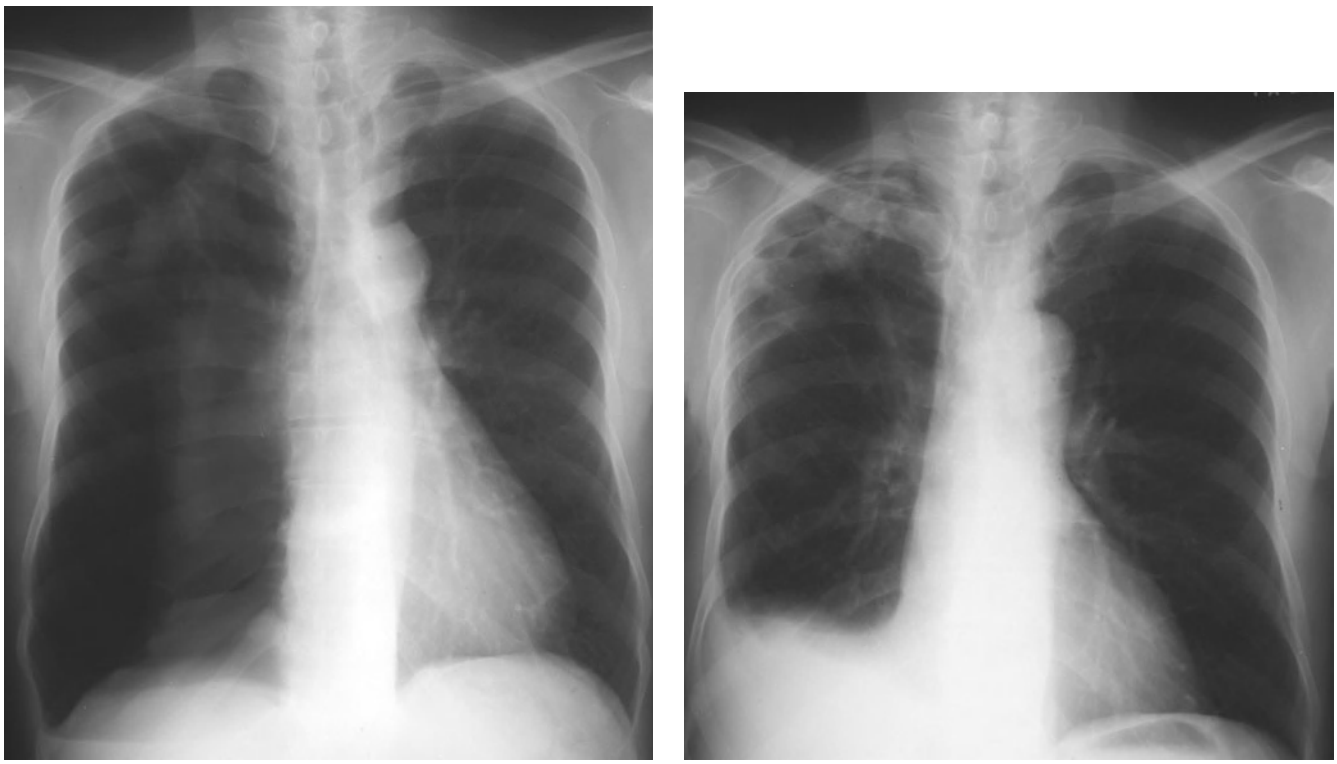
Computed tomography (CT) scans offer a more detailed examination of the parenchyma and the lymph nodes than can be done with plain chest x-ray alone. The chest CT in patients with primary tuberculosis typically demonstrates lobar consolidation in association with mediastinal or hilar adenopathy. The consolidation is usually well defined, dense, homogenous, and confined to a segment or lobe. CT may allow the visualization of tiny cavities that were not recognized on the plain chest x-ray. Reactivation tuberculosis may be characterized by the presence of centrilobular nodules or branching linear structures (tree in bud) with or without bronchial wall thickening, lobular consolidation, cavity formation, bronchiectasis, and/or fibrotic changes. Debate exists over whether CT scans can dependably discriminate active tuberculosis from latent infection. Some authors argue that findings such as the tree in bud and/or areas of centrilobular nodules are more consistent with active disease.

Complications of Pulmonary Tuberculosis

Minor endobronchial disease of the distal bronchi is a frequent occurrence in tuberculosis. Resected lung specimens frequently show either ulceration or stenosis of the draining bronchioles or bronchi. However, significant bronchial stenosis of major bronchi is rare. The same endobronchial processes may result in bronchiectasis due to destruction of the bronchial wall. Bronchiectasis also usually involves the distal airways and has a predilection for the upper lobes. Often this bronchiectasis is associated with little sputum production (dry bronchiectasis) and may manifest itself predominantly as low-grade hemoptysis.

Pneumothorax (Fig. 140-3) is a rare but serious complication of tuberculosis that requires immediate attention. A pneumothorax is believed to occur from subpleural infection rupturing into the pleural space. This may lead to the spread of infection into the pleural space and, if left untreated, can lead to the development of an empyema with subsequent fibrothorax and associated trapped lung. A bronchopleural fistula may persist after a pneumothorax and, especially if untreated, may result in major problems from secondary or superimposed bacterial infection (mixed empyema).

Even if tuberculosis is treated and cured, the destruction of lung parenchyma that occurs during active infection



A *B*

Figure 140-3 Tuberculosis pneumothorax: A 69-year-old patient admitted with spontaneous pneumothorax (*A*). After chest tube was placed and lung re-expanded, new RUL infiltrate was seen (*B*). Bronchoscopy specimens grew out *M. tuberculosis. (Courtesy of Wallace Miller, Jr., M.D.)*

can lead to later complications. Colonization of cavities and areas of bronchiectasis may occur with a variety of infectious agents. Infection with typical respiratory flora can convert "dry" to "wet" bronchiectasis, with frequent exacerbations of purulent sputum production. *Aspergillus* species may commonly colonize and/or infect areas of badly damaged lung. One prospective study in England revealed that 25 percent of clinically healed tuberculosis patients who had residual cavities developed positive precipitins to *Aspergillus* species and 11 percent had demonstrable cavitary "balls," presumed to be aspergillomas. Three years later, these numbers had risen to 34 and 17 percent, respectively.

Hemoptysis can occur in early and late infection. Mild hemoptysis is very frequent in acute infection and may be the first symptom that leads patients to present. Larger volume hemoptysis can occur later in the disease and may be due to rupture of a Rasmussen's aneurysm (a mycotic aneurysm of a branch of the pulmonary). These bleeds are still typically fatal. Even after infection, hemoptysis can occur due to the secondary development of an aspergilloma or exacerbations of bronchiectasis.

Hyponatremia can develop during active tuberculosis due to two processes; the syndrome of inappropriate antidiuretic hormone excretion (SIADH) and a reset osmostat. The SIADH of tuberculosis is similar to all other causes of SIADH and can cause clinical symptoms with renal salt wasting. A reset osmostat, on the other hand, is characterized by decreased serum osmolality without clinical symptoms or salt wasting. Both conditions disappear with control of the infection; however, they should be differentiated from each other since SIADH requires metabolic control.

DIAGNOSIS

Tuberculin skin testing with purified protein derivative (PPD) is the current standard diagnostic test for latent tuberculous infection. In 1891 Robert Koch described a broth culture filtrate of tubercle bacilli. Although it was not the cure for tuberculosis that he first described, he did note that a subcutaneous inoculation of it led to a febrile reaction in patients with tuberculosis that did not occur in healthy individuals. Over time the technique was refined to create a intradermal reaction with a PPD. It cannot distinguish, however, between latent and active infection. False-positive skin reaction can occur with infection with non-tuberculous mycobacterial (NTM) infection or from vaccination with *M. bovis* BCG. False-negatives can occur with anergy due to immunocompromised states or recent or active infection, since it can take up to 10 weeks to develop a typical skin reaction. In 2000 the Centers for Disease Control (CDC), the American Thoracic Society, and the Infectious Disease Society of America issued guidelines for the use of PPD testing as a screening test for latent tuberculous

Table 140-1

Guidelines for the Interpretations of PPD Skin Tests

Induration >5 mm
HIV-positive patients
Recent contracts of active tuberculosis cases
Fibrotic changes on chest x-ray consistent with prior tuberculosis infection
Patients with organ transplants or other chemically immunosuppressed patients (equivalent of >15 mg/day of prednisone for 1 month or more)
Induration >10 mm
Recent immigrants from high prevalence countries
Injection drug users
Residents and employees of prisons, nursing homes, long-Term care facilities, hospitals, and shelters
Mycobacteriology laboratory personnel
Persons with silicosis, diabetes, chronic renal failure, hematological disorder, and specific malignancies (i.e., head and neck cancer), malnourished individuals, and subjects after gastrectomy and jejunoileal bypass
Children younger that 4 or those exposed to adults at high risk
Induration >15 mm
Persons with no risk factors for TB

SOURCE: *Official Statement of ATS, CDC, and IDSA, September 1999.* Am J Respir Crit Care Med *161:s221–s247, 2000.*

infection. The guidelines suggest that risk for infection should affect the cutoff used to determine a positive result. Table 140-1 illustrates the suggested cutoff values for patients with different risk factors for the presence of tuberculous infection. Newer techniques for the diagnosis of latent infection are being developed including the QuantiFERON-TB and QuantiFERON-TB Gold tests (Cellestis Limited, St. Kilda, Australia) and the T SPOT-TB test (Oxford Immunotec, Oxford, UK). These tests are based on detection of either interferon gamma by T cells exposed to *M. tuberculosis* antigens or detection of the T cells themselves. The advantages of these tests may include greater specificity (no cross reactivity with BCG and NTM) and improved sensitivity in immunosuppressed patients, and the lack of the need for follow-up in 48 to 72 hours. However, these tests are still expensive and require some laboratory expertise, which may limit their usefulness, especially in the developing world. The utility of these tests is still being evaluated in studies and they are already being widely used in the European Union.

The diagnosis of active tuberculosis often can be very difficult. A confident diagnosis of tuberculosis requires bacteriologic confirmation. It is important to remember that a positive acid-fast smear is not specific for *M. tuberculosis*. Other mycobacteria, both saprophytes and potential pathogens, are usually acid-fast, and can cause similar patterns of pulmonary disease. Thus, culture of *M. tuberculosis* is the only absolute way of confirming the diagnosis.

Freshly expectorated sputum is the best sample to stain and culture for *M. tuberculosis*. Sputum samples 24 hours old are frequently overgrown with mouth flora and are much less useful. The sensitivity of expectorated sputum (by smear, and/or culture) ranges from 34 to 80 percent in studies, and is highest in cavitary disease. If the patient is not spontaneously producing sputum, induced sputum is the next best specimen for study. It can be obtained by having the patient breathe an aerosol of isotonic or hypertonic saline for 5 to 15 minutes. A single induced sputum may have a yield of 64 percent for the diagnosis of tuberculosis by smear and 70 percent by culture. Increasing the number of induced sputum samples obtained to three increases the yield to 91 percent for smear and 99 percent for culture.

In some cases, bronchoscopy may be considered to obtain a sputum sample when none are expectorated or inducible. In 41 patients with proven tuberculosis, cultures of specimens taken during fiberoptic bronchoscopy were positive in 39 (95 percent) cases. Mycobacteria were seen on initial smear in 14 (34 percent) cases, and in eight (20 percent) cases granulomas were seen on biopsy. Similar results have been obtained in another study of 22 patients with proven mycobacterial disease and negative smears prior to bronchoscopy. The local anesthetics used during fiberoptic bronchoscopy may be lethal to *M. tuberculosis*, so specimens for culture should be obtained using a minimal amount of anesthesia. However, irritation of the bronchial tree during the fiberoptic bronchoscopy procedure frequently leaves the patient with a productive cough. Thus, collection of the postbronchoscopy sputum can be another valuable source of diagnostic material. In nine (13 percent) of the preceding cases, the postbronchoscopy sputum was the only source of positive material.

Nucleic acid amplification (NAA) assays have become a useful adjunct in the diagnosis of tuberculosis. These assays amplify *M. tuberculosis* specific amino acid sequences using a probe. The advantage of these assays is that they require a much lower bacillus load to detect the presence of tuberculosis (10 bacillus vs. 5000 to 10,000 bacilli needed for smear positivity and 10 to 100 organisms for positive culture). They are also very specific for MTB. There are new assays that may not only detect *M. tuberculosis,* but also amplify sequences specific for INH and rifampin resistance and thus may provide information on drug sensitivity as well. These sensitivity assays are not yet widely available for clinical practice and their performance in general clinical situations has not been tested. All of these assays are very expensive and require a sophisticated laboratory. Therefore, the exact role of the NAA assays remains in debate. Most authorities agree that they are useful when attempting to confirm that a positive smear is indeed due to *Mycobacterium tuberculosis*. They may also be useful in cases with negative smears but a high clinical

suspicion to suggest the diagnosis while awaiting the culture results.

In 2004, as reported to the CDC, 45 percent of pulmonary cases of tuberculosis were smear positive, 42 percent were negative, and 13 percent were not done or unknown. Sputum culture was positive in 69 percent, negative in 17 percent and unknown in 14 percent of cases. Thus, in a significant number of cases, the diagnosis of tuberculosis had been made in the absence of bacteriologic confirmation. In these cases, the diagnosis was made by a combination of a positive skin test, a compatible chest radiograph, and a therapeutic trial.

Extrapulmonary Tuberculosis

Tuberculosis can spread to almost any organ in the body and is associated with several common extrapulmonary syndromes. In the most recent CDC report of new infection in the United States, the most commonly affected sites outside the lung included lymph nodes (44 percent), pleural space (19 percent), bone and joint infection (11 percent), meninges (6 percent), peritoneal (5.5 percent), genitourinary track (4 percent), miliary (1.8 percent), and other (11 percent). Older studies in the United States show different patterns with a recent decrease in the frequency of genitourinary disease, bone and joint infection, and miliary disease. Other countries display different frequencies largely due to the prevalence of other immune-modulating diseases such as HIV.

Lymphadenitis

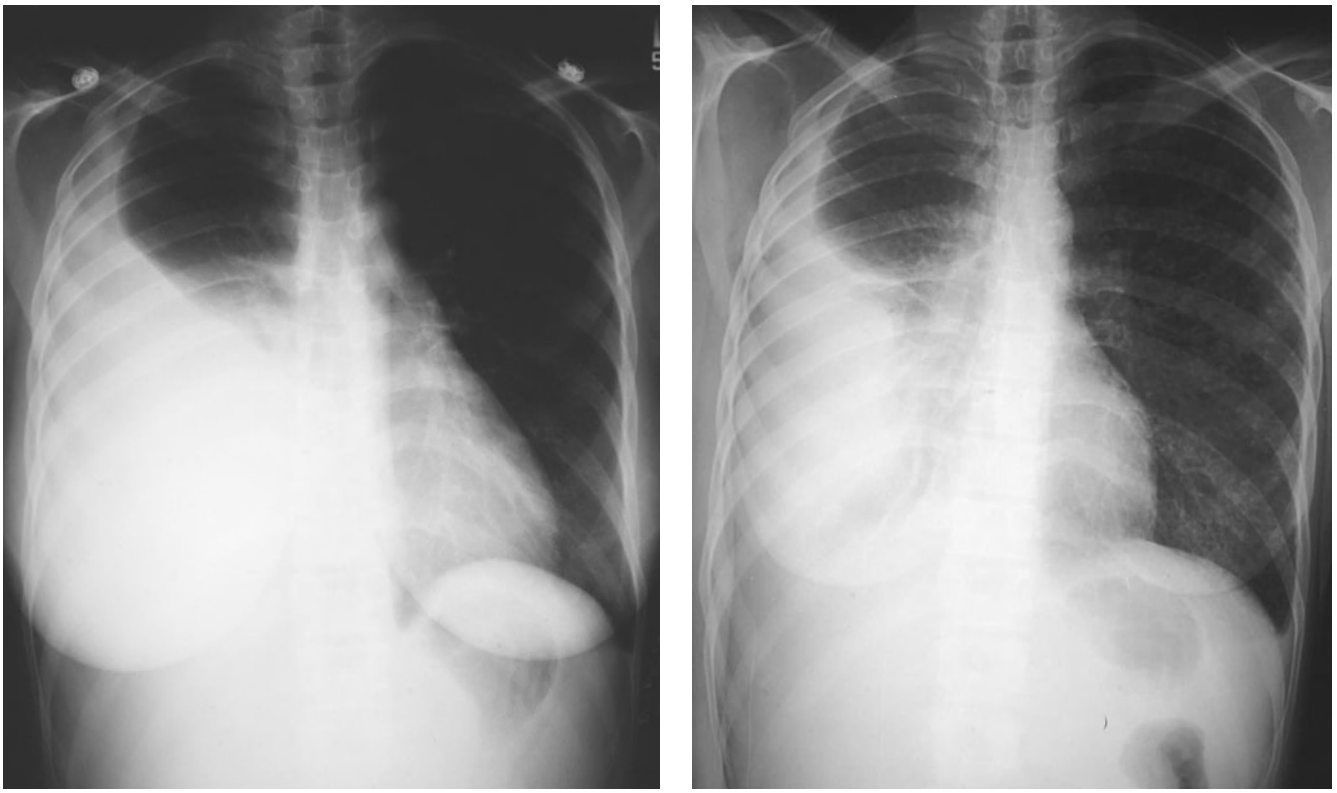
Mycobacterial infection involving the cervical lymph nodes, or scrofula, is the most common extrapulmonary manifestation of tuberculosis. Seventy percent of patients with nodal disease have cervical node involvement alone, 7 percent have inguinal involvement, 7 percent have axillary involvement, and 16 percent have multiple nodes involved simultaneously. Only 5 to 10 percent of patients have active pulmonary tuberculosis concomitantly. Therefore, constitutional symptoms such as weight loss, night sweats, or hemoptysis are unusual. There may be an enlarged single node or several nodes matted together. Infrequently these nodes are flocculent or have draining sinuses. Patients with tuberculous lymphadenitis are PPD positive in 74 to 96 percent of cases at the time of presentation. Fine-needle aspiration of the involved node can diagnose tuberculosis as the causative agent by cytology in 83 percent of cases and another 25 percent of those with negative cytology subsequently grow *M. tuberculous* on culture. In negative fine-needle aspirates, excisional biopsy may be necessary to make the diagnosis and rule out other possibilities, including lymphoma. Lymphadenitis is treated medically with antituberculous therapy, as described later in this chapter. Surgical intervention is reserved for situations in which excision is necessary for diagnosis or to remove nodes that remain enlarged after therapy. Medical therapy even for sinus tracks and/or flocculent nodes is undertaken first because of the propensity for the development of further sinuses if surgery occurs while the infection is still active.

Pleural Disease

Pleural disease accounted for 19 percent of cases of extrapulmonary tuberculosis reported to the CDC in 2004. Tuberculous pleural effusions (Fig. 140-4) are usually due to the rupture of subpleural foci of tuberculosis and an accompanying delayed hypersensitivity reaction to a small number of bacilli within the space. The effusions in tuberculosis are typically unilateral and mild to moderate in size. Miliary spread may lead to the development of bilateral effusions. The natural course of a tuberculous pleural effusion is to gradually resorb without treatment and usually resolves with minimal changes on the chest radiograph. However, these patients are at significant risk of reactivation within subsequent years.

The diagnosis of pleural effusions due to tuberculosis can be accomplished by appropriate studies of the pleura and/or pleural fluid in approximately 80 percent of cases. These studies involve evaluation of the character of the fluid, which is an exudate (pleural fluid protein greater than 4 g/dL) with a prominent lymphocytosis and few mesothelial cells. Smears of the fluid usually are negative for tubercle bacilli, but positive cultures are found in more than half of the cases. Repeated thoracenteses with culture of large quantities of fluid combined with centrifugation may also increase bacteriological yield. When one combines the histological examination and culture of the pleural biopsy specimen with study of the fluid, one has the highest rate of diagnosis (80 percent). For each undiagnosed pleural effusion, in addition to the studies for tuberculosis, studies for malignant cells, fungi, and bacteria should be performed on the aspirated fluid and any biopsy material. Elevated adenosine deaminase (ADA) is frequently found in tuberculous effusions but the utility of this test depends on the pre-test probability of tuberculosis in the individual patient. When a patient has a positive 5-TU tuberculin test (greater than 10-mm induration), his or her effusions should be presumed to be tuberculous until proved otherwise. If a patient has an undiagnosed exudative effusion and a negative tuberculin test, the tuberculin test should be repeated within 2 weeks, since it is not uncommon for patients with tuberculous effusions to have an initially negative tuberculin test. At times, a video assisted or standard thoracotomy with pathological examination of the pleura for tuberculosis, fungi, malignant cells, and bacteria may be necessary to establish the cause of a pleural effusion.

In the absence of a diagnosis and the presence of a compatible pleural effusion, consideration should be given to a trial of antituberculous therapy on the basis of a presumptive diagnosis of tuberculosis. Many patients with an undiagnosed pleural effusion later develop progressive parenchymal tuberculosis if they are not treated. However, a therapeutic trial in pleural tuberculosis is not as helpful diagnostically as one in pulmonary tuberculosis, since the natural course of pleural tuberculosis is toward resolution.



A *B*

Figure 140-4 Tuberculosis effusion. *A*. A 23-year-old patient with persistent shortness of breath postpartum whose chest radiograph demonstrated a large right pleural effusion. Thoracentesis to obtain pleural fluid was nondiagnostic. *B*. Two months later, chest radiograph revealed miliary nodules in addition to right pleural effusion and culture of bronchoscopy washing grew out *M. tuberculosis. (Courtesy of Wallace Miller, Jr., M.D.)*

Tuberculosis empyema is a rare condition due to purulent infection of the pleural space with a large bacillus burden; thus, typically AFB cultures of the fluid are positive. However, in contrast to tuberculous pleurisy, which does not require surgery, tuberculous empyema is usually accompanied by a thick pleural peel and requires surgical drainage or decortication (see complications) in addition to antituberculosis therapy.

Bone/Joint Infection

The classic description of spinal tuberculosis was written by Percival Pott in 1779. However, mummified remains from Egypt dated to 3400 B.C. show evidence of its existence. It remains the most common site of tuberculosis involvement of the bone with approximately 50 percent of bone infections with tuberculosis in the United States occurring in the spine. Pain at the site of the infection is the most common symptom. Chronic constitutional symptoms are also frequent. Neurological involvement occurs in 10 to 61 percent of patients and late presentation and cervical involvement may predispose to higher rates of disability. MRI with gadolinium has become the radiographic test of choice with bone scans and gallium scans being frequently unreliable. However, there are no pathognomic findings of Pott's disease on x-ray, so biopsy and culture remain the gold standards for diagnosis. Medical therapy is required. Surgery is restricted to those who need biopsy, unstable spinal lesions, and those with progressive neurological symptoms while on appropriate therapy. This disease, like other extrapulmonary and paucibacillary types of TB, is not only more difficult to diagnose by culture, but likely to be associated with a longer time to culture positivity than pulmonary TB. High clinical suspicion of TB in the spine should prompt consideration for empiric antituberculous therapy while cultures are pending, especially if a biopsy shows granulomatous inflammation.

Tuberculosis has been reported in all bones in the body. However, large bones/joints are more commonly affected than smaller bones/joints. Multiple simultaneously involved joints are rare. Joint infection can present as worsening arthritis with effusions and infrequently with draining sinuses. Often systemic symptoms are absent. Aspiration of the joint rarely yields the diagnosis and a biopsy of the synovial tissue is typically required. Like spinal infection, medical therapy is first line and surgery is reserved for complicated cases.

Gastrointestinal/Peritoneal

Tuberculosis can involve any part of the gastrointestinal tract. However, the most commonly affected area is the ileocecal

region. Peritoneal involvement may occur due to spread from abdominal lesions or associated lymph nodes. Most patients have fever (40 to 70 percent), pain (80 to 95 percent), diarrhea (11 to 20 percent), constipation, weight loss (40 to 90 percent), anorexia, and malaise. Despite these constitutional symptoms, pulmonary involvement is present in less than half of the affected patients. In peritoneal involvement, ascitic fluid may provide diagnostic information. The fluid typically has elevated fluid protein, elevated white count with lymphocyte predominance, and low glucose. Unfortunately, the yield of fluid culture is low (less than 20 percent). This is a volume-dependent test and if one wants to send a culture of this fluid, one should consider sending several liters to the laboratory, which can be spun down and concentrated prior to culture. Several studies have found that adenosine deaminase levels may be elevated in the ascitic fluid. However, HIV status and malignancy can alter these levels. Similar, to pleural disease, biopsy of the affected surface is necessary in most cases to confirm the diagnosis. Usually direct visualization by laparoscopy or laparotomy reveals studding of the peritoneum or mesentery, and directed biopsies of the lesions usually demonstrate granulomas instead of tumor, which is sufficient to prompt treatment.

Meningitis/Central Nervous System Involvement

Tuberculous meningitis is the most common form of central nervous system (CNS) involvement with the infection. Seeding of meninges is believed to occur from hematogenous spread of the bacilli. After the meninges are seeded, the disease can remain quiescent for a period of time until reactivation. After reactivation cell-mediated immunity leads to the formation of a thick, gelatinous exudate along the basal surface of the cerebrum. These exudates can obstruct cerebrospinal fluid (CSF), leading to hydrocephalus and encase cranial nerves, leading to further dysfunction. Additionally, the granulomas formed during the infection can coalesce to form a tuberculoma that can lead to focal neurological defects depending on their location. Finally, the infection can also lead to a vasculitis leading to infarction and stroke symptoms.

Clinical signs and symptoms of tuberculous meningitis include headache (50 to 80 percent), fever (60 to 95 percent), vomiting (30 to 60 percent), photophobia (5 to 10 percent), anorexia (60 to 80 percent), neck stiffness (40 to 80 percent), confusion (10 to 30 percent), coma (30 to 60 percent), cranial nerve palsy (30 to 50 percent), hemiparesis (10 to 20 percent), paraparesis (5 to 10 percent), and seizures (children: 50 percent; adults: 5 percent). There are no pathognomonic findings on neurological imaging, but common findings include basal meningeal enhancement, hydrocephalus, and infarction in the supratentorial brain parenchyma and brain stem. Lumbar puncture classically shows an elevated white count with a lymphocyte predominance, elevated protein, and very low glucose levels. Initial reports of yields from AFB smears and cultures from CSF were quite low. The yield can be increased by extremely careful microscopy and large volume (greater than 6 mL) analysis. In one study, increasing the volume of CSF from 2 mL to 6 mL examined increased the percentage of positive AFB cultures from 40 to 80 percent.

Genitourinary

Genitourinary (GU) tuberculosis occurs after hematogenous spread of the bacilli to the glomerulus. The infection can then spread down the GU system into the renal pelvis, ureters, bladder, epididymis, and testes. It frequently takes years to develop. The symptoms depend on the location of the burden of infection and range from symptoms of recurrent pyelonephritis, including flank pain, frequency, and dysuria, to chronic testicular pain with micturition that does not respond to typical antibacterials. The GU disease is more common in men. Untreated disease can lead to stenosis and/or stricture over time. Sterile pyuria is a classic finding. Diagnosis is made by culture of the urine, usually collected first thing in the morning on three consecutive days. Culture of ejaculate may also be positive in many cases, but does not seem to add to the yield from urine. GU tuberculosis is a significant cause of infertility in areas of the world where tuberculosis is endemic (e.g., 5 to 16 percent of cases of infertility in Indian women).

Miliary Tuberculosis

Miliary tuberculosis (Fig. 140-5) occurs when there is hematogenous spread of bacilli to multiple organs leading to the formation of small (less than 2 mm in diameter) granulomatous nodules. This widespread dissemination can occur at the time of primary infection or years later when the immune response is suppressed. Because multiple organs are involved, the symptoms are often protean, including fever, weight loss, malaise, and cough. Tuberculous meningitis occurs in 10 to 30 percent of patients with miliary disease and one-third of patients with TB meningitis have underlying miliary disease.

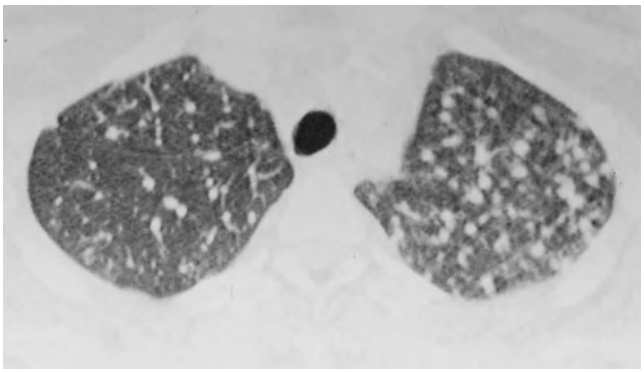


Figure 140-5 Miliary tuberculosis: A 30-year-old patient undergoing treatment for Hodgkin's disease with right neck lymphadenopathy and shortness of breath. Chest computed tomography demonstrated multiple military nodules, and sputum cultures grew out *M. tuberculosis. (Courtesy of Wallace Miller, Jr., M.D.)*

Within the lung, miliary lesions can lead to restriction and diffusion abnormalities, and in an extreme form is a cause of the adult respiratory distress syndrome (ARDS). Additionally, severe infection can lead to multiple organ dysfunction syndrome (MODS). Laboratory abnormalities can include anemia, hyponatremia, and liver function test elevation. Renal insufficiency can occur as part of MODS or because of direct parenchymal infection. Miliary tuberculosis is more common in patients with advanced HIV infection and in the elderly. Mortality is typically 25 to 30 percent in adults and 15 to 20 percent in children. Tuberculin skin tests may be negative in up to 50 percent of patients with miliary tuberculosis. Diagnosis can be difficult due to a typically low bacillus burden, and more invasive sampling techniques including BAL, bone marrow biopsy, or liver biopsy may be necessary.

TUBERCULOSIS IN SPECIAL HOSTS

Tuberculosis and Human Immunodeficiency Virus

Authorities agree that human immunodeficiency virus (HIV) infection is part of the explanation for the resurgence of tuberculosis in the United States since 1984. Prior to 1984, there had been a consistent decline in the numbers of newly reported active cases of tuberculosis. Since 1984, there has been a slight increase in the number of newly reported active cases. Several important differences have emerged regarding the clinical presentations of tuberculosis in patients with or without HIV infection. Patients with HIV infection are more likely to present with disseminated disease. Approximately 50 percent of people with HIV have extrapulmonary disease as compared to 20 percent of the general population. Additionally, they tend to have an increased number and severity of symptoms and have a more rapid progression to death unless treatment is begun.

Radiographic findings of TB in HIV correlate with the degree of immunosuppression due to the CD4 cell depletion. Hilar and mediastinal lymphadenopathy are usually associated with lower CD4 counts (i.e., less than 200/mm^3), while cavitation is seen more commonly is patients with higher CD4 counts. Additionally, HIV subjects may be more likely to have non-apical infiltrates, pleural effusions, and miliary infiltrates.

In patients with HIV infection but without the manifestations of AIDS, the tuberculin skin test is positive in 50 to 80 percent of patients with tuberculosis. Once an individual has developed AIDS, the tuberculin skin test is less likely to be positive, but reactivity may be seen in as many as 30 to 50 percent of patients. As noted, active tuberculosis should be considered in any HIV-infected patient with a tuberculin skin test that has greater than 5 mm of induration. The proportion of positive sputum smears and cultures is similar for HIV-infected and -uninfected patients. Therefore, the diagnostic algorithm of spontaneous or induced sputum followed by bronchoscopy with BAL as noted above for immunocompetent individuals should be followed. However, given the risk of rapid progression, the assumption must be that an acid-fast organism present in the sputum of a patient with HIV and pulmonary disease is *M. tuberculosis,* and treatment should be initiated pending definitive identification of the organism.

Tuberculosis in Children

In contrast to adults, tuberculosis in children often represents primary infection rather than the result of reactivation. Additionally, pediatric TB occurs more frequently in the very young, with greater than 60 percent of cases in children less than 5 years old and 26 percent in children less than 2 years old. When compared with adults, children (less than 15 years of age) have more lymphatic (15.5 vs. 6.8 percent) and meningeal involvement (2.1 vs, 0.9 percent). They are also less likely to have cavitary disease (4.9 vs. 27 percent in adults). HIV co-infection was lower in children and the proportion of multi-drug–resistant organisms was similar. Death rates were significantly lower in children (11.2 vs. 0.7 percent). Additionally there are two forms of TB unique to pediatrics. Congenital TB is rare and due to transmission in utero of the bacillus from mother to fetus. These children typically present within the first weeks of life with nonspecific symptoms, including cough and increased work of breathing, fever, hepatosplenomegaly, poor feeding, lethargy, and skin lesions. Mortality for congenital tuberculosis is high at around 40 percent. Neonatal tuberculosis occurs with transmission after birth and more frequently has CNS and miliary involvement.

Tuberculosis in the Elderly

Recent studies have begun to suggest that not only is increasing age a risk factor for the development of active tuberculosis, but the disease itself may present differently in the elderly, making it harder to recognize and diagnose. One study in South Africa prospectively examined 93 consecutive patients over the age of 60 admitted with pulmonary tuberculosis. Among these patients, "atypical" radiographic findings were the norm rather than the exception. For instance, only 7 percent had purely apical infiltrates, while 48 percent had mid and lower lung zones only, and 46 percent had mixed infiltrates between upper and lower lung fields. A pleural reaction was common (46 percent) and cavities were not (33 percent), with half of those seen in the lower and mid-lung fields. In addition the investigators found that systemic abnormalities of routine blood work were common, including anemia (66 percent), elevated erythrocyte sedimentation rates (90 percent), hyponatremia (60 percent), and hypoalbuminemia (83 percent). However, not all studies have confirmed these differences. One recent meta-analysis of 12 studies of tuberculosis found that the elderly were less likely to have symptoms such as fever, sweating, hemoptysis, and cavitary lung disease. They were more likely to have dyspnea and significant co-morbidities. In this study, the only differences seen in radiographic patterns between young adults and the elderly

was an increased incidence of miliary disease in the older population.

TREATMENT OF TUBERCULOSIS

History of the Treatment of Tuberculosis

In the late 1800s, before chemotherapeutic agents had been discovered, patients with TB were isolated in sanitariums for nutrition and rest. Lung collapse therapy was performed by pneumothorax or various surgical techniques that frequently left patients disfigured for life. In 1946, streptomycin was introduced as an effective antituberculosis drug and initially was used in TB patients by Feldman and Henshaw. However, it quickly became evident that streptomycin monotherapy resulted in relapse and the emergence of drug resistance. PAS, which was also used initially as monotherapy, could reduce the emergence of resistance to streptomycin; thus, two-drug therapy was born. In 1953, isoniazid (INH) and pyrazinamide (PZA) were released for therapy, and an era of truly effective chemotherapy began. Following the development of ethambutol (EMB) in 1964, INH and EMB became the cornerstone of an 18-month treatment regimen. Rifampin (RMP) was developed in 1965 and released for use in 1971. In the early 1980s, it was found that RMP and INH reduced the duration of therapy to 9 months. Addition of PZA to this regimen shortened the period of treatment to 6 months. Thus, in the 60 years since the introduction of the first effective drugs for the treatment of TB, the care of these patients has been transformed from long hospitalizations and a lifetime of fear of relapse to a relatively short outpatient treatment regimen and cure. The challenge today is not so much how to treat TB as how to ensure that patients receive the proper treatment. Failure to deliver proper care is the major cause for the development of drug-resistant strains and the fear for the recrudescence of this dreaded malady. Thus, directly observed therapy (DOT) has been adopted as the preferred method for insuring completion of effective therapy.

Theoretical Basis for Effective Treatment Strategies

Effective chemotherapy for tuberculosis is based on the observation that only actively replicating organisms can be killed. In addition, the environment in which the organism lives can affect not only its growth rate but also its susceptibility to different antibiotics. Mycobacteria that are living extracellularly in pulmonary cavities are metabolically very active and are rapidly growing in a hyperoxic and neutral pH environment. There organisms are highly susceptible to Streptomycin, INH, and ethambutol. Mycobacteria that live extracellularly in closed caseous lesions are less active metabolically and grow slowly in a hypoxic and neutral pH environment. These organisms are susceptible to rifampin and INH. Mycobacteria that live in the acidic, hypoxic environment of macrophages have a slow or intermittent growth, and PZA and rifampin are effective antibiotics. Finally, some mycobacteria may be trapped in fibrosis and encapsulated and may be completely dormant. These organisms are unaffected by antibiotics and the cellular immune system.

A second major consideration for effective chemotherapy is the presence of drug-resistant mutants. These mutants develop spontaneously at a rate of 10^{-7} to 10^{-10} mutations per bacterium per generation. Since cavitary lesions can contain 10^8 to 10^9 bacilli, it is likely that in cavitary lesions, some bacilli are resistant to any single drug. In addition, the probability of resistance to one drug is independent of the development of resistance to any other drug. Therefore, the probability of spontaneous resistance to two drugs is extremely low. Thus, antituberculosis chemotherapy should always consist of at least two effective drugs to prevent the emergence of drug-resistant mycobacteria.

Finally, because tuberculosis is an infectious disease and a public health threat, all providers, public and private, must ensure that patients complete effective chemotherapy. This is important because failure to complete effective chemotherapy is the most likely cause for the emergence of drug-resistant organisms. Thus, DOT has become the standard method of insuring completion of adequate chemotherapy. Adding individual incentives and enablers to DOT has resulted in greater than 90 percent of patients completing chemotherapy for pulmonary tuberculosis.

Specific Antituberculosis Drugs

First-Line Drugs

Isoniazid

Because of its bactericidal effect and low cost, INH is the most important drug used for the treatment of TB. INH should be included in all regimens except when a high proportion of INH-resistant organisms are present. INH is the hydrazide of isonicotinic acid, which most probably acts by inhibiting mycolic acid synthesis by mycobacteria. For INH to be effective, three things must occur. First, the drug has to be taken up by the organisms. Second, INH needs to be activated by a catalase-peroxidase enzyme within mycobacteria. Third, this activated form of INH then interferes with mycolic acid synthesis. Mutations that result in resistance of mycobacteria to INH have been reported in at least four different genetic loci. The most important is the katG gene, which encodes a catalase-peroxidase enzyme. Mutations at codon 315 have been associated with high levels of resistance and virulent organisms. Other genes associated with resistance to IHN are the inhA which codes for a protein involved in fatty acid elongation, the ahpC gene, which encodes a protein for alkyl hydroperoxidase reductase, and the oxyR gene, which encodes a protein involved in the regulation of oxidative stress. Thus, multiple molecular tests are necessary to identify all INH-resistant mycobacteria even though the katG gene seems to be the most important.

INH has a bactericidal effect for both intra- and extracellular organisms and is well absorbed from the

gastrointestinal tract, reaching serum levels equal to those following parenteral administration. The peak serum concentration of 3 to 5 μg/ml occurs 1 to 2 hours after a dose of 5 mg/kg. The small molecular size of INH allows widespread distribution. The drug can be detected in serous membranes, caseous foci, cavities, and macrophages. INH is metabolized in the liver by both acetylation and oxidation via the cytochrome P-450 system. The serum half-life is around 3 hours in slow acetylators and 1 hour in rapid acetylators. The inactive metabolites are excreted in the urine, accounting for 75 to 95 percent of a dose within 24 hours. If the serum creatinine levels are higher than 12 mg/dl, these metabolites accumulate in the body. In renal failure, INH should be administered after dialysis. The drug can be given by nasogastric tube, intramuscular injection, or intravenously if the patient is unconscious.

When INH and phenytoin are administered together, an increase in serum concentration of phenytoin will be observed since INH is a noncompetitive inhibitor of diphenylhydantoin (DPH). In such patients, the serum levels of phenytoin should be monitored and a dose reduction may be necessary. In cases of DPH intoxication, the drug should be discontinued for at least a week and then therapy restarted with low doses (100 to 200 mg/day). INH may also decrease the threshold for acetaminophen hepatotoxicity.

A major toxic manifestation of INH is peripheral neuritis. Susceptibility is highest in chronic alcoholics, persons with malnutrition, and slow acetylators. Major manifestations are sensory dysfunctions and numbness of the lower extremities. The syndrome is dose related (in 40 percent of patients at doses of 20 mg/kg per day, in 20 percent at 10 mg/kg per day, and in 1 to 2 percent at 5 mg/kg per day). Owing to its pyridoxine-like structure, INH competitively inhibits pyridoxine-requiring reactions. INH-induced depletion of pyridoxine stores can be prevented with pyridoxine 50 mg/day. Unless there is an obvious muscle weakness (i.e., atrophy or fasciculations), the symptoms of peripheral neuritis are reversible within a few weeks after withdrawal of INH and treatment with pyridoxine 100 to 200 mg/day. Autonomic dysfunctions, ataxia, muscle twitching, CNS irritability, depression, acute psychosis, and encephalopathy are other neurological symptoms that may occur after INH therapy or overdose. Pyridoxine may terminate all these adverse effects.

The other major side effect of INH is toxic hepatitis. This is related to toxic drug metabolites. After acetylation, INH converts to hydrazine, which may be changed to a toxic agent, acetyl hydrazine. In addition, as RMP inducts the enzymatic conversion of INH to acetyl hydrazine, the hepatotoxic effect is potentiated when these drugs are used together. In the first months of therapy, a mild elevation of transaminase levels may occur in 10 to 20 percent of patients receiving INH. If the enzyme levels rise above three times normal values, the drug should be discontinued. Monthly monitoring of liver enzymes is recommended for all patients on INH therapy. The frequency of tests should be increased in patients who have elevated enzyme levels. INH causes a hepatocellular type of hypersensitivity reaction and histology is indistinguishable from that of viral hepatitis. INH-induced hepatitis is age dependent, occurring in 2 to 3 percent of patients over 50 years of age but less than 1 percent of children. Fatal liver damage may occur in 1 to 2 percent of patients with INH hepatitis. This may be asymptomatic until jaundice develops. Before onset of jaundice, patients may suffer from weakness, fatigue, and generalized malaise. Therefore, patients may unknowingly continue taking INH after the onset of drug-induced hepatitis. Patients given INH should be warned about such symptoms and instructed to promptly inform their physician if such symptoms occur.

INH and RMP together produce hepatotoxicity more frequently then either drug alone. Risk factors for hepatitis are age greater than 35, slow acetylators, history of cholelithiasis, alcohol use, and preexisting liver disease. Liver transplantation has been successful in patients who develop hepatic failure from either INH alone or INH and RMP therapy. Thus, liver transplantation may be a lifesaving therapy.

Rifampin

Rifampin (RMP) is bactericidal against intracellular and extracellular bacterial populations. It is a semisynthetic antibiotic that inhibits RNA synthesis by inhibiting DNA-dependent RNA polymerase enzyme, encoded by the rpoB gene. Most strains of *M. tuberculosis* are inhibited with 0.20 μg/ml. RMP is considered to be a "sterilizing" agent. A standard oral dose of 600 mg/day may produce serum concentrations of 7 to 10 μg/ml in 1 to 2 hours. RMP is metabolized in the liver and excreted in bile. As only 30 percent of the drug is excreted in the urine, dose reduction is not necessary in renal failure. RMP is able to penetrate into caseous foci, serous membranes, and macrophages. RMP does not pass the blood-brain barrier under normal conditions, but inflammation of the meninges causes an increase in penetration. Rifampin penetrates well into tissues and can be detected in urine, tears, sweat, and other body fluids, coloring then to red-orange. Patients should be advised of this harmless discoloration. RMP can be given to unconscious patients by nasogastric tube or intravenous injection.

In nearly all isolates of *M. tuberculosis* resistant to RMP, a short region of 27 codons in the center of the rpoB gene was mutated.

Major side effects of RMP are gastrointestinal upset, skin eruptions, and fever. Twenty percent of patients receiving high-dose intermittent RMP (600 to 1200 mg/day) develop an immunologically mediated influenza-like reaction, hemolytic anemia, acute renal failure, and thrombocytopenia. When these syndromes occur, RMP should be discontinued.

Another important adverse effect of RMP is its hepatic toxicity. An elevation in serum hepatic enzyme levels occurs in 5 to 10 percent of patients. Usually this resolves spontaneously, and therapy does not need to be altered or interrupted. The clinical presentation of hepatotoxicity varies from transaminase elevations to fatal hepatic necrosis. RMP is also a potent inducer of hepatic microsomal enzymes, resulting in an increased rate of metabolism of a number of drugs and, thus, a rapid elimination and diminished effects

of these drugs, which include methadone, Coumadin derivatives, glucocorticoids, estrogens, oral hypoglycemic agents, and antiarrhythmic agents. Bidirectional interactions can occur between RMP and antiretroviral agents, which complicates the treatment of TB patients on retroviral therapy.

Several studies have shown that the incidence of hepatitis in regimens containing both INH and RMP may be two to four times that of INH alone. Hepatic toxicity due to INH usually occurs after 2 months of therapy. In contrast, in INH and RMP combined therapies, jaundice may occur within the first 2 weeks of therapy and may be fulminate. The reason for this toxic effect was the accelerated production of toxic metabolites of INH due to the stimulation of hepatic microsomal P-450 system by RMP.

Rifabutin

Rifabutin (RIF) is a semisynthetic antibiotic similar to rifampin in structure and activity. RIF has a relatively low oral bioavailability of about 20 percent after single dose administration. After long-term administration RIF induces its own metabolism. The half-life for elimination of RIF is long (45 hours). As a result of a very large volume of distribution (greater than 9 L/kg), average plasma concentrations remain relatively low even after repeated administration of standard doses.

Because RIF has fewer interactions with antiretroviral agents, it is more frequently used in the treatment of TB patients on retroviral therapy. Careful monitoring of drug levels is essential in these cases. Neutropenia may necessitate stopping the drug in 2 percent of AIDS patients. Neutropenia has not been associated with RIF in non-AIDS patients. Uveitis is rare at the standard doses, but can occur in 8 percent when given at higher doses. Drugs (i.e., macrolide antibiotics, protease inhibitors, and azole antifungal agents) that reduce RIF clearance may also be associated with increased incidence of uveitis.

Gastrointestinal symptoms and polyarthralgias were reported to occur in less than 3 percent of subjects, but have not been reported in more recent literature.

Similar to RMP, RIF can cause hepatitis and causes orange discoloration of body fluids. No adjustment for renal failure is necessary. Similar to RMP, RIF penetrates inflamed meninges.

Rifapentine

Rifapentine (RPT) is a long-acting cyclopentyl-derivative of rifampin. The mean half-life for RPT elimination is over 16 hours. RPT is only used in the continuation phase of TB treatment in non-HIV patients as a once or biweekly drug. Its side effects are similar to RIF.

Pyrazinamide

Pyrazinamide (PZA) is a nicotinic acid derivative similar to INH, but it has no cross-resistance with INH. Its bacteriocidal activity at acid pH makes PZA particularly effective against slowly metabolizing intracellular bacilli. This "sterilizing" property has made PZA an essential component of short-course therapy. Regimens not including PZA require at least 9 months to succeed. This beneficial effect is limited to the first 2 to 3 months of treatment. PZA is absorbed from the gastrointestinal tract and distributed throughout the body, including the CNS. PZA is excreted from the kidneys. Serum levels of 30 to 50 μg/ml are achieved with doses of 20 to 25 mg/kg of PZA. It has a minimum inhibitory concentration of 15 to 20 μg/ml.

PZA is thought to be converted to pyrazine acid by a mycobacterial enzyme pyrazinamide. Pyrazine acid is thought to kill mycobacteria by lowering the intracellular pH. Resistance to PZA may be due to failure of the drug to be taken up by mycobacteria due to a lack of a PZA transport system in addition to mutations in the PZase gene.

The most adverse reaction of PZA is hepatotoxicity. After 2 months of therapy, 15 percent of patients who receive PZA at a dose of 3000 mg/day (40 to 50 mg/kg) develop liver dysfunctions and 2 to 3 percent develop jaundice. Liver function should be monitored closely, and the treatment should be discontinued if elevations of SGOT levels occur. Another common side effect of PZA is hyperuricemia. Occasionally, mild non-gouty polyarthralgias occur as a result of inhibition of urate excretion. This complication usually responds to nonsteroidal anti-inflammatory drugs. Clinical gout is rarely seen, and allopurinol therapy is usually indicated. Therapy is not necessary for patients who have only elevated urate levels without symptoms. Other side effects, such as skin rash and gastrointestinal intolerance are rare.

Ethambutol

Ethambutol (EMB) is a bacteriostatic agent. It has no activity on bacilli in the stationary growth phase. It is a unique butanol derivative that may block a step of cell wall synthesis. Following a 5 mg/kg oral dose, the peak serum level is approximately 4 μg/ml after 2 to 4 hours. Serum half-life is approximately 4 hours and is prolonged in renal failure. EMB may be bacteriocidal at 25 mg/kg doses, whereas it is bacteriostatic at 15 mg/kg doses. EMB is active against both intracellular and extracellular bacilli. Most strains of M. tuberculosis are inhibited in vitro by 1 to 5 μg/ml of EMB. Cerebrospinal fluid concentrations are low (1 to 2 μg/ml), even in the presence of meningeal inflammation.

The main toxicity of EMB is optic neuritis. This is manifested by central scotoma, decreased red-green color vision, decreased visual acuity, and rarely, concentric concentration of visual fields, leading to gun-barrel vision. This side effect is dose dependent and largely reversible. Optic neuritis occurs in 3 percent of patients taking 25 mg/kg but in less than 1 percent of patients taking 15 mg/kg. Patients should be questioned concerning visual symptoms, and tests of visual acuity and color vision should be performed. In cases of optic neuritis, the visual function returns after withdrawal of the drug. Like PZA, EMB may cause hyperuricemia and rarely, gout. Skin rash, drug fever, and gastrointestinal disturbance are other rarely seen side effects.

Second-Line Drugs

Second-line drugs have increased toxicity and decreased effectiveness and should only be used by physicians experienced with their use. Second-line drugs include cycloserine, ethionamide, streptomycin, amikacin, kanamycin, capreomycin, p-aminosalicylic acid, and the fluoroquinolones. Because of the concern about the emergence of drug-resistant organisms, whenever new drugs are introduced into a patient's regimen, care should be taken that the patient is always on at least two drugs to which the mycobacteria is sensitive.

Cycloserine

Cycloserine is a bacteriostatic drug. It is an analog of D-alanine and competes with it for incorporation into the cell wall. It is rapidly absorbed from the gut and is distributed to all compartments. Urine excretion accounts for 70 percent of the active form of the drug, as only 30 percent is metabolized. Common side effects include neurological and psychiatric disturbances ranging from headache, tremor, memory problems, and somnolence to psychosis (paranoid, depressive, or catatonic reactions) and seizure. Some patients with depression or anxiety have committed suicide. The usual dose is 15 to 20 mg/kg, with a maximal dosage of 1 g/day. Most of the adverse CNS effects are dose related and disappear when the medication is discontinued. To prevent serious psychic problems, periodic monitoring of mental status and serum drug levels is necessary. To diminish the potential for seizures and convulsions, pyridoxine at doses of 100 to 150 mg/day is helpful. Cycloserine may affect the elimination of phenytoin especially when taken with INH. Dose reduction of phenytoin is necessary in these cases. In the presence of renal failure, the daily dose of the drug must be reduced.

Ethionamide

Ethionamide has a structure similar to INH but cross-resistance with INH is very rare. A dose of 2.5 μg/kg has a bacteriostatic effect. Ethionamide is well absorbed from the gut and metabolized in the liver. Peak serum levels are 15 to 20 mg/ml. The optimum dosage is usually 1 g. It is almost completely and widely distributed in the body compartments. Nausea, vomiting, loss of appetite, and abdominal pain are the most common adverse effects. Serious neurological reactions include headache, restlessness, diplopia, tremors, and convulsions. It is necessary to increase the dose to the full amount gradually. As it is very irritating to the gastrointestinal tract, a bedtime dose is recommended with an anti-emetic and a hypnotic drug. Hepatitis may develop in 1 percent of patients. To monitor hepatotoxicity, monthly hepatic enzyme determination is necessary. In the presence of a fivefold elevation of liver enzyme levels, the drug should be stopped. If well tolerated, ethionamide can be a lifesaving agent in patients with drug-resistant TB.

Streptomycin

Streptomycin (SM) was the first major antituberculosis drug release. SM acts through inhibition of protein synthesis. It is effective only against extracellular bacterial populations in cavities, where the pH is neutral. SM must be administered parenterally, as it is not absorbed from the gut. Peak serum concentration of 40 μg/ml occurs approximately 1 hour after a 15 mg/kg intramuscular dose. Most strain of *M. tuberculosis* are inhibited in vitro at a concentration of 8 μg/ml. SM's half-life is 5 hours in blood.

Several mechanisms are responsible for resistance to SM. One of them is a mutation in the rpsL gene, encoding the S12 protein. This has been associated with a high level of resistance. Mutations in the rrs gene are usually associated with a low level of resistance; however, many isolates with a low level of resistance do not carry mutations in these genes. The frequency of resistance to SM in high-incidence countries limits the usefulness of SM.

Although SN has good tissue penetration, it can enter the CSF only in the presence of meningeal inflammation. Its major toxicity is irreversible eighth nerve damage, leading to vestibular dysfunction and, less frequently, deafness. It is a nephrotoxic drug like other aminoglycosides, and the frequency of renal toxicity is increased in patients with preexisting renal diseases or with simultaneous use of other nephrotoxic drugs. Renal and eighth-nerve toxicity increases in patients more than 50 years of age, and SM should be used very cautiously in these patients. Patients should be questioned regarding balance and asked to perform simple tests of vestibular function. In TB treatment, its use is usually limited to 2 months.

Amikacin and Kanamycin

Amikacin and kanamycin are closely related aminoglycoside antibiotics that act on ribosomes, inhibition protein synthesis. Both have eighth nerve and renal toxicity. Monthly audiograms should be used to monitor both drugs. Amikacin can be given intramuscularly or intravenously. Average peak serum concentration is 21 μg/ml and the MIC is 4 to 8 μg/ml. Kanamycin is usually given intramuscularly and serum concentrations should be in a range of 15 to 20 μg/kg. There is cross resistance among amikacin, kanamycin, and streptomycin.

Capreomycin

Capreomycin is chemically distinct from aminoglycosides, but it is likely to have cross-resistance with SM, amikacin, and kanamycin. It has the same therapeutic activity, pharmacology, and toxicity.

Para-amino Salicylic Acid

Para-amino salicylic acid (PAS) was the first oral antituberculosis drug that had strong bacteriostatic effect. This effect is potentiated when it is used in conjunction with SM or INH. Ass the drug is excreted rapidly, high doses are necessary to maintain bacteriostatic activity. The usual oral daily therapeutic dose is approximately 150 mg/kg, and the total dose should not exceed 10 to 12 g/day. The 10- to 12-g/day dosage causes a high rate of adverse gastrointestinal effects, including nausea, vomiting, diarrhea, and epigastric

pain. The half-life of PAS is about 1 hour and is markedly prolonged in renal failure. PAS is well absorbed orally but does not cross the blood-brain barrier. In 5 to 10 percent of patients, PAS may also cause hypersensitivity reactions and rarely, hepatitis, hypothyroidism, or hemolytic anemia. Adverse effects may be diminished by beginning therapy with a low dose and gradually increasing to a full dose over 7 to 10 days. To avoid gastrointestinal effects, PAS should be taken after eating. Antacids may also be helpful to reduce these side effects.

Fluoroquinolones

Fluoroquinolones are broad-spectrum antibacterial agents that act by inhibiting DNA gyrase enzyme. They are the preferred oral agent for treating drug-susceptible organisms that are sensitive to these agents. There is no cross-resistance with other antituberculosis drugs. Levofloxacin is the preferred agent. Cross-resistance is present among the fluoroquinolones and is presumably a class effect. Administration of quinolones with theophylline increases serum theophylline levels and the risk of adverse effects from theophylline. Both ferrous sulfate and antacids with magnesium and aluminum may affect the absorption of the fluoroquinolones. Side effects include nausea, bloating, dizziness, insomnia, tremulousness, headache, rash, pruritus, and photosensitivity.

Deciding to Initiate Treatment

Frequently, the decision to initiate treatment for tuberculosis is made before there is culture confirmation. This is a clinical decision based on the patient presenting signs and symptoms, laboratory tests, radiological findings, microscopic examination of sputum or other specimen smears, and histological examination of any tissue specimens. When a decision is made about initiating antituberculosis therapy, physicians should consider the following issues and try to avoid common mistakes (Table 140-2).

1. Tuberculosis should be viewed not only as a disease affecting personal health requiring treatment to cure the patient, but also as a disease of public health concerns because of community transmission.
2. A positive PPD, while helpful, is not necessary for the initiation of treatment as a negative PPD is not uncommon in active tuberculosis.
3. Before starting therapy, one should attempt to confirm the diagnosis by sending material to the laboratory for culture.
4. In newly diagnosed TB patients, at least three sputum samples should be sent for culture and drug susceptibility testing before starting therapy.
5. In smear-negative cases, five or six sputum samples and, if necessary, bronchoalveolar lavage material should be sent for mycobacterial culture.
6. If no other cause can be found in a severely ill, smear-negative, presumed TB patient, antituberculosis therapy should be started immediately.

Table 140-2

Common Errors in the Management of Tuberculosis

Addition of a single drug to a falling regimen
Failure to identify preexisting or acquired drug resistance
Chest radiographs findings absent or misinterpreted
Inadequate primary regimen
Failure to identify and address noncompliance
Inappropriate isoniazid preventive therapy

7. The emergence of drug resistance is usually due to noncompliance and failure to take all of the drugs. Resistance is usually to the omitted drug. Directly observed therapy is the preferred method in all patients.
8. Therapy should never be stopped unless one is certain that the cultures are negative.

Initiation of Treatment

Currently accepted drug regimens are summarized in Table 140-3 and suggested doses are given in Table 140-4. During treatment for pulmonary tuberculosis all patients should have monthly sputum examined by smear and culture. Patients who have cavitation on the initial chest radiograph or have positive cultures after 2 months are at increased risk for relapse. In these individuals, the continuation phase of treatment should be prolonged to 7 months, making the total duration of treatment 9 months. Repeat susceptibility testing should be done if cultures remain positive after 3 months of treatment.

Monitoring for Adverse Reactions

For evaluation of standard regimens, baseline measurement of a complete blood count, hepatic enzymes, serum bilirubin, and creatinine levels should be obtained. If PZA is used, serum uric acid levels should be monitored. Patients receiving EMB should have both visual acuity measurement and a red-green color perception testing. The baseline tests have two major goals: first, to detect abnormalities that could complicate the regimen and, if necessary, make rearrangements; and second, to monitor the adverse reactions of drugs by means of comparing the baseline measurements with the follow-up results. The same tests should be repeated at monthly examinations. The patients with abnormalities detected on the baseline tests should be evaluated for the cause of the result. If symptoms suggesting drug toxicity occur, appropriate laboratory testing

Table 140-3

Drug Regimens for Pulmonary Tuberculosis Caused by Drug Susceptible Organisms

Initial Phase (8 wk)			Continuation Phase (18 wk Except Regimen 4)			Rating	
Regimen	**Drugs**	**Interval and Doses**	**Regimen**	**Drugs**	**Interval and Doses**	**HIV−**	**HIV+**
1	INH RIF PZA EMB	7 d/wk for 56 doses or 5 d/wk for 40 doses	1a	INH/RIF	7 d/wk for 126 doses or 5 d/wk for 90 doses	A	A
			1b	INH/RIF	2 ×/wk for 36 doses	A	A†
			1c*	INH/RPT	1 ×/wk for 18 doses	B	E
2	INH RIB PZA EMB	7 d/wk for 14 doses (2 wk) or 5 d/wk for 10 doses (2 wk), then 2 ×/wk for 12 doses 6 wk)	2a	INH/RIF	2 ×/wk for 36 doses	A	B†
			2b*	INH/RPT	1 ×/wk for 18 doses	B	E
3	INH RIF PZA EMB	3 ×/wk for 24 doses	3a	INH/RIF	3 ×/wk for 54 doses	B	B
4	INH RIF EMB	7 d/wk for 56 doses or 5 d/wk for 40 doses	4a	INH/RIF	7 d/wk for 217 doses (31 wk) or 5 d/wk for 155 doses (31 wk)	C	C
			4b	INH/RIF	2 ×/wk for 62 doses (31 wk)	C	C

Note: Abbreviations: EMB = ethambutol; INH = isoniazid; PZA = pyrazinamide; RIF = rifamppin; RPT = rifapentine.
Ratings: A = preferred; B = acceptable alternative; C = offer when A and B cannot be given; E = should never be given.
**Not recommended for HIV-infected patients with CD4+ cell counts <100 cells/μl.*
DOT is the preferred method for giving drugs on an intermittent basis.
† Options 1c and 2b should be used only in HIV-negative patients who have negative sputum smears at the time of completion of 2 months of therapy and who do not have cavitation on initial chest radiograph. For patients started on this regimen and found to have a positive culture from the 2-month specimen, treatement should be extended an extra 3 months.
SOURCE: *Adapted from Treatment of tuberculosis,* MMWR *52:3, 2003.*

should be performed. Patients should always be informed about the common adverse effects of drugs before starting therapy (Table 140-5).

Duration of Observation and Evaluation of Response to Treatment

Patients with Positive Pretreatment Sputum

To monitor conversion and detect the possible emergence of drug resistance, sputum smear and cultures should be obtained monthly or at least after 2, 4, and 6 months of therapy. With INH- and RMP-containing regimens, sputum should convert to negative within 2 months. If smear and culture results continue to be positive after 2 months of therapy, emerging drug resistance and noncompliance should be major concerns. A new drug susceptibility test should be performed immediately. Unless drug resistance is demonstrated, the regimen in use should be continued carefully under direct observation. If drug resistance occurs, at least two new drugs to which the organism is sensitive should be added to the therapy and administered under direct observation. Addition of a single drug to therapy should never be done since it increases the risk of the rapid development of resistance to the new drug. Bacteriologic culture and susceptibility tests should be performed at monthly intervals until the cultures become negative. Relapse of drug-sensitive infections after adequate INH- and RMP-containing treatment is very infrequent. For patients who have completed a standard regimen and have had a satisfactory bacteriologic response, follow-up after completion of therapy is not necessary. In contrast, the patient with extensive disease, immunosuppressed patients, the persistence of radiologic findings after therapy, or suspicion of poor patient compliance, are indications for prolonged follow-up.

A chest radiograph before the start of therapy is necessary to compare with one taken after the completion of therapy. Monthly chest radiographs during therapy are helpful, but not as essential as sputum examinations. A chest

Table 140-4

Doses* of Antituberculosis Drugs for Adults and Children†

Drug	Adults/Children	Daily Dose	Intermittent Dose (2 ×/wk)
First-line drugs			
Isoniazid	Adults (max.)	5 mg/kg (300 mg)	15 mg/kg (900 mg)
	Children (max.)	10–15 mg/kg (300 mg)	20–30 mg/kg (900 mg)
Rifampin	Adults‡ (max.)	10 mg/kg (600 mg)	10 mg/kg (600 mg)
	Children (max.)	10–20 mg/kg (600 mg)	10–20 mg/kg (600 mg)
Rifabutin	Adults‡ (max.)	5 mg/kg (300 mg)	5 mg/kg (300 mg)
	Children	Unknown for children	Unknown for children
Rifapentine	Adults (max.)	—	10 mg/kg (600 mg) continuation phase (once weekly)
	Children (not approved)		
Pyrazinamide	Adults (max.)	20–25 mg/kg (2.0 g)	50 mg/kg (4.0 g)
	Children (max.)	15–30 mg/kg (2.0 g)	50 mg/kg (2.0 g)
Ethambutol	Adults (max.)	15–20 mg/kg (1.6 g)	50 mg/kg (4.0 g)
	Children§ (max.)	15–20 mg/kg (1.0 g)	50 mg/kg (2.5 g)
Second-line drugs			
Cycloserine	Adults (max.)	10–15 mg/kg divided into two doses (1.0 g)¶	No data
	Children (max.)		
Ethionamide	Adults (max.)	15–20 mg/kg (1.0 g) may be divided into two doses#	No data
	Children (max.)		
Streptomycin	Adults (max.)	**	**
	Children (max.)	20–40 mg/kg (1.0 g)	20 mg/kg
Amikacin/kanamycin	Adults (max.)	**	**
	Children (max.)	15–30 mg/kg (1.0 g)	15–30 mg/kg
Capreomycin	Adults (max.)	**	**
	Children (max.)	15–30 mg/kg (1.0 g)	15–30 mg/kg
p-Aminosalicyclic acid (PAS)	Adults	8–12 g	No data
	Children (max.)	200–300 mg/kg (10 g)	
Levofloxacin	Adults	500–1000 mg	No data
	Children	††	††
Moxifloxacn	Adults	400 mg	No data
	Children	‡‡	‡‡
Gatifloxacin	Adults	400 mg	No data
	Children	§§	§§

* *Dose per weight is based on ideal body weight. Children weighing more than 40 kg should be dosed as adults.*

† *For purposes of this document adult dosing beigns at age 15 years.*

‡ *Dose may need to be adjusted when there is concomitant use of protease inhibitors or nonnucleoside reverse transcriptase inhibitors.*

§ *The drug can likely be used safely in older children but should be used with caution in children less than 5 years of age, in whom visual acuity cannot be monitored. In younger children EMB at the dose of 15 mg/kg per day can be used if there is suspected or proven resistance to INH or RIF.*

¶ *It should be noted that although this is the dose recommended generally, most clinicians with experience using cycloserine indicate that it is unusual for patients to be able to tolerate this amount. Serum concentration measurements are often useful in determining the optimal dose for a given patient.*

The single daily dose can be given at bedtime or with the main meal.

** *Dose: 15 mg/kg per day (1 g), and 10 mg/kg in persons more than 59 years of age (750 mg). Usual dose: 750–1000 mg administered intramuscularly or intravenously, given as a single dose 5–7 days/week and reduced to two or three times per week after the first 2–4 months or after culture conversion, depending on the efficacy of the other drugs in the regimen.*

†† *The long-term (more than several weeks) use of levofloxacin in children and adolescents has not been approved because of concerns about effects on bone and cartilage growth. However, most experts agree that the drug should be considered for children with tuberculosis caused by organisms resistant to both INH and RIF. The optimal dose is not known.*

‡‡ *The long-term (more than several weeks) use of moxifloxacin in children and adolescents has not been approved because of concerns about effects on bone and cartilage growth. The optimal dose is not known.*

SOURCE: *Adapted from Treatment of tuberculosis* MMWR, *52:4–5 2003.*

Table 140-5

Side Effects of Antituberculosis Drug

Drugs	Most Common Side Effects	Tests to Detect Side Effects	Remarks
Isoniazid	Peripheral neuritis, hepatotoxicity, hypersensitivity	SGOT, SGPT	Pyridoxine 50 mg as prophylaxis for neuritis, 100–200 mg as treatment
Rifampin	Hepatitis, GI upset (skin eruptions, fever)	SGOT, SGPT	Orange urine and other body secretions
Pyrazinamide	Hyperuricemia, hepatotoxicity, (skin rash, GI irritation)	Serum uric acid level, SGOT, SGPT	NSAIDS for nongouty polyarthralgias: allopurinol for frank gout
Streptomycin	8th nerve damage, nephrotoxicity	Vestibular function, audiograms, BUN/creatinine	Use in caution in older patients or those with renal disease
Ethambutol	Optic neuritis (reversible), (hyperuricemia, gout, skin rash, drug fever, GI iritation)	Red-green color discrimination and visual acuity	Use with caution when eye test is not feasible
Ethionamide	GI intolerance, endocrine disturbances, hepatitis, hypersensitivity	SGOT, SGPT	Consider antiemetics or bedtime dosing
Cycloserine	Neurological and psychiatric distubances	Serum levels of drug, regular evaluation of mental status	Pyridoxine
Capreomycin, kanamycin, amikacin, viomycin	Hearing loss, vestibular damage, renal toxicity, electrolye disturbances	Audiogram, vestibular examinations, BUN/creatinine	Use with caution in older patients or those with renal disease
p-amino-salicylic acid (PAS)	GI intolerance, hepatitis, hypersenstivity	SGOT, SGPT	Consider antacids or dosing at meal time
Ciprofloxacin, ofloxacin	GI intolerance, headache, restlessness, hypersensitivity, drug interactions	Monitoring for drug interactions	Avoid antacids, iron, zinc, and sucralfate, which decrease absorption
Clofazimine	Abdominal pain, skin discolorations (both dose related), photosensitivity		Consider dosing at mealtime, avoid sunlight

radiograph taken at the end of therapy will also help for comparison with any future films.

Patients with Negative Sputum

In patients with radiographic abnormalities and clinical findings consistent with TB, diagnostic tests should be performed to isolate *M. tuberculosis.* If an alternative diagnosis cannot be established, treatment against TB should be started while culture results are awaited. For this group of patients, clinical evaluation and chest radiographs are the major indicators of response to therapy. If cultures are negative and radiographic changes have not occurred after 3 months of an INH- and RMP-containing regimen, the abnormality is probably due to another disease or a TB fibrotic scar if the patient is PPD positive.

Retreatment of Patients Who Have Relapsed

Patients whose sputum is persistently positive after 5 to 6 months of therapy are considered treatment failures. A current sputum specimen should be obtained for the susceptibility testing. While susceptibility results are pending, the original therapy may be continued, or at least three new drugs added to the therapy. DOT should be done if that has not already been done. When the new susceptibility test results are received, a new regimen should be adopted in accordance with the results of the susceptibility tests. Patients who relapse after completing a regimen containing both INH and RMP, and whose organisms were susceptible to the drugs at the onset of treatment, may be restarted on their original therapy, since the organisms are still usually susceptible. In contrast, patients who relapse after taking a regimen that did not contain both INH and RMP should be assumed to be infected with an organism that is resistant to all previous drugs and managed accordingly.

Adherence and Directly Observed Therapy

Nonadherence to therapy is a major reason for failure of antituberculosis treatment. To overcome this problem, therapy should be given under DOT, if possible. A medical or other responsible person should observe as the patient ingests antituberculosis drugs. A health care worker may observe the patient in the "field" (patient's home, place of work, school, etc.) or the clinic. Following the initial therapy of daily treatments for the first 2 weeks, DOT may be administered. While DOT is especially useful in alcoholic, drug addictive or homeless patients, as their risk of nonadherence is very high, DOT increases successful completion of treatment in all groups. The cost of DOT is insignificant compared with the cost of hospitalization for advanced TB or multi-drug–resistant TB.

Treatment of Drug-Resistant Tuberculosis

Patients can become infected with *Mycobacteria* resistant to drugs in two ways. The first is to become infected with resistant organisms. This is called primary resistance. The second is that the resistant organism develops in TB patients during therapy. This is called secondary resistance. Multi-drug–resistant TB (MDT-TB) is defined as organisms that are resistant to both INH and RMP and requires the use of second-line drugs. Extensively or extremely resistant TB (XDR-TB) is not only resistant to INH and RMP but also resistant to three or more of the six classes of second-line drugs. MDR-TB has been reported to be higher than 20 percent in South Africa and XDR-TB as high as 2 percent.

During the initial phase of treatment with a single drug, most of the susceptible bacilli are destroyed, but the small number of resistant mutants continues to grow and, after 2 weeks to several months, the resistant bacilli outgrow the susceptible bacilli; this is known as the "fall and rise" phenomenon. This is most likely to occur when the bacillary population is very large (i.e., cavitary TB). Mutants with multiple mutations may be selected out, resulting in organisms with resistance to multiple drugs. Basically, nonadherence to prescribed therapy and the use of inadequate therapy regimens cause the development of drug resistance. The best treatment for drug-resistant TB is to make sure the patient receives adequate treatment initially and prevent the emergence of drug resistance.

Treatment of drug resistant TB should only be done in close consultation with experts in the management of drug-resistant TB. The initial course of treatment for drug-resistant TB represents the patient's best hope for cure. Inappropriate therapy can lead to serious morbidity and mortality.

Surgery

Surgery is rarely used for the treatment of TB. Before the chemotherapeutic era, surgery was used as an adjunct to "resting" of the lungs. Operations such as artificial pneumothorax, artificial pneumoperitoneum, plombage, artificial phrenic nerve paralysis, thoracoplasty, pulmonary resection, cavity drainage, and decortication were performed as important adjunctive treatment for managing cavity lesions, progressive focal disease, empyemas, and fibrothorax. Today, surgery has a role for treatment failure, such as multi-drug resistant TB with localized disease, chronic empyema, bronchopleural fistula, life-threatening hemoptysis unresponsive to arteriographic embolization, and closed pleural evacuation.

Adjunctive Corticosteroid Therapy

Corticosteroids do not play a major role in treatment of TB, but they are useful in some types of diseases. In fulminant military disease, ARDS, and obstructive lymphadenopathy, 20 to 30 mg/day of prednisone is helpful to relieve symptoms, improve oxygenation, and abolish fever. Patients with tuberculous meningitis at stages 2 and 3 (uncomplicated cases) seem to benefit from corticosteroid therapy. Prednisone should be begun at 60 to 80 mg/day and gradually decreased after 1 to 2 weeks. Corticosteroid therapy has been recommended in treatment of pericardial TB to prevent constriction.

Special Treatment Situations

Tuberculosis in HIV-infected individuals is associated with a high mortality. This is usually in patients with advanced HIV and may be due to stimulation of HIV replication secondary to tuberculosis. However, the effective use of antiretroviral therapy may change this. The treatment of persons with HIV infection is essentially the same as the treatment of patients without HIV infection with two exceptions. First, once-weekly INH-rifapentine should not be used in the continuation phase; and second, twice-weekly INH-RIF should not be used in patients with a CD4+ lymphocyte count less than 100/μl. A major concern about the treatment of tuberculosis in patients who are HIV+ is the interaction of rifampin with the anti-retroviral agents (see above).

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Mycobacterial Infections and HIV Infection

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Mycobacterial infections are important complications of human immunodeficiency virus (HIV) disease. During the past two decades, the emerging HIV pandemic has resulted in dramatic increases in illness caused by mycobacteria. In particular, the spread of HIV has caused sharp increases in tuberculosis rates in endemic countries, as well as in those with previously declining rates. Although the incidence of *Mycobacterium avium*-complex infection among HIV-infected persons has decreased significantly since the introduction of highly active antiretroviral therapy, *M. avium* complex remains an important pathogen for those who are not receiving or are unable to tolerate such therapy. By lowering cell-mediated immune responses, HIV infection increases the susceptibility to new mycobacterial infections, as well as the risk of progression from latent tuberculosis infection to active disease. Infections with other nontuberculous mycobacteria, such as *M. kansasii*, *M. genavense*, and *M. haemophilum*, are also associated with HIV infection.

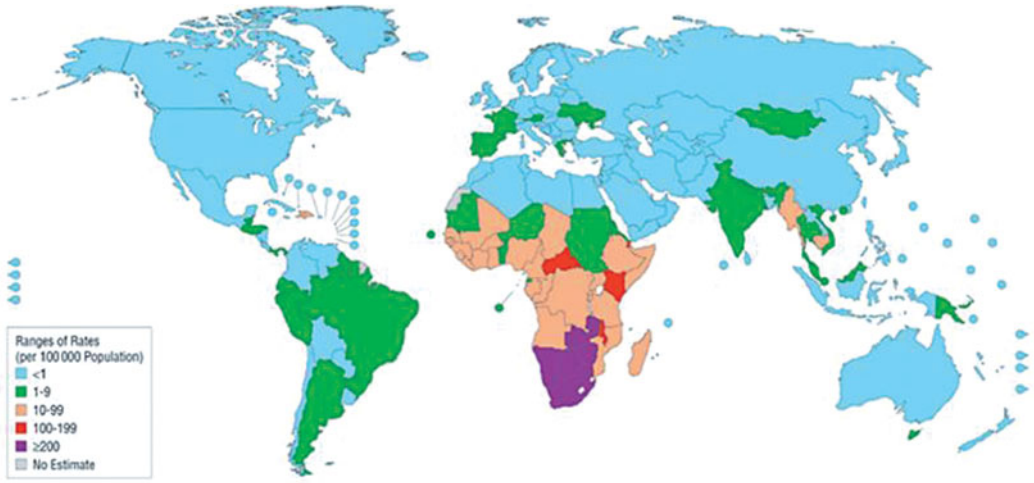
In developing countries, tuberculosis is exceedingly common in patients with HIV infection, while *M. avium* complex is more unusual. Figure 141-1 shows the worldwide prevalence of co-infection with HIV and *M. tuberculosis*. The World Health Organization estimates that at least 11 million adults are infected with both agents. Throughout the world, mycobacterial infections are common complications of HIV-associated immunodeficiency. This chapter will review the clinical and therapeutic aspects of HIV-related mycobacterial infections.

MYCOBACTERIUM TUBERCULOSIS

Epidemiology

HIV infection is increasingly common in populations with a high prevalence of *M. tuberculosis* infection. In the United States, for example, HIV is prevalent in injection drug users, people from racial and ethnic minority groups, and residents of inner cities—populations with historically high rates of tuberculosis. Recent data suggest an exceedingly high prevalence of HIV (80 percent) among injection drug users with tuberculosis in New York City. The increased susceptibility of these co-infected persons to developing active tuberculosis has contributed to a significant rise in tuberculosis rates in the United States. Prior to the HIV epidemic, new cases of tuberculosis were stably decreasing between 1953 and 1984 at a rate of 5 percent per year. With the spread of HIV, new cases of tuberculosis began to rise, peaking in 1992 at 26,673 new cases that year.

The risk of tuberculosis among HIV-infected individuals is dependent on the prevalence of tuberculosis in the community, the degree of immune suppression from HIV, and the



Corbett, E. L. et al. Arch Intern Med 2003;163:1009-1021.

Figure 141-1 Estimated numbers of cases with HIV and tuberculosis co-infection per 100,000 population (all ages) by country in 2000. (*Courtesy of Mario C. Raviglione, M.D., World Health Organization.*)

accessibility to treatment for latent tuberculosis infection. In developing countries, where the prevalence of tuberculosis infection in adults may exceed 50 percent, the spread of HIV has caused sharp increases in tuberculosis case rates. Substantial increases in tuberculosis morbidity related to HIV infection have occurred in sub-Saharan African countries, Thailand, and Latin American countries. A recent analysis of global tuberculosis trends estimates that approximately one-tenth of all cases worldwide are attributable to HIV, ranging from 1 percent in the Western Pacific, to one-third of all cases in Africa. Despite a low overall prevalence of tuberculosis, one-fourth of tuberculosis cases in the United States are attributable to HIV, reflecting the vulnerability of certain subpopulations to co-infection with HIV and *M. tuberculosis*. As case rates of tuberculosis have increased due to the HIV epidemic, additional problems have emerged, including outbreaks of tuberculosis in HIV-infected persons in hospitals or other congregate living facilities, and the rise of multidrug-resistant tuberculosis.

Pathogenesis

HIV is the strongest known risk factor for development of tuberculosis. In patients with latent tuberculosis infection the acquisition of HIV infection results in progressive impairment of cell-mediated immunity, which is required for the successful containment of tubercle bacilli. A number of immunologic defects have been noted in patients with *M. tuberculosis* and HIV infections, including reductions in CD4 cell levels, impaired T-cell proliferation, decreased cytolytic T-cell responses, deranged intracellular killing, and reduced cytokine elaboration in response to mycobacterial antigen challenge. The risk of reactivation of latent tuberculosis infection increases dramatically in patients with HIV co-infection, from 5 to 10 percent per lifetime in immunocompetent hosts to 5 to 10 percent per year in co-infected patients. The risk of reactivation rises as CD4 cell levels decline.

The early natural history of *M. tuberculosis* infection is also greatly affected by HIV disease. Although it is not clear if HIV-infected persons are more likely to acquire *M. tuberculosis* infection after exposure to infectious cases, it has been definitively shown that there can be rapid progression to clinical disease following initial tuberculosis infection in HIV-infected individuals. For example, in a residential care facility for HIV-infected persons in San Francisco, 38 percent of susceptible residents developed active pulmonary tuberculosis with an identical strain of *M. tuberculosis* (identified with restriction fragment length polymorphism analysis) within 120 days of exposure to the index case. The rapid progression of tuberculosis infection to tuberculosis disease in persons with HIV infection has resulted in numerous outbreaks of tuberculosis in institutions such as hospitals, nursing homes, and prisons, as well as in community settings. Molecular epidemiological studies have shown that approximately 40 percent of tuberculosis cases in urban areas of the United States are epidemiologically clustered, indicating recent transmission and primary disease. In these settings, HIV infection is significantly associated with clustering of tuberculosis cases.

Because *M. tuberculosis* is a virulent pathogen even in the normal host, tuberculosis tends to occur relatively early in the course of HIV infection. In general, HIV-seropositive patients tend to have higher CD4 counts than patients with opportunistic infections such as *Pneumocystis jiroveci* pneumonia. A recent retrospective cohort analysis of over 20,000

mineworkers in South Africa showed that the risk of tuberculosis doubled within the first year of HIV infection, prior to any significant reduction in CD4 cell counts. HIV-infected patients also appear to be at higher risk for re-infection, probably because of an impaired capacity to mount long-lasting protective immune responses. Using DNA fingerprinting, a study of South African HIV-infected mineworkers who had completed treatment for pulmonary tuberculosis showed that recurrence of tuberculosis was a consequence of re-infection rather than relapse. Interestingly, several cross-sectional studies and a prospective cohort study have shown that HIV-infected individuals with pulmonary tuberculosis are less likely than HIV-uninfected patients to transmit *M. tuberculosis* to close contacts. Possible explanations for the decreased contagiousness of HIV-infected individuals may include a lower sputum bacillary burden, decreased duration of smear-positivity due to rapid progression and earlier presentation to medical care, weakened cough with more severe disease, or greater social isolation.

While HIV has a major effect on the natural history of tuberculosis, there is also evidence that tuberculosis may affect the course of HIV disease. Experimental evidence indicates that *M. tuberculosis* increases HIV replication and enhances susceptibility to viral infection at the cellular level. A number of retrospective studies have shown worsened survival in HIV-infected persons with tuberculosis. The largest prospective cohort study to evaluate the impact of tuberculosis on survival of HIV-infected individuals demonstrated a threefold increased risk of death in patients with CD4 counts greater than 200 cells/mm^3, but no significant effect on individuals with more advanced immunosuppression. However, other studies have shown that a high viral load and low CD4 cell count precede the onset of tuberculosis, implying that the latter is a marker of advanced HIV disease, rather than the cause of accelerated immunosuppression. Furthermore, another study showed that there was no significant difference in viral load or CD4 cell counts in 111 HIV-infected patients during the treatment of active tuberculosis. Therefore, although treatment of tuberculosis may have a modest effect on the course of HIV infection, clearly the most important intervention in controlling HIV progression is institution of highly active antiretroviral therapy.

Clinical Manifestations

Depending on the degree of immune suppression, the clinical features of tuberculosis in HIV infection may differ significantly from those seen in patients without HIV infection. Patients with higher CD4 counts (greater than 300 cells/mm^3) tend to have more typical presentations, involving the lungs predominantly with upper-lobe infiltrates, with or without cavitation. As CD4 cell levels decline, tuberculosis is more likely to present atypically, including extrapulmonary involvement and disseminated disease, with low rates of tuberculin skin test reactivity. Unusual findings on chest radiographs in these patients are common, including lower

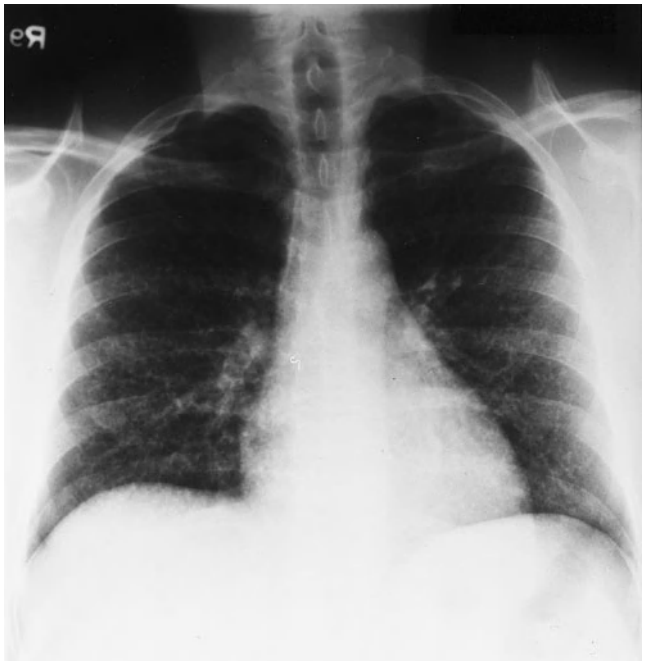


Figure 141-2 Chest radiograph from a 40-year-old HIV-infected man with HIV and miliary tuberculosis.

lung zone involvement and diffuse interstitial or alveolar infiltrates, which may mimic *P. jiroveci* pneumonia (Fig. 141-2). Hilar adenopathy is seen more frequently in patients with HIV infection, but cavitation and pleural effusions are uncommon, especially with advanced HIV disease. The most frequent sites of extrapulmonary involvement include lymph nodes, the urinary tract, meninges, and bone marrow. Mycobacteremia is not unusual, particularly in patients with low CD4 cell counts. One study found that mycobacterial blood cultures were positive in 49 percent of HIV-infected tuberculosis patients with CD4 counts less than or equal to 100 cells/mm^3, as opposed to 11 percent for patients with CD4 counts greater than 100/mm^3. However, despite the increased frequency of atypical manifestations of tuberculosis among HIV-infected patients, pulmonary disease tends to predominate in most series.

The diagnosis of tuberculosis in the HIV-infected patient requires a high index of suspicion and the use of appropriate diagnostic tests. The presence of acid-fast bacilli on sputum or tissue sample smears has a high positive predictive value for the diagnosis of tuberculosis, even in populations where *M. avium* complex is more common. However, only two-thirds to three-fourths of HIV-infected patients with pulmonary tuberculosis will have a positive acid-fast smear on a sputum sample. Since the diagnostic yield of sputum smears depends to some extent on cavitation, the sensitivity of this test may be lower in patients with advanced immunosuppression who are less likely to develop cavitary lesions. The number of bacilli in the sputum of HIV-infected patients may be lower than in the sputum of HIV-uninfected

patients, but sputum concentration through centrifugation may improve detection of acid-fast bacilli in these samples. Bronchoalveolar lavage and transbronchial biopsy are useful in diagnosing HIV-related pulmonary tuberculosis, as well as in evaluating for the presence of other pathogens, such as *P. jiroveci*. Biopsy is particularly useful in patients with pulmonary nodules or intrathoracic lymphadenopathy, since identification of granulomas or caseous necrosis is strongly suggestive of tuberculosis. Given the moderate sensitivity of acid-fast smears, presumptive therapy should be initiated in patients suspected of having tuberculosis after diagnostic tests have been performed and cultures are pending.

Tuberculin skin testing using protein purified derivative (PPD) has lower sensitivity in diagnosing tuberculosis in patients with HIV infection than in other populations. Because the tuberculin skin test loses sensitivity with progressive immune suppression, induration of greater than or equal to 5 mm is considered positive in HIV-infected individuals. In one study, only 14 percent of HIV-infected drug users had a reaction of at least 5 mm induration to PPD, whereas 25 percent of HIV-seronegative drug users had a reaction of at least 10 mm induration. In addition, the sensitivity of the tuberculin skin test declines as CD4 cell levels fall. However, even in the setting of advanced HIV disease, almost half of patients with active tuberculosis have a positive PPD, and the test maintains a high positive predictive value for the diagnosis of tuberculosis.

Nucleic acid amplification tests have good sensitivity and specificity for the diagnosis of tuberculosis in respiratory specimens that are smear-positive for acid-fast bacilli, but the sensitivity declines significantly in smear-negative samples. Although these tests have not been extensively validated in HIV-infected individuals, they appear to maintain the same specificity with slightly lower sensitivity as compared to HIV-uninfected individuals. The Quantiferon assay, an enzyme-linked immunosorbent assay (ELISA)-based test quantifying interferon-γ in plasma after stimulation of whole blood with PPD, was shown to have a relatively high agreement with the tuberculin skin test in HIV-negative persons in areas with a relatively low prevalence of tuberculosis. However, concordance between these two tests is relatively low in HIV-infected patients. T-cell–based assays using *M. tuberculosis*-specific antigens, including ESAT-6 and CFP-10, may be useful in the diagnosis of active and latent tuberculosis infection in HIV-infected persons. These assays appear to have increased specificity as compared to the tuberculin skin test, particularly in bacille Calmette-Guérin (BCG)–vaccinated individuals, but they are relatively expensive and require laboratory-based expertise, thus limiting their potential use in areas of the world with the highest prevalence of tuberculosis and HIV co-infection.

Treatment and Prevention

As in HIV-uninfected individuals, the successful treatment of tuberculosis in patients with HIV infection relies heavily on directly observed therapy involving a four-drug induction phase followed by a two-drug continuation phase. Despite similar responses to therapy, patients with HIV infection have a higher overall mortality and are at higher risk for tuberculosis reinfection than HIV-uninfected patients. Concurrent opportunistic infections, drug interactions, and immune reconstitution may complicate the therapy of patients with tuberculosis and HIV infection.

Retrospective and prospective studies have shown that treatment regimens which include isoniazid and rifampin supplemented by pyrazinamide and ethambutol (or streptomycin) for the first 2 months are effective in treating HIV-infected patients with active tuberculosis. Sputum conversion, time to defervescence, and resolution of radiographic abnormalities occurs as rapidly in HIV-infected patients as those without HIV infection. After successful completion of therapy for tuberculosis, relapse rates are similar for HIV-infected and HIV-uninfected persons (i.e., between 2 and 5 percent), although HIV-infected persons remain at increased risk for exogenous reinfection. In addition, mortality rates are higher for patients with HIV and tuberculosis co-infection, since these patients are at increased risk for infection with opportunistic pathogens.

Patients with HIV infection are generally more likely to experience adverse reactions from first-line antituberculosis medications. For example, dermatologic reactions are common in HIV-infected individuals receiving isoniazid and rifampin. The use of thiacetazone in developing countries has been linked with severe mucocutaneous hypersensitivity and toxic epidermal necrolysis in HIV-infected patients, and should be avoided in this population. Adverse reactions are especially common in patients treated concomitantly with antituberculosis medications and antiretroviral therapy. Peripheral neuropathy is common in patients receiving isoniazid and the antiretrovirals stavudine and didanosine. In addition, concurrent therapy for HIV and tuberculosis infections leads to many potential drug interactions. Use of rifampin, which is a potent inducer of cytochromes P450, can result in subtherapeutic levels of protease inhibitors or non-nucleoside reverse transcription inhibitors, leading to antiretroviral treatment failure. Rifabutin, the rifamycin with the least potential for induction of cytochromes P450, is recommended for use in patients receiving protease inhibitors. However, protease inhibitors, especially ritonavir, cause a marked reduction in the metabolism of rifabutin, resulting in supratherapeutic rifabutin levels and increased toxicity. Therefore, rifabutin doses must be decreased when used together with protease inhibitors (except saquinavir). In contrast, rifabutin doses must be increased when this drug is used with efavirenz. Rifampin may be used with efavirenz, but some experts recommend increasing the efavirenz dose to 800 mg daily. None of the rifamycins should be used with delavirdine because they may reduce delavirdine concentrations by up to 90 percent. Despite the numerous potential interactions, rifamycins should be included in the treatment of tuberculosis in HIV-infected patients, since non-rifamycin–based

regimens are generally more complicated to administer and are associated with higher rates of relapse.

One concern in treating patients with tuberculosis and HIV infection is paradoxical worsening associated with immune reconstitution upon initiation of highly active antiretroviral therapy, which may occur in up to one-third of cases. The immune reconstitution inflammatory syndrome usually occurs within 6 weeks of antiretroviral initiation in patients with very low initial CD4 counts who experience a rapid rise in CD4 cells or decline in HIV viral load over a short period of time. The syndrome is consistent with an enhanced inflammatory response to *M. tuberculosis* with the rapid improvement of immune function, manifesting as high fevers, lymphadenopathy, and respiratory compromise. Although data from randomized trials are lacking, nonsteroidal anti-inflammatory agents are often used for mild cases, and corticosteroids at doses of approximately 1 mg/kg per day may be used for more severe presentations. Steroids should be tapered very slowly over the course of weeks to months, depending on the clinical response. Although some authorities have advocated delaying the initiation of antiretroviral therapy until the completion of 2 months of therapy for active tuberculosis, it appears that the risks of AIDS-defining illnesses and mortality outweigh any benefits associated with delaying HIV therapy. Therefore, antiretroviral therapy should not be delayed in individuals with CD4 counts below 100 cells/mm^3.

Given the high rate of reactivation of latent tuberculosis infection in patients with HIV infection, treatment of latent tuberculosis infection in these patients is paramount. Two meta-analyses of randomized clinical trials performed in the United States, Africa, and Latin America prior to 1998 showed that treatment of latent tuberculosis infection in HIV-infected persons with isoniazid for 6 to 12 months reduces the risk of tuberculosis by over 40 percent but does not affect mortality. Because subgroup analyses of prospective, randomized trials in HIV-uninfected persons indicate that the maximal beneficial effect of isoniazid is achieved by 9 months of therapy, the same duration of therapy for latent tuberculosis infection is recommended for HIV-infected persons. Short-course regimens for the treatment of latent tuberculosis infection have been investigated in HIV-uninfected and HIV-infected patients. Four months of therapy with rifampin appears to have equivalent efficacy to 9 months of isoniazid, but special attention is required to the multiple potential drug interactions with antiretroviral agents, particularly with protease inhibitors. The combination of rifampin and pyrazinamide for 2 months appears to have similar efficacy and safety as isoniazid for 12 months in the treatment of latent tuberculosis infection in HIV-seropositive persons, and the former regimen is associated with greater medical adherence. However, several studies have reported a significantly increased risk of hepatotoxicity associated with rifampin and pyrazinamide in HIV-seronegative persons, occurring in as many as 10 percent of cases. Interestingly, this regimen is not associated with hepatotoxicity in HIV-infected patients. This discrepancy has led to speculation that the hepatotoxicity associated with this regimen is immune-mediated or that there is reduced bioavailability of the medications in HIV infection. Because of these concerns, the Centers for Disease Control has issued a recommendation against the use of rifampin and pyrazinamide in HIV-seronegative individuals and a warning for HIV-seropositive persons.

MYCOBACTERIUM AVIUM COMPLEX

Epidemiology

Disseminated *Mycobacterium avium* complex is the most common bacterial opportunistic infection in HIV-1-infected adults in the developed world, with an annual frequency of 10 to 20 percent in patients with AIDS who are not receiving antiretroviral therapy. The rate of *M. avium*-complex infection among HIV-infected persons has decreased significantly since the introduction of highly active antiretroviral therapy. In the Johns Hopkins HIV cohort, the incidence of disseminated *M. avium* complex fell steeply from 9 cases per 100 person years in 1993 to 0.5 cases per 100 person years in 2003 (Fig. 141-3). A multivariate Cox proportional hazards analysis showed that predictors for developing disseminated *M. avium* complex in this cohort of patients with CD4 counts less than 200 cells/mm^3 were enrollment between 1990 and 1995, younger age, and no use of highly active antiretroviral therapy. However, persons with HIV infection and advanced immunosuppression who are not receiving or are unable to tolerate highly active antiretroviral therapy continue to be at risk for disseminated *M. avium* complex. In addition to causing substantial morbidity in advanced HIV disease, disseminated *M. avium* complex is an independent predictor of mortality, even after adjustment for CD4

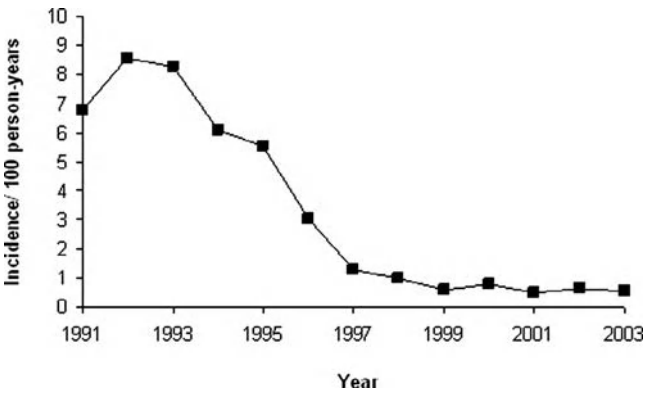


Figure 141-3 Incidence of *M. avium*-complex infection inpatients with a CD4 count less than 200 cells/mm^3 in the Johns Hopkins HIV clinic cohort, 1991–2003. (*Methods are described in Moore RD, Chaisson RE: Natural history of opportunistic disease in an HIV-infected urban clinical cohort. Ann Intern Med 124:633–642, 1996.*)

lymphocyte count. Because of the frequency, severity, and effect on survival of *M. avium*-complex infections, physicians caring for patients with HIV infection should be familiar with the treatment and prevention of this important complication of AIDS.

M. avium complex is acquired from the environment and is not spread from person to person. The organism is a common environmental mycobacterium, which is concentrated in soil and water and is also found in a number of animal reservoirs throughout the world. Although the organism is found widely in the environment, there is marked geographic variability in the incidence of *M. avium*-complex disease among HIV-infected individuals. For example, disseminated *M. avium* complex is frequently seen in AIDS patients in the United States, but the disease is unusual in African AIDS patients. In addition, *M. avium*-complex bacteremia is more prevalent among HIV-infected patients in the southern United States, as compared with those in the northern states and Canada. There are several potential explanations for the observed differences in worldwide distribution of *M. avium*-complex infection. Environmental concentrations of *M. avium* complex may be higher in areas of increased prevalence of disease, such as in the acidic swamps of the southeastern United States, although most environmental *M. avium* complex isolates are not linked to human disease. A possible explanation for the lower prevalence of *M. avium*-complex disease in African countries is that HIV-infected persons living in these countries may succumb to tuberculosis or other pyogenic infections at CD4 cell levels sufficient to protect against *M. avium* complex. Alternatively, prior exposure of these populations to other mycobacterial infections, including tuberculosis or BCG vaccination, may result in protection against disseminated *M. avium*-complex disease. However, African HIV-infected persons who migrate to Europe have rates of *M. avium*-complex disease similar to those of European HIV-infected patients, suggesting that differences in environmental concentrations of this organism may be responsible for observed geographic disparities in prevalence of *M. avium*-complex disease. It is also possible that *M. avium* complex is isolated and reported less frequently in African countries as a result of inadequate diagnostic capabilities or clinical evaluation.

The environmental sources responsible for most human *M. avium*-complex infections are not known. Studies using molecular epidemiological techniques have shown that some patients with AIDS and disseminated *M. avium* complex may acquire infection from hospital hot-water supplies or community potable water sources. Other possible epidemiological risk factors have been identified, including history of gastrointestinal endoscopy or bronchoscopy, consumption of raw seafood or hard cheese, and tobacco use. However, no study has convincingly established any connection between environmental exposures and subsequent *M. avium*-complex disease. Therefore, specific recommendations for avoiding particular exposures in HIV-infected patients cannot be made with confidence.

Pathogenesis

The *M. avium*-complex family comprises numerous organisms of varying serotypes from the species *M. avium* and *M. intracellulare*. In HIV-infected persons, *M. avium*-complex infection most commonly presents as disseminated disease and isolated pulmonary involvement is rare. This may reflect differences in organism tropism and virulence, as the majority of bacteremic strains in patients with AIDS are *M. avium*, whereas *M. intracellulare* is more commonly associated with pulmonary infection in HIV-seronegative persons with underlying structural lung disease.

M. avium complex is acquired from environmental sources either by inhalation or ingestion of organisms, leading to pulmonary and gastrointestinal infection, respectively. In healthy hosts, infection is usually self-limited or may not be recognized clinically, and is apparent only by reactivity to delayed-hypersensitivity skin testing. In HIV-infected persons, colonization of the respiratory and gastrointestinal tracts increases the risk of disseminated *M. avium*-complex significantly, although most patients with *M. avium*-complex bacteremia do not have evidence of prior colonization. Chin et al reported that for HIV-infected patients with CD4 less than or equal to 50/mm^3 who were colonized with *M. avium* complex, the risk of *M. avium*-complex bacteremia was 60 percent within 1 year. Specifically, colonization of the stool increased the risk of disseminated *M. avium*-complex sixfold and colonization of the sputum increased the risk more than twofold. However, two-thirds of patients who ultimately developed *M. avium*-complex bacteremia had no evidence of prior colonization. Thus, culture of these sites to detect colonization has limited use as a screening test.

The most important predictor of disseminated *M. avium*-complex is low CD4 lymphocyte count. Prospective studies have shown that as CD4 counts decline to below 100 cells/mm^3 the annual incidence of *M. avium*-complex bacteremia rises substantially. The annual risk of *M. avium*-complex bacteremia is between 10 and 20 percent for patients with CD4 counts below 50 cells/mm^3, and most patients with *M. avium*-complex bacteremia have CD4 lymphocyte counts below 20 cells/mm^3. On the other hand, patients with CD4 counts of at least 100 cells/mm^3 are very unlikely to develop *M. avium*-complex bacteremia in the subsequent year. Several other immunologic abnormalities contribute to the development of disseminated *M. avium* complex in HIV-infected patients. Although the ability of macrophages to phagocytose *M. avium* complex in patients with advanced AIDS is not impaired, intracellular killing is reduced and the organisms multiply within macrophages. This intracellular killing defect may result from diminished cytokine production (especially interferon-γ and interleukin-12), leading to reduced activation of macrophages. The important role of interferon- γ in control of *M. avium*-complex infection has been clearly demonstrated, as patients who have genetic defects in the interferon- γ regulatory pathway are predisposed to disseminated infection with *M. avium* complex and other

nontuberculous mycobacteria. In addition, cell-mediated killing of infected macrophages and granuloma formation, which are important mechanisms of control of *M. avium*-complex infection, are also substantially impaired in patients with AIDS.

After initial infection is established, the infection spreads via local lymphatics. Eventually, as cell-mediated immunity wanes because of progressive HIV infection, *M. avium* complex disseminates hematogenously. *M. avium*-complex bacteremia is associated with elevations of serum tumor necrosis factor-α and interleukin-6 levels, which may account for the common constitutional symptoms of fever, night sweats, and cachexia. The organisms are taken up by mononuclear phagocytic cells throughout the body, and reticuloendothelial organs such as the liver, spleen, and bone marrow are the most frequently affected sites.

Clinical Manifestations

Common symptoms of disseminated *M. avium* complex include fever, weight loss, night sweats, fatigue, and diarrhea. The pace of the illness is usually insidious, and symptoms are often present for many weeks before the diagnosis is established. Clinical signs and laboratory abnormalities frequently include cachexia, lymphadenopathy, hepatosplenomegaly, anemia, neutropenia, and elevated liver-associated enzymes. However, these clinical and laboratory features are relatively nonspecific and are frequently observed in other opportunistic infections and malignancies associated with advanced HIV infection. Case-control studies have shown that patients with AIDS and disseminated *M. avium* complex are significantly more likely than matched controls to have fever, night sweats, weight loss, and respiratory and gastrointestinal symptoms, as well as abnormal laboratory values, including raised serum alkaline phosphatase and lactate dehydrogenase, and reduced hemoglobin levels.

M. avium-complex infection may be limited to the lymph nodes, gastrointestinal tract, or lungs in some patients. In particular, pulmonary *M. avium*-complex infection, including focal pneumonia and endobronchial lesions, may occur with or without bacteremia. However, isolated *M. avium*-complex infection involving the lungs without evidence of dissemination is extremely unusual in patients with AIDS, and most cases occur in the setting of immune reconstitution syndrome. Figure 141-4 shows the radiographic findings of chronic *M. avium*-complex pulmonary disease in a patient with long-standing bacteremia. Cavitary disease with extensive infiltrates is common in this setting and pulmonary impairment may be acute or chronic. Disseminated *M. avium* complex may be difficult to distinguish clinically from disseminated tuberculosis, especially in the presence of pulmonary involvement. Clinical features that favor the diagnosis of disseminated tuberculosis include an absence of previous AIDS-defining illnesses, the presence of acid-fast bacilli in sputum smears, and chest radiographic findings of hilar enlargement; clinical features that favor the diagnosis of disseminated *M. avium* complex include hepatosplenomegaly, elevated serum alkaline phosphatase, and leukopenia.

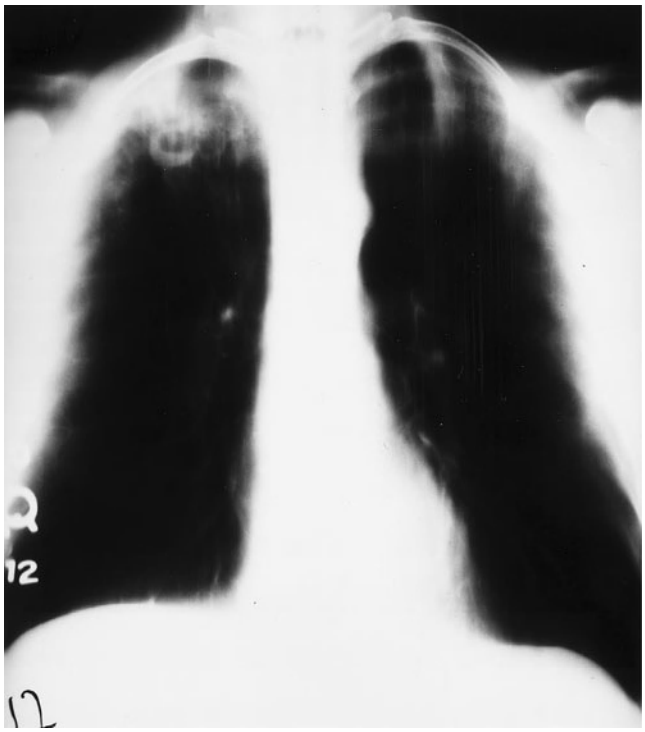


Figure 141-4 Radiographic presentation of *M. avium*-complex pulmonary disease in a patient with HIV infection. Chest radiograph showing cavitary infiltrates in a 37-year-old man with AIDS and long-standing *M. avium*-complex bacteremia.

The diagnosis of disseminated *M. avium* complex is usually made by isolation of organisms from blood or bone marrow cultures. Patients in whom *M. avium* complex is identified in other tissues should also have blood cultures performed to detect disseminated disease. Culture results may be obtained expeditiously with the use of Bactec and other rapid culture assays. DNA-RNA hybridization probes allow for speciation within 1 to 2 days after growth in liquid media. Isolation of *M. avium* complex in sputum or stool specimens does not necessarily indicate systemic disease, although, as noted above, colonization increases the risk for disseminated *M. avium* complex significantly. Presumptive therapy may be initiated in patients with CD4 counts below 50 cells/mm^3 and compatible symptoms while cultures are pending, but long-term treatment should be based on isolation of the organism in culture. If blood cultures are negative in patients with suspected disseminated *M. avium* complex, a bone marrow aspirate and biopsy may confirm the diagnosis.

Treatment and Prevention

Treatment outcomes of patients with AIDS and disseminated *M. avium* complex have improved substantially since the introduction of the extended-spectrum macrolides, which are now considered the cornerstone of any potent regimen. Clarithromycin and azithromycin given alone significantly

reduce levels of bacteremia and are associated with clinical improvement. Although both drugs are clearly effective against disseminated *M. avium* complex, several studies directly comparing these two drugs when used in combination with ethambutol suggest trends toward more rapid clearance of bacteremia with clarithromycin. Lower doses of clarithromycin (less than or equal to 1 g/day total) are associated with fewer gastrointestinal side effects and improved survival as compared to higher doses. The mechanism of increased mortality with higher doses (1000 mg twice daily) of clarithromycin is not known, and there is no evidence of any specific organ system–related toxicity. Macrolide monotherapy for disseminated *M. avium* complex is associated with clinical relapses secondary to selection of preexisting, innately macrolide-resistant *M. avium*-complex clones during therapy. Drug-resistant organisms usually begin to emerge after 2 to 3 months of therapy, and the majority of patients will experience recrudescence of symptoms after 4 or more months of therapy.

Combination therapy for disseminated *M. avium* complex is necessary to prevent the emergence of macrolide resistance. Treatment regimens should consist of clarithromycin or azithromycin with at least one other antimycobacterial agent (Table 141-1). The combination regimen of clarithromycin and ethambutol, which is the standard treatment regimen, is clinically active and prevents relapses with drug-resistant organisms in a large proportion of patients. The addition of clofazimine to this regimen does not improve efficacy and is associated with increased mortality. Recent data suggest that the addition of rifabutin to clarithromycin and ethambutol may be associated with a reduction in clarithromycin-resistance, and possibly improved survival. The aminoglycosides and fluoroquinolones have in vitro and in vivo activity against *M. avium* complex, but are generally reserved for patients who are failing first-line therapy.

A major limitation to the treatment of *M. avium*-complex disease is the occurrence of adverse drug reactions. Clarithromycin and azithromycin are associated with dose-related gastrointestinal side effects, which occur in up to one-half of patients. Common complaints include abdominal pain, nausea, vomiting, and diarrhea. Dose reduction or drug holiday may alleviate symptoms and permit further treatment. Taste and smell perversion occurs in 5 to 15 percent of macrolide-treated patients. Hepatotoxicity and rash are less common. Ethambutol is generally well tolerated, although gastrointestinal intolerance may occur. When dosed at less than 20 mg/kg daily, optic neuritis is rare. Rifabutin is associated with orange discoloration of urine, tears, and sweat in one-third to one-half of patients. Other adverse reactions include nausea, rash, and neutropenia. Uveitis is frequent with high doses (450 to 600 mg daily) of rifabutin, particularly when clarithromycin and fluconazole are coadministered. These drugs inhibit clearance of rifabutin by cytochromes P450, resulting in higher serum concentrations of rifabutin.

Routine testing of all *M. avium*-complex isolates for drug susceptibility is not currently recommended. Patients who develop systemic symptoms consistent with disseminated *M. avium* complex following apparent initial clinical response should also undergo testing for other opportunistic infections. Testing for relapse of *M. avium* complex involves obtaining blood cultures, which should be held in the laboratory for 4 to 6 weeks, since drug therapy may delay growth. If the organism is isolated on blood cultures, clarithromycin susceptibility should be performed. For patients who are known or suspected to be failing therapy, at least two new agents from different classes should be added or substituted. Azithromycin should not be substituted for clarithromycin, since cross-resistance to these agents is expected. Although no formal studies have been performed, suggested treatment for patients with clarithromycin-resistant *M. avium*-complex infection includes a fluoroquinolone (moxifloxacin or levofloxacin) in combination with ethambutol and rifabutin. Amikacin may be given initially, but extended treatment is challenging because of toxicity and the need for parenteral administration. Therapy with interferon-γ appears to be effective against disseminated *M. avium* complex in patients without HIV, but its efficacy in patients with AIDS has not been studied.

As with underlying tuberculosis infection (discussed above), HIV-infected patients with previously treated or subclinical *M. avium*-complex infection may develop immune reconstitution inflammatory syndrome soon after initiation of highly active antiretroviral therapy. This pathological inflammatory response may be seen in up to one-third of cases with HIV and *M. avium*-complex co-infection, usually manifesting as fever, abdominal pain, and lymphadenopathy. Although there are scarce data regarding the proper

Table 141-1

Regimens for the Treatment of Disseminated *M. avium* complex in Patients with HIV Infection

Preferred Regimens	Additional Drugs for Macrolide-Resistant Infections
Clarithromycin 500 mg twice daily or 1000 mg extended release once daily + ethambutol 15 mg/kg daily (± rifabutin 300 mg once daily) *or* Azithromycin 600 mg once daily + ethambutol 15 mg/kg daily (± rifabutin 300 mg once daily)	Moxifloxacin 400 mg daily *or* Levofloxacin 500–750 mg once daily + ethambutol 15 mg/kg daily + rifabutin 300 mg once daily ± amikacin 10–15 mg/kg IV daily

Table 141-2

Indications for Starting and Stopping Prophylaxis and Treatment for *M. avium*-Complex Infection in HIV-Infected Patients

Indication	When to Start	When to Stop
Prophylaxis	CD4 <50/mm^3	Increase in CD4 count to >100/mm^3 after at least 3 months of HAART
Treatment of disseminated infection	Positive blood culture	Negative blood cultures for 1 year + increase in CD4 count to >100/mm^3 after at least 3 months of HAART

HAART, highly active antiretroviral therapy.

Table 141-3

Regimens for the Prevention of *M. avium*-Complex Infection in Patients with Advanced HIV Infection

Preferred Regimens	Alternative Regimens
Clarithromycin 500 mg twice daily (or 1000 mg extended release once daily)	Rifabutin 300 mg once daily
Azithromycin 1200 mg once weekly	Azithromycin 500–600 mg once daily

management of this condition, most authorities recommend the use of nonsteroidal anti-inflammatory agents for mild cases, and systemic steroids for more severe presentations. Corticosteroids should be tapered over weeks to months, depending on the clinical response.

Although data on the discontinuation of chronic maintenance treatment for *M. avium*-complex infection are scarce, clinical evidence from other opportunistic infections support the safe discontinuation of treatment for *M. avium*-complex infection after completion of a greater than 12-month course, assuming there are no *M. avium*-complex–specific signs and symptoms, and there is a sustained rise (greater than 6 months) in CD4 cell count to greater than or equal to 100 cells/mL after highly active antiretroviral therapy.

Because disseminated *M. avium* complex is a predictable late complication of HIV infection that occurs in a large proportion of patients, chemoprophylaxis to prevent disease is desirable. In particular, patients who have a CD4 count less than or equal to 50 cells/mm^3 are at increased risk for *M. avium*-complex infection and should receive chemoprophylaxis (Table 141-2). Although official guidelines do not include criteria for initiation of prophylaxis on the basis of HIV plasma RNA (viral load) measurements, high viral loads (greater than or equal to 100,000 copies/mL) appear to be independently associated with *M. avium*-complex infection. Once-weekly azithromycin and twice-daily clarithromycin are both very effective in preventing *M. avium*-complex bacteremia in persons with low CD4 cell counts. Moreover, azithromycin prophylaxis reduces the risk of *Pneumocystis carinii* pneumonia and bacterial infections, and clarithromycin prophylaxis reduces the risk of bacterial respiratory tract and soft-tissue infections by 44 percent, and also significantly reduces mortality. Although azithromycin achieves low serum levels, the drug is concentrated in macrophages, the primary cells infected by *M. avium* complex. Therefore, the drug has a long half-life in tissue, permitting once weekly dosing.

Rifabutin is somewhat effective in preventing *M. avium*-complex bacteremia, but it is not currently recommended as first-line prophylaxis because of its modest efficacy, numerous potential drug interactions, high cost, lack of widespread availability, and potential for development of rifampicin cross-resistance in tuberculosis patients. The addition of rifabutin to either of the macrolide regimens does not appear to be significantly more effective in preventing *M. avium*-complex bacteremia, selection of macrolide-resistant organisms, or death, but is associated with increased medication-related toxicities. Therefore, current guidelines recommend clarithromycin 500 mg twice daily or azithromycin 1200 mg once weekly as first-line agents for the prevention of disseminated *M. avium* complex in HIV-infected patients with a CD4 count less than 50 cells/ mm^3 (Table 141-3). Alternative doses of clarithromycin and azithromycin are possible, although they have not been studied in human clinical trials for *M. avium*-complex prophylaxis. There have been no studies directly comparing the two drugs, and the choice of agent is based on perceptions of relative convenience, cost, tolerability, and effectiveness.

Primary prophylaxis for *M. avium* complex may be safely withheld in HIV-infected patients whose CD4 cell counts have risen to greater than or equal to 100/ mm^3 for more than 3 months in response to antiretroviral therapy (Table 141-2). Continuation of *M. avium*-complex prophylaxis in the setting of immune reconstitution after initiation of antiretroviral therapy confers no clinical benefit, and increases pill burden, costs, and the potential for drug toxicity and selection of drug-resistant organisms. A recent cohort study of over 46,000 HIV-infected persons showed that implementation of these discontinuation guidelines significantly increased the proportion of eligible patients who discontinued primary

prophylaxis from 17 percent in 1996 to 85 percent in 2002, and there was no increased risk of disseminated *M. avium* complex observed. Primary prophylaxis should be reintroduced if the CD4 count falls to less than or equal to 50 to 100 cells/mm^3.

Other Mycobacteria

Patients with HIV infection are susceptible to a number of other mycobacterial infections, although these are less common than tuberculosis or *M. avium* complex. *Mycobacterium kansasii* is generally considered to be one of the most pathogenic nontuberculous mycobacteria, and isolation of this organism on sputum cultures is associated with clinical disease in approximately 50 percent of patients. *M. kansasii* infections may closely mimic tuberculosis, causing cavitary lung lesions or diffuse pulmonary infiltrates in severely immunocompromised patients. Before the onset of the HIV epidemic, *M. kansasii* infections were extremely unusual. *M. kansasii* infections are more frequently seen with advanced HIV infection, often in the setting of concomitant opportunistic infections, than is disease caused by *M. tuberculosis*. Bacteremia, osteomyelitis, septic arthritis, pericarditis, and soft-tissue infections are also seen. Without treatment, the disease is generally progressive. Although recent American Thoracic Society (ATS) guidelines do not distinguish between HIV-positive and HIV-negative patients and recommend treating pulmonary *M. kansasii* infection only in the presence of multiple positive cultures and clinical and radiographic abnormalities, some experts advocate initiation of therapy after a single positive culture in HIV-infected patients. In HIV-infected patients with pulmonary *M. kansasii* infection, predictors of survival include higher CD4 counts, antiretroviral therapy, negative smear microscopy, and adequate treatment for *M. kansasii* infection, but not ATS diagnostic criteria. Treatment with isoniazid, rifampin, and ethambutol for 18 months is recommended, and until sputum cultures remain culture-negative for at least 12 months. All isolates are resistant to pyrazinamide, but sulfamethoxazole and clarithromycin are active against this organism. *M. genavense* may cause disseminated disease in patients with advanced immunodeficiency, including bacteremia and involvement of lymph nodes, liver, spleen, and gastrointestinal tract. The diagnosis is suggested in HIV-infected patients with an *M. avium*-complex–like illness who have weakly positive (low-growth index) cultures that cannot be speciated or who have negative cultures despite the presence of acid-fast bacilli in tissue samples. Isolation of *M. genavense* may be facilitated by use of acidic liquid media and prolonged incubation of cultures (mean growth in blood cultures is approximately 6 weeks). Although formal studies are lacking, disseminated *M. genavense* is usually treated with two or more of the following drugs: ethambutol, rifampin, rifabutin, clofazimine, and clarithromycin. *M. haemophilum* may cause skin and soft-tissue infections in AIDS patients, and infections with *M. fortuitum*, *M. chelonei*, *M. xenopi*, and *M. sherrisii* have been reported in HIV-infected patients.

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Diseases due to Non-Tuberculous Mycobacteria

Jay A. Fishman

Mycobacterium tuberculosis and *M. leprae* are among the most important mycobacterial species causing disease in humans. However, many other species of non-tuberculous mycobacteria (NTM) are common as environmental inhabitants and are increasingly recognized in infections of the lungs and systemically, generally in patients with immune compromise. The non-tuberculous mycobacteria are not obligate human parasites, as are *M. tuberculosis* and *M. leprae*. Prior to the AIDS epidemic, most cases presented as indolent, cavitating pulmonary infections in persons with other underlying lung diseases such as chronic obstructive pulmonary disease (COPD) or previous tuberculosis. During the 1980s pulmonary and disseminated infections due to the more common NTM (*Mycobacterium avium, M. intracellulare*, some *M. scrofulaceum*, some unclassified) emerged as complications of acquired immunodeficiency syndrome (AIDS) and were termed *M. avium* complex or MAC infections (described by Chaisson in Chapter 141). Subsequently, a syndrome of predominantly mid-lung zone bronchiectasis with MAC pulmonary infection was described in otherwise healthy middle-aged women. Mycobacterial infections after solid organ and hematopoietic transplantation have increased in frequency, reflecting both increased exposure and/or improved diagnostic methods. In the absence of mandatory infection reporting, the true incidence of NTM disease in the general population and transplant recipients can only be estimated. In the United States, the rate of NTM isolation based on laboratory surveillance is estimated to be 7.5 to 8.2 per 100,000 population. However, in the absence of clinical information, the incidence of disease due to NTM cannot be determined. In recipients of hematopoietic stem cell transplants (HSCT) the incidence of NTM infection ranges from 0.4 percent to 4.9, 50 to 600 times greater than the general population. Among renal transplant recipients, the incidence of NTM infection is between 0.16 and 0.38 percent. Slightly higher rates are reported in recipients of heart (0.24 to 2.8 percent), and lung (0.46 to 2.3 percent) transplants. The one systematic study of mycobacterial infection in liver transplant recipients reported an incidence of 0.04 percent, which may reflect local epidemiology, underdiagnosis, or a true, low incidence of infection. Newer guidelines of the American Thoracic Society (2007) can be used to guide therapy in most hosts.

ORGANISM AND DISEASE

Microbiology

Over 125 NTM species have now been identified and speciated. Many of these have been implicated in human disease.

A comprehensive list of all validated NTM species is available online at www.bacterio.cict.fr/m/mycobacterium.html. The increased number of species reflects improved microbiologic techniques for isolating NTM from clinical specimens and to the use of 16S rRNA gene sequencing as a standard for defining new species. To simplify understanding of these organisms, particularly as applied to clinical circumstances, they often are grouped into complexes of closely related species. The *M. avium* complex, for example, consists of many serotypes, including *M. avium, M. intracellulare,* and *M. scrofulaceum.* Certain species are associated with human disease more often than others and are presumed to be more virulent.

Key aspects of laboratory evaluation include:

1. Be aware that these organisms may be present, and request mycobacterial cultures in appropriate specimens. The gram stain will not detect mycobacteria. The preferred staining procedure is the fluorochrome method, although the Ziehl-Neelsen method and Kinyoun stain are less sensitive alternatives. NTM are often more sensitive to the acid-fast decolorization procedure.
2. Specimens should be cultured on both liquid and solid media. Species that are often associated with cutaneous and lymph node disease may require special growth conditions and/or lower incubation temperatures, including *M. haemophilum*, *M. genavense*, and *M. conspicuum.* Methods for the isolation of NTM in clinical laboratories have been approved by the Clinical and Laboratory Standards Institute (CLSI), formerly known as the National Committee for Clinical Laboratory Standards (NCCLS).
3. Molecular testing is used primarily (initially) to distinguish *M. tuberculosis* from NTM species. DNA probes exist for some common NTM species (*M. avium* complex or MAC, *M. kansasii*, and *M. gordonae*).
4. NTM should be identified to the species level.
5. ATS guidelines suggest that routine susceptibility testing be limited for MAC isolates (clarithromycin) and for *M. kansasii* isolates (rifampin). However, many centers perform more extensive testing due to the frequency of resistance, drug intolerance, and in HIV infection and transplant recipients, drug interactions.
6. For "rapid growers" in particular (*M. fortuitum*, *M abscessus*, *M. chelonae*), isolates should used for extended antibiotic in vitro susceptibility testing. Testing should include amikacin, imipenem, meropenem, moxifloxacin and gatifloxacin (*M. fortuitum* only), doxycycline, a sulfonamide or trimethoprim-sulfamethoxazole, cefoxitin, clarithromycin, linezolid, and amikacin, and tobramycin (*M. chelonae* only).

Some specific guidelines have been adopted to avoid potential sources of contamination, especially tap water, in specimen collection. Specimens should be submitted without fixatives. Refrigeration of samples at 4°C should be used if transportation to the laboratory is delayed for over 1 hour.

Respiratory Specimens

To establish the diagnosis of NTM lung disease, sputum is often induced or collected via bronchoscopy (Table 142-1). Alternatively, three early-morning specimens may be collected on different days. Respiratory specimens can be shipped to the laboratory on ice. Recent treatment with macrolides or fluoroquinolones often affects the yield of NTM recovery and should be avoided. Lung or other tissue (lymph node) biopsy specimens can be used for cultures also. Individuals with NTM lung disease may also have bacteremia. Blood cultures should be obtained specifically for NTM, although rapid growers normally grow in standard blood culture bottles.

Epidemiology and Pathogenesis

NTM are ubiquitous in the environment, often isolated from soil and water, including treated water sources (*M. kansasii*, *M. xenopi*, and *M. simiae*). There has been no documentation of animal-to-human or human-to-human transmission of NTM, including that in highly susceptible hosts (e.g., those with cystic fibrosis). In general, the environmental source of human disease is unidentified. NTM may cause both asymptomatic infection and symptomatic disease in humans. NTM disease is often detected in asymptomatic patients awaiting organ transplantation with diffuse nodular or interstitial lung disease. Skin test studies in adults indicate that a substantial proportion have had prior infection with NTM, notably in the southeastern United States. While disease is often asymptomatic (and often in individuals with other underlying lung disease), in the immunologically normal host, NTM has not been shown to lead to latent infection. However, disease may be exacerbated by immune suppression.

The most common clinical manifestation of NTM disease is probably lung disease, but lymphatic, skin/soft tissue, and disseminated disease are underdiagnosed. CDC reports that of NTM isolates reported to the Public Health Laboratory System (PHLIS) database between 1993 and 1996, 75 percent were pulmonary, 5 percent were from blood, 2 percent from skin/soft tissue, and 0.4 percent from lymph nodes. Disseminated NTM infections occurs in HIV-infected patients with CD4+ T-lymphocyte counts below 50/cc. In individuals with congenital immune deficiencies such as chronic granulomatous disease, there may be defects in production of interferon (IFN)-γ or interleukin (IL)-12, or defects in receptors or pathways controlling responses to IFN-γ. These IFN-γ pathway defects include receptor and signaling mutations in the nuclear factor-κB essential modulator, IFN-γ receptor 1 and receptor 2, IL-12 receptor 1 subunit, IL-12 subunit p40, and the signal transducer and activator of transcription 1 (STAT1). These defects are important given the role of macrophages in the innate immune response to NTM

Table 142-1

Bacteriologic Criteria for Diagnosis of NTM Pulmonary Disease

Normal Host or Local Immunosuppression*	Systemic Immunosuppression†
At least three available sputum/bronchial wash samples within 1 yr • Three positive cultures with negative AFB smears **OR** • Two positive cultures and one positive AFB smear	Same
OR	**OR**
Single available bronchial wash and inability to obtain sputum samples • Positive culture with 2+, 3+, or 4+ growth **OR** • Positive culture with a 2+, 3+, or 4+ AFB smear	Single available bronchial wash and inability to obtain sputum samples • Positive culture with 1+ growth **OR** • Positive culture with a 2+, 3+, or 4+ AFB smear
OR	**OR**
Tissue biopsy • Any growth bronchopulmonary tissue biopsy • Granuloma and/or AFB on lung biopsy with one or more positive cultures from sputum/bronchial wash • Any growth from usually sterile extrapulmonary site	Same

**Alcoholism, bronchiectasis, cyanotic heart disease, cystic fibrosis, prior mycobacterial disease, pulmonary fibrosis, smoking/COPD.*
†Leukemia, lymphoma, SOT, HIV, other systemic immunosuppression.

with IL-12 and IFN-γ essential for intracellular killing of mycobacteria.

Recent experience with inhibitors of tumor necrosis factor (TNF-α) suggests that TNF also is essential in the prevention of disease activation. These agents have been used in a variety of chronic inflammatory conditions, including inflammatory bowel disease and rheumatoid arthritis. The effect of these agents may persist for months to years after administration. In addition to NTM infection, such agents have been associated with activation of *Aspergillus species*, histoplasmosis, coccidioidomycosis listeriosis, and *M. tuberculosis.*

Pulmonary Disease

Older physicians are well aware that disease due to NTM in immunologically normal hosts tends to occur in the setting of structural lung disease, such as bronchiectasis, chronic obstructive pulmonary disease (COPD), old cavitary TB, mesothelioma and pneumoconioses, and with pulmonary alveolar proteinosis (Fig. 142-1). Bronchiectasis and NTM infection may coexist. As noted, some women without obvious immune defects have developed pulmonary NTM disease and tend to have characteristics that include scoliosis, pectus excavatum, mitral valve prolapse, and joint hypermobility. The relationship between these physical traits and NTM infection is unknown.

The histology of disease is indistinguishable from that caused by *M. tuberculosis*, although classical granulomata are often less "tight" in NTM infections. The general pattern is that of bronchiectasis, bronchiolar and peribronchiolar inflammation, and granuloma formation. Disease should be treated as caused by *M. tuberculosis* until identification

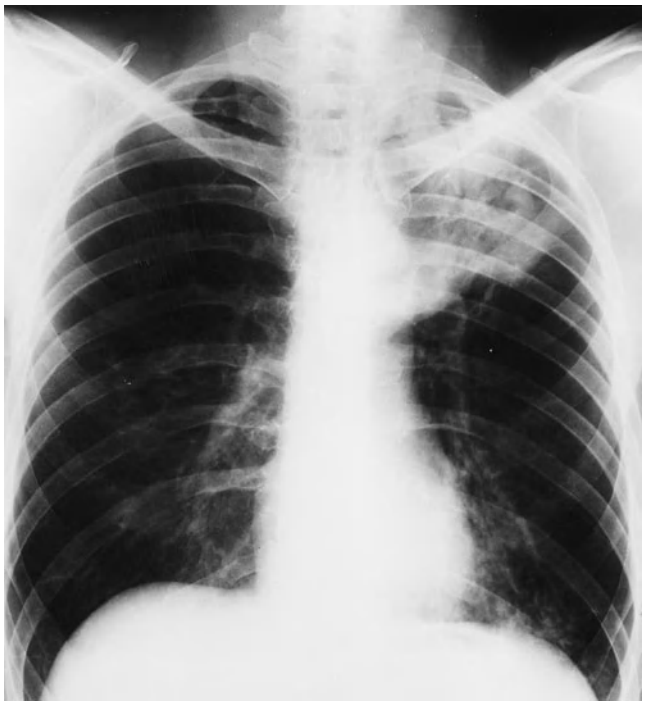

Figure 142-1 PA chest radiograph showing exudative infiltrate and probable cavitation in left upper lung.

of the organism proves otherwise. The granulomatous response may not occur in patients with overwhelming infection or severe underlying innate or cellular immune deficiency.

CLINICAL PRESENTATION AND RADIOGRAPHY

Most patients have preexisting structural lung disease (Figs. 142-2 and 142-3) and present with chronic cough or sputum production, often with nonspecific signs, including dyspnea, fatigue, malaise, low-grade fevers, and weight loss. Cavitary disease may be associated with hemoptysis and chest pain. Physical examination is generally unrewarding, with diffuse rhonchi and wheezes on auscultation. As noted, some women have a characteristic morphotype and are often thin, with scoliosis, pectus excavatum, and mitral valve prolapse.

Three forms of disease merit comment: hypersensitivity pneumonitis with NTM infection, infection in cystic fibrosis, and infection in transplant recipients. The hypersensitivity lung disease has been termed "hot tub lung." It is unknown whether the hot tub itself plays a role in the pathogenesis of this syndrome, but a unique form of hypersensitivity pneumonitis may be seen after exposure to NTM and hot tubs, undrained spas, and occasionally contaminated showers, with aerosolization devices. A similar syndrome is seen in metal workers associated with exposures to metalworking fluids (paraffins, pine oils, and polycyclic aromatic hydrocarbons) containing mycobacteria. This syndrome is associated almost exclusively with *M. immunogenum*, a rapidly growing mycobacterium. Onset of symptoms is subacute and is generally in non-smokers without a clear disposition to infection. Chest radiographs and chest CT scans have diffuse small nodules with ground-glass infiltrates. Lung biopsy generally reveals centrilobular and bronchocentric non-necrotizing granulomata, although some cases may have necrotizing granulomas, bronchiolitis and organizing pneumonia, or interstitial inflammation.

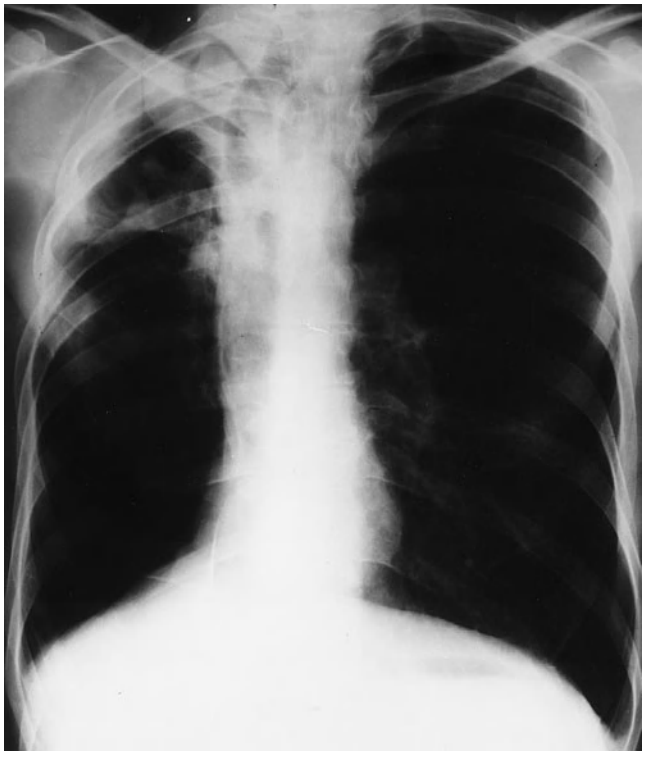

Figure 142-2 PA radiograph view of the chest showing extensive bilateral emphysema with cavitary destruction of right upper lobe.

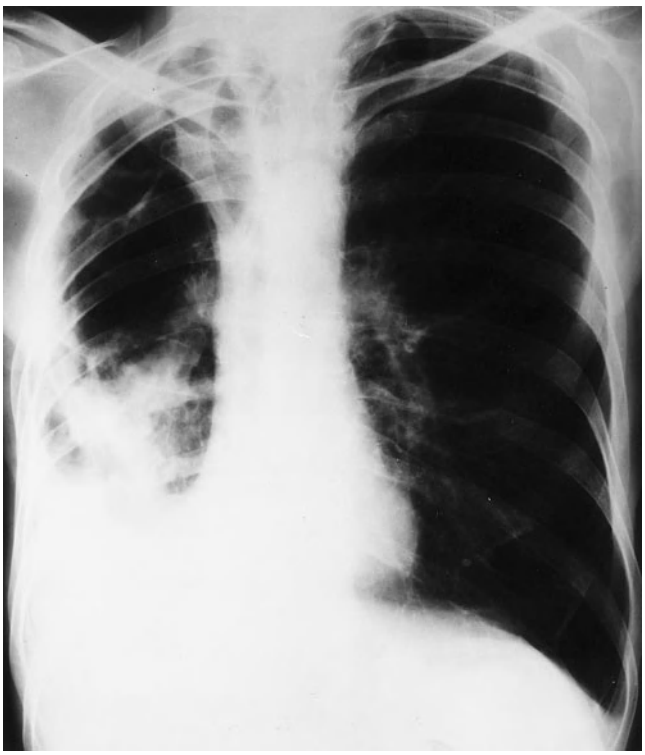

Figure 142-3 PA chest radiograph $2^1/_2$ years later showing pleural involvement and further marked progression of disease and destruction of the right lung.

In cystic fibrosis, NTM are increasingly isolated, often with uncertain clinical significance. As a result, such patients should have episodic sputum cultures for NTM, notably in advance of macrolide therapy.

In solid organ transplant recipients, the most common manifestations of NTM infection include cutaneous and pleuropulmonary disease. Catheter-related infection is the most commonly reported manifestation of NTM disease in hematopoietic stem cell transplant recipients. In such hosts, skin and pulmonary lesions should be biopsied for histology, special staining, and microbiologic cultures, including bacteria, *Nocardia* species, fungi, and mycobacteria. Mycobacterial infections associated with catheters may be documented by tunnel or blood (isolator) cultures. The pattern of NTM infection in transplantation differs from that of HIV-infection

Table 142-2

Interactions Between Drugs Used to Treat NTM and Immunosuppressive Medications

NTM Medication	Immunosuppresive Agent	Anticipated Reaction
Rifamycins (rifampin > rifabutin)	Calcineurin Inhibitors (CNI) (cyclosporin, tacrolimus) Sirolimus Steroids	Decreased level of CNI Loss of sirolimus efficacy Decreased steroid effectiveness
Macrolides (clarithromycin, azithromycin)	Calcineurin Inhibitors (CNI) (cyclosporin, tacrolimus)	Increased CNI level and risk of toxixcity
Ethambutol	NS*	N/A†
Aminoglycosides (streptomycin, amikacin)	Calcineurin Inhibitors (CNI) (cyclosporin, tacrolimus)	Possible additive or synergistic risk of renal impairment
Clofazamine	NS*	N/A†
Fluoroquinolones	NS*	N/A†
Isoniazid	NS*	N/A†
Doxycycline	NS*	N/A†
Cefoxitin	NS*	N/A†
Imipenem	Cyclosporin	May result in neurotoxicity (mental confusion, agitation, tremor)

**NS = no significant inteaction.*
†N/A = not applicable.

(less commonly *Mycobacterium avium* complex), which limits extrapolation of therapeutic data from HIV-infected individuals to this population. Drug interactions are common and outlined in Table 142-2.

Radiographic patterns are non-specific also, with fibrosis, small or large cavities, and predominantly interstitial disease, or with classical nodules (less than 5 mm by CT scans) and bronchiectasis. In general, the diffuseness of the disease is out of proportion to clinical illness. Radiographs often have multiple thin-walled cavities and significant pleural involvement, in addition to tree-and-bud appearance. Apical pleural disease is less common than with tuberculosis (Figs. 142-1, 142-4, 142-5). Most abnormalities are found in the lower and mid-lung fields.

TREATMENT

The approach to treatment varies with the species (Table 142-3). Many patients respond to regimens of several drugs, but toxicity and drug interactions are common (Table 142-2). Therapy should be based on antimicrobial susceptibility testing. During therapy, monitoring for toxicity of drugs is essential. Such testing should include visual acuity (ethambutol and rifabutin), liver enzymes (clarithromycin, azithromycin, rifabutin, rifampin, isoniazid, and ethionamide), auditory and vestibular function (streptomycin, amikacin, clarithromycin, and azithromycin), renal function (streptomycin and amikacin), and leukocyte and platelet counts (rifabutin). Red-green color discrimination (ethambutol) and drug interactions are also common. Clarithromycin enhances rifabutin toxicity (especially uveitis), whereas the rifamycin (rifampin more than rifabutin) lowers clarithromycin serum drug levels.

Some patients (e.g., those with localized pulmonary disease or hemorrhage) merit consideration for lung resection. This may be beneficial in patients with developing drug resistance.

Pulmonary *M. avium* Complex

Therapy is covered in detail by Chaisson in Chapter 141. In general, this is a syndrome of HIV infection and presents

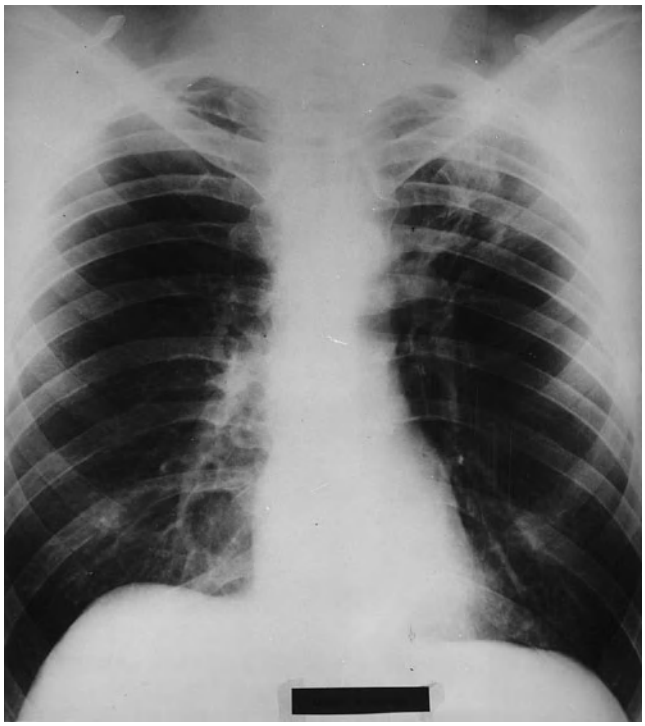

Figure 142-4 PA chest radiograph 2 months later showing decreased infiltration.

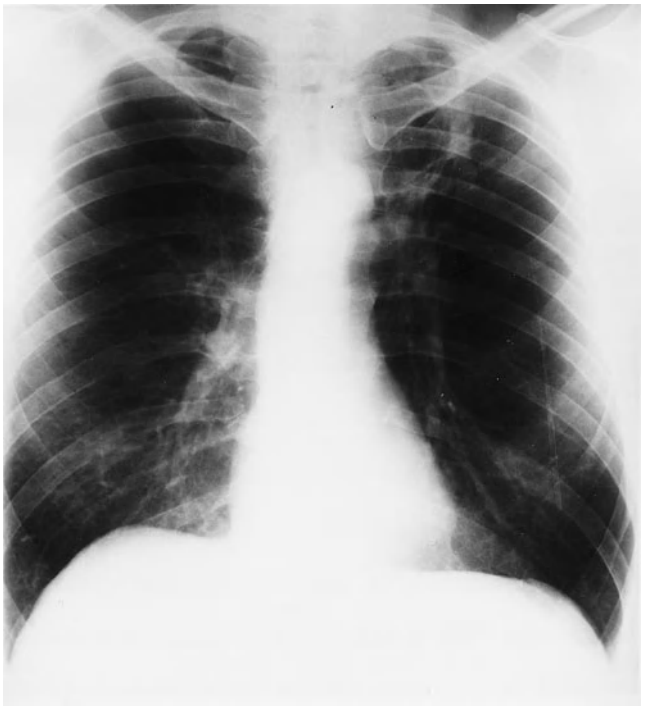

Figure 142-5 PA chest radiograph 7 years later showing a stable scar in left upper lung.

Table 142-3

Dosages of Drugs Used in Treating Adults with NTM Infection

Rifampin	600–900 mg per day in a single dose
Isoniazid	300–600 mg per day in a single dose
Ethambutol	25 mg/kg daily in a single dose until cultures are negative for 6 months, then 15 mg/kg daily thereafter
Streptomycin, capreomycin, kanamycin, amikacin	15 mg/kg up to 1 gm, once daily 5 days a week–when cultures are negative or significant toxicity occurs, dosages can be reduced and/or the drug given less frequently
Azithromycin	500–1000 mg per day in a single dose
Clarithromycin	500–750 mg twice daily
Ciprofloxacin	500–750 mg twice daily
Ofloxacin	800 mg per day in a single dose
Clofazimine	100–200 mg per day in a single dose
Rifabutin	300–600 mg per day in a single dose
Ethionamide	500–1000 mg per day usually in divided dose; give highest tolerated dose
Cycloserine	500–1000 mg per day usually in divided doses; give highest tolerated dose

with nodular and bronchiectatic lung disease. Intermittent therapy and monotherapy are not recommended due to the emergence of resistance. It should also be noted that patients respond best to the first course of MAC treatment; therefore, adherence and use of a multi-drug regimen are essential. Treatment is with three times weekly dosing of clarithromycin 1000 mg or azithromycin 500 mg, ethambutol 15 to 25 mg/kg, and rifampin 600 mg. For fibrocavitary or severe nodular/bronchiectatic disease, a daily regimen is used that includes clarithromycin 500 to 1000 mg/day or azithromycin 250 mg/day, ethambutol 15 mg/kg per day, and rifampin 10 mg/kg per day (maximum 600 mg). For prolonged therapy, visual acuity and color vision testing are recommended. The primary microbiologic goal of therapy is 12 months of negative sputum cultures while on therapy. A macrolide with a single companion drug, ethambutol, may be adequate for nodular/bronchiectatic MAC disease. Patients are considered treatment failures if they have not had response (microbiologic, clinical, or radiographic) after 6 months of appropriate therapy or achieved culture negativity of sputum after 12 months of therapy. Common factors in such patients include medication nonadherence and emergence of a macrolide-resistant MAC isolates.

M. kansasii

This organism is susceptible to anti-tuberculous agents, including rifampin and rifabutin. Response to a three-drug regimen of isoniazid, rifampin, and ethambutol plus pyridoxine (50 mg/d) is excellent. Isoniazid is sometimes given at doses higher than those recommended by guidelines (5 mg/kg per day to a maximum of 300 mg/d) because of the relative resistance of *M. kansasii* to this drug. Doses of 400 to 600 mg daily have been used in resistant cases. The rifampin dose is 10 mg/kg per day to a maximum of 600 mg daily, and ethambutol is given at 15 mg/kg per day. An initial 2 months of ethambutol at 25 mg/kg per day is no longer recommended. The total duration of treatment is 18 to 24 months, although good results with 12 months of therapy have been reported. Other drugs usually given in three-drug combinations are effective for retreatment of disease that has become resistant to rifampin; they include ethionamide, cycloserine, streptomycin, capreomycin, and kanamycin. Relapse after treatment with rifampin-containing regimens is uncommon.

M. marinum

This organism usually causes superficial skin infections following trauma and exposure to infected water (swimming pool granuloma). The disease often disappears with topical care. When the disease is more prolonged or extensive, treatment with isoniazid and rifampin is often successful. Minocycline or a trimethoprim-sulfa drug is sometimes useful when this approach fails.

M. abscessus

Soft-tissue abscesses related to trauma or surgery are the most common form of disease, but pulmonary disease is no longer rare. *M. abscessus* is the third most frequently recovered NTM pulmonary pathogen in the United States. These patients are generally women, non-smokers, without previously recognized lung disease, presenting with symptoms of bronchiectasis. Our patients have had a mixed radiographic picture with patchy interstitial-alveolar disease with upper lobe predominance. CT scanning reveals small nodules with bronchiectasis. Some have had cavity formation or scant hemoptysis. Dual infection with MAC is common. Disease is slowly progressive. *M. abscessus* has complicated lung transplant surgery causing sternal osteomyelitis.

M. abscessus isolates are uniformly resistant to standard antituberculous agents. Resistance to clarithromycin (23S rRNA gene) and amikacin (16S rRNA gene) can occur during therapy because *M. abscessus has* only a single gene copy. Drugs that may be useful include clarithromycin, amikacin, and cefoxitin. Some isolates respond to imipenem or linezolid. Combination therapy is mandatory for significant disease, usually for a minimum of 4 to 6 months.

No antibiotic regimens based on in vitro susceptibilities have been shown to produce long-term sputum conversion for patients with *M. abscessus* lung disease. For macrolide-resistant *M. abscessus* isolates or macrolide intolerance, a combination of parenteral drugs should be used based on in vitro susceptibilities. We have recently had some success with newer classes of drugs, the oxazolidinones (linezolid), the glycylcyclines (tigecycline), and the ketolides (telithromycin). Long-term therapy with linezolid has resulted in some peripheral neuropathy and marrow suppression. Tigecycline therapy has a problem with gastrointestinal intolerance and must be given intravenously. Telithromycin has not been well studied in vitro against NTM isolates.

M. chelonae and *M. fortuitum*

M. chelonae is a rapid grower that causes pulmonary disease similar to that of *M. abscessus. M. chelonae* isolates are susceptible to doxycycline, ciprofloxacin, tobramycin (more often than amikacin), clarithromycin, imipenem, clofazimine, and linezolid. *M. chelonae* are resistant to cefoxitin. Pulmonary disease due to *M. fortuitum* is also similar to that of *M. abscessus* but is most common in patients with gastroesophageal reflux disorders with recurrent aspirational lung disease. *M. abscessus may also be seen in such patients.* Dual therapy with an active agent should be given for 12 months or until clinical resolution of disease. *M. fortuitum* isolates are usually susceptible to clarithromycin and azithromycin, fluoroquinolones, doxycycline and minocycline, sulfonamides, amikacin, imipenem, and in about half to cefoxitin. Acquired resistance to macrolides is common.

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PART

XVII

Acute Respiratory Failure

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143
CHAPTER

Respiratory Failure: An Overview

Michael A. Grippi

Respiratory failure is a condition in which the respiratory system fails in one or both of its gas-exchanging functions—i.e., oxygenation of, and carbon dioxide elimination from, mixed venous (pulmonary arterial) blood. Hence, respiratory failure is a syndrome rather than a disease. Many diseases result in respiratory failure, as discussed elsewhere in this text.

Respiratory failure may be acute or chronic. The clinical presentations of patients with acute and chronic respiratory failure usually are quite different. While acute respiratory failure is characterized by life-threatening derangements in arterial blood gases and acid-base status, the manifestations of chronic respiratory failure are more indolent and may be clinically inapparent.

Although the causes of respiratory failure are diverse, common underlying pathophysiological mechanisms and management strategies merit a general discussion. This chapter begins with a focus on the definition of respiratory failure and underscores distinctions between acute and chronic varieties. Hypoxemic and hypercapnic respiratory failure are described, and the pathophysiological underpinnings of each type are reviewed. The concepts of ventilatory supply and demand are considered before an overview of the many categories of disease that result in respiratory failure. Finally, an approach to clinical evaluation and management is outlined, followed by a summary of complications and comments on prognosis.

CLASSIFICATION OF RESPIRATORY FAILURE

As noted previously, respiratory failure is characterized by inadequate blood oxygenation or carbon dioxide removal. "Adequacy" is defined by tissue requirements for oxygen uptake and carbon dioxide elimination. In the absence of bedside techniques for direct measurement of these metabolic parameters, clinicians must rely on arterial blood gas values.

Respiratory failure may be classified as *hypercapnic* or *hypoxemic* (Fig. 143-1). *Hypercapnic respiratory failure* is defined as an arterial P_{CO_2} (Pa_{CO_2}) greater than 45 mmHg. *Hypoxemic respiratory failure* is defined as an arterial P_{O_2} (Pa_{O_2}) less than 55 mmHg when the fraction of oxygen in inspired air (F_{IO_2}) is 0.60 or greater. In many cases, hypercapnic and hypoxemic respiratory failure coexist. Disorders that initially cause hypoxemia may be complicated by respiratory pump failure (see below) and hypercapnia. Conversely, diseases that produce respiratory pump failure are frequently complicated by hypoxemia due to secondary pulmonary parenchymal processes (e.g., pneumonia or atelectasis) or vascular disorders (e.g., pulmonary embolism).

Distinctions between *acute* and *chronic* respiratory failure are summarized in Table 143-1. In general, acute hypercapnic respiratory failure is defined as a Pa_{CO_2} greater than 45 mmHg with accompanying acidemia (pH less than 7.30). The physiological effect of a sudden increment in Pa_{CO_2} depends on the prevailing level of serum bicarbonate anion. In patients with chronic hypercapnic respiratory failure—e.g., due to chronic obstructive pulmonary disease (COPD)—a long-standing increase in Pa_{CO_2} results in renal "compensation" and an increased serum bicarbonate concentration. A superimposed acute increase in Pa_{CO_2} has a less dramatic effect than does a comparable increase in a patient with a normal bicarbonate level.

Table 143-1

Distinctions between Acute and Chronic Respiratory Failure

Category	Characteristic
Hypercapnic respiratory failure	Pa_{CO_2} >45 mmHg
Acute	Develops in min to h
Chronic	Develops over several days or longer
Hypoxemic respiratory failure	Pa_{O_2} <55 mmHg when F_{IO_2} ≥0.60
Acute	Develops in min to h
Chronic	Develops over several days or longer

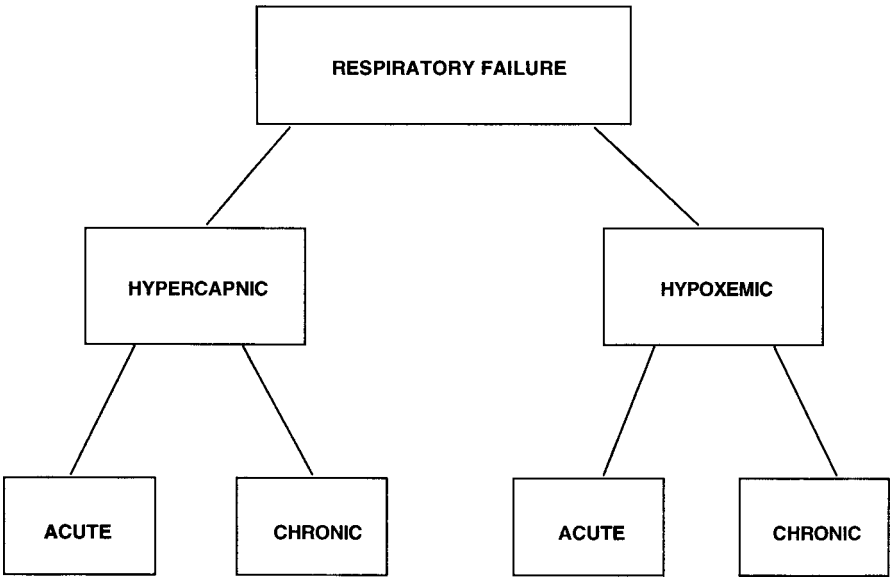

Figure 143-1 Classification of respiratory failure. Although depicted as distinct entities, hypercapnic and hypoxemic respiratory failure frequently coexist. Either may be acute or chronic.

Distinction between acute and chronic hypoxemic respiratory failure may not be readily made on the basis of arterial blood gas values. The presence of markers of chronic hypoxemia (e.g., polycythemia or cor pulmonale) provides clues to a long-standing disorder, whereas abrupt changes in mental status suggest an acute event.

It is important to bear in mind that even though the definition of hypoxemic respiratory failure rests on measurement of Pa_{O_2}, the major threat of arterial hypoxemia is inadequate tissue oxygenation, reflected in tissue *oxygen delivery*. Tissue oxygen delivery is determined by the product of cardiac output and blood *oxygen content* (see Chapter 13); the latter, in turn, depends on hemoglobin concentration and oxygen saturation. Therefore, factors that lower cardiac output or hemoglobin concentration, or inhibit dissociation of oxygen from hemoglobin at the tissue level, may promote tissue hypoxia without technically producing respiratory failure.

PATHOPHYSIOLOGY

Respiratory failure can arise from an abnormality in any of the "effector" components of the respiratory system—central nervous system, peripheral nervous system, respiratory muscles and chest wall, airways, or alveoli (Fig. 143-2). A defect in any of the first four components, which constitute the "respiratory pump," may cause coexistent hypercapnia and hypoxemia; at least initially, disorders of the alveoli are more apt to result in hypoxemia.

Hypoxemic Respiratory Failure

As described in Chapters 10, 11, and 12, four pathophysiological mechanisms account for the hypoxemia seen in a wide variety of diseases: alveolar hypoventilation, ventilation-perfusion mismatch, shunt, and diffusion limitation. Alveolar hypoventilation occurs in neuromuscular disorders that affect the respiratory system. In the absence of underlying pulmonary disease, the hypoxemia accompanying alveolar hypoventilation is characterized by a normal alveolar-arterial oxygen gradient, as defined by Eq. (1):

$$P_{A_{O_2}} - Pa_{O_2} = [P_{I_{O_2}} - Pa_{CO_2}/R] - Pa_{O_2} \qquad (1)$$

where

$P_{A_{O_2}}$ = alveolar P_{O_2}
Pa_{O_2} = arterial P_{O_2}
$P_{I_{O_2}}$ = inspired P_{O_2}
Pa_{CO_2} = arterial P_{CO_2}
R = respiratory exchange ratio

In contradistinction, disorders in which any of the other three mechanisms are operative are characterized by widening of the alveolar-arterial oxygen gradient, which is normally less than 20 mmHg. With ventilation-perfusion mismatching, areas of low ventilation relative to perfusion contribute to the hypoxemia. Similarly, with shunt, either intrapulmonary or intracardiac, deoxygenated mixed venous blood bypasses ventilated alveoli, resulting in "venous admixture." Finally, diseases that increase the diffusion pathway for oxygen from the alveolar space to pulmonary capillary impair oxygen transport across the alveolar-capillary membrane.

Although changes in minute and alveolar ventilation can change Pa_{CO_2} considerably, this is not so for Pa_{O_2}. Increases in minute ventilation and, secondarily, in alveolar ventilation, modestly increase Pa_{O_2}. Indeed, at a Pa_{O_2} above 55 to 60 mmHg, the effect of increasing ventilation on oxygen content is minimal, since the oxyhemoglobin dissociation curve is flat in this range.

Hypercapnic Respiratory Failure

At a constant rate of CO_2 production ($\dot{V}_{CO_2}$), Pa_{CO_2} is determined by the level of alveolar ventilation. The relationship

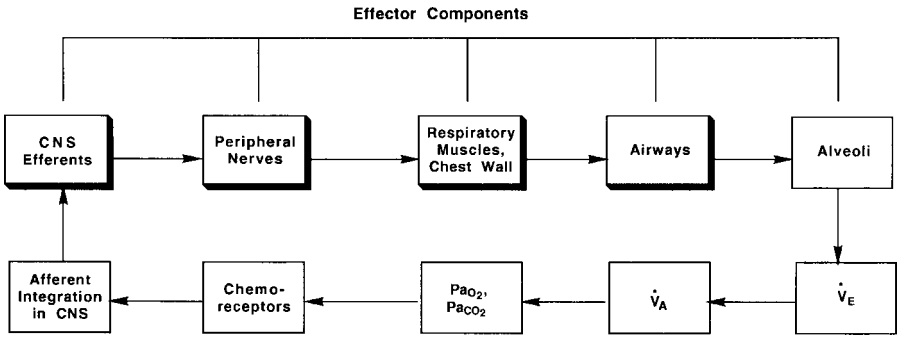

Figure 143-2 Functional components of the respiratory system and its controller. Abnormalities in any of the effector components can result in respiratory failure. The central and peripheral nervous systems, respiratory muscles and chest wall, and airways constitute the "respiratory pump" (shaded boxes). Hypercapnia is the hallmark of respiratory pump failure, while hypoxemia constitutes the primary disturbance in alveolar disorders producing respiratory failure. *(From Lanken PN: Respiratory failure: An overview, in Carlson RW, Geheb MA (eds),* Principles and Practice of Medical Intensive Care. *Philadelphia, WB Saunders, 1993, pp 754–763.)*

between alveolar ventilation, rate of CO_2 production, and Pa_{CO_2} is described by Eq. (2):

$$\dot{V}_A = K \cdot \dot{V}_{CO_2}/Pa_{CO_2} \qquad (2)$$

where

$\dot{V}_A$ = minute alveolar ventilation
K = a constant
$\dot{V}_{CO_2}$ = rate of CO_2 production

When $\dot{V}CO_2$ is constant, Pa_{CO_2} is determined by $\dot{V}_A$, which, in turn, is dictated by two factors: minute ventilation ($\dot{V}_E$) and the relationship between $\dot{V}_E$ and $\dot{V}_A$. The latter is determined by the proportion of $\dot{V}_E$ that constitutes dead space ventilation—i.e., the dead space to tidal volume ratio (V_D/V_T):

$$\dot{V}_E = K \cdot (\dot{V}_{O_2} \cdot RQ)/(Pa_{CO_2}/[1 - V_D/V_T]) \qquad (3)$$

where

$\dot{V}_{O_2}$ = rate of O_2 consumption
RQ = respiratory quotient (the respiratory exchange ratio in the steady state)
V_D = dead space volume
V_T = tidal volume

Inspection of Eq. (3) indicates that disorders reducing $\dot{V}_E$ or increasing the proportion of dead space ventilation may result in hypercapnia.

Ventilatory Supply vs. Demand

A useful theoretical construct for understanding the pathophysiological basis for hypercapnic respiratory failure is the relationship between ventilatory supply and ventilatory demand (Fig. 143-3).

Ventilatory supply is the maximal spontaneous ventilation that can be maintained without development of respiratory muscle fatigue; ventilatory supply is also known as *maximal sustainable ventilation* (MSV).

Ventilatory demand is the spontaneous minute ventilation, which, when maintained constant, results in a stable Pa_{CO_2} (assuming a fixed rate of CO_2 production).

Normally, ventilatory supply greatly exceeds ventilatory demand. Hence, major changes in minute ventilatory requirements (e.g., during exercise) may occur without hypercapnia. In lung disease, significant abnormalities may be present before ventilatory demand encroaches on MSV. Consequently, hypercapnia is a late finding. When ventilatory demand exceeds MSV, Pa_{CO_2} increases.

As a general rule, MSV is approximated as one-half the *maximal voluntary ventilation,* or MVV (see Chapter 34). A 70-kg adult has an MVV of about 160 L/min, an MSV of 80 L/min, and, under basal conditions, a $\dot{V}_E$ of approximately 6 to 7 L/min (90 ml/kg/min). Normally, therefore, there is a 10- to 15-fold difference between resting $\dot{V}_E$ and MSV. In disease states, the $\dot{V}_E$ requirement may approach a markedly

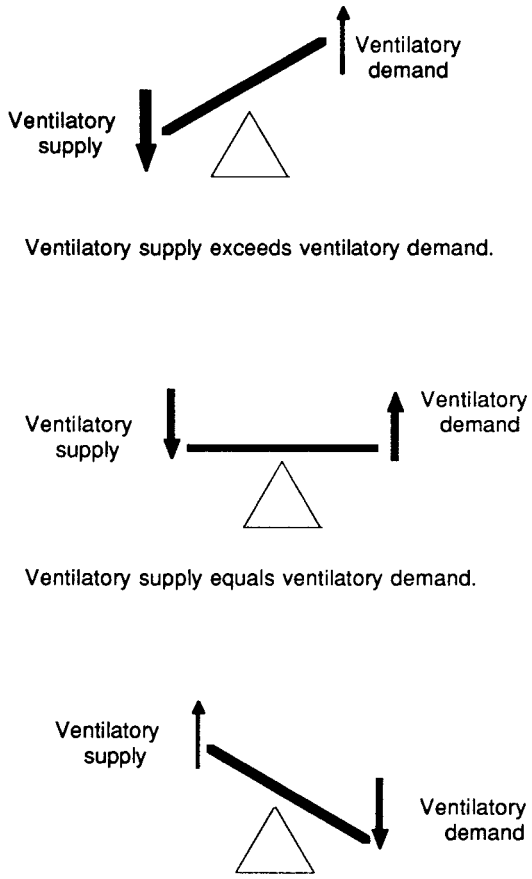

Figure 143-3 Relationship between ventilatory supply (maximal sustainable ventilation) and ventilatory demand (overall level of ventilation specified by the central nervous system controller). Relative size of the arrows indicates levels of supply and demand in each of the three circumstances illustrated. *A*. Normal. Ventilatory supply greatly exceeds ventilatory demand. Physiological "reserve" is maintained. *B* .Ventilatory supply is decreased and ventilatory demand increased (e.g., acute asthma attack). "Borderline" respiratory failure exists. *C* . Ventilatory demand exceeds ventilatory supply (e.g., sepsis in a patient with chronic obstructive pulmonary disease). Respiratory muscle fatigue develops, and hypercapnic respiratory failure ensues. See text for details. *(From Lanken PN: Pathophysiology of respiratory failure, in Grippi MA (ed), Pulmonary Pathophysiology. Philadelphia, JB Lippincott, 1995, pp 267–280.)*

reduced MSV. Further reductions in MSV result in ventilatory demand exceeding supply, and hypercapnia occurs.

Factors that Reduce Ventilatory Supply or Increase Ventilatory Demand

Disruption of any component of the efferent arm of the respiratory control system may diminish ventilatory supply (Table 143-2). While a variety of diseases produce specific abnormalities along the efferent pathway (e.g., phrenic nerve and respiratory muscle disorders), some result in respiratory

Table 143-2

Factors That Diminish Ventilatory Supply

Factor	Examples
Decreased respiratory muscle strength	
Muscle fatigue	Recovery from acute respiratory failure, high respiratory rates, increased inspiratory time
Disuse atrophy	Prolonged mechanical ventilation, following phrenic nerve injury
Malnutrition	Protein-calorie starvation
Electrolyte abnormalities	Low serum phosphate or potassium concentrations
Arterial blood gas abnormalities	Low pH, low Pa_{O_2} high Pa_{CO_2}
Fatty infiltration of diaphragm	Obesity
Unfavorable alteration in diaphragm length–tension relationship	Flattened domes of diaphragm caused by hyperinflation
Increased muscle energy requirement or decreased substrate supply	
High elastic work of breathing	Low lung or chest wall compliance, high respiratory rate
High resistive work of breathing	Airway obstruction
Reduced diaphragm perfusion	Shock, anemia
Decreased motor neuron function	
Decreased phrenic nerve output	Polyneuropathy, Guillain-Barré syndrome, phrenic nerve transection or injury, poliomyelitis
Decreased neuromuscular transmission	Myasthenia gravis, use of paralyzing agents
Abnormal respiratory mechanics	
Airflow limitation	Bronchospasm, upper-airway obstruction, excessive airway secretions
Loss of lung volume	After lung resection, large pleural effusion
Other restrictive defects	Pain-limited inspiration; tense abdominal distention due to ileus, peritoneal dialysis fluid, or ascites

muscle fatigue—the biochemical, cellular, and molecular mechanisms of which remain poorly understood.

As described previously, ventilatory demand can be assessed according to Eq. (3):

$$\dot{V}_E = K \cdot (\dot{V}_{O_2} \cdot RQ)/(Pa_{CO_2}/[1 - V_D/V_T]) \qquad (3)$$

Any factor that affects terms on the right-hand side of the equation may result in ventilatory demand exceeding supply. Selected clinical examples are given in Table 143-3.

CATEGORIES OF RESPIRATORY FAILURE

Although many different diseases cause respiratory failure, they may be grouped conveniently according to primary abnormalities in the individual effector components of the respiratory system.

Abnormalities of the Central Nervous System

A variety of pharmacologic, structural, and metabolic disorders of the central nervous system (CNS) are characterized by suppression of the neural drive to breathe. The resultant hypoventilation and hypercapnia may be acute or chronic.

An overdose of a narcotic or other drug with sedative properties is a common cause of respiratory failure. While the most striking clinical picture occurs with an acute overdose, long-standing use of some agents (e.g., methadone) may result in chronic hypercapnia.

"Structural" CNS abnormalities producing hypercapnic respiratory failure include meningoencephalitis, localized tumors or vascular abnormalities of the medulla, and strokes affecting medullary control centers. Usually, respiratory failure is observed in the context of other neurological findings.

Table 143-3

Factors That Increase Ventilatory Demand

Factor	Clinical Examples
Increased V_D/V_T	Acute asthma, emphysema, late phase of acute respiratory distress syndrome, pulmonary emboli
Increased V_{O_2}	Fever, sepsis, trauma, shivering, increased work of breathing, massive obesity
Increased RQ	Excessive carbohydrate feeding
Decreased Pa_{CO_2}	Hypoxemia, metabolic acidosis, anxiety, sepsis, renal failure, hepatic failure

Source: Data from Lanken PN: Pathophysiology of respiratory failure, in Grippi MA (ed), Pulmonary Pathophysiology. *Philadelphia, JB Lippincott, 1995, pp. 267–280.*

A variety of metabolic derangements may produce hypercapnia through depression of respiratory control centers. Examples include severe myxedema, hepatic failure, and advanced uremia. In addition, elevation of P_{CO_2} in the CNS results in neural depression, further enhancing CO_2 retention. A common clinical setting in which elevation of Pa_{CO_2} is observed is chronic metabolic alkalosis (e.g., due to diuretic use), as detailed in Chapter 14.

Finally, obesity-hypoventilation syndrome is characterized by hypercapnia due to hypoventilation on a central basis. The underlying mechanisms have not yet been elucidated.

Abnormalities of the Peripheral Nervous System or Chest Wall

A wide variety of disorders of the peripheral nerves, neuromuscular junction, and chest wall may be associated with hypercapnic and hypoxemic respiratory failure. While the hallmark is an inability to maintain a level of $\dot{V}_E$ appropriate for the rate of CO_2 production, many of these disorders are complicated by impaired expiratory muscle strength, atelectasis, and aspiration. Through mechanisms outlined previously, hypoxemia develops in conjunction with the hypercapnia.

Among the most common neuromuscular causes of hypercapnic respiratory failure are Guillain-Barré syndrome, myasthenia gravis, polymyositis, the muscular dystrophies, and a large number of metabolic muscle disorders. In addition, acute poliomyelitis and traumatic spinal cord injury are associated with hypercapnia. Development of respiratory muscle fatigue during prolonged weaning from mechanical ventilation may cause recurrent hypercapnia in the critical care setting.

Pharmacologic causes of hypercapnia in the intensive care unit are frequently encountered. Use of depolarizing and nondepolarizing paralyzing agents, particularly in conjunction with systemic corticosteroids (e.g., in management of status asthmaticus), cholinergic crisis during therapy of myasthenia gravis, and administration of aminoglycosides to patients with myasthenia are examples.

Primary disorders of the chest wall constitute another important category of neuromuscular respiratory failure. The prototype is severe kyphoscoliosis. Additional examples include flail chest (see Chapter 100), extensive thoracoplasty, morbid obesity, and massive abdominal distention due to ascites or distended loops of bowel.

In each of these disorders, a common pathophysiological sequence develops. Because of inadequate activation of inspiratory muscles or limited thoracic excursion, tidal volume falls. While an increase in respiratory rate compensates initially for the fall in $\dot{V}_E$ (and in $\dot{V}_A$), $\dot{V}_E$ eventually declines. In addition, the sigh mechanism is impaired, which, in conjunction with the low tidal volume, results in atelectasis and reduced lung compliance. Reduced lung compliance produces a further fall in tidal volume and an increase in the elastic work of breathing (see Chapter 9). Hence, ventilatory supply becomes limited, while ventilatory demand increases due to a rise in V_D/V_T (as a result of atelectasis and other factors noted below). An imbalance between ventilatory supply and demand arises, and hypercapnia ensues. Furthermore, an impaired gag reflex in the setting of bulbar weakness, coupled with impaired cough due to respiratory muscle involvement, may result in aspiration pneumonia and secondary hypoxemia.

In addition to the pathophysiology described, structural abnormalities of the thoracic cage (e.g., severe kyphoscoliosis) are characterized by an increase in the elastic component of the work of breathing. This results in a higher $\dot{V}_{O_2}$ and a higher proportion of total O_2 consumption by the respiratory muscles (normally, less than 5 percent of $\dot{V}_{O_2}$).

Abnormalities of the Airways

Obstructive diseases of the airways—either upper or lower—are common causes of acute and chronic hypercapnia. Examples in the upper airways include acute epiglottitis, aspirated foreign body, tracheal tumor, and narrowing of the trachea or glottis by fibrotic tissue. Disorders of the lower airways include COPD, asthma, and advanced cystic fibrosis. The underlying mechanisms are multifaceted and variable. However, several common pathophysiological pathways are operative.

Airway narrowing results in a greater transthoracic pressure gradient requirement for inspiratory airflow. The resistive component of the work of breathing is increased, and the increase is associated with an elevation in $\dot{V}_{O_2}$. In addition, tidal volume falls and dead space ventilation increases. Respiratory muscle fatigue may develop; the consequences of a shallow breathing pattern ensue.

Finally, in some disorders (e.g., acute asthma or an exacerbation of COPD), air trapping and lung hyperinflation occur, resulting in diaphragm flattening and worsening diaphragm mechanics (see Chapters 9, 41 and 42). The overall effect is a growing imbalance between ventilatory supply and demand.

Abnormalities of the Alveoli

Although diseases characterized by diffuse alveolar filling frequently result in hypoxemic respiratory failure, hypercapnia may complicate the picture. Common clinical examples in this category include cardiogenic and noncardiogenic pulmonary edema, diffuse pneumonia, extensive pulmonary hemorrhage, aspiration of stomach contents, and near-drowning.

Diffuse alveolar filling creates a large right-to-left shunt as pulmonary blood flows through nonventilated or poorly ventilated regions of the lung. In addition, coexisting interstitial edema may impair diffusion across the alveolar-capillary membrane, further impairing oxygenation of mixed venous blood.

In extensive, acute pulmonary disease characterized by alveolar filling, ventilatory demand is high because of hypoxemia and increases in V_D/V_T, the elastic work of breathing (due to reduced lung compliance), the resistive work of breathing (due to airway narrowing and increased airway reactivity), and the neural drive to breathe (mediated by pulmonary parenchymal vagal fibers). In conjunction with heightened ventilatory demand, ventilatory supply is reduced because of alveolar flooding, reduced lung elasticity, respiratory muscle fatigue, and, possibly, reduced blood supply to the diaphragm secondary to shock. Once again, the imbalance between ventilatory supply and demand results in hypercapnia.

APPROACH TO THE PATIENT

The diagnosis of acute or chronic respiratory failure begins with clinical suspicion of its presence. Confirmation of the diagnosis is based on arterial blood gas analysis (Table 143-1). Evaluation for an underlying cause must be initiated early, frequently in the presence of concurrent treatment for acute respiratory failure. While the diagnosis of chronic respiratory failure is usually easily established with clinical findings of chronic hypoxemia (with or without findings of hypercapnia), the diagnosis of acute respiratory failure requires more careful analysis.

Signs and symptoms in acute respiratory failure reflect the underlying disease process and associated hypoxemia or acidemia due to hypercapnia. Localized pulmonary findings reflecting the acute causes of hypoxemia (e.g., pneumonia, pulmonary edema, asthma, or COPD) may be readily apparent. Alternatively, the predominant findings may be systemic (e.g., hypotension due to sepsis). The principal manifestations may even be remote from the thorax—e.g., abdominal pain in acute pancreatitis or leg pain due to a long bone fracture—each associated with acute (adult) respiratory distress syndrome (ARDS) (see Chapter 145). Frequently, neurological or cardiovascular symptoms and signs predominate. Neurological manifestations include restlessness, anxiety, confusion, seizures, or coma. Asterixis may be seen with severe hypercapnia. Common cardiovascular findings include tachycardia and a variety of arrhythmias. Finally, there may be few or no findings other than a complaint of dyspnea, as in some patients with hypoxemia due to pulmonary embolism.

Once respiratory failure is suspected on clinical grounds, arterial blood gas analysis is performed to confirm the diagnosis, to assist in the distinction between acute and chronic forms, to assess the magnitude and metabolic impact, and to help guide management (Table 143-4).

PRINCIPLES OF MANAGEMENT

The principles of management of patients in acute respiratory failure include those that are cause-specific and those that are more general. Triage of the patient to the proper clinical setting, airway maintenance, correction of hypoxemia and hypercapnia, and management of the underlying cause are of paramount importance.

Triage Decisions

The first step in management is to determine the appropriate setting for care—admission to a standard inpatient facility or to an intensive or intermediate care unit. Factors that constitute the basis for this decision include the acuity of the respiratory failure; the degree of hypoxemia, hypercapnia, and acidemia; the presence of co-morbid conditions (e.g., cardiac disease or renal insufficiency); and the clinical direction that the patient takes over the first few minutes or hours of observation. At one end of the spectrum is the patient with fulminant hypoxemic respiratory failure, metabolic acidosis, and imminent cardiovascular collapse, who needs emergent intubation, mechanical ventilation, and admission to a critical care unit. At the other end of the spectrum is the patient with COPD and chronic, compensated hypercapnic respiratory failure, who requires observation in an intermediate care unit. Notably, in recent years, a number of studies have indicated that use of noninvasive mechanical ventilation may obviate the need for endotracheal intubation in selected patients with hypercapnic or acute, hypoxemic respiratory failure (other than ARDS-related). Although studies also point to the potential role of noninvasive mechanical ventilation in recurrent respiratory failure following extubation, a multicenter, randomized trial found no reduction in mortality or in the need for reintubation with its use.

Airway Management

Assurance of an adequate airway is key in the patient with acute respiratory distress. Whether emergency intubation is

Table 143-4

Changes in Arterial Blood Gases, $P_{A_{O_2}}$–Pa_{O_2}, and Ventilation in Acute Respiratory Failure

Failed Respiratory System Component	pH	Pa_{CO_2}	Pa_{O_2}	$P_{A_{O_2}}$–Pa_{O_2}	$\dot{V}_E$	$\dot{V}_A$
Central nervous system	↓	↑	↓*	NL or ↑†	↓	↓
Peripheral nervous system or chest bellows	↓	↑	↓*	NL or ↑†	↓	↓
Airways						
In acute asthma						
Early phase (before respiratory failure)	↑	↓	NL	↑	↑	↑
"Crossover point"	NL	NL	NL or ↓	↑	↑	NL
With development of respiratory muscle fatigue	↓	↑	↓	↑	↓‡	↓
In COPD						
Non–CO_2 retainer	↓	NL or ↑§	↓	↑	↑	↓
CO_2 retainer						
Baseline	NL to ↓	↑	↓	↑	NL or ↑	↓
Flare	↓	↑↑	↓↓	↑	NL, ↑ or ↓‡	↓
Alveoli						
Before respiratory muscle fatigue develops	↑	↓	↓↓	↑↑	↑	↑
After respiratory muscle fatigue develops	↓	↑	↓↓	↑↑	↓	↓

*Pa_{O_2} *may decrease when pneumonia or atelectasis occurs as a complication.*
†($P_{A_{O_2}}$–Pa_{O_2}) *widens when pneumonia or atelectasis occurs as a complication.*
‡$\dot{V}_E$ *declines when frank respiratory muscle failure occurs.*
§Pa_{CO_2} *may increase during an exacerbation.*
Note: ↑ = increased; ↑↑= very increased; ↓= decreased; ↓↓= very decreased; NL = in normal range.
Source: Data from Lanken PN: Pathophysiology of respiratory failure, in Grippi MA (ed), Pulmonary Pathophysiolosy. *Philadelphia, JB Lippincott, 1995, pp. 267–280.*

required depends on the clinical circumstances described previously. For patients with chronic respiratory insufficiency, the need for intubation depends on critical arterial blood gas values and the patient's early acute course. When progressive hypoxemia or hypercapnia is observed over the first few minutes or hours of care, intubation and mechanical ventilation are warranted.

Correction of Hypoxemia and Hypercapnia

Once the airway is secured, the clinician must turn attention to the treatment of hypoxemia—the most life-threatening aspect of acute respiratory insufficiency. The goal is to assure adequate oxygen delivery to tissues, generally achieved with a Pa_{O_2} of about 60 mmHg (assuming an adequate hematocrit and cardiac output). In patients who have coronary or cerebrovascular disease, a slightly higher level of arterial oxygenation may be desirable in order to provide a "buffer" for any sudden, unpredictable changes in gas exchange.

The means by which supplemental oxygen is administered is determined by the clinical circumstances. While some patients may simply require nasal prongs or a face mask to achieve an adequate Pa_{O_2}, others are best treated with controlled-flow oxygen delivered via a Venturi mask—e.g.,

the patient with COPD and chronic hypercapnia (see Chapters 42 and 149). Generally, if an acceptable level of oxygenation, as judged by arterial blood gases, cannot be attained using a face mask, or if administration of supplemental O_2 causes hypercapnia to worsen significantly (e.g., in some patients with COPD), either noninvasive mechanical ventilation or endotracheal intubation and mechanical ventilation will be required.

While correcting hypoxemia, the clinician must also address any coexisting hypercapnia and respiratory acidosis. Once again, the immediacy of correction depends on the magnitude of the acidosis and its attendant effects (e.g., elevation of serum potassium). A partly compensated respiratory acidosis in a patient with COPD usually constitutes a less urgent clinical circumstance than does profound respiratory acidosis in a patient with a drug overdose.

Search for an Underlying Cause

Finally, as therapy is initiated to correct the hypoxemia, hypercapnia, and acidosis of respiratory failure, a search for the cause of the problem and its management must be undertaken. In some cases, the cause and management are straightforward (e.g., administration of a narcotic antagonist to the patient with a narcotic overdose). In others, a more protracted course may be in store (e.g., long-term ventilator management of fulminant ARDS due to sepsis).

In both brief and prolonged cases of respiratory failure, attention to details of management is important in order to minimize the risks of complications of therapy, as discussed below.

MONITORING PATIENTS WITH ACUTE RESPIRATORY FAILURE

Repeated assessment of the patient with incipient or resolving respiratory failure, as well as the patient with frank hypoxemic or hypercapnic failure, is critical in formulating decisions about therapy. Monitoring methods range from routine bedside observations to use of invasive techniques.

For many patients with acute respiratory failure, simple observation of respiratory rate, tidal volume, use of accessory muscles, and presence of paradoxical breathing movements provides evidence of worsening respiratory failure and the need for mechanical ventilation. The patient with asthma or an acute exacerbation of COPD will frequently manifest rapid, shallow breathing and paradoxical thoracoabdominal breathing movements as respiratory mechanics deteriorate.

Once placed on mechanical ventilation, the patient must be monitored carefully for ventilator-associated complications (see below). In addition, placement of indwelling arterial and venous catheters, patient immobilization, and use of a broad range of pharmacologic agents present additional potential threats to the acutely ill patient.

While many monitoring techniques are routine and may be universally applicable to patients in a critical care setting (e.g., pulse oximetry), others may be of particular importance in selected clinical circumstances. For example, routine assessment of static respiratory system compliance in a mechanically ventilated patient with ARDS or pulmonary fibrosis may provide an early warning of barotrauma. In the patient with status asthmaticus requiring mechanical ventilation, development of hypotension due to intrinsic positive end-expiratory pressure (PEEP) or "auto-PEEP," as discussed in Chapters 152 and 153, may signal the need to alter ventilator settings or implement sedation or pharmacologic paralysis.

COMPLICATIONS OF ACUTE RESPIRATORY FAILURE

The respiratory patient in a critical care unit must navigate not only the obstacles presented by the underlying pulmonary process, but also the hazards associated with use of mechanical devices and pharmacologic agents. Complications of acute respiratory failure may be broadly categorized as pulmonary, cardiovascular, gastrointestinal, renal, infectious, nutritional, and other (Table 143-5). For details in each of these areas, the reader is referred to other chapters in this text.

Pulmonary

Common pulmonary complications of acute respiratory failure include pneumonia (discussed in detail elsewhere), pulmonary emboli, pulmonary barotrauma, pulmonary fibrosis, and complications directly related to use of mechanical devices.

Pulmonary emboli have been reported in up to one-fourth of patients with respiratory failure in intensive care units. The diagnosis is difficult in this setting, since patients typically have diffuse underlying lung disease, abnormal gas exchange, and many coexisting potential causes for the clinical, radiographic, and physiological consequences of pulmonary emboli.

Pulmonary barotrauma, identified as the presence of extra-alveolar air in structures that do not normally contain air, may occur in patients receiving mechanical ventilation for a variety of indications. It is particularly common in patients with ARDS. Manifestations of barotrauma include pulmonary interstitial emphysema, pneumothorax, pneumomediastinum, pneumoperitoneum, subcutaneous emphysema, tension lung cysts, and subpleural air cysts.

Pulmonary fibrosis may follow acute lung injury associated with ARDS. In addition, use of high inspired concentrations of oxygen may enhance development of fibrosis in the presence of acute lung injury.

Based on recent studies, a strategy of "low stretch" ventilation has emerged for managing patients with acute lung injury or ARDS and is aimed at minimizing the risks of ventilator-induced pulmonary damage, as discussed in

Table 143-5

Complications of Acute Respiratory Failure

Pulmonary
Pulmonary emboli
Pulmonary barotrauma (interstitial emphysema, pneumothorax, subcutaneous emphysema, pneumoperitoneum, tension lung cyst, subpleural air cyst)
Pulmonary fibrosis
Related to Use of Mechanical Devices
Complications of mechanical ventilation (infection, arterial desaturation, hypotension, barotrauma, others)
Complications of insertion and maintenance of pulmonary artery catheter (pneumothorax, air embolism, arrhythmias, infection, thrombosis, pulmonary artery rupture)
Complications of tracheal intubation
Related to prolonged intubation attempt (hypoxemic brain injury, cardiac arrest, seizures, others)
Related to right main bronchus intubation (hypoventilation, pneumothorax, atelectasis)
Self- or inadvertent extubation
Endotracheal tube dislodgment
Endotracheal tube cuff leak
Injury to pharynx, larynx, trachea
Complications of tracheotomy (pneumothorax, bleeding, tube dislodgment, tracheoinnominate fistula, tracheoesophageal fistula, tracheal stenosis)
Gastrointestinal
Hemorrhage (including "stress" ulceration)
Ileus
Diarrhea
Cardiovascular
Hypotension
Arrhythmias
Decreased cardiac output
Myocardial infarction
Pulmonary hypertension
Renal
Acute renal failure
Fluid retention
Infectious
Nosocomial pneumonia
Bacteremia
Sepsis
Paranasal sinusitis
Nutritional
Complications of underlying malnutrition (decreased respiratory muscle strength, immune suppression, others)
Complications of enteral feeding (pneumothorax, pleural effusion, sinusitis, aspiration, diarrhea)
Complications of parenteral feeding (pneumothorax, sepsis, hyperglycemia, hyperosmolar coma, hypophosphatemia, liver function test abnormalities)
Complications of refeeding (hypercapnia)
Other
Psychiatric (anxiety, depression, confusion, sleep dysfunction, psychosis)
Hematological (anemia, thrombocytopenia)

Chapters 144 and 145. In addition, new approaches to the use of intravenous sedation, namely, daily interruption of the infusion, has been shown to reduce both the duration of mechanical ventilation and length of stay in the intensive care unit.

Common device-related complications include those due to pulmonary artery flotation catheters, endotracheal intubation, and tracheotomy.

Cardiovascular

Common cardiovascular complications in patients with acute respiratory failure include hypotension, reduced cardiac output, arrhythmias, pericarditis, and acute myocardial infarction. These complications may be related to the underlying disease process, mechanical ventilation, or use of pulmonary artery flotation catheters.

Gastrointestinal

A variety of gastrointestinal complications of acute respiratory failure, particularly during mechanical ventilation, have been well described. The major ones include hemorrhage, gastric distention, ileus, diarrhea, and pneumoperitoneum. "Stress" ulceration is extremely common in patients with acute respiratory failure. Associated risk factors include trauma, shock due to a variety of causes, sepsis, renal failure, and liver disease.

Infectious

Nosocomial infections are a frequent complication of acute respiratory failure. Principal among these are pneumonia, sepsis, and urinary tract infections. Each typically occurs with the use of mechanical devices, including endotracheal and tracheotomy tubes, indwelling central venous and pulmonary artery catheters, and urinary bladder catheters.

The incidence of nosocomial pneumonia in the critically ill may be as high as 70 percent for patients in intensive care units, particularly in those with ARDS. The need for prolonged mechanical ventilation is a harbinger for development of nosocomial pneumonia. Not unexpectedly, nosocomial pneumonia occurring in the medical intensive care unit is associated with a significantly increased length of stay and higher mortality. Guidelines have been developed for treatment of patients with ventilator-associated pneumonia.

Renal

Acute renal failure and abnormalities in electrolyte and water homeostasis are not uncommon in critically ill patients with acute respiratory failure; the former is observed in approximately 10 to 20 percent of patients in intensive care units. Development of acute renal failure in a patient with acute respiratory failure carries a poor prognosis and a high mortality. The causes of acute renal failure are numerous and include prerenal azotemia and acute tubular necrosis due to hypotension or use of nephrotoxic drugs.

Nutritional

Nutritional complications of acute respiratory failure include the effects of malnutrition on respiratory performance and complications related to the administration of enteral or parenteral nutrition. Complications of enteral nutritional support relate to initial insertion of the catheter (e.g., tracheal or pleural space penetration, pneumomediastinum, pneumothorax, and pleural effusion) and its maintenance (e.g., paranasal sinusitis and aspiration). In addition, vomiting, abdominal distention, and diarrhea are common. Complications of parenteral nutrition are mechanical (e.g., pneumothorax during catheter insertion), infectious (e.g., catheter-related sepsis), or metabolic (e.g., metabolic acidosis, hyperglycemia and hyperosmolar coma, and hypophosphatemia). Hypercapnia, induced by enteral as well as parenteral nutrition, can complicate management of patients who have limited ventilatory reserve.

PROGNOSIS

Interpretation of studies addressing the prognosis of patients with acute respiratory failure is subject to a number of constraints, including marked clinical variability in the patients studied, predominance of studies from intensive care units in large university teaching hospitals, and variability in treatment methods employed over the time span of studies performed. In addition, many studies report only hospital mortality, not long-term survival or quality of life. Finally, findings from large-population studies are difficult to extrapolate to prediction of outcome in a single patient. Nonetheless, several generalizations can be made regarding the prognosis of patients hospitalized with acute respiratory failure.

Morbidity and Mortality in Acute Hypoxemic Respiratory Failure

As expected, mortality in hypoxemic respiratory failure depends on the underlying cause. A number of studies have addressed outcome in patients with ARDS.

Mortality in ARDS appears to have improved in recent years, with overall survival now at about 60 percent. Patients who develop sepsis after trauma have a lower mortality than do patients with sepsis that complicates medical disorders. Not surprisingly, younger patients (those under the age of 70 years) have better survival rates than do older patients. Notably, patients with preexisting lung disease, higher F_{IO_2} or PEEP requirements, or a lower Pa_{O_2} may not necessarily have a poorer chance of survival.

Approximately two-thirds of patients who survive an episode of ARDS will manifest some impairment of

pulmonary function one or more years after recovery. The abnormalities include both obstructive and restrictive defects, as well as a reduction in diffusing capacity. The pulmonary function findings do not appear to correlate with whether low or high tidal volumes were used during mechanical ventilation. Pulmonary function abnormalities that persist beyond one year after recovery are unlikely to resolve thereafter. Furthermore, despite recovery of pulmonary function, many survivors of ARDS have persistent functional disabilities one year after discharge, largely due to muscle wasting and weakness.

Approximately three-fourths of survivors of ARDS have neurocognitive findings at hospital discharge; in about one-half, the findings persist at 2 years postdischarge. Indeed, reduced quality of life and persistent neurocognitive defects represent long-term morbidities of survival in ARDS.

Morbidity and Mortality in Acute Hypercapnic Respiratory Failure

In general, several parameters presage a higher mortality in patients admitted with hypercapnic respiratory failure: (1) the patient's "physiological reserve," as determined by concurrent cardiopulmonary, renal, hepatic, or neurological disease and the patient's age; (2) the underlying cause of the acute deterioration; (3) the severity of the respiratory failure, as defined by arterial pH and P_{CO_2}; and (4) development of complications after onset of acute respiratory failure—e.g., sepsis, pneumonia, renal failure, or gastrointestinal bleeding. Cachexia and home confinement before hospitalization may also presage a poorer outcome. These harbingers appear to hold true regardless of whether the patient requires mechanical ventilation.

For patients with COPD and acute respiratory failure, overall mortality has declined from approximately 26 percent to 10 percent according to more recent studies. Not unexpectedly, older patients who are significantly more acidemic, hypotensive, or uremic appear to have a higher mortality. The magnitude of the hypoxemia or hypercapnia at the time of presentation may not reliably foretell mortality.

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144

Acute Respiratory Distress Syndrome: Pathogenesis

Michael A. Matthay

This chapter focuses on the pathogenesis of acute lung injury (ALI) and the acute respiratory distress syndrome (ARDS). Chapter 145 discusses clinical features and clinical management.

PATHOPHYSIOLOGY OF PULMONARY EDEMA IN ACUTE LUNG INJURY

Pulmonary edema occurs when fluid is filtered into the lungs faster than it can be removed. Accumulation of fluid may have major consequences on lung function because efficient gas exchange cannot occur in fluid-filled alveoli. Lung structure relevant to edema formation and the forces governing fluid and protein movement in the lungs has been the subject of classic and more recent reviews and chapters, as noted in the "Suggested Reading" included at the end of this discussion.

Vascular Fluid and Protein Exchange

The essential factors that govern fluid exchange in the lungs are expressed in the Starling equation for the microvascular barrier:

$$Jv = LpS[(Pc - Pi) - \sigma d(\pi c - \pi i)] \quad (1)$$

where

- Jv = the net fluid-filtration rate (volume flow) across the microvascular barrier
- Lp = the hydraulic conductivity ("permeability") of the microvascular barrier to fluid filtration (a measure of how easy it is for water to cross the barrier)
- S = the surface area of the barrier
- Pc = the pulmonary capillary (microvascular) hydrostatic pressure
- Pi = the interstitial ("perimicrovascular") hydrostatic pressure
- πc = the capillary (microvascular) plasma colloid osmotic (or oncotic) pressure
- πi = the interstitial (perimicrovascular) fluid osmotic pressure
- σd = the average osmotic reflection coefficient of the barrier (a measure of the effectiveness of the barrier in hindering the passage of solutes from one side of the barrier to the other)

The Starling equation predicts the development of two different kinds of pulmonary edema. *Increased pressure pulmonary edema* occurs when the balance of the driving forces increases,

forcing fluid across the barrier at a rate that can no longer be accommodated by lymphatic drainage. *Increased permeability pulmonary edema* occurs in the presence of ALI that damages the normal barriers to fluid filtration and allows increased flux of liquid and protein into the extravascular compartments of the lungs.

Thus, pulmonary edema results from increases in either hydrostatic driving pressures (increased pressure edema) or barrier conductance (increased permeability edema), or both. What distinguishes the two types is barrier permeability, which is normal in increased pressure edema, but abnormal in increased permeability edema. Fluid flow into the lungs is driven across the barrier in both types of edema by the balance of pressures. ALI or ARDS results primarily from an increase in lung vascular permeability, although some cases may be made worse by the presence of elevated lung vascular hydrostatic pressures.

Increased Permeability Pulmonary Edema

Increased permeability pulmonary edema is caused by an increase in liquid and protein conductance across the barriers in the lungs. The essential feature is that the integrity of the barrier to fluid and protein flow into the lung interstitium and the alveoli is altered. Increased permeability edema is sometimes called *noncardiogenic pulmonary edema*, and the resulting clinical syndromes in humans are commonly lumped together as *acute lung injury* or the *acute respiratory distress syndrome*.

Accumulation of fluid and protein increases when the lung endothelial and epithelial barriers are injured. If the rate of fluid accumulation exceeds the rate at which it can be removed, increased permeability edema occurs. Because the barriers limiting fluid and protein flow into the lungs do not function normally when the lungs are injured, the lungs are not protected against edema by the usual safety factors. Although increases in fluid and protein filtration across the lung endothelium can be removed by lymphatics and drained away from the alveolar walls as in increased pressure edema, much more fluid and protein are filtered at any given sum of driving pressures because the barriers to their flow are much less restrictive than normal. Edema formation in injured lungs is very sensitive to hydrostatic driving pressures. Driving pressures are often increased when the lungs are injured because of the vasoconstrictive effects of inflammatory mediators such as thromboxanes, which may shift the main site of resistance to postcapillary venules, thus increasing hydrostatic pressure at the microvascular fluid exchange sites, or because of effects on the heart as well as on the circulation. For example, elevated left atrial pressure, pulmonary venoconstriction, or an increase in cardiac output in sepsis can increase hydrostatic pressure at the microvascular fluid exchange sites.

Because the barriers are leaky, the protective osmotic pressure differences across them are lost; driving pressure is unopposed by osmotic pressure, and even normal hydrostatic pressure results in significant fluid and protein extravasation into the interstitial and alveolar spaces. The ability of the lymphatics to pump the excess filtrate away is increased when the lungs are injured. Maximal lung lymph flow increases more when the microvascular wall has been injured than when hydrostatic pressure alone is increased, but even this augmented lymphatic-pumping capability is taxed at lower driving pressures. If the epithelial barrier is injured, edema may accumulate readily in alveoli, because most of the resistance to fluid and protein flow into the alveoli is in the epithelial barrier. Increased permeability edema is often rapid in onset and progression because injured barriers offer much less resistance to flow and because hydrostatic driving pressure is unopposed by increases in osmotic pressure difference. Clinically, many patients with increased permeability edema have a low intravascular hydrostatic pressure, commonly measured as a low or normal pulmonary capillary wedge pressure. In some cases, this reflects the low intravascular pressures associated with the underlying disease process, such as sepsis.

Lung Physiology

The effects of increased permeability edema on lung mechanics and gas exchange depend, in part, on the magnitude of edema accumulation. As with increased pressure edema, the major effects on pulmonary mechanics occur with alveolar flooding. In experimental lung injury, functional residual capacity is decreased as a consequence of alveolar flooding; the loss of units which can be ventilated accounts for most of the decrease in static lung compliance. Computed tomography has provided new insights into structure-function relationship in human ALI. In the early stage of lung injury, when alveolar edema predominates, the lungs are characterized by a more homogeneous alteration of vascular permeability, and edema can accumulate evenly in all lung regions with a nongravitational distribution.

Measurements of pulmonary mechanics in mechanically ventilated patients with ALIs show a decrease in static lung compliance as a consequence of the loss of ventilated lung units. In addition, airflow resistance is increased as a result of decreased lung volume. Bronchospasm may add to the increase in airflow resistance and may be partially reversed in some patients by administration of inhaled bronchodilators. Chest wall compliance is reduced, probably because of alterations in the intrinsic mechanical properties of the chest wall by abdominal distention, chest wall edema, and pleural effusion. Some investigators have reported differing respiratory mechanics and response to positive end-expiratory pressure (PEEP) during mechanical ventilation in patients with ARDS originating from pulmonary disease (e.g., pneumonia, which causes consolidation) versus ARDS due to extrapulmonary disease (which causes edema and subsequent alveolar collapse).

Although the effects of surface forces on decreased lung compliance in ALI were once believed to be small, results of experiments in isolated rabbit lungs indicate that increased permeability edema may produce more severe mechanical

changes than equivalent degrees of increased pressure edema. In contrast, experiments in awake sheep have demonstrated that similar degrees of pulmonary edema, regardless of mechanism, cause similar changes in compliance and gas exchange. Other studies indicate that dynamic and static lung compliances are decreased early in evolving lung injury.

Surfactant is strongly thromboplastic, and coagulation may compound surfactant depletion when plasma proteins enter the airspaces. The injured lung may release substances that can interfere with the normal, low surface tension in the alveoli. In addition, activated neutrophils may impair surfactant function in vitro and degrade major surfactant apoproteins through a combination of proteolysis and oxidant-radical–mediated mechanisms. In studies using bronchoalveolar lavage, human lung surfactant obtained from patients at risk for ALI and from those with established ALIs has been reported to be abnormal in chemical composition and functional activity. Abnormalities may also be caused by interactions between surfactant and edema proteins, since plasma proteins (especially fibrin monomers, but also fibrinogen and albumin) interfere with surfactant function. Proteinaceous edema fluid has been associated with surfactant inhibition in several experimental models.

Gas exchange is severely compromised in increased permeability edema because of both intrapulmonary shunting of blood and ventilation-perfusion inequalities. New evidence indicates that patients with early ALI have a marked increase in pulmonary dead space fraction. This finding indicates that many ventilated lung units are not well perfused, although intrapulmonary shunting may also contribute to the elevated dead space. Not surprisingly, minute ventilation is typically twice normal (approximately 12 L/min) at the onset of ARDS.

MECHANISMS OF ACUTE LUNG INJURY

This section focuses on the characteristic pulmonary pathological findings in patients with ALI and ARDS and the mechanisms responsible for ALI.

Pathological Findings

Based on several studies that included a preponderance of postmortem pathology, the light and electron microscopic appearances of human and animal lung tissue in ALI have been described. Exudative, proliferative, and fibrotic changes usually appear in sequence.

The earliest changes are marked by widespread alveolar and interstitial edema and hemorrhage. Hyaline membranes, composed of precipitated plasma proteins, fibrin, and necrotic debris are frequently found (Fig. 144-1). The alveolar epithelium may be more extensively damaged than is the vascular endothelium, even if the underlying insult is bloodborne. Widespread, local areas of destruction of type I alveolar epithelial cells alternate with normal-appearing alveoli. The injured alveolar epithelium is swollen, disorganized, discontinuous, and, frequently, detached from basement membranes, which may be otherwise intact. The alveolar surface may be covered by hyaline membranes. Type I cells are more severely damaged than type II cells. The thin cytoplasmic extensions of cells far from the nucleus, which cover the thin side of the alveolar-capillary barrier, may be most severely affected. The interstitium is widened by edema (especially in peribronchovascular cuffs) and may be filled with leukocytes, platelets, red blood cells, fibrin, and debris (especially near the alveolar walls). The microvascular endothelium is relatively preserved; it usually shows little other than irregular, focal thickening due to cytoplasmic swelling or vacuoles and greater numbers of luminal leukocytes.

After about 5 to 10 days, the exudative phase is followed by a proliferative phase. The relative contributions of the original insult, repair processes, and effects of therapies on this and subsequent phases are not well known. Some abnormalities occurring after the initial exudative phase appear to be related to effects of traditional modes of mechanical ventilation that used tidal volumes between 12 and 15 ml/kg predicted body weight.

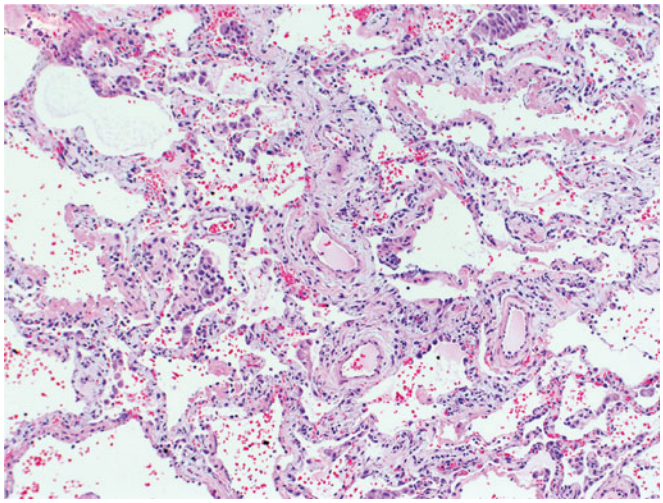
Reabsorption of some of the edema fluid characterizes the proliferative phase. Fibrin may be prominent in alveoli and interstitium, and infiltration with inflammatory cells and fibroblasts, which may have been activated very early in the course of lung injury, may be seen. The alveolar epithelium is often cuboidal and made up largely of proliferating type II cells. The air-blood barrier may be thickened by interstitial and epithelial enlargement. The pulmonary vascular bed may be partially or completely disrupted, and structural alterations may reduce its surface area.

Approximately 2 weeks after the initial insult, a final stage may be observed in which fibrotic changes of the alveolar ducts, alveoli, and interstitium predominate. Alveoli may be obliterated, alveolar walls coalesced, and functional lung units lost. The lungs may be emphysema-like, with extensive bullous changes. Notably, even severe changes at any stage may be reversible during a slow recovery back toward normal lung function.

Mediators

The most common clinical disorders associated with the development of ALI are pneumonia, sepsis, gastric aspiration, and major trauma. Other, less common causes include transfusion-associated lung injury, drug overdose, severe acute pancreatitis, and near drowning. The initiating insult to the lungs occurs either via the airways or the bloodstream.

The exact mechanisms by which the lungs are injured have been the subject of intense investigation in humans, animals, and cellular systems. Human studies have provided descriptive data about the events that occur in the airspaces before and after the onset of lung injury. Studies using bronchoalveolar lavage or collection of pulmonary edema fluid



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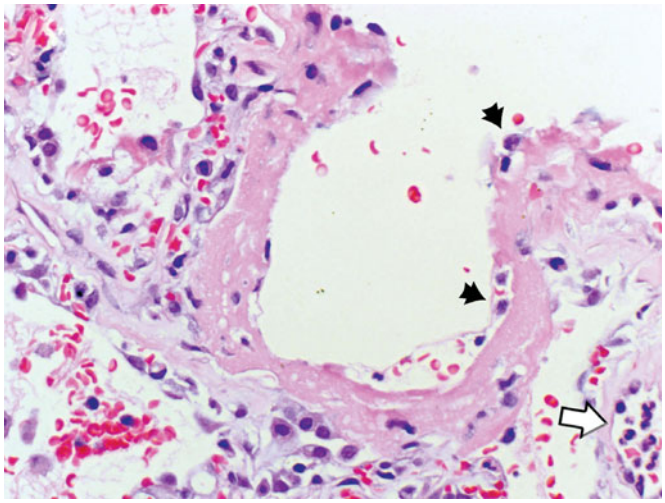

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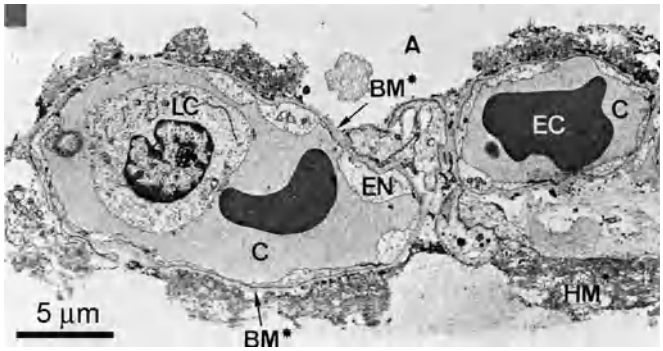

C

Figure 144-1 *A*. A low-power light micrograph of lung biopsy specimen collected 2 days after onset of ALI/ARDS secondary to gram-negative sepsis demonstrates key features of diffuse alveolar damage, including hyaline membranes, inflammation, intra-alveolar red blood cells and neutrophils, and thickening of the alveolar-capillary membrane. *B*. High-power view of a different field illustrates dense hyaline membrane and diffuse alveolar inflammation. Polymorphonuclear leukocytes are imbedded in the proteinaceous hyaline membrane structure (black arrows). The white arrow points to the edge of an adjacent alveolus, which contains myeloid leukocytes. (*Histological sections in A and B courtesy of Dr. K. Jones, University of California, San Francisco). C.* Electron micrograph from a classic analysis of ALI/ARDS showing injury to capillary endothelium and alveolar epithelium. LC = leukocyte within the capillary lumen; EC = erythrocytes; EN = blebbing of the capillary endothelium; BM = exposed basement membrane where the epithelium has been denuded; C = capillary; A = alveolar space. (*From The ARDS Network: Ventilation with lower tidal volumes as compared with traditional tidal volumes for acute lung injury and the acute respiratory distress syndrome.* N Engl J Med *342:1301–1308, 2000, with permission.*)

in patients following the onset of ALI have demonstrated a major acute inflammatory response beginning prior to clinical recognition of ALI. The response peaks during the first 1 to 3 days of clinically defined ALI and resolves slowly over 7 to 14 days in patients who remain intubated. These studies have shown the complexity of the evolving inflammatory responses, characterized by accumulation of acute response cytokines and their naturally occurring inhibitors, oxidants, proteinases and antiproteinases, lipid mediators, growth factors, and the collagen precursors involved in the repair process.

Hypotheses regarding the mechanisms of lung injury have been tested in animal models and in vitro studies, and several reviews have summarized the findings. The existing animal models do not completely reproduce all of the aspects of ALI in humans, in part because human ALI evolves over a longer period of time than can be studied in the laboratory. In addition, the lungs of humans are exposed not only to the initial injurious insult, but also to the therapies that are used to treat ALI, such as mechanical ventilation. Experiments using isolated cells have been helpful in testing specific concepts, but the complexity and redundancy of intact biologic systems is not reproduced in simplified experimental systems. By design, most experimental work limits study to one causative agent, thereby reducing actual clinical complexity to the simplicity of a single experimental pathway. Increased permeability edema in humans is likely to be caused by interactions among a number of different pathways acting in parallel or series.

Studies in isolated organs and small animals in which hemodynamic variables are not measured can be difficult to evaluate. Indices of lung injury, usually measured by the appearance of markers in lungs, lavage fluid, or perfusate, are not determined solely by the barrier function of the microvasculature. Indeed, when vascular endothelium is injured, fluid and protein movement from the vascular space into the lungs is sensitive to hydrostatic driving pressures and filtration surface area. Hence, the effects of experimental interventions may be caused by changes in these parameters and not by changes in microvascular barrier function.

The effects of microvascular driving pressures and surface area can be difficult to evaluate, even in large, instrumented animals. In sheep and goats, interpretation of lung lymph fluid and protein flow changes are further complicated by contributions of extrapulmonary lymphatics, physical forces acting on lymphatics, and possible intranodal modification of lymph. Data from experimental animal models suggest that at least two broad categories of mechanisms of ALI are operative: (1) those that are *indirect* (i.e., require the participation of intermediary mechanisms, e.g., host defenses); and (2) those that are *direct* (i.e., do not require intermediary mechanisms; injury probably occurs as a result of contact between an offending substance and lung tissue). These categories overlap, since once the lungs are injured, inflammatory responses occur, which may compound the primary mechanism of injury. Three major hypotheses regarding the mechanism of ALI are discussed below. Although discussed separately, they are interrelated.

Role of Infection

ALI develops in 20 to 45 percent of patients with severe sepsis. Increased microvascular permeability to albumin has been shown to accompany human sepsis, and infection and the sepsis syndrome are major causes of ALI in humans. Patients who develop shock in response to known or suspected infection have a particularly high incidence of ALI, and the mortality of patients with ALI associated with infection (i.e., sepsis syndrome) is increased. ALI also appears to predispose the lungs to infection, and delayed infection is an important cause of morbidity in patients who survive the initial lung insult.

The mechanism by which infection and sepsis syndrome injure the lungs is not certain. The lung injury is likely related to factors other than direct damage by bacteria or other microorganisms, since the prognosis appears unrelated to documented bacteremia or pneumonia. In experimental animals, intravenous infusions of live *Pseudomonas aeruginosa* or endotoxins from *Escherichia coli* or surgically induced peritonitis result in increased permeability pulmonary edema. Instillation of endotoxin into the airways of sheep also leads to lung inflammation with variable degrees of lung injury. *P. aeruginosa* produces lung injury in pigs, and *E. coli* endotoxin administration injures the lungs of baboons and dogs; neutrophilic alveolitis is observed in rats and mice. ALI caused by endotoxin in sheep is thought to be an inflammatory response mediated, at least in part, by neutrophils and tumor necrosis factor (TNF). Endotoxin may also affect the clotting system and metabolic functions of the lungs, as well as predispose the lungs to development of pulmonary infections by increasing adherence of bacteria to injured endothelium. Exoproducts of bacteria, such as elastase and *Pseudomonas* exoenzyme U, also have been shown to injure the lungs.

In addition to a direct role in the pathogenesis of lung injury, bacterial products may also have an indirect role by sensitizing the lungs to the effects of mechanical stretch. Gram-negative lipopolysaccharide causes an acute inflammatory response in the lungs of humans. Bacterial endotoxin enhances the responses of human alveolar macrophages to positive pressure ventilation; pretreatment of rats with intravenous endotoxin enhances cytokine production in the lungs during mechanical ventilation ex vivo. Furthermore, mechanical ventilation using moderate or large tidal volumes increases the sensitivity of lung macrophages to endotoxin in vitro and the expression of the endotoxin recognition molecule, CD14, on lung cells in vivo. Endotoxin recognition pathways are increased in the lungs of patients with ARDS, and the biologic effects of endotoxin are amplified in the lungs of patients with lung injury. The synergism between bacterial products and mechanical stretch suggests that interrupting these pathways might limit some forms of ALI in humans.

Increased permeability edema is associated with impaired antibacterial defenses. In animal models, bacterial infections worsen ALI. The cause of impaired bacterial defenses in acute ALI is not known. Bactericidal properties of the alveolar lining material might be altered in injured or flooded lungs, and alterations in surfactant concentration and function may be important. Although neutrophils may be present in large numbers in the bronchoalveolar lavage fluid of patients with ALI, evidence indicates that the function of the neutrophils is compromised.

Role of Inflammation

Substantial evidence implicates host defenses and inflammatory responses in the underlying mechanism of many ALIs. Neutrophils are a vital component of host defenses, and patients with severe neutropenia are at increased risk of bacterial and fungal infections. On the other hand, neutrophils release toxic oxygen radicals, proteases, and other biologically active mediators that initiate inflammation. Other important cells in pathogenesis include alveolar and pulmonary intravascular macrophages, and eosinophils.

Normally, the pulmonary circulation contains a very large pool of marginated neutrophils that change shape in order to squeeze through the lung capillaries. When neutrophils are activated, they stiffen and become less distensible. These neutrophils are retained for longer periods of time in the pulmonary microcirculation. Endothelial activation leads to increased expression of leukocyte adhesion molecules, providing a second mechanism to slow the transit of neutrophils. Trapped neutrophils respond to chemotactic

gradients generated by chemokines produced by alveolar macrophages and mesenchymal cells and migrate into the airspaces. Activated neutrophils generate and release toxic substances (e.g., oxygen metabolites and granular constituents, such as proteases, and cationic lysosomal enzymes) that disrupt the function of the microvascular and epithelial barriers. Normally, these barriers limit liquid and protein flow out of the vascular space and into the alveolar spaces, mitigating development of permeability edema.

Inflammatory responses also have the potential to induce lung cell injury by activating cell death pathways, leading to apoptosis. Bacterial products, such as *Pseudomonas* Exoenzyme U and mechanical stretch, may lead to direct cellular necrosis. Apoptosis is mediated by a family of death receptors, including TNF and Fas receptors. The Fas ligand (FasL) is a 45 kD peptide that is shed from the cell surface by the action of metalloproteinases. Biologically active soluble FasL (sFasL) accumulates in the lungs of patients with ARDS, inducing apoptotic death of human lung epithelial cells in vitro. Human sFasL induces epithelial cell death in the lungs of rabbits; a monoclonal antibody that activates membrane Fas causes alveolar wall apoptosis and fibrosis in the lungs of mice.

Apoptosis and inflammation pathways intersect, as stimulation of membrane Fas induces cytokine production in human macrophages and inflammation in the lungs of rabbits and mice. In addition, lung injury may be able to trigger apoptosis pathways in distant organs, such as the kidney, perhaps by increasing the concentrations of circulating sFasL. Thus, inflammatory responses may trigger cell death pathways, and cell death pathways triggered by sFasL may induce inflammation in the lung alveolar environment. Recent human studies implicate apoptosis in human lung injury.

Role of Direct Toxicity

Inflammation is not required for all forms of ALI. ALI or ARDS can develop in neutropenic patients. A clinical trial using granulocyte colony-stimulating factor to increase the number and activation state of circulating neutrophils in patients with severe pneumonia was not associated with an increased incidence of ARDS. Lung injuries that do not require the participation of neutrophils have been described in animal models.

Direct lung injury is also thought to occur in humans. Putative agents that directly injure the lungs include mechanical forces during mechanical ventilation, toxic and corrosive chemicals and gases (e.g., hydrochloric and other acids, ozone, ammonia, chlorine, phosgene, nitrogen dioxide, the vapors of cadmium and mercury, combustion products, and oxygen, especially at high concentrations), ionizing radiation, aspiration of fresh water (near drowning) or hydrocarbon compounds (e.g., kerosine, gasoline, and dry-cleaning fluid), high temperatures (parenchymal lung burns from fires or explosions), and mechanical injuries (e.g., lung contusion from nonpenetrating chest trauma or blast injury from explosions or lightning). Many of these injuries develop rapidly, supporting the idea that injury is caused directly by contact with the respiratory epithelium in the airways and/or alveolar walls.

Inflammatory pathways are likely to be rapidly activated following many types of direct lung injury, as probably occurs following aspiration of gastric secretions—one of the most common clinical causes of ALI. Lung injury occurs rapidly, especially to the epithelium. The injury is probably related, in part, to the low pH of the aspirated stomach contents (aspiration of gastric contents with pH greater than 2.5 is relatively benign; aspiration of gastric contents with pH less than 2.5 causes severe pulmonary injury). Aspirated acid is almost immediately neutralized. However, within hours, proinflammatory mediators are released, the injured lung is infiltrated with neutrophils, fibrin accumulates in the alveolar spaces, and further structural damage is seen on histological examination.

Biologic Markers

Considerable interest exists in finding a simple test of blood, urine, or bronchoalveolar lavage fluid that would identify patients at risk for, or in the earliest stages of, ALI, or that might predict clinical outcome.

Although products of complement activation have been proposed as markers, their serum levels correlate poorly with lung injury. Measurement of circulating endotoxin is not appropriately sensitive or specific for the presence or risk of developing lung injury. The same is true for measurements of release or activity of angiotensin-converting enzyme. Von Willebrand factor (VWF) antigen may be useful as a plasma marker of impending ALI in patients with nonpulmonary sepsis. Recent work confirms that VWF levels are elevated in the edema fluid and plasma of patients with ALI and correlate with poor clinical outcomes. While increases in other biochemical and inflammatory markers, including surfactant protein D and interleukin-6, correlate somewhat with lung injury and mortality, no simple biologic marker currently serves in the same diagnostic capacity as do cardiac enzymes in evaluation of suspected acute myocardial infarction.

Because neutrophils are implicated in the mechanism of many lung injuries, their detection in the lungs, assessment of their function, or assay of the toxic metabolites they release might be useful. For example, increased hydrogen peroxide levels have been measured in the breath and urine of patients with ALI, presumably reflecting the presence of oxygen metabolites in the injured lungs. Evidence of increased oxidant activity has been reported in bronchoalveolar lavage fluid in patients with lung injury.

Finally, other mediators of inflammation in ALI have been studied. For example, increased levels of TNF are detected in blood and bronchoalveolar lavage fluid in lung injury, but an association between TNF levels and development of ARDS has not been found. Furthermore, elevated TNF levels are found in patients with severe congestive heart failure. Lipoxygenase products of arachidonic acid metabolism have been detected in pulmonary edema fluid, bronchoalveolar lavage fluid, plasma, and urine, and elastase has been

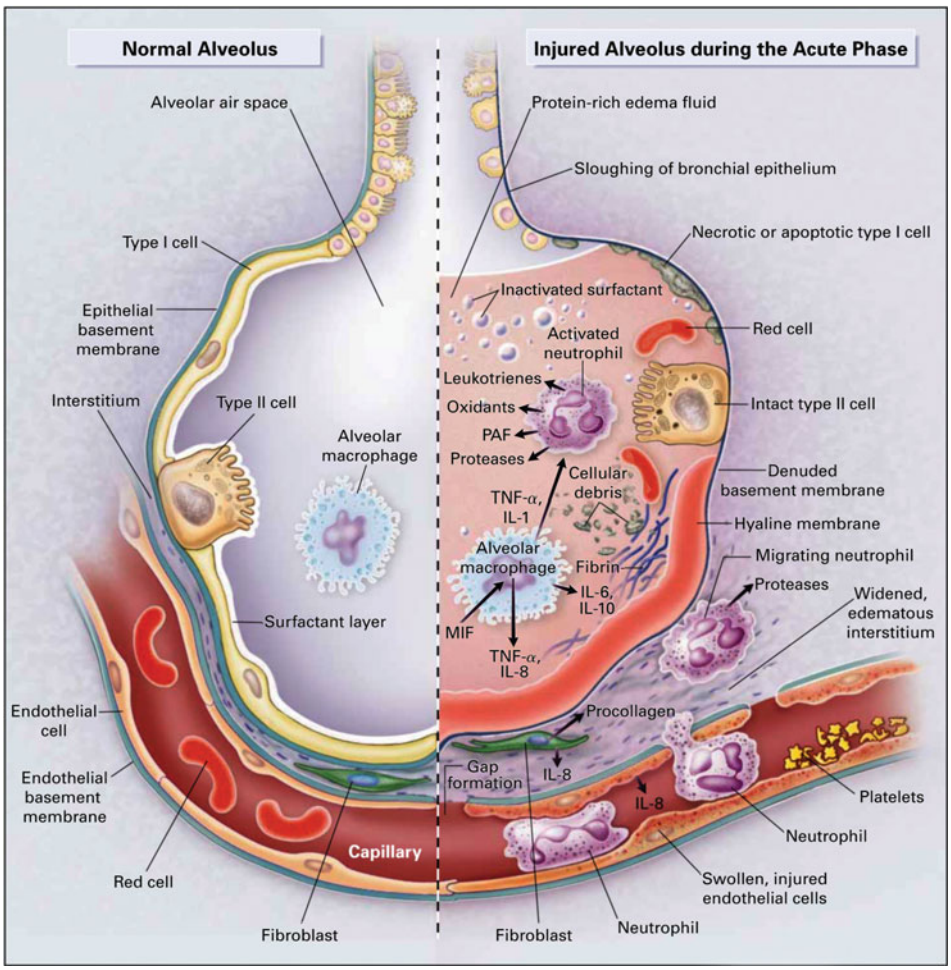

Figure 144-2 Multiple cellular responses and mediators contribute to alveolar-capillary membrane injury (*right-hand side*) and the transition from normal alveolar structure and function (*left-hand side*) in the acute phase of ALI/ARDS. Original investigations of the pathogenesis of ALI/ARDS searched for single mediators that provided final common pathways to inflammation and alveolar edema. Current concepts of pathogenesis involve multiple molecular factors of several classes, a variety of responding cells, and an imbalance between injurious and reparative signals and pathways. See text and Ware & Matthay (2000) and Matthay & Zimmerman (2005). *(Reprinted from Matthay MA, Zimmerman GA: Acute lung injury and the acute respiratory distress syndrome: Four decades of inquiry into pathogenesis and rational management.* Am J Respir Cell Mol Biol *33:319–327, 2005, with permission.)*

detected in bronchoalveolar lavage fluid in the setting of lung injury.

ALI follows a wide variety of insults of varying severity. Furthermore, many abnormalities detected in ALI are found in other diverse, severe illnesses that do not involve the lungs. Therefore, the likelihood that any single marker that unequivocally identifies the risk or the presence of ALI will be found seems remote. An investigative focus on particular subgroups of patients with common causes of injury, coupled with study of much larger groups of more definitively diagnosed patients, might prove helpful. An approach that has not received much attention is investigation of the sensitivity and specificity of combinations of biologic markers. The new field of proteomics will expand this type of investigation and, perhaps, identify patterns of protein abnormalities that can be found in plasma, urine, edema fluid, and bronchoalveolar lavage in patients with ARDS.

Figure 144-2 depicts multiple pathways involved in the pathogenesis of ALI and ARDS in the context of normal and injured alveoli. Emphasis is placed on potential pathways for injury across the vascular endothelium and alveolar epithelium.

VENTILATOR-ASSOCIATED LUNG INJURY

The most important development of the last 10 years in our understanding of the pathogenesis and treatment of ALI is recognition that the long-standing practice of mechanically ventilating patients with ALI or ARDS using high tidal volumes and airway pressures actually worsens the injury. Animal studies first suggested the potential contributory role of high tidal volumes and elevated airway pressures in the

pathogenesis of lung injury; subsequently, clinical trials confirmed the findings.

Animal Studies

Animal experiments have shown that ventilation using high tidal volumes may increase vascular filtration pressures; produce stress fractures of microvascular endothelium, alveolar epithelium, and basement membranes; and cause lung rupture (so-called ventilation-induced lung injury). The injury appears to be due to increased lung excursions at high volumes ("volutrauma"), rather than the high-airway pressure, per se, since it can be prevented by limiting thoracic motion (e.g., by placing the chest in a cast). The concept of volutrauma was first established in 1974 when investigators found that modestly elevated tidal volumes, especially in the absence of PEEP, caused lung edema in rats. Several years later, additional animal studies further demonstrated the potential injurious role of high tidal volumes and elevated airway pressures, an effect termed *ventilator-induced lung injury* (VILI). Subsequent experiments demonstrated that VILI could also induce release of several proinflammatory cytokines, injuring the lung and other organs—a process referred to as "biotrauma." These animal studies stimulated clinical investigation that revolutionized the care of patients with ALI or ARDS.

Clinical Studies

The compelling evidence from animal experiments and small clinical trials prompted clinical studies aimed at testing the potential benefit of lower tidal volumes and reduced airway pressures in management of ALI or ARDS. In a large, multicenter, National Heart Lung and Blood–sponsored trial of 861 patients, mortality was reduced from 40 to 31 percent using a tidal volume of 6 ml/kg/ideal body weight and a limited plateau airway pressure of less than 30 cm H_2O. In this trial, use of small tidal volumes was associated with a lower incidence of nonpulmonary organ failure. The protocol for carrying out the lung protective ventilatory strategy is described in detail in Table 144-1. The results of the trial have transformed the management of patients with ALI or ARDS. A follow-up clinical trial has shown that ventilation using the limited tidal volume and plateau pressure of the original study is associated with an overall reduction of mortality to 26 percent. In the follow-up study, although elevated levels of PEEP did not decrease mortality, the basic lung protective strategy was validated as effective.

The beneficial mechanism underlying the low tidal volume strategy is unclear. An Italian study has shown that use of low tidal volumes in patients with ARDS attenuates the inflammatory response in both lungs and bloodstream, as measured by reductions in neutrophil and cytokine concentrations in bronchoalveolar lavage and cytokines in circulating blood. Other studies have confirmed a number of these findings. In addition, a reduction in alveolar epithelial injury appears likely, based on a decline in plasma surfactant protein D levels. Additional clinical and experimental studies are underway. A reduction in lung endothelial and epithelial injury, attenuated inflammatory responses, reduced edema formation, and more rapid resolution of lung edema are likely part of the mechanism(s).

RESOLUTION OF ACUTE LUNG INJURY

In the last two decades, considerable progress has been made in understanding the mechanisms responsible for resolution of lung edema. More limited progress has been made in understanding the resolution of lung inflammation.

Considerable advances have been made in our understanding of the clearance of fluid and solute from alveoli. Active sodium and chloride transport across the alveolar and distal airway epithelial barriers into the interstitium drives edema fluid removal from the airspaces. The uninjured alveolar epithelium has a remarkable ability to rapidly clear fluid from the airspaces. Even when mild-to-moderate alveolar injury occurs, salt and water transport capacity is often preserved. In severe injury, when the barrier is disrupted, the capacity to clear edema is lost. The vascular endothelium becomes the limiting barrier between the vascular space and airspace. Clinically, the capacity to remove some alveolar edema fluid (as indicated by increase in edema fluid to plasma protein concentration ratio) in the first 12 hours following ALI is a favorable prognostic finding; the associated mortality rate is only 20 percent. In contrast, an inability to resorb alveolar edema fluid early in the course of injury is associated with a mortality of nearly 80 percent. Thus, the function of the alveolar epithelial barrier early in the course of ALI may be a useful prognostic index, serving as a marker of the severity and extent of injury.

In uninjured, ex vivo human lungs, alveolar fluid clearance is increased by administration of salmeterol. In addition, experimental studies have shown that even in the presence of ALI and alveolar edema, alveolar fluid clearance can be increased pharmacologically (e.g., by catecholamines), thereby representing a potential therapeutic intervention.

Clearance of protein from flooded alveoli is much slower (1 to 2 percent per hour) than clearance of fluid (10 to 20 percent per hour), resulting in an increased concentration of protein in airspaces. If the alveolar edema formed during increased lung vascular permeability clots, its removal from flooded alveoli may be slowed. Clotting may occur because extravasation of plasma into airspaces can lead to clotting system activation by surfactant or macrophage-derived procoagulants.

Most of the interstitial water in pulmonary edema lies in the peribronchovascular loose connective-tissue spaces, rather than in alveolar walls. Because the lymphatic capillaries are arranged to drain only the alveolar wall interstitium, this route for edema removal is not significant for most interstitial edema. A study in goats showed that lung lymph originates mainly from alveolar wall interstitial fluid. The contribution

Table 144-1

National Institute of Heart, Lung, and Blood, ARDS Network: Lung Protective Ventilatory Strategy

Ventilator mode	Volume assist-control
Tidal volume	≤ 6 ml/kg PBW
Plateau pressure	≤ 30 cmH_2O
Ventilation set rate, pH goal	6–35, adjusted to achieve arterial
	pH ≥7.30, if possible
Inspiratory flow, I:E	Adjust flow to achieve I:E = 1:1–1:3
Oxygenation goal	55 ≤Pa_{O_2} ≤80 mmHg or 88 ≤Sp_{O_2} ≤95%
F_{IO_2}/PEEP Combinations	

F_{IO_2}	0.3	0.4	0.4	0.5	0.5	0.6	0.7	0.7	0.7	0.8	0.9	0.9	0.9	1.0
PEEP, cmH_2O	5	5	8	8	10	10	10	12	14	14	14	16	18	18, 22, 24

(Further increases in PEEP to 34 cmH_2O allowed, but not required)

Weaning	Attempts to wean by pressure support required when F_{IO_2}/PEEP ≤0.40/8

PBW = predicted body weight

Male PBW = 50 + 2.3 [height (inches) − 60] *or*
50 + 0.91[height (cm) − 152.4]
Female PBW = 45.5 + 2.3[height (inches) − 60] *or*
45.5 + 0.91[height (cm) − 152.4]

I:E = *ratio of inspiratory to expiratory duration*
Pa_{O_2} = *partial pressure of oxygen in arterial blood*
Sp_{O_2} = *oxyhemoglobin saturation measured by pulse oximetry*
Source: Adapted from Acute Respiratory Distress Syndrome Network: Ventilation with low tidal volumes as compared with traditional tidal volumes for acute lung injury and the acute respiratory distress syndrome. N Engl J Med *342:1301–1308, 2000, with permission.*

of the lung lymphatic system to clearance of interstitial edema in bronchoalveolar cuffs and interlobular septa is small. The maximum possible contribution by lung lymphatics to clearance of interstitial edema liquid is less than 10 percent, with airway loss of liquid through evaporation occurring at about twice the rate of lymphatic clearance.

In a study of in situ perfused sheep lungs with experimentally induced low- and high-protein pulmonary edema, interstitial liquid was resorbed into the circulation in inverse proportion to its protein concentration. Only a very small fraction of interstitial edema was cleared by the lung lymphatics during recovery from either type of edema.

Some fluid from the loose peribronchovascular interstitium may drain directly into the bloodstream by crossing the walls of blood vessels in the lungs. A study of isolated sheep lungs made edematous by raising vascular pressures showed that the primary route of edema clearance is by vascular resorption (60 percent of filtered water cleared over 3 hours, including 42 percent by resorption into the bloodstream and 18 percent by lymphatic, pleural, and mediastinal drainage).

Edema may also drain into the pleural space. Pleural effusions are more common in increased pressure pulmonary edema (25 to 50 percent of patients; usually on the right if unilateral). However, they occur in ALI as well (35 percent of patients). As much as 25 to 30 percent of edema fluid may leave the lungs through the pleural space. A significant portion of the interstitial edema probably follows the prevailing pressure gradient in the lungs to drain into the mediastinum, where it may be picked up by the lymphatics.

Short-term alveolar protein clearance appears to proceed primarily by paracellular diffusion. The process depends

on the size of the proteins. Most proteins are cleared intact, rather than as degraded, smaller fragments. However, a few specific proteins (e.g., vasoactive intestinal peptide and gastrin) are degraded before being cleared.

Receptor-mediated clearance may play a role. An albumin-binding protein (albondin) is expressed on lung microvascular endothelial cells. An antibody to this protein reacts with cellular proteins of alveolar epithelial cells, which also appear to have albondinlike binding sites for albumin. In addition, a polymeric immunoglobulin receptor has been described. The significance of these receptors in protein clearance is, however, unclear.

Finally, the general consensus is that transcytosis (transport via vesicles) is not a major mechanism for clearing bulk quantities of albumin or other proteins from the alveolar space. Over the long term, phagocytosis and catabolism by macrophages account for most protein clearance from the alveolar spaces. All insoluble, precipitated proteins are removed in this way. Macrophages are also ultimately responsible for removing senescent and dead neutrophils and other debris. The presence of a small, ciliated surface area of the distal airspaces suggests that the mucociliary route accounts for only a minor fraction of alveolar protein clearance. Complete clearance of alveolar protein from pulmonary edema by any route is slow.

Little is known about the mechanisms and signals that regulate endothelial barrier function or how increased endothelial permeability is returned to normal.

CONCLUSIONS

Among the major advances in respiratory medicine and physiology over the last three decades has been the acquisition of important new knowledge on the physiology of fluid, solute, and protein transport in healthy and diseased lungs. Pulmonary edema, defined as the abnormal accumulation of extravascular lung fluid, is a pathological state that occurs when fluid is filtered into the lungs faster than it can be removed.

The many causes of pulmonary edema are grouped into two main pathophysiological categories: (1) increased pressure edema, which results from an increase in hydrostatic or osmotic forces (or both) that act across the barriers that normally restrict movement of fluid and solutes in the lungs; and (2) increased permeability edema, which is seen in ALI in which a breakdown of the normal barrier properties of lung endothelium or epithelium develops. Although these two different types of pulmonary edema share many features, usually they can be distinguished by careful clinical, radiological, and physiological evaluation. They also differ in treatment and prognosis.

Major advances in the treatment of ALI have occurred because of the successful application of lung protective ventilatory strategies early in the course of the illness (Table 144-1). A low tidal volume (6 ml/kg/ideal body weight), coupled with a plateau pressure limit (less than 30 cm H_2O) has resulted in the first therapy demonstrated to reduce mortality in patients with ALI.

Recently, the National Heart, Lung, and Blood Institute Acute Respiratory Distress Syndrome Network published the results of the Fluid and Catheter Treatment Trial (FACTT), a large randomized trial comparing a liberal fluid management strategy to a conservative fluid management strategy in patients with ALI. Patients were also randomized to receive either a pulmonary arterial catheter or a central venous catheter for monitoring and fluid management. There were no differences in clinical outcomes between the pulmonary or central venous catheter utilization. In contrast, there was a marked difference in outcome between the liberal and the conservative fluid management arms of the study. Patients in the conservative fluid management arm had 2.5 more ventilator-free days than those in the liberal fluid management arm with concordant improvements in pulmonary physiology. There was also a 2.9 percent reduction in the 60-day mortality rate in the conservative fluid management arm compared with the liberal fluid management arm, although this difference did not reach statistical significance.

New insights into the pathogenesis of ALI suggest that other therapies may also prove to be efficacious in reducing mortality in this common form of severe acute respiratory failure. A major development has been the ability to conduct large, prospective, randomized, clinical trials (e.g., those sponsored by the National Heart, Lung, and Blood Institute) to test a variety of therapies important in supportive patient care, including use of mechanical ventilation, intravenous fluids, and a variety of pharmacologic agents. Such trials have led to a better understanding of the pathogenesis of human ALI and have confirmed the importance of ventilator-associated lung injury. In addition, ancillary pathogenetic studies carried out on biologic samples from clinical trials have advanced our understanding of underlying mechanisms. In the future, additional human studies will be needed to explore new therapeutic strategies suggested by basic investigation conducted in animal models of ALI.

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Acute Lung Injury and the Acute Respiratory Distress Syndrome: Clinical Features, Management, and Outcomes

Jason D. Christie • Paul N. Lanken

DESCRIPTION AND DEFINITIONS

In 1967, Ashbaugh and co-authors described a syndrome characterized by the acute onset of dyspnea, severe hypoxemia, diffuse lung infiltrates, and decreased respiratory system compliance in the absence of evidence for congestive heart failure. The syndrome, initially called acute respiratory distress in adults (to contrast it with acute respiratory distress in neonates), is now known as the acute respiratory distress syndrome (ARDS). Following the initial report, other authors utilized various definitions that incorporated elements related to time of onset, presence of hypoxemia and radiographic infiltrates, and absence of overt congestive heart failure.

In 1988, Murray and others introduced the Lung Injury Score (LIS), an assessment tool for ARDS that reflects the extent of radiographic infiltrates, severity of hypoxemia and reduced respiratory system compliance, and level of positive end expiratory pressure (PEEP) used in mechanically ventilating affected patients. The LIS incorporates these four parameters that are graded on a scale of 0 to 4: (1) the ratio of Pa_{O_2} to FI_{O_2} (Pa_{O_2}/FI_{O_2}); (2) total respiratory compliance; (3) level of PEEP; and (4) extent of radiographic infiltrates (assessed by noting the number of quadrants in the chest radiograph containing infiltrates). The LIS equals the sum of the scores for the four variables divided by four. In clinical studies, a score of 2.5 or more is generally used as a threshold for severe disease.

Consensus Definitions of Acute Lung Injury and Acute Respiratory Distress Syndrome

Prior to 1994, published studies used non-uniform definitions of ARDS, prompting an American European Consensus

Table 145-1

American European Consensus Conference Criteria for Acute Lung Injury (ALI) and the Acute Respiratory Distress Syndrome (ARDS)

Clinical Variable	Criteria for Acute Lung Injury	Criteria for Acute Respiratory Distress Syndrome
Onset	Acute	Acute
Hypoxemia	$Pa_{O_2}/FI_{O_2} \leq 300$mm Hg	$Pa_{O_2}/FI_{O_2} \leq 200$ mmHg
Chest radiograph	Bilateral infiltrates consistent with pulmonary edema	Bilateral infiltrates consistent with pulmonary edema
Noncardiac cause	No clinical evidence of left atrial hypertension or, if measured, pulmonary artery occlusion pressure $\leq$ 18mmHg	No clinical evidence of left atrial hypertension or, if measured, pulmonary artery occlusion pressure $\leq$ 18 mmHg

Source: Bernard GR, Artigas A, Brigham KL, et al: The American-European Consensus Conference of ARDS: Definitions, mechanisms, relevant outcomes, and clinical trial coordination. Am J Respir Crit Care Med *149:818, 1994.*

Conference (AECC) to develop standardized definitions for ARDS and acute lung injury (ALI): a broader category that encompasses ARDS. The AECC definitions included the acute onset of illness, bilateral chest radiographic infiltrates consistent with pulmonary edema, poor systemic oxygenation, and absence of evidence for left atrial hypertension (Table 145-1). The syndrome is ALI when the ratio of Pa_{O_2} to FI_{O_2} (Pa_{O_2}/FI_{O_2}) is less than or equal to 300 and ARDS when the ratio is less than or equal to 200.

The AECC coined the term ALI to facilitate diagnosing patients earlier in the course of their ARDS and identify patients who have a milder form of acute hypoxemic respiratory failure than ARDS. The AECC definitions of ALI and ARDS are intentionally broad in order to encompass different types of acute hypoxemic respiratory failure occurring in a wide variety of settings. Most patients with ALI progress to ARDS, prompting some to use the composite abbreviation ALI/ARDS to describe all patients with a Pa_{O_2}/FI_{O_2} less than or equal to 300 who meet the other AECC criteria (Table 145-1).

Limitations of Consensus Definitions

Despite standardization of definitions of ALI and ARDS, little data are available to support their reliability and validity. In fact, various components of the definitions remain problematic: (1) The chest radiograph is subject to variability in interpretation; (2) Pa_{O_2}/FI_{O_2} may vary according to ventilator parameters, e.g., PEEP, and at extremes of FI_{O_2}; and (3) accuracy in excluding the presence of heart failure may be influenced by measurement methodology and timing, as discussed below.

Although interpretation of chest radiographs can be inaccurate and variable among observers, formal training can reduce variability.

The Pa_{O_2}/FI_{O_2} criterion is influenced by the level of PEEP and other transient factors, including the presence or absence of airway secretions or inadequate sedation. Increasing PEEP generally increases Pa_{O_2} at a given FI_{O_2}. The consequent increase in Pa_{O_2}/FI_{O_2} may result in a ratio that no longer meets inclusion criteria for ALI. Conversely, without any PEEP, values of Pa_{O_2}/FI_{O_2} less than 300 may reflect simple atelectasis rather than ALI or ARDS. Adding PEEP may recruit sufficient atelectatic lung to raise Pa_{O_2}/FI_{O_2} greater than 300, thereby excluding such patients from meeting this criterion for ALI.

Finally, diagnostic criteria for left atrial hypertension on purely clinical grounds may be inaccurate. Use of a pulmonary artery catheter may also be inconclusive, since the pulmonary artery occlusion pressure (PAOP) in ALI/ARDS may be higher than 18 mm Hg due to intravascular volume loading, particularly in the setting of goal-directed management paradigms for sepsis (see Chapter 146). Conversely, some patients with pulmonary edema due to congestive heart failure and high left atrial pressures have normal pulmonary artery occlusion pressures by the time the catheter is inserted and PAOP is measured.

Several clinical trials have used the aforementioned standardized definitions of ALI and ARDS to specify study inclusion criteria for their study populations. Using the AECC definitions of ALI and ARDS in clinical trials that have shown therapeutic benefit adds important validity to the definitions. Clinicians can generalize the results of these trials to clinical decisions involving their own patients if they meet the same criteria for ALI or ARDS as used in the clinical trial. Further refinement of the reliability and validity of definitions of ALI and ARDS are important future directions for clinical studies. More reliable definitions will not only improve estimates of the public health impact of these syndromes, but also will decrease misclassification errors that can be especially

problematic for research aimed at clarifying mechanisms in ALI and ARDS, e.g., genetic epidemiological studies.

EPIDEMIOLOGY

Over the last several decades, the epidemiology of ALI and ARDS has become more clearly delineated.

Incidence and Mortality Rate

A landmark epidemiologic study of the incidence of ALI and ARDS in the United States between 1999 and 2000—the King County Lung Injury Project (conducted in King County, Washington)—represents the first broad, population-based epidemiological study of ALI and ARDS in the United States using standardized definitions. Study results included an estimated incidence of ALI of 78.9 per 100,000 person-years and an age-adjusted incidence of 86.2 per 100,000 person-years. The incidence of ARDS was estimated as 58.7 per 100,000 person-years with an age-adjusted incidence of 64.0 per 100,000 person-years. The incidence of ALI increased dramatically with age, with an incidence of 306 per 100,000 person-years for ages 75 through 84 years. By extrapolation, an estimated 190,600 cases of ALI and 141,500 cases of ARDS occur each year in the United States (Table 145-2).

Table 145-2

Estimated Incidence, Hospital Days and Intensive Care Unit (ICU) Days for Acute Lung Injury (ALI) and Acute Respiratory Distress Syndrome (ARDS) in the United States (US)

Variable	ALI	ARDS
Crude incidence, per 100,000 person-years	78.9	58.7
Age-adjusted incidence, per 100,000 Person-years	86.2	64.0
Estimated annual Number of cases in US	190,600	141,500
Estimated annual number of hospital days in US	3,622,00	2,746,000
Estimated annual number of days in ICU in US	2,154,000	1,642,000

From Rubenfeld GD, Caldwell E, Peabody E, et al: Incidence and outcomes of acute lung injury. N Engl J Med *353:1685, 2005.*

Although prior estimates of the incidence of ALI and ARDS had been lower, those studies were limited by incomplete and nonvalidated data, inaccuracies in the definition of the syndromes, and use of administrative coding. Thus, the estimates from King County Lung Injury Project serve as the best indicator of the public health impact of ALI and ARDS in the United States.

During the time of observation in the King County Lung Injury Project study, the mortality from ALI was 38.5 percent and from ARDS was 41.1 percent. These figures translate into an estimated 74,500 annual deaths from ALI in the United States. To put this mortality rate in perspective, more people die annually from ALI than from AIDS, asthma, and breast cancer combined. Other than lung cancer, ALI is responsible for more annual deaths than any cause of cancer, including lymphomas, leukemias, and breast, prostate, colon, ovarian, and pancreatic cancers (Table 145-3). Although the mortality rates from ALI and ARDS may have fallen since the King County Lung Injury Project was conducted in 1999–2000 (due to usage of low tidal volume ventilation strategies), ALI and ARDS likely still have a major public health impact.

Table 145-3

Estimated Annual Number of Deaths in the US from Selected Causes

Cause	Number of Deaths
ALI*	74,500
ARDS	59,000
Asthma	4,621
AIDS	18,017
Breast cancer	40,870
Leukemia	22,570
Lung cancer	163,510
Lymphoma	20,610
Ovarian cancer	16,210
Pancreatic cancer	31,800
Prostate cancer	30,350

** Includes 59,000 deaths from ARDS.*
Source: Data for ALI and ARDS are from Rubenfeld GD, Caldwell E, Peabody E, et al: Incidence and outcomes of acute lung injury. N Engl J Med *353:1685, 2005; all other are from CDC National Center for Health Statistics* (http://www.cdc.gov/nchs/).

Furthermore, as the population of the United States becomes older, the incidence of ALI and its associated annual death rate can be expected to rise.

Precipitating Causes

The severe extensive lung inflammation in ALI and ARDS represents the common final pathogenetic process in response to a large variety of precipitating causes, which result in either direct or indirect (systemic) lung injury. In general, *direct* causes of ALI include those that originate within the lung, such as aspiration of gastric contents or viral pneumonia. Examples of *indirect* causes include severe systemic inflammatory response syndrome (SIRS) or severe sepsis, ingested toxins, hypotension, and ischemia-reperfusion injury. Although some causes of ALI may fit into either category (e.g., multilobar pneumonia with septic shock), the classification scheme is useful both for considering the many predisposing causes of ALI and their varying mechanisms of lung injury and for future development of therapies aimed at different categories of ALI. Table 145-4 lists precipitating causes of ALI and ARDS according to this construct.

Factors Influencing Risk of ALI and ARDS

Not all patients with an underlying cause (e.g., sepsis) for ALI or ARDS develop the syndrome. In addition to inherent risk differences within at-risk populations, specific clinical variables may be important.

Clinical variables found to be associated with an increased risk of ARDS include chronic alcohol abuse, hypoproteinemia, advanced age, increased severity, and extent of injury or illness as measured by injury severity score (ISS) or APACHE score, hypertransfusion of blood products, and possibly, cigarette smoking. Diabetes mellitus decreases the risk of ALI. Since many of the studies addressing this issue are retrospective or based on a single center's experience, the consistency and generalizability of identified risk factors have not been confirmed. Nonetheless, the mechanistic underpinnings of these probable associations are the subject of ongoing research.

Factors Influencing Mortality from ALI and ARDS

Clinical variables at the onset of ALI and ARDS that are associated with increased mortality include advanced age, lower Pa_{O_2}/FI_{O_2}, high plateau pressure (i.e., low respiratory system compliance), greater extent of pulmonary infiltrates, chronic liver disease, nonpulmonary organ dysfunction, increased global severity of illness, hypoproteinemia, and greater length of hospitalization prior to onset of ALI/ARDS. In addition, an increased dead space fraction has been identified as a risk factor for increased mortality, possibly indicating the importance of early loss of the pulmonary vascular bed as a sign of greater disease severity. Although various precipitating causes of ALI and ARDS carry somewhat different prognoses, the strategy of low tidal volume ventilation utilized by the National Institutes of Health (NIH) National Heart, Lung, and Blood Institute (NHLBI)–sponsored ARDS Clinical Trials Network (ARDSNet) as part of its clinical trials appears to be equally efficacious in all subgroups.

Table 145-4

Common Direct and Indirect (Systemic) Precipitating Causes of ALI and ARDS

Direct Precipitating Cause	Indirect (Systemic) Precipitating Cause*
Aspiration of gastric fluids	Acute pancreatitis
Bacterial pneumonia (diffuse), e.g., Legionnaire's disease	Blood transfusions with transfusion-related acute lung injury (TRALI)
Chest trauma with lung contusion	Post-cardiopulmonary bypass
Near-drowning	Primary graft failure of lung transplantation
Pneumonia due to *Pneumocystis carinii*	Severe sepsis and septic shock
Toxic inhalations, e.g., smoke inhalation, inhaled crack cocaine	Toxic ingestions, e.g., aspirin, tricyclic antidepressants
Viral pneumonia, e.g., influenza, severe acute respiratory syndrome (SARS)	Trauma with multiple fractures and the fat-emboli syndrome

** In indirect or systemic mechanism of lung injury, the lung injury results from deleterious effects on the alveolar epithelium by inflammatory or other mediators delivered via the pulmonary circulation (see Chapters 144 and 146 Matthay Deutschman for details).*

Source: Christie JC, Lanken PN: Acute lung injury and the acute respiratory distress syndrome, in Hall JB, Schmidt GA, Wood LDH (eds): Principles of Critical Care, *3d ed. New York, McGraw-Hill, 2005; p 518, reproduced with permission.*

CLINICAL PRESENTATION AND DIAGNOSIS

The clinical presentation and diagnosis of ALI/ARDS are fundamentally related to the syndrome's pathophysiological changes, regardless of the underlying etiology. A brief description of the pathology and pathophysiology is provided before a detailed discussion of clinical aspects of the disorder. The reader is also referred to Chapter 144 for additional details on disease mechanisms.

Pathology and Pathophysiology

A number of inter-related mechanisms contribute to the development and clinical course of ALI and ARDS. Inflammatory cytokines, oxygen radicals, activation of coagulation and complement, platelet and immune cell activation, generation of proteases, and abnormal fluid fluxes resulting in edema fluid generation and defective epithelial alveolar fluid clearance have all been hypothesized to play a role in the early stages. In addition, factors specific to apoptosis, edema fluid resolution, and fibrosis and repair, as well as the response to mechanical ventilation are likely to play a role in the pathophysiology of the later phases of ALI and ARDS.

Pathologically and clinically, ALI can be divided into *early* and *late phases* of lung injury (Fig. 145-1). In the early phase (first few hours or days), light microscopy shows interstitial and alveolar edema, capillary congestion, and intra-alveolar hemorrhage with minimal evidence of cellular injury. Electron microscopy reveals changes of endothelial cell swelling, widening of intercellular junctions, increased numbers of pinocytotic vesicles, and disruption and denudation of the basement membrane. Inflammatory cell infiltration of the lung interstitium may also be seen. Protein-rich pulmonary edema and its clinical effects are most pronounced in the early exudative phase. Hyaline membranes containing condensed fibrin and plasma proteins form over the next several days. Later in the exudative phase, inflammatory cells become more numerous within the lung interstitium, and extensive necrosis of type I alveolar epithelial cells is present.

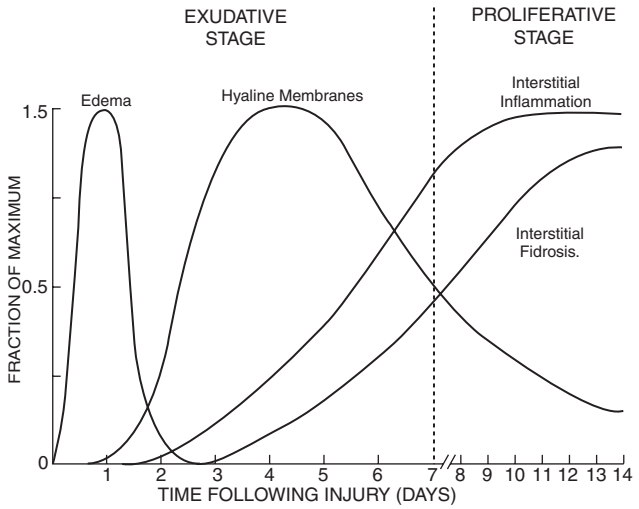


Figure 145-1 Schematic representation showing time course of evolution of the acute respiratory distress syndrome (ARDS). The early or exudative phase is characterized by a pulmonary capillary leak with interstitial and alveolar edema and hemorrhage followed by hyaline membrane formation. Within as short a period of time as 7 to 10 days, a proliferative phase may appear with marked interstitial and alveolar inflammation and cellular proliferation, followed by fibrosis and disordered healing (see text for discussion). *(Reproduced with permission from Katzenstein AA, Askin FB: Surgical Pathology of Non-Neoplastic Lung Diseases, 2nd ed. Philadelphia, Saunders, 1990.)*

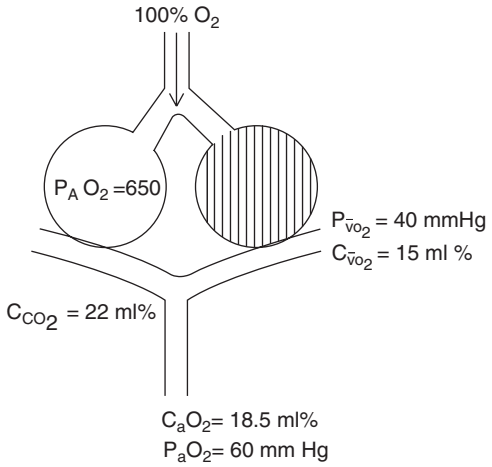


Figure 145-2 Diagram of a two-compartment model of lung perfusion and ventilation demonstrating basis for failure of oxygenation in ALI and ARDS. When large portions of the lung are nonventilated due to alveolar collapse or flooding (hatched area), blood flow to these units with mixed venous P_{O_2} ($P\bar{v}_{O_2}$) of 40 mmHg and content of 15 vol percent is effectively "shunted" through the lungs without being resaturated. Thus, despite a high concentration of supplemental oxygen (100 percent in this example) and high alveolar P_{O_2} in ventilated unit, these blood flows mix in accord with their oxygen contents, i.e., the resulting left atrial blood has an oxygen content that is the weighted mean of the oxygen content of the shunted and non-shunted blood. In this example of a 50 percent shunt, the left atrial and systemic arteries have an arterial P_{O_2} of 60 mmHg. CaO_2 = arterial oxygen content; C_{CO_2} = capillary oxygen content; $C\bar{v}O_2$ = mixed venous oxygen content; P_A = alveolar pressure; Pa_{O_2} = arterial P_{O_2}; $P\bar{v}_{O_2}$ = partial pressure of oxygen in the mixed venous blood. *(Reproduced with permission Christie JD, Lanken PN: Acute Lung Injury and The Acute Respiratory Distress Syndrome, in Hall JB, Schmidt GA, Wood LDH (eds.): Principles of Critical Care, 3rd ed. New York, McGraw-Hill, 2005; p 516.)*

Pathologists refer to this constellation of findings as *diffuse alveolar damage* (DAD).

Pathophysiologically, in the exudative phase, alveolar edema and alveolar collapse, i.e., atelectasis due to loss of normal surfactant-related stabilization of alveoli, interfere with oxygenation. Surfactant is both washed out of alveoli and inactivated by the alveolar edema. The hypoxemia in ALI/ARDS is typically resistant to supplementary oxygen, reflecting an increased right-to-left shunt (Fig. 145-2). Continued perfusion of alveoli that lack ventilation because of alveolar edema results in ventilation-perfusion ($\dot{V}/\dot{Q}$) ratios of zero, thereby defining physiological shunt. Furthermore, the effects of this type of shunt are exacerbated by shuntlike contributions from alveoli with very low ventilation-perfusion ratios.

Disordered healing and proliferation of fibrous tissue dominate the late phase of ARDS or persistent ARDS, i.e., the *proliferative or fibroproliferative* phase. Type II alveolar cells, fibroblasts, and myofibroblasts proliferate in this phase, which can occur as early as 7 to 10 days after initial injury. The late phase of ARDS is characterized by an increased dead space fraction, high minute ventilation requirement,

pulmonary hypertension, and further reduction in lung compliance.

Clinical Presentation

The development of ALI and ARDS usually follows a rapid course, occurring most often within 12 to 48 hours of the predisposing event. At its onset, patients with ALI and ARDS often become anxious, agitated, and dyspneic. Inflammatory changes in the lung decrease lung compliance, which, in turn, leads to an increased work of breathing, small tidal volumes, and tachypnea. Marked tachypnea and dyspnea are invariably present in subjects with ALI. If breathing ambient air or low-flow supplementary oxygen, patients with ALI typically have initial arterial blood gas results showing a Pa_{O_2} less than 50 to 55 mm Hg and pulse oximetry recordings of less than 85 percent arterial O_2 saturation. The hallmark of ALI and ARDS is hypoxemia that is resistant to oxygen therapy because of the large right-to-left shunt (Fig. 145-2).

Initially, patients may be able to compensate by hyperventilating, thereby maintaining an acceptable Pa_{O_2} with an acute respiratory alkalosis. Typically, patients deteriorate over several hours, requiring endotracheal intubation and mechanical ventilation. However, the need for mechanical ventilation is not necessary for establishing the diagnosis of ALI or ARDS. Selected patients with milder lung injury and a normal level of consciousness can be treated successfully with high-flow oxygen therapy, with or without a continuous positive airway pressure (CPAP) mask, or noninvasive assisted ventilation.

Differential Diagnosis

The differential diagnoses for acute hypoxemic respiratory failure, in general (Table 145-5), and for ALI and ARDS, in particular (Table 145-6), are extensive. Identifying the specific etiology of the diffuse infiltrates in ALI or ARDS is important because several, e.g., acute eosinophilic pneumonia or diffuse alveolar hemorrhage, have specific therapies. Table 145-6 lists the major clinical and diagnostic characteristics of these disorders.

The setting in which respiratory failure occurs usually provides important diagnostic information. ALI and ARDS commonly arise following development of a typical predisposing factor (Table 145-4). Sepsis, pneumonia, trauma, transfusion of blood products, and gastric aspiration account for the majority of cases.

When an inciting event is obvious and diagnostic criteria (Table 145-1) are met, establishment of a clinical diagnosis of ALI or ARDS is not difficult. Under such circumstances, management can be instituted immediately. However, in the absence of a clear predisposing event, or when conflicting or ambiguous information exists, the other causes listed in Table 145-6 should be considered and relevant clues from the history and physical examination sought. For example, cardiogenic edema is most often accompanied by systolic left ventricular or valvular dysfunction, and the appropriate history and physical findings (e.g., a heart murmur or ventricular gallop) are often present. Electrocardiographic and laboratory-based evidence (e.g., serum troponin I levels) of cardiac ischemia suggest cardiogenic edema as a likely cause. Additional important tests that help to differentiate ALI and ARDS from other causes of acute hypoxemic respiratory failure are discussed below.

Table 145-5

Differential Diagnosis of Acute Hypoxemic Respiratory Failure (AHRF)

1. ALI or ARDS
2. Acute (or "flash") cardiogenic pulmonary edema
3. Bilateral aspiration pneumonia
4. Lobar atelectasis of both lower lobes
5. Severe unilateral lower lobe atelectasis, especially when patient is receiving vasodilators, such as intravenous nitrates, calcium-channel blockers, or sodium nitroprusside, that blunt hypoxic vasoconstriction
6. Acute loss of ventilation to one lung due to complete or near-complete obstruction of its mainstem bronchus, e.g., due to a mucus plug or blood clot
7. Loss of ventilation to one or both lungs due to large pneumothorax/pneumothoraces
8. Loss of ventilation to one or both lungs due to large pleural effusion(s)
9. Diffuse alveolar hemorrhage, especially in patients post–bone marrow transplantation
10. Massive pulmonary embolus
11. Acute opening of a patent foramen ovale in patient with preexisting pulmonary hypertension

Abbreviations: ALI = acute lung injury; ARDS = acute respiratory distress syndrome.
Source: Christie JD, Schmidt G, Lanken PN: Acute respiratory distress syndrome: http://pier.acponline.org/physicians/diseases/d349/d349.html*, July 2004. Physicians' Information and Education Resource. Philadelphia, American College of Physicians, reproduced with permission.*

Approach to Clinical Diagnosis

A number of diagnostic methods are extremely valuable in evaluating suspected ALI or ARDS. Each is briefly described below.

Chest Radiograph

The chest radiograph is a simple and widely available test used to assess patients with acute hypoxic respiratory failure. In cases of *established* ALI or ARDS, the chest radiograph typically demonstrates findings of diffuse, bilateral alveolar infiltrates consistent with pulmonary edema (Fig. 145-3). However, especially early in the course of the disorder, the infiltrates associated with ALI and ARDS may be variable: mild or dense, interstitial or alveolar, patchy or confluent.

Table 145-6

Differential Diagnosis of ALI and ARDS

Disorder	Characteristics	Comments
Pulmonary edema due to left heart failure.	History of cardiac disease, enlarged heart on chest radiograph, third heart sound.	Rapid improvement with diuresis and/or afterload reduction.
Noncardiogenic pulmonary edema	History of one or more precipitating causes (Table 145-4), crackles absent or not prominent, normal cardiac size on chest radiograph.	Usual etiology for ALI and ARDS. Rarely some patients with ALI or ARDS have no obvious precipitating cause.
Diffuse alveolar hemorrhage (DAH)	Often associated with autoimmune diseases (e.g., vasculitis) or following bone marrow transplantation. Often patients do not have bloody sputum. Renal disease or other evidence of systemic vasculitis may be present. Hemosiderin-laden macrophages in bronchoalveolar lavage fluid can confirm diagnosis of DAH. May respond to apheresis, corticosteroids, or cyclophosphamide, depending on etiology.	May meet diagnostic criteria for ARDS (Table 145-1), but has different pathophysiology and management.
Acute eosinophilic pneumonia	Cough, fever, pleuritic chest pain, and myalgia are often present. Patients often do not have peripheral blood eosinophilia, but generally have greater than 15% eosinophils in bronchoalveolar lavage fluid. Usually responds rapidly to high-dose corticosteroid therapy.	May meet diagnostic criteria for ARDS (Table 145-1), but has diffeent pathophysiology and management.
Lupus pneumonitis	Usually associated with active lupus. May respond to high-dose corticosteroid therapy or cyclophosphamide	May meet diagnostic criteria for ARDS, but has different pathophysiology and management.
Acute interstitial pneumonia (AIP)	Slower onset than ARDS (over 4–6 weeks) with progressive course. However it may present in advanced state, mimicking ARDS.	Associated with >90% mortality. AIP includes Hamman-Rich syndrome.
Pulmonary alveolar proteinosis (PAP)	Slower onset than ARDS (over 2–12 months) with progressive course. Can be treated with whole lung lavage.	Characteristic "crazy paving" pattern on high-resolution CT scan of chest.
Bronchiolitis obliterans with organizing pneumonia (BOOP) or cryptogenic organizing pneumonia	May be precipitated by viral syndrome. Slower onset than ARDS (over >2 weeks) with progressive course. However it may present in advanced state, mimicking ARDS. May respond to high-dose corticosteroid therapy.	

(*Continued*)

Table 145-6

(*Continued*)

Disorder	Characteristics	Comments
Hypersensitivity pneumonitis	Typically slower onset than ARDS (over weeks) with progressive course. However, it may present in advanced state, mimicking ARDS. May respond to high-dose corticosteroid therapy and removal from offending agent.	
Leukemic infiltration	May be rapid in onset during active disease states. Usually leukemia is clinically apparent.	
Drug-induced pulmonary edema and pneumonitis	May follow use of heroin, other opioids, overdose of aspirin, tricyclic antidepressants, or exposure to paraquat.	May progress to overt ARDS.
Acute major pulmonary embolus (PE)	Occurs acutely, occasionally accompanied by severe hypoxemia that may be resistant to O_2 therapy like ARDS, and by hypotension, requiring pressors, mimicking ARDS with sepsis. Patients typically have risk factors for acute PE and may not have common precipitating causes of ARDS.	Chest radiograph in ARDS should have bilateral infiltrates consistent with pulmonary edema. Chest radiograph in acute major PE may have unilateral or no infiltrates. Acute major PE needs a confirmatory study, e.g., CT scan with pulmonary embolism protocol.
Sarcoidosis	The onset is not acute, but its clinical recognition may be. Oxygenation is often impaired and the chest radiograph can be diffusely abnormal.	Historical features and the frequent presence of hilar adenopathy in sarcoidosis usually eliminate confusion with ARDS.
Interstitial pulmonary fibrosis	The onset is not acute, but its clinical recognition may be. Oxygenation is often impaired and the chest radiograph can be diffusely abnormal.	Prior chest radiographs and a history of chronic and progressive dyspnea characterize the collection of diseases causing interstitial pulmonary fibrosis.

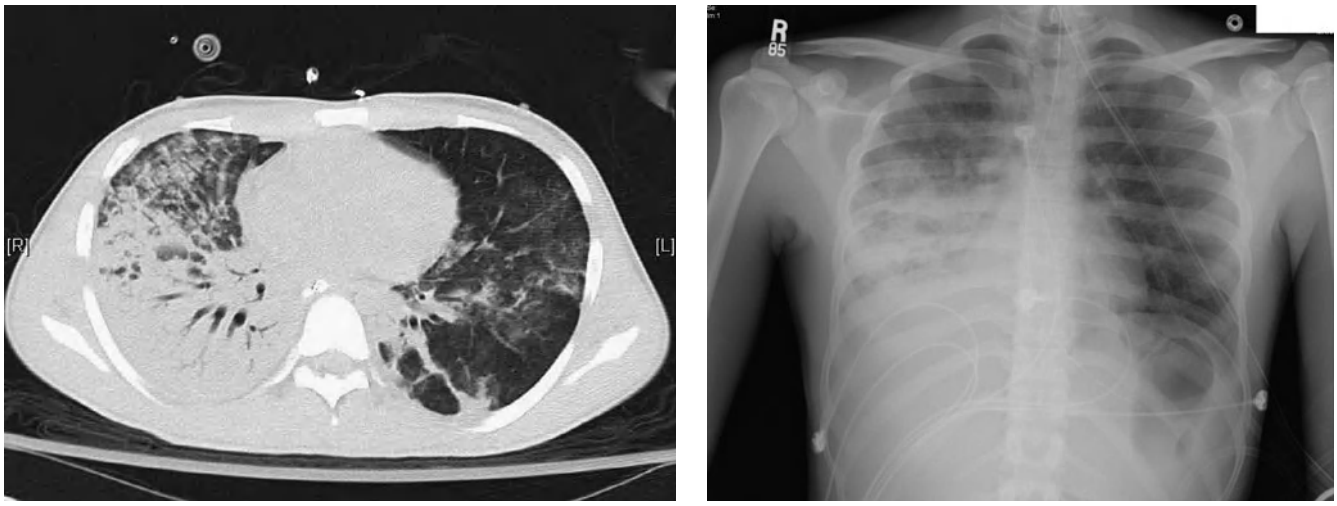
Abbreviations: AIP = acute interstitial pneumonia; ARDS = acute respiratory distress syndrome; CT = computed tomography; DAH = diffuse alveolar hemorrhage.

Source: Christie JD, Schmidt G, Lanken PN: Acute respiratory distress syndrome. http://pier.acponline.org/physicians/diseases/d349/d349.html, *July 2004. Physicians' Information and Education Resource. Philadelphia, American College of Physicians, reproduced with permission.*

In addition, the radiographic infiltrates may not correlate well with the degree of hypoxemia. For example, a patient with early ALI and ARDS may have profound hypoxemia in the setting of patchy asymmetrical infiltrates that may be interpreted as pneumonia or segmental atelectasis. Routine chest radiographs cannot reliably distinguish hydrostatic edema, i.e., cardiogenic edema, from ALI and ARDS. Nonetheless, several criteria suggest *cardiogenic* edema: increased heart size, increased width of the vascular pedicle, vascular redistribution toward upper lobes, the presence of septal lines, or a perihilar ("bat's wing") distribution of the edema. Lack of these findings, in conjunction with patchy peripheral infiltrates that extend to the lateral lung margins, suggests ALI or ARDS. In the proper clinical setting, despite a variable radiographic appearance, the presence of bilateral infiltrates and moderate or severe hypoxemia ($Pa_{O_2}/F_{I_{O_2}}$ less than or equal to 300 mmHg) should raise the possibility of ALI or ARDS.

Laboratory Studies

Although no laboratory test is specific for the diagnosis of ARDS, arterial blood gas analysis is essential for confirming the diagnosis of ALI or ARDS. $Pa_{O_2}/F_{I_{O_2}}$ is markedly abnormal in patients with ALI and ARDS (Table 145-1). In addition to the profound oxygen therapy–resistant hypoxemia that is the hallmark of ALI and ARDS, acute respiratory alkalosis



A *B*

Figure 145-3 Chest CT and plain radiograph in ARDS. *A*. Chest CT scan reveals asymmetric lung injury, with dense consolidation at the right base, patchy alveolar infiltrates in the right anterior lung field, and patchy ground-glass infiltrates throughout the right lung. *B*. Chest radiograph obtained concurrently with chest CT scan shown in panel (*A*). Dense infiltrates at right base, patchy infiltrates in the right upper lung zone, and more subtle infiltrates in the left lung are demonstrated. The panels illustrate the subtle findings of lung injury that are more apparent on the CT scan than on the chest radiograph.

may also occur in the early stage. If a patient with ALI and ARDS then develops respiratory muscle fatigue, hypercapnia results. In late-stage ALI, patients typically have increased minute ventilation requirements due to an increasing dead-space fraction, despite possible improvement in oxygen exchange.

In addition to arterial blood gas measurements, several other laboratory studies may be helpful in investigating other causes of respiratory failure and evaluating additional aspects of critical illness associated with ALI or ARDS. For example, cardiac enzymes (creatine phosphokinase and troponins) are useful for evaluating the presence of myocardial infarction or cardiac ischemia in patients at risk because of increased age or other factors. The results should be interpreted in conjunction with electrocardiographic findings, since elevations in cardiac enzymes, especially troponins, have been reported in patients with sepsis or septic shock in the absence of coronary artery disease.

Another cardiac-related laboratory test that may be useful in this clinical context is plasma brain natriuretic peptide (BNP), which is secreted by the cardiac ventricles, and, to a lesser extent, the atria. BNP measurements are often utilized in the evaluation of acute shortness of breath in patients presenting to an emergency department. In this group, a BNP greater than 500 pg/ml indicates that congestive heart failure (CHF) is likely with a positive predictive value greater than 90 percent. In the same group, a BNP less than 100 pg/ml suggests that congestive heart is unlikely with a negative predictive value greater than 90 percent. However, interpretation of an elevated BNP in patients who are critically ill is problematic. Reports indicate that BNP increases with renal failure, and that elevations of BNP greater than 500 pg/ml may occur in patients with sepsis and normal left ventricular function. Nonetheless, one can reasonably exclude a cardiac cause for acute pulmonary edema in patients in the intensive care unit if BNP is less than 100 pg/ml.

Echocardiography

Echocardiography is a useful noninvasive method to evaluate potential cardiac causes of acute hypoxemic respiratory failure. Cardiogenic pulmonary edema is suggested by echocardiographic findings of mitral valve stenosis or regurgitation, left ventricular dilatation and systolic dysfunction, or regional left ventricular wall motion abnormalities. Although these findings do not rule out coexisting lung injury, they are helpful in the initial evaluation and management, even in the presence of ALI or ARDS.

Invasive Hemodynamic Monitoring

Although right-heart catheterization has been performed often in patients with pulmonary edema, the benefits of the procedure are controversial and the topic of recent investigations (see Chapter 152). Several studies have demonstrated that physician interpretation of data obtained from right heart catheters is inconsistent and often erroneous. Furthermore, one observational study suggested that routine right-heart catheterization is harmful in critically ill patients with acute hypoxemic respiratory failure.

The utility of the pulmonary artery occlusion pressure, also known as pulmonary artery wedge pressure (PCWP), in the diagnosis of ALI or ARDS is questionable. Studies have shown that many patients who originally met criteria for ALI or ARDS (i.e., had a pulmonary artery occlusion pressure less

than or equal to 18 mm Hg) often have subsequent measurements with the PAOP greater than 18 mm Hg.

Finally, recent results from the ARDSNet Fluid and Catheter Treatment Trial (FACCT) support the contentions that the AECC's decision to use a PAOP of greater than 18 mmHg to exclude ALI/ARDS was arbitrary and that the threshold of greater than 18 mmHg needs re-examination.

FACTT was a large, randomized clinical trial that used a two-by-two factorial design to test a fluid-conservative management strategy against a fluid-liberal management strategy in ALI and ARDS and to assess safety and efficacy of a central venous catheter (CVC) or pulmonary artery catheter (PAC) to guide fluid management. In FACTT, 29 percent of 513 patients enrolled in the PAC arm of the trial were found to have a PAOP greater than 18 mm Hg at the time of initial measurement (following passage of the catheter shortly after enrollment and randomization). Before enrollment, FACTT investigators believed that these patients lacked a primary cardiogenic cause for their pulmonary edema. Approximately one half of these subjects had PAOPs of 19 or 20 mmHg. Since the vast majority (97 percent) of this group had a normal cardiac index (greater than or equal to 2.5 $L/m^2/min$), and a mortality similar to other subjects in FACTT, the elevated PAOP (greater than 18 mmHg) likely reflected intravascular volume loading rather than cardiogenic pulmonary edema.

Bronchoalveolar Lavage

Bronchoscopy with bronchoalveolar lavage (BAL) is an important tool in the evaluation of patients who have ALI or ARDS of unclear origin. In general, BAL can be performed safely in patients with ALI or ARDS, except in those with a very low Pa_{O_2} or requiring high levels of PEEP. The principal reason for performing bronchoscopy in ALI or ARDS is to rule in or rule out acute processes that may have specific therapies.

For example, acute eosinophilic pneumonia is a rare disorder characterized by diffuse eosinophilic infiltrates in the lungs (Table 145-6). When the precipitating cause for ALI or ARDS is uncertain, performance of BAL and measurement of the percent eosinophil count in the lavage fluid is helpful in establishing a diagnosis of this corticosteroid-responsive disorder.

Likewise, BAL can be diagnostic for diffuse alveolar hemorrhage (see Chapter 77). In this case, the bronchoscopy may or may not reveal fresh blood in the trachea and major bronchi. However, BAL generally demonstrates a blood-tinged fluid, which contains red blood cells and hemosiderin-laden macrophages. Diffuse alveolar hemorrhage may occur following bone marrow transplantation or as a result of rheumatologic or other immunologic disorders, including Goodpasture's syndrome, Wegener's granulomatosis, systemic lupus erythematosus, or anti-phospholipid antibody syndrome.

APPROACH TO TREATMENT

Goals of Management

Management of patients with ALI or ARDS can be complicated and challenging because clinicians are often faced with simultaneous failure of both respiratory and nonrespiratory organ systems (Table 145-7). Unfortunately, only a limited set of controlled clinical trials are available to support an evidenced-based approach. For example, even large, multicenter, randomized clinical trials, such as those done by ARDSNet, are limited in the number of variables that can be tested. As a result, patient management rests on a combination of relevant evidence-based medicine, extrapolations from basic and clinical research, and experience-based approaches.

Diagnosis and Treatment of Precipitating Causes and Other Comorbidities

The first step in the therapy of ALI or ARDS is identification and treatment of the precipitating cause(s) and any other life-threatening medical or surgical issues (Fig. 145-4).

Table 145-7

Goals of Management of Patients with ALI and ARDS

Treatment of respiratory system abnormalities
Diagnose and treat the precipitating cause of ALI/ARDS, if possible (Table 145-8)
Maintain oxygenation, preferably using nontoxic $F_{I_{O_2}}$ (<0.7), PEEP, or mechanical ventilation
Prevent ventilator-induced lung injury (VILI) by using a low tidal volume ventilatory strategy (Table 145-9) with a limit ($\leq$30 cm H_2O) on static end-inspiratory airway pressure (plateau pressure)
Keep pH in normal range without compromising goal to prevent VILI (but reverse a life-threatening acidosis, even if it prevents meeting goal to prevent VILI)
Enhance patient-ventilator synchrony and patient comfort by use of sedation, amnesia, opioid analgesia, and pharmacological paralysis, if necessary
Liberate or wean from mechanical ventilation when patient can breathe without assisted ventilation
Treatment of non-respiratory system abnormalities
Support or treat other organ system dysfunction or failure
General critical care (preventive and homeostatic measures)
Adequate early nutritional support

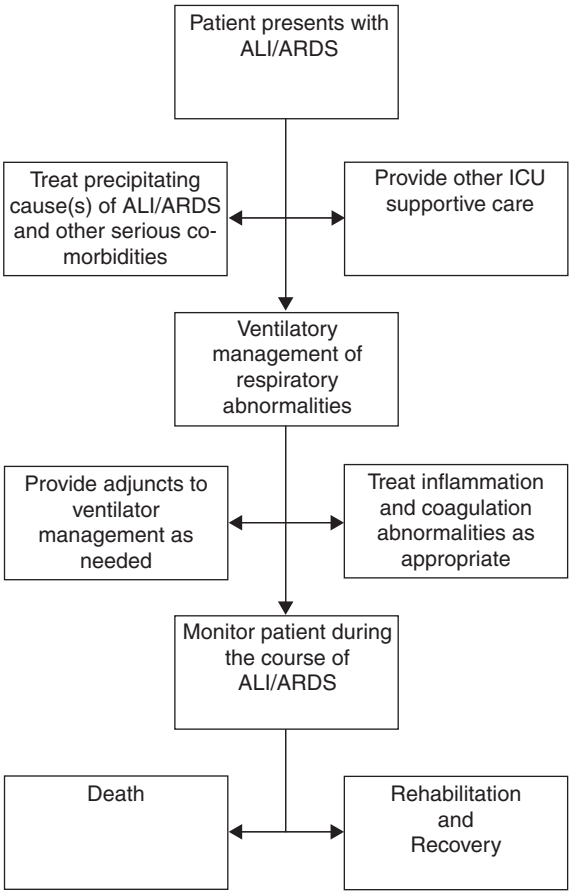


Figure 145-4 Summary of treatment approach to ALI and ARDS. Note that, "Treat inflammation and coagulation abnormalities as appropriate," is currently limited. Examples include treatment of patients with severe sepsis and multiple organ dysfunction using recombinant drotrecogin alpha (activated) and administration of replacement-dose corticosteroids in patients with severe sepsis and septic shock who have relative adrenal insufficiency. In the ARDSNet "LaSRS" clinical trial, physiological improvement, but no mortality benefit, was found with high-dose corticosteroid therapy for persistent (late phase) ARDS (see text for details). *(Reproduced with permission Christie JD, Lanken PN: Acute lung injury and the acute respiratory distress syndrome, in Hall JB, Schmidt GA, Wood LDH (eds): Principles of Critical Care, 3rd ed. New York, McGraw-Hill, 2004; p 525.)*

Since ALI and ARDS are *syndromes* based on nonspecific radiographic and physiologic criteria, establishing a diagnosis of ALI or ARDS is *not* equivalent to diagnosing the precipitating cause. The fact that early identification and treatment directed at the inciting cause(s) of ALI and ARDS are imperative for resolution of lung injury and respiratory failure cannot be overemphasized. Treatable inciting causes of ALI and ARDS include a variety of infectious and noninfectious disorders (Table 145-8).

Management of Respiratory Failure

Management of respiratory failure in ALI or ARDS rests on assurance of adequate oxygenation and carefully crafted ventilatory strategies, as outlined below.

Table 145-8

Treatable Inciting Causes of ALI and ARDS

Infectious etiologies
Bacterial or other sepsis, e.g., fungemia, responsive to antimicrobial therapy
Diffuse bacterial pneumonias, e.g., Legionella species
Diffuse viral pneumonias, e.g., cytomegalovirus, influenza A
Diffuse fungal pneumonias, e.g., Candida species, Cryptococcus
Pneumocystis carinii pneumonia
Other diffuse lung infections, e.g., military tuberculosis
Noninfectious etiologies
Diffuse alveolar hemorrhage post–bone marrow transplantation
Diffuse alveolar hemorrhage due to vasculitis, e.g., Goodpasture syndrome
Acute eosinophilic pneumonia
Lupus pneumonitis
Toxic drug reactions, e.g., aspirin

Source: Christie JD, Lanken PN: Acute lung injury and the acute respiratory distress syndrome, in Hall JB, Schmidt GA, Wood LDH (eds.): Principles of Critical Care, 3rd ed. *New York, McGraw-Hill, 2004; p 525, reproduced with permission.*

Maintaining Adequate Oxygenation

As noted, the pathophysiological hallmark of ALI and ARDS is hypoxemia that is resistant to oxygen therapy. Maintaining adequate arterial oxygenation is the primary goal of both traditional and newer ("lung protective") approaches to assisted ventilation.

As expected with shunt physiology, administration of supplementary oxygen provided by high-flow oxygenation systems, e.g., a non-rebreather face mask, is generally ineffective in reversing the oxygenation deficit. Exceptions to this rule are some patients with mild or transient cases of ALI or ARDS that are otherwise uncomplicated by other organ system failures.

In order to reduce the shunt, positive end-expiratory pressure (PEEP) is employed. When utilized in sufficient amounts, PEEP generally results in correction of the hypoxemia to patients with ALI, thereby allowing $F_{I_{O_2}}$ to be lowered from high potentially toxic concentrations. Although PEEP is usually used in conjunction with mechanical ventilation, in selected cases it may be effective when applied by means of a continuous positive airway pressure (CPAP) mask or as the lower level of bilevel noninvasive ventilation. The effect of PEEP-induced improvement in arterial oxygenation is attributed predominantly to recruitment of collapsed alveoli. However, application of PEEP may also mediate a redistribution of alveolar fluid into the interstitium and decrease the absolute magnitude of shunt by reducing cardiac output.

Acutely ill patients in intensive care units typically receive assisted ventilation via an endotracheal tube. In selected non-ARDS disorders, e.g., COPD or acute cardiogenic pulmonary edema, noninvasive ventilation has been shown to be as effective as invasive ventilation. Although the routine use of noninvasive ventilation for patients with ALI or ARDS lacks compelling evidence, the data are limited. One reason for limited study of noninvasive ventilation in ALI or ARDS is concomitant nonrespiratory organ failure (e.g., due to septic shock). Except for select subgroups, e.g., immunosuppressed patients with hypercapnic respiratory failure who are hemodynamically stable, one should generally avoid use of noninvasive ventilation for patients with ALI and ARDS.

Lung-Protective Mechanical Ventilation

As described in Chapter 153, over the past 30 years investigators have convincingly shown that large tidal volumes delivered during mechanical ventilation can injure lungs of normal animals, producing a pathologic pattern resembling ALI in humans. In animal models of acute lung injury, use of large tidal volume ventilation has been found to augment preexisting injury. In addition, repetitive opening and closing of alveoli during inspiration and expiration induces acute lung injury in normal animals. The injury can be prevented by application of sufficient PEEP. Finally, overexpansion of alveoli in normal lungs of sheep induces multiorgan failure, with recent studies of other species showing that lung overexpansion results in systemic release of proinflammatory cytokines—providing a likely mechanism for these remote deleterious effects. These observations support the concept that the lung, rather than the gut, is the "engine of inflammation."

Concurrent with the previously described observations, clinical investigators studying patients with ALI or ARDS using computed tomography observed that, in contrast to the typical diffuse-appearing pattern noted on plain chest radiographs, the pattern of consolidation, atelectasis, and normal alveoli is actually heterogeneous (Fig. 145-3). The key physiological implication of these observations is that a ventilator-delivered tidal volume is preferentially distributed to the open alveoli, which represent only a small fraction of the entire lung. Reference by Gattinoni, Pesenti and coworkers to this fraction as "the baby lung" emphasized the potential danger of delivering traditional tidal volumes of 10 to 15 ml/kg actual body weight and the associated risk for alveolar overexpansion and lung injury. Notably, tidal volumes of 10 to 15 ml/kg actual body weight (equivalent to approximately 12 to greater than 15 ml/kg predicted body weight) were used originally in critically ill patients with ALI or ARDS as a complementary strategy to PEEP in recruiting atelectatic alveoli.

These productive lines of basic and clinical research strongly support the hypothesis that mechanical ventilation using limited tidal volumes should be less injurious to the lungs of patients with ALI and ARDS and should result in better outcomes (i.e., decreased mortality) compared with use of traditional, large tidal-volume ventilation.

In summary, the goals of lung-protective ventilation are to avoid injury due to overexpansion of alveoli during inspiration (so-called "volu-trauma") and injury due to repetitive opening and closing of alveoli during inspiration and expiration (so-called "atelecta-trauma") (Fig. 145-5). The injurious effects of mechanical ventilation on the lung have been referred to as "ventilator-induced lung injury or VILI." The term "bio-trauma" encompasses the direct lung injury and the concomitant release of inflammatory cytokines that produce remote cell death or organ injury. Clinical strategies underlying contemporary applications of mechanical ventilation in treatment of ALI or ARDS are described below.

ARDSNet Ventilator Strategies: Low vs. Traditional Tidal Volumes

Based on the aforementioned considerations, the ARDSNet conducted a randomized trial (ARMA) in the mid-to-late 1990s to test the hypothesis that low tidal volume ventilation, combined with limited end-inspiratory (plateau) pressure, would lower mortality and ventilator days among survivors of ARDS compared with use of traditional tidal volumes. The trial included 861 subjects. The low tidal volume arm consisted of a tidal volume of 6 ml/kg predicted body weight, as long as the end-inspiratory pressure (Pplat) was 30 cm H_2O or less; if Pplat exceeded 30 cm H_2O, the tidal volume could be decreased to as low as 4 ml/kg. The traditional tidal volume arm used a tidal volume of 12 ml/kg predicted body weight, as long as the Pplat remained less than 50 cm H_2O. Both arms included explicit goals and protocols as the bases for ventilator adjustments and determination of the time and means of weaning (Table 145-9).

Important results of this clinical trial are summarized in Table 145-10. The difference in actual tidal volumes resulted from protocol-driven target tidal volumes in each study arm. As expected, the mean plateau pressure for the lower tidal volume group was less than 30 cm H_2O (25 cm H_2O), since the protocol required decreasing the tidal volume from 6 ml/kg predicted body weight to as low as 4 ml/kg if Pplat exceeded 30 cm H_2O. Of note, the traditional tidal volume group had a mean Pplat of 33 cm H_2O on study day one—a value less than the threshold of 35 cm H_2O that some clinicians had believed represented a safe threshold.

Despite the fact that the clinical trial used an arbitrary threshold of 30 cm H_2O for Pplat in the lower tidal volume arm, it should not be assumed that any Pplat at or below 30 cm H_2O is safe. If a "safe" upper limit of Pplat exists, its value is unknown. Lack of such a safe threshold is supported by the finding of an absence of any significant interaction between differences in mortality and quartiles of static respiratory compliance (Fig. 145-6*A*) or quartiles of plateau pressures (Fig. 145-6*B*). These results suggest that the lower tidal volume ventilatory strategy tends to be effective across a wide range of baseline static compliances and plateau pressures. Likewise, a statistical model of mortality proportion vs. Day 1 Pplat that combined data from both arms of this clinical trial suggests that, in general, the lower Pplat the lower the associated mortality (Figure 145-7).

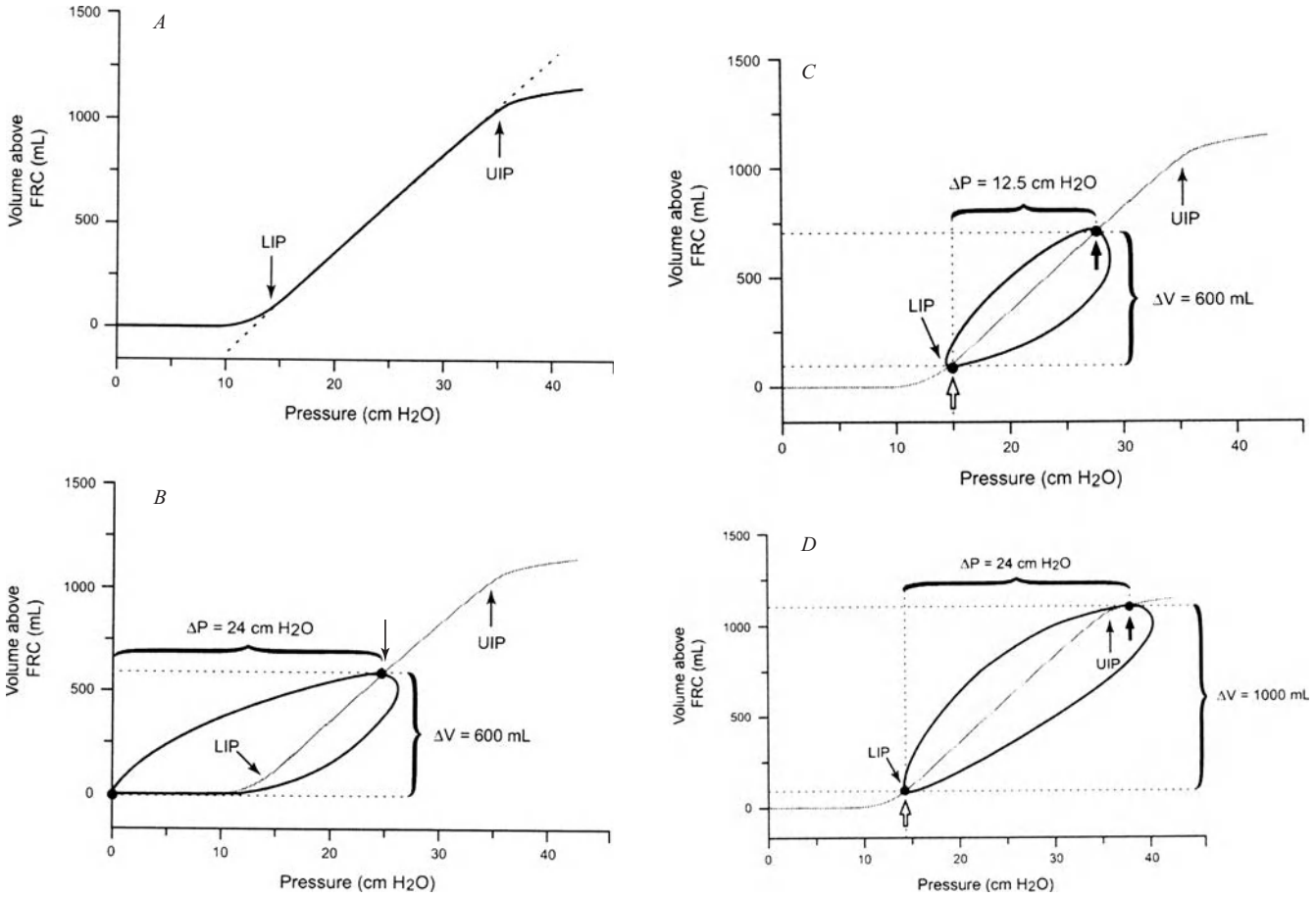


Figure 145-5 *A.* Schematic inspiratory static pressure-volume (P-V) curve of the respiratory system (lung and chest wall combined) in ARDS. Lower inflection point (LIP) is approximately 14 cm H_2O, and upper inflection point (UIP) is approximately 35 cm H_2O. Abscissa is respiratory system recoil pressure; ordinate is lung volume above functional residual capacity (FRC) *B.* Same static P-V curve as (*A*), plus dynamic P-V curve of 600 mL tidal volume starting below the LIP (PEEP = 0). This tidal volume results in a plateau pressure (closed arrow) below the UIP (24 cm H_2O). Static compliance (Cstat = $\Delta V/\Delta P$ = 600 ml/24 cm H_2O) is 25 ml/cm H_2O. *C*. PEEP of 15 cm H_2O has moved the starting point for the 600 ml tidal volume up the static P-V curve to a new FRC (open arrow), which is at the LIP. The tidal volume results in a plateau pressure of 27.5 cm H_2O (closed arrow), which is well below the UIP. Cstat ($\Delta V/\Delta P$ = 600 ml/12.5 cm H_2O) is increased to 48 ml/cm H_2O. D. Dynamic P-V curve of a 1000 ml tidal volume, starting at 14 cm H_2O PEEP, results in a plateau pressure of 37.5 cm H_2O (closed arrow). Despite an increase in Cstat ($\Delta V/\Delta P$ = 1000 ml/24 cm H_2O = 41.5 ml/cm H_2O), compared with Cstat derived from the 600 mL tidal volume in (*B*), the plateau pressure associated with the 1000 ml tidal volume exceeds the UIP. Delivery of an inflation volume that results in a plateau pressure exceeding the UIP implies alveolar overdistension and is believed to put the lung at risk for ventilator-induced lung injury (see text). *(Reproduced with permission from Lanken PN: Acute respiratory distress syndrome, in Lanken PN, Hanson CW III, Manaker S (eds): The Intensive Care Unit Manual. Philadelphia, Saunders, 2001, pp 824–825.)*

These considerations are important, since some clinicians may believe that they can achieve the improved mortality rate simply by lowering tidal volumes to the point where Pplat is at or slightly less than 30 cm H_2O, instead of following the ARDSNet low tidal volume strategy of using a tidal volume of 6 ml/kg predicted body weight. In addition, recognition of the need to use predicted, rather than actual, body weight is important, since the latter has been estimated to be about 20 percent greater than the former (due to fat and extravascular fluid). In summary, clinicians should employ the *entire* ARDSNet protocol (Table 145-9) rather than selected parts in attempting to achieve comparably favorable mortality results.

Lung Protection due to Higher PEEP

The initial ARDSNet trial (ARMA) described above did not address the question of whether application of higher levels of PEEP than used traditionally is beneficial. The possibility of improved outcomes using higher levels of PEEP was suggested by both basic and clinical studies conducted by Amato and colleagues in the early 1990s. To address whether higher levels of PEEP combined with low tidal volumes decreases

Table 145-9

NIH NHLBI ARDS Clinical Trials Network Low Tidal Volume Ventilation Strategy

Part I: Ventilator setup and adjustment

1. Calculate ideal body weight (IBW)* (also known as predicted body weight [PBW])
2. Use Assist/Control mode and set initial TV to 8 ml/kg IBW (if baseline TV >8 ml/kg)
3. Reduce TV by 1 ml/kg at intervals ≤2 h until TV = 6 ml/kg IBW
4. Set initial rate to approximate baseline $\dot{V}_E$ (but not >35 bpm)
5. Adjust TV and RR to achieve pH and plateau pressure (Pplat) goals below.
6. Set inspiratory flow rate above patient demand (usually >80 L/min); adjust flow rate to achieve goal of I:E ratio of 1:1.0–1.3

Part II: Oxygenation goal: Pa_{O_2} = 55–80 mmHg or Sp_{O_2} = 88–95%

1. Use these incremental F_{IO_2}-PEEP combinations to achieve oxygenation goal:

F_{IO_2}	0.3	0.4	0.4	0.5	0.5	0.6	0.7	0.7
PEEP	5	5	8	8	10	10	10	12
F_{IO_2}	0.7	0.8	0.9	0.9	0.9	1.0	1.0	1.0
PEEP	14	14	14	16	18	20	22	24

Part III. Plateau pressure (Pplat) goal: ≤ 30 cm H_2O

1. Check Pplat (use 0.5-sec inspiratory pause), Sp_{O_2}, total RR, TV and ABG (if available) at least every 4 h and after each change in PEEP or TV.
2. If Pplat >30 cm H_2O, decrease TV by 1 ml/kg steps (minimum 4 ml/kg IBW)
3. If Pplat <25 cm H_2O and TV < 6 ml/kg, increase TV by 1 ml/kg until Pplat > 25 cm H_2O or TV = 6 ml/kg.
4. If Pplat < 20 cm H_2O and breath stacking occurs, one may increase TV in 1 ml/kg increments (to a maximum of 8 ml/kg)

Part IV. pH goal: 7.30–7.45

Acidosis management: pH < 7.30

1. If pH = 7.15–7.30, increase RR until pH > 7.30 or Pa_{CO_2} < 25 mmHg (maximum RR = 35); if RR = 35 and Pa_{CO_2} < 25 mmHg, may give NaH_{CO_3}.
2. If pH < 7.15 and NaH_{CO_3} considered or infused, TV may be increased in 1 ml/kg steps until pH > 7.15 (Pplat goal may be exceeded)

Alkalosis management: pH > 7.45: Decrease RR, if possible

**Male IBW = 50 + 2.3 [height (inches) − 60]; female IBW = 45.5 + 2.3 [height (inches) − 60]*

Abbreviations: ABG = arterial blood gas; RR = respiratory rate on ventilator; SpO_2 = Oxygen saturation by pulse oximetry; TV = tidal volume; $\dot{V}_E$ = minute ventilation.

From the NIH NHLBI ARDS Clinical Trials Network (Complete protocol is available at www.ardsnet.org*).*

Source: Lanken PN: Acute respiratory distress syndrome, in Lanken PN, Hanson CW III, Manaker S (eds): The Intensive Care Unit Manual, *Philadelphia, Saunders Co., 2001, p. 828, reproduced with permission.*

mortality, the ARDSNet conducted a second ventilator clinical trial (ALVEOLI) in which each of two groups received the same low tidal volume ventilatory strategy, but one group was treated using an additional 4 to 5 cm H_2O of PEEP. Mortality rates at day 60 were below 30 percent for both groups and were not significantly different, even after adjustment for imbalances in baseline variables. Similarly, ventilator-free days were not significantly different. Therefore, at present, whether maintenance of PEEP above a certain point (corresponding to the lower inflection point in Fig. 145-5) improves clinical outcome is unknown. Recent studies by Gattinoni and co-workers showed that, while some patients with ALI have little or no recruitment (opening previously collapsed or fluid filled airspaces) with increased levels of PEEP, in others PEEP shows marked recruitment. This suggests that future clinical trials using higher PEEP be restricted to subjects with ALI in whom PEEP increments can reliably result in recruitment.

Recommended Core Ventilator Management

We recommend that as the core ventilator management in ALI and ARDS clinicians follow the ARDSNet low tidal volume ventilatory strategy (Table 145-9). Because higher levels of

Table 145-10

Results of NIH NHLBI ARDS Clinical Trials Network Low Tidal Volume vs. Traditional Tidal Volume Clinical Trial ("ARMA")

Variable or Outcome	Units	Low Tidal Volume Ventilatory Strategy Mean ± SD	Traditional Tidal Volume Ventilatory Strategy Mean ± SD	*p* Value
Tidal volume on day 1	mL/kg PBW	6.2 ± 0.9	11.8 ± 0.8	<0.05
Plateau pressure on day 1	cm H_2O	25 ± 7	33 ± 9	<0.05
PEEP on day 1	cm H_2O	9.4 ± 3.6	8.6 ± 3.6	<0.05
Pa_{O_2}:FI_{O_2} on day 1		158 ± 73	176 ± 76	<0.05
Pa_{CO_2} on day 1	mmHg	40 ± 10	35 ± 8	<0.05
Death before discharge or 180 days	%	31.0	39.8	0.007
Breathing without assistance at day 28	%	65.7	55.0	<0.001
No. of ventilator-free days by day 28		12 ± 11	10 ± 11	0.007
No. of days without failure of nonpulmonary systems by day 28		15 ± 11	12 ± 11	0.006

Abbreviations: PBW = predicted body weight (see footnote of Table 145-9 for details); PEEP = positive end expiratory pressure; SD = standard deviation; ventilator-free days by day 28, number of days alive and not receiving assisted ventilation between days 1 and 28.
Source: Acute Respiratory Distress Syndrome Network. New Engl J Med *342:1301, 2000.*

PEEP have not yet been found to improve outcomes, unless new evidence arises to the contrary, we also recommend that clinicians follow the same combinations of FI_{O_2} and PEEP used in the first ARDSNet trial, ARMA (Table 145-9).

Because of constraints of sample size, the ARDSNet trial tested the low-volume strategy only against use of tidal volumes of 12 ml/kg predicted body weight. Notably, a strategy using 6 ml/kg has not been shown to be superior to a strategy using tidal volumes of 8 to 10 ml/kg. However, based on the previous descriptions of ventilator-induced lung injury and bio-trauma, we believe it is prudent for clinicians to strictly follow the ARDSNet protocol as their core management strategy in ALI or ARDS. Modifications should be considered only in special cases, e.g., when contraindications for permissive hypercapnia exist (Table 145-11).

Other Approaches to Ventilator Management

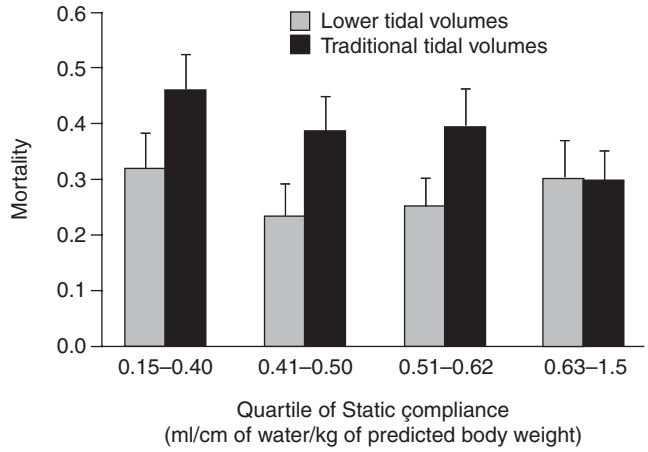
In addition to the low-volume protocol described, several additional approaches may be used in the management of ALI or ARDS and are discussed briefly below.

Pressure Control Mode

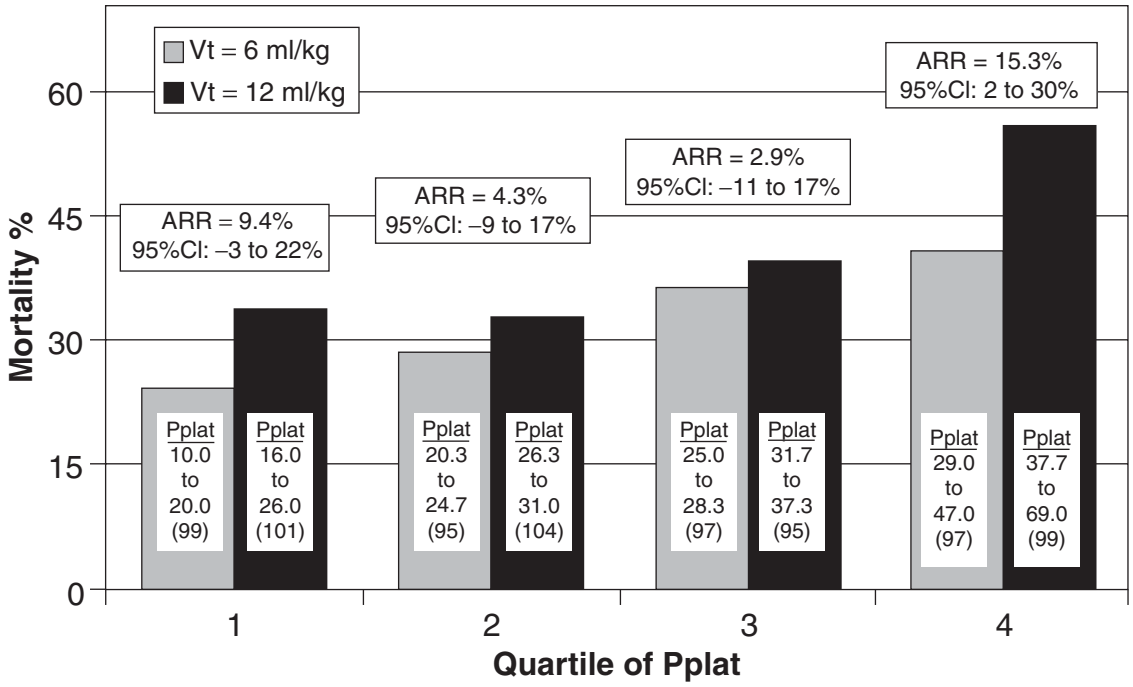
The ARDSNet low tidal volume strategy used the volume-assist-control mode—a familiar device setting and the only ventilator intervention that has been shown thus far to improve long-term survival in patients with ALI and ARDS. However, other modes of ventilation can also provide low tidal volume ventilation, including pressure control ventilation (PCV).

PCV can limit maximal peak airway pressure as well as end-inspiratory pressure (Fig. 145-8A) and, hence, is favored by some clinicians. However, the end-inspiratory pressure in PCV can be underestimated. For example, using PCV with an inspiratory pressure of 30 cm H_2O and a PEEP of 10 cm H_2O, the end-inspiratory pressure is 40 cm H_2O (the sum of the two pressures). Some may misinterpret this combination as equivalent to a Pplat of 30 cm H_2O and assume that it is a "safe" value according to interpretation of ARDSNet results. As discussed previously, however, no Pplat is known to be safe, even when end-inspiratory pressure is calculated correctly. Furthermore, use of PCV to mimic both tidal volume and Pplat used in the ARDSNet trial remains problematic. The benefit seen from using the ARDSNet strategy may have been due as much to the use of low tidal volume as to lower Pplat.

Inverse ratio ventilation (IRV) with PCV is based upon an inspiratory time (I) greater than expiratory time (E), i.e., I:E greater than 1 (Fig. 145-8B). Some case reports identify



A



B

Figure 145-6 ARDSNet ARMA study. *A*. Mortality rates (mean ± SE) according to quartile of static respiratory system compliance before randomization and subsequent treatment group. Data represent a subset of 861 subjects enrolled, including 257 patients assigned to the low tidal volume ventilatory strategy and 260 to the high tidal volume strategy. Mortality in the low tidal volume group was at least 30 percent lower than for those receiving traditional tidal volumes in each of the lowest three quartiles. Although the low tidal volume strategy was not advantageous for patients in the quartile with the highest static compliance, a test for interaction between treatment group and static compliance quartile at baseline was not statistically significant. Results support the concept that the low tidal volume ventilation strategy is beneficial for patients with ALI or ARDS across a spectrum of static compliances, not just for those with the stiffest lungs. (*Reproduced with permission from Acute Respiratory Distress Syndrome Network*. N Engl J Med *342: 1301, 2000.*) *B*. Mortality according to quartiles of end-inspiratory pressure (plateau pressure, Pplat) and treatment group on study day 1 in 787 subjects for whom Pplat data are available (including 270 subjects for whom pre-randomization static compliance measurements were not available). Pplat was measured using protocol-dictated tidal volumes (rather than clinician-determined tidal volumes, as used in assessing static respiratory system compliance). Subjects with the stiffest lungs are likely to have Pplat in the fourth quartile (far right). Range of Pplat (cm H_2O) and number of subjects (parentheses) are shown in each bar of the graph (ARR = absolute risk reduction; CI = confidence interval). Lower tidal volume ventilation appears to benefit patients with ALI or ARDS across a range of Pplat. The hypothesis that a "safe" upper limit exists for Pplat, below which ventilator-induced lung injury does not occur, is *not* supported by the data. *(Reproduced with permission from Hager DN, Krishnan JA, Hayden DL, et al: Am J Respir Crit Care Med 172:1241, 2005.)*

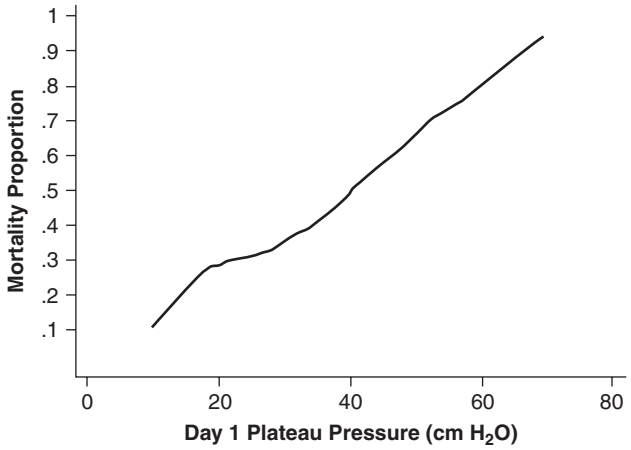


Figure 145-7 Lowess (locally weighted regression and smoothing) plot (bandwidth, 0.4) of mortality proportion and day 1 plateau pressure (Pplat, cm H_2O) for 787 patients enrolled in the ARDSNet ARMA study. Plot includes same subjects and Pplat shown in Fig. 145-6B. When expressed using this estimating method, the data do not support a safe upper limit for Pplat, the presence of which would be suggested by a leveling in mortality proportion, rather than a further decrease, as the plot demonstrates. The Lowess method is a nonparametric smoother that uses overlapping neighborhoods of data to estimate a local effect. A bandwidth of 0.4 means that 20 percent of the data on either side of a given Pplat contribute to a local estimate of mortality at that Pplat; data at the high and low ends of the curve represent fewer observations. As data are smoothed using a tricubic weight function, points furthest from the Pplat of interest are assigned the least weight and approach zero. *(Reproduced with permission from Hager DN, Krishnan JA, Hayden DL, et al: Tidal volume reduction in patients with acute lung injury when plateau pressures are not high. Am J Respir Crit Care Med 172:1241, 2005.)*

Table 145-11

Contraindications for Permissive Hypercapnia and Acute Respiratory Acidosis

Increased intracranial pressure from any cause (trauma, mass lesion, malignant hypertension)
Acute cerebrovascular disorders, e.g., stroke
Acute or chronic myocardial ischemia
Severe pulmonary hypertension
Right ventricular failure
Uncorrected severe metabolic acidosis
Sickle cell anemia
Tricyclic antidepressant overdose
Patients taking beta-blockers
Pregnancy (due to potential for decreased fetal blood flow from vasodilation-induced steal syndrome; in addition, shift to the right of the O_2 dissociation curve decreases the maternal-fetal gradient for O_2)

patients with refractory hypoxemia who responded to PCV-IRV. This may be due to effects of auto-PEEP (intrinsic PEEP) or other mechanisms involving alveolar recruitment following prolonged exposure to IRV. IRV with auto-PEEP plus applied PEEP may compromise cardiac output and increase the risk of nonpulmonary organ dysfunction. Clinicians should consider using PCV-IRV only as a "salvage" mode of ventilation (Table 145-12).

Modes That Allow Spontaneous Breathing during Positive Pressure Ventilation

Two ventilatory modes of modern microprocessor-based devices that permit spontaneous breathing to occur at any phase of the respiratory cycle during assisted ventilation include biphasic airway pressure (BIPAP) and airway pressure release ventilation (APRV). In each, airway pressure cycles between higher and lower levels of PEEP at preset time intervals. Controlled studies using these ventilator modalities are limited. One report found that use of APRV in patients with ARDS decreased intrathoracic pressure, improved ventilation-perfusion mismatch and cardiac output, and decreased shunt and dead space fractions compared with pressure support ventilation (matched for the same airway pressure limits or minute ventilation). However, clinically important outcomes were not compared.

BIPAP and APRV can be expected to decrease the use of neuromuscular blocking agents in patients with ALI or ARDS since both allow spontaneous breathing and potentially less patient-ventilator dyssynchrony. However, whether such newer modes of ventilation are better than, equal to, or worse than the ARDSNet lower tidal volume ventilatory strategy remains unknown. Until more clinical evidence supports their superiority or equivalency, their routine use cannot be recommended.

High Frequency Oscillatory Ventilation Mode

The U.S. Food and Drug Administration has approved an adult high frequency oscillatory ventilator (HFOV) for management of patients with ARDS. Theoretically, HFOV may be regarded as the ultimate low tidal volume ventilator with a capacity to ventilate a patient using a very small tidal volume midway between the upper and lower inflection points of the pressure-volume curve (Fig. 145-5).

Clinically, use of HFOV has been shown to be equivalent to "usual" care. However, the trial comparing HFOV with usual care was conducted at a time when usual care did *not* include low tidal volume ventilation. Since its application generally requires neuromuscular paralysis, HFOV is unlikely to be utilized in patients with mild ALI or ARDS because of the risk of paralytic agent–related quadriparesis and lack of

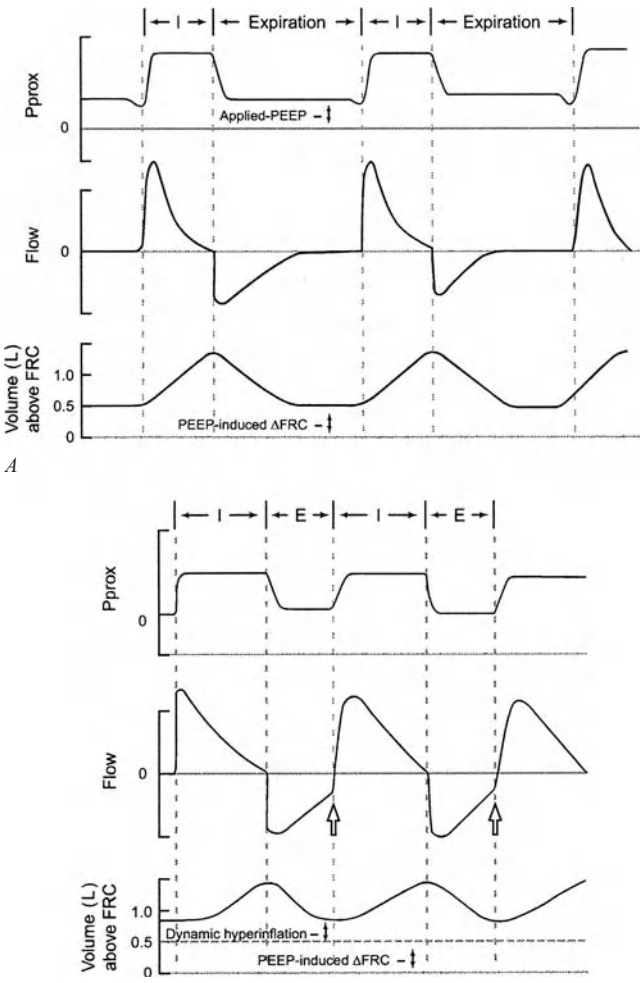


Figure 145-8 Schematic depiction of pressure, flow, and volume waveforms during pressure control ventilation (PCV) with applied PEEP. Abscissa is time and ordinates (from top to bottom) are proximal airway pressure (P_{prose}), inspiratory flow and volume above functional residual capacity (FRC). Other abbreviations: I, inspiration, ΔFRC, change in FRC. *A*. The inspiratory-to-expiratory (I:E) time is about 1:2. The pressure waveform resembles pressure support ventilation, and the flow pattern is characterized by marked deceleration. Applied PEEP increases FRC (PEEP effect). *B*. I:E time is reversed (I > E), representing pressure-controlled inverse ratio ventilation (PC-IRV). As a result, the next breath starts before expiratory flow has returned to zero (open arrows), resulting in auto-PEEP and dynamic hyperinflation. The latter is superimposed on the increased FRC due to the applied PEEP. *(Reproduced with permission from Lanken PN: Acute respiratory distress syndrome, Lanken PN, Hanson CW III, Manaker S (eds): The Intensive Care Unit Manual. Philadelphia, Saunders, 2001, p 829.)*

efficacy data comparable to the ARDSNet protocol used in ARMA (Table 145-9). Some clinicians may use high frequency ventilation as a "salvage" mode (Table 145-16). However, its use, even in those circumstances, is not supported by controlled clinical trials.

Adjuncts to Lung Protective Mechanical Ventilation

A number of adjunctive measures to mechanical ventilation have assumed importance in the management of patients with ALI and ARDS. In some cases, the physiological or pharmacologic basis for the measure's beneficial effect is apparent; in others, the mechanism is unknown.

Overview

Use of adjuncts to lung protective ventilation is generally based on extrapolations from animal or basic studies, or from clinical studies using physiological markers as surrogates for clinically meaningful endpoints, e.g., mortality or ICU length of stay or ventilator-free days. However, extrapolation from such studies to clinical practice is problematic. For example, the only intervention that thus far proved to result in improved survival in ALI and ARDS—the ARDSNet low tidal volume ventilatory strategy—also resulted in patients in the low-volume group with significantly lower Pa_{O_2}/FI_{O_2} after enrollment compared with those receiving traditional tidal volume ventilation (Table 145-10). If the trial had used improvement in Pa_{O_2}/FI_{O_2} as a surrogate marker for better survival, the results would have been interpreted as showing that low tidal volume ventilation results in *higher* not a *lower* mortality.

In general, both efficacy and safety data supporting use of the following adjunctive therapies in ALI or ARDS are lacking. Thus, these interventions should be used cautiously, if at all.

Permissive Hypercapnia

Permissive hypercapnia is defined as clinician-allowed hypercapnia during assisted ventilation, despite an ability to achieve a level of minute ventilation sufficient to maintain a normal Pa_{CO_2} (36 to 44 mmHg). Because patients may develop hypercapnia during lower tidal volume ventilation, which is recommended as the core ventilator strategy, permissive hypercapnia should no longer be considered an "adjunct." (Although the ARDSNet lower tidal volume strategy did stipulate maintenance of minute ventilation while decreasing tidal volume in order to decrease the secondary rise in Pa_{CO_2}, permissive hypercapnia was allowed as a consequence of the protocol. The response to the resulting respiratory acidosis was left to the local investigator's discretion.)

Fluid Management

The ARDSNet Fluid and Catheter Treatment Trial (FACTT), which used a two-×-two factorial design, tested the hypothesis that a management strategy of fluid restriction (conservative fluid management) would improve clinically important outcomes in ALI compared with more generous fluid management strategy (liberal fluid management). Although the strategy of liberal fluid management was based upon a protocol to determine fluid balance, patients' net fluid balance during the first 7 days of the trial resembled that resulting from the non–protocol-directed care in the first two ARDSNet clinical trials (ARMA and ALVEOLI).

FACTT investigators developed a detailed fluid management protocol that, except for patients in shock (MAP less

than 60 mmHg or on vasopressors for hypotension), used four basic input variables (assessed every 1 to 4 hours) to determine the fluid management instructions: (1) mean arterial blood pressure (MAP); (2) urine output; (3) effectiveness of circulation; and (4) intravascular pressure (central venous pressure [CVP] or pulmonary artery occlusion pressure [PAOP]). In both arms of the study, the protocol goals were MAP greater than 60 mmHg (or vasopressor independence); urine output greater than 0.5 ml/kg predicted body weight/hour; and evidence for effective circulation, including a cardiac index greater than or equal to 2.5 L/min/m^2in patients with pulmonary artery catheters (PACs) or, in those with central venous catheters (CVCs), absence of physical examination findings indicating hypoperfusion of extremities. In the group randomized to conservative fluid strategy, the target intravascular pressure was a CVP less than 4 mmHg or PAOP less than 8 mmHg. In contrast, for those randomized to the liberal fluid strategy, targets were a CVP of 4 to 8 mmHg or PAOP of 8 to 12 mmHg.

Despite marked differences in cumulative net fluid balance between the conservatively and liberally managed groups, the two showed no statistically significant difference in mortality at 60 days, which was the study's primary outcome (Table 145-12). Nonetheless, compared with the liberal strategy, the conservative strategy resulted in statistically significant improvements in several clinically important outcomes, including decreased duration of assisted ventilation and length of stay in the intensive care unit (Table 145-12). Moreover, the conservative strategy did not worsen the incidence of shock, number of days in shock, frequency or extent of other organ system failures, or rate of use of dialysis. These results support the use of a conservative fluid strategy in managing patients with ALI or ARDS who are not in shock.

Table 145-12

Results of ARDSNet FACTT (Fluids and Catheter Treatment Trial): Conservative Fluid Management Stategy vs. Liberal Fluid Management Strategy

Result	Conservative Strategy ($n = 503$)	Liberal Strategy ($n = 497$)	p Value
Cumulative net fluid balance from day 1 to day 7 (ml)			
All patients	−139 ± 491	6992 ± 502	<0.001
Patients in shock at entry	2904 ± 1008	10, 138 ± 922	<0.001
Patients not in shock at entry	−1576 ± 519	5287 ± 576	<0.001
Death at 60 days (%)	25.5	28.4	0.30
Ventilator-free days from day 1 to Day 28*	14.6 ± 0.5	12.1 ± 0.5	<0.001
ICU-free days from day 1 to day 28*	13.4 ± 0.4	11.2 ± 0.4	<0.001
Organ-failure-free days from day 1 to day 7*,†			
Cardiovascular failure‡	3.9 ± 0.1	4.2 ± 0.1	0.04
CNS failure§	3.4 ± 0.2	2.9 ± 0.2	0.02
Renal failure‡	5.5 ± 0.1	5.6 ± 0.1	0.45
Hepatic failure‡	5.7 ± 0.1	5.5 ± 0.1	0.12
Coagulation abnormalities‡	5.6 ± 0.1	5.37 ± 0.1	0.23
Dialysis to day 60			
Patients (%)	10	14	0.06
Days of dialysis	11.0 ± 1.7	10.9 ± 1.4	0.96

Plus-minus values are means ± SE. Abbreviations: CNS = central nervous system.

* *This was an* a priori *secondary outcome. Death at 60 days was the primary outcome.*

† *Definitions of organ failure: Cardiovascular failure = systolic blood pressure <90 mmHg or receiving a vasopressor other than dopamine at 5 μg/kg/min or less; CNS failure = Glasgow Coma Scale of 12 or less; renal failure = serum creatinine ≥ 2 mg/dl (177 μmol/L); hepatic failure = serum bilirubin ≥ 2 mg/dl (34 μmol/L); coagulation abnormalities = platelet count of 80,000/μl or less. Number of days without organ failure is determined by subtracting the number of days with organ failure from the lesser of 28 or from number of days until death.*

‡ *This difference was not significant from day 1 through day 28.*

§ *This difference was still statistically significant from day 1 through day 28.*

Table 145-13

Results of ARDSNet FACTT (Fluids and Catheter Treatment Trial): Use of Pulmonary Arterial Catheter (PAC) vs. Use of Central Venous Catheter (CVC) to Direct Fluid and Hemodynamic Management Protocols

Result	Pulmonary Artery Catheter Group ($n = 513$)	Central Venous Catheter Group ($n = 487$)	p Value
Death at 60 days (%)	27.4	26.3	0.69
Ventilator-free days from day 1 to day 28*	13.2 ± 0.5	13.5 ± 0.5	0.58
ICU-free days from day 1 to day 28*	12.5 ± 0.5	12.0 ± 0.4	0.4
Number of catheters inserted†	2.47 ± 0.05	1.64 ± 0.04	<0.001
Number of complications per catheter	0.08 ± 0.01	0.06 ± 0.01	0.35
Total number of catheter-related complications per group†	100	41	

±values are means ± SE.

** This was an* a priori *secondary outcome. Death at 60 days was the primary outcome.*

† This includes the sheath for PAC, PAC, and CVC for subjects in the PAC group and sheath (n = 6) and CVC for subjects in the CVC group.

Hemodynamic Management

Using the trial's two-×-two factorial design, the ARDSNet FACTT investigators also compared the safety and efficacy of PACs with CVCs in directing fluid and hemodynamic protocols, as described. Mortality and other important clinical outcomes, such as ventilator-free days, ICU-free days, and organ-failure-free days by study day 28 were no different in patients managed with a PAC versus a CVC (Table 145-13). However, use of the PAC was associated with a significantly higher complication rate during catheter insertion—primarily, cardiac arrhythmias. The excess events were attributed principally to the need for passing both a sheath and catheter; none of the adverse events was fatal.

Based on the results, the FACTT investigators recommend using a CVC to guide a hemodynamic and fluid management. However, in specific cases, clinicians may elect to use a PAC in selected circumstances, e.g., in addressing the response to volume resuscitation, determining the adequacy of cardiac output, measuring the oxygen saturation of mixed venous blood, calculating the degree of intrapulmonary shunt, or searching for equalization of diastolic pressures during suspected cardiac tamponade.

Prone Positioning

About two-thirds of patients with ALI or ARDS improve their oxygenation after being placed in a prone position. Mechanisms that may explain the improvement include: (1) increased functional residual capacity; (2) change in regional diaphragmatic motion; (3) perfusion redistribution; and (4) improved clearance of secretions. Studies of the distribution of ventilation-to-perfusion ratios in animal models suggest that gravity is less influential on the distribution of perfusion in the prone rather than supine position. This finding, coupled with the observation that edema fluid migrates to the dependent portions of the lung (as demonstrated on computed tomography) in patients with ALI who have been turned prone, suggested that ventilation-perfusion relationships might be favorably altered in the prone position.

Patients managed in the prone position need special attention to prevent pressure necrosis of the nose, face, and ears. Extra care is also needed to ensure security and patency of the endotracheal tube. Pressure on the eye may result in retinal ischemia, especially in hypotensive patients. Others may experience cardiac arrhythmias or hemodynamic instability when turned prone.

In a large clinical trial of prone positioning in patients with ALI and ARDS published in 2001 by Gattinoni and colleagues, subjects were randomly placed prone for 6 or more hours daily for 10 days or were left in the supine position. Although the investigators found that oxygenation was transiently improved with prone positioning, they demonstrated no survival advantage. A more recent study of prone positioning in children with ALI also demonstrated lack of benefit.

Because no controlled clinical trial has showed improved survival with prone positioning, and because the technique carries known risks, even in experienced hands, it cannot be recommended for routine use in patients with ALI or ARDS. However, some clinicians may opt to use

prone positioning as salvage therapy for severe hypoxemia (Table 145-16).

Recruitment Maneuvers

Lung recruitment maneuvers are defined as the application of continuous positive airway pressure (CPAP) aimed at "recruiting" or opening totally or partially collapsed alveoli. The alveoli are then kept inflated during expiration using an appropriately high level of PEEP. In one study of a "lung protective" strategy utilizing low tidal volume ventilation and extra-high PEEP, recruitment manuvers were performed by maintaining a CPAP level of 35 to 40 cm H_2O for 30 seconds. Others advocate application of equivalent or higher pressures for longer periods.

No controlled clinical trial supports the efficacy of recruitment maneuvers alone to improve clinically important outcomes, such as mortality or ventilator-free days. Studies of recruitment maneuvers have generally used physiological end points, e.g., improvement in oxygenation. In a subset of patients treated with high levels of PEEP in the ARDSnet trial comparing high versus low PEEP in ARDS, no clinically relevant improvements in arterial saturation were noted. However, complications such as transient hypotension and slight drops in arterial saturation during the manuver were reported. On the other hand, other clinical studies have reported that recruitment maneuvers improve oxygenation in patients on relatively low levels of PEEP, receiving large tidal volumes, or maintained on paralytics.

Because no controlled clinical trials demonstrate efficacy in clinically relevant end points and there are potentially adverse effects, routine use of recruitment maneuvers is not recommended in ALI or ARDS. Likewise, in the absence of data showing efficacy, routine use of ventilator "sighs" exceeding peak pressures of 30 cm H_2O (the threshold used in the ARDSnet clinical trial that showed improved survival) is also not recommended. Some clinicians may use recruitment maneuvers with higher pressures as part of salvage therapy for patients with severe refractory hypoxemia (Table 145-16).

Inhaled Nitric Oxide

In 1993 Roissant and colleagues published a study of inhaled nitric oxide (NO) as a novel therapy for ARDS. Given via inhalation, NO selectively vasodilates pulmonary capillaries and arterioles that subserve *ventilated* alveoli, diverting blood flow to these alveoli and away from areas of shunt. Lowering of the pulmonary vascular resistance, accompanied by lowering of the pulmonary artery pressure, appears maximal at very low concentrations (0.1 ppm) in patients with ARDS. Beneficial effects on oxygenation take place at somewhat higher inspired concentrations of NO (1 to 10 ppm).

Table 145-14

Results of ARDSNet Late Steriod Rescue Study ("LaSRS") in Patients with Persistent ARDS: *A Priori* Protocol-Defined Outcomes and Adverse Events

Variable or Outcome	Methylprednisolone-Treated Group	Placebo-Treated Group	*p* Value
Mortality at day 60 (%) (95% CI)	28.6 (20.8–38.5)	29.2 (20.8–39.4)	1.0
No. of ventilator-free days at day 28	11.2 ± 9.4	6.8 ± 8.5	<0.001
No. of ICU-free days at day 28	8.9 ± 8.2	6.2 ± 7.8	0.02
No. of serious adverse events associated with myopathy or neuropathy	0	9	0.001
60-Day mortality according to time from onset of ARDS (means)			
7–13 days (%)	27	36	0.26
No. of patients	66	66	
>14 days (%)*	35	8	0.02
No. of patients	23	25	

± *values are mean ± SD.*

* $p = 0.02$ *for the interaction with treatment-group assignment (Wald's test).*

Abbreviations: SD = standard deviation; ventilator-free days by day 28, number of days alive and not receiving assisted ventilation between days 1 and 28; ICU-free days by day 28, number of days alive and not *in ICU between days 1 and 28*

Source: Acute Respiratory Distress Syndrome Network. N Engl J Med *354:1671, 2006.*

Rapid inactivation of NO by hemoglobin prevents unwanted systemic hemodynamic side effects, but also requires continuous delivery of gas through the ventilator circuit. Thus, if continuous delivery of NO is interrupted (e.g., during patient transport or due to NO supply exhaustion), precipitous and life-threatening hypoxemia and right-sided heart failure may occur.

Inhaled NO has been studied in one large contolled clinical trial in patients with ALI and ARDS (not due to sepsis) who had no other organ failures. Inhaled NO did not improve survival, although some patients experienced transient improvements in oxygenation. Based on this trial, the routine use of inhaled NO in ALI is not recommended.

Some clinicians may consider using inhaled NO as a salvage intervention (Table 145-16). However, a much less costly alternative, inhaled prostacyclin (epoprostenol/ilo- prost), is available. The initial daily cost of inhaled NO is several thousands of dollars, while the daily cost of inhaled prostacyclin is several hundreds of dollars. Although less well studied than inhaled NO, inhaled prostacyclin seems to improve oxygenation to the same degree in a majority of patients with ALI or ARDS.

Tracheal Gas Insufflation

Tracheal gas insufflation (TGI) consists of delivering fresh gas through a modified endotracheal tube at a point just above the carina. The additional gas flow (i.e., flow provided in addition to the standard tidal volumes delivered by the ventilator) tends to remove CO_2-rich gas from the trachea and smaller airways. It has the effect of reducing anatomic dead space. Although acute lung injury decreases the ability of TGI to reduce Pa_{CO_2}, permissive hypercapnia and higher Pa_{CO_2} values increase its relative effectiveness. For example, in one study of patients with ARDS, TGI using 100 percent humidified oxygen, delivered throughout the respiratory cycle at a flow of 4 L/min, lowered Pa_{CO_2} from 108 to 84 mmHg.

Because TGI carries a number of potential risks (e.g., tracheal erosion, oxygen toxicity related to an increased $F_{I_{O_2}}$, and hemodynamic compromise or barotrauma due to TGI-induced auto-PEEP and a larger tidal volume than the ventilator is set to deliver), its routine use is not recommended. However, once again, some clinicians may employ it as a salvage intervention for patients with high levels of Pa_{CO_2} (e.g., greater than 100 mmHg).

Extracorporeal Membrane Oxygenation (ECMO) or Extracorporeal CO_2 Removal ($ECCO_2R$)

The use of extracorporeal gas exchange, such as ECMO or $ECCO_2R$, is based on the hypothesis that more patients will survive if the lung is allowed to recover from its injury by "resting" it by using extracorporeal gas exchange temporarily. Although this hypothesis was initially stimulated by the desire to decrease the risk of pulmonary oxygen toxicity, its assessment can now be justified in regard to the techniques' potential roles in reducing ventilator-induced lung injury (VILI).

In the 1970s, a large-scale study on use of ECMO in patients with severe ARDS demonstrated that it offered no survival benefit to patients whose mortality was extremely high (approximately 90 percent). Similarly, a randomized controlled trial in severely ill patients with ARDS reported in 1994 did not find improved survival using $ECCO_2R$. Despite these findings, some clinicians believe that ECMO, with its continually improving technology, may be beneficial in subgroups of patients with ARDS when treated before 7 days of mechanical ventilation. A number of related techniques also have been utilized, including veno-venous ECMO to assist in CO_2 elimination. Some specialized centers continue to offer ECMO to adults with severe ARDS and consider the technique as a safe life-saving salvage intervention (Table 145-16).

Corticosteroids

The general consensus among intensivists is that corticosteroids have little or no role to play in treating the acute phase of ALI or ARDS. However, the role of corticosteroids in later phases of ALI or ARDS has been controversial.

A number of small case series suggest that high-dose corticosteroid therapy may be beneficial during the proliferative phase of ARDS, based on the rationale of preventing lung scarring that occurs during this phase of ALI as a result of alveolar inflammation. Potential risks include immunosuppression of debilitated, instrumented patients managed in environments harboring multiple antibiotic-resistant organisms and potential long-term neuromuscular weakness associated with use of high-dose corticosteroids and paralytic agents.

In 2006, the ARDSNet investigators published results of a double blind, random, controlled clinical trial (Late Steroid Rescue Study or LaSRS) designed to evaluate benefits and risks of moderately high doses of corticosteroids in 180 patients with persistent ARDS (ARDS lasting 7 to 21 days) (Tables 145-15 and 145-16). It found no differences in 60- or 180-day mortality rates. Although parameters of respiratory function, including $Pa_{O_2}/F_{I_{O_2}}$, plateau pressure, respiratory system compliance, and time to, and rate of, liberation from mechanical ventilation improved after corticosteroid administration, the corticosteroid treated group included more patients who returned to assisted ventilation. Furthermore, no statistically significant differences between treated and untreated groups in ICU or hospital days by 180 days were observed. In addition, more adverse events related to weakness occurred in the treated group than in those receiving placebo. Finally, patients treated with corticosteroids after 14 days of persistent ARDS had a significantly increased mortality (Table 145-15). Hence, the results of this study do not support the routine use of steroids for late-phase ARDS in general, and they argue against their use if ARDS has been present for 14 days or longer.

Beta-Agonists

Basic research supports the hypothesis that beta-agonists may improve the outcomes of patients with ALI or ARDS. Beta-agonists stimulate removal of fluid from flooded alveoli by stimulating the epithelial sodium pump and promoting active

Table 145-15

Results of ARDSNet Late Steroid Rescue Study ("LaSRS") in Patients with Persistent ARDS: *Post-hoc* Analyses of Outcomes and Adverse Events at 180 Days

Variable or Outcome	Methylprednisolone-Treated Group	Placebo-Treated Group	*p* Value
180-Day mortality (%) (mean) (95% CI)	31.5 (22.8–41.7)	31.9 (23.2–42.0)	1.0
No. of days of assisted ventilation in survivors up to 180 days (median) (interquartile range)	11 (6–22)	18 (10–33)	0.006
No. of days of ICU stay in survivors up to 180 days (median) (interquartile range)	17 (10–31)	20 (11–31)	0.29
No. of days of hospitalization in survivors up to 180 days (median) (interquartile range)	26 (19–43)	29 (19–40)	0.73
180-Day mortality according to time from onset of ARDS (means)			
7–13 days (%)	27	39	0.14
No. of patients	66	66	
>14 days (%)*	44	12	0.01
No. of patients	23	25	

* $p = 0.006$ *for the interaction with treatment-group assignment (Wald's test).*
Abbreviations: SD = standard deviation.
Source: Acute Respiratory Distress Syndrome Network. N Engl J Med *354:1671, 2006.*

transport of sodium out of the alveoli (with water following passively according to osmotic gradients). This mechanism is possible, however, only with an intact epithelial membrane. Following preliminary reports suggesting that use of beta-agonists may be effective in fluid removal in patients with ALI or ARDS, the ARDSNet clinical investigators began a large, randomized, double-blinded, controlled clinical trial of inhaled albuterol to test the hypothesis in 2006. Their results are pending.

Experimental Adjuncts to Lung-Protective Ventilation

Two experimental adjuncts to lung-protective ventilation deserve comment: use of exogenous surfactant and partial liquid ventilation.

Exogenous Surfactant

Both animal and human studies have shown that in ALI surfactant levels are decreased or proportions of various surfactants are abnormal, resulting in decreased surface tension-lowering activity. Surfactant therapy in infants with respiratory distress syndrome (RDS) due to prematurity improves gas exchange and lung mechanics, decreases the requirement for CPAP, lessens barotraumas, and improves survival. However, results of trials using surfactant therapy in adults with ALI or ARDS have been disappointing to date.

The first large, prospective, randomized controlled trial of inhaled surfactant in patients with ARDS due to severe sepsis was reported in 1996 and showed no benefit. Concerns about appropriate dosing of the agent, alternative modes of agent delivery, timing of therapy, types of subjects treated, and the precise surfactant formulation employed prompted investigators to view the study as inconclusive with regard to advising against use of exogenous surfactant in adults with ARDS. However, another large randomized, controlled trial reported in 2004 also found no improvement in survival; additional trials are underway.

In contrast, in children (infants to adolescents), one encouraging report on use of exogenous surfactant in ALI or ARDS demonstrated improvement in overall mortality, but not in ventilator-free days, which was the study's primary end point. Further positive studies in children likely will be necessary to gain FDA approval for this indication.

Table 145-16

"Rescue" or "Salvage" Interventions Used in Patients with ARDS and Severe Hypoxemia Resistant to Conventional Mechanical Ventialation and PEEP

Corticosteroids
Extracorporeal CO_2 removal ($ECCO_2R$)
Extracorporeal membrane oxygenation (ECMO)
High frequency oscillatory ventilation (HFOV)
Inhaled nitric oxide (NO) or inhaled prostacyclin (epoprostenol/iloprost)
Pressure controlled inverse ratio ventilation (PC-IRV)
Prone positioning
Recruitment maneuvers
Tracheal gas insufflation (TGI)

Currently, exogenous surfactant for adults is available only as an experimental agent.

Partial Liquid Ventilation

Clinical studies on use of partial liquid ventilation using oxygen-carrying perfluorocarbons instilled into the trachea of adults and children with ALI suggest that this mode of therapy has the potential to improve gas exchange. Partial liquid ventilation may improve oxygenation in part because the perfluorocarbon, by virtue of the hydraulic column created, is able to recruit dependent alveoli that PEEP is not. A practical problem with the technique is that agent used (perflubron) is radiodense, thereby complicating interpretation of chest radiographs in detecting infection or in following resolution of the ALI or ARDS. One clinical trial reported in 2006 reported that patients treated with partial liquid ventilation showed trends to worse survival, longer ventilator-free days and more complications.

CLINICAL COURSE, OUTCOME, AND LONG-TERM SEQUELAE

The clinical course and outcomes of ALI and ARDS have been better delineated in recent years. Both pulmonary and nonpulmonary outcomes have been investigated.

Clinical Course and Duration

The course of illness varies considerably in severity and duration among patients. ALI and ARDS may last for a few days or even less (e.g., ARDS from opioid exposure, with the patient recovering rapidly after the initial insult). Alternately, ARDS from other causes may last several months and involve a prolonged ICU course. Patients can recover or die at any point in the course of ALI or ARDS. The median duration of mechanical ventilation is approximately 9 days. Up to 20 percent of patients remain on mechanical ventilation for longer than 2 weeks, and about 10 percent still require assisted ventilation at 28 days (representing approximately 15 percent of those still alive at 28 days). Notably, as shown in LaSRS, a longer duration of mechanical ventilation for ALI/ARDS does not translate into a higher mortality. Most ARDS-related deaths occur within the first 2 weeks, with one-third occurring by day 7, two-thirds by day 14, and three-fourths to four-fifths by day 28.

The mortality rate of patients on mechanical ventilation after 2 to 4 weeks of persistent ARDS is about 30 percent over the ensuing 2 to 6 months. These rates are similar to the overall mortality rate (at 180 days) for patients enrolled in ARDSNet clinical trials in which low tidal volume ventilation was used. The findings highlight the importance of continued supportive care in the ICU and vigilance aimed at reducing nosocomial complications.

Trends in Mortality Rates

Mortality rates for patients with ARDS have decreased since the early 1980s. In one hospital using the same definition of ARDS throughout the period analyzed, the mortality rate was 68 percent in 1982, 29 percent in 1996, and in the mid–30 percent range in 1997 and 1998. Obviously, the decrease cannot be ascribed to widespread application of low tidal volume ventilation strategies, since the decline was observed prior to publication of the ARDSNet ARMA study in May 2000. The improvement is likely attributable to improvements in general ICU care, including prevention of nosocomial pneumonias and other infections, earlier institution of enteral nutrition, routine use of stress ulcer prophylaxis, and improved ICU teamwork. Notably, however, the case fatality rate for patients with ARDS due to sepsis remained the same over this time frame, while that for patients with ARDS due to trauma or other causes decreased significantly.

Mortality rates for patients with ALI but without ARDS (see previously described definitions in Table 145-1) are lower by about one-third than for those with ARDS. The decreased mortality presumably reflects the decreased severity of the oxygenation defect in ALI compared with ARDS (Table 145-1).

Causes of Death

Approximately one-third of ARDS-related deaths occur in the first 7 days. Most are related to the underlying disease

or injury, i.e., to events occurring before the onset of ARDS. The majority of patients who die succumb after 7 days, with these late deaths also commonly due to the underlying injury or illness. Other causes include complications occurring contemporaneously with or after the onset of ARDS. The most common cause of death in this group of patients is sepsis and associated multiple organ system failure. Of note, only a relatively small fraction of patients—10 to 20 percent of all patients with ARDS—die a respiratory death due to irreversible hypoxemia or refractory respiratory acidosis. Therefore, not surprisingly, clinical trials of interventions aimed selectively at improving gas exchange (e.g., use of inhaled nitric oxide or exogenous surfactant) have not demonstrated improved survival.

Long-Term Sequelae

Recent studies indicate that many survivors of ALI have medical problems and a compromised quality of life both of which persist well beyond their initial ICU stay. Impaired pulmonary, neurologic, musculoskeletal, cognitive, and psychosocial functions have been documented in ALI survivors. Furthermore, survivors have a poorer quality-adjusted survival than do critically ill subjects without ALI.

Research into these disorders is in the early stages; the etiology and pathophysiology of are incompletely understood. Recognition of the problems affecting ALI survivors and referral for appropriate evaluation and therapy constitute important components of overall care. With improved therapy of ALI resulting in greater survival rates, clinicians should anticipate an increase in the prevalence of long-term sequelae.

Health-Related Quality of Life

Health-related quality of life (HRQL) has become increasingly recognized as important to the evaluation of patient-centered outcomes in recovery from a variety of illnesses. A number of studies have evaluated HRQL in ALI survivors. Tools used to assess HRQL include the Medical Outcomes Study 36-Item Short Form Health Survey (SF-36), St. George's Respiratory Questionnaire, Quality of Well Being Scale, and Sickness Impact Profile. Each has illustrated impaired quality of life in survivors of ALI compared with various control populations, including critically ill subjects without ALI and patients with chronic diseases (including cystic fibrosis). In general, impairments in HRQL improve over the first 3 months following discharge from the ICU and appear to plateau by 1 year. Studies of interventions to improve HRQL are under way.

Pulmonary Sequelae

Studies of pulmonary function following ALI and ARDS are affected by inconsistent disease definitions, methodological problems due to lack of patient follow-up, and heterogeneity of preexisting pulmonary diseases. Consequently, a range of lung function impairments has been reported following recovery. Although a proportion of survivors of ALI may have impaired diffusion capacity or restrictive or obstructive abnormalities, restoration of normal lung function occurs in a substantial proportion. In the Toronto ARDS Outcomes study, restrictive and diffusion abnormalities observed at 3 months improved toward normal by 1 year. Given the severely impaired physical function domains reported in HRQL surveys and the relatively mild pulmonary impairment, investigation has more recently focused on other limitations and causes of symptoms in ALI survivors (see below).

Physical and Neuromuscular Sequelae

In the previously noted Toronto ARDS Outcomes study, persistent physical impairment in survivors of ARDS was assessed. Despite improvement in pulmonary function at 1 year following their ICU stay, this cohort had low exercise capacity, weakness, and decreased muscle mass. Risk factors for these findings included multiorgan dysfunction in the ICU, prolonged duration of ARDS, treatment with corticosteroids during the ICU stay, and increased co-morbid disease burden. Although the basis for many of the abnormalities is not clear, a number of patients demonstrated a range of abnormalities, including critical illness polyneuropathy, ICU-acquired myopathy (critical illness myopathy), entrapment neuropathy, and heterotopic ossification.

Cognitive and Psychological Sequelae

Cognitive impairments can cause major limitations in the ability to return to work, affect mood, and lead to increased health care expenditures. Study of long-term cognitive function in ARDS survivors indicates that many have impaired memory, reduced attention, and decreased concentration and processing speed. The abnormalities were associated with the number and severity of hypoxemic episodes in the ICU. Similar to physical abnormalities, cognitive dysfunction seemed to be worse in the first 3 months following hospital discharge; it improved until 1 year and then reached a plateau.

Depression and anxiety are frequent following ARDS. Several studies indicate that the prevalence of depression symptoms is as high as 50 percent following recovery. These emotional problems are likely multifactorial, including prior hypoxic brain injury and delirium and subsequent limitation of physical function. In addition, some authors have suggested the presence of a major component of post-traumatic stress disorder (PTSD) in survivors of ALI. Because these disorders are potentially treatable using pharmacological, behavioral, and cognitive therapies, clinicians should ask ARDS survivors about possible depression and anxiety, which, in turn, may improve HRQL.

Finally, in accord with the concept that the ICU team treats patients as well as their families, clinicians need to be aware that familial caregivers of patients who are survivors of ALI or ARDS experience long-term health effects. In particular, they are at increased risk for emotional distress (associated with various factors, including patient depression) and a lower HRQL over all domains tested on the Medical

Outcomes Short Form 36. Clinicians providing long term follow-up care for patients with ALI or ARDS should aim to ensure adequate social and other support for their familial caregivers.

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146

Sepsis, Systemic Inflammatory Response Syndrome, and Multiple Organ Dysfunction Syndrome

Stuart F. Sidlow • Clifford S. Deutschman

The systemic inflammatory response syndrome (SIRS) and multiple organ dysfunction syndrome (MODS) are diseases of medical progress. Prior to advances in critical care medicine that have characterized the past three decades, SIRS and MODS were unknown. However, our ability to treat shock, manage acute renal insufficiency, support patients in pulmonary failure, and even to transplant organs such as the liver has unmasked these new syndromes. Indeed, initial reports on MODS, which, at the time was called *sequential system failure* or *multiple system organ failure,* heralded the ability to rescue patients from such diverse catastrophic events as ruptured abdominal aortic aneurysm, severe trauma, pancreatitis, multiple transfusions, and progressive infections. Attempts to manage MODS have led, in turn, to a host of important biochemical, metabolic, and physiological discoveries.

This chapter defines the clinical findings that constitute sepsis, SIRS, and MODS and places these disorders in context by relating them to a continuum of clinical abnormalities and syndromes. In addition, the natural history of these disorders is reviewed briefly. Several pathogenic hypotheses, management strategies, and intriguing new forms of therapy are examined.

DEFINITIONS, NATURAL HISTORY, AND EPIDEMIOLOGY

The characteristic response to inflammatory stimuli, including surgery and trauma, classically has been referred to as *the stress response* (Fig. 146-1)—the evolutionary importance of which is facilitation of survival and tissue repair. Initially, an orchestrated neural-endocrine-humoral response directs substrate delivery to the most vital organs—the heart and brain. This response is accomplished through

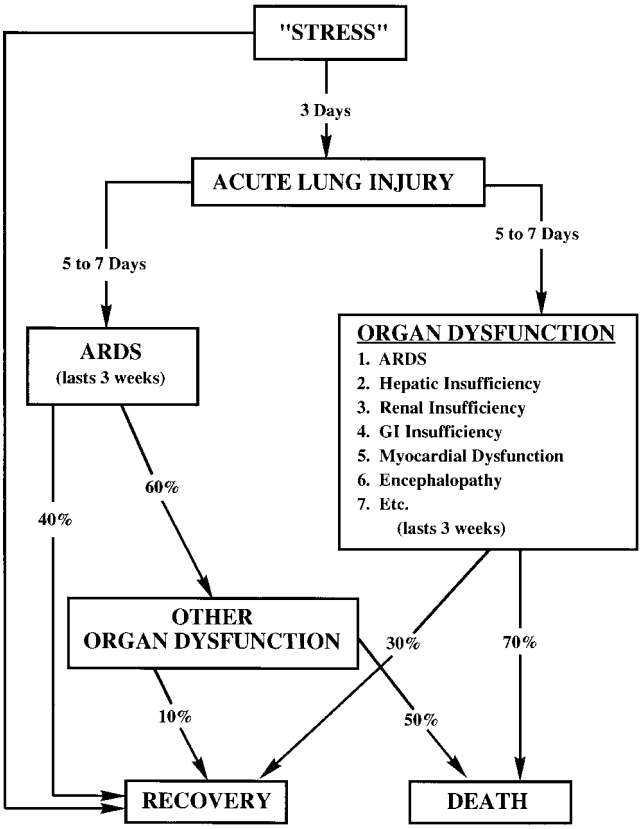

Figure 146-1 Diagrammatic representation of the two classic patterns of MODS pathogenesis. Percentages indicate the proportion of patients following the pathway. Patients develop respiratory insufficiency after an initial insult. In some cases (left side of diagram) this persists for 2 to 3 weeks, and the patients then rapidly develop abnormalities of other organ systems. Over the course of the next week, patients either recover or die. In a second group of patients, multiple-organ dysfunction rapidly follows the onset of respiratory insufficiency. These abnormalities persist for 2 to 3 weeks. Over the next week, patients then either recover or die.

Table 146-1

Diagnostic Criteria

SIRS
Temperature >38°C or <36°C
Heart rate >90 beats/minute
Respiratory rate >20 breaths/min or P_{CO_2} <32 mmHg
WBC $>12\times10^9$/L or $<2\times10^9$/L or >10% immature forms

Sepsis
SIRS + identified or suspected infection

Sever Sepsis
Sepsis + dysfunction of 1 or more organ systems

Septic Shock
Sepsis + hypotension (BP <90 mmHg or a reduction of >40 mmHg from baseline in the absence of other causes) despite adequate fluid resuscitation and perfusion abnormalities (e.g., lactic acidosis, oliguria, altered mental status)

MODS
No current definitions

From Levy MM, Fink MP, Marshall JC, et al: 2001 SCCM/ESICM/ACCP/ATS/SIS International Sepsis Definitions Conference. Crit Care Med *31:1250–1256, 2003.*

vasoconstriction, fluid retention, and translocation of intracellular water to the vasculature. In the absence of exogenous support, death from shock ensues if these endogenous mechanisms are inadequate. Following resuscitation from the initial period of shock, hypermetabolism develops. The driving force behind this second phase is repair of damaged tissue, with white blood cells serving as the primary effectors of the process. To support the increased white blood cell mass, substrate is mobilized from endogenous sources and glucose reserves are rapidly depleted. Because white blood cells are obligate glucose users, muscle (both skeletal and smooth) is broken down to provide precursors for hepatic gluconeogenesis. In addition, amino acids are used to synthesize structural proteins and enzymes. Energy to support the liver, heart, and other organs is derived from fat and amino acids, since utilization of glucose by tissues other than blood cells and neurons is blocked. Generalized capillary recruitment and leak allows glucose delivery to the avascular tissue of the wound. The amount of fluid in the extracellular compartment, particularly in the extravascular matrix, increases dramatically. Continued fluid retention and movement of water out of cells fill the dilated, leaky vasculature. Vasodilatation is accompanied by an increase in cardiac output, which further facilitates delivery of substrate.

By the fourth day after injury or surgery, neovascularization of damaged tissue occurs. Along with a sharp increase in substrate delivery to the tissue of the newly vascularized wound, a decrease occurs in capillary leak accompanied by generalized increases in vascular tone and in the mobilization and excretion of fluid in the matrix. Water also returns to cells. In most cases, the patient recovers uneventfully.

In an unknown percentage of patients, the inflammatory process becomes persistent, progressing to the systemic inflammatory response syndrome, or SIRS. This process is defined by the presence of two or more of the criteria listed in Table 146-1. Because these are normal responses postsurgery or following trauma, these criteria must persist beyond days 3 to 5 for the disorder to be termed SIRS.

Although SIRS is a useful term in comparing studies in the literature, some have challenged the notion that it is a useful diagnostic entity. One alternative approach is the so-called "PIRO" classification system (Table 146-2), which considers **P**redisposition, **I**nfection, **R**esponse, and **O**rgan Dysfunction in evaluating patients in the context of a systemic

Table 146-2

The PIRO system for Staging Sepsis

Domain	Present	Future	Rationale
Predisposition	Premorbid illness with reduced probability of short-term survival. Cultural or religious beliefs, age, sex.	Genetic polymorphisms in components of inflammatory response (e.g., TIR, TNF, IL-1, CD14): enhanced understanding of specific interactions between pathogens and host diseases.	In the present, premorbid factors impact on the potential attributable morbidity and mortality of an acute insult; deleterious consequences of insult heavily dependent on genetic predisposition (future).
Insult infection	Culture and sensitivity of infecting pathogens; detection of disease amenable to source control.	Assay of microbial products (LPS, mannan, bacterial DNA): gene transcript profiles.	Specific therapies directed against inciting insult require demonstration and characterization of that insult.
Response	SIRS, other signs of sepsis, shock, CRP.	Nonspecific markers of activated inflammation (e.g., PCT or IL-6) or impaired host responsiveness (e.g., HLA-DR); specific detection of target of therapy (e.g., protein C, TNF, PAF).	Both mortality risk and potential to respond to therapy vary with nonspecific measures of disease severity (e.g., shock); specific mediator-targeted therapy is predicated on presence and activity of mediator.
Organ dysfunction	Organ dysfunction as number of failing organs or composite score (e.g., MODS, SOFA, LODS, PEMOD, PELOD).	Dynamic measures of cellular response to insult—apoptosis, cytopathic hypoxia, cell stress.	Response to preemptive therapy (e.g., targeting micro-organism or early mediator) not possible if damage already present; therapies targeting the injurious cellular process require that it be present.

TLR, Toll-like receptor; TNF, tumor necrosis factor; IL, interleukin; LPS, lipopolysaccharide; SIRS, systemic inflammatory response syndrome; CRP, C-reactive protein; PCT, procalcitonin; HLA-DR, human leukocyte antigen-DR; PAF, platelet-activating factor; MODS, multiple-organ dysfunction syndrome; SOFA, sepsis-related organ failure assessment; LODS, logistic-organ dysfunction system; PEMOD, pediatric multiple-organ dysfunction; PELOD, pediatric logisticorgan dysfunction.

SOURCE: *Table created using data from Angus et al (2003); Gerlach et al (2003); Vincent, Opal et al (2003); and Vincent, Wendon et al (2003).*

inflammatory response. While not yet widely accepted, this classification system has the potential to address some of the concerns over the SIRS designation.

Whatever one calls the syndrome that develops when inflammation becomes persistent, the clinical entity does exist, often driven by an underlying source, such as a nidus of infection or in undrained hematoma. Such occurrences generally reflect extensive trauma, delayed resuscitation, surgery complicated by extensive, rapid blood loss, or inflammation, as occurs with pancreatitis or aspiration pneumonitis. If a clear source of infection is present, the disorder is classified as sepsis. Further details are summarized in Table 146-3. Although sepsis or SIRS may be complicated by hypotension, lactic acidosis, acute lung injury, or oliguria, obvious organ dysfunction is not present. When organ dysfunction does arise, the syndrome is termed "multiple-organ dysfunction syndrome", or MODS.

STRESS RESPONSE, SIRS, SEPSIS, AND MODS

Virtually all organs become dysfunctional in MODS. However, defining which abnormalities in individual organs constitute dysfunction is problematic. Although many different criteria have been used, none are universally accepted. Indeed, two Consensus Conference Committees of the American College of Chest Physicians (ACCP) and the Society for Critical

Table 146-3

General Criteria for Organ Dysfunction

System	Mild	Severe
Pulmonary	Hypoxia/hypercarbia requiring assisted ventilation for 3–5 d	ARDS requiring PEEP >10 cm H_2O and F_{IO_2} >0.5
Hepatic	Bilirubin 2–3 mg/dl or other LFTs twice normal, PT elevated to twice normal	Jaundice with bilirubin >8–10 mg/dl
Renal	Oliguria (<500 ml/d) or increasing creatinine (2–3 mg/dl)	Dialysis
Gastrointestinal	Intolerance of GI feeding >5 d	Stress ulceration with need for transfusion, acalculous cholecystitis
Hematologic	PTT >125% of normal, platelets <50,000–80,000 per mm^3	DIC
CNS	Confusion	Coma
PNS	Mild sensory neuropathy	Combined motor and sensory deficit
Cardiovascular	Decreased ejection fraction, persistent capillary leak	Hypodynamic state not responsive to pressors

ARDs = acute respiratory distress syndrome; PEEP = positive end-expiratory pressure; LFTs = liver function tests; PT = prothrombin time; PTT = partial thromboplastin time; DIC = disseminated intravascular coagulation; CNS = central nervous system; PNS = peripheral nervous system.
SOURCE: *From Deitch EA: Multiple organ failure: Pathophysiology and potential future therapy.* Ann Surg *216:117–134, 1992.*

Care Medicine (SCCM) declined to recommend the adoption of specific definitions. The basis for this position may reflect the understanding that just as MODS falls along a continuum of abnormalities, so, too, is there spectrum of abnormalities in each organ system. Furthermore, the transition from adaptive response to organ dysfunction may be clinically obscure, and distinctions among sepsis, SIRS, and MODS are often simply semantic.

Some generally used criteria for organ dysfunction in other systems are detailed in Table 146-3. However, these criteria reflect the gaps in our understanding of MODS. More detailed investigations into the pathobiology of MODS should provide more useful diagnostic criteria.

CLINICAL PATTERNS OF SIRS AND MODS

Two well-defined forms of SIRS/MODS are recognized (Fig. 146-1). In either, development of acute lung injury or the acute respiratory distress syndrome (ARDS) is of key importance to the natural history. ARDS is the earliest manifestation in almost all cases.

In the more common form of SIRS/MODS, damage to the lungs predominates and often is the only evidence of organ dysfunction until very late in the disease. This predominantly pulmonary form of MODS is identical to ARDS, which is described in depth elsewhere (see Chapters 144 and 145). However, it is important to point out that the natural history of patients with this type of MODS is well established. Most often, these patients present with an initiating pulmonary affliction (e.g., pneumonia, aspiration, lung contusion, near-drowning, exacerbation of COPD, lung hemorrhage, or pulmonary embolism) that progresses to a condition that meets the diagnostic criteria for ARDS. Ventilator-dependent pulmonary dysfunction, often accompanied by encephalopathy and a mild coagulopathy, persists for some time. At some point, the patient either begins to recover or progresses to develop fulminant dysfunction in other organ systems, most often hepatic, renal, or cardiovascular. A large proportion of patients with multiple organ involvement do not survive. The pulmonary origin of this form of SIRS/MODS is useful diagnostically since the population at risk can often be defined; data indicate a better prognosis in this subgroup.

Diagnosis of the second form of SIRS/MODS is more problematic. Although the earliest manifestation of the syndrome continues to be pulmonary, most often there is an underlying source that is remote from the lung. This group consists of patients who have experienced major trauma (including isolated head injuries, intra-abdominal sepsis,

extensive blood loss, pancreatitis, vascular catastrophes, such as ruptured or dissecting aneurysms, and a host of other conditions). Acute lung injury and ARDS develop early, but dysfunction in other organs soon becomes evident.

Most studies have found the liver to be the next most commonly involved organ. Indeed, if one considers bleeding associated with an elevated prothrombin time to reflect a hepatic abnormality, the liver may well become dysfunctional even in cases classified as primary pulmonary MODS. Gastrointestinal, cardiovascular, and renal dysfunction are cited equally as the next most common signs of organs failure.

Compensated organ dysfunction persists for some time before the patient either recovers or deteriorates further and dies. The diversity of the population at risk makes early diagnosis of the second form of SIRS/MODS difficult. Furthermore, since many of these patients have undergone surgical procedures, development of mild hypoxemia and increased lung water—normal findings after surgery—may obscure early recognition of ARDS. Thus, SIRS/MODS may not be appreciated until dysfunction in several organ systems has become well established.

Improvements in our ability to support patients with MODS have led to recognition of a third syndrome—referred to (for lack of a better term) as "chronic critical illness." At some point, critically ill patients may become quite stable (i.e., unchanging), but their physiology remains remarkably abnormal. Typically, they require exogenous support of major organ systems. A "hyperimmune" state gives way to one of immunosuppression. Most hormonal systems cease to work properly either because of resistance to hormonal effects or to depletion of hormonal synthesis and storage. These abnormalities reflect a state of endocrine "burn-out" that currently has no specific treatment.

EPIDEMIOLOGY

Accurate determination of the incidence of SIRS/MODS is difficult, predominantly a reflection of the diverse etiologies of the syndromes. The incidence of primary pulmonary SIRS/MODS (i.e., ARDS) is estimated to be in excess of 150,000 cases per year. With regard to the second form of SIRS/MODS, the estimated number of cases in the United States is 750,000 per year. The incidence of MODS following trauma that necessitates admission to the ICU may be as high as 14 percent.

Mortality from MODS remains distressingly high. Estimated mortality from ARDS per se is approximately 35 to 40 percent. Involvement of additional organ systems increases the likelihood of a poor outcome; the presence of dysfunction in three or more organ systems virtually ensures death. Some investigators have reported lower mortality rates; others have shown that mortality is a function of the duration of organ failure. The incidence and mortality of MODS may be increasing. Although there is a lack of consensus in this regard, clearly, once the disease has progressed to the point of multi-organ failure, the patient is at substantial risk for death.

PATHOPHYSIOLOGY

The major factor limiting treatment of MODS is the lack of a clear understanding of the underlying pathophysiological defect. In fact, if not viewed carefully, the changes associated with SIRS/MODS may simply resemble an extension of those observed after uncomplicated stress. Thus, patients recovering from major surgery undergo increases in metabolic rate, oxygen consumption, and carbon dioxide production. Relative glucose intolerance and hyperglycemia also occur. The vasculature is dilated, and the cardiac output increases to promote oxygen transport. In fact, lactate production may increase, reflecting the overall increase in metabolism rather than tissue hypoxia.

Although simple stress and SIRS/MODS have in common altered intermediary metabolism, a hyperdynamic circulation, and systemic signs of inflammation, two important distinctions have been consistently observed. First, noted previously, they differ in time course. Whereas postoperative hypermetabolism runs its course over 5 to 7 days and resolves with neovascularization, the time course of SIRS/MODS is longer, usually 3 to 4 weeks. The second distinction consists of subtle differences in metabolic and physiological parameters. In simple stress and early SIRS, the increase in metabolic demand can be met by an increase in oxygen supply or in oxygen extraction. However, as the disease progresses toward MODS, the ability to extract, and possibly, utilize, oxygen is lost in some tissue beds. This situation is unstable, because oxygen demand on the cellular level is increased. Similarly, in simple stress there appears to be a block in peripheral glucose utilization.

Glucose intolerance becomes more pronounced in SIRS/MODS, possibly because of a defect in the enzyme pyruvate dehydrogenase, which catalyzes conversion of pyruvate to acetyl coenzyme A (acetyl CoA). As a result, increases in tissue metabolic demand cause an increase in the activity of the Krebs cycle and in the generation of lactate (aerobic glycolysis). Consequently, serum lactate increases in direct proportion to the increase in pyruvate. If a microcirculatory perfusion deficit develops, increases in lactate exceed increases in pyruvate. These changes in glucose metabolism become progressively less responsive to modulation by insulin. Ultimately, futile cycling occurs of alanine and lactate between the liver and periphery.

The onset of hepatic dysfunction is heralded by increments in serum lactate that are disproportionate to the increments in pyruvate. Fat metabolism is markedly altered as well. Stress is characterized by levels of ketosis that are disproportionately low for the degree of starvation. It also elicits an increase in hepatic gluconeogenesis, which, in turn, causes hyperinsulinemia.

Stress is associated with lipolysis, decreased lipogenesis, and increased oxidation of long- and medium-chain triglycerides. In early SIRS/MODS, lipogenesis undergoes further decrease. However, oxidation of long-chain triglycerides by the liver also decreases, in association with a decrease in expression of key beta-oxidative enzymes. Ultimately, fat intolerance arises as the liver continues to fail.

In the setting of SIRS/MODS, with significant abnormalities of both glycolysis and beta-oxidation, amino acids become an important source of fuel. As oxidation of amino acids increases, so does urea production. Exogenous protein can be an important energy source, but ultimately, hepatic failure compromises ureagenesis and limits this energy source, as well.

On the physiological level, vasodilatation and peripheral edema become more pronounced. Cardiac output increases as afterload decreases, but ultimately, the heart also fails as energy sources are depleted. Renal mechanisms are then called upon to conserve fluid and to excrete urea. The generalized edema limits the ability to concentrate the urine maximally, thereby leading to two incompatible goals. As a result, the renal system also becomes dysfunctional. One additional hallmark of progressive SIRS/MODS is a loss of the normal hormonal modulation of cellular processes. Thus, insulin-mediated glucose uptake decreases and blood pressure becomes unresponsive to all but the most potent vasopressors, while a glucagon-induced alteration in gluconeogenesis disappears. The mechanisms by which these changes occur are unknown.

A large number of hypotheses have been advanced to explain the pathophysiology of SIRS/MODS. From these have emerged two general concepts concerning etiology. In one, the predominant effect is in the microcirculation: along with an overall decrease in peripheral vascular tone, demand and supply at the microcirculatory level are mismatched, resulting in misdistribution of flow. In the second, the defect is predominantly one of cellular and, indeed, mitochondrial, metabolism. All hypotheses invoke a process that "activates" an inflammatory cascade that "mediates" end-organ responses. In time, these responses become dysfunctional. It is generally accepted that dysfunction in some way results from an inability to meet metabolic demands because of either inadequate flow or direct metabolic block.

HYPOTHESES OF UNDERLYING MECHANISMS

A number of hypotheses have been advanced regarding the underlying basis of SIRS/MODS.

Cytokine Hypothesis

Cytokines are mediators produced and secreted by a number of cells, most notably inflammatory and endothelial cells. These mediators bind to receptors on the cell membrane and initiate intracellular events that alter cell behavior. The cell whose behavior is altered may be the same cell that produces the cytokine (autocrine), a nearby cell (paracrine), or a distant cell (endocrine). Cytokines activate a number of intracellular signal transduction pathways. The ultimate effect may be direct (e.g., activation of membrane channel or an intracellular protein) or may result in stimulation of gene expression. Cytokines that have been implicated in SIRS/MODS include tumor necrosis factor-α (TNF-α), interleukin-1 (IL-1), IL-6, and interferon-γ (INF-γ).

Following simple stress, TNF-α or IL-1 are produced by inflammatory cells drawn to the site of injury or inflammation and by local endothelial cells. These cytokines are then released into the circulation and affect distant organs. The behavior of TNF-α on the liver serves as a useful paradigm.

A 26-kD form of TNF-α is produced by local cells and is expressed on the cell surface. This form of TNF-α is, through unknown mechanisms, active in control of debridement and infection at the local level. Ultimately, however, 26-kD TNF-α is cleaved by a matrix metalloproteinase to a 17-kD circulating form. The blood carries the 17-kD form from remote organs. The 17-kD form is capable of not only producing vasodilatation (perhaps, via a nitric oxide-linked pathway), but also of stimulating other inflammatory and noninflammatory cells. For example, in the liver, TNF-α stimulates resident macrophages (Kupffer cells) to produce more TNF-α, as well as other cytokines, such as IL-1 and especially IL-6. TNF-α, IL-1, and IL-6 then induce hepatocytes to express the genes for a number of proteins called acute-phase reactants. These secreted proteins have diverse activities that help control the inflammatory response. Since low levels of TNF-α (and IL-1) are released from the initial site of inflammation, the process should be self-limited.

In the cytokine theory of MODS, over-production of TNF-α, IL-1, or IL-6 and resultant uncontrolled inflammation are postulated. The net result is prolonged, uncontrollable vasodilatation and damage to viable organs by activated macrophages and other inflammatory cells.

In support of this theory, high levels of circulating TNF-α, IL-1, IL-6, and INF-γ have been found in fulminant septic shock (e.g., as in disseminated meningococcemia). Similarly, in animal models in which endotoxin is administered intravenously, serum levels of TNF-α and IL-1 are increased. Studies in animals and human volunteers indicate that TNF-α is probably the most proximal mediator, initiating the expression and release of the other cytokines. TNF-α is cytotoxic to a number of cells, initiating programmed cell death (apoptosis) in culture. Antibodies to TNF-α are protective in lethal endotoxemic and bacteremic animal models, while certain intracellular proteins can block TNF-α–induced apoptosis. Finally, administration of TNF-α to animals results in a syndrome that mimics septic shock, whereas giving low doses of this cytokine to humans mimics certain metabolic aspects of SIRS. Substantial data indicate, however, that this view of SIRS/MODS is simplistic.

In animal models of bacterial peritonitis, neutralizing TNF-α in the serum increases mortality. Reported levels of cytokines in the blood of septic patients vary considerably among studies. Also, clinical trials of anti-TNF-α in human SIRS have been disappointing. Recent data indicate that serum levels do not reflect tissue levels, and that the cell-associated, 26-kD form (and not the 17-kD circulating form) of TNF-α mediates organ injury. Evidence from studies of IL-6 knockout mice indicates that this cytokine is an important component of hepatic regeneration; therefore, it may be protective, rather than injurious. Since a host of other mediators and pathways are activated in SIRS, a reasonable conclusion is that cytokines are important mediators of certain aspects of SIRS/MODS, but that other factors are at work.

Microcirculatory Hypothesis

The common link in the microcirculatory hypothesis is that the failure of cells or organs to receive adequate levels of oxygen or some important nutrient or substrate triggers SIRS/MODS. Low blood flow, as is likely to occur in hypotension or shock, contributes to cellular dysfunction. However, the release of vasoactive mediators and vascular congestion secondary to microthrombi and leukocytes are also held to be important.

Reperfusion of ischemic tissue may be as important a determinant of tissue injury as decreased flow itself. In particular, the generation of oxygen free radicals and peroxidation of membrane lipids following reperfusion may contribute to tissue injury. Sources of free radicals include the conversion of molecular oxygen to superoxide by xanthene oxidase, activated leukocytes, mitochondria, and prostaglandin synthase. The first two sources are probably the most important.

Circulatory shock, microvascular compromise, and free radical generation are likely to affect the endothelium directly. Endothelial cells are active in free radical formation, provide a point of attachment for leukocytes, and may be exquisitely sensitive to hypoxia. Furthermore, they not only produce, but are also affected by, vasoactive mediators. These interactions provide the link between the cytokine and microvascular hypotheses.

Cytokines activate endothelial cells to elaborate other vasoactive substances and to express surface proteins that promote leukocyte adhesion; endothelial cells are also important participants in the formation of microthrombi. In support of the microvascular hypothesis, circulatory shock often occurs before MODS; autopsy data indicate the presence of microvascular injury in patients with MODS; and microthrombi containing platelets, neutrophils, and fibrin are common in MODS. Antibodies to CD18, which block leukocyte adhesion, do occur in circulatory shock and are protective in some forms of ischemia-reperfusion injury; they are not protective against liver injury or leukocyte adherence in experimental sepsis. The microthrombi, microvascular constriction, and free radicals are valuable in limiting the spread of infection.

Gut Hypothesis

The syndrome that is now designated as SIRS once was believed to be the result of uncontrolled infection, presumably due to the endotoxin released by gram-negative bacteria. However, organisms other than gram-negative bacteria have been implicated, and in many patients, neither microorganisms nor a source of bacteria can be identified.

The gut hypothesis contends that inflammation is due, in part, to bacteria in the gastrointestinal tract (or their associated endotoxin) that translocate to the mesenteric lymph nodes, liver, and circulation. Various insults have been shown to lead to such translocation of bacteria or endotoxin, and the intestinal barrier is disrupted in many clinical situations that can precede MODS. As a rule, translocation involves a combination of insults, including an alteration in the indigenous gastrointestinal flora, that results in bacterial overgrowth, impaired host defenses, and physical disruption of the intestinal barrier.

The gut hypothesis overlaps the cytokine and microcirculatory hypotheses. Bacteria or endotoxin activates white blood cells and induces production of cytokines. Each can alter the behavior of both endothelial cells and the coagulation system, leading to microvascular aggregation and production of free radicals, which can, in turn, create a self-sustaining cycle that culminates in MODS. Exposure to intestinal flora activates hepatic macrophages (Kupffer cells), releases cytokines, and damages hepatic cells, reinforcing the hypothesis that translocated bacteria are important in the pathogenesis of SIRS/MODS.

"Two-Hit" Hypothesis

A second insult, subsequent to an initial "hit," may be of major importance in the pathogenesis of SIRS/MODS. According to this hypothesis, an initial period of hypotension "primes" the trauma patient for SIRS/MODS (i.e., the initial insult activates other processes that amplify the effects of the initial event, however mild).

Priming could involve activation of white blood cells or platelets, disruption of the intestinal mucosal barrier, or the induction of free radicals and the enzymes (such as xanthene oxidase) that produce these reactive species. Although this hypothesis overlaps with others, such as the cytokine, microcirculatory, and gut hypotheses, animal studies in which a single insult is followed by a second, more severe insult have shown that the first "hit" is actually protective.

Connectionist Hypothesis

By viewing biologic systems as composed of oscillators, with the oscillations reflecting a continuously changing series of external events, we can regard the loss of either the external stimuli or the ability to respond to these stimuli as pathological. On the basis of this approach, and with the application of nonlinear modeling, the transition from SIRS to MODS has been depicted as an erosion in the ability of different organs to

communicate with each other. For example, in experimental sepsis, hepatocellular metabolic pathways, such as glucogenesis, respond inadequately to hormonal stimulation. Similarly, beat-to-beat cardiac variability in human volunteers is lost during experimental endotoxemia. The connectionist hypothesis supplements, rather than substitutes for, the hypotheses presented above.

Other Hypotheses

Other hypotheses are being explored. For example, one possibility under investigation is that the seemingly diffuse abnormalities in SIRS and MODS may be related to deficits in hepatic metabolism. Consistent with this hypothesis is the observation that gluconeogenesis, beta-oxidation, and ureagenesis are impaired in septic animals. These alterations are due, in part, to a decrease in the transcription of genes coding for key enzymes in each pathway. Furthermore, when important transcription factors are examined, a potential link between pulmonary and hepatic dysfunction becomes clear.

Similarly, another theory holds that dysfunction at the mitochondrial level may be responsible for the improper response in MODS—specifically, inadequate oxygen utilization by cells may be operative. This mechanism, coupled with inadequate oxygen delivery (as described in the microcirculatory hypothesis) results in a mismatch between oxygen demand or supply and oxygen utilization. Recent studies reveal a defect in cytochrome oxidase, the terminal complex in the electron transport chain, in septic myocardium.

Regardless of which is the dominant "cause" or "effect" of SIRS or sepsis, the net result is that dysfunction of multiple systems results in physiological detriment to the patient and threatens survival.

MANAGEMENT

Management of patients with SIRS/MODS is challenging and focuses on treatment of major end-organ damage.

Pulmonary Dysfunction

Pulmonary dysfunction most often takes the form of secondary ARDS. This topic is covered in depth in Chapter 145.

Source Control

The key to prevention and elimination of SIRS/MODS is source control. The clinician must exhaustively search for and eliminate the nidus of inflammation, whether it is a hematoma, abscess, wound infection, or sinusitis. This is critical to reversing the process. While conducting the search for the offending source or microorganism, empiric use of broad-spectrum antibiotics is advised; subsequently, the regimen is tailored based on culture and sensitivity reports from the microbiology laboratory.

Perfusion Management

In the face of inflammation, perfusion should be optimized. It is nearly impossible to restore the body to pre-insult hemodynamic status until the inflammatory response has run its course. Supportive care is key. That inadequate tissue perfusion potentiates SIRS and may catalyze progression to MODS should be recognized. This is especially true for the kidneys, which are sensitive to hypoperfusion, even in the absence of underlying renal pathology. Moreover, hypoperfusion of the kidneys activates the renin-angiotensin-aldosterone system. Since angiotensin II is the major determinant of portal perfusion of the liver, and since hepatic dysfunction figures prominently in MODS, disturbances in the renin-angiotensin-aldosterone system may contribute to disturbance in hepatic function. Disturbances in ventilation-perfusion relationships secondary to pulmonary hypoperfusion may contribute to arterial hypoxemia.

Fluids should be administered liberally in SIRS/MODS. Determination of the appropriate volume of fluid to administer is problematic, however, largely because end-organ function, the best index of adequate perfusion, is already impaired. One practical rule of thumb is to achieve a stroke volume of approximately 1 ml/kg of body weight. If the administration of fluid does not increase stroke volume, cardiac dysfunction is probably present and administration of additional fluid is not likely to be helpful.

Rational Use of Inotropes and Vasopressors

Animal and human studies indicate that SIRS/MODS renders the cardiovascular system relatively resistant to the effects of native and synthetic catecholamines. Therefore, powerful agents are required to achieve any hemodynamic effect. Also, the vasodilatation may represent a compensatory response to a metabolic defect; hence, induced vasoconstriction may worsen this defect.

One practical expedient is to treat hypotension when evidence of myocardial ischemia develops, usually at a diastolic pressure of about 40 mmHg. Norepinephrine is the drug of choice. This agent constricts somatic (muscle) beds, but it appears to spare the splanchnic circulation, thereby transferring fluid from the periphery to the central, visceral compartment. As a second-line therapy to increase visceral tone once maximum effect using norepinephrine has been achieved, a low, nontitrated dose of vasopressin at 0.01 to 0.04 units/h may be added. Endogenous vasopressin release is diminished in sepsis, suggesting a role for vasopressin "replacement," rather than "therapy." Dopamine, which had long been a preferred agent in sepsis, is no longer advocated, since it is a nonspecific agonist and may cause maldistribution of flow. Dopamine has been demonstrated to be detrimental to renal function. If cardiac output remains low despite adequate fluid resuscitation and vasopressor therapy, an inotrope,

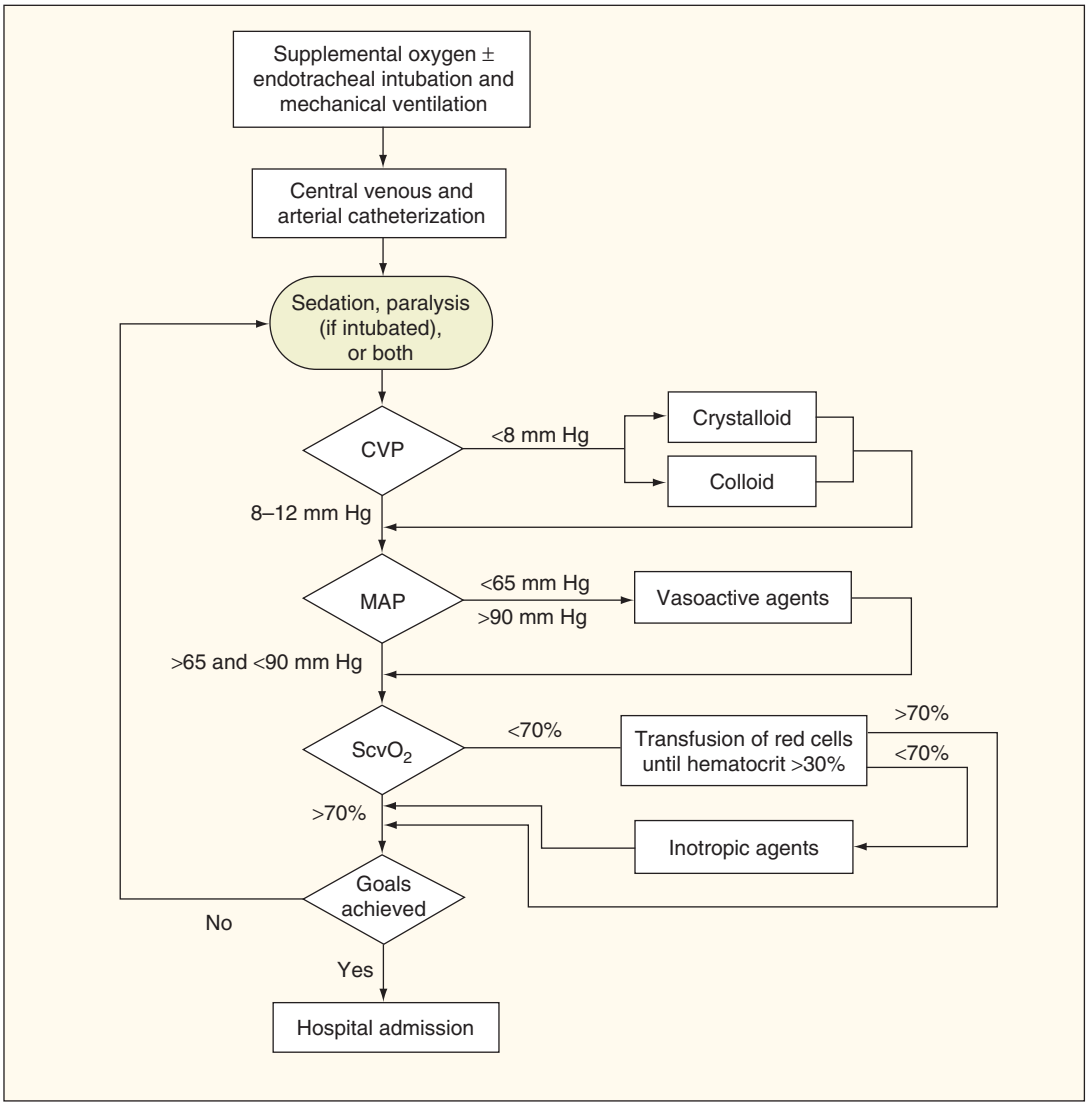

Figure 146-2 Goal-directed therapy for septic shock. *(From* Clinical Practice Guidelines, *Hospital of the University of Pennsylvania.)*
Resuscitation in Septic Shock: Hemodynamic Considerations in Goal-Directed Therapy
Resuscitation should continue with predetermined end points:

1. Target mean arterial pressure (MAP) of 65 mmHg
2. Urinary output of >0.5 ml/kg/h
3. Central venous pressure (CVP) of 12–15 mmHg
4. Stroke volume (SV) of 0.7–1.0 ml/kg

If early aggressive fluid resuscitation does not restore MAP within 30 min (refractory shock), add norepinephrine.

If norepinephrine dose exceeds 10 μg/min, add nontitrated dose of vasopressin at 0.04 μg/min.

If patient remains hyperdynamic with impaired myocardial contractility, add inotrope with goal SV of 0.7–1.0 ml/kg. Dobutamine is first line, followed by epinephrine. Impaired myocardial contractility is defined as decreased ejection fraction (EF), ventricular dilation, impaired contractile response to volume loading, or low peak systolic/end-systolic volume ratio.

End points for assessing resuscitation are arterial blood pressure, heart rate, urinary output, and skin perfusion.
From Clinical Practice Guidelines, *Hospital of the University of Pennsylvania, Philadephia, PA.*

such as dobutamine, may be added to increase cardiac contractility.

Recent studies emphasize *goal-directed therapy* in the management of sepsis (Fig. 146-2). This includes promptly achieving a mean arterial pressure (MAP) greater than 65 mmHg, a central venous pressure (CVP) of 8 to 12 mmHg, a venous oxygen saturation (Sv_{O_2}) greater than 70 percent, a hemoglobin concentration greater than 10 g/dl, and a lactate concentration less than 4.0 mm. After initial resuscitation, unless there is active cardiac disease, acute hemorrhage, or continuing lactic acidosis, a hemoglobin concentration of 7 g/dl is acceptable.

Metabolic Management

As SIRS progresses to MODS, the intrinsic metabolic defect associated with the disorder worsens. Although glucose intolerance is apparent very early in the course of the disease, progressive hyperglycemia may develop. Additionally, there is progressive azotemia as amino acids are deaminated and carbon skeletons enter the Krebs cycle. Ultimately, hepatic dysfunction becomes so severe that even this process becomes impaired. The intrinsic defect appears to be a decrease in the transcription of genes encoding certain key enzymes in metabolic pathways. Although compensation can occur early in the course, ultimately this fails.

To meet caloric needs, most clinicians rely on a formula that is relatively hypocaloric and protein-rich. The resultant increase in blood urea nitrogen is generally well tolerated in adequately hydrated patients. This contrasts with the results of overfeeding with fat or glucose. However, if the increase in blood urea nitrogen is a manifestation of uremia, rather than an isolated consequence of protein overfeeding, dialysis may become necessary.

We believe that administration of exogenous insulin should be avoided early in SIRS/MODS. Most often, the need is precipitated by use of fluids that contain exogenous glucose. Employment of tight glycemic control is controversial in sepsis, although it has been shown to be effective overall in critically ill patients. These studies show an improvement primarily in patients in the ICU for more than 5 days. Thus, it is our belief that "insulin resistance" represents one additional manifestation of "endocrine burn out" in chronic critical illness.

In the acute phase of critical illness, insulin may lower serum glucose levels, but it does so by driving glucose into fat cells. Insulin does not increase glucose oxidation in any tissue. Moreover, even though insulin may block catabolism of skeletal muscle, it does not have this effect on smooth muscle. Therefore, vascular and gastrointestinal smooth muscle may be mobilized, worsening the defects in these organ systems.

Use of corticosteroids in sepsis is another controversial topic. Patients requiring high doses of vasopressors may have a component of adrenal insufficiency. However, the criteria for defining adrenal insufficiency in critically ill patients are difficult to define. If normal diagnostic criteria are met (low baseline cortisol or failure to increase serum levels 30 to 60 minutes following administration of adrenocorticotropic hormone [ACTH] or an ACTH analogue), corticosteroid administration is reasonable. Adrenal insufficiency, too, may be a manifestation of endocrine burnout in chronic critical illness.

Novel Medications

Recent studies have evaluated the use of recombinant human Activated Protein C (rhAPC) in patients who are in severe sepsis or MODS. The rationale for use is that the inflammatory response results in a procoagulant state. By reversing this response, patients may have a greater survival rate. Indeed, in carefully selected subgroups (those who are less severely ill, with Acute Physiology, Age, and Chronic Health Evaluation (APACHE) scores under 25), administration of rhAPC modestly increases survival. Furthermore, low-risk patients do not benefit.

The specifics of renal replacement therapy are beyond the scope of this chapter. However, in acute renal failure from MODS, the replacement of choice is early continuous venovenous hemodialysis (CVVHD). Hemodynamic stability is greater with CVVHD than with intermittent hemodialysis. In addition, animal studies have demonstrated a shortened course of sepsis using hemodiafiltration. Unfortunately, these results have not been confirmed in human studies.

CONCLUSION

SIRS/MODS represent a major cause of mortality and morbidity. The nature of the underlying pathological defect is unknown. Current treatment is supportive and centers on assurance of adequate ventilation and oxygenation, appropriate fluid resuscitation, metabolic support, an intensive search for an excisable or drainable inflammatory site, and avoidance of secondary organ injury.

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Acute Respiratory Failure in the Surgical Patient

Robert M. Kotloff

Advances in surgical technique, anesthesia and analgesia, and postoperative supportive care have facilitated application of sophisticated surgical procedures to an expanding spectrum of patients. Emboldened by diminished operative mortality rates, clinicians are increasingly willing to subject older and sicker patients to rigorous, but potentially life-saving, surgical interventions. In most instances, the success or failure of the surgery is defined not in the operating room, but postoperatively, when the adverse effects of surgery may first become apparent and when intercurrent complications may jeopardize the patient's well-being.

The respiratory system is particularly vulnerable to the effects of general anesthesia and surgery, and postoperative respiratory impairment is common. While generally mild and well-tolerated in otherwise healthy, young patients, postoperative respiratory compromise may have serious consequences in the elderly and in patients with preexisting lung disease. Potentially devastating postoperative complications, such as pneumonia, aspiration, and acute respiratory distress syndrome (ARDS) may lead to respiratory failure independent of the patient's presurgical status. Overall, pulmonary complications account for approximately 25 percent of postoperative deaths. This figure is, in fact, conservative, since many patients with respiratory failure can be supported on mechanical ventilation, only to die of other nonrespiratory complications (e.g., sepsis, gastrointestinal bleeding, and multi-organ failure). In addition to their effect on mortality, respiratory complications exact a toll in lengthening ICU and hospital stay, delaying convalescence, and escalating the cost of care. Therefore, clinicians who provide preoperative evaluation and postoperative care must be familiar with the factors that predispose to pulmonary impairment in the surgical patient. Many of these concepts are considered in Chapter 38. This chapter focuses on the most serious of the perioperative respiratory complications—acute respiratory failure.

IDENTIFICATION OF THE HIGH-RISK PATIENT

In a review of over 7000 patients undergoing various gastrointestinal, urological, gynecological, and orthopedic procedures, respiratory failure requiring mechanical ventilation beyond 24 h occurred in only 0.8 percent. Among 81,719 patients undergoing both elective and emergency noncardiac procedures in hospitals belonging to the Veterans Affairs (VA) health system, respiratory failure (defined as mechanical ventilation beyond 48 h after surgery or need for reintubation) occurred in 3.4 percent. Though the overall risk of respiratory failure in these studies is relatively low, it is clear that risk varies markedly, depending on a number of factors related to the procedure and the patient. While risk of postoperative respiratory failure is negligible in the young, healthy nonsmoker undergoing elective knee surgery, it is significant in the elderly patient with underlying chronic obstructive pulmonary disease (COPD) undergoing emergent repair of a thoracoabdominal aortic aneurysm. Factors that have been most thoroughly studied in association with postoperative respiratory failure are discussed in greater detail below.

Type of Operative Procedure

Procedures that involve the upper abdomen or thorax are associated with the highest rates of postoperative pulmonary complications, including respiratory failure (Table 147-1). In large part, the risk is attributable to the profound derangement in pulmonary mechanics that accompanies these procedures (see below). Thoracoabdominal aneurysm repair carries the greatest risk of postoperative respiratory failure.

Table 147-1

Incidence of Respiratory Failure Following Various Surgical Procedures

Procedure	Incidence of Postoperative Respiratory Failure
TAAA repair	8–33%
AAA repair	5–24%
Lung resection	4–15%
CABG	5–8%
All types*	0.8%

TAAA = thoracoabdominal aortic aneurysm; AAA = abdominal aortic aneurysm; CABG-coronary artery bypass grafting.
**Refers to general survey of gastrointestinal, urological, gynecological, and orthopedic procedures.*

Given the need for both abdominal and thoracic incisions, as well as division of the diaphragm and costal margin, this observation is not surprising. Other procedures with significant risk include abdominal aortic aneurysm repair, upper gastrointestinal surgery, thoracotomy, and open heart surgery. Lower abdominal procedures carry a much smaller risk than those involving the upper abdomen; procedures involving the extremities carry a negligible risk.

In some cases, the surgical approach can be modified to lessen the risk of postoperative pulmonary complications in patients who are marginal operative candidates because of advanced age or co-morbid conditions. For example, use of a transverse abdominal incision appears to carry less risk than a vertical midline incision. Cholecystectomy performed by laparoscopic technique is associated with a lower incidence of pulmonary complications compared with the conventional open approach. For thoracic procedures, median sternotomy and muscle-sparing lateral thoracotomy are better tolerated than posterolateral thoracotomy. However, these approaches provide more limited access to the thorax than does the standard thoracotomy incision, and they are generally inadequate for resection of the left lower lobe or for tumors involving the posterior chest wall, diaphragm, or superior sulcus. Additionally, removal of bulky tumors via the muscle-sparing approach may be problematic. Video-assisted thoracoscopic surgery (VATS) also appears to be a less morbid thoracic procedure (Chapter 37). Studies suggest that VATS results in reduced postoperative pain and hospital length of stay compared with thoracotomy and may cause less early impairment in lung function. Whether this procedure carries a diminished risk of postoperative pulmonary complications has not been definitively established.

Chronic Obstructive Pulmonary Disease

In the previously noted study of over 80,000 patients undergoing noncardiac surgery in VA hospitals, multivariate analysis revealed that a history of COPD was an independent risk factor for postoperative respiratory failure. Overall, the risk of respiratory failure associated with COPD (odds ratio of 1.8) was considerably lower than that associated with the type of surgery (odds ratio of 14.3 for abdominal aortic aneurysm repair and 8.1 for thoracic surgery). Notably, preoperative pulmonary function parameters were not examined in this study, precluding assessment of the relationship between severity of COPD and risk of postoperative respiratory failure.

Studies focusing on outcomes following specific, high-risk procedures shed additional light on the risks posed by COPD. The incidence of respiratory failure following thoracotomy and lobectomy or pneumonectomy exceeds 50 percent for patients with COPD and a predicted postresection forced expiratory volume in 1 sec (FEV_1) less than 40 percent of normal, but it is minimal for those with more adequate pulmonary reserve. Within the subset of patients with a predicted postresection FEV_1 less than 40 percent, those who maintain an acceptable functional status (as indicated by peak oxygen consumption of greater than or equal to 10 to

15 ml/kg/min on cardiopulmonary exercise testing) appear to have a low risk of respiratory failure following definitive lung resection procedures. The use of VATS in combination with less extensive resection of lung tissue (e.g., wedge resection or segmentectomy) appears to be well tolerated by patients with severe lung disease, with only a 4 percent incidence of respiratory failure and a 1 percent mortality rate documented in one recent study of 100 patients with an FEV_1 less than 35 percent predicted.

Studies of the risk posed by COPD among patients undergoing thoracoabdominal aortic aneurysm repair have yielded conflicting results. In one prospective study of over 1400 patients, COPD was found to be an independent risk factor for respiratory failure, defined as the need for mechanical ventilation in excess of 48 h. Respiratory failure developed in 53 percent of patients with COPD and in only 23 percent of patients without this disorder. The risk of respiratory failure correlated linearly with preoperative spirometry, precluding identification of a particular set of "threshold" values. In contrast, two other studies of thoracoabdominal aneurysm surgery employing similar statistical methods did not identify COPD as a significant predictor of postoperative respiratory failure.

The impact of COPD on outcome following coronary artery bypass grafting (CABG) has also been examined. In one study, patients with a history of COPD had higher rates of mechanical ventilation exceeding 48 h (18.9 percent vs. 3.7 percent) and reintubation (13.5 percent versus 3.7 percent) compared with age-matched controls. In a recent study of over 8000 consecutive patients undergoing CABG, the incidence of postoperative respiratory failure was 5.6 percent. Among preoperative characteristics, COPD was identified as a risk factor for respiratory failure, with an odds ratio (OR) of 1.9. This was, nonetheless, considerably less than the risk posed by such factors as renal insufficiency (OR 3.9), congestive heart failure on admission (OR 4.1), and emergency (rather than elective) surgery (OR 5.8).

Following major abdominal vascular surgery, including abdominal aortic aneurysm repair and aortobifemoral bypass grafting, approximately 25 percent of patients require ventilatory support for more than 24 h. While an extensive smoking history and low preoperative Pao_2 are predictive of the need for prolonged postoperative ventilatory support, the severity of COPD, as defined by preoperative spirometry, is not. Indeed, no prospective evaluation of patients undergoing abdominal surgery of any type has shown that pulmonary function studies can reliably identify patients at increased risk of serious postoperative pulmonary complications.

What conclusions can be drawn from this complex and conflicting body of literature? Clearly, the presence of severe COPD with a predicted postoperative FEV_1 of less than 30 to 40 percent in association with poor functional status should be viewed as an absolute contraindication to thoracotomy and extensive lung resection (lobectomy or pneumonectomy). COPD appears to increase the risk of respiratory failure to a far lesser degree following other types of surgical procedures. Acknowledging current uncertainties about the full contribution of COPD to postoperative risk in these settings, the presence of significant lung disease should prompt a careful analysis of the necessity of the surgery planned. However, it should not preclude surgery deemed likely to extend patient survival or to markedly improve quality of life.

Patients with COPD scheduled for surgery should undergo a preparatory pulmonary regimen intended to optimize lung function and minimize airway secretions. This regimen should include smoking cessation, institution or intensification of inhaled bronchodilator therapy, and use of oral antibiotics in the presence of purulent secretions or a "loose" cough. Patients should be instructed on the use of incentive spirometry or cough and deep breathing techniques prior to surgery. A short course of oral corticosteroids should be considered in patients who have a significant bronchospastic component to their disease. Such a preparatory regimen is simple and inexpensive and has been shown to have a favorable impact on the incidence of postoperative pulmonary complications. Other than the assurance of strict compliance with the regimen, there is no reason to believe that hospitalization is superior to outpatient preparation of the patient.

Smoking

Smoking has been shown to be a risk factor for postoperative pulmonary complications in general and for prolonged ventilatory support in particular. Smoking does not appear simply to be a surrogate marker of COPD; rather it poses risk that is independent of the magnitude of pulmonary impairment. Detrimental effects of smoking include bronchial irritation with resultant excessive airway secretions, impairment in mucociliary clearance, and elevation of carboxyhemoglobin levels with consequent impairment in oxygen uptake and tissue oxygen utilization. While preoperative smoking cessation has been shown to diminish the risk of postoperative pulmonary complications, a minimum of 8 wk of abstinence is required to achieve this risk reduction (see Chapter 38 for additional details).

Predicting Risk of Respiratory Failure

Recently, a multifactorial risk index for predicting postoperative respiratory failure was published. The model was derived from analysis of the VA population of over 80,000 patients undergoing noncardiac surgery and was validated in a second VA population of nearly 100,000 patients. Preoperative variables independently predictive of an increased risk of postoperative respiratory failure (mechanical ventilation for greater than 48 h or reintubation) were identified by multivariate analysis, and each variable was assigned a point value reflecting the relative risk that it posed (Table 147-2). Based upon the total number of points, patients were assigned to one of five risk classes that predict the overall probability of respiratory failure (Table 147-3). The model performed well when validated in the second cohort of patients. However, as it was derived from a population of male patients cared for at VA facilities and did not include cardiac procedures, its applicability to

Table 147-2

Respiratory Failure Risk Index

Preoperative Predictor	Point Value
Type of surgery	
Abdominal aortic aneurysm	27
Thoracic	21
Neurosurgical, upper abdominal, peripheral vascular	14
Neck	11
Emergency surgery	11
Albumin (<30 g/L)	9
Blood urea nitrogen (>30 mg/dL)	8
Partially or fully dependent functional status	7
History of COPD	6
Age (years)	
≥70	6
60–69	4

Source: Adapted from Arozullah MA, et al: Multifactorial risk index for predicting, postoperative respiratory failure in men after major noncardiac surgery. Ann Surg *22:242–253, 2000.*

Table 147-3

Respiratory Failure Index Scores and Predicted Probability of Postoperative Respiratory Failure

Class	Point Total	Predicted Probability of PRF
1	≤10	0.5%
2	11–19	2.2%
3	20–27	5.0%
4	28–40	11.6%
5	>40	30.5%

Source: Adapted from Arozullah MA, et al: Multifactorial risk index for predicting, postoperative respiratory failure in men after major noncardiac surgery. Ann Surg *22:242–253, 2000.*

other patient populations is uncertain. Therefore, additional studies are required before use of this predictive index can be endorsed.

IMPACT OF ANESTHESIA AND POSTOPERATIVE ANALGESIA ON PULMONARY FUNCTION

An additional important consideration in patients undergoing surgical procedures is the effect of anesthesia on pulmonary function.

General Anesthesia

Use of general anesthetic agents is associated with a number of well-characterized alterations in pulmonary mechanics, gas exchange, and respiratory drive. In the controlled environment of the operating room, these physiological derangements are clinically inconsequential and easily overcome by simple adjustments of the ventilator. However, lingering effects of general anesthesia after completion of surgery may impede efforts to extubate the patient or may precipitate respiratory failure in the recovery room.

Administration of general anesthesia, whether by the inhaled or intravenous route, results in an almost immediate loss of diaphragmatic and intercostal muscle tone, a cephalad shift of the diaphragm, and a decrease in the transverse thoracic diameter. These dimensional alterations in thoracic volume result in a 20 percent reduction in functional residual capacity (FRC) and in development of compressive atelectasis. As demonstrated using computed tomography (CT) to image patients during and after general anesthesia, patients develop crescent-shaped areas of atelectasis in dependent areas of the lung within 10 min of induction. Atelectatic areas comprise approximately 2 to 10 percent of total lung volume and disappear with the application of positive end-expiratory pressure (PEEP). Dependent atelectasis develops after administration of either inhalational or intravenous anesthetics. A notable exception is ketamine, a drug that is unique in its maintenance of respiratory muscle tone. The degree of atelectasis appears unaffected by whether the patient is breathing spontaneously or is mechanically ventilated.

Areas of dependent atelectasis perturb the normal balance of ventilation and perfusion in the lung. Persistent perfusion of nonventilated atelectatic areas results in an increase in the shunt fraction, which may approach 15 percent. The magnitude of shunt correlates directly with the volume of atelectatic lung and may be further magnified by impairment of hypoxic pulmonary vasoconstriction induced by certain inhalational anesthetics. Elderly patients, those who are obese, and patients with underlying COPD are most likely to develop clinically apparent hypoxemia in response to general anesthesia; the effect may persist into the early postoperative period.

The inhaled anesthetic agents in common usage are respiratory depressants that blunt the response to both hypoxemia and hypercapnia. These agents depress the ventilatory response to CO_2 in a dose-dependent fashion. They have a negligible effect on the hypercapnic response at the low concentrations encountered during emergence from anesthesia. In contrast, hypoxemic drive is markedly attenuated even at very low, subanesthetic concentrations of the volatile agents. As a result of deposition of these agents in muscle and fat, concentrations sufficient to depress hypoxic drive persist for several hours after termination of anesthesia. This can result in significant postoperative respiratory depression in patients who, by virtue of chronic hypercapnia, are dependent upon a hypoxic ventilatory drive to breathe.

Neuraxial Anesthesia

It is common practice for those providing preoperative assessment of high-risk patients to recommend the use of neuraxial (i.e., spinal or epidural) anesthesia, predicated on the impression that this route of administration lessens the adverse impact of anesthesia on the respiratory system. Neuraxial anesthesia does possess a number of favorable physiological features. In contrast to the effects of general anesthesia, neuraxial anesthesia preserves diaphragmatic innervation and function. External intercostal muscle paralysis is induced by thoracic levels of neuraxial anesthesia, but the level is generally two dermatomes below the sensory level because of the lesser sensitivity of motor neurons to the effects of the anesthetic agent. Hypoxic pulmonary vasoconstriction is unaffected by neuraxial anesthesia, and the ventilatory response to CO_2 is unimpaired; indeed, the CO_2 response may be heightened. Despite the ostensibly favorable effects of neuraxial anesthesia on respiratory mechanics and respiratory drive, a clinically significant benefit over general anesthesia has not been consistently demonstrated. Pending further studies, neuraxial anesthesia should not be viewed as clearly superior to general anesthesia in the compromised patient.

Postoperative Analgesia

Postoperative analgesia is an essential component of the care of the surgical patient. Analgesia is important not only in ensuring patient comfort, but also in mitigating the adverse effects of pain on respiratory function and airway clearance. Inadequate pain relief can lead to splinting and patient reluctance to cough and deep breathe; the end result is promotion of retained secretions, atelectasis, hypoxemia, and, possibly, pneumonia. For major surgical procedures, particularly those involving the chest and upper abdomen, administration of opiates via the parenteral or epidural route has become the analgesic method of choice. Studies comparing the effect of epidural and parenteral opiates on pulmonary function are conflicting. While most have documented the superior analgesic effect of the epidural route, this has not invariably translated into improvement in respiratory mechanics and gas exchange or a lower incidence of postoperative pulmonary complications. This suggests that factors other than pain (see below) contribute significantly to alterations in pulmonary function that accompany thoracic or abdominal surgery. Nonetheless, this should not lead to the false impression that pain control is superfluous; failure to adequately control pain will exacerbate postoperative pulmonary dysfunction.

The use of narcotic analgesia in the postoperative period is associated with a small, but not insignificant, risk of precipitating respiratory depression. The reported incidence of respiratory depression varies based on the criteria employed. A meta-analysis of published studies revealed an incidence of 0.3 percent defined by the need to administer naloxone, 3.3 percent defined by the presence of hypercapnia, and 17 percent defined by oxygen desaturation. The risk may be slightly lower in association with the epidural, as opposed to parenteral, route of administration. Elderly patients are particularly susceptible to the respiratory depressant effects of opiates, likely reflecting an impaired ability to metabolize these agents. Respiratory depression in the postoperative patient is most likely to occur during the initial 24 h following surgery. It is typically accompanied by a decreased level of consciousness and a slow respiratory rate. Treatment consists of administration of naloxone in 0.1 to 0.4 mg aliquots. Ventilation should be supported with a face mask and Ambu bag, reserving intubation for failure of naloxone to swiftly rectify the problem.

IMPACT OF SURGERY ON POSTOPERATIVE PULMONARY FUNCTION

Surgery involving the upper abdomen and thorax results in a pronounced impairment in pulmonary function in the postoperative period. The impairment is more severe and prolonged than that due to administration of general anesthesia alone. Typically, upper abdominal and thoracic procedures are associated with a fall in lung volumes, development of atelectasis, and hypoxemia. These adverse effects commonly necessitate short-term administration of low-flow, supplemental oxygen, but when severe, or when accompanied by underlying lung disease, may precipitate respiratory failure.

Upper Abdominal Surgery

Vital capacity declines by 50 percent within 24 h following upper abdominal surgery. Although the vital capacity improves with time, marked impairment persists for as long as 7 d after the surgery. In contrast, vital capacity falls by only 25 percent following lower abdominal procedures; it returns to normal by the third postoperative day. Underlying these profound changes after upper abdominal surgery is the development of diaphragmatic dysfunction, as reflected in a reduction in transdiaphragmatic pressure with tidal respirations and in a shift from abdominal to rib cage breathing.

Two main theories have been proposed to explain the observed impairment in diaphragmatic function. One theory is that there is a primary alteration in diaphragmatic contractility induced by local irritation, inflammation, surgical trauma, or pain. This theory has been rendered improbable with the demonstration that external stimulation of the phrenic nerves produces normal peak transdiaphragmatic pressure in patients recovering from upper abdominal surgery. In other words, when maximally stimulated, the diaphragm functions in a normal fashion.

The alternative, and currently favored, theory proposes that diaphragmatic dysfunction results from diminished phrenic nerve output. The basis for the attenuation in neural drive remains a matter of speculation, although several putative pathways can be rationally eliminated. For example, general anesthesia is known to depress output from the central respiratory centers, as well as to inhibit synaptic transmission. However, as noted previously, the effects of general anesthesia on diaphragmatic tone are transient and modest. Additionally, the degree of dysfunction observed after upper abdominal procedures is not seen following general anesthesia for procedures on the lower abdomen and extremities. An inhibitory arc initiated by abdominal nociceptors for pain is unlikely, given that achievement of adequate pain control by epidural opiates fails to consistently improve pulmonary function or to normalize diaphragmatic performance. In contrast, the epidural administration of anesthetic agents such as bupivacaine does ameliorate diaphragmatic dysfunction following upper abdominal surgery. Since these agents produce sympathetic blockade in addition to pain control, it has been argued that visceral sympathetic afferents are responsible for providing an inhibitory signal that downgrades central neural drive and phrenic nerve activity, thereby leading to impaired diaphragmatic function. Supporting the notion of a reflex inhibitory arc mediated by visceral afferents is the demonstration in experimental animals that mechanical gallbladder stimulation strongly inhibits electromyographic activity and motion of the diaphragm.

Cardiac Surgery

Although CABG—the most commonly performed cardiac surgical procedure—has been most intensively scrutinized with respect to its impact on the respiratory system, other related cardiac procedures (e.g., valve replacement) are likely to have similar effects. Lung volumes decrease by approximately 30 percent after CABG; their return to preoperative values may take several months. Lung function may decline to a greater degree when internal mammary harvesting and grafting are employed. Gas exchange is also impaired after CABG, as evident in the development of hypoxemia and significant widening of the alveolar-arterial oxygen gradient. In 125 patients who had daily room air arterial blood gas determinations prior to and following CABG, Pa_{O2} fell from approximately 75 mmHg preoperatively to a nadir of 55 mmHg on postoperative day 2. The Pa_{O2} improved, but remained below preoperative values, at the end of the first postoperative week. A similar pattern and magnitude of decline in oxygenation have been demonstrated in other studies, with the development of hypoxemia associated with an increase in calculated shunt fraction from 3 percent preoperatively to a peak of 19 percent postoperatively. The increase in shunt fraction is readily accounted for on the basis of atelectasis, which is invariably present postoperatively, especially on the left side.

A number of factors have been implicated in the development of post-CABG pulmonary dysfunction and atelectasis. Alterations in chest wall compliance and motion may result from division of the sternum, harvesting of the internal mammary artery, and traumatic injury to the costovertebral joints and first rib induced by retraction. Intraoperative lung retraction may directly injure the left lower lobe, leading to contusion and atelectasis, and, perhaps, accounting for the predilection for radiographic infiltrates on the left side. An alternative explanation for post-CABG left lower lobe atelectasis is intraoperative injury to the left phrenic nerve and consequent diaphragmatic paralysis or paresis. The phrenic nerve is vulnerable to stretch and ischemic injury during sternal retraction, dissection of the left internal mammary artery, or prolonged distention of the pericardium. Additionally, thermal injury to the nerve may occur with the cardioplegic technique of instilling iced slush into the open pericardial sac. The actual incidence of phrenic nerve dysfunction after CABG is best defined in studies employing electrophysiological techniques, which have documented unequivocal evidence of phrenic nerve injury in 10 percent of patients. This suggests that phrenic nerve injury accounts for only a minority of the observed cases of left lower lobe atelectasis.

Finally, cardiopulmonary bypass (CPB) may contribute to pulmonary impairment after cardiac surgery. The duration of CPB has been linked to the severity of postoperative atelectasis; whether this relationship is causal is unclear. It has been hypothesized that the use of CPB leads to abnormal surfactant production—possibly due to ischemic, thermal, or toxic injury to the alveolar epithelium—predisposing to the development of atelectasis. More clearly established is the ability of the bypass pump to induce a capillary leak syndrome, marked by extravasation of fluid into the alveolar interstitium and, rarely, into the airspaces. This process is thought to result from exposure of blood to nonendothelial surfaces, resultant activation of neutrophils, complement and other inflammatory cascades, and sequestration of neutrophils within the microvasculature. While this rarely may lead to full-blown ARDS (see discussion below), the consequences are usually more subtle, manifesting as a widened arterial-alveolar oxygen gradient and diminished lung compliance. The recent introduction of "off-pump" CABG has permitted a greater appreciation of the adverse impact of CPB on postoperative lung function. For example, a recent large, multicenter comparative analysis from the United Kingdom of CABG with or without CPB demonstrated significant reductions in the rates of prolonged mechanical ventilation (more than 24 h), reintubation or tracheostomy, and ARDS or pulmonary edema

or pneumonia among the group that underwent off-pump CABG.

Lung Resection

Unique to lung resection surgery is the immediate loss of lung function due to removal of lung parenchyma. The magnitude of the loss can be estimated reliably from preoperative quantitative lung scanning in conjunction with standard spirometry (Chapter 38). The impact of lung resection on pulmonary function is further magnified in the perioperative period by other factors. For example, the standard posterolateral thoracotomy incision represents significant chest wall trauma, with rib retraction and resection, and transection of intercostal, latissimus dorsi, trapezius, and serratus anterior muscles. As a result, total respiratory compliance may fall by as much as 75 percent; work of breathing increases; and lung volumes decline dramatically, out of proportion to the surgical loss of functional lung. Following standard thoracotomy and lung resection (either lobectomy or wedge resection), FEV_1 and FVC fall to 25 percent of preoperative values at 1 hour, and to 30 percent at 24 h. When a more limited, muscle-sparing incision is used, the impact on pulmonary function is markedly attenuated.

As with cardiac and upper abdominal surgery, atelectasis is frequently present after lung surgery and results in impaired oxygenation. Phrenic nerve activity remains normal and diaphragmatic function during tidal breathing is preserved, although maximal diaphragmatic strength may be reduced.

CAUSES OF POSTOPERATIVE RESPIRATORY FAILURE

The development of acute respiratory failure in the surgical patient should prompt a systematic assessment of the likely causes (Table 147-4). In approaching this life-threatening problem, one must consider the nature and magnitude of preexisting pulmonary disease, type of surgery performed, drugs administered intra- and postoperatively, and predominant derangement in gas exchange (i.e., hypoxemia or hypercapnia). In conjunction with important information derived from the physical examination and chest radiograph, the analysis should readily identify factors responsible for, or contributing to, respiratory failure. The following discussion focuses on the more common or unique causes of postoperative respiratory failure in the surgical setting.

Atelectasis

Atelectasis is the most common pulmonary complication encountered in the surgical patient, particularly following thoracic and upper abdominal procedures. As discussed previously, anesthesia and surgical manipulation act in concert to produce regional atelectasis through incompletely defined mechanisms, including diaphragmatic dysfunction and diminished surfactant activity. The atelectasis is typically basilar and segmental in distribution, obscuring the hemidiaphragms radiographically. A distinct and less common cause of postoperative atelectasis is plugging of central airways by retained secretions. This problem is encountered in the surgical patient whose efforts to clear secretions are compromised by depressed consciousness, inadequate pain control, or a weak, ineffective cough. When situated in a mainstem bronchus, mucus plugs can result in collapse of an entire lung; more distal obstruction leads to lobar collapse. An abrupt termination of the proximal bronchial air shadow and the absence of air bronchograms within the atelectatic portion of the lung are clues to the possible presence of mucus plugging.

While often clinically insignificant, postoperative atelectasis may lead to severe hypoxemia and respiratory distress. The magnitude of hypoxemia is dictated by the extent of atelectasis, the presence and severity of underlying lung disease, and the integrity of the hypoxemic pulmonary vasoconstrictive response. Impairment of hypoxemic pulmonary vasoconstriction by vasodilatory drugs, commonly administered to surgical patients for treatment of underlying hypertension or ischemic heart disease, prevents the compensatory diversion of blood flow away from nonventilated areas of the lung and magnifies the shunt fraction.

Respiratory distress due to atelectasis usually evolves insidiously over the first several postoperative days. Supplemental oxygen requirements increase in association with worsening basilar infiltrates noted on the chest radiograph. The clinicoradiographic picture may be indistinguishable from that of pneumonia. While fever and leukocytosis suggest infection, these signs are common and nonspecific. When atelectasis is due to central airway occlusion by mucus plugs, hypoxemia and respiratory distress may develop quickly. A chest radiograph obtained immediately after the onset of symptoms may be surprisingly unrevealing if sufficient time has

Table 147-4

Causes of Postoperative Respiratory Failure

Factors extrinsic to the lung

- Depression of central respiratory drive (anesthetics, opioids, sedatives)
- Phrenic nerve injury or diaphragmatic dysfunction
- Obstructive sleep apnea

Factors intrinsic to the lung

- Atelectasis
- Pneumonia
- Aspiration of gastric contents
- Acute lung injury (ARDS)
- Volume overload or congestive heart failure (CHF)
- Pulmonary embolism
- Bronchospasm or COPD

not passed to permit resorption of gas from the airspaces of the nonventilated lung. Careful examination of the patient, however, will reveal an absence of breath sounds over the involved lung, providing an important clue to the presence of central airway obstruction and obviating pursuit of other considerations, such as pulmonary embolism.

Treatment of respiratory failure due to atelectasis is directed toward the combined goals of adequate oxygenation and re-expansion of lung segments. Supplemental oxygen should be titrated to achieve an arterial oxyhemoglobin saturation of at least 90 percent. Refractory hypoxemia, severe respiratory distress, progressive hypercapnia, or inability of the patient to clear copious airway secretions should prompt immediate intubation and mechanical ventilatory support. This life-saving intervention permits more efficient delivery of oxygen, secures access for suctioning of the airways, and facilitates performance of bronchoscopy should it be necessary. Moreover, the positive pressure and large tidal volumes delivered by the ventilator are often effective in rapidly re-expanding collapsed lung segments. In less dire circumstances, noninvasive delivery of continuous positive airway pressure (CPAP) via a nasal or face mask may be equally effective.

Fiberoptic bronchoscopy has a limited role in the treatment of serious postoperative atelectasis; its indiscriminate use should be avoided. The immediate use of fiberoptic bronchoscopy does not result in more rapid or complete resolution of acute lobar atelectasis when compared with standard chest physiotherapy consisting of deep breathing, coughing, suctioning of the intubated patient, aerosolized bronchodilator treatments, chest percussion, and postural drainage. Resolution of atelectasis appears to be dictated not by the treatment modality employed, but by radiographic evidence of central airway patency. In this regard, both chest physiotherapy and bronchoscopy are highly effective in the absence of an air bronchogram. In contrast, the presence of an air bronchogram, which indicates that the atelectasis is not due to proximal airway obstruction, is associated with minimal response to either modality. Therefore, simple and standard respiratory therapy techniques applied to either the spontaneously or mechanically ventilated patient form the mainstay of treatment for lobar atelectasis. Fiberoptic bronchoscopy should be reserved for those situations where chest physiotherapy is contraindicated (e.g., chest trauma, immobilized patient), poorly tolerated, or unsuccessful. In these circumstances, the decision to employ bronchoscopy should be tempered by the presence of an air bronchogram.

A number of other measures are commonly employed in the treatment of atelectasis. Judicious use of analgesia is an essential adjunct, permitting the patient to breathe deeply, cough forcefully, and comfortably participate in chest physiotherapy maneuvers. Care must be taken to avoid excessive sedation which will offset the beneficial effects of pain control. In the setting of marked hypoxemia, attempts should be made to discontinue vasoactive drugs with the potential to influence the pulmonary vascular bed; examples include nitrates, nitroprusside, calcium channel blockers, angiotensin-converting enzyme inhibitors, and hydralazine. Mucolytics, such as N-acetylcysteine, are commonly administered in an effort to promote clearance of tenacious secretions; however, their efficacy in this setting has not been well documented. Some clinicians and respiratory therapists advocate the use of nasotracheal suctioning of the nonintubated patient with a weak and ineffective cough. However, this technique is associated with considerable discomfort and, in the opinion of this author, is an inefficient and highly transient means of clearing secretions from the tracheobronchial tree.

The important role of prophylactic maneuvers in reducing the incidence and magnitude of postoperative atelectasis in high-risk patients should not be overlooked. These techniques, intended to promote periodic full lung expansion, include intermittent positive pressure breathing (IPPB), cough and deep breathing exercises, and incentive spirometry. All three techniques have been shown to be equally efficacious and superior to no therapy in the prevention of postoperative pulmonary complications following abdominal surgery, although their efficacy following cardiac surgery has recently been called into question. IPPB has largely been abandoned due to its expense, need for specially trained personnel and close patient supervision, and tendency to produce abdominal distention. For maximal benefit, prophylactic measures should be taught and instituted prior to surgery and used hourly in the postoperative period. Early ambulation of the postsurgical patient has been found to be as effective as respiratory therapy maneuvers in the prevention of postoperative atelectasis and should be strongly encouraged.

Pneumonia

Pneumonia is the second most common nosocomial infection and the most lethal, with an associated mortality rate of 20 to 50 percent. Pneumonia represents a principal cause of postoperative respiratory compromise and may precipitate acute respiratory failure, as well as complicate respiratory failure in the patient who is ventilator-dependent for other reasons. In epidemiological surveys, surgery has been identified as an independent risk factor for nosocomial pneumonia. In particular, the risk is greatest following standard thoracic and upper abdominal procedures, where an incidence of 15 to 20 percent has been documented. Lung transplant recipients represent an emerging population with a similarly high risk of postoperative pneumonia. In contrast, the risk of pneumonia is only 5 percent following lower abdominal surgery, and it is even less frequently encountered following procedures remote from the chest and abdomen. Overall, the incidence of nosocomial pneumonia is up to fivefold greater among patients in surgical ICUs than among patients in medical ICUs.

Epidemiological studies have identified a number of other risk factors for nosocomial pneumonia, but these studies fail to fully distinguish those factors that are causally linked from those that are simply surrogate markers. Factors reflective of poor preoperative health, including a low serum albumin level, presence of COPD, extensive smoking history, advanced age, protracted preoperative hospital stay, and high

status according to the American Society of Anesthesiologists' (ASAs) preanesthesia classification, have been linked to an excessive risk of pneumonia. A direct relationship between duration of surgery and incidence of postoperative pneumonia has been demonstrated. Other identified risk factors include presence of a nasogastric tube, use of antacids or H_2-blockers for stress ulcer prophylaxis, immunosuppression, impaired consciousness, and witnessed aspiration. Perhaps the most important and consistently identified risk factor is the need for prolonged mechanical ventilatory support. Overall, mechanically ventilated patients have a 3- to 21-fold increased risk of pneumonia compared with nonventilated patients. Moreover, the risk of pneumonia is linked to the duration of ventilatory support, approximating 1 percent per day on the ventilator.

The microbiological profile of nosocomial pneumonia is distinctly different from that of community-acquired infection. Gram-negative aerobic bacilli of the Enterobacteriaceae family prevail, collectively accounting for approximately one-third of all infections. Other highly virulent gram-negative rods which are commonly encountered are *Pseudomonas aeruginosa* and *Acinetobacter* species. Of the gram-positive organisms, *Staphylococcus aureus* predominates, while the pneumococcus, the most common bacterial respiratory pathogen in the community setting, plays an insignificant role. Often the pneumonia is polymicrobial; studies employing bronchoscopic culture techniques or postmortem cultures of lung tissue have identified more than one organism in up to 46 percent of cases.

While organisms may reach the lower respiratory tract by several routes, microaspiration of oropharyngeal secretions appears to be the predominant mechanism in the pathogenesis of nosocomial pneumonia. A critical initiating event in this pathway is colonization of the oropharynx with gram-negative aerobic bacilli, a process that characteristically occurs in response to serious illness or surgical stress. Clinically occult aspiration of these virulent organisms is facilitated by a number of iatrogenic measures imposed upon the surgical patient. Paramount among these is the placement of an endotracheal tube, which impairs swallowing, stents open the glottis, and permit pooling of secretions above the tube cuff. The inflated cuff is an imperfect barrier and allows intermittent seepage of secretions into the lower airways. Prolonged intubation has also been associated with postextubation swallowing dysfunction. Depressed consciousness as a consequence of general anesthesia and postoperative analgesia further contributes to the risk of aspiration.

Recent attention has focused on the stomach as an additional source of bacteria in the development of nosocomial pneumonia. While the acidic milieu of the stomach normally inhibits bacterial growth, the common use of H_2-blockers and antacids as stress ulcer prophylaxes overrides this natural barrier and promotes gastric colonization with gram-negative enteric organisms. Gastroesophageal reflux, a common feature of the critically ill patient, permits bacteria-laden gastric contents to enter the respiratory tract either directly or by first colonizing the oropharynx. This route of migration has been confirmed by recovery of technetium-99m (^{99m}Tc)-labeled gastric contents in endobronchial secretions and by the demonstration in some patients that organisms cultured from the airways first appeared in the stomach. Perhaps the most compelling, albeit circumstantial, evidence derives from several studies that have shown a higher incidence of nosocomial pneumonia in patients receiving H_2-blockers or antacids compared with those given sucralfate, a drug that does not result in alkalinization of gastric pH. However, conflicting data abound, and firm conclusions about the role of gastric colonization in the pathogenesis of nosocomial pneumonia await the outcome of larger and more methodologically rigorous studies.

The fate of organisms introduced into the lower respiratory tract is dependent upon the integrity of mechanical and immunologic pulmonary defense mechanisms. Impairment of the mucociliary escalator (e.g., due to recent cigarette smoking or underlying COPD), weak and ineffective cough, and use of immunosuppressive medications (e.g., corticosteroids) favor the proliferation of organisms and the development of pneumonia. It is widely held that postoperative atelectasis predisposes to pneumonia by entrapping bacteria. However, studies demonstrating a lack of concordance between the degree of atelectasis and the subsequent risk of pneumonia challenge this contention.

The constellation of fever, leukocytosis, purulent sputum, and radiographic infiltrates has traditionally defined the presence of pneumonia. While these diagnostic criteria are reasonably accurate in the previously healthy outpatient, they are notoriously nonspecific in the setting of recent surgery, particularly with prolonged use of mechanical ventilation. In one autopsy series, traditional clinical and radiographic criteria provided the correct antemortem diagnosis in only 70 percent of cases. Alternative etiologies of radiographic infiltrates include atelectasis, pulmonary edema, infarction or hemorrhage due to pulmonary emboli, pulmonary contusion, and chemical pneumonitis. Cultures of sputum and tracheal aspirates are poorly reflective of the bacterial flora of the distal airways, since these specimens are contaminated by colonizing organisms in the oropharynx and upper respiratory tract. In an attempt to enhance diagnostic certainty, bronchoscopic sampling of the distal airways using a sterile sheathed brush or bronchoalveolar lavage has been advocated. While the absence of a "gold standard" for the diagnosis of pneumonia has complicated attempts to define the accuracy of these techniques, rates of false-positive and false-negative results have generally fallen in the range of 30 percent. It is questionable, therefore, whether the performance of bronchoscopy actually contributes significantly to a reduction in the degree of diagnostic uncertainty. These concerns, coupled with the need to perform the procedure prior to institution of antibiotics and to collect and process specimens in a fastidious and standardized fashion, have severely limited the use and acceptance of currently available bronchoscopic techniques. Despite all of the pitfalls, most clinicians continue to rely on conventional assessment strategies in establishing a diagnosis of pneumonia and in determining the need for therapy.

Empiric treatment of nosocomial pneumonia is broad in spectrum and includes effective coverage of gram-negative organisms (including *Pseudomonas*) and *S. aureus*. The initial choice of antibiotics is influenced by the particular epidemiological profile and microbiologic susceptibility patterns at a given institution; many ICUs are currently plagued by highly resistant organisms, such as *Acinetobacter* and methicillin-resistant *Staphylococcus*, which have unusual, but predictable, susceptibilities.

Preventive strategies intended to diminish the risk of pneumonia are an important consideration in the care of the surgical patient. Prevention begins in the preoperative phase with emphasis on abstinence from cigarette smoking for a minimum of 8 wk prior to elective surgery. Following surgery, nasogastric and endotracheal tubes should be removed as soon as possible. Postoperative analgesia must be titrated to permit the patient to comfortably and vigorously cough, but excessive sedation impairing protection of the airway and enhancing the risk of aspiration must be avoided.

For the high-risk, ventilator-dependent patient, maintenance of a semierect position has been shown to diminish the magnitude of clinically occult aspiration of gastric contents and the incidence of pneumonia. While the use of sucralfate has been associated with a lower incidence of gastric colonization and nosocomial pneumonia compared with agents that raise gastric pH, additional corroborating studies are required before a firm recommendation to preferentially employ sucralfate in stress ulcer prophylaxis can be made.

An emerging approach to pneumonia prevention in the high-risk patient is selective digestive decontamination (SDD), intended to prevent or diminish the magnitude of gram-negative colonization of the aerodigestive tract. Regimens have varied among studies, but they typically consist of some combination of antibiotics applied topically to the oropharynx, instilled into the stomach as a slurry, and/or administered systemically. A recent meta-analysis of prospective, randomized trials concluded that SDD reduced the incidence of pneumonia and decreased overall mortality among critically ill surgical patients. Some studies have demonstrated emergence of resistant pathogens, while others have not. Despite the proven efficacy of this approach in high-risk surgical patients, SDD is not yet widely used.

Acute Lung Injury

The hallmark of acute lung injury is the presence of noncardiogenic pulmonary edema resulting from widespread damage to the alveolar-capillary membrane. Referred to clinically as acute respiratory distress syndrome (ARDS), the syndrome is defined by the constellation of hypoxemic respiratory failure, diffuse pulmonary infiltrates, and a normal pulmonary artery occlusion pressure or absence of clinical evidence of elevated left atrial pressure. ARDS represents the end result of a variety of insults that either involve the lung directly (e.g., aspiration of gastric contents) or trigger pulmonary inflammation as part of a systemic process (e.g., sepsis). Many of the risk factors associated with development of ARDS are commonly encountered in surgical patients (Table 147-5). In decreasing order of risk, these include sepsis, massive blood transfusion, pulmonary contusion, aspiration of gastric contents, and multiple fractures. Causes of acute lung injury of particular relevance to the surgical patient, and, in some cases, unique to this population, are described in greater detail below.

Table 147-5

Incidence of ARDS by Risk Factor

Risk Factor	Incidence of ARDS
Sepsis	41%
Massive transfusions	36%
Pulmonary contusion	22%
Aspiration	22%
Multiple fractures	11%

Sourc: Data adapted from Hudson LD, et al. Clinical risks for development of the acute respiratory distress dyndrome. Am J Respir Crit Care Med *151:293–301, 1995.*

Aspiration of Gastric Contents

Aspiration of gastric contents can rapidly lead to widespread acute lung injury and is an important cause of ARDS in the surgical patient. It is the third leading cause of anesthesia-related deaths, accounting for 10 to 30 percent of fatal outcomes. Aspiration typically occurs when the mechanisms of glottic closure and cough, which normally protect the airway, are compromised. In the surgical patient, the period of maximal vulnerability for aspiration spans from the induction of general anesthesia to full return of consciousness postoperatively. A number of factors combine to enhance the risk of aspiration during this period. Most important is the blunting of consciousness that accompanies induction and administration of general anesthesia. Insufflation of air into the stomach during induction may cause gastric distention and promote vomiting. Vomiting may also be provoked by noxious stimulation of the posterior oropharynx during intubation or extubation. Reflux of gastric contents is facilitated by medication-induced relaxation of the lower esophageal sphincter, placement of the patient in a supine position, and manipulation of the bowel during abdominal procedures. At the completion of surgery, extubation is commonly performed at a time when the patient, while able to ventilate adequately, may not yet be capable of fully protecting the airway. Indeed, upper-airway reflexes remain significantly impaired for up to 2 h after recovery from anesthesia, even at a time when mental alertness has returned. Moreover, translaryngeal intubation, even

when brief, may cause residual glottic dysfunction for up to 8 hours following removal of the tube. While the risk of aspiration diminishes beyond the immediate perioperative period, it remains a concern in the patient receiving narcotic analgesia, which may not only induce vomiting, but also depress consciousness.

The risk of aspiration during the immediate perioperative period was delineated in a survey of over 215,000 general anesthetic procedures performed at the Mayo Clinic. Aspiration was defined as the presence of bilious or particulate matter in the airways or the development of a new infiltrate on the immediate postoperative chest radiograph. The overall incidence of aspiration was only 0.03 percent, but the incidence was nearly fourfold higher (0.11 percent) in the setting of emergency surgery. In addition to the use of general anesthesia, other predisposing factors were present in over one-half of the patients who aspirated. These included gastrointestinal obstruction, swallowing dysfunction, altered sensorium, previous esophageal surgery, and a recent meal. The majority of events occurred during laryngoscopy (in preparation for insertion of the endotracheal tube) and during tracheal extubation. Twenty percent of patients who aspirated required postoperative mechanical ventilation in excess of 6 h; 5 percent died as a direct result of this complication.

Acidic gastric content introduced into the airways is rapidly disseminated throughout the bronchial tree and lung parenchyma, producing an almost instantaneous chemical burn. In addition, acid aspiration triggers a more delayed inflammatory response, with release of inflammatory cytokines and recruitment of neutrophils into the lung. The result is injury to the alveolar-capillary membrane, with flooding of the interstitium and airspaces by proteinaceous edema fluid. Surfactant levels drop precipitously due to both direct acid denaturation and diminished production, leading to alveolar instability and atelectasis. The magnitude of lung injury is directly related to the pH and volume of aspirated material. Initial studies in animals suggested that a pH of less than 2.5 and a volume in excess of 0.4 ml/kg are critical threshold values for the induction of lung injury. While these values are now often quoted in the literature, their validity has been challenged by more recent studies demonstrating significant injury in association with lower volumes and higher pH. In particular, aspiration of bile is capable of inducing widespread injury even at a pH as high as 7.19. The presence of large food particles may further exacerbate the problem by causing airway obstruction and atelectasis. Notably, infection does not normally play a significant role in the initial lung injury from aspiration of acidic gastric contents, as the low pH serves to maintain relative sterility of the inoculum. However, gastric colonization with bacteria can occur in patients maintained on acid suppressive agents, those receiving enteral feeds, and those with gastroparesis or small bowel obstruction.

The diagnosis of aspiration is most firmly established in the setting of witnessed vomiting or recovery of gastric contents from the airways. More often, the diagnosis is suspected circumstantially in a patient with risk factors and a compatible clinicoradiographic picture. Massive aspiration presents in a characteristic fashion, with the development of fever, tachypnea, and diffuse crackles within several hours of the event. Wheezing is appreciated in approximately one-third of patients and may be due either to obstruction of airways by particulate matter or, more commonly, to reflex bronchospasm. Hypoxemia is universally present with massive aspiration and is sufficiently severe in the majority of patients to mandate use of mechanical ventilation. The initial presence of apnea or shock is particularly ominous and portends a high risk of subsequent death. Initial radiographic patterns vary, depending upon the volume, causticity, and distribution of the aspirated material. However, three general patterns have been described: (1) extensive bilateral consolidation resembling diffuse pulmonary edema; (2) widespread, but discrete, patchy infiltrates involving dependent areas of the lung; and (3) focal consolidation, usually localized to one or both lung bases.

The clinical course following massive aspiration is variable, but it typically diverges along one of several pathways. A minority of patients follow a fulminant course marked by refractory hypoxemia and shock that eventuates in death within several days. More commonly, patients demonstrate progressive radiographic and clinical improvement over the first several days. Although most of these patients will go on to full recovery, a subset demonstrates secondary deterioration due to the development of ARDS or nosocomial pneumonia. The overall mortality rate associated with massive aspiration is approximately 30 percent and exceeds 50 percent in those patients with initial shock or apnea, secondary pneumonia, or ARDS.

Treatment of respiratory failure secondary to aspiration is supportive and includes mechanical ventilatory strategies generic to other forms of ARDS (detailed below). Bronchoscopy is indicated only when large-airway obstruction by particulate matter is suspected on the basis of a localized wheeze or lobar atelectasis. Because acid is disseminated and endogenously neutralized within seconds, large-volume bronchoalveolar lavage is ineffective in attenuating the degree of injury and is not recommended. Studies of the administration of systemic corticosteroids in the treatment of aspiration pneumonitis have been inconclusive and do not currently justify their use. Similarly, use of prophylactic antibiotics is generally discouraged in the absence of supportive data and because of fear that this practice will preferentially select more highly resistant organisms. Some authors do advocate use of empiric antibiotics for that subset of patients at risk for gastric colonization with bacteria, as described above. Additionally, up to 40 percent of patients will develop a superimposed bacterial pneumonia within several days of the aspiration event, often heralded by a new fever, new or progressive infiltrates, and purulent sputum. Broad-spectrum antibiotic therapy is indicated at that time.

The high morbidity and mortality associated with aspiration and the lack of effective therapy once the event has occurred have focused attention on measures to prevent this complication. The most straightforward and widely used measure is the convention of overnight fasting prior to

elective surgery. However, despite prolonged fasting, up to one-third of patients will maintain a gastric volume in excess of 0.4 ml/kg (approximately 25 to 30 ml in the average adult), and up to three-fourths will have a gastric pH below 2.5. Administration of H_2-blockers and proton-pump inhibitors can effectively raise the pH and reduce the volume of gastric contents, suggesting a potentially appealing strategy. Currently, prophylactic administration of antisecretory agents is recommended only for patients deemed to be at increased risk for aspiration. Unfortunately, there is generally insufficient time to allow these agents to act in the setting of emergency surgery, where the risk of aspiration is highest. In high-risk patients, rapid sequence induction of anesthesia should be employed to shorten the time between loss of consciousness and tracheal intubation. During induction, manual pressure should be applied to the cricoid cartilage (Sellick maneuver) and maintained until the endotracheal tube is in proper position and the cuff is inflated. Postoperatively, extubation should be performed only when consciousness and the gag reflex have returned to a level sufficient to permit adequate protection of the airway.

Postpneumonectomy Pulmonary Edema

Over the past 25 years, a number of published reports have documented the rapid development of pulmonary edema in the remaining lung of some patients following pneumonectomy. Initially attributed to overzealous fluid administration in the operating room, it has since been demonstrated that this complication occurs in the face of a normal pulmonary artery occlusion pressure. In addition, the edema fluid is protein-rich, arguing that the driving force behind edema formation is increased vascular permeability, rather than increased hydrostatic pressure. Postmortem studies confirm the universal presence of pathological features of acute lung injury. The exact mechanism responsible for lung injury after pneumonectomy remains obscure. One theory suggests that mechanical stress due to single lung ventilation in the operating room may cause ultrastructural damage to the alveolar epithelium, while diversion of the entire cardiac output through this remaining lung may similarly cause endothelial injury. Other factors that may contribute to edema formation include surgical trauma and disruption of lymphatic drainage.

In a study employing stringent criteria for excluding patients with congestive heart failure (CHF) or known risk factors for ARDS, the incidence of postpneumonectomy pulmonary edema was 2.6 percent. Other studies employing variable criteria have documented an incidence of 1 to 7 percent. For unclear reasons, the complication is encountered more frequently following right pneumonectomy. The observed mortality rate associated with postpneumonectomy pulmonary edema is in the range of 50 to 100 percent.

Cardiopulmonary Bypass

ARDS has been documented to develop immediately following use of cardiopulmonary bypass in approximately 1 percent of cases. While factors unrelated to the use of CPB may be at play, there is compelling evidence from both animal models and clinical studies to suggest that CPB activates a number of inflammatory mechanisms that could lead to acute lung injury. It is well established, for example, that CPB results in neutrophil activation, likely through mechanical sheer stress and exposure to the artificial surfaces of the bypass circuit. Additionally, an increased expression of cell surface adhesion molecules has been demonstrated, which may promote neutrophil binding to pulmonary endothelium and release of proteolytic enzymes and reactive oxygen species. The central role played by neutrophils in causing acute lung injury following CPB is supported by several lines of evidence: (1) bronchoalveolar lavage fluid from patients undergoing CPB contains an increased number of neutrophils; (2) plasma levels of neutrophil elastase and myeloperoxidase are increased; and (3) inhibition of neutrophil activation with pentoxifylline as well as neutrophil depletion attenuate the degree of pulmonary dysfunction. A number of other inflammatory mediators are released in association with CPB, including complement, proinflammatory cytokines, and prostaglandins.

Post-CPB ARDS is frequently accompanied by evidence of a systemic inflammatory response including fever, leukocytosis, and multi-organ system failure. Mortality associated with this complication is in the range of 60 to 90 percent.

Amiodarone

Amiodarone-induced pulmonary toxicity usually presents as a subacute illness characterized by cough, dyspnea, fever, and patchy pulmonary infiltrates. Less commonly, use of amiodarone has been linked to the development of ARDS immediately following cardiac and thoracic surgery. In most of the reported cardiac cases, amiodarone was administered preoperatively for varying periods of time for control of arrhythmias. The majority of patients had no evidence prior to surgery of the more indolent form of amiodarone pulmonary toxicity. More recently, development of ARDS has been described in patients whose only exposure to amiodarone occurred in the postoperative period, when the drug was initiated as prophylaxis or treatment for atrial arrhythmias following lung resection. In one report, postoperative ARDS developed in 11 percent of patients receiving amiodarone and in only 1.8 percent of untreated patients. The specific perioperative factors that act in concert with amiodarone to produce acute lung injury remain to be defined. Some authors have suggested that exposure to high levels of supplemental oxygen may be a contributing factor. The diagnosis rests on exclusion of other causes, rather than on specific diagnostic tests or histology.

Transfusion-Related Acute Lung Injury

The transfusion of blood and blood products has been linked to the development of ARDS in two ways. Epidemiologically, an association between massive blood transfusion (greater than 15 U/24 h) and ARDS has been noted, but it remains

unclear whether this link is truly causal or is indirect and reflective only of the critically ill nature of the patient requiring such massive transfusion support. More clearly defined mechanistically is the induction of acute lung injury by leukoagglutinating antibodies, a process that has been termed "transfusion-related acute lung injury" (TRALI). These antibodies are typically contained in blood products derived from multiparous female donors, whose exposure to foreign human leukocyte antigen (HLA) or granulocyte antigens occurred during prior pregnancies. When transfused into a recipient with these same antigens, these antibodies result in leukoagglutination and activation of recipient granulocytes or monocytes within the pulmonary microvasculature, triggering increased capillary permeability and development of noncardiogenic pulmonary edema. Less commonly, TRALI can be caused by the interaction between leukoagglutinating antibodies from the recipient and donor-derived leukocytes. TRALI has rarely been associated with infusion of biologically active mediators derived from breakdown of the cellular component of stored blood products.

The true incidence of TRALI is difficult to determine since this entity is underrecognized and frequently misdiagnosed. One study involving 36 cases over a 2-year period documented an incidence of 0.02 percent per unit and 0.16 percent per patient transfused. Most cases were detected in surgical patients in the immediate postoperative period, a fact that likely reflects the frequent need for transfusions in this setting and the close monitoring of cardiopulmonary function in the postanesthesia recovery area.

Mild episodes of TRALI may present as dyspnea and fever. More severe cases are characterized by the abrupt onset of respiratory distress, hypoxemia, and diffuse pulmonary infiltrates within 2 to 4 h of transfusion. Accompanying features include fever, chills, and hypotension; urticaria is present in a minority of patients. Respiratory distress and hypoxemia are of sufficient magnitude to require mechanical ventilatory support in most patients. The differential diagnosis includes volume overload, CHF myocardial infarction, and aspiration. The reaction tends to be self-limited and is typically characterized by rapid clearing of infiltrates and improved oxygenation within several days. However, a more protracted course of greater than 1 wk can be seen in approximately 20 percent of patients; a mortality rate of 5 to 10 percent has been reported.

When TRALI is suspected, the blood bank should be notified and all units that have been transfused should be assayed for the presence of leukoagglutinating antibodies. Any blood product containing plasma or plasma proteins is capable of inducing this reaction. Indeed, packed red blood cells, which contain only 60 to 100 ml of plasma, are one of the more common culprits.

Ischemia-Reperfusion Injury

The restoration of blood flow to previously ischemic tissue may, paradoxically, worsen tissue injury. This ischemia-reperfusion effect involves a "two-hit" mechanism. Tissue ischemia leads to formation of xanthine oxidase and its substrate, hypoxanthine, while reperfusion supplies molecular oxygen that fuels the reaction to produce oxygen free radicals injurious to cells. Neutrophils recruited to the site of ischemia-reperfusion serve as an additional source of oxygen free radicals, as well as proteolytic enzymes. Within the lung, ischemia-reperfusion produces diffuse injury to the alveolar epithelium and resultant noncardiogenic pulmonary edema. This mechanism underlies the development of acute lung injury in two important clinical settings: lung transplantation (Chapter 101) and pulmonary thromboendarterectomy.

Noncardiogenic pulmonary edema is a nearly universal feature of the freshly implanted lung allograft, but it is usually mild and self-limited. In approximately 10 percent of cases, however, the allograft is severely injured, with widespread and persistent alveolar edema causing profound hypoxemia and low pulmonary compliance, necessitating mechanical ventilatory support beyond the immediate posttransplant period. This entity, termed *primary graft dysfunction*, is nonimmunologic in nature and is believed to represent a severe form of ischemia-reperfusion injury. Primary graft failure occurs despite acceptable ischemic times below the perceived safe threshold of 6 h. Injury is manifest exclusively in the allograft, sparing the native lung in cases of single lung transplantation. The presence of unilateral lung injury may create difficulties in postoperative ventilator management. This is particularly true in the presence of underlying COPD, when positive-pressure breaths and PEEP are preferentially applied to the highly compliant emphysematous lung, leading to progressive hyperinflation, mediastinal shift, and potentially catastrophic impairment in gas exchange and hemodynamics. This situation can be effectively addressed with insertion of a double-lumen endotracheal tube, enabling use of independent lung ventilation and selective application of PEEP to the edematous allograft, while ventilating the native lung using low-airway pressures and a prolonged expiratory phase to minimize hyperinflation.

Pulmonary thromboendarterectomy is an established surgical technique for definitive treatment of chronic thromboembolic pulmonary hypertension (Chapter 82). Although operative mortality has decreased dramatically to less than 10 percent, reperfusion pulmonary edema remains a common postoperative complication. It is most often encountered within the initial 24 h after surgery, but its onset may occasionally be delayed for up to 72 h. A striking characteristic is the radiographic restriction of edema to those lung zones supplied by previously obstructed vessels. Exacerbating the degree of shunt and hypoxemia associated with this complication is the redistribution of blood from previously well-perfused segments to newly endarterectomized vessels supplying edematous areas of lung—a phenomenon referred to as "pulmonary artery steal." Fortunately, the degree of reperfusion edema and attendant hypoxemia is mild in the majority of cases. In approximately 10 percent of cases, however, the presence of severe hypoxemia necessitates prolonged mechanical ventilatory support with high levels of oxygen and application of PEEP.

Treatment and Outcome

Detailed discussion of the management of ARDS is beyond the scope of this chapter but is covered elsewhere in this text (Chapter 145) and in recent reviews. However, several fundamental aspects of care should be underscored. First and foremost, clinical management remains supportive; specific therapies aimed at ameliorating lung injury or accelerating healing are presently lacking. Care largely centers on use of mechanical ventilation, adjusted to maintain adequate gas exchange, while minimizing potentially harmful effects of high concentrations of oxygen, high tidal volumes, and high-airway pressures, all of which can induce further acute lung injury. To this end, efforts should be made to reduce the F_{IO_2} to 0.6 or less, accepting an arterial saturation in excess of 90 percent and using PEEP to recruit atelectatic areas of the lung and improve oxygenation. A "low stretch" ventilatory pattern should be employed, using tidal volumes of less than or equal to 6 ml/kg and limiting maximum plateau airway pressures to less than or equal to 30 cm H_2O. This ventilatory strategy, to which clinicians should strictly adhere, has been shown to decrease mortality associated with ARDS.

Inhaled nitric oxide preferentially vasodilates vessels supplying well-ventilated areas of the lung and has been shown to reduce shunt fraction and improve oxygenation in patients with severe ARDS. Unfortunately, these beneficial effects are typically short-lived, and multiple phase III clinical trials have failed to show a meaningful impact on duration of mechanical ventilation or mortality. Similarly, placing patients in the prone position can improve oxygenation but has not, to date, been shown to impact survival.

Sedatives should be administered to maintain patient comfort and promote synchronous breathing with the ventilator. Paralysis of the patient is occasionally required in the acute situation of life-threatening hypoxemia or hypercapnia, but prolonged use of neuromuscular blocking agents is discouraged because of the risk of a debilitating myopathy.

Despite aggressive support, the overall mortality from ARDS approximates 30 percent. The mortality rate is significantly higher in the elderly and in those with concurrent failure of other organ systems. On the other hand, patients with acute lung injury due to TRALI tend to have a more favorable prognosis.

Phrenic Nerve Injury and Diaphragmatic Dysfunction

Phrenic nerve injury is a well-described complication of CABG. In the past, this complication arose chiefly from the use of iced saline slush placed in the pericardium for topical cooling of the heart. Thermal injury causes both demyelination and axonal degeneration of the nerve, with slowing of conduction and impaired activation of the diaphragm. The use of topical cooling techniques has fallen out of favor largely because of this potential complication. However, the phrenic nerves can also be injured by traction, ischemia, use of diathermy, or transection during sternal retraction and harvesting of the internal mammary arteries. Unilateral phrenic nerve injury, typically involving the left phrenic nerve, has been reported in up to 10 percent of patients undergoing CABG. Bilateral phrenic nerve injury was reported to occur in 1 to 3 percent of cases in the era of widespread topical cardioplegia usage but is now a rare event. Phrenic nerve injury is not restricted to CABG; it is also seen in association with other cardiac procedures, thoracic surgery, neck surgery, and liver transplantation.

Although typically inconsequential in the otherwise healthy patient, unilateral diaphragmatic paralysis can lead to significant respiratory compromise in patients with underlying chronic lung disease or those who are otherwise marginal. In patients with COPD, for example, the duration of postoperative mechanical ventilation and the rate of reintubation are higher for those with than those without unilateral phrenic nerve injury following CABG. Bilateral diaphragmatic paralysis results in marked impairment in pulmonary function and frequently leads to respiratory failure. In the proper setting, phrenic nerve injury should be suspected when attempts to wean a postoperative patient from mechanical ventilation result in progressive hypercapnia or atelectasis. The spontaneously breathing patient will often complain of orthopnea, which may be misinterpreted by the unsuspecting clinician as indicative of CHF. However, orthopnea is actually due to further impairment in diaphragmatic function resulting from loss of gravitational assistance in the supine position. The detection of inspiratory thoracoabdominal paradox—an inward movement of the abdominal wall with simultaneous expansion of the thorax—is an important bedside clue to the presence of bilateral diaphragmatic paralysis and is best evoked in the supine position. The chest radiograph may also hold important clues, demonstrating either unilateral or bilateral elevation of the diaphragms and accompanying basilar atelectasis. However, these findings are not specific for phrenic nerve injury and may also be due to splinting or abdominal distention. A reduced maximum inspiratory pressure recorded at the mouth is another sensitive but nonspecific indication of significant diaphragmatic dysfunction.

Unilateral diaphragmatic paralysis can be readily diagnosed by fluoroscopic inspection, which reveals paradoxical upward movement of the affected hemidiaphragm with a maximal inspiratory effort ("sniff"). The situation is more problematic with bilateral diaphragmatic dysfunction. In this setting, patients often assume an altered breathing pattern marked by active contraction of the abdominal muscles during expiration, forcing the flaccid hemidiaphragms upward. With subsequent inspiration, the abdominal muscles relax and the hemidiaphragms descend briefly, potentially creating the false impression that they are functional. Because of this, fluoroscopy may not be confirmatory in these patients.

The "gold standard" for confirmation of phrenic nerve injury is electrophysiological testing, although even this methodology is occasionally flawed. The phrenic nerve is stimulated transcutaneously in the neck, and the diaphragmatic electromyogram (EMG) is recorded by surface

electrodes placed in the seventh intercostal space at the costochondral junction. Demonstration of a prolonged latency between nerve stimulation and diaphragmatic action potential confirms a diagnosis of demyelinating injury. It is more difficult to interpret the significance of diminished amplitude or complete absence of the surface recording of the diaphragmatic EMG. This finding could represent either phrenic nerve injury or transection or failure to properly localize the diaphragm, which is typically shifted caudally in the postoperative patient and, therefore, away from the surface electrodes. Direct puncture of the diaphragm with a recording electrode may be employed to clarify this issue, but the technique requires a high level of expertise and carries a risk of pneumothorax.

Nontraumatic causes of phrenic nerve injury and diaphragmatic dysfunction can also lead to prolonged respiratory failure and delayed weaning in the surgical patient. Phrenic neuropathy can be a component of a more generalized polyneuropathy of critical illness, commonly encountered in the wake of an episode of severe sepsis or systemic inflammatory response syndrome. A critical illness myopathy affecting the diaphragms and other muscles of respiration can be encountered under the same circumstances. Finally, diaphragmatic dysfunction can arise as a component of a myopathy induced by the concurrent use of high-dose systemic corticosteroids and neuromuscular blocking agents.

Patients with diaphragmatic dysfunction are generally well-suited for noninvasive positive pressure ventilatory support if they are awake and able to effectively handle respiratory secretions. Tracheostomy is indicated for patients with ineffective cough and those who cannot be weaned from conventional mechanical ventilation. The prognosis for patients with thermal or traction injury of the phrenic nerve is favorable; recovery is typically complete, but often protracted. In symptomatic patients with unilateral diaphragmatic paralysis due to transection of the phrenic nerve, surgical plication of the flaccid hemidiaphragm usually results in improved pulmonary function and can lead to successful liberation from mechanical ventilation.

Pulmonary Embolism

An increased risk of pulmonary embolism (PE) accompanies a number of surgical procedures, including upper abdominal, neurosurgical, cardiac, major urological, and lower extremity orthopedic procedures. Other, nonsurgical risk factors that predispose the patient to PE may also be present, including obesity, immobility, and underlying malignancy.

While alterations in gas exchange typify pulmonary embolism, frank hypoxemic respiratory failure is relatively uncommon and suggests massive clot burden. Lesser degrees of clot burden may produce equally devastating physiological impairment in patients with underlying pulmonary disease. In the presence of severe hypoxemia, there is little remaining cardiopulmonary reserve. Failure to establish a correct diagnosis and to swiftly and appropriately intervene can prove lethal.

Unfortunately, little information pointing specifically to a diagnosis of PE is easily gleaned at the bedside. The patient is often dyspneic, and tachypnea and tachycardia are observed on physical examination. However, these features are common in many postoperative patients because of pain and atelectasis. More informative, but infrequently detected, is evidence of acute cor pulmonale (e.g., distended neck veins, a parasternal heave, right-sided third heart sound, and accentuation of the pulmonic component of the second heart sound). An electrocardiogram may also demonstrate evidence of right heart strain, with an "S1Q3T3" pattern or new right bundle branch block. The chest radiograph is most suggestive of PE when it is normal in the face of severe hypoxemia. When abnormal, the greatest use of the chest radiograph is in identifying other causes of hypoxemia, such as pneumonia, pneumothorax, or ARDS. Echocardiography is commonly performed in the setting of hypotension; evidence of a dilated right ventricle in the face of a normal or underfilled left ventricle should raise suspicion for massive PE.

The choice of diagnostic studies is dictated by the urgency of the situation. In the setting of life-threatening hypoxemia or hemodynamic instability, pulmonary angiography provides the most definitive and expeditious means of establishing the diagnosis. Pulmonary angiography also permits the immediate placement of an inferior vena cava filter or performance of catheter embolectomy or thrombus fragmentation, as needed. In more stable patients, CT angiography is emerging as the imaging procedure of choice. Until its performance characteristics in the ICU patient population are better defined, however, a negative CT angiogram in the setting of high clinical suspicion should not necessarily be viewed as definitively excluding PE.

While anticoagulation with heparin forms the mainstay of therapy for the otherwise stable patient, the presence of life-threatening hypoxemia and/or hemodynamic instability should prompt consideration of alternative or additional interventions. Since additional clot burden could be fatal, insertion of an inferior vena cava filter is generally advised in this setting. Certainly this intervention is mandatory when anticoagulation is contraindicated. Thrombolytic therapy should also be considered in the critically ill patient, but its use in the postoperative period is limited by the risk of precipitating bleeding at the site of recent surgery. This risk appears to fall to an acceptable level beyond the seventh postoperative day; the exception is intracranial surgery, which contraindicates use of lytic agents for at least 2 months. Several interventional radiologic techniques—thrombus fragmentation, suction embolectomy, and intraembolic infusion of low-dose thrombolytics—as well as surgical embolectomy are alternative considerations in the deteriorating patient for whom systemic thrombolytics are either contraindicated or unsuccessful.

Obstructive Sleep Apnea

Obstructive sleep apnea (OSA) is a common disorder affecting 2 to 4 percent of the adult population. It is characterized by

repetitive upper-airway obstruction during sleep, resulting in periodic arterial desaturation, hypercapnia, and arrhythmias. Because of alterations in oropharyngeal anatomy that commonly accompany obesity and OSA, orotracheal intubation at the time of induction may be difficult. The immediate postoperative period is a particularly precarious time for patients with this disorder, as the use of volatile anesthetics, opioids, and sedatives diminish the activity of the upper-airway musculature and increase the frequency and duration of obstructive apneas. Failure to recognize and appropriately support patients with OSA in the perioperative period can lead to serious complications, including respiratory arrest, hypoxemia, confusion, and ventricular arrhythmias. Institution of nasal continuous positive airway pressure immediately after extubation permits safe administration of analgesic and sedative agents, without undue risk of precipitating life-threatening airway obstruction. It is estimated that as many as 80 percent of patients with OSA are undiagnosed; a high index of suspicion, therefore, is required in the surgical patient to intervene appropriately when upper-airway obstruction is anticipated or observed.

USE OF NONINVASIVE POSITIVE PRESSURE VENTILATION

For patients with respiratory failure refractory to conservative measures, endotracheal intubation is the standard means to facilitate mechanical ventilatory support. However, in recent years, a greater appreciation for the untoward effects of endotracheal intubation has emerged. In addition to airway trauma, these include an increased risk of nosocomial pneumonia and sinusitis and the frequent need for heavy sedation that, while addressing patient discomfort, often prolongs the process of weaning and extubation. The desire to avoid endotracheal intubation has prompted interest in the use of noninvasive positive pressure ventilation (NIPPV), employing a tight-fitting nasal or full-face mask as the interface between patient and ventilator.

There is ample evidence supporting the benefits of NIPPV in the treatment of a variety of causes of respiratory failure in the medical patient, but only recently have data emerged confirming its safety and efficacy in the postoperative setting. The most compelling study randomized patients with hypoxic respiratory failure following lung resection surgery to standard therapy (supplemental oxygen, bronchodilators, chest physiotherapy) with or without NIPPV. Compared to the control group, the use of NIPPV was associated with a marked reduction in the need for endotracheal intubation (20.8 percent versus 50 percent) and in mortality at 3 months (12.5 percent versus 37.5 percent). While there has been concern about using NIPPV following esophageal or gastric surgery, recent experience suggests that this can be accomplished safely. In this setting, care must be taken to avoid gastric distention, using a nasogastric tube for decompression if necessary, and the magnitude of positive pressure ventilation employed should be limited to less than 12 cm H_2O. Since NIPPV often requires a period of acclimation, it should not be used in unstable patients. Other contraindications to its use include depressed or agitated mental status, inability to protect the airway, and compromised airway clearance due to copious secretions or weak cough.

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CHAPTER

Pump Failure: The Pathogenesis of Hypercapnic Respiratory Failure in Patients with Lung and Chest Wall Disease

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The ventilatory pump accomplishes bulk transfer of air to and from the alveoli. Accordingly, diseases that perturb the mechanical properties of any component of the ventilatory pump (i.e., the bony rib cage, the extra- and intrathoracic conducting airways, and the respiratory muscles) may interfere with CO_2 elimination and O_2 uptake. If disturbances in the function of the ventilatory pump are sufficiently severe, alveolar hypoventilation and respiratory acidosis may ensue.

Hypercapnic respiratory failure is defined as a steady-state Pa_{CO_2} while awake at more than 45 mmHg, the upper limit of normal. This definition is somewhat arbitrary but has proved clinically useful.

Conceptually, diseases that cause hypercapnic respiratory failure do so by deranging respiratory mechanics and lung dead-space volume (e.g., chronic obstructive pulmonary disease [COPD], asthma, or kyphoscoliosis) or by impairing the contractile properties of the respiratory muscles (e.g., neuromuscular disease). Diseases that impair respiratory mechanics increase the elastic or resistive load against which the respiratory muscles must contract. On the other hand, neuromuscular diseases impair the strength or endurance properties of the respiratory muscles and impair their ability to generate swings in intrathoracic pressure sufficient to maintain ventilation.

A variety of compensatory neural mechanisms that sense alterations in blood gas tensions or ventilatory performance elicit increases in the neuromuscular drive to breathe—which, in turn, helps preserve alveolar ventilation. In fact, in most patients, rather marked abnormalities in ventilatory pump performance are required before hypercapnic respiratory failure ensues. Conceptually, the susceptibility to develop CO_2 retention in the setting of lung, chest wall, or respiratory muscle dysfunction, therefore, depends on the balance between the severity of the derangement in ventilatory pump function and the intensity of the respiratory neuromuscular drive to breathe.

This chapter deals with the pathogenic mechanisms at work in the development of CO_2 retention in lung and chest wall diseases. The compensatory/adaptive mechanisms that help preserve ventilation (e.g., respiratory chemosensitivity, motor responses to alterations in the mechanics of breathing, and intrinsic changes in respiratory muscle strength and endurance) and the decompensating/maladaptive responses that predispose to CO_2 retention (e.g., respiratory muscle wasting and fatigue and a rapid, shallow pattern of breathing) will be discussed.

COMPENSATORY/ADAPTIVE MECHANISMS

Respiratory Chemosensitivity

Overview—Regulation of Ventilation

Hypoxia and hypercapnia stimulate chemoreceptors in the arterial circulation (peripheral chemoreceptors) and ventrolateral medulla (central chemoreceptors) that reflexively increase motor activity to the respiratory skeletal muscles of the chest wall and upper airway. Contraction of the muscles of the chest wall (e.g., diaphragm, intercostals, abdominals, and neck muscles) deforms the ventilatory pump and moves air. Contraction of the muscles of the upper airway (genioglossus, alae nasae, posterior arytenoids, pharyngeal dilators, sternohyoid, etc.) increases the caliber of the upper airway and diminishes its susceptibility to collapse during inspiration.

Chemoreceptor-induced increases in inspiratory and expiratory muscle activity are proportional to the severity of abnormalities in blood gas tensions and represent a feedback control loop that restores blood gas tensions toward normal by enhancing alveolar ventilation. The magnitude of the swings in intrathoracic pressure and resistance and compliance of the upper airway are determined by these changes in respiratory motor activity. The maintenance of blood gas tensions within a relatively narrow, normal range from neonatal life to senescence attests to the power of this homeostatic mechanism.

Hypoxic and hypercapnic chemical drives to breathe exert the following stereotypic effects on the activity of chest wall and upper-airway muscles. Peak respiratory muscle electrical activity and its rate of rise are increased. For the inspiratory muscles, these changes in muscle electrical activity increase the rate of change and peak inspiratory intrathoracic pressure, inspiratory airflow, and tidal volume. For the expiratory muscles, increased electrical activity enhances the rate of expiratory airflow. For the upper-airway muscles, the resistance to inspiratory airflow decreases.

Chemosensitivity-induced increases in respiratory activity also affect the timing of respiratory motor activity as reflected in the duration of inspiration (T_I) and expiration (T_E). Hypoxia and hypercapnia lead to decreased T_I and T_E, allowing the frequency of breathing to increase. Reductions in T_E are generally out of proportion to T_I, thereby increasing the fraction of the respiratory cycle spent in inspiration. This partitioning of the respiratory cycle is reflected in the T_I/T_T ratio, where T_T is the total breath cycle duration (i.e., the sum of T_I and T_E).

Hypoxia and hypercapnia differ in their effects on the activity of the inspiratory muscles after the cessation of inspiratory airflow, the so-called postinspiratory inspiratory activity (PIIA). Hypoxia increases PIIA in both chest wall inspiratory muscles and muscles that constrict the laryngeal aperture. Accordingly, hypoxia has a braking effect on the rate of expiratory airflow. As T_E decreases with increasing hypoxic drive, end-expiratory lung volume increases. PIIA-induced increases in lung volume increase the caliber of the intrathoracic airways and the O_2 content of the lung. Hypoxia-induced PIIA affects the load on the respiratory muscles in complex fashion; that is, PIIA reduces inspiratory resistive work of breathing but increases the inspiratory elastic and expiratory resistive work of breathing. It has been suggested, however, that the net effect of hypoxia-induced PIIA is a reduction in overall energy expenditure during breathing. In contrast, hypercapnia diminishes the duration of PIIA.

Indices of Respiratory Motor Output

Ventilation is a well-accepted index of respiratory motor output. Traditionally, ventilation was viewed as the product of tidal volume (V_T) and respiratory rate (which is equal to $60/T_T$). More recently, ventilation has been viewed as the product of separate "drive" and "timing" components. The

average rate of inspiratory airflow, V_T/T_I—which reflects the rate of rise of inspiratory muscle activity and intrathoracic pressure—is increased when blood gas tensions are deranged. Accordingly, V_T/T_I has been taken as a reflection of the activity of mechanisms that regulate the drive to breathe. Of note, V_T/T_I may also be increased by excitatory inputs arising from respiratory mechanoreceptor afferents (e.g., vagal irritant receptors) and higher central nervous system (CNS) structures engaged in thermoregulation and emotion (i.e., hypothalamic and limbic areas). Conversely, the T_I/T_T ratio has been taken as a reflection of the activity of mechanisms that regulate respiratory timing. The T_I/T_T ratio is strongly affected by afferent input from mechanoreceptors in the lungs, airways, and respiratory muscles, as well as increasing chemical drive. For example, T_I/T_T increases in anesthetized animals when vagal stretch receptors are stimulated by increases in lung volume and is decreased by bronchoconstriction-induced activation of vagal irritant receptors.

In subjects with normal lung function, V_T/T_I and ventilation are accurate reflections of inspiratory muscle electrical activity and the rate of rise of intrathoracic pressure. On the other hand, diseases that adversely affect the mechanical properties of the ventilatory pump (e.g., obstructive lung disease, kyphoscoliosis) interfere with the translation of changes in intrathoracic pressure into ventilation and airflow. Conversely, conditions that impair respiratory muscle contractility (e.g., neuromuscular diseases, respiratory muscle fatigue) interfere with the translation of inspiratory muscle electrical activity into intrathoracic pressure changes. Accordingly, V_T/T_I reflects the intensity of motor outflow to the inspiratory muscles produced by increasing chemical drive only when the mechanical properties of the ventilatory pump and inspiratory muscle strength are normal. When the ventilatory pump function is abnormal, respiratory motor outflow is best assessed from respiratory muscle electrical activity (i.e., diaphragm electromyography [EMG] activity), a complicated measurement largely confined to the research laboratory.

A simpler, clinically useful measurement that reflects the neuromuscular drive to breathe and the driving pressure to inspiratory airflow is the airway occlusion pressure. The occlusion pressure is the pressure generated at the airway opening 100 ms after the onset of an occluded inspiratory effort (i.e., P_{100} or $P_{0.1}$) initiated at end-expiratory lung volume. Since the airway is occluded, the inspiratory muscles contract quasi-isometrically, a condition in which muscle force correlates closely with muscle electrical activity. Measurements are made early in inspiration (100 ms) to prevent behavioral responses elicited in response to airway occlusion from altering the shape/trajectory of the pressure waveform. The lack of flow or volume change during the measurement means that the occlusion pressure is unaffected by abnormalities in the flow-resistive or compliance properties of the ventilatory pump. The occlusion pressure, therefore, has been used to assess the drive to breathe in patients with lung diseases (e.g., COPD and asthma) and chest wall diseases (e.g., kyphoscoliosis) during resting and chemically stimulated breathing. On the other hand, the occlusion pressure depends on the ability of the inspiratory muscles to convert neural activity into force and pressure. Accordingly, like ventilation, occlusion pressure may not reflect respiratory motor-neuron activity when the inspiratory muscles are weak (e.g., neuromuscular disease) or fatigued.

Hypoxic Response

Under isocapnic conditions, ventilation (or occlusion pressure) increases in curvilinear fashion as P_{O_2} falls. However, hypoxic responses depend importantly on the prevailing level of Pa_{CO_2} (i.e., the O_2–CO_2 interaction). When Pa_{CO_2} is in the hypocapnic range, arterial P_{O_2} must fall considerably (to approximately 55 to 60 mmHg or less) before respiratory activity increases. Hypercapnia profoundly increases the response to hypoxia by shifting the threshold of the response toward higher levels of P_{O_2} and augmenting the change in ventilation elicited for a given reduction in P_{O_2}.

Although the physiological stimulus for the hypoxic response is the Pa_{O_2} of the blood perfusing the peripheral chemoreceptors, for convenience the oxyhemoglobin saturation assessed with a pulse oximeter has been taken as a reflection of the stimulus. Use of the oxyhemoglobin saturation linearizes the relationship between the hypoxic stimulus, ventilation, and occlusion pressure. The intensity of the hypoxic response has been assessed from the slope of the change in ventilation (or occlusion pressure) relative to the change in O_2 saturation (i.e., $\Delta V_E/\Delta$ % O_2 sat) and from the intercept of the relationship (e.g., ventilation at O_2 saturation of 85 percent).

Hypercapnic Response

In contrast to the response to hypoxia, the ventilatory and occlusion pressure responses to hypercapnia under iso-oxic conditions are linear over a relatively wide range of Pa_{CO_2} above and below the resting level of 40 mmHg. The intensity of the ventilatory and occlusion pressure response to CO_2 has been assessed from the slope of the relationship of V_E to Pa_{CO_2} (i.e., $\Delta V_E/\Delta Pa_{CO_2}$) and from the intercept of the relationship (i.e., V_E at Pa_{CO_2} 50 mmHg).

The ventilatory response to hypercapnia is strongly affected by the prevailing level of Pa_{O_2} and is heightened as Pa_{O_2} decreases. In fact, hypoxemic and hypercapnic stimuli interact multiplicatively to enhance inspiratory and expiratory motor activity. Worsening hypoxemia enhances the ventilatory response to hypercapnia in accordance with the O_2–CO_2 interaction. The strength of a subject's chemosensitivity to O_2 and CO_2 and, in particular, to the O_2–CO_2 interaction is a powerful feedback mechanism opposing the tendency to retain CO_2 in patients with ventilatory pump dysfunction.

Consequently, treatment of the hypercapnic, hypoxemic patient with supplemental O_2 may decrease V_T/T_I and T_I/T_T and, hence, worsen hypercapnia in accordance with O_2–CO_2 interaction. Increases in Pa_{O_2} in hypoxic, hypercapnic subjects move the O_2 response to the right (less stimulus)

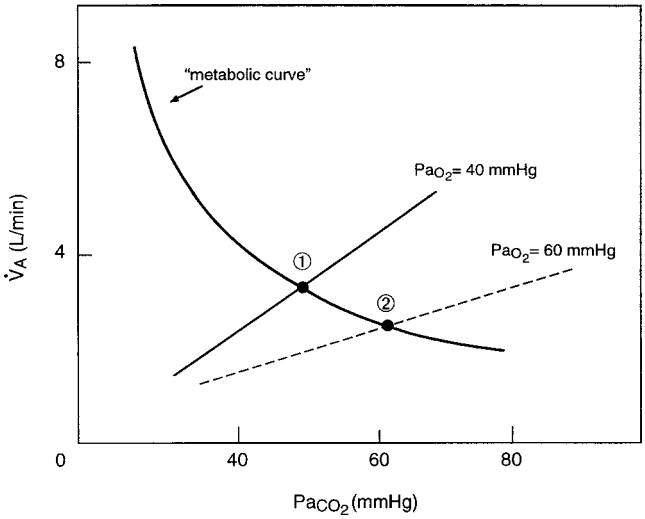

Figure 148-1 Theoretical effects of supplemental O_2 on the ventilatory response to CO_2 and steady-state arterial P_{CO_2} in subjects with COPD in hypercapnic respiratory failure. Increasing Pa_{O_2} decreases alveolar ventilation and increases Pa_{CO_2} as dictated by effects of O_2 on the CO_2 ventilatory response. The two straight lines represent hypercapnic ventilatory response curves at Pa_{O_2} of 40 and 60 mmHg. As may be seen, increasing Pa_{O_2} produces a downward, rightward shift of the ventilatory response. In contrast, the hyperbolic line intersecting the ventilatory response lines is the metabolic CO_2–ventilation curve, which represents the effect of increasing alveolar ventilation (independent variable) on Pa_{CO_2} (the dependent variable) when CO_2 production is normal (~200 ml/min). Steady-state alveolar ventilation and Pa_{CO_2} at rest are dictated by intersection of the ventilatory response curves with the metabolic curve (points 1 and 2). Note the increase in Pa_{CO_2} as the ventilatory response with Pa_{O_2} 60 mmHg intersects at a lower alveolar ventilation and higher Pa_{CO_2} (point 2) compared to the higher ventilatory response when Pa_{O_2} was 40 mmHg (point 1).

and decrease the slope and shift the intercept of the ventilatory response to *hypercapnia* to the right (Fig. 148-1). Shifts in the CO_2 response with increases in the prevailing Pa_{O_2} mean that a higher CO_2 stimulus is required to maintain ventilation at the baseline level. Accordingly, ventilation falls and Pa_{CO_2} rises. The magnitude of the rise in Pa_{CO_2} in patients with COPD in acute respiratory failure produced by supplemental O_2 varies widely among subjects as determined by their chemosensitivity.

Of note, hypercapnia induced by supplemental O_2 in patients with COPD is multifactorial and reflects increases in lung dead-space volume as well as reductions in alveolar ventilation. Hypoxemia causes bronchoconstriction via increases in parasympathetic outflow to airway smooth muscle. Accordingly, relief of hypoxemia causes bronchodilation and increased dead-space volume.

Role of Blunted Chemosensitivity in Development of Respiratory Failure

Chemosensitivities to hypoxemia and hypercapnia are hereditofamilial and ethnic traits that vary widely interindividually

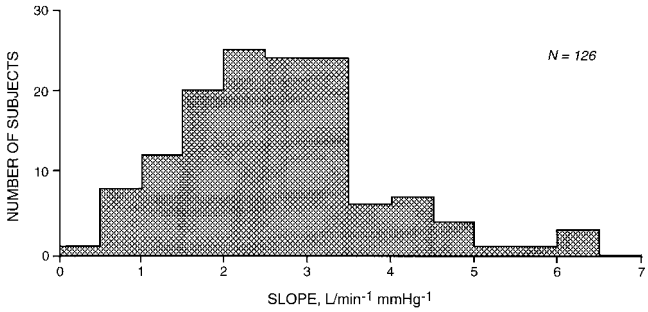

Figure 148-2 Variability of the slopes of the ventilatory responses to progressive hypercapnia (i.e., V_E/P_{CO_2}) in a normal population. Shown is the frequency distribution histogram of the slopes in 126 normal South African medical students. Note the considerable interindividual variation in CO_2 responsiveness. In some healthy subjects, the ventilatory response is blunted to less than 1 L/min/mmHg P_{CO_2}. *(Based on data from Irsigler GB: Carbon dioxide response lines in young adults: The limits of the normal response. Am Rev Respir Dis 114:529–536, 1976, with permission.)*

(Fig. 148-2). In a given subject, responses to hypoxemia and hypercapnia correlate weakly, so that subjects with strong responses to hypercapnia also tend to have strong responses to hypoxia. Respiratory chemosensitivity to both hypoxemia and hypercapnia declines with age. The decline in chemosensitivity with aging may explain why elderly subjects with lung disease (e.g., COPD) or chest wall disease (e.g., kyphoscoliosis) develop hypercapnic respiratory failure more frequently than young adults. When chemosensitivity is low, subjects with diseases of the ventilatory pump are predisposed to develop hypercapnic respiratory failure.

In patients with advanced COPD, the severity of airway obstruction required to cause CO_2 retention varies widely from subject to subject (Fig. 148-3). Subjects with the greatest respiratory effort responses to changes in Pa_{CO_2}—as measured by diaphragm EMG, respiratory work of breathing, or occlusion pressure—have arterial Pa_{CO_2} values closer to normal than subjects with blunted responses to CO_2 but the same severity of lung dysfunction. Accordingly, when chemosensitivity is low, subjects with diseases of the ventilatory pump are predisposed to develop hypercapnic respiratory failure. However, since CO_2 retention per se may blunt the response to acute hypercapnia, studies in patients in respiratory failure have not been able to determine whether blunted CO_2 responses are a cause or consequence of respiratory failure.

The tendency for chemosensitivity to be inherited has been used in a number of subsequent studies to assess the role of hypoxic and hypercapnic responses in the pathogenesis of CO_2 retention in the setting of obstructive lung disease. Study of relatives with normal lung function and blood gases has been employed to circumvent the effects of CO_2 retention on respiratory chemosensitivity in patients with COPD.

In general, normal relatives of hypercapnic patients with COPD have lower ventilatory responses to hypoxia and hypercapnia than relatives of eucapnic patients with COPD

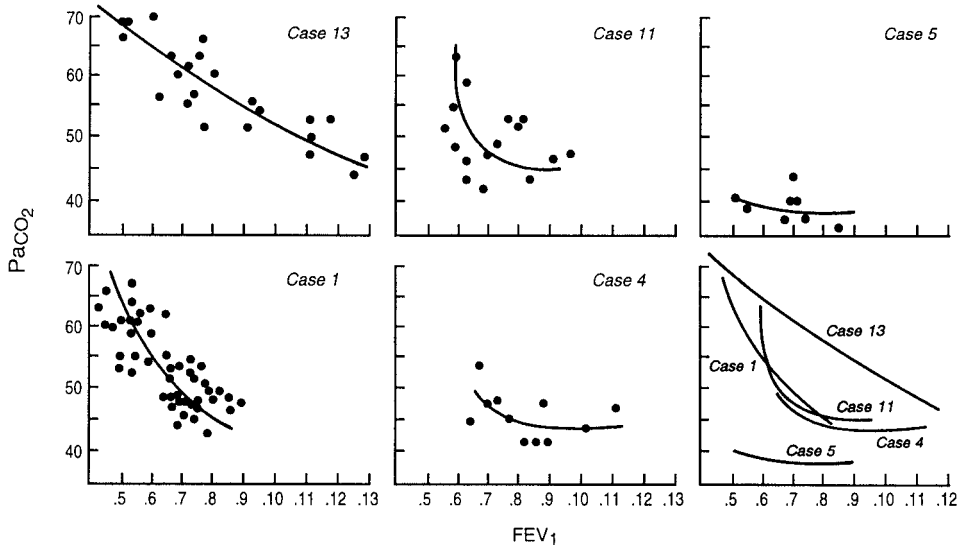

Figure 148-3 Results of repeated measurements of arterial P_{CO_2} and FEV_1 (liters) in five patients with advanced COPD. Free-hand curves of the data are shown plotted together in the lower right graph. Note that cases 1, 11, and 13 show marked increases in P_{CO_2}, with relatively small changes in FEV_1, whereas cases 4 and 5 do not. *(Based on data from Lane DJ, Howell JBL, Giblin B: Relation between airways obstruction and CO_2 tension in obstructive airways disease. Br Med J 3:707–709, 1968, with permission.)*

(Fig. 148-4). Among the offspring of patients with COPD with equally severe airway obstruction, the slopes of the ventilatory responses to isocapnic hypoxemia and hyperoxic hypercapnia are 30 to 40 percent lower in the offspring of hypercapnic patients than in offspring of eucapnic patients. Similarly, the slopes of the ventilatory and airway occlusion pressure responses to isocapnic hypoxia in the offspring of hypercapnic patients are approximately 40 percent of the values obtained in the offspring of normocapnic patients. In one study, the Pa_{O_2} of COPD patients while in a stable state and the Pa_{O_2} and Pa_{CO_2} during COPD exacerbations correlated with the

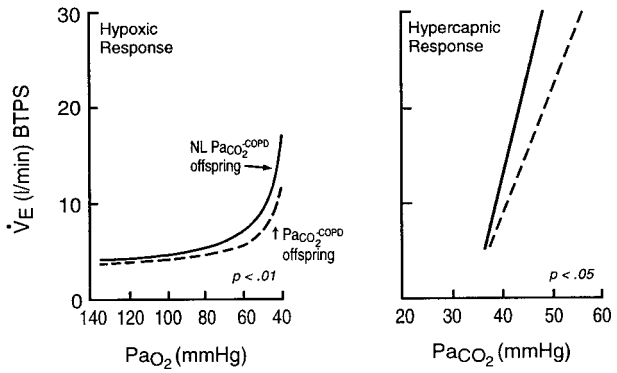

Figure 148-4 Mean isocapnic hypoxia and hyperoxic hypercapnic ventilatory response curves of 12 offspring of hypoventilating patients with COPD (solid line) and 10 offspring of eucapnic COPD patients (dashed line). Ventilatory responses to hypoxia and hypercapnia are significantly lower in the offspring of hypercapnic COPD than in the offspring of eucapnic COPD patients. *(Based on data from Mountain R, Zwillich CW, Weil JV: Hypoventilation in obstructive lung disease: The role of familial factors. N Engl J Med 297:521–525, 1978, with permission.)*

hypoxic ventilatory response of their sons. It appears that blunted chemosensitivities to hypoxia and hypercapnia are likely to be premorbid characteristics of hypercapnic patients with COPD, which contribute to the development of respiratory failure.

A number of reports describe patients with asthma and respiratory failure who had blunted ventilatory responses to hypoxia and hypercapnia and whose healthy immediate family members also showed blunted hypoxic and hypercapnic responses. Respiratory responses to hypoxia and hypercapnia in patients with asthma who have near-fatal attacks differ from those of asthmatics who did not have near-fatal attacks and age-matched, normal subjects. The slopes of the ventilatory and occlusion pressure responses to hypoxia in the patients with a history of near-fatal asthma are approximately 33 percent of the responses of the asthmatics without near-fatal attacks or normals, which are similar. Hypercapnic responses tend to be lower in the near-fatal asthmatic groups than in the other two groups, but the differences are smaller in magnitude.

Responses to Heightened Respiratory Load

A complex array of mechano- and proprioceptors whose afferents project to respiratory neurons in the brain stem and higher CNS structures provides the respiratory controller with information about the mechanics of breathing and performance of the ventilatory pump. The sensory receptors providing this afferent feedback and the CNS structures that integrate this feedback into a coordinated respiratory response (see below) are not perfectly understood. However, mechanoreceptors in the intercostal muscles that sense muscle tension and length (Golgi tendon receptors and spindle

organs, respectively) and pressure and flow sensors in the lower (vagal irritant receptors) and upper airway (larynx and mouth) clearly play a role in shaping the neuromuscular response to alterations in the mechanics of breathing.

Diseases of the airways (COPD and asthma) or chest wall (kyphoscoliosis) change the resistance and compliance properties of the ventilatory pump and, hence, stimulate mechanoreceptors in the ventilatory pump. In normal subjects and those with COPD, mechanoreceptor afferent inputs increase inspiratory neuromuscular output as reflected in airway occlusion pressure in response to bronchoconstriction or external resistances or elastance. Changes in ventilation during acute increases in airway resistance are inversely related to changes in occlusion pressure. Thus, the magnitude of the motor response to increases in respiratory load determines the ventilatory response.

External ventilatory loads that can be consciously detected and alter the intensity of the sensations associated with breathing elicit increases in respiratory effort as reflected by the diaphragm EMG and occlusion pressure. Increases in effort occur abruptly within the first loaded breath and in feedforward fashion; that is, the experience of the previous breath elicits a response in anticipation that the load will still be present. These responses are eliminated by general anesthesia and dulled if not absent in stages III and IV and REM sleep. The afferent input to the CNS elicited by external ventilatory loads probably arises from spindle and tendon organs in the respiratory muscles that project to the sensorimotor cortex and medullary respiratory neurons. The motor response to external ventilatory loads is thought to be behavioral.

The magnitude of the respiratory motor response to external loads varies widely from subject to subject and may be a hereditofamilial trait. Of considerable importance, some subjects with COPD demonstrate lesser occlusion pressure responses to acutely applied external resistive loads than age-matched normal subjects. It has been suggested that the blunted respiratory motor response to external loads may be a form of sensory adaptation to chronic increases in respiratory resistance. The fact that occlusion pressure responses of patients with COPD to external elastic loads and patients with asthma to external resistive loads are normal supports this concept. Of interest, the blunted motor response to external loads in some patients with COPD may reflect an increase in endogenous opiates within the CNS, since naloxone administration immediately enhances the response.

In subjects with COPD, bronchoconstriction increases airway occlusion pressure in proportion to increases in airway resistance and to a greater extent than with external flow-resistive loads. Bronchoconstriction increases the activity of vagal "irritant" receptors in the airway, which exert an inspiratory augmenting effect on breathing. Irritant receptors may also be excited chemically by inflammatory mediators (e.g., histamine, prostaglandin $F_{2\alpha}$) and, in contrast to external loads, elicit simple monosynaptic reflexes not abolished by sleep or anesthesia.

Mechanoreceptor inputs modify the respiratory motor responses to chemical stimuli to breathing. Increases in the elastic or resistive load to inspiration augment inspiratory muscle electrical activity and the airway occlusion pressures to hypoxia and hypercapnia. Subjects with asthma show heightened occlusion pressure responses to hypoxia and hypercapnia for this reason. Increases in the inspiratory neuromuscular drive to breathe allow ventilation to be maintained in the face of abnormalities in respiratory mechanics. Respiratory motor activity (i.e., occlusion pressure) also tends to be increased when the respiratory muscles are weak. In all likelihood, this reflects the fact that the maintenance of force output by a weakened muscle requires an increase in activation by the CNS.

Increased ventilatory loads also alter the pattern of breathing in load-dependent fashion. Subjects breathing against resistive loads breathe slowly and deeply, with an increase in tidal volume and prolongation of T_I and T_E. In contrast, subjects breathing against elastic loads tend to breathe with smaller tidal volumes and a reduced T_I and T_E; that is, they demonstrate a rapid and shallow pattern of breathing. Slow, deep breathing during resistive loading and rapid, shallow breathing during elastic loading diminish the resistive and elastic work of breathing, respectively. Alterations in breathing pattern when the mechanics of breathing are deranged are believed to be attempts to minimize the work of breathing, muscle tension, or energy expended.

Integrated Motor Responses

Respiratory motor responses to heightened chemical or mechanoreceptor drives to breathe elicit highly coordinated patterns of muscle activity that optimize the mechanical output of the respiratory musculature contracting in concert. These responses may take the following forms: (1) simple reflex-mediated recruitment of additional agonists, which exert similar mechanical effects on the chest wall; (2) sequential activation of inspiratory and expiratory muscles, which exert opposing effects on chest wall structures; and (3) complex behavioral acts that use nonrespiratory muscles to effect changes in body posture and expiratory airflow, minimizing dyspnea.

For example, hypercapnia and hypoxia recruit the external intercostal and parasternal muscles during inspiration in a stereotypic rostral-to-caudal direction, and the internal intercostals and triangularis sterni during expiration in the opposite direction. Preferential activation of the inspiratory external intercostal and parasternal muscles in the rostral-most interspaces decreases the impedance of the rib cage to rostral movement and, hence, facilitates thoracic expansion. Conversely, recruitment of the expiratory internal intercostals and triangularis sterni in the most caudal interspaces decreases the impedance to caudal movement and facilitates thoracic deflation. In addition, recruitment of the parasternal intercostal muscles facilitates inspiratory pressure as tidal volume increases. The parasternal intercostal muscle fiber length, which is optimum for tension development, is shorter than that of the diaphragm and occurs at higher lung volume. Accordingly, the parasternal muscles become mechanically more effective than the diaphragm as lung volume increases above functional residual capacity (FRC).

Moreover, hypercapnia and hypoxia increase phasic and tonic inspiratory activity in the dilator muscles of the upper airway (e.g., posterior arytenoid, alae nasae, genioglossus). Increases in activity of the dilator muscles of the upper airway decrease the load on the chest wall pumping muscles by decreasing the resistance to inspiratory airflow through the upper airway. Increased activity of these muscles also diminishes the susceptibility of the upper airway to collapse as inspiratory efforts become greater and subpharyngeal pressure becomes more subatmospheric.

In addition, phasic increases in abdominal expiratory muscle electrical activity during expiratory airflow accelerate lung emptying, thereby allowing the time of expiration to decrease. When sufficiently intense, activation of the abdominal muscles reduces end-expiratory lung volume and improves the ability of the diaphragm to generate pressure by favorably affecting its precontraction length, radius of curvature, and alignment with the rib cage. Reductions in end-expiratory lung volume achieved by the expiratory muscles also allow elastic work to be stored in the passive recoil of the chest wall and released suddenly at the onset of inspiration. Sudden release of the recoil pressure of the chest wall thereby "assists" the inspiratory muscles by contributing to the driving pressure to inspiratory airflow. A portion of the inspiratory load is thus assumed by the expiratory muscles.

Finally, hyperinflated, dyspneic patients with COPD often assume a stereotypic body posture that improves diaphragm, neck accessory, and pectoral girdle muscle mechanical advantage. This posture is forward flexion of the trunk, extension of the head and neck, bracing of the pectoral girdle by rounding of the shoulders, and grasping of the thighs with the arms. The effect of this posture is to increase abdominal pressure (thus increasing diaphragm precontraction length and radius of curvature); provide more favorable alignment of the scalenes and sternomastoid with the upper rib cage; and anchor the pectoral girdle muscles, allowing them to apply an inspiratory action on the rib cage. In this posture, transdiaphragmatic pressure is increased and diaphragm and sternomastoid muscle EMG activity is decreased. Patients with advanced COPD also spontaneously adopt pursed-lip breathing to slow expiratory airflow, thus minimizing dynamic airway compression.

Effects of Sleep

Responses to chemical stimuli to breathing are powerfully influenced by CNS state (e.g., sleep vs. waking). Slow-wave and REM sleep depress O_2 and CO_2 chemosensitivity, with greatest depression occurring in REM sleep. While the subject is awake, apnea does not occur in the presence of even marked hypocapnia, and ventilation is largely independent of changes in P_{CO_2}. Rather, ventilation persists even when Pa_{CO_2} is less than about 30 to 35 mmHg. Persistence of ventilation in the setting of hypocapnia (the so-called wakefulness drive to breathe) probably represents the effects on medullary neurons of inputs activated by auditory, visual, and tactile stimuli. In contrast, in the sleeping or anesthetized state, the ventilatory response to CO_2 extrapolates to zero ventilation in the hypocapnic range. In fact, apnea occurs when P_{CO_2} falls only 4 to 6 mmHg below waking eucapnic levels. Sleep-related changes in chemosensitivity, therefore, underlie the recurrent periods of apnea and hyperpnea and exaggerated hypercapnia that occur in some patients with diseases of the lung and chest wall.

The increase in respiratory motor activity induced by derangements in respiratory mechanics is also state-dependent; that is, heightened activity in awake subjects is absent in sleeping or anesthetized subjects. REM sleep, in particular, impairs the "load" response and causes collapse of the upper rib cage during inspiration, which adversely affects the level of ventilation as well as its distribution. Descending inhibitory drives to spinal α– and spindle γ– motor neurons in REM sleep cause atonia of all the respiratory muscles except the diaphragm. Muscle spindle γ-efferent activity determines spindle sensitivity by progressively contracting the intrafusal fiber. Accordingly, reductions in muscle spindle γ-efferent activity diminish spindle organ sensitivity and interfere with a mechanism for augmenting respiratory muscle spinal α– motor neuron activity. The diminished or absent load response during sleep and anesthesia probably explains the exaggerated increases in Pa_{CO_2} that occur during these periods in patients with lung and chest wall disease. In fact, REM sleep is the period in which Pa_{CO_2} is highest and Pa_{O_2} lowest in patients with stable COPD (Fig. 148-5).

Changes in Respiratory Structure

Respiratory Muscles

The respiratory muscles are highly plastic and undergo changes in structure, biochemistry, and contractile properties in response to chronic increases in load or changes in precontraction length. Chronic increases in inspiratory muscle activity enhance their strength and endurance. In animal models, chronic increases in inspiratory load produced by emphysema or inspiratory resistive loading increase diaphragm endurance and the content of oxidant enzymes (e.g., succinic dehydrogenase and citrate synthase) essential for high-energy phosphate synthesis. In patients with chronic asthma, inspiratory and expiratory muscle endurance assessed from the time course of the fall in maximum static pressure is about 40 percent greater than in normal controls. The effect of COPD per se on inspiratory muscle endurance has not been assessed. In subjects with COPD, however, daily training with inspiratory resistive ventilatory loads increases inspiratory muscle strength by about 40 percent as reflected by maximum static inspiratory pressure ($P_{I_{max}}$) over an 8- to 10-week period.

Hyperinflation impairs the force- and pressure-generating ability of the inspiratory muscles by decreasing muscle precontraction length and unfavorably changing muscle alignment with the chest wall. In particular, severe hyperinflation alters diaphragm shape (i.e., flattening) and decreases the zone of apposition with the rib cage. Flattening of the diaphragm displaces the vector of contraction force from a rostral-caudal direction to a medial-lateral direction and diminishes the ability of the diaphragm to increase abdominal

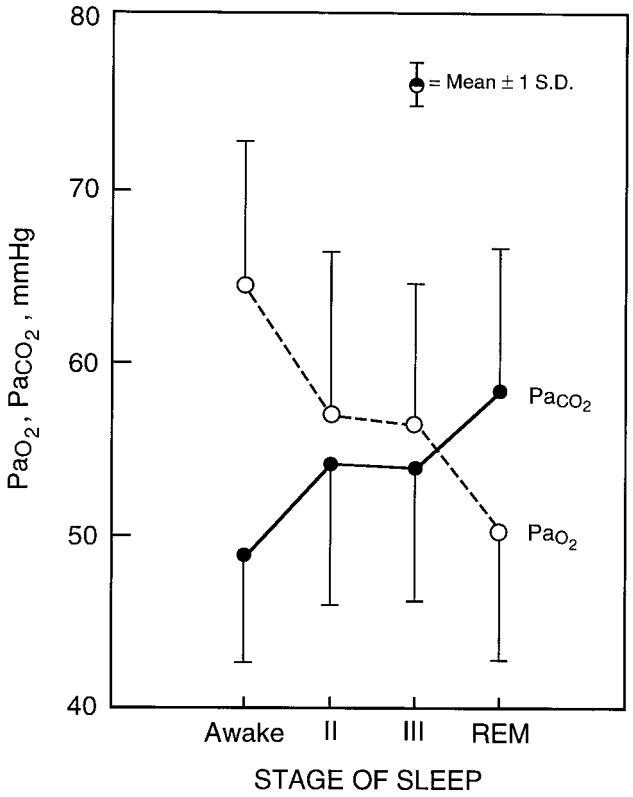

Figure 148-5 Changes in steady-state arterial P_{CO_2} during sleep in eight patients with stable COPD. Note that arterial P_{CO_2} increases and arterial P_{O_2} decreases during sleep. Greatest changes occur during REM sleep. For Pa_{CO_2}, average increase is 10 mmHg. *(Based on data from Koo KW, Sax DS, Snider GL: Arterial blood gases and pH during sleep in chronic obstructive pulmonary disease. Am J Med 58:663–670, 1975, with permission.)*

pressure. Reductions in the zone of apposition diminish the inflationary effects on the lower rib cage produced by increases in abdominal pressure induced by the diaphragm. In extreme cases of hyperinflation, the diaphragm may exert an expiratory action on the lower rib cage and retract the lower rib cage on inspiration (Hoover's sign).

In part, hyperinflation-induced impairment in the action of the diaphragm is compensated for by adaptive changes in the intrinsic muscle length–tension characteristic. In emphysematous animals, the active and passive length–tension curve of the costal diaphragm is displaced toward shorter lengths, thereby allowing maximum tension to be developed at significantly shorter lengths and higher lung volumes (Fig. 148-6). The shift in the length–tension curve appears to be the reverse of normal growth, in which muscle length is increased by addition of sarcomeres in series. A similar adaptation in the diaphragm seems to occur in chronically hyperinflated, stable outpatients with COPD.

Chest Wall Anatomy

Chronic hyperinflation elicits adaptive changes in the pressure-volume (P-V) characteristic of the passive chest wall. In animal models of emphysema, the static deflation, chest

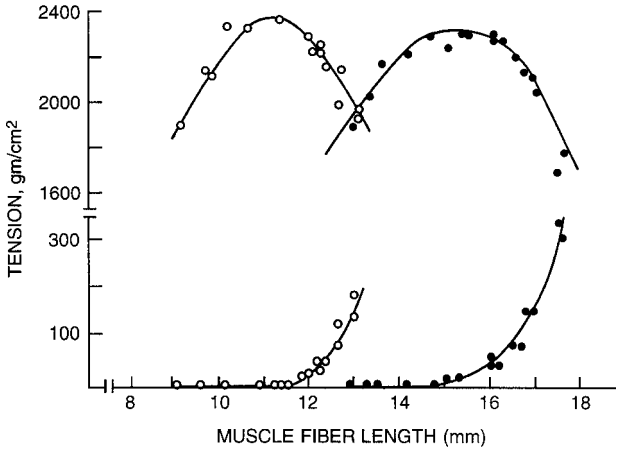

Figure 148-6 Active (upper trace) and passive (lower trace) length-tension (L-T) relationship of costal diaphragm of emphysematous (open circles) and normal hamsters (solid circles), assessed in vitro during electrical stimulation. Note that in emphysematous animals, the L-T curve is displaced toward shorter fiber lengths. This adaptive change in emphysematous animals allows the diaphragm to generate maximal tension (force) at shorter fiber lengths and helps preserve diaphragm contractile performance in the face of considerable hyperinflation. *(From Supinski GS, Kelsen SG: Effect of elastase-induced emphysema on the force-generating ability of the diaphragm. J Clin Invest 70:978–988, 1982, with permission.)*

wall P-V curve is shifted up and to the left, so there is a decrease in elastic recoil at any given lung volume. Shifts in the passive P-V curve are accomplished by a structural remodeling of the rigid structures in the chest wall. The length of the sternum and the lengths of the ribs in anteroposterior and transverse dimensions are increased. This displacement of the chest wall P-V curve diminishes the inspiratory elastic work of breathing during hyperinflation and preserves the zone of apposition of the diaphragm. An increase in the zone of apposition of the diaphragm in hyperinflation preserves the appositional force exerted by the diaphragm on the lower rib cage by virtue of changes in abdominal pressure. If present in patients with COPD, the process is reversible, since recent observations of the thorax after volume reduction surgery or lung transplantation for COPD indicate that the shape of the chest wall can quickly revert to normal.

DECOMPENSATING/MALADAPTIVE RESPONSES

Respiratory Muscle Fatigue

Overview/Definition

Studies in the laboratory and in the clinic indicate that the respiratory skeletal muscles, like muscles in the limbs, fatigue under conditions of intense activity, leading to respiratory failure. Conditions that increase the level of phasic inspiratory muscle activity, or the duty cycle of breathing, or that decrease the maximal pressure-generating capacity of

the muscle, make fatigue more likely. For example, derangements in the mechanical properties of the lung or chest wall or increases in ventilatory drive increase inspiratory muscle contractile activity. Of note, increases in ventilatory drive increase both the peak inspiratory pressure and T_I/T_T ratio, the latter by causing greater reductions in the duration of expiration than in that of inspiration.

Decreases in inspiratory muscle strength caused by aging, protein-calorie malnutrition, or electrolyte imbalances predispose to fatigue at any given level of inspiratory impedance or ventilation by decreasing $P_{I_{max}}$. Finally, on the basis of data from animal models, reductions in diaphragm blood flow are likely to decrease the level of muscle activity that leads to fatigue.

Respiratory muscle fatigue has been defined as a loss in muscle capacity to develop force or shorten, resulting from muscle fiber activity under load; it is reversible by rest. In contrast, respiratory muscle weakness has been defined as impairment in the capacity of a fully rested muscle to generate force.

Fatigue is viewed as developing when the muscle is highly active and generating appreciable levels of force. Recovery from fatigue is generally observed over a short time (e.g., minutes to hours). On the other hand, muscle weakness is commonly caused by muscle fiber atrophy, metabolic derangements that impair the ability of actomyosin cross-bridges to generate force (e.g., acidosis or electrolyte abnormalities that affect intracellular calcium flux), or chronic reductions in muscle precontraction length that impose a mechanical disadvantage (e.g., hyperinflation of the thorax and its effects on the inspiratory muscles). Implied in the definition of weakness is the idea that alterations in muscle function are secondary to alterations in muscle structure or lung volume and hence induce changes in muscle function that are more slowly reversible than fatigue (e.g., days to weeks). In the clinical setting, however, the distinction between muscle weakness and fatigue is difficult and not easily accomplished. Moreover, a close association exists between respiratory muscle weakness and respiratory muscle fatigue. In fact, weak muscles are predisposed to fatigue (see below).

Fatigue produces complex effects on muscle mechanical output. Fatigue prolongs contraction and relaxation time and depresses the force generated at a given stimulus frequency and fiber length, and reduces the velocity of shortening against a given load.

Depending on the cause of the fatigue, depression of force output can occur at primarily subtetanizing frequencies of muscle stimulation (e.g., less than 15 to 20 Hz), a condition called low-frequency fatigue, or at frequencies above 50 Hz, a condition called high-frequency fatigue (Table 148-1, Fig. 148-7). The biochemical and biophysical processes that underlie low-frequency and high-frequency fatigue differ. Muscle force responses to tetanizing frequencies of stimulation (i.e., above 50 Hz) are primarily determined by the processes of neuromuscular transmission and muscle excitation. In contrast, muscle mechanical output at subtetanizing frequencies is determined primarily by the processes of excitation-contraction coupling (e.g., calcium release from the sarcoplasmic reticulum, calcium-troponin interactions), perhaps caused, in part, by O_2 free radical–induced injury.

Table 148-1

Classification of Respiratory Muscle Fatigue

Central
Refers to decreases in phrenic motor output mediated by spinal or supraspinal mechanisms
Peripheral
Refers to fatigue occurring at the level of the muscle itself
Transmission
Failure of mechanisms operative in muscle excitation ("high-frequency" fatigue)
Contractile
Failure of mechanisms involved in excitation-contraction coupling or contractile protein function ("low-frequency" fatigue)

Of interest, recovery from high-frequency fatigue is more rapid (minutes) than recovery from low-frequency fatigue (hours) (Fig. 148-8). Moreover, the two forms of fatigue have different physiological consequences. High-frequency fatigue impairs muscle force output under conditions in which the muscle is maximally driven by the CNS (i.e., when muscle strength is being evaluated). Low-frequency fatigue, on the other hand, impairs force generation during resting breathing, when phrenic motor unit discharge rates are typically about 15 Hz. Since low- and high-frequency fatigue reflect impairments occurring at the level of the muscle, they have been termed *peripheral fatigue.*

Performance of strenuous ventilatory tasks may also elicit an additional, qualitatively different response—i.e., a reduction in central motor output and failure of the CNS to fully activate the respiratory muscles. That is, the diaphragm EMG or phrenic neurogram may decrease late in the performance of strenuous respiratory efforts before the point of exhaustion. This reduction in motor activity may limit task performance. The failure of CNS mechanisms to fully activate the muscle near the point of exhaustion has been termed *central fatigue.* The mechanisms underlying central fatigue are poorly understood. It is not clear whether central fatigue represents a behavioral response elicited by the unpleasant sensations present during ventilatory loading or is mediated reflexively or by changes in brain neurotransmitter levels.

Detection of Respiratory Muscle Fatigue

Diaphragm muscle fatigue has been diagnosed in humans from changes in the response of the muscle to electrical stimulation (i.e., the force-frequency relationship), the power

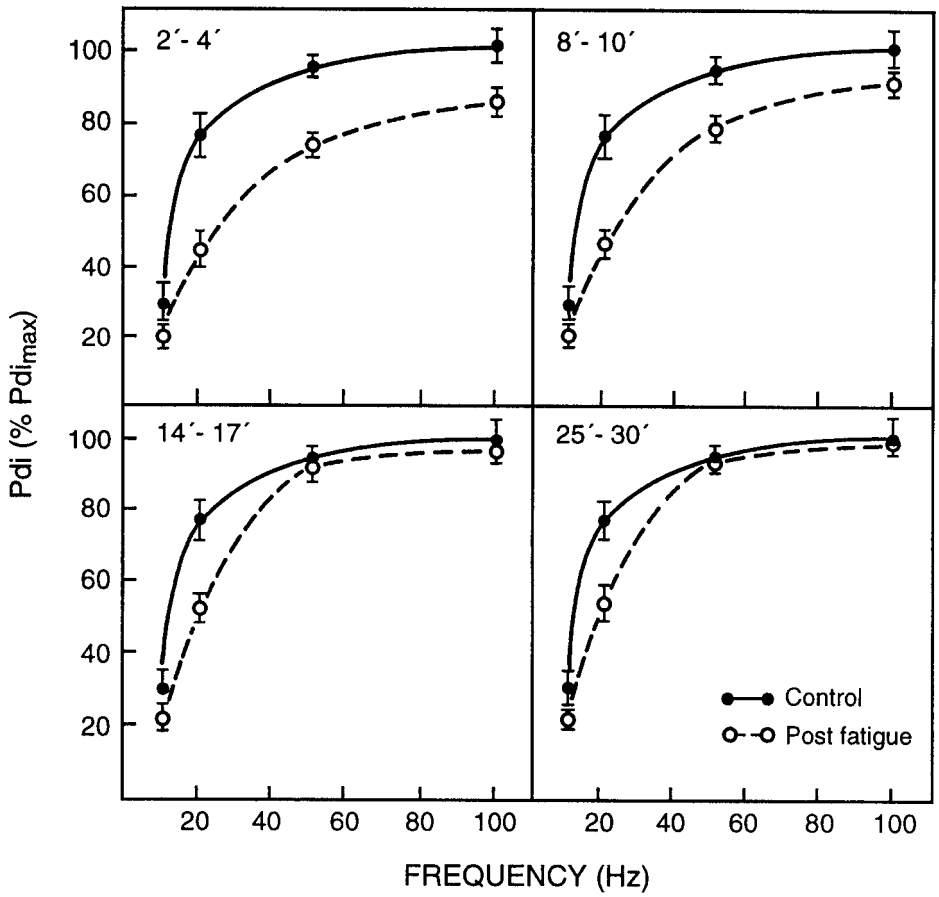

Figure 148-7 Force-frequency relationship of the human diaphragm during electrophrenic stimulation showing rate of recovery from high- and low-frequency fatigue. Data obtained in four subjects before and after a period of inspiratory resistive loading to exhaustion. At the point of exhaustion, the subject was unable to generate targeted values of transdiaphragmatic pressure (Pdi). Note the decrease in Pdi in response to low (20 Hz) and high (50 Hz) electrical stimulation immediately after loading, indicating the presence of both high- and low-frequency fatigue. Note also that high-frequency fatigue disappears within 14 to 17 min. In contrast, low-frequency fatigue persists beyond the period of observation (>30 min). *(Based on data from Aubier M, Farkas A, De Troyer RT, et al: Detection of diaphragmatic fatigue in man by phrenic stimulation. J Appl Physiol 50:538–544, 1981, with permission.)*

spectral content of the EMG, and $P_{I_{max}}$. As will be seen, the force-frequency relationship and EMG power spectrum analyses are complex and require sophisticated electronics and instrumentation. Consequently, their use has been confined to the research laboratory. On the other hand, $P_{I_{max}}$ is convenient and easily performed at the bedside but suffers from relative nonspecificity.

Electrical Stimulation

The force-frequency relationship represents a way of assessing muscle mechanical output over a wide range of stimulus intensities. Since fatigue shifts the force-frequency curve downward (and possibly to the left), the magnitude of the shift in the force-frequency relationship can be used to assess the severity of low- and high-frequency fatigue and the time course of recovery.

Electrical stimulation of the muscle of interest has several advantages. It allows the muscle to be activated in response to a standard stimulus without the cooperation of the subject. Hence, neurological deficits, decreased effort, and central fatigue, which may diminish muscle activation, are circumvented and peripheral fatigue can be detected.

EMG Power Spectrum

Fatigue alters the power-EMG spectral content of the raw EMG of the respiratory muscles analyzed by fast Fourier transform (Fig. 148-8). In the fresh diaphragm, the power (or voltage) contained in the EMG waveform reaches a maximum between approximately 85 and 105 Hz, and thereafter declines. (Maximum power in the EMG of the diaphragm, parasternal intercostal, and sternocleidomastoid occurs at somewhat different frequencies, however.) Fatigue-inducing contractions cause a leftward shift of the power spectral density, so that more of the power in the EMG is contained in a lower-frequency domain. The power-spectral density of the contracting diaphragm changes almost immediately with fatiguing contractions and considerably before the mechanical output of the muscle fails. The diaphragmatic EMG power

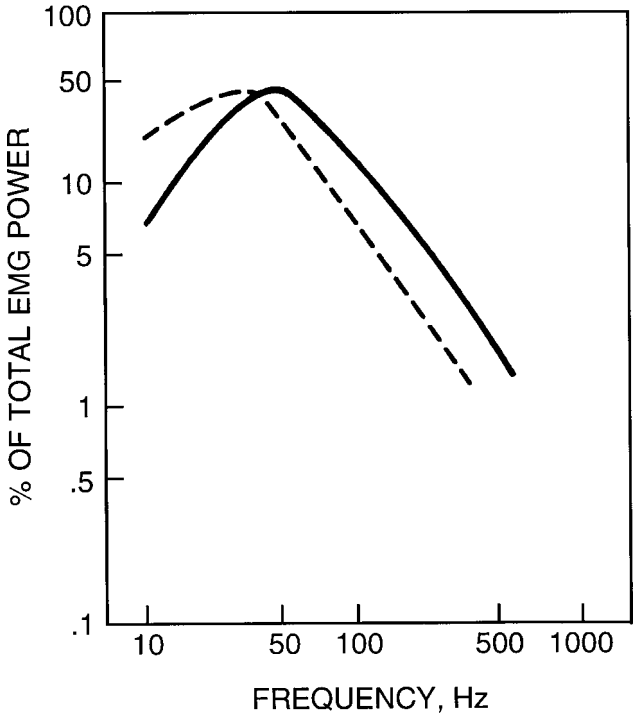

Figure 148-8 Schematic representation of the power-spectral density of a respiratory muscle EMG determined by fast Fourier transform. Note the concave appearance of the relationship. Note that fatigue (dashed line) decreases and increases power in the high- and low-frequency domains, respectively, thereby shifting the relationship toward the left. *(Based on data from Moxham J, Edwards RHT, Aubier M, et al: Changes in EMG power spectrum (high-to-low ratio) with force fatigue in humans. J Appl Physiol 53:1094–1099, 1982, with permission.)*

spectrum can be obtained from the raw EMG of the muscle, recorded from surface electrodes on the chest wall or within the esophagus. It is, therefore, relatively noninvasive and well tolerated. Moreover, the EMG power spectrum, unlike maximal static pressure, can be measured continuously—i.e., breath by breath—and does not require subject cooperation. Accordingly, the EMG power spectrum has proved to be a useful tool to study the pathophysiological mechanisms of human respiratory muscle fatigue. A significant caveat in the use of the power spectrum is the suggestion that it may be unable to detect low-frequency fatigue.

Pathogenesis of Respiratory Muscle Fatigue

Studies designed to examine the pathogenetic mechanisms that lead to respiratory muscle fatigue have largely focused on the diaphragm. The diaphragm has been the primary focus of attention for several reasons. First, it is the major respiratory muscle. Second, anatomic considerations allow the mechanical output of the diaphragm (i.e., transdiaphragmatic pressure) and its EMG, an index of phrenic motor outflow and fatigue state, to be assessed relatively easily. Finally, the cervical phrenic nerves can be electrically stimulated, thereby allowing the mechanical output of the muscle to be assessed under standard conditions as well as during volitional contractions.

Muscle Activity

In seminal studies, Roussos and Macklem observed that the time of onset of diaphragm fatigue was *not* related to the magnitude of the phasic inspiratory swings in Pdi during loading alone or to Pdi_{max} alone. Rather, the time of onset of mechanical failure of the diaphragm was a unique curvilinear function of the ratio of Pdi generated on each breath over Pdi_{max} (Pdi/Pdi_{max}) (Fig. 148-9). Values of Pdi/Pdi_{max} less than 40 to 50 percent could be maintained indefinitely; values greater than this threshold were associated with progressively more rapid exhaustion. These results made several important points. First, diaphragm fatigue depended on the relative intensity of contraction (i.e., muscle force output as a percentage of its strength). Second, contractions below some critical threshold could be sustained indefinitely and did not lead to fatigue.

Subsequent studies demonstrated that the timing as well as the intensity of diaphragmatic contractions determined the time of onset of mechanical failure of that muscle. Increases in the ratio of the T_I over the T_T increased the rapidity of onset of fatigue at any given Pdi/Pdi_{max} ratio. That is, increasing the duration of diaphragm contraction relative to the period during which the diaphragm is relaxed, the duty cycle of breathing, predisposes to fatigue. In fact, diaphragm fatigue appears to be largely a function of the product of $Pdi/Pdi_{max} \times T_I/T_T$, which has been termed the *diaphragm tension–time index* (TTI) (Fig. 148-10). The TTI is, in essence, the integrated area under the pressure waveform over time. The TTI is usually expressed not in absolute terms of pressure per unit of time but, rather, in relative terms as a dimensionless value (i.e., as a percentage of the maximum) to reflect the importance of relative changes in pressure and timing of contraction. The TTI determines muscle energy use as reflected in the O_2 consumption.

A threshold for the onset of fatigue occurs at a TTI of approximately 15 to 20 percent of maximum (Fig. 148-10). The greater the TTI above this value, the more rapidly fatigue ensues.

Subsequent studies in normal subjects demonstrated that mechanical failure of the inspiratory muscles as pressure generators can be accelerated at a given TTI by increasing the V_T/T_I. Increases in V_T/T_I reflect an increase in the velocity of inspiratory muscle shortening. Since the greater the velocity of shortening and the more rapid actomyosin cross-bridge cycling, the greater the rate of adenosine triphosphate splitting, this is not surprising. Also of interest, respiratory maneuvers associated with high levels of ventilation appear to selectively fatigue the diaphragm, whereas maneuvers that produce high levels of pressure primarily fatigue the intercostal and neck muscles.

Muscle Blood Flow

Diaphragm fatigue may relate, in part, to a compromise of muscle blood flow during intense contractions. The

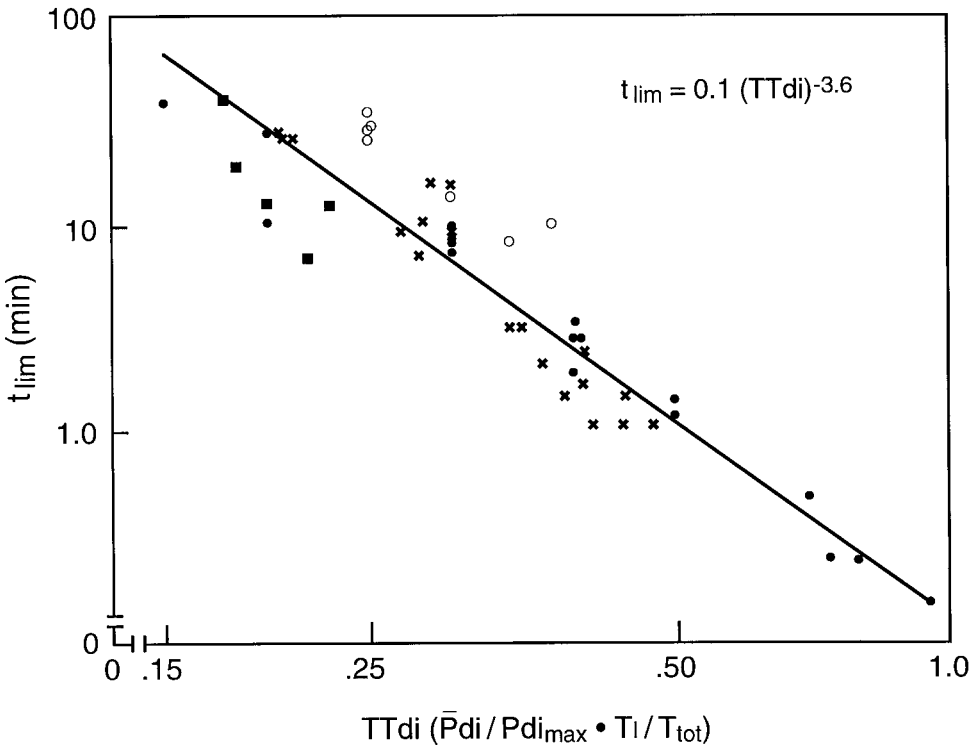

Figure 148-9 Relationship between the intensity of diaphragm contractile activity reflected in the diaphragm tension-time index (TTdi)—i.e., the product of $Pdi/Pdi_{max} \times T_I/T_T$ and the time of onset of mechanical failure of the diaphragm, Tlim. The two scales are logarithmic. Data obtained in normal subjects during strenuous volitional contractions during inspiratory resistive ventilatory loading. Note that above approximately 15 percent TTdi, Tlim decreases progressively with increasing TTdi. These data indicate that a fatigue threshold exists for the human diaphragm above TTdi 15 to 20 percent and that above this threshold, diaphragm endurance is a unique function of the TTdi. *(Based on data from Bellemare F, Grassino A: Evaluation of human diaphragm fatigue. J Appl Physiol 53:1196–1206, 1982, with permission.)*

relationship of diaphragm blood flow to muscle contractile activity is complex and depends, like fatigue itself, on both the intensity and timing of contractions. The level and pattern of diaphragm activation, therefore, determine not only muscle energy use but also the availability of metabolic fuel (i.e., glucose, free fatty acids, and other nutrients).

Contractions of low intensity increase blood flow. In contrast, contractions in excess of 20 to 30 percent of Pdi_{max} mechanically compromise blood flow and cause postcontraction hyperemia. When the diaphragm contracts rhythmically, the T_I/T_T also affects diaphragm blood flow. At Pdi/Pdi_{max} values that compromise blood flow during contraction (i.e., above 20 to 30 percent), blood flow occurs solely during the phase of muscle relaxation. Consequently, increases in the T_I/T_T ratio decrease overall blood flow by encroaching on relaxation time. Diaphragm blood flow is, therefore, a function of the TTI rather than Pdi/Pdi_{max} or the T_I/T_T alone. Blood flow increases up to a TTI of 20 to 30 percent and thereafter falls progressively with further increases in TTI. Compromise of diaphragm blood flow when TTI is greater than 20 to 30 percent of maximum may lead to a condition in which the metabolic needs of the muscle outstrip the availability of energy supply. Alternatively, the importance of blood flow may lie in washing out toxic metabolites (e.g., hydrogen and phosphate ions) from the muscle. The diaphragmatic TTI associated with limitation of blood flow is also a complex function of the level of systemic arterial pressure. Reductions in arterial pressure produced in animal models by bleeding decrease blood flow at any given level of TTI and reduce the Pdi value at which blood flow is mechanically impeded.

Of considerable importance, diaphragm blood flow may also be a determinant of steady-state diaphragm contractile function in COPD patients in acute respiratory failure. In small numbers of COPD patients, 30 to 50 percent increases in diaphragm blood flow with intravenous dopamine (8 μg/kg/min) caused rapid, approximately 40 percent increases in Pdi during electrophrenic twitch contractions. These findings require confirmation before vasodilator therapy to improve diaphragm function can be advocated. However, they suggest the possibility that diaphragm blood flow may be compromised by intense contractile activity in patients with severe lung disease.

Rapid, Shallow Breathing

Patients with abnormalities in ventilatory pump function breathe rapidly and shallowly in respiratory failure. Respiratory rate is increased and tidal volume is decreased.

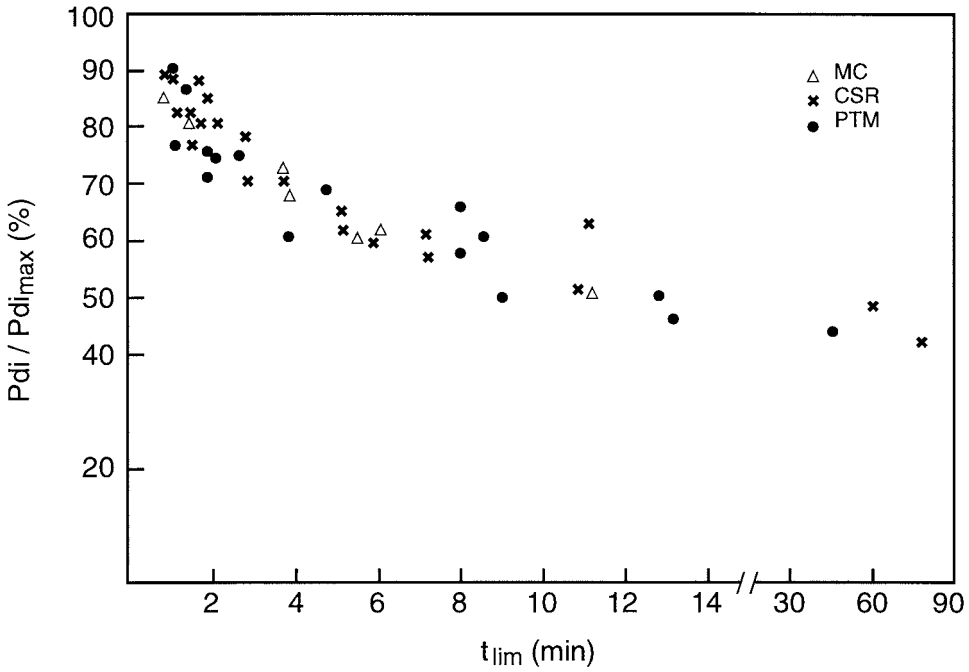

Figure 148-10 Effect of increasing Pdi/Pdi_{max} (i.e., the ratio of peak inspiratory Pdi) during resistance breathing over maximum static Pdi (ordinate) at the time of onset of mechanical failure of the diaphragm, Tlim (abscissa). Data from three normal subjects (shown as separate symbols). Note that progressive increases in Pdi/Pdi_{max} are associated with more rapid onset of diaphragm fatigue. Note also the curvilinear nature of the relationship, with apparent asymptote between 40 and 50 percent Pdi/Pdi_{max}, which represents a fatigue threshold. *(Based on data from Roussos CS, Macklem PT: Inspiratory muscle fatigue, in Macklem PT, Mead J (eds), Handbook of Physiology, section 3: The Respiratory System, vol III: Mechanics of Breathing, part 2. Bethesda, MD, American Physiological Society, 1986, pp 511–527, with permission.)*

Reductions in T_I are out of proportion to reductions in T_E, so the duty cycle of breathing (T_I /T_T) is reduced to less than normal values (below 40 percent). Average inspiratory airflow (V_T/ T_I) tends to be normal, despite abnormalities in mechanics, because of increases in the neuromuscular drive to breathe as reflected in the airway occlusion pressure. Reductions in T_I have the effect of increasing the dead-space-to-tidal-volume ratio (V_D/V_T) and predisposing to alveolar hypoventilation.

A rapid, shallow pattern of breathing with an abnormally low T_I/T_T ratio and reduced tidal volume is extremely common in patients with COPD during acute exacerbations and tends to get better with improvements in clinical condition. Rapid, shallow breathing appears to cause CO_2 retention rather than result from it. It can be produced in patients with COPD by histamine-induced bronchoconstriction and reversed by topical airway anesthesia. Patients with neuromuscular disease in whom the ability to generate inspiratory pressure is impaired require more intense motor outflow to the respiratory muscles to maintain tidal volume. Patients with respiratory muscle weakness also tend to breathe rapidly and shallowly.

The pattern of breathing has been quantified in adults receiving ventilatory support for acute respiratory failure from the ratio of respiratory rate (breaths per minute) divided by tidal volume (liters). This useful parameter has been termed the *rapid shallow breathing index* (RSBI). It has proved to be an extremely powerful way of assessing weanability in adults with a variety of medical and surgical conditions. The greater the value, the more rapid and shallow is the pattern of breathing. Values for the RSBI exceeding 100 are associated with a high probability of failure to wean from mechanical ventilation. The RSBI lends itself to a more general use in patients with disorders of the ventilatory pump not requiring mechanical ventilation.

Rapid, shallow breathing leading to CO_2 retention exerts a number of deleterious effects. First, CO_2 retention decreases Pa_{O_2} and arterial pH. Decreases in Pa_{O_2} result in accordance with the alveolar air equation. In general, a 1 mmHg increase in P_{CO_2} causes a 1.25 mmHg reduction in Pa_{O_2} (assuming a respiratory quotient of 0.8; larger respiratory quotient values are associated with smaller changes in Pa_{O_2}). Second, renal compensation for hypercapnia-induced respiratory acidosis stimulates bicarbonate resorption. Increases in body fluid bicarbonate restore pH toward normal values but blunt the ventilatory response to further increases in CO_2. Third, hypercapnia depresses diaphragm contractility; that is, Pdi is decreased at a given level of diaphragm electrical activity in proportion to the increase in P_{CO_2}.

However, rapid, shallow breathing may also confer beneficial effects to subjects with severe ventilatory pump dysfunction. First, CO_2 retention increases the CO_2 partial-pressure gradient between the alveolus and atmosphere. Accordingly, during hypercapnia the same volume of metabolically produced CO_2 can be excreted at a lower level

of alveolar and minute ventilation and O_2 cost of breathing than during eucapnia. As such, CO_2 retention affords a mechanism to diminish the activity level of the inspiratory muscles and their propensity to fatigue. Normal humans and animal models fatigued by inspiratory resistive loads in the laboratory spontaneously minimize the diaphragm TTI after fatigue by adopting a shallow, rapid pattern of breathing. In fact, a large study of stable outpatients with advanced COPD indicates that the inspiratory muscle TTI is below the fatigue threshold even in markedly hypercapnic (above 60 mmHg) subjects (see below). Second, rapid, shallow breathing minimizes the magnitude of dynamic hyperinflation in patients with severe COPD who breathe on the envelope of the maximum expiratory flow-volume loop; that is, reductions in tidal volume and decreases in the T_I /T_T ratio diminish the volume to be exhaled and prolong the expiratory time available to reach FRC.

The balance between the beneficial and deleterious effects of CO_2 retention is difficult to define with precision; however, the balance probably is determined by the magnitude and rapidity of the changes in Pa_{CO_2} and pH and their effect on the cardiovascular and central nervous systems. Relatively small (5 to 15 mmHg) changes in Pa_{CO_2}, produced gradually over days to weeks and leaving pH at levels of 7.25 to 7.30, are likely to be well tolerated and, on balance, beneficial. On the other hand, Pa_{CO_2} changes that occur rapidly and reduce pH to less than 7.25 are likely to exert net negative effects. In fact, respiratory acidosis to pH values under 7.25 is life-threatening and generally considered an indication for intubation and mechanical ventilation. Cardiac function and sympathetic regulation of peripheral vascular resistance are impaired at this level of pH. Patients become encephalopathic (i.e., somnolent and unable to care for themselves and control their airway secretions). Obviously, hypercapnia of such magnitude is to be avoided.

Pathogenesis of Rapid, Shallow Breathing

The neurophysiological mechanisms driving the altered pattern of breathing are obscure. Moreover, whether changes in breathing pattern in animal models and humans are reflexively induced or behaviorally mediated, or reflect changes in brain neurotransmitter levels (e.g., endorphins), is unclear. However, chemosensitivity-induced alterations in respiratory activity do *not* appear to be the explanation. Hypoxia- and hypercapnia-induced reductions in T_E are disproportionately greater than reductions in T_I, so the T_I/T_T ratio increases. Moreover, V_T/ T_I and the tidal volume increase rather than decrease.

Reflexes originating from mechanoreceptors in the contracting rib cage muscles and diaphragm (i.e., Golgi tendon organs, spindle organs, and type III and type IV endings) probably play a role in shaping the rapid, shallow pattern of breathing. In deeply anesthetized animals, stretch of the intercostal muscles or an increase in diaphragm tension may abruptly terminate inspiration. Activation of vagal irritant receptors in the airway may also produce rapid, shallow breathing. In animal models, rapid, shallow breathing produced acutely by inhalation of allergen or inflammatory mediators (e.g., histamine, bradykinin) can be prevented by vagal blockade. These observations suggest that rapid, shallow breathing in bronchoconstriction may be mediated by vagal sensory endings in the airways.

Finally, changes in the pattern of breathing may represent a behavioral response to minimize the sense of dyspnea. The sense of dyspnea is a complex perceptual construct that is not fully understood but is probably multifactorial. In fact, an important determinant of the sense of dyspnea is the magnitude of the CNS motor command to the inspiratory muscles as reflected in the peak inspiratory intrathoracic pressure. Studies indicate that the sense of breathlessness increases for any set of respiratory mechanical conditions with increases in peak inspiratory pressure, the duration of inspiration, or respiratory rate. In particular, the magnitude of the sense of dyspnea depends on inspiratory pressure (P) swings as a percent of maximum (P/P_{max}), the duration of inspiration relative to the total breath cycle (T_I/T_T), and the respiratory rate (freq). However, the relative importance of these three terms is quite different. The peak inspiratory pressure has a far greater effect than the duration of inspiration, which in turn has a greater effect than breathing frequency. The sensation of dyspnea can be expressed quantitatively by each of these parameters raised to a power:

$$\text{Dyspnea} = P^{1.3} \times {T_I/T_T}^{1.14} \times \text{freq}^{-0.97}$$

Increases in intrathoracic pressure required to maintain airflow and tidal volume in patients with abnormalities in ventilatory pump function increase the sense of dyspnea. Given the greater exponential value for P than for the timing variables, it can be seen that the magnitude of the swing in inspiratory pressure is the predominant determinant of dyspnea. Thus, at a given level of minute ventilation and set of respiratory mechanics, the pattern of breathing determines the intensity of breathlessness. When the mechanics of breathing are deranged by COPD or kyphoscoliosis, diminishing peak inspiratory intrathoracic pressure (i.e., tidal volume) and increasing respiratory rate (i.e., a rapid, shallow pattern of breathing) tend to minimize the sense of breathlessness.

At equivalent levels of airway resistance and inspiratory effort, the sense of dyspnea is greater during bronchoconstriction than during external resistive loading, probably because of the activation of vagal irritant receptors. Differences in the intensity of dyspnea at any given level of airway obstruction, therefore, may depend on the site of airway obstruction (i.e., intra- vs. extrathoracic). Also, the sense of dyspnea at a given level of peak intrathoracic pressure, T_I/T_T ratio, and frequency of breathing are increased in the setting of inspiratory muscle fatigue, probably because a greater motor command is required to generate a given level of intrathoracic pressure. Finally, it should be apparent from the above equation that the sense of dyspnea depends on the same variables that determine respiratory muscle fatigability. However, respiratory muscle fatigue, in contrast to dyspnea, does not

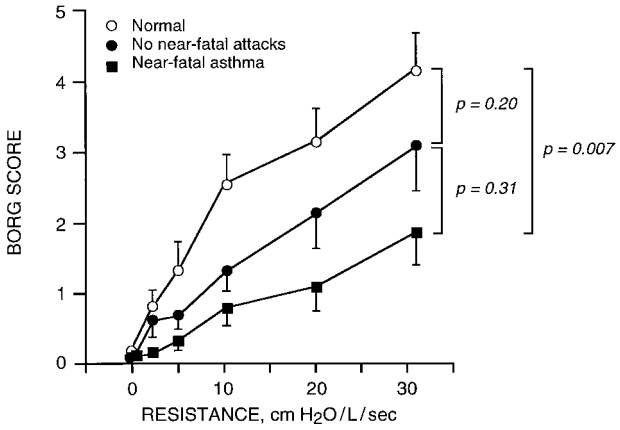

Figure 148-11 Severity of dyspnea experienced during breathing against external resistive ventilatory loads in normal subjects, patients with asthma but no near-fatal attacks, and patients with near-fatal asthma. Y axis indicates the intensity of dyspnea (i.e., Borg score). Increasing numerical values on the Borg score indicate increasing dyspnea. Note that at any given level of external resistance, dyspnea was significantly less in patients with near-fatal asthma than in the normal group. *(Based on data from Kikuchi Y, Okabe S, Tamura G, et al: Chemosensitivity and perception of dyspnea in patients with a history of near-fatal asthma. N Engl J Med 330:1229–1234, 1994, with permission.)*

appear to depend on the pattern in which TTI is developed; that is, whether a given TTI is arrived at by a higher P/P_{max} or a higher T_I/T_T is irrelevant in the development of fatigue, but it *is* important in the generation of respiratory sensations.

Perceptual acuity of the respiratory sensations elicited when the mechanical properties of the ventilatory pump are deranged is a major determinant of the pattern of breathing and tendency to develop CO_2 retention in subjects with COPD. For example, when airway resistance is increased experimentally, patients with COPD who retain CO_2 are those with the greatest perceptual acuity for changes in intrathoracic pressure. That is, spontaneous tidal volume and T_I are smallest in patients with COPD who have the highest perceptual acuity for changes in intrathoracic pressure.

On the other hand, when airway resistance was increased experimentally by external resistive loads, asthmatics with near-fatal attacks experienced less dyspnea at any level of resistance than normal subjects (Fig. 148-11). Accordingly, in patients with COPD the acuity of respiratory perception plays an important role in the pathogenesis of respiratory failure. The mechanism by which respiratory perception contributes to respiratory failure awaits clarification.

Undernutrition

Undernutrition, defined as a body weight less than 90 percent of the ideal, is extremely common in patients with COPD, occurring in about 25 percent of stable outpatients and about 40 percent of hospitalized patients. Undernutrition is an independent risk factor for mortality. For a given level of lung function, undernourished patients with COPD have a greater 5-year mortality than normally nourished subjects. The respiratory muscles, like skeletal muscles in other parts of the body, atrophy under conditions of chronic protein-calorie deficiency. In patients without lung disease, $P_{I_{max}}$ is significantly smaller in those who are undernourished than in those who are well-nourished. In those with COPD at autopsy, the mass (i.e., weight and thickness) of the diaphragm is diminished in undernourished compared to well-nourished subjects. Both slow and fast fibers in respiratory muscles (e.g., the diaphragm and intercostals) atrophy in subjects with advanced COPD. In patients with COPD, resting Pa_{CO_2} is inversely related to $P_{I_{max}}$. The weaker the subject, the greater the Pa_{CO_2}. Reductions in $P_{I_{max}}$ predispose to inspiratory muscle fatigue by increasing the Pdi/Pdi_{max} ratio and, hence, the TTI during breathing against a given set of lung mechanics. Of practical importance, aggressive nutritional repletion, which increases body weight, augments $P_{I_{max}}$ and Pdi_{max}. Thus, respiratory muscle wasting and atrophy are reversible in undernourished patients with COPD.

The pathogenesis of body wasting in subjects with chronic diseases like COPD is unclear. However, increases in the work of breathing and respiratory muscle activity increase resting energy expenditure by as much as 50 to 100 percent above normal. In normal subjects in whom basal energy requirements are similarly increased by heavy physical labor (e.g., lumberjacks), caloric intake is increased appropriately to meet metabolic demands and body weight is preserved. Accordingly, the root of the problem in undernourished patients with COPD may be "relative anorexia," so that increases in basal caloric requirements are not accompanied by adequate caloric intake. Undernourished patients with COPD have higher blood levels of the cachexia factor tumor necrosis factor-α than well-nourished COPD subjects.

SPECIFIC DISEASES

Chronic Obstructive Pulmonary Disease

Patients with advanced COPD develop CO_2 retention because of abnormalities in the gas exchange and mechanical properties of the lung. The relationship between the severity of COPD as reflected by the forced expiratory volume in 1 s (FEV_1) and steady-state resting P_{CO_2} is curvilinear (Fig. 148-12). In general, Pa_{CO_2} does not increase above normal until the FEV_1 decreases to about 20 to 25 percent of predicted normal values.

The effects of COPD on lung gas exchange are complex. Simply put, increases in lung dead space and abnormalities in ventilation/perfusion relationships impair CO_2 elimination and O_2 uptake. Increases in physiological dead space require greater than normal levels of ventilation and tidal volume to maintain eucapnia. Maintenance of "normal tidal volume" in the setting of increased dead space predisposes to CO_2 retention because of an unfavorable V_D/V_T. Normally, during resting breathing, ventilation is 4 to 5 L/min, of which alveolar ventilation is approximately 70 to 80 percent.

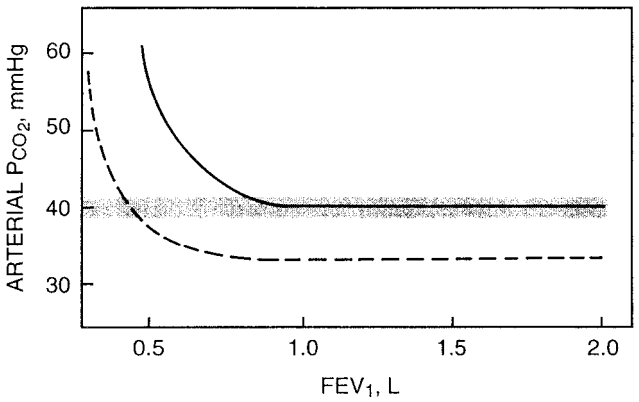

Figure 148-12 Relationship between the severity of airway obstruction reflected in the FEV_1 and steady-state arterial P_{CO_2} in COPD and asthma. Shaded area represents normal range of arterial P_{CO_2}. The relationship is curvilinear, so CO_2 retention occurs only after FEV_1 is considerably reduced. The asthmatic curve (dashed line) lies below and to the left of the curve for COPD, indicating that much greater levels of obstruction are necessary before arterial P_{CO_2} rises. *(From Fishman AP: Pulmonary Diseases and Disorders. New York, McGraw-Hill, 1980, vol 1, p 426, with permission.)*

In COPD, abnormalities in lung gas exchange for O_2 and CO_2 (i.e., increased dead-space volume and alveolar-arterial O_2 gradient) require greater than normal levels of ventilation to maintain eucapnia and euoxia. Consequently, in subjects with advanced COPD, minute ventilation is typically two to three times the normal value (i.e., 10 to 15 L/min). Minute ventilation is increased still further in hypoxemia. Increases in ventilation require increases in airflow, tidal volume, and the duty cycle of breathing.

Hyperinflation and heightened airway resistance are common in patients with advanced COPD. Hyperinflation and increases in FRC in patients with COPD are multifactorial. First, emphysema decreases lung (and possibly chest wall) elastic recoil pressure. Second, tonic activation of chest wall inspiratory muscles throughout the respiratory cycle enhances transpulmonary pressure. Third, activation of laryngeal constrictor muscles and pursed-lip breathing during expiration slow the rate of expiratory airflow. Fourth, severely obstructed patients breathing on the envelope of the maximum expiratory flow-volume curve may have insufficient time during expiration to exhale to passively determined FRC.

In advanced COPD, increases in airway resistance and hyperinflation require greater than normal swings in intrathoracic pressure to generate normal levels of airflow and tidal volume. In consequence, the respiratory neuromuscular drive to breathe, peak inspiratory intrathoracic pressure, and the TTI of the inspiratory muscles are increased considerably. Normally, at rest, respiratory muscle O_2 consumption is less than 2 percent of total body O_2 consumption (i.e., about 5 ml/min or less). In contrast, patients with advanced cardiopulmonary disease may have levels of respiratory muscle O_2 uptake greater than 50 percent of total body O_2 uptake (i.e., in excess of 125 ml/min).

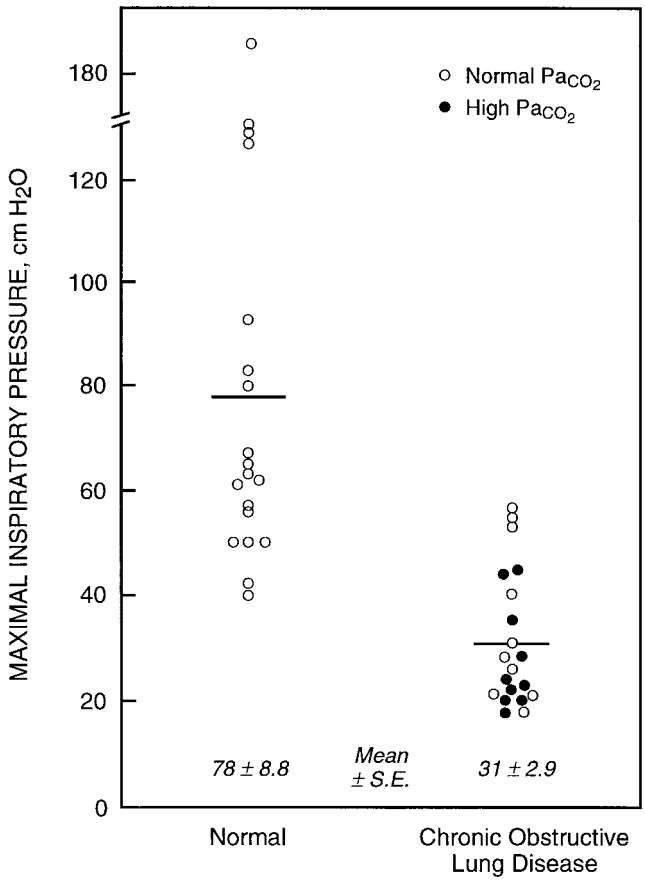

Figure 148-13 Inspiratory muscle strength as reflected in the maximum static inspiratory pressure ($P_{I_{max}}$) at functional residual capacity (FRC) in subjects with advanced COPD and age-matched normal subjects. Each symbol represents a single subject. Note that in COPD subjects, because of hyperinflation and muscle wasting, $P_{I_{max}}$ is reduced to approximately 40 percent of the value in normal subjects. Note the tendency for hypercapnic subjects to have even lower values of $P_{I_{max}}$ than eucapnic COPD subjects. *(Based on data from Sharp JT, van Lith P, Nuchprayoon C, et al: The thorax in chronic obstructive lung disease. Am J Med 44:39–46, 1968, with permission.)*

In subjects with severe COPD, hyperinflation reduces inspiratory muscle mechanical advantage, which decreases the capacity of the inspiratory muscles to generate pressure (P_{max}). P_{max} values in patients with COPD may be as low as one-third to one-half that of age-matched normal subjects (Fig. 148-13). Moreover, aging- and malnutrition-associated changes in the diaphragm may further impair Pdi_{max} in subjects with COPD. COPD typically becomes disabling in the sixth and seventh decades of life, a period of life at which Pdi normally falls. For example, Pdi_{max} is about 25 percent less in healthy men over 65 years of age than in healthy men under 35 years of age.

Respiratory Muscle Fatigue in COPD

Severe COPD is arguably the clinical condition most likely to cause inspiratory muscle fatigue. The combined effects of increases in inspiratory muscle activity and decreases in

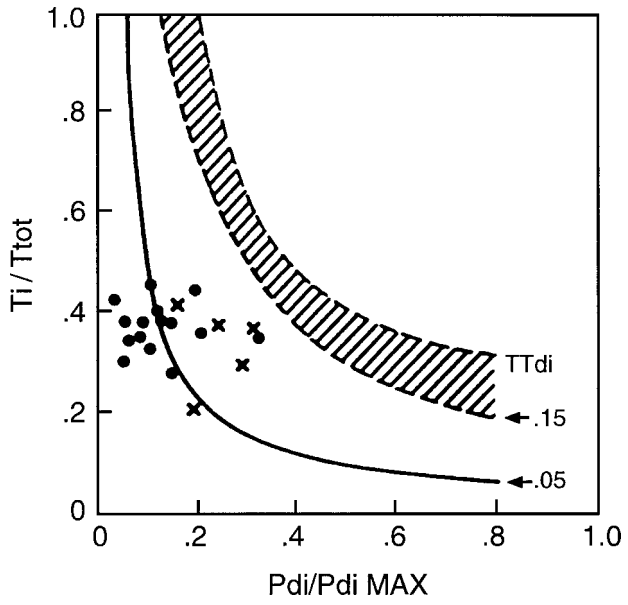

Figure 148-14 Diaphragmatic tension-time index (TTdi) in 20 stable outpatients with COPD breathing room air at rest. Each symbol represents a separate COPD subject. Shaded area represents the fatigue threshold in normal subjects. Most COPD subjects breathe well below the fatigue threshold and cluster around 0.05 TTdi. *(Based on data from Bellemare F, Bigland-Ritchie B: Central components of diaphragmatic fatigue assessed by phrenic nerve stimulation. J Appl Physiol 62:1307–1316, 1987, with permission.)*

muscle strength in severe COPD increase the diaphragm TTI during resting breathing in elderly COPD patients considerably above the normal value of 1 to 2 percent. The TTI may, in fact, approach the fatigue threshold (i.e., 15 to 20 percent) in patients with COPD (Fig. 148-14). These and similar data indicate that diaphragm activity is increased in patients with advanced COPD, and that the diaphragm is highly susceptible to fatigue when breathing is increased above spontaneous levels by minor increases in tidal volume or T_I/T_T. The diaphragm TTI is higher in hypercapnic than in eucapnic COPD subjects, but even in hypercapnic subjects it does not exceed the fatigue threshold. Mean TTI, even for hypercapnic subjects, is approximately 10 percent. Therefore, hypercapnia per se does not indicate the presence of diaphragm fatigue even in patients with severe COPD. Rather, hypercapnia may be a manifestation of a breathing strategy (i.e., rapid, shallow breathing) that minimizes inspiratory muscle activity and, hence, prevents fatigue.

On the other hand, inspiratory muscle fatigue may be a relatively common occurrence during the hyperpnea of exercise and could contribute to exercise limitation in COPD subjects. A high percentage (about 50 percent) of subjects with moderate to severe COPD demonstrate EMG evidence of scalene or diaphragm (or both) fatigue during exercise. Of interest, improvement in exercise performance and elimination of the EMG signs of fatigue can be achieved following inspiratory resistance training.

Subjects with COPD in acute respiratory failure requiring mechanical ventilation are more likely to show evidence of inspiratory muscle fatigue. During weaning from mechanical ventilation, diaphragm EMG changes indicative of fatigue precede the increases in Pa_{CO_2}. These findings suggest that diaphragm fatigue contributes to ventilator dependence after the onset of hypercapnic respiratory failure in at least some critically ill subjects.

In COPD patients being weaned from mechanical ventilation during a bout of acute respiratory failure, the tracheal occlusion pressure is usually greater than 6 cm H_2O and EMG evidence of diaphragm fatigue is present during spontaneous breathing. Patients with persistently elevated tracheal occlusion pressure values (above 6 cm H_2O) and EMG evidence of diaphragm fatigue generally cannot be successfully weaned from mechanical ventilation. In contrast, sternomastoid muscle fatigue is evident in fewer than 10 percent of COPD patients hospitalized for worsening respiratory distress.

In summary, most subjects with stable COPD adopt a pattern of breathing that minimizes the diaphragm TTI and prevents inspiratory muscle fatigue. Behavioral mechanisms may be operative in an attempt to minimize the sensation of dyspnea. On the other hand, inspiratory muscle fatigue contributes to the morbidity of a subgroup of patients with COPD by preventing weaning from mechanical ventilation, and possibly by impairing exercise performance. The reported number of COPD subjects with respiratory muscle fatigue is small, however, and may represent a highly select population. Further studies are needed to define the extent of this problem.

Asthma

The pathophysiology of CO_2 retention appears to be generally similar in patients with asthma and COPD, but the likelihood of developing CO_2 retention is less in asthma than in COPD. That is, the level of expiratory airway obstruction required to produce CO_2 retention in subjects with acute asthma is greater than that required in subjects with COPD (Fig. 148-14). Several possibilities may explain this tendency. First, it appears that inspiratory drive is higher in patients with asthma than in those with COPD. The airway occlusion pressure is considerably higher at any given level of Pa_{CO_2} in patients with asthma than in normal subjects or patients with COPD. The heightened inspiratory drive in patients with asthma may in part arise from irritant receptors within the airway, which have an augmenting effect on inspiratory motor neuron activity. Furthermore, the inspiratory muscles are stronger, and ventilatory responses to CO_2 and hypoxia are greater, in the younger asthmatic than in COPD subjects. These differences are not simply due to age, as the endurance of the inspiratory and expiratory muscles is greater in asthmatic than in age-matched normal subjects. The increased respiratory muscle endurance in subjects with asthma may be a response to chronic increases in inspiratory muscle load. Finally, greater lung elastic recoil in asthma than in COPD tends to preserve maximal expiratory airflow.

Neuromuscular Disease

Subjects with neuromuscular disease and weak inspiratory muscles tend to breathe rapidly and shallowly. Despite this breathing pattern, these subjects tend to have hypocapnia at rest, and hyperventilate at any given level of CO_2 during progressive hypercapnia. Increases in ventilation are associated with increases in airway occlusion pressure. Heightened occlusion pressure in the setting of weak inspiratory muscles suggests that the drive to the inspiratory muscles early in inspiration is greater than normal.

The pathogenesis of hypercapnic respiratory failure is very different in patients with neuromuscular disease than in patients with COPD. Patients with neuromuscular disease demonstrate an impaired ability to sigh (i.e., a greater than twofold increase in the tidal volume) because of inspiratory muscle weakness. Inability to sigh decreases lung compliance by interfering with the redistribution of surfactant within the alveolar space. Progressive stiffening of the lung leads to microatelectasis and ultimately lobar atelectasis. Breathing high concentrations of O_2 accelerates this process. In addition, expiratory muscle weakness impairs the cough mechanism and causes retention of secretions.

The best indicators of a tendency to develop CO_2 retention in patients with neuromuscular disease are reductions in inspiratory muscle strength ($P_{I_{max}}$) and forced vital capacity (FVC). Reductions in $P_{I_{max}}$ and FVC to less than 30 and 25 percent of predicted, respectively, are associated with CO_2 retention. Suffice it to say, hypercapnia is a late manifestation of neuromuscular disease and requires marked impairment in inspiratory and expiratory muscle function. With diaphragm dysfunction, hypercapnia may occur during sleep (especially REM sleep) even when the subject is eucapnic while awake.

Obesity

Obesity imposes a stress on the respiratory system both by altering lung mechanics and the work of breathing (see Chapter 92). The mass loads applied to the thorax and abdomen by excess fatty tissue decrease chest wall compliance and end-expiratory lung volume resulting in increases in the elastic and resistive work of breathing. Furthermore, by diminishing airway caliber, obesity predisposes to premature airway closure and even atelectasis. The resultant low ventilation-perfusion ratios of these lung regions increase alveolar-arterial O_2 gradient and cause arterial hypoxemia. In fact, hypoxemia is the most common respiratory abnormality in the morbidly obese.

In addition, the excessive body mass results in increased CO_2 production and O_2 consumption. Increases in metabolism may be two to three times normal in morbidly obese subjects. These metabolic changes require significant increases in minute and alveolar ventilation in order to maintain eucapnia and hence, increasing ventilatory demands. For example, a doubling in CO_2 production requires a doubling in alveolar ventilation to maintain eucapnia. Finally, arterial hypoxemia, which is common, induces a further increase in ventilation.

Given these stresses, the maintenance of normal blood gas tensions requires a considerable increase in respiratory motor output and the work of breathing. Increased work of breathing appears to explain the common occurrence of dyspnea in the morbidly obese person.

Not all morbidly obese subjects develop hypercapnic respiratory failure, however. Although body weight alone does not predict the development of hypercapnia, approximately 30 percent of severely obese subjects with a body mass index (BMI) of more than 35 kg/m^2 and almost 50 percent with a BMI of 50 kg/m^2 or greater have unexplained daytime hypercapnia. Observations of eucapnic and hypercapnic obese subjects demonstrate that eucapnic subjects have greater increases in diaphragm electrical activity with increases in CO_2 than hypercapnic subjects. Obese subjects with hypercapnic respiratory failure may have impaired chemosensitivity to hypercapnia and hypoxemia.

A subset of obese subjects with hypercapnia also have daytime hypersomnolence, polycythemia, pulmonary hypertension, and cor pulmonale. This constellation of signs and symptoms has been termed the *obesity hypoventilation syndrome* (see Chapter 92.) Of interest, leptin may be involved in the pathogenesis of hypercapnic respiratory failure in obese individuals. Leptin stimulates ventilation and a deficiency of leptin has been associated with hypoventilation. Clearly excessive body weight is the primary pathogenetic factor, since weight reduction into the normal range, however difficult this may be to accomplish, corrects the problem.

Kyphoscoliosis

Kyphoscoliosis decreases chest wall and lung compliance, presumably as a result of atelectasis and deformation of the lungs (see Chapter 92). The elastic work of breathing is markedly increased. In addition, the mechanical action of the respiratory muscles may be impaired by changes in configuration of the bony structures on which the respiratory muscles insert. Ventilation-perfusion mismatch and increase in the alveolar-arterial O_2 gradient are common. As expected in patients with diminished respiratory compliance, subjects with kyphoscoliosis breathe rapidly and shallowly. The tendency to develop CO_2 retention is a function of the severity of the restrictive process in kyphoscoliosis, as reflected in the Cobb angles, and is predicted separately for the magnitude of scoliosis and kyphosis.

Hypercapnic respiratory failure tends to develop late in life, even if the severity of the spinal deformity has not changed since childhood; that is, stability of the Cobb angles of kyphosis and scoliosis does not preclude development of hypercapnic respiratory failure. It is not clear why respiratory failure ensues late in life. However, several possibilities exist. Aging adversely affects compliance of the chest wall, leading to an increase in the elastic work of breathing. In addition, aging diminishes respiratory muscle strength. Finally, chemosensitivity to O_2 and CO_2 declines with advancing age, and it seems likely that the subject's ability to compensate

for derangements in blood gas tensions is progressively impaired.

ASSESSMENT OF PATIENTS WITH ABNORMALITIES OF THE VENTILATORY PUMP

Symptoms

Dyspnea appears to be an early manifestation of respiratory muscle impairment in neuromuscular disease and typically occurs before the development of CO_2 retention. Breathlessness in the supine position is characteristic of isolated diaphragm dysfunction. In the supine position, the increased hydrostatic pressure imposed by the abdominal viscera represents an increased inertial load on the diaphragm.

Physical Findings

Physical signs of ventilatory pump dysfunction revolve around evidence of accessory respiratory muscle recruitment, abnormal thoracoabdominal movement, and rapid, shallow breathing.

Use of Accessory Muscles

Inspection and palpation demonstrate accessory respiratory muscle use. Intense respiratory efforts are associated with visible activation of the neck accessory muscles, interosseous intercostals, and abdominal expiratory muscles and flaring of the alae nasae.

Abnormal Thoracoabdominal Movement

Normally, in the supine position, the anterior abdominal wall displays a prominent outward movement during inspiration. With impaired diaphragm function, as occurs in diaphragm weakness or fatigue, the abdominal wall may move inward on inspiration. This is called *abdominal paradox.* Abdominal paradox reflects cephalad movement of the contracting diaphragm in response to the negative intrathoracic pressure generated by the inspiratory action of the neck and intercostal muscles. Abdominal paradox may also be present in patients with marked derangements in lung mechanics, in whom inspiratory intrathoracic pressure swings exceed 30 percent of maximum. Abdominal paradox, therefore, is not specific for diaphragm weakness or fatigue.

Abdominal paradox, resulting from ineffectual contractions of the diaphragm, should be distinguished from *pseudo-abdominal paradox,* resulting from strong contractions of the expiratory muscles during expiration, with rapid relaxation during early inspiration. For example, intense contraction of the transverse abdominis muscles causes inward movement of the lateral abdominal wall and outward movement of the anterior abdominal wall during expiration. Subsequent relaxation of the abdominal muscles with the onset of inspiration causes outward movement of the lateral abdominal wall and inward movement of the anterior abdominal wall. Tenseness of the lateral abdominal wall during expiration easily distinguishes *pseudo-* from true *abdominal paradox.*

Maximum Static Inspiratory Pressure

Perhaps the most practical method of assessing the function of the inspiratory muscles contracting in aggregate is from the pressure generated during maximal volitional contractions against an occluded airway at FRC. This parameter is discussed in greater detail in Chapter 93. In brief, however, reductions in $P_{I_{max}}$ indicate inspiratory muscle weakness or high-frequency fatigue. Improvements in $P_{I_{max}}$ occurring over several hours to several days in a patient with COPD suggest that lung volume is improving toward normal and that the mechanical disadvantage imposed on the inspiratory muscles is disappearing. More rapid improvements (occurring over hours) may indicate resolution of high-frequency fatigue or elimination of the metabolic disturbances (e.g., hypercapnia or hypophosphatemia) that depress inspiratory muscle function. Of note, $P_{I_{max}}$ is not affected by low-frequency fatigue.

$P_{I_{max}}$ depends on patient cooperation and motivation. With training, however, patients can provide reproducible values. Performance of the maneuver at FRC, where respiratory system recoil is zero, is preferred; that is, at FRC, changes in airway pressure during inspiratory efforts equal the pressure generated by the inspiratory muscles (P_{mus}).

Maximum static expiratory pressure at FRC ($P_{E_{max}}$) has been used in the laboratory setting to assess the endurance properties of the expiratory muscles. The $P_{E_{max}}$ has not been used extensively in the clinical setting, however, because of the perception that it is more difficult to obtain consistent values than $P_{I_{max}}$ with breathless subjects.

TREATMENT

Abnormalities in respiratory mechanics and gas exchange are the most important pathogenetic factors in the development of respiratory failure. Accordingly, therapy should be directed toward achieving maximum improvement in airway, lung, and respiratory muscle function. For example, in patients with COPD or asthma, an intensive regimen of bronchodilators (e.g., β_2-adrenergic agonists, anticholinergics, and theophylline) and anti-inflammatory therapy (e.g., corticosteroids) can correct respiratory failure by diminishing airway resistance, FRC, lung dead-space volume, the alveolar-arterial O_2 partial-pressure gradient, and the work of breathing. Improvements in lung function in certain patients with advanced COPD and emphysema may also be accomplished by lung-volume reduction surgery (volume-reduction pneumectomy) or lung transplantation. Lung-volume reduction surgery removes 20 to 30 percent of the most emphysematous regions of lung and appears to improve

FRC, FEV_1, ventilatory capacity, inspiratory muscle function, and elastic recoil pressure of the lung. In patients with myasthenia gravis, cholinesterase inhibitors can improve inspiratory muscle strength and vital capacity and reverse atelectasis, which causes hypercapnia. Additionally, noninvasive positive-pressure ventilation (NIPPV) has become one of the most important modalities for treating hypercapnic respiratory failure (see below).

Abnormalities in Chemosensitivity

Respiratory failure caused by impaired chemosensitivity is difficult to treat, since drug treatments to improve chemosensitivity to hypoxia or hypercapnia are not very effective. Since it was observed that women exhibit alveolar hypoventilation during pregnancy and the luteal phase of the menstrual cycle, progestational agents have been used for many years to treat idiopathic hypoventilation syndromes. In some subjects, medroxyprogesterone acetate, given orally in a dose of 20 mg three times a day, acts centrally to augment the ventilatory responses to hypercapnia and hypoxemia and can improve resting arterial blood gas tensions. Medroxyprogesterone is generally well tolerated in women but may produce feminizing side effects in men. The onset of action of the drug is slow. Several weeks may be required before a response is observed. Theophylline, in doses that produce blood levels in the therapeutic range (10 to 15 μg/ml), also has weak respiratory stimulatory effects, which may contribute to a reduction in Pa_{CO_2} in patients with COPD. Theophylline also produces modest improvements (about 10 to 20 percent) in diaphragm contractile function in this population. Finally, in some patients with hypercapnia, elimination of medications having CNS respiratory depressant effects (e.g., opiate analgesics, benzodiazepine anxiolytics) can lead to improvements in Pa_{CO_2}.

Hypoxemia leading to pulmonary artery hypertension and cor pulmonale may be the most serious complication of chronic hypercapnic respiratory failure. Supplemental O_2 is usually indicated in patients with chronic hypercapnic respiratory failure. Supplemental O_2 may produce exaggerated increases in Pa_{CO_2} in patients with disorders of ventilatory control in whom the ventilatory response to CO_2 is blunted but the O_2 response is preserved. Accordingly, blood gas tensions should be monitored closely when O_2 is applied initially. During sleep, patients with disorders of the control of breathing typically display exaggerated increases in Pa_{CO_2} (e.g., 15 to greater than 30 mmHg) with hypoxemia and severe respiratory acidosis. In these subjects, mechanically assisted ventilation (typically with nasal positive-pressure ventilation), with or without O_2, may be required during the sleeping period. Nasal positive-pressure ventilation is an effective way of improving blood gas tensions during sleep. In fact, improvements in blood gas tensions achieved by nocturnal mechanical ventilation may carry over to the waking period in these patients, perhaps by preventing nocturnal increases in serum bicarbonate or hypoxic depression of CNS function.

Table 148-2

Principles of Therapy for Respiratory Muscle Fatigue

Decrease inspiratory swings in transdiaphragmatic pressure (Pdi)
Improve the mechanics of breathing (i.e., decrease airway resistance, improve thoracic compliance and static lung volume)
Decrease ventilatory drive (i.e., relieve hypoxemia, hypercapnia, metabolic acidosis, fever, pulmonary congestion/inflammation, acute respiratory distress syndrome
Increase Pdi_{max}
Correct hyperinflation
Correct muscle atrophy induced by protein-calorie deficiency
Correct electrolyte and blood gas abnormalities (i.e., hypoxemia, hypercapnia, hypophosphatemia, hypokalemia, hypocalcemia, hypomagnesemia)
Optimize muscle blood flow and substrate availability
Correct low cardiac output state (e.g., cardiogenic shock, hypovolemic shock).
Correct hypoxemia, anemia, hypoglycemia

Respiratory Muscle Weakness or Fatigue

The treatment of respiratory muscle weakness depends on pathogenic mechanisms. For example, inspiratory muscle weakness related to the hyperinflation of COPD is best treated by aggressive improvement of airway function. On the other hand, decreases in muscle strength caused by electrolyte abnormalities (e.g., hypophosphatemia) or protein-calorie malnutrition are best dealt with by repletion of the deficits.

The treatment of respiratory muscle fatigue has not been systematically studied. However, several approaches based on theoretical considerations appear to be applicable (Table 148-2). It is clear that diaphragm fatigue is a result of muscle overactivity (i.e., a TTI greater than 20 percent). Accordingly, attempts should be made to decrease the TTI of the inspiratory muscles to values below the fatigue threshold by improving lung mechanics or reducing ventilatory drive. In patients with abnormalities in airway resistance and hyperinflation secondary to severe COPD, this can best be accomplished with bronchodilators and corticosteroids. Reductions in ventilatory drive in hypoxic or febrile patients can be accomplished by administration of O_2 or antipyretics.

Unloading the inspiratory muscles by reducing the TTI may be sufficient to prevent or reverse fatigue and allow the muscle to recover. In some cases, however, respiratory muscle fatigue may be sufficiently advanced so that the muscle must

be placed at complete rest. Mechanical ventilation and ventilatory muscle rest are certainly indicated when the pH is less than 7.25 or the patient appears unable to maintain ventilation and stable blood gas tensions. The precise duration of mechanical ventilation to rest the inspiratory muscles in patients with respiratory muscle fatigue is unclear. However, no attempts at weaning should be made until the conditions that initiated fatigue are reversed. Since low-frequency fatigue persists for 24 h or more, it may not be advisable to wean patients with respiratory muscle fatigue from mechanical ventilation for at least 24 h, even if the factors that caused fatigue have been corrected.

Chronic Ventilatory Support/Nasal Positive-Pressure Ventilation

Mechanically assisted ventilation, especially at night, may be helpful in reducing arterial P_{CO_2} and increasing P_{O_2} in the chronically hypercapnic subject. Nasal positive-pressure ventilation (NPPV) affords an effective, practical approach to treat selected subjects with chronic hypercapnia secondary to either impaired chemosensitivity or abnormalities in respiratory mechanics. In particular, selected subjects with the obesity hypoventilation syndrome, kyphoscoliosis, or neuromuscular disease have been successfully maintained on NPPV for prolonged periods.

NPPV is particularly effective in hypercapnic respiratory failure. NPPV obviates the need for airway intubation, provides considerable patient comfort, and is easy to use. Many different types of masks exist. The most commonly used are oral or oronasal masks with a soft rubber seal. An oronasal mask may be more comfortable for mouth breathing patients. By setting the magnitude of the inspiratory positive airway (IPAP) and expiratory pressures (EPAP), tidal volume is determined. Small, portable, simple-to-operate bilevel ventilators (BiPAP) that deliver phasic pressure changes are available. Many bilevel machines allow manipulation of the pressure rise time during inhalation so that exhalation time and patient comfort can be maximized. No ideal pressure settings effective for all patients exist. Settings should be adjusted to maximize patient comfort and ventilation. The effectiveness of a given setting can be assessed by observing the degree of chest expansion and measuring the Pa_{CO_2}. Disadvantages of NPPV include aerophagia and air leaks secondary to poorly fitting masks.

The use of NPPV during acute hypercapnic respiratory failure secondary to COPD has been demonstrated repeatedly to reduce mortality, reduce the need for airway intubation, and rapidly improve respiratory rate, Pa_{CO_2}, and pH. Recently NPPV has been successfully used over a prolonged period for the treatment of the obesity hypoventilation syndrome. In morbidly obese patients (mean BMI 44 kg/m^2), NPPV decreased the Pa_{CO_2} by an average of 17 mmHg and increased the Pa_{O_2} by 24 mmHg after an average of 50 months.

NPPV is also used in neuromuscular disease, particularly for nocturnal hypoventilation or progressive hypercapnic respiratory failure (see Chapters 93 and 94). NPPV prolongs and improves the quality of life in amyotrophic lateral sclerosis. Its use in this disorder is discussed in detail in Chapter 94. Unfortunately, the majority of the neuromuscular disorders are progressive and many patients develop bulbar symptoms and thus have difficulty controlling their secretions.

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CHAPTER

Oxygen Therapy and Pulmonary Oxygen Toxicity

Michael F. Beers

Following Joseph Priestley's discovery of molecular oxygen and Lavoisier's subsequent demonstration of respiratory gas exchange, use of inhaled oxygen in treatment of a variety of clinical disorders accelerated rapidly during the late eighteenth century. However, a backlash of criticism developed as studies demonstrated that, under ambient conditions, the oxygen-carrying capacity of arterial blood was nearly maximal, and that further increases in the fraction of inspired O_2 produced no appreciable additional physiological benefit. Furthermore, in 1899, Lorrain-Smith confirmed the early suspicions of Priestley, Lavoisier, and others regarding the potential toxicity of inhaled oxygen, describing the pulmonary

pathological alterations associated with excessive oxygen exposure. As a result of these observations, by the start of the twentieth century, use of oxygen as a therapeutic modality fell into disrepute.

However, in the early 1920s supplemental oxygen breathing was rigorously reevaluated. Through pioneering efforts by Meakins, Baruch, and others, the concept of a therapeutic window for oxygen inhalation was established. Many investigators independently demonstrated that a reduction in oxygen availability had serious physiological consequences, and that in pathological states, the detrimental consequences of hypoxia could often be circumvented by administration of oxygen. Thus, use of inhaled oxygen again became mainstream therapy, but as adjuvant treatment for cardiac and pulmonary diseases specifically accompanied by hypoxemia and hypoxia.

Over the past 80 years, with the advent of improved oxygen delivery systems, mechanical ventilation, the modern intensive care unit, and long-term home oxygen administration, oxygen has become widely available and frequently prescribed. Nevertheless, despite a large clinical experience, many persistent uncertainties inhibit rational use of supplemental oxygen. As with any drug, indications for, and contraindications to, its use exist. Consensus conferences and numerous studies have resulted in establishment of guidelines defining clinical criteria for proper use of supplemental oxygen. Unfortunately, in current practice, oxygen therapy is often prescribed without careful evaluation of its potential benefits and side effects and without adequate supervision. In a retrospective study of 90 consecutive hospitalized patients, oxygen therapy was prescribed inappropriately in 21 percent; monitoring was inadequate in 85 percent; and documentation of physiological criteria for termination of therapy was lacking in 88 percent of all patients. Prospective collected data have also indicated that less than 50 percent of hospitalized patients receiving supplemental oxygen do so at the prescribed dosage and flow.

This chapter provides the basis for the rational use of inhaled oxygen therapy. A review of the physiology of tissue oxygenation is followed by a discussion of the current indications and guidelines for acute oxygen therapy, the role of long-term oxygen therapy, and the pathophysiological basis for pulmonary oxygen toxicity. Because prescribed oxygen is administered typically under normobaric conditions, oxygen therapy and its toxic consequences are considered in this setting (i.e., at one atmosphere of pressure).

TISSUE OXYGENATION

The physiological basis for oxygen therapy has been well documented for over 40 years. While treatment and prevention of arterial hypoxemia are the most common indications for oxygen therapy, the ultimate goal in its use is correction or avoidance of tissue hypoxia. In 1965, Chance first demonstrated that a partial pressure of oxygen (P_{O_2}) in mitochondria of 18 mmHg or more is required to generate the high-energy phosphate bonds (as adenosine triphosphate) essential for all major cellular biochemical functions. At rest, the average adult man consumes about 225 to 250 ml of oxygen per min; this rate of consumption may increase as much as 10-fold during exercise. Ongoing oxygen utilization in peripheral tissues dictates a very small oxygen reserve which is consumed quickly (within 4 to 6 min of cessation of spontaneous ventilation). A complete understanding of the concepts of oxygen delivery and utilization is required for careful assessment of the hypoxic patient and implementation of proper therapy.

Oxygen Delivery and Utilization

Transport of oxygen from atmospheric air to tissue mitochondria (the ultimate sites of oxygen utilization) requires the integrated function of the pulmonary, cardiovascular, and hematologic systems. Under normal conditions, a pronounced drop in P_{O_2} between ambient atmosphere and tissues is observed (Fig. 149-1). The measured basal tissue P_{O_2} (i.e., mixed venous P_{O_2} or $\bar{v}_{O_2}$) is only marginally greater than the threshold value for mitochondrial anaerobic metabolism measured in vitro (as illustrated in Fig. 149-1 by the dashed line at a P_{O_2} of 20 mmHg). The consequence of such a steep oxygen concentration gradient and a marginal tissue reserve is that a variety of environmental and pathological factors can significantly impact on tissue oxygenation by altering P_{O_2} at one of these intermediary stages. Hence, tissue hypoxia develops whenever oxygen delivery is inadequate to meet metabolic demands.

Oxygen delivery to the periphery is determined by two major factors: (1) oxygen content of arterial blood and (2) blood flow (i.e., cardiac output). Oxygen delivery is calculated as the product of cardiac output and arterial oxygen content. Total oxygen delivery is calculated as:

$$D_{O_2} = CO \times Ca_{O_2} \times 10 \quad (1)$$

where

D_{O_2} = oxygen delivery, ml/min
CO = cardiac output, L/min
Ca_{O_2} = O_2 content of arterial blood, ml/dl

The oxygen content of arterial blood is determined by the hemoglobin concentration, its degree of saturation with molecular oxygen, and the fractional amount of oxygen physically dissolved in solution. The amounts of both bound and dissolved oxygen are related directly to the oxygen tension in arterial blood (Pa_{O_2}), while the percentage of hemoglobin saturated with oxygen is a function of Pa_{O_2}, as described by the oxyhemoglobin dissociation curve (see Chapter 13). In turn, the amount of oxygen dissolved in solution is a function of the solubility coefficient of oxygen and the Pa_{O_2}. Hence, total arterial oxygen content is calculated as:

$$Ca_{O_2} = ([Hgb] \times 1.34 \times Sa_{O_2}) + (Pa_{O_2} \times 0.0031) \quad (2)$$

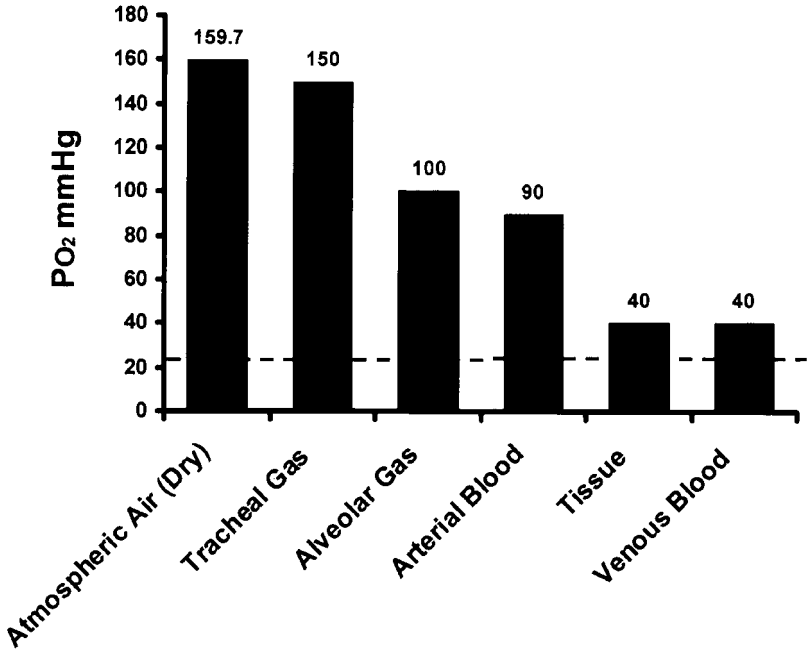

Figure 149-1 Graphical representation of sequential steps in the drop in oxygen tension (P_{O_2}) at various stages of oxygen transport from atmosphere to peripheral tissues. Values depicted are calculated using the alveolar gas equation and data from Chance (*J Gen Physiol* 49:163–195, 1965). Dashed line represents the approximate intracellular anaerobic threshold.

where

[Hgb] = hemoglobin concentration, g/dl
1.34 = O_2 carrying capacity of hemoglobin at 37°C, ml/g hemoglobin
Sa_{O_2} = measured $\%O_2$ saturation of hemoglobin
0.0031 = solubility coefficient for oxygen

Mechanisms of Hypoxia

Aerobic metabolism requires a balance between oxygen delivery (Do_2) and oxygen utilization ($\dot{V}o_2$). A biphasic relationship between Do_2 and $\dot{V}o_2$ has been observed (Fig. 149-2). During normal aerobic metabolism, oxygen transport and oxygen utilization are independent variables. Whereas the amount of oxygen delivered to tissues per unit time defines the upper limit of oxygen availability for the body's total metabolic needs, delivery of oxygen under normal circumstances always exceeds peripheral oxygen utilization. In this "supply-independent" region of the graph, oxygen consumption is commensurate with the rate of adenosine 5′-triphosphate (ATP) production and represents a measure of tissue cellular energy requirements. If oxygen delivery falls below a critical threshold (Do_2 critical), or if utilization exceeds delivery (e.g., during strenuous exercise), tissues must shift from aerobic to anaerobic metabolism to supply adequate energy for total metabolic needs. When an imbalance arises, excessive lactic acid production ensues, resulting in progressive acidosis, disrupted cellular metabolism, and, potentially, cell death.

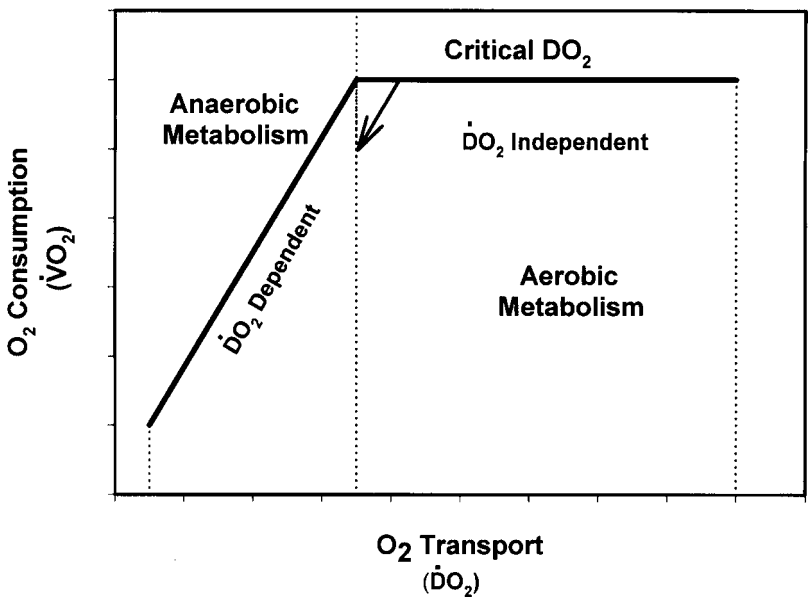

Figure 149-2 Relationship between oxygen consumption ($\dot{V}_{O_2}$) and oxygen transport (D_{O_2}). The critical D_{O_2}, indicative of the transition from supply-dependent to supply-independent conditions, is denoted by the arrow. Anaerobic metabolism exists under supply-dependent conditions and ensues when oxygen consumption exceeds oxygen supply.

Table 149-1

Causes of Tissue Hypoxia

Categroy	Clinical Correlate	Pa_{O_2}	$\bar{V}_{O_2}$	Cardiac Output
Hypoxemia	See Table 149-2	↓	↔ or ↓	↓ or ↑ or ↔
Impaired delivery				
Circulatory (forward flow)	Hypovolemia; heart failure	↔	↓	↓
Distributive	Sepsis; arterial insufficiency	↓ or ↔	↔ or ↓	↑ or ↔
Defective Blood-O_2 Transport	Inherited abnormal hemoglobins			
	Acquired abnormal hemoglobin (Carbon monoxide poisoning)	↔	↔ or ↓	↑ or ↓
	Anemia			

Table 149-1 lists the major causes of tissue hypoxia, which are mechanistically divided into three broad categories: (1) arterial hypoxemia, (2) reduced oxygen delivery, and (3) excessive or dysfunctional tissue utilization.

Maintenance of tissue oxygenation depends on the proper integration of three separate components: (1) the cardiovascular system, which determines cardiac output and blood flow distribution; (2) the blood, which determines hemoglobin concentration; and (3) the respiratory system, which determines Pa_{O_2}. Although causes of hypoxemia primarily reflect failure of proper oxygen loading of the blood (low Pa_{O_2}) due to abnormal function of the respiratory system, defects in oxygen transport may result from either dysfunction of the cardiovascular system or hematologic issues. Finally, "misuse" of delivered oxygen, resulting from either defects in cellular metabolism or excessive demand, represents another class of disorders characterized by hypoxia. Each of these three categories is discussed below.

Arterial Hypoxemia

Hypoxemia may be defined as a validated deficiency of oxygen tension in the arterial blood. A P_{O_2} below the range of normal for age-matched subjects establishes the presence of arterial hypoxemia. Table 149-2 summarizes the major causes of hypoxemia. Since the driving force for oxygen transport across the alveolar barrier into the blood depends on both the concentration of oxygen in the alveolus (Pa_{O_2}) and overall respiratory function, arterial hypoxemia results only from reduction of the inspired oxygen tension or respiratory dysfunction.

The most common pathophysiological causes of hypoxemia in lung disease include ventilation-perfusion mismatch, true shunt, or a diffusion barrier. In some

Table 149-2

Causes of Arterial Hypoxemia and Response to Oxygen Therapy

Cause	Clinical Examples	Effect of Oxygen Therapy
Decreased oxygen intake	Altitude	Rapid increase in Pa_{O_2}
Ventilation-perfusion imbalance	Chronic obstructive pulmonary disese	Moderately rapid increase in Pa_{O_2}
Shunt	Atrial septal defect Pulmonary arteriovenous fistula	Rapid but variable increase in Pa_{O_2} depending on size of shunt
Diffusion defect	Interstitial pneumonitis	Moderately rapid increase in Pa_{O_2}
Alveolar hypoventilation	Chronic obstructive pulmonary disease	*Initial response*: Increase in Pa_{O_2} *Late response*: Variable depending upon whether supplemental O_2 depresses minute ventilation

nonpulmonary disorders, a low mixed-venous oxygen tension is responsible (Chapters 11 and 12). Alveolar hypoventilation, which also results in hypoxemia, acts indirectly through mechanisms that increase alveolar P_{CO_2} and secondarily decrease alveolar P_{O_2}. To a varying degree, most causes of arterial hypoxemia (with shunt physiology as the exception) can be improved by administration of supplemental oxygen. However, the magnitude of the response differs, based on the etiology.

Reduced Oxygen Delivery

In the setting of a normal Pa_{O_2}, tissue hypoxia may result from abnormalities in any of the determinants of oxygen delivery, including circulatory causes, abnormal blood oxygen transport, or maldistribution of blood flow.

Circulatory hypoxia results when fully oxygenated blood is delivered to tissues in insufficient quantity or at an inadequate level to support tissue metabolic needs. Usual etiologies include low cardiac output states, systemic hypovolemia, and arterial insufficiency of peripheral tissues. Compensation is partially effected at the tissue level initially by increased oxygen extraction from blood, resulting in lowering of mixed-venous oxygen tension ($\bar{v}_{O_2}$). Thus, a low $\bar{v}_{O_2}$ is the hallmark of circulatory hypoxia. Because Pa_{O_2} may be normal and the hemoglobin normally saturated, oxygen administration is unlikely to be of great help in the majority of these disorders.

Tissue hypoxia may also result from *abnormal blood-oxygen transport,* in which the oxygen-carrying capacity of the blood is reduced, as manifested primarily by a decrease in the total hemoglobin content (i.e., anemia), or secondarily as a consequence of abnormal hemoglobin-O_2 affinity. States of abnormal hemoglobin-O_2 affinity are characterized by an inability to bind oxygen (e.g., hemoglobinopathies) or to release oxygen to tissues (e.g., low levels of 2,3-diphosphoglycerate). Acquired defects result typically from binding of a ligand with stronger affinity for hemoglobin than oxygen (e.g., carbon monoxide) or a toxic alteration in hemoglobin structure (e.g., methemoglobin). Under these circumstances, cardiac output is increased as an adaptive response, and $\bar{v}_{O_2}$ is normal or decreased. Although not a primary therapy, oxygen administration may play an adjunctive role. In certain situations, including carbon monoxide poisoning, hyperbaric oxygen therapy (Chapter 62) may be helpful.

Finally, tissue hypoxia may result from *maldistribution* of a normal or supranormal cardiac output. Examples include microvascular perfusion defects observed in classical septic shock or in the more recently recognized systemic inflammatory response syndrome (SIRS) (Chapter 146). Maldistribution of perfusion leading to tissue hypoxia has also been described in other situations, such as experimental interleukin-2 therapy. The hallmark of a maldistributive hypoxia is the development of precapillary shunting in peripheral tissues. Thus, cardiac output is normal or increased, and $\bar{v}_{O_2}$ is usually low. Because of the presence of peripheral shunting, supplemental oxygen is usually not effective in increasing local cellular oxygen tension.

Cellular Causes of Hypoxia

Hypoxia may also arise from misuse of oxygen at the tissue level. Cellular hypoxia results from inhibition of either intracellular enzymes or oxygen-carrying molecules involved in intermediary metabolism and energy generation. In hydrogen cyanide poisoning, Pa_{O_2}, hemoglobin concentration, percentage of hemoglobin saturation, and tissue perfusion are normal. However, peripheral utilization of oxygen is impaired as cyanide binds to cytochrome oxidase and inhibits intramitochondrial transport of electrons to molecular oxygen. This event blocks production of ATP via oxidative phosphorylation, resulting in lactic acidosis as anaerobic metabolism is triggered. In addition, oxygen extraction is often impaired, leading to a normal or increased $\bar{v}_{O_2}$. Although oxygen therapy is usually not effective, 100 percent oxygen is often administered while the patient is treated with specific antidotes.

"Demand hypoxia" results when tissue oxygen utilization is supernormal and exceeds the rate of oxygen delivery. Common causes include maximal exercise and hypermetabolic states, such as thyrotoxicosis. As in circulatory hypoxia, $\bar{v}_{O_2}$ is decreased, but in contrast, cardiac output is normal or, more likely, increased. Because oxygen-carrying capacity is normal, oxygen administration is often ineffective, and definitive treatment requires control of the underlying disorder.

RECOGNITION AND ASSESSMENT OF TISSUE HYPOXIA

The correct use of oxygen therapy requires clinical recognition of tissue hypoxia, careful evaluation of the pathophysiological basis for the hypoxia, understanding of factors that predict those hypoxic patients likely to receive benefit, and continued assessment of the optimal dosage. The benefit must be balanced against potential toxicity. In most circumstances, tissue hypoxia is not directly measurable, and detection is usually accomplished through a combination of clinical and laboratory parameters. In cases of isolated arterial hypoxemia, awareness of tissue hypoxia is enhanced through inference of abnormal measurements of arterial oxygen saturation.

Clinical Manifestations

Clinical manifestations of hypoxia are highly variable and nonspecific and depend on both duration of the hypoxia (acute or chronic) and the individual's fitness. Symptoms and signs associated with acute hypoxia, outlined in Table 149-3, include changes in mental status, dyspnea, tachypnea, respiratory distress, and cardiac arrhythmias. Alterations in mental status range from impaired judgment to confusion or coma. Cyanosis, often considered a hallmark of hypoxia, occurs only when the concentration of reduced hemoglobin

Table 149-3

Signs and Symptoms of Acute Hypoxia

System	Signs and Symptoms
Respiratory	Tachypnea, breathlessness, dyspnea, cyanosis
Cardiovascular	Increased cardiac output, palpitations, tachycardia, arrhythmias, hypotension, angina, vasodilatation, diaphoresis, and shock
Central nervous	Headache, impaired judgment, inappropriate behavior, confusion, euphoria, delierium, restlessness, papilledema, seizures, obtundation, coma
Neuromuscular	Weakness, tremor, asterixis, hyper-reflexia, incoordination
Metabolic	Sodium and water retention, lactic acidosis

in the blood is 1.5 g/dl or greater. However, this is not a reliable sign, as it is absent in anemia and during periods of poor peripheral perfusion.

Laboratory and Other Objective Assessments

Because of the variability of presentation and nonspecificity of the symptoms and signs of hypoxia, the laboratory assessment of the state of tissue oxygenation is desirable. Unfortunately, the current state of the art remains imprecise. Quantification of the degree of oxygenation of individual tissues is difficult. The $\bar{v}_{O_2}$ represents an approximation of mean tissue P_{O_2}, and a level of less than 30 mmHg indicates overall tissue hypoxia. However, measurements of $\bar{v}_{O_2}$ require pulmonary artery catheterization and, therefore, are limited to intensive care settings.

In most clinical situations, direct determinations of Pa_{O_2}, arterial hemoglobin oxygen saturation, and serum lactate levels are surrogate markers for tissue hypoxia. Pa_{O_2} determinations are made invasively with blood samples obtained from arterial puncture or indwelling arterial catheters, while noninvasive assessment of percent saturation of blood hemoglobin is routinely available by infrared pulse oximetry. Both are useful in excluding arterial hypoxemia; neither directly measures tissue P_{O_2}. Inadequate tissue oxygen delivery is inferred from moderate decreases in Pa_{O_2}, and the inference is usually warranted in acutely ill patients whose Pa_{O_2} is less than 50 mmHg or in whom blood lactate levels are elevated. However, this judgment may be unsubstantiated in patients who are chronically hypoxemic and who have developed compensatory mechanisms. In addition, assumptions about the adequacy of tissue oxygenation may not be warranted in clinical settings in which factors other than arterial hypoxemia are responsible for the development of hypoxia (Table 149-1).

INDICATIONS FOR OXYGEN THERAPY

In every sense, oxygen must be thought of as a drug having a therapeutic window based on the dose and duration of administration. In addition, the cost of both short-term oxygen therapy for hospitalized patients and long-term therapy for patients with chronic lung disease dictates a rational understanding regarding its administration. For example, in the United States, using data from the Health Care Financing Administration, total annual Medicare expenditures for therapy and equipment range from $1.3 to $1.8 billion. Thus, indications for use of supplemental oxygen must be clear. Oxygen should be administered in precise amounts, and patients should be monitored for both efficacy and toxicity of treatment. Despite the facts that the scientific foundation underlying these principles is incomplete and that all-inclusive guidelines have been difficult to develop, the economic implications and requirements for laboratory monitoring have prompted development of recommendations for oxygen therapy. These recommendations allow the physician flexibility in exercising appropriate clinical judgment in prescribing oxygen in a cost-effective manner, in both acute and chronic settings.

Short-Term Oxygen Therapy

Recommendations for administration of supplemental oxygen, based upon guidelines of the American College of Chest Physicians, the National Heart, Lung and Blood Institute, and other organizations, are summarized in Table 149-4.

Tissue Hypoxia Associated with Arterial Hypoxemia

In the acute setting, the most common indication for supplemental oxygen, regardless of the underlying etiology, is arterial hypoxemia. For a normal, middle-aged adult, the usual level of hypoxemia at which oxygen therapy is instituted is a Pa_{O_2} of less than 60 mmHg. Based on the oxyhemoglobin dissociation curve, this value for Pa_{O_2} results in a hemoglobin saturation of about 90 percent. Because of the sigmoidal shape of the curve at this Pa_{O_2}, a further decrease in oxygen tension results in a considerable drop in oxygen saturation.

Ventilation-perfusion mismatch is the most common pathophysiological cause of arterial hypoxemia (see Chapter 11). The magnitude of the response to administration of supplemental oxygen depends upon the range and degree of ventilation-perfusion mismatch within individual lung regions. Therefore, repeated measurements of Pa_{O_2} or Sa_{O_2}

Table 149-4

Guidelines for the Use of Acute Oxygen Therapy

Accepted Indications

Acute hypoxemia (Pa_{O_2} < 60 mmHg; Sa_{O_2} < 90%)
- Cardiac and respiratory arrest
- Hypotension (systolic blood pressure < 100 mmHg)
- Low cardiac output and metabolic acidosis (bicarbonate < 18 mmol/L)
- Respiratory distress (respiratory rate > 24/min)

Questionable Indications

- Uncomplicated myocardial infarction
- Dyspnea without hypoxemia
- Sickle cell crisis
- Angina

** Data from Fulmer JD, Snider GL:* Chest *86:234–247, 1984.*

should be performed to document an effective response to a particular F_{IO_2}.

Hypoxemia secondary to right-to-left shunting is often less responsive to administration of supplemental oxygen. Mixing of shunted and unshunted blood results in a large fall in Pa_{O_2}. When the shunt fraction is greater than 20 to 25 percent, hypoxemia may persist, despite an F_{IO_2} of 1.0.

Finally, alveolar hypoventilation is often easily corrected with supplemental oxygen. However, recognition and correction of the underlying cause and immediate restoration of ventilation are the primary aims of treatment.

Although a Pa_{O_2} of 60 mmHg is a reasonable goal in the initial treatment of arterial hypoxemia, in certain clinical situations the acceptable threshold level may be adjusted upward or downward. For example, in patients with low oxygen-carrying capacity (e.g., severe anemia), or in flow-limited states (e.g., acute angina pectoris), increases in Pa_{O_2} beyond 60 mmHg (yielding increases in Sa_{O_2} from 90 to 100 percent) may result in marginal, but potentially important, increases in tissue oxygen delivery. Conversely, the "acceptable" Pa_{O_2} may have to be set at a lower level in patients with abnormal control of respiration, such as those with an acquired reduced hypoxic ventilatory drive due to chronic carbon dioxide (CO_2) retention.

Tissue Hypoxia with Normal Pa_{O_2}

The efficacy of supplemental oxygen in diseases that cause arterial hypoxemia is well-established. However, in cases where tissue hypoxia may exist without concomitant arterial hypoxemia, treatment should be directed ultimately to correcting the underlying cause. In these cases, Pa_{O_2} is an inadequate index of the need for, or the potential to benefit from, oxygen therapy. When available, alternative indices of tissue oxygenation should be used; oxygen therapy should be initiated and modified, based on the indices. Nevertheless, in some disorders, oxygen therapy has often been used even if Pa_{O_2} is not at a substantially depressed level. There is not always a consensus about the proper uses of oxygen in these circumstances.

Acute Myocardial Infarction

Hypoxemia is extremely common in acute myocardial infarction. In such patients, oxygen administration is of unquestioned benefit. Data supporting use of oxygen therapy in nonhypoxemic patients with acute myocardial infarction is controversial. Double-blinded studies of the value of oxygen in uncomplicated myocardial infarction demonstrate no significant effects on morbidity or mortality.

Inadequate Cardiac Output (Low-Flow States)

Oxygen has been recommended for temporary treatment of inadequate systemic perfusion resulting from cardiac failure. Although this practice seems reasonable, no clinical studies to date have proved the value of oxygen therapy in this setting. Oxygen therapy is used in conjunction with inotropic agents and other devices to assist cardiac output as definitive treatment is undertaken.

Trauma and Hypovolemic Shock

Oxygen has been advocated as adjunctive therapy in the setting of acute trauma. The low-flow state induced by acute hemorrhage is best treated by increasing the supply of circulating hemoglobin. However, supplemental oxygen as supportive therapy seems warranted until red blood cells become available for transfusion.

Carbon Monoxide Intoxication

In carbon monoxide poisoning, the Pa_{O_2} is a poor guide to the need for oxygen therapy. Despite a normal or "supranormal" Pa_{O_2}, a state of significant tissue hypoxia exists, as often indicated by a severe metabolic acidosis. Because of the high concentration of carbon monoxide–bound hemoglobin (carboxyhemoglobin), administration of supplemental oxygen does not increase tissue oxygen delivery. However, administration of pure oxygen markedly shortens the half-life of circulating carbon monoxide (80 min vs. 320 min on room air). Thus, oxygen administration for carbon monoxide poisoning constitutes an accepted therapy. Hyperbaric oxygen administration represents the current standard of care for those patients with high carboxyhemoglobin levels and evidence of end-organ ischemia-reperfusion damage (Chapter 62).

Miscellaneous Disorders

Use of supplemental oxygen as adjuvant therapy in sickle cell crisis, in accelerating resorption of air in pneumothorax, and for relief of dyspnea without hypoxemia remains controversial.

Long-Term Oxygen Therapy

In recent years, use of long-term oxygen therapy in the chronically ill patient has increased. In the United States, over 800,000 patients currently receive long-term oxygen therapy; most are patients with arterial hypoxemia. Patients with chronic obstructive pulmonary disease (COPD) represent the largest group of patients, and most of the data regarding clinical efficacy of supplemental oxygen come from studies of these patients.

Early studies of oxygen therapy in COPD showed that continuous supplemental oxygen administered for 4 to 8 weeks decreased the hematocrit, improved exercise tolerance, and lowered pulmonary vascular pressures. In the early 1980s, two well-controlled studies demonstrated the value of long-term oxygen administration in patients with chronic hypoxemia due to COPD. Both the Nocturnal Oxygen Therapy Trial (NOTT) and the British Medical Research Council Domiciliary (BMRCD) study documented a significant reduction in mortality in patients receiving supplemental oxygen compared with controls who received no supplemental oxygen. Although the treatment groups in the two studies are not directly comparable (patients in NOTT received either continuous or nocturnal oxygen, whereas those in BMRCD received nocturnal oxygen or no supplementation), nocturnal oxygen (greater than 15 h/day) is better than no oxygen; continuous supplemental oxygen imparts the most benefit. The greatest efficacy is seen in patients with polycythemia, pulmonary hypertension, or hypercapnia. Although similar studies in other groups of patients with chronic hypoxemia are not available, extension of the concept of long-term oxygen therapy for patients with resting hypoxemia from a variety of cardiopulmonary diseases, including restrictive lung disease, cystic fibrosis, and chronic cardiac disease, has become widely accepted in clinical practice.

Table 149-5 lists the currently accepted indications for long-term oxygen therapy. In addition to chronic arterial hypoxemia at rest, continuous-flow oxygen therapy is indicated for patients with exercise-induced hypoxemia (i.e., exercised-induced arterial desaturation). Current data suggest that supplemental oxygen improves exercise endurance, as measured by either treadmill walking or bicycle ergometry. However, since ventilatory, rather than circulatory, factors often limit exercise in patients with airflow obstruction, increasing oxygen saturation is not a reliable predictor of improved exercise performance in all patients.

A third group of patients who benefit from chronic oxygen administration are those who develop significant decreases in arterial oxygen during sleep. Included are patients with primary sleep-disordered breathing (e.g., obstructive sleep apnea and obesity hypoventilation syndrome) and patients with primary lung disease who exhibit nocturnal desaturation. For the first part of this group, oxygen therapy may need to be coupled with invasive or noninvasive ventilatory support for treatment of hypercarbia; the latter part of the group can often make use of low-flow oxygen to blunt arterial desaturation.

Table 149-5

Indications for Long-Term Oxygen Therapy

Continuous Oxygen

1. Resting Pa_{O_2} < 55 mmHg or oxygen saturation < 88%
2. Resting Pa_{O_2} of 56–59 mmHg or oxygen saturation of 89% in the presence of any of the following indicative of cor pulmonale:
   a. Dependent edema suggesting congestive heart failure
   b. P pulmonale on the electrocardiogram (P wave > 3 min in standard leads II, III, or aVF)
3. Polycythemia (hematocrit > 56%)
4. Resting Pa_{O_2} > 59 mmHg or oxygen saturation > 89% reimbursable only with additional documentation justifying the oxygen prescription and a summary of more conservative therapy that has failed.

Noncontinuous Oxygen*

1. During exercise: Pa_{O_2} < 55 mmHg or oxygen saturation < 88% with a low level of exertion
2. During sleep Pa_{O_2} < 55 mmHg or oxygen saturation 88% with associated complications, such as pulmonary hypertension, daytime sommolence, and cardiac arrhythmias

** Oxygen flow rate and number of h-day must be specified.*

In all patients, the need for additional supplemental oxygen should be based on measurements of arterial saturation. Certificates of medical necessity can then be completed appropriately. Most data support the notion that strategies for delivery of long-term oxygen should include early follow-up for assessing efficacy, followed by routine reevaluation at fixed intervals.

TECHNIQUES OF OXYGEN ADMINISTRATION

In either the acute or chronic setting, once the need for supplemental oxygen is established, one of several types of delivery devices can be used to supply the patient with O_2-enriched gas. The choice of delivery system is based upon a variety of criteria, including: (1) the degree of hypoxemia, (2) the requirement for precision of delivery, (3) patient comfort, and (4) cost. The devices discussed below are reserved primarily for conscious patients who are capable of protecting their airways. Not included in the discussion are details on the use of endotracheal intubation (Chapter 151) or mechanical ventilation (Chapter 153).

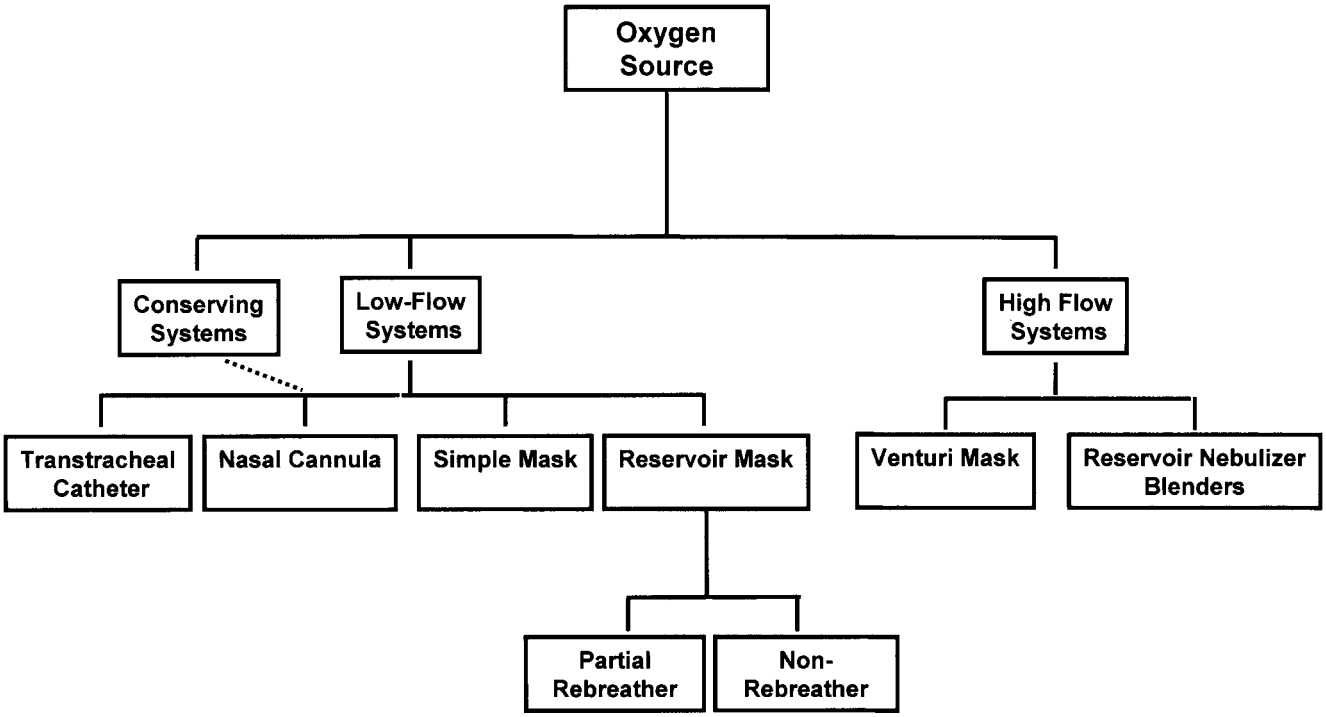

Figure 149-3 Commonly used classes of oxygen delivery systems. See text for complete descriptions.

Oxygen Delivery Systems in the Acute Setting

A variety of delivery systems are available for short-term oxygen administration. The systems vary in complexity, expense, efficiency, and precision of oxygen delivery. Other than anesthesia breathing circuits, virtually all oxygen delivery systems are non-rebreathing (full or partial). In non-rebreathing circuits, the inspiratory gas is not made up of any portion of the exhaled volume, and the only inhaled CO_2 is that which is entrained from ambient room air. Rebreathing is avoided through use of one-way valves to sequester expired from inspired gases. In addition, in all these systems, inspired gas mixtures must be presented in sufficient volume and at flows to allow compensation for the high-flow demands often exhibited by critically ill patients.

The major types of oxygen delivery systems are outlined in Fig. 149-3. They can be divided into low-flow and high-flow varieties, each of which can deliver humidified, inspired gases. Each has advantages and drawbacks.

Low-Flow Oxygen Devices

Low-flow oxygen delivery systems provide a fraction of the patient's minute ventilatory requirement as pure oxygen; the remainder of the ventilatory requirement is fulfilled by addition of another gas, usually entrained room air. Flows supplied through these devices are low (less than 6 L/min), and they cannot deliver constant inspired oxygen concentrations, since small fluctuations in each tidal volume lead to variations in the amount of entrained room air. Consequently, in patients with an abnormal or variable ventilation pattern, marked variation in the fraction of inspired oxygen may exist. Patient-related factors that affect the fractional concentration of inspired oxygen include: (1) shallow breathing, which results in entraining less room air and, therefore, a higher concentration of inspired oxygen; (2) deep, hyperpneic breathing, which enhances entraining of more room air; and (3) changes in respiratory frequency, which affect exhalation time, thereby producing variable filling of the device's inspiratory reservoir. When the delivery of a constant F_{IO_2} is required (e.g., in patients with chronic CO_2 retention), low-flow systems should not be used.

Nasal Cannulae

Nasal catheters and cannulae are the most widely used devices for delivering low-flow oxygen. They are simple, inexpensive, easy to use, and well-tolerated. As for all low-flow systems, the F_{IO_2} may vary greatly, depending on the oxygen flow, inspiratory flow, and minute ventilation. With low-flow nasal cannulae set to deliver oxygen to the nasopharynx at flows between 1 and 6 L/min, the F_{IO_2} ranges between 0.24 and 0.44 (Table 149-6). Flows above 6 L/min do not significantly increase F_{IO_2} above 44 percent; these higher flows may result in drying of mucous membranes.

Oxygen Masks

Simple plastic oxygen masks which cover the nose and mouth are capable of delivering concentrations of oxygen up to 50 to 60 percent. Depending on mask size, these devices provide a self-contained reservoir of 100 to 200 ml of additional gas,

Table 149-6

Approximate Fraction of Inspired Oxygen with Low- and High-Flow Oxygen Devices

100% O_2 Flow Rate (L/min)	F_{IO_2} (%)
Low-Flow Systems	
Nasal cannula	
1	24
2	28
3	32
4	36
5	40
6	44
Transtracheal catheter	
0.5–4	24–40
Oxygen mask	
5–6	40
6–7	50
7–8	60
Mask with reservoir bag	
6	60
7	70
8	80
9	90
10	>99
Non-rebreathing	
4–10	0.60–1.00
High-Flow System	
Venturi mask*	
3 (80)	0.24
6 (68)	0.28
9 (50)	0.35
12 (50)	0.40
15 (41)	0.50

**Numbers in parentheses indicate total flow of entrained room air in the Venturi mixture.*

thereby facilitating increases in the achievable fraction of inspired oxygen above 0.44. Simple face masks require a flow of inspired oxygen of 5 to 6 L/min to avoid accumulation of CO_2 within the mask.

Conventional oxygen masks suffer from the limitations of all face masks. They interfere with drinking, eating, and expectorating, and they can become displaced, particularly at night as the patient sleeps. In addition, use of face masks increases the risk of aspiration by concealment of vomitus or containment of regurgitant materials. Therefore, when using these devices, the risk-benefit ratio should be considered. As with nasal cannulae, respiratory mucous membrane drying from the inspired gas mixture is possible. Humidification of inspired gas reduces the magnitude of the problem.

Masks with Reservoir Bags

To deliver an F_{IO_2} of greater than 0.6 to patients who do not have artificial airways, a reservoir bag (600 to 1000 cc) can be attached to a simple face mask (Fig. 149-4). A source of continuous oxygen at flow rates of 5 to 8 L/min is needed to ensure adequate distention of the bag and to flush out CO_2 from the mask. If there are no one-way valves on the reservoir bag, the apparatus is referred to as a *partial non-rebreathing mask* (Fig. 149-4*A*). Partial non-rebreathing masks can deliver oxygen in concentrations of 80 to 85 percent. The true non-rebreathing mask makes use of a one-way valve between the mask and the bag so that the patient can only inhale from the reservoir bag and exhale through separate valves on either side of the mask (Fig. 149-4*B*). A very high F_{IO_2} can be achieved when these masks fit tightly against the patient's face. However, tight-fitting molded masks, including those used to deliver continuous positive airway pressure (CPAP), are often uncomfortable and are not suitable for use for more than a few hours.

High-Flow Oxygen Delivery Devices

High-flow oxygen delivery systems maintain the selected F_{IO_2} by incorporating a reservoir whose volume exceeds the patient's anatomic dead space or by delivering oxygen at a very high flow. In quantitative terms, the flow of all high-flow systems exceeds four times the patient's actual minute volume; otherwise, entrainment of room air at peak inspiration arises.

Common clinical indications for use of a high-flow oxygen delivery system are: (1) treatment of hypoxic patients who depend on their hypoxic drive to breathe but who require controlled increments in F_{IO_2}, and (2) young, vigorous patients with hypoxemia who have an abnormal ventilatory pattern and whose ventilatory requirements may exceed the delivery capabilities of low-flow systems. When a clinical indication exists for a tightly controlled, high F_{IO_2}, or when high flows are necessary, a high-flow delivery system should be used.

Jet-Mixing Venturi Masks

Another high-flow oxygen delivery device is the Venturi mask, the operation of which is based on the Venturi modification of the Bernoulli principle of fluid physics for gaseous jet-mixing (Fig. 149-5). As forward flow of inspired gas increases, the lateral pressure adjacent and perpendicular to the vector of flow decreases, resulting in entrainment of gas. In a Venturi mask, a jet of 100 percent oxygen flows through a fixed constrictive orifice, past open side ports, thereby entraining room air. The flow of jetting gas passing through, and then out of, the central orifice of the mask increases in velocity, and the resultant pressure drop along the sides of the jet draws room air into the face mask via the side ports. The amount of air entrained and, therefore, the resultant F_{IO_2}, depend on the size of the side ports and flow of oxygen. Since both of these parameters are fixed, the resultant oxygen-room air mixing ratio is held steady, resulting in a well-controlled, constant F_{IO_2}. Exhalation occurs through valved exhalation ports. The range of F_{IO_2} obtainable through adjustments in the amount

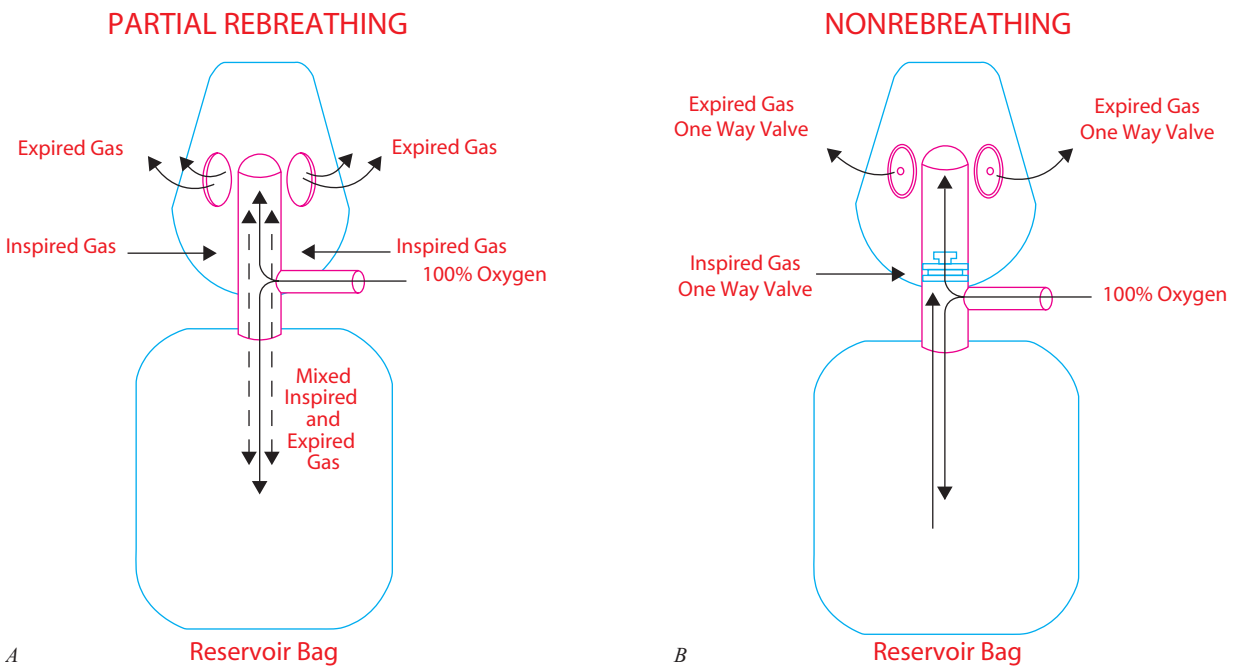

Figure 149-4 Mask-reservoir bag systems, illustrating airflows with partial rebreathing (*A*) and nonrebreathing (*B*) masks. Arrows indicate direction of airflow. See text for details.

of entrained room air and oxygen flow (i.e., the "entrainment ratio") is broad (Table 149-6). Masks currently in use deliver inspired gas with an F_{IO_2} between 0.24 and 0.50.

Since the Venturi mask reliably provides an accurate F_{IO_2} up to 0.50, it is an ideal device for use in treatment of hypoxemia in patients with COPD and chronic respiratory failure characterized by a blunted hypercarbic respiratory drive. Although the F_{IO_2} usually can be regulated precisely, technical factors can alter the value. For example, water drops may clog the oxygen injector device, resulting in changes in gas flow. In addition, development of back pressure by occluded exhalation ports may lead to decreases in the volume of entrained room air and a resultant increase in F_{IO_2}.

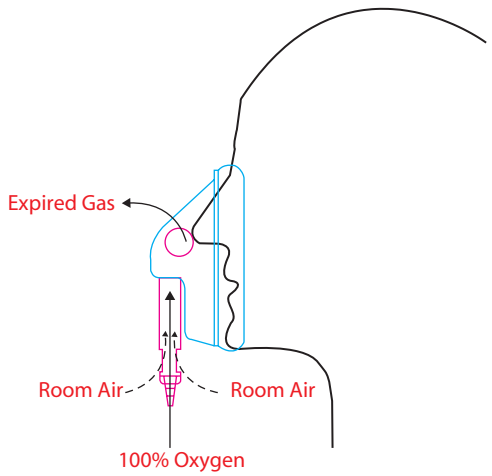

Figure 149-5 Venturi mask. Arrows denote direction of airflow. See text for details.

Other High-Flow Systems

Reservoir nebulizers and humidifiers are used to provide supplemental oxygen or highly humidified gas (including room air). Provision of high humidification is often important as adjuvant management of increased airway secretions. Usually, this delivery system is combined with endotracheal tubes or tracheostomy collars, and, therefore, its use is limited to patients with artificial airways. However, such delivery systems have also been used in combination with aerosol masks, face tents, and CPAP masks. If high-flow rates (in excess of 40 L/min) are supplied, they can usually provide a constant and predictable F_{IO_2}.

Air-oxygen blenders consist of precision metering devices that convert high-pressure wall sources of compressed air and oxygen (at 50 to 70 psi) to usable, predictable flows of up to 100 L/min at an F_{IO_2} ranging from 0.21 to 1.0. These devices also require pressure-reduction valves and an inlet pressure monitor to ensure consistency of F_{IO_2} against minor fluctuations in wall pressure. Although they provide a predictable F_{IO_2}, the devices have some disadvantages. They are noisy and require specialized personnel to set up and monitor the instrumentation.

Long-Term Oxygen Delivery Systems

A variety of modes of oxygen delivery and oxygen administration devices are available for use in the home and other chronic care settings. Gas supplies for long-term oxygen therapy include oxygen concentrators and compressed gas or liquid oxygen sources. Most patients requiring a stationary source of supplemental oxygen use oxygen concentrators.

Because the concentrators weigh about 35 lb and require wall current, their use is limited as a fixed source of oxygen. Unless patients are immobile or confined to bed, both stationary and mobile oxygen delivery systems should be employed. Both compressed gas and liquid oxygen portable systems are available, but the liquid system containers are easier to refill than high-pressure cylinders. The major disadvantages of liquid oxygen are higher cost and the requirement for pressure-relief venting.

The delivery devices for long-term oxygen therapy include most of the low-flow devices described previously. Most patients who receive chronic oxygen use nasal cannulae and oxygen flow rates of 2 to 4 L/min.

To improve the efficiency of oxygen delivery and to limit both the need for repetitive home delivery and cost, a number of devices have been designed to "conserve" home oxygen. These include reservoir nasal cannulae, electronic conserving devices, and transtracheal catheters.

The reservoir nasal cannulae have a pouch that stores 20 ml of extra oxygen during expiration and delivers the oxygen as a bolus at the onset of the next inspiration. Electronic demand devices, triggered by the onset of inspiration, deliver a pulse of oxygen early in the breath. Oxygen conservers include those that deliver a fixed volume per breath (pulse devices) and those that deliver a variable volume, which is commensurate with the length of inspiration (demand devices). Pulse-type devices deliver fixed volumes for each flow setting each time a pulse is triggered and do not deliver any more or less volume as the length of the patient's inspiration time varies. Some pulse devices deliver with every breath, others with alternate breaths. By comparison, demand devices vary the amount of oxygen delivered during each and every breath, consistent with the duration of inhalation. Following the initial gas bolus, demand devices deliver (at an equivalent flow) a continuous flow for the remainder of the inspiration. These devices provide a variable volume at each flow setting, depending on the length of inspiration, and they have lower levels of savings at low breath rates. In addition, demand devices tend to deliver volumes equal to or greater than those achieved using continuous flow therapy in most settings; in the event of conserver malfunction, they revert automatically to continuous flow without patient interaction.

Transtracheal catheters improve oxygen delivery by bypassing the anatomic dead space of the upper airway, effectively using the upper airway as an oxygen reservoir during inspiration and expiration. Transtracheal oxygen is delivered directly into the trachea via a hollow catheter implanted surgically under local anesthesia, or inserted percutaneously using the Seldinger technique. In numerous studies, transtracheal catheters have been shown to effect reductions in total oxygen usage of 50 to 75 percent. Other advantages of transtracheal oxygen systems include their inconspicuousness, lack of nasal or facial irritation due to oxygen flow, and infrequency of catheter displacement during sleep. Disadvantages include an increased incidence of infection, development of potentially fatal "mucus balls," and catheter breakage which necessitates replacement.

PULMONARY OXYGEN TOXICITY

Potential adverse effects of exposure to increased oxygen tensions at one atmosphere include alterations of normal physiological functions and oxygen-mediated tissue damage.

Physiological changes to high concentrations of oxygen involve perturbations of both pulmonary and extrapulmonary homeostasis; they are easily correctable, if recognized promptly. Extrapulmonary physiological effects of hyperoxia include suppression of erythropoiesis, systemic vasoconstriction, and depression of cardiac output. These effects are usually clinically insignificant. In contrast, pulmonary physiological effects of hyperoxia include depression of hypoxic ventilatory drive, pulmonary vasodilation, and absorption atelectasis. Each is clinically relevant.

In addition to producing adverse physiological effects, oxygen in high concentrations is cytotoxic. Whereas all respiring cells are potentially susceptible to the toxicity derived of hyperoxia, the major clinical adverse effects are related to lung damage.

Molecular and Cellular Mechanisms of Oxygen Toxicity

The molecular and cellular bases for tissue injury in oxygen toxicity are thought to be mediated biochemically by reactive free radicals, the formation of which directly depends on the oxygen concentration. Since oxygen concentration is directly proportional to partial pressure, breathing 100 percent O_2 at an altitude of 5000 feet (0.8 ata), 80 percent O_2 at sea level (1 ata), or 40 percent O_2 in a hyperbaric chamber (2 ata) for the same duration results in a similar toxicity profile.

Aerobic cells utilize oxygen both as a metabolic substrate for the generation of ATP via the electron transport chain, and as a cofactor in intermediary metabolism involving oxidation or hydroxylation of various substrates. Molecular oxygen (O_2), per se, is relatively nonreactive and nontoxic. However, modification of molecular oxygen by addition of electrons (e^-) can result in formation of highly reactive free radicals. The consequences of the sequential addition of single electrons to molecular oxygen are illustrated in the following reaction:

$$\begin{array}{cccc} e^- & e^- + 2H & e^- & e^- + H \\ & & O_2 \rightarrow O_2\cdot^- \rightarrow H_2O_2 \rightarrow OH\cdot \rightarrow H_2O & (3) \end{array}$$

Superoxide anion ($O_2^{\cdot -}$), hydrogen peroxide (H_2O_2), and hydroxyl radical ($OH\cdot$) represent 1-, 2-, and 3-electron reduction products of oxygen, respectively. Singlet oxygen ($O_2\cdot$), a potent electrophile, is also generated as a by product of oxygen-dependent metabolism. During normal cellular metabolism, almost all molecular oxygen is converted completely to water, and the enzymes responsible for the reduction reactions (e.g., cytochrome oxidase, cytochrome P450, dopamine-β-hydroxylase) release few or no O_2 intermediates. However, under certain conditions, these cellular

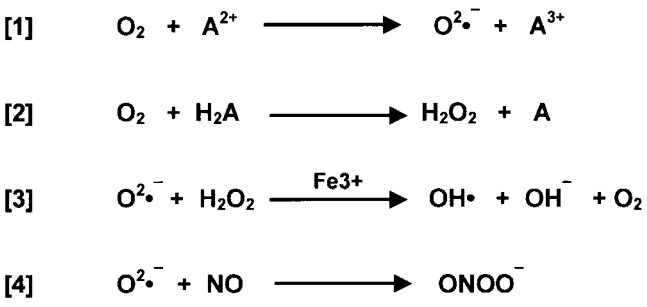

Figure 149-6 Generation of free radicals. Mechanisms for generation of toxic species of oxygen include: (1) superoxide anion (O_2^-) generation by 1-electron reduction of molecular oxygen (O_2) through a variety of electron donors (A^{2+}); (2) hydrogen peroxide (H_2O_2) generation by 2-electron reduction of O_2, usually via enzymatic catalysis; (3) interaction of superoxide and hydrogen peroxide in the presence of metals which generate hydroxyl radical; and (4) production of peroxynitrite by diffusion-limited reaction of superoxide and nitric oxide.

enzymes, as well as others, can be misused by serving as incomplete electron donors (i.e., fewer than four electrons) to molecular oxygen, generating and releasing the reactive O_2 intermediates shown in Eq. (3) above.

Figure 149-6 depicts general mechanisms responsible for generation of toxic metabolites of oxygen reduction. $O_2\cdot^-$ (reaction 1) and H_2O_2 (reaction 2) are each generated by both enzymatic and nonenzymatic processes. Although both molecular species may have direct toxic effects, their interaction via the Haber-Weiss cycle, in the presence of metal ions (typically, Fe^{3+}), may generate hydroxyl radicals (reaction 3) which represent the most highly reactive and potentially dangerous of the O_2-derived products.

Superoxide has also clearly been shown to interact with other molecular species, such as nitric oxide (NO), which result in production of the free radical, peroxynitrite (ONOO), as illustrated in reaction 4 in Fig. 149-6. The second-order rate constant for the reaction of NO and $O_2\cdot^-$ to form peroxynitrite is 6.7×10^9 $M^{-1}s^{-1}$. This represents a reaction rate that is three times faster than the clearance of superoxide by superoxide dismutase.

Mechanisms of Pulmonary Cellular Toxicity

The previously described generalized mechanisms of oxygen toxicity and metabolic intermediates are probably operative in the lung. Hyperoxia has been shown to stimulate increases in oxygen radical production in whole rat lungs, lung mitochondria, lung microsomes, lung nuclear membranes, and in cultured pulmonary endothelial cells, providing important support for the free radical hypothesis. Likewise, peroxynitrite formation has been detected in cultured cells in some animal models of acute lung injury, as well as in infants with bronchopulmonary dysplasia.

Mitochondria appear to be the major subcellular source of $O_2\cdot^-$ which is produced by the oxidation of ubisemiquinone as part of the normal mitochondrial electron transport chain and by autooxidation of NADH dehydrogenase. Additional $O_2\cdot^-$ is generated by: (1) the endoplasmic reticulum (and microsomes), through the auto-oxidation of flavins (e.g., cytochrome P450) or other components, as well as during turnover of NADPH-cytochrome c reductase; and (2) plasma membranes, by auto-oxidation of cytochromes and during prostaglandin synthesis. H_2O_2 is produced at most of the aforementioned sites by the dismutation of $O_2\cdot^-$ and via oxidase activity (e.g., urate oxidase) in peroxisomes. $HO\cdot$ is generated where concentrations of $O_2\cdot^-$ and H_2O_2 are greatest (i.e., near their production sites). Because peroxynitrite is generated by a diffusion-limited reaction, it may be formed as physiological pH at any cellular sites that contain significant amounts of NO and $O_2\cdot^-$.

The biochemical alterations produced by modification of cellular components by oxygen radicals and peroxynitrite are depicted in Table 149-7. Lipid peroxidation and protein oxidation are thought to represent important mechanisms

Table 149-7

Biochemical Alterations and Cellular Dysfunction from Free Radical Damage

Cell Component	Cellular Manifestation
Oxygen Radicals	
Lipids	Damage to cell and organelle membranes
Lipid peroxidation	
Surfactant	Altered lung mechanics
Eicosanoids	Changes in cellular metabolism and intracellular signaling
Proteins	Inactivation of enzymes and transport proteins; Altered cellular and intercellular permeability
Nucleic acids	Inhibition of cell growth and division
Pyridine nucleotides	Altered intermediary metabolism
Complex carbohydrates	Altered recognition of macromolecules
Peroxynitrite	
Proteins	
Nitrotyrosine formation	Inactivation of enzymes and transport proteins
Sulfhydryl groups	
Nucleic acids	
8-Nitroguanine formation	Cell death
Lipid peroxidation	Cell and organellar membrane damage

of direct O_2 radical toxicity. Lipids containing unsaturated fatty acids are particularly susceptible to injury. Lipid hydroperoxides produced as intermediates are extremely toxic and can propagate the peroxidation process in an autocatalytic manner. Proteins are inactivated by reaction of radicals with sulfhydryl groups, through cross-linkage of proteins, or oxidation of constituent amino acids. Destruction of lipid and protein results in damage to cellular and organellar membranes, inactivation of key enzymes, and disruption of cellular transport mechanisms. In addition, DNA, pyridine nucleotides, and complex carbohydrates are susceptible to oxidative processes, leading to mutagenesis, growth inhibition, and alteration of intermediary metabolism. Peroxynitrite is a powerful oxidant and, as such, has been shown to oxidize many cellular components. Of particular interest is its interaction with proteins, resulting in oxidation of sulfhydryl groups and formation of nitrotyrosine residues.

Cellular Antioxidant Defenses

The half-life and tissue levels of most reactive oxygen species are low, in part due to an elaborate network of cellular antioxidant defenses. Antioxidant mechanisms include any cellular process which (1) prevents formation of free radicals, (2) converts oxidants to less reactive species, (3) "compartmentalizes" reactive species away from important cellular structures, or (4) initiates repair of molecular injury by free radicals.

Cellular oxygen radical defenses are classified into three basic categories: (1) enzymatic scavenging systems, which directly catalyze removal of free radicals; (2) enzyme-cofactor systems, which use a recyclable (renewable) intermediate to remove or prevent formation of O_2 radicals; and (3) nonenzymatic free radical scavengers, which re-reduce O_2 radicals or quench radical-producing reactions.

The major enzymatic O_2 radical scavenger in the lungs is superoxide dismutase (SOD). SOD is a metalloprotein present in three distinct forms, each of which has a metallic cofactor. Copper-zinc SOD is a dimeric protein which is predominantly cytosolic; manganese SOD is found mainly in mitochondria. Copper SOD, a tetrameric peptide, has been isolated from plasma. All forms of SOD catalyze the dismutation of $O_2 \cdot^-$ to H_2O_2 at very high rates. Hydrogen peroxide is subsequently removed enzymatically by either the glutathione (GSH) redox cycle (see below) or by catalase.

The GSH redox cycle is the most important cellular scavenger of H_2O_2. It represents a unique system that uses multiple enzymes and a renewable, low-molecular-weight scavenger. GSH peroxidase removes both H_2O_2 and lipid peroxides at the expense of GSH oxidation. GSH is regenerated by GSH reductase, using NADPH as a cofactor.

Low-molecular-weight, nonenzymatic free radical scavengers include ascorbic acid (vitamin C), α-tocopherol (vitamin E), and β-carotene (vitamin A). These nonrecyclable compounds are derived from extrinsic (dietary) sources.

PATHOPHYSIOLOGY OF OXYGEN TOXICITY

The toxic effects of oxygen on the lung occur when free radical production during hyperoxic exposure overwhelms intrinsic antioxidant defenses. Excess free radicals interact with cellular components, resulting in cytotoxic events which produce a characteristic cascade of biochemical, cellular, morphologic, and physiological changes. The biochemical reactions, in turn, result in a sequence of characteristic cellular and morphologic changes.

Primary Morphologic and Cellular Changes

Based primarily on data from animal models and some limited human studies, four basic phases constitute the development of oxygen toxicity in lung tissue. The first three phases—initiation, inflammation, and destruction—occur during exposure to both lethal and sublethal doses of hyperoxia. The fourth phase—proliferation and fibrosis—occurs if there is re-exposure to sublethal oxygen levels. If lethal exposure persists, ongoing tissue destruction and death are observed.

Initiation Phase

The initiation phase of oxygen toxicity comprises the first few hours and continues throughout the duration of exposure. Initiation follows short-term exposure to lethal doses of O_2 and occurs over longer periods, with sublethal hyperoxia. In each setting, the initiation phase is associated with enhanced rates of oxygen radical formation; however, there is no significant evidence of morphologic injury. Decreased rates of protein synthesis, alterations in tracheobronchial clearance of particulates, and changes in endothelial cell function have been described.

Inflammatory Phase

The earliest morphologic changes in the lung in response to hyperoxia occur as a consequence of primary cellular damage. They involve subtle changes in endothelial cell structure, resulting in pericapillary accumulation of fluid. Increased leakage from the pulmonary microcirculation via disruptions in the endothelial lining follows, along with accumulation of proteinaceous fluid, formation of hyaline membranes, and an influx of inflammatory blood cell elements with release of mediators. This combination of events gives rise to a pathological picture resembling noncardiogenic pulmonary edema, including morphologic characteristics of diffuse alveolar damage—a process frequently associated with acute respiratory distress syndrome (ARDS) and other forms of lung injury (see Chapters 144 and 145).

Destruction Phase

Overt cellular destruction begins shortly after the inflammatory phase. From a large body of in vitro and in vivo evidence it now appears that two major patterns of cell death, apoptosis and necrosis, occur in the lung in response

to hyperoxia. Apoptotic signaling pathways appear to involve both the cell death receptor (CD40-CD40 ligand) and mitochondria-dependent pathways with activation of caspase family members. The earliest evidence for impending cellular destruction appears at the ultrastructural level. Observed changes in lung epithelial and endothelial cells include membrane damage, vacuolarization of cytoplasm, mitochondrial swelling, and nuclear degeneration. Soon thereafter, frank cell death is seen, and exposure of the basement membrane occurs.

Proliferation and Fibrosis Phase

If exposure to toxic levels of O_2 is terminated, a subacute or chronic stage, termed the *proliferative phase,* develops. The cellular proliferative response blunts the destructive phase and may enhance survival. Proliferation of type II pneumocytes occurs as alveolar remodeling takes place. In addition, an influx and proliferation of interstitial cells (fibroblasts, monocytes, and macrophages) appears to be mediated by both cytokine and autocrine factors; collagen deposition is seen as well. In baboons, lung histology and function have been shown to return to normal within 6 months of recovery from severe oxygen toxicity. However, in other settings, the end result may be, instead, varying degrees of fibrosis or emphysema. The complete complement of regulating factors remains to be defined.

In the aggregate, the pathophysiological and morphologic changes associated with hyperoxic stress are similar to other forms of diffuse alveolar damage. An initial inflammatory response (exudative phase) is followed by fibrosis and repair (proliferative phase), a sequence not dissimilar from other forms of ARDS.

Secondary Changes

The cellular changes that occur in response to toxic oxygen exposure also produce secondary changes in lung function. The increased capillary permeability that occurs with cellular damage results in decreased lung compliance, an increased alveolar-arterial oxygen gradient, and a decreased carbon monoxide diffusing capacity. Hyperoxia has also been reported to alter the pulmonary surfactant system. Alveolar surfactant material recovered from animals exposed to hyperoxic conditions exhibits markedly decreased surface tension–lowering capabilities. One potential explanation appears to be inactivation of the biophysical activity of surfactant by serum proteins which leak into the alveolar space.

CLINICAL SYNDROMES OF OXYGEN TOXICITY

The scenario of clinical events following exposure to hyperoxic environments is well-described as summarized in Table 149-8.

Table 149-8

Sequence of Pulmonary Changes during Hyperoxic Exposure in Humans

O_2 at 1 atm	Exposure Duration	Manifestions
100%	>12 h	Decreased tracheobronchial clearance; decreased forced vital capacity; cough; chest pain
	>24 h	Altered endothelial function
	>36 h	Increased alveolar-arterial oxygen gradient; decreased carbon monoxide diffusing capacity
	>48 h	Increasing alveolar permeability; pulmonary edema; surfactant inactivation
	>60 h	Acute respiratory distress syndrome
60%	7 days	Mild chest discomfort without changes in lung mechanics; possible changes in morphometry
24–28%	Months	Subclinical pathological changes; no clinical toxicity documented

Acute Toxicity: Tracheobronchitis and Acute Respiratory Distress Syndrome (ARDS)

Normal volunteers exposed to 100 percent O_2 experience symptoms within 12 to 24 h. The earliest manifestations represent effects on the tracheobronchial mucosa and include substernal chest pain and nonproductive cough. Measurements of tracheobronchial function show decreased particle clearance as early as 6 h after the start of exposure to 100 percent O_2. Systemic symptoms, including malaise, nausea, anorexia, and headache may be seen.

The onset of acute pulmonary oxygen toxicity usually follows an asymptomatic period during which no physiological changes are seen. In normal volunteer subjects given 100 percent O_2 for 6 to 12 h, no abnormalities were noted in the alveolar-arterial oxygen gradient, pulmonary artery pressure, vascular resistance, cardiac output, pulmonary extravascular lung water, or chest radiograph. By 24 h, significant decreases in their vital capacities were found, and at 48 h of exposure to 98 percent oxygen, decrements in static compliance and carbon monoxide diffusing capacity were seen. In patients with irreversible brain damage given 100 percent O_2, the

alveolar-arterial gradient increased precipitously after 40 to 60 h. The longest voluntary exposure to 100 percent O_2 reported is 110 h; the subject developed severe dyspnea, a marked decrease in pulmonary function, and acute respiratory failure.

Chronic Pulmonary Syndromes

Although not well understood in humans, the subacute and chronic phases of oxygen toxicity are well documented in animals and appear to be related to dose and duration of exposure. The best-known clinical syndrome of chronic pulmonary oxygen toxicity occurs in newborns receiving oxygen for treatment of neonatal respiratory distress syndrome. Persistent morphologic changes with healing may produce the chronic disorder bronchopulmonary dysplasia. The effects of long-term exposure of adults to inspired oxygen concentrations of 60 to 100 percent are less clear, although morphometric changes after 13 days of exposure in brain-dead patients have been described. Data on longer exposures, including exposure to lower levels of inspired oxygen, are unavailable.

Diagnosis

Pulmonary oxygen toxicity develops insidiously after a variable lag period, during which the biochemical and cellular changes described previously occur. Early clinical detection of oxygen toxicity during this lag period is impossible; tests to identify biochemical changes (e.g., lipid peroxidation) would improve diagnostic accuracy. However, such tests are currently unavailable for clinical use. Although reversible (early) physiological, anatomic, and biochemical changes can be detected following short exposure to hyperoxia, humans can tolerate 100 percent oxygen at sea level for 24 h without serious pulmonary injury. Currently, the diagnosis of hyperoxic lung injury depends on a nonspecific symptom complex or abnormal pulmonary function in the proper clinical setting.

Symptoms and Signs

Development of chest pain, tachypnea, or cough in a patient breathing elevated concentrations of oxygen should alert the clinician to the possibility of oxygen toxicity. The best index of oxygen toxicity may be the individual's subjective symptom of retrosternal chest pain. Unfortunately, in a critically ill patient who requires mechanical ventilation or who has an altered mental status, detection of subjective complaints is difficult or impossible. On physical examination, the presence of crackles suggestive of interstitial or alveolar edema may be noted as a nonspecific finding.

Pulmonary Function Tests

Decreases in vital capacity, pulmonary compliance, or carbon monoxide diffusing capacity, as well as a widening of the alveolar-arterial oxygen gradient, have been observed during hyperoxic exposures. Monitoring serial changes in vital capacity has been proposed as a means of detecting and following injury from oxygen exposure. However, the practicality and cost-effectiveness of such testing remains unsubstantiated.

Radiographic Changes

The chest radiographic findings of increased interstitial markings or alveolar filling are similar to those found in other causes of diffuse alveolar damage; the findings are nonspecific and are insensitive as early markers.

Potentiation of Oxygen Toxicity

Susceptibility of cells or organisms to oxygen toxicity can be modified by factors other than intrinsic cellular antioxidant mechanisms. Many therapeutic drugs act synergistically with hyperoxia, accelerating free radical production and worsening oxygen toxicity. Bleomycin has been shown to increase lung injury and fibrosis through enhanced production of $O_2.^-$. Potentiation of oxygen toxicity by disulfiram occurs through inhibition of cytosolic superoxide dismutase by diethyldithiocarbamate, which is produced in vivo from the conversion (reduction) of disulfiram. The metabolism of nitrofurantoin and paraquat results in production of superoxide or hydroxyl radicals, and O_2 has been shown to increase their cytotoxicity. Variability of dietary intake can also modify oxygen tolerance. Protein malnutrition, as well as dietary deficiency of any of the antioxidant quenchers, may alter the response to hyperoxia. Protein deficiency is thought to potentiate toxicity from hyperoxia due to a lack of sulfur-containing amino acids which are crucial for GSH synthesis. The adverse effects of vitamin A and vitamin E deficiencies are also well described.

Prevention and Therapy

As with other drugs, oxygen should be administered judiciously, in doses designed to achieve therapeutic efficacy with limited toxicity. Because early detection of oxygen toxicity has remained elusive and specific therapy is lacking, avoidance of pulmonary toxicity during oxygen therapy remains the cornerstone of management. The best approach is to monitor the efficacy of the inspired oxygen concentration and to adhere to guidelines to use doses that have not been found to be associated with major side effects.

The primary therapeutic goal associated with use of supplemental oxygen is assurance of adequate tissue oxygenation without use of toxic levels of F_{IO_2}. A significant obstacle in achieving this goal centers around monitoring the efficacy of oxygen therapy and assessing the adequacy of tissue oxygenation. As noted previously, the clinical approach entails correction of arterial hypoxemia as the cause of tissue hypoxia and assessment of the response to supplemental oxygen administration through measurement of Pa_{O_2} or use of continuous, cutaneous, infrared pulse oximetry.

Extrapolations about the state of tissue oxygenation from measurement of $\bar{v}_{O_2}$ using an indwelling pulmonary artery catheter can be used in the critical care setting. Transcutaneous estimations of tissue P_{O_2} and, hence, intracellular oxygen sufficiency, remain experimental. Based upon general consensus, the following guidelines can be offered regarding oxygen administration at 1 atmosphere.

Oxygen in concentrations up to 100 percent can be administered in the transport and initial management of critically ill patients. In patients who are not on mechanical ventilation, evidence of respiratory depression should be monitored. If needed, an F_{IO_2} of 1.0 can be used for up to 24 h without significant lung injury. During this period, management should be directed toward improving pulmonary gas exchange, optimizing oxygen delivery, and limiting tissue metabolic demands so that inspired O_2 concentration can be decreased to the lowest possible levels.

Oxygen at an F_{IO_2} of 0.5 or less can be administered safely to most patients for weeks, although factors specific to individual patients (e.g., prior bleomycin use) may dictate a lower tolerance. The maximal safe duration for oxygen exposures between an F_{IO_2} of 0.5 and 1.0 is less certain, although these concentrations probably can be tolerated longer than 24 h. The safe upper limit of F_{IO_2} for chronic oxygen therapy in the ambulatory setting is largely undefined.

SUMMARY

Use of supplemental oxygen is a powerful tool in the management of critically ill patients as well as those with chronic cardiopulmonary disease, but it represents a double-edged sword. Concomitant with initiation of its use in management of hypoxemia, careful assessment for the underlying etiology of the hypoxemia and implementation of therapeutic measures aimed at its reversal should be undertaken. The proper prescription of oxygen is based upon general principles that are applied to the administration of any other drug. Knowledge of the various techniques of oxygen administration, establishment of clear therapeutic end points, monitoring of the efficacy of treatment, and awareness of the potential toxicity of oxygen are required.

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Pulmonary Pharmacotherapy

Karen J. Tietze • Scott Manaker

A wide spectrum of therapeutic agents are currently employed in the treatment of respiratory disorders, including obstructive lung diseases. This chapter reviews the rationale for, and clinical use of, these agents in current clinical practice. A brief discussion of potentially useful therapeutic drug strategies for the future is also provided.

BRONCHODILATORS

Pharmacologic management of obstructive airway diseases is based heavily upon bronchodilation produced by β-adrenergic agonists, muscarinic antagonists, and methylxanthines. In addition, magnesium and inhaled diuretics may ultimately prove to be effective bronchodilators suitable for clinical use.

β-Adrenergic Agonists

The β-adrenergic agonists mimic the actions of norepinephrine at neuroeffector and synaptic junctions. Norepinephrine is the major neurotransmitter in the sympathetic nervous system; therefore, this class of drugs is referred to as *adrenergic agonists* or *sympathomimetics.* Adrenergic receptor stimulation catalyzes the conversion of adenosine triphosphate (ATP) to cyclic-3′5′-adenosine monophosphate (cAMP) by activating adenyl cyclase, a cofactor in the production of cAMP. The increase in cAMP triggers the intracellular events that mediate pulmonary and extrapulmonary responses. The two major types of adrenergic receptors are the alpha and beta receptors; at least two alpha and two beta receptor subtypes have been identified. The β-adrenergic agonists (Table 150-1) are indicated in the treatment of bronchospasm associated with acute and chronic asthma, bronchitis, emphysema, exercise, and other obstructive pulmonary diseases. Selection of a specific agent and route of administration depends on underlying patient risk factors and the receptor specificity of the drug.

Pharmacology

Adrenergic receptor stimulation produces a wide range of responses, depending on the effector organ and the specific

Table 150-1

Adrenergic Agonists

	Receptor Activity			Dosage Forms					
	Alpha	**Beta$_1$**	**Beta$_2$**	**Duration**	**MDI**	**DPI**	**Neb**	**Inj**	**Oral**
Agent									
Catecholamines									
Epinephrine	+	+	+	Very Short	X[*,†]		X	X	
Isoproterenol		+	+	Short				X	
Isoetharine		+	+	Short			X		
Resorcinols									
Metaproterenol		±	++	Short	X		X		X[#,**]
Terbutaline		±	+++	Short				X	X[#]
Saligenins									
Albuterol		±	+++	Short	X[‡]		X		X[#,¶,**]
Levalbuterol		±	+++	Short	X[§]		X		
Salmeterol		±	+++	Long		X			
Other									
Pirbuterol		±	+++	Short	X[†]				
Formoterol		±	+++	Long		X			

Duration: short = 2 to 6 h; long = 8 to 12 h

Note: Abbreviation: MDI = metered dose inhaler; Neb = solution for nebulization; Inj = injectable dosage form; X = marketed dosage formulation; ± = present but minimal effect; + = mild effect; ++ = considerable effect; +++ = major effect.

[*] *Nonprescription product.*

[†] *Contains chlorofluorocarbons.*

[‡] *Some products contain chlorofluorocarbon and some products contain hydrofluoroalkane.*

[§] *Contains hydrofluoroalkane.*

[#] *Immediate-release dosage formulation.*

[¶] *Sustained-release dosage formulation.*

[**] *Syrup.*

receptor. Although bronchial smooth-muscle relaxation results from β_2-adrenergic receptor stimulation, none of the currently marketed agonists are completely specific for β_2-adrenergic receptors.

The α-adrenergic receptor is generally associated with constrictor/contractor responses, including constriction of arteries and veins and contraction of the uterus, radial and sphincter muscles of the iris, urinary bladder, and stomach sphincters. β_1-Adrenergic receptor stimulation increases heart rate, atrial and ventricular contractility, and cardiac conduction velocity. Effects from β_2-adrenergic receptor stimulation include relaxation of bronchial and uterine smooth muscle, dilatation of arteries and veins, and several metabolic effects, including glycogenolysis, gluconeogenesis, and induction of hepatic pancreatic beta cell secretion.

Structure-Activity Relationships

The parent compound for the adrenergic agonists, phenylethylamine (Fig. 150-1), consists of a benzene ring and an ethylamine side chain. Substituents can be added to the alpha or beta carbons of the ethylamine side chain, the terminal amine group, or one or more of the carbons in the aromatic ring.

The basic chemical structures of the adrenergic agonists include the catecholamines, resorcinols, and saligenins (Fig. 150-1). The catecholamines were the first adrenergic agonists to be marketed. The resorcinols (metaproterenol and terbutaline) have hydroxyls at positions 3 and 5 of the aromatic ring. This promotes oral bioavailablity and prolongs the duration of effect by protecting the molecules from catechol-o-methyl transferase degradation. Terbutaline, with a large substituent on the terminal amine, is selective for β_2-adrenergic receptors. The saligenins (albuterol and salmeterol) have a hydroxyl at position 4, various carbon moieties on position 3 of the aromatic ring, and large substituents on the terminal amine. These large substituents confer a longer duration of action and β_2-adrenergic receptor specificity, particularly for salmeterol. Salmeterol's long side chain results in increased lipophilicity, protecting the structure from

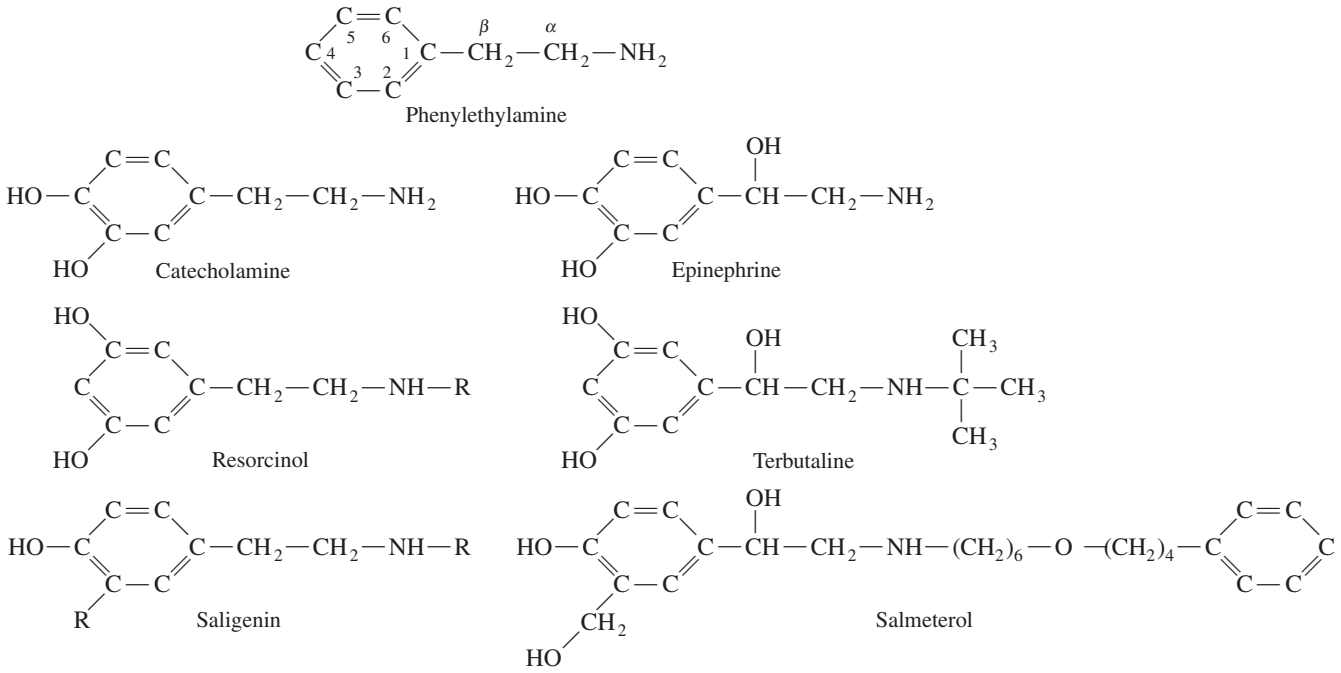

Figure 150-1 Structures of adrenergic agonists.

metabolism by catechol-o-methyl transferase and allowing the compound to bind both to the beta receptor and to an adjacent exoreceptor site. In theory, the exoreceptor binding site anchors the drug close to the beta receptor, further prolonging its action. Albuterol is a 1:1 mixture of the R- and S-enantiomers. The R-albuterol enantiomer is the active moiety; the S-albuterol enantiomer is inactive. Although early animal and clinical studies suggested that the S-albuterol enantiomer might antagonize the effects of the R-albuterol enantiomer, a clear clinical advantage of levalbuterol, the first pure enantiomer (R-albuterol) has not been demonstrated. Formoterol is a phenylethanolamine derivative with a phenyl-isopropyl group attached to the terminal amine. Physicochemical properties account for formoterol's long duration of action. Pirbuterol differs from all other adrenergic agonists in that the aromatic ring is a pyridine, instead of a benzene.

Drug Delivery

The β-adrenergic agonists may be administered systemically or by inhalation; however, not all drugs are marketed in every dosage form. Systemic dosage forms include oral, subcutaneous, and intravenous preparations. Systemic administration decreases the β_2-adrenergic receptor selectivity of the drug due to exposure to various metabolic enzymes, including catechol-o-methyl transferase, monoamine oxidase, and sulfatase. These enzymes change the chemical structure of the drug, decreasing the β_2-adrenergic receptor selectivity. The oral route of administration is generally reserved for patients who cannot successfully use metered-dose inhalers (e.g., children or the elderly). Sustained-release, oral dosage forms may be useful in controlling nocturnal symptoms of asthma, although not as effectively as the long-acting, inhaled adrenergic agonists. The subcutaneous route is generally reserved for patients too dyspneic to inhale the drug, and parenteral drug administration is generally employed for pediatric patients.

The preferred route of β-adrenergic agonist administration is by inhalation. Local application of small amounts of drug directly to the airways decreases the amount available for systemic absorption, minimizing systemic side effects. Inhaled β-adrenergic agonists are available in several dosage forms, including wet aerosols, aerosols from metered-dose inhalers, and dry powder forms. Most commonly, wet aerosols are delivered by jet or ultrasonic nebulizer, whereas metered-dose inhalers are primarily marketed as "press and breathe" devices. Historically, nebulized drug delivery was standard practice for children, emergency treatment of asthma exacerbations, hospitalized patients, and severely obstructed patients. However, nebulized drug delivery is labor intensive; significant cost savings can be realized, without sacrificing efficacy, by using metered-dose inhalers coupled with spacer devices.

Drug delivery by metered-dose inhaler is highly dependent on administration technique. Less than 10 percent of the dose is delivered to the lung using optimal inhalation technique; the rest of the drug is deposited in the mouth. Spacer devices eliminate the split-second timing necessary with proper metered-dose inhaler technique and decrease the amount of drug deposited in the oropharynx (an important factor with inhaled corticosteroids); however, they do not provide a therapeutic advantage over correct use of a metered-dose inhaler alone.

Metered-dose inhalers initially contained chlorofluorocarbon (CFC) propellants. In 1978, international concerns regarding the ozone-depeleting properties of CFCs led to a generalized ban on CFC-containing products. In 2005, the Food and Drug Administration (FDA) announced that CFC-containing MDIs, previously exempt from the ban on CFC production and importation, will not be produced, marketed, or sold in the United States after December 31, 2008. CFC-containing MDIs are being replaced by hydrofluoroalkane (HFA)-containing MDIs and a variety of dry powder inhalers (DPIs).

Clinical Use

The β_2-adrenergic agonists are considered first-line drugs in the treatment of both asthma and chronic obstructive pulmonary disease (COPD). In asthma, the short-acting inhaled β_2-adrenergic agonists are preferred for treating acute symptoms and for preventing exercise-induced bronchospasm. The subcutaneous route of administration is generally reserved for patients unresponsive to frequent, high-dose, inhaled β_2-adrenergic agonists; uncooperative patients; or patients too severely dyspneic to inhale the dose. Subcutaneous or parenteral administration should not be used in patients with angina or a recent history of myocardial infarction. Oral adrenergic agonists may be appropriate for children too young to cooperate with inhaled drug administration; sustained-release, oral adrenergic agonists decrease nocturnal symptoms, but they are less effective than long-acting β_2-adrenergic agonists.

In COPD, β_2-adrenergic agonists provide modest symptomatic relief and improvement in pulmonary function. Long-acting inhaled β_2-adrenergic agonists are standard bronchodilator therapy for patients with moderate and severe COPD. Standard doses of inhaled β_2-adrenergic agonists appear as effective as inhaled anticholinergic drugs for relief of acute exacerbations of COPD. The value of subcutaneous drugs and high-dose short-acting bronchodilators in the management of COPD has not been determined.

The intensity and duration of response to β_2-adrenergic agonists is dose- and frequency dependent. For patients with asthma, higher doses result in incrementally greater bronchodilation. The dose-response relationships are less well defined for COPD. The dose-response curve in asthma led to the development of intensive inhaled β_2-adrenergic agonist drug regimens for the treatment of severe, acute exacerbations. Typically, the nebulized drug is administered every 20 min for three to six doses; some patients respond better to continuous nebulized drug delivery. These regimens are generally well tolerated, although cardiac stimulation is common.

The long-acting β_2-adrenergic agonists are add-on agents for patients with moderate or severe asthma when usual doses of inhaled corticosteroids are inadequate and for patients with moderate to severe COPD. The long-acting β_2-adrenergic agonists are also alternate add-on agents for patients with symptoms of nocturnal asthma. The long-acting β_2-adrenergic agonists have no role in the treatment of acute asthma or an acute exacerbation of COPD; all patients should have a short-acting inhaler and should be instructed on how and when to use each type of β_2-adrenergic agonist.

Tolerance

Tolerance, or receptor subsensitivity, is defined as a decreased response to receptor stimulation. Although tolerance to the nonbronchodilator effects of β-adrenergic agonists, including tremor, tachycardia, prolongation of the QT_c interval on the electrocardiogram, hypoglycemia, hypokalemia, and vasodilator response, has been demonstrated, data on tolerance to the bronchodilator effects of β-adrenergic agonists are limited and conflicting.

Tolerance to the long-acting drugs may make patients less responsive to short-acting β_2-adrenergic agonists during an acute attack or may mask inadequate control of inflammation. Although the mechanism for tolerance to the long-acting drugs has not been precisely identified, one hypothesis is that prolonged drug-receptor interaction may induce receptor down-regulation. Concomitant disease-modifying drug therapy (e.g., corticosteroids) may also modify the development of tolerance by modulating adrenoceptor function.

Safety

The β_2-selective adrenergic agonists produce less cardiovascular toxicity than do the nonselective agents, but β_2-selectivity does not protect from all adverse events. Biochemical abnormalities associated with the β_2-adrenergic agonists include hyperglycemia, hyperinsulinemia, lipolysis, hypokalemia, hypomagnesemia, and lactic acidosis. These side effects are most pronounced with parenteral and oral drug administration; they are minimal with usual doses of inhaled agents. Furthermore, the biochemical abnormalities are more pronounced in drug-naïve normal volunteers than in asthmatic patients, suggesting that tolerance develops following chronic drug administration.

β_2-adrenergic agonists cause dose- and route-dependent hyperglycemia by stimulating glycogenolysis and gluconeogenesis. This effect may be clinically most important in asthmatic patients with diabetes mellitus or during pregnancy. β_2-adrenergic agonists increase plasma insulin by directly stimulating pancreatic islet cells; indirect increases occur secondary to the hyperglycemic response. β_2-adrenergic agonists induce the release of free fatty acids from adipose tissue. Although hyperinsulinemia and high concentrations of free fatty acids have been linked with cardiovascular morbidity and mortality, tolerance minimizes these effects. β_2-adrenergic receptor stimulation also induces muscle glycogenolysis, increasing lactate production.

The β_2-adrenergic agonists induce hypokalemia by directly stimulating the uptake of potassium into skeletal muscle cells. β_2-adrenergic receptor stimulation induces the cellular uptake of magnesium; hypomagnesemia may induce arrhythmias or worsen symptoms of coronary artery disease. Other

adverse β_2-adrenergic agonist effects include: (a) an increased baseline tremor by creating an imbalance in fast- and slow-twitch muscle groups; (b) tachycardia by direct chronotropy and through reflex peripheral vasodilatation and decreased venous return; and (c) central nervous symptoms, such as appetite suppression, headache, nausea, and sleep disturbances. The nervousness reported by many patients is probably a response to the peripheral tremors rather than a result of direct stimulation of the central nervous system.

β-adrenergic agonist use has increased coincident with the increase in asthma morbidity and mortality in the United States and other countries. This observation has promoted interest in the possible relationship between asthma mortality and use of these agents. The first link was made during the 1960s when the newly marketed nonselective β-adrenergic agonist isoproterenol was associated with an increase in asthma morbidity and mortality in the United Kingdom. Although never conclusively proved, the increase in asthma morbidity and mortality was blamed partly on the lipolytic effect of the drug, which increases the potential for myocardial ischemia, and partly on the high-dose formulation. In the 1970s, when fenoterol was linked to an increased death rate in New Zealand, part of the increased mortality was attributed to the hypokalemic effect of fenoterol.

Interest in the association between regular use of short- and long-acting β-adrenergic agonists and asthma morbidity and mortality was heightened by several reports that use of multiple fenoterol or albuterol inhalers per month was associated with an increased risk of death. A subsequent meta-analysis of case-control studies reported only a very weak, although statistically significant, relationship between the use of nebulized β agonists and death from asthma. Although this weak relationship was more likely in adults than adolescents, data from large, well-designed trials are needed to assess accurately the risk of death associated with long-acting β-adrenergic agonists.

Anticholinergics

Atropine and other anticholinergic alkaloids from plant extracts have been used for thousands of years to relieve respiratory symptoms in humans with airway diseases. Historically, clinical use of atropine and atropinelike agents has been limited by anticholinergic side effects, including dry mouth and skin, tachycardia, and meiosis; higher doses produce difficulties in speaking, swallowing, urinating, and mentating, as well as other neurologic side effects.

Pharmacology

Muscarinic receptors control airway smooth muscle function. Activation of airway M_1 and M_3 muscarinic receptors results in bronchial smooth muscle contraction and mucus secretion. M_2 "autoreceptor" activation results in decreased acetylcholine (Ach) release; blockade of M_2 receptors increases airway Ach. The ideal anticholinergic drug would selectively block M_1 and M_3 receptors and have no effect on M_2 receptors.

Quaternary ammonium atropine derivatives were developed to avoid the systemic side effects associated with tertiary derivatives, such as atropine. The quaternary ammonium compounds do not penetrate the blood-brain barrier, are minimally absorbed systemically, and have longer durations of action than atropine. Ipratropium bromide (FDA approved in 1998) and tiotropium bromide (FDA approved in 2004) are closely related quaternary ammonium drugs that differ in terms of muscarinic receptor binding affinities and receptor-drug complex half-lives. Ipratropium bromide nonselectively blocks M_1, M_2, and M_3 receptors. Tiotropium bromide has a greater affinity for muscarinic receptors than ipratropium bromide, but it dissociates rapidly from M_2 receptors, resulting in prolonged M_1- and M_3-drug complex half-lives compared to ipratropium bromide. Inhalation of ipratropium bromide produces bronchodilation in seconds to minutes, with a peak effect after 1 to 2 h. Inhalation of a single dose of tiotropium bromide produces a peak FEV_1 in 1 to 3 h; the duration of effect is about 32 h. The trough FEV_1 increases after multiple doses, reflecting carryover bronchodilation from the prolonged half-life.

Clinical Use

Ipratropium bromide and tiotropium bromide are most efficacious in patients with COPD, including emphysema and chronic bronchitis. In such patients, ipratropium bromide and tiotropium bromide are equally or more effective than β-adrenergic agonists in increasing FEV_1 and reducing airway resistance. Limited data suggest that tiotropium bromide may be superior to ipratropium bromide and the long-acting β_2-adrenergic agonist, salmeterol, in long-term management of moderate to severe COPD. The increased cost of tiotropium bromide may be offset by reduced overall health care expenditures. Chronic inhalation of ipratropium bromide or tiotropium bromide does not lead to development of tolerance or tachyphylaxis.

The combination of inhaled anticholinergic and β-adrenergic agonist produces greater improvement in FEV_1 and specific conductance than does administration of either agent alone. Most large-scale studies of patients with COPD demonstrate that the addition of oral corticosteroids does not increase maximal flow over that achieved by the administration of a β-adrenergic agonist with inhaled ipratropium bromide.

In contrast, ipratropium bromide is less effective than β-adrenergic agonists in the treatment of chronic asthma, and the role of tiotropium is not established. Some asthmatics may gain more relief of bronchospasm from inhalation of ipratropium bromide than β-adrenergic agonists. However, this unusual response requires initial evaluation with an empiric trial of ipratropium bromide and should be reserved only for patients whose moderate to severe asthma is difficult to control. A recent meta-analysis of 32 randomized controlled trials of anticholinergics in treatment of children

and adults with acute asthma found that compared with use of inhaled β_2-adrenergic agonists alone, addition of inhaled anticholinergics significantly reduced hospitalizations and increased spirometric parameters 1 to 2 h after treatment.

Safety

Consistent with their very low systemic bioavailability, both ipratropium bromide and tiotropium bromide are remarkably free of side effects. Transient dry mouth of mild intensity has been reported in 16 percent of patients inhaling tiotropium bromide and in up to 10 percent of patients inhaling ipratropium bromide. Side effects of tiotropium bromide typically appear after 3 to 5 wk of continued use, reflecting the slow linear tissue accumulation of the drug. Neither ipratropium bromide nor tiotropium bromide change pulmonary hemodynamics, ventilation-perfusion matching, oxyhemoglobin saturation, heart rate, or urinary flow; however, blurred vision and pupillary dilation may occur if either drug inadvertently contacts the eye. Both drugs should be used with caution in patients with myasthenia gravis, narrow-angle glaucoma, prostatic hyperplasia, or bladder neck obstruction. Tiotropium bromide should be used with caution in patients with moderate to severe renal insufficiency (Cl_{cr} less than 30 to 50 ml/min).

Although systemic administration of muscarinic anticholinergics decreases mucus formation, neither ipratropium bromide nor tiotropium bromide have much effect on respiratory secretions. Ipratropium bromide inhalation produces a clinically insignificant decrease in mucus viscosity and does not change mucus transport or ciliary beat frequency. Tiotropium bromide does not appear to adversely affect mucus transport.

Concomitant use of drugs with anticholinergic properties may increase the risk of side effects with either ipratropium bromide and tiotropium bromide.

Methylxanthines

Theophylline and aminophylline, the ethylenediamine salt of theophylline, are used to treat asthma and the obstructive component of COPD. Other pulmonary diseases for which theophylline may have a role include obstructive sleep apnea, apnea of prematurity, and airway obstruction secondary to pulmonary edema.

Potentially beneficial therapeutic effects of theophylline include bronchial smooth-muscle relaxation, enhanced mucociliary transport, inhibition of mediator release, suppression of permeability edema, decreased pulmonary hypertension, increased right ventricular ejection fraction, improved diaphragmatic contractility, and central stimulation of ventilation. Although bronchial smooth-muscle relaxation is most likely responsible for the majority of theophylline's beneficial therapeutic effects in the treatment of obstructive lung disease, the anti-inflammatory and diaphragmatic effects may contribute to the overall efficacy of the drug.

Pharmacology

Despite having been marketed and studied for several decades, the precise cellular mechanism of theophylline's bronchodilating action is unknown. It is unlikely that theophylline bronchodilates via adenosine antagonism. However, many of the extrapulmonary effects associated with theophylline, including cardiac stimulation, anxiety, tremors, seizures, diuresis, gastric secretion, and free fatty acid release have been attributed to adenosine antagonism.

Anti-inflammatory Effects

Anti-inflammatory actions attributed to theophylline include inhibition of neutrophil and mononuclear cell migration, leukotriene B_4 generation, T-cell proliferation, and lymphokine production; increased activity and number of suppressor T cells; and stabilization or inactivation of macrophages and platelets. The anti-inflammatory effect of theophylline appears to be qualitatively different than that of corticosteroids, resulting from the selective inhibition of phosphodiesterase IV at low serum theophylline concentrations. Although there has been a great deal of interest in the immunomodulatory effect of the methylxanthines, the clinical relevance of this effect remains unknown.

Diaphragmatic Effects

Theophylline increases diaphragmatic strength and contractility, actions potentially mediated by transmembrane calcium movement. Most data are from in vitro studies or from normal volunteers; results from controlled clinical trials in patients with COPD are limited and conflicting. Theophylline may be potentially most beneficial in patients with hypoxic and hypercapnic COPD when dosed to midtherapeutic plasma concentrations.

Structure-Activity Relationships

Theophylline and aminophylline are 1,3-dimethylxanthines. Other methylxanthines, including theobromine (3,7-dimethylxanthine) and caffeine (1,3,7-trimethylxanthine), differ in the positions of the methyl substituents on the xanthine molecule. N-1 substituents are important for adenosine antagonism, whereas N-3 substituents augment bronchodilator activity. Substituents at N-7 decrease bronchodilator potency; substituents at N-9 decrease the potency of the xanthine.

Clinical Use

For bronchodilation, the target theophylline serum concentration is generally accepted as 10 to 20 mg/L. The therapeutic range for other effects (e.g., anti-inflammatory properties, enhanced diaphragm capability, respiratory stimulation) may be different, prompting interest in a lower (5 to 15 mg/L) target range. Approximately 50 percent of maximal bronchodilation is achieved at a serum level of 10 mg/L; only an additional 17 percent increase is observed at 20 mg/L.

The precise clinical role of theophylline is unclear. Relatively noncontroversial indications include severe

bronchodilator-dependent COPD; severe, systemic, corticosteroid-dependent asthma; nocturnal asthma uncontrolled with adrenergic agonists; and acute, severe asthma progressing to respiratory failure.

Safety

Adverse effects associated with theophylline include nausea, vomiting, diarrhea, irritability, insomnia, supraventricular tachycardia, ventricular arrhythmias, and seizures. Although the risk of adverse effects increases at serum concentrations greater than 20 mg/L, patients also may experience serious adverse effects within the usual therapeutic range. Because of this narrow therapeutic index, emphasis should be placed on achieving the midtherapeutic range for serum theophylline levels (10 to 15 mg/L), while accepting a broader range (5 to 20 mg/L) as appropriate.

Magnesium Sulfate

Magnesium blocks calcium entry into smooth-muscle cells, thereby relaxing muscle fibers. Several small trials randomized patients upon presentation to the emergency room to receive either 2 g of magnesium sulfate intravenously over 20 min or placebo, in addition to standard therapy. Intravenous magnesium administration demonstrated no overall beneficial effect, although in retrospective analysis, the degree of airflow obstruction and rate of hospital admission were reduced for patients with severe asthma.

Subsequent case reports and small series suggested similar results could be obtained with inhalation of various doses of inhaled magnesium. The few randomized clinical trials reported to date seem to demonstrate similar small reductions in the degree of airflow obstruction and rate of hospital admission following magnesium sulfate inhalation in patients with severe asthma presenting to the emergency room setting.

Despite these limited clinical data demonstrating efficacy of magnesium sulfate, the recommendation from the Global Initiative for Asthma is that intravenous magnesium sulfate be considered in therapy of acute severe asthma. Recent survey data reveal that 21 percent of children receiving intensive care for asthma in the United States between 2000 and 2003 received parenteral or inhaled magnesium sulfate therapy during their hospitalization.

Inhaled Diuretics

While inhaled magnesium may act as a direct bronchodilator, inhaled diuretics may act upon the airways through a variety of mechanisms to achieve bronchodilation, reduce mucosal inflammation, or interrupt sensory nerve reflex responses to irritants. Inhaled furosemide has no role in the treatment of exacerbations of acute asthma, and additional information is needed before use of inhaled diuretics can be recommended for prevention of exercise- or irritant-induced asthma.

ANTI-INFLAMMATORY AGENTS

Corticosteroids are the mainstay of current anti-inflammatory regimens; other agents in clinical use include mast cell stabilizers, leukotriene receptor antagonists, and synthetic inhibitors of leukotrienes.

Corticosteroids

Corticosteroids are cortisollike drugs that influence metabolic pathways and have an anti-inflammatory effect. By reducing airway inflammation, corticosteroids are clearly useful in the management of asthma, but they have a more limited and targeted role in the management of COPD.

Pharmacology

Glucocorticoids (i.e., cortisol) are produced by the adrenal cortex via the hypothalamic-pituitary axis in response to physical and emotional distress. Although the usual daily secretion of cortisol is approximately 10 to 20 mg, as much as 400 to 500 mg per day can be secreted during periods of severe stress. Although the cellular mechanisms are incompletely understood, corticosteroids stimulate the transcription and creation of certain proteins, such as lipocortin-1, and inhibit DNA transcription, resulting in decreased cytokine production. The clinical effects of corticosteroids are delayed for several hours following administration, reflecting the time needed to create new proteins or inhibit cytokine production. Leukocytes, mucous glands, and blood vessels are glucocorticoid targets.

The inhaled glucocorticoids differ in potency, lipophilicity, relative receptor binding affinity, and pharmacokinetics. Since glucocorticoid preparations are marketed and prescribed in relatively equipotent doses, potency may be the least important differentiating characteristic. However, lipophilicity and relative glucocorticoid receptor binding and dissociation affinities are important discriminants among the inhaled corticosteroids. These characteristics determine the rate of receptor association and dissociation and the amount of drug absorbed systemically following inhalation. All corticosteroids undergo hepatic metabolism. Orally administered drugs, including drug swallowed after inhalation, undergo significant first-pass metabolism.

Mometasone furoate and fluticasone propionate, with an esterified lipophilic group at the 17-α positon, are the most lipophilic of the marketed inhaled corticosteroids; beclomethasone dipropionate, budesonide, triamcinolone acetonide, and flunisolide follow in descending order of lipophilicity. The relative receptor binding affinity and receptor association follow the same order as lipophilicity. Mometasone furoate differs from other inhaled corticosteroids in that it is less specific for glucocorticoid receptors; in addition, the drug demonstrates agonist activity at progesterone receptors and partial agonist activity at mineralocorticoid receptors.

Clinical Use

Corticosteroids are the cornerstone of therapy in the treatment of asthma; the role of glucocorticoid therapy in COPD is more limited.

Asthma

The role of airway inflammation in asthma is well established, and high-dose systemic (parenteral or oral) corticosteroids are standard therapy for patients experiencing severe acute exacerbations of asthma. Parenteral administration of corticosteroids is often used preferentially due to the inability of some patients to swallow medications while in respiratory distress or because of lack of oral access after intubation. Dose-ranging studies of intravenous corticosteroids have not established a minimum effective dose, although as little as 120 mg/d of methylprednisolone (in divided doses administered every 6 h) is effective in asthmatic adults having an acute exacerbation. The time to initial response, as evidenced by augmentation of FEV_1 with bronchodilator administration, begins as early as 1 h after corticosteroid administration; maximal response is achieved in 8 to 12 h. Parenteral corticosteroid therapy is usually maintained for 24 to 72 h, with subsequent conversion to oral prednisone at 60 mg daily when the FEV_1 reaches a threshold of 50 percent of predicted normal. This dose may be maintained for 2 to 7 d, followed by gradual tapering of the dose over 1 to 3 wk. Parenteral methylprednisolone is emerging as the corticosteroid of choice, due to its lower mineralocorticoid and greater glucocorticoid effects than hydrocortisone.

Oral corticosteroid therapy is seldom indicated for chronic stable asthma. Oral therapy is maintained at the lowest dose possible to sustain control of symptoms and optimize peak expiratory flow in conjunction with inhaled β_2-adrenergic agonists. Hydrocortisone, methylprednisolone, or prednisone are most commonly used. Unlike prednisone, the first two agents do not require hepatic metabolism for therapeutic activity and are preferred in patients with significant liver disease.

Inhaled corticosteroids offer direct delivery to the lung and reduced risk of systemic effects. To achieve the same effect as higher potency agents, the lower potency agents are given in higher doses; adverse effects are more likely to occur.

The combination of an inhaled corticosteroid and a long-acting bronchodilator is better than either agent alone in terms of improving lung function and preventing asthma exacerbations; in patients with moderate-to-severe asthma, the combination of low-dose inhaled corticosteroid appears to be as effective as high-dose inhaled corticosteroid alone.

Poor adherence with inhaled corticosteroid regimens is an ongoing issue. Inhaled corticosteroids initially required four-times-a-day dosing schedules, but they are now usually prescribed twice daily. Mometasone furoate, the newest inhaled corticosteroid, is FDA approved for once daily administration. Although data are limited, patients with stable mild to moderate asthma might benefit from a trial of once-daily inhaled corticosteroids. Twice-daily dosage regimens may be more effective for patients with severe or difficult-to-control asthma.

Chronic Obstructive Pulmonary Disease

The mechanism underlying the beneficial effects of corticosteroids in COPD is not fully known, but changes in inflammatory gene transcription and modulation of β_2-adrenergic receptor function appear to play a role.

No evidence exists that systemic corticosteroids prevent exacerbations in patients with stable COPD or that steroid responsiveness can be predicted. A common clinical practice has been to test steroid response by measuring the change in FEV_1 following a trial of systemic corticosteroids and then limiting subsequent corticosteroid therapy to steroid responders. However, in a 3-y, large, randomized, double-blind, placebo-controlled prospective trial, no significant relationship between initial steroid response and subsequent FEV_1 decline was found.

Short courses (10 to 15 d) of moderate doses (40 mg/d of prednisone) of systemic corticosteroids in combination with standard bronchodilator therapies are effective for treating acute exacerbations of COPD in outpatients, inpatients, and patients in the emergency room who have moderate or severe COPD. However, the role of systemic corticosteroids in the treatment of patients with COPD who are receiving mechanical ventilation is unknown. Chronic maintenance therapy with inhaled corticosteroids reduces the incidence of acute exacerbations by 20 to 30 percent and improves health status in patients with stage III or IV COPD and a history of frequent exacerbations.

Definitive data regarding the clinical usefulness of combining inhaled corticosteroids and long-acting bronchodilators are lacking. Guidelines published in 2004 recommend the combination of inhaled corticosteroid and long-acting bronchodilator for patients with severe or very severe disease and frequent exacerbations.

Safety

Short-term use (less than 14 d) of systemic corticosteroids is associated with mild glucose intolerance, fluid retention that may progress to edema and hypertension, proximal muscle weakness (especially with large parenteral doses), and mood alteration. Long-term systemic corticosteroids prolong the short-term effects; in addition, peptic ulcer disease, cataracts, increased risk of infection, and impaired wound healing occur. Truncal obesity, hirsutism, acne, moon-shaped facies, striae, and ecchymoses contribute to a cushingoid appearance. Disruption of bone metabolism predisposes patients to osteoporosis and resultant vertebral and long-bone fractures; inhibition of long-bone growth is the major complication in children who receive systemic corticosteroids. Suppression of the hypothalamic-pituitary-adrenal axis diminishes body cortisol stores, which, in turn, reduces the capacity of the body to confront stress, such as trauma, surgery, or infection.

Inhaled corticosteroids are less systemically bioavailable due to poor absorption from the tracheobronchial tree. The most common adverse effect is local irritation of the oropharynx, cough, and bronchospasm. Dysphonia may arise from vocal cord myopathy induced by the presence of corticosteroid in the oropharynx. Thrush is easily avoided by rinsing the mouth after each use of a corticosteroid inhaler, using a spacer device to decrease deposition of drug particles in the mouth, and keeping the inhaler mouthpiece clean. Newer inhaled corticosteroids, such as fluticasone, undergo extensive first-pass metabolism to inactive substances, thereby decreasing concentrations of active drug and the potential for systemic adverse effects. Long-term studies of inhaled corticosteroids have not documented significant adrenal suppression.

Steroid Resistance

Patients with asthma who are unresponsive to usually sufficient doses of corticosteroids are described as *steroid resistant.* Steroid resistance has been formally defined by a smaller than 15 percent increase in FEV_1 after 7 d of oral prednisolone administered at a dose of 20 mg daily in bronchodilator-responsive asthmatics. Steroid resistance must be distinguished from steroid dependency, which is usually defined as the need for systemic corticosteroids for maintaining control of asthma.

Steroid resistance may involve reduced metabolism of oral corticosteroids to the active compound or accelerated drug clearance. An impaired cellular response to corticosteroids has been observed in steroid-resistant asthmatics, and altered receptor binding or the presence of antilipocortin antibodies may contribute to the phenomenon.

Corticosteroid-Sparing Agents

Chronic systemic corticosteroid therapy required for the treatment of severe airflow obstruction often results in numerous side effects. Therefore, many anti-inflammatory agents have been evaluated in an effort to identify alternatives to systemic corticosteroid therapy.

Troleandomycin

Since the 1960s, anecdotal clinical observations suggested that the macrolide antibiotic, troleandomycin, might reduce corticosteroid requirements in patients with severe asthma by decreasing steroid metabolism. However, results from double-blind, randomized trials are mixed. To date, the weight of evidence suggests that troleandomycin has little or no clinical effect at relieving airway obstruction or inflammation independent of its effects on corticosteroid metabolism. Troleandomycin has little role in the current therapy of severe, steroid-dependent asthma.

Methotrexate

From initial observations in patients with rheumatoid arthritis and coexistent asthma, methotrexate therapy appeared to ameliorate both asthmatic and arthritic symptoms. Currently, no clear documentation exists of the clinical efficacy of methotrexate administration in severe, steroid-dependent asthma. Due to significant side effects, potentially fatal complications and long-term toxicity concerns, prudency argues for limiting methotrexate administration in severe, steroid-dependent asthmatics to empiric trials in individual patients or investigations in large-scale, controlled clinical trials.

Cyclosporine

Used widely in organ transplantation, cyclosporine inhibits lymphokine synthesis, thereby blocking the activation of T cells. The absence of significant drug interactions with β-adrenergic agonists, corticosteroids, or theophylline makes cyclosporine particularly attractive as an anti-inflammatory agent for use in asthma. However, only one of three small, double-blind, placebo-controlled studies suggested that cyclosporine increased peak expiratory flow and FEV_1, reduced exacerbations of airway obstruction, or reduced oral prednisolone dosage by over 60 percent. Hypertrichosis, hypertension, reversible nephrotoxicity, and a large number of nonspecific side effects limit widespread use of cyclosporine in the management of asthma.

Other Agents

The search continues for anti-inflammatory agents with potential efficacy in asthma. A broad spectrum of agents have been touted, including gold salts, pooled immunoglobulins, azathioprine, colchicine, dapsone, hydroxychloroquine, ketotifen, nonsteroidal anti-inflammatory agents, and inhaled heparin. The original studies purporting the efficacy of these various agents comprise mainly anecdotal reports or small case series. Use of these drugs in obstructive airway disease should be restricted to well-designed, controlled clinical trials.

Mast Cell Stabilizers

Cromolyn sodium and nedocromil exert anti-inflammatory actions by stabilizing mast cells. This blockade of mast cell degranulation prevents inflammatory mediator release, which is partially responsible for the bronchoconstriction and epithelial injury that are characteristic of asthma.

Cromolyn Sodium

Cromolyn sodium was the first mast cell stabilizer to be approved for clinical use in asthma and is widely employed in pediatric asthmatics.

Pharmacology

Cromolyn sodium is a potent inhibitor of inflammatory responses. Cromolyn sodium diminishes early phase reactions in asthma by blocking the release of intracellular calcium and inhibiting enzymes responsible for mast cell degranulation; cromolyn reduces late phase reactions in asthma by inhibiting production of the enzymes necessary for superoxide

generation. Cromolyn sodium may also exhibit tachykinin antagonism, accounting for some of its anti-inflammatory properties. In vitro, cromolyn sodium potentially inhibits the activation of inflammatory cells, antibody-induced granulocyte cytotoxicity, IgE production by atopic cells, and monocyte IgG production.

Clinical Use

Cromolyn sodium is indicated for the management of asthma in children and atopic young adults. Cromolyn sodium, alone or in combination with β_2-adrenergic agonists, improves exercise tolerance, enhances sleep quality, reduces asthma exacerbations, and facilitates patient acceptance of therapy. Patients diagnosed with asthma prior to the age of 4 years, patients less than 17 years of age, and patients with long-term asthma (more than 5 y) may experience maximal benefit from cromolyn sodium therapy. Cromolyn sodium significantly improves seasonal allergic asthma symptoms. Long-term use of cromolyn sodium (at least 12 wk) four times daily is recommended for effective control of chronic bronchial hyperresponsiveness, while a shorter treatment duration (up to 6 wk) usually suffices for control of seasonal allergic attacks.

Cromolyn sodium prophylaxes against exercise-induced asthma in children as efficaciously as do beta$_2$ agonists. Premedication with cromolyn sodium, inhaled β_2-adrenergic agonist, or both, 15 to 30 min prior to vigorous exercise is recommended for children and adults. Cromolyn sodium is a useful adjunct to bronchodilators in adults with atopic asthma; it may provide added benefit when administered in conjunction with inhaled corticosteroids.

Safety

Cromolyn sodium causes few adverse effects, even after long-term use. Its efficacy in preventing childhood asthma symptoms and safety record make cromolyn sodium a first-line agent, in conjunction with β_2-adrenergic agonists, in management of asthma in children.

Nedocromil

Nedocromil also stabilizes mast cells in the bronchial mucosa, but it has a broader anti-inflammatory spectrum than cromolyn sodium. Nedocromil blocks activation of eosinophils and neutrophils, further reducing inflammation. Dose-dependent inhibition of IL-4-induced IgE and IgG production has been demonstrated in vitro. Nedocromil is useful prophylactically against asthma exacerbations, but not therapeutically for acute bronchospasm.

The similar pharmacology of cromolyn sodium and nedocromil have prompted direct comparisons of the two agents in asthmatics. Nedocromil appears to be more effective as a bronchodilator-sparing agent than cromolyn sodium in adults, but it provides a similar level of protection against exercise-induced asthma in children. Lack of long-term experience with nedocromil relegates it to second-line status as an adjunct to bronchodilators in the management of asthma.

Leukotriene Antagonists and Inhibitors

The leukotriene antagonists and inhibitors are the first new class of asthma drugs to be developed in several decades. Advances in our understanding of the inflammatory pathogenesis of asthma and the role of leukotrienes as inflammatory mediators have generated great interest in the development of and therapeutic potential for these drugs.

Leukotrienes are synthesized from arachidonic acid, a fatty acid stored in phospholipids of cell walls. Numerous stimuli, including IgE receptor activation, antigen-antibody interactions, and activation of phospholipase A_2 induce release of arachidonic acid from phospholipids. Arachidonic acid is converted to a variety of products via several unrelated pathways; the 5-lipoxygenase pathway is the pathway of importance in asthma. Leukotriene A_4 (LTA_4) is metabolized by two different pathways to either the nonpeptide LTB_4 or the cysteinyl leukotrienes (LTC_4, LTD_4, and LTE_4). LTB_4 recruits and activates inflammatory cells but has no effect on bronchial tone or reactivity. The cysteinyl leukotrienes stimulate smooth-muscle contraction, increase vascular permeability, and enhance bronchial hyperresponsiveness; thus, they have a major role in the pathogenesis of asthma.

Leukotriene action may be inhibited by either selective receptor blockade or interference with synthesis. Most clinical experience has been with the LTD_4 receptor antagonists, since LTC_4, LTD_4, and LTE_4 interact with a common LTD_4 receptor. Inhibition of 5-lipoxygenase (5-LO) reduces the generation of all leukotrienes.

Clinical Use

Two LTD4 receptor antagonists (montelukast and zafirlukast) and one 5-LO inhibitor are FDA-approved and marketed in the United States. The leukotriene receptor antagonists are alternate anti-inflammatory medications for long-term use in children and adults with mild to moderate asthma, including aspirin- or exercise-induced asthma and asthma associated with concomitant allergic rhinitis. To date, data are insufficient to assess the role of antileukotriene receptor antagonists in the management of acute exacerbations of asthma or COPD. Inhaled glucocorticosteroids in doses of 400 μg/d of beclomethasone equivalent are more effective than the leukotriene receptor antagonists in adults with mild or moderate asthma. However, addition of a leukotriene receptor antagonist to therapy that includes an inhaled corticosteroid results in some further improvement in lung function.

Safety

Montelukast and zafirlukast are well tolerated. Montelukast chewable tablets contain phenylalanine and therefore are contraindicated in patients with phenylketonuria. Hepatotoxicity has been reported with zileuton. Zileuton is contraindicated in patients with active liver disease and in patients with serum transaminase levels exceeding three times the upper limit of normal. Baseline liver function tests should be obtained prior to initiating therapy with zileuton, and patients should be monitored closely for the duration of therapy. Zileuton must

be discontinued if serum transaminase levels exceed five times the upper limit of normal.

The leukotriene receptor antagonists have numerous drug interactions.

Immunoglobulin E Antibody

Pharmacology

Omalizumab is a recombinant humanized antibody developed for therapy of allergic diseases that has significant efficacy in severe atopic asthmatics. By specifically binding with high affinity to immunoglobulin E (IgE), but not to other immunoglobulins, omalizumab does not activate mast cells or basophils. Clinical efficacy depends upon almost total elimination of circulating IgE; therefore, the role of omalizumab is limited to those asthmatics with elevated IgE levels. Parenteral administration of omalizumab produces rapid binding of circulating IgE, with serum levels slowly rebounding over the subsequent 4 to 6 wk.

Several randomized, double-blind placebo controlled studies of omalizumab have been completed in patients more than 12 years of age with moderate to severe atopic asthma refractory to high-dose inhaled corticosteroids; patients also received inhaled, long-acting β agonists and oral leukotriene antagonists. Use of omalizumab resulted in reproducible decreases in asthmatic flares, reduced inhaled and oral steroid dosage, and improved quality of life.

Clinical Use

Omalizumab therapy is indicated for moderate to severe asthmatics who have serum IgE levels exceeding 30 IU/ml (75 ng/ml) and an allergic basis for their asthma, as demonstrated by positive skin testing or radioallergosorbent tests (RAST) to common antigens. As a chronic therapy, omalizumab treatment should not be initiated in the setting of an acute asthma flare. Subcutaneous administration of omalizumab every 2 to 4 wk is required to maintain reductions in circulating IgE, with required dose and frequency dependent upon body weight and initial serum IgE level. Up to three separate subcutaneous injections, each not exceeding 150 mg at a single site, may be required at each administration. Subsequent serum IgE measurements are unnecessary, as levels are expected to plummet to negligible levels and slowly rebound after each administration of the drug.

The total duration of necessary therapy is unclear, although a review every 6 to 12 mo is commonly employed to assess whether improved asthma control has been achieved (as indicated by reduced inhaled and oral steroid usage, fewer emergency medical encounters and hospitalizations, and decreased overall medical costs).

Safety

Minor local skin reactions at the injection sites occur in almost one-half of patients. A diffuse urticarial rash has been reported, but it is extremely uncommon. Severe hypersensitivity reactions, including anaphylaxis, are rarely observed. Nonetheless, close observation, including frequent assessment of vital signs, is recommended for at least 2 h following initial drug administration; similar monitoring is warranted for at least 1 h following each subsequent administration.

MUCOKINETIC AGENTS

Chronic sputum production or inspissated airway secretions plague most patients with obstructive lung disease. Some mucokinetic agents are effective in promoting the clearance of obstructed airways.

Dornase Alpha

Purulent, viscous secretions contribute to airway obstruction and chronic pulmonary infections in patients with cystic fibrosis, chronic bronchitis, and bronchiectasis. High concentrations of mucus contribute to the increased viscosity of bronchial secretions in these conditions. Polymorphonuclear leukocytes recruited to ward off chronic pulmonary infections eventually degenerate, releasing DNA into the extracellular environment. Although recombinant human deoxyribonuclease I (DNAse) metabolizes DNA liberated from airway leukocytes, the high concentration of DNA released in these chronic conditions overwhelms the endogenous ability of the lungs to clear the DNA. Exogenous administration of DNAse promots clearance of airway DNA by reducing mucus viscosity, increasing mucus clearance, diminishing airway obstruction, and preventing recurrent pulmonary infections.

Results of randomized clinical trials of nebulized DNAse as short-term adjunctive therapy in patients with cystic fibrosis demonstrate modest dose-dependent improvement in pulmonary function and reduction in symptoms. Placebo-controlled investigations of DNAse in adults with chronic bronchitis or bronchiectasias not due to cystic fibrosis reveal prolonged antibiotic therapy requirements, no enhancement of pulmonary function, and no improvement in quality of life.

N-Acetylcysteine

N-acetylcysteine (NAC) lyses disulfide bonds in mucus proteins, reducing airway mucus viscosity. Increased mobilization of mucus and decreased inspissation with use of inhaled NAC has been reported in patients with asthma or COPD. However, randomized placebo-controlled trials in COPD have demonstrated no objective benefit of treatment with NAC.

Due to the in vivo conversion of NAC to the potent antioxidants, glutathione and cysteine, recent investigations have focused on NAC as an immunomodulator. Since antioxidant formation is distinct from the local mucolytic effect, oral NAC has been investigated in most studies. Unfortunately, intravenous NAC in patients with acute lung injury

or the acute respiratory distress syndrome (ARDS) offers no significant reduction in mortality or disease progression.

Iodinated Agents

Some iodinated compounds have mucolytic-expectorant properties. When ingested, iodide is liberated and stored in secretory glands of the tracheobronchial tree. Upon stimulation by coughing or inhalation of irritant substances, iodide promotes secretion of respiratory tract fluid and mucoproteins and augments ciliary activity. Increased mucus mobilization and decreased mucus viscosity result.

Adverse events appear to be infrequent, although thyroid dysfunction may be induced by the iodine load and has been reported after long-term use in elderly patients with COPD. Clinicians should use iodinated compounds with caution in elderly patients or those with preexisting thyroid dysfunction.

Sodium Bicarbonate

Sodium bicarbonate solutions (2 to 7.5 percent) are frequently used as vehicles for bronchodilators and N-acetylcysteine. By raising the pH of the respiratory tract fluids, aerosolized sodium bicarbonate weakens the saccharide structure of airway mucus, increasing its susceptibility to proteases and promoting its removal through enhanced ciliary activity. These effects are additive when used with N-acetylcysteine and cause reduction in mucus viscosity. Local irritation from hypertonic sodium bicarbonate solutions may occur; cough and bronchospasm have been observed in some patients. Therefore, bronchodilators should be given prior to sodium bicarbonate aerosols.

Guaifenesin

Guaifenesin remains the only agent approved by the FDA as an expectorant, based upon a single placebo-controlled trial in patients with chronic bronchitis in whom guaifenesin significantly reduced sputum volume and improved sputum quality. These patients also experienced subjective relief of respiratory congestion, and no adverse effects were reported. However, the purported expectorant properties of guaifenesin have not been substantiated in well-controlled studies.

PHYSIOLOGICAL REPLACEMENTS

Replacement therapy comprises a novel class of agents to replace deficient, or augment existing, endogenous substances. To date, replacement therapy has been employed only in adults with α_1-antitrypsin deficiency or neonates with respiratory distress syndrome. However, clinical studies of replacement therapy are underway in patients with a wide spectrum of obstructive and other lung diseases.

α_1-Antitrypsin

α_1-Antitrypsin is a glycoprotein synthesized and secreted by hepatocytes. A protease inhibitor, α_1-antitrypsin, blocks the actions of neutrophil-derived elastase in the lung. Inherited deficiency of α_1-antitrypsin promotes development of emphysema in adulthood; tobacco smoking rapidly accelerates the clinical presentation and severity of the emphysema. Since 1988, α_1-antitrypsin replacement therapy has been available for intravenous administration as a purified product derived from pooled human plasma.

Clinical Use

Weekly or monthly intravenous infusion of α_1-antitrypsin to deficient patients increases α_1-antitrypsin levels in serum and bronchoalveolar lavage specimens and restores antielastase activity in serum and alveolar lining fluid. Numerous case reports and small series dispute whether α_1-antitrypsin replacement reduces the accelerated rate of decline in pulmonary function associated with α_1-antitrypsin deficiency. Currently, α_1-antitrypsin replacement therapy is recommended for patients with α_1-antitrypsin deficiency who are older than 18 years of age and have both abnormal pulmonary function tests and a serum α_1-antitrypsin level less than 11 mM. Replacement therapy for α_1-antitrypsin deficient patients is not recommended after lung transplantation.

Side Effects

α_1-Antitrypsin replacement therapy is remarkably nontoxic, and current preparations have few side effects other than mild fever. Repeated administration of α_1-antitrypsin does not shorten the serum half-life, suggesting that α_1-antitrypsin antibodies do not develop, even in patients with complete deficiency.

Pulmonary Surfactant

The administration of pulmonary surfactant to premature infants with, or at risk for, respiratory distress syndrome has become the standard of care. Surfactant administration decreases mortality from respiratory distress syndrome by 30 to 40 percent and reduces morbidity due to pneumothoraces, interstitial emphysema, bronchopulmonary dysplasia, and intraventricular hemorrhage.

Endogenous pulmonary surfactant is an emulsion of phospholipids, cholesterol, and apoproteins that reduces surface tension within alveoli. Natural surfactant is commercially available and is prepared from lung tissue or lavages from a variety of species. Synthetic surfactant is available from a number of commercial sources, although the optimal composition of the material remains to be determined.

Pulmonary surfactants reduce oxygen toxicity by scavenging free radicals, and the surfactants may be cytoprotective for alveolar cell surfaces. Pulmonary surfactants suppress mediator release by inflammatory cells and may deactivate inflammatory mediators upon release. In vitro studies indicate that surfactant suppresses lymphocyte mitogenic

responses, leading to a decrease in inflammatory cell influx. Pulmonary surfactant has both antibacterial and antiviral properties which are mediated by an increase in alveolar macrophage phagocytosis. Surfactant may promote airway clearance by changing the physical properties of mucus, as well as by increasing ciliary beat frequency. Finally, pulmonary surfactant may directly relax airway smooth muscle. This spectrum of putative biologic activities may directly interrupt the pathogensis of airway inflammation, chronic infection, and bronchoconstriction seen in most obstructive lung diseases.

Limited clinical data are available to document the effects of pulmonary surfactant in adults. In anecdotal case reports and small patient series, surfactant administration to patients with respiratory failure has produced occasional increases in Pa_{O_2}, although usually no change in radiographic, physiological, or respiratory findings were reported. However, in two large, double-blind, randomized, placebo-controlled trials, administration of synthetic surfactant for 5 days yielded no demonstrable physiological benefit and no significant decrease in mortality rate measured at 30 days.

RESPIRATORY STIMULANTS

Respiratory stimulants are a group of pharmacologically unrelated agents used to treat diverse pathophysiological conditions, including obstructive or central sleep apnea, COPD, postanesthesia respiratory depression, and acute mountain sickness.

Acetazolamide

Acetazolamide is a noncompetitive inhibitor of carbonic anhydrase that induces a weak diuresis and mild metabolic acidosis. Currently, acetazolamide is approved for the prophylaxis of acute mountain sickness and has been proposed as an alternative therapy for chronic mountain sickness. Sometimes used to treat patients with chronic hypercapnia and drug-induced or compensatory metabolic alkalosis, acetazolamide may have both indirect and direct respiratory stimulant properties. The increased hydrogen concentration indirectly stimulates respiration via peripheral and medullary chemoreceptor stimulation. Acetazolamide may also directly stimulate respiration by increasing cerebral blood flow through mechanisms unrelated to the metabolic acidosis.

Recently, a small, double-blind, placebo-controlled study demonstrated acetazolamide improves nocturnal oxyhemoglobin saturations and reduces hematocrit in patients with chronic mountain sickness. However, further large scale studies will be required before acetazolamide can be recommended over standard therapies, including phlebotomy or relocation to lower altitude.

Limited data from short-term trials of acetazolamide in hypercapnic patients are available. In small numbers of patients with hypercapnic obstructive lung disease, acetazolamide produces modest reductions in Pa_{CO_2} and pH, while improving $P_{A_{O_2}}$. Long-term safety and efficacy data are unavailable, and larger studies will be required before acetazolamide therapy can be recommended for hypoventilation associated with either sleep-disordered breathing or hypercapnic obstructive lung disease.

Almitrine

Almitrine bismesylate stimulates peripheral chemoreceptors in the carotid body and has no central respiratory stimulant effect. Also a pulmonary vasoconstrictor, almitrine improves ventilation-perfusion matching and, therefore, has received attention in small case series as adjunctive therapy for hypoxemic respiratory failure from ARDS. Although marketed in Europe, almitrine bismesylate is not available in the United States. Toxicities and side effects include right ventricular strain from pulmonary arterial vasoconstriction, peripheral neuropathy, weight loss during long-term therapy, and diuretic activity.

Methylxanthines

Aminophylline and theophylline are methylxanthine bronchodilators that augment the central ventilatory response to hypoxia, likely through adenosine receptor activation in the carotid body and or brain stem ventilatory control centers. Limited data suggest theophylline reduces periodic breathing at high altitude. Used to treat apnea of prematurity and infants with periodic breathing, methylxanthines are less useful in the treatment of obstructive sleep apnea or in stimulating adult respiration in normobaric environments.

Doxapram

Doxapram is a short-acting, parenterally administered, peripheral chemoreceptor agonist and central respiratory stimulant. Doxapram has been approved for postanesthesia respiratory depression or apnea, drug-induced central nervous system respiratory depression, and short-term use as a respiratory stimulant in acute respiratory insufficiency superimposed on chronic pulmonary disease. Limited case reports and small studies describe doxapram as a respiratory stimulant in COPD complicated by acute respiratory failure.

Medroxyprogesterone

Medroxyprogesterone is a gestational respiratory stimulant. Although its mechanism of action is unclear, medroxyprogesterone increases minute ventilation and produces hypocapnia in normal subjects. However, it does not improve breathing disturbances during sleep in normocapnic patients with obstructive sleep apnea. Limited data reveal medroxyprogesterone stimulates minute ventilation in patients with hypercapnic obstructive lung disease, without improving nocturnal oxygenation.

Protriptyline

Protriptyline is a tricyclic antidepressant that is cited frequently as an effective respiratory stimulant in patients with obstructive sleep apnea. The mechanism of action may include suppression of rapid eye movement (REM) sleep and increased tone in the upper airway muscles. Protriptyline is contraindicated in patients with glaucoma or prostatic hypertrophy, and anticholinergic side effects limit its usefulness.

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Intubation and Upper Airway Management

C. William Hanson III • Erica R. Thaler

The first known use of positive pressure ventilation (PPV) as a medical intervention dates back to the sixteenth century, as described in Vesalius' *de Humani Corporis Fabrica*:

> But that life may in a manner of speaking be restored to the animal, an opening must be attempted in the trunk of the trachea, into which a tube of reed or cane should be put; you will then blow into this, so that the lung may rise again and the animal take in air. Indeed with the slight breath in the case of the living animal, the lung will swell to the full extent of the thoracic cavity, and the heart become strong . . . for when the lung, long flaccid, has collapsed, the beat of the heart and arteries appears wavy, creepy, twisting; but when the lung is inflated at intervals, the motion of the heart and arteries does not stop. . . .

Vesalius subsequently resuscitated a Spanish nobleman by inflating his lungs through the trachea, resulting in resumption of cardiac activity and nearly in Vesalius' death at the hands of the Inquisitors. Vesalius, an excellent anatomist who disproved many of the cherished teachings of Galen that had been accepted as absolute truth for 13 centuries, was viewed as a heretic by his peers. In fact, one described him as "an impious madman who is poisoning all of Europe with his vaporings."

Because of lack of enthusiasm in response to Vesalius' findings, a 100-year hiatus attended the next attempt at endotracheal ventilation. In 1667, Robert Hooke, a prominent mathematician, geologist, and paleontologist kept a dog alive by intermittently insufflating air into its trachea using a set of bellows. One century later, in 1744, John Fothergill, one of the founders of the British Humane Society, described successful mouth-to-mouth resuscitation.

Because of concerns over development of emphysema and tension pneumothorax as complications of PPV (recognized as early as 1827), research on artificial ventilation in the nineteenth and early twentieth centuries focused on negative-pressure ventilation (NPV). Iron lungs, tank ventilators, cuirass ventilators, and a variety of strange and remarkable differential pressure chambers and boxes were developed in the United States and Europe. The devices were powered by hand, water, steam, or electricity, and, in some cases, by the patient himself. However, PPV became incorporated into the resuscitation strategy of the Dutch Humane Society, which advocated mouth-to-mouth ventilation in conjunction with external thoracic and abdominal compression. In 1776, John Hunter described an apparatus that blew fresh air into the lungs with one set of bellows and sucked "bad" air out with a second set.

By the end of the nineteenth century, a surge in the evolution of thoracic surgery led to the use of tracheal intubation and PPV through cuffed tubes as acceptable components of medical care. An American surgeon, Joseph O'Dwyer,

designed a series of metal tubes that were inserted between the vocal cords of children afflicted with diphtheria. Rudolph Matas referred to O'Dwyer's devices in describing "intralaryngeal intubation" and "insufflation" and noted that, "the procedure that promises the most benefit in preventing pulmonary collapse in operations is . . . the rhythmic maintenance of artificial respiration by a tube in the glottis." In the early part of the twentieth century, Franz Kuhn, a German surgeon, described techniques for oral and nasal intubation using flexible metal tubes introduced into the trachea with the assistance of the operator's index finger; the procedure was preceded by application of topical anesthesia using cocaine. The airway was then sealed with a supralaryngeal flange and gauze packing.

Among the further advances that followed was the first laryngoscope created by Alfred Kirstein in Berlin. However, his model was never widely accepted. Chevalier Jackson developed a U-shaped laryngoscope that otorhinolaryngologists still use for endoscopy but was never adopted by anesthesiologists. In 1913, Janeway described an endotracheal tube with a removable cuff, an anesthesia ventilator, and a battery-powered laryngoscope. From 1900 to 1920, Dorrance, Elsberg, Löwen, and Sievers published methods for tracheal intubation and PPV.

The most influential figure in the history of endotracheal intubation is Sir Ivan Magill. Along with Stanley Rowbotham, he used anesthetics on Royal Army casualties during World War I (in particular, on patients with disfiguring facial injuries). Their patients were often intubated nasally to allow freer access to the face by the surgeon. Magill's inventions include the Magill forceps, which is still used to facilitate nasal intubation, semirigid endotracheal tubes fashioned from mineralized rubber, and the Magill circuit, an L-shaped laryngoscope. He is also credited with describing the "sniffing position."

Arthur Guedel, an American contemporary of Magill, refined the cuffed endotracheal tube and, by extensive experimentation on animal tracheas, determined that the best position for the cuff was just below the vocal cords. He popularized use of the cuffed endotracheal tube by publicly anesthetizing his pet dog, "Airway," and immersing the animal in a tank of water. Upon awakening, the dog shook itself off and departed the arena.

In current practice, access to the trachea through the nasopharynx or oropharynx takes advantage of laryngoscope blades invented in the 1940s by Robert Miller, a Texas clinician, and Robert Macintosh, an Oxford professor. The Miller blade was an advance over similar straight blades; it was designed to pick up the epiglottis and expose the vocal cords. The curved Macintosh blade differed from previous models and was designed for insertion between the epiglottis and tongue. Although many variants of the two blades are available today, including those with different angulations, prisms, and fiberoptic bundles, the Miller and the Macintosh blades remain the mainstays of the anesthesiologist's armamentarium.

The first departments of anesthesiology were founded in the early 1940s. Thereafter, the skills required for management of the upper airway and endotracheal intubation became widely disseminated in the United States and the United Kingdom.

UPPER AIRWAY ANATOMY AND CLINICAL RELEVANCE

The two functional conduits between the trachea and atmosphere—the oropharynx and the nasopharynx (Fig. 151-1)—join at the level of the base of the skull to form the hypopharynx. The oropharynx includes the base of the tongue,

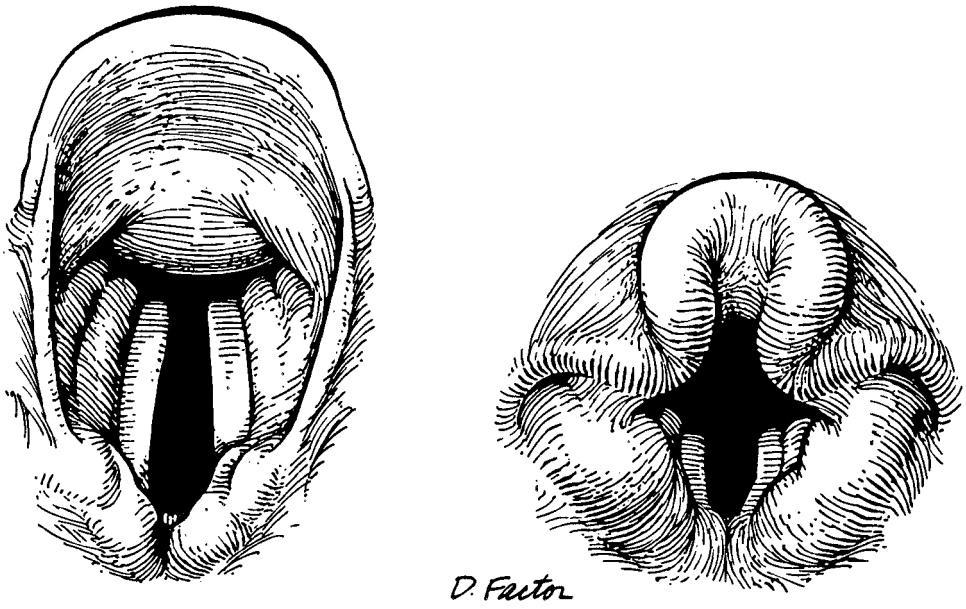

Figure 151-1 Comparative anatomy of adult and infant airways. *(Courtesy of Barash P, et al (eds.):* Clinical Anesthesia, *Philadelphia, Lippincott, 1989, p 544, D. Factor, illustrator.)*

uvula, and tonsils. The nasopharynx is separated from the oropharynx by the mobile soft palate. The hypopharynx includes the vallecula, which is the space posterior to the tongue and anterior to the cervical esophageal inlet. Typically, the adult epiglottis is crescentic, moderately stiff, and thin. Because of its ligamentous attachments, the adult epiglottis can be lifted indirectly using a curved laryngoscope blade applied to the base of the tongue. The U-shaped infant epiglottis is longer and floppier than the epiglottis of the adult. Therefore, a straight blade is typically required to lift the infant epiglottis directly during endotracheal intubation.

The adult and infant airways differ in several other respects. The narrowest portion of the adult airway is the rima glottidis, the area between the vocal cords; in contradistinction, the cricoid is the narrowest portion of the infant's airway. The infant larynx is also situated relatively more cephalad than the larynx of the adult; in addition, the vocal cords of the infant are angled, whereas the vocal cords of the adult are perpendicular to the airway.

In an awake patient, with the head in the neutral position (i.e., neither flexed nor extended), air moves freely through both the oropharynx and nasopharynx. In most normal subjects, the same is true during sleep. Abnormalities of any of the component parts of the upper airway can impede airflow during respiration while awake; alternatively, impeded airflow may only become evident during sleep (e.g., as snoring or obstructive apnea). Consequently, a directed history and physical examination should be performed prior to any procedure on the airway.

A history of nasal polyps or nasal septal deviation mandates caution prior to nasotracheal intubation, transnasal passage of a fiberoptic scope, or insertion of a nasal airway. The patient's sleeping partner is often the best source of information about snoring and apnea, manifestations that may result from a variety of upper airway abnormalities, including soft tissue redundancy, masses, polyps, stenosis, or lymphoid hypertrophy from the nose to the hypopharynx and larynx. Vocal changes or abnormalities may suggest abnormalities of the vocal cords and warrant preintubation evaluation.

The physical examination of the airway is preceded by a conversation with the patient. Hoarseness, stridor, tachypnea, and coughing suggest potential upper airway problems. The examination then can be pursued systematically beginning with the nasopharynx. The patient's ability to breathe through a single nostril (when the mouth is closed and the other nostril occluded) indicates that the passage is relatively patent. Asymmetry often exists between the two sides and, whenever possible, instrumentation should be performed on the more patent side.

The ability to open the mouth is limited in patients with temporomandibular joint disease. The temporalis muscle may be scarred or fibrotic (e.g., secondary to prior radiation) resulting in restricted mandibular mobility. Fractures to the mandible produce limited ability to open the mouth that, when the limitation is caused by muscle spasm, disappears with anesthesia. Some fractures functionally affect the mobility of the jaw, irrespective of anesthetic state. Inability to open the mouth more than 40 mm is considered to be clinically significant.

The patient's dentition should also be assessed prior to elective management of the airway. Protruding maxillary incisors ("buck teeth") interfere with direct laryngoscopy by restricting the extent to which the laryngoscope blade can be aligned with the trachea. Dental caps and other prostheses are fragile and easily damaged during laryngoscopy. The laryngoscope may become lodged in gaps between the maxillary teeth during instrumentation and interfere with intubation. Severe dental caries or periodontal diseases make it easier to dislodge teeth during airway instrumentation. The edentulous patient often has an atrophic mandible and large tongue and may be difficult to ventilate by mask because of poor fit of the mask. Intubation of the trachea in such a patient becomes difficult because the tongue, no longer constrained by the teeth, interferes with visualization of the larynx.

Abnormalities of the tongue, hard palate, tonsillar pillars, and hypopharyngeal structures can impede or prevent intubation. Normally the tongue is small and sufficiently flexible to be displaced by a laryngoscope blade during visualization of the vocal cords. However, the tongue is enlarged in obese patients, those with angioedema or impaired lymphatic drainage (e.g., after cervical surgical procedures or trauma), or in the setting of certain neoplasms. Burns, scars, or radiation of the submandibular soft tissue prevent lateral displacement of the tongue into the oropharynx during laryngoscopy. Similarly, in patients with small jaws ("receding chins"), displacement or flattening of the tongue during laryngoscopy is difficult, making intubation a challenge. A hyomental distance (the distance from the hyoid bone to tip of the mandible) of less than 6 cm should raise awareness of potential difficulty with intubation.

A cleft or high, arched palate is seen in a variety of congenital abnormalities of the facial bones, including the Treacher-Collins, Pierre Robin, Klippel-Feil, Goldenhar, Beckwith-Wiedemann, and Crouzon's syndromes, as well as the mucopolysaccharidoses. Affected patients are difficult or impossible to intubate using standard approaches.

Intraoral, oropharyngeal, hypopharyngeal, and laryngeal lesions, as well as tonsillar hypertrophy, can interfere with both laryngoscopy and ventilation by mask. The epiglottis can be infiltrated, inflamed, floppy, or enlarged by fat. The retropharyngeal and lateral pharyngeal spaces are continuous with and therefore subject to expansion by processes that involve the mediastinum (e.g., the presence of edema, blood, pus, or soft-tissue emphysema). Patients with epiglottitis and parapharyngeal swelling often exhibit a characteristic posture, sitting upright in the sniffing position and drooling.

The preferred position for visualization of the vocal cords is the sniffing position (Fig. 151-2). However, this position may be unsuitable in some patients or impossible to achieve in others.

The normal range for flexion and extension of the neck ranges from 90 to 165 degrees. A variety of disorders limit this range. Patients with cervical osteophytes or ankylosing spondylitis, who are often fixed in an anteroflexed head

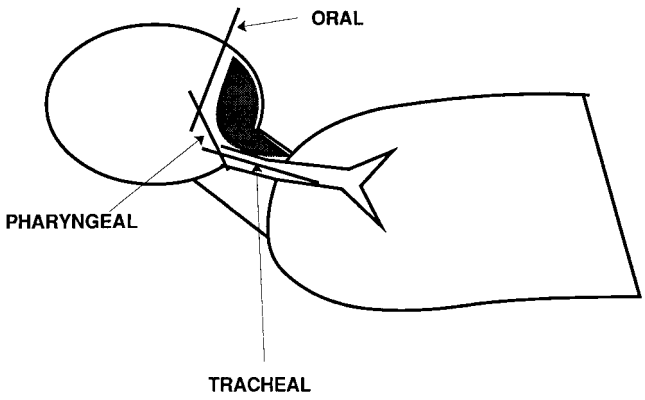

Figure 151-2 The sniffing position with the oral, pharyngeal, and tracheal axes.

position, may be difficult to intubate. Halo fixation imposes similar constraints. Rheumatoid arthritis, which may affect the cervical spine even in asymptomatic patients, may be problematic. By the age of 75 years, the normal aging process results in as much as a 20 percent reduction in cervical spine mobility. Injury to the cervical spine or the presence of a cervical collar also impairs the ability of the laryngoscopist to position the head. Finally, patients with short, muscular necks have limited neck mobility and redundant soft tissue in the mouth and submandibular space, making airway visualization a challenge.

A variety of other anatomic features, including large breasts or a barrel chest, can complicate airway management by interfering with the excursion of the butt of the laryngoscope blade. During pregnancy, the oral and pharyngeal mucosae are swollen and bleed easily. When associated with a diminished functional residual capacity and increased volume of acidic gastric contents, intubation becomes quite hazardous.

Based upon anatomical considerations, clinicians commonly employ the Mallampati scale (Table 151-1) to evaluate objectively the airway's suitability for placement of the endotracheal tube. The ability to visualize the soft palate, fauces, tonsillar pillars, and uvula is used to predict the degree of difficulty in exposing the larynx. A careful examination of the airway, coupled with attention to difficulties during prior procedures and the physical features described above, permit adequate preparation for instrumentation of the difficult airway.

Table 151-1

Mallampati Scale for Characterizing the Airway

Class I Soft palate, fauces, uvula, and tonsillar pillars visible
Class II Soft palate, fauces, and uvula visible
Class III Soft palate and base of uvula visible
Class IV Soft palate only visible

UPPER AIRWAY MANAGEMENT

Airway management is well suited to the use of algorithms. The American Society of Anesthesiologists has a "difficult airway" algorithm for use in the operating room. In addition, algorithms for the critical care unit and trauma setting have been developed. In using an algorithm-based approach, the first decision branch point typically addresses the need for endotracheal intubation, since short-term respiratory insufficiency often can be managed noninvasively.

Factors that must be considered in the care of patients with respiratory compromise include the level of consciousness, clinical context (e.g., the perioperative setting, emergency circumstances, etc.), anticipated duration of respiratory problem, risk of gastric aspiration, airway patency, concurrent medical problems, and anticipated relative ease of noninvasive (i.e., spontaneous or mask ventilation) vs. invasive (i.e., endotracheal intubation) management of the airway.

In the patient with neurological depression due to injury of the central nervous system, noninvasive management is usually inappropriate due to the potential for developing hypercarbia or hypoxia and exacerbation of the primary injury. Conversely, in the patient sedated or obtunded by drugs or seizures, the clinical state is often brief in duration, so temporizing measures may be appropriate.

Several factors differentiate elective perioperative airway management from emergency care. During surgery, an anesthesiologist or anesthetist is constantly present; the patient is properly prepared (i.e., the stomach is empty and a drying agent has been administered) and the environment is designed to facilitate airway management (i.e., there is ready access to suction, a ventilator, etc.). Under these circumstances, caregivers may choose to sedate the patient to the point of semiobtundation. Conversely, in an emergency, the setting is usually less than optimal. Airway management is usually only one component of the care rendered during cardiac or trauma resuscitation, and definitive airway intervention is essential in order to allow care providers to concentrate on other problems.

Potentially quickly reversible processes (e.g., some attacks of asthma or episodes of pulmonary edema) may be appropriately managed without intubation. In other instances (e.g., blunt chest injury), the initial problem can be expected to worsen, and early intubation is warranted.

The volume and acidity of the patient's gastric contents must be factored into any decision about management of the airway. Aspiration of solid food can be catastrophic, as can large volumes of acidic, enzymatically active gastric fluid. Most studies have indicated that aspirated stomach contents with a pH lower than 2.5 or volume greater than 0.5 to 1.0 cc/kg are likely to cause lung damage. The lung damage is manifested by loss of ciliated and nonciliated epithelial cells in the trachea, destruction of type I and II pneumocytes, depletion of surfactant, and increased vascular permeability (see Chapter 144). Pain and narcotics may alter gastric emptying or change gastric pH, as can a number of disease states, such as intestinal obstruction, diabetic gastroparesis, and obesity. Unless the patient has fasted for more than 8 h and is not subject to the confounding factors noted above, a full stomach should be presumed, and airway management handled accordingly.

The patient's coexisting medical problems and expected course must also be considered in management of the airway. For example, endotracheal intubation can be a dangerous stress to a patient with coronary artery disease and can be performed more safely after suitable preparation than under emergency circumstances. As another example, a patient with Fournier's gangrene and normal lungs is appropriately managed by maintaining intubation and sedation between trips to the operating room for debridement, rather than by performing multiple extubations and reintubations. Similarly, elective intubation and mechanical ventilation can prevent aspiration or atelectasis in a patient with hepatic encephalopathy who is awaiting liver transplantation, thereby improving the likelihood of a successful outcome.

Some degree of airway obstruction can be managed without intubation by proper positioning of the head, use of an oral or nasal airway, or application of positive airway pressure (PAP) by mask. A rolled towel or small pillow placed behind the neck or occiput reproduces the sniffing position. Oral and nasal airways can alleviate airway obstruction due to redundant airway soft tissue or muscle relaxation. The application of positive pressure to the mouth and nose (mask continuous positive airway pressure or mask CPAP) distends the soft tissue of the airway. For this reason, nasal mask CPAP is frequently used in the management of obstructive sleep apnea (see Chapter 97). These measures can be used as short-term, temporizing alternatives to intubation in the patient who is ventilating spontaneously in the intensive care unit or operative setting.

Although a growing literature exists on the use of noninvasive ventilation in a variety of settings that previously would have mandated endotracheal intubation, anesthesia is frequently administered in the operating room by mask using positive pressure. True mask ventilation is readily accomplished in the anatomically normal patient. However, some anatomic features, such as a beard, flat or sharp nose, or sunken cheeks (in the edentulous patient) can make mask-assisted ventilation difficult or impossible.

Indications for tracheal intubation (Table 151-2) fall broadly under several categories: respiratory failure, airway protection, hemodynamic instability, and perioperative management. If intubation is indicated, the clinician must decide upon the route and technique.

Table 151-2

Indications for Intubation of the Trachea

Ventilatory failure Cardiac arrest, primary lung disease, neuromuscular disease or weakness
Airway obstruction Primary airway process, neurogenic obstruction
Airway protection Upper airway bleeding or injury (burn), central nervous system depression
Pulmonary toilet Inability to manage secretions

TECHNIQUES AND EQUIPMENT

Although expertise is a function of experience, several principles are generally applicable in any approach to airway management. The first applies to correct head positioning, which facilitates mask management, oral or nasotracheal intubation, and fiberoptic examination of the airway. Incorrect positioning impedes each procedure.

The previously noted sniffing position refers to extension of the head on the neck while the neck is flexed on the thorax (Fig. 151-3). The hypopharynx is at its maximal circumference in this position, and the tongue is farthest from the posterior pharyngeal wall. Anterior displacement of the jaw can be accomplished by pulling it forward or applying pressure on the angle of the mandible (the "jaw thrust" maneuver).

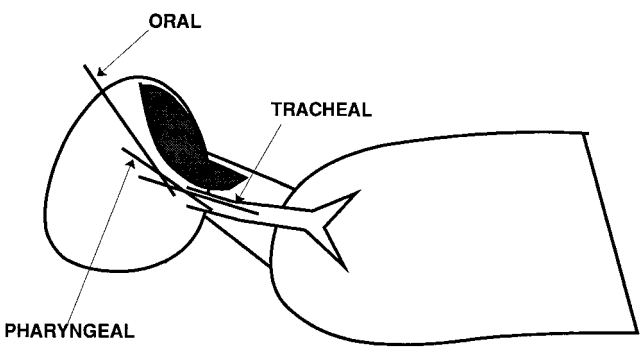

Figure 151-3 The sniffing position modified by additional head extension for oral intubation, with alignment of the oral, pharyngeal, and tracheal axes.

This serves to open further the retrolingual space. Pulling the tongue forward while grasping it with gauze or an instrument accomplishes the same goal. The position is appropriate for spontaneous respiration because it limits soft-tissue obstruction to airflow.

Nasotracheal intubation is easiest in the sniffing position, because the tip of the endotracheal tube is best aligned with the larynx and least likely to be deflected by the walls of the pharynx. Nasal and oral fiberoptic procedures are also easier in this position in which the oral, pharyngeal, and tracheal axes are well aligned (Fig. 151-3). The sniffing position may be modified by further head extension and flattening of the back of the tongue by the laryngoscope blade during oral intubation.

A second general principle underlining airway management is that saliva and blood interfere with mask ventilation, direct visualization of the airway, and fiberoptic procedures. When circumstances permit, pretreatment with an antisialogogue, such as atropine, glycopyrrolate, or scopolamine, significantly diminishes saliva production. Suction must be available prior to initiation of any elective procedure (as well as on the emergency cart) to clear secretions or deal with regurgitation of gastric contents. A suction tip with a large bore, such as the Yankauer tonsil suction tip, is commonly used; suction should be maximized in order to clear thick, viscous oral secretions.

A third general principle of airway management refers to preparation of the patient and airway. Small, titrated doses of sedatives, topical anesthesia, and vasoconstrictor agents markedly enhance the ease with which procedures, such as fiberoptic, nasotracheal, or oral intubation, are performed while the patient is awake. Narcotics are more likely to suppress the cough reflex than are other agents. Topical cocaine has anesthetic and vasoconstrictor properties, but because of its classification as a controlled agent, the combination of lidocaine and phenylephrine is often used as an alternative. The light source of a laryngoscope or fiberoptic scope should be checked prior to instrumentation, and, with the latter, the focus adjusted. Finally, a backup plan for airway management is essential in case the primary plan should go awry.

Finally, perhaps the most important principle of airway management is that a source of oxygen and means of ventilation should be available. This implies that the pressure in nearby oxygen tanks should be checked, as should the proximity of a source of wall oxygen. In the absence of an oxygen source, a self-inflating resuscitation bag can provide a method for ventilation, obviously using only room air (see below). Bags used for most anesthesia circuits require a gas source for inflation.

AIRWAYS

A large variety of nasal and oral airways, designed for children and adults of different sizes (Fig. 151-4), are available. Nasal airways are generally made of flexible rubber and have a beveled tip, permitting insertion through narrow nasal passages. Oral airways are curved, designed to lie over and behind the tongue. Some are fashioned with slots for ready passage of a suction catheter, whereas others have a central channel designed to accommodate a fiberoptic scope. Binasal airways are designed to be fitted to a ventilation circuit, permitting ventilation in anesthetized patients without endotracheal intubation.

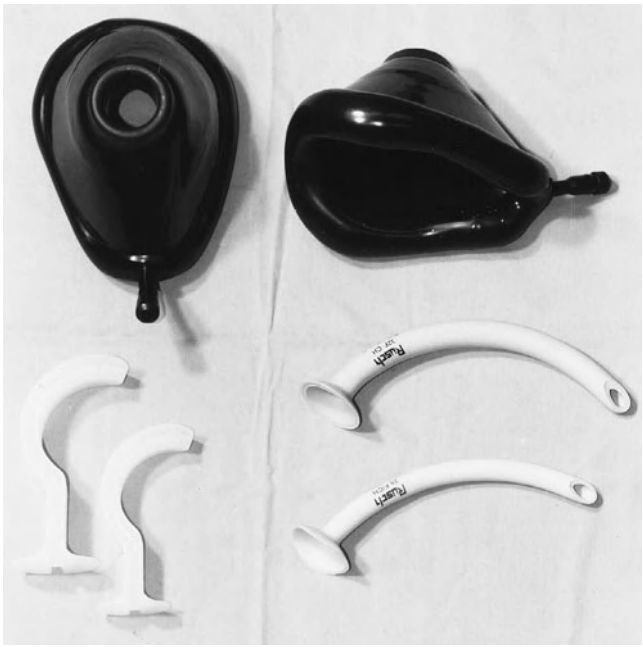

Figure 151-4 Oral and nasal airways and face masks.

RESUSCITATION BAGS

Resuscitation bags are available in many styles (Fig. 151-5) and are designed with several common features. They are self-inflating, and can, therefore, be used in the absence of a gas source. An internal flap valve system directs inflowing gas to the patient or reservoir, permitting application of positive pressure by mask or endotracheal tube and venting exhaled gas to the atmosphere. Inspired oxygen concentration is ordinarily limited to 40 to 60 percent when oxygen inflow is 10 L/min; bag reinflation is rapid, since room air is entrained with each breath. Addition of an oxygen reservoir, usually in the form of a sleeve or tail at the back of the bag, permits administration of oxygen concentrations of 75 to 90 percent at 10 to 15 L/min. Some bags are equipped with adjustable valves for application of positive end-expiratory pressure.

MASKS

Although a large variety of masks are available (Fig. 151-4), all have three features in common: the body, seal, and

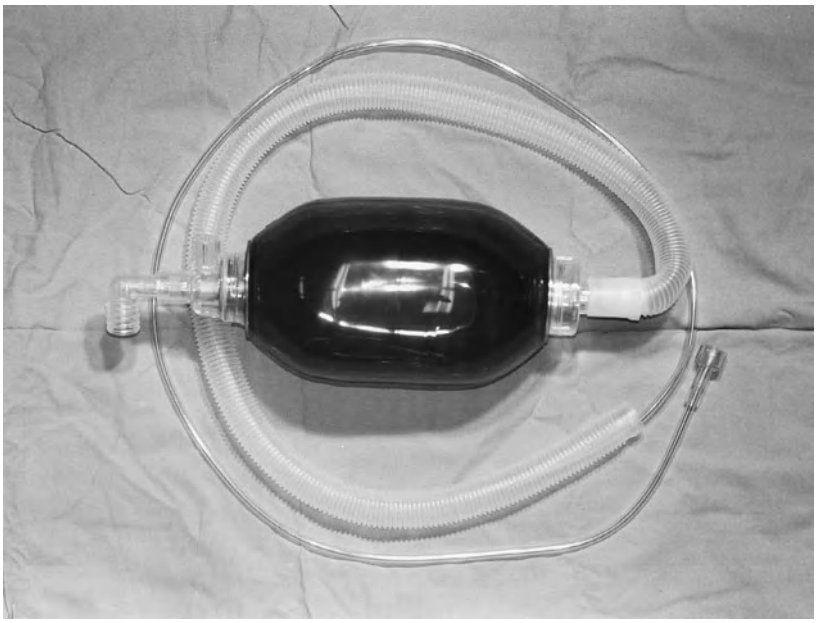

Figure 151-5 Self-inflating resuscitation bag.

connector. The body is usually made of malleable or moldable material and adjustable to individual facial anatomy. The body of some masks is made of clear plastic to allow diagnosis of regurgitation of gastric contents. The seal is usually a cushioned rim (which can be inflated or deflated) attached to the body, although some are detachable. Some seals are flanged and not cushioned. The connector is designed with a universal fitting (22-mm internal diameter) for attachment to any ventilating circuit. Many are equipped with retaining straps for attachment to mask straps (which pass behind the patient's head, freeing the hand of the operator).

EXTRAGLOTTIC AIRWAY DEVICES

A number of extraglottic or supraglottic airway devices exist, and new ones are described every year. Some are cuffed, while others are uncuffed; some are nasally inserted, while others are orally inserted. A few devices are based on cannulation of the esophagus. The most familiar devices are cuffed, orally inserted, hypopharyngeal airways, such as the laryngeal mask airway (LMA) and the laryngeal tube airway (LTA).

The LMA (Fig. 151-6) is analogous to the facial mask: It has a compliant cuff that is applied to the dorsal surface of the larynx, isolating the airway from the mouth and esophagus. The LMA came into common intraoperative usage in the early 1990s. While used most extensively in surgical patients, the LMA has also been used for awake, fiberoptic bronchoscopy, in the intensive care unit, and in emergency resuscitation. Variants are specifically designed to be flexible, disposable, or to permit passage of an endotracheal tube through the device's lumen. The LMA is inserted through the mouth into the hypopharynx; its correct positioning is verified by assessment of breath sounds.

The LTA is similar to the LMA. The device has two cuffs, one of which is designed to seal the lower pharynx and esophagus and the other the upper pharynx. A lumen exists between the two.

The esophageal obturator airway (EOA) is similar to the LTA in that it also has two cuffs and a single lumen. However, the distal end of the device is designed to lie in the esophagus. A newer device, the Combitube (Armstrong Medical Industries), addresses a concern that the tip of the EOA may inadvertently enter the trachea, making ventilation impossible. The Combitube is designed to permit ventilation and airway isolation regardless of whether its tip lies in the esophagus or trachea.

TRACHEAL INTUBATION

Four approaches are commonly employed in tracheal cannulation: nasal, oral, laryngeal, and tracheal. The first two are noninvasive, whereas the latter two require surgical incisions.

Nasotracheal intubation can be done "blindly" (i.e., without tracheal lumen visualization) or using a laryngoscope and forceps. A blind nasotracheal intubation, when performed by a skilled operator, allows rapid control of the airway in an awake patient and minimal suppression of protective airway reflexes. The technique is used widely by paramedics in prehospital patient care, as a component of many difficult airway algorithms, and as an integral part of Advanced Trauma Life Support algorithms.

In performing blind nasotracheal intubation in a nonemergency setting, the operator examines the nasal passages for patency, septal deviation, or the presence of polyps.

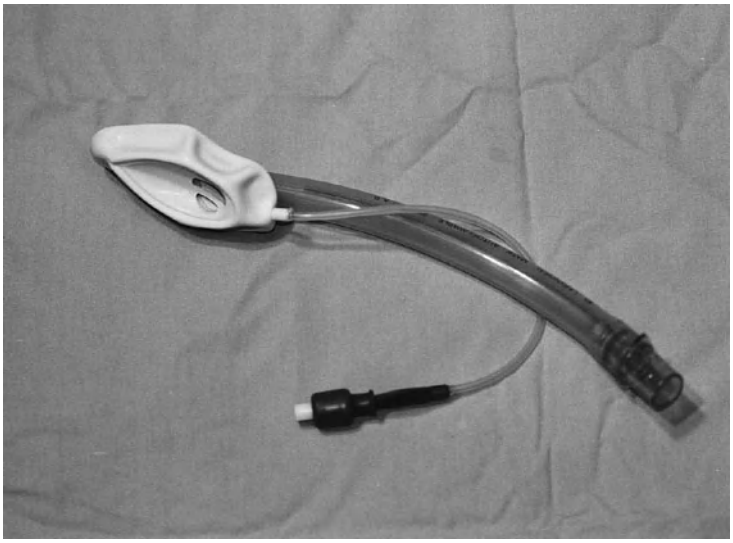

Figure 151-6 The laryngeal mask airway.

If the patient is able to cooperate, the larger nasal passage is selected by alternately occluding each nostril and choosing the one with better airflow. A topical anesthetic and vasoconstrictor agent are sprayed in the nostril or applied with cotton pledgets. Anesthetic is also sprayed into the back of the mouth in order to anesthetize the hypopharynx.

An appropriately sized tube (6 to 7 mm for women, 7 to 8 mm for men) is selected and lubricated. Lubrication eases passage of the tube and minimizes abrasion of the nasal mucosa, making bleeding less likely. The patient is placed in the sniffing position and the tube inserted and advanced using slow, firm pressure. The natural slope of the tube is oriented so that the tip initially points toward the occiput and curves in a caudad direction as it is advanced.

During the procedure in an awake patient, the operator listens for breath sounds as the tip approaches the vocal cords. A commercially available whistle attachment (Bamm, Great Plains Ballistics, Inc., Lubbock, TX) enhances the operator's ability to hear breath sounds (Fig. 151-7). The tube is

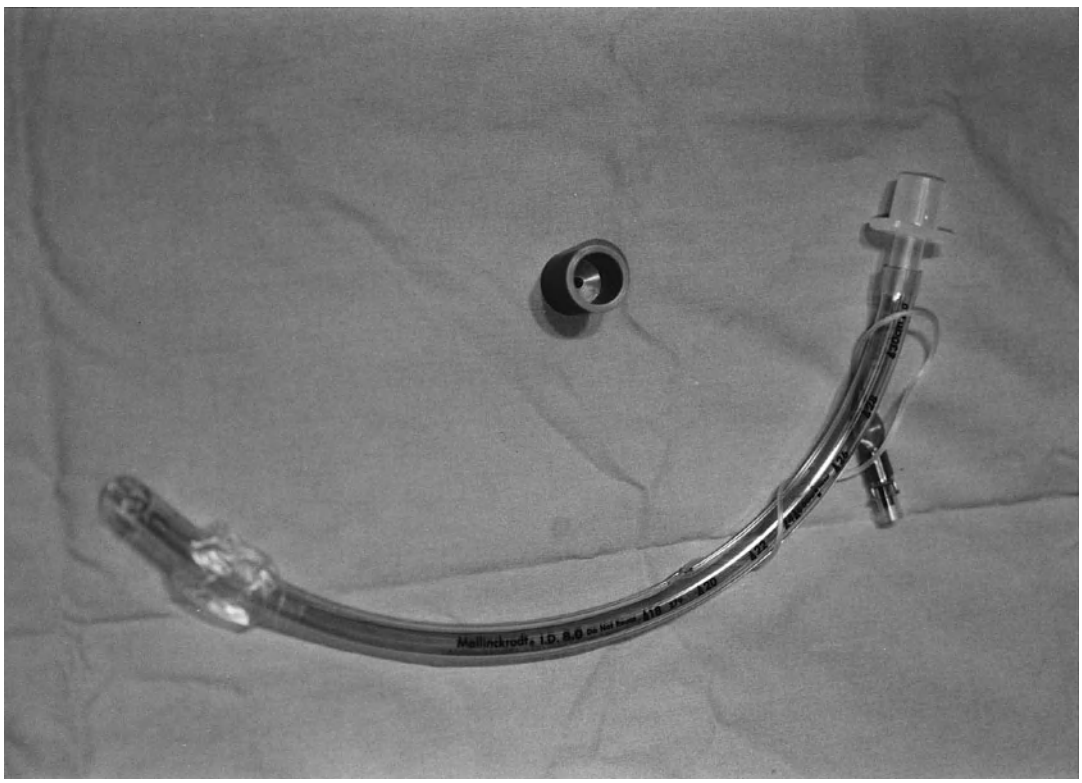

Figure 151-7 Standard endotracheal tube with whistle tip attachment to amplify breath sounds during blind nasal intubation.

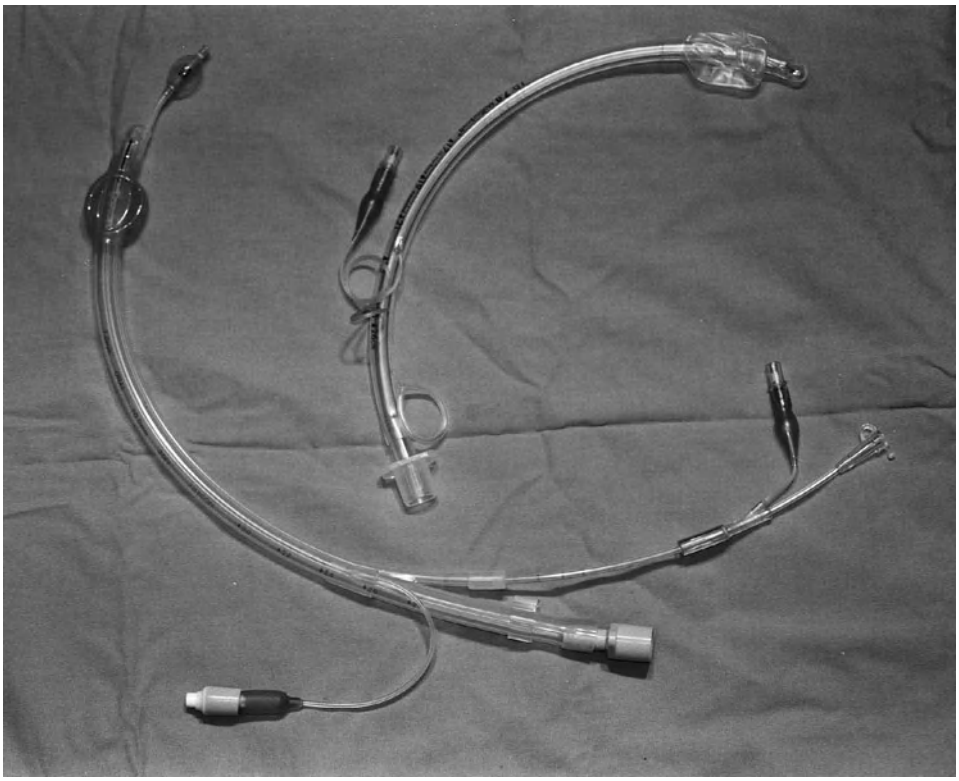

Figure 151-8 Endotracheal tube modified with a "trigger" permitting anteroflexion of the tip of the tube during blind nasal intubation. Univent tube for lung isolation (see text).

advanced into the airway during *inspiration*. Slight clockwise or counterclockwise rotation of the tube at the nose can be used to correct for lateral misalignment. A commercially available endotracheal tube (Endotrol, Mallinckrodt, Athlone, Ireland) allows the operator to anteroflex the tip of the tube with a "trigger" at the connector (Fig. 151-8). This is especially effective in patients with anteriorly positioned vocal cords or those who cannot assume the sniffing position (e.g., due to the presence of a cervical collar).

When nasotracheal intubation is performed in an anesthetized patient, the endotracheal tube tip is advanced into the hypopharynx above the vocal cords, laryngoscopy is performed, and the tube is then advanced into the trachea under direct visualization. Magill forceps (Fig. 151-9) are often used to grasp the tube and direct its tip between the vocal cords. Care must be taken to avoid grasping the tube by the cuff, which is easily perforated.

Correct position of the tube can be verified using a number of methods. Audible or palpable air passage (in the spontaneously breathing patient), a visible vapor trail within the tube, or auscultatory evidence of breath sounds over the lung fields are standard approaches. End-tidal capnometry showing phasic variation in carbon dioxide levels is the gold standard and has become more feasible in nonoperative settings because of the development of portable and disposable devices.

Extensive literature exists on the pros and cons of nasal versus oral intubation in the intensive care environment. Nasal intubation is associated with a higher incidence of bleeding, nasal discomfort, and hemodynamic alterations during tube placement. A minimal increase in the dead space of the equipment (less than 10 cc) without significant difference in airflow resistance occurs with nasotracheal intubation compared with the orotracheal route. Literature regarding the incidence of sinusitis and pneumonia as a result of each of the two methods is conflicting; one prospective, randomized trial showed no differences. In general, early tracheostomy is increasingly preferred in critically ill patients who are likely to be intubated for prolonged periods.

By far, direct laryngoscopy with orotracheal intubation is the most common approach that is applied to secure the airway. With the patient's head in the sniffing position, the operator inserts a Macintosh or Miller blade (Fig. 151-10) into the right side of the mouth using the left hand (regardless of the handedness of the operator). While some anatomic situations make it advantageous to use one blade rather than the other (e.g., the Miller blade in the setting of an anatomically anterior larynx), most operators become familiar with one blade and use it preferentially.

The blades of both instruments are flanged to keep the tongue to the left and out of the visual field. Larger adult blades (Macintosh no. 4 or Miller no. 3) are used for patients with long mandibles, whereas shorter blades (Macintosh no. 3 or Miller no. 2) are used in normal patients. Smaller blades are used for children.

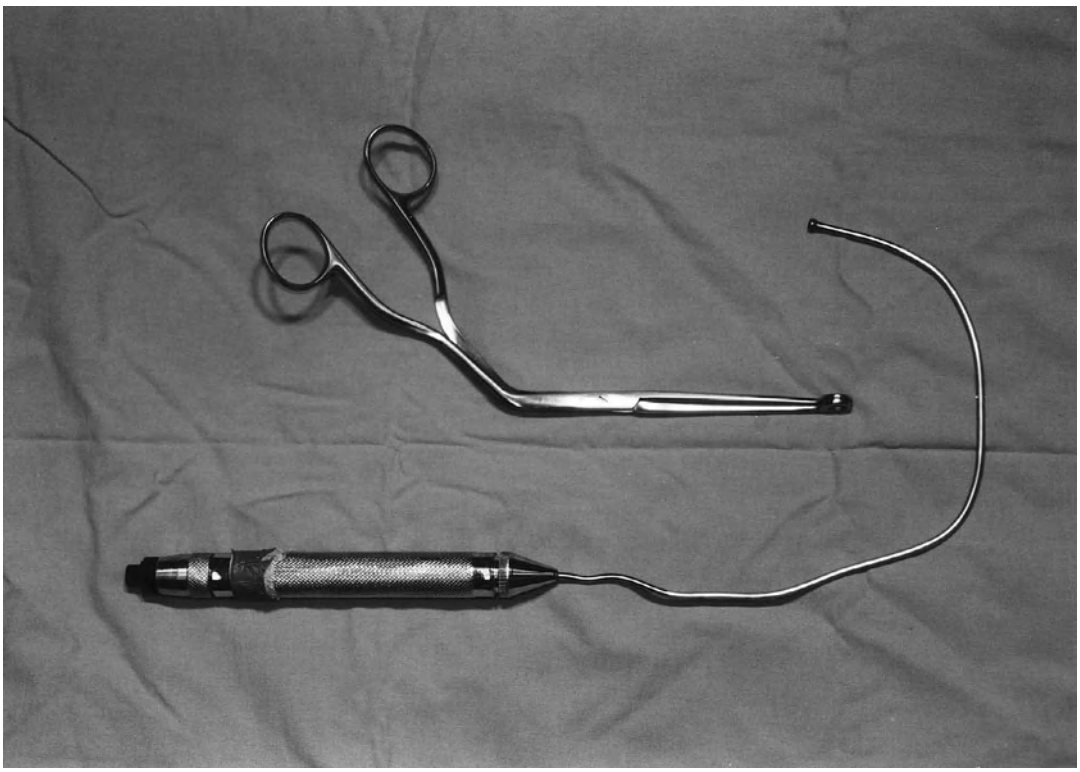

Figure 151-9 Magill forceps (see text) and light wand for transillumination of the trachea during blind oral intubation.

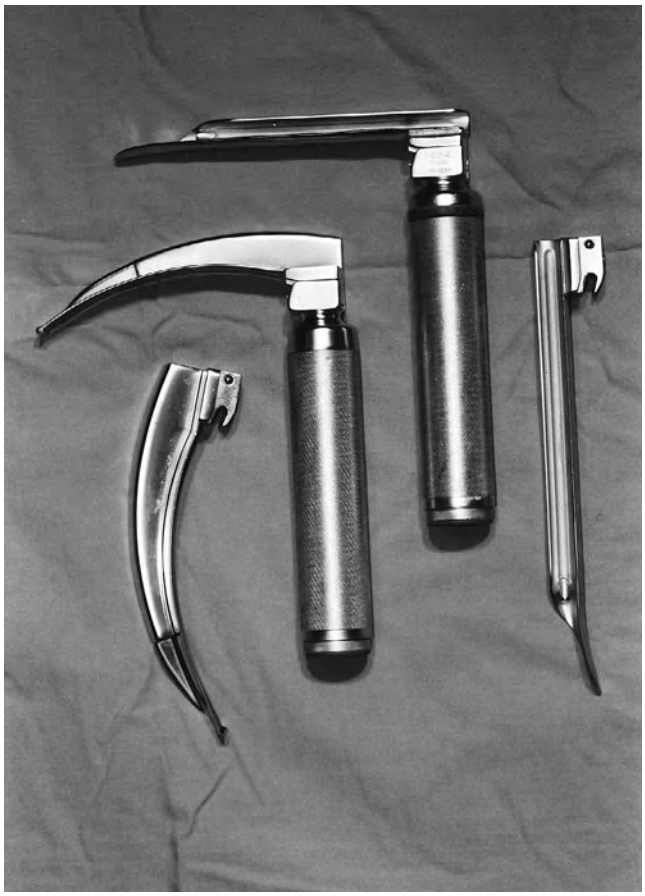

Figure 151-10 Macintosh and Miller blades.

During the procedure, the operator's right hand pulls the upper and lower lips out of the way, so that they are not caught and injured between the blade and teeth. The tip of the laryngoscope blade is advanced along the tongue until the epiglottis is visible. If the Macintosh blade is used, it is advanced between the tongue and epiglottis; when the Miller blade is used, the epiglottis is elevated directly. The cords should be visible immediately below the epiglottis. Most infants are intubated using a Miller blade. The shape, length, and pliancy of the infant epiglottis are such that it must be "picked up" by the tip of the Miller laryngoscope so that the cords can be seen.

Because some patients are difficult to intubate due to anatomic considerations, a number of alternate approaches have evolved. These include fiberoptic laryngoscopy, by which the trachea is entered using a bronchoscope and an endotracheal tube advanced into the airway over the device. A flexible light wand (see Fig. 151-9) can be used to transilluminate and identify the airway; an endotracheal tube is then advanced into the airway using the wand as a stylet. Retrograde techniques involve percutaneous cannulation of the trachea in the neck and retrograde passage of a wire or catheter into the oropharynx. The wire is grasped and secured to an endotracheal tube and used to guide its passage back into the trachea.

Percutaneous cricothyrotomy kits are available for emergency access to the airway, as are percutaneous tracheostomy kits. Percutaneous ventilation has been taught in airway management portions of Advanced Cardiac Life Support (ACLS), Advanced Trauma Life Support (ATLS), and

Table 151-3

Indicators of a Potentially Difficult Airway

Poor mouth opening
Temporomandibular joint disease
Mandibular fracture
Dental problems
"Buck" anterior teeth
Caries
Dental hardware (caps, dentures)
Gaps
Abnormalities of the tongue
Large (e.g., in obesity)
Swollen Edema (surgical) Angioedema (allergic)
Fixed Scarring (radiation) Tumor
Presence of other intraoral structures
Tumors
Enlarged tonsils
Small jaw
"Anterior larynx"
Decreased neck mobility
Cervical disease or injury Suspected fracture Rheumatoid arthritis Ankylosing spondylitis
Increased age (presence of cervical osteophytes)
Congenital syndromes
Cleft palate
Treacher-Collins
Pierre Robin
Klippel-Feil

Pediatric Advanced Life Support (PALS) courses. The technique requires insertion of a needle or intravenous catheter through the cricothyroid membrane in order to insufflate oxygen during emergency airway management.

Anatomic features indicative of the difficult airway are listed in Table 151-3. While a full discussion of the management of the potentially problematic airway is beyond the scope of this chapter, adequate preparation by the operator can prevent a catastrophe.

Early assessment of the anatomy to determine whether difficulty with intubation alone or intubation and ventilation should be anticipated is important. An anteriorly placed larynx is usually associated with difficulty in intubation alone, whereas an obese patient is more likely to present a challenge with regard to both intubation and ventilation.

An additional important determination is whether interventional airway management is actually necessary. Can the procedure be performed under regional, rather than general, anesthesia? If regional anesthesia cannot be employed, awake intubation using sedation and topical airway anesthesia may be an excellent alternative. Direct laryngoscopy and fiberoptic bronchoscopy are equally appropriate adjuncts in intubating cooperative patients.

If difficulty in airway management is unexpectedly encountered in an already anesthetized patient, ensuring adequate ventilation and oxygenation is critical. A mask or, if necessary, one of the invasive approaches described above, may be used. Establishment of reliable ventilation allows time for alternate approaches, including abandonment of the procedure (allowing the patient to awaken) or tracheostomy.

A large number of endotracheal tubes are commonly employed in a variety of clinical settings.

Single-lumen, reusable, red rubber tubes with separate cuffs were used as recently as the mid-1970s, and red rubber double-lumen tubes were in common use 5 to 10 years ago. Disposable tubes are now widely available, and a host of different design modifications have been made to make the tubes safer and accommodate different surgical procedures.

The cuff of the adult tube has been changed from a low-volume, noncompliant cuff to a higher volume, very compliant cuff; a corresponding decrease in the incidence of tracheal stenosis has been observed. Pediatric tubes are generally uncuffed because children are more vulnerable to development of subglottic stenosis due to tube contact with the trachea. Uncuffed tubes also maximize the cross-sectional area of the airway. Oral and nasal RAE tubes (Fig. 151-11) are preconfigured to permit facial and oral surgery without interference from the proximal portion of the endotracheal tube.

A variety of special tubes are used for laser surgery. These tubes are less likely to burn when contacted by the laser beam. Reinforced or anode tubes have an embedded wire or nylon filament spiral in the wall of the tube that prevents kinking or collapse due to external pressure (see Fig. 151-11). The Hi-Lo Jet endotracheal tube (Mallinckrodt) has four

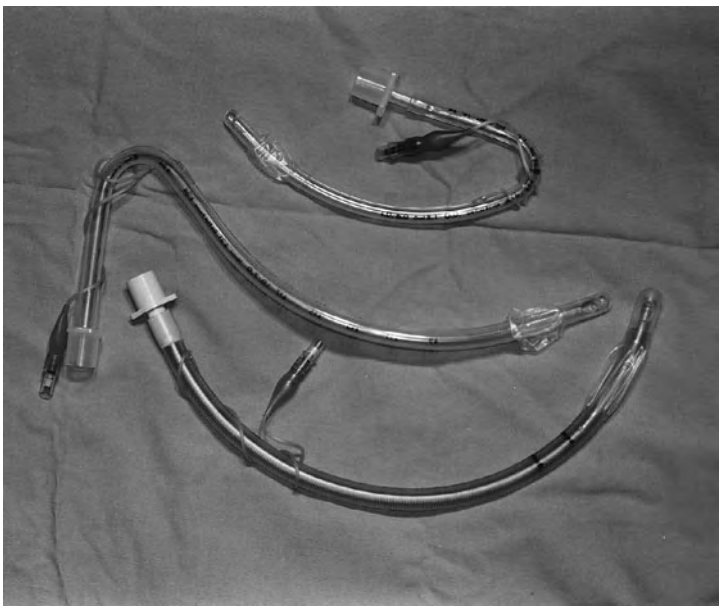

Figure 151-11 Oral and nasal preshaped tubes (RAE tubes). Anode, wire-wrapped tubes to prevent kinking.

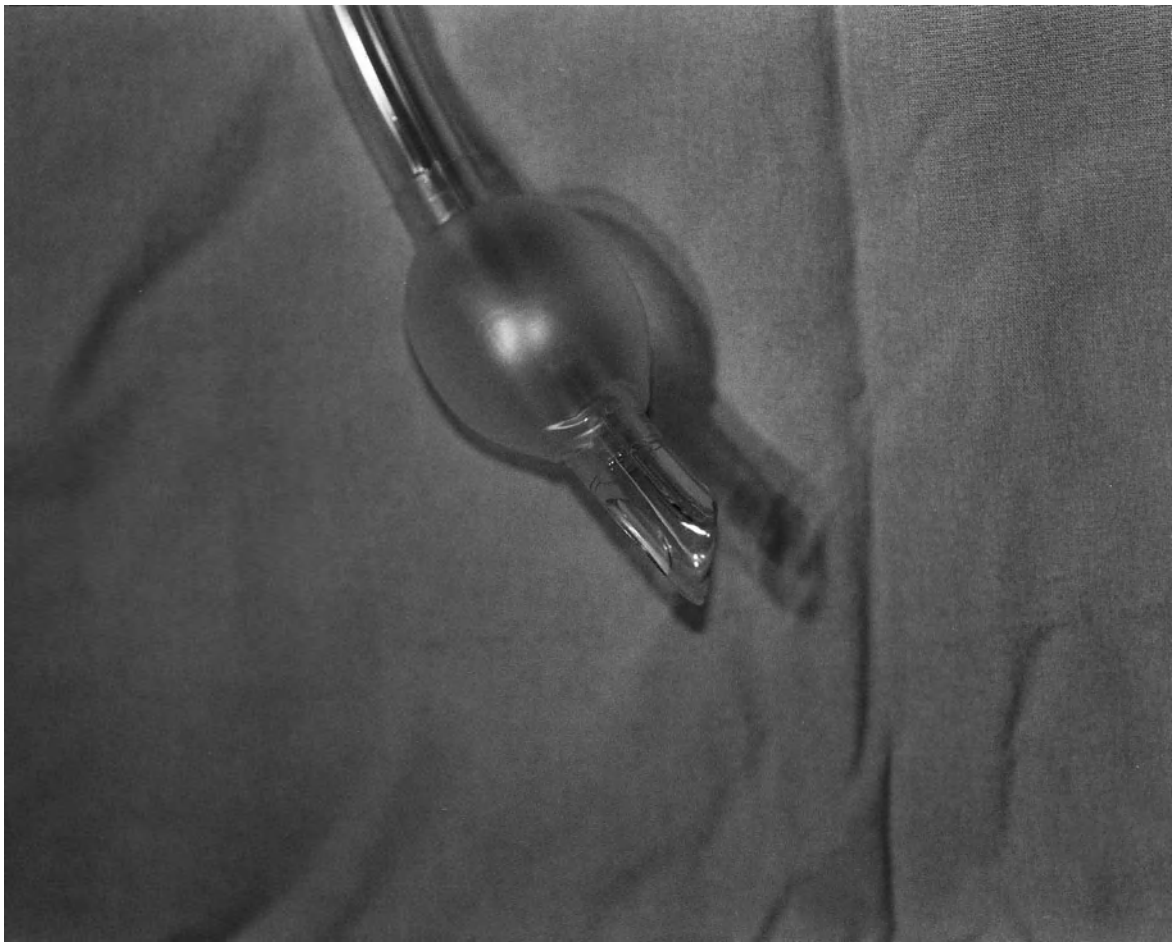

Figure 151-12 Endotracheal tube tip with Murphy eye and bevel (see text).

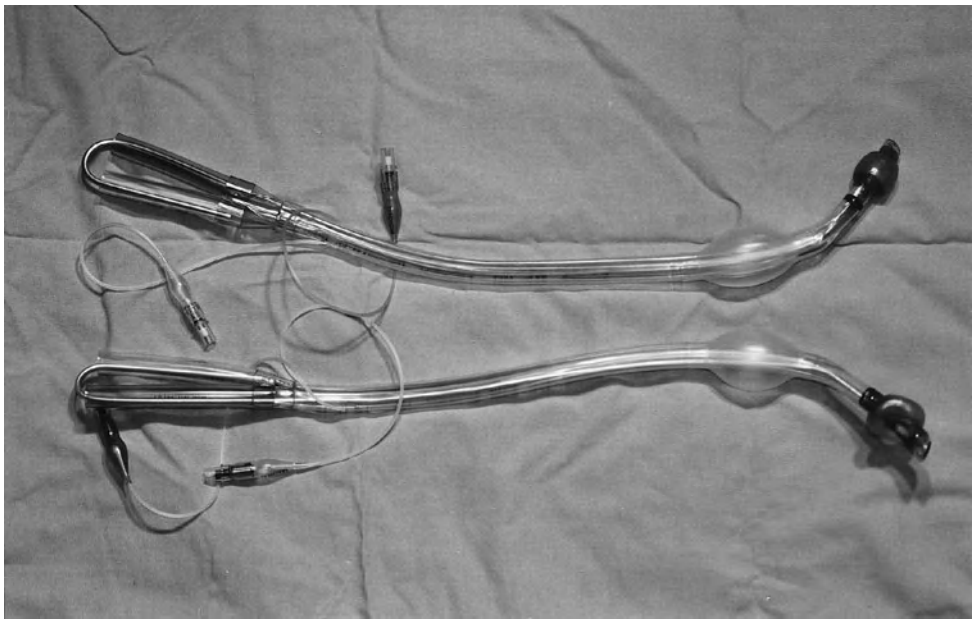

Figure 151-13 Right- and left-sided double-lumen endotracheal tubes. Note oblique bronchial cuff on the right-sided tube to accommodate right upper-lobe bronchial orifice.

lumens: one for entrained gas, a second for jet ventilation, a third for cuff inflation, and a fourth for pressure monitoring.

All single lumen tubes have a 15 mm outer diameter and connect to any standard ventilation device. Most also have a radioopaque stripe that permits tube localization on chest roentgenograms. The tip of the tube is beveled (Fig. 151-12); the bevel faces to the left because endotracheal tubes are generally inserted from the right by right-handed operators. An extra hole (Murphy eye) lies opposite to the bevel on many tubes and is designed to permit suctioning or antegrade gas flow if the bevel becomes occluded.

Finally, disposable double-lumen endotracheal tubes are now available. The Carlens and White tubes that were used in the past were equipped with a carinal hook for correct tube placement. These tubes have largely been abandoned in favor of the Robertshaw design, which has tracheal and bronchial cuffs and no hook. The tube is available in four adult sizes (35, 37, 39, and 41 French) in both right- and left-sided designs (Fig. 151-13). The right-sided tube has an oblique bronchial cuff to accommodate the takeoff of the right upper lobe orifice. Correct placement of a double-lumen tube has become easier with development of bronchoscopes small enough to pass through the narrow tube lumens.

An alternative to the double-lumen tube (the Univent tube, introduced in 1982) has a self-contained endobronchial blocker. The tube is inserted in the standard fashion, and the endobronchial blocker is then advanced (blindly or under direct vision) into the right or left main bronchus. A central lumen in the endobronchial blocker allows for inflation or deflation. While the bronchial blocker is integrated into the Univent tube construction, the same functionality can be achieved by using the Arndt wire-guided endobronchial blocker (Cook Critical Care, Bloomington, IN). The device is a multiport airway adapter, which can be used without a tube change (unlike the Univent tube) and can be "swapped" for a standard Y-piece connector, when desired.

CONCLUSION

While some of the skills developed by the early pioneers may be lost to current practitioners (Fig. 151-14), advances in pharmacology, equipment, and equipment manufacturing

Figure 151-14 Earlier diagnostic airway intervention. *(From Kirstein:* Archiv Laryngol Rhinol *3:156–164, 1895. Courtesy of Cushing/ Whitney Medical Library.)*

standards have greatly facilitated airway management and have made new surgical procedures possible.

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Hemodynamic and Respiratory Monitoring in Acute Respiratory Failure

Barry D. Fuchs • Patrick Neligan

GENERAL PRINCIPLES

Patients with acute respiratory failure (ARF) sustain significant morbidity and mortality, with adverse outcomes resulting from both the primary insult responsible for the ARF and secondary complications, many of which are preventable. Admission of these patients to the intensive care unit (ICU) allows more for intensive monitoring in an attempt to diminish risks and guide therapeutic interventions. This chapter reviews methods currently available for monitoring hemodynamics and respiratory function in patients with ARF.

A number of important goals of ICU monitoring can be identified. One is to ensure adequacy of respiratory and circulatory functions in patients who appear clinically stable. Another is to provide close surveillance for early signs of respiratory and circulatory instability, with the presumption that early detection improves outcome. In addition, measurement of the response to therapeutic interventions, including application of supportive devices, such as endotracheal tubes and mechanical ventilators, is routinely performed in the ICU. Although life-saving, these devices, like all therapeutic interventions, are associated with risks that must be monitored. Finally, monitoring respiratory and hemodynamic derangements over hours to days provides valuable insight about prognosis, since the trend in physiological derangements over time predicts outcomes far better than does the severity of abnormalities on admission. Consequently, failure to improve over days, despite full support and appropriate treatment, suggests the need for alternative therapeutic strategies, including patient comfort as the primary goal of care.

Physiological parameters normally vary in critically ill patients. Furthermore, the devices used to measure these parameters are often imprecise and, at times, inaccurate. Therefore, clinical assessment and decision making should not be based, in general, on single data points. Rather, *trends* in data add reliability to interpretation of measurements.

INDICATIONS FOR MONITORING HEMODYNAMICS

When managing patients with ARF, intensivists are regularly required to make judgments about circulatory function

that can often be made confidently using routine monitoring equipment. However, several clinical questions become more challenging without application of more invasive or sophisticated measuring devices. These questions include:

1. For the patient with pulmonary edema, is the edema cardiogenic or noncardiogenic in origin?
2. Is hypoperfusion causing, or contributing to, the patient's end-organ dysfunction?
3. Recognizing the risk of worsening hypoxemia in ARF following administration of intravenous fluids, should the patient with ARF who presents with or develops shock be given fluids? If so, how much?
4. For those patients with volume overload, given the risk of causing or exacerbating organ dysfunction, how much fluid should be removed by using diuretics or dialysis to reduce lung water and improve respiratory function?

The first question requires an estimate of ventricular preload, the second an estimate of cardiac output, and the third and fourth an assessment of the inter-relationship of both preload and cardiac output.

Varieties of both noninvasive and invasive techniques are available to monitor hemodynamics and are discussed below.

METHODS FOR MONITORING HEMODYNAMICS

Assessment and monitoring of hemodynamics are based on a spectrum of clinical tools, ranging from a detailed history and physical examination to a variety of noninvasive and invasive techniques.

History and Physical Examination

While patients with ARF may require heavy sedation, some do not, and the clinician should routinely attempt to obtain a focused history from all intubated patients.

The physical examination is equally important, providing valuable visual, auditory, and tactile information. Alterations in the general appearance of the patient, including restlessness, agitation, delirium or ventilator dyssynchrony, may be readily apparent and should be investigated as a potential first sign of a serious underlying circulatory problem, particularly in the heavily sedated patient. Alterations in heart rate and blood pressure often accompany significant pathophysiological changes (e.g., severe hypoxemia), but they may also be seen as a side effect of medications or cardiac ischemia. A reduction in blood pressure, while attributable to many potential causes, may be a late manifestation of shock and always requires emergent evaluation. Unfortunately, changes in vital signs have limited sensitivity and specificity. In one study of normal subjects, a 25 percent reduction in blood volume resulted in no change in vital signs. In addition, a variety of nonhemodynamic conditions (e.g., pain or anxiety) may cause significant changes in vital signs.

The remainder of the physical examination may provide information about the adequacy of perfusion and help to establish the type and cause of shock. The adequacy of cardiac output is assessed by evaluating heart rate, mean arterial pressure, pulse pressure, urine output, mental status, and extremity and skin perfusion (as reflected by peripheral temperature, capillary refill, and absence of mottling or livedo reticularis). Estimates of right and left ventricular filling pressure based on assessment of jugular venous distention or the presence or absence of lung crackles provides a presumptive diagnosis of the type of shock and helps guide initial resuscitation. When coupled with other physical findings (e.g. unequal breath sounds) the specific etiology of shock may be determined.

Despite the potential usefulness of a careful physical examination, several studies have shown that clinical assessment correlates poorly with objective measurements of central hemodynamics, including cardiac filling pressures and cardiac output. Thus, if accurate hemodynamic measurements are needed to make safe clinical decisions, use of more sophisticated monitoring devices or diagnostic evaluation is required.

Arterial Blood Pressure

Mean arterial pressure (MAP) is the primary determinant of cerebral and myocardial blood flow. In the setting of hypotension, cardiovascular homeostatic mechanisms maintain MAP in a narrow range, in part through compensatory vasoconstriction in other, less vital, organs. However, MAP is not a useful measure of the adequacy of cardiac output. A low MAP may accompany shock, but it is a late manifestation, occurring when cardiovascular reserves are exhausted. Conversely, acute elevations in MAP may also be associated with injury to vital organs.

Patients with chronic hypertension should be maintained at a higher MAP, given the likelihood of vascular wall thickening which may limit vasodilator capacity for autoregulation. A general rule is that the MAP should be maintained within 25 percent of the patient's baseline value in order to minimize the likelihood of myocardial or cerebral ischemia. In contrast, patients with chronic liver disease may have adequate organ perfusion despite a low MAP. Nevertheless, normalizing the MAP is a primary goal in circulatory resuscitation. In patients with a normal baseline MAP, resuscitation to a goal greater than or equal to 65 mmHg has been recommended, since higher resuscitation targets fail to improve organ perfusion. Once the MAP resuscitation goal is met, other parameters more sensitive to organ perfusion are used to guide the adequacy of resuscitation.

Measurement of arterial blood pressure may be accomplished using invasive or noninvasive methods. Although in healthy patients noninvasive measurements of blood pressure

correlate well with invasive measurements, invasive methods are preferred in patients with ARF. Noninvasive methods are unreliable in shock states, which are not uncommon in patients with ARF. Continuous monitoring of arterial blood pressure during resuscitation or titration of vasoactive agents minimizes the chance of missing a critically low or high recording between measurements. Furthermore, an indwelling arterial catheter is often required for monitoring arterial blood gases.

In contrast to MAP, the pulse pressure provides information about cardiac output that is useful in the assessment of shock. Pulse pressure is determined primarily by stroke volume and aortic compliance. Since the latter doesn't change beat-to-beat and is assumed to be normal in most patients (except the elderly), pulse pressure changes in proportion to stroke volume. Thus, in a patient with tachycardia, a normal or stable pulse pressure suggests normal or high cardiac output, while a reduced pulse pressure indicates a low cardiac output.

In animals subjected to graded hemorrhage, the magnitude of respiratory phase-related changes in systolic arterial pressure and pulse pressure correlate with the degree of hypovolemia. Numerous studies have corroborated these findings, establishing a potential role for use of systolic and pulse pressure variation in determining fluid responsiveness in critically ill patients. Indeed, in the hypovolemic patient, central veins collapse more easily following a positive pressure breath, and ventilator-induced changes in right atrial pressure are greatest when the right atrium is underfilled and most compliant. Furthermore, hypovolemia increases the likelihood that mechanical insufflation will collapse pulmonary capillaries, increasing pulmonary vascular resistance and decreasing left ventricular filling. Finally, when the left ventricle is underfilled and operating on the steep (linear) portion of its Starling curve, it is more sensitive to changes in right ventricular output. Hence, the greater the variation in systolic and pulse pressure during a single cycle of mechanical ventilation, the more underfilled the ventricles and the more likely the response to a fluid challenge ("preload responsiveness").

These principles may also be used to monitor the titration of positive end-expiratory pressure (PEEP) by assessing variation in systolic or pulse pressure as PEEP is applied. PEEP can reduce cardiac output, thereby limiting or negating any improvement in arterial oxygenation on oxygen delivery. When systolic or pulse pressure begins to vary with each mechanical breath, the level of PEEP has likely decreased cardiac preload, suggesting the need for a fluid challenge.

Respiratory variations in systolic and pulse pressure have been shown to accurately predict fluid responsiveness in critically ill patients with respiratory failure, with or without septic shock. Once validated, these findings may be more useful in predicting fluid responsiveness than other, more traditional, estimates of cardiac preload, including central venous pressure, pulmonary artery occlusion pressure, or left ventricular end-diastolic volume (LVEDV).

Laboratory Tests

Two laboratory tests deserve special mention for their potential role in hemodynamic monitoring: B-type natriuretic peptide (BNP) and lactic acid.

Serum levels of BNP (either B-type or N-terminal pro-B-type) correlate with the degree of cardiac dysfunction and have shown promise as a tool to diagnose, monitor, and predict outcome of patients with congestive heart failure (CHF) in outpatient and emergency department settings. Accordingly, interest has arisen in using BNP as a noninvasive test to monitor volume status in critically ill patients.

Unfortunately, in patients with ARF, BNP levels do not correlate with pulmonary artery occlusion pressure. BNP increases with right heart dysfunction, sepsis (with or without cardiac dysfunction), and ARF, reflecting low test specificity. Furthermore, hypotensive patients who are in a non–steady-state condition may present acutely with an elevated BNP, despite hypovolemia, because of preexisting cardiac disease. On the other hand, a *low* BNP level may be useful in ruling out cardiac dysfunction.

In assessing the net "result" of cardiac performance, namely, end-organ perfusion, an absolute value for cardiac output or index cannot be used to diagnose shock. In addition to the physical examination and assessment of selected parameters, including urine output and central or mixed venous oxygen saturation (see below), measurement of venous lactate levels represents a useful screening tool for determining the adequacy of global and regional hemodynamics.

Elevated lactate levels have also been shown to correlate with patient outcome in the ICU, although in individual patients, lactate clearance (change in level over time) is a more accurate predictor of outcome. With newer assays and sampling techniques (e.g., by finger stick) lactate levels are readily available.

In patients with ARF, lactic acidosis is most commonly caused by cellular hypoxia due to hypoperfusion or hypoxemia. Although cellular hypoxia may contribute to lactic acidosis associated with sepsis, particularly early in its course, endotoxin and other mediators may also cause lactate release due to cytopathic hypoxia via direct inhibition of the mitochondrial enzyme that metabolizes pyruvate. When a patient has an elevated lactate not explained by hypoxemia, global and regional hypoperfusion must be excluded immediately. If the physical examination and central or mixed venous oxygen saturations (see below) are normal (suggesting normal cardiac output), ischemic bowel or extremity compartment syndrome must be considered, as should "occult sepsis," certain drugs, or liver disease.

Central Venous Catheterization

Since most patients with ARF require a central venous catheter (CVC) for administration of medications, no additional rationale or risk-benefit considerations are required to justify insertion of the line. However, the type of catheter inserted determines the extent of monitoring permitted. All

CVCs, regardless of lumen diameter or length, can be used to transduce central venous pressure (CVP) and measure central venous blood oxygen saturation (Scv_{O_2}), a surrogate for true mixed venous oxygen saturation (Sc_{O_2}). However, in order to monitor Scv_{O_2} continuously, a special oximetric catheter (Pre-SEP, Edwards Scientific) is required.

The internal jugular (IJ) or subclavian vein (SV) is the preferred access site, since femoral lines are associated with increased rates of infection and deep venous thrombosis. The choice between SV and IJ sites is dependent on many factors, but, in general, the IJ is safer because the vein is compressible, amenable to ultrasound localization, and associated with a reduced rate of pneumothorax. However, the Centers for Disease Control and Prevention (CDC) recommends the SV site over the IJ because of a presumed lower risk of infection. Both sites are reasonable, and the decision is a function of specific patient issues and operator experience and preference.

Central Venous Pressure

CVP is the downstream pressure that governs the rate of venous return to the right heart; it represents a good approximation of mean right atrial (RA) pressure. CVP can be measured accurately through a variety of catheter types, including triple lumen, tunneled, and percutaneously placed varieties. Commonly employed CVP catheter sites include the IJ, subclavian, and femoral veins.

CVP has been used to assess volume status in the diagnosis and management of shock and to infer the etiology of pulmonary edema. However, numerous studies have demonstrated flaws in this approach. Although, in some cases, a very low (less than 5 mmHg) or a very high (greater than 20 mmHg) CVP may be helpful in guiding decisions about volume status, in most patients, a single CVP value is rarely helpful.

The central venous or RA pressure is the pressure within the RA relative to atmospheric pressure. However, right ventricular preload, which is best defined as right ventricular end-diastolic volume (RVEDV), is equally dependent on the extracardiac (i.e., intrathoracic) pressure and right ventricular compliance, neither of which can be determined reliably at the bedside. Applied or intrinsic PEEP and intra-abdominal hypertension, among other conditions, may also increase extracardiac pressure.

Even if CVP correlated with RVEDV, the latter correlates poorly with LVEDV in patients with ARF because of discordance in ventricular afterload and contractility. Indeed, lung disease and the PEEP used to treat it increase pulmonary vascular resistance and may produce right ventricular failure. Furthermore, since the pericardium limits ventricular dilatation, ventricular interdependence further increases the disparity in LVEDVs and RVEDVs when differential contractility or loading conditions are present. This occurs because ventricular dilatation displaces the septum laterally and compresses the adjacent ventricle. Use of CVP in lieu of measurement of pulmonary artery occlusion pressure (PAOP) in determining whether pulmonary edema is of cardiogenic or noncardiogenic origin is equally tenuous.

In contrast, measurement of dynamic changes in CVP and the diameters of the superior and inferior vena cavae in response to changes in intrathoracic pressure provides more clinically useful information about cardiac preload. The basis for these dynamic responses is similar to that discussed previously. Unfortunately, lack of standardization, rigorous validation of the techniques, or outcome studies preclude recommending routine clinical use.

Mixed Venous Oxygen Saturation

Normally, the circulation delivers oxygen to tissues at a rate sufficient to maintain an intracellular (mitochondrial) oxygen tension above a critical threshold. If oxygen delivery (D_{O_2}) fails to meet tissue oxygen requirements (V_{O_2}), shock exists and anaerobic metabolism ensues; if prolonged, cell death occurs.

If D_{O_2} decreases and tissue V_{O_2} remains constant, a reduction in the oxygen content in mixed venous blood (Sv_{O_2}) is observed, reflecting an increase in oxygen extraction which occurs as a result of increased diffusion. The reduced D_{O_2} causes mitochondrial and tissue P_{O_2} to fall, which, in turn, increases the gradient for oxygen diffusion from capillary blood to tissue. The result is a reduction in end-capillary and, hence, venous P_{O_2}.

Since blood flow to organs is not equally distributed, and since rates of oxygen utilization are heterogeneous among organs, the venous oxygen content of blood draining from organs varies. The mixed venous oxygen content measured in the pulmonary artery (Sv_{O_2}), which reflects "global" oxygen delivery, represents a weighted average of the product of blood flow and oxygen content from all organs. Thus, Sv_{O_2} is not sensitive to localized tissue ischemia (e.g., bowel ischemia)—an important limitation of this monitoring tool.

Based on an understanding of the determinants of Sv_{O_2}, the clinician can use the Fick equation (Eq. 1, below) to elucidate the mechanism of shock and, perhaps, to target therapy:

$$V_{O_2} = CO \times (\text{arterial } O_2 \text{ content} - \text{venous } O_2 \text{ content}) \quad (1)$$

where CO is cardiac output. Recalling that O_2 content of either arterial or venous blood is the sum of hemoglobin (Hgb)-bound oxygen (1.34 ml O_2/g Hgb × [Hgb]/100 ml blood × % hemoglobin saturation) and dissolved oxygen (0.003 ml O_2/mm Hg), the following expression (Eq. 2) for mixed venous O_2 is derived:

$$Sv_{O_2} \sim (\text{arterial } O_2 \text{ content} \times [\text{Hgb}] \times CO)/V_{O_2} \quad (2)$$

Thus, if Sa_{O_2} is stable, Sv_{O_2} decreases if either CO or [Hgb] decreases or V_{O_2} increases. Since Sa_{O_2} and [Hgb] are readily measured and changes in V_{O_2} can be grossly estimated, the cause of a decrease in Sv_{O_2} can usually be determined quickly. Compared with alternative methods of monitoring CO, Sv_{O_2} reflects the adequacy of CO relative to oxygen requirements, which is a more valuable measurement than is

the absolute CO. In this regard, Sv_{O_2} is also more sensitive than measurement of blood lactate (see below) as a measure of the adequacy of CO.

Goal-Directed Therapy

Recent studies indicate that when a central venous oxygen saturation (Scv_{O_2}) of greater than or equal to 70 percent is achieved early in the resuscitation of patients with severe sepsis, survival increases significantly. Indeed, achievement of this target as part of "goal-directed therapy" has been embraced by the critical care community, and a consensus guideline for treatment of sepsis has been published. The guideline, developed by experts from 11 multidisciplinary, international critical care societies, recommends routine monitoring of central venous oxygen saturation to guide initial resuscitation of patients with severe sepsis.

Pulmonary Artery Catheterization

The pulmonary artery catheter (PAC) was first introduced into clinical practice in 1970. Since that time, the PAC has been the most commonly used device for monitoring hemodynamics in critically ill patients. It is also the most controversial. The PAC represents a reference standard for testing the accuracy and precision of noninvasive methods of assessing volume status and hemodynamic parameters. Indeed, the breadth of directly measured and derived parameters obtained using a PAC is unparalleled. However, more recently, use of the catheter has been curtailed because of data suggesting increased complications with its use and no evidence of any benefit to patient outcome.

Pulmonary Artery Occlusion Pressure

The PAC is used to estimate right and left ventricular filling pressures, PAOP or "wedge" pressure, and cardiac output.

When the balloon of the catheter, "wedged" into a branch of the pulmonary artery, is inflated, a static column of blood is created downstream from the catheter tip, which extends to the point of confluence with other, unoccluded pulmonary veins. Without blood flow, a pressure drop across the static column of blood is absent, making the column a direct extension of the fluid column between the tip of the PAC and the pressure transducer. In the absence of disease in the pulmonary veins, left atrium, or mitral valve, the mean end-expiratory PAOP approximates left ventricular end-diastolic pressure (LVEDP). If "a" and "v" waves are visible in the transduced pressure recording, the mean value of the "a" wave (halfway between the top of the "a" wave and the bottom of x descent) is used to indicate the PAOP.

PAOP is also used to estimate pulmonary capillary pressure in determining whether pulmonary edema is due to increased capillary permeability or hydrostatic pressure. In contrast to measuring PAOP as an estimate of LVEDP, the mean of the end-expiratory tracing is always used, even when large "v" waves are present, since the systolic pressure spike ('v" wave) is transmitted with an equal contribution to the capillary hydrostatic pressure. If PAOP never exceeds 18 mmHg, hydrostatic pulmonary edema can be excluded; however, transient spikes in left atrial pressure occurring between normal PAOP measurements can be missed. A PAOP greater than 18 mmHg is consistent with a hydrostatic cause of pulmonary edema, but high-permeability edema cannot be excluded.

Cardiac Output

Cardiac output (CO) is measured routinely in the ICU using the thermodilution (TD) technique. The principle of TD is that by lowering the temperature of blood flowing through the right heart by injecting a bolus of saline at room temperature, the resultant change in blood temperature over time, as recorded by a thermistor at the distal port of the PAC (i.e., the area under the curve of a plot of temperature versus time), will provide an approximation of CO.

With TD, CO can be measured intermittently using manual methods, or continuously using automated techniques. The manual method is based on the average value determined from 4 to 6 successive 10-ml boluses of saline injected into the proximal right atrial port of the PAC. For continuous measurements a specialized catheter with a proximal thermal filament, which heats the blood repeatedly using a brief thermal pulse, is used. Although limitations of TD methods are recognized—most notably, errors in measurement in the setting of tricuspid regurgitation—the technique provides a reasonably accurate measurement of CO. Measurement of CO using TD and a PAC is considered the gold standard to which other CO technologies are compared.

CO can also be measured indirectly with the PAC using the Fick method, based on the fact that CO is equal to oxygen consumption (V_{O_2}) divided by the difference in O_2 content across the circulation (i.e., the arteriovenous O_2 difference). Since V_{O_2} is usually not measured directly, the method is limited by inaccuracies in estimating V_{O_2} using body surface area alone in a critically ill patient. Hence, in patients with ARF, CO should be measured using TD unless significant tricuspid regurgitation is present. Application of the Fick method may be reasonable when values obtained by TD are unexpected.

Oxygen consumption varies significantly over time in any given patient and among patients with ARF. Furthermore, since CO normally increases directly in proportion to V_{O_2} and inversely with hemoglobin concentration and O_2 saturation, no normal or range of normal for CO has been established in patients with ARF. Normalizing CO to body surface area for comparison with reference values is also tenuous. From a management perspective, the most important questions in these patients are whether CO is adequate for the patient's needs, whether CO can be improved with intravenous fluids, and whether fluid can be removed by diuresis or dialysis without significant compromise of CO.

Outcome Studies

In the mid-1990s, a study addressing the effectiveness of the PAC purported to show that use of the PAC increased

mortality. The report stimulated a great deal of concern about the safety and use of the PAC and promoted significant efforts at improving education about use of the catheter. Use of the PAC fell dramatically following publication of the study.

Subsequently, several randomized controlled trials were conducted to assess the value of the PAC in a variety of critically ill patients. The findings can be summarized as follows: use of the PAC does not alter patient outcome in patients undergoing high-risk surgery, those with septic shock, acute respiratory distress syndrome (ARDS) or CHF, or in patients deemed critically ill enough to require the PAC.

Cautions in Using Pulmonary Artery Catheters

Based on the outcome studies summarized previously, one can legitimately question whether the PAC should be used at all in patients with ARF. Proponents of PAC use cite several observations as the basis for their argument. The studies only evaluated whether use of the PAC improved overall outcome. None included explicit, standardized treatment protocols to direct patient management using the catheter. In addition, no systematic effort was made to minimize errors in measurement and interpretation of data, particularly errors due to respiratory variation (see below). In all but one of the studies inclusion criteria were based on disease or condition, rather than a specific clinical question, thus making it difficult to rule out a potential benefit with more selective application of the catheter.

Given all of the information provided by use of the PAC, why have studies failed to show improved patient outcomes? Several hypotheses have been proposed, including an adverse physical effect of the PAC, inaccurate data, and misinterpretation of data, promoting misguided therapeutic interventions. Although physical complications from use of the PAC are well recognized, most are related to insertion of the central venous catheter through which the PAC is inserted. The few physical complications attributable to PAC, itself, are rare. In contrast, studies do support the notion that inaccuracies in pressure measurements or misinterpretation of data may lead to misguided treatment decisions and adverse outcomes.

Studies using standardized tests demonstrate that clinicians from a variety of countries, disciplines, and levels of experience have inadequate knowledge about the PAC and difficulty reading pressure measurements accurately. In one study, the difficulty in reading tracings was due primarily to misidentification of end-expiration; interobserver variability in PAOP measurements was greatest when recordings showed marked phasic respiratory variation.

Traditionally, clinicians have been taught to record all vascular pressures at end-expiration in order to minimize the effect of intrathoracic (i.e., juxtacardiac) pressure. Unfortunately, widely available resources for PAC education have misleading instructions on identification of end-expiration; in particular, these resources suggest that end-expiration in patients on mechanical ventilation is defined by the lowest point on the vascular pressure waveform. However, it is well known that patients may actively inspire during assist-control

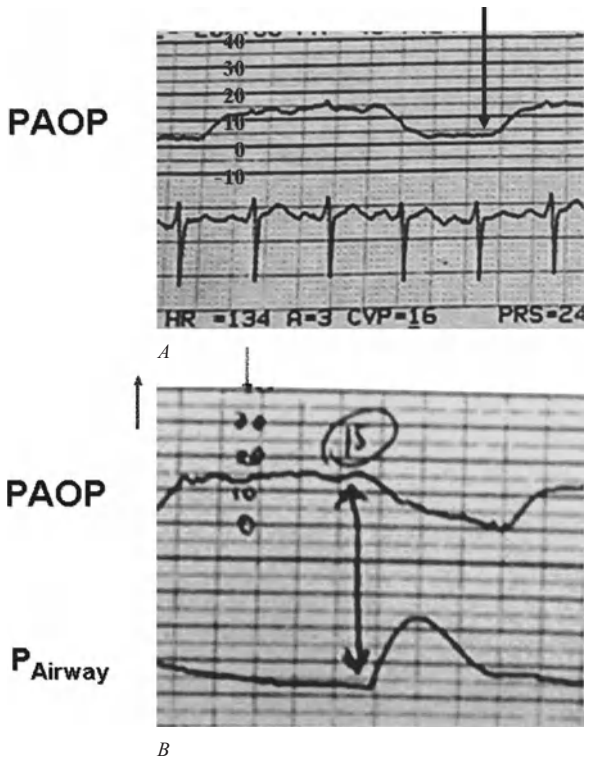

Figure 152-1 *A*. In this patient on mechanical ventilation in the AC-mode, pulmonary artery occlusion pressure (PAOP) is read conventionally at the lowest vascular pressure (arrow), which is 3 mmHg. *B*. With airway pressure (P_{AW}) displayed concurrently, in place of the electrocardiogram tracing, it becomes obvious that vascular pressure falls throughout inspiration due to inspiratory effort. The true end-expiratory time point is shown by the arrow, which is a PAOP of 15 mmHg.

mechanical ventilation, causing intrathoracic (and, hence, vascular) pressure to fall, rather than rise. Consequently, in such patients the lowest point on the vascular pressure waveform corresponds to end-inspiration, while end-expiration coincides with the highest point on the tracing (Fig. 152-1 *A*). Erroneous selection of the nadir pressure results in vascular pressure readings (including CVP and PAOP) that may markedly underestimate the true values; the magnitude of the error is proportional to patient inspiratory effort. The significance of this potential error has likely increased in the last 5 years because of a trend toward use of minimal sedation and reduced tidal volumes in patients with ARF, each of which may increase respiratory effort and further lower pleural pressure during inspiration.

Attempts to visually quantify and coordinate patient ventilatory efforts with the waveform displayed on a bedside monitor can be problematic, especially with higher respiratory frequencies observed in patients ventilated with lower tidal volumes. Addition of a simultaneous airway pressure (P_{AW}) signal to strip chart recordings of CVP and PAOP may provide a reliable signal for accurately timing end-expiration and significantly reduce interobserver variability (Fig. 152-1 *B*). Intensivists who use the PAC should consider concurrent

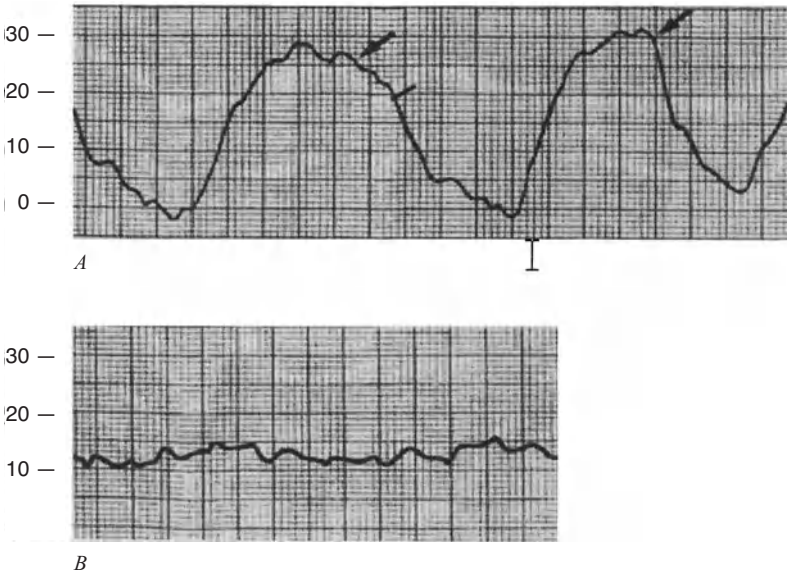

Figure 152-2 *A*. In this patient on mechanical ventilation in AC-mode, an airway pressure (P_{AW}) tracing (not shown) confirms that end-expiratory pulmonary artery occlusion pressure (PAOP) is 25 mmHg (arrows) with respiratory variation of greater than 20 mmHg. *B*. Immediately after paralysis with succinylcholine repeat PAOP is 12 mmHg with minimal respiratory variation.

monitor display of P_{AW} and vascular pressures when recordings show significant (greater than 8 mmHg) respiratory variation in CVP or PAOP.

Patients with significant phasic respiratory variation may also *exhale* forcefully, and significant errors in interpretation of hemodynamic data may occur despite measurement of P_{AW}. Expiratory muscle use during exhalation increases abdominal pressure, which is transmitted directly across the relaxed diaphragm, resulting in increased end-expiratory pleural pressure. This, in turn, increases all vascular pressures in the thorax. Since transmural filling pressures of the right and left ventricles are unchanged, if unrecognized, forced expiration causes CVP and PAOP to be overestimated by an amount directly proportional to expiratory muscle effort (Fig. 152-2).

The significance of forced expiration raises two important questions:

1. How does one account for the effect of forced expiration when interpreting CVP or PAOP?
2. How does one recognize when forced expiration is present?

With regard to the first question, studies performed in patients with significant respiratory variation in PAOP demonstrated that the PAOP before and after muscular paralysis was similar to the PAOP measured as the midpoint between values recorded at end-expiration (peak) and end-inspiration (nadir) prior to paralysis—a value more closely approximated by the mean PAOP (Figs. 152-2 and 152-3).

Recognition of forced expiration is necessary to determine when to apply this "midpoint" rule in the measurement of PAOP. In the absence of significant (greater than 8 mmHg) respiratory variation in PAOP, one can rule out forced expiration. Abdominal inspection and palpation usually confirm forced expiration if inward movement of the lateral and anterior abdominal walls occurs during expiration. Of note, if significant respiratory variation occurs in the absence of forced expiration (from isolated inspiratory muscle effort alone), the pressures read at end-expiration are accurate. If it is not clear from the physical examination whether forced expiration is present, simultaneous measurement of CVP or PAOP and intra-abdominal pressure can be performed. Forced expiration is easily identified if PAOP and intra-abdominal pressure increase concordantly during expiration (Fig. 152-4), and is ruled out if the phasic changes in the two pressure recordings are discordant.

Additional factors may result in misinterpretation of PAOP as an estimate of left ventricular preload. For example, PAOP may correlate poorly with LVEDV because of alterations in juxtacardiac pressure (e.g., from increases from set or occult PEEP or intra-abdominal hypertension) or ventricular compliance (e.g., due to ischemia or hypoxia). Finally,

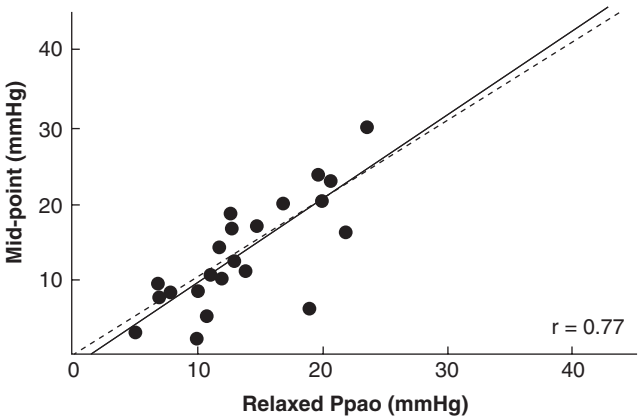

Figure 152-3 Relationship between the relaxed pulmonary artery occlusion pressure (PAOP) (post-paralysis) and the midpoint PAOP (obtained during active respiratory effort). (*From Hoyt JD, Leatherman JW: Interpretation of the pulmonary artery occlusion pressure in mechanically ventilated patients with large respiratory excursions in intrathoracic pressure.* Intensive Care Med *23:1125, 1997.) (Reproduced with permission.)*

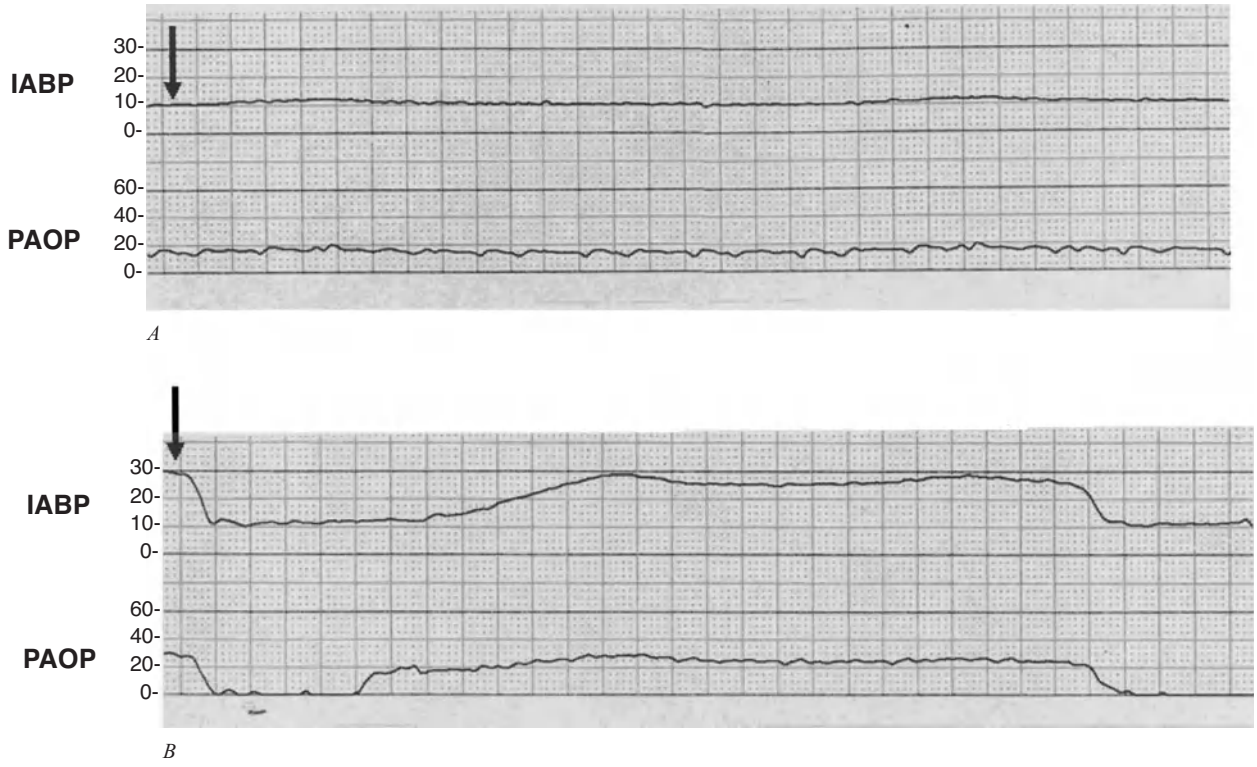

Figure 152-4 Arrows indicate end-exhalation. *A*. In this strip chart recording from a patient on AC-mechanical ventilation, there is minimal respiratory variation in pulmonary artery occlusion pressure (PAOP). Note, intra-abdominal blood pressure (IABP) rises during inhalation and falls during exhalation, paralleling the change in PAOP. *B*. On the same ventilator settings with less sedation, there is marked respiratory variation (~30 mmHg) in PAOP. PAOP falls during inspiration consistent with active respiratory effort. Forced exhalation is confirmed by seeing a rise in IABP during exhalation (~20 mmHg), in parallel with the PAOP. If IABP falls during exhalation in this setting, forced exhalation can be ruled out (not shown).

because of pericardial constraint of ventricular enlargement, right ventricular overload may cause PAOP and LVEDV to change reciprocally (increases in PAOP associated with decreases in LVEDV).

Given the limitations of using pressure measurements to estimate cardiac preload (end-diastolic volume), a modified PAC was developed to allow continuous measurements of RVEDV using TD. The catheter contains a proximally located thermal filament which emits thermal pulses to heat the blood, while a sensitive and rapidly responsive thermistor located at the distal end of the catheter records temperature in the pulmonary artery. Input from the electrocardiogram allows timing of ventricular systole and a beat-to-beat analysis of the temperature decay curve. Right ventricular ejection fraction is computed from the exponential slope of the temperature decay curve and mean heart rate; RVEDV is calculated as stroke volume divided by ejection fraction. Studies have shown that RVEDV correlates well with CO, and specified thresholds of RVEDV may distinguish patients with hypovolemia who are fluid-responsive. However, other studies have not corroborated these thresholds and have failed to show that RVEDV can reliably predict preload responsiveness. Thus, routine use of these catheters cannot be recommended.

Even if the problems with measuring, recording, and interpreting PAOP and CO could be eliminated, PAC-guided care will likely be limited by lack of standardized guidelines for treatment based on the hemodynamic data obtained.

Noninvasive Alternatives to the Pulmonary Artery Catheter

A variety of noninvasive techniques, including echocardiography, have been used as alternatives to PACs. They are described briefly below.

Echocardiography

Echocardiography is the most commonly used technique for cardiac imaging in critically ill patients, providing unique and important diagnostic information for the evaluation of shock, including assessment of biventricular volumes, contractility, valvular function, and pericardial anatomy.

In patients who are adequately resuscitated, but who continue to have low output shock, early use of echocardiography to assess biventricular volumes and function is important. In the setting of an elevated PAOP and low CO, systolic dysfunction cannot be differentiated from any of the many states of ventricular compression, including cardiac

tamponade, massive pleural effusion, mediastinal fluid collections, auto-PEEP, pneumothorax, or ventricular interdependence. When right ventricular dysfunction is suspected as the primary cause of shock, echocardiographic findings may assist in establishing the etiology.

The presence of pulmonary arterial hypertension, which can be estimated in most critically ill patients, suggests pulmonary embolism, nonthrombotic pulmonary embolism, ARDS, or severe lung hyperinflation; right ventricular infarction is unlikely. Furthermore, in the setting of pulmonary hypertension, the echocardiogram may point to an acute process (e.g., pulmonary emboli, rather than chronic pulmonary hypertension), if regional akinesia of the right ventricular free wall and normal apical wall motion is found ("McConnell sign"). The diagnosis of acute pulmonary embolism is highly likely if a free floating clot is seen in the right atrium or ventricle, and the diagnosis is confirmed if a clot is visualized in the proximal pulmonary arteries.

Both volumetric and Doppler-based techniques have been developed to allow echocardiographic estimates of cardiac preload and CO. Volumetric measurements using two-dimensional imaging of ventricular size during diastole and systole provide the basis for estimates of preload, stroke volume, and contractility. Signs of hypovolemia on the two-dimensional echocardiogram include a hyperdynamic ventricle and appearance of "kissing walls" at end-systole. CO can be determined using volumetric estimates of stroke volume, calculated as the difference in end-systolic and end-diastolic volumes. However, Doppler-based measurements of CO are more accurate.

The Doppler method relies on the principle that flow in a cylinder (e.g., the aorta) is equal to cross-sectional area of the aorta times the blood-flow velocity. Velocity, in turn, is determined according to the principle that when ultrasonic waves are emitted perpendicular to flowing blood, the change in frequency of the sound waves reflected back is proportional to the blood-flow velocity. Stroke volume is derived from these two measurements; when multiplied by heart rate, CO is determined. Doppler-based estimates of CO have been shown to correlate reasonably well with those obtained by TD.

Doppler techniques can also be used to estimate PAOP by assessing the relative velocity of blood flow through the mitral valve during early and late diastole. However, estimates of PAOP using this technique do not correlate well with direct measurements using a PAC. In any event, given the limitations of PAOP as a measure of preload, there is little utility in estimating PAOP using this technique, except to provide a rough estimate about whether or not pulmonary edema is on a cardiogenic basis.

Echocardiography is performed at the bedside using either the transthoracic esophageal (TTE) or transesophageal (TEE) routes. Since rapidity of diagnosis is important, TTE is the initial study of choice in the ICU, given the technique's widespread availability. TTE provides adequate assessment in the vast majority of mechanically ventilated patients; morbid obesity and emphysema may necessitate TEE. TEE is also recommended as the initial study to rule out aortic dissection. Although considered a very low-risk procedure, TEE is not risk free. TTE is associated with trauma to the upper gastrointestinal tract and is contraindicated in patients with known or suspected pathology of the esophagus or cervical spine.

One of the major limitations of both TTE and TEE is that neither allows for continuous hemodynamic monitoring. To fill this need, an esophageal catheter with a distal Doppler probe that allows measurement of CO continuously has been developed. The device is easy to use and eliminates the need for a specialist in Doppler signal acquisition, although some operator experience is required to ensure proficiency. Numerous studies have evaluated the accuracy of these devices relative to TD-based assessment of CO. A recent review concluded that esophageal Doppler does not provide accurate assessment of absolute CO, but its validity is high for monitoring changes in CO in critically ill patients.

Finally, imaging dynamic changes in the diameter of the central veins and assessment of the velocity of aortic blood flow may predict preload responsiveness. Using portable echocardiography in completely sedated patients in septic shock respiratory collapse of the inferior or superior vena cavae in response to a large (8 to 10 ml/kg) mechanically delivered breath suggests hypovolemia and potential fluid responsiveness.

In conclusion, bedside echocardiography is the diagnostic study of choice for unexplained or persistent circulatory shock. For patients who require continuous monitoring of CO, esophageal Doppler is a reasonable alternative to a PAC. The technique can be used to guide fluid resuscitation for optimization of CO in acute shock and guide a diuresis strategy to minimize pulmonary edema without adversely affecting peripheral perfusion. Although esophageal Doppler monitoring has been increasingly used as a substitute for a PAC, we still favor use of the PAC over esophageal Doppler for monitoring hemodynamics continuously in selected patients.

Other Methods

Several other noninvasive methods have been developed for determining CO, including expired carbon dioxide (CO_2) analysis (indirect Fick method), lithium dilution method, measurement of thoracic impedance, and pulse contour analysis. The techniques are approved by the Food & Drug Administration (FDA) and are currently available, but none have been validated sufficiently to justify their routine use in critically ill patients.

Indirect Fick Method

By imposing a brief period of partial rebreathing through the addition of dead space to the breathing circuit, changes in CO_2 elimination and end-tidal CO_2 concentration can be effected. Comparison of the new resultant steady-state values compared to baseline allows calculation of CO using the Fick principle. The technique has serious limitations in patients

with ARF. Spontaneous breathing and hypocapnea limit its accuracy. Steady-state conditions must be achieved to assure accuracy, and intrapulmonary shunt affects the sensitivity of the measurement.

Thoracic Electrical Bioimpedance

Thoracic electrical bioimpedance is based on the principle that the chest is an electrical conductor whose impedance is altered by changes in blood volume and blood-flow velocity with each heartbeat. By placing electrical current-transmitting and voltage-sensing electrodes on the chest, stroke volume may be calculated based on an equation incorporating values for the baseline and maximum rate of change in chest impedance. Unfortunately, although noninvasive, measurement of thoracic electrical bioimpedance is confounded by too many factors in patients with ARF to support its routine clinical use.

Transpulmonary Indicator Dilution Techniques: Thermodilution and Lithium Dilution

Transpulmonary indicator dilution techniques are based on intravenous injection of an indicator solution (e.g., cold saline or lithium chloride) and measurement of the change in temperature or lithium concentration, respectively, over time using a special arterial catheter. For the TD technique, the catheter is equipped with a thermistor at its tip; for the lithium-based technique, blood samples must be drawn successively for external measurement using a lithium-sensitive electrode. The greater the degree of indicator dilution (i.e., the *less* the change in temperature or lithium concentration) over time, the greater the CO. Values derived from each of these techniques correlate well with PAC-determined values. However, more data are needed to determine the accuracy of these techniques under a wide variety of clinical conditions.

Pulse Contour Analysis

This method is based on the concept that changes in the contour of the arterial pressure waveform are proportional to stroke volume and are dependent on the mechanical properties of the aorta. Since the latter is relatively constant from beat to beat, changes in the pulse pressure correlate with changes in stroke volume. The technique requires calibration with an independent measurement of CO—currently accomplished by combining the indicator dilution technique (to determine mean CO) with assessment of beat-to-beat variability in the arterial pressure waveform (as a measure of stroke volume). Most studies have shown fair to good agreement of the technique with that of PAC-based measurements. Major limitations include the requirements for a femoral or axillary arterial catheter and frequent recalibration in patients who are hemodynamically unstable. Although the technique is promising, more studies are required to validate its usefulness and applicability in critically ill patients with ARF.

METHODS FOR MONITORING RESPIRATORY FUNCTION

A number of respiratory parameters are routinely monitored in patients with ARF and are discussed briefly below.

Oxygenation

In the ICU, oxygenation is generally monitored using pulse oximetry, arterial blood gas analysis, or transcutaneous methods.

Pulse Oximetry

Pulse oximeters are universally deployed in the monitoring of perioperative and critically ill patients. Unique as monitoring devices, they provide useful data regarding oxyhemoglobin saturation (Sp_{O_2}), heart rate, pulse volume, and tissue perfusion.

Pulse oximeters use the spectrophotometric characteristics of pulsatile arterial blood to determine oxygen saturation and heart rate. Oxygenated blood absorbs light at 660 nm (red light), while deoxygenated blood absorbs light preferentially at 940 nm (infrared light). The oximeter consists of two light-emitting diodes (wavelengths, 600 nm and 940 nm) and two light-collecting sensors that measure the amount of red and infrared light emerging from tissues traversed by the light rays. The relative light absorption by oxyhemoglobin and deoxyhemoglobin is analyzed by the device and an oxygen saturation is calculated. The sensing function of the device is directed at pulsatile arterial blood, while local "noise" arising from the tissues is ignored. The result is a continuous qualitative measurement of oxyhemoglobin saturation.

Use of pulse oximetry has not been shown to improve clinical outcomes, but epidemiological data have demonstrated a significant reduction in anesthesia-related morbidity. Although the technique accurately predicts arterial oxygen tension, the relationship between Pa_{O_2} and Sp_{O_2} is nonlinear, as dictated by the oxyhemoglobin dissociation curve. Accuracy falls off substantially at low-oxygen tensions, and saturation readings of less than 80 percent cannot be used reliably to guide oxygen therapy.

The use of pulse oximeters is limited by a number of factors. The devices are designed to measure levels of oxygenated and deoxygenated hemoglobin, but no provision is made for measurement error in the presence of dyshemoglobinemias, including carboxyhemoglobinemia and methemoglobinemia. Since carboxyhemoglobin absorbs red light, conventional oximeters cannot distinguish oxy- from carboxyhemoglobin. In clinical situations where carbon monoxide poisoning is suspected, co-oximetry is essential. Co-oximeters measure reduced hemoglobin, oxyhemoglobin, carboxyhemoglobin, and methemoglobin.

An additional source of error in using oximeters is abnormal patient movement (e.g., due to agitation). Low blood flow, hypotension, vasoconstriction, or hypothermia reduce pulsatility of capillary blood, resulting in underreading or

no reading of oxygen saturation. Conversely, increased venous pulsation, such as occurs with tricuspid regurgitation, may result in an erroneously low reading by the device. Finally, oximetry-determined saturation is inaccurate on the steep part of the oxyhemoglobin dissociation curve. While the *trend* between directly measured arterial saturation and Sp_{O_2} appears accurate, the correlation between the two is not; a drop in Sp_{O_2} below 90 percent must be considered a potentially significant clinical event.

Arterial Blood Gases

Blood gas analyzers have been available for 40 years and provide accurate measurement of Pa_{O_2}, Pa_{CO_2}, and pH. From these primary determinations, a number of parameters are calculated, including serum bicarbonate, base deficit or base excess, and oxyhemoglobin saturation.

Through application of the alveolar gas equation (see Chapters 11 and 34) arterial blood gas analysis is used commonly in calculating the alveolar-arterial oxygen gradient, a number that reflects the severity of ventilation-perfusion abnormalities. A significant limitation of the alveolar-arterial oxygen gradient is that it varies directly with FI_{O_2}; consequently, changes in the value may not reflect changes in the underlying disease process. An alternative calculation—the ratio of Pa_{O_2} to FI_{O_2}, ("PF ratio"), which does not vary with FI_{O_2}—has been used as a measure permitting comparisons of gas exchange at differing levels of FI_{O_2}.

The PF ratio has been incorporated into consensus definitions of ARDS and acute lung injury (ALI). A PF ratio less than or equal to 300 defines ALI; a ratio less than or equal to 200 defines ARDS. Neither the alveolar-arterial oxygen gradient nor the PF ratio takes into account differences in mean airway pressure. Although comparisons using the PF ratio would be more accurate if arterial blood was sampled uniformly at end-expiration and in the absence of PEEP, clinical constraints may preclude such sampling conditions.

Transcutaneous Oxygen Monitoring

The commonly employed oxygen electrode is based on a modification of the electrode developed in 1956. The device is constructed of a platinum wire tip surrounded by glass. Covered by a polyurethane membrane which is permeable to oxygen, the electrode responds in a linear fashion to oxygen in the gaseous or liquid phase over a concentration range of 1 to 100 percent. The margin of error is less than 1 percent.

Although the oxygen electrode has been employed predominantly for blood gas measurements, it can be modified for use in the continuous, noninvasive measurement of transcutaneous oxygen tension (Ptc_{O_2}). Electrode heating of the skin changes the structure of lipoproteins in the stratum corneum from the gel to the sol state, allowing rapid diffusion of oxygen from subcutaneous tissues through the skin. In addition, electrode heating prevents local vasoconstriction, ensuring that Ptc_{O_2} closely reflects Pa_{O_2}. In hemodynamically stable patients who have good tissue perfusion, Ptc_{O_2} accurately represents P_{O_2}; however, the values are not identical, with Ptc_{O_2} approximately equal to 80 percent of Pa_{O_2}. Under conditions of hypoperfusion, the relationship may vary dramatically. In addition, various tissues have different values for Ptc_{O_2}, depending on local perfusion, skin thickness, and anatomic location (e.g., trunk versus limb). In order to prevent burns, the electrodes must be changed every 4 to 6 h, and the membrane must be changed and calibrated before each use. Despite these limitations and lack of widespread use, transcutaneous oxygen monitoring remains a useful device in multicomponent oxygen monitoring systems.

Ventilation

Clinical assessment of CO_2 metabolism is usually considered with regard to the amount of gas that is dissolved in plasma (Pa_{CO_2}), the amount present in the exhaled tidal volume (end-tidal CO_2), and the total extracellular content (total CO_2 or bicarbonate concentration). In the setting of respiratory failure, these measurements provide information on adequacy of ventilation, percentage of physiological dead space, acid-base balance, and nutritional status.

In progressive chronic respiratory failure, as the ability to eliminate CO_2 declines, total body CO_2 stores (bicarbonate) increase. The ratio of total CO_2 to bicarbonate concentration provides an indication of the acuity of the respiratory failure. Changes in Pa_{CO_2} may also be related to changes in base deficit or excess.

Assessment of CO_2 elimination forms the basis of calculating the ratio of dead space to tidal volume—a useful physiological construct in gauging the severity of underlying lung disease in respiratory failure. Through application of the modified Bohr equation (see Chapter 34), the ratio of dead space to tidal volume (V_D/V_T) is calculated in Eq. (3) as follows:

$$V_D/V_T = (Pa_{CO_2} - PE_{CO_2})/Pa_{CO_2} \qquad (3)$$

where PE_{CO_2} is mean expired CO_2. PE_{CO_2} can be measured using a metabolic monitor that collects expired gas over 5 min. Alternatively, main stream or side stream capnometry can be used to measure PE_{CO_2}.

In the normal lung, alveolar P_{CO_2} is equivalent to Pa_{CO_2} and can be estimated by sampling expired end-tidal gas. However, in the presence of significant physiological dead space (as in ARF), end-tidal CO_2 grossly underestimates Pa_{CO_2}. Given this limitation, aside from confirming endotracheal tube placement, end-tidal CO_2 measurements are not used routinely in managing patients with ARF.

Endotracheal Tube Placement

Monitoring endotracheal tube (ETT) position is an important aspect of critical care. An extremely common complication of intubation is misplacement of the ETT, with passage into the right main bronchus. Ideally, the ETT tip should be located 4 to 5 cm above the carina. In the case of a tracheotomy,

the tube tip should be located about halfway between the tracheotomy stoma and the carina.

ETT placement can be confirmed in several ways: (1) by assessing for the presence of bilateral breath sounds during breath delivery, (2) by palpation of the ETT cuff in the jugular notch, (3) with chest radiography, or (4) using fiberoptic bronchoscopy.

In addition to tube placement, pressure within the ETT cuff should be measured regularly. The cuff is inflated to create a seal between the side wall of the ETT and the tracheal wall. Since capillary perfusion pressure of the tracheal mucosa is approximately 25 cm H_2O, cuff pressure should be kept below this level to prevent ischemia, which may lead to ulceration, inflammation, and, if severe, tracheal dilatation. In addition, the injured tracheal segment may develop fibrosis and, ultimately, stenosis. On the other hand, evidence exists that low cuff pressures may increase the risk of pneumonia, presumably by promoting microaspiration. Thus, the current recommendation for optimal tracheal cuff pressure is 20 to 25 cm H_2O.

Following intubation and ETT positioning, the tube cuff should be slowly and progressively inflated just to the point of loss of gas leak occurring with ventilation—the so-called "minimal occluding pressure" technique (some experts advocate use of the "minimal leak" technique). To measure cuff pressure, an aneroid manometer is connected to the cuff's pilot tube (the tube from which the balloon is inflated). If excessive cuff pressure is required to maintain an adequate tracheal seal, the ETT is likely too narrow for the patient's trachea. If cuff pressure increases over time, tracheomalacia should be suspected and the tube changed to one with a foam cuff.

The presence of a cuff leak may be problematic, particularly in patients who are critically ill. Signs of leak include an audible noise during inspiration, audible patient phonation, frothy mouth secretions with each breath, a difference between set and exhaled tidal volumes, inadequate ventilatory volumes, hypoxemia, and the presence of a thrill over the trachea. Cuff leaks may be caused by rupture or herniation of the cuff, proximal displacement of the ETT, pilot tube valve malfunction, or inadvertent cuff deflation.

Respiratory System Mechanics

Assessment of respiratory system mechanics may be useful in differentiating the etiology of ARF (e.g., restrictive versus obstructive disease or upper versus lower airway obstruction), troubleshooting the cause of new episodes of clinical instability, assessing the effectiveness of therapeutic interventions (e.g., use of bronchodilators or application of PEEP), or minimizing the risk of ventilator-induced lung injury.

Airway Pressure

Airway pressure is an important variable which is routinely monitored during mechanical ventilation. Respiratory pressures are usually referenced to atmospheric pressure ("single-ended" pressures). Electromechanical transducers (or aneroid manometers), which convert pressure to electrical current, may be located in the patient's ventilator circuit or esophagus. The most common site of pressure transduction is the wye connector (the connector that joins the inspiratory and expiratory limbs of the ventilator circuit), although the distal ETT can also be used. Pressure measured within the ventilator or ventilator circuit is referred to as "airway pressure," P_{AW} (or, more correctly, airway opening pressure, P_{AO}), while that measured at the tip of the ETT is referred to as "tracheal pressure," P_{TR}. Pressure measured within the esophagus is referred to as "esophageal pressure," P_{ES}.

Five different pressure measurements are commonly made during the respiratory cycle: (1) peak airway pressure (P_{PEAK}), (2) plateau pressure (P_{PLAT}), (3) mean airway pressure (P_{MEAN}), (4) positive end-expiratory pressure (PEEP), and (5) auto-PEEP (also called intrinsic PEEP). Measurement of tracheal pressure at the tip of the distal ETT provides an assessment of pressure in the native airway, as the effect of flow through the ETT is eliminated. Esophageal pressure provides an estimate of pleural pressure. Although not used routinely in clinical practice, esophageal pressure can be used to estimate transpulmonary pressure, which is a more accurate measure of alveolar distending pressure than is plateau pressure.

Accurate measurement of airway resistance requires that airway pressures be determined using constant flow conditions (i.e., a square flow-wave profile) (Fig. 152-5). Most modern ventilators make the flow-wave profile adjustment automatically when the "mechanics function" of the device is selected. In addition, since airway pressures are altered by respiratory muscle contraction, patients must be fully relaxed and exert minimal breathing effort. These conditions may be accomplished by using ventilator settings designed to fully support the patient (e.g., by providing a level of ventilatory support that exceeds patient demand, or administration of sedation). For quality control, ventilator waveforms should

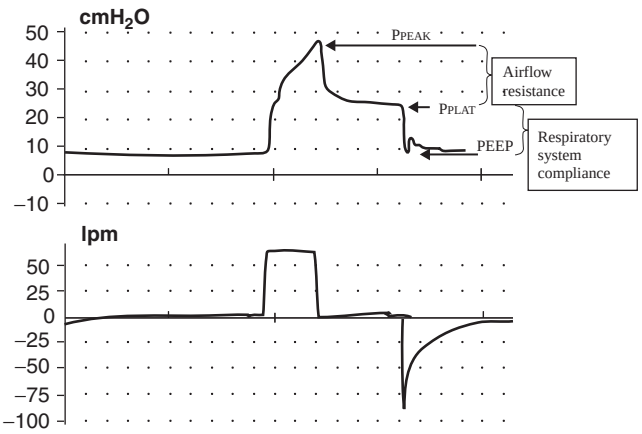

Figure 152-5 Inspiratory hold maneuver during constant flow in a volume-controlled breath. Note the significant difference between the patient's peak airway pressure (48 cm H_2O) and plateau pressure (26 cm H_2O), indicative of increased airways resistance.

be assessed during the mechanics maneuver to ensure the conditions have been met.

P_{PEAK} represents the total pressure the ventilator must generate in order to overcome the impedance of the respiratory system, including airflow resistance, elastic load (lung and chest wall distention), and any threshold load due to dynamic hyperinflation (from auto-PEEP). When interpreting P_{PEAK}, in addition to impedance, several other factors must be considered, including peak flow rate, waveform profile (square or decelerating), and tidal volume. This is a very important point in clinical practice, since P_{PEAK} may erroneously be considered as the primary determinant of barotrauma. When a high P_{PEAK} is observed (as commonly seen in obstructive lung diseases), an attempt to lower P_{PEAK} by reducing inspiratory flow rate may achieve the opposite effect. The risk of barotrauma may be increased by the resulting increment in plateau pressure that occurs as a consequence of reduced expiratory time and increased auto-PEEP.

P_{PLAT} reflects the pressure within the alveoli at end-inhalation and is the most important pressure to monitor in preventing barotrauma. The goal is less than or equal to 30 mmHg in all cases of ARF, including those due to obstructive airway disease. P_{PLAT} is measured at end-inspiration during a period of zero flow, which is achieved by applying an inspiratory "hold" during volume-controlled ventilation (see Fig. 152-5). P_{PLAT} is always lower than P_{PEAK} by an amount equal to the pressure required to drive inspiratory flow through the ventilator circuit, ETT, and airways.

For the patient with a high P_{AW}, the clinician can determine rapidly whether the problem is resistive (airway) or elastic (lung or chest wall) in nature by assessing the pressure gradient between P_{PEAK} and P_{PLAT} and between P_{PLAT} and total PEEP (set PEEP plus auto-PEEP) (see Fig. 152-5). For instance, if the differential between P_{PEAK} and P_{PLAT} increases, airflow resistance must have increased; potential causes include bronchospasm, a kink in the ETT, and increased airway secretions. In contrast, if the rise in P_{AW} is unaccompanied by an increase in the P_{PEAK}–P_{PLAT} pressure gradient (i.e., both P_{PEAK} and P_{PLAT} increase relative to total PEEP), the elastic load must have increased; causes include loss of lung volume (e.g., right main bronchus intubation; lobar atelectasis; or an alveolar filling process, such as pneumonia or CHF) or a stiffer chest wall apparatus (e.g., pleural effusion or intra-abdominal hypertension).

These routinely measured airway pressures are also used to calculate additional important measures of respiratory mechanics, including airway resistance and respiratory compliance.

Dividing the P_{PEAK}–P_{PLAT} pressure gradient by inspiratory flow rate yields *airway resistance*. The normal value depends on the size of the ETT, but it is typically about 5 to 15 cm H_2O/L/s.

Respiratory system compliance, expressed as ml/cm H_2O, is calculated as tidal volume divided by the difference between P_{PLAT} and total PEEP. Failure to consider auto-PEEP in the calculation results in overestimation of compliance. Normal respiratory system compliance is greater than 60 ml/cm H_2O.

Auto-PEEP

Auto-PEEP (also known as "intrinsic" PEEP) refers to the positive pressure within alveoli at end-expiration that has not been generated by a ventilator. A form of naturally occurring auto-PEEP may be observed with forced exhalation that occurs during heavy exercise. In this case, lung mechanics may be normal, and expiratory muscle force maintains positive intrathoracic and airway pressures throughout expiration; functional residual capacity (FRC) may be normal or decreased.

In contrast, two other types of auto-PEEP are associated with dynamic hyperinflation. In one, auto-PEEP results from a high minute ventilatory requirement, as occurs in ARDS, where insufficient expiratory time promotes incomplete expiration before delivery of the next breath. In the other, more common variety, auto-PEEP results primarily from delayed emptying of alveoli due to airflow obstruction, as most commonly seen in status asthmaticus or an acute exacerbation of chronic obstructive pulmonary disease.

The development of auto-PEEP is determined by three factors: tidal volume, expiratory time, and the respiratory system expiratory time constant (the product of resistance and compliance). Auto-PEEP poses significant problems in pressure-targeted mechanical ventilation, where the additional PEEP reduces ventilator driving pressure, and consequently, tidal volume. In contrast, in volume-targeted ventilation, auto-PEEP causes P_{AW} and P_{PLAT} to increase, which, in turn, increase end-inspiratory lung volumes and alveolar "stretch."

In a mechanically ventilated patient, auto-PEEP is most easily identified by examining the ventilator flow waveform and observing that expiratory flow does not return to zero before initiation of the next breath (Fig. 152-6). Quantification of the magnitude of auto-PEEP is achieved by implementing a prolonged "expiratory hold" maneuver, during which equilibration of pressure throughout the ventilatory circuit is achieved (Fig. 152-7). A mechanically ventilated patient who is generating spontaneous breaths presents a challenge for measurement of auto-PEEP, as airway occlusion usually incites increased respiratory drive. Under these circumstances, an esophageal balloon catheter may be used to estimate pleural pressure, and auto-PEEP calculated by measuring the magnitude of the negative deflection in esophageal pressure from the start of inspiratory effort to onset of inspiratory flow. This method underestimates auto-PEEP in patients with significant airway obstruction.

If auto-PEEP arises as a result of hyperinflation due to expiratory flow limitation in a spontaneously breathing, ventilated patient, external PEEP upto, but not exceeding, the level of auto-PEEP can be applied to offset the increased work of breathing associated with the additional inspiratory threshold load. The applied PEEP does not impact expiratory flow or lung volume. The applied PEEP should be no greater than 85 percent of the measured auto-PEEP.

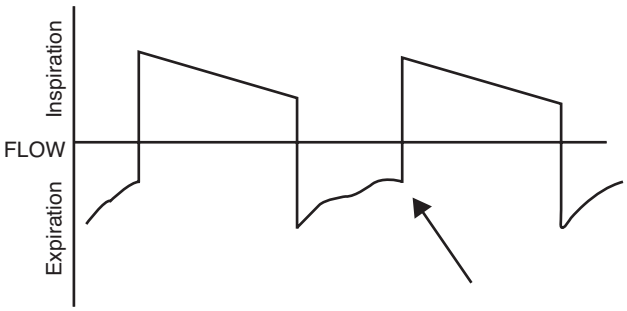

Figure 152-6 The presence of auto-PEEP is identified from the flow waveform. The next breath commences before expiratory flow returns to zero.

Pressure-Volume Curves

In the normal lung, compliance is greatest at FRC, decreasing progressively as lung volume increases (Fig. 152-8). In patients with diffuse parenchymal lung disease (e.g., ARDS) FRC declines, and pressure application at low lung volume yields little increase in volume. With increasing levels of inflation pressure, a point is reached (the lower inflection point, or LIP) beyond which compliance improves dramatically. With further increments in inflation pressure, another point is reached beyond which the pressure-volume curve flattens, defining the upper inflection point (UIP).

A significant reduction in mortality has been demonstrated in patients with ARF using PEEP levels greater than LIP as part of a ventilator protocol based on pressure-control, inverse-ratio, and pressure-limited techniques. The findings may relate to a reduction in the lung injury thought to be related to phasic opening and closing of lung units ("atelectrauma") and resulting epithelial disruption, local inflammation, cytokine release, and tissue destruction. Therefore, some have advocated as an optimal ventilation strategy for minimizing ventilator-induced lung injury (VILI) application of

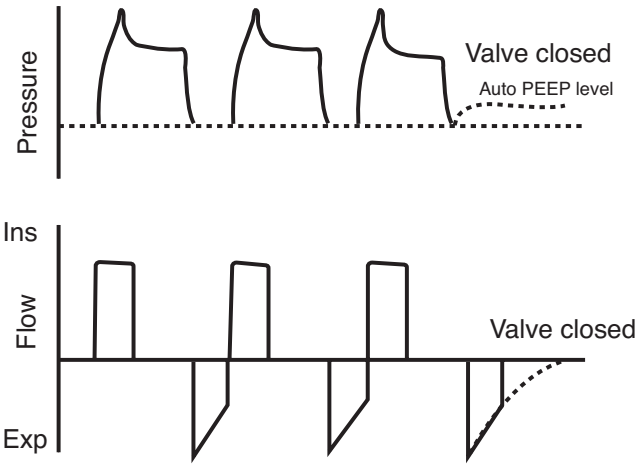

Figure 152-7 Expiratory hold technique to quantify auto-PEEP. The expiratory valve is closed during an expiratory "hold" at the end of a set expiratory time. When flow equals zero, airway pressure rises to the auto-PEEP level.

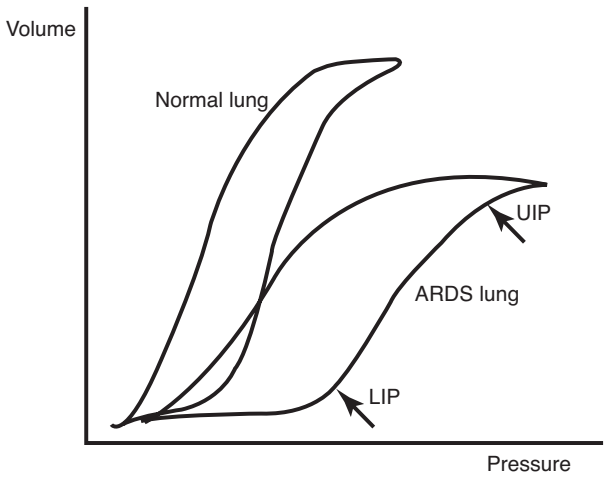

Figure 152-8 Pressure-volume curves of normal and diseased lungs. In the curve in acute respiratory distress syndrome (ARDS), two inflection points have been identified: a lower inflection point (LIP) and an upper inflection point (UIP).

a PEEP level 2 cm H_2O above the LIP and maintenance of P_{PLAT} just below the UIP. However, although many believe that the LIP represents the critical opening pressure of the majority of atelectatic alveoli, alveolar recruitment has been shown to continue for the duration of inspiration. In addition, investigators have found no such inflection point in patients with obvious alveolar recruitment demonstrated by computed tomography (CT).

Esophageal Pressure

Measurement of respiratory system compliance includes the mechanical properties of the lung *and* chest wall. By measuring pleural pressure, the transmural distending pressure of the lung can be calculated. Although regional variation in pleural pressure exists, measurement of lung compliance is based on the *change* in pleural pressure, rather than its absolute value.

Pleural pressure is usually estimated from esophageal pressure, which is recorded using an esophageal catheter. The typical device consists of a latex balloon which is 10 cm long and has several holes. The catheter is inserted into the lower esophagus (usually to a depth of about 40 cm). At this level, artifact from the beating heart is minimized. The adequacy of esophageal balloon positioning is confirmed by having the patient perform inspiratory attempts against an occluded airway. The esophageal pressure changes should be equal (±10 percent) to airway pressure changes. In the paralyzed patient, external chest compressions are used to create pressure fluctuations.

Ventilator Waveforms

Most modern ventilators include a spirometer or flow monitor to measure the volume and flow of gas passing through the ventilator circuit with each breath. Data are analyzed by a microprocessor in the ventilator and are graphically represented

as waveforms. The most commonly displayed waveforms include volume, pressure, and flow. Plots of flow versus volume (flow-volume loops) and pressure versus volume can be constructed electronically from the measurements. Monitoring of ventilator waveforms provides useful information about patient-ventilator synchrony, circuit leaks, patient-ventilator disconnection, development of auto-PEEP, and airway obstruction.

Inspiratory Muscle Strength

Respiratory muscle strength may be assessed by measuring maximum inspiratory and expiratory pressures generated against an occluded airway. This is most easily measured using an aneroid manometer. Inspiratory strength is measured at FRC, where the length-tension relationship of the inspiratory muscles is optimal. The pressure determined by this maneuver is known as the negative inspiratory force (NIF) or maximal inspiratory pressure (MIP). Clearly, the measurement is dependent on the intensity of the inspiratory effort, which may be suboptimal in uncooperative or unconscious patients. The problem can be circumvented by performing the maneuver off the ventilator, using a one-way valve; the NIF is measured over 10 sequential breaths or 30 s. By measuring over time, progressively lower lung volumes are reached and the inspiratory drive increases progressively, promoting a maximal effort. Although the utility of the NIF as a predictor of weaning outcome has fallen out of favor, it remains a useful measurement in troubleshooting reasons for ventilator dependence.

Maximal expiratory pressure (MEP) is measured at total lung capacity, where the expiratory muscle length-tension relationship is optimal. Although not routinely employed in clinical practice, MEP may have use in predicting extubation outcome in selected patient populations.

Imaging in Acute Lung Injury

A variety of imaging techniques may be useful in monitoring patients with ARF, including diaphragm ultrasound, electrical impedance activity (EIT), and CT.

The thickness of the diaphragm changes dynamically between the relaxed phase and maximum inspiration. Ultrasound can be used to evaluate changes in diaphragm thickness in the so-called "zone of apposition," where the lateral portions of the diaphragm lie adjacent and parallel to the lateral chest walls. The technique is noninvasive, inexpensive, and free of ionizing radiation. Diaphragm ultrasound has proved useful in the diagnosis of diaphragm paralysis in the context of ARF.

EIT is a relatively new bedside imaging technique in which an image of gas distribution within the chest is constructed during different phases of respiration. Although the technique's spatial resolution is limited in comparison with CT, its temporal resolution is better. With EIT, a series of eight pairs of electrodes are placed around the chest circumference and a current applied between electrode pairs. The resulting electrical potential is measured, and the process is repeated for numerous configurations of applied current. Potential applications for the technique include titration of PEEP, evaluation of alveolar recruitment maneuvers, and investigation of phasic atelectasis. At present, EIT remains a research tool.

The use of CT has dramatically changed the way in which clinicians view ARDS. Because of the diffuse, widespread distribution of abnormalities seen on conventional radiographs, ARDS was traditionally considered a homogeneous pathological process. However, application of CT imaging in ARDS has demonstrated that the disorder is quite heterogeneous. Furthermore, the advent of high-resolution, multidetector scanners will expand the number of applications of this technology—for example, in the diagnosis of the etiology of the lung injury (pulmonary versus extrapulmonary), nature of the injury (pneumonia versus lung contusion), or progression of injury from inflammation to fibrosis. In addition, the presence of complications (e.g., occult barotrauma or pleuropulmonary infection) and the response to interventions (e.g., adjustment of PEEP, implementation of alveolar recruitment maneuvers, incorporation of spontaneous breathing during mechanical ventilation, or determination of the need for insertion of chest drains) will be more readily discerned.

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Principles of Mechanical Ventilation

Martin J. Tobin

The historical evolution of mechanical ventilation is rich and built on advances in many fields, including endeavors by anatomists, chemists, explorers, physiologists, and clinicians. In 1543, Vesalius demonstrated that positive-pressure ventilation could be used to resuscitate a dying animal. Bellows ventilation was advocated by various lay bodies in the resuscitation of near-drowning victims late in the eighteenth century. In 1827, however, Leroy demonstrated that overzealous bellows inflation could result in pneumothoraces. Official bodies condemned the technique, and, thus, early in its infancy, positive-pressure ventilation was banned from use. Around this time, negative-pressure ventilators were developed and later popularized as a panacea for a wide variety of ailments.

The modern era of mechanical ventilation was ushered in by Bjorn Ibsen in response to epidemic of bulbar poliomyelitis in Copenhagen in 1952. In the first 3 weeks of the epidemic, 31 patients had been treated with negative-pressure respirators, and 27 had died. Ibsen advised immediate tracheostomy and the use of positive-pressure ventilation with manual positive pressure from a rubber bag, as was then customary in the operating room. Hundreds of medical students worked in relays, delivering bag ventilation during the epidemic; shortly thereafter, machines were introduced to deliver positive-pressure ventilation. Over the following 40 years, ventilators changed enormously in appearance, becoming more sophisticated and versatile and having enhanced capabilities for monitoring and alarming.

OBJECTIVES AND INDICATIONS FOR MECHANICAL VENTILATION

The objectives of mechanical ventilation are listed in Table 153-1. In isolation, hypoxemia of mild to moderate severity can be managed by administration of oxygen (O_2) through a face mask. With more severe hypoxemia secondary to shunt or ventilation-perfusion ($\dot{V}_A/\dot{Q}$) mismatching, it is difficult to guarantee the delivery of a high fractional inspired oxygen concentration ($F_{I_{O_2}}$) through a face mask. Moreover, these patients are commonly in considerable distress. Thus, intubation helps by ensuring delivery of the required $F_{I_{O_2}}$, and positive-pressure ventilation helps by recruiting collapsed lung units, leading to improved matching of ventilation and perfusion.

Table 153-1

Objectives of Mechanical Ventilation

Improve pulmonary gas exchange
Reverse hypoxemia
Relieve acute respiratory acidosis
Relieve respiratory distress
Decrease oxygen cost of breathing
Reverse respiratory muscle fatigue
Alter pressure-volume relationships
Prevent or reverse atelectasis
Improve lung compliance
Prevent further lung injury
Permit lung and airway healing
Avoid complications

SOURCE: *From: Tobin MJ: Mechanical ventilation.* N Engl J Med *330:1056–1061, 1994, with permission.*

Acute progressive respiratory acidosis is a major indication for mechanical ventilation, although simpler measures can sometimes reverse the process. For example, among patients with acute severe asthma and hypercapnia, hypercapnia resolves with standard bronchodilator therapy, without the need for mechanical ventilation, in more than 90 percent of patients. If a patient has severe respiratory depression that is expected to be slow in resolving (e.g., certain drug overdoses), intubation and mechanical ventilation should be instituted without delay.

A substantial proportion of patients who require (and benefit from) mechanical ventilation have relatively normal arterial blood gases but have clinical signs of increased work of breathing: nasal flaring; vigorous activity of the sternomastoid muscles; tracheal tug; recession of the suprasternal, supraclavicular, and intercostal spaces; paradoxical motion of the abdomen; and pulsus paradoxus. This picture of a patient "tiring out" is the most common reason for instituting mechanical ventilation. The increase in work of breathing may be the result of increased airway resistance, increased stiffness of the lungs or chest wall, or the presence of a threshold inspiratory load secondary to auto- or intrinsic positive end-expiratory pressure ($PEEP_i$).

Increased respiratory work increases the O_2 cost of breathing to as much as 50 percent of total O_2 consumption. By decreasing respiratory work, mechanical ventilation allows precious O_2 stores to be rerouted to other vulnerable tissue beds. To substantially reduce patient effort, the ventilator must cycle in unison with the patient's central respiratory rhythm (Fig. 153-1). For perfect synchronization, the period of mechanical inflation must match the period of neural inspiratory time (the duration of inspiratory effort), and the period of mechanical inactivity must match the neural expiratory time. Work of breathing is increased in patients with atelectasis or acute lung injury because breathing occurs on the low, flat portion of the pressure-volume curve. By shifting tidal ventilation to the steep, compliant portion of the curve, mechanical ventilation can decrease respiratory work.

Commonly listed indications for mechanical ventilation include acute respiratory failure, exacerbation of chronic respiratory failure (e.g., secondary to infection, bronchoconstriction, or heart failure), coma, and neuromuscular disease. Many patients with these same conditions, however, do not require ventilator assistance. Indeed, the most common, and honest, reason that mechanical ventilation is instituted is a tautology: A physician thinks that "the patient looks like he (or she) needs to be placed on the ventilator." Mechanical ventilation is most commonly instituted based on a physician's clinical gestalt, formed through assessing a patient's signs and symptoms, rather than because a patient satisfies a certain set of criteria on a checklist. It is important to ground this decision on solid knowledge of pulmonary pathophysiology.

MODES OF MECHANICAL VENTILATION

The term *mode* refers to the relationship among various breath types (mandatory, assisted, supported, and spontaneous), as well as inspiratory phase variables.

Controlled Mechanical Ventilation

In controlled mechanical ventilation, the ventilator delivers all breaths at a preset rate, and the patient cannot trigger the machine. In the volume-targeted mode, the breaths have a preset volume—so-called volume-controlled ventilation. When the breaths are pressure limited and time cycled, the mode is termed *pressure-controlled* ventilation. Use of volume-controlled ventilation is largely restricted to patients who are apneic as a result of brain damage, sedation, or paralysis.

Assist-Control Ventilation

In the assist-control mode, the ventilator delivers a breath either when triggered by the patient's inspiratory effort (pressure- or flow-triggered) or, independently, if such an effort does not occur within a preselected time period. All breaths are delivered under positive pressure by the machine, but unlike controlled mechanical ventilation, the patient's triggering effort can exceed the preset rate. If the patient's spontaneous rate drops below the preset back-up rate, controlled ventilation is provided. The pressure to achieve the set tidal volume may be provided solely by the machine or, in part, by the patient. By design, delivered tidal volume is not influenced by patient effort. The more the patient contributes, the less pressure is provided by the machine, and ventilator-generated pressure bears an inverse relationship to patient-generated pressure.

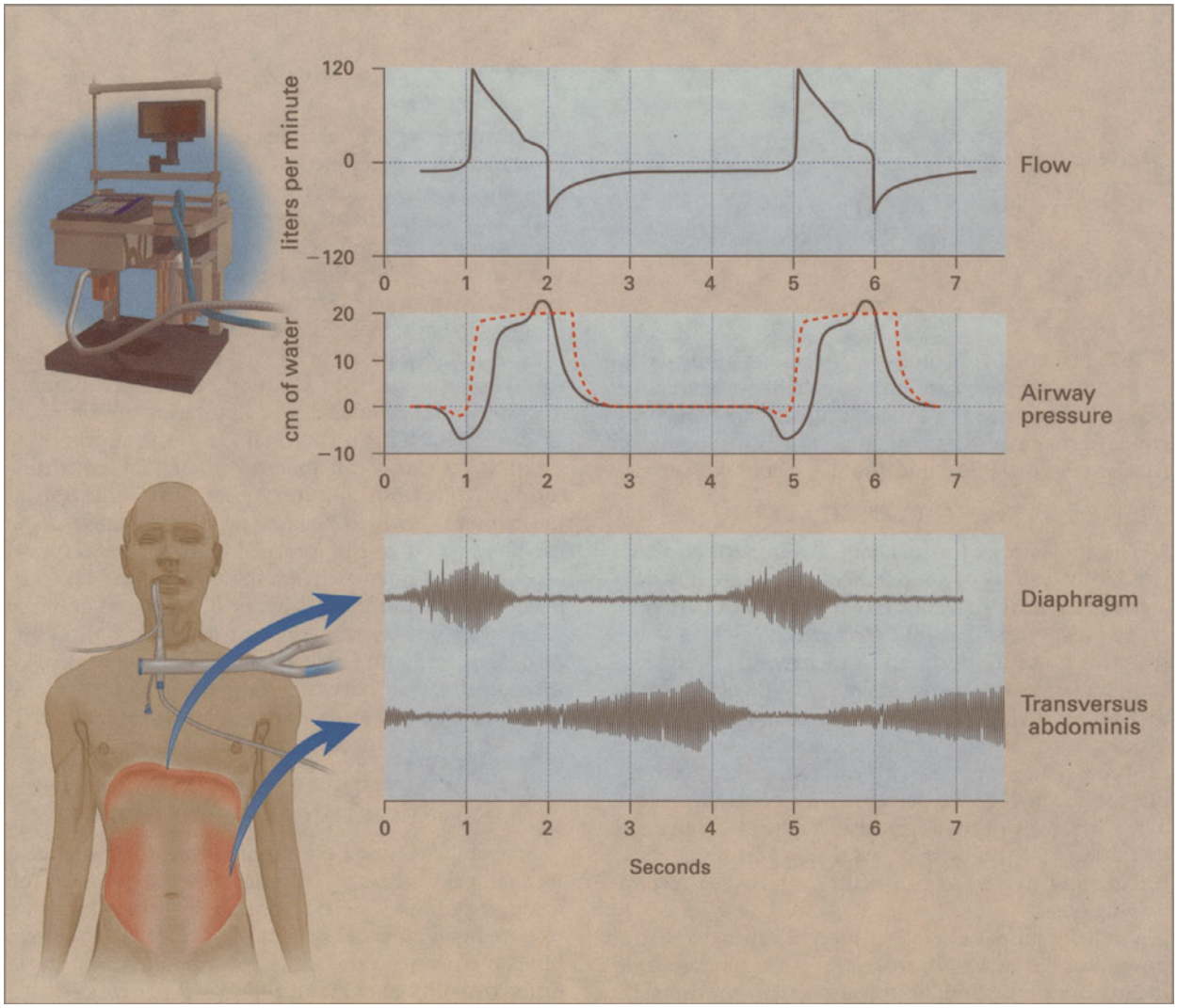

Figure 153-1 Flow, airway pressure, and inspiratory and expiratory muscle activity in a patient with chronic obstructive pulmonary disease who received pressure-support ventilation at an airway pressure of 20 cm H_2O. The electromyograms in the lower portion of the figure show inspiratory muscle activity in the patient's diaphragm and expiratory muscle activity in the transversus abdominis. The patient's increased inspiratory effort caused the airway pressure to fall below the set sensitivity (−2 cm H_2O), and inadequate delivery of flow by the ventilator resulted in a scooped contour on the airway-pressure curve during inspiration. While the ventilator was still pumping gas into the patient, his expiratory muscles were recruited, causing a bump in the airway-pressure curve. That the flow never returned to zero throughout expiration reflected the presence of $PEEP_i$. The broken red line shows airway pressure in another patient, who generated just enough effort to trigger the ventilator and in whom there was adequate delivery of gas by the ventilator. *(Data are from Jubran A, Van de Graaff WB, Tobin MJ: Variability of patient-ventilator interaction with pressure support ventilation in patients with chronic obstructive pulmonary disease.* Am J Respir Crit Care Med *152:129–136, 1995; Parthasarathy S, Jubran A, Tobin MJ: Cycling of inspiratory and expiratory muscle groups with the ventilator in airflow limitation.* Am J Respir Crit Care Med *158:1471–1478, 1998. Reproduced with permission from Tobin MJ: Advances in mechanical ventilation.* N Engl J Med *344:1986–1996, 2001.)*

The ventilator cycles off when the preset tidal volume is reached, and machine inspiratory time may be shorter or longer than the patient's intrinsic (neural) inspiratory time. If the set tidal volume is reached before the end of neural inspiratory time, the machine cycles off while the patient's inspiratory effort continues. If the patient's inspiratory effort ceases before the set tidal volume is reached, the machine increases pressure to provide continued inspiratory flow. The amount of active work performed by a patient ventilated in the assist-control mode is critically dependent on the trigger sensitivity and inspiratory flow settings. Even when these settings are selected appropriately, patients actively perform about one-third of the work performed by the ventilator during passive conditions.

Intermittent Mandatory Ventilation

With intermittent mandatory ventilation (IMV), the patient receives periodic positive-pressure breaths from the ventilator at a preset volume and rate, but the patient can also breathe

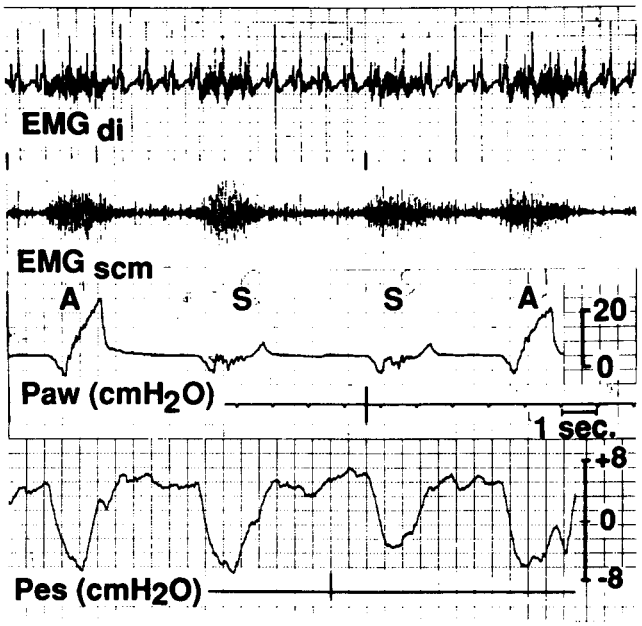

Figure 153-2 Electromyograms of the diaphragm (EMGdi) and sternocleidomastoid muscles (EMGscm) in a patient receiving synchronized intermittent mandatory ventilation. Similar intensity and duration of electrical activity during assisted (A) and spontaneous (S) cycles are demonstrated. P_{aw} = airway pressure; P_{es} = esophageal pressure. *(From Imsand C, Feihl F, Perret C, et al: Regulation of inspiratory neuromuscular output during synchronized intermittent mechanical ventilation.* Anesthesiology *80:13–22, 1994, with permission.)*

spontaneously between these mandatory breaths. A problem unforeseen at the time IMV was introduced is the difficulty that patients encounter in trying to adapt to the intermittent nature of ventilator assistance. It had been assumed that the degree of respiratory muscle rest achieved by IMV would be proportional to the number of mandatory breaths delivered. Studies, however, have demonstrated that inspiratory effort is equivalent for spontaneous and assisted breaths during IMV (Fig. 153-2). Indeed, the tension-time index for both spontaneous and assisted breaths is above the threshold associated with respiratory muscle fatigue at IMV rates of 14 breaths per minute or less. At a moderate level of machine assistance (at which the ventilator accounts for 20 to 50 percent of total ventilation), electromyographic activity of the diaphragm and sternocleidomastoid muscles is equivalent for assisted and spontaneous breaths. These findings suggest that respiratory center output is preprogrammed and does not adjust to breath-to-breath changes in load, as occur during IMV. As a result, IMV may contribute to development of respiratory muscle fatigue or prevent its recovery.

Pressure-Support Ventilation

Pressure-support ventilation is patient triggered, like assist-control ventilation and IMV, but differs in that it is pressure targeted and flow cycled. The physician sets a level of pressure that augments every spontaneous effort, and the patient can alter respiratory frequency, inspiratory time, and tidal volume. Tidal volume is determined by the pressure setting, the patient's effort, and pulmonary mechanics, in contrast to assist-control ventilation and IMV, in which a guaranteed volume is delivered. With volume-targeted ventilation, the inspiratory flow setting is a crucial determinant of patient work. There is no flow setting with pressure-support ventilation, although the initial peak flow determines the speed of pressurization and the initial pressure ramp profile.

The level of pressure delivered by the ventilator is usually adjusted in accordance with changes in the patient's respiratory frequency. However, the frequency that signals a satisfactory level of respiratory muscle rest has never been well defined, and recommendations range from 16 to 30 breaths per minute.

Several investigators have shown that pressure support is very effective in decreasing the work of inspiration. The degree of inspiratory muscle unloading, however, is variable, with a coefficient of variation of up to 96 percent among patients. Pressure-support does not decrease $PEEP_i$ in patients with chronic obstructive pulmonary disease (COPD). Thus, at a pressure support of 20 cm H_2O, $PEEP_i$ may account for two-thirds of total inspiratory effort.

Cycling to exhalation is triggered by a decrease in inspiratory flow to a preset level, such as 5 L/min or 25 percent of peak inspiratory flow, depending on the manufacturer's algorithm (Fig. 153-3). The algorithm for "cycling-off" of mechanical inflation causes problems in patients with COPD, because increases in resistance and compliance produce a slow time constant (of the respiratory system). The longer time needed for flow to fall to the threshold value can cause mechanical inflation to persist into neural expiration.

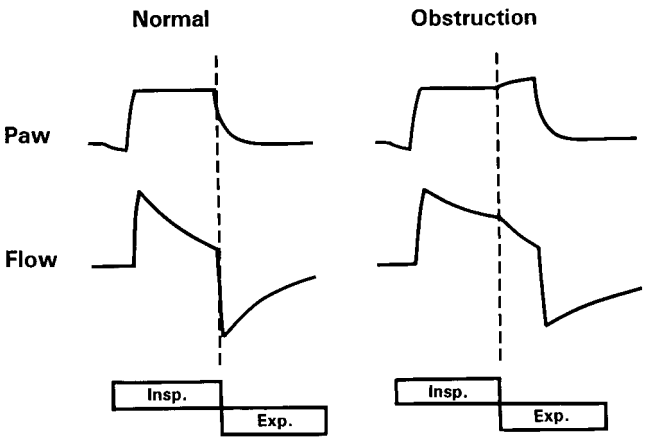

Figure 153-3 Airway pressure (P_{aw}) and inspiratory (Insp) and expiratory (Exp) flow during pressure support ventilation in patients with normal and obstructed airways. Patient effort triggers the ventilator to deliver a preset pressure, and inspiratory assistance continues until the flow rate falls to 25 percent of the peak inspiratory flow. In patients with airway obstruction who have a prolonged time constant, more time is required for flow to decrease to this threshold value, so that neural expiration commences before the termination of mechanical inflation. The resulting activation of the expiratory muscles hastens the fall in flow, but it also results in dyssynchrony between the patient's neuromuscular activity and the mechanical phase of the ventilator—so-called "fighting the ventilator."

In 12 patients with COPD receiving pressure support of 20 cm H_2O, investigators found that five recruited their expiratory muscles while the machine was still inflating the thorax. Interestingly, the patients who recruited their expiratory muscles during mechanical inflation had an average time constant of 0.54 seconds, as compared with an average of 0.38 seconds in the patients who did not exhibit expiratory muscle activity. The persistence of mechanical inflation into neural expiration is very uncomfortable, as well recognized with use of inverse-ratio ventilation.

New Modes

New modes of mechanical ventilation are frequently introduced. Each has an acronym, and the jargon is inhibiting to those unfamiliar with it. Yet each new mode involves nothing more than a modification of the manner in which positive pressure is delivered to the airway and of the interplay between mechanical assistance and the patient's respiratory effort. The purpose of a new mode may be to enhance respiratory muscle rest, prevent deconditioning, improve gas exchange, prevent lung damage, enhance coordination between ventilator assistance and patient respiratory effort, and foster lung healing; the priority given to each goal varies.

VENTILATOR SETTINGS

Ventilator settings are based on the patient's size and clinical condition. Determination of the settings is a dynamic process, based on a patient's physiological response, rather than on a fixed set of numbers. The settings require repeated readjustment over the period of ventilator dependency. Such an iterative process requires careful respiratory monitoring.

Triggering

Many ventilators employ pressure triggering, whereby a decrease in circuit pressure is required to initiate ventilator assistance. Patients reach the set sensitivity by activating their inspiratory muscles. When the threshold is reached, however, inspiratory neurons do not simply switch off. Consequently, the patient may expend considerable inspiratory effort throughout a machine-cycled inflation. The level of patient effort during this post-trigger phase is closely related to a patient's respiratory drive at the point of triggering. As such, measures that decrease respiratory drive may enhance respiratory muscle rest during mechanical ventilation.

If respiratory drive at the point of triggering is important, one might expect that effort during the time of triggering would determine patient effort during the remainder of inspiration. To elucidate this issue, investigators applied graded levels of pressure support in eleven critically ill patients. They achieved a fourfold reduction in overall patient effort. Yet patient effort during the time of triggering did not change. The constancy of effort during the trigger phase was probably secondary to different factors becoming operational as the level of ventilator assistance was varied (Fig. 153-4). Thus, increases in the level of ventilator assistance do

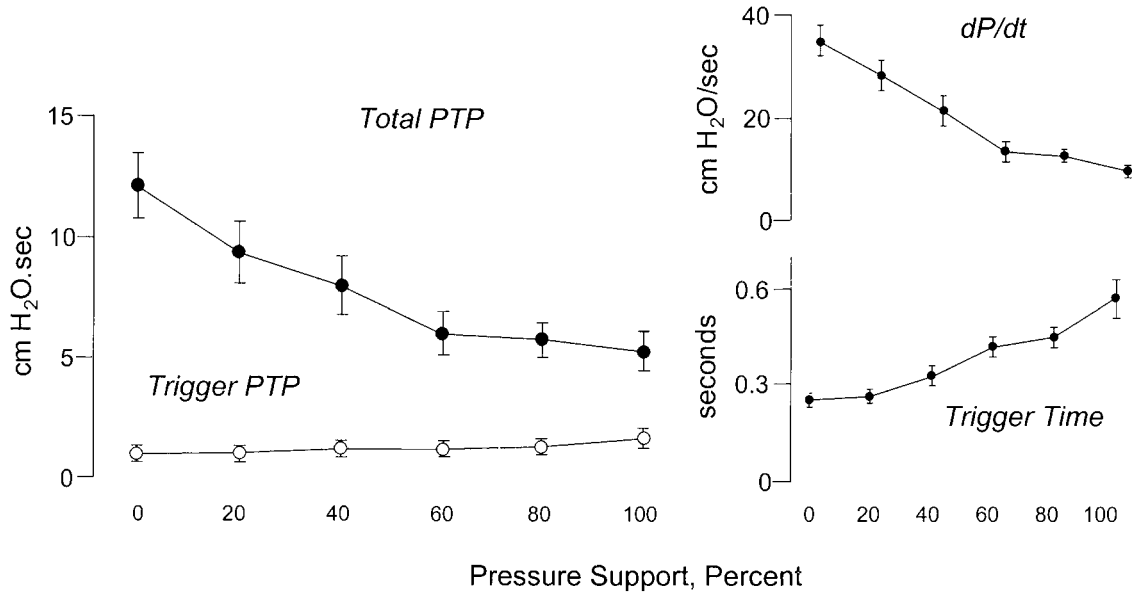

Figure 153-4 Graded increases in pressure support produced a decrease in total pressure-time product (PTP) per breath (closed symbols), although PTP during the trigger phase (open symbols) did not change (left panel). The constancy of PTP during triggering probably resulted from different factors becoming operational at different levels of assistance (right panel). At low levels of pressure support, respiratory drive (dP/dt) and $PEEP_i$ were high, but triggering time was short, resulting in a large change in pleural pressure over a brief interval. At high levels of pressure support, dP/dt and $PEEP_i$ were low, but triggering time was long, resulting in a smaller change in pleural pressure over a longer time. *(Based on data from Leung P, Jubran A, Tobin MJ: Comparison of assisted ventilator modes on triggering, patient effort, and dyspnea.* Am J Respir Crit Care Med *155:1940–1948, 1997; Tobin MJ, Jubran A, Laghi F: Patient-ventilator interaction.* Am J Respir Crit Care Med *163:1059–1063, 2001, with permission.)*

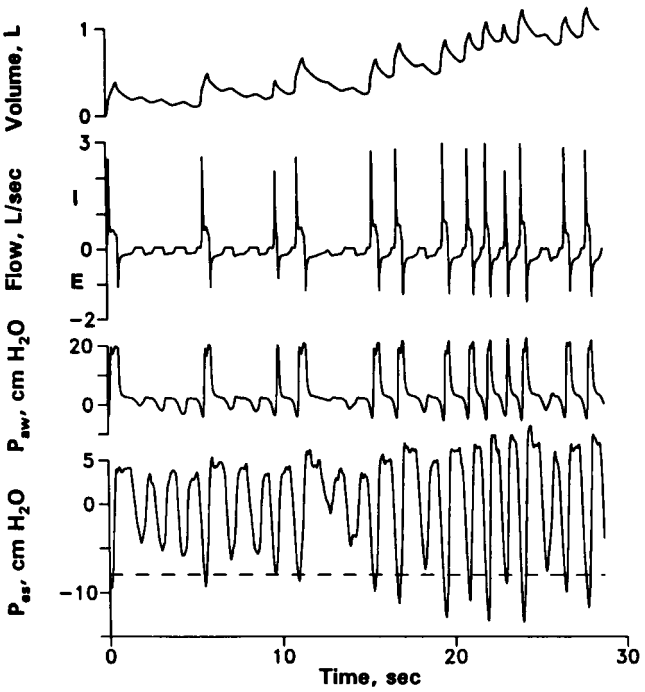

Figure 153-5 Recordings of tidal volume, inspiratory (I) and expiratory (E) flow, airway pressure (P_{aw}), and esophageal pressure (P_{es}) in a patient with COPD receiving pressure-support ventilation. Approximately half of the patient's inspiratory efforts do not succeed in triggering the ventilator. Triggering occurs only when the patient generates P_{es} more negative than −8 cm H_2O (indicated by the interrupted horizontal line), a pressure equal in magnitude to the opposing elastic recoil pressure. Expiratory flow exhibits a biphasic pattern, with momentary braking signaling ineffective inspiratory effort. Thus, monitoring of expiratory flow provides a more accurate measurement of the patient's intrinsic respiratory rate than does the number of machine cycles displayed on the bedside monitor. *(From Tobin MJ, Jubran A:* Pathophysiology of failure to wean from mechanical ventilation. *Schweiz Med Wochenschr 124:2138–2145, 1994, with permission.)*

not substantially decrease patient effort during the time of triggering.

The display of airway pressure and flow tracings on ventilator screens has increased awareness that inspiratory effort is frequently insufficient to trigger the ventilator. At high levels of mechanical assistance, up to one-third of a patient's inspiratory efforts may fail to trigger the machine (Fig. 153-5).The number of ineffective triggering attempts increases in direct proportion to the level of ventilator assistance. Surprisingly, unsuccessful triggering is not the result of poor inspiratory effort. In a study of factors contributing to ineffective triggering, effort was noted to be more than one-third greater when the threshold for triggering the ventilator was not reached than when it was. Breaths that do not reach the threshold for triggering the ventilator have higher tidal volumes and shorter expiratory times than do breaths that do trigger the ventilator. Consequently, elastic-recoil pressure builds up within the thorax in the form of $PEEP_i$. To trigger the ventilator, the patient's inspiratory effort has to first generate a negative intrathoracic pressure in order to counterbalance the elastic recoil; it then must reach the set sensitivity.

The time at which a patient initiates an expiratory effort (in relation to the cycling of the ventilator) partly determines the success of the ensuing inspiratory effort in triggering the machine. The relationship between the onset of expiratory muscle activity and termination of mechanical inflation by the ventilator has been quantified. At a pressure support of 20 cm H_2O, mechanical inflation continues for a longer time into neural expiration in the breaths preceding nontriggering attempts. Continuation of mechanical inflation into neural expiration counters expiratory flow, and also decreases the time available for unopposed exhalation. Consequently, elastic recoil increases. In turn, a greater inspiratory effort will be needed to achieve effective triggering. In this way, the time at which a patient commences an expiratory effort (in relation to cycling-off of mechanical inflation) partly determines the success of the ensuing inspiratory effort in triggering the ventilator.

Tidal Volume

In the past, use of a tidal volume setting of 10 to 15 ml/kg had been the standard recommendation. This setting is still used by many anesthesiologists for patients without lung disease who are undergoing surgery. Since the early 1990s, however, lower tidal volumes have been used when ventilating patients in medical intensive care units (ICUs). The change in practice was precipitated by research in experimental animals that provided convincing evidence of severe lung injury induced by alveolar overdistension. A 1990 retrospective study of patients with the acute respiratory distress syndrome (ARDS) revealed a 60 percent decrease in the expected mortality rate with use of lower tidal volumes. Subsequent randomized trials, including that conducted by the ARDS Network investigators, revealed a significantly lower mortality with a tidal volume of 6 ml/kg compared with a tidal volume of 12 ml/kg. Three other controlled trials, however, did not reveal a lower mortality using the lower tidal volume.

To understand the discrepant findings among the five randomized trials, a meta-analysis was undertaken. The analysis focused on plateau pressure, which is the airway pressure during an end-inspiratory pause. The low tidal volume arms of the three negative studies had plateau pressures that were at least as low as in the two positive studies. Thus, authors of the meta-analysis concluded that use of low tidal volumes did not lower mortality. The control arms of the three negative studies had plateau pressures that were comparable to those of usual practice (as reflected by plateau pressures before randomization). The control arms of the two positive studies, however, had plateau pressures higher than those used in usual practice (plateaus above 35 cm H_2O versus plateaus of 29 to 31 cm H_2O). Thus, the conclusion from the meta-analysis was that the control arms of the two positive studies were associated with increased mortality.

A subsequent analysis of the data from the ARDS Network study revealed that respiratory compliance had a major

influence on the response to the setting of tidal volume. If compliance was low before randomization, lowering of tidal volume decreased mortality from 42 to 29 percent. If compliance was high, however, lowering of tidal volume increased mortality from 21 to 37 percent. Thus, a low tidal volume is not appropriate for every patient with ARDS. Instead, it is essential to characterize each patient's pathophysiology and to customize the ventilator settings accordingly.

Respiratory Rate

Correct setting of the ventilator rate depends on the mode of ventilation employed. With assist-control ventilation, the ventilator supplies a breath in response to each patient effort. With this mode, physicians commonly pay little attention to the machine rate, which may be set much lower than the patient's spontaneous rate. This gap results in two problems: (a) If the patient has a sudden decrease in respiratory center output, a low machine rate results in serious hypoventilation. (b) A large discrepancy between the patient's spontaneous rate and the machine's back-up rate results in a respiratory cycle with an inverse inspiratory-to-expiratory time (I:E) ratio.

Development of an inverse I:E ratio arises because inspiratory time (T_I) on the machine remains fixed at the initial setting and does not change in response to increases in the patient's spontaneous rate (Fig. 153-6). For example, if the machine rate is initially set at 12 breaths per minute (T_{TOT} of 5 seconds) and T_I set at 1.65 seconds (either set directly or indirectly as a consequence of the volume and flow settings), then T_E will be 3.35 seconds. The I:E ratio will be 1:2. If the patient's spontaneous respiratory rate is increased to 25 breaths per minute, T_{TOT} will be 2.4 seconds. Because T_I remains fixed at 1.65 seconds, T_E will be 0.75 s, and the I:E ratio will be 2:1. Such inverse-ratio ventilation is very uncomfortable and may lead to increased sedative use, or even to use of neuromuscular blockade, simply because of inappropriate

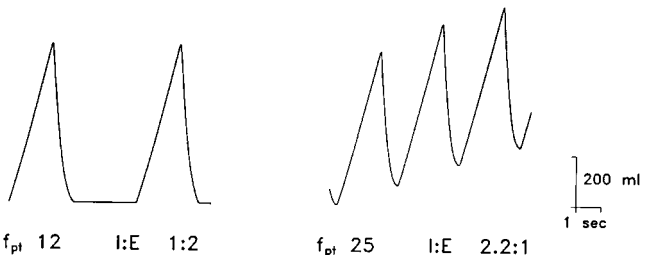

Figure 153-6 Effect of interaction between a patient's respiratory rate and the ventilator back-up rate on inspiratory time–expiratory time ratio (I:E) during assist-control ventilation. Ventilator back-up rate is 12 breaths per minute and inspiratory time (T_I) 1.65 seconds. *Left panel.* If the patient's intrinsic respiratory (f_{pt}) rate is also 12 breaths per minute, the total respiratory cycle time (T_{TOT}) is 5.0 seconds, the expiratory time (T_E) is 3.35 seconds, and the I:E ratio is 1:2. *Right panel.* If the patient's respiratory rate increases to 25 breaths per minute, the new T_{TOT} is 2.4 seconds, T_E is 0.75 seconds, and I:E is 1:0.45 (or, as more conventionally noted, 2.2:1).

setting of the back-up rate. Based on these considerations, the back-up rate during assist-control ventilation should be set at approximately four breaths less than the patient's spontaneous rate.

With IMV, the ventilator (or mandatory) rate is initially set high and then gradually reduced according to patient tolerance. Unfortunately, titration is often based on data from arterial blood gases, and even a small number of ventilator breaths can result in acceptable values for Pa_{O_2} and Pa_{CO_2} but achieve little or no respiratory muscle rest in patients with increased work of breathing. In ventilator-dependent patients, work of breathing at IMV rates of 14 breaths per minute or less may be sufficient to induce respiratory muscle fatigue.

With PS ventilation, the ventilator rate is not set.

Inspiratory Flow Rate

Clinicians initially set the inspiratory flow rate at a default value, such as 60 L/min. Many critically ill patients, however, have an elevated respiratory drive, and the initial flow setting may be insufficient to meet flow demands. As a result, patients will struggle against their own respiratory impedance and that of the ventilator. Consequently, work of breathing increases. Clinicians sometimes increase flow in order to shorten the inspiratory time and increase the expiratory time. However, an increase in flow causes immediate and persistent tachypnea; as a result, expiratory time may be shortened. In a study of healthy subjects, increases in inspiratory flow from 30 L/min to 60 and 90 L/min caused increases in respiratory rate of 20 and 41 percent, respectively.

One of the main reasons that clinicians increase inspiratory flow is to decrease inspiratory time, in hope of allowing more time for expiration and, thereby, decreasing $PEEP_i$, especially in patients with COPD. Because increased flow usually leads to an increase in respiratory rate, the expected shortening of expiratory time might actually increase $PEEP_i$.

An investigation of this phenomenon was conducted in 10 patients with COPD (Fig. 153-7). As with healthy subjects, an increase in flow from 30 to 90 L/min caused respiratory rate to increase from 16 to 21 breaths per minute. Despite the increase in rate, $PEEP_i$ fell from 7.0 to 6.4 cm H_2O. The decrease in $PEEP_i$ arose because of an increase in expiratory time (from 2.1 to 2.3 seconds), which allowed more time for lung deflation. Why did expiratory time increase? An increase in inspiratory flow is usually achieved by shortening of mechanical inspiratory time. The shortened inspiratory time combined with time-constant inhomogeneity of COPD causes overinflation of some lung units to persist into neural expiration. Continued inflation during neural expiration causes stimulation of the vagus nerve, which prolongs expiratory time.

When adjusting the flow rate and trigger sensitivity, examination of the contour of the airway pressure waveform is helpful (Fig. 153-8). Ideally, the waveform should show a smooth rise and convex appearance during inspiration. In

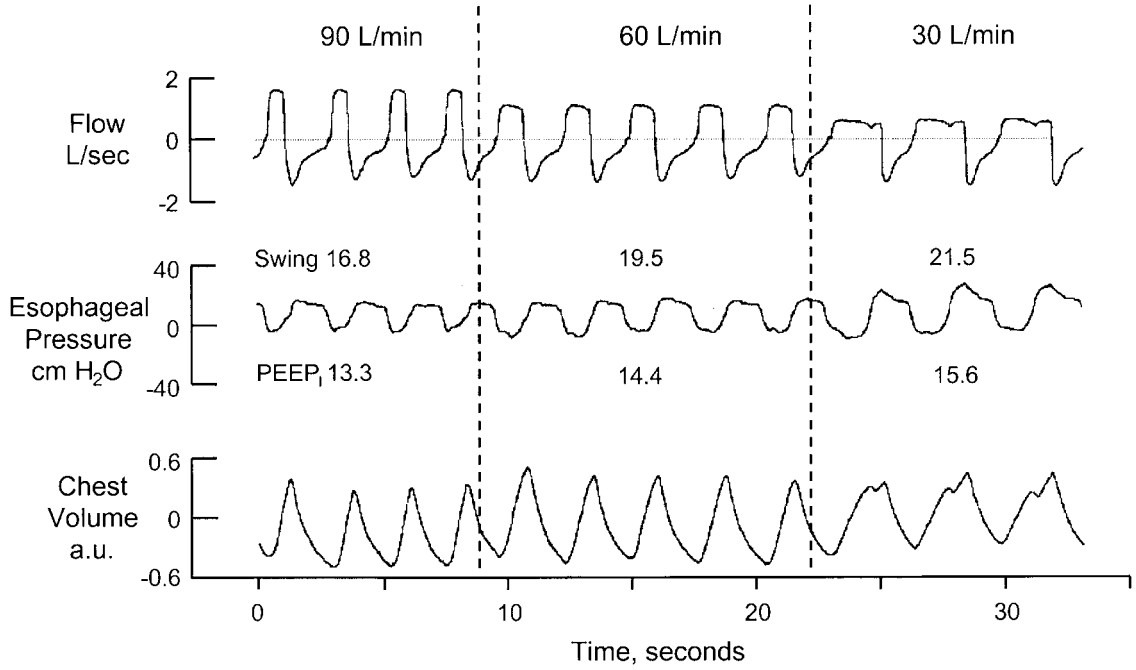

Figure 153-7 Continuous recordings of flow, esophageal pressure (Pes), and the sum of rib cage and abdominal motion, in a patient with chronic obstructive pulmonary disease receiving assist-control ventilation at a constant tidal volume. As flow increased from 30 to 60 and 90 L/min (from right to left), frequency increased (from 18 to 23 and 26 breaths/min, respectively), $PEEP_i$ decreased (from 15.6 to 14.4 and 13.3 cm H_2O, respectively), and end-expiratory lung volume also fell. Increases in flow from 30 L/min to 60 and 90 L/min also led to decreases in the swings in Pes from 21.5 to 19.5 and 16.8 cm H_2O, respectively. *(Reproduced from Laghi F, Segal J, Choe WK, et al: Effect of imposed inflation time on respiratory frequency and hyperinflation in patients with chronic obstructive pulmonary disease.* Am J Respir Crit Care Med *163:1365–1370, 2001.)*

contrast, a prolonged negative phase, with excessive scalloping of the tracing, indicates unsatisfactory settings of sensitivity or flow.

Fractional Inspired Oxygen Concentration

Correction of hypoxemia and its prevention are major goals in mechanically ventilated patients. Many predictive equations have been published to aid in selecting an appropriate

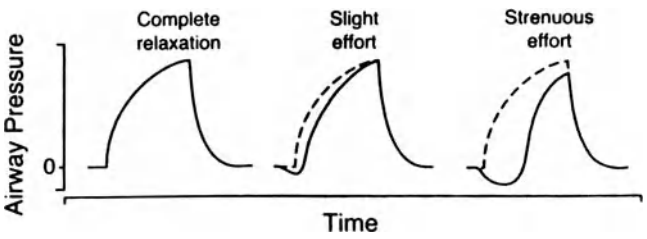

Figure 153-8 Airway-pressure waveforms recorded during assist-control ventilation. The tracings represent changes in airway pressure during inspiration in a completely relaxed patient, and in patients making slight (center tracing) and strenuous efforts (tracing on right) to breathe. The distance between the dashed line (representing controlled ventilation) and the solid line (representing spontaneous breathing) is proportional to the patient's work of breathing. *(From Tobin MJ: Mechanical ventilation.* N Engl J Med *330:1056–1061, 1994, with permission.)*

$F_{I_{O_2}}$, but none is sufficiently accurate to substitute for a trial-and-error approach. Initially, $F_{I_{O_2}}$ is set at a high value (often 1.0) to ensure adequate oxygenation. Thereafter, the lowest $F_{I_{O_2}}$ that achieves satisfactory arterial oxygenation should be selected. The usual target is a Pa_{O_2} of 60 mmHg or an arterial saturation (Sa_{O_2}) of 90 percent; higher values do not substantially enhance tissue oxygenation. Although it is customary to wait 30 min to assess the response to a change in $F_{I_{O_2}}$, the effect is usually well defined within 10 min. When using arterial blood samples to assess oxygenation, a target of 90 percent for Sa_{O_2} is appropriate. If pulse oximetry is employed, a Sp_{O_2} target may result in values for Pa_{O_2} as low as 41 mmHg. In white patients, a target of 92 percent for Sp_{O_2} indicates satisfactory oxygenation. In black patients, however, this target may still result in significant hypoxemia.

In experimental animals, hyperoxia produces diffuse alveolar damage, with histologic changes that are indistinguishable from ARDS resulting from any other cause. No diagnostic tests distinguish O_2-induced injury from progression of the underlying disease. Thus, the possibility of O_2 toxicity should be considered in any patient receiving an $F_{I_{O_2}}$ of more than 0.50 to 0.60 for 24 to 48 hours or longer. Healthy human subjects who inhale 100 percent O_2 develop acute tracheobronchitis, manifested as substernal discomfort, cough, sore throat, nasal congestion, eye and ear discomfort, paresthesias, and fatigue. Symptoms begin within 4 hours; bronchoscopic features of tracheal inflammation are evident after

6 hours. Retrosternal discomfort also occurs with an $F_{I_{O_2}}$ of 0.75 but not with an $F_{I_{O_2}}$ of 0.50. Hyperoxia causes absorption atelectasis in lung units with low $\dot{V}_A/\dot{Q}$ ratios, because the rate of absorption of O_2 from the alveoli into the bloodstream is faster than the rate of replenishment from inspired gas. Such atelectasis results in a small shunt (approximately 3 percent) in healthy elderly subjects and requires only about 6 minutes to develop.

A decrease in vital capacity is probably the best indicator of O_2 toxicity. In several studies of healthy volunteers breathing 50 percent O_2 over 7 to 28 days, little, if any, change in vital capacity was observed. When healthy subjects breathed 100 percent O_2, a decrease in static lung compliance was observed within 3 hours. This decrease resolved readily with deep breathing, suggesting that the decreased compliance was caused by absorption atelectasis, rather than direct toxicity. Exposure of healthy subjects to 100 percent O_2 for as long as 4 days resulted in only modest reductions in vital capacity, and gas exchange function returned to normal with air breathing.

Overall, studies in human subjects reveal much less parenchymal injury than has been observed in animals. It has been suggested the risk of O_2 toxicity might be greater in patients who have coexisting lung injury, but ironically, indirect data suggest that patients with ARDS have a reduced risk of O_2 toxicity. Exuded plasma proteins and intra-alveolar hemorrhage provide a medium that is rich in antioxidant enzyme capacity and helps to protect against O_2 toxicity. Death in experimental animals exposed to prolonged hyperoxia is usually attributed to acute lung injury. Several investigators, however, have reported a terminal course characterized by severe cardiac embarrassment associated with focal areas of myocardial necrosis on microscopy.

In the face of potential O_2 toxicity, the only possible strategy is to reduce the $F_{I_{O_2}}$ to the lowest level compatible with adequate systemic oxygenation. Thus, excess O_2 demand should be minimized, and measures to enhance systemic oxygenation optimized. Although excessive O_2 administration should be avoided, there is more to fear from severe hypoxemia than from the potential damage that might result from hyperoxia.

Positive End-Expiratory Pressure

The beneficial effects of positive end-expiratory pressure (PEEP) include improvement in arterial oxygenation, improvement in lung compliance, alleviation of excessive respiratory work secondary to $PEEP_i$ in patients with airflow limitation, and, possibly, a decrease in lung injury resulting from repeated alveolar collapse and reopening. The principal beneficial effect of PEEP is an increase in Pa_{O_2}, which permits a decrease in $F_{I_{O_2}}$ and a reduction in the risk of O_2 toxicity. The major mechanism for the increase in Pa_{O_2} with PEEP is an increase in end-expiratory lung volume (Table 153-2).

Patients with ARDS develop alveolar instability and collapse (see Chapters 144 and 145). Consequently, functional residual capacity falls below closing volume, and small airways close during tidal breathing, leading to intrapulmonary shunt and hypoxemia. PEEP increases end-inspiratory lung volume by distending lung units that are already open, preventing collapse of unstable alveoli at end-expiration, recruiting collapsed lung units, and redistributing liquid within the lung. The decrease in venous admixture with PEEP is proportional to alveolar recruitment. It had been thought that the decrease in venous admixture with PEEP resulted largely from a decrease in cardiac output. This view has been shown to be erroneous.

Table 153-2

Mechanisms of Increased Pa_{O_2} with PEEP

Increase in end-expiratory lung volume
Distention of patent lung units
Recruitment of collapsed lung units
Redistribution of fluid within the lung
Decrease in shunt
Increase in end-expiratory lung volume
Decrease in cardiac output

At one time PEEP was thought to decrease extravascular lung water by "pushing" alveolar fluid back into the circulation. On the contrary, PEEP can actually increase lung water. As alveoli expand with application of PEEP, interstitial pressure in the extra-alveolar space decreases, leading to an increase in transmural pressure across the vessel wall. If intravascular pressures remain the same or increase, the filtration of fluid across the vessel wall increases, causing an increase in pulmonary edema; if PEEP causes a decrease in cardiac output and vascular pressures, lung water does not change. The beneficial action of PEEP in pulmonary edema is produced by redistribution of edema fluid from the alveolar space into the perivascular cuffs. This redistribution of lung water, in association with an increase in end-expiratory lung volume, is the major mechanism underlying the increase in Pa_{O_2} with PEEP.

In patients with acute respiratory distress syndrome, PEEP is often used for the purpose of recruiting previously nonfunctioning lung tissue (see Chapter 145). Selecting the right level of PEEP for a given patient is difficult, however, because the severity of injury varies throughout the lungs. PEEP can recruit atelectatic areas, but it may also overdistend normally aerated areas. In one study involving six patients with acute lung injury, the use of PEEP at 13 cm H_2O resulted in recruitment of nonaerated portions of lung, with a gain of 320 ml in lung volume; however, three patients had overdistention of already aerated portions of lung, with an excess volume of 238 ml.

Overall, about 30 percent of patients with acute lung injury either do not benefit from PEEP or experience a fall in Pa_{O_2}. With the patient in the supine posture, PEEP generally

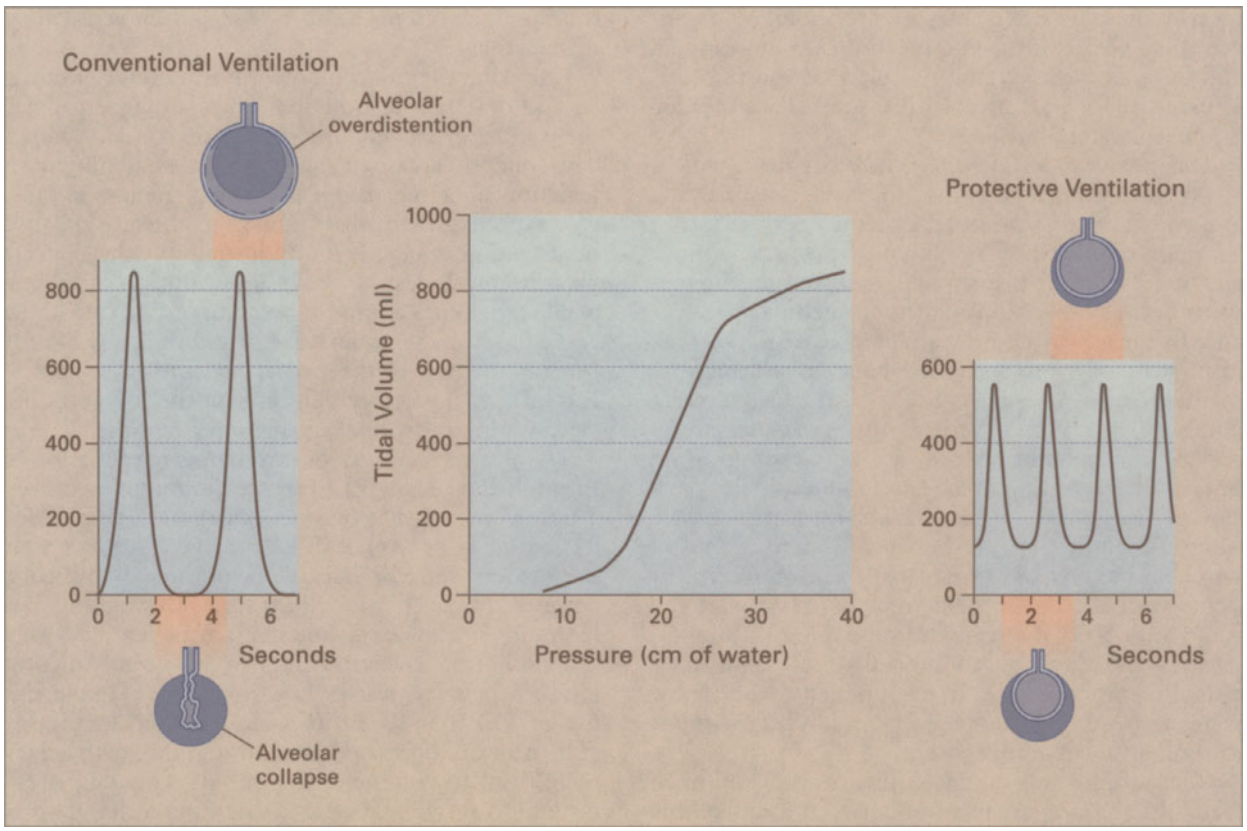

Figure 153-9 Respiratory pressure-volume curve and the effects of traditional versus protective ventilation in a 70-kg patient with acute respiratory distress syndrome. The lower and upper inflection points of the inspiratory pressure-volume curve (center panel) are at 14 and 26 cm H_2O, respectively. With conventional ventilation at a tidal volume of 12 ml/kg and zero end-expiratory pressure (left panel), alveoli collapse at the end of expiration. The generation of shear forces during the subsequent mechanical inflation may tear the alveolar lining, and attaining an end-inspiratory volume higher than the upper inflection point causes alveolar over-distention. With protective ventilation at a tidal volume of 6 ml/kg (right panel), the end-inspiratory volume remains below the upper inflection point; the addition of PEEP at 2 cm H_2O above the lower inflection point may prevent alveolar collapse at the end of expiration and provide protection against the development of shear forces during mechanical inflation. *(Reproduced Tobin MJ: Advances in mechanical ventilation.* N Engl J Med *344:1986–1996, 2001, with permission.)*

recruits the regions of the lung closest to the apex and sternum. Conversely, PEEP can increase the amount of nonaerated tissue in the regions close to the spine and diaphragm. Among patients in the early stages of ARDS, those with pulmonary causes, such as pneumonia, are less likely to benefit from PEEP than are patients with nonpulmonary causes, such as intra-abdominal sepsis or extrathoracic trauma. This distinction may be related to the type of morphologic involvement: Pulmonary causes of ARDS are characterized by alveolar filling, whereas nonpulmonary causes are characterized by interstitial edema and alveolar collapse. In the later stages of ARDS, remodeling and fibrosis may eliminate this distinction between pulmonary and nonpulmonary causes.

Even if a pressure-volume curve is not performed at the bedside, it is useful to select the PEEP level according to this conceptual framework (Fig. 153-9). A level above the lower bend in the pressure-volume curve is thought to keep alveoli open at the end of expiration, thereby preventing injury that can result from shear forces created by the opening and closing of alveoli. This level of PEEP may also prevent an increase in the amount of nonaerated tissue and, thus, atelectasis. However, the notion that the lower bend of the pressure-volume curve signals the level of PEEP necessary to prevent end-expiratory collapse, and that pressure above the upper bend signal alveolar overdistention, is a gross oversimplification. The relation between the shape of the pressure-volume curve and events at the alveolar level is confounded by numerous factors and is the subject of ongoing research and debate. An understanding of this relation is also impeded by the difficulty in distinguishing collapsed lung units from fluid-filled units on computed tomography scans.

BRONCHODILATOR THERAPY

Several obstacles are encountered when inhaled drugs are administered to ventilated patients. As a result, drug deposition to the lower respiratory tract is less than that in

ambulatory patients. Determinants of aerosol deposition include the configuration of the endotracheal tube and ventilator circuit, ventilator mode and settings, and patient-related factors.

Nebulizers have been used traditionally for the delivery of bronchodilators, but they have a number of disadvantages. Nebulizer contamination causes aerosolization of bacteria, and lack of attention to this matter by health care providers has led to epidemics of nosocomial pneumonia. Tidal volume and inspiratory flow must be adjusted to compensate for nebulizer flow. This factor is inconsequential in most adults, but instances of hypoventilation have occurred in patients who are unable to trigger the ventilator. Another shortcoming of nebulizers is the considerable variation in efficiency of different commercial brands, as well as among various batches of the same brand.

In contrast, metered-dose inhalers (MDIs) are easy to administer, involve less personnel time, and provide reliable dosing. Moreover, when MDIs are used with a collapsible cylindrical spacer, it is not necessary to disconnect the ventilator circuit for each treatment. Thus, risk of ventilator-associated pneumonia is decreased. Using MDIs instead of nebulizers results in substantial cost savings. The combination of an MDI and a chamber device achieves a four- to sixfold greater delivery of aerosol than MDI actuation into a connector attached directly to the endotracheal tube or into an in-line device that lacks a chamber. Aerosol delivery is increased with use of a higher tidal volume and longer fractional inspiratory time (T_I/T_{TOT}). Aerosol delivery is decreased by a high inspiratory flow rate; heating and humidification of inhaled gas reduce aerosol deposition by about 40 percent. When an aerosol is carried by a low-density gas, such as an 80:20 helium-oxygen mixture, aerosol delivery from a MDI is increased by more than 50 percent.

A dose-response study of four, eight, and 16 puffs of albuterol (administered with an MDI and cylindrical spacer) conducted in ventilated patients with COPD (Fig. 153-10) demonstrated a decrease in airway resistance after four puffs of albuterol; no additional effects were noted after cumulative doses of 12 and 28 puffs. In another study in ventilated patients with COPD, the bronchodilator effect of a single dose of four puffs of albuterol was sustained for at least 60 minutes. The bronchodilator effect obtained with four puffs of albuterol from an MDI was comparable to that obtained with six to 12 times the same dose given by a nebulizer.

Based on research conducted over the past decade, it is possible to formulate specific steps to achieve maximum bronchodilator effect with use of MDIs in ventilated patients (Table 153-3). Therapy can be given in combination with either controlled or assisted ventilation, provided aerosol administration is synchronized with inspiratory flow. Based on the recommended technique for use of an MDI in ambulatory patients, some authors recommend use of a postinspiratory breath hold; with optimal technique, however, this maneuver does not influence bronchodilator response in ventilated patients. Although humidification of the circuit reduces aerosol deposition, it is advisable not to bypass the humidifier. Even with a humidified circuit, significant bronchodilation can be achieved with as few as four puffs of a bronchodilator aerosol when the MDI technique is carefully executed.

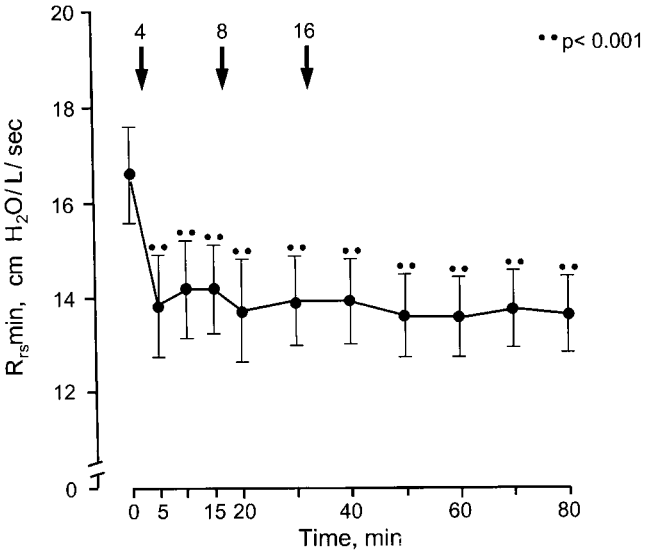

Figure 153-10 Effect of albuterol on minimal inspiratory resistance (Rrs_{min}) in 12 stable mechanically ventilated patients with chronic obstructive pulmonary disease. Significant decreases in resistance occurred within 5 minutes of administration of four puffs of albuterol. The addition of eight and 16 puffs (cumulative doses of 12 and 28 puffs, respectively) did not achieve a significantly greater effect than that with four puffs ($p > 0.05$). Bars represent SE. $^{**}p < 0.001$. *(Modified from Dhand R, Duarte AG, Jubran A, et al: Dose-response to bronchodilator delivered by metered-dose inhaler in ventilator-supported patients.* Am J Respir Crit Care Med *154:388–393, 1996, with permission)*

MONITORING AND COMPLICATIONS

Several devices can be used to monitor pulmonary gas exchange, respiratory neuromuscular function, respiratory mechanics, and patient-ventilator interaction. Use of the derived information permits the physician to better tailor ventilator settings to an individual patient's requirements, with the promise of enhancing patient comfort. Monitoring of key variables helps to minimize the risk of iatrogenic complications and alerts the physician to the likelihood of an impending catastrophe, allowing sufficient time for the institution of lifesaving measures. A detailed discussion of techniques used for monitoring of ventilator-supported patients can be found in Chapter 152 and in other textbooks.

Patients receiving mechanical ventilation are at risk for numerous complications, including O_2 toxicity, volutrauma and air leaks, decreased cardiac output, and endotracheal tube–related issues. These problems are discussed elsewhere in this volume.

Table 153-3

Technique for Using Metered-Dose Inhalers in Mechanically Ventilated Patients

1. Assure V_T > 500 ml (in adults) during assisted ventilation.
2. Aim for an inspiratory time (excluding the inspiratory pause) >0.30 of total breath duration.
3. Ensure that the ventilator breath is synchronized with the patient's inspiration.
4. Shake the metered-dose inhalers vigorously.
5. Place canister in actuator of a cylindrical spacer situated in inspiratory limb of ventilator circuit.*
6. Actuate metered-dose inhalers to synchronize with precise onset of inspiration by the ventilator.†
7. Allow a breath hold at end-inspiration for 3–5 s.
8. Allow passive exhalation.
9. Repeat actuations after 20–30 s until total dose is delivered.‡

** With metered-dose inhalers, it is preferable to use a spacer that remains in the ventilator circuit to avoid disconnecting the ventilator circuit for each bronchodilator treatment. Although bypassing the humidifier can increase aerosol delivery, it prolongs each treatment and requires disconnecting the ventilator circuit.*

† In ambulatory patients with metered-dose inhalers placed inside the mouth, actuation is recommended briefly after initiation of inspiratory airflow. In mechanically ventilated patients using a metered-dose inhaler and spacer combination, actuation should be synchronized with onset of inspiration.

‡ The manufacturer recommends repeating the dose after 1 min. Metered-dose inhalers' actuation within 20–30 s after the previous dose does not compromise drug delivery.

SOURCE: *Modified from Dhand R, Tobin MJ: Inhaled bronchodilator therapy in mechanically ventilated patients.* Am J Respir Crit Care Med *156:3–10, 1997.*

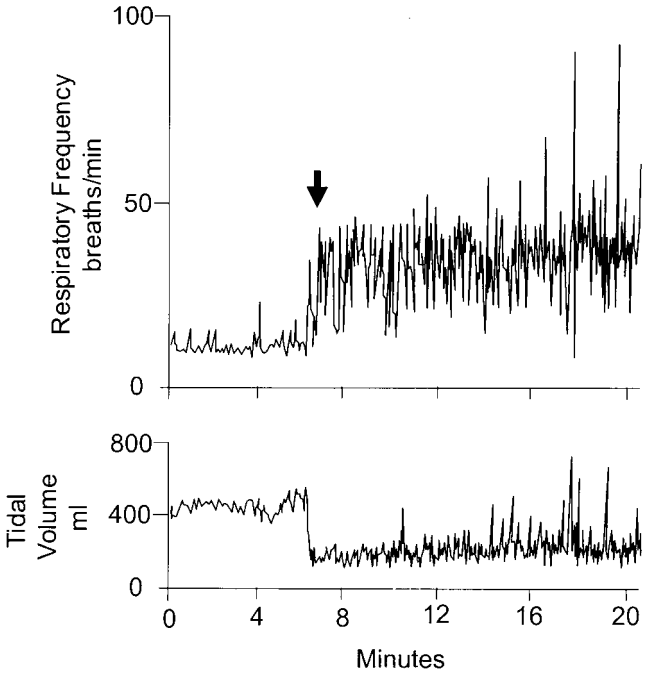

Figure 153-11 A time-series, breath-by-breath plot of respiratory frequency and tidal volume in a patient who failed a weaning trial. The arrow indicates the point of resuming spontaneous breathing. Rapid, shallow breathing developed almost immediately after discontinuation of the ventilator. *(From Tobin MJ, Perez W, Guenther SM, et al: The pattern of breathing during successful and unsuccessful trials of weaning from mechanical ventilation.* Am Rev Respir Dis *134:1111–1118, 1986, with permission.)*

WEANING

The term *weaning* literally means a slow, gradual decrease in the amount of ventilator support. However, the term is used more commonly to refer to all methods of discontinuing mechanical ventilation.

Causes of Weaning Failure

After discontinuation of mechanical ventilation, up to 25 percent of patients experience respiratory distress severe enough to necessitate the reinstitution of ventilator support. Our understanding of the basis for weaning failure in patients has advanced considerably in recent years. Among patients who cannot be weaned, disconnection from the ventilator is followed almost immediately by an increase in respiratory frequency and fall in tidal volume; that is, rapid, shallow breathing (Fig. 153-11). As a trial of spontaneous breathing is continued over the next 30 to 60 minutes, respiratory effort increases considerably, reaching more than four times the normal value at the end of this period (Fig. 153-12). The increased effort is caused mainly by worsening respiratory mechanics. Respiratory resistance increases progressively, reaching about seven times the normal value at the end of a failed weaning trial; lung stiffness also increases, reaching five times the normal value; and gas trapping, measured as $PEEP_i$, more than doubles over the course of the trial. Before weaning is started, however, respiratory mechanics in such patients are similar to patients in whom subsequent weaning is successful. Thus, unknown mechanisms associated with the act of spontaneous breathing cause the worsening of respiratory mechanics in patients who are weaning failures.

In addition to the increase in respiratory effort, an unsuccessful attempt at spontaneous breathing causes considerable cardiovascular stress. Patients can experience substantial increases in right- and left-ventricular afterload during a trial of spontaneous breathing, with increases of 39 and 27 percent in pulmonary and systemic arterial pressures, respectively. The changes are most likely attributable to the extreme negative swings in intrathoracic pressure. At the completion of a weaning trial, the level of O_2 consumption is equivalent in patients who can be weaned and in those who cannot. How the cardiovascular system meets the O_2 demand differs in the two groups of patients.

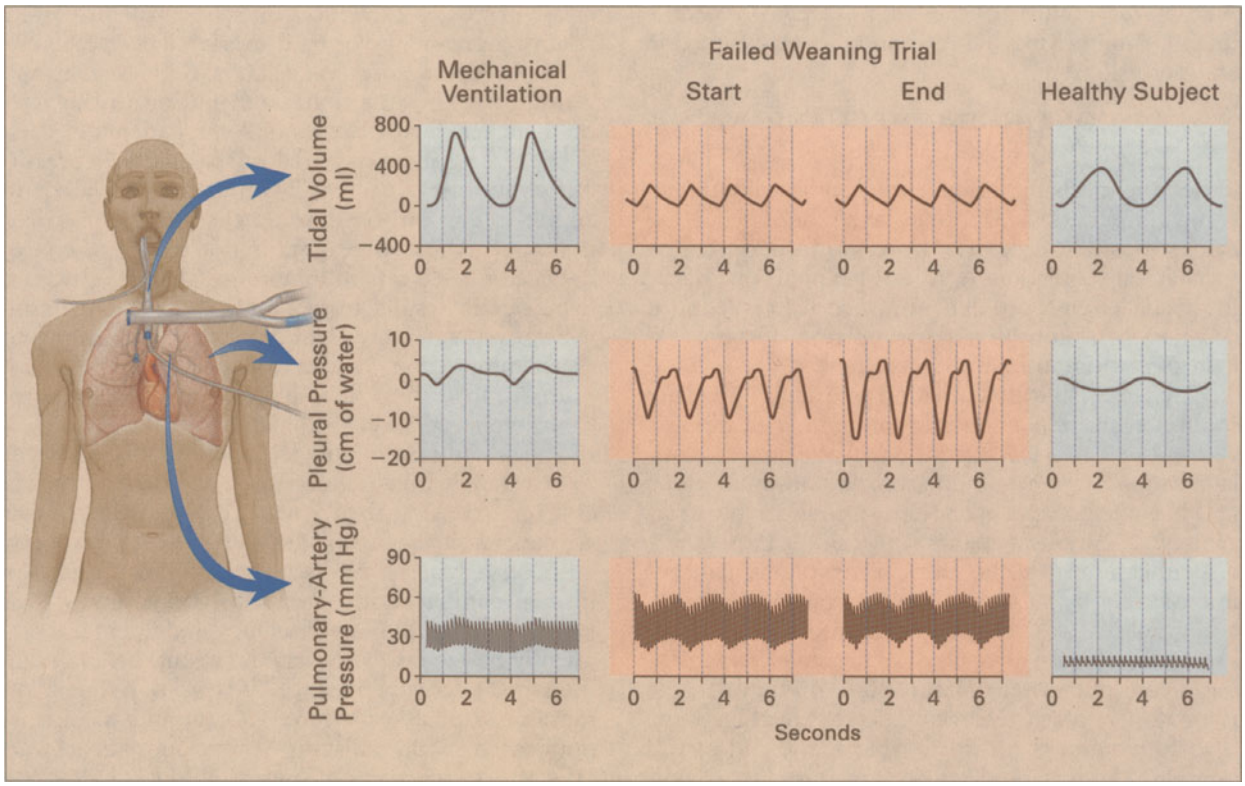

Figure 153-12 Tidal volume, pleural pressure, and pulmonary-artery pressure during assist-control ventilation and at the start and end of a failed weaning trial. During mechanical ventilation, the patient's inspiratory effort is in the normal range, and the pulmonary-artery pressure is 45/22 mmHg. At the start of the weaning trial, tidal volume falls to 200 ml, respiratory frequency increases to 33 breaths per minute, and a swing of 11 cm H_2O in pleural pressure is noted; the pulmonary-artery pressure at the end of expiration is 60/28 mmHg. At the end of the trial, 45 minutes later, the tidal volume and respiratory frequency are unchanged, a swing in pleural pressure of 19 cm H_2O is evident, and $PEEP_i$ is 4 cm H_2O; pulmonary artery pressure is 60/31 mmHg. The values in a healthy subject are tidal volume, 380 ml; respiratory frequency, 17 breaths per minute; pleural-pressure swing, 3 cm H_2O; and pulmonary artery pressure, 18/8 mmHg. *(Data are from Tobin MJ, Perez W, Guenther SM, et al: The pattern of breathing during successful and unsuccessful trials of weaning from mechanical ventilation.* Am Rev Respir Dis *134:1111–1118, 1986; Jubran A, Mathru M, Dries D, et al: Continuous recordings of mixed venous oxygen saturation during weaning from mechanical ventilation and the ramifications thereof.* Am J Respir Crit Care Med *158:1763–1769, 1998; Jubran A, Tobin MJ: Pathophysiologic basis of acute respiratory distress in patients who fail a trial of weaning from mechanical ventilation.* Am J Respir Crit Care Med *155:906–915, 1997. Reproduced from Tobin MJ: Advances in mechanical ventilation.* N Engl J Med *344:1986–1996, 2001, with permission.)*

In patients who are successfully weaned, O_2 demand is met through an increase in O_2 delivery, mediated by the expected increase in cardiac output on discontinuation of positive-pressure ventilation. In patients who cannot be weaned, O_2 demand is met through an increase in O_2 extraction; these patients have a relative decrease in O_2 delivery. The greater O_2 extraction causes a substantial decrease in mixed venous O_2 saturation, contributing to the arterial hypoxemia that occurs in some patients.

Over the course of a trial of spontaneous breathing, about half of patients in whom the trial fails have an increase in Pa_{CO_2} of 10 mm Hg or more. The hypercapnia is not usually a consequence of a decrease in minute ventilation. Instead, hypercapnia results from rapid, shallow breathing, which causes an increase in dead-space ventilation. In a small proportion of patients who cannot be weaned, primary depression of respiratory drive may be responsible for the hypercapnia.

Timing of the Weaning Process

One of the major challenges in the management of ventilator-supported patients is deciding on the right time to discontinue mechanical ventilation. If the physician is too conservative and postpones weaning onset, the patient is placed at an increased risk of life-threatening, ventilator-induced complications. Conversely, if weaning is begun prematurely, the patient may suffer cardiopulmonary or psychological decompensation of sufficient severity to set back a patient's clinical course.

In randomized trials of different weaning techniques, most patients who had received mechanical ventilation for a week or longer were able to tolerate ventilator discontinuation on the first day that weaning-predictor tests were measured. It is likely that many of these patients would have tolerated extubation a day or so earlier. As such, one of the main sources of weaning delay is the failure of the physician to *think* that the patient *just might* come off the ventilator. It is possible to speed up the weaning process by undertaking physiological assessment early in the patient's clinical course.

A cardinal precept of diagnostic testing is to begin with a screening test and follow with a confirmatory test. The characteristics of these test types differ. A single diagnostic test rarely fulfills both functions. The fundamental job of a weaning-predictor test is screening. Because the goal is to not miss anyone with the condition under consideration, a good screening test has a very low rate of false-negative results; to achieve this goal, a higher false-positive rate is acceptable. Thus, an ideal screening test has a very high sensitivity. The ratio of respiratory frequency to tidal volume (f/V_T) meets this requirement; numerous studies have documented that its sensitivity is 0.90 or higher.

The f/V_T ratio must be calculated during spontaneous breathing. Measurements of f/V_T in the presence of pressure support or CPAP will result in inaccurate predictions of weaning outcome. The higher is the f/V_T ratio, the more rapid and shallow the breathing and the greater the likelihood of unsuccessful weaning. A ratio of 100 discriminates between successful (less than 100) and unsuccessful (greater than 100) attempts at weaning.

Because the results of screening tests are often negative, an ideal screening test should be simple, expeditious, and safe. Measurement of f/V_T takes a minute or so to perform. In contrast, a trial of spontaneous breathing takes one-half to 2 hours to perform, during which time attendants commonly leave the patient's room. Accordingly, a spontaneous breathing trial does not satisfy the criteria for a desirable screening test, and commencing weaning with such a trial is likely to prolong the weaning process.

If clinicians obtain weaning-predictor tests at the earliest point that a patient might tolerate extubation, the results will be negative at least half the time. In studies of weaning-predictor tests, however, positive results have been obtained at least 75 percent of time. Such a high rate of positive test results indicates that clinicians were being too slow in initiating the weaning process.

When a screening test is positive, the diagnostician proceeds to a confirmatory test. A positive confirmatory test result essentially rules in a condition: The likelihood of a patient tolerating a trial of extubation is very high. An ideal confirmatory test has a very low rate of false-positive results, i.e., a high specificity. The specificity of a weaning trial is not known and will never be known, since its determination would require an unethical experiment—extubating all patients who fail a weaning trial and noting how many require reintubation.

Weaning Trials

Four methods can be used for conducting a weaning trial. The oldest is to perform trials of spontaneous breathing several times a day, using a T-tube circuit that contains an enriched supply of O_2. Initially 5 to 10 minutes in duration, T-tube trials are extended and repeated several times a day until the patient can sustain spontaneous ventilation for several hours. This approach has become unpopular because it requires considerable time on the part of ICU staff.

For many years, IMV was the most popular methods of weaning. With IMV, the mandatory rate from the ventilator is reduced in steps of one to three breaths per minute, and an arterial blood gas is obtained about 30 minutes after each rate change. Unfortunately, titrating the number of breaths from the ventilator in accordance with the results of arterial blood gases can produce a false sense of security. As few as two to three positive-pressure breaths per minute can achieve acceptable blood gases, but these values provide no information regarding the patient's work of breathing (which may be excessive). As noted previously, at IMV rates of 14 breaths per minute or less, patient inspiratory efforts are increased to a level likely to cause respiratory muscle fatigue. Moreover, this occurs not only with the intervening spontaneous breaths, but also with ventilator-assisted breaths. Consequently, use of IMV may actually contribute to the development of respiratory muscle fatigue or prevent its recovery.

When pressure support is used for weaning, the level of pressure is reduced gradually (decrements of 3 to 6 cm H_2O) and titrated on the basis of the patient's respiratory frequency. When the patient tolerates a minimal level of pressure support, he or she is extubated. What exactly constitutes a "minimal level of pressure support" has never been defined. For example, pressure support of 6 to 8 cm H_2O is widely used to compensate for the resistance imposed by the endotracheal tube and ventilator circuit. It is reasoned that a patient who can breathe comfortably at this level of pressure support will be able to tolerate extubation. However, if the upper airways are swollen because an endotracheal tube has been in place for several days, the work engendered by breathing through the swollen airways is about the same as that caused by breathing through an endotracheal tube. Accordingly, any amount of pressure support overcompensates and may give misleading information about the likelihood that a patient can tolerate extubation.

The fourth method of weaning is to perform a single daily T-tube trial, lasting for 30 to 120 minutes. If this trial is successful, the patient is extubated. If the trial is unsuccessful, the patient is given at least 24 hours of respiratory muscle rest with full ventilator support before another trial is performed.

Until the early 1990s, it was widely believed that all weaning methods were equally effective, and the physician's judgment was regarded as the critical determinant. However, the results of randomized, controlled trials clearly indicate that the period of weaning is as much as three times as long with IMV as with trials of spontaneous breathing. In a study involving patients with respiratory difficulties on weaning,

trials of spontaneous breathing halved the weaning time as compared with pressure support; in another study, the weaning time was similar with the two methods. Performing trials of spontaneous breathing once a day is as effective as performing such trials several times a day but is much simpler. In a recent study, half-hour trials of spontaneous breathing were as effective as 2-hour trials. This study, however, involved all patients being considered for weaning, not just those for whom there were difficulties with weaning.

In conclusion, to minimize the likelihood of either delayed weaning or premature extubation, a two-step diagnostic strategy is recommended: measurement of weaning predictors followed by a weaning trial. The critical step is for the physician to contemplate the possibility that a patient *just might* be able to tolerate weaning. Such diagnostic triggering is facilitated through use of a screening test, which is the rationale for measurement of weaning-predictor tests. It is important not to postpone this first step by waiting for a more complex diagnostic test, such as a T-tube trial.

Extubation

Decisions about weaning and extubation are commonly conflated. When a patient tolerates a weaning trial without distress, a clinician feels reasonably confident that the patient will be able to sustain spontaneous ventilation after extubation. Before removing the endotracheal tube, however, the clinician also has to judge whether or not the patient will be able to maintain a patent upper airway after extubation.

Of patients who are expected to tolerate extubation without difficulty, about 10 to 20 percent fail and require reintubation. Mortality among patients who require reintubation is more than six times as high as mortality among patients who can tolerate extubation. The reason for the higher mortality is unknown. It might be related to the development of new problems after extubation or complications associated with reinsertion of a new tube. A more likely explanation is that the need for reintubation reflects greater severity of the underlying illness.

Because of the high mortality associated with reintubation, clinicians are eager to avoid this problem. The major diagnostic test used to predict the success of an extubation attempt is a weaning trial. In contrast to the many studies that have evaluated the reliability of diagnostic tests that predict the outcome of a trial of weaning, the diagnostic accuracy of weaning trials in predicting the outcome of a trial of extubation is unknown. Moreover, the accuracy is impossible to determine, because the experiments necessary to measure the sensitivity and specificity of a weaning trial (for predicting extubation outcome) are unethical.

CONCLUSION

Since the previous edition of this textbook, we have gained a better understanding of the pathophysiology associated with unsuccessful weaning and have learned how to wean patients more efficiently. We have also learned how ventilator settings influence survival in patients with ARDS. Less progress has been made in determining how the ventilator can best be used to achieve maximal respiratory muscle rest, which is the most common reason for providing mechanical ventilation.

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Nutrition in Acute Respiratory Failure

Lisa M. Bellini

OVERVIEW OF MALNUTRITION

Malnutrition is a disorder of body composition in which nutritional intake is less than required, resulting in reduced organ function, abnormalities in blood chemistry, reduced body mass, and worsened clinical outcomes. Malnutrition in the setting of acute respiratory failure (ARF) may be a preexisting condition due to underlying advanced lung disease, such as chronic obstructive pulmonary disease (COPD) (see Chapters 41 and 42); alternatively, it may develop during the course of acute illnesses that promote hypermetabolism, as occurs in acute respiratory distress syndrome (ARDS) (see Chapter 145). Regardless of the starting point, ARF results in alterations in substrate metabolism that are manifest as nutritional deficiencies and altered body composition. As the body tries to conserve protein, fat is metabolized as a principal source of energy. When fat stores are depleted, visceral and muscle protein catabolism and gluconeogenesis become the main processes for generating energy. Nutritional assessment in these settings is critical. Evaluation usually consists of determination of clinical, anthropometric, chemical, and immunologic parameters that reflect altered body composition. The assessment must be considered in light of the patient's underlying condition, as no single test is diagnostic of malnutrition.

Incidence of Malnutrition in the Intensive Care Unit

Physicians may contribute to malnutrition in the hospital setting by failing to recognize it as a complication of illness or injury and addressing it inadequately. Recognition of malnutrition does not insure that adequate nutrition repletion will

occur. When enteral feeding is undertaken in the intensive care unit (ICU), inadequate nutrition is frequently delivered because of underestimation of patients' nutritional needs and inappropriate cessation of feedings. A prospective study of patients requiring enteral feedings in an ICU found that physician prescriptions provided a mean of only 66 percent of goal caloric requirements; furthermore, a mean of only 78 percent of the ordered volume was actually infused. Cessation of enteral feeds was judged avoidable in 66 percent of cases, including circumstances when feeding was discontinued at midnight for a procedure on the following day, or was stopped for simple bedside tasks, such as bathing the patient or placement of intravenous lines. An additional study of patients with COPD presenting with ARF (with slightly over one-half requiring mechanical ventilation) revealed malnutrition in 60 percent. Malnutrition was more frequent in those that required mechanical ventilation (74 percent versus 43 percent).

In 1997, the American College of Chest Physicians (ACCP) published a consensus statement on nutrition in the ICU, aimed at guiding patient selection, timing and route of administration, nutrient use, and monitoring of nutrition support. In a study of over 1500 critically ill medical patients who had an ICU length of stay greater than 96 h, cumulative caloric intake reached only about 50 percent of ACCP-recommended guidelines. Notably, patients receiving 33 to 65 percent of recommended caloric targets were more likely to achieve spontaneous ventilation prior to discharge from the ICU, while those receiving more than 65 percent of targets were less likely to be weaned or to be discharged alive from the hospital. The findings suggest that current caloric targets may overestimate patient needs, since moderate caloric intake was associated with a better outcome.

Incidence of Malnutrition in Advanced Lung Disease

The finding that patients with advanced lung disease suffer from changes in body composition manifest by progressive weight loss has long been recognized. Thirty to seventy percent of patients with COPD have clinical evidence of malnutrition. Malnutrition associated with advanced lung disease, so-called "pulmonary cachexia syndrome," has been associated with increased mortality and decline in functional status. Although COPD has been best studied, current thinking is that all advanced lung diseases are characterized by progressive reduction in lean body mass, which is a function of many variables, including aging, exercise, metabolism, tissue hypoxia, inflammation, and use of certain medications. Importantly, basal metabolism in patients with advanced lung disease does not follow the expected normal age-related decline. Many patients are hypermetabolic, presumably secondary to an increased work of breathing. In fact, patients with COPD have a 10-fold increase in daily energy expenditure over the normal baseline of 36 to 72 calories per day.

EFFECTS OF MALNUTRITION

The effects of malnutrition may be considered with respect to the underlying pathophysiology, consequences of malnutrition during critical illness, and effects of nutritional supplementation.

Pathophysiology and Complications of Malnutrition

A reduction in food intake results in loss of fat, muscle, skin, and, ultimately, bone and viscera. Body mass declines and extracellular fluid volume increases. Nutritional requirements fall as an individual's body mass decreases, probably reflecting more efficient utilization of ingested food and a reduction in work capacity at the cellular level. However, the combination of decreased tissue mass and reduction in work capacity impedes homeostatic responses to stressors, such as acute respiratory failure.

Malnutrition causes a number of deleterious consequences, including increased susceptibility to infection, poor wound healing, increased frequency of decubitus ulcers, overgrowth of bacteria in the gastrointestinal tract, and abnormal nutrient losses in stool. These alterations result in increased morbidity and mortality in malnourished, hospitalized patients. One study of over 2000 hospitalized veterans found a 30-day mortality rate of 62 percent among those whose serum albumin concentrations fell below 2.0 g/dl. A study of over 4300 patients in ICUs revealed that those with a low body mass index (BMI) on admission (due to preexisting malnutrition) were at increased risk of death during hospitalization and at 6 mo following BMI measurement. A BMI on admission below the 15th percentile was associated with a 23 percent increase in 6-mo mortality.

Adequate nutrition is essential for reversing the physiological derangements described and for recovery from ARF. Supplemental nutrition has been demonstrated to improve morbidity and mortality in certain groups of patients, likely related to contraction of previously expanded extracellular fluid volume and repletion of protein reserves.

Protein Calorie Malnutrition and Critical Illness

Metabolic derangements are amplified during periods of critical illness, including ARF; protein calorie malnutrition is particularly detrimental in this situation. The stress of critical illness inhibits the body's natural conservation responses to malnutrition; aggressive nutritional support instituted early during a critical illness may be protective.

Hypermetabolism associated with critical illness causes a redistribution of macronutrients (fat, protein, and glycogen) from the labile reserves of adipose tissue and skeletal muscle to more metabolically active tissues, such as bone, liver, and other viscera. Within a few days, this response may lead to the onset of protein calorie malnutrition, defined as

a negative balance of 100 g of nitrogen and 10,000 kcal. The rate of development of malnutrition in critically ill patients is a function of preexisting nutritional status and degree of hypermetabolism.

In the 1940s, Cuthbertson described two phases of the metabolic response to shock: (a) an initial "ebb" phase, and (b) a later, hypercatabolic "flow" phase. The initial "ebb" phase lasts 12 to 24 h and is characterized by fever, increased oxygen consumption, decreased body temperature, and vasoconstriction. These adaptive changes reflect activation of the sympathetic nervous system and pituitary-adrenal axis, reflected in rapid rises in plasma concentrations of epinephrine, norepinephrine, adrenocorticotropic hormone, growth hormone, cortisol, and other corticosteroids. The "flow" phase, which lasts for the remainder of the acute illness, is marked by hypercatabolism and is mediated primarily by catecholamines. The hypercatabolism exceeds anabolism, resulting in net negative nitrogen balance and a shift to utilization of fat as the major fuel source. Subsequent to Cuthbertson's description, a third or "anabolic" phase was described, beginning with the onset of recovery and characterized by normalization of vital signs, improved appetite, and diuresis. The difference between the last two phases relates primarily to the level of energy expenditure.

Effects of Nutritional Supplementation in Acute Respiratory Failure

Supplemental nutrition may improve respiratory muscle strength and restore ventilatory drive and altered lung defenses. Patients with advanced lung disease often have increased ventilatory drive with a blunted response to hypoxemia. Supplemental nutrition in malnourished patients with advanced lung disease may help restore ventilatory drive, increasing the chances for successful weaning. Malnutrition in advanced lung disease may also increase the risk of infection through a detrimental effect on cell-mediated immunity and reduced cellular resistance of respiratory mucosa to bacterial infection. Introduction of an endotracheal tube may exacerbate the latter effect.

Several retrospective studies suggest that supplemental nutrition may facilitate weaning from mechanical ventilation. Although a randomized, prospective controlled trial on the effects of supplemental nutrition on weaning has yet to be done, current evidence supports the notion that nutritional support is an important determinant of weaning success.

ASSESSMENT OF NUTRITIONAL STATUS

Early detection of malnutrition in ARF enables prompt and aggressive intervention using supplemental nutrition. No single measurement or assessment tool can adequately characterize nutritional status, and the diagnosis of malnutrition remains somewhat subjective. However, both functional and biochemical parameters should be examined to identify patients at increased risk for developing malnutrition and its complications.

Functional Assessment

Functional nutritional assessment consists of a medical history, physical examination, and appraisal of muscle and organ function. Identification of preexisting malnutrition (i.e., malnutrition occurring prior to the onset of respiratory failure) is made by careful attention to the history of present illness and relevant past medical and surgical history, a focused dietary history, and review of the patient's medications and social habits. This information usually needs to be obtained from the patient's family. The degree to which the patient's usual weight deviates from estimated ideal body weight should be considered; the period of time over which the weight has changed is important in evaluating the severity of weight loss.

Historical data should be used to estimate the nutritional consequences of the current hospitalization. Prehospitalization weights should be documented, and any weight changes since hospitalization should be noted and evaluated in the context of concomitant diuresis or fluid supplementation.

Physical examination may suggest the presence of nutritional and metabolic deficiencies. Temporal muscle wasting, sunken supraclavicular fossae, and decreased adipose stores are easily recognized signs of starvation. Careful inspection of the hair, skin, eyes, mouth, and extremities may reveal additional stigmata of protein calorie malnutrition or vitamin and mineral deficiencies.

An assessment of muscle mass and function may yield information about a patient's protein reserves and overall nutritional status. Estimation of muscle mass and fat stores can be obtained from anthropometric measurements, such as arm circumference or triceps skin fold measurements. These methods are simple, safe, cost effective, and standardized; however, interpretation of results remains controversial, limiting their use in the intensive care setting.

Cardiovascular, respiratory, and gastrointestinal functions should be evaluated with regard to both evidence of malnutrition-related dysfunction and the ability of the patient to tolerate nutritional supplementation. Administration of large fluid volumes associated with parenteral nutrition may be limited by impaired cardiovascular function. Abdominal distention may make use of enteral supplementation difficult.

Newer methods of nutritional assessment that have not been well studied to date include magnetic resonance imaging (MRI), whole body conductance and impedance, and neutron activation.

Metabolic Assessment

Information from select laboratory tests may complement the functional assessment and should be evaluated in every patient during the standard nutritional evaluation.

Serum albumin concentration is the most frequently used laboratory measure of nutritional status; values less than 2.2 g/dl generally reflect severe malnutrition. Although serum albumin is used popularly as an indicator of nutritional status, its value as a surrogate for visceral protein status is limited. Because albumin has a long half-life of 14 to 20 d, its serum level does not accurately reflect acute changes in nutritional status. Furthermore, serum albumin concentration rises rapidly in response to exogenously administered albumin and fluctuates in conditions such as dehydration, sepsis, trauma, and liver disease, irrespective of nutritional status.

Prealbumin (transthyretin) is a more reliable indicator of nutritional status than is albumin because its half-life of 24 to 48 h makes its plasma concentration more reflective of current nutritional state. However, as is the case with albumin, the concentration of prealbumin is diminished in renal and liver disease. Transferrin, with a half-life of 9 d, makes it intermediate between prealbumin and albumin with regard to its sensitivity for identifying incipient malnutrition.

Although serum chemistry values are important in determining the specifics of nutritional support, they do not directly reflect nutritional status. Serum sodium, potassium, chloride, total carbon dioxide, blood urea nitrogen, glucose, iron, magnesium, calcium, and phosphate, as well as prothrombin and partial thromboplastin times, should be measured on admission and rechecked periodically.

Adequacy of cellular immunity may be estimated by measuring total lymphocyte count (TLC) and delayed-type hypersensitivity testing using a series of common antigens (e.g., *Candida, Trichophyton,* tuberculin, diphtheria, and a glycerin control). Compromise of cell-mediated immunity due to malnutrition is suggested by a TLC less than or equal to 1000/mm^3 or lack of skin test induration greater than 5 mm above the glycerin control at 48 h (unless another cause of lymphocyte dysfunction is present). Delayed-type hypersensitivity testing is least useful during an acute illness, because cell-mediated immunity may be depressed in this setting, even in the absence of malnutrition. Furthermore, technical application and interpretation are variable.

INDICATIONS FOR NUTRITIONAL SUPPORT

Adequate nutrition is essential for recovery from ARF. Indications for enteral or parenteral nutritional support include preexisting nutritional deprivation, anticipated or actual inadequate oral caloric intake, and significant multiorgan system disease (Table 154-1).

Although supplemental nutrition is a lower priority during the resuscitative phase of respiratory failure, it's use becomes increasingly important once a patient is stabilized and should be initiated as soon as feasible. Critically ill patients should not be allowed to remain in a state of unopposed starvation because this increases morbidity and mortality, particularly in the setting of multisystem organ failure. Several studies support early initiation of nutritional support in the ICU. A randomized multicenter trial of almost 500 critically ill patients found that early initiation of nutritional support reduced duration of hospitalization from 35 to 25 d; a trend toward reduced mortality was also noted. A related study of medical patients admitted to the ICU indicated that low caloric intake was independently associated with nosocomial blood stream infection.

Table 154-1

Indications for Nutritional Support

Preexisting malnutrition (i.e., BMI <19)
Anticipated inadequate oral intake
Significant multiorgan system disease

GOALS OF NUTRITIONAL SUPPORT

The goals of nutritional support are different in the different phases of critical illness, which are distinguished on the basis on energy expenditure. In the first several days of critical illness (the "ebb" and "flow" nutritional phases described previously), hypercatabolism exceeds anabolism, resulting in net negative nitrogen balance and a shift to utilization of fat as the major fuel source. During this time, the goal of metabolic support is to maintain vital organ structure and function and attenuate the complications of sepsis, shock, and multisystem organ failure. Metabolic support can blunt the negative nitrogen balance and minimize further protein wasting. However, such support cannot reverse the negative nitrogen balance entirely until patients enter the third, or anabolic, phase of critical illness. At this point, nutritional goals shift to achieving a positive nitrogen balance and repleting protein stores.

ROUTE OF ADMINISTRATION AND COMPLICATIONS

Nutritional support may be administered enterally or parenterally. Clinical circumstances dictate which method is employed.

Enteral

Enteral nutrition is preferred over parenteral nutrition because of its lower cost, fewer and less severe complications, lower rates of infection, better rates of wound healing, and association with lower gut mucosal permeability. Enteral feeding requires adequate gastric motility. Impaired gastric

Table 154-2

Complications of Nutritional Support

	Enteral	Parenteral
Mechanical	Aspiration Pharyngitis Otitis Sinusitis Airway occlusion	Bleeding Pneumothorax Infection Thromboembolism
Metabolic	Hyperglycemia Hyper-, hypophosphatemia Hyper-, hypokalamia Hyper-, hyponatremia Hyper-, hypocalcemia Hyper-, hypomagnesemia	Hyperglycemia Hyper-, hypophosphatemia Hyper-, hypokalemia Hyper-, hyponatremia Hyper-, hypocalcemia Hyper-, hypomagnesemia Metabolic acidosis Azotemia Elevated liver–associated enzymes
Gastrointestinal	Diarrhea Bowel/abdominal distention Vomiting Constipation	

emptying can be assessed by checking gastric residual volumes of the tube feedings. Volumes greater than 150 ml should prompt consideration of decreasing the infusion rate, alternative use of intravenous nutritional supplementation, or small bowel feeds. The efficacy of gastric motility agents has not been proved.

Complications of enteral feeding fall into three categories: mechanical, gastrointestinal and metabolic (Table 154-2). The most common complication of enteral feeding is diarrhea, the cause of which may be difficult to discern in the critical care setting, when patients are receiving multiple medications that may be responsible. Evaluation of enteral feeding as the cause of diarrhea begins with adjustment of a single parameter at a time, e.g., infusion volume, rate, or osmolality. Persistent diarrhea despite use of a low infusion volume infusion of a neutral formula should prompt investigation of other causes and, when appropriate and not contraindicated, use of antimotility agents.

Parenteral

Although parenteral nutrition is *presumed* to be preferable to no nutrition in patients who cannot tolerate enteral feedings, this hypothesis has not been rigorously tested. In fact, a meta-analysis of 26 studies that enrolled over 2200 patients did not demonstrate a decrease in mortality or complications in those receiving total parenteral nutrition (TPN) compared with those receiving standard care with intravenous dextrose until able to receive an oral diet. The parenteral route is recommended for those patients in whom enteral nutrition is not possible or is insufficient for meeting nutritional goals.

Complications of parental nutrition can be divided into mechanical and metabolic categories (Table 154-2). Most mechanical complications are related to establishing access for the infusion. Infection is a primary concern. Metabolic complications include the same as with enteral feeding, as well as metabolic acidosis, azotemia, and an increase in liver-associated enzymes.

BASIC NUTRITIONAL PRESCRIPTION

The initial parental nutrition regimen for patients with ARF, but without underlying lung disease, centers around administration of a concentrated, low-volume solution to replete electrolytes and address acid-base issues. Thereafter, caloric and protein content (and hence, volume) are increased over several days, progressing over a period of days (Table 154-3).

Enteral regimens typically begin with the agent at full concentration, delivered at a rate of 10 to 20 ml per h. The rate can be increased by 10 to 20 ml every 12 to 24 h until the goal rate is reached. This process should take no more than 4 d.

Table 154-3

Basic Nutrition Prescription

Calculate caloric need based on BEE:

BEE (men) = 66.5 + 13.7W + 5H − 6.8A

BEE (women) = 655.1 + 9.6W + 1.8H − 4.7A

where W = weight, kg
H = height, cm
A = age, years

Multiply total caloric need by stress factor, if applicable:

Stress	*Examples*	*Multiplier*
Mild	Stable postoperative state	1.0–1.25
Moderate	Pneumonia, peritonitis	1.25–1.5
Severe	Sepsis, burn, cancer, BMI <19	1.5–2.5

Administer total calories in a volume consistent with the total fluid needs of the patient. One ml of water is necessary for each kcal administered.

Consider recommended distribution of macronutrients:

Macronutrient	*% Total Calories*
Glucose	30–70%
Fat	15–30%
Protein	15–20%

Consider recommended micronutrients and electrolytes, as necessary:

Micronutrient	*Dose*	*Frequency of Administration*
Multivitamin	1 unit	Weekly
Vitamin K	10 mg	Weekly
Mineral aliquot	Premixed	Daily
Iron	2 mg	Daily
Zinc	5–10 mg	Daily

A patient's fluid and electrolyte status must not be compromised by use of nutritional supplementation. The initial volume of the supplement must be based upon careful assessment of the patient's volume. Electrolyte balance is restored and maintained through daily assessment of losses and requirements. Simultaneously, glycemic control is achieved by balancing glucose and insulin requirements. Once these metabolic parameters are stabilized, attention centers on insuring that protein and calorie needs are met (see below). Vitamins, trace elements, and lipids are added to complete the nutrition prescription. Despite the association of low albumin with severe malnutrition, administration of supplemental albumin does not improve morbidity or mortality.

Energy Requirements

Energy needs are calculated on the basis of *basal energy expenditure* (BEE). BEE is the amount of energy required to perform metabolic functions at rest; it is influenced by both body size and illness. BEE is estimated using the Harris-Benedict equations (1) and (2):

For men:

$$\text{BEE} = 66.5 + (13.7 \times \text{weight}) + (5 \times \text{height}) - (6.8 \times \text{age}) \quad (1)$$

For women:

$$\text{BEE} = 655.1 + (9.6 \times \text{weight}) + (1.8 \times \text{height}) - (4.7 \times \text{age}) \quad (2)$$

where weight is expressed in kg, height in cm, and age in years

In using these equations, weight is the usual or actual weight of the patient for those without significant weight loss; for those with significant weight loss, current weight is used; for obese patients, ideal body weight is used.

Traditionally, use of BEE measurements in critical illness has involved multiplication by a "stress factor" of 0.5 to 2.5. Application of the stress factor may result in overfeeding and may predispose the patient to liver steatosis, hyperglycemia, electrolyte imbalances, respiratory compromise due to increased CO_2 production, and macrophage

dysfunction. Use of the standard Harris-Benedict equation (without the stress factor) in determining the BEE of critically ill patients yields an average estimate of 25 kcal/kg body weight per day. Evidence suggests that total energy expenditure is maximal during the second week of critical illness, at which time it may reach 50 to 60 kcal/kg per day.

Glucose Requirements

Glucose administration may provide 30 to 70 percent of total daily calories. The amount is adjusted based on serum glucose measurements, aiming to keep levels less than 144 mg/dl. Administration of insulin may be required.

Protein Requirements

The patient's protein requirements depend upon the degree of metabolic stress to which he or she is exposed. Generally, 15 to 20 percent of daily calories may be administered as protein or amino acids. Importantly, mild or moderately stressed underweight patients have the protein requirements as severely stressed normal or obese patients (2 to 2.5 g/kg/day). Based upon periodic metabolic monitoring, formula protein content should be adjusted to promote positive nitrogen balance and support synthetic function.

Fat Requirements

Fat is added to the formula to prevent essential fatty acid deficiency. In general, 15 to 30 percent of calories should be administered as polyunsaturated fatty acids.

Micronutrients

Phosphate, magnesium, potassium and zinc should be administered in amounts necessary to keep serum levels normal. Consensus on the administration of vitamins, minerals, or trace elements is currently lacking.

Immunonutrition

Interest is growing in assessment of specific enteral formulations, particularly those with high concentrations of arginine, glutamine, nucleotides, or omega-3 fatty acids, to improve patient mortality and decrease infectious complications. In addition to providing nutritional support, these formulations appear to offer beneficial effects on immunologic and inflammatory responses to critical illness. However, results from randomized trials and systematic reviews have yielded equivocal results.

Glutamine

Glutamine is a precursor for nucleotide synthesis and an important fuel source for rapidly dividing cells, such as gastrointestinal epithelia. Animal experiments have shown that glutamine supplementation can prevent or ameliorate the gastrointestinal mucosal atrophy seen during prolonged parenteral nutrition. Glutamine may facilitate gastrointestinal mucosal healing after damage by radiotherapy or chemotherapy. Possible benefits of glutamine supplementation have been evaluated in more than 30 controlled trials, most of which, unfortunately, have significant methodologic problems or are too small to permit definitive conclusions. A meta-analysis of 14 randomized trials found that glutamine, especially when given parenterally and at high doses, may improve outcome in postoperative and critically ill patients. However, at present, identification of indications for glutamine supplementation awaits the results of larger clinical trials.

Arginine and Omega-3 Fatty Acids

Arginine is an amino acid with important roles in nitrogen and ammonia metabolism and in the generation of nitric oxide. Animals subjected to wounds or fractures demonstrate improved rates of wound healing, nitrogen retention, and growth when given supplemented dietary arginine. In addition, rats administered arginine-supplemented parenteral nutrition show increased ability to synthesize acute phase proteins when challenged with sepsis. Fatty acids of the omega-3 series have profound effects upon cell membrane fluidity and stability, receptor expression and function, and activation of intracellular signaling pathways.

Multiple randomized trials of "immunonutritional" formulations have been undertaken, primarily in the setting of critical medical illness or routine postoperative recovery. Results have been mixed: Immunostimulation may help counteract the immunosuppressive effects of surgery, but they also may aggravate the systemic inflammatory response in patients with critical illness.

MONITORING

The most important goal of monitoring nutrition supplementation is avoidance of overfeeding and metabolic derangements.

Nitrogen Balance

Monitoring of nitrogen balance is the best method of assessing effectiveness of supplemental nutritional therapy. Nitrogen balance is determined by measuring concurrent protein intake and urinary excretion of urea nitrogen (UUN) over 12 or 24 h. Urea nitrogen is a waste product of protein metabolism that is minimally resorbed by the kidney. Nitrogen balance is the difference between the intake and loss of nitrogen. A positive or negative protein balance is used to determine the adequacy of protein intake. Nitrogen balance is calculated using the following equation:

$$\text{Nitrogen balance} = (\text{protein intake}/6.25) - (\text{UUN} + 4) \quad (3)$$

where protein intake and UUN are each expressed in grams

The factor 6.25 is based on dietary protein containing 16 percent nitrogen. The factor 4 accounts for the obligatory, nonurea nitrogen losses in skin and feces. The current recommendation is to monitor nitrogen balance every 5 to 6 d.

In the initial stages of critical illness, the goal of nutritional therapy is to maintain a nitrogen balance of zero. A negative balance of 0 to 5 represents moderate stress, while a negative balance greater than 5 represents severe stress. Once the anabolic or recovery phase is entered, the goal is to maintain a positive nitrogen balance to allow for repletion of protein stores.

Glucose Control

Hyperglycemia and insulin resistance are common in critically ill patients, even in the absence of a history of diabetes mellitus. These problems are often compounded by initiation of parenteral or enteral feeding. The general approach to managing such patients traditionally has focused on keeping blood glucose levels under 200 mg/dl (11.1 mmol/L). A prospective, controlled trial of over 1500 mechanically ventilated patients in surgical ICUs suggested that tighter blood glucose control may have a profound effect on mortality.

Patients were assigned randomly to intensive insulin therapy (target blood glucose of 80 to 100 mg/dl [4.4 to 5.6 mmol/L]) or standard care (target blood glucose of 180 to 200 mg/dl [10 to 11.1 mmol/L]). Mortality while in the ICU and overall in-hospital mortality were lower in the more rigorously controlled group (4.6 versus 8 percent and 7.2 versus 10.9 percent, respectively). Over 97 percent of patients in the rigorously controlled group received intravenous insulin, compared with 33 percent in the control group. Episodes of hypoglycemia (glucose less than 40 mg/dl [2.2 mmol/L]) were more common in the rigorously controlled group (5 versus 0.7 percent); however, no episodes of hemodynamic instability or seizures were observed in association with hypoglycemia.

In addition, retrospective analysis of the data noted that glycemic control, rather than cumulative insulin dose, was more closely associated with improvements in outcome, including mortality, bacteremia, and development of critical illness, polyneuropathy. In-hospital mortality was significantly higher in patients whose mean blood glucose was 110 to 150 mg/dL (6.1 and 8.3 mmol/L) versus those with a mean level under 110 mg/dl (6.1 mmol/L).

In a subsequent, prospective, observational study of 523 adult critically ill patients, survival also correlated with glucose control, rather than cumulative insulin dose. The authors of this study suggested that a slightly higher target serum glucose (less than 144 mg/dl, rather than 110 mg/dl) might optimize survival and decrease the risk of iatrogenic hypoglycemia.

Other Monitoring

Daily monitoring of potassium, sodium, BUN, calcium, magnesium, phosphate, and zinc concentrations is usually recommended. Worsening prerenal azotemia may be related to protein administration and should prompt re-evaluation of the protein contribution to total calories. Triglyceride monitoring should be performed weekly. If triglyceride levels are greater than 500 mg/dl, total calories, percent of calories derived from fatty acids, or both, should be reduced. Visceral protein levels (serum prealbumin and transferrin) should be monitored weekly, recognizing that their levels may not represent a response to feeding. Liver-associated enzymes should be assessed weekly. Mild elevations should not prompt a change to liver-specific formulas (see Table 154-2).

SPECIAL CONSIDERATIONS IN PATIENTS WITH ADVANCED LUNG DISEASE

Several issues are unique in regard to nutritional support of patients with advanced lung disease who have ARF. Supplemental nutrition is associated with an obligate increase in basal metabolic rate and has a profound effect on gas exchange. Since the breakdown of nutrition products consumes oxygen and generates carbon dioxide, supplemental nutrition increases ventilatory demand. Patients with advanced lung disease have limited ability to respond to increases in ventilatory demand, making difficult ventilatory management and weaning. The desire to limit carbon dioxide production in mechanically ventilated patients has led to a number of studies exploring use of varying nutrient compositions on this metabolic parameter. Comparison of isocaloric formulas containing pure carbohydrates with those containing a mixture of carbohydrates and lipids has demonstrated that the mixtures generally produce lower rates of carbon dioxide production. In fact, excessive carbon dioxide production is well documented when carbohydrate intake is greater than energy demand (i.e., one and one-half times or more the resting energy expenditure). Utilization of exogenous protein as a substrate for anabolism requires nonprotein calories, such as carbohydrates or fat. Thus, increasing protein intake beyond what is appropriate for critical illness is unlikely to play a major role in regulating ventilatory demand.

Administration of lipids intravenously may adversely impact oxygenation in certain situations. Lipid infusions have been associated with transient reductions in diffusion capacity in noncritically ill patients. Although results of studies of lipid infusions in critically ill patients are conflicting, a mechanism for reduced oxygenation appears to be related to modulation of lung prostaglandins levels. Changes in gas exchange typically are clinically insignificant and are eliminated with infusions under 4 to 8 h in duration.

Current recommendations call for patients with advanced lung disease to receive mixed carbohydrate-fat diets in which the fat compromises 20 to 40 percent of total calories. The increase in carbon dioxide production using a mixed carbohydrate-fat diet is minimal; furthermore, if calories provided match energy expenditure, consequences

should be of little clinical significance. Use of very high fat (providing more than 40 percent of calories) or very low fat (providing fewer than 15 percent of calories) diets is not recommended. The former may reduce carbon dioxide production, but are usually poorly tolerated and result in diarrhea and abdominal discomfort. The latter do not deliver enough essential fatty acids in critically ill, stressed patients and usually increase carbon dioxide production.

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Treatment of Agitation in the Intensive Care Unit

John P. Kress • Jesse B. Hall

Critically ill patients often require sedatives and analgesics, especially when mechanical ventilation is necessary. Most patients with respiratory failure experience a subjective sense of respiratory distress; furthermore, endotracheal intubation and positive pressure ventilation are uncomfortable for most patients in the intensive care unit (ICU). Patients in the ICU frequently experience pain. As a result, most receive analgesics along with sedatives while undergoing mechanical ventilation. Indeed, a recent multicenter international cohort study reported that 68 percent of mechanically ventilated patients received sedation for a median number of 3 days; 13 percent of mechanically ventilated patients received neuromuscular blocking agents at some point during mechanical ventilation.

Many sedative and analgesic drugs are available for managing agitation in the ICU. Recent studies reporting outcomes of critically ill patients have advanced our understanding of sedative and analgesic pharmacology in this setting. Drugs used for treatment of agitation in the ICU are extremely potent. A growing awareness of their enduring effects when the agents are used without discretion has dramatically impacted strategies for their administration.

SEDATION

Sedation is an important part of the management plan for many patients in critical care units. This section focuses on indications for use of sedative drugs, assessment of their efficacy, and clinical use of the most commonly employed agents.

Indications

Sedation requirements vary widely in mechanically ventilated patients. Although nonpharmacologic approaches, such as comfortable positioning in bed and verbal reassurance, are reasonable initial considerations, treatment using pharmacologic agents is frequently needed. Effective prescribing of sedatives in critically ill patients begins with an understanding of indications for their use.

Anxiety occurs frequently in patients undergoing mechanical ventilation and is one of the most common indications for sedation. Anxiety may result from uncomfortable experiences, such as the presence of an endotracheal tube; uncertainty of one's surroundings, diagnosis or prognosis; or isolation from family and friends. In addition, anxiety

frequently occurs in conjunction with pain, and analgesia should be considered concurrently with sedation; this topic is discussed in detail in a subsequent section.

Dyspnea is common in mechanically ventilated patients and may be a source of distress requiring sedation. Excessive coughing may contribute to patient-ventilator dyssynchrony in some patients. Many patients requiring mechanical ventilation suffer from cardiopulmonary instability and impaired gas exchange. Sedatives may be required to facilitate routine nursing care, particularly in mechanically ventilated patients. Procedures such as endotracheal suctioning, dressing changes, and repositioning often elicit distress requiring sedatives.

Autonomic instability and elevated endogenous catecholamine activity are common in mechanically ventilated patients and may lead to hemodynamic changes (e.g., tachycardia, hypertension) that may elicit myocardial ischemia, particularly in patients at risk for coronary artery disease. Sedatives may be administered to counter such autonomic hyperactivity. Elevations in oxygen consumption (V_{O_2}) and carbon dioxide production (V_{CO_2}) may compromise patients. Reduction of oxygen consumption can stabilize the balance between oxygen supply and demand by reducing V_{O_2}. The reduction may be critical in mechanically ventilated patients with shock or severe hypoxemic respiratory failure.

Amnesia is often cited as an indication for sedation of mechanically ventilated patients. For those mechanically ventilated during surgical procedures, the importance of amnesia is indisputable. In contrast, for patients mechanically ventilated during critical illness, the necessity of continuous amnesia is far less certain. Although amnesia for certain periods during the course of a critical illness requiring mechanical ventilation is logical (e.g., with performance of invasive procedures), complete amnesia for extended periods in the ICU does not appear to be beneficial. In fact, recent findings suggest that prolonged amnesia in the ICU may be detrimental to long-term neuropsychiatric recovery from critical illness. One circumstance in which amnesia is mandatory is during administration of neuromuscular blocking drugs.

The relationship between delirium and sedation is well established. Delirium—defined as an acutely changing or fluctuating mental status, inattention, disorganized thinking, and an altered level of consciousness that may or may not be accompanied by agitation—occurs in most critically ill patients. Hyperactive or agitated delirium may occur with anxiety, as well as sepsis, fever, encephalopathy (e.g., hepatic or renal), withdrawal syndromes (e.g., alcohol, tobacco, or illicit drugs) or use of certain medications. Hyperactive delirium is frequently treated with neuroleptic medications, such as haloperidol.

A much greater percentage of mechanically ventilated patients exhibit a hypoactive form of delirium. Whether hypoactive delirium responds to pharmacologic therapy is unclear. Available evidence suggests that sedative medications are more likely to exacerbate, rather than alleviate, hypoactive delirium.

Assessing Adequacy of Sedation

Assessment of the adequacy of sedation requires awareness and consideration of its indications. A reliable instrument for categorizing the level of sedation is necessary, and several sedation scales are currently available for use in the ICU.

The Ramsay scale is the most frequently utilized in clinical investigations of sedation. While it offers the benefit of simplicity, the Ramsay scale does not effectively measure quality or degree of sedation with regard to the indications outlined above. In addition, the scale has not been validated objectively.

More recently, other sedation scales, such as the Sedation Agitation Scale (SAS) and the Richmond Agitation-Sedation Scale (RASS) have been examined thoroughly for validity and reliability. The RASS is, perhaps, the most extensively evaluated scale. The scale's utility in detecting changes in sedation status over consecutive days of critical care and against constructs of level of consciousness and delirium have been validated. Furthermore, the RASS has been shown to correlate with doses of sedative and analgesic medications administered to critically ill patients. Because of their more rigorous scientific validation, the RASS and SAS are preferable to the Ramsay Scale.

Assessment of sedation adequacy is performed at the bedside. Guidance from nurses is useful, as changes in level of sedation are typically noticed first by the bedside nurse. In practice, protocols for sedative administration must take into account that, most often, drug administration is titrated by the nurse. Theoretically, optimal sedation results in a state in which all indications for sedation are addressed while the patient is fully communicative with caregivers. Although a communicative state of wakefulness during sedative administration is ideal and achievable, for many patients, the stresses of mechanical ventilation do not permit its attainment. Instead, many mechanically ventilated patients require sedation to a point at which constant communication is impossible.

An automated electronic device to monitor the sedation level would be useful in the care of mechanically ventilated patients. One such device, the bispectral index monitor, has been shown to track the level of consciousness under general anesthesia. The monitor is based on processing of raw EEG signals into a discrete, scaled number from 0 to 100, which reflects the level of cortical activity (0 indicating absence of cortical activity and 100 indicating full wakefulness). Preliminary data suggest a good correlation between the bispectral index and the SAS and RASS. However, the device has not been thoroughly evaluated in the ICU and awaits more extensive validation before its role in the critical care setting is established.

Selection of Agent

Once an indication for sedation is established, the clinician must choose one or more drugs. The use of commonly employed agents and their pharmacologic properties are outlined below.

Benzodiazepines

Benzodiazepines potentiate gamma-aminobutyric acid (GABA) receptor-mediated inhibition of the central nervous system (CNS). The GABA receptor complex regulates a cell membrane chloride channel by increasing intracellular flow of chloride ions. This activity causes hyperpolarization of neurons, raising their excitability threshold. The GABA receptor can be competitively antagonized using the synthetic agent, flumazenil, thereby reversing the pharmacologic effects of benzodiazepines. Midazolam, lorazepam, and diazepam are the three available parenteral benzodiazepines.

The onset of action of midazolam is rapid (0.5 to 5 min), and the duration of action following a single dose is short (approximately 2 h). All parenteral benzodiazepines are lipid soluble and have a large volume of distribution; therefore, they are widely distributed throughout body tissues. The duration of action following a single bolus of a parenterally administered benzodiazepine is dependent mainly on the rate of redistribution to peripheral tissues, especially adipose tissue. Midazolam undergoes hepatic metabolism and renal excretion. Alpha hydroxyl midazolam is a pharmacologically active metabolite that may accumulate in patients with impaired renal function. When midazolam is administered to critically ill patients by continuous infusion over extended periods, accumulation of the drug in peripheral tissues can occur, leading to prolonged clinical effects. Obese patients with larger volumes of distribution, and elderly patients with decreased hepatic and renal function, may be even more prone to prolonged effects.

Parenteral lorazepam has a somewhat slower onset of action (5 min) compared to midazolam due to lower lipid solubility and resultant reduced ability to cross the blood-brain barrier. The duration of action following a single dose is longer than that of midazolam (typically 6 to 10 h), depending on the dose given. Critically ill patients requiring mechanical ventilation may show a wide range of responses to the drug.

Parenteral diazepam has a rapid onset of action (1 to 3 min) and a limited duration of action (30 to 60 min) following a single dose, due to high lipid solubility. However, once peripheral tissues become saturated, recovery from the drug's effects can be prolonged for days. Diazepam has several active metabolites that may impair recovery time. Because of the tendency for drug accumulation with diazepam, it is rarely used in patients in the ICU.

Pharmacodynamic effects of all three of the benzodiazepines described are similar. All cause a dose-dependent suppression of awareness along a spectrum from mild reduction in responsiveness to obtundation. They are potent anxiolytic drugs and reliably produce amnesia. All benzodiazepines have anticonvulsant properties; lorazepam is the preferred agent for treatment of generalized seizures. Rarely, paradoxical agitation may occur in patients given benzodiazepines; the agitation may accelerate with additional doses and is more frequently observed in elderly patients.

All benzodiazepines induce a dose-dependent depression of respiratory drive. Benzodiazepine-induced depression of ventilation is less extreme than that seen with opiates; however, concurrent use of both agents may have a synergistic effect. Distinguishing benzodiazepine- from opiate-induced respiratory depression may be difficult. A pattern of reduced tidal volume and slightly increased respiratory rate is more characteristic of a benzodiazepine's effect, while opiates tend to produce slow, deep breathing.

Benzodiazepines have minimal cardiovascular effects in euvolemic patients; a slight decrease in blood pressure without a significant change in heart rate may be observed. Effects are potentiated in the presence of hypovolemia. For patients with elevated endogenous sympathetic drive, more profound decreases in blood pressure may be seen.

Table 155-1 summarizes the pharmacologic properties of the parenteral benzodiazepines. Dependence and withdrawal can be seen in patients receiving benzodiazepines for extended periods after the drugs are discontinued. Benzodiazepine withdrawal may be difficult to detect, since the signs (e.g., autonomic hyperactivity) are relatively nonspecific, particularly in critically ill patients. Accordingly, a high index of suspicion is necessary, especially for patients who have received these drugs for a protracted period.

Propofol

Propofol appears to act on the GABA receptor, although not at the same site as do the benzodiazepines. The drug is hydrophobic and must be prepared for administration as a lipid emulsion. The lipid solubility leads to rapid onset of sedation, since time required to cross the blood-brain barrier is short. High lipid solubility also permits rapid redistribution of propofol to peripheral tissues; therefore, the duration of effect is typically measured in minutes. With prolonged, continuous infusions, the duration of effect may be increased slightly, but rarely does it last beyond 60 min from the time the infusion is discontinued. When a propofol infusion is stopped, the drug is slowly redistributed back to the plasma from peripheral tissue stores; however, the redistribution is usually not clinically significant because of the drug's high lipid affinity. Propofol is ultimately metabolized primarily in the liver. The elimination half-life is 4 to 7 h and there are no active metabolites.

Propofol has predictable pharmacodynamic effects on the CNS, acting as a hypnotic agent and causing dose-dependent depression of responsiveness and awareness. The drug is also a potent anxiolytic and amnestic agent. Indeed, at high infusion rates, propofol is commonly used for general anesthesia. In addition, propofol is currently viewed by most authorities as an effective anticonvulsant, although preliminary reports of its impact on seizure threshold were conflicting. Propofol has no detectable analgesic activity and is not recommended as the sedative in management of mechanically ventilated patients, since pain control is important in this setting.

Table 155-1

Properties of Commonly Used Benzodiazepines

	Midazolam	Lorazepam	Diazepam
Typical starting dose	1–2 mg	0.5–1 mg	5–10 mg
Onset of action	0.5–2 min	3–5 min	1–3 min
Duration of action after single dose	2 h	6–10 h	1–6 h
Metabolism	Hepatic	Hepatic (less influenced by age and liver disease)	Hepatic
Elimination	Renal	Renal	Renal
Anxiolysis	4+	4+	4+
Analgesia	No effect	No effect	No effect
Hypnosis	4+	4+	4+
Amnesia	4+	4+	4+
Anticonvulsant activity	3+	4+	3+
Effectiveness in reducing dyspnea	1+	1+	1+
Cardiovascular effect	Venodilation	Venodilation	Venodilation
Respiratory effect	Hypcventilation	Hypoventilation	Hypoventilation
Common side effects	Paradoxical agitation	Paradoxical agitation	Paradoxical agitation

1+ = *minimal effect;* 2+ = *mild effect;* 3+ = *moderate effect;* 4+ = *large effect.*

Propofol causes ventilatory depression and even apnea in some patients. Because propofol-induced apnea is unpredictable and not always dose dependent, the drug should not be used in settings in which the airway can not be readily secured. Typically, the respiratory pattern seen with propofol is characterized by a decrease in tidal volume and slight increase in respiratory rate.

Propofol may cause significant decreases in blood pressure, especially in patients with hypovolemia. Venodilation and mild myocardial depression are observed. The hemodynamic effects of propofol generally are more pronounced than those of the benzodiazepines. The drug should be administered cautiously in patients with cardiac disease.

Development of hyperlipidemia is a well described complication of propofol. As described previously, the drug is delivered in an intralipid carrier. A 1 percent solution of propofol provides 1.1 kcal/ml; consequently, parenteral lipid feedings must be adjusted accordingly when a propofol infusion is given. Serum triglyceride levels should be checked frequently and the propofol stopped if hypertriglyceridemia is noted.

Propofol can support growth of bacteria and fungi; therefore, strict aseptic technique and frequent replacement of infusion tubing are essential to prevent blood stream infection.

Finally, the "propofol infusion syndrome," which manifests as dysrhythmias, heart failure, metabolic acidosis, hyperkalemia, and rhabdomyolysis is a rare complication of propofol use. The syndrome appears more likely to occur when high doses (greater than 80 μg/kg/min) and or high concentrations (2 versus 1 percent) of the drug are used. An unpublished, randomized, controlled trial of propofol in pediatric patients reported a drug concentration-dependent increase in 28-d mortality in propofol-treated patients (8 percent with 1 percent propofol; 11 percent with 2 percent propofol) compared with those given other sedatives (4 percent).

Butyrophenones

Butyrophenones, such as haloperidol, are sometimes used for sedation of mechanically ventilated patients. These drugs induce a state of tranquility, and patients often demonstrate

a detached affect. Butyrophenones appear to antagonize dopamine, especially in the basal ganglia, although their exact site of action is not known.

The time of onset of the effect of intravenously administered haloperidol is 2 to 5 min; the half-life is 2 h. Starting doses of 1 to 10 mg are used typically, and the dose is titrated depending on desired endpoint. Haloperidol is metabolized in the liver.

As noted, patients receiving haloperidol appear calm and detached. Consequently, the butyrophenones are typically reserved for acutely agitated or hyperactive patients. Patients may appear indifferent to their surroundings; occasionally, a state of cataleptic immobility is seen.

Haloperidol provides no amnesia, has no effect on seizure activity, and has minimal analgesic properties. Haloperidol and other butyrophenones are the drugs of choice for agitated delirium.

Recent data suggest reduced mortality in mechanically ventilated patients treated with haloperidol. However, the findings are preliminary and retrospective in nature. Nevertheless, such reports have created an interest in use of the drug as a sedative in the ICU. More studies are needed to validate these preliminary findings.

When used as a single agent, haloperidol has no significant respiratory depressant activity; there is little attenuation of respiratory depression when used in conjunction with opiates. Hypoxic pulmonary drive is maintained. Reliable maintenance of respiratory function is an attractive feature of haloperidol, since most sedative or analgesic drugs cause respiratory depression.

Concern over adverse cardiovascular effects has limited use of haloperidol as a sedative in critically ill patients. Haloperidol is known to prolong the QT interval in some patients; although rare, torsade de pointes has been noted in patients receiving the drug. The drug also mildly antagonizes the α_1 receptor and may decrease the neurotransmitter function of dopamine, resulting in mild hypotension.

Extrapyramidal effects are occasionally seen with haloperidol, but they are much less common with intravenous, than oral, butyrophenones. When these complications occur, treatment with diphenhydramine or benztropine may be necessary. The neuroleptic malignant syndrome (NMS) is another extremely rare problem thought to result from central dopaminergic blockade, leading to extrapyramidal side effects, muscle rigidity, and excess heat generation. NMS is a life-threatening complication manifested by "lead pipe" muscle rigidity, fever, and mental status changes. Bromocriptine, dantrolene, and pancuronium have all been used to successfully treat NMS.

Dexmedetomidine

Dexmedetomidine is a selective α_2 agonist with both sedative and analgesic properties. Patients receiving this drug appear to be sedated when undisturbed, but they are easily aroused with minimal stimulation. Dexmedetomidine is unique in that patients treated with the agent may transition between sedate and awake states quickly and easily without discontinuing the infusion. Consequently, frequent neurological examinations can be performed. The drug is approved for short-term use (less than 24 h) in patients initially receiving mechanical ventilation.

Dexmedetomidine has been shown to be analgesic-sparing in postoperative patients. The drug causes no respiratory depression; therefore, it can be continued after discontinuation of mechanical ventilation and extubation. Side effects include bradycardia and hypotension, especially with hypovolemia or high endogenous sympathetic tone. Vasoconstriction and hypertension with increasing doses of dexmedetomidine also have been described. To date, the majority of studies of dexmedetomidine have evaluated postoperative patients in the ICU. Unfortunately, dexmedetomidine has not been extensively studied as an agent for long-term administration in critically ill, mechanically ventilated patients. Table 155-2 summarizes the pharmacologic properties of propofol, haloperidol, and dexmedetomidine.

Ketamine

Ketamine is a so-called "dissociative" anesthetic with a molecular structure similar to phencyclidine. Patients receiving the drug experience a state of mind in which perception is separated from sensation; i.e., patients feel detached from their surroundings ("dissociative state"). While patients appear unaware of their environment, they keep their eyes open and are able to maintain a protective cough reflex. In addition, they may demonstrate coordinated movements that appear without purpose.

Ketamine has profound analgesic properties, but it does not produce respiratory depression. Hypertension and tachycardia may be observed and reflect increased activity of the sympathetic nervous system. Some, but not all, patients experience amnesia. The common side effects of emergence delirium and severe hallucinations greatly limit use of the drug in mechanically ventilated patients. As a phencyclidine derivative, ketamine recently has gained popularity as an illicit drug. Benzodiazepines may reduce the incidence and severity of ketamine-related hallucinations.

Barbiturates

Barbiturates, such as thiopental and pentobarbital, are potent agents that cause amnesia and unconsciousness. They have no role as sedatives in mechanically ventilated patients because of their propensity to cause hemodynamic instability and exert prolonged effects due to accumulation in peripheral tissues because of high lipid solubility. Thiopental is sometimes used to induce anesthesia in facilitating endotracheal intubation. These drugs may be used to induce a pharmacologic coma in patients with severe brain injury.

Inhalational Anesthetics

Inhalational anesthetics are used widely in the operating room to maintain general anesthesia in mechanically ventilated patients. The exhaled anesthetics must be effectively scavenged to prevent pollution of the ICU environment, since the agents

Table 155-2

Properties of Other Sedative Agents

	Propofol	Haloperidol	Dexmedetomidine
Typical starting dose	1–2 mg/kg	0.5–1 mg	0.5–1.0 μg/kg over 10 min; 0.2–0.7 μg/kg/h infusion
Onset of action	0.5–1 min	2–5 min	5–10 min
Duration of action after single dose	2–8 min	2 h	30–60 min
Metabolism	Hepatic, renal, pulmonary?	Hepatic	Hepatic
Elimination	Renal	Renal	Renal
Anxiolysis	4+	3+	3+
Analgesia	No effect	No effect	2+
Hypnosis	4+	2+	3+
Amnesia	4+	No effect	1+
Anticonvulsant activity	3+	No effect	No effect
Effectiveness in reducing dyspnea	1+	No effect	No effect
Cardiovascular effect	Venodilation, arteriolar dilation, myocardial depression	Venodilation, arteriolar dilation	Venodilation, arteriolar dilation, bradycardia, occasional hypertension
Respiratory effect	Hypoventilation	No effect	No effect
Common side effects	Increased triglycerides	Neuroleptic malignant syndrome (rare), extrapyramidal effects (rare)	Hypotension, bradycardia

1+ = *minimal effect;* 2+ = *mild effect;* 3+ = *moderate effect;* 4+ = *large effect*

are not metabolized to any significant degree. Delivery and scavenging of inhalational anesthetics is technically challenging and has limited use of these agents outside the operating room. However, some studies have reported successful use of these drugs in mechanically ventilated, critically ill patients. For example, isoflurane, which has analgesic, amnestic, and hypnotic properties, has been described as an effective single agent for mechanically ventilated patients in the ICU.

ANALGESIA

The observations that most mechanically ventilated patients experience some level of discomfort and have limited ability to communicate fully mandates an aggressive, pre-emptive strategy for use of analgesia. Failure to achieve adequate analgesia may result in a mechanically ventilated patient developing agitation that is inadequately treated with sedatives alone. As a result, inappropriate escalation of sedative doses may result in excessive administration of the drug.

Indications

Pain from surgical incisions or trauma is usually obvious, but other indications for pain control in the ICU are often covert. These include endotracheal suctioning or placement of invasive catheters, such as arterial or venous lines. For many patients, the mere presence of an endotracheal tube is painful. Preexisting problems, such as skeletal fractures from

metastatic cancer or prolonged immobility during bed rest, may also be sources of pain. If all potential causes of pain are not recognized and addressed, discomfort and agitation often persist.

Pain in critically ill, mechanically ventilated patients can increase endogenous catecholamine activity and cause myocardial ischemia, hypercoagulability, a hypermetabolic state, sleep deprivation, anxiety, or delirium. These problems are diminished by adequate treatment.

Because failure to recognize pain as a cause of agitation may lead to inappropriate administration of nonanalgesic sedatives, an aggressive approach to managing pain in mechanically ventilated patients has been strongly recommended by consensus groups. Clinicians should actively search for sources of pain. Ability to discern its presence may be difficult because of impaired communication with mechanically ventilated patients. Furthermore, clinical parameters, such as changes in vital signs, are often not reliable indicators. Therefore, a high level of vigilance toward a need for analgesia is essential in critically ill patients, especially those undergoing mechanical ventilation.

Despite consensus recommendations, management of pain in the ICU is often inadequate. Ineffective communication and delirium may contribute to the problem. Concern over addiction to opiates is not a valid reason for inadequate analgesia in critically ill patients. In addition, an arbitrary limit should not be placed on drug doses.

For most patients, intravenous administration of opiate analgesics is preferred. Intramuscular injections are not recommended because of injection-related pain and unpredictable drug absorption in critically ill patients. Dosing strategies for intravenous administration of opiates include continuous infusions and intermittent dosing.

Intermittent opiate dosing regimens can be divided into scheduled administration, administration on an as-needed (prn) basis, and patient-controlled analgesia (PCA). Strategies employing an as-needed basis may lead to fluctuations between inadequate and excessive analgesia. Patients alert enough to respond to their own pain needs may benefit from a PCA-based regimen, although the majority of mechanically ventilated patients are not alert enough to utilize a PCA device.

Transdermal opiates may be continued in patients who are treated chronically with these medications; however, transcutaneous absorption is unpredictable during critical illness. Certainly, this route should not be used for treating acute pain in mechanically ventilated patients.

Use of clinical tools to categorize pain, such as scales or scoring systems, may be helpful. In general, simpler scales are more effective, since communication for many mechanically ventilated patients is limited. Although it has not been evaluated in critically ill, mechanically ventilated patients, the visual analogue scale (VAS) has excellent reliability and validity.

The VAS uses a self-reported measure of pain intensity that consists of a 10 cm line inscribed on paper; verbal anchors—"no pain" and "severe pain"—define the ends of the scale. The scale may provide useful information in patients alert enough to respond. A similar scale is the numeric rating scale. This scale also consists of a horizontal line with numeric markings: 1 and 10 anchoring the extremes of the pain intensity scale. The numeric rating scale may be preferred because it can be completed by writing, speaking, or using hand gestures. In addition, it may demonstrate better performance across various age groups.

Selection of Agent

Nonpharmacologic analgesic strategies are occasionally helpful and should be considered. For example, malpositioning of invasive catheters (e.g., an endotracheal tube impinging on the main carina) is a problem that may be easily remedied. Likewise, optimal patient positioning in the bed may at least partially relieve low back pain, pain from chest tubes and surgical incisions, etc. However, in spite of attention to these issues, most patients require administration of pharmacologic agents. Opiates are the most commonly used analgesic agents for critically ill patients.

Opiates

Opiate receptors are found in both the central nervous system and peripheral tissues. The two most clinically important opiate receptors are the mu and kappa types. Mu receptors include two subtypes: μ_1, which mediate analgesia, and μ_2, which mediate respiratory depression, nausea, vomiting, constipation, and euphoria. Kappa receptors mediate other effects, including sedation, miosis, and spinal analgesia. Opiates may have some anxiolytic properties, but they do not provide reliable amnesia. Commonly utilized opiates are discussed in detail below.

Morphine is the most commonly used opiate and is the standard against which all other opiates are compared. When given intravenously, morphine has a relatively slow onset of action (typically, 5 to 10 min) due to its low lipid solubility. As a result, movement of the drug across the blood-brain barrier is delayed. The duration of action after a single dose is approximately 4 h. However, when the drug is given repeatedly, drug accumulation and a prolonged effect are the rule.

Morphine is metabolized in the liver through glucuronide conjugation; an active metabolite (morphine-6-glucuronide) is generated that may accumulate, especially in renal failure. Drug elimination occurs in the kidney.

Fentanyl is a highly lipid-soluble, synthetic opiate. Its lipid solubility allows rapid movement across the blood-brain barrier and a quick onset of action. Redistribution of fentanyl into peripheral tissues leads to a short duration of action after a single dose (0.5 to 1 h). However, when fentanyl is given repeatedly, tissue stores become saturated and the clinical effect can be prolonged. Fentanyl has no active metabolites and does not release histamine.

Hydromorphone is similar to morphine with regard to its onset of action. However, since hydromorphone has

no active metabolites, the drug's duration of action following long periods of administration may be less than that of morphine.

Meperidine is a lipid-soluble opiate that moves rapidly across the blood-brain barrier and has a rapid onset of action (3 to 5 min). The higher lipid solubility leads to peripheral redistribution, so that duration of action after a single dose may be shorter than that of morphine (1 to 4 h). Meperidine undergoes hepatic metabolism and renal elimination. Metabolites of meperidine may accumulate and lead to neurotoxic effects, including seizures. Because many other opiates with better safety profiles are available, this drug probably should not be used in the ICU.

Remifentanil is another synthetic, lipid-soluble drug with a rapid onset of action. The drug is unique because of its rapid metabolism via hydrolysis by nonspecific blood and tissue esterases. Consequently, the pharmacokinetic profile of remifentanil is not affected by hepatic or renal insufficiency. The drug must be given by continuous infusion because of its rapid metabolism and quick recovery time.

To date, remifentanil has not been studied extensively for long-term use in the critical care setting. Most studies report experiences with short-term use in neurosurgical and cardiothoracic surgical units. Some studies suggest that when remifentanil is used during general anesthesia, the incidence of postoperative respiratory failure may be reduced, presumably because patients wake up more rapidly. As a result, extubation in the operating room may reduce the need for routine postoperative care in the ICU.

Opiate Toxicities

All opiates cause centrally mediated, dose-dependent respiratory depression mediated by μ_2 receptors in the medulla. The typical breathing pattern seen with opiates is a reduced respiratory rate with preservation of tidal volume. The response to hypercapnia is decreased and the ventilatory response to hypoxia is obliterated. The respiratory depressive properties of opiates are frequently exploited in mechanically ventilated patients suffering from dyspnea or coughing.

The hemodynamic effects of opiates are less profound than are the respiratory effects. Hypovolemic patients whose blood pressure is sustained by sympathetic hyperactivity may become hypotensive following administration of opiates. Most opiates cause a decrease in heart rate because of decreased sympathetic activity. The histamine release caused by morphine rarely leads to hemodynamic compromise. Meperidine is unique in that it may cause tachycardia, perhaps through an anticholinergic mechanism. Remifentanil may cause bradycardia and hypotension, particularly when administered concurrently with drugs having vasodilating properties, such as propofol. Hypertension after remifentanil dosing, although described, is uncommon.

Gastrointestinal dysfunction, including drug-related ileus, is seen frequently in mechanically ventilated patients receiving opiates. Methylnaltrexone, a specific antagonist of μ_2 receptors in the gut, has been reported to attenuate opiate-induced ileus in humans. However, use of methylnaltrexone in critically ill, mechanically ventilated patients has not been studied.

The neurotoxic effects of meperidine, including seizures, have been discussed previously.

Muscle rigidity occasionally occurs with use of synthetic opiates, such as fentanyl and remifentanil; however, it is not observed with naturally occurring opiates like morphine. The finding may be seen when high doses of the drugs are injected rapidly. The mechanism of opiate-induced skeletal muscle rigidity, although not fully understood, is thought to involve supraspinal activity of the drugs in the striata and substantia nigra. In the most extreme cases, chest wall muscle rigidity may make ventilation impossible. Neuromuscular blockade (e.g., using succinylcholine) is necessary to reverse the rigidity. Fortunately, the problem is extremely rare with the doses of opiates used in management of mechanically ventilated patients.

Findings of drug dependence and withdrawal may be seen in patients receiving opiates for extended periods. Patients who abuse opiates are at risk when hospitalized for a critical illness. Signs and symptoms are nonspecific and include: pupillary dilation, sweating, lacrimation, rhinorrhea, piloerection, tachycardia, vomiting, diarrhea, hypertension, yawning, fever, tachypnea, restlessness, irritability, increased sensitivity to pain, nausea, cramps, muscle aches, dysphoria, insomnia, symptoms of opioid craving, and anxiety. Patients without prior illicit drug use may also experience opiate withdrawal when pharmacologically administered opiates are stopped suddenly. Whether any pre-emptive strategies, such as downward dose titration or regular interruption of dosing, can attenuate or prevent opiate withdrawal is not known.

In one study of trauma patients in a surgical ICU, a high incidence of withdrawal was noted in those receiving opiates or sedatives for more than 1 week. Patients manifesting withdrawal findings received higher doses of opiates and benzodiazepines than did those not experiencing withdrawal. A potential role for long-acting opiates, such as methadone, in overcoming this problem is logical, although it has not been studied. Table 155-3 summarizes the pharmacologic properties of commonly used opiates.

STRATEGIES FOR USE OF SEDATIVES AND ANALGESICS IN THE INTENSIVE CARE UNIT

Since no single drug can achieve all of the indications for sedation and pain control in the ICU, a combination of drugs, each titrated to specific end points, may be a more effective strategy. The strategy may permit use of lower doses of individual drugs, thereby reducing problems of drug accumulation.

In the ICU, sedatives and analgesics are almost always administered intravenously. Administration by continuous infusion or intermittent boluses has been advocated. Intermittent administration may lead to fluctuations in level of

Table 155-3

Properties of Commonly Used Opiates

	Morphine	Meperidine	Fentanyl	Methadone
Usual starting dose	2–5 mg	20–50 mg	25–50 μg	5–10 mg
Onset of action	10 min	3–5 min	0.5–1 min	10–20 min
Duration of action after single dose	4 h	1–4 h	0.5–1 h	6–24 h
Metabolism	Hepatic	Hepatic	Hepatic	Hepatic
Elimination	Renal	Renal	Renal	Renal
Anxiolysis	1+	2+	2+	1+
Analgesia	4+	4+	4+	4+
Hypnosis	No reliable effect	No reliable effect	No reliable effect	No reliable effect
Amnesia	No reliable effect	No reliable effect	No reliable effect	No reliable effect
Seizure threshold	No effect	May decrease	No effect	No effect
Effectiveness in reducing dyspnea	4+	4+	4+	4+
Cardiovascular effect	Venodilation	Venodilation	Venodilation	Venodilation
Respiratory effect	Hypoventilation	Hypoventilation	Hypoventilation	Hypoventilation
Common side effects	N/V, ileus, itching	N/V, seizure, ileus, itching	N/V, ileus, itching	N/V, ileus, itching

1+ = *minimal effect;* 2+ = *mild effect;* 3+ = *moderate effect;* 4+ = *large effect.*
N/V = nausea and vomiting.

sedation and increase demands on nursing time, potentially diverting attention from other aspects of patient care. The perceived benefits of continuous infusions include a more consistent level of sedation and better patient comfort. The convenience of the continuous infusion strategy for both patients and caregivers is likely the greatest reason for its popularity.

Ideally, strategies for sedation and analgesia in critically ill patients should be based upon pharmacokinetic and pharmacodynamic principles. Unfortunately, patients in the ICU frequently exhibit unpredictable alterations in pharmacodynamics, making establishment of precise guidelines for drug administration impossible. For instance, when "short-acting" benzodiazepines, such as midazolam and lorazepam, are administered in the ICU, the drugs accumulate in tissue stores and produce prolonged clinical effects. Other circumstances that confound prediction of pharmacologic behavior of sedatives and analgesics include altered hepatic or renal function, complex drug-drug interactions, altered protein binding, and circulatory instability. The multicompartmental pharmacokinetics typical of critically ill patients defy simple bedside pharmacokinetic profiling. Consequently, clinicians must titrate sedatives and analgesics against discernible clinical end points. Indeed, some critically ill patients require extraordinarily high doses of sedatives; such doses may be much greater than those described in the literature or recommended by the drug manufacturer.

Since oversedated patients are easier to manage than undersedated patients, clinicians are usually very aggressive in using sedation in the ICU. This is appropriate during the state of agitation that is often seen early during critical illness. However, maintenance of deep sedation after agitation resolves may lead to the problems described previously.

Recent clinical studies in critical care have led to evidence-based treatment strategies for many common conditions. For example, over the last decade improved outcomes

for critically ill patients with ARDS, sepsis, acute renal failure, status asthmaticus, and cancer have been reported. As sicker patients survive the acute phases of critical illness, more aggressive levels of sedation and analgesia may be necessary. This is especially true for those managed using unconventional ventilator strategies (e.g., permissive hypercapnia, low stretch, prone positioning, and pressure-controlled ventilation), since these modalities may be inherently distressing to many patients.

Although it is not without problems, deep sedation may be the only realistic option for some patients. Ideally, a head-to-toe daily assessment for the presence of organ failure should be routine for every critically ill patient. This is particularly true during the resuscitative phases of ICU care, when assessment of the adequacy of end-organ perfusion and organ function is vital, including neurological assessment.

The mental status examination is an important gauge of brain perfusion. Since brain injury is a devastating complication of critical illness, acute cerebral dysfunction must be detected quickly and corrected, if possible, before permanent injury arises. A thorough neurological examination, including assessment of mental status, may detect problems early and obviate the need for urgent diagnostic studies or therapeutic interventions. However, use of sedatives may limit a clinician's ability to serially follow a patient's neurological status.

A protocol-driven approach to sedation has been shown to alleviate many of the problems noted previously. A protocol directed by bedside nurses can shorten the duration of mechanical ventilation, ICU and hospital lengths of stay, and need for tracheostomy. Protocols may help assure adequate analgesia and sedation, based on frequent patient assessment and goal-directed titration of drugs.

A daily respite from sedatives may eliminate the tendency of clinicians to "lock in" to a high sedative infusion rate, which—while appropriate early in ICU care—may be unnecessary on subsequent days. Recently, the practice of routine daily interruption of continuous sedative infusions has been shown to reduce sedation-related complications, duration of mechanical ventilation, and ICU length of stay. The strategy allows patients to remain awake and interactive, thereby potentially reducing the amount of sedatives and opiates given and need for diagnostic studies to evaluate unexplained alterations in mental status. Although interruption of sedative infusions may lead to abrupt awakening and agitation, anticipation of these developments by the ICU team can reduce the incidence of complications, such as self-extubation.

Literature evaluating long-term consequences of recovery from respiratory failure and sedation is limited. Available data suggest that post-ICU depression is common in those who require mechanical ventilation during critical illness. Posttraumatic stress disorder (PTSD) following recovery has been reported, as well. As noted previously, studies suggest that lack of awareness related to sedation or underlying illness is associated with development of PTSD and that preservation of awareness during mechanical ventilation may reduce the risk.

CONCLUSIONS

Critically ill patients frequently exhibit agitated behavior. Sedation and pain control are important components of treatment, especially in those requiring mechanical ventilation. Treatment of agitation should be directed to specific, individualized goals.

All currently available drugs used to treat agitation have limitations. Complications related to use of these agents are common. Rather than seeking an ideal drug, clinicians should employ strategies of drug administration that are based upon principles of sedative pharmacology in critical illness. When sedative drugs are administered, recognition of specific goals allows rational management strategies to be implemented, leading to improved short- and long-term outcomes.

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Decision Making in the Intensive Care Unit

Bruno DiGiovine • Mark A. Kelley

Care of the critically ill patient is a complex interplay of science, health care economics, ethics, and the art of medicine. In the intensive care unit (ICU), the health care team utilizes costly technology to rescue patients from the extremes of illness. This struggle places emotional strain on patients, their families, and health care professionals as they balance the desire for cure with concerns for dignity, comfort, and patient autonomy. In this difficult scenario, the physician must provide facts to patients and their families about the severity of illness and prognosis. The prognostic information should include not only predictions about risk of death, but also likely outcomes in terms of quality of life if the patient survives. A description of the objective information available on the outcome of critically ill patients is provided later in this chapter.

Critical care in the United States utilizes expensive health care technology. Recently, general health costs have escalated to approximately 15 percent of the U.S. gross national product, and critical care accounts for as much as 10 percent of the health-related costs. Whether this investment in critical care results in improved health for the nation has been questioned, as has whether most patients even desire this type of treatment. Consequently, considerable research has been performed in defining the prognosis of critically ill patients, through both historical case series and objectively derived predictive instruments.

This chapter focuses on three specific areas. First is a description of the prognosis of patients with the most common conditions found in the medical ICU, such as respiratory failure and sepsis. A discussion of what is known about quality of life after recovery from these conditions is included. The second area is an overview of the outcome instruments that have been developed to predict mortality in the ICU, while the third covers social issues in critical care, such as expectations of patients and their families, advanced directives, and stratification of critically ill patients by resource utilization. The last section also addresses the ways in which access to prognostic information affects practitioners.

OUTCOMES OF MEDICAL CONDITIONS COMMONLY SEEN IN THE INTENSIVE CARE UNIT

Much has been written about the prognosis of certain syndromes and diagnoses prompting admission to the ICU. In general, diagnoses can be divided into two categories. The first is the group of disorders that result in critical illness in the course of chronic illnesses, such as chronic obstructive pulmonary disease (COPD) or cancer. In these disorders, the prognosis depends on the status of the underlying disease. The second category is an acute illness, such as acute respiratory distress syndrome (ARDS) or severe sepsis. Although the mortality for patients with these diagnoses is certainly affected by underlying disease, many of the prognostic factors measured in the ICU have a direct impact on the prognosis.

Consideration of quality of life after surviving these illnesses is important, since families often make decisions based mainly upon issues surrounding quality of life. This is most obvious if one considers a patient in a coma in whom the prognosis of eventual neurological recovery impacts decision making much more than the likelihood of the patient surviving into the immediate future.

Respiratory Failure

Acute respiratory failure (ARF) has been one of the most widely studied critical conditions. Studies have focused on three disorders: COPD, status asthmaticus, and ARDS.

Chronic Obstructive Pulmonary Disease

Acute hypercapnic respiratory failure in COPD is usually defined as the presence of an arterial CO_2 tension (Pa_{CO_2}) that exceeds 50 mmHg, or an increase of 10 mmHg or more from baseline. Recently, a reduction in the hospital mortality of this condition has been improved through use of noninvasive positive pressure ventilation (NPPV). In controlled trials of NPPV (as reviewed by the Cochrane Airways group), the overall hospital mortality in the treatment group was half of that in the usual care group (11 versus 22 percent). However, little evidence exists for an improved prognosis in the era of of NPPV for patients who are intubated. This has been confirmed by recent studies showing that patients who require critical care have hospital mortalities of 20 to 25 percent.

Nevertheless, the long-term prognosis of patients with COPD who are hospitalized remains quite guarded. A prospective study of 17,440 patients admitted to the ICU for acute respiratory failure from COPD demonstrated a 1-year mortality of 59 percent. Long-term mortality was similar for patients who received mechanical ventilation as for those who did not. Indeed, this observation recently has been reinforced by a study addressing the long-term outcomes of patients who received NPPV for COPD-related acute respiratory failure in which the 1-year mortality was 49 percent.

These studies point out that long-term survival in COPD is a function of the underlying severity of the patient's disease, rather than the severity of the exacerbation. Indeed, a recently published metric that incorporates measures of body mass index, airflow obstruction, dyspnea, and exercise capacity (as determined using the 6-minute walk test)—the so-called "BODE index"—is an accurate predictor of long-term mortality. This, or other validated prognostic metrics, may prove useful in determining prognosis in the ICU.

Based on these observations, a reasonable conclusion is that patients with COPD admitted to the ICU for acute respiratory failure have a hospital survival rate that exceeds 70 percent. Hospital survival for these patients is influenced by the overall severity of illness, rather than degree of respiratory failure, whether acute or chronic. However, survival at 2 years is less than 50 percent and is influenced by severity of the lung disease.

Status Asthmaticus

Previously reported hospital mortality rates for patients with status asthmaticus requiring mechanical ventilation ranged from 10 to 38 percent. Subsequent studies report fatality rates of 3 to 8 percent. Possible explanations for the improved outcome are the conservative use of mechanical ventilation to avoid barotrauma and the aggressive use of bronchodilators. Women have a higher risk than men of fatal asthma.

Patients with near-fatal asthma, when followed prospectively, have an alarming mortality. The mortality rate of near-fatal asthma is 10 percent at 1 year of follow-up, 14 percent at 3 years, and up to 25 perecent at 6 years. Anoxia and prehospital asphyxiation are typical presentations. The statistics emphasize that the critically ill patient with asthma may require special follow-up after discharge in order to prevent recurrence of near-fatal asthma.

Acute Rsepiratory Distress Syndrome

ARDS is a common cause of hypoxic respiratory failure that frequently accompanies such conditions as sepsis, shock, and transfusion of blood products (see Chapter 145). Mortality in ARDS is often analyzed by dividing deaths into early (less than 72 hours after ARDS onset) and late groups. Early deaths are thought to be related to the presenting illness or injury, while late deaths are presumably due to complications arising after onset of ARDS. Prognosis and mortality late in the illness appear more dependent on the presence of infection and failure of other organs, particularly the liver, kidney, and central nervous system.

In recent years, survival has improved for patients with ARDS. Two NIH-sponsored trials of controlled ventilation in ARDS have demonstrated that, in specialized centers, hospital mortality ranges from 25 to 31 percent. Reasons for the improvement are unclear, but a study at one referral center showed that the improved mortality appears limited to certain underlying diagnoses. In particular, investigators have found that the case-fatality for sepsis-related ARDS has remained at about 55 percent since 1981, while that related to trauma and other risk factors has dropped from approximately 65 to 25 percent.

Multiple organ failure is a strong prognostic factor in the outcome of ARDS. Mortality approaches 80 percent with failure of two or more organs (brain, liver, lung, heart, kidney) and reaches 90 percent with failure of three or more. In a report examining prognostic factors among patients with ARDS, the initial ratio of Pa_{O_2} to inspired oxygen fraction (Pa_{O_2}/FI_{O_2}) had only a modest influence on mortality. More important were the presence of multiorgan failure, primary ICU diagnosis, and treatment location before ICU admission. Hence, although the magnitude of initial hypoxemia reflects the severity of ARDS, outcome is determined by the interplay of mutliple organ systems.

For patients with ARDS, considerable information exists regarding quality of life in survivors. In many, quality of life, as measured by the SF-36 and other tools, appears to be reduced for up to 2 years. At 2 years, almost a quarter of survivors report moderate to severe depression, and a similar fraction report moderate to severe anxiety; almost half (47 percent) demonstrate neurocognitive impairment.

Recent studies have demonstrated that an important factor affecting quality of life after ARDS is decreased pulmonary function. Pulmonary function testing reveals diminished function in a large number of survivors. As many as 80 percent of patients have decreased diffusion, although impairment is mild in the majority. In addition, 20 to 50 percent have a restrictive pattern, while 20 percent also have an obstructive component. Notably, one study found that over 30 percent of ARDS survivors were less than fully ambulatory at 1 year.

Persistent symptoms one year after recovery correlate with the duration of mechanical ventilation, the lowest recorded lung compliance, and the requirement of an Fi_{O_2} greater than 0.6 for more than 24 hours. No link between choice of ventilatory strategy and long-term outcome has as yet been demonstrated.

Sepsis and the Systemic Inflammatory Response Syndrome

Based on a consensus conference held jointly in 1992 by the American College of Chest Physicians and the Society of Critical Care Medicine, *sepsis* is defined as a combination of the *systemic inflammatory response syndrome* (SIRS) and confirmed or suspected infection. SIRS is defined clinically as the presence of two or more of the following: (a) body temperature greater than 38°C or less than 36°C; (b) heart rate greater than 90 beats/min; (c) respiratory rate greater than 20 breaths/min or Pa_{CO_2} less than 32 mmHg; (d) WBC greater than 12,000 cells/mm^3 or less than 4000 cells/mm^3 or greater than10 percent immature (band) forms. *Severe sepsis* is defined as sepsis that occurs in association with organ failure. When hypotension is present also, the patient is said to have *septic shock*.

The epidemiology of sepsis has been elucidated in recent years using ICD-9 codes to evaluate the disorder's national impact and outcome. Studies have pointed to a reduction in hospital mortality from sepsis over the last two decades. Average mortality from sepsis was 27.8 percent from 1979 though 1984 and 17.9 percent from 1995 through 2000. Despite the decrease, overall sepsis-related mortality in the population has increased because of an increased incidence of sepsis in elderly persons. Studies have highlighted the importance of organ failure in predicting mortality; patients with three or more failing organs have a mortality rate of approximately 70 percent.

Nontraumatic Coma

The prognosis of patients with nontraumatic coma has been the subject of several prospective studies. In such patients, neurologic observations must be made in the absence of central nervous system (CNS) depressant drugs or status epilepticus. Patients without brain stem function (e.g., as indicated by the absence of corneal reflexes) within the first 12 hours, or without pupillary reflexes within the first 72 hours after the onset of coma, have little chance of meaningful neurological recovery. Although nontraumatic coma is frequently encountered in patients in whom cerebral hypoxia has resulted from cardiopulmonary resuscitation, the prognosis of nontraumatic coma is independent of etiology.

Prognostic information exists not only for neurological recovery, but also for mortality. When patients are assessed on day 3 of coma, five independent risk factors for death at 2 months can be identified: (a) age greater than or equal to 70 years; (b) abnormal brain stem response; (c) absent verbal response; (d) absent withdrawal to pain; and (e) level of creatinine in blood greater than or equal to 1.5 mg/dl. When none of these factors are present, mortality is 20 percent; with one factor, 33 percent; with two factors, 60 percent; with three factors, 94 percent; with four factors, 96 percent; and with all five factors, 100 percent. For patients with three or more risk factors, aggressive care beyond 3 days does not improve outcome and comes at a very high economic cost.

Malignancy

Continuous improvements in oncologic treatment make mortality predictions for care in the ICU difficult. For example, studies published prior to 2000 cited a 50 percent in-hospital mortality for cancer patients entering the ICU for nonoperative care; if mechanical ventilation was required, mortality exceeded 70 percent. However, in a study published in 2005, patients with cancer who underwent mechanical ventilation had a mortality rate of 50 percent. Predictors of a poor outcome included older age, poor performance status, recurrent or progressive cancer, or presence of organ failure.

Similar improved outcomes appear to be the case for bone marrow transplant (BMT) recipients. Previous studies showed a very poor prognosis, with in-hospital mortality exceeding 70 percent; patients who required ventilatory support had an in-hospital mortality in excess of 95 percent. However, recent reports of patients who have undergone stem cell BMT have been more optimistic: when admitted to the ICU for any cause, patients had a 50 percent in-hospital mortality.

Cardiopulmonary Resuscitation

The outcome of cardiopulmonary resuscitation (CPR) is influenced by the setting in which it is performed (in hospital versus out of hospital), age of the patient, and underlying diseases. When discussing goals for patient care in the ICU, physicians may attempt to offer a prognosis on outcome if the patient should experience a cardiopulmonary arrest. Recent data from the Cleveland Clinic demonstrated a 23 percent survival to hospital discharge in patients experiencing cardiopulmonary arrest—a rate that compares favorably to pooled analyses of worldwide data, in which survival rate to hospital discharge was 15 percent. Long-term outcome of discharged patients appears favorable, with nearly three-quarters surviving for 1 year.

Finally, cardiopulmonary arrests due to ventricular tachycardia or ventricular fibrillation are associated with better survival rates than those caused by asystole or pulseless electrical activity. Similarly, witnessed arrest, arrest in an ICU, respiratory arrest, short duration of CPR, and absence of comorbidities are associated with better chances of survival.

Age

Controversy exists over whether age is an independent predictor of mortality in critically ill patients. Approximately half of all patients in the United States admitted to the ICU are over 65 years of age. The percentages are much lower in other western countries. Past reports suggested a correlation between increasing age and hospital mortality. However, more recent investigations using prognostic scoring systems have found that age is a weak variable in portending the likelihood of death. More predictive power rests with such factors as underlying disease, previous functional status, and number of failing organs. Nonetheless, older age is associated with a greater likelihood of disease and poor functional status; no large studies have compared patients in different age groups who have similar severity of disease.

Two other elements that have been examined in relation to patient age and critical care include utilization of ICU resources and the cost and quality of life. About 10 percent of critically ill patients consume about 50 percent of ICU costs. Although one might envision that the elderly compose a large fraction of these high-resource patients, this is not the case. Functional assessment of quality of life in the elderly following critical care has yielded mixed results. Some studies find no differences in functional outcome between elderly and young patients; others suggest that the elderly are more impaired after critical care. The studies have not been stratified for severity of illness, making comparisons between the two age groups difficult.

Acquired Immunodeficiency Syndrome

The natural history of HIV infection changed dramatically after the introduction of highly active antiretroviral therapy (HAART). The change has also affected the prognosis of HIV-infected patients in the ICU.

Two studies have shown improvement in prognosis for patients with AIDS treated in the ICU in the era of HAART compared with prior times, with survival rates increasing from 50 to 60 percent to 70 to 75 percent. The improvement is related to a change in the general epidemiology of critical care for affected patients; in particular, fewer admissions to the ICU during the HAART era are for respiratory failure. HIV-infected patients entering the ICU are more likely to be black, less likely to be homosexual, and more likely to be users of injection drugs.

SEVERITY OF ILLNESS SCORING SYSTEMS AND MORTALITY PREDICTION

The complexity of critically ill patients has exposed the limitations of historical methods of prognostication, such as case studies and clinical judgment. From the time of Socrates, physicians have accurately predicted outcome in patients at the extreme ends of the spectrum of disease severity. For example, even inexperienced clinicians can predict the high likelihood of death in a patient with multiple organ failure and shock. Similarly, clinicians can correctly judge that patients admitted to the ICU only for monitoring of an arrhythmia have an excellent prognosis.

The challenge in formulating a prognosis is that most patients entering the ICU fall somewhere between the two ends of the spectrum, and the outcome of most patients cannot be accurately assessed by simple application of clinical judgment. A patient presenting with sepsis and hypotension might have a predicted mortality ranging from 15 to 40 percent, depending on underlying diseases, source of the infection, and other organ system dysfunction.

A number of compelling reasons exist for defining the severity of disease and prognosis in all patients in the ICU. Furthermore, assessment of quality of ICU care is difficult without a means to compare severity of disease among different ICUs. In an era of public accountability, critical care physicians must ensure that patients are provided the best possible care. Objectively measuring the severity and prognosis of the disease enables a rational description of patients in the ICU and lays the foundation for quality assessment. In addition, utilization of severity scoring systems provides a stable platform for research in critical care therapeutics and economics. An objective scoring system stratifies patients by disease severity, thereby permitting measurement of therapeutic effects and economic consequences. Finally, scoring systems of severity may be useful in clinical decision making, especially in mapping the trajectory of the patient's critical illness.

Methods Employed in Developing Severity-Scoring Systems

Severity-scoring systems utilized in critical care settings assign numeric values to various degrees of illness. The scores

are then applied in a mathematical formula to calculate predicted mortality. To a great extent, the ultimate importance of the severity score is its power to predict mortality. Two characteristics are essential in judging predictive instruments: discrimination and calibration.

Discrimination is the ability of a predictive model or scoring system to discriminate between patients who ultimately die and those who ultimately live. Typically, predictive models are based upon sensitivies and specificities for various levels of probability of death. A graphed compilation of sensitivities and specificities across different probability cutoffs results in generation of a receiver operating characteristic (ROC) curve, the area under which is a measure of the discriminative ability of the model. In effect, the curve provides a measure of how well the scoring system works over a range of predictions, but it does not assess how well the model works at any specific probability.

Calibration describes how well the prediction model performs at each specific probability cutoff. For example, a group of patients may have a predicted probability of death of 0.1. Data analysis would include determination of whether 10 percent of this group actually died. Similar analyses could be performed for other probabilities (e.g., 0.2, 0.3, etc.). For all groups, a determination can then be made with regard to how well the resultant curve predicts actual mortality. Overall assessment of the relationship of observed to predicted mortality is a measure of calibration. As noted previously, although the time-honored method of outcome prediction using clinical judgment tends to be highly discriminatory at extremes of probability, the method tends to be poorly calibrated.

Characteristics of discrimination and calibration are depicted in Fig. 156-1. A predictive instrument with perfect calibration and discrimination has predicted mortalities identical to observed mortalities over the complete range of mortality prediction. This corresponds to the line of identity seen on the graph. A poorly calibrated instrument has wide variability around the line of identity and a well calibrated instrument less variability. Therefore, the ideal prediction instrument has minimal variability and comes as close as possible to the line of identity.

Several steps are used in developing ICU severity-scoring systems. The first is to assess a representative patient population from a variety of ICUs. The key clinical characteristics of the patients are then analyzed statistically using methods of multivariate analysis and logistic regression. Variables with the most discriminatory power for predicting mortality are then tested and validated in another patient population. Based on this process, severity-scoring system and mortality prediction algorithms are derived.

A number of important features characterize currently available instruments for assessing outcome: (a) They measure an outcome of clinical significance. Most critical care–based severity-scoring systems have focused on in-hospital mortality but interest is increasing in tools to assess post-discharge mortality and functional status. (b) The instruments are easy to use. Data collection on critically ill patients

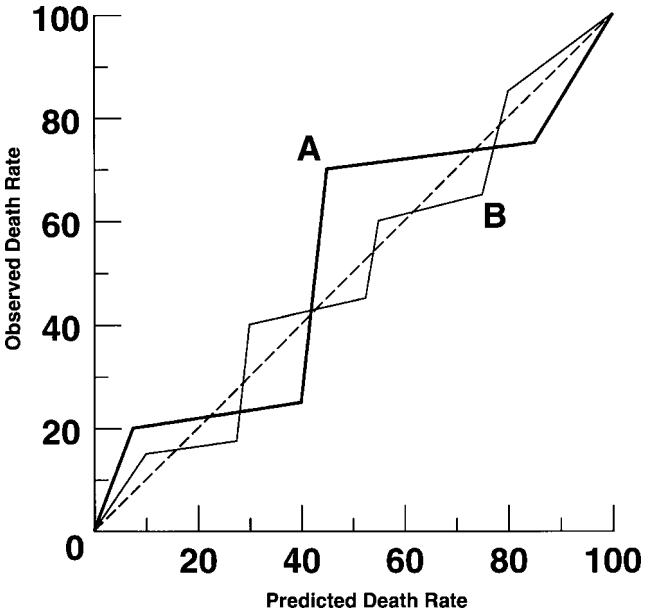

Figure 156-1 Calibration curves for two hypothetical scoring instruments. Perfect calibration is described by the line of identity. Instrument (*A*) has a wide variation around the identity line. Instrument (*B*) has less variability and therefore is better calibrated across the range of death rates. *(Data from Cowen J, Kelley M: Predicting intensive care unit outcome: Errors and bias in using predictive scoring systems.* Crit Care Clin *1053-1072, 1994.)*

can be time consuming and costly. Therefore, outcome instruments focus on data that are simple to record and reproduce. (c) The instruments have limitations in their application. Notably, they do not accurately predict outcome for populations that are not included in their sets of derivation data. For example, ICU severity-scoring systems are not applicable to all hospitalized patients. Understanding these limitations is important in preventing misuse of the instruments.

Acute Physiology, Age, and Chronic Health Evaluation Scoring System

The Acute Physiology, Age, and Chronic Health Evaluation (APACHE) scoring system has two versions (II and III) that are widely used in the United States. APACHE II was derived from studies in 13 hospitals, based on approximately 6000 patients. The instrument assigns points for age, underlying disease, and several other elements of chronic health status; it adds points for physiological variables measured in the first 24 h of ICU admission. The total severity score is entered into a logistic regression equation, which provides a predicted mortality.

APACHE II has excellent calibration and discrimination, but it has several flaws. The first is that the instrument is not as accurate when applied to patients in the ICU who are transferred from other inpatient facilities. The mortality of these patients is generally underestimated by APACHE II as a result of an effect known as "lead time bias." A similar phenomenon has been recognized to affect prediction using the updated version of APACHE, i.e. the APACHE III. The

second flaw is that the derivation database is not powerful enough to allow stratification of patients by certain disease categories, such as liver failure, respiratory failure, etc. Therefore, APACHE II cannot accurately predict outcome for any specific patient subgroup. Nevertheless, some have suggested that it can be used to decide whether to use certain medical therapies in patients with severe sepsis.

The updated version of APACHE II, called APACHE III, addresses these problems. APACHE III was derived from 40 representative hospitals and more than 17,000 patients. This instrument includes many of the variables in APACHE II but adds the location of prior treatment and the disease that required admission to the ICU. APACHE III also updates prognosis daily, based on newly measured physiological variables.

The APACHE instruments have been published widely and studied internationally. Their discrimination and calibration have been well validated; flaws in older versions have been corrected. However, the APACHE scores require a great deal of data collection and an investment in expensive proprietary computer technology. In addition, whether specific disease subgroups can be assessed, even using the expanded APACHE III database, remains unclear.

Simplified Acute Physiological Score

The simplified acute physiological score (SAPS) was developed as an alternative tool to the data-intensive APACHE instrument. SAPS provides a summary score after 24 h of ICU admission. It concentrates on physiological variables, as well as such elements as type of admission and underlying diseases. SAPS II uses 17 variables: 12 physiological variables, age, type of admission, and three underlying disease variables (AIDS, metastatic cancer, hematologic malignancy). The scoring system was derived from 8500 patients and validated on a sample of 4500 patients. The model provides a score that is entered into a mathematical formula the solution of which provides a prediction of in-hospital mortality. SAPS II does not require a principal ICU diagnosis, which is mandated with APACHE III. Based on published data, SAPS II has excellent discrimination and calibration.

Mortality Prediction Model

Like SAPS, the mortality prediction model (MPM) was developed to simplify the scoring of severity in critically ill patients. MPM was originally developed in one hospital, but its second version (MPM II) had a derivation database of 12,610 patients from many hospitals. MPM requires that patients be placed in categories that correspond to certain scores. The categories are based on several physiological assessments, chronic diagnoses, acute diagnoses, and other characteristics, such as type of admission, age, and use of CPR or mechanical ventilation. The total score is derived from 15 easily obtainable variables.

The MPM score is determined immediately upon ICU admission (MPM 0) but can be updated after 24 h (MPM 24). The update contains five of the admission variables and eight additional variables, such as arterial blood gases, creatinine, prothrombin time, urine output, etc. Like SAPS II, MPM II has excellent calibration and discrimination. Since MPM 0 utilizes measurements that are made immediately upon ICU admission, the measurement time may define a patient population that is different from that assessed 24 h after treatment and after the evolution of other diagnoses. Only the MPM 24 can be compared to SAPS and APACHE, since all three instruments use measurements performed within the first 24 h of admission.

USE OF SEVERITY SCORES IN THE INTENSIVE CARE UNIT

Development of reliable severity scoring systems in critical care has opened the field to a wide range of opportunities in health care management and research. Severity-scoring systems can be considered with regard to their potential uses in resource allocation, quality management, and clinical decision making.

Allocation of Resources

Allocation of ICU resources is grounded in the fundamental principle of *fairness*, which itself has several potential interpretations. The first is the concept of *equality,* which implies that all patients are entitled to the same access and level of ICU care. The second principle is the principle of *equity,* according to which a patient's level of care does not jeopardize that of others. A third concept, *utilitarianism,* places the overall benefit to society above that of the individual. The final application of fairness is *distribution according to medical need,* regardless of social issues (see Chapter 157).

In the United States, medical need has traditionally dictated allocation of critical care resources. Recently, outcomes and outcome prediction in critical care have raised the issue of medical suitability. This concept dictates that outcome of care, as well as medical need, should be used to assess application of ICU resources. The critical care community has summarized these issues in a consensus statement on the triage of critically ill patients. The guiding principles in this statement are patient advocacy, equitable distribution of care, and provision of care on the basis of expected benefit.

Outcome instruments have been useful in management of hospital resources. Severity scores have been used to identify patients who no longer need intensive nursing and who can be placed in lower-cost settings. Physician and nursing staffs can be queried with respect to the patient's need for the ICU and appropriate adjustments made. These analyses may extend beyond the hospital walls to include a regional approach to critical care. Like trauma patients, critically ill patients may be triaged by severity of illness, so that the most complex cases are treated in larger ICUs.

Quality Management

Because of the rising costs of health care, patients and insurers have sought methods to compare the value of choosing certain providers. This "health care value" has been defined conceptually as quality divided by cost. While the economic side of this equation is straightforward to measure, quantifying the quality of care is more elusive.

In critical care, severity-scoring instruments have been useful in assessing quality of ICU care. Some uncontrolled studies using predictive scoring instruments suggest that patient outcome is better in ICUs staffed by trained intensivists. Interhospital comparisons of hospital mortality have been widely published, since several states have mandated outcome measurements in all hospitals.

Institutional comparisons using predictive instruments may be misleading. Two studies using APACHE II demonstrated that previous site of treatment can influence the accuracy of APACHE II. In the first report, APACHE II underestimated mortality in an ICU that accepted transfers from other institutions. In the second, APACHE II underestimated mortality for patients previously treated in the hospital but overestimated mortality for patients admitted from the emergency room. As previously described, this phenomenon, called "lead-time bias," has been adjusted in APACHE III. Nevertheless, investigators have shown that patients accepted in transfer have a worse prognosis than expected based upon their APACHE III score. These examples demonstrate that even well-designed instruments, such as APACHE II and III, can have unanticipated problems, making institutional comparisons challenging.

Controversies abound concerning the accuracy and relevance of measuring quality of care. The critical care arena offers several advantages over the general health care setting in assessing quality of care: (a) The patient population in ICUs is well defined, and the provision of care is well circumscribed; (b) substantial evidence exists that the degree of illness in the ICU is the major determinant of patients' hospital mortality; (c) the predictive instruments described have considerable power to risk-adjust ICU populations and to permit evaluation of ICU effectiveness and efficiency. Therefore, severity-scoring systems provide a foundation for assessing quality of critical care.

Clinical Decision Making

Severity-scoring systems can be helpful in predicting outcome across the entire range of prognosis. However, in assessing an individual patient in the ICU, only the extremes of probability are of practical importance. For purpose of triage, patients who are clearly terminal, or who do not require intensive care, should be identified. For such assessment, clinical judgment, often based on historical case series, is as accurate as any outcome instrument. Patients in between the extremes of prognosis are usually eligible for critical care.

A concept of continuous prognostication has been introduced into the APACHE III instrument. Using this technology, disease severity and prognosis can be updated continuously to plot the trajectory of the patient's illness. The updated severity score may have more predictive power than that obtained in the first 24 h of ICU admission. The implication is that continuous monitoring of disease severity may assist in critical decisions, such as limiting or withdrawing therapy. This idea has evolved into the concept of "potentially ineffective care" that categorizes patients with a poor prognosis who consume an inordinate amount of resources.

The challenge is that there may be a substantial disparity between how health care workers use prognostic information and how patients and their families use this information. In Canada, a survey demonstrated that health care workers could not even agree among themselves on criteria for withdrawing life support. Two studies have documented that do-not-resuscitate orders are increasingly common in ICUs. However, one of these reports indicated that patients and their families did not always participate in this process.

Given these considerations, one might ask whether having reliable prognostic information actually influences physician behavior. The question was answered by The Study to Understand Prognoses and Preferences for Outcomes and Risks of Treatment (SUPPORT).

SUPPORT consisted of an observational period that, in addition to measuring prognosis, demonstrated significant differences in the outcome expectations of health care workers, patients, and families. The intervention component of the study attempted to bridge the communication gap by sharing updated prognoses and establishing better methods of communication among the health care providers, patients, and families. Surprisingly, the study showed that this intervention had no measurable effect on clinical decision making. The ICU teams continued to emphasize the technological quest for cure, rather than concentrating on the patients' desires to avoid suffering and prolonged, painful dying. The investigators concluded that, at least in the five tertiary academic centers that were part of the study, critical care providers appear to be insensitive to the needs and expectations of patients.

SUPPORT pointed out that simply providing prognostic information will not, by itself, change decision making in the ICU. The reasons for this are likely multiple, but all revolve around the need for better communication among physicians, patients, and their families. Studies have shown that even when physicians are confident about prognosis, they share their assessment with the patient only 37 percent of the time, perhaps, stemming from a belief that physicians must not extinguish patient hope.

However, methods exist for providing honest prognosis while allowing patients to continue to hope for the best outcome. In fact, SUPPORT suggests that patients may have more limited and realistic expectations of high technology than do critical care physicians. Further training on how to best to negotiate issues of trust, uncertainty, and affect in dealing with end-of-life are of benefit to all health care professionals. With such training, physicians will be able to use prognostic information from severity-scoring systems to facilitate

doctor-patient communication and support rationale decision making about the level of care.

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Ethics in the Intensive Care Unit

Paul N. Lanken

Patient care in a modern intensive care unit (ICU) presents a striking contrast. On the one hand, by definition, the ICU is the health care setting in which depersonalized, "high-tech" medicine is practiced and in which the "technological imperative" is often played out. On the other hand, the ICU also is a health care delivery site in which the deeply humanistic concerns of bioethics are evident on a day-to-day basis. *Ethics,* in simple terms, is the discipline that concerns itself with defining the right action for the right reasons. *Bioethics* generically refers to the ethics encompassing health care and health care professionals as well as basic biological and physical scientific research relevant to human health and disease.

Many ethical dilemmas in the ICU share common themes. For example, advanced technology and a high level of professional intervention in the ICU can keep patients alive for prolonged periods. However, this same capacity for delivering life-sustaining care often fails to achieve what patients really want and what also has been the traditional goal of critical care medicine: restoring patients to sufficiently good health to permit them to leave the ICU with a good quality of life. Ethical dilemmas that characterize critical care medicine often arise from this interface between the ability to prolong life by expensive and sometimes scarce technology and an inability to cure patients or even restore them to their

baseline. The relevant ethical question often is whether this technology is being used wisely, i.e., whether the patient's life *should* be prolonged. The question becomes even more complex for practitioners and patients' families when different ethical principles suggest conflicting answers.

Although the practice of critical care medicine encompasses a broad range of bioethical issues, several are particularly common, including end-of-life decision making, medical futility, resource allocation, and "do not attempt resuscitation" (DNAR) orders. These issues are some of the most challenging for ICU practitioners and constitute the focus of this chapter.

FUNDAMENTAL PRINCIPLES OF BIOETHICS

Overview

These fundamental principles of bioethics are particularly relevant in the ICU: (a) beneficence and nonmaleficence; (b) respect for patient autonomy; and (c) justice. *Ethical dilemmas* in the ICU arise when two or more of these principles are in conflict (Fig. 157-1) and when health care providers must violate one or more ethical principles to resolve the conflict. Determining which principle is the overriding one is the goal of ethical analysis applied to such conflicts.

Each of these principles also relates to certain moral entities (Fig. 157-1). The principle of beneficence primarily involves physicians, nurses, other health care providers, and health care institutions, all of which are moral agents, i.e., entities with inherent values and moral responsibilities that arise from their established roles and positions in society. Respect for patient autonomy relates to patients, their families, and surrogate decision makers or proxies—i.e., individuals who speak on behalf of those patients who lack the capacity to make medical care decisions.

Justice refers to fairness in the distribution of limited resources, i.e., *distributive justice.* This principle is usually discussed in terms of two levels of applicability. First, on the level of *macroallocation* of resources, distributive justice entails governmental and institutional decisions on the relative importance of funding health care among a number of social goods and services, e.g., education and defense. Macroallocation also refers to the distribution of health care resources among various regions and communities, e.g., funding for Medicare, Medicaid, and the Veterans Administration health care system. Second, on the level of *microallocation* of resources, *distributive justice* refers to decision making about an individual patient or resource allocation within an individual ICU, hospital, or local health care system.

Beneficence and Nonmaleficence

The principle of *beneficence* refers to the traditional aim of medicine and nursing to provide services that benefit the patient. Beneficence may be broadly interpreted to include the principle of *nonmaleficence*, i.e., doing no harm to the patient. The Hippocratic maxim *primum non nocere,* which can be translated as "First of all do no harm," reflects the fundamental importance of this principle for physicians. These two principles—beneficence and

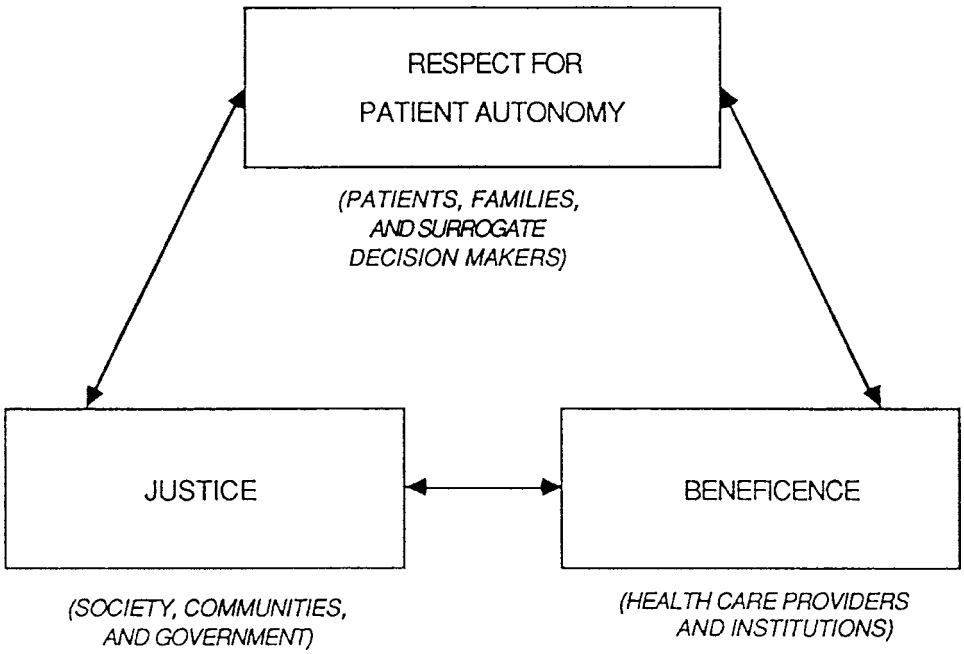

Figure 157-1 Basic ethical principles and related moral agents commonly involved in intensive care unit ethical dilemmas: respect for patient autonomy, beneficence (which includes the principle of nonmaleficence), and justice. Opposing arrows represent potential conflicts between principles.

nonmaleficence—commonly conflict when the patient suffers pain as a consequence of receiving beneficial care, e.g., the discomfort of suctioning while intubated. The bioethical conflict is resolved when it reasonably can be concluded that the discomfort of suctioning is more than balanced by its beneficial effects and that the actions are in accord with the patient's preferences.

In the Hippocratic tradition of beneficence and nonmaleficence, physicians had not only the responsibility, but also the authority to determine what was best for their patients. This has evolved to the more contemporary notion, especially prominent in the United States, that the patient, rather than the physician, determines what is best for the patient. The U.S. physician's role has evolved from the traditional authoritarian or paternalistic model to that of someone whose role is to share decision-making responsibility with the patient through educating and making recommendations. In this interpretation, the principles of beneficence and nonmaleficence are congruent with the principle of respect for patient autonomy.

Respect for Patient Autonomy

The principle of *respect for patient autonomy* is embodied by the legal concept of *self-determination:* A competent adult has a right to determine what will be done to his or her body. This principle also relates closely to the legal principle of an individual's right to privacy. According to these principles, the patient has the right to decide whether or not to undergo interventions that are available and medically appropriate. It is important to recognize that autonomy is a right to choose, not a right to demand and receive any desired treatment. The principle of respect for autonomy is also the basis for informed consent. Except in emergency circumstances, a competent adult must give informed consent prior to receiving medical care, especially that which involves potentially hazardous interventions. Under emergency conditions, i.e., when the patient's life, limb, or other vital functions are at risk without the intervention, consent is presumed. In the United States, there is a widespread societal and professional consensus that health care providers should not only respect a patient's autonomy but also enhance it through shared medical decision making. Outside of the United States, ICU physicians are much more likely to follow the paternalistic tradition of decision making, i.e., make decisions, including decisions to withhold or withdraw life support, on behalf of their patients.

Distributive Justice

In the ICU setting, the principle of justice refers to the principle of *distributive justice.* As alluded to previously, this principle pertains to defining fairness in allocating resources among individuals when not all can receive the resources. Aristotle stated the concept of distributive justice as the "principle of formal justice," according to which equals should be treated equally and unequals unequally. Although it appears rather straightforward, this formulation cannot be applied easily, because specific criteria need to be identified and agreed upon when judging if two individuals are equal or unequal. When applied to distributive justice, various ethical theories define different values as the most relevant criterion for making such judgments, as described below.

Egalitarian Theory

The *egalitarian theory* of justice holds that all individuals have equal intrinsic worth and therefore distributions should not be made based on perceptions of individuals' different social worth. One egalitarian strategy for fair allocation of health care resources is that patients having the same medical need should have the same medical resources. An example of this is health care funding in the United States for patients with end-stage renal disease (ESRD), all of whose medical expenses are covered by Medicare. Another egalitarian approach holds that each person should have an equal chance of receiving a scarce resource. Examples include dialysis centers that, prior to Medicare funding, held lotteries to determine who would receive chronic dialysis, and centers that took applicants on a "first come, first served" basis. Although the latter practice resembles a "natural lottery," it is biased due to unequal access to the health care system by poor (uninsured) and wealthy patients due to financial constraints and timeliness of referrals.

Utilitarian Theory

Other theories of ethics are based on different criteria. The *utilitarian* theory of justice is centered on the principle of utility and contends that a fair decision should maximize utility as its consequence. For example, the maxim "The greatest good for the greatest number" reflects utilitarianism. According to this theory, a country with limited health care resources could justify disproportionate spending on public health interventions benefiting many citizens, rather than on critical care beds that benefit relatively few. In the United States, prior to universal Medicare coverage for chronic dialysis, some centers based treatment access on perceived social worth—a utilitarian schema. Patients were prioritized according to whether they were employed, their type of employment, family status, and other measures of perceived social worth. Not unexpectedly, successful dialysis candidates resembled the white, male, middle-class constituents of the anonymous selection committees (so-called "God Committees" because they made life-and-death decisions). When this approach was publicized, it was criticized as unfair and discriminatory, and ensuing public outcry was the impetus for universal Medicare funding for patients with ESRD.

Libertarian Theory

The *libertarian* point of view holds that health care resources should be allocated according to one's own resources and ability to pay for them. Private health insurance in the United States is an example of the libertarian view.

Deontological Theories

Deontological, or duty-based, theories of justice are based on rules that define ethical behavior. One influential deontological theory developed by the philosopher John Rawls relates to social institutions in general. From Rawls' theory were derived the concepts of provision of fair, decent, minimum health care benefits for all, and fair, equal opportunity. The latter concept supports provision of *more than an equal share* of resources to those who are disadvantaged in order to promote a basic level of societal functioning. On this basis, health care resources should be allocated according to need of the individual patient in order to preserve or restore a basic level of functioning.

Another deontological principle that affects the distribution of limited resources is the so-called rule of rescue. This principle refers to the duty of society to expend resources to save an identified individual's life if society has the means to do so. The rule underlies well-publicized rescue efforts for *individuals* whose lives are in danger. Equally predictable but unidentifiable (i.e., anonymous) statistical deaths are not accorded the same moral obligation. Emphasis on the practice of "rescue-type" medicine in the United States, including the burgeoning of ICUs, has been heavily influenced by the rule of rescue.

RELATIONSHIP BETWEEN HEALTH CARE LAW AND ETHICS

Ethical behavior and legal requirements are generally not completely congruous. For example, some argue that the traditional application of the law to health care providers is a type of "minimal morality." For example, states *require* that practitioners providing medical or nursing care be licensed. In contrast, the professional ethics of these practitioners represents ideal professional behavior: Care *should* always be provided in accord with the principle of beneficence. For many clinical issues, the relationship between ethical and legal viewpoints is even more complex.

The legality of what health care professionals do may change, depending on external circumstances. For example, health care law may vary considerably over time between two different jurisdictions. Similarly, what is regarded as ethical or unethical behavior for physicians may change. As an example, consider active euthanasia by physicians. Although controversial, all major U.S. professional medical societies consider the practice of euthanasia as unethical. Furthermore, according to state law, it is illegal in the United States. However, over the past 10 years, euthanasia administered by physicians with certain safeguards has become both legal and professionally accepted in the Netherlands and Belgium.

As these considerations highlight, health care providers should view bioethics not as a fixed body of knowledge, but rather as a continually evolving field similar to clinical medicine.

PRINCIPLES REGARDING END-OF-LIFE CARE IN THE INTENSIVE CARE UNIT

During the last three decades a broad societal consensus has developed regarding the ethics of withholding or withdrawing life-sustaining therapies or life support. This consensus was catalyzed, for the most part, by a bioethical foundation developed by the President's Commission in the early 1980s and a series of precedent-setting judicial decisions, including the 1972 Spence decision in the District of Columbia on informed consent, the 1976 New Jersey Supreme Court decision regarding Karen Ann Quinlan, the 1984 California Supreme Court decision regarding Bartling, and culminating with the 1990 U.S. Supreme Court decision regarding Nancy Cruzan. Based this consensus, one can derive a number of principles that can guide health care professionals in making decisions related to withholding and withdrawing life-sustaining therapy. These principles are discussed in this and subsequent sections.

Principle 1

Informed adults with adequate decision-making capacity can forgo any life-sustaining medical therapy, even if the action results in their death.

The key words and phrases in Principle 1 are *adult, informed,* and *adequate decision-making capacity.* The principle applies only to adults, since children generally lack the personal autonomy required by legal or ethical standards. An adult must have appropriate information, provided in an understandable manner, in order to arrive at an informed decision. In addition, he or she must have sufficient mental capacity to evaluate the specific decision being considered. Assessment of adequacy of decision-making capacity is described below.

Principle 2

Forgoing life-sustaining therapy includes not only the withholding *of therapy, such as cardiopulmonary resuscitation, but also the* withdrawal of *interventions, such as mechanical ventilation, artificial nutrition, and hydration. There is no substantive ethical or legal difference between withholding and withdrawing life-sustaining therapy.*

Controversy over the moral distinctions between actions and omissions leading to a patient's death ended when consensus developed that withdrawing care is ethically equivalent to withholding care. Likewise, in general, there are no legal distinctions between withholding and withdrawing. Nonetheless, patients, families, and health care providers often perceive differences between them and their psychological effects.

The legal issue of whether artificial nutrition and hydration provided by an oral, nasal, or percutaneous feeding tube constitutes medical care was decided when the U.S. Supreme Court deemed it so in its 1990 decision on Nancy Cruzan. This decision established a constitutionally protected legal

right to refuse any medical care by competent adults or by appropriate surrogate decision makers acting in accord with the patient's previously expressed preferences or values.

Principle 3

Surrogate decision makers should decide whether to forgo life-sustaining therapy on behalf of patients who have lost decision-making capacity based on knowledge of what the patient would have wanted under similar circumstances. In the absence of such knowledge, decisions should be based on the patient's best interests.

Surrogate decision makers are commonly one or more members of the patient's immediate family. However, others may serve in this role under a number of circumstances. When a patient has legally designated someone as health care proxy by means of a durable power of attorney for health care, the designee must be the surrogate decision maker, even if he or she is not a member of the patient's family. When the patient has not arranged for a valid durable power of attorney but has otherwise identified someone as health care proxy, either in writing or verbally, his or her choice should be respected. Finally, when the patient has not designated a health care proxy or where state statutes do not specify a formal legal hierarchy that determines the order of selection of a surrogate, the presumption is that a close family member who knows the patient well should be the surrogate decision maker. In these circumstances, the patient's attending physician, as an advocate for protecting the patient's interests, has the responsibility for evaluating the appropriateness of a surrogate decision maker.

Legal Standards for Surrogate Decision Makers

Surrogate decision makers should use one of these two ethical and legal standards: (a) the *substituted judgment standard* and (b) the *best interests standard.*

Under the substituted judgment standard, the surrogate decision maker expresses what the patient would have preferred under the circumstances. The decision maker must have knowledge either about the preferences of the patient, as expressed orally or in writing in an advanced directive, e.g., a living will, or about the patient's values and life goals, from which valid inferences can be made.

Under the best interests standard, such knowledge is lacking, and the surrogate decision maker along with the caregivers must weigh the *benefits* of life-sustaining therapy against its *burdens.* The decision is based on the outcome of the balance. For example, the benefits of life, chance of survival, and chance of full recovery with a high quality of life are weighed against the burdens of pain, additional suffering, and poor eventual quality of life.

Principle 4

When in doubt about a patient's preferences, health care providers should err on the side of sustaining life.

Although the essence of Principle 4 is obvious, less obvious is a corollary to the principle: Health care providers who decide to sustain a patient's life should be willing to stop life-sustaining therapy if it is later determined that the patient would not have wanted it or that it was not in his or her best interests. Consistent with this principle is the concept of a "therapeutic trial of life support." Despite uncertainty about their effectiveness, life-sustaining therapies may be started in order to determine whether they will benefit the patient. Once therapy is under way, the decision to continue it or not can be made by an objective assessment, rather than a prediction, of its effectiveness.

For example, the question often arises whether a patient with acute respiratory failure complicating severe chronic obstructive pulmonary disease, once intubated and ventilated, can be successfully weaned from mechanical ventilation over a certain period of time that is acceptable to the patient. In many cases, the question can be resolved only by a time-limited therapeutic trial of assisted ventilation. In certain instances, when it can be agreed before the therapeutic trial, the ventilator can be withdrawn and the patient allowed to die if extubation or progress toward extubation is not made after an agreed-upon period. Such a therapeutic trial is preferable to not attempting potentially beneficial therapy because of uncertainty or the patient's fear that once such therapy is started, the ventilator would be continued indefinitely, even against his or her preferences.

Principle 5

Providing the patient or surrogate decision maker has been informed and consented, it is ethically appropriate to relieve pain and other suffering, such as dyspnea, even if doing so has the potential to hasten the patient's death

Giving medication to relieve pain and suffering that may hasten death as a side effect should not be confused with active euthanasia or assisted suicide. When acting in accord with Principle 5, the health care provider's intention should be to relieve pain and suffering. This follows from the principle of beneficence. In contrast, the intention when performing active euthanasia or assisted suicide is to *cause* the patient's death. Withdrawal of mechanical ventilation to allow patients to die from disease is ethically and legally distinct from active euthanasia or assisted suicide. However, in the past some authors have referred to such withdrawal as *passive euthanasia.* Since this term may be confused with active euthanasia, it should be avoided when referring to acts of withholding or withdrawing life support.

Principle 6

It is inappropriate to force physicians or other health care providers to comply with a patient's request to forgo life-sustaining therapy if compliance violates the health care provider's personal moral values. Under these circumstances, responsibility for care of the patient should be transferred to another provider who can respect the patient's request.

This principle affirms individual values and acknowledges the pluralistic nature of society, especially in the United States. Although the principle respects the right of the health care provider to act in accord with personal values, despite conflict with the patient's preferences, it continues to support the patient's autonomy. There may be difficulty in implementing this principle if the health care provider who is in conflict with the patient is uncooperative. For example, if the attending physician refuses to comply with the patient's or family's request to withdraw life support because of his or her personal moral values, the family may have to assert themselves in having that physician transfer the patient to another, more supportive, physician.

ETHICS RELATED TO FUTILE MEDICAL INTERVENTIONS

The issue of a patient's family demanding continuation of what health care providers judge as futile interventions remains controversial. While some suggest that there are limits to the respect for patient autonomy and that there is no ethical "right" to receive useless or futile interventions, others argue that the definition of medical futility is so subjective that use of the term, and decision making based upon it, are unjustified.

Principle 7

Health care professionals are not obligated to provide medical interventions that are judged as futile, even if requested by the patient or family. Futile life support may be limited without consent of the patient or surrogate decision maker.

Although Principle 7 lacks the strong consensus that supports the six preceding ethical principles, limiting life-sustaining therapy that has been judged futile has, in one form or another, already been incorporated into clinical practice. One may ask whether the term *futile life support* is inherently contradictory. If an intervention supports life, how can it be futile?

First, in response, one should make a distinction between *physiological futility* and *medical futility.* An intervention that is judged to be *physiologically futile* is one that is not expected to or does not achieve the relevant physiological function as an end point. For example, cardiopulmonary resuscitation (CPR) is judged to be physiologically futile at the point when health care providers decide to stop an unsuccessful resuscitation. The CPR has failed in its goal of restoring a spontaneous circulation. In the same sense, CPR may be regarded as physiologically futile in a patient with refractory septic shock who has a cardiac arrest after progressively worse hypotension despite use of maximal vasopressor therapy. Under these circumstances—a cardiac arrest occurring despite maximal medical therapy—the conclusion that CPR would have virtually no chance of being successful (beyond possibly a brief time period) appears reasonable. An attempt at cardiopulmonary resuscitation would prolong the patient's dying somewhat but could also do physical harm to the patient, e.g., by fracturing ribs, etc. Prolonging dying is not one of the goals of medicine and, under these circumstances, CPR would violate the principle of nonmaleficence. Arguably, some see forcing health care providers to perform CPR with virtually no prospect of success as violating the ethical integrity of the medical profession.

Although there is modest consensus about physiological futility, medical futility is more difficult to define. Some have suggested that an intervention can be judged to be medically futile if reasoning and experience indicate that the intervention would have a high likelihood of failing to result in "meaningful survival." In applying this definition, the key words are *high likelihood,* which acknowledges the uncertainties inherent in clinical decision making, and *meaningful survival.* Meaningful survival signifies that survival has a quality and duration that are of value to the particular individual. Importantly, *quality of life* refers to the *patient's* point of view, not that of the health care provider. As an extension of this definition, some organizations of critical care specialists have recommended that survival of patients with permanent loss of consciousness, such as those in a persistent vegetative state, should be regarded as meaningless. Using this criterion, a life-sustaining intervention for such patients can be judged to be medically futile and, therefore, not obligatory.

Because application of the concepts of physiological or medical futility as the basis for withholding or withdrawing life-sustaining intervention can be misapplied due to their subjective definitions, appropriate guidelines and safeguards for their application should be incorporated within a health care institution's written policies. This is especially important to ensure due process for patients and families. Furthermore, appropriate resources, such as institutional ethics committees or consulting bioethicists, should be available to provide consultations to clinicians and families. In contrast to the legacy of high-level, important court decisions affirming a patient's right to forgo life-sustaining therapy, case law on use of physiological or medical futility as the basis for withdrawal of life support is quite limited and, at present, inconclusive.

ETHICAL PRINCIPLES RELATED TO MICROALLOCATION OF ICU RESOURCES

Microallocation includes the process of admitting patients who are competing for a limited number of ICU beds or providing specific scarce resources to patients within the ICU—e.g., use of continuous renal replacement therapy or extracorporeal life support (ECLS). Microallocation encompasses concepts of both triage and rationing. *Triage* is the system of prioritizing patients according to severity of illness and, under some circumstances (e.g., in combat or disasters with mass casualties), according to the degree of benefit accrued to the patient by access to medical care. It entails consideration

of the impact of caring for one patient on the system's capacity to care for others. In the broad sense, *rationing* is an economic term that refers to the process of deciding among competing goals when resources are limited. In a narrow sense, rationing implies depriving some patients of beneficial care when not all can receive that care. One example is the use of waiting lists for solid organ transplants.

In contrast to the constantly inadequate number of solid organs for transplantation, ICU bed shortages often occur intermittently. Furthermore, in the face of *persistent* excess demand, ICU shortages can be addressed by spending more money to open more ICU beds, whereas the same does not solve the problem of scarcity of solid organs.

Compared to the obvious impact of an insufficient supply of solid organs on mortality, the impact on patient outcomes of situations when ICU demand exceeds ICU supply is unclear. This may be due to the presence of flexibility in ICU supply and demand compared to the circumstances of shortage of solid organs. Flexibility of *supply* arises from using "intermediate care" units for patients who do not necessarily need critical care but who still require monitoring and more care than provided on a general inpatient unit. There is also flexibility in *demand* since patients who normally would be admitted to an ICU postoperatively often can be held in postanesthesia care units. In response to severe ICU bed shortages, elective surgical cases may be canceled. Finally, emergency departments may be able to function for limited periods in a similar holding capacity in response to ICU bed shortages.

The following principles are derived from fundamental legal and ethical principles and can serve as guides to making microallocation decisions in the ICU despite lack of an explicit societal consensus in how to allocate care and expensive health care resources.

Principle 8

Each individual's life is equally valuable.

This principle affirms two fundamental concepts: (a) All individuals are equal; and (b) all human life is valuable. The principle reflects the egalitarian concept that all individuals are equal because of their same intrinsic worth, which in turn arises from their humanity and human dignity. On this basis, each individual should receive respect and equal treatment. According to this principle, access to ICU resources and other services should *not* be prioritized according to perceptions of relative social worth among individuals. Patients should not be regarded as more or less valuable to society by virtue of their social class, employment status, family status or ethnicity, etc.

The principle has its roots in legal principles derived from concepts of due process in the Constitution of the United States. Although there is no legal right to health care in general for citizens of the United States, there is a legal obligation for health care providers to administer care in emergency situations. Because care in the ICU is similar to emergency care from the perspective of the need to address urgent and often life-threatening medical needs, one could argue that for patients in need, ICU care is as much a right as emergency care. Although this remains an unresolved legal issue, external accrediting and state regulatory bodies hold health care institutions accountable to have resources available to meet the medical needs of their patients.

Principle 9

Vulnerable members of the community should be protected.

This principle reiterates Principle 8 that all members of the community should be treated as having equal value. However, Principle 9 goes beyond a simple sense of equality by highlighting that additional safeguards should be taken to ensure that society's vulnerable members are treated fairly.

One of these safeguards is protection against potential tyranny of the majority. For example, consider a policy in which the majority of subscribers of a health maintenance organization (HMO) decide to not fund beneficial critical care for premature infants or the elderly in order to make money available for other health care purposes. Such a policy would adversely affect these vulnerable groups, whether or not the majority's motives were judged to be altruistic (e.g., improving public health programs) or self-serving (e.g., providing free cosmetic surgery).

Historical justifications for this precaution reflect past events when society has restricted access to education, employment, or health care for certain vulnerable groups, such as the poor, the handicapped, or ethnic and racial minorities. In accord with John Rawls' principle of fair equality of opportunity, there is an egalitarian duty to provide extra (not equal) resources to those who are disabled or disadvantaged as a means of helping them function effectively in society. For example, education of handicapped children is supplemented by provision of additional resources. The supplementation provides the handicapped with a fair equality of opportunity to achieve a basic level of education. The same rationale justifies provision of additional health care resources, such as critical care, to patients in greater need rather than provision of each person with an equal amount, irrespective of need.

Current legal protections for certain vulnerable groups in the United States also reflect this principle. For example, as potential subjects in clinical research, children and other persons with absent or limited autonomy, such as the mentally retarded or prisoners, are accorded extra protection.

Principle 10

Access to intensive care should be based on the patient's medical need and the potential benefit of such care; judgments about whether a benefit is worthwhile should reflect not only the values of the patient and health care providers but also the values of the community.

This principle affirms that decisions to admit and care for patients in the ICU should be primarily based on *medical* appropriateness. In general, this principle holds that patients with the same degree of medical need should be treated

the same. However, the principle also recognizes that different medical interventions can be used for the same medical need and have a range of potential benefits from minimally (marginally) beneficial to clearly beneficial. On this basis, patients should receive critical care only when they have sufficient medical need and when critical care provides a sufficient degree of potential benefit, i.e., exceeds a certain threshold.

Evaluating the value of receiving critical care is a complicated process that incorporates three points of view: those of the health care provider, patient, and community. The health care provider's professional knowledge is required for assessing the patient's medical needs, deciding which interventions can meet those needs, and predicting the likelihood of success. In addition, although medical benefit denotes how well an intervention meets the patient's needs, only the patient can determine if the potential benefit of an intervention has sufficient personal value to justify receiving it. Finally, the community and health care institution—the parties ultimately paying for the resources—have a legitimate role in deciding whether the potential benefit of a certain intervention has sufficient value to society to make it worth the financial cost. For example, the question of whether a marginally beneficial therapy should be covered by a health care plan needs a societal perspective that extends beyond medical expertise and patient opinion. Denial of care because of very low potential benefit should reflect the community's values and priorities for using its resources.

Communities and their health care institutions may place different values on the same services. For example, one health care institution may decide that patients in states of permanent unconsciousness should be restricted from care in the ICU. Another may decide the opposite, holding that sanctity of life prevails above all other considerations. A health care system, its members, and its providers might decide not to provide critical care for all patients with irreversibly fatal diseases when death is imminent. In a financially closed system, such as one with full capitation or a global budget, money saved by such a decision could fund a comprehensive hospice home care program for the same category of patients. Involvement of health care providers in decision making provides a safeguard from the tyranny of the majority of the community, whereby vulnerable members are treated unfairly by denying reimbursement for clearly beneficial therapies.

Principle 11

Although health care providers have a primary obligation to benefit their patients, this duty has limits when it unfairly compromises the availability of resources for others.

The primary professional duty of health care providers is to promote their patients' best interests. This responsibility is derived from the principles of beneficence and fidelity and constitutes the core of the physician-patient relationship. Some have argued the physician-patient relationship bestows on the physician a *fiduciary-like responsibility* to his or her patients. Under this responsibility, physicians are obligated to put their patients' interests above their own and those of others when providing medical care. This obligation for physicians is needed because of marked inequalities of medical knowledge and experience between health care providers and patients. It also recognizes the patient's vulnerability and dependency on the health care provider due to sickness and disability.

In a closed system in which physicians put their patients' interests foremost without regard for limited resources, a situation arises that some have likened to the "tragedy of the commons." In this analogy, each herdsman is only motivated by self-interest and keeps adding cows to a common grazing area. Overgrazing eventually results in tragic consequences for all of the cows. Likewise, if health care providers keep spending limited health care resources on their own patients without regard for costs or availability of resources for other patients, the resources will be depleted eventually. The result is their unavailability for all. From these considerations arises the need for limits on the physician's duty. However, limitations cause an inherent tension for physicians between duty to patients and obligation to support a system whose availability of resources could be compromised by unchecked promotion of patient interests (e.g., by expending resources in the pursuit of minimal but expensive marginal benefits).

Even though health care providers should practice cost-effective medicine whenever possible—i.e., they should select the less costly of two therapies with equivalent effectiveness—in the absence of a closed system and explicit limits, providers are not obligated to withhold beneficial care from patients solely because of personal concerns over cost.

Allocation rules for the ICU should be made at the institutional level and not at the level of the individual practitioner. Individual physicians may have subjective biases about issues that constitute worthy bases for allocation decisions. Decision making on an institutional basis provides additional safeguards that the process is fair since institutional policy making is generally an explicit process that has built-in mechanisms for internal review and external scrutiny.

SPECIFIC ETHICAL QUESTIONS AND CONSIDERATIONS IN THE ICU

Principles 1 through 11 can be illustrated more fully when applied to a number of important ethical questions commonly arising in the ICU.

Can intubated patients in the ICU really express their preferences?

Although communication may be a difficult and slow process, selected patients receiving mechanical ventilation may be quite lucid, especially when not receiving sedation. At these times, it is not uncommon for health care professionals to communicate with the patient verbally and for the patient to write responses or questions. When the patient cannot write (e.g., due to neuromuscular weakness) more creative means of communication can be tried. Examples include

having the patient blink in response to yes or no questions and creating controlled leaks around the tracheal cuff to allow patients to phonate during the inspiratory phase of mechanical ventilation.

Should one assume that patients in the ICU are capable of valid decision making?

Under ordinary circumstances in medical practice, one should presume that adult patients have adequate decision-making capacity. In fact, the law presumes an adult to be competent until judged by a court to be legally incompetent. However, one can argue that a critically ill patient in an ICU generally lacks decision-making capacity. Many factors may compromise the decision-making capacity of a critically ill patient: effects of the underlying disease; use of sedatives, narcotics, and other mind-altering medications; sleep deprivation; pain; anxiety; disorientation; and fear. Adopting this point of view, health care providers should carefully assess the patient's decision-making capacity, relying on his or her communication, as discussed below.

What if the family or surrogate decision maker of a critically ill, incapacitated patient overrides the patient's previously known preferences regarding life-sustaining therapy?

In general, according to the principle of respect for patient autonomy, the patient's preferences should guide therapy, even if the patient's family or surrogate decision maker opposes these preferences. However, if the patient's surrogate has a valid durable power of attorney over the patient's health care decisions, the surrogate can legally exercise control over decisions—although it should be quite unusual for the person holding a durable power of attorney to ignore a patient's preferences. Regardless of the legal status of the surrogate, in the event of a conflict, the recommended first step for health care providers is discussion of differences directly with the surrogate. If needed, a request for informal or formal consultation from the hospital's ethics committee or bioethicist can be taken as the next step. In these circumstances, the principle of beneficence and the health care provider's fiduciary relationship with the patient obligate the health care provider to act as the patient's advocate. Only in rare instances should the conflict have to be resolved in a court of law.

What if health care providers do not agree with the patient's or surrogate's preferences regarding life support?

When health care providers disagree with patients or their surrogates regarding life support, physicians and nurses have little choice except to transfer care to other health care professionals. (This assumes, of course, that the decisions are made by an informed patient with adequate decision-making capacity or by a surrogate who has a valid durable power of attorney.) A classic example of this type of conflict is refusal of blood products on religious grounds by a Jehovah's Witness despite the presence of life-threatening gastrointestinal bleeding. In this case, health care providers must respect the patient's legal and ethical right to refuse the blood, even if such action results in the patient's death. When conflicting bioethical principles arise (Fig. 157-1), respect for patient autonomy overrides beneficence. Under different circumstances—e.g., if the patient is a child of a Jehovah's Witness and is a minor—health care providers can regularly obtain a court order to give blood products, despite the parents' opposition.

When preferences are expressed by a surrogate decision maker who lacks a valid durable power of attorney, the strength of the surrogate's directives is less compelling. If the patient's health care providers are concerned that the surrogate may not be acting in the patient's best interests, they should seek consultation with the ethics committee to resolve the conflict.

Is a "slow code" or "Hollywood code" ever ethically acceptable?

A "slow code" occurs when health care providers perform CPR with less than the usual intensity or speed; the intent of such an approach is to allow the patient to die. The premise is that resuscitating the patient is inappropriate. A "Hollywood code" carries the same meaning as "slow code" but includes the pretense that the code is genuine. The deception in both of these practices makes them ethically problematic and unacceptable. These practices may be employed in hospitals that do not have policies allowing DNR orders on the basis of physiological futility when CPR is considered extremely unlikely to be successful for patients. One way to discourage these types of codes is for institutions to support their physicians' authority to use their professional judgment in not providing inappropriate or ineffective interventions.

If CPR or another life-sustaining intervention is judged to be futile, what should health care providers do? Can they be forced to provide futile interventions?

When health care providers judge that CPR or other life support is futile, they should discuss this with the patient (if possible) or the patient's surrogate decision maker. Sometimes the surrogate or family agrees with the physician's judgment that limitation of life support is appropriate. Some families may even be thankful and relieved that the physician has taken responsibility for the decision to withhold or stop the intervention. If the surrogate opposes withholding CPR or other interventions that are judged futile, attempts to reach agreement through further discussion and consultation with the ethics committee should be made. If these efforts are unsuccessful, attempts should be made to transfer the patient to another physician in the same or another institution for provision of the particular intervention in question. However, patients for whom judgments of futility apply are often too unstable to be moved to another institution. Ultimately, if the patient cannot be transferred and if it is allowed by hospital policy, the physician should write a DNR order on the basis of futility and should inform the surrogate. If such DNR orders are not permitted by hospital policy and if the patient cannot be transferred to another hospital, the physician faces a limited number of alternatives: (a) acquiescence and provision of futile care; (b) resignation from the case by transferring care to another physician in the same institution; or (c) procurement of a court order to limit therapy on the basis of futility.

Is the current system of "first come, first served" regarding ICU admissions fair? Which patients should be discharged from a full ICU in order to make room for new patients?

Whether the admissions policy of an ICU is fair or unfair can be assessed by first considering the policy in relation to this basic principle of distributive justice: Equals should be treated equally and unequals treated unequally. If admission is granted solely on the basis of whether a patient's severity of illness meets a threshold, and if critical care can provide more than certain minimal threshold of potential benefit, the patient should be admitted to an available bed. This practice constitutes an example of "equals being treated equally," where the overriding criteria for equality or inequality are a sufficient degree of medical need and the potential for deriving benefit. If policies limit admissions to the ICU based solely on gender, race, ethnicity, or age—even if a patient meets thresholds for severity of illness and derivation of potential benefit—equals are being treated unequally and the decision is considered unfair.

If patients do not meet the thresholds for degree of illness or potential benefit, they should not be admitted, even if requested by the patient or his or her family. This scenario is an example of unequals (i.e., those with lower medical needs) being treated unequally (e.g., not being admitted to the ICU), where a sufficient degree of illness or potential benefit are the determinative criteria. These same considerations should govern not only decisions to admit patients to the ICU, but also decisions to continue care in the ICU.

What are the alternatives when a critically ill patient needs admission to a full ICU? Providers could refuse to admit the patient, irrespective of the relative degrees of illness among the new and old patients, assuming all existing ICU patients meet the criteria of sufficient medical need and derivation of potential benefit. This decision is consistent with the "first come, first served" rule. The waiting patient could be admitted to another ICU in the same hospital or stabilized and transferred to another hospital where an ICU bed is available. Alternatively, providers could transfer the least sick patient in the full ICU to another ICU in the same hospital or an intermediate care unit in order to make room for the new patient (assuming the new patient is clinically more in need than the transferred patient). Resources in the intermediate care unit might need to be increased temporarily to care for the transferred patient adequately. In addition, one could discharge the ICU patient with the poorest prognosis in order to make room for the new patient (assuming the new patient had a better prognosis than the one discharged). Unless differences in prognoses are striking, deciding on the relative benefits of critical care among patients is subject to bias and value judgments—a problematic issue from an ethics standpoint.

Currently available objective estimates of outcome in an ICU may improve decision making regarding resource allocation by decreasing subjectivity (see Chapter 156). However, these estimates can be misleading when used in this regard. The estimated risk of death assumes that the patient has received critical care; hence, a low predicted risk of death would not constitute firm grounds in *excluding* a patient from the ICU. It is clear that objective determination about who would do well in an intermediate care unit instead of an ICU would be useful in making these kinds of triage decisions. In addition, it is unclear how accurate the current generation of objective prognostic systems is in comparing relative risks of survival. For example, is a predicted mortality risk of 40 percent significantly different from a 50 percent risk? Finally, even if these systems predict mortality risks greater than 90 percent, it is unlikely that families of critically ill patients would accept a 5 or 10 percent chance of survival as too low to continue ICU care.

When should an individual patient's consumption of scarce or expensive resources be limited?

When a provided resource meets a patient's medical needs, the resource should be limited only if the patient is consuming a *disproportionate share;* that is, if continued consumption would threaten availability for others. For example, a patient who has persistent variceal hemorrhage, despite all possible therapeutic attempts, may require an almost continuous infusion of blood products to prevent death from exsanguination. When availability of the blood bank's supply of that type of blood product may be compromised, it is appropriate to stop transfusions. Some would argue that there is an *obligation* to do so. Such a decision by clinicians and appropriate consultants should be communicated to the family (since the patient is likely to be encephalopathic under these circumstances). However, deciding on the point at which a patient's share of a resource is disproportionate may be difficult.

With regard to consumption of limited or expensive resources, physicians face an ethical dilemma between two conflicting professional roles: (a) as patient advocate, keeping the patient alive in accord with the principles of beneficence and respect for autonomy; and (b) as a "wise steward" of a health care system's limited resources. Few guidelines exist that address the tension created by these dual roles. Although the limited resource in the example provided above was blood, the same argument could apply to health care costs. Money is as limited a resource as tangible medical products and interventions in a large health care system that is financially closed. In a closed system, money spent on behalf of one patient decreases funds available for other patients. One important future ethical challenge for health care providers in the ICU is integration of these roles as financial resources become even more constrained.

"DO NOT ATTEMPT RESUSCITATION" (DNAR) ORDERS IN THE INTENSIVE CARE UNIT

DNAR Orders and Terminology

End-of-life decisions have a prominent role in the management of patients in intensive care units. For critically ill patients, DNAR orders are common, and the majority of patients dying in intensive care units have DNAR orders at the time of their death. Clinicians practicing critical care must be familiar with the details of DNAR decision making. Because in-hospital resuscitations are much more likely to fail

than succeed, many hospitals have changed what was originally written as "Do Not Resuscitate" or DNR orders to the more realistic descriptor, "Do Not Attempt Resuscitation" or DNAR orders.

When to Discuss Withholding or Withdrawing Life-Sustaining Therapy

Ideally, a patient's primary care provider should have discussed the patient's preferences for withholding or withdrawing life support well before admission to an ICU. If done with medically informed foresight, the primary care provider should have discussed and clarified how use of life support fit into the patient's overall plan for medical care, in accord with the patient's life goals and values. At the time of this discussion, the patient should have been encouraged to prepare a written advance directive and designate a surrogate decision maker and preferably a durable power of attorney. Preferences for degrees of medical interventions under various specific scenarios that patients might reasonably encounter should have been discussed. For example, in the case of a patient with severe lung disease who has previously needed mechanical ventilation, what are the patient's preferences regarding re-intubation and duration of assisted ventilation? Does the patient want to be intubated again if clinically indicated? What should be done if the patient cannot be weaned after 1 week or after 2 or more weeks?

After a patient is admitted to an ICU, the patient, a family member, surrogate decision maker, or health care provider may initiate discussion about whether continued or new life support is appropriate. If the patient has an advance directive, the patient's ICU caregivers should explore its meaning and applicability to first clarify why the patient was admitted to the ICU. If the advance directive simply indicates that life support should be withdrawn when there is no reasonable hope for meaningful recovery (a common phrase in many living wills), one needs to understand how to interpret "reasonable" and "meaningful recovery" before being able to offer appropriate recommendations regarding continuing, withholding, or withdrawing life support.

However, if the patient lacks a written advance directive (which is the case in the vast majority of admissions), he or she may have talked to family or friends about preferences regarding life support (e.g., a preference "not to be kept alive by machines"). Alternatively, even if the patient has not expressed anything specifically about life support, family or close friends might agree about what the patient's preferences would be based on their knowledge of his or her life goals and values.

In circumstances in which a patient's prognosis is very poor and provision of CPR or other interventions would be futile or highly burdensome, the attending physician should initiate end-of-life discussions with the patient's family or surrogate decision maker as early as possible. In general, ICU attending physicians should meet with the patient's family within the first 48 hours of ICU admission specifically to discuss the patient's condition, prognosis, and what is known about the patient's preferences related to continuing or forgoing life support.

Assessment of a Patient's Decision-Making Capacity

Competency should be distinguished from *decision-making capacity.* An adult is legally competent until a court of law decides otherwise; children, as minors (unless emancipated by parenthood or marriage), lack legal competency. In contrast, decision-making *capacity* refers to a patient's functional ability, which is often determined by the patient's attending physician. Many legally competent patients lack adequate decision-making capacity when critically ill or heavily sedated. Conversely, a patient who is legally incompetent may retain some decision-making capacity, e.g., a teenager who has opinions about his or her medical care.

If a patient has adequate decision-making capacity in relation to a specific decision, then the patient should be able to demonstrate a set of abilities relating to comprehension, making comparisons, value judgments, and communication (Table 157-1). Adequate decision-making capacity in relation to a specific decision is generally present when the patient demonstrates all of the following: (a) comprehension; (b) comparative judgment; (c) communication; (d) appreciation of consequences; and (e) ability to make a choice. The patient should be able to understand information about his or her medical condition, its prognosis, and treatment alternatives, including having no treatment at all. The patient should also be able to judge and compare the medical alternatives and outcomes relative to personal values and life goals. Finally, the patient should be able to communicate preferences consistently. One should specify the context of the assessment for decision-making capacity, since in some cases patients may have adequate capacity for certain decisions but not for others.

The attending physician is responsible for assessing the patient's decision-making capacity. The process includes review of the patient's medical history, performance of mental status examinations, and consultation with the patient's

Table 157-1

Standards for Determining Decision-Making Capacity

Ability to communicate a choice
Ability to make a reasonable treatment choice
Ability to appreciate the decision and its consequences
Ability to rationally manipulate the information
Ability to understand the fundamental meaning of the decision

nurses and family. If doubt or conflict arises about the determination, additional information should be obtained, e.g., by requesting a psychiatric consultation.

Identification and Role of Surrogate Decision Makers

As is often the case, when a patient in the ICU lacks decision-making capacity, the physician commonly turns to a surrogate decision maker. The choice of proxy may be legally mandated in states that have established a legal hierarchy, e.g., spouse first, parents next, etc. Another legal mandate is an individual having a valid durable power of attorney for health care decisions. In the absence of a legal directive, if the patient has informally designated someone as surrogate decision maker, that choice should be followed with some exceptions. In most cases, the surrogate decision maker will be a close family member. An appropriate surrogate should be willing to serve in that role and to accept responsibility for making the patient's decisions, preferably based on knowledge of the patient's preferences, values, and life goals. This knowledge allows the surrogate to act on the basis of a substituted judgment, i.e., what the patient would have wanted under the circumstances.

In unusual cases, no individual who knows the patient or is willing to serve as a surrogate decision maker can be identified. In such circumstances, it is desirable to find a relatively neutral party (generally not a hospital employee) to act as surrogate—e.g., the chairperson of a hospital's ethics committee. If this is not possible, prior to their implementation, knowledgeable health care providers who are not involved in the case should review DNAR decisions. The aim of the review is to ensure that the process of determination of DNAR status is sound, i.e., the decision is based on a best interests standard or a futility judgment with appropriate due process.

Deciding on the DNAR Order

A DNAR order actually consists of much more than a proscription of CPR. In most hospitals, it also refers to withholding or withdrawing one or more life-sustaining therapies. For a patient in the ICU, these therapies may include antiarrhythmic drugs (chemical cardioversion), intubation, mechanical ventilation, dialysis, blood products, intravenous pressors, antibiotics, and parenteral and enteral nutrition.

How should limitation of certain treatments be decided? One approach is to define the goals of therapy that are applicable to the patient. Once these goals are established, one can decide which therapies are compatible with them. In some institutions, DNAR orders have been classified into three levels, each with a different goal of treatment (Table 157-2).

Table 157-2

Do Not Attempt Resuscitation (DNAR) Orders: Levels of Intervention and Associated

		Therapeutic Goals
Level	**Interventions**	**Goals of Therapy**
A	All therapies except cardiopulmonary resuscitation (CPR)	Patient is to receive all medically indicated therapies to preserve life and restore function, including those to *prevent* cardiac or respiratory arrest. However, if patient suffers cardiopulmonary arrest, *no* resuscitative attempts will be made unless specified in advance (e.g., only drug therapy permitted). Patient will not be intubated or mechanically ventilated. Restrictions may be temporarily suspended during general anesthesia or other invasive procedures if agreed upon previously. "No ICU transfer" may also be specified.
B	No additional therapy and no CPR	Therapy already under way to be continued as medically indicated, but in general, no additional treatment given except for patient comfort. Goal is maintenance of *status quo* while discussions evolve or prognosis becomes more certain. If cardiac or pulmonary arrest occurs, no resuscitative attempts to be made.
C	Palliative care only	Treatment limited to nursing care and therapy whose goal is comfort. Treatment for relief of pain, anxiety, or dyspnea may be used, even if the treatment worsens cardiac or respiratory function. All life-sustaining interventions, including artificially provided food and water, will be discontinued unless exceptions agreed upon, e.g., continued mechanical ventilation.

As a first step in the decision-making process, health care providers should meet with the patient's family or surrogate decision maker to inform them about the current medical situation, review the goals of therapy, and reassess the appropriateness of the level of current treatment in relation to the goals. The discussion should include the patient unless he or she lacks sufficient decision-making capacity. Attendance should include the attending physician, the patient's primary care physician (if applicable), consultants (when relevant for explanations and discussions of prognosis), house staff, and one or more ICU nurses and respiratory therapists caring for the patient. These meetings promote open communication among parties, help all to feel involved in the decision-making process, and facilitate understanding and acceptance of the results. "Family meetings," in which families have the opportunity to grieve while making DNAR decisions, have become common and a way of life in the practice of critical care medicine.

Carrying Out the DNAR Order

After deciding on the limits of therapy, the attending physician should document the meeting's discussion in the medical record and the justification for the DNAR order. The order should be written in a clearly identifiable location in the record as well as communicated orally to other health care providers. Details of DNAR policies vary among institutions. For example, in some states, the signature of a capable patient or surrogate decision maker may be required for a DNAR order. In the usual case, just prior to removal from assisted ventilation, bolus intravenous doses of opioids and benzodiazepines should be given pre-emptively to sedate the patient and control anxiety, pain, and dyspnea. After the desired level of sedation has been achieved, the patient is extubated and the dosage of opioids and sedatives is titrated to maintain patient comfort. A physician, nurse, or respiratory therapist may do this. If a staff member is uncomfortable with removal of life support, he or she should be given the option of not participating. Ultimately, the physician who writes the DNAR order must be prepared to extubate or remove the patient from the ventilator if necessary.

PROVIDING PALLIATIVE CARE TO ICU PATIENTS

Palliative care aims to restore or maintain quality of life and prevent needless physical or emotional suffering. Titrating opioids and sedatives to prevent the patient from suffering pain, dyspnea, or anxiety is one form of palliative care. Another is addressing the patient's and family's needs for relief of spiritual or existential suffering as well as bereavement care. It is a multidisciplinary process.

After removal from assisted ventilation, ICU patients may be legitimately kept in the ICU for palliative care. Although this may seem paradoxical to some, the patient's needs may demand an intense level of nursing and physician intervention to keep him or her comfortable, e.g., by frequent adjustments of the dose of opioid or sedative. Continued care in the ICU also has the advantage of providing continuity of care by the same physician and nursing team.

However, for patients whose needs for palliative care can be met by a less intense level of nursing and medical care, thought should be given to transferring that patient to another room outside of the ICU, e.g., in a step-down unit. This is especially important if medically needy patients require an ICU and there are no open ICU beds available. On the one hand, transfer of such patients should be given a higher priority if the demand for ICU beds is high and supply is tight, and if the patient's post-assisted ventilation course is estimated to be prolonged, i.e., longer than 1 to 2 days. Some hospitals have special palliative care units for such patients with specially trained nursing and medical staff and pleasant and private surroundings for the patient and his or her family.

On the other hand, transfer out of the ICU should be given lower priority if demand for ICU beds is modest and supply of open beds is good, and if the patient's course is anticipated to be measured in terms of hours. It makes little sense in such situations to transfer a patient out of an ICU bed for him or her to die during transport or several hours later in another unit.

Resolution of Conflicts

Good communication during the decision-making process, as a rule, prevents the occurrence of conflicts. However, if communication is poor among physicians and nurses, conflicts are common. Conflicts may also occur between the patient's family and the health care team. Conflicts may arise when one party favors forgoing life support and the other does not—for example, if the family wants full critical care continued despite pessimism about the patient's recovery on the part of the health care team. Alternatively, a family may wish to stop life support while the attending physician is reluctant to do so.

Resolution of conflicts begins with open communication among all parties. It may be helpful to consult with the hospital's ethics committee. Reviewing hospital policy, identifying legal myths or real limits, and getting all parties around the same table for discussion may resolve the conflict. Rarely should conflicts have to be referred for judicial review. If the situation reaches an impasse, it may be prudent to offer to transfer the patient to another attending physician in the same hospital or to another hospital rather than go to court.

CONCLUSION

In today's critical care environment, death in the ICU usually occurs after life-sustaining therapy is withheld or withdrawn. Many ethical considerations in the ICU arise from the frequency and complexity of this process. Health care providers

face ethical dilemmas in which decisions violate one or more ethical principles in order to respect an overriding ethical principle. Weighing ethical principles in limiting life support is supported by a broad ethical, legal, and professional consensus. As a general rule, the overriding principle is respect for patient autonomy, and hospital policies regarding DNAR orders should reflect this. Despite well-written policies, conflicts still occur, and other resources—e.g., ethics committees or consulting bioethicists—are frequently helpful in their resolution. Only in very rare cases should a conflict have to be resolved in court.

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A

Normal Values: Typical Values for a 20-Year-Old Seated Man

Ventilation (BTPS)	
Tidal volume (V_T), L	0.6
Frequency (f), breaths/min	12
Minute volume (V_E), L/min	7.2
Respiratory dead space (V_D), ml	150
Alveolar ventilation, V_A, L/min	5.4
Lung Volumes and Capacities (BTPS)	
Inspiratory capacity (IC), L	3.0
Expiratory reserve volume (ERV), L	1.9
Vital capacity (VC), L	4.9
Residual volume (RV), L	1.4
Functional residual capacity (FRC), L	3.2
Total lung capacity (TLC), L	6.3
Residual volume/total lung capacity × 100 (RV/TLC), %	22
Mechanics of Breathing	
Forced vital capacity (FVC), L	4.9
Forced expiratory volume, first second (FEV_1), L	4.0
Maximum voluntary ventilation (MVV), L/min	170
Forced expiratory volume in 1 s/forced vital capacity × 100 (FEV_1/FVC), %	83
Forced expiratory volume in 3 s/forced vital capacity × 100 (FEV_3/FVC), %	97
Forced expiratory flow during middle half of FVC (FEF_{25-75}), L/s	4.7
Forced inspiratory flow at the middle of FIVC (FIF_{50}), L/s	5.0
Static compliance of the lungs (Cst, l), L/cm H_2O	0.2
Compliance of lungs and thoracic cage (CRS, respiratory system compliance) L/cm H_2O	0.1
Airway resistance at FRC (Raw), cm H_2O/L/s	1.5
Pulmonary resistance at FRC, cm H_2O/L/s	2.0
Airway conductance at FRC (G_{aw}), L/s/cm H_2O	0.66
Specific conductance (G_{aw}/V_1)	0.22
Maximum inspiratory pressure, mmHg	−75
Maximum expiratory pressure, mmHg	120
Distribution of Inspired Gas	
Single-breath N_2 test (ΔN_2 from 750 to 1250 ml in expired gas), % N_2	<1.5
Alveolar N_2 after 7 min of breathing O_2, % N_2	<2.5
Closing volume (CV), ml	400
CV/VC × 100, %	8
Closing capacity (CC), ml	1900
CC/TLC × 100, %	30
Slope of phase III in single-breath N_2 test, % N_2/L	<2
Gas Exchange	
O_2 consumption at rest (STPD), ml/min	240
CO_2 output at rest (STPD), ml/min	192
Respiratory exchange ratio (R), CO_2 output/O_2 uptake	0.8

ALVEOLAR GAS	
PA_{O_2}, mmHg	105
PA_{CO_2}, mmHg	40
ARTERIAL BLOOD	
Pa_{O_2}, mmHg	95
Sa_{O_2}, %	98
pH	7.41
Pa_{CO_2}, mmHg	40
Pa_{O_2}, while breathing 100% O_2, mmHg	640
Alveolar Ventilation	
Alveolar ventilation, L/min	4.2
Physiological dead space/tidal volume × 100 (V_D/V_T), %	<30
Alveolar-arterial oxygen-gradient, (A-a) P_{O_2}, mmHg	10
Diffusing Capacity	
Diffusing capacity at rest for CO, single-breath (D_{LCOsb}), ml CO/min/mmHg	29
Diffusing capacity per unit alveolar volume (D_L/V_A)	4.8
Control of Ventilation	
Ventilatory response to hypercapnia, L/min/per Δ Pa_{CO_2} mmHg	>0.5
Ventilatory response to hypoxia, L/min per ΔS_{O_2} (%)	>0.2
Arterial blood P_{O_2} during moderate exercise, mmHg	95
Pulmonary Hemodynamics	
Pulmonary blood flow (cardiac output), L/min	5.4
Pulmonary artery systolic/diastolic pressure, mmHg	25/8
Pulmonary capillary blood volume, ml	100
Pulmonary "capillary" (wedge) blood pressure, mmHg	<10

B

Terms and Symbols in Respiratory Physiology

GENERAL SYMBOLS

P	Partial pressure in blood or gas. P_{O_2} = partial pressure of O_2
$\bar{X}$	A bar over the symbol indicates a mean value. $\bar{P}$ = mean pressure, as distinct from instantaneous pressure
$\dot{X}$	A time derivative (rate) is indicated by a dot above the symbol $\dot{V}_{O_2}$ = oxygen consumption per minute, ml $\dot{V}_{CO_2}$ = CO_2 production per minute, ml
% X	Percent sign preceding a symbol indicates percentage of the predicted normal value
X/Y%	Percent sign following a symbol indicates a ratio function with the ratio expressed as a percentage. Both components of the ratio must be designated. $FEV_1/FVC, \% = 100 \times FEV_1/FVC$
XA, Xa	A small capital letter or a lower-case letter on the same line following a primary symbol is a qualifier to further define the primary symbol. Alternatively, subscript letters may be used. XA = X_A, Xa = X_a Additional qualifiers of the primary symbol may be identified as shown. $P_{E_{CO_2}}$ = Pressure of CO_2 in the expired air, mmHg

GAS PHASE SYMBOLS

Primary Symbols

V	Volume of gas
$\dot{V}$	Flow of gas
F	Fractional concentration of a gas

QUALIFYING SYMBOLS

I	Inspired V_I = inspired volume
E	Expired V_E = expired volume $\dot{V}_E$ = expired volume per minute
A	Alveolar V_A = alveolar volume $\dot{V}$ = alveolar ventilation per minute
T	Tidal V_T = tidal volume
D	Dead space V_D = volume of dead space $\dot{V}_D$ = dead-space ventilation per minute
B	Barometric P_B = barometric pressure
STPD	Standard conditions: temperature 0°C, pressure 760 mmHg, and dry (0 mmHg water vapor)
BTPS	Body conditions: body temperature and ambient pressure, saturated with water vapor at these conditions
ATPD	Ambient temperature and pressure, dry
ATPS	Ambient temperature and pressure, saturated with water vapor at these conditions
an	Anatomic
p	Physiological
f	Respiratory frequency, per minute
max	Maximum
t	Time

BLOOD PHASE SYMBOLS

Primary Symbols

Q	Volume of blood
$\dot{Q}$	Blood flow $\dot{Q}$ = cardiac output, L/min

C	Concentration in the blood phase C_{O_2} = concentration of oxygen in blood, ml of O_2 per 100 ml of blood
S	Saturation in the blood phase S_{O_2} = Saturation of hemoglobin with O_2, percent

Qualifying Symbols

a	Arterial Ca_{O_2} = concentration of O_2 in arterial blood, ml of O_2 per 100 ml of blood
c	Capillary Cc_{O_2} = concentration of O_2 in capillary blood, ml of O_2 per 100 ml of blood
c′	Pulmonary end-capillary Pc'_{O_2} = partial pressure of O_2 in end-capillary blood, mmHg
v	Venous Cv_{O_2} = concentration of O_2 in venous blood, ml of O_2 per 100 ml of blood
$\bar{v}$	Mixed venous $C\bar{v}_{O_2}$ = concentration of O_2 in mixed venous blood, ml of O_2 per 100 ml of blood

VENTILATION AND LUNG MECHANICS TESTS AND SYMBOLS

Static Lung Volumes*

Primary Compartments

RV	Residual volume. Volume of air remaining in the lungs after maximum expiration.
CV	Closing volume. Volume of air expired from the onset of airways closure to residual volume. May be expressed as a fraction of VC: CV/VC, %.
ERV	Expiratory reserve volume. Maximum volume of air expired from the resting end-expiratory level.
V_T	Tidal volume. Volume of air inspired or expired with each breath during quiet breathing. When tidal volume is used in gas-exchange formulations, this symbol is used.
IRV	Inspiratory reserve volume. Maximum volume of air inspired from the end-tidal inspiratory level.

* Expressed as BTPS.

Lung Capacities*

IC	Inspiratory capacity. The sum of IRV and TV.
IVC	Inspiratory vital capacity. Maximum volume of air inspired from the point of maximum expiration, i.e., from RV
VC	Vital capacity. Maximum volume of air expired from the point of maximum inspiration, i.e., from TLC
FRC	Functional residual capacity. Sum of RV and ERV. FRC is the volume of air remaining in the lungs at the resting end-expiratory position.
TLC	Total lung capacity. Volume of air in the lungs after maximum inspiration. Also, the sum of all volume compartments of the lungs.
RV/TLC,%	Residual volume to total lung capacity ratio, expressed as a percentage.
CC	Closing capacity. Closing volume plus residual volume, may be expressed as a percentage of TLC: CC/TLC, %.

Forced Respiratory Maneuvers During Spirometry†

FVC	Forced vital capacity. The maximum volume of air forcibly expired from total lung capacity.
FIVC	Forced inspiratory vital capacity. Maximum volume of air forcibly inspired starting from residual volume.
FEV*t*	Timed forced expiratory volume. Volume of air expired in a specified time in the course of the forced vital capacity maneuver. FEV_1 = volume of air expired during the first second of the FVC.
FEV*t*/FVC, %	Ratio of time forced expiratory volume to forced vital capacity, expressed as a percentage.
FEF*x*	Forced expiratory flow, related to some portion of the FVC curve. Modifiers refer to the amount of the FVC that has been expired at the time of measurement.
$FEF_{200-1200}$	Forced expiratory flow between 200 and 1200 ml of the FVC (formerly called the maximum expiratory flow rate).
FEF_{25-75}	Forced expiratory flow during middle half of the FVC (formerly called the maximum midexpiratory flow rate or MMEF).

* Combinations of volumes for practical purposes.
† All values at BTPS.

PEF	Peak expiratory flow. Highest value for expiratory flow.
$\dot{V}_{max_x}$	Maximum flow when x percent of the FVC has been expired. $\dot{V}_{max_{75}}$ = flow (instantaneous) when 75 percent of the FVC has been expired.
FIFx	Forced inspiratory flow. As in the case of the FEF, appropriate modifiers designate the volume at which flow is being measured. Unless otherwise specified, the volume qualifiers indicate the volume inspired from RV at the point of measurement. FIF_{25-75} = forced inspiratory flow during the middle half of the FIVC.
MVV	Maximum voluntary ventilation. Volume of air exhaled during maximum breathing efforts within a specified time period. If breathing frequency is set by the examiner, it is indicated by the qualifier. MVV_{60} = MVV at a breathing frequency of 60 per minute.
PImax	Maximum inspiratory pressure. The maximum pressure generated during an inspiratory effort.
PEmax	Maximum expiratory pressure. The maximum pressure generated during an expiratory effort.

Measurements Related to Ventilation

$\dot{V}_E$	Expired volume per minute (BTPS)
$\dot{V}_I$	Inspired volume per minute (BTPS)
$\dot{V}_{CO_2}$	Carbon dioxide production per minute (STPD)
$\dot{V}_{O_2}$	Oxygen consumption per minute (STPD)
R	Respiratory exchange ratio, the ratio of CO_2 output to O_2 intake in the lungs
$\dot{V}_A$	Alveolar ventilation per minute (BTPS)
$\dot{V}_D$	Ventilation per minute of the physiological dead space (BTPS) defined by the equation $\dot{V}_D = \dot{V}_E \frac{Pa_{CO_2} - P_{E_{CO_2}}}{Pa_{CO_2} - P_{I_{CO_2}}}$
V_D	Volume of the physiological dead space, calculated as $\dot{V}_D/f$.
V_D/V_T	Ratio of dead space to tidal volume. The fraction, usually expressed as a percentage, of each breath that does not contribute to CO_2 elimination.

Mechanics of Breathing*

Pressure Terms

Paw	Pressure at any point along the airways
Pao	Pressure at the airway opening
Ppl	Pleural pressure
P_A	Alveolar pressure
Pbs	Pressure at the body surface
Pes	Esophageal pressure: used to estimate Ppl
P_A–Pbs	Transthoracic pressure
P_A–Ppl	Transpulmonary pressure
Ppl–Pbs	Pressure difference across the chest wall
Paw–Ppl	Transbronchial pressure, estimated as difference between airway and pleural pressures.

Flow-Pressure Relationships†

R	General symbol for frictional resistance, defined as the ratio of pressure difference to flow.
Raw	Airway resistance, calculated from pressure difference between airway opening (Pa_o) and alveoli (P_A) divided by the airflow, $cmH_2O/L/s$.
R_L	Total pulmonary resistance, measured by relating flow-dependent transpulmonary pressure to airflow at the mouth.
Rti	Tissue resistance (viscous resistance of lung tissue), calculated as difference between R_L and Raw.
Rus	Resistance of the airways on the upstream (alveolar) side of the point in the airways where intraluminal pressure equals Ppl, i.e., equal pressure point. Measured during a forced expiration.
Rds	Resistance of the airways on the downstream (mouth) side of the point in the airways where intraluminal pressure equals Ppl, i.e., equal pressure point. Measured during a forced expiration.
Gaw	Airway conductance, reciprocal of Raw.
Gaw/V_L	Specific conductance, airway conductance, expressed per liter of lung volume at which Gaw is measured.

*All pressures expressed relative to ambient pressure unless otherwise specified.

†Unless otherwise specified, resistance measurements are assumed to be made at FRC.

Volume-Pressure Relationships

C — General symbol for compliance of the lungs, chest wall, or total respiratory system. Volume change per unit change in applied pressure. For the lungs, the applied pressure is the pressure difference across the lungs, or transpulmonary pressure, Pao–Ppl; for the chest wall, the applied pressure is the transthoracic pressure, Ppl–Pbs; for the entire respiratory system, the applied pressure is Pao–Pbs.

C_L — Lung compliance. Value for the volume change divided by the transpulmonary pressure.

Cw — Chest wall compliance. Value for the volume change divided by the transthoracic pressure.

Cdyn — Dynamic compliance. Value for compliance determined at time of zero gas flow at the mouth during uninterrupted breathing. The respiratory frequency appears as a qualifier. $Cdyn_{40}$ = dynamic compliance at a respiratory frequency of 40 per minute.

Cst — Static compliance, value for compliance determined on the basis of measurements made during a period of zero airflow.

C/V_L — Specific compliance. Compliance divided by the lung volume at which it is determined, usually FRC.

Pst — Static pulmonary pressure at a specified lung volume.
Pst_{TLC} = static recoil pressure of the lung measured at TLC (maximum recoil pressure)

DIFFUSING CAPACITY TESTS AND SYMBOLS

D_Lx — Diffusing capacity of the lung expressed as volume (STPD) of gas (x) uptake per minute per unit alveolar-capillary pressure difference for the gas used. A modifier can be used to designate the technique:

D_{LCO}/sB = Single-breath CO diffusing capacity

D_{LCO}/ss = Steady-state CO diffusing capacity

D_M — Diffusing capacity of the alveolar-capillary membrane (STPD).

θ — Reaction rate coefficient for red blood cells. Determined as the volume of gas (stpd) that will combine per minute with 1 unit volume of blood per unit of gas tension. If the specific gas is not stated, θ is assumed to refer to CO and is a function of existing O_2 tension.

V_C — Capillary blood volume. This should be Qc for consistency with other symbols, but Vc is entrenched in the literature. In the equation that follows for $1/D_L$, Vc represents the effective pulmonary capillary blood volume, i.e., capillary blood volume in intimate association with alveolar gas.

$1/D_L$ — Total resistance to diffusion, including resistance to diffusion of test gas across the alveolar-capillary membrane, through plasma in the capillary, and across the red blood cell membrane (1/Dm), the resistance to diffusion with the red cell arising from the chemical reaction of the test gas and hemoglobin ($1/\theta Vc$), according to the formulation

$$\frac{1}{D_L} = \frac{1}{D_M} + \frac{1}{\theta Vc}$$

D_L/V_A — Diffusing capacity per unit of alveolar volume. D_L is expressed STPD, and V_A is expressed in liters, BTPS.

BLOOD GAS SYMBOLS

Symbols for these values are readily composed by combining general symbols. Some examples include the following:

Pa_{CO_2} — Arterial CO_2 tension, mmHg

Sa_{O_2} — Arterial O_2 saturation, percent

CcO_2 — Oxygen content of pulmonary end-capillary blood, ml of O_2 per 100 ml of blood

$(A\text{-}a)Po_2$ — Alveolar-arterial difference in the partial pressure of O_2, mm Hg

$Ca_{O_2}–C\bar{v}_{O_2}$ — O_2 content difference between arterial and mixed venous blood (arteriovenous O_2 difference), ml of O_2 per 100 ml of blood

PULMONARY SHUNT SYMBOLS

$\dot{Q}_s$ — Flow of blood via shunts. This is usually determined as percent of cardiac output ($\dot{Q}$) while breathing 100% O_2, according to the equation

$$\frac{\dot{Q}_s}{\dot{Q}} = \frac{CcO_2 - CaO_2}{CcO_2 - C\bar{v}O_2} \times 100$$

where
CcO_2 = O_2 content of end-capillary blood
CaO_2 = O_2 content of arterial blood
$C\bar{v}o_2$ = O_2 content of mixed venous blood

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Note: Page numbers followed by *f* and *t* indicate figures and tables, respectively.

Q

T